TESIS DOCTORAL

Methods for the epidemiological investigation of vaccine effectiveness in the elderly using large-linked databases

Autor:

Héctor Santiago Izurieta

Directora:

Ruth Gil Prieto

Programa de doctorado en Epidemiología y Salud Pública Interuniversitario

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Antecedentes

La premisa fundamental de esta tesis es la necesidad de usar datos de efectividad vacunal provenientes del análisis de los encuentros entre el sistema de salud rutinario y el paciente durante la práctica médica rutinaria para la toma de decisiones regulatorias. Estos datos tienen obvias ventajas, entre las cuales destaco las siguientes:

(1) Abren la posibilidad de usar bases de dato masivas, de decenas de millones de usuarios y miles de millones de contactos con el sistema, como las de Medicare, el seguro de salud de los ancianos de los Estados Unidos, que reembolsa los servicios de salud de cerca del 98% de la población de personas de 65 años y mayores, y asegura además a personas de cualquier edad con invalidez o insuficiencia renal.

(2) Disponen de denominadores directamente conocidos y bastante precisos y actualizados: los beneficiarios de cada uno de los servicios reembolsados por Medicare, y de numeradores conocidos también directamente, generalmente exactos.

(3) Dada la utilización ya casi generalizada de la entrada directa de datos en la práctica clínica habitual en los Estados Unidos, y las ventajas económicas y de eficiencia que se obtienen con el reembolso rápido de servicios médicos, una importante ventaja es la de obtener datos para el análisis en tiempo ´´casi real´´.

(3) Dado que los datos utilizados son producto de la práctica habitual, el costo incrementado de la utilización de estos enormes recursos para la investigación en salud púbica se limita casi únicamente al manejo y envío de datos (ciertamente cuando los datos utilizados son obtenidos a través de acuerdos interinstitucionales entre oficinas del mismo gobierno).

Las grandes bases de datos observacionales, que llamaremos datos de la atención de salud en el mundo real (real-world data) se diferencian de los datos derivados de estudios experimentales (como los estudios clínicos controlados utilizados para la aplicación de licencia de nuevos productos) en que, a diferencia de los estudios experimentales, no controlamos

implícitamente los sesgos (´´bias´´). Por lo tanto, cuando usamos datos de atención de salud en el mundo real deberemos considerar siempre la posibilidad (o quizás más acertadamente la certitud) de que los resultados así obtenidos no reflejen la asociación real entre la exposición (por ejemplo, a una vacuna) y el evento a estudiar (episodio de la enfermedad supuestamente evitada por esa vacuna), sino que estos resultados sean desviados del ´´resultado verdadero´´ por una variedad de razones, que llamamos sesgos. Ejemplos frecuentes de sesgo en estudios que usan bases de datos como las de Medicare son el subregistro de vacunados (lo cual clasificaría erróneamente a un ´´verdadero vacunado´´ como ´´no vacunado´´ por lo cual el estudio subestimaría la efectividad real de la vacuna al ´´contaminar´´ el grupo de supuestos ´´no vacunados´´ con individuos que habían recibido vacuna sin haber sido detectados por la base de datos como vacunados. Otro ejemplo de sesgo es el caso de que el individuo vacunado, de enfermarse, tenga menor probabilidad de acudir a la consulta al creer que la enfermedad será controlada fácilmente o de que su médico, que lo sabe vacunado y cree que la vacuna es altamente eficaz, lo diagnostique como sufriendo una enfermedad otra que la que se estudia, lo cual sesgaría el estudio al hacer disminuir el número de casos entre los vacunados, desviando el estimado de efectividad hacia hallar una efectividad vacunal mayor que la real. El caso más típico de sesgo por causas no identificadas en la base de datos (´´unmeasured confounders´´) es el del individuo de vida sana que se vacuna más regularmente que otros con menos disciplina en el cuidado de su salud, esto suele ser llamado efecto del vacunado saludable (´´healthy vaccinee effect´´). En este caso, al comparar a los vacunados, entre los cuales estos ´´individuos de vida sana´´ estarían excesivamente representados, aumentaríamos hipotéticamente la estimación de efectividad de la vacuna. Sin embargo, estos ´´individuos de vida sana ´´ tienen, asimismo, tendencia a acudir más al médico cuando están enfermos, lo cual tendría el efecto contrario, disminuir el estimado de efectividad. Estos ejemplos ilustran la complejidad del problema, y evidencian que, frecuentemente, no se puede saber a priori ni siquiera la dirección del presunto sesgo, menos aún su magnitud en una población y tiempo determinados. Ello evidencia la necesidad de que, en estudios que utilicen datos de la atención de salud en el mundo real, se detecten y evalúen a tiempo los posibles sesgos, y se corrijan sus efectos en el diseño y/o en el análisis con metodologías adecuadas a la base de datos que se está usando. Ello mejoraría la validez del estudio y su utilidad para la toma de decisiones regulatorias y de salud pública.

Objetivos

El objetivo común de los cuatro estudios presentados en esta tesis (que pueden verse, acompañados de sus datos suplementarios, en la sección Resultados (´´Results´´), es la utilización de datos de servicios de salud reembolsados por Medicare (´´Claims´´) para investigar la efectividad de vacunas en ancianos de 65 años y mayores. He seleccionado estos estudios por su utilidad para la toma de decisiones regulatorias y de salud pública, y porque presentan desafíos metodológicos para la identificación y corrección de posibles sesgos derivados de la utilización de datos de la atención de salud en condiciones reales.

Métodos

Los estudios presentados en esta tesis han sido todos realizados utilizando datos de Medicare, una de las bases de datos de servicios de salud para ancianos más grandes de occidente. Medicare cubre a aproximadamente un 98% de los individuos de 65 años y mayores de los Estados Unidos, y los datos derivados de contactos de pacientes asegurados por Medicare con los servicios de salud pueden obtenerse casi en tiempo real, como lo hemos demostrado en estudios previos. Durante el periodo de desarrollo inicial de esta tesis hicimos una primera exploración sobre el uso de la base de datos de Medicare para estudios de efectividad vacunal. Este estudio de prueba inicial (´´proof of concept study´´) fue completado a fines del año 2015, y sirvió de base para el desarrollo de los cuatro estudios que constituyen los resultados de esta tesis, este estudio será explicado brevemente aquí, pues es esencial al desarrollo de esta tesis. En otras palabras, los métodos de los estudios resultado de esta tesis se basaron inicialmente en los utilizados en este estudio de prueba inicial en Medicare. Para cada estudio subsecuente, dependiendo de factores que incluyen la pregunta o preguntas a responder, la población de interés para el estudio a realizar, los grupos de riesgo a comparar, y las características fundamentales del producto a estudiar,

utilizamos innovaciones y adaptaciones que describiremos en detalle en la sección de métodos de cada uno de los proyectos. Este estudio de prueba inicial (Efectividad comparativa de las vacunas de influenza a alta dosis (HD) vs. dosis standard (SD) para consultas médicas y hospitalizaciones por influenza entre beneficiaries de Medicare de 65 años de edad y mayores durante la temporada 2012-2013 (´´Comparative effectiveness of high-dose vs. standard dose influenza vaccines against medical office visits and hospitalizations among Medicare beneficiaries ages 65 years and older during the 2012-2013 season´´), fue publicado en Lancet Infectious Diseases a fines del año 2015 (Izurieta, Thadani et al, Lancet Infect Dis 2015). I iniciamos el estudio subsecuentemente a la licencia dada por la Agencia de Medicamentos y Alimentos de los Estados Unidos (U.S. Food and Drug Administration) a una vacuna de influenza trivalente inactivada de alta dosis a fines del año 2009. Esta licencia fue otorgada en base a resultados serológicos favorables, usando el mecanismo de licencia acelerada (´´Accelerated approval regulations´´), que no requiere demostración previa de eficacia, y es utilizado solamente para productos de alta prioridad para los cuales la demostración de eficacia previa a la licencia no es posible o retrasaría excesivamente la licencia. Dada la incertidumbre existente en esa época sobre la factibilidad de un estudio de eficacia aleatorio subsecuente a la licencia, y sobre la dificultad de que ese estudio aleatorio, de completarse, pudiese estudiar también efectos severos de influenza (hospitalizaciones), decidimos iniciar paralelamente un estudio observacional de efectividad vacunal. El objetivo de este estudio fue determinar si la vacuna HD era más efectiva que las tradicionales vacunas SD con tres veces menos hemaglutinina, para la prevención de visitas médicas y hospitalizaciones relacionadas con la influenza entre los beneficiarios de Medicare en los Estados Unidos. Para ello, utilizamos un diseño de cohortes retrospectivo con códigos de facturación (´´Claims´´), e identificamos cohortes de beneficiarios ≥65 años que recibieron vacunas sea HD o SD en farmacias ambulatorias que ofrecían y administraban ambas vacunas durante la temporada de influenza 2012-2013. Definimos los diagnósticos a analizar utilizando códigos de facturación relevantes en Medicare. La variable resultado para el análisis primario fue la infección probable por influenza, definida por la implementación de una prueba rápida de diagnóstico de influenza, seguida de la administración de oseltamivir, un inhibidor de la neuraminidasa utilizado únicamente para tratar influenza. La variable resultado para el análisis secundario fue la hospitalización o la visita a urgencias con un diagnóstico de influenza. Estimamos etonces la efectividad relativa ambas vacunas usando una comparación de las tasas de influenza entre beneficiarios de Medicare que recibieron la vacuna HD con beneficiarios que recibieron una de las vacunas con SD

durante periodos de alta circulación de influenza. Para estos análisis utilizamos modelos de regresión de Poisson univariados y multivariados. Estudiamos un total de 929.730 vacunados con HD y 1.615.545 con SD. Los sujetos incluidos en cada cohorte estaban bien balanceados con respecto a edad, otras características demográficas, y presencia de afecciones médicas subyacentes. La vacuna HD fue 22% más efectiva que la vacuna SD para la prevención de visitas médicas con un diagnóstico de influenza y también 22% más efectiva para la prevención de hospitalizaciones o visitas a urgencias con un diagnóstico de influenza. En conclusión, este estudio, que fue calificado de ´´innovador´´ por el editorial que lo acompañó (Hak et al, Lancet Infect Dis 2015), utilizó datos de más de dos millones y medio de ancianos registrados en Medicare, vacunados durante la temporada de gripe 2012-2013, y demostró que la vacuna HD fue significativamente más efectiva que la SD para la prevención de visitas médicas, hospitalizaciones y visitas a urgencias por influenza. Una copia de este estudio, y de sus datos suplementarios, puede encontrarse en la sección Anexos (´´Annex´´) de esta tesis.

Resultados

Efectividad comparativa de las vacunas de influenza a alta dosis (HD) vs. dosis standard (SD) para prevenir muertes subsecuentes a influenza entre beneficiarios de Medicare de 65 años y mayores: estudio de cohortes retrospectivo, 2012-2013 y 2013-2014. (Shay et al, JID 2017).

Un ensayo de fase IV patrocinado por el fabricante de la vacuna de influenza HD y un estudio observacional implementado por nosotros en millones de beneficiarios de Medicare, mostraron que los vacunados con HD tuvieron una menor incidencia de visitas médicas y hospitalizaciones por influenza. Ninguno de estos estudios pudo estudiar la consecuencia última de influenza, la mortalidad. El objetivo de este nuevo estudio fue evaluar la efectividad de la vacuna HD comparada con las vacunas SD para la prevención de muertes asociadas con influenza durante dos temporadas. Para ello identificamos beneficiarios de Medicare mayores de 65 años que recibieron vacunas HD o SD en farmacias que ofreciesen ambas vacunas durante 2012-2013 y 2013-2014. El resultado primario fue muerte en los 30 días siguientes a una hospitalización o visita a urgencias con un código CIE-9-MC de influenza. Estimamos la efectividad vacunal durante los periodos de alta actividad de influenza en las diez regiones de los Estados Unidos mediante el uso de modelos multivariados de regresión de Poisson. Investigamos a 1.039.645 ancianos vacunados con HD y 1.683.264 vacunados con SD en la temporada 2012-13 y a 1.508.176 vacunados con HD y 1.877.327 vacunados con SD durante 2013-14. Hallamos que ambos grupos eran comparables en cuanto a características demográficas, enfermedades crónicas e indicadores médicos de fragilidad.

Hubo 83 muertes subsecuentes a influenza en el grupo de HD (0,028/10,000 personas/ semana), y 162 muertes en el grupo de SD (0,038/10,000 personas/semana). La tasa de mortalidad fue 57% menor en 2013-2014, cuando los virus A (H1N1=pdm09 fueron dominantes, en comparación con 2012-2013, cuando predominaron los virus A(H3N2). En la temporada 2012-13, la vacuna HD fue 36.4% más efectiva para reducir la mortalidad; en 2013-2014, fue 2.5% más efectiva, pero este resultado no fue estadísticamente significativo (IC 95% - 47% a 35%).

En conclusión, la vacuna HD fue significativamente más efectiva que las vacunas SD para prevenir muertes subsecuentes a influenza en 2012-2013, pero no en 2013-2014. Sin embargo, en ambas temporadas, la vacuna HD fue más efectiva para prevenir hospitalizaciones, aunque el efecto estimado para 2012-2013 fue de mayor magnitud. Una mayor circulación de virus A (H3N2) en 2012-2013 y de virus A (H1N1)pdm09 en 2013-2014 pudo haber influido en estos hallazgos. Junto a la publicación, la revista presentó un editorial que comentó positivamente sobre nuestro estudio (Monto A, JID 2017).

Efectividad comparativa de la vacuna de influenza cultivada en células comparada con las vacunas cultivadas en huevos durante la temporada 2017-2018.´´ (Izurieta et al, JID 2018)

Un análisis del ´´Centers for Disease Control and Prevention (CDC)´´ realizado durante la temporada 2017-2018 (dominada por influenza A(H3N2)), mostró que, en conjunto, las vacunas de influenza usadas entre individuos de 65 años y mayores tuvieron una efectividad del 20%. Algunos autores han sugerido que esta extremadamente baja efectividad puede haberse debido a la adaptación de los virus vacunales al crecimiento en huevos. Nuestro objetivo fue evaluar la efectividad relativa de una nueva vacuna tetravalente de cultivo celular comparada con las vacunas cultivadas en huevos. El componente A(H3N2) de la vacuna celular de influenza para la temporada 2017-2018 fue íntegramente producido en cultivo celular, pero los componentes influenza B y A(H1N1) tuvieron, en cambio, un pasaje inicial en huevos. Usamos un diseño de cohortes retrospectivo con regresión de Poisson para evaluar la

efectividad relativa de cinco tipos de vacunas de influenza utilizadas por beneficiarios de Medicare de 65 años y mayores vacunados durante la temporada 2017-18. Usamos la técnica llamada ´´Inverse probability of treatment weighting´´ para ajustar las diferencias en la distribución de covariables en las cohortes a comparar. Los beneficiarios elegibles recibieron uno de los cinco tipos de vacuna evaluados: cuadrivalente de cultivo celular, cuadrivalentes de cultivo en huevos, trivalentes cultivadas en huevo de dosis alta (HD), con adjuvante, o de dosis estándar (SD). La variable resultado para el análisis primario fue el encuentro hospitalario (hospitalización o visita a urgencias) con diagnóstico de influenza. La variable resultado para el análisis secundario fue la visita médica con diagnóstico de influenza, definida por una prueba rápida de influenza durante la visita seguida de tratamiento con oseltamivir (un antiviral utilizado solamente para influenza). Estudiamos más de 13 millones de beneficiarios. En el análisis interino realizado a mediados de temporada, cuando el dominio de las cepas A(H3N2) era casi absoluto, la vacuna de cultivo celular tuvo una efectividad relativa (RVE) 16.5% mayor que la vacuna cuadrivalente cultivada en huevos. En el análisis subsecuente de final de temporada, la vacuna de cultivo celular tuvo una efectividad 9-10% más alta que la tetravalente cultivada en huevos. En la comparación entre cinco tipos de vacunas, la cultivada en células (RVE 11%) y la HD cultivada en huevos (RVE 8%) fueron las más efectivas.

En conclusión, la diferencia entre el análisis interino, realizado durante un período en el que dominaron solamente los virus A/H3N2, y el análisis de final de temporada, que incluyó períodos en los que los virus del linaje B /Yamagata circularon frecuentemente, sugiere que la mayor efectividad relativa que encontramos para la vacuna de cultivo celular podría haber sido impulsado por diferencias de efectividad para el componente A/ H3N2, el único componente de esta vacuna cultivado 100% en células sin paso alguno por cultivos en huevo. Esta modesta efectividad diferencial explica solo parcialmente la baja efectividad del conjunto de las vacunas utilizadas reportada por el CDC. Este estudio fue comentado muy favorablemente en un editorial escrito por el equipo de influenza del CDC (Flannery and Fry, JID 2018), el cual enfatiza la necesidad de continuar estudios comparativos y de desarrollar nuevas vacunas para influenza utilizando los resultados obtenidos por nosotros.

Uso de estatinas y riesgo de influenza entre ancianos vacunados con dosis standard (SD) o dosis alta (HD) en Medicare durante 2010-2015. (Izurieta et al, CID 2017)

Las estatinas se utilizan para reducir el riesgo de enfermedad cardiovascular, estudios recientes sugieren que pueden estar asociadas con un mayor riesgo de infecciones por influenza entre los vacunados. Nuestro objetivo fue evaluar la asociación entre el uso de estatinas y la efectividad de las vacunas de influenza entre los beneficiarios de Medicare vacunados. En este estudio de cohortes retrospectivo, identificamos beneficiarios de Medicare de 65 años y mayores que recibieron vacunas contra la influenza en dosis altas (HD) o dosis estandar (SD), en farmacias, durante las temporadas 2010-2011 hasta 2014-2015. Excepto por la hipertensión, los pacientes con enfermedad cardíaca previa fueron excluidos para no sesgar el estudio. Los usuarios de estatinas se compararon con los no usuarios por tipo de vacuna, sexo, grupo de edad, región de residencia, encuentros médicos previos y comorbilidades. Utilizamos modelos multivariables de Poisson para estimar las asociaciones entre el uso de estatinas durante los 15 días previos o subsecuentes a la fecha de vacunación y el riesgo de visitas médicas por influenza. La variable de resultado para el análisis primario fue una visita médica por influenza, definida por la realización de una prueba rápida de influenza durante la visita, seguida de la administración de oseltamivir. La variable de resultado para el análisis secundario fue el encuentro hospitalario relacionado con influenza (hospitalización o visita a urgencias con un código ICD-9-CM para influenza). Incluimos 1,403,651 usuarios de estatinas emparejados (´´matched´´) con no usuarios. Las cohortes emparejadas estaban bien equilibradas, con diferencias de medias estandarizadas (´´Austin standardized mean differences´´) <0,03 para todas las covariables evaluadas. Analizamos eventos solamente durante períodos de alta circulación de influenza. Identificamos 2,419 visitas médicas por influenza (1.41 / 10,000 persona-semana) entre los usuarios de estatinas y 2,235 (1.31 / 10,000 persona-semana) entre los no usuarios. El riesgo relativo ajustado (RR) para las visitas médicas por influenza fue 1.086

(intervalo de confianza [IC] del 95% [1.025-1.150]) entre los usuarios de estatinas en comparación con los no usuarios. El RR para las hospitalizaciones relacionadas con la influenza fue 1.096 (IC del 95%: 1.013-1.185). Los resultados fueron similares para los vacunados con HD y SD, y para los usuarios de estatinas sintéticas y no sintéticas.

En conclusión, estos resultados sugieren que la recepción de estatinas en el momento de la vacunación de influenza aumenta modestamente el riesgo de la enfermedad en adultos mayores.

Efectividad y duración de la efectividad de la vacuna Zostavax entre beneficiarios de Medicare de 65 años de edad y mayores. (Izurieta et al, CID 2017)

En los Estados Unidos, decenas de millones de adultos mayores están a riesgo de contraer herpes zoster (HZ) y sus complicaciones. Zostavax, la vacuna viva atenuada contra el herpes zoster, reduce el riesgo, aunque persisten preguntas sobre su efectividad y la durabilidad de la protección en la práctica clínica habitual. Nuestro objetivo fue investigar la efectividad de Zostavax y su duración. Este estudio de cohortes retrospectivo incluyó beneficiarios de más de 65 años desde enero del año 2007 hasta julio del 2014. Realizamos ajustes múltiples para corregir los posibles sesgos. Los beneficiarios vacunados con Zostavax se compararon con (a) beneficiarios no vacunados con Zostavax (análisis primario) y (b) con beneficiarios no vacunados con Zostavax que habían recibido una vacuna antineumocócica (análisis secundario entre grupos vacunados). Analizamos los casos de visitas médicas y encuentros hospitalarios con diagnóstico de HZ, incluimos también zoster oftálmico (´´OZ´´) y neuralgia postherpética (´´PHN´´). Entre los beneficiarios elegibles (edad promedio de 77 años), el análisis primario encontró una efectividad para visitas médicas por HZ del 33% y 19% en los primeros 3 y en los años 4 o más subsecuentes a la vacunación, respectivamente. En el análisis secundario, la efectividad fue, respectivamente, del 37% y 22%. En el análisis primario, la efectividad para PHN fue del 57% y del 45%, respectivamente. La efectividad para casos de HZ hospitalizados fue, respectivamente, del 74% y 55%. Las diferencias en efectividad por grupo de edad no fueron significativas.

En conclusión: Tanto en el análisis primario como en el secundario, Zostavax brindó protección contra HZ en todas las edades, pero la efectividad disminuyó con el tiempo. La efectividad fue mayor y mejor conservada en el tiempo para eventos severos como hospitalizaciones por HZ y neuralgia post herpética. Este estudio, que publicamos en CID (Izurieta et al, 2017) fue acompañado por un editorial muy positivo escrito por el Doctor Steven Black, uno de los autores más conocidos internacionalmente en temas de efectividad y seguridad vacunal.

Discusión

Una evidencia de la calidad y relevancia de los estudios presentados y discutidos en esta tesis incluye el hecho de que todos han sido todos publicados en revistas médicas internacionales de elevado prestigio (´´Lancet Infectious Diseases´´, ´´Clinical Infectious Diseases ´´, y ´´Journal of Infectious Diseases´´), que cuatro de ellos han sido acompañados por editoriales muy positivos escritos por expertos conocidos internacionalmente (que incluyo en la sección Anexos (´´Annex´´)), y que han mostrado ya impacto en la toma de decisiones. Estos estudios tuvieron éxito en varios aspectos de la investigación en efectividad vacunal: (a) en la selección de cohortes con una baja probabilidad de incluir individuos frágiles (cohortes de vacunados en farmacias en las cuales se administraron ambas vacunas en estudio), lo cual disminuyó además la probabilidad de que los grupos tuvieran diferencias importantes en cuanto a la distribución geográfica de la enfermedad; (b) en la definición de algoritmos que incluyen, para visitas médicas, el tratamiento de la enfermedad, lo cual permitió aumentar la especificidad; (c) en la definición de periodos de alta circulación de la enfermedad, lo cual permitió aumentar aún más la especificidad para enfermedades estacionales como la influenza; (d) en la obtención de estimaciones de efectividad para eventos raros y graves, incluyendo la muerte, que no resultaría práctico estudiar en ensayos clínicos; (e) en la obtención de resultados muy cercanos a los obtenidos durante los ensayos clínicos, lo cual apoya la validez de nuestros estudios; (f) en estudiar la modificación del efecto causada por un fármaco utilizado concomitantemente a la administración de una vacuna, y (g), al estimar no solamente la efectividad comparativa sino también la duración de la efectividad, difícil de obtener en estudios clínicos aleatorios. Estas experiencias exitosas, además de

proporcionarnos información potencialmente útil para la toma de decisiones regulatorias, podrían asimismo contribuir a la fase de planificación de estudios que podrían formar parte de los compromisos y requisitos posteriores a la licencia de nuevas vacunas.

Tuvimos menos éxito en otros aspectos, incluyendo: (a) asegurando la generalizabilidad de los resultados del estudio (a menudo usamos restricciones para aumentar la validez de los resultados, sacrificando así parcialmente la generalizabilidad de los resultados a todos los ancianos; (b) en el control del sesgo para eventos menos serios, y por tanto más fácilmente influenciables por diferencias en el uso de servicios de salud, como visitas médicas. No obstante, nuestro uso exitoso de cohortes más grandes (no restringido a los vacunados en farmacia) en nuestra reciente comparación de la efectividad de las vacunas de cultivo celular frente a las basadas en huevo, muestra que nuestros estudios no necesitarían sacrificar la generalizabilidad de los resultados al conjunto de la población de ancianos.

Tras completar esta tesis, hemos seguido desarrollando nuevos métodos. Hemos completado recientemente la exploración del uso de encuestas de Medicare para validar la comparabilidad de las cohortes en nuestros estudios en cuanto a la tendencia a usar (o evitar) los servicios de salud, al nivel de educación, la capacidad para caminar sin ayuda, y otras variables que podrían influir en el sesgo. Hemos continuado asimismo realizando otros estudios de efectividad comparativa de las vacunas de cultivo celular frente a las producidas con la técnica clásica de cultivo en huevos, hemos iniciado investigaciones sobre el efecto de la edad y el sexo en la efectividad vacunal comparativa y sobre la posible interacción de otros medicamentos con la efectividad vacunal. Asimismo, continuamos desarrollando otros métodos para medir y ajustar el efecto de sesgos causados por variables no incluidas en los datos de medicare.

Conclusiones

(1) Estos estudios han servido para brindar a los investigadores en efectividad vacunal orientaciones para seleccionar cohortes con una probabilidad uniforme y baja de incluir individuos frágiles, lo que

disminuye el riesgo de desequilibrios que podrían socavar gravemente la comparabilidad de los grupos a estudiar.

(2) Los estudios han contribuído a definir algoritmos de reclamaciones de pago de servicios por visitas médicas, que han demostrado su validez al nosotros obtener repetidamente resultados sorprendentemente similares a los de estudios aleatorios realizados en poblaciones similares durante las mismas temporadas. Con ello demostramos que estos algoritmos podrían acercarse a lograr una especificidad suficiente para realizar estudios de efectividad con fines regulatorios.

(3) Estos trabajos también han ayudado a definir de manera innovadora períodos de alta circulación de influenza. Fuimos los primeros en utilizar la distribución nacional de antivirales contra influenza en Medicare para definir los períodos de circulación de influenza, con una calidad similar (o incluso mayor) a la de la vigilancia actual, realizada usando porcentaje de aislamoientos virales, y con la ventaja de estar disponible mucho más rápido y más barato que cualquier sistema existente, creando una herramienta de vigilancia que continuamos explorando.

(4) Al obtener estimaciones de efectividad para complicaciones graves de influenza muy comparables a las obtenidas durante ensayos clínicos, y al obtener estimaciones para eventos muy raros, incluída la muerte, nuestros estudios han demostrado la capacidad de los datos de uso de servicios médicos en condiciones reales para proporcionar datos no disponibles en estudios aleatorios.

(5) Los estudios presentados en esta tesis también han demostrado la capacidad del uso de datos de servicios médicos en condiciones reales para identificar diferencias significativas de efectividad y para detectar interacciones entre medicamentos y vacunas, incluso cuando la magnitud de los efectos estudiados es pequeña.

BACKGROUND

Justification

In most industrialized countries, the elderly are at high risk of serious disease and death from vaccine-preventable diseases such as influenza and pneumonia, as compared with younger persons.[1-4] Individuals aged ≥65 years account for more than 90% of all U.S. influenza deaths. [1-4] Despite this serious public health concern, ethical considerations, including, once a vaccine is licensed, the presumption of clinical equipoise (genuine uncertainty in the expert medical community over whether the vaccine will be beneficial) no longer exists, which complicates (and often impedes) the use of randomized trials to confirm efficacy against serious disease or death, or among specific subpopulations such as the elderly. For instance, until recently, only one randomized, placebo-controlled study of the efficacy of inactivated influenza vaccines in the elderly has been published.[5] Thus, most information on the benefits of influenza and other vaccines in persons aged ≥65 years are obtained from observational studies.

In influenza studies, for instance, estimates of the effectiveness of inactivated influenza vaccines in preventing serious influenza-associated outcomes among people aged ≥65 years have varied widely, suggesting zero to moderate effectiveness.[6-8] The extreme disparities in results obtained from observational studies of vaccine effectiveness among the eldery, the frequent absence of adjustments for influential covariates including surrogates for frailty, the insufficient accounting of the effects of seasonality and other limitations suggest that, at least in some such studies, bias and confounding could have contributed to explain the findings.[9,10]

Although better information on the efficacy of vaccines is needed, post-licensure randomized trials to confirm efficacy are often unfeasible/unethical. Observational studies, instead, can be performed more cheaply, rapidly, and in larger populations, but they are often subject to bias. Thus, there is an increasing need for large observational effectiveness studies in which bias is either decreased or accounted for.

The XXI Century Cures Act

In December, 2016, the U.S. Congress passed the XXI Century Cures Act,[11] which changes the way in which the Food and Drug Administration (FDA) approves some medical products,[12] including encouraging FDA to provide faster tracks for the licensing of new products, sometimes with data on efficacy surrogates (as opposed to efficacy outcomes). It also encourages the Department of Health and Human Services (HHS) to promote innovation in the development of vaccines that minimize the burden of infectious diseases and stress the need for ensuring timely and adequate recommended utilization guidelines for qualified countermeasures, including pandemic and epidemic products.[11,12] Thus, regulators have been increasingly considering the use of real world data (RWD), data relating to contacts between the patient and the health system, to the patient use of services, health status and/or the delivery of health care routinely collected from a variety of sources, to respond to some of the regulatory questions post-licensure, giving priority to the understanding of and methods for the use of real world evidence (RWE) to obtain reliable and timely post- marketing evidence of the effectiveness of regulated products.[13-18]

Limitations in the use of randomized clinical trials for licensure

Prior to licensure of a product, regulators require verification of the product's safety and efficacy, mainly through implementation of randomized trials. The internal validity of these trials is often reached at the expense of generalizability, since populations enrolled in such studies may often differ in significant ways from those seen in clinical practice. Moreover, the cost of performing clinical trials have increased, without substantial decreases in the time required for their completion.[19] During the last few years, the availability, connectivity and processing speed of electronic medical data have substantially increased, providing Sponsors and the regulator with significant amounts of large linked medical care data in record time.[13,20] One of regulator's priorities is to make medical products that are safe and effective available as quickly as possible, but requiring large clinical studies prior to licensure requires significant time and resources, and many safety and effectiveness questions relevant for regulators just can't be answered pre-licensure.[13]

Vaccine approval scenarios

"Traditional" approval

Under a traditional approval pathway, the licensure of vaccines or other biologic products is based on the demonstration that a product is "safe, pure and potent". Here, we interpreted "potency" to mean effectiveness, based on substantial evidence from adequate and well-controlled clinical investigations.

"Non-traditional" approval scenarios

There are two scenarios, accelerated and animal rule approval. The accelerated approval (21 CFR 601): It is based on adequate and well-controlled trials establishing effect on a surrogate endpoint that is "reasonably likely" to predict clinical benefit. In this scenario, the applicant must study the biological product further following licensure to verify and describe clinical benefit (such studies must be adequate and well-controlled). The animal rule approval (21 CFR 601.90 - 601.95), applies when human efficacy studies are not ethical and field trials are not feasible.

Could non-traditional approval scenarios be relevant for regulators?

The post-marketing determination/verification of effectiveness could be useful for vaccines designed to prevent diseases with highly variable and difficult to predict circulation patterns (e.g., pandemic influenza), long incubation periods (cancer vaccines such as human papilloma virus vaccines), when randomized efficacy studies might be unfeasible (unethical)/unaffordable/unacceptably long. They could also be useful to confirm protection for specific high-risk groups, serious and very rare outcomes such as hospitalizations and death, and to support new indications for already licensed and recommended vaccines.

An important constraint for the use of real-world data: Bias

Bias is a "Systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure's effect on the risk of disease" (Schlesselman and Stolley, 1982). The main types of bias are:

Selection bias: participant selection that distorts the exposure-outcome relationship from that in the target population (e.g. health seeking behavior bias)

Information bias: When information is collected differently between groups, leading to misclassification of exposure or outcome (e.g. vaccination status misclassification)

Confounding: the observed association between exposure and disease differs from the truth because of a third variable (e.g. unmeasured confounding)

Strategies to address bias:

Ways to address selection and other bias include adjustments, evaluating health seeking behavior differences, differences in disease risk, and/or in frailty (which also influence outcome severity), validation of the comparability of cohorts, verification/confirmation of exposures, outcomes, etc. In some cases, the use of negative endpoints can help determine of bias is affecting the study results. All these strategies will be explored in this thesis.

Partnerships to investigate effectiveness

Understanding the need to promote and develop the use of real world data for studies of effectiveness post-licensure, while addressing the constraints generated by the unavoidable challenge that bias and confounding bring to the analysis of real-world data, we initiated a series of investigations to monitor the absolute effectiveness, comparative effectiveness, duration of effectiveness and interactions between drugs and vaccines that could affect vaccine effectiveness.[14-18] These studies are the product of inter-institutional collaborations, and are a continuation of already existing projects to assess the safety of vaccines, which includes studies of the association between influenza vaccines and Guillain Barré Syndrome (GBS), initiated during 2003, that still continue.[21,22]

Using a claims dataset

In the United States, CMS is the primary medical insurance provider for a large majority of the elderly population through Medicare. CMS holds claims records for the medical care received by a large percentage of the 65 years and older population. These records have strong potential for use in a study of the high-dose influenza vaccine among the elderly. Since these records include a wide range of demographic and healthcare information, they can be used to determine high-dose vaccination field effectiveness in different age and risk groups. However, claims data has some limitations. Diagnoses on claims for respiratory illnesses are often imprecise since many conditions have similar symptoms. In addition, the vaccination status of individuals without vaccination claims in CMS is unknown, since they may have been vaccinated outside of CMS or their claims may not have been submitted. Even with these limitations, CMS claims information is a viable tool for analyzing vaccine effectiveness in the elderly since the information is comprehensive, collected continuously, and covers a large percent of the population of interest. This study uses CMS data to select cohorts of study that focus on relatively homogenous populations in terms of health, socioeconomic status, and geographic region, with access to both the high-dose and seasonal-dose vaccine. Then, claims data is used to identify adverse outcomes related to influenza in vaccinated populations. These adverse outcomes are analyzed with consideration to the amount of influenza circulating at the time of event. With this information, this study can compare the effectiveness of the seasonal and high- dose vaccines in different phases of influenza circulation.

Special concerns regarding the investigation of vaccines

Among medical products, vaccines have characteristics which make the use of RWD particularly compelling. Mainly during the last century, vaccines have dramatically decreased the worldwide incidence (or completely eliminated) highly infectious life-threatening diseases such as smallpox, poliomyelitis, neonatal tetanus, congenital rubella syndrome, measles and many others.[23,24] For vaccines to provide such outstanding public health benefits, they often had to be administered to large proportions of the susceptible population, including also healthy individuals and persons at low infection risk.[23,24] In part linked to the need to administer vaccines to millions of healthy individuals (many at low or very low risk for the diseases being prevented) regulators usually require larger safety clinical trials for vaccines than for drugs. [11,25] Moreover, the safety of vaccines is also monitored post-licensure through large passive (e.g. VAERS) and active (e.g. Sentinel, VSD, CMS) vaccine safety networks.[21,22,26-30] Until recently, however, real world data were not systematically used by the FDA to monitor the effectiveness of vaccines post-licensure.[16,18]

Because some vaccines are produced to prevent epidemics or pandemics that are sporadic in nature (e.g. meningitis and influenza pandemics, Ebola outbreaks), it is not always possible to wait for the disease to occur prior to performing efficacy trials. Also, even when pre-licensure efficacy studies are feasible, they can take significant time and, in some cases, the immediate consequences of a disease outbreak and the lack of a viable therapeutic alternative are such that there are no valid alternatives to the use of a vaccine for which efficacy has not yet been proven but for which the safety profile is good and there is a reasonable expectation

of efficacy based on immunogenicity or animal data.[31-33] In such cases, FDA can use accelerated approval or animal rule regulations[34,35] to license such vaccines, using either immune markers to infer effectiveness, or efficacy studies in animal models, conditional to the implementation of efficacy or effectiveness studies post-licensure. Once the vaccine is approved, however, clinical equipoise (genuine uncertainty in the expert medical community over whether the vaccine will be beneficial) may no longer exist and, in such cases, it becomes difficult to justify ethically a randomized placebo-controlled efficacy study post-licensure.[36] In such cases, effectiveness studies using real world data can be the best alternative.[16-18] Other considerations make a compelling case for the use of real world evidence to provide evidence of effectiveness: (a) pre-licensure clinical trials are often conducted with healthier populations and in specialized environments, subject to multiple restrictions. Therefore, their findings are difficult to generalize to the larger, more inclusive populations of patients, clinicians and health care systems that exist in real world practice;[37] moreover, many vaccines are licensed to prevent diseases caused by organisms susceptible to frequent mutations (e.g. influenza), and, given the need to rapidly vaccinate susceptible populations during epidemics, vaccine efficacy can't be assessed prior to each epidemic by a drifted strain[14,38,39]. Also, once multiple vaccines with similar indications are marketed, evaluating their comparative effectiveness and risk/benefit profiles using randomized studies may sometimes be unethical. Also, the rarity of serious vaccine adverse events and the potential for small differences in efficacy could make such studies impractical, time-consuming, and overly expensive.[21,22]

Influenza

The disease and the agent

Influenza is one of the most notorious human ailments. First described by Hippocrates in 412 BC, it is among the oldest and most common human diseases. It affects large portions of the world population in seasonal epidemics each year. While the symptoms of the flu are often mild, the ever-changing influenza virus can lead to deadly pandemics. Surveillance and vaccine preparation - two important activities of influenza control - are therefore indispensable to prevent its potentially deadly effects.

Influenza viruses are classified as A, B and C. Influenza A and B are the two types that cause epidemic human disease. Influenza A viruses are further categorized into subtypes on the basis of two surface antigens: hemagglutinin (H) and neuraminidase (N). The development of antigenic variants through a process called antigenic drift is the virologic basis for seasonal flu epidemics. A more fundamental shift in the hemagglutinin and neuraminidase of influenza viruses can cause pandemics instead. [6,8]

Clinical Signs and Symptoms:

Influenza viruses are spread from person-to-person primarily through the coughing and sneezing of infected persons. The incubation period for influenza is 1-4 days, with an average of

2 days. Persons can be infectious starting with the first symptoms through approximately 5 days after illness onset; children can be infectious for a longer period. Uncomplicated influenza illness is characterized by the abrupt onset of constitutional and respiratory signs and symptoms (e.g., fever, myalgia, headache, severe malaise, nonproductive cough, sore throat, and rhinitis). It typically resolves after several days for most persons, although cough and malaise can persist for more than 2 weeks. In some persons, the disease can exacerbate underlying medical conditions (e.g., pulmonary or cardiac disease), lead to secondary bacterial pneumonia or primary influenza viral pneumonia, or occur as part of a co-infection with other viral or bacterial pathogens. [6,8]

Influenza epidemiology

In temperate and cold climates, influenza (the flu) usually causes winter epidemics: December-March in the Northern Hemisphere; June-September in the Southern Hemisphere. In tropical and subtropical areas, influenza epidemics can occur either twice a year or even throughout the year. As mentioned before, these seasonal epidemics occur due to antigenic drift. [8]

More rarely, major antigenic changes (a new hemagglutinin or neuraminidase) occur in the viruses and can cause pandemics (worldwide outbreaks of an influenza virus subtype to which the human population has no protection). The most severe infectious disease disaster of the 20th century was the "Spanish" influenza pandemic of 1918, which killed more than 40

million persons worldwide. Other more recent pandemics were the 1957 "Asian" flu, the 1968 "Hong-Kong" flu, and, more recently, the 2009-10 H1N1 swine influenza pandemic. In 2009, a new pandemic influenza A (H1N1) virus spread globally, leading to the accelerated production of monovalent 2009 Influenza A (H1N1) vaccines (pH1N1) by manufacturers in the Americas, Europe, and Asia. Rapid and extensive monovalent vaccine administration was implemented worldwide.

Influenza Surveillance

Respiratory illness caused by influenza is difficult to distinguish from illness caused by other respiratory pathogens on the basis of symptoms alone. The reported sensitivity and specificity of clinical definitions for influenza-like illness that include fever and cough have ranged from 63% to 78% and 55% to 71%, respectively, compared with viral culture. Sensitivity and predictive value of clinical definitions can vary, depending on the degree of cocirculation of other respiratory pathogens and the level of influenza activity. For these reasons, and also because the influenza strains identified during one season are useful to help define the influenza strains to be recommended for the next season, virologic surveillance is the most important element of influenza surveillance. Work absenteeism due to influenza could be a problem among otherwise healthy adults. Although this and other low-risk groups can also benefit from vaccination, in a CDC-led investigation, Carolyn Bridges and other researchers performed a two-year cost analysis of influenza vaccination in a work setting and found that, from a public health perspective, there were no savings when giving the flu shot to healthy adults.[8]

Antivirals for influenza

The first recommended influenza antivirals were Amantadine and, subsequently, rimantadine. Nonetheless, increase in resistance to these drugs made the CDC to no longer recommend them for treating influenza. Currently, the following antivirals with FDA license are recommended by CDC for use in the United States during the 2018-2019 influenza season: Three of them are neuraminidase inhibitors, effective against influenza A and influenza B viruses: oseltamivir phosphate (oral), zanamivir (inhaled), and, more recently, peramivir (intravenous). Another recently licensed antiviral is not a neuraminidase inhibitor, it is instead an endonuclease inhibitor that interferes with viral RNA transcription and can, therefore, block replication of the virus.[7]

Influenza vaccines

A person's immunity to the surface antigens reduces the likelihood of infection and severity of disease if infection occurs. Antibody against one influenza virus type or subtype confers limited or no protection against another influenza virus type or subtype. Furthermore, even when a person, following vaccination, has developed a response,

antibodies to one antigenic variant of influenza virus might not protect against a new antigenic variant of the same type or subtype. Antigenic drift is the reason for the incorporation of one or more new strains in each year's influenza vaccine. It is also the basis for the recommendation of yearly influenza vaccination. In the U.S., seven vaccines are currently marketed, a live- attenuated vaccine, a cell-cultured inactivated vaccine, and four egg-based vaccines (high dose trivalent, adjuvanted trivalent, standard dose trivalent, standard dose quadrivalent, and recombinant). Among them, only the live-attenuated vaccine is not licensed for use in the elderly.[8]

Because manufacturers normally need months to prepare a new vaccine, the World Health Organization (WHO) meets every year (usually in March) to recommend the influenza strains to be included in the vaccine for the Northern Hemisphere's winter (usually December to March). Until 1998, the vaccine recommended for the Northern Hemisphere was used for the Southern Hemisphere winter half a year later. Studies by Regnery, Savy et al. have shown that, for eight out of ten winters analyzed, the vaccine recommended for the Northern Hemisphere did not match the strains that circulated during the following Southern Hemisphere winter. For this reason, since 1998, WHO holds a second yearly meeting (usually in September), to recommend influenza vaccine strains for the Southern Hemisphere. Because of the often-unusual patterns of virus circulation in these areas, deciding the best time for vaccination in tropical and subtropical areas is more challenging and needs to be studied on a case-by-case basis.

Can real-world data be used to compare the effectiveness of different vaccine products? What are the constraints? The case of influenza.

Understanding influenza vaccine effectiveness in the elderly is crucial to minimizing hospitalizations and death due to influenza. The elderly face a higher risk for severe influenza-related complications than other age groups, because immune systems often weaken with age.[2,3] The elderly also respond to vaccination with lower antibody titers to influenza hemagglutinin when compared with younger adults.[40] Researchers are investigating alternate formulations and higher doses of the influenza vaccine for improved vaccine effectiveness in the elderly.

The effectiveness of the standard-dose inactivated influenza vaccine among people ages 65 years and older is subject to controversy. Current study conclusions vary widely between very high estimates of effectiveness that suggest that the influenza vaccine reduces the risk of death from all causes by 50% and very low estimates that conclude the vaccine has no effectiveness.[10,41] Only one small (<2000 subjects) post-licensure clinical trial has been published, and its estimates of effectiveness depended upon serological diagnosis of influenza.[5] Recent research suggests that use of a serologic endpoint for influenza diagnosis tends to overestimate the effect of inactivated vaccines, because once antibody titers increase in response to the vaccine, they reach an "antibody ceiling" and cannot rise further in response to infection.[42]

Regulatory implications for the study of comparative influenza vaccine effectiveness

The comparison of the effectiveness of HD and SD influenza vaccines, was chosen for our first comparative effectiveness studies because of its potential regulatory usefulness, under the assumption that two products used for the same indication and recommendations in a given population (in this case elderly individuals ages 65 years and older) could be compared using observational studies. Our objective was to compare the effectiveness of the high dose influenza vaccine (HD), licensed by FDA for persons ages >65 years in December 2009[32] under accelerated approval regulations (applicable to products for treating or preventing serious illnesses that provide meaningful therapeutic benefit over existing treatments) with the standard dose (SD) influenza vaccines.[16,18] The outcomes selected included serious and rare influenza-related outcomes such as hospitalizations and deaths, particularly relevant because the investigation of such rare and serious outcomes in a randomized study would not only be very challenging to implement, but also extremely expensive and time consuming. To further test the use of RWE we focused on a more pressing HHS priority, the timely evaluation of the comparative effectiveness of influenza vaccines used among the U.S. elderly, a key element of

U.S. (and global) influenza pandemic preparedness.[43]

Accelerated approval of a high-dose influenza vaccine for the elderly

In December 2009, under accelerated approval regulations, the FDA licensed an injectable inactivated trivalent influenza vaccine (Fluzone High-Dose, Sanofi-Pasteur) that contains four times the amount of influenza virus hemagglutinin antigen as compared to standard-dose trivalent influenza vaccines (SD), for use among adults ages >65 years.[33,44] Licensure was supported by superior hemagglutinin inhibition (HI) responses for 2 of 3 vaccine strains. For licensure, efficacy of the vaccine was characterized by immunogenicity. Data from three studies among the elderly indicated that Fluzone High-Dose elicited higher hemagglutination inhibition titers against all three influenza virus strains included in the vaccine as compared to standard-dose Fluzone.[45-47] A two-season study conducted by Sanofi-Pasteur on the Fluzone High-Dose vaccine using a cohort of 30,000 older adults found that the High-Dose vaccine is 24·2 percent more effective in preventing influenza in older adults than the standard vaccine.[48] This study can be expanded upon by characterizing vaccine effectiveness in different age groups and in patients with different risk factors to understand the usefulness of the high- dose vaccine in the Medicare population. Because the post-licensure commitments agreed upon with the manufacturer did not include the evaluation of efficacy against rare outcomes such as hospitalizations and death, which would have required extremely large populations, unpractical for a randomized study, and because of a public health need to estimate benefits against influenza strains that often drift from year to year, we decided to use multiple years of Medicare claims data from beneficiaries aged ≥65 years for this purpose. Because we wanted the control population to be comparable to the HD recipients, particularly in regard to health seeking behaviors, we decided to use SD recipients as comparison group.

Issues when investigating influenza vaccine effectiveness

Study outcomes

Investigating influenza vaccine effectiveness is challenging. Vaccine effectiveness varies based on the adequacy of the antigenic match between the vaccine and the circulating influenza strain, the specific population vaccinated, the interval between vaccination and disease exposure, the age of vaccine administration, and the vaccinee's immune system, among other factors. Since influenza diagnostic tests are used infrequently, secondary infections such as bacterial pneumonia often cause influenza patient hospitalization. In addition, respiratory syncytial virus, other respiratory viruses, and other non-viral pathogens often cause lower respiratory tract infections in winter.[1] Therefore, identifying outcomes that can be used as surrogates for influenza-related complications is difficult. In addition, characteristics of the vaccinated population provide other complications in assessing the effectiveness of the influenza vaccine. Vaccine effectiveness is hard to assess for the very frail, since they are less likely to receive vaccines. In addition, vaccines are administered in a wide variety of settings, including nursing homes, hospitals, outpatient settings, and pharmacies. The patients that receive vaccination in these locations differ greatly in demographic and health characteristics.

Using medical office visits outcomes in influenza comparative effectiveness studies

To perform our studies comparing the effectiveness of the HD vs SD influenza vaccines, we had to resolve a number of issues. We faced the challenge of determining if our cohorts were comparable not only for the multiple covariates available in the Medicare databases, but also for unmeasured variables that might have influenced the likelihood of vaccination and/or the outcome risk. Thus, to perform our comparisons using medical office visits as the outcome, we needed to decrease the likelihood of including non-ambulatory (frail) individuals, adjust for temporal and geographic factors influencing socioeconomic characteristics, closeness to care, influenza circulation, and access to HD vaccine. We also needed to resolve the potential bias associated with the participation of persons who entered Medicare because of disability and those who lived in assisted living facilities. Moreover, we needed to evaluate the study cohorts with regard to covariates measured in Medicare by evaluating differences in baseline covariates, and correct the differences found. More important, because routine medical practice in the U.S. does not include the systematic verification of influenza diagnoses by PCR or culture, we had to create algorithms for influenza case definition that did not include virological case confirmation.[16,18] An advantage, and also a challenge, associated with our use of medical office visit outcomes in studies of the comparative effectiveness of influenza vaccines was the availability of contemporary results from randomized trials of the same vaccines. This would allow us to confirm that our methods succeeded in allowing us to obtain comparative effectiveness estimates similar to those from the randomized studies performed during the same seasons.[48,49 50]

Interactions: The effect of age and sex

As previously stated, a number of randomized and observational studies have suggested that the HD vaccine has higher efficacy, effectiveness, and superior immune responses compared to the SD vaccines in some, but not all, seasons.[16,18,48,50-52] For the 2011−12 and 2012−13 influenza seasons, a manufacturer-sponsored randomized trial with 31,989 participants demonstrated that, compared with Sanofi's SD vaccine, the HD vaccine was associated with improved protection against laboratory-confirmed influenza illness (relative efficacy 24.2%, 95% confidence interval (CI) 9.7−36.5%), overall influenza related serious adverse events (relative effectiveness 17.7%, 95% CI 6.6−27.4%), and superior immune responses for adults ≥65 years.[48,51] A retrospective cohort study with more than 2.5 million Medicare beneficiaries ≥65 years found that, for the 2012−13 season, HD vaccine recipients were less likely to have influenza office visits (RVE (RVE) 22%, 95% CI 15−29%) and influenza hospitalizations (RVE 22%, 95% CI 16−27%) than SD vaccinees.[16] Shay *et al.* found that the HD vaccine showed better protection against post-influenza mortality than SD vaccines in the 2012−13 (RVE 36.4%, 95% CI 9−56%) but not in the 2013−14 season (RVE 2.5%, 95% CI - 47−35%) among Medicare beneficiaries ≥65 years.[18] Izurieta *et al.* compared RVE of cell- cultured and egg-based influenza vaccines among Medicare beneficiaries ≥65 years in the 2017−18 season and showed that HD was more effective than SD in preventing influenza hospital encounters (RVE 8.7%, 95% CI 6.5−10.9%).[14] The same study found that the cell- cultured SD vaccine had higher RVE than traditional trivalent and quadrivalent SD vaccines.[14]

Several studies have investigated HD relative efficacy, effectiveness, or immunogenicity by age and suggested potential age effect modification. DiazGranados *et al.* analyzed clinical trial data by age group and showed that the point estimate of the relative vaccine efficacy for laboratory-confirmed influenza caused by any influenza strain (regardless of similarity to the vaccine) was higher for participants ages ≥75 years (32.4%, 95% CI 8.1−50.6%) than for those ages 65−74 years (19.7%, 95% CI 0.4−35.4%), although the difference was not statistically significant[50]. However, the study did not have a separate group for people ≥85 years. An unadjusted FDA sub-analysis of the HD relative vaccine efficacy trial[53] found a slightly increasing trend with age for vaccine efficacy of HD relative to SD, even though results were not statistically significant, possibly due to the small number of subjects in the subgroups. In a retrospective cohort observational study among elderly U.S. veterans, Richardson and collaborators showed that, during 2010−11, the risk of hospitalization for influenza or pneumonia was significantly lower among patients receiving HD versus SD vaccine only for patients ≥85 years[54]. Although there are potential limitations in the Richardson study,[55,56] the findings raise questions regarding potential effect modification of HD RVE by age, at least for some seasons.

Due to sex difference in human biological aging and other characteristics, men and women can have different exposures, health status, and morbidity and mortality risks as they age[57-60]. Sex-related differences in influenza vaccine effectiveness and immunogenicity have been observed in studies for both younger (18−64 years) and older (≥65 years) adults.[61-64] The unadjusted FDA sub-analysis of the HD relative vaccine efficacy trial[53] found potential differences in efficacy by sex for culture-confirmed influenza associated with protocol-defined

influenza-like illness caused by viral types/subtypes antigenically similar to those contained in the vaccine. However, no significant difference in relative vaccine efficacy by sex was found for the primary endpoint (laboratory-confirmed influenza associated with protocol defined influenza-like illness caused by any viral types/subtypes).

The above-mentioned research suggests that the RVE of HD versus SD influenza vaccines could potentially be modified by age, sex, and factors related to the influenza season, such as severity of influenza circulation and differences between the vaccine and circulating influenza strains. This study aims mainly to investigate potential effect modification by age on the RVE of HD versus SD influenza vaccines for people ≥65 years. We hypothesize that the RVE of HD versus SD influenza vaccines may be higher among older vaccine recipients. Therefore, in future studies, we plan to investigate the potential effect modification of age and sex on the relative effectiveness of the HD vs the SD influenza vaccines.

The study of influenza-associated mortality

Results from the Sanofi-sponsored post-licensure randomized, controlled trial of high- versus standard- dose vaccine among ~30,000 subjects aged ≥65 year had shown superior efficacy of the high-dose vaccine for prevention of laboratory-confirmed influenza infections (relative efficacy, 24.2%; 95% CI, 9.7 to 36.5). However, despite the relatively large number of subjects enrolled, this study was not powered to characterize efficacy of these inactivated influenza vaccines (IIV) against not only serious influenza-related outcomes, such as

hospitalizations, but, more important, against death associated with influenza infections. Using a retrospective cohort design with Medicare claims, we had already identified cohorts of beneficiaries aged ≥65 years who received high- or standard-dose IIV from outpatient pharmacies during the 2012-2013 influenza season.[16]

Our "proof-of-concept" 2012-13 season study on the comparative effectiveness of the High Dose vs. Standard Dose influenza vaccines among the elderly had provided results that were consistent with the findings of the clinical trials performed by the Sponsor.[16,65] Among 929,730 high-dose vaccine and 1,615,545 standard-dose vaccine recipients, we had found that the high-dose vaccine was 22% more effective than standard-dose vaccine for prevention of influenza infections, a finding very similar to those from the manufacturer's randomized trial, and 22% more effective for prevention of the influenza hospitalizations.[16,65] Nonetheless, important questions remained, including if the comparative effectiveness findings from one season (the influenza A(H3N2)-dominated 2012-13 season) could be extrapolated to another (in this case, the A(H1N1)-dominated 2013-14 season). Results from multiple observational studies of inactivated influenza vaccine effectiveness have been quite variable, with estimates of the effectiveness of standard-dose inactivated influenza vaccines in preventing serious influenza-associated outcomes among people aged ≥65 years ranging from no effects, to moderate effectiveness, and even unrealistically high estimates.[10,41,67] Although results from some of these studies were likely the product of methodological issues, the effectiveness of influenza vaccines does change between seasons. Also, neither our study nor the clinical trials had been able to resolve a fundamental question: was the High Dose vaccine more effective than the Standard Dose to prevent influenza-associated mortality? Persons aged ≥65 years are not only at greater risk for influenza-related complications,[2,3] as stated previously, but also account for more than

90% of all influenza-associated deaths.[4] Unhappily, evaluating effectiveness to prevent influenza deaths, one of the most important reasons for influenza vaccines to be promoted among the elderly, require a significantly larger sample than what could be obtained in a modern clinical trial. Reducing influenza complications and, specifically, influenza deaths, were important reasons for the influenza vaccination of the elderly program. During the 1957 influenza A(H2N2) pandemic it already became evident that the elderly (and persons suffering chronic health conditions such as chronic pulmonary and cardiac diseases) were at the greatest risk of death, [68,69] but the clinical trials performed among the elderly continue to assess mainly laboratory-confirmed infections, not deaths.[48,70] The mean reason is that, because of the low incidence of influenza-related deaths during annual epidemics, their investigation in the context of a controlled trial would require enormous financial resources, and very significant time. Thus, no good evidence exists of the effectiveness and comparative effectiveness of influenza vaccines against death. The outcomes used in the largest modern placebo-controlled study of influenza vaccine efficacy among the elderly showed a 58% efficacy (95% confidence interval [CI] 26% - 77%) against clinical illness with serologic evidence of influenza infection.[71]

The December, 2009 accelerated approval licensing of the High Dose trivalent vaccine) for use among adults aged $\geq$65 years, which contains four times the antigen amount found in the standard dose vaccine (60 micrograms of antigen per strain),[44] was based on higher hemagglutination inhibition (HAI) titers among persons ages ≥65 years. [62,72,73] Post-licensure, the manufacturer agreed to perform a randomized trial comparing the high-dose versus standard-dose vaccine during two seasons (2011-12 and 2012-13). This study of subjects aged ≥65 years[48] showed that the High Dose vaccine was more efficacious in preventing laboratory-confirmed influenza infections (relative efficacy, 24.2%) than the Standard dose vaccine.

Nonetheless, these results, which used a relatively frequent outcome, already had wide confidence intervals (95% CI, 9.7% - 36.5%). Thus, although this trail was large (it included some 30,000 people), it did not have sufficient power to estimate efficacy against death. In our 2012-13 real world evidence stud among Medicare beneficiaries aged ≥65 years vaccinated in 2012-2013 with high-dose versus standard-dose vaccines, which we restricted to individuals vaccinated in pharmacies,[16] we found that High-dose vaccine was 22% (95% CI 15%-29%) more effective than standard-dose vaccines in preventing influenza-related office visits, which was consistent with results from the post-licensure trial, which used polymerase-chain reaction- confirmed influenza infection as the outcome[48]. Although that study also found a 22% (95% CI 16%-27%) reduction in the rates of influenza hospitalizations among individuals who had received the High dose vaccine, we did not evaluate the risk of influenza-related deaths either.[16] Thus, for the 2012-13 and 2013-14 seasons study, our main aim was to evaluate the comparative effectiveness against influenza-related deaths among Medicare beneficiaries. We also wanted to determine if our 2012-13 season finding of a higher vaccine effectiveness for the High Dose vaccine could also be found during an influenza A(H1N1)-dominated season.

Can these studies also address the challenges of studying interaction between drugs and influenza vaccines?: The statins issue as an example for an investigation using real world data.

Based on the experience already gained with these types of studies, we decided to perform an analysis on the effect of statins on influenza vaccine effectiveness among the elderly. Our recently published research used a retrospective cohort study and data from CMS to evaluate the effectiveness of the high-dose influenza vaccine to standard dose vaccine in the US elderly. That study[16] evaluated nearly a million Medicare beneficiaries vaccinated with a HD vaccine and a similar number of beneficiaries vaccinated with a SD vaccine, and found the high-dose vaccine was ~22% more effective. The consistency of findings between the sponsor's clinical trial and FDA's observational study was reassuring. This experience reassured us that we could use methods developed in these projects to perform an observational study to evaluate the effect of other products, such as drugs, including statins, on vaccine effectiveness, using the same influenza vaccine working group, adding as well other scientists with specific expertise in the investigation and regulation of cholesterol-lowering drugs. The objective of the study, for both High Dose (HD) and Standard Dose (SD) influenza

vaccines, would be to determine the relative risk and risk difference in influenza outcomes among influenza vaccinees who were statin users and statin nonusers.

We were interested in this study as a proof-of-concept that would help us respond to the question of whether our Medicare databases could address such complex issue.

Because statins are widely used worldwide, particularly among the elderly, to decrease the risk of heart disease, [74-78] and influenza vaccines are the main tool for prevention of influenza disease, which causes significant respiratory morbidity and mortality among the elderly,[2-4] determining the accuracy of these findings, and, if true, establishing the real magnitude of the effect, became a priority.

Three observational studies have raised the possibility that the immunogenicity and effectiveness of inactivated influenza vaccines may be lower among recent statin users.[79,80] The fact that they were performed using different methodologies in a diversity of settings have increased the level of concern. The effect found in these studies was large, raising the possibility of a need for a change in the indications for statins and/on in vaccination recommendations. In a post-hoc analysis of data from a randomized clinical trial, Black and collaborators evaluated the effect of statins on the immune response to inactivated influenza vaccines, finding significantly lower hemagglutination inhibition (HI) titers to vaccine antigens among patients who had received statins from 28 days before to 22 days after vaccination. Among statin users, HI titers for the three vaccine antigens were 38% to 67% lower than among non- users.[79] A nine-season retrospective cohort study performed in an integrated health care delivery organization (Kaiser Permanente) found that influenza vaccine effectiveness (VE) during periods of widespread

influenza circulation was 18% lower for participants who had >1 month of statin therapy prior to vaccination compared to non-users.[80] In a test-negative design study of influenza vaccine effectiveness (VE), McLean and collaborators found an adjusted VE against influenza A(H3N2) infection of -21% (95% CI -85% to 20%) among statin users and 45% (95% CI 27%-59%) among non-users.

Although the studies suggested that the effectiveness and immunogenicity of inactivated influenza vaccines could be lower among recent statin users, they presented limitations that could affect the validity of their findings:

(1) Black S et al, JID 2015:[79] In a post-hoc analysis from a randomized trial of the comparative safety and immunogenicity of MF-59 adjuvanted trivalent influenza vaccine (aIIV3) and unadjuvanted (IIV3) in >14 000 adults aged >65 years of age during the of 2009–2010 and 2010–2011 influenza seasons, the authors performed a cross-sectional observational study of >5000 individuals to evaluate the impact of statin therapy on the immune response to influenza vaccination. Comparison of hemagglutination-inhibiting geometric mean titers (GMTs) to influenza A(H1N1), A(H3N2), and B strains revealed that titers were 38% (95% confidence interval [CI], 27%–50%), 67% (95% CI, 54%–80%), and 38% (95% CI, 28%–29%) lower, respectively, in subjects receiving chronic statin therapy compared with those not receiving chronic statin therapy. This apparent immunosuppressive effect of statins on the vaccine immune response was most dramatic in individuals receiving synthetic statins (which are more frequently used in the U.S. market), compared to fermentation-derived (natural occurring) statins. These effects were similar in both the adjuvanted and unadjuvanted vaccine groups. The study had some limitations: (a) it did not assess VE (only immunogenicity), and it is unclear how immunogenicity correlates with

clinical efficacy; (b) participants were recruited among clinical trial participants, and therefore, they may have been healthier than the overall population and results may not be as generalizable; (c) since receipt of statins was not randomly assigned, it is possible that the observed effect could be due to other factors. Among these factors: (a) patients receiving statins had higher rates of comorbidities potentially associated with risk of influenza complications, and (b) they may have been more likely to have received unadjuvanted influenza vaccines in the years before the study (receipt of influenza vaccine in the previous season has been associated with a decreased immune response in the subsequent season in some studies).

(2) Omer et al, JID 2015:[80] In a retrospective cohort study over nine influenza seasons using research databases of a large U.S. managed care organization, investigators ascertained influenza vaccination status, statin use and medically attended acute respiratory illness (MAARI) of cohort members for each season. Incidence rate ratios (IRRs) of MAARI were estimated using Poisson regression and stratified by vaccine use and statin use. Using a ratio of ratios approach, they compared IRRs from periods of widespread (and local) influenza circulation to IRRs from periods before influenza circulation and used relative IRRs to compute VE. After adjustment for age, comorbidities, and other covariates, the influenza VE against MAARI was significantly lower among statin users than nonusers during periods of widespread influenza circulation (12.6% vs 26.2%). The authors concluded that, in this study, statin therapy was associated with reduced influenza VE against MAARI. The study had some limitations: (a) influenza activity was not defined based on virologic surveillance but by monitoring the percent of sentinel doctors' visits for "influenza-like illness"; (b) participants could have received vaccination in places other than the MCO; (c) participants who did not

stay in the MCO for the whole season were excluded, thus increasing the likelihood of excluding patients who died of influenza; (d) the outcomes were based on MAARI cases, as opposed to confirmed influenza; (e) not all prescriptions are filled at network pharmacies, and thus statins use misclassification may have occurred; (f) because statin users may utilize preventive services more often, their MAARI events may have been more likely to be identified, although the use of a rate of ratios approach may mitigate the effects of this problem;

(g) statin users may have received other prescriptions of drugs that could affect VE or they could to be obese, which could also affect VE; (h) all influenza seasons were combined in one overall analysis, although there could be effect modification by season;

(i) most participants were ages <65 years, and thus, results may not be representative of older individuals; (j) the distribution of participants was not well balanced overall (among non-statin users who were vaccinated, there were almost twice as many females as males); (k) health seeking behaviors (e.g well-care visits, other vaccinations) were different for vaccinated and unvaccinated participants, as well as for statin user and non-statin user participants; (l) the study appeared to have limited power to evaluate in the effect of statins by sex in the adjusted analysis, despite combining all seasons; and (m) investigators did not account for the effect of influenza vaccination in a prior year.

(3) McLean et al, JID 2016:[81] In a test-negative design study of influenza   vaccine effectiveness (VE), McLean and collaborators found an adjusted VE against influenza A(H3N2) infection of -21% (95% CI -85% to 20%) among statin users and 45% (95% CI 27%-59%) among non-users. That study also had important limitations : (a) Although they found significant effects among users of non-synthetic statins, no effect was found for

users of synthetic statins; (b) no dose-effect response was noted; (c) a significant effect was found for influenza A(H3N2) but not for other strains; and (c) the study had limited power, given its relatively small sample size.[81]

Also, multiple studies have reported that statins may have clinically relevant anti-inflammatory effects independent of their lipid-lowering effects. [82-88] It is possible that these immuno-modulatory effects could both impair the immune response to influenza vaccination and decrease the risk of pneumonia and severe influenza outcomes.[88-95] These investigators found significant effects among users of non-synthetic but not among synthetic statin users; no dose-effect response was noted.[81]

Given the limited published data, we decided to conduct a retrospective cohort study to evaluate the effects of statins, including potential differences by statin type and dose, on the risk of influenza-related outcomes among Medicare beneficiaries aged >65 years who received influenza vaccination in community pharmacies.[16,18,96]

Investigating the comparative effectiveness of multiple vaccines: Comparing the effectiveness of the cell-cultured influenza vaccine with egg-based vaccines

As indicated previously, influenza is responsible for a significant share of U.S. morbidity and mortality. Some 140,000-710,000 influenza-related hospitalizations and 12,000-56,000 deaths occur annually, with most of the burden occurring among individuals ages >65 years.[2,4,8] Seasonal strain-specific vaccination is the main tool for influenza prevention.[97] A preliminary

estimate of the effectiveness of influenza vaccines during the A(H3N2)-dominated 2017-18 season by the U.S. influenza vaccine effectiveness network, using a test-negative design, found 20% (95% CI -9 to 41%) and 17% (95% CI -22% to 44%) VE against any influenza strain and against influenza A(H3N2) viruses, respectively, among persons ages $\geq$65 years.[98] A prior interim analysis of the U.S. data, and studies in Australia and Canada, had also found low effectiveness against A(H3N2) strains that circulated during 2017-18.[99-101] Although there were differences in the dominant A(H3N2) influenza virus clades that circulated in these countries,[100] the low effectiveness found caused concern. One hypothesis for this low effectiveness is the adaptation of influenza virus to growth in eggs.[100] Two vaccines not manufactured in eggs are licensed and distributed in the U.S.: a recombinant protein vaccine consisting of virus hemagglutinin (HA) produced in insect cells, not included in our study due to the limited number of users, and a sub-unit vaccine prepared from influenza viruses propagated in mammalian cells (i.e. cell-cultured).[102,103] The A(H3N2) virus used for the manufacture of the cell-cultured vaccine for the 2017-18 season did not undergo egg adaptation prior to culture in cells, while the 3 other components, the A(H1N1) virus and both influenza B vaccine seeds, originated from egg isolates.[104] All other influenza vaccines are produced in eggs, although some differences are potentially relevant to the evaluation of effectiveness: one is high-dose[33] (contains 60 mcgs of each HA antigen per dose), others are standard-dose (15 mcg/dose). Among standard-dose vaccines, one is adjuvanted,[105] some are trivalent (contain antigens from subtype A(H1N1) and A(H3N2) strains, and a single type B (B/Victoria) lineage strain), while others are quadrivalent (contain antigens from both A subtypes and from two type B lineage strains). The RVE (RVE) for the ensemble of these vaccines has never been evaluated. We used real-world data from

Medicare claims to conduct both an interim evaluation, with data as of January 19, 2018, and an

end-of-season analysis, with data updated as of August 4, 2018, of the RVE of cell-cultured vs.

egg-based influenza vaccines administered to U.S. beneficiaries ages $\geq$65 years during the

2017-2018 season.

Herpes Zoster: Disease and complications

Herpes zoster (HZ) is a painful condition resulting from the reactivation of the varicella–

zoster virus (VZV) from a latent state in sensory nerve ganglia. The disease manifests as a

vesicular rash, characteristically unilateral and restricted to a single dermatome, accompanied

by radicular pain along the dermatome. Older populations are particularly affected, as the

incidence and severity of HZ increases with age. There is a marked increase in the incidence of

HZ after age 50, which correlates with aging-related decline in cell-mediated immunity. Studies

in Canada, Israel, Japan, Taiwan and the USA reported age-adjusted HZ incidence rates of 8 to

11 per 1000 person-years in populations aged $\geq$65 years, while incidence in the general

population was lower, ranging from 3.4 to 5.0 per 1000 person-years. [106;107] Complications of

herpes zoster include ophthalmic zoster (OZ), bacterial superinfections of skin lesions and

disseminated VZV infections, particularly among immunocompromised patients. [108] The most

common serious complication of HZ is postherpetic neuralgia (PHN), which has been defined as

pain that persists more than 90 days after onset of rash or cutaneous healing. [109] Adults aged

>70 years have a four-fold increased risk of PHN compared to those younger than 60

years. [110,111]

The first Herpes Zoster vaccine: Zostavax

The Herpes Zoster live-attenuated vaccine, ZOSTAVAX® (Zoster Vaccine, Live; Merck & Co., Inc., Whitehouse Station, NJ) was initially licensed in the U.S. in May 25, 2006 to prevent HZ, following a clinical trial on over 38,000 participants ages 60 years or older with no history of HZ, immunosuppression or other conditions that could interfere with study participation. [53] This study showed that the vaccine (HZV) reduced HZ incidence by 51% (95%CI: 44%, 58%) and PHN by 67% (95%CI: 48%, 79%). [53,112]

Investigating the effectiveness of a herpes zoster vaccine

In many cases, we need to obtain a reliable measure of absolute effectiveness, this usually means comparing a group of vaccinated individuals with another group of unvaccinated individuals. The main concerns for performing these studies are that, almost invariably, the populations to be studied are different not only with respect to their likelihood of getting vaccinated but also regarding the risk of the disease prevented by the vaccine being investigated. To address this issue, we decided to evaluate whether, using Medicare claims data, we could successfully evaluate vaccine effectiveness against an unvaccinated cohort. For this proof-of-concept study we decided to evaluate, using a population of Medicare Fee-for- service beneficiaries, the rate of Herpes Zoster outcomes among a group of vaccinees vs. an unvaccinated cohort.

Nonetheless, vaccinated and unvaccinated cohorts in Medicare are often different with respect to important potential confounders. One consideration is the fact that the population eligible to receive the study vaccine does not necessarily include the whole population of CMS beneficiaries. Specifically, in the case of the Zostavax effectiveness study, the vaccine has three main contraindications:[113]

(1) Zostavax should not be administered to individuals with a history of anaphylactic/anaphylactoid reaction to gelatin, neomycin or any other component of the vaccine. Nonetheless, a neomycin allergy manifested as contact dermatitis is not a contraindication.

(2) It should not be administered to pregnant women, given that naturally occurring varicella-zoster virus infection is known to sometimes cause fetal harm. The package insert recommendation specifically states that pregnancy should be avoided for 3 months following Zostavax administration.

(3) It should not be administered to individuals who are immunodeficient or immunosuppressed due to disease or therapy, as serious or fatal disseminated vaccine strain varicella-zoster virus disease may occur. The main list of causes of immunodeficiency or immunosuppression includes "primary or acquired immunodeficiency states, AIDS or other clinical manifestations of infection with human immunodeficiency viruses, leukemia, lymphoma or other malignant neoplasms affecting the bone marrow or lymphatic system, and immunosuppressive therapy."

Of the three contraindications described above, the one about pregnancy is not relevant

for a study among the elderly. Also, because our studies in CMS use claims, not medical records, we are unable to specifically identify individuals with a history of anaphylactic/anaphylactoid reaction to gelatin or neomycin. Nonetheless, such anaphylactic reactions are rare, and should not, a priori, affect a HZ disease comparison. The contraindication regarding immunosuppression, however, is relevant to our study because the conditions described (primary or acquired immunodeficiency states, AIDS or other clinical manifestations of infection with human immunodeficiency viruses, leukemia, lymphoma or other malignant neoplasms affecting the bone marrow or lymphatic system, and immunosuppressive therapy) are usually associated with severe morbidity, including herpes zoster, and are not so infrequent among the U.S. elderly. Therefore, prior to performing a Zostavax effectiveness study, we must identify and exclude relevant immunocompromising conditions. Moreover, for similar reasons, we should also identify and exclude immunocompromising drugs. We will describe the procedures followed to perform these exclusions and the codes used in the methods section.

An additional problem, not limited to claims-based studies, is the definition of study outcomes. Although defining hospitalizations or medical office visits for herpes zoster is fairly straightforward, giving the high positive predictive value of this diagnosis, defining other important outcomes using claims, particularly post-herpetic neuralgia, would require the use of algorithms, this will be described in detail in the methods section.[17,107,108,114-121]

The main problem for a comparison between a vaccinated and an unvaccinated population, however, is the cohort balance. Although Zostavax, the vaccine included in this particular study, is available to the (part D) Medicare-eligible population free-of-cost, the individuals who are more likely to use preventive services, including vaccinations, are different from those who don't. Therefore, we developed a list of covariates that are likely to reflect those

differences. The list includes demographic factors, socio-economic conditions, healthcare utilization, frailty characteristics, and functional immunocompromising chronic conditions. The table below (Table *i*) shows the imbalance between the herpes zoster vaccinated and unvaccinated cohorts with respect to these covariates.

Table *i*: Cohort balance prior to matching in a study of the effectiveness of a herpes zoster vaccine in the Medicare population

Demographic Variables	Vaccinated		Unvaccinated		Austin Std. Diff
Base Population	946,077		6,715,986		
Age (Continuous)	946,073		6,715,203		
Mean	76.61		78.06		0.21
SD	6.15		7.58		
Age (Categories)					
65-69	106,175	11%	923,193	14%	0.08
70-74	292,409	31%	1,574,338	23%	0.17
75-79	262,863	28%	1,508,504	22%	0.12
80-84	172,307	18%	1,275,867	19%	0.02

85-89	84,236	9%	879,397	13%	0.13
90-94	24,194	3%	420,045	6%	0.18
95-99	3,628	0%	116,978	2%	0.13
100+	265	0%	17,664	0%	0.06
Gender					
Male	316,749	33%	2,426,752	36%	0.06
Female	629,328	67%	4,289,234	64%	0.06
Race					
White	850,089	90%	5,390,931	80%	0.27
Black	22,086	2%	722,205	11%	0.35
Asian	44,649	5%	207,048	3%	0.08
Hispanic	10,905	1%	256,832	4%	0.17

Other	18,348	2%	138,970	2%	0.01
Low-Income Subsidy Status					
Receives LIS	205,438	22%	2,731,085	41%	0.42
No LIS	740,639	78%	3,984,901	59%	0.42

Note: For Austin standardized differences, the accepted threshold is 0.01

As can be seen in the highlighted cells, which show standardized mean differences (SMDs) larger than the conventionally accepted 0.10, the vaccinated and the unvaccinated populations were significantly different with respect to all important potential confounder categories included, with the exception of gender. Because these confounders have the potential to alter the association between HZ vaccination and HZ risk, we needed to take a series of steps to correct the imbalances in covariates included in the study. Therefore, prior to performing an absolute effectiveness study such as this one, we had to make the two populations as comparable as possible to regard to important potential confounders.

Are unmeasured confounders an unsurmountable issue in real-world evidence studies?

Other important issues also needed to be resolved, including regarding the effect of confounders unmeasured in the database such as likelihood to seek medical care when sick. This is a persistent problem for studies that compare a vaccinated and unvaccinated population. This is not easy to resolve and will be discussed extensively in this thesis. One approach to diminish the effect of such a problem is the use of a comparison cohort restricted to persons who received another vaccine.[17] Such approach, however, is not without problems.[17] A number of studies have used negative outcomes and other methods to detect such imbalances, with varying degrees of success.[122] In the methods section we will present the approaches we decided to use,

and the success of our effort will also be discussed in this thesis.

Are real-world effectiveness studies appropriate for investigating the duration of effectiveness of a herpes zoster or other vaccines?

An issue difficult also to resolve using (more expensive) clinical trial studies, is the duration of effectiveness of regulated vaccines. Clinical trials usually last only for sufficient time to establish short-term effectiveness, but that is usually not sufficient to determine how long vaccines work. This is of particular concern for a vaccine such as Zostavax, which did not show high effectiveness in randomized studies. Therefore, we decided to also estimate the duration of effectiveness for Zostavax. An advantage for this analysis is that an external comparison cohort may not be necessary.

Our objective was to estimate the absolute effectiveness and duration of effectiveness of Zostavax among Medicare beneficiaries ages 65 years and older. We chose multiple herpes zoster (HZ) outcomes including: (a) outpatient outcomes (medical office visits, which are frequent and less severe than hospitalizations; (b) less frequent and more severe outcomes including ophthalmic zoster and post-herpetic neuralgia (PHN)), and (c) rare and serious events including HZ hospitalizations and emergency room visits. We defined HZ medical office visits using two case definitions, with and without requiring antiviral treatments for HZ. We restricted the comparison to beneficiaries who had aged into Medicare (e.i. individuals who did not enter

Medicare prior to age 65 years because of special conditions such as renal failure) and were Medicare beneficiaries ages 65 years and older since at least the date of Zostavax licensure, and compared vaccinees with two well matched cohorts: (a) unvaccinated Medicare beneficiaries, and (b) beneficiaries not vaccinated with Zostavax who had received another unrelated vaccine (pneumovax).

Unmeasured confounders issues when comparing a Zostavax vaccinated group with an unvaccinated cohort

Unmeasured confounders are probably the main unresolved problem regulators face when trying to use observational study "real-world data to make regulatory decision. As indicated above, the 21st Century Cures Act [11] directs the regulators to "develop a regulatory framework to evaluate how real world evidence[13] can potentially be used to support approval of new indications for approved drugs or to support or satisfy post-approval study requirements". [25] This is not without difficulties. In clinical trials, the comparison groups (e.g. vaccine and placebo recipients) are usually randomized, guaranteeing that subjects assigned to the test vaccine are not systematically different from controls regarding measured and unmeasured variables. Thus, investigators can directly estimate treatment effects. In RWE studies, the decision to vaccinate is not made at random; it is instead made by parties such as the medical provider, patient, or insurance company. Therefore, the vaccinated and unvaccinated groups are often not balanced with respect to potential confounders that could

affect the associations being studied. These imbalances, if not well controlled, generate bias which may affect the direction and magnitude of the association being investigated.

Using matching and other techniques, investigators can control for potential measured confounders, but not for unmeasured variables. As the magnitude and direction of the potential bias due to unmeasured confounders cannot be estimated, it limits the use of RWE for regulatory decision-making.

Medicare claims and enrollment databases offer a powerful source of RWE for FDA's investigation of post-market vaccine safety and effectiveness. Medicare provides health insurance to some 58.5 million beneficiaries in the United States, of whom 49.8 million are 65 years or older.[123] While Medicare databases include information on a vast array of demographics, health conditions, and services delivered, they do not contain comprehensive information on behavioral and impaired mobility measures. Estimates based on Medicare claims data may therefore be biased. One possible solution is to incorporate information from external sources to evaluate covariate balance and adjust for confounders unavailable in the database.

The Medicare Current Beneficiary Survey (MCBS)[124] is a continuing, multipurpose survey of a nationally representative sample of the Medicare population conducted by the Centers for Medicare and Medicaid Services (CMS) since 1991, with approximately 16,000 respondents yearly. Participants are selected from a stratified sample of the Medicare population based on age and disability status.[124,125] MCBS data can therefore be linked back to the Medicare claims database to provide additional beneficiary behavioral and impaired mobility information.[126] A

potential solution to the issues arising from unmeasured confounders is to use MCBS data to assess the balance of covariates unavailable in the claims-based databases among cohorts in our vaccine effectiveness studies, and use multiple imputation techniques to evaluate the potential bias in study results by adjusting for a select set of MCBS covariates. Because the MCBS population comprises only a small portion (0.1%-0.2%) of the Medicare population, such a study should treat beneficiaries who had not participated in the survey as observations with missing information. Therefore, multiple imputation by chained equations approach could be used to impute variables that have been identified as potential confounders.

OBJECTIVE

The objective of this project is the development and implementation of methods and analytical strategies for the use of large-linked databases in the epidemiological investigation of the effectiveness of vaccines in the elderly. This should facilitate the use of real-world data such as the one available in Medicare for regulatory and public health decision-making.

METHODS

Proof of concept phase:

A proof of concept study in which we evaluated the effectiveness of high-dose compared with standard dose trivalent inactivated influenza vaccine (TIV) against outpatient and inpatient influenza among a sample of U.S. Medicare beneficiaries aged ≥65 years was initiated shortly before the submission of this thesis proposal, and was published during the following months in Lancet infectious diseases.[16] The methods initially developed during this "proof of concept" phase were the starting points for those used in the studies included in this thesis. These methods were also further improved during the development of the thesis, as will be seen in the following chapters.

Because a high-dose trivalent inactivated influenza vaccine was licensed in 2009 by the US Food and Drug Administration (FDA) on the basis of serological criteria, we sought to establish whether high-dose inactivated influenza vaccine was more effective for prevention of influenza- related visits and hospital admissions in US Medicare beneficiaries than the standard-dose inactivated influenza vaccine. In this retrospective cohort study, we identified Medicare beneficiaries aged 65 years and older who received high-dose or standard-dose inactivated influenza vaccines from community pharmacies that offered both vaccines during the 2012–13 influenza season. Outcomes were defined with billing codes on Medicare claims. The primary outcome was probable influenza infection, defined by use of a rapid influenza test followed by dispensing of the neuraminidase inhibitor oseltamivir (a medication that is only used against influenza). The secondary outcome was a hospital or

emergency department visit listing a Medicare billing code for influenza. In this proof of concept phase, in which pharmacy matching was used, we estimated relative vaccine effectiveness by comparing outcome rates in Medicare beneficiaries among recipients of High Dose (HD) vs. Standard Dose (SD) influenza vaccines during periods of high influenza circulation, determined by virologic surveillance. Univariate and multivariate Poisson regression models were used for analyses.

Our main findings were the following: Between August 1, 2012 and January 31, 2013, we studied 929 730 recipients of high-dose vaccine and 1 615 545 recipients of standard-dose vaccine. Participants enrolled in each cohort were well balanced with respect to age and presence of underlying medical disorders. The high-dose vaccine (0.86 outcomes per 10 000 person-weeks) was 22% (95% CI 15–29) more effective than the standard-dose vaccine (1.01 outcomes per 10 000 person-weeks) for prevention of outpatient influenza consultations (rapid influenza test followed by oseltamivir treatment) and 22% (95% CI 16–27%) more effective for the prevention of influenza hospital admissions. In conclusion, this retrospective cohort study in US Medicare beneficiaries shows that, in people 65 years of age and older, high-dose inactivated influenza vaccine was significantly more effective than standard-dose vaccine in prevention of influenza- related medical encounters. Additionally, the large population in our study enabled us to show, for the first time, a significant reduction in influenza-related hospital admissions in high-dose compared to standard-dose vaccine recipients, an outcome not shown in randomized studies.

These results provided important new information to be considered by policy makers recommending influenza vaccinations for elderly people[16]. More important, results from this proof of concept study, as well as from other two studies presented as results of this project,[14,18] have been cited to support the findings of randomized studies implemented under

experimental conditions but with significantly less power.[48,50,51,55,65,66]. Our findings have also

been commented favorably in comparison with less stringent observational vaccine

effectiveness studies[55].

Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US Medicare beneficiaries in preventing post-influenza deaths: a retrospective cohort study, 2012-13 and 2013-14

Data sources

Influenza

Data was gathered from the administrative files for Medicare, which provides

government sponsored health insurance coverage to about 40 million US residents of ages 65

and over, and to about 9 million persons under the age of 65 who are disabled or have end

stage renal disease. For each beneficiary, Medicare enrollment data was linked to claims from

the inpatient (Medicare Part A), office-based medical care (Part B) settings, as well as claims

for prescription drugs (Part D) to track influenza trends, define outcomes, and determine

population characteristics. Pharmacy data was drawn from the Provider Enrollment, Chain,

and Ownership System (PECOS). The proportion of samples testing positive for influenza

infection among samples submitted to laboratories collaborating with the National Respiratory

and Enteric Virus Surveillance System (NREVSS) was used to define the intensity of influenza

circulation during each week of a calendar year. This CDC-sponsored nationwide laboratory-based surveillance system monitors temporal and geographic patterns associated with the detection of influenza and other respiratory and enteric viruses. With NRVESS data, we defined high-, medium-, and low-intensity influenza weeks by using   previously published criteria. To identify likely episodes of influenza related illness in the outpatient setting, it is necessary to have access to prescription drug (Part D) claims for beneficiaries. For analyses involving this outcome, the study population is further subset to those beneficiaries who are also enrolled in Medicare Part D on the date of vaccination.

Study Cohort

The study's base population was drawn from fee-for-service Medicare beneficiaries aged ≥65 years who had a Healthcare Common Procedure Coding System (HCPCS) or Current Procedural Terminology (CPT) code for a high-dose influenza vaccination (CPT of 90662) or standard-dose vaccination (CPT of 90655-90661 or 90724; HCPCS of G0008, Q2035-Q2038) between August 1st, 2012 and January 31st, 2013 for the 2012-13 season and August 1st, 2013 and January 31st, 2014 for the 2013-14 season. Each beneficiary was required to be enrolled in Medicare parts A and B on the date of vaccination and for a period of at least 6 months prior to vaccination, so that data were available to detect comorbidities. For each season, beneficiaries diagnosed with influenza prior to vaccination or recorded as having both the high- and standard-dose vaccines between August 1st and May 31st of the following year were excluded from the study. Additionally, beneficiaries who entered Medicare for reasons other than being above the age of 65 – being disabled or having end stage renal disease – were excluded from the analysis. The remaining population was subset to only those beneficiaries

who received the vaccine at a community pharmacy. This restriction was applied to ensure that the eligible population met a minimum standard of self-care ability, demonstrated by the ability to request vaccination at an outpatient pharmacy. We hypothesized that this restriction would reduce the likelihood of confounding bias in the receipt of an influenza vaccine associated with physical or mental frailty. To account for temporal and geographical factors that may affect the availability of or access to the high-dose vaccine, the study population was further restricted to those beneficiaries who received a standard- or high-dose vaccine at a community-located pharmacy which vaccinated at least one other beneficiary with the alternate vaccine in the 2 weeks preceding or following the vaccination index date.

Vaccines

The 2012-2013 influenza vaccines used in the Northern hemisphere contained antigens representing the following viruses: an A/California/7/2009 (H1N1)pdm09-like virus, an A/Victoria/361/2011 (H3N2)-like virus, and a B/Wisconsin/1/2010-like virus. For the 2013-14 season, trivalent vaccines contained the following antigens: an A/California/7/2009 (H1N1)pdm09-like virus, an A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011 (A/Texas/50/2012), and a B/Massachusetts/2/2012-like virus. B/Wisconsin/1/2010 and B/Massachusetts/2/2012 are both B/Yamagata lineage viruses, and thus good serologic cross-reactivity is expected. Thus, the vaccine components used for the 2012-2013 and the 2013-2014 influenza vaccines were very similar, suggesting that pooled estimates of vaccine effects over these two seasons might be possible.

Outcomes and Follow-Up

The three outcomes of interest for this study are (i) influenza hospitalizations, (ii) deaths occurring within 30 days of hospital admission for influenza, and (iii) likely episodes of an influenza-related illness resulting in a clinical encounter at a community-based health care provider. The influenza hospitalization outcome occurred at the time of a hospital inpatient admission or an emergency department visit with a diagnosis of influenza, defined use of an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code or 488.xx. An influenza-associated death was defined as death within 30 days of admission for influenza. The 30-day window is an appropriate time window during which acute or subacute effects of an influenza hospitalization might be associated with death (refs). Similar to the hospitalized influenza outcome, the fatal influenza hospitalization outcome was defined to have occurred on the date of the inpatient hospitalization or Emergency department. Both these outcomes are evaluated in the vaccinated population that includes people both with and without Medicare Part D enrollment. The final outcome of interest – influenza related illness – was defined by an outpatient medical encounter with the provision of a rapid influenza diagnostic test (RIT) coded with CPT 87804, followed by the dispensing of oseltamivir for treatment (oseltamivir, 75 mg twice daily for 5 days) within a 2-day period. This influenza-related illness outcome was evaluated in a cohort that represented a subset of eligible beneficiaries who were enrolled in Medicare Part D on the day of influenza vaccination, as this criterion permitted the identification of the dispensing of a therapeutic course of oseltamivir. To define oseltamivir prescription, we used Medicare NDCcodes.

Follow-up time began 14 days after the date of vaccination and continued until the

occurrence of the first of the following events: death, disenrollment from Medicare Part A/B, or an outcome. In the case of the influenza related illness, beneficiaries were censored if they disenrolled from Medicare Part D. Beneficiaries contributed person-time to the analysis for each week that they remained in the study. For each of the 10 Census regions of the United States, each calendar week was classified as low, medium, or high influenza period, based on an estimated level of influenza activity during that week in that region. High, medium, and low periods of influenza activity were defined as weeks when the proportion of respiratory samples that tested positive for influenza was at the 75th or greater percentile, the 55th through 74th, and less than the 55th percentile, respectively, based on NREVSS data from all regions from August 2012 through August 2014.

Covariates

Baseline covariate data were collected for all study subjects in the 6 months prior to their date of vaccination. Covariates included demographic variables as well as pre-existing medical conditions The remaining population was subset to only those beneficiaries who received the vaccine at a community pharmacy. This restriction was applied to ensure that the eligible population met a minimum standard of self-care ability, demonstrated by the ability to request vaccination at an outpatient pharmacy. We hypothesized that this restriction would reduce the likelihood of confounding bias in the receipt of an influenza vaccine associated with physical or mental frailty. To account for temporal and geographical factors that may affect the availability of or access to the high-dose vaccine, the study population was further restricted to those beneficiaries who received a standard- or high-dose vaccine at a

community-located pharmacy which vaccinated at least one other beneficiary with the alternate vaccine in the 2 weeks preceding or following the vaccination index date.

Table *iii*: List of covariates used in adjusted Poisson model.

Covariates	
Age	**Low Income Subsidy (LIS)**
65 to 74	Not LIS
75 to 84	No Copay
85 +	Low Copay
Gender	High Copay
Female	15% Copay
Male	
Race	**Medical Conditions**
White	Diabetic
Black	At least one inpatient hospitalization
Hispanic	At least one high risk condition
Asian	Asthma Diagnosis
Native	Blood Disorder Diagnosis
Unknown	Chronic Lung Disease Diagnosis

Regions	Heart Disease Diagnosis
1: CT, ME, MA, NH, RI, VT	Kidney Disorder Diagnosis
2: NJ, NY, PR, VI	Liver Disorder Diagnosis
3: DE, DC, MD, PA, VA, WV	Neurological Disorder Diagnosis
4: AL, FL, GA, KY, MS, NC, SC, TN	Weakened Immune System Diagnosis
5: IL, IN, MI, MN, OH, WI	
6: AR, LA, NM, OK, TX	
7: IA, KS, MO, NE	
8: CO, MT, ND, SD, UT, WY	
9: AZ, CA, HI, NV, AS, FS, GU, PU	
10: AK, ID, OR, WA	

Medicare hierarchical medical condition categories

We used Centers for Medicare and Medicaid Services (CMS) hierarchical conditions categories (HCCs) to compare the acute and chronic medical conditions diagnosed in recipients of high-dose and standard-dose inactivated influenza vaccines in the 6 months prior to the date of immunization. The HCCs were developed to guide Medicare in making payments to private health care plans for the health expenditure risk of beneficiaries enrolled in these plans.[127] The HCCs are used with an individual's demographic data to determine a risk score, which is a relative measure of how costly that individual is anticipated to be to the plan. The HCCs and the risk model used by CMS were recently reviewed in a compressive white paper available from CMS (https://www.cms.gov/CCIIO/Resources/Forms-Reports-and-Other- Resources/Downloads/RA-March-31-White-Paper-032416.pdf). The ICD-9-CM and HCPCS codes used to define the disease categories listed in Table 1 have been used only with Medicare data file and are available on request from the authors of the study.

Indicators of frail health status

We used indicators for dementia, falls, fractures, home oxygen use, home use of a urinary catheter, and use of walkers or wheelchairs to define states associated with frail health that might represent confounders of the vaccine – outcome associations that we studied. Beneficiaries were placed into these seven categories by using ICD-9-CM Diagnosis (DGN) and Procedure (PRC) codes, and HCPCS codes, as can be seen in Table *iv*.

Table *iv*: Frailty indicators

Indicator	Code source	Data source used*	Diagnosis position
Dementia	DGN	IP/OP	All
Falls	DGN	IP/OP	All
Fracture	DGN/HCP/PRC	IP/OP	All
Home Oxygen	DGN/HCP/PRC	IP/OP/DM	All
Urinary Catheter	DGN/HCP/PRC	IP/OP/DM	All
Walker Use	HCP	IP/OP/DM	--
Wheelchair Use	DGN/HCP	IP/OP/DM	All

* IP, inpatient; OP, outpatient; and DM, durable medical equipment, data files were accessed in defining the indicator

Indicator of low income status

The Medicare Prescription Drug, Improvement and Modernization Act of 2003 (MMA), established the Medicare Prescription Drug Program, or Medicare Part D, which provides prescription drug coverage to Medicare beneficiaries who enroll in the program. The MMA also provides for a low-income subsidy (LIS) for extra help with prescription drug costs for eligible

individuals whose income and resources are limited. The LIS is a subsidy paid by the U.S. government to the drug plan in which the Medicare beneficiary enrolls, and it subsidy provides assistance with the premium, deductible and co-payments of the program. Beneficiaries apply for the low-income subsidy (LIS) through either the Social Security Administration or their State Medicaid agency. Medicare beneficiaries who wish to enroll in the Medicare Prescription Drug Program must choose a prescription drug plan through which to receive the benefit.

Power estimates

Data from the phase IV clinical trial,[48] a follow-up post-hoc analysis of the trial data stratified by factors that may influence influenza vaccine response,[50] and our previous observational study[16] suggested that receipt of high-dose versus standard-dose influenza vaccine might reduce post-influenza mortality by 20-30%, if the results from less severe outcomes were similar in magnitude to putative effects for the prevention of deaths. As the laboratory, randomized trial, and observational data all demonstrated a benefit with receipt of high-dose compared with standard-dose vaccines,[16,48,50,51,62,72,73] we conducted a 1-tailed power analysis to estimate the effects that we could detect at 80% and 90% statistical power, with an alpha = 0.05. Using data on deaths occurring after influenza hospitalizations in the entire cohort, we estimated that the study had 80% power to identify a RVE of 30% or higher for the primary outcome, post-influenza deaths. We also had 80% power to detect comparative effectiveness of 6% or higher for the hospitalized influenza and 8% for the influenza-related illness secondary outcomes. These statistics used data combined for both seasons – we also made estimates for each season individually, if seasonal effect modification was suggested. See power analyses results in Table *v*.

Table *v*: Power analysis for all outcomes, one tailed, by season

Outcome	N_{SD}	N_{HD}	Follow-up time	Number of events	Baseline rate	Comparative effectiveness threshold*	
			10 000 person-weeks		10 000 person-weeks	Power = 80%	Power = 90%
Post-influenza Death							
2012-13 Season	1,683,264	1,039,645	3,121	151	0.05	34.3	39.3
2013-14 Season	1,877,327	1,508,176	4,156	94	0.02	43.4	49.5
Combined	3,560,591	2,547,821	7,278	245	0.03	29.5	34.0
Hospitalized Influenza							
2012-13 Season	1,683,264	1,039,645	3,121	3,848	1.23	8.0	9.3
2013-14	1,877,327	1,508,176	4,156	2,192	0.53	10.2	11.9

Season							
Combined	3,560,591	2,547,821	7,278	6,040	0.83	6.3	7.4
Influenza-related Illness							
2012-13 Season	950,318	580,648	1,736	2,308	1.33	10.2	11.9
2013-14 Season	1,270,144	1,003,067	2,782	1,806	0.65	11.2	13.1
Combined	2,220,462	1,583,715	4,519	4,114	0.91	7.6	8.9

*If comparative effectiveness is lower than the comparative effectiveness threshold, then the study does not have the power to identify a statistically significant difference from zero, at an alpha of 0.05.

Statistical Analysis

To assess whether the beneficiaries in the two cohorts were similar, the differences in baseline covariates across cohorts were evaluated using standardized mean differences, calculated as the difference in means or proportions of a variable divided by the pooled standard deviation of the variable. A standardized mean difference of 0.1 or greater indicated a substantial difference in means or proportions between groups. The standardized mean difference is an effect-size measure that not influenced by population size, and thus provided

a more meaningful measure of the difference in the two large cohorts than simple mean

differences.

Outcome rates were calculated as the number of outcomes per person-time for each

cohort. The crude RVE (RVE) was estimated during the high season. The primary analysis

included only events occurring in the high influenza period during each season. RVE was

estimated by using the formula: RVE = (1 − rate high-dose recipients / rate standard-dose

recipients) x 100. A multivariate Poisson model, which adjusted for all covariates listed in the

table below, was used to model the outcomes in the high-influenza season, and used to derive

an adjusted RVE in the high season from the model-estimated rate ratio. Because both the

seasons and the vaccines administered in 2012-13 and 2013-14 were similar, the primary

analysis pooled outcomes from both seasons. Two different multivariate Poisson models will

be fit to the pooled data; both models included a covariate for season to account for the

differences in outcome rates across seasons, while one model also included a treatment-season

interaction term. The interaction term was used to assess whether there was a difference in

relative effectiveness by season. The log-likelihood ratio test was used to evaluate which of the

two models better fit the data; a p-value of <0.1 was used to indicate a substantial difference

in model fit.

Comparative effectiveness of cell-cultured vs egg-based influenza vaccines during the 2017-18 season.

Data Sources

We used Medicare administrative files providing data on enrollment, inpatient and outpatient care, physician office visits, and prescription drugs as the primary data source. We used respiratory sample data from the National Respiratory and Enteric Virus Surveillance System to define periods of high influenza circulation within seasons,[16,18] the National Plan and Provider Enumeration System plus the National Council for Prescription Drug Programs databases to identify pharmacies, and the Minimum Data Set to identify nursing facilities.

Observation Period

The study included the period from August 6, 2017 to August 4, 2018. For the interim analysis, we used data available up to January 19, 2018.

Study Population

We included Medicare beneficiaries ages ≥65 years who received an egg-based or cell- cultured influenza vaccination from August 6, 2017 through January 31, 2018, with data available as of August 4, 2018. For the interim analysis, we only included beneficiaries vaccinated prior to January 4, 2018, with data available as of January 19, 2018. We required continuous enrollment in fee-for-service Medicare Parts A and B in the six months prior to vaccination to allow for identification of chronic medical conditions. We excluded

beneficiaries enrolled in Medicare Part C, and those residing in nursing homes on vaccination date because their medical encounters may not be reliably captured. We also excluded beneficiaries who received an earlier influenza vaccination in the same season, and those for whom region of residence was not defined in the Department of Health and Human Services (DHHS) regions.[16,18] The selection process, and the attrition of cohorts participants after each step, are described in Figure *i*.

Figure *i*: Selection Process for Defining Influenza Vaccine Cohorts among Medicare Beneficiaries in the 2017-2018 Influenza Season (ilustration)

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┌─────────────────────────────────────────────────┐
│              Base Population:                      │
│  Beneficiaries who received an influenza           │
│  vaccination within the specified time frame       │
│  for the season                                    │
└─────────────────────────────────────────────────┘
                      │
                      ▼
┌─────────────────────────────────────────────────┐
│  Beneficiaries with continuous Medicare Part       │
│  A/B enrollment for the 6 months prior to their    │
│  vaccination date                                  │
└─────────────────────────────────────────────────┘
                      │
                      ▼
┌─────────────────────────────────────────────────┐
│  Beneficiaries at least 65 years of age            │
└─────────────────────────────────────────────────┘
                      │
                      ▼
┌─────────────────────────────────────────────────┐
│  Beneficiaries who received only one influenza     │
│  vaccine type on index day, were not in a nursing  │
│  home facility on vaccination day, and did not     │
│  receive any influenza vaccine prior to index date │
│  in the season                                     │
└─────────────────────────────────────────────────┘
                      │
                      ▼
┌─────────────────────────────────────────────────┐
│  Beneficiaries residing in one of the ten HHS      │
│  regions                                           │
│  Final study population                            │
└─────────────────────────────────────────────────┘
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Influenza Vaccine Exposure

We classified eligible beneficiaries into five cohorts based on the type of vaccine received. Vaccinations were identified using Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes for the cell-cultured quadrivalent vaccine (CPT 90674 & 90756), as well as the four egg-based vaccine types: quadrivalent (CPT 90630, 90685-90688), high-dose trivalent (CPT 90662), adjuvanted trivalent (CPT 90653), and standard-dose trivalent (CPT 90656-90658; HCPCS Q2034-Q2038). Other influenza vaccines were not utilized in sufficient numbers for study inclusion. An unvaccinated cohort was not included because we were unable to reliably identify unvaccinated beneficiaries from Medicare claims alone, since they may have been vaccinated outside of the system.

Study Outcomes

The primary outcome was influenza hospital encounters, defined as inpatient hospitalizations/emergency department visits listing an International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) code for influenza (ICD-10 codes J09.xx, J10.xx, J11.xx, J129). We also performed a post-hoc analysis using only inpatient stays as outcomes, and a pre-specified secondary analysis of influenza-related office visits, defined as community-based physician office visits or hospital outpatient visits with a rapid influenza diagnostic test performed (RIT, CPT 87804) followed by a therapeutic course of Oseltamivir (75 mg twice daily for 5 days) prescribed within 2 days of the test.[16,18]

Person-Time under Observation

Follow-up time began 14 days after vaccination (to allow for development of vaccine-specific immunity) and continued until one of the following occurred: outcome of interest, Medicare disenrollment, end of study period, death, admission into a nursing home, or administration of a subsequent influenza vaccine. To increase the positive predictive value of outcomes, we focused the analyses only on person-time observed in regions and weeks with high levels of influenza circulation.[1,16,18] Each week of the influenza season within each DHHS region was classified as a high influenza circulation period if the proportion of respiratory samples that tested positive for influenza was $\geq$15%.[1,16,18]

Variables of Interest

For each beneficiary, we collected data on demographics, Medicaid eligibility, reason for entry into Medicare, DHHS region of residence, prior medical encounters, chronic medical conditions, and frailty indicators in the six months prior to vaccination. We adjusted for all study covariates as potential confounders. We assessed the covariate balance between cohorts using standardized mean differences (SMDs). SMDs of less than 0.1 represented negligible imbalance.[128]

Statistical Analyses

Our main analysis focused on the comparison between the cell-cultured and egg-based

standard-dose quadrivalent vaccines to ensure comparability. For the adjusted analysis, we used inverse probability of treatment weighting (IPTW) to adjust for imbalances between cohorts on all covariates.[129] Stabilized IPTW weights were derived from propensity scores, representing each beneficiary's probability of receiving the cell-cultured over egg-based vaccines, conditional on covariates.[130] We calculated propensity scores using a logistic regression model with vaccine cohort as the dependent variable and all covariates as independent variables. Weight values greater than five were truncated to five to limit the bias that outlier beneficiaries could have on results.[131] We ran a univariate Poisson regression model on the weighted population to estimate the adjusted rate ratio (RR) between the two cohorts. The adjusted RVE was defined as $(1 - RR) \times 100\%$. As sensitivity analyses, we ran a weighted univariate Poisson model for which weights were not truncated and a doubly-robust model that implemented covariate adjustment along with IPTW weighting.[132]

To provide further context, we conducted an analysis that also included the egg-based high-dose, adjuvanted, and standard-dose trivalent vaccines, using IPTW to adjust for covariate imbalances. We calculated five propensity scores for each participant using separate logistic regression models, with each score representing the probability of receiving a particular vaccine type relative to any other.[133] The outcome models and sensitivity analyses conducted were similar to those we used for the two-way vaccine comparison.

We conducted the analyses using R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS v. 9.4 (SAS Institute Inc., Cary, NC). We performed all analyses with de-identified data collected for administrative purposes by the Centers for Medicare & Medicaid Services (CMS). This study was approved by the FDA's Research Involving Human Subjects Committee.

Derivation of Vaccine Effectiveness Estimates for All Vaccine Cohorts

Although the main study objective was to evaluate comparative effectiveness, more specifically between cell-cultured vs egg-based influenza vaccines, we also decided to provide hypothetical vaccine effectiveness estimates for each study vaccine in the 2017-18 season among beneficiaries ages ≥65. These estimates were approximated using the CDC interim VE estimate for the season, [98,101] assuming a ±10 point difference, given that, as indicated previously, we are unable to reliably identify unvaccinated beneficiaries using Medicare claims (given that the influenza vaccine is often also offered free of charge at the workplace, or in public health clinics, which do not report the vaccinees to CMS.

The steps for calculating VE estimates for each vaccine type are described below. The calculation assumes that the vaccine effectiveness and share of each vaccine type among our study population is comparable to that of the population used by the CDC to produce interim VE estimates across all vaccine types for the 2017-18 season.[98,101,134]

- Set of treatments defined as T = [1, 2, 3, 4, 5],
    - 1 = Cell-cultured Quadrivalent, 2 = Egg-based Adjuvanted, 3 = Egg-based HD Trivalent, 4 = Egg-based SD Trivalent, 5 = Egg-based SD Quadrivalent (reference group)
- *Pt*= Proportion of beneficiaries that received vaccine type *t* among the total study population
- *IRx*= Incidence rate of cohort *x*

Definitions:

- *RRxy=IRx/IRy*

- *RVExy=(1-RRxy)*100%*

- *VEx=(1-RRx,*unvaccinated*)*100%*

- *VEall=18%* based on CDC's interim VE estimates for the 2017-18 season

VE Estimate Calculation:

1. We know that the incidence rate in the vaccinated population is the *weighted average of the rate ratios for each vaccine* compared to the egg-based quadrivalent vaccine multiplied by the incidence rate amongst the egg-based quadrivalent vaccinated cohort.

2. By definition, the rate ratio of the vaccinated population to the unvaccinated population is described as:

   - *RRall, unvaccinated=IRall/IRunvaccinated*

3. Rearranging the equations, we get an estimate of the rate ratio for the egg-based quadrivalent cohort against the unvaccinated population:

Note: The proportion of the total study population in each vaccine cohort is provided in Table 1 of the article. The estimated rate ratio for each vaccine cohort, using the egg- based quadrivalent cohort as the reference group, can be derived from the vaccine effectiveness estimates provided in Table 3 and Table 4 of the article.

4. Replacing values, we can derive the rate ratio of the egg-based quadrivalent vaccinated cohort to the unvaccinated population as 0.892:

5. We derive the rate ratio for all other vaccine categories, using the rate ratios for the vaccine to the egg-based quadrivalent vaccine (derived from the RVEs in Table 3 and Table 4 of the article), and the rate ratio for the egg-based quadrivalent vaccine to the unvaccinated population.

6. We derive VE for each vaccine group from the rate ratios (approximately 10.8% for the egg-based quadrivalent vaccine).

Statin use and risks of influenza-related outcomes among older adults receiving standard-dose or high-dose influenza vaccines through Medicare during 2010-2015

Data sources

Medicare administrative files were the primary data source. Medicare provides health insurance coverage to ~49 million U.S. residents aged >65 years, as well as to ~9 million younger beneficiaries who are disabled or have end-stage renal disease.[80] Medicare administrative files include data on enrollment, inpatient and outpatient care, physician office visits, and prescription drugs. Pharmacy data were derived from the National Plan and Provider Enumeration System and the National Council for Prescription Drug Programs databases. Respiratory sample data were drawn from the National Respiratory and Enteric Virus Surveillance System.[135]

Participants

Medicare beneficiaries aged >65 years who received high-dose (HD) or standard-dose (SD) influenza vaccines at community pharmacies from August through January of each influenza season in the study period, defined as August 1, 2010 through August 1, 2015. We restricted enrollment to beneficiaries vaccinated in a pharmacy setting, because previous studies demonstrated this restriction produced vaccinated cohorts well balanced for factors associated with increased risks for serious complications of influenza infection.[16,18] Beneficiaries were included for each season in which they received a vaccination.[16,18] Vaccinations were identified using Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes for high dose (CPT 90662), trivalent standard dose (CPT 90654, 90656-90661, 90673, and 90724; HCPCS Q2034-Q2039), and quadrivalent standard dose influenza vaccinations (CPT 90630, 90686, and 90688). Beneficiaries who received more than one influenza vaccination in the same season were excluded.

We required continuous enrollment in fee-for-service Medicare Parts A (hospitalization), B (outpatient medical care), and D (prescription drugs) for at least 1 year prior to vaccination to permit identification of chronic medical conditions. Participants whose Medicare eligibility depended on disability or end-stage renal disease prior to age 65 years were excluded.[16,18] Beneficiaries enrolled in Medicare Part C (i.e., Medicare advantage plans) were excluded because their medical encounters may not be reliably captured in claims data.[16] Additionally, beneficiaries were excluded if they resided in a nursing home or skilled nursing facility (SNF), received hospice care or chemotherapy, were diagnosed with HIV or cancer other than skin cancer, or underwent organ transplant in the year prior to vaccination. [17] Medical condition exclusion criteria were identified using HCPCS, CPT, or International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

As statins are prescribed specifically to treat persons with hyperlipidemia to prevent complications of atherosclerotic cardiovascular disease, which may be associated with more serious complications of influenza, we excluded beneficiaries who received a diagnosis of atherosclerotic cardiovascular disease in the year prior to vaccination (e-Table 1).

Study outcomes

The primary outcome was a community-based physician office visit or hospital outpatient visit containing a claim for a rapid influenza diagnostic test (CPT coded 87804) followed by a claim for a therapeutic course of oseltamivir (75 mg twice daily for 5 days) prescribed within 2 days of the test claim, which we have referred to here as "influenza-related office visits".[16] The secondary outcome was a hospitalization or emergency department visit with an ICD-9-CM code for influenza (codes 487.xx and 488.xx), which we have referred to here as "influenza hospitalizations".

Statin exposure

Participants were classified as statin users or non-users. Statin users were eligible beneficiaries with a sufficient supply of statins to cover the 15 days before through 15 days after vaccination, with a maximum allowable gap of 2 days. Adherent statin users were defined as beneficiaries who received at least two prescriptions of statins in the period from 6 months before to 15 days after vaccination and had a medication possession ratio (MPR) of ≥ 0.8.[136] Non-

users were defined as beneficiaries with no evidence of receiving statins during the period extending from 6 months before to 15 days after vaccination. Beneficiaries who did not meet the criteria for either group were excluded.

Person-time under observation

Follow-up began 14 days after vaccination, to permit development of vaccine-specific immunity. [137] It ended when one of the following endpoints was reached: a study outcome of interest, disenrollment from Medicare Parts A, B, or D, diagnosis of cardiovascular or immunosuppressive conditions, organ transplant, chemotherapy, admission to a SNF or nursing home, transfer to hospice care, end of influenza season, or death. Each week in each influenza season for each geographic region of the United States as defined by the Department of Health and Human Services (HHS) was classified as a high-, medium-, or low-intensity influenza period. These periods were defined, respectively, as weeks in which the proportion of respiratory samples that tested positive for influenza was above the 75th percentile, within the 55th and 74th percentile, or below the 55[th]percentile.[16]

Control for confounding

Data on demographics, socioeconomic status, medical encounter history, medical conditions, and health status were collected for each beneficiary during the year prior to vaccination.[138,139] We used a combination of exact matching and propensity score matching to adjust for potential confounders.[129,140] Propensity scores were calculated using a logistic

regression model with statin use as the dependent variable. For each statin user, we first identified a group of non-users who were identical by vaccine type, sex, age group (65-69, 70-74, 75-79, 80-84, and 85+ years), and HHS region of residence, and then selected the non-user with the nearest propensity score.[129] Balance in baseline covariates between the cohorts was assessed using standardized mean differences (SMDs). We considered SMDs of less than 0.1 to represent a negligible imbalance.[128]

Statistical analyses

Rates for each study outcome in the low, medium, and high intensity influenza periods were calculated as the number of outcomes divided by person-time in weeks. We focused on the high-intensity influenza periods to increase the specificity of outcomes. We used three Poisson regression models to estimate rate ratios between statin users and non-users. The first model adjusted for influenza season, to account for differences in influenza circulation by season. The second model included all covariates used in the matching process in addition to season. In the third model, an interaction term between season and statin exposure was added to Model 2, to evaluate if associations between statin use and outcome risks varied by season. The Akaike Information Criterion (AIC) was used to evaluate model fit.[141] Two-tailed P values ≤ 0.05 were considered statistically significant.

We conducted several additional analyses to address specific questions. To evaluate if statin effects varied by receipt of HD or SD vaccine, we fit a model including an interaction for vaccine type and statin exposure. We also examined the effect of synthetic (atorvastatin,

fluvastatin, rosuvastatin) vs non-synthetic (simvastatin, pravastatin, lovastatin, and pitavastatin) statin use, and intensity of statin treatment exposure on influenza-related outcomes (e-Table 2). For the statin-type analysis, the statin user cohort was split into synthetic and non-synthetic statin cohorts.[81] In the statin-intensity analysis, the statin user cohort was split into low, moderate and high intensity statin cohorts based on active ingredient and prescribed dose.[142] To investigate the effect of the relationship between statin type and intensity, we fit a model comparing users of different statin type and intensity combinations. In a post-hoc analysis, the statin intensity analysis was repeated with cohorts weighted with stabilized inverse probability of treatment weights (IPTW) to address residual imbalances found in the statin-intensity cohorts.

To assess if our findings might reflect the effect of persistent use of a common medication, rather than statin-specific effects, we performed "negative exposure" analyses. [143] These analyses replicated the study methodology for the primary and secondary outcomes using an alternate exposure in place of statin use, to evaluate if observed differences were due to bias from unmeasured confounders.[143] Null results would suggest lack of confounding. Negative exposures considered were use of hydrochlorothiazide medications (HCTZs) not combined with another drug in a single pill and use of proton pump inhibitors (PPIs).

Analyses were conducted using R 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria) and SAS v. 9.4 (SAS Institute Inc., Cary, NC). All analyses were performed with de-identified data collected for administrative purposes by the Centers for Medicare & Medicaid Services.

Effectiveness and duration of effectiveness of the Zostavax vaccine among Medicare beneficiaries ages 65 years and older

Study Population

Medicare beneficiaries ages 65 years or older enrolled in fee-for-service Medicare Parts A (inpatient services), B (outpatient services), and D (prescription drugs) were analyzed retrospectively, comparing those who received a claim for HZV to those who were unvaccinated. Exposure to the HZV was identified using National Drug Codes (NDCs) for ZOSTAVAX, with the vaccination date used as the index date. Vaccinations between January 1, 2007 and July 31, 2014 were eligible for use as index dates. For the unvaccinated cohort, index dates were assigned to match the distribution of vaccination dates, subject to eligibility requirements.

Beneficiaries were included in the analyses if they had 12 months of continuous enrollment in Medicare A, B, and D. Additionally, to ensure that unvaccinated beneficiaries were truly unvaccinated, beneficiaries were included in analyses only if they were enrolled in Medicare Part D since at least May 2006, when HZV was first licensed. Beneficiaries were excluded if they had an overlapping nursing home, skilled nursing facility, or hospice stay, an HZ diagnosis in the 12 months prior a claim for an immunocompromising medical condition in the 12 months prior, or immunosuppressive treatment in the 6 months prior to their index date (Appendix I-II).

Cohort Follow-up

Start of follow-up began 30 days after cohort entry, similar to the Shingles Prevention Study [112]. Beneficiaries were followed continuously until: a subsequent HZV claim, death, disenrollment from fee-for-service Medicare, end of study (July 31, 2014), admission to a nursing home, skilled nursing facility, or hospice, occurrence of the outcome of interest, or an immunosuppressive drug claim in the first two months after index date.

Outcomes

Incident HZ cases were defined using *International Classification of Diseases, Ninth Revision* (ICD-9-CM) codes (053.XX for HZ and 053.2X for OZ). Cases were captured in institutional and non-institutional care settings and categorized into five separate outcomes: outpatient HZ, hospitalized HZ, outpatient OZ, hospitalized OZ, and PHN. We do not present our hospitalized OZ results because of low sample size and overall similarity to findings on hospitalized HZ. For inpatient cases, HZ in the first diagnosis position only was used, as it has the highest reported Positive Predictive Value (PPV) for identifying hospitalizations due to HZ (86%) [116]. For outpatient cases, outcomes in any diagnosis position were considered with reported PPVs ranging from 85.2% to 98% [111,117].

Detection of PHN may be biased when ascertainment is restricted to medically-attended care, and particularly challenging when using administrative data [117,121]. Nonetheless, PHN is an important consequence of HZ, especially in older adults, so we evaluated it as an outcome in

an exploratory analysis. PHN was defined using a modified version of the algorithm in Klompas et al. [117]. Cases of PHN were identified based on the presence of ICD-9 053.xx in the 90-180 days after an incident HZ diagnosis in combination with at least one of the following events: (1) a new prescription of a PHN treatment (Appendix III) in the 0-60 days from incident HZ diagnosis, (2)the presence of HZ with nervous system complications (ICD-9 053.1x) in the 90-180 days from incident HZ diagnosis, or (3) the presence of a new diagnosis for neuralgia (ICD-9 729.2x) in the 0-180 days from incident HZ diagnosis.

Covariates

This study accounted for well-studied risk factors of HZ, including age, gender, and race, in addition to other potential risk factors believed to be associated with risk of HZ or propensity to seek care once HZ is contracted (Appendix IV) [118,144-146]. To achieve balance between cohorts, 1:1 propensity score matching was used, with propensity scores estimated from a logistic regression using all covariates. Beneficiaries were matched using this propensity score and the minimum Mahalanobis distance for key covariates: age, gender, race, and low-income subsidy status [147].

Definitions of medical conditions and prescription drugs

Because the Zostavax package insert contraindicates the use of this vaccine among persons with immunosuppressive conditions, including primary or acquired immunodeficiency states, AIDS or other clinical manifestations of infection with human immunodeficiency viruses, leukemia, lymphoma or other malignant neoplasms affecting the bone marrow or lymphatic system, and immunosuppressive therapy), and these conditions may be linked to the occurrence and severity of herpes zoster, we identified codes for such conditions for study exclusion (Table *vi*).

Table *vi*: Immunocompromising conditions used as an exclusion criterion- Zostavax study

Frankly Immunocompromising Conditions	ICD-9 Diagnosis Codes
HIV Infection	042, 079.53, 795.71
Hodgkin's Disease	201
Non-Hodgkin's Lymphoma	200, 202.0, 202.1, 202.2, 202.3, 202.5, 202.6, 202.7, 202.8, 202.9
Leukemia	202.4, 203.1, 204, 205, 206, 207, 208
Multiple Myeloma	203.0
Neoplasm	203.8, 238.6, 238.72, 238.73, 238.74, 238.75, 238.76, 238.77, 238.79
Immune System Disorder	273.3, 277.89, 279.0, 279.2, 279.3, 279.4, 279.5, 279.8, 279.9
White Blood Cell Disease	279.10, 279.11, 279.12, 279.13, 279.19, 284.09, 284.89, 288.01, 288.02, 288.1, 288.2, 288.4, 288.50, 288.64, 288.8, 289.53
Other Hematological Diseases	289.50, 289.59, 289.8, 289.9

Conditions were defined using all diagnosis positions in inpatient, outpatient, and non- institutional settings.

Because drugs with immunocompromising effects can also affect the occurrence and severity of herpes zoster events, we also produced a list of such medications and excluded individuals who had received them around the time of vaccination (see table below). This list of drugs was used in three ways: (1) as a baseline exclusion criterion, (2) censoring reason in the 2 months after cohort entry, and (3) a time-varying covariate during follow-up. For the latter, a beneficiary was considered immunocompromised during the time from prescription fill date up until the end of days' supply plus an additional 30-day grace period. If a subsequent prescription was filled within the 30-day grace period of the first prescription, use was aggregated, and the 30-day grace period was applied at the end of the 'episode'. Because immunocompromising drug use within 2 months of cohort entry was a censoring criterion, only use in the period afterwards was considered.

Table *vii*: Immunocompromising drugs used for exclusion in the Zostavax effectiveness study

IC Drug Categories	Drug Names
Antineoplastics	Altretamine, Bendamustine, Busulfan, Carboplatin, Cisplatin, Oxaliplatin, Thiotepa, Chlorambucil, Cyclophosphamide, Ifosfamide, Mechlorethamine, Melphalan, Carmustine, Lomustine, Streptozocin, Temozolomide, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitomycin, Mitoxantrone, Plicamycin, Pegaspargase, Azacitidine, Capecitabine, Cladribine, Clofarabine, Cytarabine, Decitabine, Floxuridine, Fludarabine, Fluorouracil, Gemcitabine, Nelarabine, Pemetrexed, Pralatrexate, Thioguanine, Alemtuzumab, Obinutuzumab, Ofatumumab, Rituximab, Brentuximab, Gemtuzumab, Ibritumomab, Tositumomab, Pomalidomide, Cabazitaxel, Docetaxel, Eribulin, Etoposide, Ixabepilone, Paclitaxel, Teniposide, Vincristine, Vinblastine, Vinorelbine, Romidepsin, Everolimus, Dasatinib, Erlotinib, Gefitinib, Ibrutinib, Imatinib, Lapatinib, Nilotinib, Ponatinib, Bortezomib, Irinotecan, Iodine, Radium, Samarium, Strontium, Sipuleucel-T, Dacarbazine, Denileukin, Hydroxyurea, Omacetaxine, Pentostatin, Procarbazine, Ifosfamide & Mesna
Mercaptopurines	Mercaptopurine
Methotrexates	Methotrexate
Immunomodulators	Anakinra, Adalimumab, Golimumab, Leflunomide, Etanercept, Abatacept, Rilonacept, Canakinumab, Tocilizumab, Tofacitinib, Penicillamine
Immunosuppressants	Certolizumab, Infliximab, Thalidomide, Lenalidomide, Cyclosporine, Lymphocyte, Anti-thymocyte, Mycophenolate, Everolimus, Sirolimus, Tacrolimus, Basiliximab, Daclizumab, Muromonab, Belatacept
Azathioprines	Azathioprine
Central Nervous System Agents	Teriflunomide, Natalizumab, Fingolimod
Corticosteroids	Betamethasone, Budesonide, Cortisone, Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone

To define post-herpetic neuralgia in this claims-based study, drugs used to treat herpes zoster-related pain, specifically neuralgia, had to be defined. Table *viii* lists below shows the codes we used in the study.

Table viii**: Anti-PHN drug categories used to define postherpetic neuralgia outcomes for the Zostavax effectiveness study**

Postherpetic Neuralgia Drug Categories	Drug Names
Analgesics/Opioids	Fentanyl, Methadone, Morphine, Oxycodone, Tramadol, Buprenorphine, Butorphanol, Codeine, Hydrocodone, Hydromorphone, Ketamine, Levorphanol, Meperidine, Oxymorphone, Propoxyphene, Tapentadol
Anticonvulsants	Gabapentin, Pregabalin

We used propensity score matching to make the herpes zoster vaccinated and unvaccinated cohorts comparable. The covariate categories we used included demographic factors, socio-economic conditions, healthcare utilization, frailty characteristics, and functional immunocompromising chronic conditions. Table *ix* lists all the covariates used by category.

Table *ix*: Covariates used in the propensity score matching model for the Zostavax

effectiveness study

Covariate	Condition	ICD-9 Diagnosis/Procedure and HCPCS Codes
Demographic factors	Age	--
	Gender	--
	Race	--
	Year of Cohort Entry	--
	Reason for Entrance into Medicare	--
Socio-economic conditions	Metropolitan Statistical Area (urban/rural status)	--
	Low Income Subsidy (LIS) Status	--
	Household Income by ZIP Code of Residence	--
Healthcare utilization characteristics	Hospital Visits	--
	ER Visits	--
	Physician Office Visits	--
	Flu Vaccine Indicator	HCPCS: 90470, 90655, 90656, 90657, 90658, 90659, 90660, 90661, 90662, 90663, 90724, G0008, G9141, G9142
	Pneumococcal Vaccine Indicator	HCPCS: 90669, 90732, G0009
Frailty characteristics	Dementia	ICD-9: 094.1, 290.0, 290.1, 290.10, 290.11, 290.12, 290.13, 290.2, 290.20, 290.21, 290.3, 290.4, 290.40, 290.41, 290.42, 290.43, 291.1, 291.2, 292.82, 294, 294.0, 294.1, 294.10, 294.11, 331.0, 331.1, 331.11, 331.19, 331.82
	Home Oxygen	ICD-9: V46.2, 93.96; HCPCS: 99503, 99504, E0424, E0425, E0430, E0431, E0433, E0434, E0435, E0439, E0440, E0441, E0442, E0443, E0444, E0445, E0550, E0560, E1390, E1391, E1392, E1405, E1406, K0671
	Urinary Catheter	ICD-9: 996.64, V53.6, 57.94, 57.95, 96.48, 97.64; HCPCS: 51702, 51703, A4311, A4312, A4313, A4314, A4315, A4316, A4338, A4340, A4344, A4346, A4355
	Walker Use	HCPCS: E0130, E0135, E0140, E0141, E0143,

		E0144, E0147, E0148, E0149, E0154, E0155, E0156, E0157, E0158, E0159, L1520
	Wheelchair Use	ICD-9: E88.43, V46.3, V53.8; HCPCS: 97542, E0192, E0950, E0951, E0952, E0953, E0954, E0955, E0956, E0957, E0958, E0959, E0960, E0961, E0962, E0963, E0964, E0965, E0966, E0967, E0968, E0969, E0971, E0972, E0973, E0974, E0977, E0978, E0981, E0982, E0983, E0984, E0985, E0986, E0990, E0992, E0995, E1002, E1003, E1004, E1005, E1006, E1007, E1008, E1009, E1010, E1011, E1012, E1013, E1014, E1015, E1016, E1017, E1018, E1019, E1020, E1021, E1025, E1026, E1027, E1028, E1029, E1030, E1050, E1060, E1070, E1083, E1084, E1085, E1086, E1087, E1088, E1089, E1090, E1093, E1100, E1130, E1140, E1150, E1160, E1161, E1170, E1171, E1172, E1180, E1190, E1195, E1200, E1210, E1211, E1212, E1213, E1220, E1221, E1222, E1223, E1224, E1225, E1226, E1227, E1228
Functional immunocompromising chronic conditions	Diabetes	ICD-9: 250; HCPCS: G0108, G0109, G0245, G0246, G0247, G8015, G8016, G8017, G8018, G8019, G8020, G8021, G8022, G8023, G8024, G8025, G8026, G8332, G8333, G8334, G8335, G8336, G8385, G8386, G8390
	Kidney Disease	ICD-9: 585, 586, 587
	Heart Disease	ICD-9: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 414, 428, 37.66; HCPCS: 0050T, 33973, 33974, 33975, 33977, 33978, 33980, 92970, 92971, G8027, G8028, G8029, G8030, G8031, G8032, G8184
	Lung Disease	ICD-9: 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505, 506, 507, 508.1, 508.8, 508.9, 514, 515, 518.0, 518.1, 518.2, 518.3, 518.83; HCPCS: 32141, 32491, G8093, G8094
	Liver Disease	ICD-9: 571

Conditions were defined using all diagnosis positions in inpatient, outpatient, durable medical equipment, and non-institutional settings.

Falsification outcomes

HZV recipients might differ from non-recipients in their ability or desire to access care for HZ, introducing ascertainment bias. We adopted the approach in Tseng et al.[144] to check for such bias: hazard ratios were calculated for 13 acute symptomatic conditions (Table *x*) in the vaccinated and matched unvaccinated cohorts. Because these conditions were unrelated to HZ, as a group, the hazard ratios were expected to cluster around 1.0; any deviations from 1.0 would alert us to potential biases.

Table *x*: Falsification outcomes list used in the Zostavax effectiveness study

Falsification Outcomes	ICD-9 Diagnosis Codes
Lipomas	214.1, 214.8, 214.9
Gout	274.0, 274.9
Eyelid Disorders	373.00, 373.2, 373.11
Thrombosis	451.9, 453.8, 453.9
Hemorrhoids	455.0, 455.2, 455.3, 455.6
Renal Stones	592.0, 592.9, 788.0
Ingrown Nail	703.0
Epistaxis	784.7
Wound of Hand or Finger	882.0, 883.0, 883.1, 883.2
Cataracts	366.10, 366.14, 366.16, 366.17, 366.19
Cholelithiasis and Cholecystitis	574.00, 574.10, 575.10
Wrist Fracture	813.05, 813.23, 813.41, 813.42, 813.44, 813.81
Hip Fracture	820.00, 820.01, 820.02, 820.03, 820.8, 820.9, 820.09, 820.10, 820.11, 820.12, 820.13, 820.19

Conditions were defined using all diagnosis positions in inpatient, outpatient, and non-institutional settings.

Statistical analysis

Incident outcome rates were calculated by dividing the number of cases by the total person-years of observation. Cox regression models were used to estimate the hazard ratios for incident HZ and PHN in the vaccinated compared with the unvaccinated population, in which time intervals were interacted with vaccine status. A doubly robust Cox regression model was used that adjusted for all baseline characteristics.[148,149]. Additionally, for those beneficiaries in the cohorts who were started on immunosuppressive therapies after the index date, drug use was included in the model as a time-varying covariate. Vaccine effectiveness (VE) was calculated as (1-HR) x 100, where HR is the estimated hazard ratio between the two cohorts for a particular time interval, unless noted otherwise.

We also ran a secondary analysis using analogous methods but on a different comparator population. In this analysis, HZ vaccinees were compared to beneficiaries who received a pneumococcal vaccine (PV; Pneumovax®23, Merck & Co Inc, Whitehouse Station, New Jersey) but did not receive HZV. PV beneficiaries were followed from vaccination as their index date. Additional analyses were performed on both primary and secondary populations to investigate whether there was effect modification due to age, gender, and race.

This study was performed as part of the SafeRx Project, a joint initiative of the Centers for Medicare & Medicaid Services (CMS) and the U.S. Food and Drug Administration (FDA). It was approved by the Research in Human Subjects Committee of FDA's Center for Biologics

Evaluation and Research. Analyses were performed using R 3.0.2 (R Foundation for Statistical

Computing, Vienna, Austria) and SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Comparative effectiveness of high-dose versus standard- dose influenza vaccines among US Medicare beneficiaries in preventing post-influenza deaths: a retrospective cohort study, 2012-13 and 2013-14

Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccines Among US Medicare Beneficiaries in Preventing Postinfluenza Deaths During 2012–2013 and 2013–2014

David K. Shay,[1] Yoganand Chillarige,[2] Jeffrey Kelman,[3] Richard A. Forshee,[4] Ivo M. Foppa,[1,5] Michael Wernecke,[2] Yun Lu,[4] Jill M. Ferdinands,[1] Arjun Iyengar,[2] Alicia M. Fry,[1] Chris Worrall,[3] and Hector S. Izurieta[4,6]

[1]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia; [2]Acumen LLC, Burlingame, California; [3]Centers for Medicare and Medicaid Services, Washington, District of Columbia; [4]Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland; [5]Battelle Memorial Institute, Atlanta, Georgia; and [6]Department of Health Sciences, Universidad Rey Juan Carlos, Madrid, Spain

(See the editorial commentary by Monto on pages 500–2.)

Background. Recipients of high-dose vs standard-dose influenza vaccines have fewer influenza illnesses. We evaluated the comparative effectiveness of high-dose vaccine in preventing postinfluenza deaths during 2012–2013 and 2013–2014, when influenza viruses and vaccines were similar.

Methods. We identified Medicare beneficiaries aged ≥65 years who received high-dose or standard-dose vaccines in community-located pharmacies offering both vaccines. The primary outcome was death in the 30 days following an inpatient or emergency department encounter listing an influenza *International of Classification of Diseases, Ninth Revision, Clinical Modification* code. Effectiveness was estimated by using multivariate Poisson regression models; effectiveness was allowed to vary by season.

Results. We studied 1 039 645 recipients of high-dose and 1 683 264 recipients of standard-dose vaccines during 2012–2013, and 1 508 176 high-dose and 1 877 327 standard-dose recipients during 2013–2014. Vaccinees were well-balanced for medical conditions and indicators of frail health. Rates of postinfluenza death were 0.028 and 0.038/10 000 person-weeks in high-dose and standard-dose recipients, respectively. Comparative effectiveness was 24.0% (95% confidence interval [CI], .6%–42%); there was evidence of variation by season (*P* = .12). In 2012–2013, high-dose was 36.4% (95% CI, 9.0%–56%) more effective in reducing mortality; in 2013–2014, it was 2.5% (95% CI, −47% to 35%).

Conclusions. High-dose vaccine was significantly more effective in preventing postinfluenza deaths in 2012–2013, when A(H3N2) circulation was common, but not in 2013–2014.

Keywords. influenza vaccines; influenza, human; comparative effectiveness; death.

Much of the impetus to expand influenza immunization programs has been prompted by a desire to reduce serious complications of influenza infections, including death. It has been recognized at least since the 1957 A(H2N2) pandemic that older persons and those with some chronic health conditions, including pulmonary and cardiac compromise, are at the greatest risk of severe influenza outcomes [1, 2]. Recent randomized trials of influenza vaccines conducted in older populations have used more common outcomes as endpoints, typically laboratory-confirmed infections [3, 4]. Trials assessing influenza-associated mortality are unfeasible, given the low likelihood of

death following influenza infection during seasonal epidemics, even among the older persons at greatest risk. In fact, the best evidence available from randomized placebo-controlled studies of inactivated influenza vaccines among older persons demonstrated vaccine efficacy of 58% (95% confidence interval [CI], 26%–77%) for the prevention of symptomatic clinical illness associated with serologic evidence of influenza illness [5].

Several approaches to improving the clinical effectiveness of influenza vaccines for older adults are being investigated. In December 2009, the US Food and Drug Administration (FDA) licensed an injectable inactivated trivalent influenza vaccine containing more antigen (60 μg vs 15 μg per strain) for use among adults aged ≥65 years, hereafter referred to as "high-dose vaccine" [6]. High-dose vaccine was approved under FDA accelerated approval regulations, for which licensure was based on studies showing that high-dose vaccine elicited higher hemagglutination inhibition (HAI) titers in adults aged ≥65 years than standard-dose vaccine for influenza A(H1N1) and A(H3N2) viruses, and noninferior titers for B viruses [7–9]. A manufacturer-sponsored postlicensure randomized

trial of high-dose vs standard-dose vaccine among approximately 30 000 subjects aged ≥65 years was conducted during 2011–2012 and 2012–2013 [3]. It demonstrated that high-dose vaccine was more efficacious in preventing laboratory-confirmed influenza infections (relative efficacy, 24.2% [95% CI, 9.7%–36.5%]). Despite its large size, this trial was not powered to estimate the comparative efficacy of these vaccines against more serious influenza illnesses as primary outcomes. In an observational study among Medicare beneficiaries aged ≥65 years who were vaccinated in 2012–2013 with high-dose vs standard-dose vaccines in pharmacies [10], we found that high-dose vaccine was 22% (95% CI, 15%–29%) more effective than standard-dose vaccines in preventing influenza-related office visits. This finding was consistent with the relative efficacy of high-dose vaccine in the postlicensure trial, which used culture- or polymerase chain reaction (PCR)–confirmed influenza infection as the primary outcome [3]. We also found a 22% (95% CI, 16%–27%) reduction in influenza hospitalizations in the high-dose group [10].

Here we assess the risk of death after a diagnosed influenza infection among Medicare beneficiaries who received influenza vaccines in 2012–2013 or 2013–2014. Based on results from previous randomized and observational studies [3, 10, 11], we hypothesized that high-dose vaccine would prevent 20%–30% more influenza-associated deaths than standard-dose vaccine.

METHODS

Data Sources

Data were collected from Medicare administrative files (see https://www.medicare.gov/sign-up-change-plans/decide-how-to-get-medicare/whats-medicare/what-is-medicare.html for a summary). Medicare provides US government–sponsored health insurance to >40 million US residents aged ≥65 years and to approximately 9 million persons aged <65 years who are disabled or have end-stage renal disease. We linked enrollment data for beneficiaries receiving fee-for-service care with claims from inpatient (Medicare Part A) and outpatient care (Part B) settings, as well as claims for prescription drugs dispensed in outpatient settings (Part D). Pharmacy data were drawn from the Provider Enrollment, Chain, and Ownership System, the National Plan and Provider Enumeration System, and the National Council for Prescription Drug Programs databases. The proportion of respiratory samples testing positive for influenza viruses among samples submitted to laboratories collaborating with the National Respiratory and Enteric Virus Surveillance System (NREVSS) was used to monitor the intensity of influenza activity during the study period [12].

Participants

The base population was drawn from Medicare beneficiaries aged ≥65 years enrolled in fee-for-service care through Medicare parts A and B. Enrollment on the date of vaccination and for at least 6 months prior to vaccination was required, so that data were available to detect comorbid medical conditions. Beneficiaries with Part C coverage (managed care plan enrollment) were excluded because regulations regarding coverage for medications and vaccines are more homogenous among those receiving fee-for-service care. Beneficiaries who first enrolled in Medicare for any reason other than reaching 65, specifically being disabled or having end-stage renal disease, were excluded. We selected beneficiaries who received inactivated influenza vaccines from 5 August 2012 through 31 January 2013 for the 2012–2013 season, and from 4 August 2013 through 31 January 2014 for the 2013–2014 season. Dates were formatted to reflect the reporting of NREVSS influenza virus data—weekly, from Sunday through Saturday. Beneficiaries recorded as receiving both high-dose and standard-dose vaccines between 1 August and 31 May of the following year were excluded. From this group of beneficiaries, we obtained the study population. They were beneficiaries who received an influenza vaccination at a community-located pharmacy. This restriction was applied to identify beneficiaries who met a minimum standard of physical and mental health, demonstrated by an ability to visit a pharmacy and request an influenza vaccination [10]. To help adjust for temporal and geographical factors that influenced the availability of or access to high-dose vaccine, the study population was further restricted to those beneficiaries who received a standard- or high-dose vaccine at a community-located pharmacy that vaccinated at least 1 Medicare beneficiary with the alternative influenza vaccine in the 14 days preceding or following each vaccination date. Figure 1 summarizes the cohort selection process.

Influenza Vaccine Exposure

Participants were defined as exposed to high-dose or standard-dose vaccines by using Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes for high-dose vaccine (CPT 90662 code) or standard-dose vaccine (CPT codes 90655–90661 or 90724; HCPCS codes G0008, Q2035–Q2038). The 2012–2013 influenza vaccines dispensed in the northern hemisphere contained antigens representing the following viruses: an A/California/7/2009 (H1N1)pdm09-like virus, an A/Victoria/361/2011(H3N2)-like virus, and a B/Wisconsin/1/2010-like virus [13]. For the 2013–2014 season, trivalent vaccines contained the following antigens: an A/California/7/2009(H1N1)pdm09-like virus, an A(H3N2) virus antigenically like the cell-propagated prototype virus A/Victoria/361/2011(A/Texas/50/2012), and a B/Massachusetts/2/2012-like virus [14]. B/Wisconsin/1/2010 and B/Massachusetts/2/2012 are both B/Yamagata lineage viruses, and thus serologic cross-reactivity was expected with these 2 antigens. The vaccine components used in the 2012–2013 and 2013–2014 influenza vaccines were similar, suggesting that pooled estimates of vaccine effects might be possible.
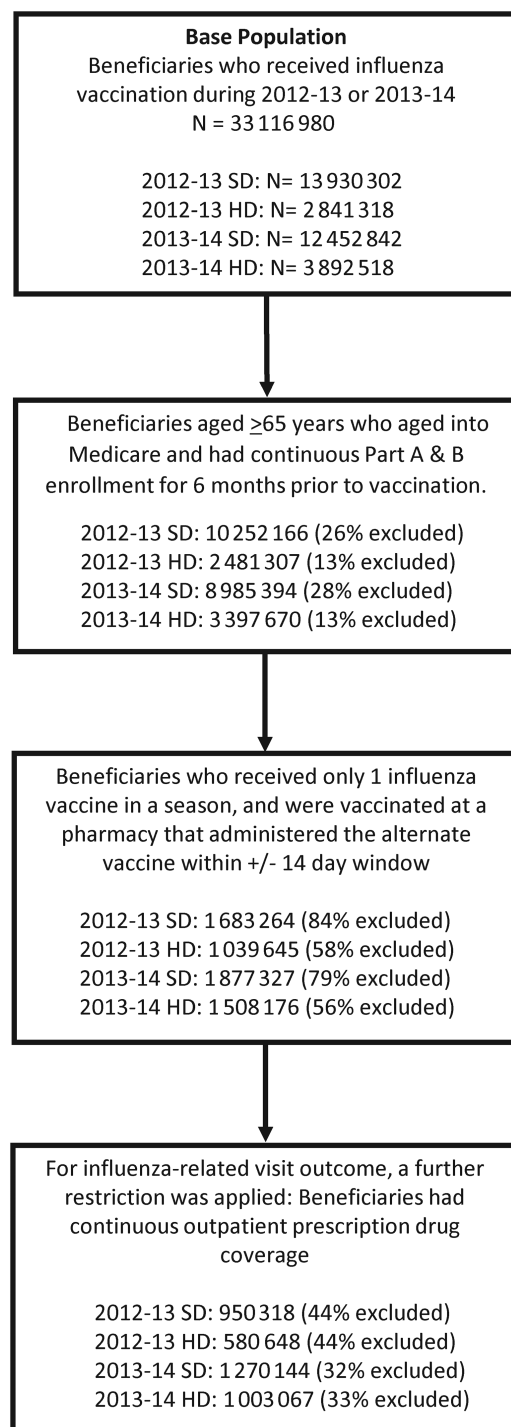
Figure 1. Cohort selection process. Abbreviations: HD, high-dose influenza vaccine; SD, standard-dose influenza vaccines.

Outcomes

The primary outcome was postinfluenza death, defined as a death occurring in the 30 days following a Medicare claim for an inpatient hospitalization or an emergency department visit with a diagnosis of influenza, identified using the *International Classification of Diseases, Ninth Revision, Clinical Modification*

(*ICD-9-CM*) codes 487.xx and 488.xx. To permit comparison of our findings with those from previous randomized and observational studies [3, 10, 11], we included 2 secondary outcomes: (1) hospitalizations and emergency department visits listing an *ICD-9-CM* code for influenza; and (2) likely influenza-related office visits, defined by a visit with claims for a rapid influenza diagnostic test (CPT code 87804) and for dispensing of a treatment regimen of oseltamivir (75 mg twice daily for 5 days) within 2 days of the test. The latter outcome was examined in a cohort restricted to participants who were enrolled in Medicare Part D on the day of influenza vaccination, so that we could identify prescriptions for a therapeutic course of oseltamivir.

Person-time Under Observation

Follow-up time began 14 days after the date of the vaccination, to permit the development of vaccine-specific immunity [15], and continued until the first of the following events: disenrollment from Medicare Part A or B; the outcome of interest; or death. For the influenza-related illness outcome, beneficiaries were also censored if they disenrolled from Medicare Part D. Using numbers of postinfluenza deaths in the entire cohort, we estimated we had adequate power to detect a 30% reduction in postinfluenza deaths in the high-dose vaccine group (Supplementary Table 1).

Variables of Interest

Demographic characteristics (age, sex, race, and ethnicity), and region of residence as characterized by the Department of Health and Human Services (DHHS) were collected for each participant. During the 6-month period prior to receipt of an influenza vaccine, we categorized preexisting medical conditions with the Hierarchical Condition Categories used for Medicare risk adjustment [16]. Participants were identified in the following categories: asthma, blood disorders, chronic lung disease, diabetes, heart disease, kidney disorders, liver disorders, neurological conditions, and immune system dysfunction. Several indicators of frail physical health were also collected for each participant (see Supplementary Materials).

Data Analyses

To determine whether the 2 cohorts were similar, differences in baseline covariates were evaluated using standardized mean differences, calculated as the difference in means or proportions of a variable divided by its pooled standard deviation. Standardized mean differences are not influenced by population size, and may provide a more meaningful measure of differences in large cohorts than standard hypothesis tests. A standardized mean difference of ≥0.1 between groups was considered meaningful [17].

Each calendar week during the study period in each DHHS region was classified into low, medium, or high influenza periods, based on detections of influenza viruses during that week

and in that region. High, medium, and low periods of influenza activity were defined as weeks when the proportion of respiratory samples that tested positive for influenza was the ≥75th, 55th–75th, or <55th percentile for each region/season, respectively [10].

Rates of each study outcome were calculated as the number of events during influenza periods divided by person-time measured in weeks. To improve specificity, our analyses focused on events occurring during high influenza periods. Three Poisson regression models were used. In the first, comparative vaccine effectiveness (VE) was estimated during high influenza periods with a covariate for season (2012–2013 or 2013–2014). A second model included all covariates listed in Table 1, to adjust for potential residual confounding after restricting participation to beneficiaries who were vaccinated in pharmacies. In the first 2 models, we pooled outcomes from 2012–2013 and 2013–2014. A third added a vaccine-season interaction term to the second, to evaluate whether effectiveness varied substantially by season. A log-likelihood ratio test was used to assess whether the interaction term statistically improved model fit; a *P* value of <.1 was considered significant. VE was estimated as [(1 – rate high-dose recipients/rate standard-dose recipients) × 100] and 95% CIs were estimated. Analyses were conducted using R 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria) and SAS version 9.4 (SAS Institute Inc, Cary, North Carolina). All analyses were performed with de-identified data collected for administrative purposes by the Centers for Medicare and Medicaid Services, and thus informed consent was not required by the US DHHS.

RESULTS

During the study period, >33 million Medicare beneficiaries aged ≥65 years received influenza vaccinations (Figure 1). In 2012–2013, 17% of vaccinees received the high-dose vaccine (2.8 million beneficiaries), while 24% received the high-dose vaccine in 2013–2014 (3.9 million beneficiaries). We studied 5 797 090 persons who received high-dose or standard-dose vaccines at 29 669 community-located pharmacies during the 2 seasons. During 2012–2013, 1 039 645 of 2 722 909 (38.2%) subjects meeting entry criteria received high-dose vaccine; during 2013–2014, 1 508 176 of 3 385 503 (44.5%) received high-dose vaccine. For the influenza-related illness outcome, requiring outpatient prescription-drug coverage reduced the number of subjects to 1 530 966 and 2 273 211 in the 2012–2013 and 2013–2014 seasons, respectively.

Subjects receiving high-dose or standard-dose vaccine were similar with respect to baseline covariates, including health conditions, low-income status, and indicators of frail health. Low and virtually identical proportions of high-dose and standard-dose recipients used home oxygen, wheelchairs or walkers, or had claims for falls, fractures, or dementia (Table 1),

suggesting that substantial confounding of vaccine exposure by health status was unlikely. There were differences by region of residence among high-dose and standard-dose vaccinees (Table 1). When we restricted the population further to those who received prescription drug coverage, the findings were very similar (Supplementary Table 2). The characteristics of beneficiaries who received standard- or high-dose vaccine in the first and the second study seasons did not differ (Supplementary Table 3).

Rates of postinfluenza death, hospitalized influenza, and influenza-related visits were plotted by vaccine type and by low, medium, and high influenza period in Figure 2. Rates for each outcome were higher during the first season, when A(H3N2) viruses predominated in the United States. The likelihood of postinfluenza death was 57% lower during 2013–2014, when A(H1N1)pdm09 viruses predominated.

During both seasons, 83 postinfluenza deaths occurred in the high-dose group during 30 079 255 person-weeks of observation (rate, 0.028/10 000 person-weeks), and 162 deaths in the standard-dose group during 42 696 182 person-weeks (rate, 0.038/10 000 person-weeks), representing a risk difference of −0.01/10 000 person-weeks (95% CI, −.019 to −.002), and an incidence rate ratio of 0.73 (95% CI, .59–.95). When examined by season of occurrence, differences in the rate of each outcome by vaccine type were greater in 2012–2013 (Figure 2).

Estimates of comparative effectiveness for influenza-related illness, hospital-diagnosed influenza, and postinfluenza death were similar in models that adjusted only for season and those that included covariates for potential confounders (Table 2). However, comparative effectiveness varied significantly by season for influenza-related illness (*P* value for season-vaccine interaction = .006) and for hospital-diagnosed influenza (*P* = .041); for postinfluenza death, the *P* value was .12. Given the consistently higher estimates of comparative effectiveness during the first season of the study, we presented season-specific estimates for each outcome (Table 2). During 2012–2013, comparative VE for the primary outcome of postinfluenza death was 36.4% (95% CI, 9%–56%), while during the following season it was minimal and not significant (2.5% [95% CI, −47% to 35%]).

DISCUSSION

In our study population, we found a significant reduction of approximately 35% in postinfluenza deaths associated with receipt of high-dose vs standard-dose vaccines in 2012–2013, but not in 2013–2014. The 2012–2013 reduction was accompanied by significant decreases of approximately 20% in influenza-related visits and hospital-based influenza diagnoses. The latter 2 findings are consistent with the results from our previous study (which used slightly different eligibility criteria and only 2012–2013 data) [10], and those from analyses of a manufacturer-sponsored

Table 1.   Characteristics of Study Participants for Postinfluenza Mortality and Influenza Hospitalization Outcomes, by Influenza Vaccine Type and Season

Characteristic	2012–2013 Season			2013–2014 Season		
	Standard Dose	High Dose	Standardized Mean Difference	Standard Dose	High Dose	Standardized Mean Difference
Population	1 683 264	1 039 645		1 877 327	1 508 176	
Age group, y						
65–74	52.1%	49.8%	0.05	51.2%	49.4%	0.04
75–84	34.7%	36.6%	0.04	34.9%	36.7%	0.04
≥85	13.1%	13.7%	0.02	13.9%	14.0%	0.00
Sex						
Male	40.7%	42.1%	0.03	40.3%	41.7%	0.03
Female	59.3%	57.9%	0.03	59.7%	58.3%	0.03
Race/ethnicity						
White	93.6%	93.1%	0.02	92.9%	92.7%	0.01
Black	2.6%	2.9%	0.02	2.8%	3.0%	0.01
Asian/Pacific Islander	1.3%	1.4%	0.01	1.4%	1.5%	0.01
Hispanic	0.6%	0.7%	0.01	0.8%	0.8%	0.00
Other, non–North American Native	1.3%	1.4%	0.01	1.3%	1.4%	0.01
North American Native	0.1%	0.2%	0.01	0.1%	0.1%	0.00
Unknown	0.4%	0.4%	0.01	0.7%	0.6%	0.01
DHHS region of residence						
Region 1: CT, ME, MA, NH, RI, VT	6.2%	4.0%	0.10	6.7%	4.6%	0.09
Region 2: NJ, NY, PR, VI	7.8%	5.6%	0.09	8.3%	6.6%	0.07
Region 3: DE, DC, MD, PA, VA, WV	8.1%	10.0%	0.07	8.4%	10.4%	0.07
Region 4: AL, FL, GA, KY, MS, NC, SC, TN	23.4%	27.2%	0.09	21.8%	26.8%	0.12
Region 5: IL, IN, MI, MN, OH, WI	19.6%	12.9%	0.18	19.6%	13.7%	0.16
Region 6: AR, LA, NM, OK, TX	11.2%	10.9%	0.01	12.2%	10.7%	0.05
Region 7: IA, KS, MO, NE	4.9%	3.3%	0.08	5.0%	3.2%	0.09
Region 8: CO, MT, ND, SD, UT, WY	2.9%	4.7%	0.10	2.6%	4.3%	0.09
Region 9: AZ, CA, HI, NV, AS, FS, GU, PU	11.9%	14.9%	0.09	11.5%	13.8%	0.07
Region 10: AK, ID, OR, WA	3.9%	6.6%	0.12	3.7%	5.9%	0.10
Proportion of beneficiaries enrolled in Medicare Part D	56.5%	55.9%	0.01	67.7%	66.5%	0.02
Low-income subsidy status[a]						
Proportion with 15% copay	0.8%	0.8%	0.00	0.7%	0.6%	0.00
Proportion with high copay	4.8%	4.9%	0.01	4.4%	4.3%	0.01
Proportion with low copay	4.9%	5.2%	0.02	4.5%	4.5%	0.00
Proportion with zero copay	1.1%	1.1%	0.01	1.0%	1.0%	0.01
Chronic medical conditions[b]						
At least 1 high-risk disorder	61.9%	62.9%	0.02	63.0%	64.6%	0.03
Asthma	3.8%	3.9%	0.01	4.0%	4.3%	0.02
Blood disorders	15.1%	15.6%	0.01	15.5%	16.3%	0.02
Chronic lung disease	13.8%	14.4%	0.02	13.9%	14.7%	0.02
Diabetes	20.1%	20.3%	0.01	21.1%	21.4%	0.01
Heart disease	33.1%	34.1%	0.02	33.7%	35.1%	0.03
Kidney disorders	6.9%	7.3%	0.01	7.7%	8.2%	0.02
Liver disorders	2.2%	2.3%	0.00	2.3%	2.4%	0.01
Neurological or neurodevelopmental conditions	11.1%	11.3%	0.01	11.3%	11.6%	0.01
Weakened immune system	12.1%	12.4%	0.01	12.1%	12.8%	0.02
Indicators of frail health status[c]						
Home oxygen use	2.4%	2.5%	0.01	2.4%	2.5%	0.00
Wheelchair use	0.1%	0.1%	0.00	0.1%	0.1%	0.00
Walker use	1.1%	1.1%	0.00	1.1%	1.0%	0.01
Dementia	3.2%	3.1%	0.00	3.4%	3.2%	0.02
Urinary catheter use	0.1%	0.1%	0.00	0.1%	0.1%	0.00
Falls	3.1%	3.1%	0.00	3.3%	3.2%	0.00
Fractures	1.1%	1.1%	0.00	1.1%	1.1%	0.00

Abbreviations: AK, Alaska; AL, Alabama; AR, Arkansas; AS, American Samoa; AZ, Arizona; CA, California; CO, Colorado; CT, Connecticut; DC, Washington, D.C.; DE, Delaware; DHHS, Department of Health and Human Services; FL, Florida; FS, Federated States of Micronesia; GA, Georgia; GU, Guam; HI, Hawaii; IA, Iowa; ID, Idaho; IL, Illinois; IN, Indiana; KS, Kansas; KY, Kentucky; LA, Louisiana; MA, Massachusetts; MD, Maryland; ME, Maine; MI, Michigan; MN, Minnesota; MO, Missouri; MS, Mississippi; MT, Montana; NC, North Carolina; ND, North Dakota; NE, Nebraska; NH, New Hampshire; NJ, New Jersey; NM, New Mexico; NV, Nevada; NY, New York; OH, Ohio; OK, Oklahoma; OR, Oregon; PA, Pennsylvania; PR, Puerto Rico; PU, Republic of Pulau; RI, Rhode Island; SC, South Carolina; SD, South Dakota; TN, Tennessee; TX, Texas; UT, Utah; VA, Virginia; VI, U.S. Virgin Islands; VT, Vermont; WA, Washington; WI, Wisconsin; WV, West Virginia; WY, Wyoming.

[a]Low-income subsidy status among beneficiaries enrolled in Medicare Part D. This subsidy provides assistance with the premium, deductible, and co-payments of the program. See Supplementary Materials for details.

[b]Medical conditions defined by the appearance of specific *International Classification of Diseases, Ninth Revision, Clinical Modification* codes in the 6 months prior to vaccination; see Supplementary Materials for details.

[c]These indicators were defined by the appearance of specific Healthcare Common Procedural Codes in the 6 months prior to vaccination; see Supplementary Materials for details.
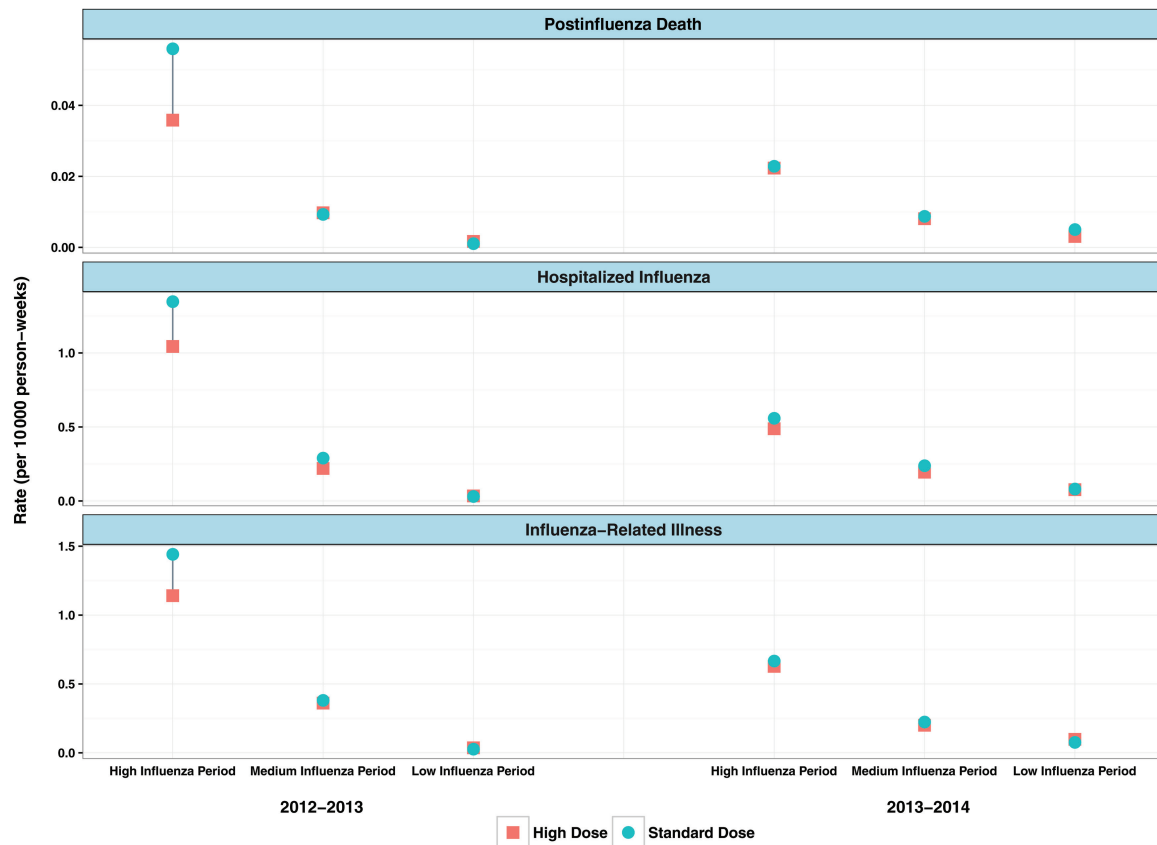
Figure 2. Outcome rates (per 10 000 person-weeks) for each of 3 influenza outcomes, by influenza season and during periods of high, medium, and low influenza activity.

trial [3, 11]. The internal and external consistency of our findings suggests that the use of high-dose vaccine in Medicare beneficiaries during 2012–2013 prevented additional influenza-related deaths. Despite 31 million person-weeks of follow-up time during 2012–2013, the magnitude of this reduction in mortality was not precisely estimated (95% CI, 9%–56%). As the outcomes of greatest interest when considering alternative vaccination strategies are often rare (eg, influenza-related mortality or serious vaccine adverse events), large postlicensure observational studies are vital in understanding the comparative effects

of new vaccine formulations—randomized trials are unable to answer all relevant policy questions. Multiple seasons of observational data analyzed with appropriate longitudinal methods will be critical to providing valid information to those considering alternative influenza vaccine recommendations.

Persons aged 65 years and older experience the highest rates of many serious complications of influenza—including prolonged hospitalization, the need for intensive care, and death—during most interpandemic influenza seasons [18–21]. During seasonal epidemics in which influenza A(H3N2) viruses predominate, rates

Table 2. Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccine in Preventing Each of 3 Influenza Outcomes

| | Simple Poisson Model[a] | | Covariate-Adjusted Poisson Model[b] | | Covariate-Adjusted Poisson Model With Season-Vaccine Interaction[c] | | | | |
| | | | | | 2012–2013 Season | | 2013–2014 Season | | Term for Season-Vaccine Interaction |
Outcome	CE	(95% CI)	CE	(95% CI)	CE	(95% CI)	CE	(95% CI)	P Value
Postinfluenza death	23.5	(.3–41.3)	24.0	(.6–41.8)	36.4	(9–55.6)	2.5	(−46.8 to 35.3)	.12
Hospitalized influenza	18.8	(14.4–23)	18.6	(14.1–22.9)	22.1	(16.6–27.3)	12.7	(4.9–19.9)	.041
Influenza-related illness	14.2	(8.5–19.4)	15.3	(9.7–20.6)	22.0	(14.8–28.6)	6.8	(−2.3 to 15.1)	.006

Abbreviations: CE, comparative effectiveness; CI, confidence interval.

[a]Model included vaccine status and a covariate for season.

[b]Added to simple model were covariates for each of the factors listed in Table 1.

[c]An interaction term for vaccine status and study season was added to the covariate-adjusted model.

of serious complications are higher, often by a factor of 2 to 3 [21, 22]. Influenza A(H3N2) virus circulation was common during the 2012–2013 influenza season [14], leading to higher rates of influenza-associated outcomes; thus, we had improved power during the first season to detect a difference in our rarest outcome, postinfluenza mortality. During the 2013–2014 influenza season, receipt of high-dose vaccine was associated with a significant reduction only in the rate of hospitalized influenza. This reduction was smaller in magnitude than that found in the 2012–2013 season. There are several plausible reasons that the comparative effectiveness of high-dose vaccine was reduced or absent during 2013–2014, including differences in the individuals who received high-dose vaccine by season, differences in the circulation patterns of specific influenza viruses by season, and differences in the antigenic relatedness of vaccine and wild-type viruses by season.

Although more high-dose vaccine was used in 2013–2014, both in terms of total vaccinations administered and in the proportion of participants who received it, we found no evidence that the characteristics of high-dose recipients differed by season. On the other hand, A(H3N2) viruses predominated in 2012–2013 [14], and 90% of influenza A detections in 2013–2014 were A(H1N1)pdm09 viruses [23]. Data from the randomized trial suggested that relative efficacy of high-dose vaccine might be greater for A(H3N2) than for A(H1N1) viruses, but this difference was not statistically significant (23.3% [95% CI, 6.0%–37.5%] and 11.1% [95% CI, –160% to 70.2%], respectively) [3]. Therefore, it is uncertain if our findings might reflect a difference in comparative effectiveness by A subtype. Influenza B viruses circulated in both seasons, representing 20%–30% of influenza detections [14, 23], so differences in B virus activity are unlikely to explain our findings. There was no evidence of antigenic drift in A(H1N1)pdm09 viruses during the 2 study seasons: 99% of A(H1N1)pdm09 viruses characterized were antigenically similar to A/CA/7/2009-like viruses [14, 23]. The great majority of A(H3N2) viruses characterized in 2012–2013 were antigenically similar to cell culture–propagated A/Victoria/361/2011 viruses [24]. A change in the A(H3N2) vaccine strain from A/Victoria/361 in 2012–2013 to A/Texas/50 in 2013–2014 was recommended because ferret antisera made with egg-propagated A/Victoria/361 did not recognize more recent cell culture–propagated A(H3N2) viruses well. Ferret antisera made with egg-propagated A/Texas/50/2012 (which was genetically closely related to A/Victoria/361) better recognized the viruses that were tested [24]. Low effectiveness of the 2012–2013 vaccine against reverse transcription PCR–confirmed A(H3N2) virus infections was found [25]. Low effectiveness was based mainly on mutations associated with adaptation to growth in eggs, and not on mutations associated with antigenic drift [25]. Without samples of postvaccination sera and of the infecting influenza viruses from participants, we cannot conclude that 2012–2013 high-dose vaccine led to a broader or improved immune response than did standard-dose vaccine, although we

can expect that its administration did lead to higher HAI titers to that season's wild-type H3N2 viruses on a population level, based on published immunogenicity data [3, 26, 27].

During 2012–2013, estimates of influenza VE were 39% (95% CI, 29%–47%) for medically attended A(H3N2) infections among US subjects of all ages; estimates were lower and nonsignificant among those aged ≥65 years (11% [95% CI, –41% to 43%]) [28]. Given the greater relative severity of A(H3N2) seasons in older adults, this low effectiveness estimate (which should be interpreted in light of its broad CI) highlights the need to improve VE for recent A(H3N2) strains, especially among those aged ≥65. We lacked data on infecting viruses, and cannot make subtype-specific VE estimates. However, how comparative VE varies during seasons dominated by different influenza types/subtypes deserves further investigation as new vaccines are introduced.

This study has limitations. The lack of laboratory results in Medicare data means that none of our outcomes represented laboratory-confirmed influenza infections. As our comparative effectiveness results for influenza-related visits (defined by a claim for a rapid influenza test followed by receipt of oseltamivir) were concordant with those from a randomized trial that used laboratory-confirmed influenza illness as a primary outcome [3], we may have identified a valid proxy for a medically attended influenza infection in the Medicare population. Our 2 more serious outcomes were defined only by influenza diagnoses made in a hospital setting. Some data suggest that use of influenza diagnostic tests by clinicians has increased since the 2009 pandemic; thus, the diagnosis of serious influenza infections may have improved recently [29, 30]. As in all observational research, it is possible that our findings were biased with residual confounding. In vaccine studies focusing on older adults, residual confounding associated with chronic conditions which are not well characterized by a simple dichotomous indicator—for example, a clinical history of chronic heart failure—can be especially problematic [31, 32]. The consistency of our findings with those of the randomized trial of high-dose vaccine suggests that we have successfully addressed this issue through restriction of the study population to those vaccinated in community pharmacies. It is possible that knowledge by a care provider of the influenza vaccine type a participant received affected decisions to test for or to diagnose influenza. However, the lack of published clinical results for high-dose vaccine during the study period and the lack of recommendations to favor high-dose over standard-dose influenza vaccines make such a bias unlikely. A final limitation is that restricting participation to those Medicare beneficiaries vaccinated in pharmacies may decrease the generalizability of our findings. On the other hand, it is essential that comparative effectiveness studies address the possibility of confounding by indication, and the use of restriction to minimize this bias in large observational studies has been advocated [33, 34].

Our findings suggest that high-dose influenza vaccines and perhaps other vaccines designed to elicit higher HAI immune responses among older adults may yield the most benefits during seasons when influenza A(H3N2) viruses are widespread. A recent meta-analysis estimated that the effectiveness of standard-dose inactivated vaccines among adults aged >60 years for laboratory-confirmed A(H3N2) infection was only 24% [35]. The authors concluded that influenza vaccines offering better protection against A(H3N2) infection are critically needed. The availability of A(H3N2) vaccines offering substantially better protection for older adults and their widespread use in this population could lead to meaningful reductions in influenza-associated morbidity and mortality.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

References

1. Louria DB, Blumenfeld HL, Ellis JT, Kilbourne ED, Rogers DE. Studies on influenza in the pandemic of 1957–1958. II. Pulmonary complications of influenza. J Clin Invest **1959**; 38:213–65.

2. Eickhoff TC, Sherman IL, Serfling RE. Observations on excess mortality associated with epidemic influenza. JAMA **1961**; 176:776–82.

3. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med **2014**; 371:635–45.

4. McElhaney JE, Beran J, Devaster JM, et al; Influence65 Study Group. AS03-adjuvanted versus non-adjuvanted inactivated trivalent influenza vaccine against seasonal influenza in elderly people: a phase 3 randomised trial. Lancet Infect Dis **2013**; 13:485–96.

5. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. JAMA **1994**; 272:1661–5.

6. Licensure of a high-dose inactivated influenza vaccine for persons aged >or=65 years (Fluzone High-Dose) and guidance for use—United States, 2010. MMWR Morb Mortal Wkly Rep **2010**; 59:485–6.

7. Couch RB, Winokur P, Brady R, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. Vaccine **2007**; 25:7656–63.

8. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis **2009**; 200:172–80.

9. Keitel WA, Atmar RL, Cate TR, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. Arch Intern Med **2006**; 166:1121–7.

10. Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. Lancet Infect Dis **2015**; 15:293–300.

11. DiazGranados CA, Robertson CA, Talbot HK, Landolfi V, Dunning AJ, Greenberg DP. Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines. Vaccine **2015**; 33:4988–93.

12. Appiah GD, Blanton L, D'Mello T, et al; Centers for Disease Control and Prevention (CDC). Influenza activity—United States, 2014-15 season and composition of the 2015-16 influenza vaccine. MMWR Morb Mortal Wkly Rep **2015**; 64:583–90.

13. Centers for Disease Control and Prevention. Update: influenza activity—United States, 2011–12 season and composition of the 2012–13 influenza vaccine. MMWR Morbid Mortal Wkly Rep **2012**; 61:414–20.

14. Centers for Disease Control and Prevention. Influenza activity—United States, 2012–13 season and composition of the 2013–14 influenza vaccine. MMWR Morbid Mortal Wkly Rep **2013**; 62:473–9.

15. Potter CW, Oxford JS. Determinants of immunity to influenza infection in man. Br Med Bull **1979**; 35:69–75.

16. Pope GC, Kautter J, Ellis RP, et al. Risk adjustment of Medicare capitation payments using the CMS-HCC model. Health Care Financ Rev **2004**; 25:119–41.

17. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med **2009**; 28:3083–107.

18. Bonmarin I, Belchior E, Bergounioux J, et al. Intensive care unit surveillance of influenza infection in France: the 2009/10 pandemic and the three subsequent seasons. Euro Surveill **2015**; 20.

19. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA **2004**; 292:1333–40.

20. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA **2003**; 289:179–86.

21. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993–2008. Clin Infect Dis **2012**; 54:1427–36.

22. Estimates of deaths associated with seasonal influenza—United States, 1976–2007. MMWR Morbid Mortal Wkly Rep **2010**; 59:1057–62.

23. Epperson S, Blanton L, Kniss K, et al; Influenza Division, National Center for Immunization and Respiratory Diseases, CDC. Influenza activity—United States, 2013-14 season and composition of the 2014-15 influenza vaccines. MMWR Morb Mortal Wkly Rep **2014**; 63:483–90.

24. Barr IG, Russell C, Besselaar TG, et al; Writing Committee of the World Health Organization Consultation on Northern Hemisphere Influenza Vaccine Composition for 2013–2014. WHO recommendations for the viruses used in the 2013-2014 northern hemisphere influenza vaccine: Epidemiology, antigenic and genetic characteristics of influenza A(H1N1)pdm09, A(H3N2) and B influenza viruses collected from October 2012 to January 2013. Vaccine **2014**; 32:4713–25.

25. Skowronski DM, Janjua NZ, De Serres G, et al. Low 2012-13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses. PLoS One **2014**; 9:e92153.

26. DiazGranados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V, Greenberg DP. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty. Vaccine **2015**; 33:4565–71.

27. DiazGranados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V, Greenberg DP. Effect of previous-year vaccination on the efficacy, immunogenicity, and safety of high-dose inactivated influenza vaccine in older adults. Clin Infect Dis **2016**; 62:1092–9.

28. McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the United States during 2012–2013: variable protection by age and virus type. J Infect Dis **2015**; 211:1529–40.

29. Lindegren ML, Griffin MR, Williams JV, et al. Antiviral treatment among older adults hospitalized with influenza, 2006–2012. PLoS One **2015**; 10:e0121952.

30. Williams LO, Kupka NJ, Schmaltz SP, Barrett S, Uyeki TM, Jernigan DB. Rapid influenza diagnostic test use and antiviral prescriptions in outpatient settings pre- and post-2009 H1N1 pandemic. J Clin Virol **2014**; 60:27–33.

31. Garvin JH, Redd A, Bolton D, et al. Exploration of *ICD-9-CM* coding of chronic disease within the Elixhauser Comorbidity Measure in patients with chronic heart failure. Perspect Health Inf Manag **2013**; 10:1b.

32. Jackson ML, Nelson JC, Jackson LA. Why do covariates defined by *International Classification of Diseases* codes fail to remove confounding in pharmacoepidemiologic studies among seniors? Pharmacoepidemiol Drug Saf **2011**; 20:858–65.

33. Psaty BM, Siscovick DS. Minimizing bias due to confounding by indication in comparative effectiveness research: the importance of restriction. JAMA **2010**; 304:897–8.

34. McGrath LJ, Ellis AR, Brookhart MA. Controlling time-dependent confounding by health status and frailty: restriction versus statistical adjustment. Am J Epidemiol **2015**; 182:17–25.

35. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis **2016**; 16:942–51.

Supplemental materials for:

Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US Medicare beneficiaries in preventing post-influenza deaths: a retrospective cohort study, 2012-13 and 2013-14

1.   **Power estimates**

Data from the phase IV clinical trial,[1] a follow-up post-hoc analysis of the trial data stratified by factors that may influence influenza vaccine response,[2] and our previous observational study[3] suggested that receipt of high-dose versus standard-dose influenza vaccine might reduce post-influenza mortality by 20-30%, if the results from less severe outcomes were similar in magnitude to putative effects for the prevention of deaths. As the laboratory, randomized trial, and observational data all demonstrated a benefit with receipt of high-dose compared with standard-dose vaccines,[1-7] we conducted a 1-tailed power analysis to estimate the effects that we could detect at 80% and 90% statistical power, with an alpha = 0.05. Using data on deaths occurring after influenza hospitalizations in the entire cohort, we estimated that the study had 80% power to identify a relative vaccine effectiveness of 30% or higher for the primary outcome, post-influenza deaths. We also had 80% power to detect comparative effectiveness of 6% or higher for the hospitalized influenza and 8% for the influenza-related illness secondary outcomes. These statistics used data combined for both seasons – we also made estimates for each season individually (Supplemental Table 1), if effect modification by season was suggested.

2.   **Medicare hierarchical condition categories**

We used Centers for Medicare and Medicaid Services (CMS) hierarchical conditions categories (HCCs) to compare the acute and chronic medical conditions diagnosed in recipients of high-dose and standard-dose inactivated influenza vaccines in the 6 months prior to the date of immunization. The HCCs were developed to guide Medicare in making payments to private health care plans for the health

expenditure risk of beneficiaries enrolled in these plans.[8] The HCCs are used with an individual's demographic data to determine a risk score, which is a relative measure of how costly that individual is anticipated to be to the plan. The HCCs and the risk model used by CMS were recently reviewed in a compressive white paper available from CMS (https://www.cms.gov/CCIIO/Resources/Forms-Reports-and-Other-Resources/Downloads/RA-March-31-White-Paper-032416.pdf). The ICD-9-CM and HCPCS codes used to define the disease categories listed in Table 1 have been used only with Medicare data file and are available on request from the authors of the study.

3. Indicators of frail health status

We used indicators for dementia, falls, fractures, home oxygen use, home use of a urinary catheter, and use of walkers or wheelchairs to define states associated with frail health that might represent confounders of the vaccine – outcome associations that we studied. Beneficiaries were placed into these seven categories by using ICD-9-CM Diagnosis (DGN) and Procedure (PRC) codes, and HCPCS codes, as follows:

Indicator	Code source	Data source used*	Diagnosis position
Dementia	DGN	IP/OP	All
Falls	DGN	IP/OP	All
Fracture	DGN/HCP/PRC	IP/OP	All
Home Oxygen	DGN/HCP/PRC	IP/OP/DM	All
Urinary Catheter	DGN/HCP/PRC	IP/OP/DM	All
Walker Use	HCP	IP/OP/DM	--
Wheelchair Use	DGN/HCP	IP/OP/DM	All

* IP, inpatient; OP, outpatient; and DM, durable medical equipment, data files were accessed in defining the indicator

The specific codes used to define these indicators are available on request from the authors.

4. Indicator of low income status

The Medicare Prescription Drug, Improvement and Modernization Act of 2003 (MMA), established the Medicare Prescription Drug Program, or Medicare Part D, which provides prescription drug coverage to Medicare beneficiaries who enroll in the program. The MMA also provides for a low-income subsidy (LIS) for extra help with prescription drug costs for eligible individuals whose income and resources are limited. The LIS is a subsidy paid by the U.S. government to the drug plan in which the Medicare beneficiary enrolls, and it subsidy provides assistance with the premium, deductible and co-payments of the program. Beneficiaries apply for the low-income subsidy (LIS) through either the Social Security Administration or their State Medicaid agency. Medicare beneficiaries who wish to enroll in the Medicare Prescription Drug Program must choose a prescription drug plan through which to receive the benefit. Details regarding the income requirements for the program can be found here: https://secure.ssa.gov/poms.nsf/lnx/0603001005.

5. Supplemental tables

Supplemental Table 1. Power analysis for all outcomes, one tailed, by season							
Outcome	N_{SD}	N_{HD}	Follow-up time	Number of events	Baseline rate	Comparative effectiveness threshold*	
			10 000 person-weeks		10 000 person-weeks	Power = 80%	Power = 90%
Post-influenza Death							
2012-13 Season	1,683,264	1,039,645	3,121	151	0.05	34.3	39.3
2013-14 Season	1,877,327	1,508,176	4,156	94	0.02	43.4	49.5
Combined	3,560,591	2,547,821	7,278	245	0.03	29.5	34.0
Hospitalized Influenza							
2012-13 Season	1,683,264	1,039,645	3,121	3,848	1.23	8.0	9.3
2013-14 Season	1,877,327	1,508,176	4,156	2,192	0.53	10.2	11.9

Combined	3,560,591	2,547,821	7,278	6,040	0.83	6.3	7.4
Influenza-related Illness							
2012-13 Season	950,318	580,648	1,736	2,308	1.33	10.2	11.9
2013-14 Season	1,270,144	1,003,067	2,782	1,806	0.65	11.2	13.1
Combined	2,220,462	1,583,715	4,519	4,114	0.91	7.6	8.9

*If comparative effectiveness is lower than the comparative effectiveness threshold, then the study does not have

the power to identify a statistically significant difference from zero, at an alpha of 0.05.

Supplemental Table 2. Characteristics of study participants for influenza-related visit outcome, by influenza vaccine type and season						
Demographic Variables	2012-2013 Season			2013-2014 Season		
	Standard Dose	High Dose	Std. Mean Difference	Standard Dose	High Dose	Std. Mean Difference
Base Population	950,318	580,648		1,270,144	1,003,067	
Age (years)						
65-74	54.4%	52.1%	0.05	52.9%	51.1%	0.04
75-84	33.3%	35.0%	0.04	34.0%	35.8%	0.04
85+	12.4%	12.9%	0.02	13.1%	13.2%	0.00
Gender						
Male	37.8%	39.1%	0.03	38.3%	39.6%	0.03
Female	62.2%	60.9%	0.03	61.7%	60.4%	0.03
Race						
White	93.0%	92.3%	0.03	92.3%	92.1%	0.01
Black	2.4%	2.8%	0.02	2.8%	3.0%	0.01
Asian	1.8%	1.9%	0.01	1.7%	1.8%	0.01
Hispanic	0.9%	1.0%	0.01	1.0%	1.0%	0.00
Other, Non-North American Native	0.1%	0.1%	0.01	0.1%	0.1%	0.00
North American Native	1.3%	1.4%	0.01	1.3%	1.4%	0.01
Unknown	0.5%	0.4%	0.01	0.7%	0.7%	0.01
HHS Region^						
Region 1: CT, ME, MA, NH, RI, VT	6.2%	4.1%	0.10	6.4%	4.5%	0.08
Region 2: NJ, NY, PR, VI	7.8%	6.0%	0.07	9.0%	7.3%	0.06

Region 3: DE, DC, MD, PA, VA, WV	8.2%	9.4%	0.04	8.5%	9.9%	0.05
Region 4: AL, FL, GA, KY, MS, NC, SC, TN	22.9%	26.4%	0.08	21.6%	26.4%	0.11
Region 5: IL, IN, MI, MN, OH, WI	19.1%	12.9%	0.17	19.4%	14.0%	0.15
Region 6: AR, LA, NM, OK, TX	10.7%	10.5%	0.01	11.8%	10.5%	0.04
Region 7: IA, KS, MO, NE	5.6%	3.8%	0.08	5.4%	3.5%	0.09
Region 8: CO, MT, ND, SD, UT, WY	2.9%	4.4%	0.08	2.4%	3.8%	0.08
Region 9: AZ, CA, HI, NV, AS, FS, GU, PU	12.6%	15.9%	0.10	12.0%	14.7%	0.08
Region 10: AK, ID, OR, WA	4.0%	6.6%	0.11	3.5%	5.4%	0.09
Other	0.0%	0.0%	0.00	0.0%	0.0%	0.00
Low-Income Subsidy Status						
Number of Part D Enrolled Beneficiaries	100.0%	100.0%		100.0%	100.0%	
With 15% Copay	0.8%	0.8%	0.00	0.7%	0.6%	0.00
With High Copay	4.7%	4.8%	0.01	4.3%	4.2%	0.00
With Low Copay	4.8%	5.2%	0.02	4.5%	4.5%	0.00
With Zero Copay	1.1%	1.0%	0.00	1.0%	0.9%	0.01
Health Conditions						
At Least one high-risk disorder	63.3%	64.4%	0.02	64.5%	66.1%	0.03
Asthma	4.0%	4.1%	0.00	4.3%	4.6%	0.02
Blood Disorders	15.5%	16.0%	0.01	16.0%	16.8%	0.02
Chronic Lung Disease	14.4%	15.1%	0.02	14.4%	15.2%	0.02
Diabetes	20.8%	21.1%	0.01	22.0%	22.4%	0.01
Heart Disease	33.6%	34.7%	0.02	34.3%	35.8%	0.03
Kidney Disorders	7.0%	7.3%	0.01	7.9%	8.3%	0.02
Liver Disorders	2.4%	2.4%	0.00	2.4%	2.6%	0.01
Neurological or Neurodevelopmental conditions	11.3%	11.6%	0.01	11.6%	11.9%	0.01
Weakened Immune System	12.3%	12.5%	0.01	12.3%	12.9%	0.02
Frailty Covariates						
Home Oxygen Use	2.6%	2.7%	0.01	2.5%	2.6%	0.00
Wheelchair Use	0.2%	0.2%	0.00	0.1%	0.1%	0.00
Walker Use	1.2%	1.1%	0.01	1.1%	1.0%	0.01
Dementia	3.3%	3.2%	0.00	3.5%	3.2%	0.01
Urinary Catheter Use	0.1%	0.1%	0.00	0.1%	0.1%	0.00
Falls	3.2%	3.2%	0.00	3.3%	3.3%	0.00

| Fractures | 1.1% | 1.1% | 0.00 | 1.1% | 1.1% | 0.00 |

*HHS = Department of Health and Human Services

Supplemental Table 3. Characteristics of study participants for post-influenza mortality and influenza hospitalization outcomes, by influenza vaccine type: comparisons by season						
Demographic Variables	Standard Dose			High Dose		
	2012-2013 Season	2013-2014 Season	Std. Mean Difference	2012-2013 Season	2013-2014 Season	Std. Mean Difference
Base Population	1,683,264	1,877,327		1,039,645	1,508,176	
Age (years)						
65-74	52.1%	51.2%	0.02	49.8%	49.4%	0.01
75-84	34.7%	34.9%	0.00	36.6%	36.7%	0.00
85+	13.1%	13.9%	0.02	13.7%	14.0%	0.01
Gender						
Male	40.7%	40.3%	0.01	42.1%	41.7%	0.01
Female	59.3%	59.7%	0.01	57.9%	58.3%	0.01
Race						
White	93.6%	92.9%	0.03	93.1%	92.7%	0.01
Black	2.6%	2.8%	0.01	2.9%	3.0%	0.00
Asian	1.3%	1.4%	0.01	1.4%	1.5%	0.00
Hispanic	0.6%	0.8%	0.02	0.7%	0.8%	0.01
Other, Non-North American Native	1.3%	1.3%	0.00	1.4%	1.4%	0.00
North American Native	0.1%	0.1%	0.00	0.2%	0.1%	0.01
Unknown	0.4%	0.7%	0.03	0.4%	0.6%	0.04
Regions						
Region 1: CT, ME, MA, NH, RI, VT	6.2%	6.7%	0.02	4.0%	4.6%	0.03
Region 2: NJ, NY, PR, VI	7.8%	8.3%	0.02	5.6%	6.6%	0.04

Region 3: DE, DC, MD, PA, VA, WV	8.1%	8.4%	0.01	10.0%	10.4%	0.01
Region 4: AL, FL, GA, KY, MS, NC, SC, TN	23.4%	21.8%	0.04	27.2%	26.8%	0.01
Region 5: IL, IN, MI, MN, OH, WI	19.6%	19.6%	0.00	12.9%	13.7%	0.02
Region 6: AR, LA, NM, OK, TX	11.2%	12.2%	0.03	10.9%	10.7%	0.01
Region 7: IA, KS, MO, NE	4.9%	5.0%	0.01	3.3%	3.2%	0.00
Region 8: CO, MT, ND, SD, UT, WY	2.9%	2.6%	0.02	4.7%	4.3%	0.02
Region 9: AZ, CA, HI, NV, AS, FS, GU, PU	11.9%	11.5%	0.01	14.9%	13.8%	0.03
Region 10: AK, ID, OR, WA	3.9%	3.7%	0.01	6.6%	5.9%	0.03
Other	0.0%	0.0%	0.00	0.0%	0.0%	0.00
Low-Income Subsidy Status						
Number of Part D Enrolled Beneficiaries	56.5%	67.7%	0.23	55.9%	66.5%	0.22
With 15% Copay	0.8%	0.7%	0.02	0.8%	0.6%	0.02
With High Copay	4.8%	4.4%	0.02	4.9%	4.3%	0.03
With Low Copay	4.9%	4.5%	0.02	5.2%	4.5%	0.03
With Zero Copay	1.1%	1.0%	0.01	1.1%	1.0%	0.01
Health Conditions						
At Least one high-risk disorder	61.9%	63.0%	0.02	62.9%	64.6%	0.03
Asthma	3.8%	4.0%	0.01	3.9%	4.3%	0.02
Blood Disorders	15.1%	15.5%	0.01	15.6%	16.3%	0.02
Chronic Lung Disease	13.8%	13.9%	0.00	14.4%	14.7%	0.01
Diabetes	20.1%	21.1%	0.03	20.3%	21.4%	0.03
Heart Disease	33.1%	33.7%	0.01	34.1%	35.1%	0.02
Kidney Disorders	6.9%	7.7%	0.03	7.3%	8.2%	0.03
Liver Disorders	2.2%	2.3%	0.01	2.3%	2.4%	0.01

Neurological or Neurodevelopmental conditions	11.1%	11.3%	0.01	11.3%	11.6%	0.01
Weakened Immune System	12.1%	12.1%	0.00	12.4%	12.8%	0.01
Frailty Covariates						
Home Oxygen Use	2.4%	2.4%	0.00	2.5%	2.5%	0.00
Wheelchair Use	0.1%	0.1%	0.00	0.1%	0.1%	0.01
Walker Use	1.1%	1.1%	0.01	1.1%	1.0%	0.01
Dementia	3.2%	3.4%	0.01	3.1%	3.2%	0.00
Urinary Catheter Use	0.1%	0.1%	0.00	0.1%	0.1%	0.00
Falls	3.1%	3.3%	0.01	3.1%	3.2%	0.01
Fractures	1.1%	1.1%	0.00	1.1%	1.1%	0.00

References

1.   DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *The New England journal of medicine* 2014; **371**(7):635-45.

2.   DiazGranados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V, Greenberg DP. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty. *Vaccine* 2015; **33**(36):4565-71.

3.   Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. *The Lancet Infectious diseases* 2015; **15**(3):293-300.

4.   Couch RB, Winokur P, Brady R, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. *Vaccine* 2007; **25**(44):7656-63.

5.   DiazGranados CA, Robertson CA, Talbot HK, Landolfi V, Dunning AJ, Greenberg DP. Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines. *Vaccine* 2015; **33**(38):4988-93.

6.   Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *The Journal of infectious diseases* 2009; **200**(2):172-80.

7.   Keitel WA, Atmar RL, Cate TR, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. *Archives of internal medicine* 2006; **166**(10):1121-7.

8.   Pope GC, Kautter J, Ellis RP, et al. Risk adjustment of Medicare capitation payments using the CMS-HCC model. *Health care financing review* 2004; **25**(4):119-41.

Comparative effectiveness of cell-cultured vs egg-based influenza vaccines during the 2017-18 season

MAJOR ARTICLE

Relative Effectiveness of Cell-Cultured and Egg-Based Influenza Vaccines Among Elderly Persons in the United States, 2017–2018

Hector S. Izurieta,[1,4] Yoganand Chillarige,[2] Jeffrey Kelman,[3] Yuqin Wei,[2] Yun Lu,[1] Wenjie Xu,[2] Michael Lu,[2] Douglas Pratt,[1] Steve Chu,[3] Michael Wernecke,[2] Thomas MaCurdy,[2] and Richard Forshee[1]

[1]Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland, [2]Acumen, Burlingame, California, and [3]Centers for Medicare & Medicaid Services, Washington DC; [4]Department of Epidemiology, Universidad Rey Juan Carlos, Spain

Background. The low influenza vaccine effectiveness (VE) observed during the A(H3N2)-dominated 2017–2018 season may be due to vaccine virus adaptation to growth in eggs. We compared the effectiveness of cell-cultured and egg-based vaccines among Medicare beneficiaries.

Methods. Retrospective cohort study on Medicare beneficiaries aged ≥65 years who received an influenza vaccine (cell-cultured, egg-based quadrivalent; egg-based high-dose, adjuvanted, or standard-dose trivalent) during the 2017–2018 season. We used Poisson regression to evaluate relative VE (RVE) in preventing influenza-related hospital encounters.

Results. Of >13 million beneficiaries, RVE for cell-cultured vaccines relative to egg-based quadrivalent vaccines was 10% (95% confidence interval [CI], 7%–13%). In a midseason interim analysis, this estimate was 16.5% (95% CI, 10.3%–22.2%). In a 5-way comparison, cell-cultured (RVE, 11%; 95% CI, 8%–14%) and egg-based high-dose (8%; 7%–10%) vaccines were more effective than egg-based quadrivalent vaccines.

Conclusions. The modest VE difference between cell-cultured and egg-based vaccines only partially explains the low overall VE reported by the Centers for Disease Control and Prevention, suggesting that egg adaptation was not the main contributor to the low VE found among individuals aged ≥65 years. The midseason interim analysis we performed demonstrates that our methods can be used to evaluate VE actively during the influenza season.

Keywords. influenza vaccine; vaccine effectiveness; relative vaccine effectiveness; cell-cultured vaccine.

In the United States, approximately 140 000–710 000 influenza-related hospitalizations and 12 000–56 000 influenza-associated deaths occur annually, with most of the burden occurring among individuals aged ≥65 years [1–3]. Seasonal strain-specific vaccination is the main tool for influenza prevention [4]. A preliminary estimate of the effectiveness of influenza vaccines during the A(H3N2)-dominated 2017–2018 season by the US Influenza Vaccine Effectiveness Network, using a test-negative design, found 20% vaccine effectiveness (VE) (95% confidence interval [CI] −9% to 41%) against any influenza strain and 17% VE (−22% to 44%) against influenza A(H3N2) viruses among persons aged ≥65 years [5]. A prior interim analysis of the US data, and studies of the 2017 season in Australia and

the 2017–2018 season in Canada had also found low VE against A(H3N2) strains [6–8].

Although there were differences in the dominant A(H3N2) influenza virus clades that circulated in these countries [7], the low VE found caused concern. One hypothesis for this low VE is the adaptation of influenza virus to growth in eggs [7]. Two vaccines not manufactured in eggs are licensed and distributed in the United States: a recombinant protein vaccine consisting of virus hemagglutinin (HA) produced in insect cells, not included in our study owing to the limited number of users, and a subunit vaccine prepared from influenza viruses propagated in mammalian cells (ie, cell cultured) [9, 10]. The A(H3N2) virus used for the manufacture of the cell-cultured vaccine for the 2017–2018 season did not undergo egg adaptation before culture in cells, whereas the 3 other components, the A(H1N1) virus and both influenza B vaccine seeds, originated from egg isolates [11]. All other influenza vaccines are produced in eggs, although some differences are potentially relevant to the evaluation of VE: one is high-dose (containing 60 µg of each HA antigen per dose) [12] and others are standard dose (15 µg per dose).

Among standard-dose vaccines, one is adjuvanted [13], some are trivalent, containing antigens from subtype A(H1N1) and

A(H3N2) strains and a single type B (B/Victoria) lineage strain, and others are quadrivalent, containing antigens from both A subtypes and from 2 type B lineage strains. The relative VE (RVE) for the ensemble of these vaccines has never been evaluated. We used real-world data from Medicare claims to conduct both an interim evaluation, with data available as of 19 January 2018, and an end-of-season analysis, with updated data available as of 4 August 2018, of the RVE of cell-cultured versus egg-based influenza vaccines administered to US beneficiaries aged ≥65 years during the 2017–2018 season.

METHODS

Data Sources

We used Medicare administrative files providing data on enrollment, inpatient and outpatient care, physician office visits, and prescription drugs as the primary data source. We used respiratory sample data from the National Respiratory and Enteric Virus Surveillance System to define periods of high influenza circulation within seasons [14, 15], the National Plan and Provider Enumeration System and the National Council for Prescription Drug Programs databases to identify pharmacies, and the Minimum Data Set (www.cms.gov/Research-Statistics-Data-and-Systems/Computer-Data-and-Systems/Minimum-Data-Set-3-0-Public-Reports/index.html#; accessed 22 February 2018) to identify nursing facilities.

Observation Period

The study included the period from 6 August 2017 to 4 August 2018. The study period for the interim analysis extended through 19 January 2018, using data available as of that date. The study period for the end of season analysis extended through 4 August 2018, using data available as of that date.

Study Population

We included Medicare beneficiaries aged ≥65 years who received an egg-based or cell-cultured influenza vaccination from 6 August 2017 through 31 January 2018, with data available as of 4 August 2018. For the interim analysis, we included only beneficiaries vaccinated before 4 January 2018, with data available as of 19 January 2018. We required continuous enrollment in fee-for-service Medicare parts A and B in the 6 months before vaccination to allow for identification of chronic medical conditions. Because the case definition we used for the office visits outcome required a prescription for an influenza-specific antiviral (oseltamivir), we needed access to drug prescription information. Thus, for this outcome, we also required that the beneficiary was a participant in Medicare part D throughout the high influenza season. We excluded beneficiaries enrolled in Medicare part C and those residing in nursing homes on the vaccination date because their medical encounters may not be reliably captured. We also excluded beneficiaries who received an earlier influenza vaccination during the same season and those whose region of residence was not defined in the Department of Health and Human Services (DHHS) regions [14, 15].

Influenza Vaccine Exposure

We classified eligible beneficiaries into 5 cohorts based on the type of vaccine received. Vaccinations were identified using Healthcare Common Procedure Coding System and Current Procedural Terminology (CPT) codes for the cell-cultured quadrivalent vaccine (CPT 90674 and 90756), as well as the 4 egg-based vaccine types: quadrivalent (CPT 90630 and 90685–90688), high-dose trivalent (CPT 90662), adjuvanted trivalent (CPT 90653), and standard-dose trivalent (CPT 90656–90658; Healthcare Common Procedure Coding System Q2034-Q2038). Other influenza vaccines were not used in sufficient numbers for study inclusion. An unvaccinated cohort was not included because we were unable to reliably identify unvaccinated beneficiaries from Medicare claims alone, because they may have been vaccinated outside the system.

Study Outcomes

The primary outcome was influenza-related hospital encounters, defined as inpatient hospitalizations/emergency department visits listing an *International Classification of Diseases, Tenth Revision, Clinical Modification,* code for influenza (codes J09.xx, J10.xx, J11.xx, and J129). We also performed a post hoc analysis using only inpatient stays as outcomes, and a prespecified secondary analysis of influenza-related office visits, defined as community-based physician office visits or hospital outpatient visits with a rapid influenza diagnostic test performed (CPT 87804) followed by a therapeutic course of oseltamivir (75 mg twice daily for 5 days) prescribed within 2 days after the test [14, 15].

Person-Time Under Observation

Follow-up time began 14 days after vaccination (to allow for development of vaccine-specific immunity) and continued until one of the following occurred: outcome of interest, Medicare disenrollment, end of study period, death, admission into a nursing home, or administration of a subsequent influenza vaccine. To increase the positive predictive value of outcomes, we focused the analyses only on person-time observed in regions and weeks with high levels of influenza circulation [14–16]. Each week of the influenza season within each DHHS region was classified as a high influenza circulation period if ≥15% of respiratory samples tested positive for influenza [14–16].

Variables of Interest

For each beneficiary, we collected data on demographics, Medicaid eligibility, reason for entry into Medicare, DHHS region of residence, prior medical encounters, chronic medical conditions, and frailty indicators in the 6 months before vaccination. We adjusted for all study covariates as potential

confounders. We assessed the covariate balance between cohorts using standardized mean differences (SMDs); SMDs <0.1 represented negligible imbalance [17].

Statistical Analyses

Our main analysis focused on the comparison between the cell-cultured and egg-based standard-dose quadrivalent vaccines to ensure comparability. For the adjusted analysis, we used inverse probability of treatment weighting (IPTW) to adjust for imbalances between cohorts on all covariates [18]. Stabilized IPTW weights were derived from propensity scores, representing each beneficiary's probability of receiving the cell-cultured rather than egg-based vaccines, conditional on covariates [19]. We calculated propensity scores using a logistic regression model with vaccine cohort as the dependent variable and all covariates as independent variables. Weight values >5 were truncated to 5 to limit the bias that outlier beneficiaries could have on results [20]. We ran a univariate Poisson regression model on the weighted population to estimate the adjusted rate ratio between the 2 cohorts. The adjusted RVE was defined as $(1 - \text{rate ratio}) \times 100\%$. As sensitivity analyses, we ran a weighted univariate Poisson model for which weights were not truncated and a doubly-robust model that implemented covariate adjustment along with IPTW [21].

To provide further context, we conducted an analysis that also included the egg-based high-dose, adjuvanted, and standard-dose trivalent vaccines, using IPTW to adjust for covariate imbalances. We calculated 5 propensity scores for each participant using separate logistic regression models, with each score representing the probability of receiving a particular vaccine type relative to any other [22]. The outcome models and sensitivity analyses conducted were similar to those we used for the 2-way vaccine comparison.

We conducted the analyses using R 3.4.3 (R Foundation for Statistical Computing) and SAS 9.4 (SAS Institute). We performed all analyses with deidentified data collected for administrative purposes by the Centers for Medicare & Medicaid Services (CMS). This study was approved by the Food and Drug Administration's Research Involving Human Subjects Committee. Medicare administrative data were used under a data use agreement with CMS, which was approved by the CMS privacy board.

RESULTS

More than 16 million fee-for-service Medicare beneficiaries received a cell-cultured or egg-based influenza vaccination in the 2017–2018 season through 31 January 2018. Approximately 13 million remained eligible after implementation of the study restrictions. Among all eligible vaccinees, 5% received the cell-cultured quadrivalent, 14% the egg-based quadrivalent, and 63%, 11%, and 7% received high-dose, adjuvanted, and standard-dose trivalent vaccines, respectively (Supplementary

Figure 1). Before weighting, the cell-cultured and egg-based quadrivalent cohorts were imbalanced as to pharmacy vaccination status, region, and prior outpatient non–emergency room visits (Table 1). After weighting, the 2 cohorts were balanced, with SMDs ≤0.01 for all covariates (Table 1 and Supplementary Table 1). For the 5-way comparison analysis, all cohorts were balanced after weighting, with SMDs ≤0.06 (Table 1 and Supplementary Table 1). Total person-time, outcome rates, and unadjusted RVEs for all vaccine cohorts are provided in Table 2.

The IPTW-adjusted results indicate that the cell-cultured vaccine was significantly more effective than the egg-based quadrivalent vaccine in preventing influenza-related hospital encounters (RVE, 10.0%; 95% CI, 7.0% to 13.0%) (Figure 1). These estimates were consistent for the secondary outcomes and all sensitivity analyses (Supplementary Figure 2). The 19 January interim analyses results also showed that the cell-cultured vaccine was significantly more effective in preventing influenza-related hospital encounters than the egg-based quadrivalent vaccine (RVE, 16.5%; 95% CI, 10.3% to 22.2%). However, the interim analysis point estimates for all outcomes were higher than those from the end-of-season analysis (Figure 1). Results from the IPTW-adjusted 5-way comparisons indicate that the cell-cultured and high-dose vaccines were both significantly more effective in preventing influenza-related hospital encounters than the egg-based quadrivalent and trivalent vaccines (Tables 3 and 4 and Figure 1). The adjuvanted vaccine was also slightly more effective than the egg-based quadrivalent and trivalent vaccines in preventing influenza-related hospital encounters but was less effective than both the cell-cultured and high-dose vaccines (Tables 3 and 4 and Figure 1). The RVE estimates for the post hoc inpatient stays outcome were consistent with those of the influenza-related hospital encounter outcome, although the adjuvanted vaccine was no longer significantly more effective than the egg-based quadrivalent vaccine (Tables 3 and 4 and Figure 1).

In the 2-way influenza-related office visits outcome comparison, the cell-cultured vaccine was again significantly more effective than the egg-based quadrivalent vaccine (RVE, 10.5%; 95% CI, 6.8%–14.0%) (Figure 1). The 5-way analysis showed similar differences between the cell-cultured, high-dose, and adjuvanted vaccines for all outcomes (Table 4 and Supplementary Figure 3). However, office visit estimates for the comparisons with the standard-dose trivalent and quadrivalent vaccines were not consistent with findings from the hospital encounters and inpatient stays analyses (Table 4).

DISCUSSION

This analysis of the A(H3N2)-dominated 2017–2018 influenza season, which we conducted among approximately 13 million influenza vaccinees aged ≥65 years, showed that the effectiveness of the cell-cultured quadrivalent influenza vaccine was approximately 10%–11% higher than that of the comparable

Table 1. Distribution of Covariates Across Vaccine Cohorts for the 2017–2018 Season Before Implementation of IPTW

	Distribution of Covariate, %					Maximum SMD[a]	
	Egg-Based Quadrivalent (n = 1 863 654)	Cell-Cultured Quadrivalent (n = 659 249)	Egg-Based HD Trivalent (n = 8 489 159)	Egg-Based Adjuvanted Trivalent (n = 1 473 536)	Egg-Based SD Trivalent (n = 1 018 494)	Before IPTW	After IPTW[b]
Vaccinated at pharmacy	9.2	19.3	44.3	67.4	11.6	1.50	0.03
Age bracket, y							
65–74	52.0	49.6	51.1	50.6	48.4	0.07	0.02
75–84	33.0	34.3	34.6	34.1	34.4	0.03	0.02
≥85	15.0	16.1	14.4	15.2	17.2	0.08	0.02
Sex							
Female	58.6	59.0	57.9	58.3	59.2	0.03	0.03
Male	41.4	41.0	42.1	41.7	40.8	0.03	0.03
Race							
White	85.8	84.3	89.4	90.2	81.7	0.25	0.02
Black	6.2	7.3	4.6	4.3	7.7	0.14	0.01
Asian	1.2	1.5	0.8	0.7	2.3	0.13	0.02
Hispanic	2.4	3.2	1.7	1.4	3.7	0.15	0.01
Other	4.4	3.7	3.5	3.4	4.6	0.06	0.02
Region[c]							
Region 1	6.9	4.2	6.3	6.6	5.6	0.12	0.02
Region 2	9.2	10.8	8.3	9.4	13.4	0.17	0.02
Region 3	10.9	9.7	12.3	11.3	10.6	0.08	0.02
Region 4	20.6	30.3	19.2	30.7	20.9	0.27	0.02
Region 5	18.2	11.9	18.1	12.6	14.8	0.18	0.03
Region 6	10.2	13.5	10.6	8.1	14.3	0.20	0.01
Region 7	5.4	2.4	6.5	4.2	2.8	0.20	0.02
Region 8	3.4	1.2	4.0	2.4	2.0	0.18	0.01
Region 9	10.7	12.6	10.8	9.2	13.1	0.12	0.01
Region 10	4.5	3.3	4.1	5.4	2.5	0.15	0.02
Reason for entering Medicare							
Aging	89.2	88.8	91.8	92.2	88.5	0.12	0.02
Disability	10.6	11.1	8.0	7.8	11.3	0.12	0.02
End-stage renal disease	0.2	0.1	0.2	0.1	0.2	0.04	0.02
Dual eligible	11.4	13.4	6.9	6.8	16.5	0.31	0.06
Month of vaccination							
August or September	26.0	27.4	33.5	30.9	22.5	0.25	0.03
October	44.2	41.2	43.0	44.0	47.1	0.12	0.02
November	18.3	17.7	15.4	14.9	19.2	0.11	0.01
December or January	11.5	13.7	8.1	10.2	11.3	0.18	0.01
≥1 Total hospitalizations	11.7	10.1	8.6	7.7	11.1	0.13	0.02
≥1 Outpatient ER visits	16.9	15.7	14.2	13.6	16.4	0.09	0.02
Outpatient non-ER visits							
0	32.2	43.5	36.9	40.4	37.5	0.23	0.04
1 or 2	30.8	30.0	30.9	31.0	29.9	0.02	0.01
≥3	37.0	26.5	32.2	28.7	32.6	0.23	0.05

Table 1. Continued

	Distribution of Covariate, %					Maximum SMD[a]	
	Egg-Based Quadrivalent (n = 1 863 654)	Cell-Cultured Quadrivalent (n = 659 249)	Egg-Based HD Trivalent (n = 8 489 159)	Egg-Based Adjuvanted Trivalent (n = 1 473 536)	Egg-Based SD Trivalent (n = 1 018 494)	Before IPTW	After IPTW[b]
All physician visits							
0–5	34.0	30.4	34.4	34.6	31.1	0.09	0.01
6–10	28.1	28.5	28.7	28.8	28.1	0.02	0.00
11–15	15.7	16.8	15.7	15.8	16.5	0.03	0.00
16–25	13.8	15.0	13.5	13.4	14.8	0.04	0.01
≥26	8.5	9.3	7.8	7.5	9.5	0.07	0.01
Respiratory failure and pneumonia							
Hospitalizations	2.6	2.1	1.6	1.3	2.4	0.09	0.01
ER outpatient visits	0.5	0.4	0.3	0.3	0.4	0.03	0.01
Non-ER outpatient visits	1.2	0.8	0.8	0.7	1.0	0.05	0.01
Physician office visits	4.9	4.4	3.6	3.3	4.8	0.08	0.01
Allergies							
Anaphylaxis	0.1	0.1	0.1	0.1	0.1	0.01	0.00
Drug allergy	0.3	0.3	0.3	0.3	0.3	0.01	0.00
Food allergy	0.4	0.4	0.3	0.4	0.4	0.01	0.00
Concomitant pneumococcal vaccine	8.0	6.0	9.0	8.0	5.9	0.12	0.04
Health conditions							
Asthma	6.7	6.8	6.1	5.7	6.9	0.05	0.01
Blood disorders	22.8	25.4	19.8	19.0	26.5	0.18	0.02
Chronic lung disease	20.4	21.4	17.4	16.6	21.8	0.13	0.01
Diabetes	30.3	32.9	26.4	24.3	34.6	0.23	0.02
Heart disease	42.9	45.3	39.9	38.8	45.7	0.14	0.01
Kidney disorders	16.5	16.8	14.2	12.4	17.0	0.13	0.02
Liver disorders	3.6	3.7	3.2	2.9	3.8	0.05	0.01
Neurological or neurodevelopmental conditions	17.2	19.0	14.9	15.2	19.4	0.12	0.02
Immunocompromising conditions	5.6	5.4	4.9	4.6	5.4	0.05	0.01
Other malignant neoplasms (not included elsewhere)	11.8	11.7	11.6	11.3	11.7	0.02	0.01
Frailty covariate							
Home oxygen use	4.5	4.4	3.5	3.0	4.5	0.08	0.01
Wheelchair use	0.1	0.1	0.1	0.1	0.1	0.01	0.00
Walker use	1.4	1.4	1.2	1.1	1.5	0.04	0.01
Dementia	0.8	0.9	0.6	0.6	0.9	0.04	0.01
Urinary catheter use	5.6	6.6	4.2	4.8	6.7	0.11	0.03
Falls	6.6	6.3	5.6	5.4	6.6	0.05	0.01
Fractures	1.4	1.3	1.1	1.1	1.4	0.02	0.00

Abbreviations: ER, emergency room; HD, high-dose; IPTW, inverse probability of treatment weighting; SMD, standardized mean difference; SD, standard-dose.

[a]SMD values ≥0.1 indicate that the 2 groups are imbalanced as to the specified covariates.

[b]The covariate frequencies across vaccine cohorts after IPTW is presented in Supplementary Table 1.

[c]Region 1 includes Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, and Vermont; region 2, New Jersey, New York, Puerto Rico, US Virgin Islands; region 3, Delaware, District of Columbia, Maryland, Pennsylvania, Virginia, and West Virginia; region 4, Alabama, Florida, Georgia, Kentucky, Mississippi, North Carolina, South Carolina, Tennessee; region 5, Illinois, Indiana, Michigan, Minnesota, Ohio, Wisconsin; region 6, Arkansas, Louisiana, New Mexico, Oklahoma, Texas; region 7, Iowa, Kansas, Missouri, Nebraska; region 8, Colorado, Montana, North Dakota, South Dakota, Utah, Wyoming; region 9, Arizona, California, Hawaii, Nevada, Guam, American Samoa, Commonwealth of the Northern Mariana Islands, Federated States of Micronesia, Republic of the Marshall Islands, Republic of Palau; region 10, Alaska, Idaho, Oregon, Washington.

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Table 2. Unadjusted Outcome Rates and RVEs Using the Egg-Based Quadrivalent Cohort as Reference for 2017–2018 Season

Outcome by Cohort	Outcomes, No.	Total Person-Time, ×10 000 Person-Weeks	Outcome Rate	RVE (95% CI), %
Influenza-related office visits				
Egg-based quadrivalent	9607	1829	5.25	Reference
Cell-cultured quadrivalent	3299	599	5.51	−4.8 (−9.1 to −.8)
Egg-based HD trivalent	45 941	8782	5.23	0.4 (−1.8 to 2.6)
Egg-based adjuvanted trivalent	8202	1439	5.70	−8.6 (−11.8 to −5.4)
Egg-based SD trivalent	4868	982	4.96	5.6 (2.3–8.8)
Influenza-related hospital encounters				
Egg-based quadrivalent	14 417	2472	5.83	Reference
Cell-cultured quadrivalent	4370	808	5.41	7.3 (4.1–10.4)
Egg-based HD trivalent	56 763	11 588	4.90	16.0 (14.5–17.5)
Egg-based adjuvanted trivalent	9393	1896	4.96	15.0 (12.8–17.2)
Egg-based SD trivalent	8239	1303	6.32	−8.4 (−11.4 to −5.5)

Abbreviation: CI, confidence interval; HD, high-dose; RVE, relative vaccine effectiveness; SD, standard-dose. RVEs for the egg-based quadrivalent cohort were not presented because the egg-based quadrivalent cohort was used as the reference for the RVE estimates calculation.

egg-based standard-dose quadrivalent products in preventing influenza-related hospital encounters, inpatient stays, and office visits (Figure 1). Among all 5 vaccine types investigated, RVE against influenza-related hospital encounters and inpatient stays was highest for the cell-cultured and high-dose vaccines (Tables 3 and 4). The higher effectiveness we observed for the egg-based high-dose relative to the egg-based standard-dose vaccine is consistent with findings from prior studies by our team and others [14, 15, 23].

To our knowledge, there is no prior real-world evidence of higher RVE for the cell-cultured vaccine versus the comparable egg-based vaccines, although there is virological evidence supporting this possibility [4, 6–8]. One hypothesis is that changes in the viral HA of influenza A(H3N2) virus during isolation, adaptation, and propagation in eggs of the influenza A(H3N2) vaccine strain might affect VE [4, 7, 24, 25]. However, our study does not rule out the possibility that other factors unrelated to the method of vaccine production could account for the observed differences in VE. Moreover, we did not separately analyze egg-based quadrivalent vaccines produced by different manufacturers.

The differential effectiveness we observed between the cell-cultured and egg-based quadrivalent vaccines only partially explains the 20% VE interim estimate reported by the Centers for Disease Control and Prevention (CDC) among individuals aged ≥65 years during the 2017–2018 season, low by historical standards [8]. Unlike in 2014–2015, when there was evidence of antigenic drift of the circulating A(H3N2) viruses compared with the vaccine reference viruses, there was no evidence of such HA drift in 2017–2018 [4, 26]. Other possibilities, including a neuraminidase drift, should be explored to help explain the low VE reported among persons aged ≥65 years [8, 27]. We also provide hypothetical VE estimates for each vaccine among beneficiaries aged ≥65 years, assuming a ±10 point difference from the CDC VE estimate (Supplementary Table 2) [8]. This method is described in the Supplementary Methods.

The numbers can be considered only a very rough approximation, because our study did not estimate absolute VEs, the CDC study population could have differed from ours, the absolute VE estimate from the CDC study had wide CIs (−9% to 41%), and their estimates were preliminary.

Our interim 19 January 2018 analysis shows the potential value of CMS data to provide early estimates of RVE to help with strain selection for the following season. The 19 January interim analysis was our first attempt to conduct an RVE study during the high influenza circulation period, and the conclusions from that interim analysis were consistent with those of the end-of-season analysis. Our end-of-season RVE estimate for the cell-cultured versus the comparable egg-based standard-dose quadrivalent vaccines (RVE, 10.0%; 95% CI, 7.0%–13.0%) was somewhat lower than that of our 19 January interim analysis (16.5%; 10.3%–22.2%) (Figure 1).

This finding might be explained by an increase in the proportion of influenza B circulating viruses during the late part of the season [28–30]. Unlike the A(H3N2) component of the 2017–2018 cell-cultured vaccine, which was isolated in cells, the influenza B viruses in the cell-cultured vaccine were isolated in eggs and, therefore, are antigenically similar to the comparator influenza B viruses in egg-grown vaccines. This could explain why the RVE was lower in the end-of-season analysis, which included a late increase in the circulation of B/Yamagata-lineage viruses [4, 25, 28–30]. It is also possible that differences in the magnitude of waning effectiveness across vaccine types may have contributed to the differences in results between the interim and end-of-season analyses [31]. Nonetheless, we found no major differences by month of vaccination among the vaccines used in the study after weighting was implemented (Supplementary Table 1).

One limitation of the use of Medicare data in real-world evidence studies is the lack of access to virological case confirmation data. However, because the 2017–2018 season was dominated by influenza A(H3N2), we can infer that most influenza events were probably
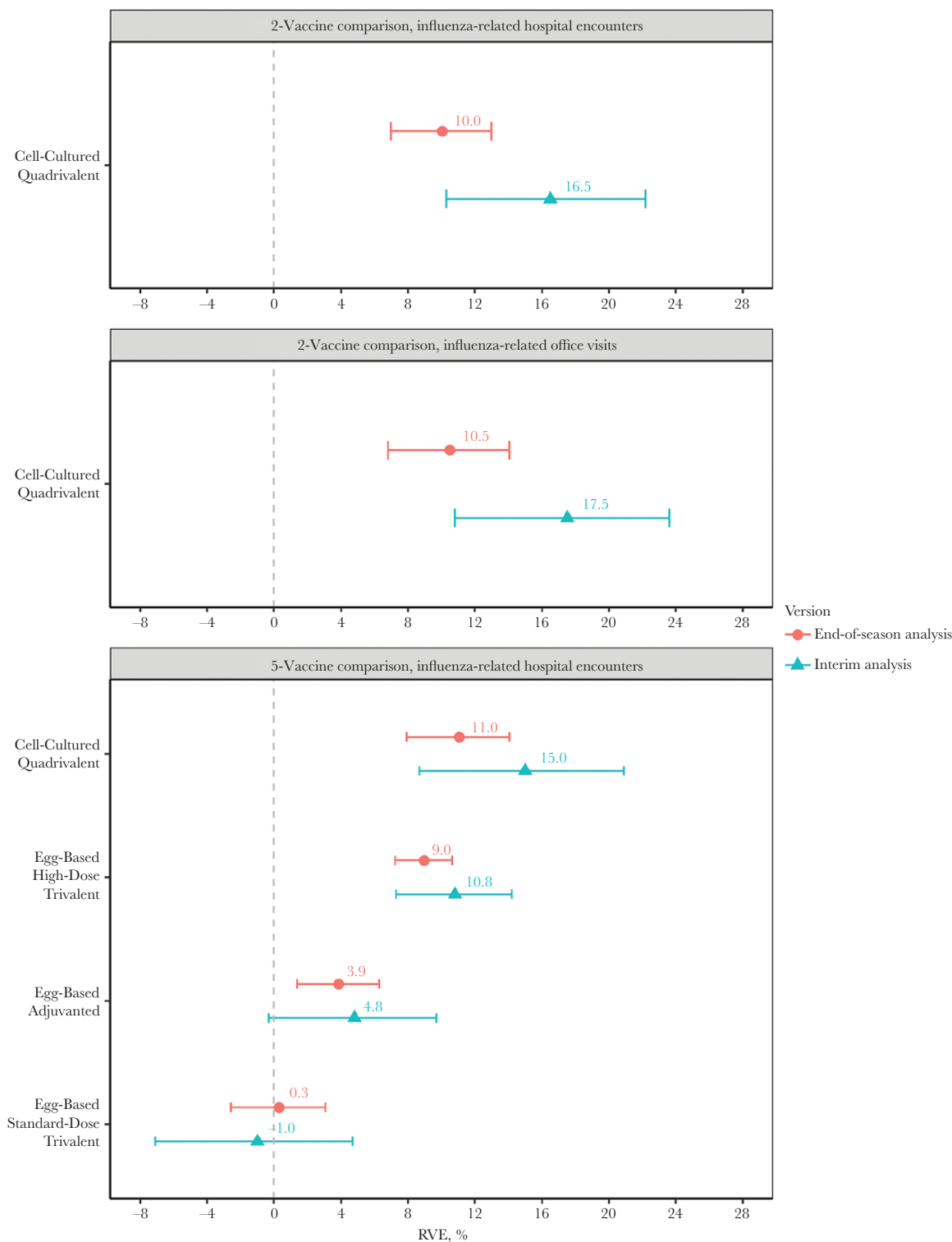
Figure 1. Inverse probability of treatment weighting–adjusted relative vaccine effectiveness (RVE) estimates for primary outcome analyses and 2-vaccine secondary outcome analysis. The RVE point estimates and 95% confidence intervals for the cell-cultured versus egg-based quadrivalent vaccine comparison are presented for both outcomes, as well as for the 5-way influenza-related hospital encounter comparison analysis for the 2017–2018 season. The egg-based quadrivalent vaccine cohort is used as the reference group for each RVE estimate presented.

caused by influenza A(H3N2). Our definition of influenza-related office visits included a rapid test followed by a prescription for a therapeutic course of oseltamivir. Although the sensitivity and specificity of

rapid influenza tests are lower than those from culture or polymerase chain reaction, rapid influenza tests can provide results to a healthcare provider within 15 minutes after sample collection [32].

Table 3.   IPTW-Adjusted Pairwise RVE Estimates for Influenza-Related Hospital Encounters in the 2017–2018 Season

Cohort	RVE by Reference Group (95% CI), %			
	Egg-Based Quadrivalent	Egg-Based SD Trivalent	Egg-Based Adjuvanted Trivalent	Egg-Based HD Trivalent
Cell-cultured quadrivalent	11.0 (7.9–14.0)[a]	10.8 (7.4–14.1)[a]	7.5 (4.1–10.7)[a]	2.3 (−.8, to 5.3)
Egg-based HD trivalent	9.0 (7.2–10.6)[a]	8.7 (6.5–10.9)[a]	5.3 (3.3–7.3)[a]	…
Egg-based adjuvanted trivalent	3.9 (1.4–6.3)[a]	3.6 (.7–6.4)[a]	…	…
Egg-based SD trivalent	0.3 (−2.6 to 3.1)	…	…	…

Abbreviations: CI, confidence interval; HD, high-dose; IPTW, inverse probability of treatment weighting; RVE, relative vaccine effectiveness; SD, standard-dose.
[a]Pairwise comparison RVE estimates that are significant at the $P \leq .05$ level.

We expect that these results guided the decision to prescribe influenza-specific antivirals [33, 34]. However, our influenza-related office visits 5-way comparison produced estimates inconsistent with the hospital encounters and inpatient hospitalizations outcomes, specifically in the comparisons with the standard-dose quadrivalent and trivalent vaccines (Table 4 and Supplementary Figure 3). These inconsistencies might be explained by potential vaccine cohort differences in health seeking behavior and in testing and treatment preferences by physicians, and they highlight the need for caution when considering results from observational studies that include outcomes particularly sensitive to differences in health-seeking and treatment preference behaviors not characterized in claims databases [35]. To resolve these issues, we have initiated projects linking surveys of Medicare beneficiaries, which provide information on frailty and on health-seeking and other behaviors, with Medicare claims databases [36]. Moreover, we a priori considered hospital encounters as our primary analysis outcome, and we included a post hoc inpatient stay–only analysis, which produced similar RVE estimates.

A strength of our study is that the population includes all eligible beneficiaries identified through Medicare fee-for-service claims. Our large sample size allowed us to perform analyses for serious outcomes including inpatient stays, difficult to obtain in any randomized trial.

However, our study has limitations. Because the analysis is observational, residual confounding could be a concern. In particular, residual confounding associated with chronic conditions not sufficiently characterized by the dichotomous indicators derived from Medicare claims can be problematic [37, 38]. However, our use of IPTW yielded well-balanced vaccine cohorts with respect to potential confounders available in the Medicare database, and our past estimates using this database have been credible [14, 15, 36].

Our consistent finding that the cell-cultured and high-dose vaccines were more effective than the comparator egg-based vaccines among persons aged ≥65 years during the 2017–2018 season, along with our findings from prior studies [14, 15, 23, 39], show that the methods we developed for using real-world data to analyze the relative effectiveness of vaccines in the Medicare population could help optimize vaccine strategies for this vulnerable population during epidemics and pandemics. However, given the potential for residual confounding in all observational studies, and the small magnitude of the differences we obtained, our findings would benefit from replication in studies in other settings and healthcare systems. We plan to conduct a rapid-response VE comparison analysis for each influenza season going forward. The critical analysis of the ensemble of real-world evidence studies performed each season should provide valuable information for epidemic influenza control

Table 4.   IPTW-Adjusted Pairwise RVE Estimates for Influenza-Related Office Visits and Inpatient Stays in the 2017–2018 Season

Outcome by Cohort	RVE by Reference Group (95% CI), %			
	Egg-Based Quadrivalent	Egg-Based SD Trivalent	Egg-Based Adjuvanted Trivalent	Egg-Based HD Trivalent
Influenza-related office visits				
Cell-cultured quadrivalent	5.7 (1.9–9.4)[a]	1.0 (−3.5 to 5.3)	11.5 (7.9–15.0)[a]	5.1 (1.6–8.4)[a]
Egg-based HD trivalent	0.7 (−1.5 to 2.9)	−4.3 (−7.4 to −1.3)[a]	6.8 (4.6–8.9)[a]	…
Egg-based adjuvanted trivalent	−6.6 (−9.7 to −3.5)[a]	−11.9 (−15.9 to −8.1)[a]	…	…
Egg-based SD trivalent	4.8 (1.5–8.0)[a]	…	…	…
Influenza-related inpatient stays				
Cell-cultured quadrivalent	9.5 (5.3–13.4)[a]	11.4 (7.0–15.7)[a]	7.1 (2.7–11.3)[a]	−0.7 (−4.8 to 3.4)
Egg-based HD trivalent	10.0 (7.8–12.3)[a]	12.0 (9.2–14.8)[a]	7.7 (5.1–10.2)[a]	…
Egg-based adjuvanted trivalent	2.5 (−.8 to 5.8)	4.7 (.9–8.3)[a]	…	…
Egg-based SD trivalent	−2.2 (−6.1 to 1.5)	…	…	…

Abbreviations: CI, confidence interval; HD, high-dose; IPTW, inverse probability of treatment weighting; RVE, relative vaccine effectiveness; SD, standard-dose.
[a]Pairwise comparison RVE estimates that are significant at the $P \leq .05$ level.

and pandemic preparedness and may help guide the future use of real-world evidence by the Food and Drug Administration and others [40–42].

References

1. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993–2008. Clin Infect Dis **2012**; 54:1427–36.
2. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. JAMA **2004**; 292:1333–40.
3. Centers for Disease Control and Prevention. Disease burden of influenza. https://www.cdc.gov/flu/about/disease/burden.htm. Accessed 7 March 2018.
4. Paules CI, Sullivan SG, Subbarao K, Fauci AS. Chasing seasonal influenza—the need for a universal influenza vaccine. N Engl J Med **2018**; 378:7–9.
5. Flannnery BCJ; for the US Flu VE Network and Ferdinands J, for the HAIVEN Network. Preliminary estimates of 2017–18 seasonal influenza vaccine effectiveness against laboratory-confirmed influenza from the U.S. Flu VE and HAIVEN networks. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2018-06/flu-02-Flannery-508.pdf. Accessed 22 August 2018.
6. Sullivan SG, Chilver MB, Carville KS, et al. Low interim influenza vaccine effectiveness, Australia, 1 May to 24 September 2017. Euro Surveill **2017**; 22:pii=17-00707.
7. Skowronski DM, Chambers C, De Serres G, et al. Early season co-circulation of influenza A(H3N2) and B(Yamagata): interim estimates of 2017/18 vaccine effectiveness, Canada, January 2018. Euro Surveill **2018**; 23.
8. Flannery B, Chung JR, Belongia EA, et al. Interim estimates of 2017-18 seasonal influenza vaccine effectiveness—United States, February 2018. MMWR Morb Mortal Wkly Rep **2018**; 67:180–5.
9. Food and Drug Administration. Flucelvax package insert. https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM502899.pdf. Accessed 22 February 2018.
10. Food and Drug Administration. Flublock package insert. https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm336020.pdf. Accessed 22 February 2018.
11. World Health Organization. Candidate vaccine viruses and potency testing reagents for development and production of vaccines for use in the northern hemisphere 2017–2018 influenza season. http://www.who.int/influenza/vaccines/virus/candidates_reagents/2017_18_north/en/. Accessed 21 March 2018.
12. Food and Drug Administration. High dose Fluzone package insert. https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm305079.pdf. Accessed 22 February 2018.
13. Food and Drug Administration. Fluad package insert. https://www.fda.gov/downloads/biologicsbloodvaccines/safetyavailability/vaccinesafety/ucm474387.pdf. Accessed 22 February 2018.
14. Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. Lancet Infect Dis **2015**; 15:293–300.
15. Shay DK, Chillarige Y, Kelman J, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US medicare beneficiaries in preventing postinfluenza deaths during 2012–2013 and 2013–2014. J Infect Dis **2017**; 215:510–7.
16. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med **2000**; 342:232–9.
17. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med **2009**; 28:3083–107.
18. Austin P. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res **2011**; 399–424.
19. Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to

directly estimate relative risk and its confidence intervals. Value Health **2010**; 13:273–7.

20. Lee BK, Lessler J, Stuart EA. Weight trimming and propensity score weighting. PLoS One **2011;6:e18174**.

21. Funk MJ, Westreich D, Wiesen C, Stürmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. Am J Epidemiol **2011**; 173:761–7.

22. McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. Stat Med **2013**; 32:3388–414.

23. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med **2014**; 371:635–45.

24. US House of Representatives. Examining U.S. Public Health preparedness for and response efforts to seasonal influenza. Testimony of Scott Gottlieb, Commissioner of Food and Drugs, Food and Drug Administration, before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, US House of Representatives. 8 March 2018. https://docs.house.gov/meetings/IF/IF02/20180308/106967/HHRG-115-IF02-Wstate-GottliebS-20180308.pdf. Accessed 16 August 2018.

25. Zost SJ, Parkhouse K, Gumina ME, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. Proc Natl Acad Sci U S A **2017**; 114:12578–83.

26. Skowronski DM, Chambers C, Sabaiduc S, et al. A perfect storm: impact of genomic variation and serial vaccination on low influenza vaccine effectiveness during the 2014–2015 season. Clin Infect Dis **2016**; 63:21–32.

27. World Health Organization. WHO Consultation and Information Meeting on the Composition of Influenza Virus Vaccines for Use in the 2018 Southern Hemisphere Influenza Season. http://www.who.int/influenza/vaccines/virus/recommendations/consultation201709/en/index2.html. Accessed 21 March 2018.

28. Gatherer D. Passage in egg culture is a major cause of apparent positive selection in influenza B hemagglutinin. J Med Virol **2010**; 82:123–7.

29. Centers for Disease Control and Prevention. Weekly U.S. influenza report: 2017–2018 influenza season week 21 ending May 26, 2018. https://www.cdc.gov/flu/weekly/index.htm. Accessed 4 June 2018.

30. Saito T, Nakaya Y, Suzuki T, et al. Antigenic alteration of influenza B virus associated with loss of a glycosylation site due to host-cell adaptation. J Med Virol **2004**; 74:336–43.

31. Ray GT, Lewis N, Klein NP, et al. Intraseason waning of influenza vaccine effectiveness. Clin Infect Dis **2018**. doi:10.1093/cid/ciy770.

32. Centers for Disease Control and Prevention. Rapid diagnostic testing for influenza: information for clinical laboratory directors, table 2. July 6th, 2013. http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm#table2. Accessed 8 January 2018.

33. Food and Drug Administration. Tamiflu® [package insert]. Foster City, CA: Gilead Science; **2018**. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno=021087. Accessed 21 February 2018.

34. Food and Drug Administration. Relenza® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; **2018**. https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021036. Accessed 21 February 2018.

35. Jackson ML, Chung JR, Jackson LA, et al. Influenza vaccine effectiveness in the United States during the 2015–2016 season. N Engl J Med **2017**; 377:534–43.

36. Izurieta HS, Wernecke M, Kelman J, et al. Effectiveness and duration of protection provided by the live-attenuated herpes zoster vaccine in the Medicare population ages 65 years and older. Clin Infect Dis **2017**; 64:785–93.

37. Garvin JH, Redd A, Bolton D, et al. Exploration of ICD-9-CM coding of chronic disease within the Elixhauser comorbidity measure in patients with chronic heart failure. Perspect Health Inf Manag **2013**; 10:1b.

38. Jackson ML, Nelson JC, Jackson LA. Why do covariates defined by International Classification of Diseases codes fail to remove confounding in pharmacoepidemiologic studies among seniors? Pharmacoepidemiol Drug Saf **2011**; 20:858–65.

39. Gravenstein S, Davidson HE, Taljaard M, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. Lancet Respir Med **2017**; 5:738–46.

40. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence—what is it and what can it tell us? N Engl J Med **2016**; 375:2293–7.

41. The Lancet Infectious D. A better pathway to approval of 21st century cures? Lancet Infect Dis **2017**; 17:117.

42. Food and Drug Administration. 21st Century cures act. https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstotheFDCAct/21stCenturyCuresAct/default.htm. Accessed 4 June 2018.

Supplementary Materials: Table of Contents

Supplementary Table 1. Distribution of Covariates across Vaccine Cohorts for the 2017-2018 Influenza Season after Implementing IPTW Weights

Covariates	Egg-Based Quadrivalent	Cell-Cultured Quadrivalent	Egg-Based HD Trivalent	Egg-Based Adjuvanted	Egg-Based SD Trivalent	Max SMD[a]
Base Population	**1,822,862**	**655,432**	**8,488,136**	**1,466,918**	**994,763**	
Vaccinated at Pharmacy						
Yes	36.9%	38.6%	38.4%	38.6%	37.0%	0.03
Age Brackets						
65-74	50.4%	51.0%	50.9%	50.7%	51.4%	0.02
75-84	33.9%	33.5%	34.3%	34.0%	33.4%	0.02
85+	15.7%	15.5%	14.9%	15.3%	15.3%	0.02
Gender						
Female	58.7%	58.7%	58.2%	58.2%	59.7%	0.03
Male	41.3%	41.3%	41.8%	41.8%	40.3%	0.03
Race						
White	88.6%	88.1%	88.2%	88.6%	88.3%	0.02
Black	5.0%	5.2%	5.2%	5.0%	5.2%	0.01
Asian	0.9%	1.0%	1.0%	0.8%	0.9%	0.02
Hispanic	1.9%	1.9%	1.9%	1.8%	2.0%	0.01
Other	3.6%	3.9%	3.7%	3.7%	3.6%	0.02
Regions						
Region 1: CT, ME, MA, NH, RI, VT	6.2%	5.9%	6.2%	6.3%	6.5%	0.02
Region 2: NJ, NY, PR, VI	9.0%	8.7%	9.0%	9.0%	9.2%	0.02
Region 3: DE, DC, MD, PA, VA, WV	11.9%	11.9%	11.7%	11.7%	11.4%	0.02
Region 4: AL, FL, GA, KY, MS, NC, SC, TN	21.0%	21.9%	21.4%	21.3%	21.0%	0.02
Region 5: IL, IN, MI, MN, OH, WI	17.2%	16.3%	17.0%	17.1%	17.6%	0.03
Region 6: AR, LA, NM, OK, TX	10.6%	10.9%	10.7%	10.7%	10.8%	0.01
Region 7: IA, KS, MO, NE	5.7%	5.6%	5.6%	5.6%	5.2%	0.02
Region 8: CO, MT, ND, SD, UT, WY	3.4%	3.3%	3.4%	3.5%	3.5%	0.01
Region 9: AZ, CA, HI, NV, AS, FS, GU, PU	10.7%	10.9%	10.8%	10.8%	10.8%	0.01
Region 10: AK, ID, OR, WA	4.2%	4.4%	4.2%	4.1%	4.0%	0.02

Supplementary Table 1. Distribution of Covariates across Vaccine Cohorts for the 2017-2018 Influenza Season after Implementing IPTW Weights (continued)

Covariates	Egg-Based Quadrivalent	Cell-Cultured Quadrivalent	Egg-Based HD Trivalent	Egg-Based Adjuvanted	Egg-Based SD Trivalent	Max SMD
Base Population	**1,822,862**	**655,432**	**8,488,136**	**1,466,918**	**994,763**	
Reason for Entering Medicare						
Aging	90.8%	90.8%	91.1%	91.4%	90.8%	0.02
Disability	9.1%	9.0%	8.7%	8.5%	9.0%	0.02
ESRD	0.2%	0.2%	0.2%	0.1%	0.2%	0.02
Dual Eligible						
Yes	9.2%	8.7%	8.5%	7.6%	8.7%	0.06
Month of Vaccination						
August & September	30.0%	29.8%	31.0%	30.3%	29.4%	0.03
October	43.9%	44.1%	43.5%	43.7%	44.3%	0.02
November	16.5%	16.5%	16.1%	16.4%	16.6%	0.01
December & January	9.6%	9.6%	9.4%	9.7%	9.7%	0.01
All Hospitalizations						
At least one	9.2%	9.6%	9.2%	9.0%	9.5%	0.02
Outpatient ER Visits						
At least one	15.0%	15.4%	14.8%	14.6%	15.2%	0.02
Outpatient Non-ER Visits						
0	36.8%	35.6%	37.0%	37.6%	36.6%	0.04
1, 2	30.7%	30.5%	30.8%	31.0%	30.8%	0.01
3 +	32.5%	33.9%	32.3%	31.4%	32.6%	0.05
All Physician Visits						
[0- 5]	34.2%	33.8%	33.9%	34.2%	34.2%	0.01
[6 - 10]	28.5%	28.5%	28.6%	28.6%	28.5%	0.00
[11 - 15]	15.7%	15.8%	15.8%	15.8%	15.7%	0.00
[16 - 25]	13.5%	13.7%	13.7%	13.5%	13.5%	0.01
26 +	8.0%	8.1%	8.0%	7.9%	8.1%	0.01
Respiratory Failure and Pneumonia						
Hospitalizations	1.8%	1.9%	1.8%	1.7%	1.9%	0.01
ER Outpatient Visits	0.4%	0.4%	0.4%	0.4%	0.4%	0.01
Non-ER Outpatient Visits	0.9%	0.9%	0.9%	0.8%	0.9%	0.01
Physician Office Visits	3.9%	4.0%	3.9%	3.9%	4.0%	0.01

Supplementary Table 1. Distribution of Covariates across Vaccine Cohorts for the 2017-2018 Influenza Season after Implementing IPTW Weights (continued)

Covariates	Egg-Based Quadrivalent	Cell-Cultured Quadrivalent	Egg-Based HD Trivalent	Egg-Based Adjuvanted	Egg-Based SD Trivalent	Max SMD
Base Population	**1,822,862**	**655,432**	**8,488,136**	**1,466,918**	**994,763**	
Allergies						
Anaphylaxis	0.1%	0.1%	0.1%	0.1%	0.1%	0.00
Drug Allergy	0.3%	0.3%	0.3%	0.3%	0.3%	0.00
Food Allergy	0.4%	0.4%	0.4%	0.4%	0.4%	0.00
Concomitant Vaccine						
Pneumococcal	7.8%	8.0%	8.4%	8.6%	7.5%	0.04
Health Conditions						
Asthma	6.2%	6.2%	6.2%	6.1%	6.1%	0.01
Blood Disorders	20.9%	20.9%	20.8%	20.2%	20.4%	0.02
Chronic Lung Disease	18.2%	18.1%	18.2%	17.9%	17.8%	0.01
Diabetes	27.4%	27.1%	27.5%	26.9%	26.5%	0.02
Heart Disease	40.7%	40.7%	40.9%	40.5%	40.1%	0.01
Kidney Disorders	14.6%	14.6%	14.7%	14.1%	14.7%	0.02
Liver Disorders	3.2%	3.3%	3.3%	3.2%	3.2%	0.01
Neurological or Neurodevelopmental conditions	16.4%	16.3%	15.8%	16.0%	16.1%	0.02
Immunocompromising Conditions	5.0%	5.1%	5.1%	4.9%	5.1%	0.01
Other Malignant Neoplasms (Non Included Elsewhere)	11.3%	11.5%	11.6%	11.4%	11.4%	0.01
Frailty Covariates						
Home Oxygen Use	3.8%	3.8%	3.7%	3.6%	3.7%	0.01
Wheelchair Use	0.1%	0.1%	0.1%	0.1%	0.1%	0.00
Walker Use	1.3%	1.3%	1.2%	1.2%	1.3%	0.01
Dementia	0.7%	0.7%	0.7%	0.7%	0.7%	0.01
Urinary Catheter Use	5.4%	5.2%	4.8%	5.2%	5.3%	0.03
Falls	6.0%	6.1%	5.8%	5.9%	6.0%	0.01
Fractures	1.2%	1.2%	1.2%	1.2%	1.2%	0.00

Abbreviation: IPTW, inverse probability of treatment weighted; SMD, standardized mean difference; HD, high-dose, SD, standard-dos

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[a] SMD values of greater than or equal to 0.1 indicate that the two groups are imbalanced on the specified covariates

Supplementary Table 2. Illustration of VE by Cohort across All Outcomes for Different Overall VE Values in the 2017-18 Season[a]

Outcome	Vaccine Type	Assumed Overall VE		
		VE = 10%	VE = 20%[b]	VE = 30%
Influenza Hospital Encounters	Egg-Based Quadrivalent	3.6%	14.3%	25.0%
	Cell-Cultured Quadrivalent	14.3%	23.8%	33.3%
	Egg-Based High-Dose	12.3%	22.0%	31.8%
	Egg-Based Adjuvanted	7.3%	17.6%	27.9%
	Egg-Based Standard-Dose Trivalent	3.9%	14.6%	25.3%
Influenza-Related Office Visits	Egg-Based Quadrivalent	9.7%	19.7%	29.7%
	Cell-Cultured Quadrivalent	14.8%	24.3%	33.8%
	Egg-Based High-Dose	10.3%	20.3%	30.2%
	Egg-Based Adjuvanted	3.8%	14.4%	25.1%
	Egg-Based Standard-Dose Trivalent	14.0%	23.6%	33.1%
Influenza Hospital Encounters - Inpatient Only	Egg-Based Quadrivalent	3.3%	14.1%	24.8%
	Cell-Cultured Quadrivalent	12.5%	22.2%	31.9%
	Egg-Based High-Dose	13.1%	22.7%	32.4%
	Egg-Based Adjuvanted	5.8%	16.3%	26.7%
	Egg-Based Standard-Dose Trivalent	1.2%	12.2%	23.1%

Abbreviations: VE, Vaccine Effectiveness

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[a] The VE estimates displayed in this table are derived using the steps outlined in the Supplementary Methods below
[b] CDC interim estimates of the overall VE across all vaccine types is approximately 20% (95% CI -9% to 41%), our estimates will be revised once final season estimates from the CDC VE network are available.

Supplementary Methods. Derivation of Vaccine Effectiveness Estimates for All Vaccine Cohorts

In Supplementary Table 2, we provide hypothetical vaccine effectiveness estimates for each study vaccine in the 2017-18 season among beneficiaries ages ≥65. These estimates were approximated using the CDC interim VE estimate for the season assuming a ±10 point difference (we were unable to reliably identify unvaccinated beneficiaries using Medicare claims).

The steps for calculating VE estimates for each vaccine type are described below. The calculation assumes that the vaccine effectiveness and share of each vaccine type among our study population is comparable to that of the population used by the CDC to produce interim VE estimates across all vaccine types for the 2017-18 season.

Notation:

- Set of treatments defined as T = $1^{4, 5}$ $^{4, 5}$,
  - 1 = Cell-cultured Quadrivalent, 2 = Egg-based Adjuvanted, 3 = Egg-based HD Trivalent, 4 = Egg-based SD Trivalent, 5 = Egg-based SD Quadrivalent (reference group)
- PP_{tt} = Proportion of beneficiaries that received vaccine type t among the total study population
- $IIII_{xx}$ = Incidence rate of cohort x

Definitions:

- $IIII_{xx,yy} = IIII_{xx}/IIII_{yy}$
- $IIRRRR_{xx,yy} = (1 - IIII_{xx,yy}) * 100\%$
- $RRRR_{xx} = (1 - IIII_{xx,UUUUUUUUUUccUUUUttcccc}) * 100\%$
  - $RRRR_{AAIIII} = 20\%$ based on CDC's interim VE estimates for the 2017-18 season

VE Estimate Calculation:

1. We know that the incidence rate in the vaccinated population is the *weighted average of the rate ratios for each vaccine* compared to the egg-based quadrivalent vaccine multiplied by the incidence rate amongst the egg-based quadrivalent vaccinated cohort. This can be represented as follows:

$$IIII_{AAIIII} = \sum_{tt}(PP_{tt} * IIII_{tt,tt=5}) * IIII_{tt=5}$$

2. By definition, the rate ratio of the vaccinated population to the unvaccinated population is described as:

$$IIII_{AAIIII,UUUUUUUUUUccUUUUttcccc} = IIII_{AAIIII}/IIII_{UUUUUUUUUUccUUUUttcccc}$$

3. Rearranging the equations from (1) and (2), we get an estimate of the rate ratio for the egg-based quadrivalent cohort against the unvaccinated population:

$$IIII_{tt=5} = IIII_{AAIIII}/\sum_{tt}(PP_{tt} * IIII_{tt,tt=5})$$

$$IIII_{tt=5} = (IIII_{AAIIII,UUUUUUUUUUccUUUUttcccc} * IIII_{UUUUUUUUUUccUUUUttcccc})/\sum_{tt}(PP_{tt} * IIII_{tt,tt=5})$$

$$RRRR_{55,UUUUUUUUUUUUUUUUUUUU} = RRRR_{AAIIII,UUUUUUUUUUUUUUUUUUUU}/\sum_{UU}(PP_{UU} * RRRR_{UU,UU=55})$$

Note: The proportion of the total study population in each vaccine cohort is provided in Table 1 of the article. The estimated rate ratio for each vaccine cohort, using the egg-based quadrivalent cohort as the reference group, can be derived from the vaccine effectiveness estimates provided in Table 3 and Table 4 of the article.

$$RR_{Age,unvaccinated} = 1 - 0.20 = 0.80$$

$$\sum_{tt}(PP_{tt} * RR_{tt,tt=5}) = 0.93$$

4. Replacing values, we can derive the rate ratio of the egg-based quadrivalent vaccinated cohort to the unvaccinated population as 0.86:

$$RR_{tt=5,unvaccinated} = \frac{0.80}{0.93} = 0.86$$

5. We derive the rate ratio for all other vaccine categories, using the rate ratios for the vaccine to the egg-based quadrivalent vaccine (derived from the RVEs in Table 3 and Table 4 of the article), and the rate ratio for the egg-based quadrivalent vaccine to the unvaccinated population:

$$RR_{tt,unvaccinated} = RR_{tt,tt=5} * 0.86$$

6. We derive VE for each vaccine group from the rate ratios (approximately 14.3% for the egg-based quadrivalent vaccine):

$$VE_{tt} = (1 - RR_{tt,unvaccinated}) * 100\%$$

Abbreviations: HD, high-dose; SD, standard-dose

Supplementary Figure 1. Selection Process for Defining Influenza Vaccine Cohorts among Medicare Beneficiaries in the 2017-2018 Influenza Season

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┌─────────────────────────────────────────────────────────┐
│  Base Population: Beneficiaries who received an influenza │
│  vaccination within the specified time frame for the     │
│  season                                                  │
│                                                          │
│         Cell-Cultured Quadrivalent: N= 986,125           │
│              Egg-Based Quadrivalent: N=                  │
│                      3,112,631                           │
│     Egg-Based High-Dose Trivalent: N= 9,114,164          │
│               Egg-Based Adjuvanted: N=                   │
│                      1,570,334                           │
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                            ▼
┌─────────────────────────────────────────────────────────┐
│  Beneficiaries with continuous Medicare Part A/B         │
│  enrollment for the 6 months prior to their vaccination  │
│  date                                                    │
│                                                          │
│   Cell-Cultured Quadrivalent: N= 927,240 (6% excluded)   │
│   Egg-Based Quadrivalent: N= 2,906,534 (7% excluded)     │
│   Egg-Based High-Dose Trivalent: N= 8,603,130 (6%        │
│   excluded)                                              │
│    Egg-Based Adjuvanted: N= 1,486,042 (5% excluded)      │
│    Egg-Based Standard-Dose Trivalent: N= 1 475 417 (6% excluded)│
└─────────────────────────────────────────────────────────┘
                            │
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┌─────────────────────────────────────────────────────────┐
│           Beneficiaries at least 65 years of age         │
│                                                          │
│   Cell-Cultured Quadrivalent: N= 678,083 (27% excluded)  │
│   Egg-Based Quadrivalent: N= 1,925,443 (34% excluded)    │
│   Egg-Based High-Dose Trivalent: N= 8,576,295 (0%        │
│   excluded)                                              │
│     Egg-Based Adjuvanted: N= 1,482,767 (0% excluded)     │
└─────────────────────────────────────────────────────────┘
                            │
                            ▼
┌─────────────────────────────────────────────────────────┐
│  Beneficiaries who received only one influenza vaccine   │
│  type on index day, were not in a nursing home facility  │
│  on vaccination day, and did not receive any influenza   │
│  vaccine prior to index date in the season               │
│                                                          │
│   Cell-Cultured Quadrivalent: N= 659,351 (3% excluded)   │
│    Egg-Based Quadrivalent: N= 1,864,057 (3% excluded)    │
│   Egg-Based High-Dose Trivalent: N= 8,490,281 (1%        │
│   excluded)                                              │
│     Egg-Based Adjuvanted: N= 1,473,796 (1% excluded)     │
└─────────────────────────────────────────────────────────┘
                            │
                            ▼
┌─────────────────────────────────────────────────────────┐
│     Beneficiaries residing in one of the ten HHS regions │
│                                                          │
│    Cell-Cultured Quadrivalent: N= 659,249 (0% excluded)  │
│              Egg-Based Quadrivalent: N= 1,863,654 (0%    │
│    excluded) Egg-Based High-Dose Trivalent: N= 8,489,159 (0% │
│         excluded) Egg-Based Adjuvanted: N= 1,473,536 (0% │
│                                         excluded)        │
│  Egg-Based Standard-Dose Trivalent: N= 1,018,494 (0% excluded) │
└─────────────────────────────────────────────────────────┘
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The number of Medicare beneficiaries remaining in the population after each step of the selection process is presented for each vaccine cohort in the study period. The percentage excluded represents the percentage of the population excluded for the specified step in the selection process.

Supplementary Figure 2. IPTW Adjusted RVE Estimates for Two-Vaccine Comparison Analyses using Egg-Based Quadrivalent Cohort as Reference
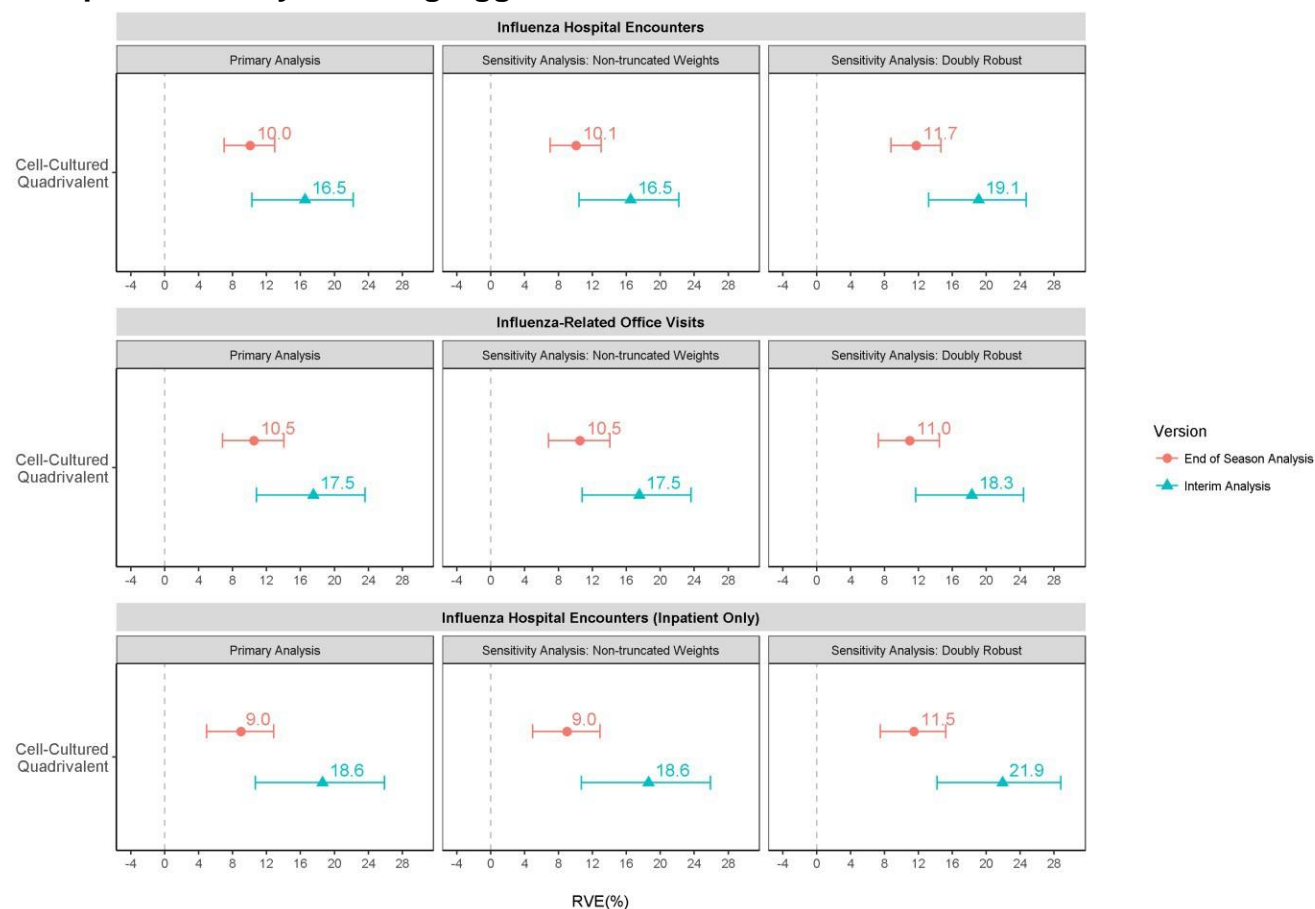
Abbreviations: IPTW, inverse probability of treatment weighting; RVE, relative vaccine effectiveness

The RVE point estimates and 95% confidence intervals are presented for the two-vaccine comparisons for all outcomes, as well as for all corresponding sensitivity analyses in the 2017-18 season. The egg-based quadrivalent vaccine cohort is used as the reference group for each RVE estimate presented.

Supplementary Figure 3. IPTW Adjusted RVE Estimates for Five-Vaccine Comparison Analyses using Egg-Based Quadrivalent Cohort as Reference
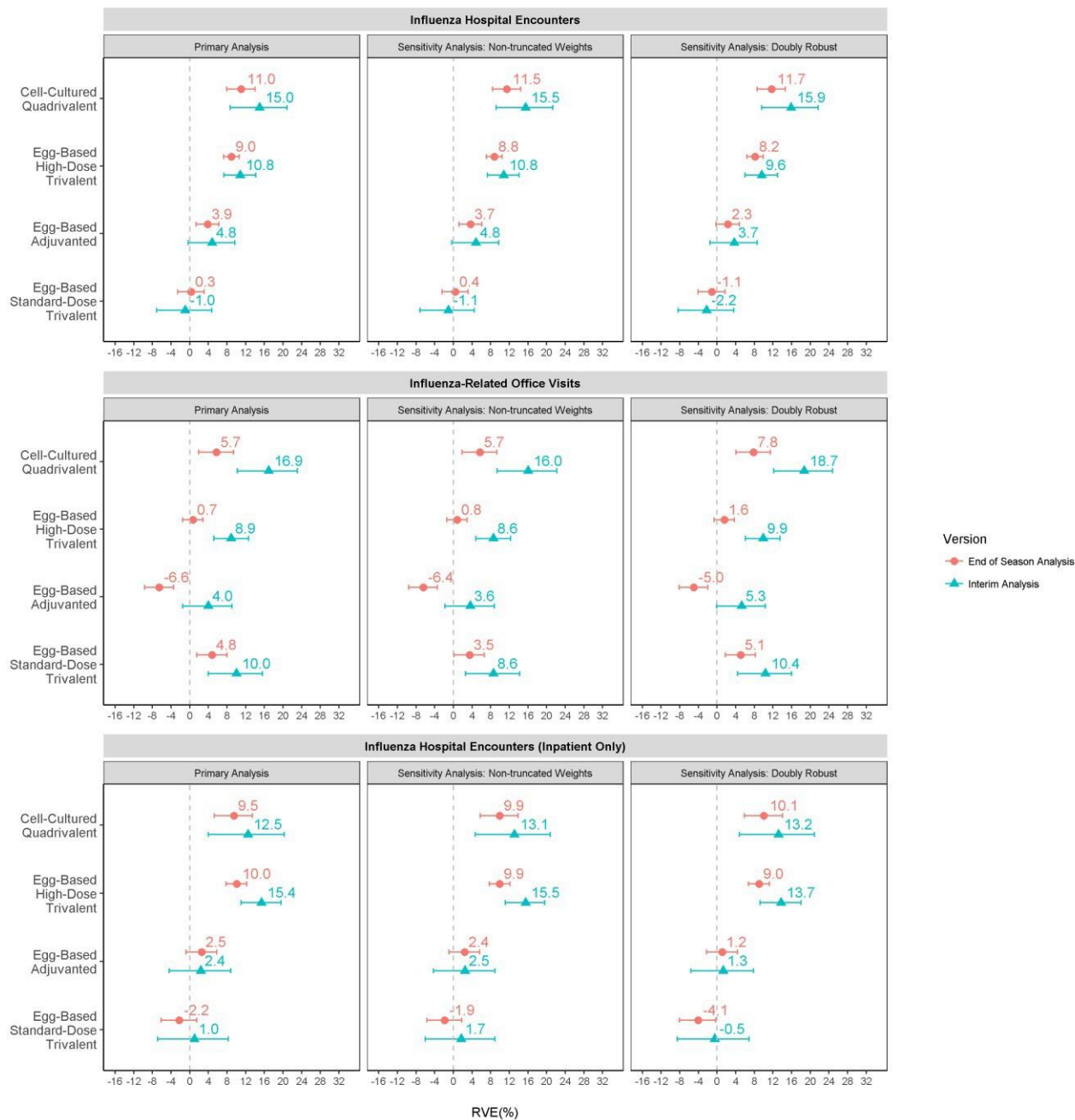
Abbreviations: IPTW, inverse probability of treatment weighting; RVE, relative vaccine effectiveness

The RVE point estimates and 95% confidence intervals are presented for the five-vaccine comparisons for all outcomes, as well as for all corresponding sensitivity analyses in the 2017-18 season. The egg-based quadrivalent vaccine cohort is used as the reference group for each RVE estimate presented. The inconsistencies we observe between the five-vaccine influenza-related office visit analysis and influenza hospital encounters analysis might be explained by the potential residual differences in office visit utilization or access to care by individuals receiving the standard-dose trivalent vaccines, which could be magnified by the relatively small number of participants who received this vaccine in our study population.

Statin use and risks of influenza-related outcomes among older adults receiving standard-dose or high-dose influenza vaccines through Medicare during 2010-2015

Statin Use and Risks of Influenza-Related Outcomes Among Older Adults Receiving Standard-Dose or High-Dose Influenza Vaccines Through Medicare During 2010–2015

Hector S. Izurieta,[1,2] Yoganand Chillarige,[3] Jeffrey A. Kelman,[4] Richard Forshee,[1] Yandong Qiang,[5] Michael Wernecke,[3] Jill M. Ferdinands,[6] Yun Lu,[1] Yuqin Wei,[3] Wenjie Xu,[3] Michael Lu,[3] Alicia Fry,[6] Douglas Pratt,[1] and David K. Shay[6]

[1]Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland; [2]Universidad Rey Juan Carlos, Madrid, Spain; [3]Acumen LLC, Burlingame, California; [4]Centers for Medicare and Medicaid Services, Washington, D.C.; [5]Center for Drugs Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland; [6]Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia

Background. Statins are used to reduce cardiovascular disease risk. Recent studies suggest that statin use may be associated with an increased influenza risk among influenza vaccinees. We used Medicare data to evaluate associations between statins and risks of influenza-related encounters among vaccinees.

Methods. In this retrospective cohort study, we identified Medicare beneficiaries aged > 65 years who received high-dose (HD) or standard-dose (SD) influenza vaccines at pharmacies from 2010–2011 through 2014–2015. Statin users were matched to nonusers by vaccine type, demographics, prior medical encounters, and comorbidities. We used multivariable Poisson models to estimate associations between statin use around the time of vaccination and risk of influenza-related encounters. Study outcomes included influenza-related office visits with a rapid test followed by dispensing of oseltamivir and influenza-related hospitalizations (including emergency room visits) during high influenza circulation periods.

Results. The study included 1 403 651 statin users matched to nonusers. Cohorts were well balanced, with standardized mean differences ≤0.03 for all measured covariates. For statin users compared to nonusers, the adjusted relative risk was 1.086 (95% confidence interval [CI], 1.025–1.150) for influenza-related visits and 1.096 (95% CI, 1.013–1.185) for influenza-related hospitalizations. The risk difference ranged from −0.02 to 0.23 for influenza-related visits and from −0.04 to 0.13 for hospitalizations, depending on season severity. Results were similar for HD and SD vaccinees and for nonsynthetic and synthetic statin users.

Conclusions. Among 2.8 million Medicare beneficiaries, these results suggest that statin use around the time of vaccination does not substantially affect the risk of influenza-related medical encounters among older adults.

Keywords. statins; influenza hospitalization; outpatient; influenza vaccination.

Statins are frequently used in the elderly to reduce the risk of cardiovascular disease [1–5]. Multiple studies have reported that statins may have clinically relevant antiinflammatory effects independent of their lipid-lowering effects [6–12]. It is possible that these immunomodulatory effects could impair the immune response to influenza vaccination [12–15]. Interestingly, studies have also suggested that statins may decrease the risk of pneumonia and severe influenza outcomes, perhaps by reducing levels of inflammatory cytokines [16–22].

Recent studies have raised concern that the immunogenicity and effectiveness of inactivated influenza vaccines may be lower among

statin users [13, 14]. In a post hoc analysis of data from a randomized clinical trial, Black and collaborators evaluated the effect of statins on the immune response to inactivated influenza vaccines and found significantly lower hemagglutination inhibition (HI) titers to vaccine antigens among patients who had received statins from 28 days before to 22 days after vaccination. Among statin users, HI titers for the 3 vaccine antigens were 38% to 67% lower than among nonusers [13]. A 9-season retrospective cohort study found that influenza vaccine effectiveness (VE) during periods of widespread influenza circulation was 18% lower for participants who had >1 month of statin therapy prior to vaccination compared to nonusers [14]. A test-negative design study of influenza VE found an adjusted VE against influenza A(H3N2) infection of −21% (95% CI, −85% to 20%) among statin users and 45% (95% CI, 27% to 59%) among nonusers. These investigators found significant effects among users of nonsynthetic but not among synthetic statin users; no dose-effect response was noted [15].

Given the limited published data, we conducted a retrospective cohort study to evaluate the effects of statins, including

potential differences by statin type and dose, on the risk of influenza-related outcomes among Medicare beneficiaries aged >65 years who received influenza vaccination at community pharmacies [23, 24].

METHODS

Data Sources

Medicare administrative files were the primary data source. Medicare provides health insurance coverage to approximately 49 million US residents aged >65 years, as well as to approximately 9 million beneficiaries who are disabled or have end-stage renal disease [14]. The files include data on enrollment, inpatient and outpatient care, physician office visits, and prescription drugs. Respiratory sample data were drawn from the National Respiratory and Enteric Virus Surveillance System [25].

Participants

The study population consisted of Medicare beneficiaries aged >65 years who received high-dose (HD) or standard-dose (SD) influenza vaccines at community pharmacies from August through January of each influenza season in the study period, defined as 1 August 2010 through 1 August 2015. We restricted enrollment to beneficiaries vaccinated at pharmacies because previous studies demonstrated this restriction produced vaccinated cohorts balanced for factors associated with increased risks for serious complications of influenza infection [23, 24]. Beneficiaries were included for each season in which they received a vaccination [23, 24]. Vaccinations were identified using Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT) codes for high-dose (CPT 90662); trivalent, standard-dose (CPT 90654, 90656–90661, 90673, and 90724; HCPCS Q2034–Q2039); and quadrivalent, standard-dose influenza vaccinations (CPT 90630, 90686, and 90688). Beneficiaries who received more than 1 vaccine type on the same date were excluded.

We required continuous enrollment in fee-for-service Medicare Parts A (hospitalization), B (outpatient medical care), and D (prescription drugs) for at least 1 year prior to vaccination to permit the identification of chronic medical conditions. Participants whose Medicare eligibility depended on disability or end-stage renal disease prior to age 65 were excluded [23, 24]. Beneficiaries enrolled in Medicare Part C (ie, Medicare advantage plans) were excluded because their medical encounters may not be reliably captured in claims data [23]. Additionally, beneficiaries were excluded if they resided in a nursing home or skilled nursing facility (SNF), received hospice care or chemotherapy, were diagnosed with human immunodeficiency virus or cancer other than skin cancer, or underwent organ transplant in the year prior to vaccination [26]. Medical condition exclusion criteria were identified using HCPCS, CPT, or *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes.

As statins are prescribed specifically to treat persons with hyperlipidemia to prevent complications of atherosclerotic cardiovascular disease, which may be associated with more serious complications of influenza, we excluded beneficiaries who received a diagnosis of atherosclerotic cardiovascular disease in the year prior to vaccination (Supplementary Table 1).

Study Outcomes

The primary outcome was a community-based physician office visit or hospital outpatient visit that contained a claim for a rapid influenza diagnostic test (CPT code 87804) followed by a claim for a therapeutic course of oseltamivir (75 mg twice daily for 5 days) prescribed within 2 days of the test claim, referred to as "influenza-related office visits" [23]. The secondary outcome was a hospitalization or emergency department visit with an ICD-9-CM code for influenza (codes 487.xx and 488.xx), referred to as "influenza hospitalizations."

We focused on high influenza circulation periods to increase specificity of our outcome [23, 24]. Each week in an influenza season was classified as a high-, medium-, or low-intensity influenza circulation period within each geographic region of the United States, as defined by the Department of Health and Human Services (HHS). These periods were defined as weeks in which the proportion of respiratory samples that tested positive for influenza within that season and region was above the 75th percentile, within the 55th and 75th percentile, or below the 55th percentile, respectively [23].

Statin Exposure

Participants were classified as statin users or nonusers. Statin users were defined as beneficiaries with a sufficient supply of statins to cover the 15 days before through 15 days after vaccination, with a maximum allowable gap of 2 days, and who received at least 2 prescriptions of statins in the period from 6 months before to 15 days after vaccination, with a medication possession ratio of ≥0.8 [27]. Nonusers were defined as beneficiaries with no evidence of receiving statins during the period extending from 6 months before to 15 days after vaccination. Beneficiaries who did not meet the criteria for either group were excluded.

Person-Time Under Observation

Follow-up began 14 days after vaccination to permit development of vaccine-specific immunity [28]. It ended when one of the following was reached: a study outcome of interest; disenrollment from Medicare Parts A, B, or D; admission to a SNF or nursing home; transfer to hospice care; end of influenza season; or death.

Control for Confounding

Data on demographics, socioeconomic status, medical encounter history, medical conditions, and health status were collected for each beneficiary during the year prior to vaccination [29,

30]. We used a combination of exact matching and propensity score matching to adjust for potential confounders [31, 32]. Propensity scores (the probability of statin use conditional on the baseline characteristics described in Table 1) were calculated using a logistic regression model, with statin use as the dependent variable. For each statin user, we first identified a group of nonusers who were identical by vaccine type, sex, age group (65–69, 70–74, 75–79, 80–84, and 85+ years), and HHS region of residence and then selected the nonuser with the nearest propensity score [31]. Balance in baseline covariates between the cohorts was assessed using standardized mean differences (SMDs). We considered SMDs of <0.1 to represent a negligible imbalance [33].

Statistical Analyses

Rates for each study outcome in the low-, medium-, and high-intensity influenza periods were calculated as the number of outcomes divided by person-time in weeks. We used 3 Poisson regression models to estimate rate ratios between statin users and nonusers (model specifications provided in the Supplementary Methods). The first model adjusted for influenza season to account for differences in influenza circulation by season. The second model included all covariates used for matching (Table 1) in addition to season. In the third model, an interaction term between season and statin exposure was added to model 2 to determine if associations between statin use and outcome risks varied by season. The Akaike information criterion was used to evaluate model fit [34]. Two-tailed P values ≤ .05 were considered statistically significant.

We conducted several additional analyses. To determine if statin effects varied by receipt of HD or SD vaccine, we fit a model including an interaction for vaccine type and statin exposure. We also examined the effect of synthetic (atorvastatin, fluvastatin, rosuvastatin) vs nonsynthetic (simvastatin, pravastatin, lovastatin, and pitavastatin) statins and intensity of statin treatment exposure on influenza-related outcomes (Supplementary Table 2). For the statin-type analysis, the statin user cohort was split into synthetic and nonsynthetic statin cohorts [15]. In the statin-intensity analysis, the statin user cohort was split into low-, moderate-, and high-intensity statin cohorts based on active ingredient and prescribed dose [35]. To investigate the effect of the relationship between statin type and intensity, we fit a model comparing users of different statin type and intensity combinations (Supplementary Table 2). In a post hoc analysis, the statin-intensity analysis was repeated with cohorts weighted with stabilized inverse probability of treatment weights (IPTWs) to address residual imbalances found in the statin-intensity cohorts (Supplementary Table 3) [31].

To determine if our findings might reflect the effect of persistent use of a common medication rather than statin-specific effects, we performed "negative exposure" analyses [36]. These analyses replicated the study methodology for the primary and secondary outcomes using alternate exposures in place of statin use to determine if observed differences were due to bias from unmeasured confounders [36]. Null results would suggest lack of confounding. Negative exposures considered were hydrochlorothiazide medications (HCTZs) not combined with another drug in a single pill and proton pump inhibitors (PPIs).

Analyses were conducted using R 3.2.0 (R Foundation for Statistical Computing, Vienna, Austria) and SAS, v. 9.4 (SAS Institute Inc., Cary, North Carolina). All analyses were performed with deidentified data collected for administrative purposes by the Centers for Medicare and Medicaid Services.

RESULTS

More than 72 million Medicare beneficiaries received influenza vaccinations during the study period. After applying inclusion criteria, 8% of vaccinees remained in the study. Of these, 28% were classified as statin users, 55% as nonusers, and 17% as neither (Figure 1). Prior to matching, the statin user and nonuser cohorts were imbalanced (SMD > 0.1) by frequency of outpatient visits; all physician visits; diabetes severity; and prevalence of hypercholesterolemia, hypertension, and chronic kidney failure. After matching, cohorts were well balanced on all defined covariates (Table 1) and on the proportion of beneficiaries vaccinated in the prior season (Supplementary Table 4).

During 17 110 929 person-weeks of observation, 2419 influenza-related office visits occurred among statin users (1.41 cases/10 000 person-weeks); 2235 visits occurred among nonusers during 17 063 761 person-weeks (1.31 cases/10 000 person-weeks) in the matched cohorts (Table 2). The risk difference ranged from −0.02 to 0.23 per 10 000 person-weeks depending on season severity (Supplementary Table 5). We identified 1316 influenza hospitalizations in statin users during 17 151 832 person-weeks (0.77/10 000 person-weeks) and 1197 influenza hospitalizations in nonusers during 17 129 468 person-weeks (0.70/10 000 person-weeks), for a risk difference ranging from −0.04 to 0.13 (Supplementary Table 5). Results from the 3 Poisson models are presented in Table 3. Statin use was associated with small but statistically significant increased relative risks (RRs) for influenza office visits (RR, 1.09; 95% confidence interval [CI], 1.03 to 1.15) and influenza hospitalizations (RR, 1.10; 95% CI, 1.02 to 1.19; Figure 2). We found no evidence that statin associations varied by receipt of HD compared to SD vaccine (interaction P values ranged from .11 to .4; Supplementary Table 6). We did not find significant differences in risk of either influenza outcome when we compared synthetic and nonsynthetic statin use (Figure 2). Use of high-intensity statins was associated with a significantly elevated risk of influenza-related visits compared to all other use intensity categories (Table 4). Moderate-intensity use was associated with an increased risk compared to nonuse. However, low-intensity use was not associated with differential risk when compared

Table 1. Distribution of Covariates in Influenza-Vaccinated Statin User and Nonuser Medicare Beneficiary Cohorts for the 2010–2015 Influenza Seasons

Covariate	Prematching			Post-Matching[a]		
	Statin User (%)	Statin Nonuser (%)	SMD[b]	Statin User (%)	Statin Nonuser (%)	SMD
Base population	1 534 590	3 046 907		1 403 687	1 403 687	
Vaccine type						
Standard dose	63.80	65.50	0.04	64.30	64.30	0.00
High dose	33.80	32.00	0.04	33.30	33.30	0.00
Quadrivalent	2.40	2.50	0.01	2.40	2.40	0.00
Age bracket, years						
65–69	27.20	29.20	0.04	27.30	27.30	0.00
70–74	31.80	30.00	0.04	31.50	31.50	0.00
75–79	20.70	18.80	0.05	20.50	20.50	0.00
80–84	12.20	12.00	0.01	12.30	12.30	0.00
85+	8.00	10.00	0.07	8.30	8.30	0.00
Gender						
Male	33.70	30.80	0.06	32.90	32.90	0.00
Female	66.30	69.20	0.06	67.10	67.10	0.00
Region						
Region 1: CT, ME, MA, NH, RI, VT	5.90	5.20	0.03	5.60	5.60	0.00
Region 2: NJ, NY, PR, VI	5.90	5.90	0.00	6.00	6.00	0.00
Region 3: DE, DC, MD, PA, VA, WV	9.20	8.70	0.02	9.00	9.00	0.00
Region 4: AL, FL, GA, KY, MS, NC, SC, TN	22.00	22.00	0.00	22.50	22.50	0.00
Region 5: IL, IN, MI, MN, OH, WI	18.40	16.90	0.04	18.10	18.10	0.00
Region 6: AR, LA, NM, OK, TX	11.20	11.90	0.02	11.20	11.20	0.00
Region 7: IA, KS, MO, NE	6.40	6.40	0.00	6.40	6.40	0.00
Region 8: CO, MT, ND, SD, UT, WY	3.40	4.10	0.04	3.50	3.50	0.00
Region 9: AZ, CA, HI, NV, AS, FS, GU, PU	12.10	13.00	0.03	12.30	12.30	0.00
Region 10: AK, ID, OR, WA	5.60	5.80	0.01	5.50	5.50	0.00
Other	0.00	0.00	0.00	0.00	0.00	0.00
Race						
White	92.30	92.60	0.01	92.40	92.30	0.00
Black	2.30	2.30	0.00	2.40	2.40	0.00
Asian	2.40	1.90	0.03	2.20	2.30	0.01
Hispanic	0.80	0.90	0.01	0.80	0.80	0.00
Other	2.30	2.20	0.00	2.20	2.20	0.00
Low-income subsidy status						
None	88.50	89.40	0.03	89.00	88.60	0.01
Zero copay	0.40	0.40	0.01	0.40	0.40	0.00
Low copay	5.50	4.70	0.04	5.10	5.30	0.01
High copay	4.90	4.80	0.00	4.70	4.80	0.01
15% copay	0.80	0.70	0.01	0.70	0.80	0.00
Month of vaccination						
August	3.70	3.10	0.04	3.60	3.60	0.00
September	32.90	29.60	0.07	32.20	32.50	0.01
October	43.50	43.20	0.01	43.70	43.50	0.00
November	12.10	13.80	0.05	12.50	12.40	0.00
December	4.50	5.70	0.05	4.70	4.60	0.00
January	3.30	4.70	0.07	3.40	3.40	0.00
All hospitalizations and observational stays						
0	95.50	95.00	0.02	95.50	95.40	0.00
1+	4.50	5.00	0.02	4.50	4.60	0.00
Outpatient non-ER visits						
0	30.10	36.40	0.13	30.40	30.60	0.00
1, 2	32.20	32.00	0.00	32.80	32.30	0.01
3+	37.70	31.60	0.13	36.80	37.00	0.01
Outpatient ER visits						
0	87.40	86.80	0.02	87.20	87.30	0.00
1	10.30	10.60	0.01	10.40	10.30	0.00

Table 1.   Continued

Covariate	Prematching			Post-Matching[a]		
	Statin User (%)	Statin Nonuser (%)	SMD[b]	Statin User (%)	Statin Nonuser (%)	SMD
Base population	1 534 590	3 046 907		1 403 687	1 403 687	SMD
2+	2.40	2.70	0.02	2.40	2.40	0.00
All physician visits						
[1–5]	14.00	22.50	0.22	14.20	14.60	0.01
[6–10]	30.20	28.10	0.05	30.40	30.10	0.01
[11–15]	22.00	18.90	0.08	21.70	21.70	0.00
[16–25]	20.70	18.10	0.07	20.50	20.50	0.00
26+	13.10	12.40	0.02	13.20	13.10	0.00
Respiratory failure and pneumonia hospitalizations						
0	99.70	99.60	0.02	99.70	99.70	0.00
1 +	0.30	0.40	0.02	0.30	0.30	0.00
Respiratory failure and pneumonia outpatient non-ER visits						
0	99.50	99.40	0.01	99.50	99.50	0.00
1+	0.50	0.60	0.01	0.50	0.50	0.00
Respiratory failure and pneumonia outpatient ER visits						
0	99.80	99.80	0.01	99.80	99.80	0.00
1+	0.20	0.20	0.01	0.20	0.20	0.00
Respiratory failure and pneumonia physician visits						
0	98.20	97.90	0.02	98.20	98.20	0.00
1+	1.80	2.10	0.02	1.80	1.80	0.00
Diabetes severity: aDCSI score (365 days prior)[c]						
0	70.00	78.10	0.19	72.00	71.10	0.02
1	9.60	7.80	0.07	9.30	9.50	0.01
2	14.20	10.60	0.11	13.50	13.80	0.01
3	3.40	2.10	0.09	3.00	3.20	0.01
4	1.90	1.10	0.07	1.60	1.70	0.01
5+	0.90	0.40	0.06	0.70	0.70	0.01
COPD complexity (365 days prior)[d]						
No COPD	93.10	92.60	0.02	92.90	92.90	0.00
Low complexity	4.30	4.30	0.00	4.40	4.30	0.00
Moderate complexity	1.80	2.30	0.03	1.90	1.90	0.00
High complexity	0.80	0.80	0.00	0.80	0.80	0.00
General medical conditions (365 days prior)						
Asthma	5.70	6.10	0.02	5.90	5.80	0.00
Bronchitis	10.10	10.10	0.00	10.30	10.20	0.00
Liver disease	1.20	1.40	0.02	1.30	1.20	0.00
Hypercholesterolemia	45.30	20.80	0.56	38.80	40.30	0.03
Hypertension	76.50	54.10	0.47	75.10	74.30	0.02
Kidney failure, chronic	6.80	3.90	0.14	5.90	6.30	0.02
Kidney failure, acute	0.80	0.60	0.02	0.70	0.70	0.00
Frailty (365 days prior)						
Dementia	2.30	2.50	0.01	2.30	2.40	0.00
Falls	3.80	4.10	0.01	3.80	3.90	0.00
Fractures	1.20	1.40	0.02	1.20	1.20	0.00
Home oxygen use	0.20	0.20	0.01	0.20	0.20	0.00
Urinary catheter use	0.00	0.10	0.00	0.00	0.00	0.00
Walker use	1.10	1.10	0.00	1.10	1.10	0.00
Wheelchair use	0.10	0.10	0.01	0.10	0.10	0.00
Anti-dementia medications	2.50	2.40	0.01	2.50	2.50	0.00
Anti-psychotics	1.60	1.60	0.01	1.60	1.60	0.00
Autoimmune conditions (365 days prior)						
Rheumatoid arthritis	2.00	2.70	0.04	2.10	2.20	0.00
Other autoimmune conditions	6.00	6.60	0.02	6.30	6.20	0.01
Immunomodulatory conditions (365 days prior)						
Immunomodulatory medications	0.30	0.30	0.02	0.30	0.30	0.00

Table 1.   Continued

	Prematching			Post-Matching[a]		
Covariate	Statin User (%)	Statin Nonuser (%)	SMD[b]	Statin User (%)	Statin Nonuser (%)	
Base population	1 534 590	3 046 907		1 403 687	1 403 687	SMD
Neoplasms	0.10	0.20	0.02	0.20	0.20	0.00
Immune disorders	0.30	0.30	0.01	0.30	0.30	0.00
White blood cell disease	0.60	0.80	0.02	0.70	0.70	0.00
Other hematological diseases	0.40	0.50	0.01	0.50	0.40	0.00
Concurrent vaccinations						
Pneumococcal vaccination	2.80	3.10	0.02	2.80	2.90	0.00

Abbreviation: COPD, chronic obstructive pulmonary disease; ER, emergency room; SMD, standardized mean difference. Following are US state and territory abbreviations: AK, Alaska; AL, Alabama; AR, Arkansas; AS, American Samoa; AZ, Arizona; CA, California; CO, Colorado; CT, Connecticut; DC, Washington, D.C.; DE, Delaware; FL, Florida; FS, Micronesia; GA, Georgia; GU, Guam; HI, Hawaii; IA, Iowa; ID, Idaho; IL, Illinois; IN, Indiana; KS, Kansas; KY, Kentucky; LA, Louisiana; MA, Massachusetts; MD, Maryland; ME, Maine; MI, Michigan; MN, Minnesota; MO, Missouri; MS, Mississippi; MT, Montana; NC, North Carolina; ND, North Dakota; NE, Nebraska; NH, New Hampshire; NJ, New Jersey; NM, New Mexico; NV, Nevada; NY, New York; OH, Ohio; OK, Oklahoma; OR, Oregon; PA, Pennsylvania; PR, Puerto Rico; PU, Palau; RI, Rhode Island; SC, South Carolina; SD, South Dakota; TN, Tennessee; TX, Texas; UT, Utah; VA, Virginia; VI, Virgin Islands; VT, Vermont; WA, Washington; WI, Wisconsin; WV, West Virginia; WY, Wyoming.

[a]The statin user and nonuser cohorts are exact matched on vaccine type, sex, age group, and region of residence and are propensity score matched on all other covariates.

[b]SMD values ≥0.1 indicate that the 2 groups are imbalanced on the specified covariates.

[c]The aDCSI score assigns points for the presence of retinopathy, nephropathy, neuropathy, cerebrovascular diseases, peripheral vascular diseases, and metabolic diseases.

[d]COPD complexity is assigned based on the presence and severity of COPD-related diagnoses.

to nonuse (Figure 2). Similar results were found in an IPTW-weighted analysis (Table 4).

Using receipt of hydrochlorothiazide medications as a negative exposure, we found no associations with either influenza-related outcome (Supplementary Table 7). However, use of PPIs was significantly associated with influenza office visits (RR, 1.21; 95% CI, 1.11 to 1.31) and influenza hospitalization (RR, 1.19; 95% CI, 1.06 to 1.32; Supplementary Table 8).

DISCUSSION

In a 5-season study that enrolled more than 2.8 million Medicare beneficiaries aged >65 years, we found that those exposed to statins around the time of vaccination had small (RD per 10 000 person-weeks ranged from −0.02 to 0.23 for office visits and from −0.04 to 0.13 for hospitalizations) but significant increased risks for influenza-related outcomes compared to nonusers (Supplementary Table 5). Over the study period, approximately 178 additional influenza-related office visits and 117 additional influenza-related hospitalizations in the study population may be attributed to statin use at the time of vaccination (Supplementary Table 5). High-intensity statin users had significantly higher risks than nonusers for both outcomes (Table 4), suggesting the possibility of a dose effect. However, results for the comparison between moderate and low-intensity users with nonusers were not consistent. We found no significant differences in influenza risks between synthetic and nonsynthetic statin users. Risk for influenza outcomes was elevated for all statin type and intensity combinations, although differences were not consistently significant (Figure 2). The majority of synthetic and nonsynthetic statin use was of moderate intensity. In a comparison of those 2 groups, we found no significant differences in influenza risk, suggesting no effect by statin type.

Our results are consistent with the direction of the effects identified by Black et al, who found 38%–62% lower HI titers, depending on influenza strain, in statin users compared to nonusers. Our findings of increased risks of approximately 10% among statin users are consistent with, albeit smaller in magnitude than, the lower HI titers observed among statin users by Black et al. While Black et al. found that patients who received nonsynthetic statins had higher HI titers than those who received synthetic statins [13], we found no significant differences in influenza risk between synthetic and nonsynthetic statin users. To account for the high correlation between type and intensity of statins, we analyzed statin treatment by combinations of type and intensity. Our results suggest significant differences in risk by statin intensity but not statin type (Table 4). Because Black et al. did not collect data on statin intensity, their findings may be confounded by statin intensity.

Direct comparisons between our findings and those from studies that included an unvaccinated group are not possible. In Medicare data, lack of a claim for influenza vaccination cannot be used to establish that a beneficiary did not receive a vaccination because it is possible that a claim was not submitted or that a vaccine claim was submitted to another payer. Thus, we cannot present VE estimates. However, we can make several observations. Omer et al. found a substantial reduction in influenza VE among statin users compared to nonusers [14]. While the Omer et al. study did not directly compare vaccinated statin users to nonusers, they did report unadjusted incidence rates for both groups. Applying the ratio-of-ratios approach used by Omer, we calculated that the ratio of the unadjusted risk of medically attended acute respiratory illness (MAARI) among vaccinated statin users and nonusers was 1.08 [14], which is consistent with our findings of 9%–10% differences in risk, despite the different
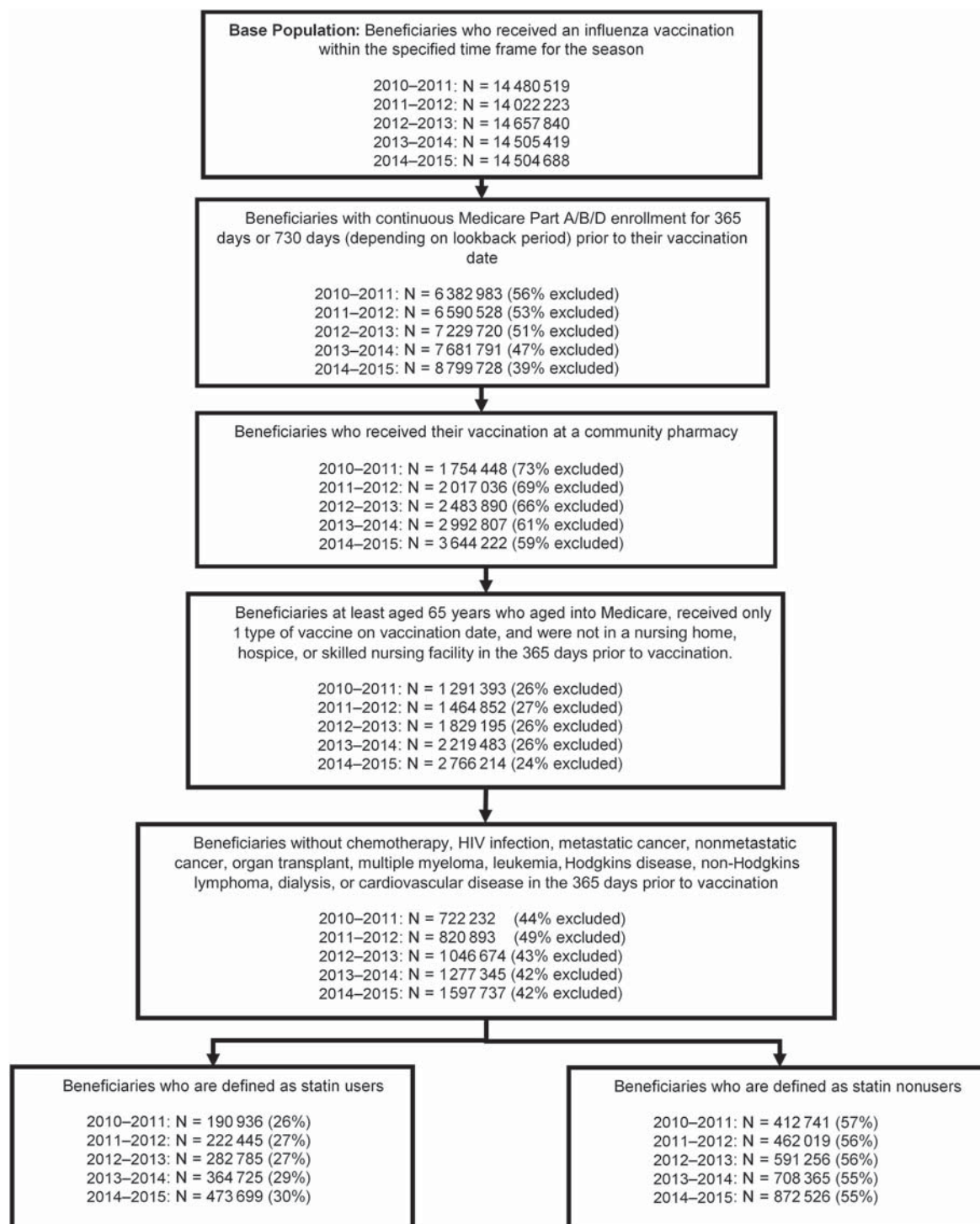
Figure 1. Selection process for defining the statin user and nonuser cohorts in the 2010–2015 influenza seasons. The number of Medicare beneficiaries remaining in the population after each step of the selection process is presented for each influenza season in the study period. The percentage excluded represents the percentage of the population excluded for the specified step in the selection process. Abbreviation: HIV, human immunodeficiency virus.

populations studied and the nonspecific outcome (MAARI) used by Omer et al.

In a 10-season study that enrolled 3285 participants aged ≥45 years, McLean et al. found that VE for real-time polymerase chain reaction–confirmed influenza outpatient visits was substantially and significantly lower in statin users for influenza A(H3N2) virus infections. However, VE against influenza A(H1N1)pdm09 or B infections did not differ by statin use [15]. Since Medicare claims data do not provide this information, we cannot compare statin effects by virus type or subtype. However,

Table 2. Outcome Rates and Raw Rate Ratios With 95% Confidence Intervals across Influenza Circulation Periods in the 2010–2015 Influenza Seasons

Outcome	Influenza Circulation Period[a]	Statin Users			Statin Nonusers			Raw Rate Ratio[b]	
		Outcome (Number)	Person-Time (10 000 Person-Weeks)	Outcome Rate (per 10 000 Person-Weeks)	Outcome (Number)	Person-Time (10 000 Person-Weeks)	Outcome Rate (per 10 000 Person-Weeks)	Rate Ratio	95% Confidence Interval
Influenza-related office visits	Low season	152	2369	0.06	140	2356	0.06	1.08	(0.86, 1.36)
	Medium season	562	1363	0.41	620	1359	0.46	0.90	(0.81, 1.01)
	High season	2419	1711	1.41	2235	1706	1.31	1.08	(1.02, 1.14)
Influenza-related hospitalizations	Low season	76	2378	0.03	102	2370	0.04	0.74	(0.55, 1.00)
	Medium season	281	1367	0.21	262	1365	0.19	1.07	(0.90, 1.27)
	High season	1316	1715	0.77	1197	1713	0.70	1.10	(1.02, 1.19)

Only cases that occurred during high influenza circulation periods, which are more likely to be associated with influenza infections, were included for all analyses.

[a]Each week of an influenza season for each region was classified as high, medium, or low influenza intensity when the proportion of respiratory samples that tested positive for influenza was above the 75th percentile, within the 55th and 74th percentile, or below the 55th percentile, respectively.

[b]Statin nonusers were used as the reference group for raw rate ratio calculations.

our study included some seasons dominated by influenza A(H3N2) and others dominated by A(H1N1), and a majority of outcomes in the study occurred during the A(H3N2)-dominant seasons of 2012–2013 and 2014–2015 (Supplementary Table 5).

We were unable to distinguish between the effect of statins on vaccine effectiveness vs the direct effect of statins on risk of influenza [12–22]. Only 8.6% of all beneficiaries in the study switched their statin-use status post-vaccination (Supplementary Table 10), reflecting a lack of power to separate these 2 effects. As a sensitivity analysis, we compared statin users and nonusers who did not switch their statin status post-vaccination and found rate ratio estimates consistent with those of the primary analysis (Supplementary Table 11).

Our study had limitations, some of which we noted in previous publications that used similar methods [23, 24]. In addition, the statin user and nonuser populations may have differed by unmeasured covariates, including body mass index, diet, smoking status, and social contacts. In an effort to minimize bias potentially associated with unmeasured confounders, including

being ambulatory, we restricted all analyses to beneficiaries vaccinated at community pharmacies [23, 24]. To further address potential unmeasured confounders, such as those reflected by chronic use of common medications, we performed negative exposures analyses with HCTZs and PPIs. We found no association between HCTZs and influenza outcomes. A significant association with PPIs was found, which might suggest the possibility of residual bias or unmeasured confounders. In retrospect, however, our choice of PPIs as a negative exposure may not have been ideal. PPIs have multiple effects beyond those on gastric pH, which may affect susceptibility to pneumonia and thus the diagnosis of infection with specific respiratory pathogens [37–40]. Thus, further investigation might be needed to determine whether this is a real effect or a result of unmeasured confounding. The cohort restrictions we used to reduce confounding, including exclusion of beneficiaries with cardiovascular conditions, may limit the generalizability of our findings; whether the associations we observed are similar in less healthy beneficiaries is unknown.

Table 3. Rate Ratio Estimates With 95% Confidence Intervals and Akaike Information Criterion Values for All Primary Analysis Poisson Models

Model	Influenza Office Visit Outcome				Influenza Hospitalization Outcome			
	Rate Ratio	P Value	95% CI	AIC	Rate Ratio	P Value	95% CI	AIC
Poisson model, season term[a]	1.08	.01	(1.02–1.14)	61c693.71	1.10	.019	(1.02–1.19)	39c372.77
Multivariate Poisson model[b,c]	1.09	.01	(1.03–1.15)	59c479.98	1.10	.022	(1.01–1.19)	38c016.18
Multivariate Poisson model, season interaction[d]				59c486.83				38c014.36
2010–2011	1.18	.286	(0.87–1.58)		0.83	.35	(0.57–1.23)	
2011–2012	0.87	.559	(0.55–1.39)		0.80	.37	(0.49–1.31)	
2012–2013	1.09	.236	(0.95–1.26)		1.08	.39	(0.90–1.29)	
2013–2014	1.09	.335	(0.91–1.30)		1.49	.00	(1.17–1.91)	
2014–2015	1.08	.023	(1.01–1.16)		1.08	.13	(0.98–1.19)	

The multivariate Poisson models in this study adjusted for all the variables used in the matching process (see Table 1). The multivariate Poisson model without season interaction is the best fitting model for the influenza office visit outcome based on its AIC value.

Abbreviations: AIC, Akaike information criterion; CI, confidence interval.

[a]Only cases that occurred during high influenza circulation periods, which are more likely to be associated with influenza infections, were included for all analyses.

[b]Statin users served as the treatment group and statin nonusers served as the reference group.

[c]The season term Poisson model only adjusts for an influenza season variable.

[d]The multivariate Poisson model with season interaction is the best fitting model for the influenza hospitalization outcome based on its AIC value.

Outcome	Analysis	Rate Ratio	95% CI
1. Influenza−Related Office Visits	Main	1.09	[1.025, 1.150]
	Statin Type		
	− Synthetic	1.084	[1.002, 1.172]
	− Nonsynthetic	1.086	[1.018, 1.159]
	Statin Intensity		
	− High−Intensity	1.228	[1.083, 1.393]
	− Moderate−Intensity	1.076	[1.011, 1.145]
	− Low−Intensity	1.045	[0.928, 1.177]
	Statin Type−Intensity		
	− Nonsynthetic, Low−Intensity	1.051	[0.931, 1.187]
	− Nonsynthetic, Moderate−Intensity	1.098	[1.024, 1.178]
	− Synthetic, Low−Intensity	0.926	[0.557, 1.538]
	− Synthetic, Moderate−Intensity	1.031	[0.941, 1.129]
	− Synthetic, High−Intensity	1.227	[1.082, 1.391]
	Vaccine Subgroup		
	− Trivalent Standard−Dose Vaccine	1.133	[1.047, 1.227]
	− High Dose−Vaccine	1.05	[0.962, 1.146]
	− Quadrivalent Standard−Dose Vaccine	0.901	[0.658, 1.183]
2. Influenza Hospitalizations	Main	1.1	[1.013, 1.185]
	Statin Type		
	− Synthetic	1.09	[0.978, 1.214]
	− Nonsynthetic	1.099	[1.007, 1.200]
	Statin Intensity		
	− High−Intensity	1.22	[1.020, 1.459]
	− Moderate−Intensity	1.088	[0.999, 1.184]
	− Low−Intensity	1.111	[0.952, 1.296]
	Statin Type−Intensity		
	− Nonsynthetic, Low−Intensity	1.108	[0.946, 1.298]
	− Nonsynthetic, Moderate−Intensity	1.119	[1.018, 1.231]
	− Synthetic, Low−Intensity	1.247	[0.706, 2.202]
	− Synthetic, Moderate−Intensity	1.041	[0.918, 1.180]
	− Synthetic, High−Intensity	1.227	[1.026, 1.467]
	Vaccine Subgroup		
	− Trivalent Standard −Dose Vaccine	1.075	[0.968, 1.194]
	− High−Dose Vaccine	1.153	[1.021, 1.303]
	− Quadrivalent Standard−Dose Vaccine	0.781	[0.498, 1.224]

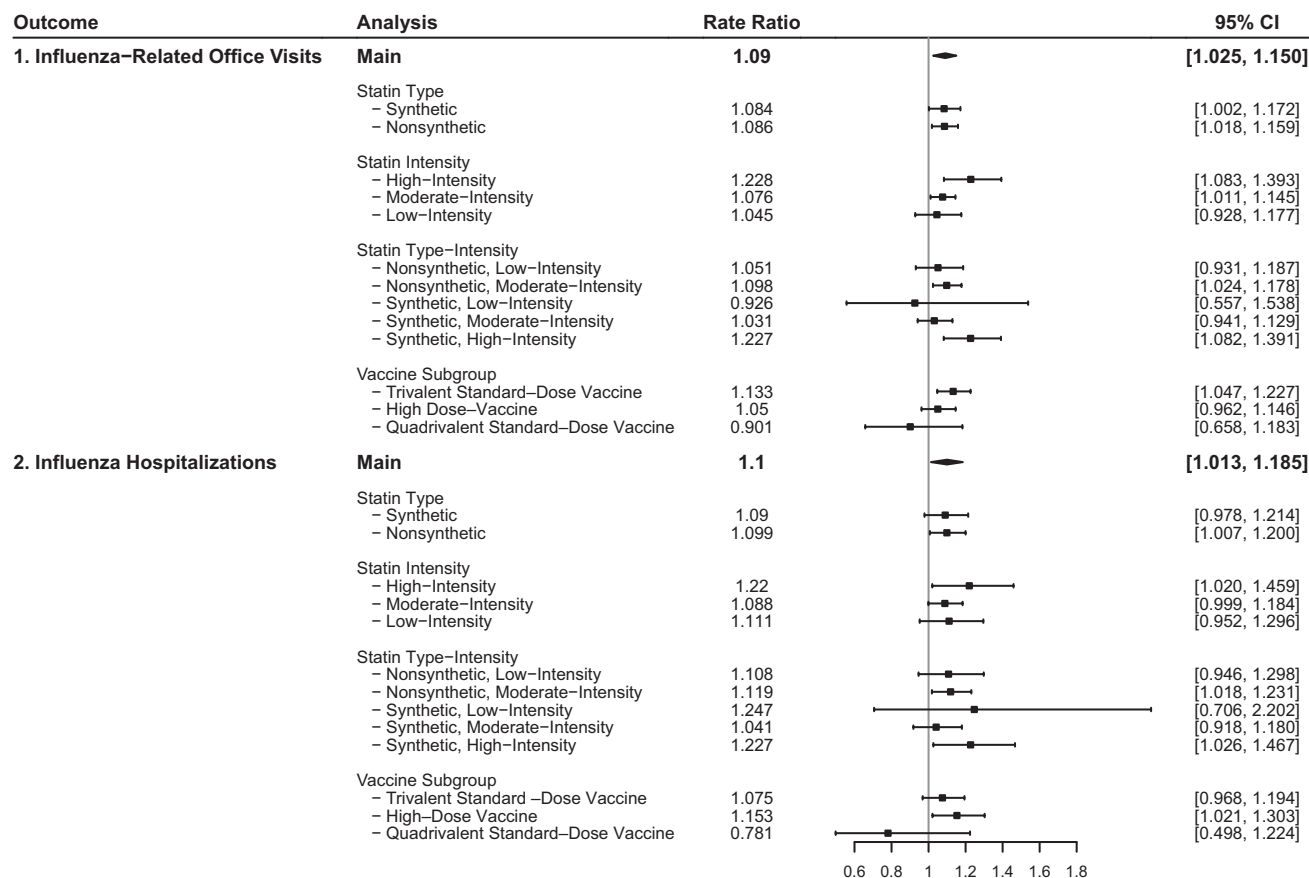(Forest plot axis: 0.6 0.8 1 1.2 1.4 1.6 1.8)

Figure 2. Multivariate Poisson regression rate ratios comparing statin users to nonusers for all outcomes among Medicare beneficiaries who received influenza vaccines at community pharmacies from 2010 through 2015. Vaccinated nonusers were used as the reference group for each comparison. For the vaccine subgroup analysis, vaccinated statin users were compared to vaccinated nonusers within each vaccine dose category, with the vaccine type and statin use interaction term *P* values ranging from .11 to .39. The relatively small proportion of quadrivalent standard-dose vaccinated beneficiaries in the study population may explain the discrepancy in rate ratios between the quadrivalent standard-dose group and the other vaccine groups. See Supplementary Table 2 for statin type and intensity classifications. Abbreviation: CI, confidence interval.

In summary, we found small associations between statin use and relative risks for influenza office visits and hospitalizations among vaccinated Medicare beneficiaries, consistent with the direction of results from an immunogenicity trial but of smaller magnitude [13]. Our findings suggest that receipt of statins around the time of influenza vaccination does not substantially affect the risk of influenza-related medical encounters among vaccinated Medicare beneficiaries. These findings should be interpreted in the context of the well-established benefits of statins for reducing the risk of cardiovascular outcomes.

Table 4. Rate Ratio Estimates of Influenza-related Office Visits With 95% Confidence Intervals for the Statin Intensity-Type Analysis from 2010 through 2015

Statin User Group	Statin Nonuser Rate Ratio	95% CI	Nonsynthetic Low-Intensity Statin User Rate Ratio	95% CI	Nonsynthetic Moderate-Intensity Statin User Rate Ratio	95% CI	Synthetic Low-Intensity Statin User Rate Ratio	95% CI	Synthetic Moderate-Intensity Statin User Rate Ratio	95% CI
Nonsynthetic low-intensity statin user	1.05	(0.93, 1.19)	…		…		…		…	
Nonsynthetic moderate-intensity statin user	1.10	(1.03, 1.18)	1.04	(0.92, 1.19)	…		…		…	
Synthetic low-intensity statin user	0.94	(0.56, 1.56)	0.89	(0.53, 1.50)	0.85	(0.51, 1.42)	…		…	
Synthetic moderate-intensity statin user	1.03	(0.94, 1.13)	0.98	(0.85, 1.13)	0.94	(0.85, 1.04)	1.10	(0.66, 1.85)	…	
Synthetic high-intensity statin user	1.25	(1.09, 1.42)	1.18	(1.00, 1.40)	1.13	(0.99, 1.30)	1.33	(0.79, 2.26)	1.21	(1.04, 1.40)

Only cases occurring during high influenza circulation periods, which are more likely to be associated with influenza infections, were included for all analyses. Propensity scores were used to derive inverse probability of treatment weights, which were used to weight the analysis cohorts.

Abbreviation: CI, confidence interval.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

References

1. Afilalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. Heart **2007**; 93:914–21.
2. Colhoun HM, Betteridge DJ, Durrington PN, et al; CARDS Investigators. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet **2004**; 364:685–96.
3. Cheung BM, Lauder IJ, Lau CP, Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. Br J Clin Pharmacol **2004**; 57:640–51.
4. Maron DJ, Fazio S, Linton MF. Current perspectives on statins. Circulation **2000**; 101:207–13.
5. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. JAMA **1997**; 278:313–21.
6. Weitz-Schmidt G, Welzenbach K, Brinkmann V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. Nat Med **2001**; 7:687–92.
7. Jain MK, Ridker PM. Anti-inflammatory effects of statins: clinical evidence and basic mechanisms. Nat Rev Drug Discov **2005**; 4:977–87.
8. Bu DX, Griffin G, Lichtman AH. Mechanisms for the anti-inflammatory effects of statins. Curr Opin Lipidol **2011**; 22:165–70.
9. Bessler H, Salman H, Bergman M, Straussberg R, Djaldetti M. In vitro effect of statins on cytokine production and mitogen response of human peripheral blood mononuclear cells. Clin Immunol **2005**; 117:73–7.
10. Ghittoni R, Napolitani G, Benati D, et al. Simvastatin inhibits the MHC class II pathway of antigen presentation by impairing Ras superfamily GTPases. Eur J Immunol **2006**; 36:2885–93.
11. Han KH, Ryu J, Hong KH, et al. HMG-CoA reductase inhibition reduces monocyte CC chemokine receptor 2 expression and monocyte chemoattractant protein-1-mediated monocyte recruitment in vivo. Circulation **2005**; 111:1439–47.
12. Mascitelli L, Goldstein MR. How regulatory T-cell induction by statins may impair influenza vaccine immunogenicity and effectiveness. J Infect Dis **2016**; 213:1857.
13. Black S, Nicolay U, Del Giudice G, Rappuoli R. Influence of statins on influenza vaccine response in elderly individuals. J Infect Dis **2016**; 213:1224–8.
14. Omer SB, Phadke VK, Bednarczyk RA, Chamberlain AT, Brosseau JL, Orenstein WA. Impact of statins on influenza vaccine effectiveness against medically attended acute respiratory illness. J Infect Dis **2016**; 213:1216–23.
15. McLean HQ, Chow BD, VanWormer JJ, King JP, Belongia EA. Effect of statin use on influenza vaccine effectiveness. J Infect Dis **2016**; 214:1150–8.
16. Fedson DS. Pandemic influenza: a potential role for statins in treatment and prophylaxis. Clin Infect Dis **2006**; 43:199–205.
17. Fedson DS. Treating influenza with statins and other immunomodulatory agents. Antiviral Res **2013**; 99:417–35.
18. Seo SH, Webby R, Webster RG. No apoptotic deaths and different levels of inductions of inflammatory cytokines in alveolar macrophages infected with influenza viruses. Virology **2004**; 329:270–9.
19. Havers F, Bramley AM, Finelli L, et al. Statin use and hospital length of stay among adults hospitalized with community-acquired pneumonia. Clin Infect Dis **2016**; 62:1471–8.
20. Vandermeer ML, Thomas AR, Kamimoto L, et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study. J Infect Dis **2012**; 205:13–9.
21. Peng J, Zhang D, Ma Y, Wang G, Guo Z, Lu J. Protective effect of fluvastatin on influenza virus infection. Mol Med Rep **2014**; 9:2221–6.
22. Laidler MR, Thomas A, Baumbach J, et al. Statin treatment and mortality: propensity score-matched analyses of 2007–2008 and 2009–2010 laboratory-confirmed influenza hospitalizations. Open Forum Infect Dis **2015**; 2:ofv028.
23. Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. Lancet Infect Dis **2015**; 15:293–300.
24. Shay DK, Chillarige Y, Kelman J, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US Medicare beneficiaries in preventing postinfluenza deaths during 2012–2013 and 2013–2014. J Infect Dis **2017**; 215:510–7.
25. Appiah GD, Blanton L, D'Mello T, et a.; Centers for Disease Control and Prevention. Influenza activity—United States, 2014–15 season and composition of the 2015–16 influenza vaccine. Morb Mortal Wkly Rep **2015**; 64:583–90.
26. Izurieta HS, Wernecke M, Kelman J, et al. Effectiveness and duration of protection provided by the live-attenuated herpes Zoster vaccine in the Medicare population ages 65 years and older. Clin Infect Dis **2017**; 64:785–93.
27. Fairman KA. Evaluating medication adherence: which measure is right for your program? J Manag Care Pharm **2000**; 6:499–506.
28. Potter CW, Oxford JS. Determinants of immunity to influenza infection in man. Br Med Bull **1979**; 35:69–75.
29. Chang HY, Weiner JP, Richards TM, Bleich SN, Segal JB. Validating the adapted diabetes complications severity index in claims data. Am J Manag Care **2012**; 18:721–6.
30. Mapel DW, Dutro MP, Marton JP, Woodruff K, Make B. Identifying and characterizing COPD patients in US managed care. A retrospective, cross-sectional analysis of administrative claims data. BMC Health Serv Res **2011**; 11:43.
31. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivariate Behav Res **2011**; 46:399–424.
32. Stuart EA. Matching methods for causal inference: a review and a look forward. Stat Sci **2010**; 25:1–21.
33. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med **2009**; 28:3083–107.
34. Akaike H. A new look at the statistical model identification. IEEE Trans Automat Contr **1974**; 19:716–23.
35. Stone NJ, Robinson JG, Lichtenstein AH, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation **2014**; 129:S1–45.
36. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology **2010**; 21:383–8.
37. Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. CMAJ **2011**; 183:310–9.
38. Filion KB, Chateau D, Targownik LE, et al; CNODES Investigators. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. Gut **2014**; 63:552–8.
39. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. JAMA **2004**; 292:1955–60.
40. Hermos JA, Young MM, Fonda JR, Gagnon DR, Fiore LD, Lawler EV. Risk of community-acquired pneumonia in veteran patients to whom proton pump inhibitors were dispensed. Clin Infect Dis **2012**; 54:33–42.

Supplementary Materials: Table of Contents

eTable 1. Cardiovascular condition codes used as exclusion criteria in defining the study population[a]

Cardiovascular Conditions	Codes	Position	Setting
Heart Failure	**ICD-9-CM DGN:** 402.x1, 404.x1, 404.x3, 428.xx **ICD-9-CM PRC:** 37.66 **HCPCS:** 33973-33978, 33980, 92970-92971, G8027-G8032, G8184	All	IP/OP/OP-ER/PB
AMI	**ICD-9-CM DGN:** 410.xx	All	IP/OP/PB
Cardiomyopathy	**ICD-9-CM DGN:** 425.xx	All	IP/OP/PB
Coronary revascularization	**ICD-9-CM DGN:** V45.81-V45.82, V45.88, **ICD-9-CM PRC:** 00.66, 36.0x-36.3x **HCPCS:** 00566, 33510-33523, 33530-33536, 33572, 92973, 92975, 92977, 92980,-92982, 92984, 92995-92996, G8518-G8167, G8170-G8172	All	IP/OP/OP-ER/PB
Other ischemic heart disease	**ICD-9-CM DGN:** 411.xx, 413.xx, 414.xx, 429.2, 429.5-429.7x, 429.9 **HCPCS:** G8033-G8041	All	IP/OP/PB
Peripheral vascular disease	**ICD-9-CM DGN:** 249.7x, 250.7x, 440.2x-440.4, 443.1, 443.81, 443.9 **ICD-9-CM PRC:** 38.13, 38.15-38.18, 39.22-39.26, 39.29, 39.50, 39.90 **HCPCS:** 34001-34203, 35301-35381, 35450-35512, 35512-35551, 35556-35571, 35583-35587, 35612-35641, 35646-35671, 35700, 35721, 35741, 35879, 35881	All	IP/OP/PB
Stroke	**ICD-9-CM DGN:** 430, 431.xx, 434.x1, 436	All	IP/OP/PB
Transient ischemic attack	**ICD-9-CM DGN:** 435.x	All	IP/OP/PB
Other cerebrovascular disease	**ICD-9-CM DGN:** 437.8-437.9, 438.xx, V12.54 **ICD-9-CM PRC:** 00.61-00.65, 38.01-38.02, 38.11-38.12, 39.74 **HCPCS:** 35301, 35390, 35501-35509, 35601-35606, 35642, 35701, 61711	All	IP/OP/PB

Abbreviations: ICD-9-CM, Ninth Revision of the International Classification of Diseases, Clinical Modification; DGN, diagnosis code; PRC, procedural code; HCPCS, Healthcare Common Procedure Coding System; IP, inpatient; OP, outpatient; OP-ER, outpatient emergency room; PB, non-institutional physician office visit

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[a] Beneficiaries with any of these cardiovascular conditions in the 6 months prior to their vaccination date were excluded from the study

eTable 2. Classifications of statin intensity and type by active ingredient and dosage[a]

Statin Type	High-Intensity Statin Therapy (lowers cholesterol by ≥ 50%)	Moderate-Intensity Statin Therapy (lowers cholesterol by 30 - 50%)	Low-Intensity Statin Therapy (lowers cholesterol by < 30%)
Synthetic	Atorvastatin ≥ 40 mg/day Rosuvastatin ≥ 20 mg/day	Atorvastatin [10 - 40) mg/day Fluvastatin ≥ 80 mg/day Rosuvastatin [5, 20) mg/day	Atorvastatin <10 mg/day Fluvastatin < 80 mg/day Rosuvastatin < 5 mg/day
Non-Synthetic		Simvastatin ≥ 20 mg/day Pravastatin ≥ 40 mg/day Lovastatin ≥ 40 mg/day Pitavastatin ≥ 2 mg/day	Simvastatin < 20 mg/day Pravastatin < 40 mg/day Lovastatin < 40 mg/day Pitavastatin < 2 mg/day

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[a] Source: Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2014;129(25 suppl 2):S1-S45.

eTable 3. Distribution of covariates across statin intensity user groups among eligible Medicare beneficiaries for the 2010-2015 influenza seasons

Covariate	Low-Intensity Statin User	Moderate-Intensity Statin User	High-Intensity Statin User	Statin Non-User	SMD (Low vs Non)a	SMD (Mod vs Non)	SMD (High vs Non)	SMD (Low vs Mod)	SMD (Low vs High)	SMD (Mod vs High)
Base Population	**181,977**	**1,053,289**	**123,093**	**1,403,469**						
Age Brackets										
65-69	25.30%	27.40%	31.50%	27.30%	0.05	0.00	0.09	0.05	0.14	0.09
70-74	30.20%	31.60%	33.40%	31.50%	0.03	0.00	0.04	0.03	0.07	0.04
75-79	20.60%	20.50%	19.40%	20.50%	0.00	0.00	0.03	0.00	0.03	0.03
80-84	13.60%	12.30%	10.20%	12.30%	0.04	0.00	0.07	0.04	0.11	0.07
85+	10.30%	8.20%	5.40%	8.30%	0.07	0.00	0.11	0.07	0.18	0.11
Gender										
Male	28.60%	33.00%	38.80%	32.90%	0.09	0.00	0.12	0.10	0.22	0.12
Female	71.40%	67.00%	61.20%	67.10%	0.09	0.00	0.12	0.10	0.22	0.12
Race										
White	91.80%	92.40%	92.50%	92.40%	0.02	0.00	0.01	0.03	0.03	0.00
Black	2.30%	2.30%	2.60%	2.40%	0.00	0.00	0.02	0.00	0.02	0.02
Asian	2.70%	2.20%	1.70%	2.20%	0.03	0.00	0.03	0.03	0.07	0.04
Hispanic	0.80%	0.80%	0.80%	0.80%	0.00	0.00	0.00	0.00	0.00	0.00
Other	2.40%	2.20%	2.30%	2.30%	0.01	0.00	0.01	0.01	0.00	0.01
Regions										
Region 1: CT, ME, MA, NH, RI, VT	6.20%	5.50%	5.60%	5.60%	0.03	0.00	0.00	0.03	0.03	0.01
Region 2: NJ, NY, PR, VI	5.70%	6.10%	6.00%	6.00%	0.01	0.01	0.00	0.02	0.01	0.00
Region 3: DE, DC, MD, PA, VA, WV	8.90%	9.10%	9.30%	9.00%	0.01	0.00	0.01	0.01	0.01	0.01
Region 4: AL, FL, GA, KY, MS, NC, SC, TN	21.70%	22.70%	23.30%	22.50%	0.02	0.00	0.02	0.02	0.04	0.02
Region 5: IL, IN, MI, MN, OH, WI	18.80%	18.10%	16.60%	18.10%	0.02	0.00	0.04	0.02	0.06	0.04
Region 6: AR, LA, NM, OK, TX	10.40%	11.30%	11.90%	11.20%	0.03	0.00	0.02	0.03	0.05	0.02
Region 7: IA, KS, MO, NE	6.40%	6.50%	5.70%	6.40%	0.00	0.00	0.03	0.00	0.03	0.03
Region 8: CO, MT, ND, SD, UT, WY	3.50%	3.50%	3.40%	3.40%	0.00	0.00	0.00	0.00	0.00	0.00
Region 9: AZ, CA, HI, NV, AS, FS, GU, PU	12.20%	12.10%	12.80%	12.30%	0.00	0.01	0.02	0.00	0.02	0.02
Region 10: AK, ID, OR, WA	6.30%	5.20%	5.40%	5.50%	0.03	0.01	0.01	0.04	0.04	0.01
Other	0.00%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00
Dual Status										
Yes	9.00%	8.90%	9.10%	8.70%	0.01	0.01	0.01	0.00	0.00	0.01

eTable 3. Distribution of covariates across statin intensity Medicare beneficiary user groups for the 2010-2015 influenza seasons (continued)

Covariate	Low-Intensity Statin User	Moderate-Intensity Statin User	High-Intensity Statin User	Statin Non-User	SMD (Low vs Non)	SMD (Mod vs Non)	SMD (High vs Non)	SMD (Low vs Mod)	SMD (Low vs High)	SMD (Mod vs High)
Base Population	**181,977**	**1,053,289**	**123,093**	**1,403,469**						
Low-Income Subsidy Status										
None	88.80%	88.80%	88.30%	89.00%	0.01	0.01	0.02	0.00	0.01	0.01
Zero Copay	0.80%	0.80%	0.70%	0.70%	0.00	0.00	0.01	0.00	0.01	0.01
Low Copay	4.60%	4.80%	5.30%	4.70%	0.01	0.00	0.03	0.01	0.03	0.03
High Copay	5.40%	5.30%	5.30%	5.10%	0.01	0.01	0.01	0.00	0.00	0.00
15% Copay	0.50%	0.40%	0.40%	0.40%	0.01	0.00	0.00	0.01	0.01	0.00
Month of Vaccination										
August	3.50%	3.70%	3.60%	3.60%	0.00	0.01	0.00	0.01	0.01	0.00
September	32.30%	32.50%	31.60%	32.20%	0.00	0.01	0.01	0.00	0.02	0.02
October	44.30%	43.40%	43.00%	43.70%	0.01	0.01	0.02	0.02	0.03	0.01
November	12.20%	12.40%	12.90%	12.50%	0.01	0.00	0.01	0.00	0.02	0.02
December	4.50%	4.70%	5.00%	4.70%	0.01	0.00	0.02	0.01	0.03	0.02
January	3.20%	3.40%	3.90%	3.40%	0.01	0.00	0.03	0.01	0.04	0.02
All Hospitalizations and Observational Stays										
0	95.50%	95.40%	95.60%	95.50%	0.00	0.01	0.00	0.00	0.01	0.01
1 +	4.50%	4.60%	4.40%	4.50%	0.00	0.01	0.00	0.00	0.01	0.01
Outpatient Non-ER Visits										
0	28.10%	31.00%	31.70%	30.40%	0.05	0.01	0.03	0.06	0.08	0.02
1, 2	31.80%	32.60%	31.60%	32.80%	0.02	0.00	0.03	0.02	0.00	0.02
3 +	40.10%	36.50%	36.70%	36.80%	0.07	0.01	0.00	0.07	0.07	0.00
Outpatient ER Visits										
0	86.80%	87.30%	87.40%	87.30%	0.01	0.00	0.00	0.02	0.02	0.00
1	10.60%	10.30%	10.10%	10.40%	0.01	0.00	0.01	0.01	0.02	0.01
2 +	2.60%	2.40%	2.50%	2.40%	0.01	0.00	0.01	0.01	0.01	0.01
All Physician Visits										
[1 - 5]	13.20%	14.90%	14.30%	14.20%	0.03	0.02	0.00	0.05	0.03	0.02
[6 - 10]	29.50%	30.20%	29.40%	30.40%	0.02	0.00	0.02	0.02	0.00	0.02
[11 - 15]	22.10%	21.70%	21.60%	21.70%	0.01	0.00	0.00	0.01	0.01	0.00
[16 - 25]	21.30%	20.30%	20.80%	20.50%	0.02	0.00	0.01	0.02	0.01	0.01
26 +	13.80%	12.90%	13.90%	13.20%	0.02	0.01	0.02	0.03	0.00	0.03
Respiratory Failure and Pneumonia Hospitalizations										
0	99.60%	99.70%	99.70%	99.70%	0.01	0.00	0.00	0.00	0.01	0.00
1 +	0.40%	0.30%	0.30%	0.30%	0.01	0.00	0.00	0.00	0.01	0.00

eTable 3. Distribution of covariates across statin intensity Medicare beneficiary user groups for the 2010-2015 influenza seasons (continued)

Covariate	Low-Intensity Statin User	Moderate-Intensity Statin User	High-Intensity Statin User	Statin Non-User	SMD (Low vs Non)	SMD (Mod vs Non)	SMD (High vs Non)	SMD (Low vs Mod)	SMD (Low vs High)	SMD (Mod vs High)
Base Population	**181,977**	**1,053,289**	**123,093**	**1,403,469**						
Respiratory Failure and Pneumonia Outpatient Non-ER Visits										
0	99.50%	99.50%	99.50%	99.50%	0.01	0.00	0.00	0.01	0.01	0.00
1 +	0.50%	0.50%	0.50%	0.50%	0.01	0.00	0.00	0.01	0.01	0.00
Respiratory Failure and Pneumonia Outpatient ER Visits										
0	99.80%	99.80%	99.80%	99.80%	0.00	0.00	0.00	0.00	0.01	0.00
1 +	0.20%	0.20%	0.20%	0.20%	0.00	0.00	0.00	0.00	0.01	0.00
Respiratory Failure and Pneumonia Physician Visits										
0	98.10%	98.20%	98.30%	98.20%	0.01	0.00	0.01	0.01	0.01	0.01
1 +	1.90%	1.80%	1.70%	1.80%	0.01	0.00	0.01	0.01	0.01	0.01
Diabetes Severity: aDCSI Score (365 days prior)[b]										
0	71.10%	71.60%	67.30%	72.00%	0.02	0.01	0.10	0.01	0.08	0.09
1	9.30%	9.40%	9.90%	9.30%	0.00	0.00	0.02	0.00	0.02	0.02
2	14.00%	13.60%	15.50%	13.50%	0.01	0.00	0.06	0.01	0.04	0.05
3	3.10%	3.10%	3.90%	3.00%	0.01	0.01	0.05	0.00	0.05	0.05
4	1.80%	1.70%	2.40%	1.60%	0.01	0.00	0.05	0.01	0.04	0.05
5+	0.70%	0.70%	1.10%	0.70%	0.01	0.00	0.04	0.00	0.04	0.04
COPD Complexity (365 days prior)[c]										
No COPD	93.00%	93.00%	93.00%	92.90%	0.00	0.00	0.00	0.00	0.00	0.00
Low Complexity	4.20%	4.30%	4.40%	4.40%	0.01	0.00	0.00	0.01	0.01	0.00
Moderate Complexity	2.00%	1.90%	1.80%	1.90%	0.01	0.00	0.01	0.01	0.01	0.01
High Complexity	0.90%	0.80%	0.80%	0.80%	0.00	0.00	0.00	0.00	0.00	0.00
General Medical Conditions (365 days prior)										
Asthma	5.90%	5.80%	5.90%	5.90%	0.00	0.01	0.00	0.01	0.00	0.01
Bronchitis	9.90%	10.30%	10.30%	10.30%	0.01	0.00	0.00	0.01	0.01	0.00
Liver Disease	1.40%	1.20%	1.30%	1.30%	0.01	0.00	0.01	0.01	0.00	0.01
Hypercholesterolemia	39.20%	40.40%	41.50%	38.80%	0.01	0.03	0.05	0.03	0.05	0.02
Hypertension	73.40%	74.20%	76.30%	75.10%	0.04	0.02	0.03	0.02	0.07	0.05
Kidney Failure - Chronic	6.40%	6.10%	7.70%	5.90%	0.02	0.01	0.07	0.01	0.05	0.06
Kidney Failure - Acute	0.70%	0.70%	0.80%	0.70%	0.00	0.00	0.02	0.00	0.02	0.01

eTable 3. Distribution of covariates across statin intensity Medicare beneficiary user groups for the 2010-2015 influenza seasons (continued)

Covariate	Low-Intensity Statin User	Moderate-Intensity Statin User	High-Intensity Statin User	Statin Non-User	SMD (Low vs Non)	SMD (Mod vs Non)	SMD (High vs Non)	SMD (Low vs Mod)	SMD (Low vs High)	SMD (Mod vs High)
Base Population	**181,977**	**1,053,289**	**123,093**	**1,403,469**						
Frailty (365 days prior)										
Dementia	2.50%	2.30%	2.10%	2.40%	0.01	0.00	0.01	0.01	0.02	0.01
Falls	4.10%	3.80%	3.70%	3.90%	0.01	0.00	0.01	0.01	0.02	0.01
Fractures	1.20%	1.20%	1.10%	1.20%	0.00	0.00	0.01	0.00	0.01	0.01
Home oxygen use	0.20%	0.20%	0.20%	0.20%	0.00	0.00	0.00	0.00	0.01	0.00
Urinary Catheter use	0.00%	0.00%	0.00%	0.00%	0.00	0.00	0.00	0.00	0.00	0.00
Walker use	1.20%	1.10%	1.00%	1.10%	0.01	0.00	0.01	0.01	0.02	0.01
Wheelchair use	0.10%	0.10%	0.10%	0.10%	0.00	0.00	0.00	0.00	0.00	0.00
Anti-Dementia Medications	2.50%	2.60%	2.40%	2.50%	0.00	0.00	0.01	0.00	0.01	0.01
Anti-Psychotics	1.60%	1.60%	1.80%	1.60%	0.00	0.00	0.01	0.00	0.01	0.01
Autoimmune Conditions (365 days prior)										
Rheumatoid Arthritis	2.50%	2.10%	2.00%	2.20%	0.02	0.00	0.01	0.02	0.03	0.01
Other Autoimmune Conditions	6.50%	6.10%	6.20%	6.30%	0.01	0.01	0.00	0.01	0.01	0.00
Immunomodulatory Conditions (365 days prior)										
Immunomodulatory Medications	0.30%	0.30%	0.30%	0.30%	0.00	0.00	0.00	0.01	0.00	0.01
Neoplasms	0.20%	0.20%	0.10%	0.20%	0.01	0.00	0.01	0.01	0.02	0.01
Immune Disorders	0.30%	0.30%	0.30%	0.30%	0.01	0.00	0.01	0.01	0.00	0.01
White Blood Cell Disease	0.80%	0.60%	0.60%	0.70%	0.01	0.00	0.01	0.01	0.02	0.00
Other Hematological Diseases	0.50%	0.40%	0.40%	0.50%	0.00	0.00	0.01	0.01	0.01	0.00
Concurrent Vaccinations										
Pneumococcal Vaccination	2.70%	2.90%	3.10%	2.90%	0.01	0.00	0.01	0.01	0.02	0.01

Abbreviations: SMD, standardized mean difference, AK, Alaska; AL, Alabama; AR, Arkansas; AS, ; AZ, Arizona; CA, California; CO, Colorado; CT, Connecticut; DC, Washington, D.C.; DE, Delaware; FL, Florida; FS, ; GA, Georgia; GU, ; HI, Hawaii; IA, Iowa; ID, Idaho; IL, Illinois; IN, Indiana; KS, Kansas; KY, Kentucky; LA, Louisiana; MA, Massachusetts; MD, Maryland; ME, Maine; MI, Michigan; MN, Minnesota; MO, Missouri; MS, Mississippi; MT, Montana; NC, North Carolina; ND, North Dakota; NE, Nebraska; NH, New Hampshire; NJ, New Jersey; NM, New Mexico; NV, Nevada; NY, New York; OH, Ohio; OK, Oklahoma; OR, Oregon; PA, Pennsylvania; PR, Puerto Rico; PU, ; RI, Rhode Island; SC, South Carolina; SD, South Dakota; TN, Tennessee; TX, Texas; UT, Utah; VA, Virginia; VI, ; VT, Vermont; WA, Washington; WI, Wisconsin; WV, West Virginia; WY, Wyoming.

[a] SMD values of greater than or equal to 0.1 indicate that the two groups are imbalanced on the specified covariates
[b] The aDCSI score assigns points for the presence of retinopathy, nephropathy, neuropathy, cerebrovascular diseases, peripheral vascular diseases, and metabolic diseases
[c] COPD complexity is assigned based on the presence and severity of COPD-related diagnoses

eTable 4. Prior season vaccinations in the matched statin user and non-user Medicare beneficiary cohorts for the 2010-2015 influenza seasons[a][b]

Prior Season Vaccine Status	Statin User	Statin Non-User	SMD
Total	1,403,651	1,403,651	
At least one vaccine claim in the prior season[c]	86.91%	85.41%	0.04
No vaccine claims in the prior season with continuous Medicare enrollment[d]	12.65%	14.11%	0.04
No vaccine claims in the prior season and no continuous Medicare enrollment[e]	0.44%	0.48%	0.01

Abbreviation: SMD, standardized mean difference

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[a] The prior season is defined as the influenza season prior to the season of the beneficiaries' index date

[b] The beneficiaries presented in this table are restricted those in the matched study cohorts

[c] Beneficiaries in this category are not restricted to those continuously enrolled in Medicare Part A, B, or D in the prior season

[d] Beneficiaries in this category are continuously enrolled in Medicare Part A, B, and D for the entirety of the prior season

[e] Beneficiaries in this category are not continuously enrolled in Medicare Part A, B, and D in the prior season

eTable 5. Risk differences between the matched statin user and non-user Medicare beneficiary cohorts for the 2010-2015 influenza seasons

Season and Outcome	Statin Users		Statin Non-users		Risk Differences[a]	
	Outcome Rate[b]	95% CI	Outcome Rate	95% CI	Risk Difference	95% CI
Influenza-related office visits						
2010-2011	0.42	(0.35 - 0.52)	0.36	(0.29 - 0.45)	0.06	(-0.06 - 0.18)
2011-2012	0.13	(0.09 - 0.18)	0.15	(0.11 - 0.20)	-0.02	(-0.08 - 0.04)
2012-2013	1.28	(1.16 - 1.42)	1.18	(1.07 - 1.31)	0.10	(-0.08 - 0.28)
2013-2014	0.64	(0.57 - 0.73)	0.59	(0.52 - 0.67)	0.05	(-0.06 - 0.16)
2014-2015	3.15	(3.00 - 3.30)	2.92	(2.77 - 3.07)	0.23	(0.02 - 0.44)
Hospitalized Influenza						
2010-2011	0.21	(0.16 - 0.28)	0.25	(0.19 - 0.32)	-0.04	(-0.13 - 0.05)
2011-2012	0.11	(0.08 - 0.16)	0.14	(0.10 - 0.19)	-0.03	(-0.09 - 0.03)
2012-2013	0.82	(0.73 - 0.93)	0.76	(0.67 - 0.86)	0.06	(-0.08 - 0.21)
2013-2014	0.39	(0.34 - 0.46)	0.26	(0.22 - 0.32)	0.13	(0.05 - 0.21)
2014-2015	1.59	(1.48 - 1.70)	1.47	(1.37 - 1.58)	0.12	(-0.03 - 0.27)

Abbreviation: CI, confidence interval

[a] Statin non-users were used as the reference group for rate difference calculations

[b] Only cases occurring during high influenza circulation periods, which are more likely to be associated with influenza infections, were included for all analyses

eTable 6. Rate ratio estimates with 95% confidence intervals and AIC values for all vaccine subgroup analysis Poisson models[a]

Outcome	Model	Rate Ratio	P-Value	95% CI	AIC
Influenza-related Office Visits	Multivariate Poisson - No Vaccine Type Interaction[bc]	1.086	0.005	(1.025 - 1.150)	**59479.98**
	Multivariate Poisson- Vaccine Type Interaction[d]				
	Standard Dose	1.133	0.002	(1.047 - 1.227)	59480.51
	High Dose	1.050	0.270	(0.962 - 1.146)	
	Quadrivalent[e]	0.901	0.452	(0.685 - 1.183)	
Influenza Hospitalizations	Multivariate Poisson - No Vaccine Type Interaction[a]	1.096	0.022	(1.013 - 1.185)	**38016.18**
	Multivariate Poisson - Vaccine Type Interaction				
	Standard Dose	1.075	0.178	(0.968 - 1.194)	38017.18
	High Dose	1.153	0.022	(1.021, 1.303)	
	Quadrivalent	0.781	0.281	(0.498, 1.224)	

[a] Only cases occurring during high influenza circulation periods, which are more likely to be associated with influenza infections, were included for all analyses

[b] The multivariate Poisson models in this study adjusted for all the variables used in the matching process (see Table 1)

[c] The multivariate models without vaccine type interaction are the best fitting models for both outcomes based on their AIC values

[d] The p-values for the vaccine type and statin use interaction term ranged from 0.11 to 0.20 for the influenza-related office visit outcome and ranged from 0.18 to 0.39 for the influenza hospitalization outcome

[e] The number of quadrivalent influenza vaccinations in the study were included for completeness, but represented a small share of all vaccinated beneficiaries

eTable 7. Outcome rates and Poisson model rate ratio estimates for the HCTZ negative exposure analysis in the 2010-2015 influenza seasons[a]

Outcome	HCTZ Users			HCTZ Non-Users			Raw Rate Ratio[b]		Poisson Model Estimated Rate Ratio	
	Outcome (#)	Person-Time (10,000 Person Weeks)	Outcome Rate (per 10,000 Person-Weeks)	Outcome (#)	Person-Time (10,000 Person Weeks)	Outcome Rate (per 10,000 Person-Weeks)	Ratio	95 % CI	Ratio	95% CI
Influenza-Related Office Visits	495	433	1.14	524	432	1.21	0.94	(0.83, 1.07)	0.94	(0.83 - 1.07)
Influenza Hospitalizations	349	434	0.80	359	434	0.83	0.97	(0.84, 1.13)	0.97	(0.83 - 1.12)

Abbreviation: HCTZ, hydrochlorothiazide

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[a] Only cases occurring during high influenza circulation periods, which are more likely to be associated with influenza infections, were included for all analyses

[b] HCTZ non-users served as the reference group for all rate ratio calculations

eTable 8. Outcome rates and Poisson model rate ratio estimates for the PPI negative exposure analysis in the 2010-2015 influenza seasons[a]

Outcome	PPI Users			PPI Non-Users			Raw Rate Ratio[b]		Poisson Model Estimated Rate Ratio	
	Outcome (#)	Person-Time (10,000 Person Weeks)	Outcome Rate (per 10,000 Person-Weeks)	Outcome (#)	Person-Time (10,000 Person Weeks)	Outcome Rate (per 10,000 Person-Weeks)	Ratio	95 % CI	Ratio	95% CI
Influenza-Related Office Visits	1,173	658	1.78	971	657	1.48	1.21	(1.11, 1.31)	1.206	(1.11 - 1.31)
Influenza Hospitalizations	718	659	1.09	602	659	0.91	1.19	(1.07, 1.33)	1.185	(1.06 - 1.32)

Abbreviation: PPI, proton pump inhibitor

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[a] Only cases occurring during high influenza circulation periods, which are more likely to be associated with influenza infections, were included for all analyses

[b] PPI non-users served as the reference group for all rate ratio calculations

eTable 9. Number of Medicare beneficiaries in the study population by outcome type and number of outcomes across the 2010-2015 influenza seasons[a]

Outcome	# Beneficiaries with no Outcome in any Season[b]	# Beneficiaries with Outcome(s) in 1 Season	# Beneficiaries with Outcomes in 2 Seasons	# Beneficiaries with Outcomes in 3 Seasons
In High Circulation Flu Season				
Influenza-Related Office Visits or Hospitalized Influenza	1,882,259	6,738	5	1
Influenza-Related Office Visits	1,884,352	4,648	3	-
Hospitalized Influenza	1,886,492	2,509	2	-
In High/Medium/Low Circulation Flu Season				
Influenza-Related Office Visits or Hospitalized Influenza	1,880,124	8,857	21	1
Influenza-Related Office Visits	1,882,847	6,144	12	-
Hospitalized Influenza	1,885,754	3,246	3	-

[a] Only cases occurring during high influenza circulation periods, which are more likely to be associated with influenza infections, were included for all analyses

[b] Column categories in the table are mutually exclusive

eMethods. Functional forms of the Poisson regression models used in the primary analysis comparing the influenza outcome rate among statin users to statin non-users in the 2010-2015 influenza seasons[a]

The log-linear functional forms of the Poisson regression models we ran for the primary study analysis and negative exposure analysis are listed below. The same models were used for the negative exposure analysis, with PPI use or HCTZ use as the treatment in place of statin use.

1) $\log(R(Y|x)) = \beta_0 + \beta_1 Tx + \beta_2\, season$

2) $\log(R(Y|x)) = \beta_0 + \beta_1 Tx + \beta_2\, season + \sum_\alpha \mu_\alpha x_\alpha$

3) $\log(R(Y|x)) = \beta_0 + \beta_1 Tx + \beta_2\, season + \beta_3\,(Tx * season) + \sum_\alpha \mu_\alpha x_\alpha$

Notation:

- Y = outcome (e.g. influenza hospitalization)
- x = complete set of study covariates
- Tx = treatment variable (e.g. statin user)
- $\sum_\alpha \mu_\alpha x_\alpha$ = study covariates and their coefficients

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[a] Only cases occurring during high influenza circulation periods, which are more likely to be associated with influenza infections, were included for all analyses

Effectiveness and duration of effectiveness of the Zostavax vaccine among Medicare beneficiaries ages 65 years and older

IDSA
Infectious Diseases Society of America

hivma
hiv medicine association

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Effectiveness and Duration of Protection Provided by the Live-attenuated Herpes Zoster Vaccine in the Medicare Population Ages 65 Years and Older

Hector S. Izurieta,[1,5] Michael Wernecke,[2] Jeffrey Kelman,[3] Sarah Wong,[2] Richard Forshee,[1] Douglas Pratt,[1] Yun Lu,[1] Qin Sun,[2] Christopher Jankosky,[1] Philip Krause,[1] Chris Worrall,[3] Tom MaCurdy,[2] and Rafael Harpaz[4]

[1]Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, Maryland; [2]Acumen LLC, Burlingame, California; [3]Centers for Medicare and Medicaid Services, Washington, DC; [4]National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; [5]Universidad Rey Juan Carlos, Madrid, Spain

(See the Editorial Commentary by Black on pages 794-5.)

Background. Tens of millions of seniors are at risk of herpes zoster (HZ) and its complications. Live attenuated herpes zoster vaccine (HZV) reduces that risk, although questions regarding effectiveness and durability of protection in routine clinical practice remain. We used Medicare data to investigate HZV effectiveness (VE) and its durability.

Methods. This retrospective cohort study included beneficiaries ages ≥65 years during January 2007 through July 2014. Multiple adjustments to account for potential bias were made. HZV-vaccinated beneficiaries were matched to unvaccinated beneficiaries (primary analysis) and to HZV-unvaccinated beneficiaries who had received pneumococcal vaccination (secondary analysis). HZ outcomes in community and hospital settings were analyzed, including ophthalmic zoster (OZ) and postherpetic neuralgia (PHN).

Results. Among eligible beneficiaries (average age 77 years), the primary analysis found VE for community HZ of 33% (95% CI: 32%–35%) and 19% (95% CI: 17%–22%), for the first 3, and subsequent 4+ years postvaccination, respectively. In the secondary analysis, VE was, respectively, 37% (95% CI: 36%–39%) and 22% (95% CI: 20%–25%). In the primary analysis, VE for PHN was 57% (95% CI: 52%–61%) and 45% (95% CI: 36%–53%) in the first 3 and subsequent 4+ years, respectively; VE for hospitalized HZ was, respectively, 74% (95% CI: 67%–79%) and 55% (95% CI: 39%–67%). Differences in VE by age group were not significant.

Conclusions. In both the primary and secondary analyses, HZV provided protection against HZ across all ages, but effectiveness declined over time. VE was higher and better preserved over time for PHN and HZ-associated hospitalizations than for community HZ.

Keywords. Herpes Zoster vaccine; vaccine effectiveness; post-herpetic neuralgia; opthalmic zoster; elderly.

Herpes zoster (HZ) is a painful condition resulting from the reactivation of the varicella–zoster virus (VZV) from a latent state in sensory nerve ganglia. The disease manifests as a vesicular rash, characteristically unilateral, and restricted to a single dermatome, accompanied by pain along the dermatome. Older populations are particularly affected as the incidence and severity increases with age. There is a marked increase in the incidence of HZ after age 50, which correlates with aging-related decline in cell-mediated immunity [1]. Studies in Canada, Israel, Japan, Taiwan, and the United States reported age-adjusted HZ incidence rates of 8 to 11 per 1000 person-years in populations ages ≥65 years, whereas incidence in the general population was lower, ranging from 3.4 to 5.0 per 1000 person-years [2, 3]. Complications of HZ include ophthalmic zoster (OZ), bacterial

superinfections of skin lesions and disseminated infections, particularly among immunocompromised patients [4]. The most common serious complication of HZ is postherpetic neuralgia (PHN) [5]. Adults older than 70 years have a 4-fold increased risk of PHN compared with those younger than 60 years [6, 7].

The live-attenuated herpes zoster vaccine, ZOSTAVAX® (Zoster Vaccine Live; Merck & Co., Inc., Whitehouse Station, NJ) was initially licensed in the United States in 2006 to prevent HZ, following a clinical trial in over 38 000 participants ages ≥60 years with no history of HZ, immunosuppression, or other conditions that could interfere with study participation [8]. In this randomized study, the vaccine (HZV) reduced HZ incidence by 51% (95% CI: 44%, 58%) [1]. Post-marketing studies have generally not been powered to fully explore the roles and interactions of factors such as time since vaccination, age, and disease outcome (e.g., PHN, OZ, and hospitalized HZ) on HZV effectiveness [1, 9–15].

Our objective in this study was to use Medicare databases to robustly evaluate the effectiveness and duration of protection provided by the live-attenuated HZV among beneficiaries ages ≥65 years by age and risk group.

METHODS

Study Population

Medicare beneficiaries ages ≥65 years enrolled in fee-for-service Medicare Parts A (inpatient services), B (outpatient services), and D (prescription drugs) were analyzed retrospectively, comparing those who received a claim for HZV to those who were unvaccinated. Exposure to the HZV was identified using National Drug Codes (NDCs) for ZOSTAVAX, with the vaccination date used as the index date. Vaccinations between January 1, 2007, and July 31, 2014 were eligible for use as index dates. For the unvaccinated cohort, index dates were assigned to match the distribution of vaccination dates, subject to eligibility requirements.

Beneficiaries were included in the analyses if they had 12 months of continuous enrollment in Medicare A/B/D, ensuring that data exist to define baseline characteristics (Figure 1). Additionally, to ensure that unvaccinated beneficiaries were truly unvaccinated, beneficiaries were included in analyses only if they were enrolled in Medicare Part D since at least May 2006, when HZV was first licensed. Beneficiaries were excluded if they had an overlapping nursing home, skilled nursing facility, or hospice stay because claims from these settings are less complete, or if they received an HZ diagnosis or claim for an immunocompromising medical condition in the 12 months prior, or immunosuppressive treatment in the 6 months prior to their index date (Appendix I–II), because these conditions and drugs are known to reduce the effectiveness of the vaccine.

Cohort Follow-up

Start of follow-up began 30 days after cohort entry [1]. Beneficiaries were followed continuously until: a subsequent HZV claim, death, disenrollment from fee-for-service Medicare, end of study (July 31, 2014), admission to a nursing home, skilled nursing facility, or hospice, occurrence of the outcome of interest, or an immunosuppressive drug claim in the first 2 months after index date.

Outcomes

Incident HZ cases were defined using *International Classification of Diseases, Ninth Revision* (ICD-9-CM) codes (053.XX for HZ and 053.2X for OZ). Cases were captured in institutional and noninstitutional care settings and categorized into 5 separate outcomes: community HZ, hospitalized HZ, community OZ, hospitalized OZ, and PHN. We do not present our hospitalized OZ results because of low sample size and overall similarity to findings on hospitalized HZ. To identify hospitalized HZ, we used inpatient claims with a primary diagnosis of HZ, which has been shown to have a positive predictive value (PPV) of 86% [15]. For community cases, outcomes in any diagnosis position were used with reported PPVs ranging from 85.2% to 98% [7, 16].

PHN is an important consequence of HZ, especially in older adults. However, detection of PHN may be biased when ascertainment is restricted to medically attended care and is particularly challenging when using administrative data [10, 16]. PHN was defined using a modified version of the algorithm in Klompas et al. [16]. Cases of PHN were identified based on the presence of ICD-9 053.xx in the 90–180 days after an incident HZ diagnosis in combination with at least one of the following events: (1) a new prescription of a PHN treatment (Appendix III) in the 0–60 days from incident HZ diagnosis, (2) the presence of HZ with nervous system complications (ICD-9 053.1x) in the 90–180 days from incident HZ diagnosis, or (3) the presence of a new diagnosis for neuralgia (ICD-9 729.2x) in the 0–180 days from incident HZ diagnosis.

Covariates

This study accounted for well-studied risk factors of HZ in addition to other potential risk factors believed to be associated with risk of HZ or propensity to seek care once HZ is contracted (Appendix IV) [11, 14, 17, 18]. To achieve balance between cohorts, 1:1 propensity score matching was used, with propensity scores estimated from a logistic regression using all covariates. Beneficiaries were matched using this propensity score and the minimum Mahalanobis distance for key covariates: age, sex, race, and low-income subsidy status [19].

Falsification Outcomes

HZV recipients might differ from nonrecipients in their ability or desire to access care for HZ or on other unmeasured confounders, introducing ascertainment or selection bias. We adopted the approach in Tseng et al. [11, 17, 20–23] to check for such bias: hazard ratios were calculated for 13 acute symptomatic conditions (Appendix V) in the vaccinated and matched unvaccinated cohorts. Because these conditions were unrelated to HZ, as a group, the hazard ratios were expected to cluster around 1.0; any deviations from 1.0 would alert us to potential biases.

Statistical Analysis

Incident outcome rates were calculated by dividing the number of cases by the total person-years of observation. Doubly robust Cox regression models were used to estimate the hazard ratios for incident HZ and PHN in the vaccinated compared with the unvaccinated population, in which time intervals were interacted with vaccine status. Doubly robust models adjust for all baseline characteristics (Appendix IV) to account for any residual confounding in post-matching analyses [24, 25]. Additionally, for those beneficiaries in the cohorts who were started on immunosuppressive therapies after the index date, drug use was included in the model as a time-varying covariate (Appendix II). Vaccine effectiveness (VE) was calculated as (1−HR) × 100%, where HR

is the estimated hazard ratio between the 2 cohorts for a particular time interval, unless noted otherwise.

The secondary analysis used analogous methods but compared HZ vaccinees to beneficiaries who received a pneumococcal vaccine (PV; Pneumovax®23, Merck & Co Inc., Whitehouse Station, New Jersey) but did not receive HZV. PV beneficiaries were followed from vaccination as their index date. Additional analyses were performed on both primary and

Table 1. Demographic and Health-related Characteristics at Baseline in Propensity Score and Mahalanobis Matched Medicare Beneficiaries in the Primary Analysis Comparing Vaccinated and Unvaccinated Cohorts From January 2007 to July 2014

Demographic Variables	Vaccinated		Unvaccinated[a]		Austin Std. Diff[b]
Base population	945 992		945 992		
Age (continuous) [c]					
Mean	77		77		0.00
SD	6.15		6.15		
Age (categories) [c]	.		.		
65–69	106 167	11%	106 077	11%	0.00
70–74	292 343	31%	292 606	31%	0.00
75–79	262 853	28%	262 935	28%	0.00
80–84	172 306	18%	172 203	18%	0.00
85–89	84 236	9%	84 174	9%	0.00
90+	28 087	3%	27 997	3%	0.00
Sex	.		.		
Male	316 743	33%	316 545	33%	0.00
Female	629 249	67%	629 447	67%	0.00
Race	.		.		
White	850 032	90%	850 118	90%	0.00
Black	22 086	2%	22 068	2%	0.00
Asian	44 621	5%	44 581	5%	0.00
Hispanic	10 905	1%	10 895	1%	0.00
Other	18 348	2%	18 330	2%	0.00
Metropolitan statistical area	.		.		
Urban	672 857	71%	672 710	71%	0.00
Rural	271 872	29%	272 045	29%	0.00
Low-income subsidy status	.		.		
No LIS	740 582	78%	740 643	78%	0.00
Hospital visits	.		.		
1	96 593	10%	97 966	10%	0.00
2+	34 458	4%	34 559	4%	0.00
ER visits	.		.		
0	765 417	81%	764 715	81%	0.00
1	131 875	14%	132 528	14%	0.00
2+	48 700	5%	48 749	5%	0.00
Physician office visits	.		.		
0–4	153 886	16%	152 646	16%	0.00
5–10	285 905	30%	287 462	30%	0.00
11–20	291 555	31%	291 723	31%	0.00
21–30	120 457	13%	120 359	13%	0.00
31+	94 189	10%	93 802	10%	0.00
Medical conditions	.		.		
Diabetes	274 517	29%	280 717	30%	0.01
Kidney disease	86 690	9%	88 333	9%	0.01
Heart disease	263 650	28%	266 710	28%	0.01
Lung disease	195 309	21%	197 762	21%	0.01
Liver disease	14 889	2%	14 828	2%	0.00

Abbreviation: ER, emergency room.

[a] Data were measured 1 year prior to index date. For the vaccinated, the index date was the date of first vaccination. For the unvaccinated, the index date was assigned to match the distribution of vaccination dates. [b] The balance of covariates between the matched cohorts was assessed using the standardized mean difference [20]. A standardized mean difference of 0.1 or less indicated a negligible difference in means or proportions between cohorts. [c] The age distribution corresponds to the eligibility restriction that required beneficiaries be enrolled in Medicare since vaccine licensure. Frailty characteristics consisted of dementia, home oxygen use, urinary catheter use, walker use, and wheelchair use. These characteristics were identified in 1%–4% of the base population, where each was balanced between vaccinated and unvaccinated cohorts.

The full list of covariates that were included in the propensity score model are provided in Appendix IV.

Table 2.   Community Herpes Zoster (HZ) Incidence by Vaccination Status in the Primary Matched Population

Characteristic	No. Community HZ Cases	Total Person-years	No. Community HZ Cases	Total Person-years	Rate/1000 person-years (95% CI)		% Community HZ Cases that led to PHN[a]	
	Vaccinated		Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Overall	27 556	2 576 815	29 383	1 952 710	10.7 (10.6, 10.8)	15.0 (14.9, 15.2)	2.9%	4.0%
Year of follow-up								
1	7 539	815 355	11 166	744 417	9.2 (9.0, 9.5)	15.0 (14.7, 15.3)	2.5%	4.1%
2	6 397	611 365	7 556	496 000	10.5 (10.2, 10.7)	15.2 (14.9, 15.6)	2.8%	3.6%
3	4 655	420 733	4 417	299 158	11.1 (10.8, 11.4)	14.8 (14.3, 15.2)	3.4%	4.1%
4	3 666	311 440	2 935	197 024	11.8 (11.4, 12.2)	14.9 (14.4, 15.4)	3.1%	4.4%
5	2 880	229 428	1 976	130 598	12.6 (12.1, 13.0)	15.1 (14.5, 15.8)	3.3%	4.6%
6	1 716	132 459	990	63 737	13.0 (12.4, 13.6)	15.5 (14.6, 16.5)	2.7%	5.3%
7+	703	56 036	343	21 776	12.5 (11.7, 13.5)	15.8 (14.2, 17.5)	1.0%	1.5%
Age								
65–69	3 940	405 346	3 944	280 504	9.7 (9.4, 10.0)	14.1 (13.6, 14.5)	2.5%	3.8%
70–74	8 869	871 173	9 782	667 538	10.2 (10.0, 10.4)	14.7 (14.4, 14.9)	2.6%	3.6%
75–79	7 465	675 940	7 860	517 660	11.0 (10.8, 11.3)	15.2 (14.9, 15.5)	2.7%	4.2%
80–84	4 696	406 809	4 959	317 050	11.5 (11.2, 11.9)	15.6 (15.2, 16.1)	3.6%	5.0%
85–89	2 019	170 667	2 179	133 734	11.8 (11.3, 12.4)	16.3 (15.6, 17.0)	3.5%	3.9%
90+	567	46 880	659	36 224	12.1 (11.1, 13.1)	18.2 (16.9, 19.6)	2.8%	3.8%
Sex								
Male	7 892	864 607	8 493	649 840	9.1 (8.9, 9.3)	13.1 (12.8, 13.4)	3.0%	4.1%
Female	19 664	1 712 209	20 890	1 302 871	11.5 (11.3, 11.6)	16.0 (15.8, 16.3)	2.8%	4.0%
Race								
White	24 559	2 339 618	26 914	1 767 930	10.5 (10.4, 10.6)	15.2 (15.0, 15.4)	2.8%	4.0%
Black	266	39 948	355	37 352	6.7 (5.9, 7.5)	9.5 (8.6, 10.5)	1.9%	4.5%
Other[b]	2 731	197 249	2 114	147 428	13.8 (13.3, 14.4)	14.3 (13.7, 15.0)	3.2%	4.1%

Abbreviations: CI, confidence interval; HZ, herpes zoster; PHN, postherpetic neuralgia.

[a] The proportion of beneficiaries that were coded for postherpetic neuralgia in the 90–180 days after an incident community herpes zoster event among beneficiaries that received a diagnosis for community herpes zoster.

[b] Asian, Hispanic, Native American, Other, and Unknown Race are included in the Race—Other category.

secondary populations to investigate whether there was effect modification due to age, sex, and race.

This study was performed as part of the SafeRx Project, a joint initiative of the Centers for Medicare and Medicaid Services (CMS) and the US Food and Drug Administration (FDA). It was approved by the Research in Human Subjects Committee of FDA's Center for Biologics Evaluation and Research. Analyses were performed using R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) and SAS 9.4 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Primary Analysis

Prior to matching, vaccinated and unvaccinated beneficiaries differed considerably. After matching, a total of 945 992 vaccinated and 945 992 unvaccinated beneficiaries were obtained, resulting in well-balanced cohorts (Table 1). The population was 67% female, 90% white, and 77 years old on average at index date. Beneficiaries were followed for up to 7.5 years with the average length of follow-up being 2.5 years. Approximately 4% of beneficiaries were censored due to death and 17% due to admittance to a nursing home, skilled nursing facility, or

hospice. During follow-up, 0.7% of eligible beneficiaries began immunosuppressive treatment.

A total of 56 964 incident zoster outcomes were detected in our matched study population. Among the 29 401 cases in the unvaccinated cohort, 29 383 (>99%) received community care, 429 (1%) were hospitalized, 2,699 (9%) experienced OZ, and 1,229 (4%) experienced PHN. In the unvaccinated, the incidence of HZ was 15.0 per 1000 person-years for community events and 0.21 per 1000 person-years for hospitalized events. About 4% of community and 9% of hospitalized cases were also coded as PHN (Table 2, eTable 1). HZ rates remained steady by calendar year in the unvaccinated cohort (eFigure 2).

Before conducting the main analysis, we assessed whether there were underlying differences between study cohorts. We compared vaccinated to unvaccinated beneficiaries using 13 falsification outcomes, which were expected to have no association with HZ. The adjusted hazard ratio (AHR) of the 13 falsification outcomes in the vaccinated and unvaccinated cohorts ranged from 0.72 (95%CI: 0.70–0.73) for hip fracture outcomes to 1.17 (95%CI: 1.15–1.20) for lipoma (Figure 2). After running the main analysis, none of the 13 outcomes had an AHR as far from the null (1.0) as that of the zoster outcomes.

Table 3a. Primary Analysis: Adjusted Vaccine Effectiveness and 95% CI Comparing Herpes Zoster Vaccinated to Unvaccinated for Community Herpes Zoster, Hospitalized Herpes Zoster, Community Ophthalmic Zoster and Postherpetic Neuralgia Outcomes by Years of Follow-up[a]

Year of Follow-up	Outpatient Herpes Zoster (No. Outcomes = 56 939) VE (95% CI)	Hospitalized Herpes Zoster[b] (No. Outcomes = 614) VE (95% CI)	Outpatient Opthalmic Zoster (No. Outcomes = 5,282) VE (95% CI)	Postherpetic Neuralgia (No. Outcomes = 2,033) VE (95% CI)
Primary model				
First 3 years	33%** (32%, 35%)	74%** (67%, 79%)	31%** (27%, 36%)	57%** (52%, 61%)
4 or more years	19%** (17%, 22%)	55%** (39%, 67%)	21%** (12%, 29%)	45%** (36%, 53%)
Yearly model				
1	38%** (37%, 40%)	77%** (68%, 84%)	38%** (32%, 44%)	70%** (63%, 76%)
2	32%** (29%, 34%)	68%** (55%, 78%)	28%** (20%, 36%)	49%** (39%, 57%)
3	25%** (22%, 28%)	75%** (60%, 84%)	22%** (11%, 32%)	50%** (39%, 59%)
4	21%** (17%, 25%)	45%* (11%, 66%)	19%** (6%, 31%)	44%** (28%, 56%)
5	17%** (12%, 22%)	52%* (15%, 73%)	21%* (4%, 34%)	40%** (21%, 54%)
6	17%** (10%, 23%)	66%** (30%, 83%)	19% (−3%, 37%)	52%** (31%, 66%)
7+	21%** (11%, 31%)	70%* (25%, 88%)	33% (−1%, 55%)	60%** (28%, 78%)

Abbreviations: CI, confidence interval; HR, hazard ratio; HZ, herpes zoster; VE, vaccine effectiveness.
[a]Significance: ** $P < .01$, * $P < .05$.
[b]Approximately 90% of hospitalized HZ cases were identified in hospital stays lasting ≥ 2 nights. VE Formula for All: 1—[(HR in Cohort) * (HR interaction of Cohort × Years of follow-up) * 100%
VE Formula for Subgroups: 1—[(HR in Cohort) * (HR interaction of Cohort × Years of follow-up) * (HR interaction of Cohort × Age/Sex/Race)] * 100% Demographic factors, socioeconomic conditions, healthcare utilization characteristics, frailty characteristics, functional immunocompromising chronic conditions, and time-varying immunocompromising drugs were adjusted in the model.

Table 3b. Primary Subgroup Analysis: Adjusted Vaccine Effectiveness and 95% CI Comparing Herpes Zoster Vaccinated to Unvaccinated for Community Herpes Zoster, Hospitalized Herpes Zoster, Community Ophthalmic Zoster, and Postherpetic Neuralgia Outcomes by Years of Follow-up[a]

Subgroups[c]	Community Herpes Zoster (No. Outcomes = 56 939) First 3 Years VE (95% CI)	4 or More Years VE (95% CI)	Hospitalized Herpes Zoster[b] (No. Outcomes = 614) First 3 Years VE (95% CI)	4 or More Years VE (95% CI)	Community Ophthalmic Zoster (No. Outcomes = 5282) First 3 Years VE (95% CI)	4 or More Years VE (95% CI)	Postherpetic Neuralgia (No. Outcomes = 2033) First 3 Years VE (95% CI)	4 or More Years VE (95% CI)
Age								
65–69	36%** (33%, 39%)	22%** (18%, 26%)	68%** (41%, 83%)	47%* (1%, 72%)	35%** (24%, 44%)	24%** (10%, 36%)	61%** (49%, 70%)	50%** (34%, 62%)
70–74	35%** (33%, 37%)	21%** (17%, 24%)	70%** (57%, 79%)	51%** (26%, 67%)	29%** (22%, 36%)	18%** (7%, 28%)	55%** (46%, 62%)	42%** (29%, 53%)
75–79	32%** (30%, 34%)	17%** (13%, 21%)	73%** (61%, 81%)	56%** (32%, 71%)	33%** (25%, 40%)	22%** (10%, 32%)	61%** (54%, 68%)	50%** (38%, 60%)
80–84	31%** (28%, 34%)	16%** (11%, 20%)	74%** (61%, 82%)	57%** (31%, 73%)	32%** (22%, 40%)	21%** (7%, 32%)	55%** (45%, 63%)	42%** (26%, 54%)
85–89	32%** (27%, 36%)	17%** (11%, 22%)	75%** (60%, 85%)	59%** (29%, 77%)	30%** (16%, 42%)	19% (0%, 35%)	47%** (27%, 61%)	32%* (4%, 52%)
90+	37%** (29%, 43%)	23%** (13%, 31%)	88%** (67%, 95%)	79%** (44%, 93%)	32%* (3%, 52%)	21% (−14%, 45%)	58%** (22%, 78%)	46% (−2%, 72%)
Sex								
Male	35%** (32%, 37%)	21%** (17%, 24%)	74%** (63%, 81%)	55%** (32%, 70%)	40%** (33%, 46%)	30%** (21%, 39%)	56%** (47%, 63%)	44%** (31%, 54%)
Female	33%** (31%, 34%)	19%** (16%, 21%)	74%** (66%, 79%)	55%** (37%, 68%)	27%** (22%, 33%)	16%** (6%, 25%)	57%** (52%, 62%)	46%** (36%, 54%)
Race								
White	35%** (34%, 36%)	21%** (18%, 24%)	74%** (67%, 79%)	55%** (39%, 68%)	31%** (27%, 36%)	21%** (12%, 29%)	58%** (53%, 63%)	47%** (38%, 55%)
Black	32%** (21%, 42%)	18%* (4%, 30%)	90%* (21%, 99%)	83% (−36%, 98%)	44%* (2%, 68%)	35% (−14%, 63%)	73%* (25%, 90%)	65%* (5%, 87%)
Asian	12%** (6%, 18%)	−6% (−15%, 1%)	70%** (51%, 82%)	49%* (13%, 71%)	29%** (12%, 43%)	18% (−3%, 35%)	39%** (17%, 55%)	22% (−7%, 44%)
Other	18%** (9%, 25%)	0% (−11%, 10%)						

Abbreviations: CI, confidence interval; HR, hazard ratio; HZ, herpes zoster; VE, vaccine effectiveness.
[a]Significance: ** $P < .01$, * $P < .05$.
[b]Approximately 90% of hospitalized HZ cases were identified in hospital stays lasting ≥ 2 nights.
[c]VE Formula for All: 1—[(HR in Cohort) * (HR interaction of Cohort x Years of follow-up) * 100%. VE Formula for Subgroups: 1—[(HR in Cohort) * (HR interaction of Cohort x Years of follow-up) * (HR interaction of Cohort x Age/Gender/Race)] * 100% Demographic factors, socio-economic conditions, healthcare utilization characteristics, frailty characteristics, functional immunocompromising chronic conditions, and time-varying immunocompromising drugs were adjusted in the model.

Table 3c. Secondary Analysis: Adjusted Vaccine Effectiveness and 95% CI Comparing Herpes Zoster Vaccinated to Pneumococcal Vaccinated for Community Herpes Zoster, Hospitalized Herpes Zoster, Community Ophthalmic Zoster and Postherpetic Neuralgia Outcomes by Years of Follow-up[a]

	Community Herpes Zoster (No. Outcomes = 45 477)		Hospitalized Herpes Zoster[b] (No. Outcomes = 452)		Community Ophthalmic Zoster (No. Outcomes = 4311)		Postherpetic Neuralgia (No. Outcomes = 1519)	
	First 3 Years	4 or More Years	First 3 Years	4 or More Years	First 3 Years	4 or More Years	First 3 Years	4 or More Years
Subgroups[c]	VE (95% CI)	VE (95% CI)	VE (95% CI)	VE (95% CI)	VE (95% CI)	VE (95% CI)	VE (95% CI)	VE (95% CI)
All	37%** (36%, 39%)	22%** (20%, 25%)	67%** (58%, 74%)	34%* (8%, 53%)	39%** (35%, 43%)	19%** (10%, 28%)	63%** (57%, 67%)	47%** (36%, 55%)
Age								
65–69	40%** (37%, 43%)	25%** (21%, 29%)	69%** (38%, 85%)	41% (-22%, 71%)	43%** (32%, 52%)	24%** (9%, 36%)	63%** (49%, 74%)	47%** (26%, 62%)
70–74	38%** (36%, 40%)	23%** (19%, 26%)	51%** (26%, 68%)	5% (-52%, 40%)	39%** (31%, 46%)	18%** (6%, 29%)	67%** (59%, 73%)	52%** (40%, 62%)
75–79	37%** (35%, 39%)	21%** (17%, 25%)	67%** (49%, 78%)	35% (-5%, 60%)	40%** (33%, 47%)	20%** (7%, 31%)	62%** (53%, 70%)	46%** (30%, 58%)
80–84	36%** (33%, 39%)	20%** (16%, 24%)	76%** (63%, 85%)	54%** (24%, 72%)	39%** (29%, 47%)	18%* (3%, 31%)	57%** (46%, 66%)	38%** (19%, 53%)
85–89	36%** (32%, 41%)	20%** (14%, 26%)	66%** (43%, 80%)	34% (-20%, 63%)	35%** (20%, 48%)	14% (-9%, 32%)	61%** (46%, 73%)	44%* (19%, 62%)
90+	32%** (23%, 40%)	15%* (3%, 26%)	81%** (42%, 94%)	62% (-19%, 88%)	29% (-7%, 53%)	5% (-45%, 37%)	60%* (13%, 81%)	42% (-28%, 73%)
Gender								
Male	39%** (36%, 41%)	24%** (20%, 27%)	63%** (46%, 75%)	26% (-16%, 53%)	48%** (42%, 54%)	32%** (21%, 41%)	63%** (55%, 70%)	48%** (34%, 59%)
Female	37%** (35%, 38%)	22%** (19%, 24%)	69%** (59%, 76%)	37%* (10%, 56%)	34%** (29%, 40%)	13%* (3%, 23%)	62%** (56%, 68%)	46%** (35%, 55%)
Race								
White	39%** (37%, 40%)	24%** (21%, 26%)	69%** (60%, 76%)	38%** (12%, 56%)	39%** (34%, 43%)	19%** (10%, 28%)	63%** (58%, 68%)	47%** (37%, 56%)
Black	36%** (22%, 47%)	20%* (3%, 34%)	86% (-19%, 98%)	71% (-142%, 97%)	26% (-52%, 64%)	2% (-103%, 59%)	90%** (59%, 98%)	86%** (41%, 97%)
Asian	23%** (17%, 29%)	4% (-4%, 12%)	48%* (7%, 71%)	-3% (-92%, 45%)	44%** (29%, 56%)	26%* (4%, 43%)	49%** (25%, 66%)	28% (-8%, 52%)
Other	24%** (15%, 33%)	6% (-6%, 17%)						

Abbreviations: CI, confidence interval; HR, hazard ratio; HZ, herpes zoster; VE, vaccine effectiveness.
[a]Significance: ** $P < .01$, * $P < .05$.
[b]Approximately 90% of hospitalized HZ cases were identified in hospital stays lasting ≥ 2 nights.
[c]VE Formula for All: 1—[(HR in Cohort) * (HR interaction of Cohort x Years of follow-up) * 100%. VE Formula for Subgroups: 1—[(HR in Cohort) * (HR interaction of Cohort x Years of follow-up) * (HR interaction of Cohort x Age/Gender/Race)] * 100% Demographic factors, socio-economic conditions, healthcare utilization characteristics, frailty characteristics, functional immunocompromising chronic conditions, and time-varying immunocompromising drugs were adjusted in the model.

In the fully adjusted analysis, vaccination was associated with a reduced risk of HZ (Table 3a). Compared to unvaccinated beneficiaries, in the first 3 years of follow-up, the adjusted vaccine effectiveness (AVE) was 33% (95% CI 32%–35%) for community HZ; AVE declined slightly by age ($P = .029$), where it was highest in ages 65–69 (36% [95% CI 33%–39%]) and lowest in ages 80–84 (31% [95% CI 28%–34%]). For hospitalized HZ and PHN, the AVE for the first 3 years of follow-up was higher: 74% (95% CI: 67%–79%) and 57% (95% CI: 52%–61%), respectively. For all outcomes, there was no evidence of effect modification by gender. Key predictors of HZ by setting are displayed in eTable 2.

For community HZ, AVE declined significantly over time (Table 3a). VE was not only higher but also better retained over time for PHN and hospitalized HZ than for community HZ. Trends on the duration of protection for the vaccine are also summarized in Figure 2. The unadjusted hazard rate for unvaccinated beneficiaries was flat in outcomes over time, whereas the

vaccinated started off with a low HZ hazard that increased over time.

Secondary Analysis

In the secondary analyses, we matched 608 982 HZV recipients to 608 982 recipients of pneumococcal vaccine (Table 3c; Supplemental Material). The AVE in the first 3 years of follow-up for community HZ (37%, 95% CI 36%–39%) was 4% higher than for the primary analysis (Table 3c). Results for all other outcomes, including HZ hospitalizations and PHN, were similar to those in the primary analysis.

DISCUSSION

We used matched cohort data from approximately 2 million Medicare beneficiaries to investigate HZ vaccine effectiveness and duration of protection, using multiple analytical approaches to identify and address potential bias. This study assesses the
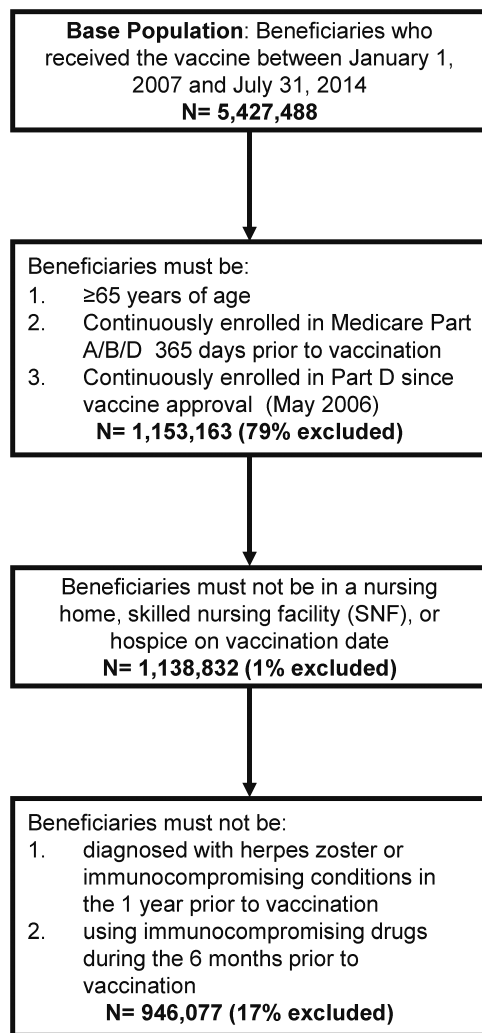
Base Population: Beneficiaries who received the vaccine between January 1, 2007 and July 31, 2014
N= 5,427,488

Beneficiaries must be:
1. ≥65 years of age
2. Continuously enrolled in Medicare Part A/B/D 365 days prior to vaccination
3. Continuously enrolled in Part D since vaccine approval (May 2006)
N= 1,153,163 (79% excluded)

Beneficiaries must not be in a nursing home, skilled nursing facility (SNF), or hospice on vaccination date
N= 1,138,832 (1% excluded)

Beneficiaries must not be:
1. diagnosed with herpes zoster or immunocompromising conditions in the 1 year prior to vaccination
2. using immunocompromising drugs during the 6 months prior to vaccination
N= 946,077 (17% excluded)

Figure 1. Vaccinated cohort flowchart.

effectiveness and durability of the live-attenuated HZV with sufficient power to examine less common outcomes such as PHN and HZ-associated hospitalizations, while controlling for a wide range of HZ risk factors and potential confounders [1, 9, 12, 26, 27]. Furthermore, our Medicare fee-for-service data are sourced from the general US population ages 65 years and older, capturing the entire range of routine clinical practice.

Among eligible study participants averaging 77 years of age, the primary and secondary analyses, respectively, found that HZV was 33% and 37% effective for the prevention of community HZ during the first 3 years postvaccination. For PHN and HZ-associated hospitalization, we found higher HZV effectiveness, 57% and 74%, respectively, for the first 3 years postvaccination in the primary analysis. The differences in these estimates, and their consistency in both the primary and secondary analyses, suggest real differences in VE for each of these endpoints. The higher VE for PHN (57%) than for community HZ (33%) suggests some incremental benefit of the vaccine in prevention of PHN beyond prevention of HZ per

se; this is also suggested by the higher proportion of HZ cases who had PHN, a complication of HZ, among unvaccinated relative to vaccinated cohorts (4.0% vs 2.9%, respectively).

These results were consistent for the primary and secondary analyses; nonetheless, the different estimates could also, in part, reflect the influence of differences in ascertainment, or other potential biases that could have differentially influenced detection of each endpoint in vaccinated versus unvaccinated beneficiaries.

Although the Shingles Prevention Study reported declines in VE with age, our study found only limited evidence of age-related declines in VE, which is a pattern previously reported [1, 11]. The difference with the SPS may relate to case finding: HZ severity increases with age [1]. HZ severity would be less likely to affect case finding in the SPS clinical trial with its active phone-based surveillance, but it would in medical sector-based studies such as ours. Although our results showed a small decline in VE for community HZ between age groups, there was no evidence of decline in other outcomes, which indicates that VE does not change substantially with increasing age. HZV also appears to protect Medicare beneficiaries despite their high burden of chronic illness. Overall, our VE results are consistent with those of other studies, although point estimates vary across studies due to differences in source population characteristics, case definitions and ascertainment, and other aspects of study methodology [11, 12]. In our study, as in other observational studies, the overall vaccine effectiveness estimates may be less accurate than relative VE estimates based on internally controlled comparisons (such as age-specific and time-specific changes in vaccine effectiveness).

In both the primary and secondary analyses, VE for community HZ declined significantly for years 4+ postvaccination to 19% and 22%, respectively, showing that HZV protection declines over time. Similar results have been published based on long-term follow-up of the original study cohort from the SPS, but the long-term follow-up study was uncontrolled and unblinded [12]. A recent prospective cohort study also showed waning of protection, though that study, conducted at a large health maintenance organization [27], had less analytic power and generalizability than our study. For PHN and HZ-associated hospitalization, protection was better preserved than for community HZ with AVEs of 45% and 55%, respectively, for years 4+ in the primary analysis. The differences found in duration of protection would need to be investigated further in other studies.

This study has several limitations. Because Medicare is an administrative database, outcomes and risk factors were not verified by medical record review. However, previous record validation studies have consistently shown relatively high positive predictive value for HZ as an outcome [11, 28–30]. Additionally, published population-based studies have indicated that over 90% of adults self-reporting HZ sought medical attention for the condition [31–34]. If measurement error were
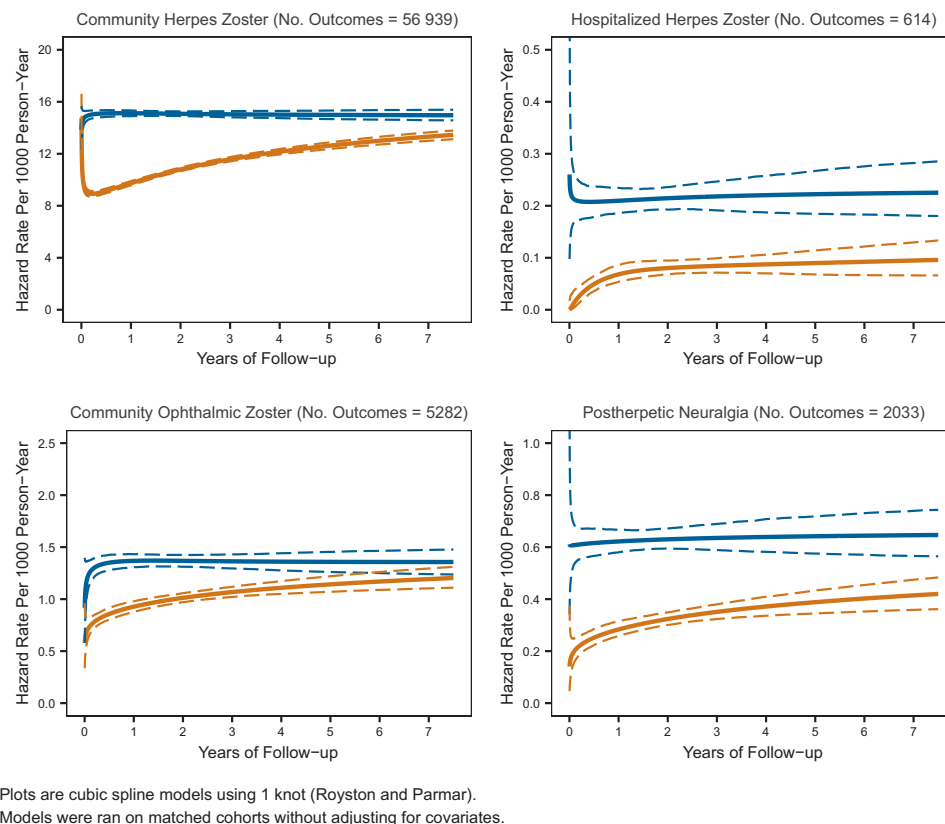
Plots are cubic spline models using 1 knot (Royston and Parmar).
Models were ran on matched cohorts without adjusting for covariates.

Figure 2. Primary analysis: fitted hazard rates and 95% confidence interval (CI) using a cubic spline model for vaccinated and unvaccinated cohorts.

a problem, we would expect VE for nonspecific outcomes like community HZ to be understated. However, when we analyzed OZ, which is a particularly distressing form of HZ that would almost certainly require medical attention, we found that HZV was similarly effective at preventing community OZ as it was for preventing community HZ. In general, analyzing more specific outcomes in observational studies may sometimes introduce biases by focusing on particular segments of the population. For example, HZ-attributable hospitalization is an imperfect surrogate for HZ disease severity, as even primary-HZ coded hospitalizations are not always attributable to HZ [15]. The rates of HZ-associated hospitalization may be influenced by other risk factors for hospitalization not directly due to HZ. In an effort to address this limitation we explored a more specific outcome with an analysis that restricted community HZ to cases receiving antiviral treatment, and found that estimated VE was only modestly increased (eTable 6).

We believe that this study is unlikely to have much error in measuring vaccination status. Our cohorts are restricted to beneficiaries enrolled in Medicare from the time HZV was licensed so that any HZV would very likely be recorded in Medicare claims. It is also unlikely that many Medicare beneficiaries would choose to pay for this vaccine out-of-pocket, so Medicare claims are likely to be nearly complete for this population. However, because we used a conservative continuous-enrollment criteria,

the average age of our cohorts was older than that for Medicare as a whole; thus, VE estimates in our study populations might have been lower than for the general Medicare population.

Vaccinees may differ from nonvaccinees with respect to both disease risk and healthcare- seeking behavior. Community HZ, in particular, can be missed among beneficiaries who tend to forgo medical care for nonserious conditions. To ensure comparability between cohorts, we matched by multiple potential confounders and conducted a vaccinee-vaccinee analysis as a secondary analysis. Falsification outcomes provide a novel supplementary approach for identifying bias. Our falsification outcomes clustered around the null (1.0), suggesting that there was no systemic bias influencing relative outcomes in vaccinees versus controls. Our aggregate use of this large number of falsification outcomes was intended to provide a more robust comparison group, under the expectation that it is unlikely that all these independently-selected conditions would share causal pathways with HZ. Nonetheless, examination of the results of the individual conditions and their variance can provide clues with which to detect and better understand residual differences between vaccine and control groups.

In the secondary analysis, VE for community HZ in the first 3 years postvaccination was only slightly higher than in the primary analysis (37% vs 33%) and was similar to the primary analysis for all other outcomes. This suggests that

any potential bias related to healthcare-seeking behavior is minimal. Indeed, although falsification outcomes did cluster more tightly around the null in the secondary analysis compared with the primary, the difference was slight. The 67% VE estimate for HZ-associated hospitalizations for the first 3 years postvaccination in the secondary analysis was only 7% lower than in the primary analysis, and differences in VE for HZ-associated hospitalizations were not statistically significant (Table 3b). Further research would be needed to confirm this.

In summary, we observed that the duration of protection against community HZ wanes over time, yet the vaccine protects against HZ regardless of age and chronic illness. We calculated that the number needed to vaccinate to avert an episode of community HZ during our study period was just 30.6 (eTable 8). Our findings provide additional evidence that the live HZV is effective at reducing the incidence of HZ and its complications when used in clinical practice among Medicare beneficiaries. Although effectiveness against community HZ was not high, the protection provided by this vaccine was higher and more durable for HZ-hospitalizations and PHN.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the author to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the author, so questions or comments should be addressed to the corresponding author.

Notes

Potential conflicts of interest: All authors: no reported conflicts. The authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Oxman MN, Levin MJ, Johnson GR, et al.; Shingles Prevention Study Group. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med **2005**; 352:2271–84.
2. Pinchinat S, Cebrián-Cuenca AM, Bricout H, Johnson RW. Similar herpes zoster incidence across Europe: results from a systematic literature review. BMC Infect Dis **2013**; 13:170.
3. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. BMJ Open **2014**; 4:e004833.
4. Tyring SK. Management of herpes zoster and postherpetic neuralgia. J Am Acad Dermatol **2007**; 57(6 Suppl):S136–42.
5. Kost RG, Straus SE. Postherpetic neuralgia–pathogenesis, treatment, and prevention. N Engl J Med **1996**; 335:32–42.
6. Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. Vaccine **2001**; 19(23–24):3076–90.
7. Yawn BP, Wollan P, St Sauver J. Comparing shingles incidence and complication rates from medical record review and administrative database estimates: how close are they? Am J Epidemiol **2011**; 174:1054–61.
8. Merck & Co., ZOSTAVAX (Zoster vaccine live): important information regarding storage and handling [package insert]. Available at: http://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi.pdf. Accessed October 1.
9. Marin M, Yawn BP, Hales CM, et al. Herpes zoster vaccine effectiveness and manifestations of herpes zoster and associated pain by vaccination status. Hum Vaccin Immunother **2015**; 11:1157–64.
10. Tseng HF, Lewin B, Hales CM, et al. Zoster vaccine and the risk of postherpetic neuralgia in patients who developed herpes zoster despite having received the zoster vaccine. J Infect Dis **2015**; 212:1222–31.
11. Tseng HF, Smith N, Harpaz R, Bialek SR, Sy LS, Jacobsen SJ. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. JAMA **2011**; 305:160–6.
12. Morrison VA, Johnson GR, Schmader KE, et al.; Shingles Prevention Study Group. Long-term persistence of zoster vaccine efficacy. Clin Infect Dis **2015**; 60:900–9.
13. Tseng HF, Tartof S, Harpaz R, et al. Vaccination against zoster remains effective in older adults who later undergo chemotherapy. Clin Infect Dis **2014**; 59:913–9.
14. Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. PLoS Med **2013**; 10:e1001420.
15. Jackson LA, Reynolds MA, Harpaz R. Hospitalizations to treat herpes zoster in older adults: causes and validated rates. Clin Infect Dis **2008**; 47:754–9.
16. Klompas M, Kulldorff M, Vilk Y, Bialek SR, Harpaz R. Herpes zoster and postherpetic neuralgia surveillance using structured electronic data. Mayo Clin Proc **2011**; 86:1146–53.
17. Leung J, Harpaz R, Molinari NA, Jumaan A, Zhou F. Herpes zoster incidence among insured persons in the United States, 1993–2006: evaluation of impact of varicella vaccination. Clin Infect Dis **2011**; 52: 332–40.
18. Zhang J, Xie F, Delzell E, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. JAMA **2012**; 308:43–9.
19. Rubin DB, Thomas N. Combining propensity score matching with additional adjustments for prognostic covariates. J Am Stat Assoc **2000**; 95:573–85.
20. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. Epidemiology **2010**; 21:383–8.
21. Prasad V, Jena AB. Prespecified falsification end points: can they validate true observational associations? JAMA **2013**; 309:241–2.
22. Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. Int J Epidemiol **2006**; 35:337–44.
23. Zaadstra BM, Chorus AM, van Buuren S, Kalsbeek H, van Noort JM. Selective association of multiple sclerosis with infectious mononucleosis. Mult Scler **2008**; 14:307–13.m
24. Bang H, Robins JM. Doubly robust estimation in missing data and causal inference models. Biometrics **2005**; 61:962–73.
25. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. Stat Med **2004**; 23:2937–60.
26. Schmader KE, Levin MJ, Gnann JW, Jr., et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50–59 years. Clin Infect Dis **2012**; 54:922–8.
27. Tseng HF, Harpaz R, Luo Y, et al. Declining effectiveness of herpes zoster vaccine in adults aged ≥60 years. J Infect Dis **2016**; 213:1872–5.
28. Mullooly JP, Riedlinger K, Chun C, Weinmann S, Houston H. Incidence of herpes zoster, 1997–2002. Epidemiol Infect **2005**; 133: 245–53.
29. Jumaan AO, Yu O, Jackson LA, Bohlke K, Galil K, Seward JF. Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992–2002. J Infect Dis **2005**; 191: 2002–7.
30. Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. Arch Intern Med **1995**; 155:1605–9.
31. Soni A, SC Hill. Average Annual Health Care Use and Expenses for Shingles among the U.S. Civilian Noninstitutionalized Population, 2003–2005 Washington, DC: Agency for Healthcare Research and Quality, **2007**.
32. Bowsher D. The lifetime occurrence of herpes zoster and prevalence of post-herpetic neuralgia: a retrospective survey in an elderly population. Eur J Pain **1999**; 3:335–42.
33. Lu PJ, Euler GL, Jumaan AO, Harpaz R. Herpes zoster vaccination among adults aged 60 years or older in the United States, 2007: uptake of the first new vaccine to target seniors. Vaccine **2009**; 27: 882–7.
34. Hales CM, Harpaz R, Bialek SR. Self-reported herpes zoster, pain, and health care seeking in the Health and Retirement Study: implications for interpretation of health care-based studies. Ann Epidemiol **2016**; 26:441–446.e3.

Supplemental Analyses on Primary Matched Population

eTable 1. Hospitalized Herpes Zoster (HZ) Incidence by Vaccination Status in the Primary Matched Population

Characteristic	No. Hospitalized HZ Cases	Total Person-years	No. Hospitalized HZ Cases	Total Person-years	Rate/1000 person-years (95% CI)		% Hospitalized HZ Cases that led to PHN[a]	
	Vaccinated		Unvaccinated		Vaccinated	Unvaccinated	Vaccinated	Unvaccinated
Overall	185	2,633,481	429	2,006,051	0.07 (0.06, 0.08)	0.21 (0.19, 0.23)	8.6%	9.3%
Year of follow-up								
1	40	818,909	155	749,423	0.05 (0.04 , 0.07)	0.21 (0.18 , 0.24)	15.0%	10.3%
2	45	619,895	113	506,696	0.07 (0.05 , 0.10)	0.22 (0.19 , 0.27)	8.9%	7.1%
3	26	431,114	72	310,139	0.06 (0.04 , 0.09)	0.23 (0.18 , 0.29)	3.8%	15.3%
4	32	322,604	36	207,350	0.10 (0.07 , 0.14)	0.17 (0.13 , 0.24)	6.3%	2.8%
5	21	240,367	25	139,447	0.09 (0.06 , 0.13)	0.18 (0.12 , 0.27)	4.8%	4.0%
6	13	140,466	18	69,056	0.09 (0.05 , 0.16)	0.26 (0.16 , 0.41)	15.4%	11.1%
7+	8	60,128	10	23,940	0.13 (0.07 , 0.27)	0.42 (0.22 , 0.78)	0.0%	10.0%
Age								
65-69	17	415,222	30	289,662	0.04 (0.03 , 0.07)	0.10 (0.07 , 0.15)	17.6%	10.0%
70-74	54	889,775	112	686,041	0.06 (0.05 , 0.08)	0.16 (0.14 , 0.20)	13.0%	6.3%
75-79	48	690,994	110	531,663	0.07 (0.05 , 0.09)	0.21 (0.17 , 0.25)	4.2%	13.6%
80-84	37	415,759	89	324,997	0.09 (0.06 , 0.12)	0.27 (0.22 , 0.34)	8.1%	9.0%
85-89	24	174,063	62	136,738	0.14 (0.09 , 0.21)	0.45 (0.35 , 0.58)	4.2%	9.7%
90+	5	47,668	26	36,949	0.10 (0.04 , 0.25)	0.70 (0.48 , 1.03)	0.0%	3.8%
Gender								
Male	54	880,919	123	664,982	0.06 (0.05 , 0.08)	0.18 (0.16 , 0.22)	9.3%	12.2%
Female	131	1,752,562	306	1,341,068	0.07 (0.06 , 0.09)	0.23 (0.20 , 0.26)	8.4%	8.2%
Race								
White	158	2,389,621	373	1,817,094	0.07 (0.06 , 0.08)	0.21 (0.19 , 0.23)	9.5%	9.7%
Black	1	40,347	8	37,863	0.02 (0.00 , 0.18)	0.21 (0.11 , 0.42)	0.0%	0.0%
Other[b]	26	203,513	48	151,093	0.13 (0.09 , 0.19)	0.32 (0.24 , 0.42)	3.8%	8.3%

[a] The proportion of beneficiaries that were coded for postherpetic neuralgia in the 90-180 days after an incident community herpes zoster event among beneficiaries that received a diagnosis for community herpes zoster.

[b] Asian, Hispanic, Native American, Other, and Unknown Race are included in the Race - Other category.

[c] As a note, approximately 90% of hospitalized HZ cases in both vaccinated and unvaccinated cohorts were identified in hospital stays lasting ≥ 2 nights.

eTable 2. Summary of Key Demographic Factors and Their Association with Herpes Zoster Outcomes in the Primary Matched Population

Characteristic	Community Herpes Zoster Adj. Hazard Ratio (95% CI)	Hospitalized Herpes Zoster Adj. Hazard Ratio (95% CI)	Community Ophthalmic Zoster Adj. Hazard Ratio (95% CI)	Postherpetic Neuralgia Adj. Hazard Ratio (95% CI)
Age				
65-69	Reference	Reference	Reference	Reference
70-74	1.07 (1.04, 1.10)	1.97 (1.41, 2.75)	1.07 (0.98, 1.17)	1.11 (0.95, 1.29)
75-79	1.11 (1.08, 1.14)	2.41 (1.72, 3.38)	1.20 (1.10, 1.32)	1.31 (1.12, 1.53)
80-84	1.14 (1.10, 1.17)	3.17 (2.23, 4.51)	1.25 (1.13, 1.39)	1.71 (1.45, 2.02)
85-89	1.17 (1.13, 1.22)	5.22 (3.59, 7.59)	1.39 (1.23, 1.58)	1.59 (1.30, 1.96)
90+	1.28 (1.20, 1.36)	7.05 (4.40, 11.31)	1.60 (1.32, 1.93)	1.63 (1.17, 2.28)
Gender				
Female	Reference	Reference	Reference	Reference
Male	0.81 (0.79, 0.82)	0.85 (0.71, 1.02)	0.92 (0.87, 0.98)	0.86 (0.78, 0.95)
Race				
White	Reference	Reference	Reference	Reference
Black	0.64 (0.59, 0.69)	0.62 (0.32, 1.21)	0.68 (0.51, 0.89)	0.63 (0.41, 0.98)
Other[a]	1.14 (1.10, 1.18)	1.25 (0.93, 1.67)	0.99 (0.87, 1.12)	1.15 (0.95, 1.38)
Chronic conditions				
Diabetes	0.95 (0.93, 0.97)	1.15 (0.97, 1.38)	0.96 (0.90, 1.02)	0.91 (0.82, 1.01)
Kidney Disease	1.03 (1.00, 1.07)	1.15 (0.88, 1.51)	1.10 (0.99, 1.22)	1.07 (0.91, 1.27)
Heart Disease	1.04 (1.02, 1.06)	1.13 (0.94, 1.35)	1.00 (0.93, 1.06)	1.02 (0.92, 1.14)
Lung Disease	1.11 (1.08, 1.13)	1.31 (1.08, 1.59)	1.08 (1.00, 1.16)	1.23 (1.10, 1.38)
Liver Disease	1.14 (1.07, 1.21)	1.54 (0.92, 2.59)	1.15 (0.92, 1.42)	0.72 (0.47, 1.11)

[a]Asian, Hispanic, Native American, Other, and Unknown Race are included in the Race - Other category

Supplemental Analyses on Secondary Matched Population

eTable 3. Community Herpes Zoster (HZ) Incidence Comparing Herpes Zoster Vaccinated (HZV) to Pneumococcal Vaccinated (PV) in the Secondary Matched Population (No. HZV= 608,982, No. PV= 608,982)

Characteristic	No. Community HZ Cases	Total Person-years	No. Community HZ Cases	Total Person-years	Rate/1000 person-years (95% CI)		% Community HZ Cases that led to PHN[a]	
	HZV		PV		HZV	PV	HZV	PV
Overall	19,509	1,799,787	25,968	1,671,445	10.8 (10.7, 11.0)	16.1 (15.9, 16.3)	2.8%	3.6%
Year of follow-up[c]								
1	4,880	525,212	8,664	564,981	9.3 (9.0 , 9.6)	15.3 (15.0 , 15.7)	2.5%	3.8%
2	4,348	411,496	6,347	406,366	10.6 (10.3 , 10.9)	15.6 (15.2 , 16.0)	2.8%	3.4%
3	3,357	302,005	4,304	277,257	11.1 (10.7 , 11.5)	15.5 (15.1 , 16.0)	3.2%	3.9%
4	2,754	232,214	3,043	194,462	11.9 (11.4 , 12.3)	15.6 (15.1 , 16.2)	2.9%	3.3%
5	2,197	175,724	2,099	131,956	12.5 (12.0 , 13.0)	15.9 (15.2 , 16.6)	3.0%	4.4%
6	1,369	106,169	1,092	69,308	12.9 (12.2 , 13.6)	15.8 (14.8 , 16.7)	2.5%	2.7%
7+	604	46,967	419	27,116	12.9 (11.9 , 13.9)	15.5 (14.0 , 17.0)	1.2%	1.2%
Age								
65-69	2,705	277,983	3,772	266,137	9.7 (9.4 , 10.1)	14.2 (13.7 , 14.6)	2.2%	2.6%
70-74	6,155	594,082	8,234	554,853	10.4 (10.1 , 10.6)	14.8 (14.5 , 15.2)	2.5%	3.6%
75-79	5,404	480,195	7,019	440,254	11.3 (11.0 , 11.6)	15.9 (15.6 , 16.3)	2.6%	3.4%
80-84	3,389	292,529	4,498	268,033	11.6 (11.2 , 12.0)	16.8 (16.3 , 17.3)	3.6%	4.3%
85-89	1,450	122,088	1,938	112,266	11.9 (11.3 , 12.5)	17.3 (16.5 , 18.0)	3.5%	4.6%
90+	406	32,904	507	29,902	12.3 (11.2 , 13.6)	17.0 (15.5 , 18.5)	2.5%	3.4%
Gender								
Male	5,506	596,089	7,479	552,387	9.2 (9.0 , 9.5)	13.5 (13.2 , 13.8)	3.0%	3.9%
Female	14,003	1,203,693	18,489	1,119,058	11.6 (11.4 , 11.8)	16.5 (16.3 , 16.8)	2.7%	3.5%
Race								
White	17,491	1,641,380	23,714	1,517,278	10.7 (10.5 , 10.8)	15.6 (15.4 , 15.8)	2.8%	3.6%
Black	168	24,936	269	27,461	6.7 (5.8 , 7.8)	9.8 (8.7 , 11.0)	1.2%	6.7%
Other[b]	1,850	133,466	1,985	126,706	13.9 (13.2 , 14.5)	15.7 (15.0 , 16.4)	2.6%	2.8%

[a] The proportion of beneficiaries that were coded for postherpetic neuralgia in the 90-180 days after an incident community herpes zoster event among beneficiaries that received a diagnosis for community herpes zoster.

[b]Asian, Hispanic, Native American, Other, and Unknown Race are included in the Race - Other category.

[c]Beneficiaries were categorized into one cohort at baseline; however, if a pneumococcal vaccinated (PV) beneficiary received the herpes zoster vaccine (HZV) after 30 days of administration, follow-up time was re-categorized into the HZV group. Thus, the HZV group was comprised of single and dual vaccinated beneficiaries, while the PV group was comprised of beneficiaries that were only vaccinated with PV.

eTable 4. Adjusted Vaccine Effectiveness and 95% CI by Years of Follow-up for Community Herpes Zoster Requiring a Prescription for Antivirals within 7-days as a Sensitivity Analysis

Population	No. Community HZ with Antivirals	First 3 Years VE (95% CI)	4 or more Years VE (95% CI)
Primary Analysis	40,876	40%** (39%, 42%)	21%** (18%, 24%)
Secondary Analysis	32,734	46%** (44%, 47%)	23%** (19%, 25%)

Significance: ** p<.01, * p<.05

VE Formula: 1 - [(HR in Cohort) * (HR interaction of Cohort x Years of follow-up) * 100%

Demographic factors, socio-economic conditions, healthcare utilization characteristics, frailty characteristics, functional immunocompromising chronic conditions, and time-varying immunocompromising drugs were adjusted in the model

Primary Analysis: This is a comparison between herpes zoster vaccinated and unvaccinated beneficiaries

Secondary Analysis: This is a comparison between herpes zoster vaccines and pneumococcal vaccines.

eTable 5. Primary Analysis: Adjusted Vaccine Effectiveness and 95% CI by Each Year of Follow-up by Outcome[a]

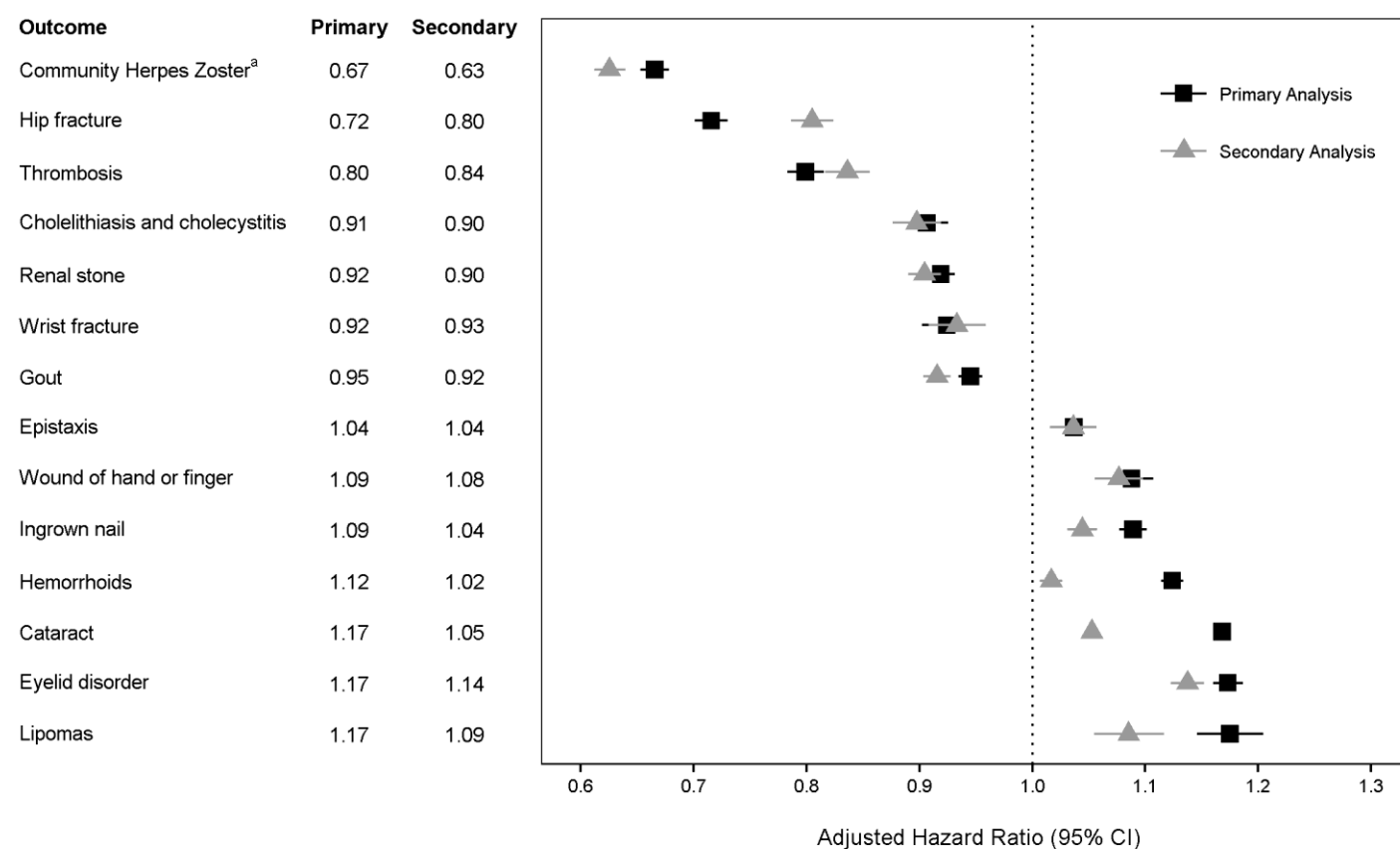| Year of Follow-up	Community Herpes Zoster (No. Outcomes = 56,939)	Hospitalized Herpes Zoster (No. Outcomes = 614)	Community Ophthalmic Zoster (No. Outcomes = 5,282)	Postherpetic Neuralgia (No. Outcomes = 2,033)
	VE (95% CI)	VE (95% CI)	VE (95% CI)	VE (95% CI)
1	38%** (37%, 40%)	77%** (68%, 84%)	38%** (32%, 44%)	70%** (63%, 76%)
2	32%** (29%, 34%)	68%** (55%, 78%)	28%** (20%, 36%)	49%** (39%, 57%)
3	25%** (22%, 28%)	75%** (60%, 84%)	22%** (11%, 32%)	50%** (39%, 59%)
4	21%** (17%, 25%)	45%* (11%, 66%)	19%** (6%, 31%)	44%** (28%, 56%)
5	17%** (12%, 22%)	52%* (15%, 73%)	21%* (4%, 34%)	40%** (21%, 54%)
6	17%** (10%, 23%)	66%** (30%, 83%)	19% (-3%, 37%)	52%** (31%, 66%)
7+	21%** (11%, 31%)	70%* (25%, 88%)	33% (-1%, 55%)	60%** (28%, 78%)

eTable 6. Secondary Analysis: Adjusted Vaccine Effectiveness and 95% CI by Each Year of Follow-up by Outcome[a]

Year of Follow-up	Community Herpes Zoster (No. Outcomes = 45,477)	Hospitalized Herpes Zoster (No. Outcomes = 452)	Community Ophthalmic Zoster (No. Outcomes = 4,311)	Postherpetic Neuralgia (No. Outcomes = 1,519)
	VE (95% CI)	VE (95% CI)	VE (95% CI)	VE (95% CI)
1	44%** (42%, 45%)	72%** (58%, 81%)	49%** (43%, 54%)	71%** (63%, 78%)
2	34%** (32%, 37%)	63%** (43%, 75%)	32%** (23%, 40%)	58%** (49%, 66%)
3	30%** (27%, 33%)	65%** (44%, 79%)	31%** (20%, 40%)	58%** (48%, 67%)
4	25%** (21%, 29%)	33% (-15%, 60%)	22%** (8%, 34%)	46%** (30%, 59%)
5	21%** (16%, 26%)	48%* (8%, 70%)	17% (-2%, 32%)	52%** (35%, 64%)
6	18%** (11%, 24%)	9% (-89%, 56%)	17% (-7%, 35%)	35% (0%, 58%)
7+	19%** (9%, 29%)	--	21% (-21%, 48%)	42% (-16%, 72%)

[a]Significance: ** p<.01, * p<.05

VE Formula: 1 - [(HR in Cohort) * (HR interaction of Cohort x Years of follow-up) * 100%

Demographic factors, socio-economic conditions, healthcare utilization characteristics, frailty characteristics, functional immunocompromising chronic conditions, and time-varying immunocompromising drugs were adjusted in the model

eTable 7. Primary and Secondary Analysis: Adjusted Vaccine Effectiveness and 95% CI by Each Year of Follow-up for Hospitalized Ophthalmic Zoster[a]

Year of Follow-up	Primary Analysis	Secondary Analysis
	Hospitalized Ophthalmic Zoster (No. Outcomes = 99)	Hospitalized Ophthalmic Zoster (No. Outcomes = 86)
	VE (95% CI)	VE (95% CI)
Primary Model		
First 3 Years	68%** (46%, 81%)	76%** (57%, 86%)
4 or More Years	64%** (25%, 82%)	9% (-117%, 62%)
Yearly Model		
1	69%** (22%, 88%)	82%** (52%, 93%)
2	70%* (15%, 89%)	86%** (51%, 96%)
3	65%** (23%, 85%)	44% (-47%, 79%)
4	80% (0%, 96%)	81% (-72%, 98%)
5	44% (-92%, 84%)	-15% (-381%, 73%)
6	55% (-81%, 89%)	-91% (-846%, 62%)
7+	76% (-44%, 96%)	--

[a]Significance: ** p<.01, * p<.05

VE Formula: 1 - [(HR in Cohort) * (HR interaction of Cohort x Years of follow-up) * 100%

Demographic factors, socio-economic conditions, healthcare utilization characteristics, frailty characteristics, functional immunocompromising chronic conditions, and time-varying immunocompromising drugs were adjusted in the model

eTable 8. Number Needed to Vaccinate (NNV) during the Study Period, by Outcome

Outcome	Rate Difference (per 1000 person year)	NNV to avert 1 case over the study period (7.5 years)
Community Herpes Zoster (No. Outcomes = 56,939)	4.35	30.6
Hospitalized Herpes Zoster (No. Outcomes = 614)	0.14	928.5
Community Ophthalmic Zoster (No. Outcomes = 5,282)	0.37	364.7
Postherpetic Neuralgia (No. Outcomes = 2,033)	0.31	423.5

eFigure 1. Fitted Hazard Rates and 95% CI Using a Cubic Spline Model for Herpes Zoster Vaccinated (HZV) and Pneumococcal Vaccinated (PV) Cohorts
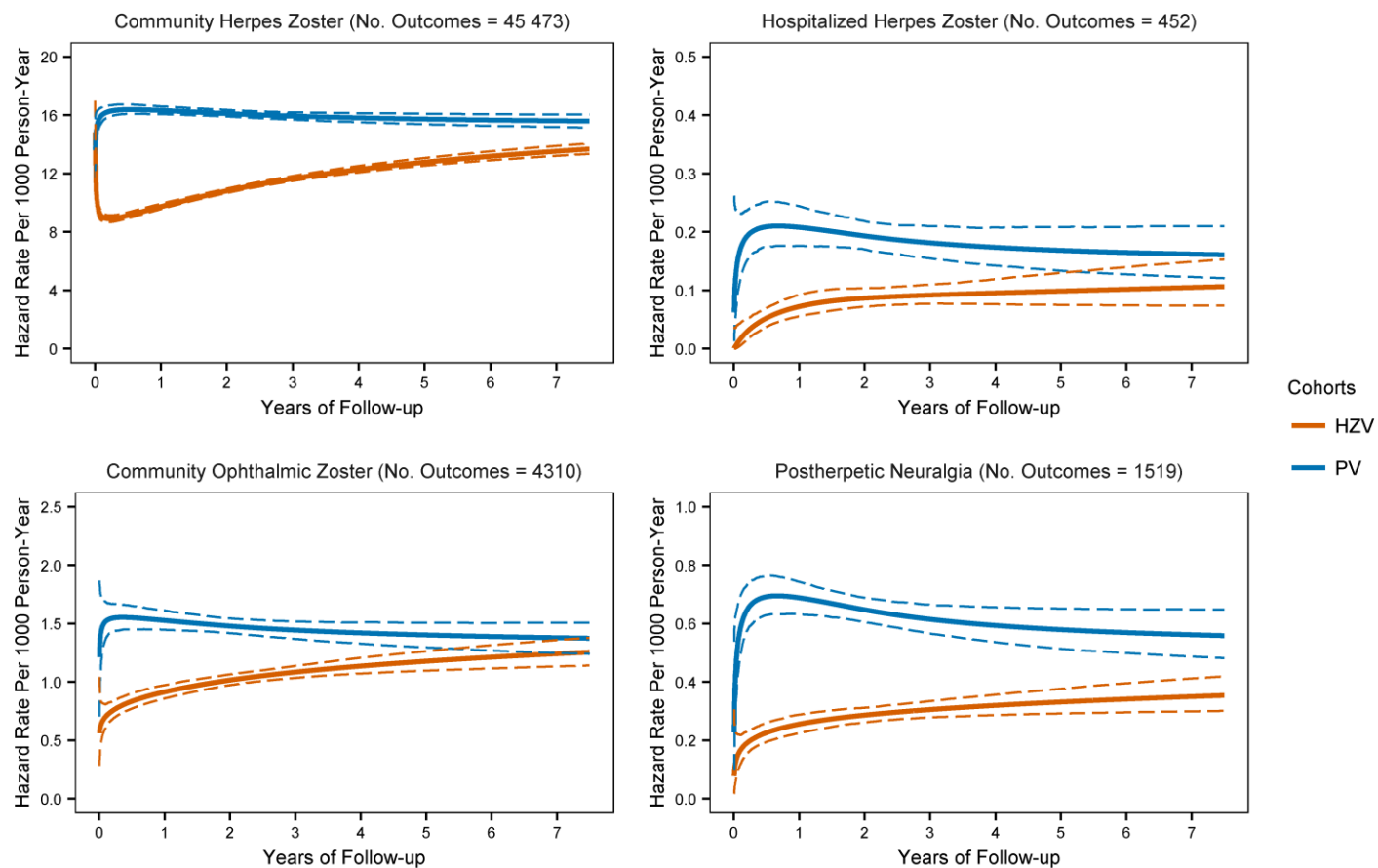
Plots are cubic spline models using 1 knot (Royston and Parmar).
Models were ran on matched cohorts without adjusting for covariates.

eFigure 2. Trend for Community Herpes Zoster in the Pre-Matched Unvaccinated Cohort (N=6,715,986)
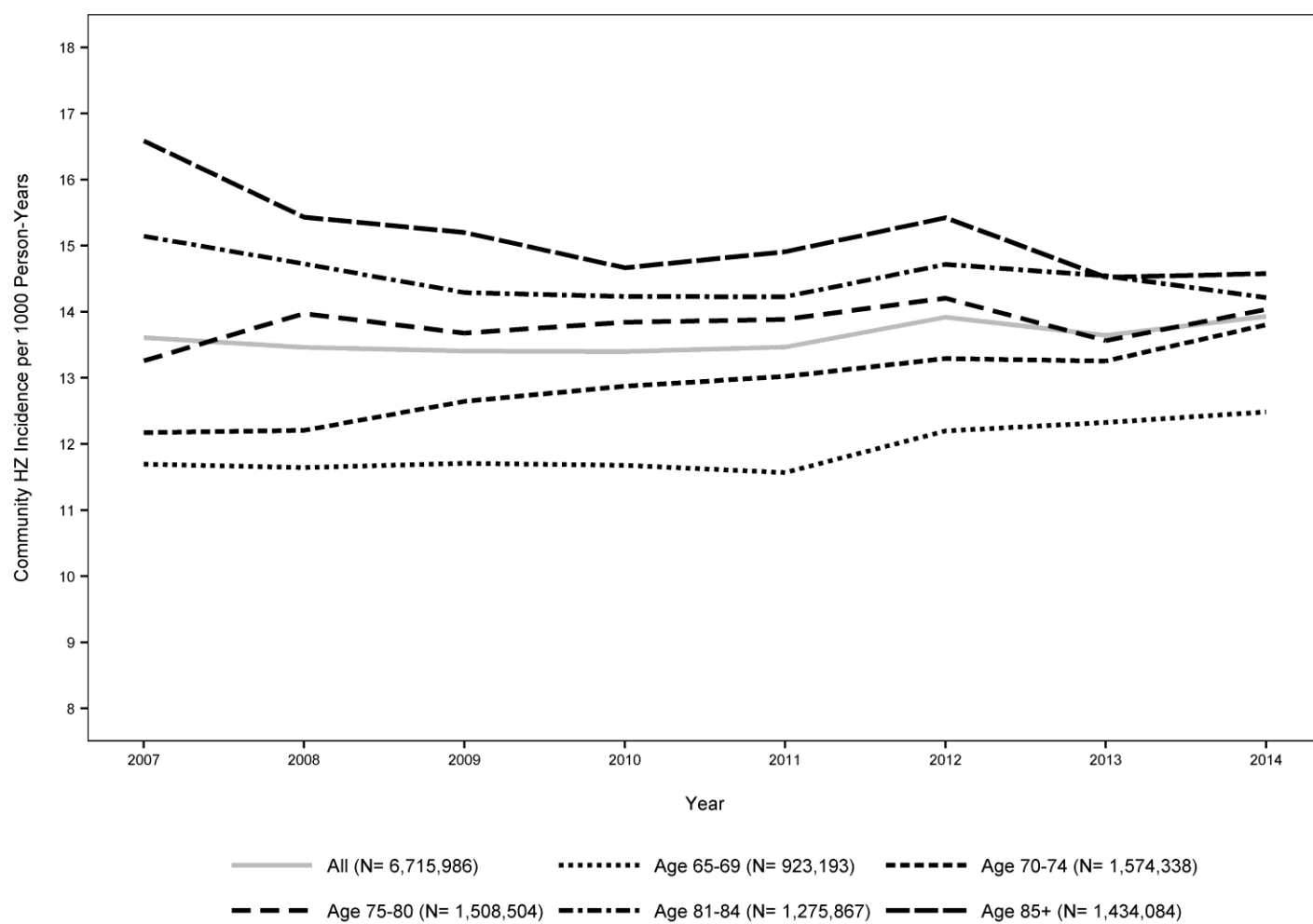
eFigure 3. Comparison of Adjusted Hazard Ratios of 13 Falsification Outcomes in the Matched Primary and Secondary Populations

Outcome	Primary	Secondary
Community Herpes Zoster[a]	0.67	0.63
Hip fracture	0.72	0.80
Thrombosis	0.80	0.84
Cholelithiasis and cholecystitis	0.91	0.90
Renal stone	0.92	0.90
Wrist fracture	0.92	0.93
Gout	0.95	0.92
Epistaxis	1.04	1.04
Wound of hand or finger	1.09	1.08
Ingrown nail	1.09	1.04
Hemorrhoids	1.12	1.02
Cataract	1.17	1.05
Eyelid disorder	1.17	1.14
Lipomas	1.17	1.09

Adjusted Hazard Ratio (95% CI)

Primary Analysis: This is the comparison between herpes zoster vaccinated and unvaccinated beneficiaries. Unvaccinated beneficiaries are the reference group.
Secondary Analysis: This is the comparison between herpes zoster vaccinees and pneumococcal vaccinees. Pneumococcal vaccinees are the reference group.
Similar to the primary and secondary analyses, the same set of demographic factors, socio-economic conditions, healthcare utilization characteristics, frailty characteristics, and functional immunocompromising chronic conditions were adjusted in each of the Falsification Outcome models.
Each Falsification Outcome model was run separately.
[a] The hazard ratio in the first 3 years of follow-up.

Appendices: Definitions of Medical Conditions and Prescription Drug Use in the Study

Appendix I. Frankly immunocompromising conditions used as an exclusion criterion

Frankly Immunocompromising Conditions	ICD-9 Diagnosis Codes
HIV Infection	042, 079.53, 795.71
Hodgkin's Disease	201
Non-Hodgkin's Lymphoma	200, 202.0, 202.1, 202.2, 202.3, 202.5, 202.6, 202.7, 202.8, 202.9
Leukemia	202.4, 203.1, 204, 205, 206, 207, 208
Multiple Myeloma	203.0
Neoplasm	203.8, 238.6, 238.72, 238.73, 238.74, 238.75, 238.76, 238.77, 238.79
Immune System Disorder	273.3, 277.89, 279.0, 279.2, 279.3, 279.4, 279.5, 279.8, 279.9
White Blood Cell Disease	279.10, 279.11, 279.12, 279.13, 279.19, 284.09, 284.89, 288.01, 288.02, 288.1, 288.2, 288.4, 288.50, 288.64, 288.8, 289.53
Other Hematological Disease	289.50, 289.59, 289.8, 289.9

Conditions were defined using all diagnosis positions in inpatient, outpatient, and non-institutional settings.

Appendix II. Immunocompromising drugs used in the study

IC Drug Categories	Drug Names
Antineoplastics	Altretamine, Bendamustine, Busulfan, Carboplatin, Cisplatin, Oxaliplatin, Thiotepa, Chlorambucil, Cyclophosphamide, Ifosfamide, Mechlorethamine, Melphalan, Carmustine, Lomustine, Streptozocin, Temozolomide, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitomycin, Mitoxantrone, Plicamycin, Pegaspargase, Azacitidine, Capecitabine, Cladribine, Clofarabine, Cytarabine, Decitabine, Floxuridine, Fludarabine, Fluorouracil, Gemcitabine, Nelarabine, Pemetrexed, Pralatrexate, Thioguanine, Alemtuzumab, Obinutuzumab, Ofatumumab, Rituximab, Brentuximab, Gemtuzumab, Ibritumomab, Tositumomab, Pomalidomide, Cabazitaxel, Docetaxel, Eribulin, Etoposide, Ixabepilone, Paclitaxel, Teniposide, Vincristine, Vinblastine, Vinorelbine, Romidepsin, Everolimus, Dasatinib, Erlotinib, Gefitinib, Ibrutinib, Imatinib, Lapatinib, Nilotinib, Ponatinib, Bortezomib, Irinotecan, Iodine, Radium, Samarium, Strontium, Sipuleucel-T, Dacarbazine, Denileukin, Hydroxyurea, Omacetaxine, Pentostatin, Procarbazine, Ifosfamide & Mesna
Mercaptopurines	Mercaptopurine
Methotrexates	Methotrexate
Immunomodulators	Anakinra, Adalimumab, Golimumab, Leflunomide, Etanercept, Abatacept, Rilonacept, Canakinumab, Tocilizumab, Tofacitinib, Penicillamine
Immunosuppressants	Certolizumab, Infliximab, Thalidomide, Lenalidomide, Cyclosporine, Lymphocyte, Anti-thymocyte, Mycophenolate, Everolimus, Sirolimus, Tacrolimus, Basiliximab, Daclizumab, Muromonab, Belatacept
Azathioprines	Azathioprine
Central Nervous System Agents	Teriflunomide, Natalizumab, Fingolimod
Corticosteroids	Betamethasone, Budesonide, Cortisone, Dexamethasone, Hydrocortisone, Methylprednisolone, Prednisolone, Prednisone

Note: This list of drugs was used in three ways: (1) as a baseline exclusion criterion, (2) censoring reason in the 2 months after cohort entry, and (3) a time-varying covariate during follow-up. For the latter, a beneficiary was considered immunocompromised during the time from prescription fill date up until the end of days' supply plus an additional 30 day grace period. If a subsequent prescription was filled within the 30 day grace period of the first prescription, use was aggregated together and the 30 day grace period was applied at the end of the 'episode'. Because immunocompromising drug use within 2 months of cohort entry was a censoring criterion, only use in the period afterwards was considered.

Appendix III. Anti-PHN drug categories used to define postherpetic neuralgia outcomes

Postherpetic Neuralgia Drug Categories	Drug Names
Analgesics/Opioids	Fentanyl, Methadone, Morphine, Oxycodone, Tramadol, Buprenorphine, Butorphanol, Codeine, Hydrocodone, Hydromorphone, Ketamine, Levorphanol, Meperidine, Oxymorphone, Propoxyphene, Tapentadol
Anticonvulsants	Gabapentin, Pregabalin

Appendix IV. Full list of covariates used in the propensity score matching model

Covariate	Condition	ICD-9 Diagnosis/Procedure and HCPCS Codes
Demographic factors	Age	--
	Gender	--
	Race	--
	Year of Cohort Entry	--
	Reason for Entrance into Medicare	--
Socio-economic conditions	Metropolitan Statistical Area (urban/rural status)	--
	Low Income Subsidy (LIS) Status	--
	Household Income by ZIP Code of Residence	--
Healthcare utilization characteristics	Hospital Visits	--
	ER Visits	--
	Physician Office Visits	--
	Flu Vaccine Indicator	HCPCS: 90470, 90655, 90656, 90657, 90658, 90659, 90660, 90661, 90662, 90663, 90724, G0008, G9141, G9142
	Pneumococcal Vaccine Indicator	HCPCS: 90669, 90732, G0009
Frailty characteristics	Dementia	ICD-9: 094.1, 290.0, 290.1, 290.10, 290.11, 290.12, 290.13, 290.2, 290.20, 290.21, 290.3, 290.4, 290.40, 290.41, 290.42, 290.43, 291.1, 291.2, 292.82, 294, 294.0, 294.1, 294.10, 294.11, 331.0, 331.1, 331.11, 331.19, 331.82
	Home Oxygen	ICD-9: V46.2, 93.96; HCPCS: 99503, 99504, E0424, E0425, E0430, E0431, E0433, E0434, E0435, E0439, E0440, E0441, E0442, E0443, E0444, E0445, E0550, E0560, E1390, E1391, E1392, E1405, E1406, K0671
	Urinary Catheter	ICD-9: 996.64, V53.6, 57.94, 57.95, 96.48, 97.64; HCPCS: 51702, 51703, A4311, A4312, A4313, A4314, A4315, A4316, A4338, A4340, A4344, A4346, A4355
	Walker Use	HCPCS: E0130, E0135, E0140, E0141, E0143, E0144, E0147, E0148, E0149, E0154, E0155, E0156, E0157, E0158, E0159, L1520
	Wheelchair Use	ICD-9: E88.43, V46.3, V53.8; HCPCS: 97542, E0192, E0950, E0951, E0952, E0953, E0954, E0955, E0956, E0957, E0958, E0959, E0960, E0961, E0962, E0963, E0964, E0965, E0966, E0967, E0968, E0969, E0971, E0972, E0973, E0974, E0977, E0978, E0981, E0982, E0983, E0984, E0985, E0986, E0990, E0992, E0995, E1002, E1003, E1004, E1005, E1006, E1007, E1008, E1009, E1010, E1011, E1012, E1013, E1014, E1015, E1016, E1017, E1018, E1019, E1020, E1021, E1025, E1026, E1027, E1028, E1029, E1030, E1050, E1060, E1070, E1083, E1084, E1085, E1086, E1087, E1088, E1089, E1090, E1093, E1100, E1130, E1140, E1150, E1160, E1161, E1170, E1171, E1172, E1180, E1190, E1195, E1200, E1210, E1211, E1212, E1213, E1220, E1221, E1222, E1223, E1224, E1225, E1226, E1227, E1228
Functional immunocompromising chronic conditions	Diabetes	ICD-9: 250; HCPCS: G0108, G0109, G0245, G0246, G0247, G8015, G8016, G8017, G8018, G8019, G8020, G8021, G8022, G8023, G8024, G8025, G8026, G8332, G8333, G8334, G8335, G8336, G8385, G8386, G8390
	Kidney Disease	ICD-9: 585, 586, 587
	Heart Disease	ICD-9: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 414, 428, 37.66; HCPCS: 0050T, 33973, 33974, 33975, 33977, 33978, 33980, 92970, 92971, G8027, G8028, G8029, G8030, G8031, G8032, G8184
	Lung Disease	ICD-9: 491, 492, 493, 494, 495, 496, 500, 501, 502, 503, 504, 505, 506, 507, 508.1, 508.8, 508.9, 514, 515, 518.0, 518.1, 518.2, 518.3, 518.83; HCPCS: 32141, 32491, G8093, G8094
	Liver Disease	ICD-9: 571

Conditions were defined using all diagnosis positions in inpatient, outpatient, durable medical equipment, and non-institutional settings.

Appendix V. Falsification Outcomes List

Falsification Outcomes	ICD-9 Diagnosis Codes
Lipomas	214.1, 214.8, 214.9
Gout	274.0, 274.9
Eyelid Disorders	373.00, 373.2, 373.11
Thrombosis	451.9, 453.8, 453.9
Hemorrhoids	455.0, 455.2, 455.3, 455.6
Renal Stones	592.0, 592.9, 788.0
Ingrown Nail	703.0
Epistaxis	784.7
Wound of Hand or Finger	882.0, 883.0, 883.1, 883.2
Cataracts	366.10, 366.14, 366.16, 366.17, 366.19
Cholelithiasis and Cholecystitis	574.00, 574.10, 575.10
Wrist Fracture	813.05, 813.23, 813.41, 813.42, 813.44, 813.81
Hip Fracture	820.00, 820.01, 820.02, 820.03, 820.8, 820.9, 820.09, 820.10, 820.11, 820.12, 820.13, 820.19

Conditions were defined using all diagnosis positions in inpatient, outpatient, and non-institutional settings.

DISCUSSION

Overview

The vaccine effectiveness studies in Medicare discussed in this thesis were all published in leading international medical journals: Lancet Infectious Diseases, Journal of Infectious Diseases and Clinical Infectious Diseases.[14-18] Moreover, four of them were accompanied by very positive journal editorials, and the fifth was consider an "Editor's Choice" upon publication.[150-153]

These studies were successful in a number of ways: (a) in selecting cohorts with a low probability of including frail individuals (pharmacy-vaccinated cohorts), which, while sacrificing generalizability, decreases the risk of imbalances that could seriously undermine cohort comparability; (b) in defining claims algorithms, including, for outpatient claims, disease treatment, which permitted sufficient outcome specificity for studying effectiveness; (c) in defining high disease circulation periods, thus allowing us to further increase outcome specificity for seasonal diseases such as influenza; (d) in obtaining effectiveness estimates for severe outcomes that were very comparable to those obtained during clinical trials, and in obtaining estimates for very rare outcomes, including death; (e) in determining effect modification from a drug used concomitantly or prior to administration of a vaccine, (f) in obtaining valid estimates when comparing vaccinated vs unvaccinated individuals, particularly for severe outcomes; and (g), in estimating comparable effectiveness and duration of effectiveness for all study outcomes. These successful experiences, besides providing us with information potentially useful for regulatory decision-making, have already allowed us to provide more pointed feedback during the planning phase of studies that could make part of

post-licensure commitments and requirements. In our initial studies we were less successful in other ways, including: (a) assuring study generalizability (we often used restriction to increase the validity of results, thus sacrificing both generalizability and sample size), (b) in verifying that we have in fact obtained highly reliable estimates for less severe outcomes, more susceptible to health seeking behavior bias. Nonetheless, our successful use of larger cohorts (not restricted to pharmacy vaccinees) in our more recent comparison of the effectiveness of cell-cultured vs. egg-based vaccines shows that studies performed using CMS claims do not need to sacrifice generalizability. Moreover, our recently initiated exploration of the use of Medicare surveys to both validate cohort balance and augment the study datasets with covariates unavailable in the claims will improve our work in a number of ways. It is because of this need to resolve potential limitations detected in our initial research that we decided to further our methods development work, particularly by using data external to the Medicare claims environment that, once linked to individuals found in the claims environment, will allow us to obtain further information on health, education and behaviors that could influence the likelihood of becoming ill (frailty) or seeking care (health care seeking behavior). These efforts, that have already produced initial success, will allow us to both verify the potential for bias and, by using imputations, correct existing bias.

The achievements so far do not suffice, however, to fully address all potential issues involved in the use of real world evidence for regulatory and public health decision-making. Thus, we are continuing our comparative effectiveness studies of cell-cultured vs. egg-based vaccines, initiated the investigation of other effect modifications, including by age and sex, in the comparative effectiveness of vaccines, have initiated other vaccine-drug interaction studies,

and are progressing even further in the development of methods to better account for both measured and unmeasured confounders in the CMS data. All these developments should open a new area of vaccine effectiveness research and, thus, allow us to open discussions regarding the systematic analysis of effectiveness interaction by drugs with immune modifying effects.

Proof-of-concept study: Comparative effectiveness of High dose (HD) vs. Standard dose (SD) influenza vaccines against medical office visits and hospitalizations among Medicare beneficiaries ages 65 years and older during the 2012-13 season

The study in context

This proof-of-concept study, which led the way for the studies included in the Results section, was the first one to provide real-world evidence comparing the effectiveness of the High dose vs Standard dose influenza vaccines. At the time of our publication, there was only one study relevant for comparison with ours, the manufacturer's double blind, randomized, active-controlled comparative effectiveness trial that included over 31,000 participants. That study reported that the high-dose vaccine was 24% (95% CI 19-37%) more effective in preventing RT-PCR-confirmed influenza infections in adults 65 years of age and older than the standard-dose vaccine.[50] Ours found that the high-dose vaccine was about 22% more effective than the standard-dose vaccine to prevent influenza illness treated in both outpatient and inpatient settings.

Our frequency matching by pharmacy resulted in a strong balance in observable potential confounders among the two groups. We had over 2.5 million study participants after applying cohort restrictions, allowing us to perform analyses by age on influenza hospitalizations, of particular interest to beneficiaries, providers, regulators and public health officials. Therefore, our finding of a significantly high comparative effectiveness for influenza- associated illnesses, confirmed for all age groups analyzed, adds important new information. Moreover, our successful use of novel methodologies both for matching and for defining outcomes, in a system that provides coverage for virtually all older U.S. adults, opens the door for conducting studies to estimate effectiveness against serious outcomes among specific risk groups in near real time, for pandemic and other new vaccines.

As indicated, we used not only medical office visits outcomes but also hospitalizations during the 2012-13 influenza season. In both setting sour results were comparable. Regarding medical office visits, we found that the high-dose influenza vaccine was 22% more effective in preventing influenza-associated illness treated in the community setting than standard-dose vaccine among U.S. Medicare beneficiaries 65 years of age and older vaccinated in pharmacies. We found a similar effect for influenza-associated hospitalizations and emergency department visits in this cohort. The relative efficacy estimates reported in a two-season randomized-controlled study of high- versus standard-dose Fluzone conducted by the manufacturer among >30,000 older adults showed that the high-dose vaccine was 24% (95% CI 19%-37%) more effective in preventing reverse transcription polymerase chain reaction (RT-PCR)-confirmed influenza infections in adults 65 years of age and older than standard-dose vaccine.[50] Interestingly, among Medicare beneficiaries 85 years of age or older enrolled in our study, we

found high-dose relative effectiveness for prevention of influenza-related outpatient illness was higher than in younger age groups, but this difference was not statistically significant. Given that the randomized trial did not have sufficient power to analyze effect modification by vaccinees ages 85 years or older, we decided to further investigate this hypothesis in a follow- up study (see Next Steps chapter).

Study findings

During the 2012-13 influenza season, we found that the high-dose influenza vaccine was 22% more effective in preventing influenza-associated illness treated in the community setting than standard-dose vaccine in a subset of U.S. Medicare beneficiaries 65 years of age and older. A similar effect was found for influenza-associated hospitalizations and emergency department visits in this cohort. Our results are comparable to the relative efficacy estimates reported in a recently completed two-season randomized-controlled study of high- versus standard-dose Fluzone conducted by the manufacturer among >30,000 older adults. In that study, the high- dose vaccine was 24% (95% CI 19%-37%) more effective in preventing reverse transcription polymerase chain reaction (RT-PCR)-confirmed influenza infections in adults 65 years of age and older than standard-dose vaccine. Among Medicare beneficiaries 85 years of age or older enrolled in our study, we found high-dose relative effectiveness for prevention of influenza- related outpatient illness was higher than in younger age groups, but this difference was not statistically significant.

A strength of our study is its population base includes patients identified through Medicare claims data, or about 98% of the U.S. population 65 years of age or older. Medicare provides inpatient and outpatient fee-for-service care for 37 million beneficiaries and

prescription coverage for 23 million of these beneficiaries as of January 2014. Given the completeness of these data, we believe that Centers for Medicare and Medicaid Services (CMS) data sources have great potential for use in observational studies among the elderly. Another strength of this study is the unusual comparability of subjects in the high-dose and standard- dose vaccine groups, which highlights the potential usefulness of studying Medicare subjects who are vaccinated in a pharmacy setting.

One potential limitation of the use of Medicare data is that the reliability of the ICD-9- CM codes used for the diagnosis of influenza in the community setting is unknown. Therefore, we developed an alternative definition for an influenza-related event that required an influenza test followed by the prescription of oseltamivir (an antiviral used exclusively for influenza). It is possible that our results are not generalizable to the whole U.S elderly population because we restricted the analysis to a subset of patients who received influenza vaccination in an outpatient pharmacy setting. Another potential limitation in the use of our definition is that providers may find specific influenza test results most helpful at the beginning and end of influenza seasons and rely on symptoms and history to identify persons with influenza infections during the peak of each season. Thus, we may have missed subjects with influenza, although we do not believe that the likelihood of influenza testing varied by vaccination status. Of course, influenza-related hospitalizations may also be associated with secondary bacterial infections, and respiratory syncytial virus (RSV), other respiratory viruses, and non-viral pathogens cause lower respiratory tract infections that are difficult to distinguish clinically from influenza infections. However, the near-perfect correlation (0.97) between influenza hospitalization claims and community claims for a RIT followed by the dispensing of oseltamivir suggests that our hospitalization outcome during periods of high influenza circulation was highly specific for

influenza-related events.

Another limitation of this study is that we did not have access to laboratory results and therefore could not use laboratory-confirmed outcomes. Instead, we created a novel outcome that combines a physician's order for a RIT followed by the prescription of an influenza-specific antiviral drug within a 2-day period following the medical encounter. Because RITs can provide a health care provider with a result within 15 minutes after sample collection, we expect that this information guided the decision to prescribe influenza-specific antivirals. Therefore, the combination of the RIT and antivirals likely provides greater specificity than a physician diagnosis of influenza or a prescription of antivirals alone.

Of concern in all observational vaccine studies is vaccination was not randomly assigned and unmeasured confounders may bias our estimates of the relative effectiveness of high-dose vaccine. However, restricting the analysis to individuals who were vaccinated at a pharmacy which offered both vaccines within a 2-week period appears to have yielded well-balanced vaccine cohorts, at least by comparing characteristics available and commonly used in pharmacoepidemiology studies, nonetheless there may be residual unmeasured confounders. This balance also may be influenced by the fact that Medicare beneficiaries do not pay for receipt of any influenza vaccine at a pharmacy. Our approach shows a strong balance in observable potential confounders (e.g., the 189 medical condition categories considered).

Nonetheless, the large number of participants in this study meant that small differences between the vaccine groups might be statistically but not meaningfully different. Because frequency matching by pharmacy yielded well-balanced cohorts, we did not attempt to further balance the cohorts with propensity-score techniques. Although the cohort restrictions applied decreased the study sample size, we still had large numbers of vaccinees in both cohorts

(approximately 930,000 high-dose and 1.6 million standard-dose recipients), and were able to perform analyses by age group and also for a serious outcome, influenza hospitalizations.

We plan to conduct similar analyses for each upcoming influenza season and to perform medical record review to validate the outcomes for a subset of participants. Our ability to detect and statistically confirm differences in effectiveness would be expected to vary with the severity of each influenza season, and with the match between the vaccine and circulating strains. Relative effectiveness also may vary by virus type and subtype, including for pandemic viruses. However, because Medicare provides coverage for virtually all older U.S. adults, we can estimate vaccine effectiveness for serious rare outcomes among specific risk groups. Such assessments typically are not possible in randomized studies of comparative treatment or prevention modalities, even when tens of thousands of participants are randomized. In the future, we expect to perform these studies using prospective active surveillance to provide results in near-real time, as done for other FDA-CMS studies, and to investigate the effectiveness of other vaccines used among the U.S. Medicare recipients.

Comparative effectiveness of High-dose versus Standard-dose influenza vaccines among US Medicare beneficiaries in preventing post-influenza deaths: a retrospective cohort study, 2012-13 and 2013-14

This was the first study ever to compare the effectiveness of High dose vs. Standard dose influenza vaccination against influenza-associated mortality[18]. It was conceived as a

follow-up to our proof-of-concept study on effectiveness against medical office visits and hospitalizations.[16] We found a significant ~35% reduction in post-influenza deaths associated with receipt of high-dose versus standard-dose vaccines in 2012-13, but not in 2013-14. The 2012-13 reduction was accompanied by significant decreases of ~20% in influenza-related visits and hospital-based influenza diagnoses. The latter two findings are consistent with the results from our previous study (which used slightly different eligibility criteria and only 2012-13 data),[16] and those from analyses of a manufacturer-sponsored trial.[48,51]. The internal and external consistency of our findings suggests that the use of high-dose vaccine in Medicare beneficiaries during 2012-13 prevented additional influenza-related deaths. Despite 31 million person-weeks of follow-up time during 2012-13, the magnitude of this reduction in mortality was not precisely estimated (95% CI 9%-56%). As the outcomes of greatest interest when considering alternative vaccination strategies are often rare (e.g., influenza-related mortality or serious vaccine adverse events), large post-licensure observational studies are vital in understanding the comparative effects of new vaccine formulations – randomized trials are unable to answer all relevant policy questions. Multiple seasons of observational data analyzed with appropriate longitudinal methods will be critical to providing valid information to those considering alternative influenza vaccine recommendations.

Person aged 65 years and older experience the highest rates of many serious complications of influenza -- including prolonged hospitalization, the need for intensive care, and death – during most inter-pandemic influenza seasons. [2-4,154] During seasonal epidemics in which influenza A(H3N2) viruses predominate, rates of serious complications are higher, often by a factor of 2 to 3.[4,155] Influenza A(H3N2) virus circulation was common during the 2012-13 influenza season,[156] leading to higher rates of influenza-associated outcomes; thus, we had

improved power during the first season to detect a difference in our rarest outcome, post-influenza mortality. During the 2013-14 influenza season, receipt of high-dose vaccine was associated with a significant reduction only in the rate of hospitalized influenza. This reduction was smaller in magnitude than that found in the 2012-13 season. There are several plausible reasons that the comparative effectiveness of high-dose vaccine was reduced during 2013-14, including differences in the individuals who received high-dose vaccine by season, differences in the circulation patterns of specific influenza viruses by season, and differences in the antigenic relatedness of vaccine and wild-type viruses by season.

Although more high-dose vaccine was used in 2013-14, both in terms of total vaccinations administered and in the proportion of participants who received it, we found no evidence that the characteristics of high-dose recipients differed by season. On the other hand, A(H3N2) viruses predominated in 2012-13,[156] and 90% of influenza A detections in 2013-14 were A(H1N1pdm09) viruses.[157] Data from the randomized trial suggested that relative efficacy of high-dose vaccine might be greater for A(H3N2) than for A(H1N1) viruses, but this difference was not statistically significant (23.3%, 95% CI 6.0-37.5% and 11.1%, 95% CI -160 to 70.2%, respectively).[48] Therefore, it is uncertain if our findings might reflect a difference in comparative effectiveness by A subtype. Influenza B viruses circulated in both seasons, representing 20-30% of influenza detections,[156,157] so differences in B virus activity are unlikely to explain our findings. There was no evidence of antigenic drift in A(H1N1pdm09) viruses during the two study seasons: 99% of A(H1N1pdm09) viruses characterized were antigenically similar to A/CA/7/2009-like viruses.[156,157] The great majority of A(H3N2) viruses characterized in 2012-13 were antigenically similar to cell culture-propagated A/Victoria/361/2011viruses.[158] A change in the A(H3N2) vaccine strain from A/Victoria/361 in 2012-13 to A/Texas/50 in 2013-14 was recommended

because ferret antisera made with egg-propagated A/Victoria/361 did not recognize more recent cell culture-propagated A(H3N2) viruses well. Ferret antisera made with egg-propagated A/Texas/50/2012 (which was genetically closed related to A/Victoria/361) better recognized the viruses that were tested.[158] Low effectiveness of the 2012-13 vaccine against RT-PCR-confirmed A(H3N2) virus infections was noted.[159] It was based not on mutations associated with antigenic drift, but mainly on those associated with adaptation to growth in eggs.[159] Without samples of post-vaccination sera and of the infecting influenza viruses from participants, we cannot conclude that 2012-13 high-dose vaccine led to a broader or improved immune response than did standard-dose vaccine, although we can expect that its administration did lead to higher HAI titers to that season's wild-type H3N2 viruses on a population level, based on published immunogenicity data.[48,50,66]

During 2012-13, estimates of influenza VE were 39% (95% CI 29%-47%) for medically attended A(H3N2) infections among US subjects of all ages; they were lower and non-significant among those aged ≥65 years (11%; 95% CI, -41% to 43%).[160] Given the greater relative severity of A(H3N2) seasons in older adults, this low effectiveness estimate (which should be interpreted in light of its broad CI) highlights the need to improve VE for recent A(H3N2) strains, especially among those aged ≥65. We lacked data on infecting viruses, and cannot make subtype-specific VE estimates. However, how comparative VE varies during seasons dominated by different influenza types/subtypes deserves further investigation as new vaccines are introduced.

This study had limitations. The lack of laboratory results in Medicare data means that none of our outcomes represented laboratory-confirmed influenza infections. As our comparative effectiveness results for influenza-related visits (defined by a claim for a rapid influenza test

followed by receipt of oseltamivir) were concordant with those from a randomized trial that used laboratory-confirmed influenza illness as a primary outcome [48] we may have identified a valid proxy for a medically attended influenza infection in the Medicare population. Our two more serious outcomes were defined only by influenza diagnoses made in a hospital setting. Some data suggest that use of influenza diagnostic tests by clinicians has increased since the 2009 pandemic; thus, the diagnosis of serious influenza infections may have improved recently,[161,162] but the limitation remains. As in all observational research, it is possible that our data were biased with residual confounding. In vaccine studies focusing on older adults, residual confounding associated with chronic conditions which are not well characterized by a simple dichotomous indicator -- for example, a clinical history of chronic heart failure -- can be especially problematic.[163,164] The consistency of our findings with those of the randomized trial of high-dose vaccine suggests that we have successfully addressed this issue through restriction of the study population to those vaccinated in community pharmacies. It is possible that knowledge by a care provider of the influenza vaccine type a participant received affected decisions to test for or to diagnose influenza. However, the lack of published clinical results for high-dose vaccine during the study period and the lack of recommendations to favor high-dose over standard-dose influenza vaccines make such a bias unlikely. A final limitation is that restricting participation to those Medicare beneficiaries vaccinated in pharmacies limits the generalizability of our findings. On the other hand, it is essential that comparative effectiveness studies address the possibility of confounding by indication, and the use of restriction to minimize this bias in large observational studies has been advocated.[165,166] Another concern is residual confounding because of differences in cohort balance with regard to both measured and unmeasured demographic, health utilization, chronic conditions and other confounders. The issue of confounders unmeasured in the database

such as level of education will be discussed in the chapter on next steps. Regarding potential confounders measured in the database, Tables *xi* and *xii* show that, both among study participants in the influenza-related visit outcome analysis, and among those included in the post-influenza mortality and influenza hospitalization outcomes, the balance of the cohorts of High dose and standard dose recipients for each of the two seasons evaluated in the study was excellent, which reassures us with respect to this concern.

Table *xi*: Characteristics of study participants for influenza-related visit outcome, by influenza vaccine type and season

Demographic Variables	2012-2013 Season			2013-2014 Season		
	Standard Dose	High Dose	Std. Mean Difference	Standard Dose	High Dose	Std. Mean Difference
Base Population	950,318	580,648		1,270,144	1,003,067	
Age (years)						
65-74	54.4%	52.1%	0.05	52.9%	51.1%	0.04
75-84	33.3%	35.0%	0.04	34.0%	35.8%	0.04
85+	12.4%	12.9%	0.02	13.1%	13.2%	0.00
Gender						
Male	37.8%	39.1%	0.03	38.3%	39.6%	0.03
Female	62.2%	60.9%	0.03	61.7%	60.4%	0.03
Race						
White	93.0%	92.3%	0.03	92.3%	92.1%	0.01

Black	2.4%	2.8%	0.02	2.8%	3.0%	0.01
Asian	1.8%	1.9%	0.01	1.7%	1.8%	0.01
Hispanic	0.9%	1.0%	0.01	1.0%	1.0%	0.00
Other, Non-North American Native	0.1%	0.1%	0.01	0.1%	0.1%	0.00
North American Native	1.3%	1.4%	0.01	1.3%	1.4%	0.01
Unknown	0.5%	0.4%	0.01	0.7%	0.7%	0.01
HHS Region^						
Region 1: CT, ME, MA, NH, RI, VT	6.2%	4.1%	0.10	6.4%	4.5%	0.08
Region 2: NJ, NY, PR, VI	7.8%	6.0%	0.07	9.0%	7.3%	0.06
Region 3: DE, DC, MD, PA, VA, WV	8.2%	9.4%	0.04	8.5%	9.9%	0.05
Region 4: AL, FL, GA, KY, MS, NC, SC, TN	22.9%	26.4%	0.08	21.6%	26.4%	0.11
Region 5: IL, IN, MI, MN, OH, WI	19.1%	12.9%	0.17	19.4%	14.0%	0.15

Region 6: AR, LA, NM, OK, TX	10.7%	10.5%	0.01	11.8%	10.5%	0.04
Region 7: IA, KS, MO, NE	5.6%	3.8%	0.08	5.4%	3.5%	0.09
Region 8: CO, MT, ND, SD, UT, WY	2.9%	4.4%	0.08	2.4%	3.8%	0.08
Region 9: AZ, CA, HI, NV, AS, FS, GU, PU	12.6%	15.9%	0.10	12.0%	14.7%	0.08
Region 10: AK, ID, OR, WA	4.0%	6.6%	0.11	3.5%	5.4%	0.09
Other	0.0%	0.0%	0.00	0.0%	0.0%	0.00
Low-Income Subsidy Status						
Number of Part D Enrolled Beneficiaries	100.0%	100.0%		100.0%	100.0%	
With 15% Copay	0.8%	0.8%	0.00	0.7%	0.6%	0.00
With High Copay	4.7%	4.8%	0.01	4.3%	4.2%	0.00
With Low Copay	4.8%	5.2%	0.02	4.5%	4.5%	0.00

With Zero Copay	1.1%	1.0%	0.00	1.0%	0.9%	0.01
Health Conditions						
At Least one high-risk disorder	63.3%	64.4%	0.02	64.5%	66.1%	0.03
Asthma	4.0%	4.1%	0.00	4.3%	4.6%	0.02
Blood Disorders	15.5%	16.0%	0.01	16.0%	16.8%	0.02
Chronic Lung Disease	14.4%	15.1%	0.02	14.4%	15.2%	0.02
Diabetes	20.8%	21.1%	0.01	22.0%	22.4%	0.01
Heart Disease	33.6%	34.7%	0.02	34.3%	35.8%	0.03
Kidney Disorders	7.0%	7.3%	0.01	7.9%	8.3%	0.02
Liver Disorders	2.4%	2.4%	0.00	2.4%	2.6%	0.01
Neurological or Neurodevelopmental conditions	11.3%	11.6%	0.01	11.6%	11.9%	0.01
Weakened Immune System	12.3%	12.5%	0.01	12.3%	12.9%	0.02
Frailty Covariates						

Home Oxygen Use	2.6%	2.7%	0.01	2.5%	2.6%	0.00
Wheelchair Use	0.2%	0.2%	0.00	0.1%	0.1%	0.00
Walker Use	1.2%	1.1%	0.01	1.1%	1.0%	0.01
Dementia	3.3%	3.2%	0.00	3.5%	3.2%	0.01
Urinary Catheter Use	0.1%	0.1%	0.00	0.1%	0.1%	0.00
Falls	3.2%	3.2%	0.00	3.3%	3.3%	0.00
Fractures	1.1%	1.1%	0.00	1.1%	1.1%	0.00

*HHS = Department of Health and Human Services

Table *xii*: Characteristics of study participants for post-influenza mortality and influenza hospitalization outcomes, by influenza vaccine type: comparisons by season

Demographic Variables	Standard Dose			High Dose		
	2012-2013 Season	2013-2014 Season	Std. Mean Difference	2012-2013 Season	2013-2014 Season	Std. Mean Difference
Base Population	1,683,264	1,877,327		1,039,645	1,508,176	
Age (years)						
65-74	52.1%	51.2%	0.02	49.8%	49.4%	0.01
75-84	34.7%	34.9%	0.00	36.6%	36.7%	0.00
85+	13.1%	13.9%	0.02	13.7%	14.0%	0.01
Gender						
Male	40.7%	40.3%	0.01	42.1%	41.7%	0.01
Female	59.3%	59.7%	0.01	57.9%	58.3%	0.01
Race						
White	93.6%	92.9%	0.03	93.1%	92.7%	0.01
Black	2.6%	2.8%	0.01	2.9%	3.0%	0.00

Asian	1.3%	1.4%	0.01	1.4%	1.5%	0.00
Hispanic	0.6%	0.8%	0.02	0.7%	0.8%	0.01
Other, Non-North American Native	1.3%	1.3%	0.00	1.4%	1.4%	0.00
North American Native	0.1%	0.1%	0.00	0.2%	0.1%	0.01
Unknown	0.4%	0.7%	0.03	0.4%	0.6%	0.04
Regions						
Region 1: CT, ME, MA, NH, RI, VT	6.2%	6.7%	0.02	4.0%	4.6%	0.03
Region 2: NJ, NY, PR, VI	7.8%	8.3%	0.02	5.6%	6.6%	0.04
Region 3: DE, DC, MD, PA, VA, WV	8.1%	8.4%	0.01	10.0%	10.4%	0.01
Region 4: AL, FL, GA, KY, MS, NC, SC, TN	23.4%	21.8%	0.04	27.2%	26.8%	0.01
Region 5: IL, IN, MI, MN, OH, WI	19.6%	19.6%	0.00	12.9%	13.7%	0.02
Region 6: AR, LA, NM, OK, TX	11.2%	12.2%	0.03	10.9%	10.7%	0.01

Region 7: IA, KS, MO, NE	4.9%	5.0%	0.01	3.3%	3.2%	0.00
Region 8: CO, MT, ND, SD, UT, WY	2.9%	2.6%	0.02	4.7%	4.3%	0.02
Region 9: AZ, CA, HI, NV, AS, FS, GU, PU	11.9%	11.5%	0.01	14.9%	13.8%	0.03
Region 10: AK, ID, OR, WA	3.9%	3.7%	0.01	6.6%	5.9%	0.03
Other	0.0%	0.0%	0.00	0.0%	0.0%	0.00
Low-Income Subsidy Status						
Number of Part D Enrolled Beneficiaries	56.5%	67.7%	0.23	55.9%	66.5%	0.22
With 15% Copay	0.8%	0.7%	0.02	0.8%	0.6%	0.02
With High Copay	4.8%	4.4%	0.02	4.9%	4.3%	0.03
With Low Copay	4.9%	4.5%	0.02	5.2%	4.5%	0.03
With Zero Copay	1.1%	1.0%	0.01	1.1%	1.0%	0.01
Health Conditions						
At Least one high-risk disorder	61.9%	63.0%	0.02	62.9%	64.6%	0.03

Asthma	3.8%	4.0%	0.01	3.9%	4.3%	0.02
Blood Disorders	15.1%	15.5%	0.01	15.6%	16.3%	0.02
Chronic Lung Disease	13.8%	13.9%	0.00	14.4%	14.7%	0.01
Diabetes	20.1%	21.1%	0.03	20.3%	21.4%	0.03
Heart Disease	33.1%	33.7%	0.01	34.1%	35.1%	0.02
Kidney Disorders	6.9%	7.7%	0.03	7.3%	8.2%	0.03
Liver Disorders	2.2%	2.3%	0.01	2.3%	2.4%	0.01
Neurological or Neurodevelopmental conditions	11.1%	11.3%	0.01	11.3%	11.6%	0.01
Weakened Immune System	12.1%	12.1%	0.00	12.4%	12.8%	0.01
Frailty Covariates						
Home Oxygen Use	2.4%	2.4%	0.00	2.5%	2.5%	0.00
Wheelchair Use	0.1%	0.1%	0.00	0.1%	0.1%	0.01
Walker Use	1.1%	1.1%	0.01	1.1%	1.0%	0.01
Dementia	3.2%	3.4%	0.01	3.1%	3.2%	0.00

Urinary Catheter Use	0.1%	0.1%	0.00	0.1%	0.1%	0.00
Falls	3.1%	3.3%	0.01	3.1%	3.2%	0.01
Fractures	1.1%	1.1%	0.00	1.1%	1.1%	0.00

Our findings suggest that high-dose influenza vaccines and perhaps other vaccines designed to elicit higher HAI immune responses among older adults may yield the most benefits during seasons when influenza A(H3N2) viruses are widespread, such as the 2012-13 season. A recent meta-analysis estimated that the effectiveness of standard-dose inactivated vaccines among adults aged >60 years for laboratory-confirmed A(H3N2) infection was only 24%.[167] The authors concluded that influenza vaccines offering better protection against A(H3N2) infection are critically needed. The availability of A(H3N2) vaccines offering substantially better protection for older adults and their widespread use in this population could lead to meaningful reductions in influenza-associated morbidity and mortality.

Resolving issues associated to the use of medical office visits outcomes in influenza comparative effectiveness studies

When comparing the effectiveness of the HD and SD influenza vaccines, as indicated in the methods section, we had to decrease the likelihood of including non-ambulatory (frail) individuals, adjust for temporal and geographic factors influencing

socioeconomic characteristics, closeness to care, influenza circulation, and access to HD

vaccine, we restricted the study population to beneficiaries who received a SD or HD

vaccine at a pharmacy that vaccinated at least one Medicare beneficiary with the

alternative influenza vaccine within +-14 days. To further decrease the likelihood of

participation by frail individuals, we also excluded persons who entered Medicare

because of disability and those who lived in assisted living facilities. We confirmed that

the cohorts were similar with regard to covariates measured in Medicare by evaluating

differences in baseline covariates using standardized mean differences.[128] Because

routine medical practice in the U.S. does not include the systematic verification of

influenza diagnoses by PCR or culture, we decided to: (a) restrict all influenza outcomes,

including office visits, hospitalizations and post-influenza deaths to those occurring

during periods of high influenza circulation (using CDC's virologic surveillance data to

select, for each region and season, the weeks during which the % of virological

specimens positive for influenza were within the top 25%)[16,18]; (b) restrict influenza

medical office visit to cases for which a rapid influenza test was performed, followed by

dispensing of oseltamivir (an influenza- specific antiviral); (c) define influenza deaths as

those occurring within 30 days following an influenza hospitalization. The restrictions

and diagnosis algorithms used in these comparative effectiveness studies allowed us to

obtain comparative effectiveness estimates very similar to those from

randomized studies that had been performed during the same seasons.[48,49,50] The

experience, as reported also by editorials about our publications,[152,153] was

successful, although the restrictions applied to our cohorts made generalization

difficult. Moreover, we could not determine if our cohorts were comparable not

only for the covariates on demographics, health consultations, and chronic conditions

available in the Medicare databases, but also for unmeasured variables that might have influenced the likelihood of vaccination and/or the outcome risk, which will be considered among the next steps in our research.

Transition from the study of the comparative effectiveness of High dose vs. Standard dose influenza vaccines to the comparative effectiveness of the quadrivalent cell- cultured vs. multiple egg-based vaccines

As discussed, the High dose influenza vaccine was licensed in 2009 under accelerated approval regulations (21 CFR 601.41), using hemagglutination inhibition (HI) antibody as the surrogate marker reasonably likely to predict clinical benefit. As per regulations, Sanofi was then obligated to conduct a randomized clinical endpoint study post licensure to confirm efficacy.

We started discussing the possibility of performing the High-Dose vs. Standard-Dose vaccine effectiveness study in Medicare once we learned of the failed attempt to establish superiority of the High-Dose vaccine, in a post-licensure randomized study during the 2009-10 season[65] (Diaz-Granados et al, Vaccine 2013). Sanofi did not repeat the study in 2010-11, due to insufficient cases of influenza because that season was too mild.

In early 2015, once we had our preliminary observational study results, we found out that the sponsor had just finalized, successfully, its two-season (2011-12 and 2012-13) randomized clinical trial.[48] Our March, 2015 publication of results of the 2012-13 observational

study in Medicare not only showed effectiveness results strikingly similar to Sanofi's efficacy trial results, but also contributed additional information useful for public health by providing results of RVE for the prevention of hospitalizations, which would be too expensive and too large (and/or long) for randomized trials to perform without unacceptably large confidence intervals. Later on, a follow-up post hoc reanalysis of the clinical trial data, although underpowered, the researchers did find hospitalization results similar to ours.[51]

Interestingly, the sponsor's randomized clinical trial did not find corresponding superior HI antibody responses for the H1N1 antigen among frail adults during the 2012-13 season.[52] In our own follow-up observational study in Medicare, which included seasons 2012-13 (A(H3N2)-dominated) and 2013-14 (A(H1N1)-dominated, we used post-influenza hospitalization mortality as the main outcome (which had not previously been studied by anybody else). This, our second comparative effectiveness observational study,[18] revealed greater effectiveness of the High-Dose vaccine during 2012-13 against mortality, but found only marginal superiority for the High-Dose vaccine during the 2013-14 A(H1N1)-dominated season A subsequent cluster- randomized nursing home study sponsored by Sanofi found results for hospitalized outcomes similar to ours;[49] however, unlike ours, the study by Gravenstein was not powered to investigate mortality outcomes.[18,49]

Thus, these two studies of the comparative effectiveness of the HD vs SD influenza vaccines[16,18] were implemented in response to a concern, results were very similar to those from randomized studies, and we also studied important outcomes too rare to be investigated in randomized studies.[153] Moreover, our observational High-Dose vs. Standard-Dose studies identified a very relevant difference in comparative vaccine effectiveness between the A(H3N2) dominated 2012-13 season and the subsequent A(H1N1)-dominated 2013-14 season.[16,18] We are

currently implementing a multi-season follow-up analysis to better understand the effect of season and age in the comparative effectiveness of High-Dose vs. Standard-Dose influenza vaccines (see chapter on Next Steps below), which was also born from a concern regarding comparative vaccine effectiveness by season, age and sex.

In summary, FDA used accelerated approval regulations to approve HD Fluzone, using the best possible surrogate (Hemagglutinin inhibition (HI) response). Nonetheless, HI does not correlate perfectly with clinical outcomes. At the time of (accelerated) licensure it wasn't clear whether Sanofi would be able to conduct a confirmatory trial within a reasonable time frame, if at all, having failed in previous years to complete the study satisfactorily.[48] Such as situation could have left FDA in the awkward position of leaving a product on the market for an unknown period of time without the relative benefit of having been verified post-licensure. Our observational real-world evidence studies then might have been useful as a fall back option. Besides, the fact that our real-world evidence studies have been cited multiple times at ACIP meetings and discussed in multiple reviews of the subject highlight their importance as contributors to the ensemble of the evidence regarding the comparative effectiveness of the High-Dose vs. Standard-Dose vaccine in different seasons and populations, thus highlighting the benefits of real-world evidence studies for both regulators and public health decision-makers.[152,153]

These studies, which include the investigation of serious and rare influenza-related outcomes such as hospitalizations and deaths, have provided results comparable to those from randomized trials performed during the same seasons.[48-50,65,152,153] The success of these efforts is particularly meaningful because, as was indicated earlier, the investigation of such rare and serious outcomes in a randomized study would be not only very challenging to implement, but

also extremely expensive and time consuming. The success of this collaboration in the use of real world evidence for the investigation of comparative vaccine effectiveness encouraged us to extend the initiative to focus on a pressing priority for the U.S. Department of Health and Human services (HHS), the timely evaluation of the comparative effectiveness of the multiple influenza vaccines used among the U.S. elderly, a key element of U.S. (and global) influenza pandemic preparedness.[43] Specifically, because of concerns expressed by influenza virologists, HHS's concern was to determine if influenza vaccines cultured in canine kidney cells (cell- cultured) were more effective than the multiple influenza vaccines produced using more traditional methods, culturing them in chicken eggs.

Relative effectiveness of cell-cultured and egg-based influenza vaccines among the U.S. elderly, 2017-18

In this analysis of the comparative effectiveness of the cell-cultured quadrivalent vaccine with four other egg-based vaccines, during the A(H3N2)-dominated 2017-18 influenza season, conducted among approximately 13 million influenza vaccinees ages ≥ 65 years, we showed that the effectiveness of the cell-cultured quadrivalent influenza vaccine was approximately 10-11% higher than that of the comparable egg-based quadrivalent standard- dose products in preventing influenza-related hospital encounters, inpatient stays and office visits. Among all five vaccine types investigated, the RVE against influenza-related hospital encounters and inpatient stays was the highest for the cell-cultured and high-dose vaccines (see Figure *ii*). The higher RVE we observed in this 2017-18 season study for the egg-based high-dose vaccine relative to the

egg-based standard-dose vaccines is consistent with findings from prior studies by our

team and others.[16,18,168]

Figure *ii*: IPTW adjusted RVE for two-vaccine comparison analyses using egg-based quadrivalent cohort as reference
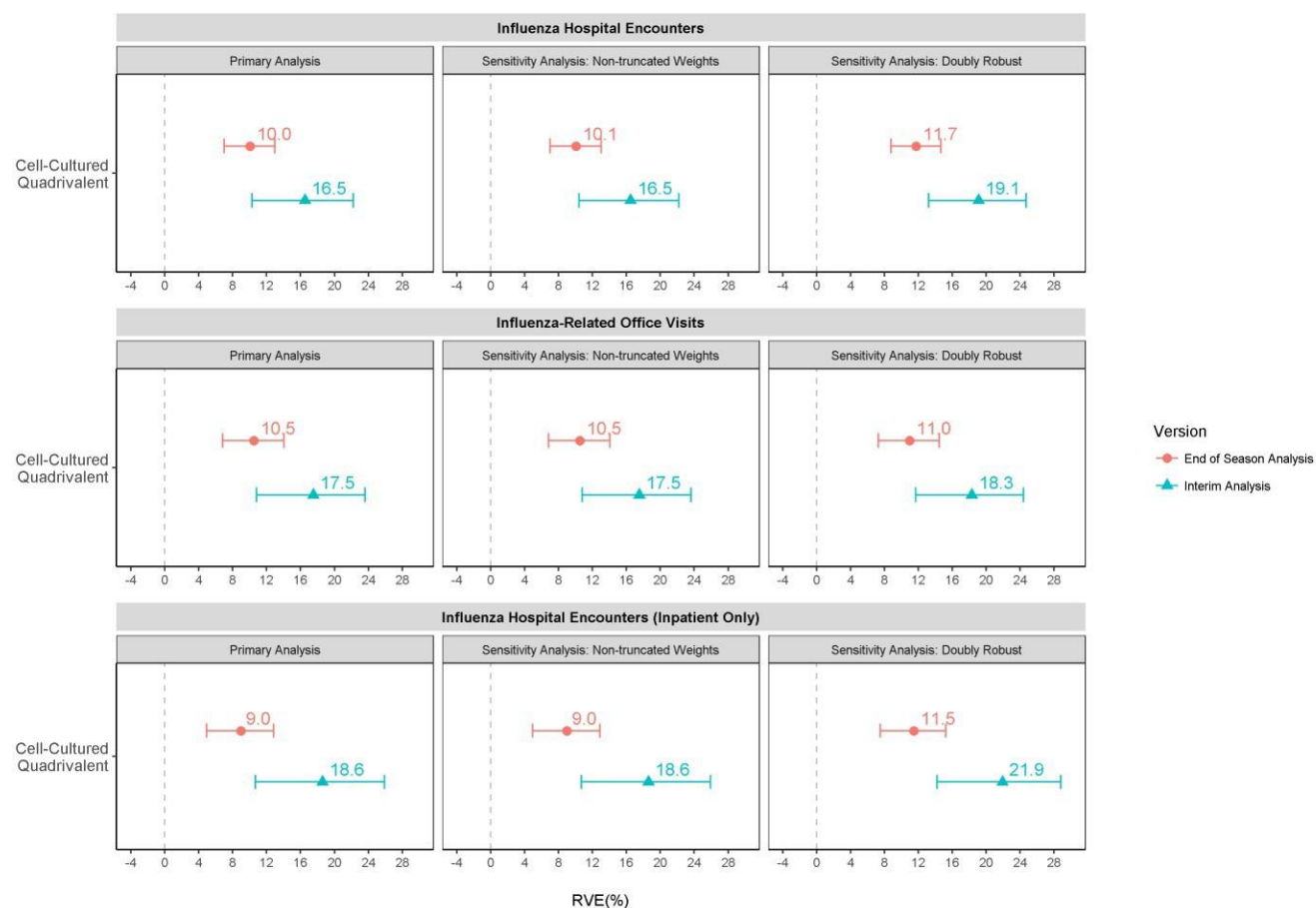
To our knowledge, there is no prior real-world evidence of higher RVE for the cell- cultured vaccine vs. the comparable egg-based vaccines, although there is virological evidence supporting this possibility.[97,99-101] One hypothesis is that changes in the viral hemagglutinin (HA) of influenza A(H3N2) virus during isolation, adaptation and propagation in eggs of the influenza A(H3N2) vaccine strain might affect VE[97,100,169,170] However, our study does not rule out the possibility that other factors unrelated to the method of vaccine production could account for

the observed differences in vaccine effectiveness. Also, we did not separately analyze egg- based quadrivalent vaccines produced by different manufacturers. The differential effectiveness we observed between the cell-cultured and egg-based quadrivalent vaccines only partially explains the 20% VE interim estimate reported by CDC among individuals ages $\geq$65 years during the 2017-18 season, low by historical standards.[101] Unlike 2014-15, when there was evidence of antigenic drift of the circulating A(H3N2) viruses compared to the vaccine reference viruses, there was no evidence of such hemagglutinin drift in 2017-18.[97,171] Other possibilities, including a neuraminidase drift, should be explored to help explain the low VE reported among persons ages ≥65 years.[101,172] We also provide hypothetical VE estimates for each vaccine among beneficiaries ages ≥65, assuming a ±10 point difference from the CDC VE estimate.[101] The results are shown in the table below. The methodology is described in the methods section.[14] The numbers can only be considered a very rough approximation since our study did not estimate absolute VEs, the CDC study population could have differed from ours, the absolute VE estimate from the CDC study had wide confidence intervals (-9% to 41%), and their estimates were preliminary.

Table *xiii*: Illustration of VE by Cohort across All Outcomes for Different Overall VE Values in the 2017-18 Season

Outcome	Vaccine Type	Assumed Overall Vaccine Effectiveness (VE)		
		VE = 10%	VE = 20%	VE = 30%
Influenza Hospital Encounters	Egg-Based Quadrivalent	3.6%	14.3%	25.0%
	Cell-Cultured Quadrivalent	14.3%	23.8%	33.3%
	Egg-Based High-Dose Trivalent	7.3%	22.0%	31.8%
	Egg-Based Adjuvanted	12.3%	17.6%	27.9%
	Egg-Based Standard-Dose Trivalent	3.9%	14.6%	25.3%
Influenza-Related Office Visits	Egg-Based Quadrivalent	9.7%	19.7%	29.7%
	Cell-Cultured quadrivalent	14.8%	24.3%	33.8%
	Egg-Based High-Dose Trivalent	10.3%	20.3%	30.2%
	Egg-Based Adjuvanted	3.8%	14.4%	25.1%
	Egg-Based Standard-Dose Trivalent	14.0%	23.6%	33.1%
	Egg-Based High-Dose Trivalent	10.3%	20.3%	30.2%
Influenza hospital encounters (Inpatient only)	Egg-Based Quadrivalent	3.3%	14.1%	24.8%
	Cell-Cultured quadrivalent	12.5%	22.2%	31.9%
	Egg-Based High-Dose Trivalent	13.1%	22.7%	32.4%
	Egg-Based Standard-Dose Trivalent	1.2%	12.2%	23.1%

As can be seen in the figure below, our end-of-season RVE estimate for the cell-cultured vs. the comparable egg-based quadrivalent standard-dose vaccines (RVE: 10.0%; 95% CI: 7.0% to 13.0%) was somewhat lower than that of our January 19 interim analysis (RVE: 16.5%; 95% CI: 10.3% to 22.2%) .This could potentially be explained by an increase in the proportion of influenza B circulating viruses (that also undergo egg-adaptation known to change antigenicity) during the late part of the season.[173-175] Unlike the A(H3N2) component of the 2017-18 cell- cultured vaccine, which was isolated in cells, the influenza B viruses in the cell-cultured vaccine were isolated in eggs and, therefore, are antigenically-similar to the comparator influenza B viruses in egg-grown vaccines. This could potentially explain why the RVE was lower in the end- of-season analysis, which included a late increase in the circulation of B/Yamagata-lineage viruses. [97,170,173-175]

In Figure *iii*, which represents the IPTW-adjusted RVE for the primary analysis (end of season) and for the secondary analyses, which represent the interim season analyses performed in January, when the H3N2 viruses had a clear domination. The RVE point estimates and 95% confidence intervals for the cell-cultured vs. egg-based quadrivalent vaccine comparison are presented for both outcomes, as well as for the five-way influenza hospital encounter comparison analysis for the 2017-18 season. The egg-based quadrivalent vaccine cohort is used as the reference group for each RVE estimate.

Figure *iii*: **IPTW interim and end-of-season analyses results comparison**
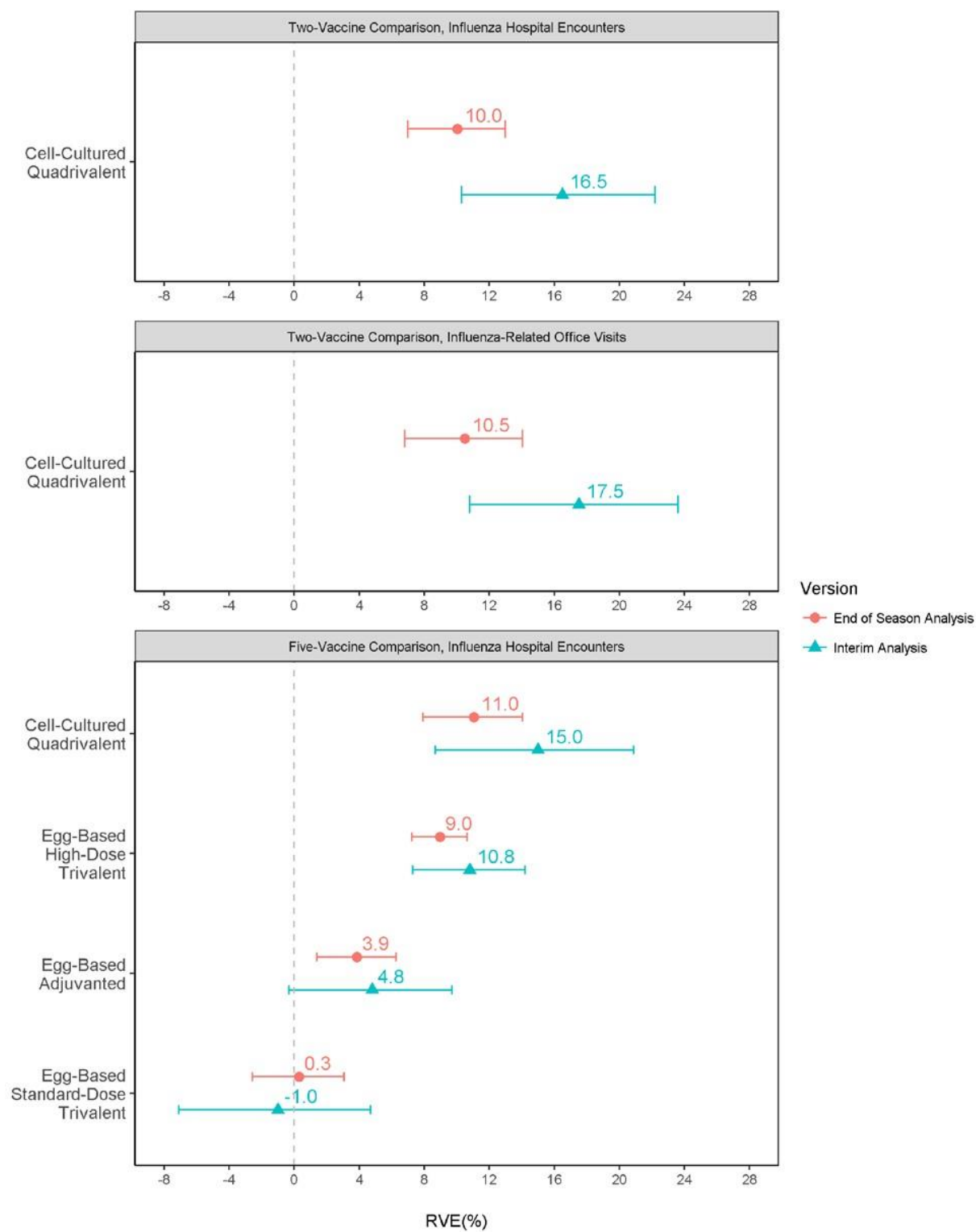
One particular issue in this study was the need to compare multiple vaccines, considering that the characteristics of the populations vaccinated with each of them could be different. A simple answer to this problem could have been to perform one-on- one matching, but that solution would have meant that the sample size would have become too small to perform some of the main analyses. Our choice was, then, to perform inverse probability of treatment weighting instead. The success of this approach is illustrated in Table *xiv*, which shows very well-balanced cohorts after weighting. Of course, this does not mean we achieved balance with respect to unmeasured covariates, which is something we will discuss in the chapter on next steps.

Table *xiv*: Distribution of covariates across vaccine cohorts for the 2017-2018 influenza season after implementing IPTW weights

Covariates	Egg-Based Quadrivalent	Cell-Cultured Quadrivalent	Egg-Based HD Trivalent	Egg-Based Adjuvanted	Egg-Based SD Trivalent	Max SMD[a]
Base Population	**1,822,862**	**655,432**	**8,488,136**	**1,466,918**	**994,763**	
Vaccinated at Pharmacy						
Yes	36.9%	38.6%	38.4%	38.6%	37.0%	0.03
Age groups						
65-74	50.4%	51.0%	50.9%	50.7%	51.4%	0.02
75-84	33.9%	33.5%	34.3%	34.0%	33.4%	0.02
85+	15.7%	15.5%	14.9%	15.3%	15.3%	0.02
Gender						
Female	58.7%	58.7%	58.2%	58.2%	59.7%	0.03
Male	41.3%	41.3%	41.8%	41.8%	40.3%	0.03
Race						
White	88.6%	88.1%	88.2%	88.6%	88.3%	0.02
Black	5.0%	5.2%	5.2%	5.0%	5.2%	0.01
Asian	0.9%	1.0%	1.0%	0.8%	0.9%	0.02
Hispanic	1.9%	1.9%	1.9%	1.8%	2.0%	0.01
Other	3.6%	3.9%	3.7%	3.7%	3.6%	0.02
Regions						
Region 1: CT, ME, MA, NH, RI, VT	6.2%	5.9%	6.2%	6.3%	6.5%	0.02
Region 2: NJ, NY, PR, VI	9.0%	8.7%	9.0%	9.0%	9.2%	0.02
Region 3: DE, DC, MD, PA, VA, WV	11.9%	11.9%	11.7%	11.7%	11.4%	0.02

Region 4: AL, FL, GA, KY, MS, NC, SC, TN	21.0%	21.9%	21.4%	21.3%	21.0%	0.02
Region 5: IL, IN, MI, MN, OH, WI	17.2%	16.3%	17.0%	17.1%	17.6%	0.03
Region 6: AR, LA, NM, OK, TX	10.6%	10.9%	10.7%	10.7%	10.8%	0.01
Region 7: IA, KS, MO, NE	5.7%	5.6%	5.6%	5.6%	5.2%	0.02
Region 8: CO, MT, ND, SD, UT, WY	3.4%	3.3%	3.4%	3.5%	3.5%	0.01
Region 9: AZ, CA, HI, NV, AS, FS, GU, PU	10.7%	10.9%	10.8%	10.8%	10.8%	0.01
Region 10: AK, ID, OR, WA	4.2%	4.4%	4.2%	4.1%	4.0%	0.02
Reason for entering Medicare						
Aging	90.8%	90.8%	91.1%	91.4%	90.8%	0.02
Disability	9.1%	9.0%	8.7%	8.5%	9.0%	0.02
ESRD	0.2%	0.2%	0.2%	0.1%	0.2%	0.02
Dual eligible						
Yes	9.2%	8.7%	8.5%	7.6%	8.7%	0.06
Month of Vaccination						
August & September	30.0%	29.8%	31.0%	30.3%	29.4%	0.03
October	43.9%	44.1%	43.5%	43.7%	44.3%	0.02
November	16.5%	16.5%	16.1%	16.4%	16.6%	0.01
December & January	9.6%	9.6%	9.4%	9.7%	9.7%	0.01
All hospitalizations						
At least one	9.2%	9.6%	9.2%	9.0%	9.5%	0.02
Outpatient ER Visits						
At least one	15.0%	15.4%	14.8%	14.6%	15.2%	0.02
Outpatient Non-ER Visits						
0	36.8%	35.6%	37.0%	37.6%	36.6%	0.04
1, 2	30.7%	30.5%	30.8%	31.0%	30.8%	0.01

3 +	32.5%	33.9%	32.3%	31.4%	32.6%	0.05
All Physician visits						
[0- 5]	34.2%	33.8%	33.9%	34.2%	34.2%	0.01
[6 - 10]	28.5%	28.5%	28.6%	28.6%	28.5%	0.00
[11 - 15]	15.7%	15.8%	15.8%	15.8%	15.7%	0.00
[16 - 25]	13.5%	13.7%	13.7%	13.5%	13.5%	0.01
26 +	8.0%	8.1%	8.0%	7.9%	8.1%	0.01
Respiratory failure and pneumonia						
Hospitalizations	1.8%	1.9%	1.8%	1.7%	1.9%	0.01
ER Outpatient Visits	0.4%	0.4%	0.4%	0.4%	0.4%	0.01
Non-ER Outpatient Visits	0.9%	0.9%	0.9%	0.8%	0.9%	0.01
Physician Office Visits	3.9%	4.0%	3.9%	3.9%	4.0%	0.01
Allergies						
Anaphylaxis	0.1%	0.1%	0.1%	0.1%	0.1%	0.00
Drug Allergy	0.3%	0.3%	0.3%	0.3%	0.3%	0.00
Food Allergy	0.4%	0.4%	0.4%	0.4%	0.4%	0.00
Concomitant Vaccine						
Pneumococcal	7.8%	8.0%	8.4%	8.6%	7.5%	0.04
Health Conditions						
Asthma	6.2%	6.2%	6.2%	6.1%	6.1%	0.01
Blood Disorders	20.9%	20.9%	20.8%	20.2%	20.4%	0.02
Chronic Lung Disease	18.2%	18.1%	18.2%	17.9%	17.8%	0.01
Diabetes	27.4%	27.1%	27.5%	26.9%	26.5%	0.02
Heart Disease	40.7%	40.7%	40.9%	40.5%	40.1%	0.01
Kidney Disorders	14.6%	14.6%	14.7%	14.1%	14.7%	0.02

Liver Disorders	3.2%	3.3%	3.3%	3.2%	3.2%	0.01
Neurological	16.4%	16.3%	15.8%	16.0%	16.1%	0.02
Immunocompromising Conditions	5.0%	5.1%	5.1%	4.9%	5.1%	0.01
Other Malignant Neoplasms (Non Included Elsewhere)	11.3%	11.5%	11.6%	11.4%	11.4%	0.01
Frailty Covariates						
Home Oxygen Use	3.8%	3.8%	3.7%	3.6%	3.7%	0.01
Wheelchair Use	0.1%	0.1%	0.1%	0.1%	0.1%	0.00
Walker Use	1.3%	1.3%	1.2%	1.2%	1.3%	0.01
Dementia	0.7%	0.7%	0.7%	0.7%	0.7%	0.01
Urinary Catheter Use	5.4%	5.2%	4.8%	5.2%	5.3%	0.03
Falls	6.0%	6.1%	5.8%	5.9%	6.0%	0.01
Fractures	1.2%	1.2%	1.2%	1.2%	1.2%	0.00

Abbreviations: IPTW, inverse probability of treatment weighted; SMD, standardized mean difference; HD, high-dose, SD, standard-dose

Another important limitation of the use of Medicare data in real-world evidence studies

is the lack of access to virological case confirmation data. However, since the 2017-18 season was

dominated by influenza A(H3N2), we can infer that most influenza events were likely caused by

influenza A(H3N2). Our definition of influenza office visits included a rapid test followed by a

prescription for a therapeutic course of oseltamivir. Although the sensitivity and specificity of

RITs are lower than those from culture or polymerase chain reaction, RITs can provide a health

care provider results within 15 minutes after sample collection.[176] We expect that these results

guided the decision to prescribe influenza-specific antivirals. [177,178] However, our influenza office

visits five-way comparison produced estimates inconsistent with the hospital encounters and

inpatient hospitalizations outcomes, specifically in the comparisons with the standard-dose

quadrivalent and trivalent vaccines. These inconsistencies might be explained by potential cohort

differences in health seeking behavior and in testing and treatment preferences by physicians,

and highlight the need for caution when considering results from observational studies that

include outcomes particularly sensitive to differences in health seeking and treatment preference

behaviors not characterized in claims databases.[134] To resolve these issues, we have initiated

projects linking surveys of Medicare beneficiaries, which provide information on frailty, health

seeking and other behaviors, with Medicare claims databases. Also, we *a priori* considered

hospital encounters as our primary analysis outcome, and also included a post-hoc inpatient stay

only analysis which produced almost identical RVE estimates.[8]

A strength of our study is that the population includes all eligible beneficiaries identified

through Medicare fee-for-service claims. Our large sample size allowed us to perform analyses

for serious outcomes including inpatient stays, difficult to obtain in any randomized trial.

However, our study has limitations. Because the analysis is observational, residual confounding

could be a concern. In particular, residual confounding associated with chronic conditions not sufficiently characterized by the dichotomous indicators derived from Medicare claims can be problematic.[163,164] However, our use of IPTWs yielded well-balanced vaccine cohorts with respect to potential confounders available in the Medicare database, and our past estimates using this database have been credible.[16-18]

Our consistent finding in this rapid response study that the cell-cultured and high-dose vaccines showed better effectiveness than the comparator egg-based vaccines among persons ages ≥65 years during the 2017-18 season, along with our findings from prior studies,[16,18,49,168] show that the methods we developed for the use of real-world data to analyze the relative effectiveness of vaccines used by the Medicare population could help optimize vaccine strategies for this vulnerable population during epidemics and pandemics.[150] However, given the potential for residual confounding in all observational studies, and the small magnitude of the differences we obtained, our findings would benefit from replication in studies in other settings and health care systems. The critical analysis of the ensemble of these real-world evidence studies should provide valuable information for epidemic influenza control and pandemic preparedness, and may help guide the future use of real-world evidence by FDA and others.[11-13,150]

Statin use and risks of influenza-related outcomes among older adults receiving standard-dose or high-dose influenza vaccines through Medicare during 2010-2015

In a 5-season study enrolling >2.8 million Medicare beneficiaries aged >65 years who

received influenza vaccines in pharmacies, we found that those exposed to statins around the day of vaccination had small (RD per 10,000 person-weeks ranged from -0.02 to 0.23 for office visits and -0.04 to 0.13 for hospitalizations) but significant increased risks for influenza-related outcomes compared with non-users. We also found that high-intensity statin users had significantly higher risks than non-users for both outcomes. However, results for the comparison between moderate and low-intensity users with non-users were not consistent. We found no significant differences in influenza risks between synthetic and non-synthetic statin users. Risk for influenza outcomes was elevated for all statin type and intensity combinations, although differences were not consistently significant. The majority of synthetic and non- synthetic statin use was of moderate intensity, and a comparison of those two groups found no significant differences in influenza risk, suggesting no effect by type of statin used.

Our results are consistent with the direction of the effects identified by Black et al., who compared HI titers among vaccinated statin users to vaccinated non-users.[79] They found 38% to 62% lower HI titers, depending on influenza strain, in statin users compared to non-users. We had no information regarding the specific influenza strains that may have caused infections in our subjects. However, our findings of increased risks of ~10% among statin users are consistent with, albeit smaller in magnitude than, the lower HI titers observed among statin users by Black et al. While Black et al. found that patients receiving non-synthetic statins had higher HI titers than those receiving synthetic statins,[79] we found no significant differences in risk for clinical influenza between synthetic and non-synthetic statin users. Type of statin received and intensity of use were correlated (i.e., high-intensity use is only possible when receiving synthetic statins). Therefore, we analyzed statin treatment by combinations defined by type and intensity to see if statin-type results might be affected by differences in statin treatment intensity. Our results

suggest significant differences in risk by statin intensity but not statin type. Because the study by

Black et al. did not collect data on statin intensity, their findings may have been confounded by

statin intensity.

Direct comparisons between our findings and those from other observational studies that

included an unvaccinated group are not possible. In Medicare claims data, lack of a claim for

influenza vaccination cannot be used to establish that a beneficiary did not receive a vaccination,

because it is possible that a claim was not submitted, or that a vaccine claim was submitted to

another payer. Thus, we cannot present VE estimates. However, we can make several

observations. Omer et al. found a substantial reduction in influenza VE among statin users

compared to non-users.[80] While the Omer et al. study did not directly compare vaccinated statin

users to non-users, they reported unadjusted incidence rates for both groups. Applying the ratio-

of-ratios approach used by Omer, we calculated that the ratio of the unadjusted risk of medically

attended acute respiratory illness (MAARI) among vaccinated statin users and non-users was

1.08.[80] These results are consistent with our findings of 9-10% differences in risk, despite the

different populations studied and the non-specific outcome (MAARI) used by Omer et al. McLean

et al. found in a 10-season study enrolling 3,285 participants aged $\geq$45 years that VE for RT-PCR-

confirmed influenza outpatient visits was substantially and significantly lower in statin users for

influenza A(H3N2) virus infection.[81] However, VE against influenza A(H1N1)pdm09 or B virus

infections did not differ by statin use.[81] Medicare claims data do not provide information on the

type/subtype of influenza virus associated with the influenza- related outcomes we used. Thus,

we cannot compare statin effects by virus type/subtype of infection. Our study period included

some seasons dominated by influenza A(H3N2) viruses and other seasons in which A(H1N1)

viruses predominated. We did not see larger differences in risk of influenza-related outcomes

during influenza A(H3N2)-predominant seasons.

Our study had limitations, some of which we noted in previous publications that used similar methods.[16,18] In addition to these, the statins user and non-user populations may have differed by unmeasured covariates, including body mass index and diet. In an effort to minimize bias potentially associated with unmeasured confounders, including being ambulatory, we restricted all analyses to beneficiaries vaccinated in community pharmacies.[16,18] To further address potential unmeasured confounders, such as those reflected by chronic use of common medications, we performed negative exposures analyses with HCTZs and PPIs. We found no association between HCTZs and influenza outcomes. A small but significant association with PPIs was found, which might suggest the possibility of residual bias or unmeasured confounders. In retrospect, however, our choice of PPIs as a negative exposure was not ideal. PPIs have multiple effects beyond their effect on gastric pH, which may affect susceptibility to pneumonia and thus the diagnosis of infection with specific respiratory pathogens.[179-182] In addition, the cohort restrictions we used to further reduce potential confounding, including also the exclusion of beneficiaries with cardiovascular conditions, may limit the generalizability of our findings. Whether the associations we observed between statin use and influenza risk are similar in less healthy beneficiaries is unknown.

In summary, we found small associations between statin use and relative risks for influenza office visits and hospitalizations among vaccinated Medicare beneficiaries, consistent with the direction of results from an immunogenicity trial.[79] The small magnitude of our findings suggests that receipt of statins around the time of influenza vaccination does not substantially affect the risk of influenza-related medical encounters among vaccinated Medicare beneficiaries. These findings should be interpreted in the context of the well- established benefits

of statins for reducing the risk of cardiovascular outcomes.

Effectiveness and duration of protection provided by the live-attenuated Herpes Zoster vaccine in the Medicare population ages 65 years and older

Success of the matching strategies used in the study

The Zostavax effectiveness is study was published in the Clinical Infectious Disease Journal (CID),[17] accompanied by a very positive editorial.[151] When we compared our results with those from clinical trials and prior observational studies we learned that our main concern, health seeking behavior bias, appeared to be less of a problem for severe outcomes, as opposed to medical office visits. This allowed us to obtain useful estimates for duration of effectiveness for post-herpetic neuralgia (PHN) and HZ hospitalization which have contributed to improve our understanding of Zostavax effectiveness. The similarity of our CID published findings on these outcomes with preliminary findings from a manufacturer sponsored observational study has provided reproducibility, which improves the credibility of observational studies. Because of the use of internal comparisons and the very large (in the millions) observational databases we used, we were also successful in evaluating duration of Zostavax effectiveness, including for very old individuals ($\geq$85 years of age). Nonetheless, our results for HZ (and ophthalmic zoster) medical visits showed VE estimates in the lower end of those shown in prior clinical studies, which could be explained by residual health seeking behavior bias, by differences in the populations studied (we used Medicare beneficiaries, and our study's mean age was 77 years), or by both.

A particularly important point to stress is the excellent balance achieved by our use of propensity score matching in the Zostavax effectiveness study. Despite significant differences in most pre-matching covariates, all post-matching covariates were well balanced (with SMDs <0.1).

For this study, we used matched cohort data from approximately 2 million Medicare beneficiaries to investigate HZ vaccine effectiveness and duration of protection, using multiple analytical approaches to identify and address potential bias. To our knowledge, this is the first study assessing the effectiveness and durability of the live-attenuated HZV [112,119,122,183,184] that directly compares vaccinated and unvaccinated cohorts with sufficient power to examine less common outcomes such as PHN and HZ-associated hospitalizations, while controlling for a wide range of HZ risk factors and potential confounders. Furthermore, our Medicare fee-for-service data are sourced from the general U.S. population ages 65 years and older, capturing the entire range of routine clinical practice.

Among eligible study participants averaging 77 years of age the primary and secondary analyses, respectively, found that HZV was 33% and 37% effective for the prevention of outpatient HZ during the first 3 years post-vaccination. In both analyses, VE for outpatient HZ declined significantly for years 4+ post-vaccination to 19% and 22%, respectively. Similar results have been published based on long-term follow-up of the original study cohort from the original HZV clinical trial, but the long-term follow-up study was uncontrolled and unblinded [184]. A recent prospective cohort study also showed waning of protection, though that study, conducted at a large health maintenance organization in California [122], had less analytic power and generalizability than our study.

For serious outcomes, including PHN and HZ-associated hospitalization, we found higher

HZV effectiveness, 57% and 74%, respectively, for the first 3 years post-vaccination than for years 4+. For both, protection was better preserved than for outpatient HZ with AVEs of 45% and 55%, respectively, for years 4+. The 57% reduction in PHN in our study among HZV recipients suggests incremental benefit beyond prevention of HZ *per se*: this is also suggested by the higher proportion of HZ cases progressing to PHN among unvaccinated relative to vaccinated cohorts (4.0% versus 2.9%, respectively). While Zostavax does not have an indication for prevention of PHN, our data suggest that it may prevent PHN, both through prevention of HZ and by reducing the likelihood that HZ that occurs among vaccinees will progress to PHN.

While vaccine effectiveness declines with increasing age, [112,144] it does appear to protect individuals with a range of chronic illnesses who are particularly vulnerable to the effects of HZ and for whom immunogenicity could theoretically be blunted.

Our results confirm those of other studies, although point estimates of vaccine effectiveness vary across studies due to differences in source population characteristics, case definitions and ascertainment, and other aspects of study methodology.[144,184] Notably, in our study, HZV was 57% effective at prevention of PHN, suggesting incremental benefit beyond prevention of HZ *per se*: of vaccinated and unvaccinated persons developing HZ, 2.9% versus 4.0% developed PHN, respectively. While Zostavax does not have an indication for prevention of PHN, our data suggest that it does indeed prevent PHN, both through prevention of HZ and by reducing the likelihood that HZ occurring among vaccinees will progress to PHN. We also found that among older individuals, vaccine effectiveness was better retained for prevention of PHN than for prevention of HZ. Furthermore, during the 3 years following vaccination, HZ- associated hospitalization was reduced by 74%.

This study has several limitations. Because Medicare is an administrative database,

outcomes and predictors were not verified by medical record review and may include errors. In general, non-specific outcomes tend to understate vaccine effectiveness, while specific outcomes may introduce biases. We explored this issue with an analysis that restricted outpatient HZ to cases receiving antiviral treatment, and found that vaccine effectiveness was modestly increased.[118] However, since HZ tends to be milder among vaccine recipients, this finding may reflect bias due to differential prescribing by vaccination status. Previous record validation studies have consistently shown relatively high positive predictive value for HZ as an outcome.[114,120,144,185] In addition, some beneficiaries may have claims for the vaccine with non-Medicare insurance, leading to errors in vaccination status. However, we attempted to address this by restricting our cohorts to beneficiaries enrolled in Medicare since HZV was licensed so that they could not have been vaccinated beforehand. It is also unlikely that many recipients paid for this expensive vaccine out of pocket. Additionally, vaccinees may differ from non- vaccinees with respect to both disease risk and healthcare seeking behavior. Outpatient HZ, in particular, is likely to be missed among beneficiaries who forgo medical care for the condition. To improve comparability between cohorts, we matched by multiple potential confounders, and also conducted an analysis comparing HZ vaccinees with beneficiaries who, instead, had received pneumococcal vaccine, which is also recommended for the elderly. We also assessed the incidence of 13 falsification endpoints (acute medical conditions unrelated to HZ) by vaccination status and found that the relative risks clustered around 1.0 in both populations. [144] We were also assured by published population-based studies indicating that over 90% of adults self-reporting HZ sought medical attention for the condition.[115,186-188] Since ophthalmic zoster (OZ) represents a particularly distressing form of HZ that would almost certainly lead to differences in cohorts, our finding that HZV was equally effective at preventing outpatient OZ and other

outpatient HZ was itself reassuring.

PHN and HZ-associated hospitalizations outcomes are more prone to artifact than outpatient HZ. Our case-definition for PHN was derived from a single validation conducted in a health system very different than Medicare[117]. The definition is based on a series of healthcare encounters lasting 90 days. Given that treatment for PHN is often frustrating or even futile, it is likely that many factors influence the prolonged pursuit of medical care among persons with chronic HZ pain.[121,189-191] Using similar methods, Tseng et al. found evidence of bias in their analysis of vaccine effectiveness for prevention of PHN, with notable bias by gender and an interaction by vaccination status. In our analysis, we found no such effects. Regarding Additionally, HZ-attributable hospitalization is an imperfect surrogate for HZ disease severity, as even primary-HZ coded hospitalizations are often not attributable to HZ.[116] The risk of HZ-associated hospitalization is likely to be influenced by risk of hospitalization as well as by the underlying risk of hospitalization as factors affecting HZ risk (including HZV). This likely explains the strong association between hospitalizations during the 12 months preceding the index date and HZ-associated hospitalization, and the reduction in protection against HZ-associated hospitalization when the comparator is restricted to pneumococcal vaccine recipients who are more similar to HZV recipients. Even though it is impossible to exclude residual bias from any observational study, regardless of methodological rigor or study outcome, this paper made significant efforts to account for multiple sources of bias, recognized by the accompanying editorial.[151]

HZ is a frequently-disabling disease among the elderly, yet it is preventable. While the duration of protection wanes over time,[184] the vaccine does protect against HZ regardless of age and chronic illness, particularly against hospitalization and PHN. Indeed, the number needed to

vaccinate (NNV) to avert an episode of outpatient HZ over our average follow-up of 2.5 years (the average follow-up time during our observation period, January 2007 to July 2014) was just 92. Yet vaccine uptake remains low at 28%.[192] We cannot generalize our findings to the full US population for which HZV is recommended since our study population was older and the population prevalence of contraindications is unknown, but clearly many hundreds of thousands of cases of HZ could have been averted since the vaccine become available had the entire population been vaccinated. It is important that health providers and health policy advocates consider the study results and take necessary action in order to increase vaccinations.

Next steps

Near-real time comparison of the effectiveness of all marketed vaccines

The largest and more deadly influenza pandemic in recorded history started in April, 1918, among soldiers at Fort Riley, Kansas, in the U.S. This pandemic, wrongly called the "Spanish Flu", killed some 20-40 million people around the world, including over 500,000 in the U.S.[193] According to one estimate, if a comparable pandemic were to occur today, it would result in close to two million U.S. deaths.[193] Concerns regarding the repeat of an influenza pandemic accelerated the development of influenza vaccines during the 1930's and 40's, but these efforts soon put in evidence the risk of antigenic drifts associated both with the natural spread of the virus and with the passage of the vaccine antigens through different cell types. Currently,

because of changes in circulation of influenza subtypes and antigenic drifts associated with annual epidemics, a new vaccine composition is decided every year by the World Health organization (WHO), following deliberations with representatives from every region, using virologic data from the main reference laboratories. These decisions are made in September for the southern hemisphere and in February for the northern hemisphere.[97] In the U.S., where, during seasonal influenza epidemics, some 12,000-56,000 influenza-related deaths occur every year, [6] over 150 million doses of influenza vaccines are administered, most of them among the elderly, who are disproportionately affected by influenza-related complications and deaths. [6,194] Although most influenza vaccines used in the U.S. are produced in eggs, there are important differences between them: some (SD) have a standard amount of antigen (15 mcgs per antigen), and are either trivalent (containing antigens from subtype A(H1N1) and A(H3N2) strains plus a single type B lineage strain), or quadrivalent (containing also antigens from a second type B lineage strain); one is adjuvanted,[105] and another (HD) is trivalent and contains 60 mcgs of each antigen per dose.[33] In addition, two recently-licensed vaccines, a sub-unit vaccine prepared from influenza viruses propagated in mammalian cells,[102] and a recombinant protein vaccine consisting of influenza virus hemagglutinin (HA) produced in insect cells,[103] are not egg-based. Differences in vaccine composition, manufacturing processes, egg and cell adaptation, and antigenic drifts (and shifts) may, sometimes dramatically, affect the effectiveness of influenza vaccines.[97,153,193,195] Although public health institutions in the U.S. and abroad already perform rapid evaluations of vaccine effectiveness each season,[97,98,100] these estimates are generally insufficiently powered to evaluate effectiveness against serious outcomes such as influenza hospitalizations, provide accurate effectiveness estimates for the elderly, or produce estimates of the comparative effectiveness of the many licensed vaccines. During the 2017-18 season,

driven by concerns regarding early findings by CDC and others of low absolute effectiveness of influenza vaccines against the dominant A(H3N2) viruses, particularly among the elderly,[100,101] and by the need to rapidly determine whether mutations arising from egg adaptation of the vaccine strain might affect VE differently comparatively to vaccines produced in egg and cell lines,[97,100,170] Using the experience gained by our studies of the comparative effectiveness of the High dose vs. standard dose influenza vaccines, in collaboration with CMS and Acumen, we decided to perform a rapid analysis of the comparative effectiveness of egg-based vs. cell-cultured vaccines during the 2017-18 season, with assistance from Acumen LLC. The preliminary analysis which, thanks to the experience obtained from prior studies of the comparative effectiveness of HD and SD influenza vaccines and other effectiveness studies[16-18,151-153] took only four weeks from study initiation to manuscript preparation found that, although cell-cultured and HD vaccines showed better effectiveness than the comparator egg-based vaccines among persons ages $\geq$65 years, the magnitude of the differences was not sufficient to explain the overall low effectiveness against influenza A(H3N2) viruses during the 2017-18 season among the elderly. Although, given the potential for residual confounding in all RWE studies, and the small magnitude of the differences obtained, such findings would benefit from replication by studies in different settings and health systems, this study has already provided insights to improve our understanding of the potential effects of manufacturing cell lines in vaccine effectiveness and, more important, has also helped stress the need for increased efforts towards the development of universal influenza vaccines for epidemic and pandemic preparedness.[97,150,153,195]

The appropriate use of RWE[13] to timely provide post-marketing data on the comparative and absolute effectiveness of regulated products has a strong potential to help regulators and public health officials make timely decisions relevant for epidemic and pandemic control, thus

helping decrease avoidable medical visits, hospitalizations and deaths.[150,151,153] To facilitate this development, we continue our efforts to provide analyses that could inform specific guidance regarding implementation and interpretation of RWE studies for regulatory decision-making, within the context of the XXI Century Cures Act.[11]

Investigation of the age and sex interaction in the evaluation of the comparative effectiveness of High dose vs. Standard dose vaccine effectiveness

A number of randomized and observational studies have suggested that the HD vaccine has higher efficacy, effectiveness, and superior immune responses compared to the SD vaccines in some, but not all, seasons.[16,18,48,50-52] For the 2011−12 and 2012−13 influenza seasons, a manufacturer-sponsored randomized trial with 31,989 participants demonstrated that, compared with Sanofi's SD vaccine, the HD vaccine was associated with improved protection against laboratory-confirmed influenza illness (relative efficacy 24.2%, 95% confidence interval (CI) 9.7−36.5%), overall influenza related serious adverse events (relative effectiveness 17.7%, 95% CI 6.6−27.4%), and superior immune responses for adults ≥65 years.[48,51] A retrospective cohort study with more than 2.5 million Medicare beneficiaries ≥65 years found that, for the 2012−13 season, HD vaccine recipients were less likely to have influenza office visits (RVE (RVE) 22%, 95% CI 15−29%) and influenza hospitalizations (RVE 22%, 95% CI 16−27%) than SD vaccinees.[16] Shay *et al.* found that the HD vaccine showed better protection against post-influenza mortality than SD vaccines in the 2012−13 (RVE 36.4%, 95% CI 9−56%) but not in the 2013−14 season (RVE 2.5%, 95% CI -47−35%) among Medicare beneficiaries ≥65 years.[18] We

compared RVE of cell-cultured and egg-based influenza vaccines among Medicare beneficiaries

≥65 years in the 2017−18 season and showed that HD was more effective than SD in preventing

influenza hospital encounters (RVE 8.7%, 95% CI 6.5−10.9%)[14]. The same study found that the

cell-cultured SD vaccine had higher RVE than traditional trivalent and quadrivalent SD vaccines.[14]

Several studies have investigated HD relative efficacy, effectiveness, or immunogenicity by age and suggested potential age effect modification. DiazGranados *et al.* analyzed clinical trial data by age group and showed that the point estimate of the relative vaccine efficacy for laboratory-confirmed influenza caused by any influenza strain (regardless of similarity to the vaccine) was higher for participants ages ≥75 years (32.4%, 95% CI 8.1−50.6%) than for those ages 65−74 years (19.7%, 95% CI 0.4−35.4%), although the difference was not statistically significant[50]. However, the study did not have a separate group for people ≥85 years. An unadjusted FDA sub-analysis of the HD relative vaccine efficacy trial found a slightly increasing trend with age for vaccine efficacy of HD relative to SD, even though results were not statistically significant, possibly due to the small number of subjects in the subgroups.[53] In a retrospective cohort observational study among elderly U.S. veterans, Richardson and collaborators showed that, during 2010−11, the risk of hospitalization for influenza or pneumonia was significantly lower among patients receiving HD versus SD vaccine only for patients ≥85 years.[54] Although there are potential limitations in the Richardson study,[55,56] the findings raise questions regarding potential effect modification of HD RVE by age, at least for some seasons.

Due to sex difference in human biological aging and other characteristics, men and women can have different exposures, health status, and morbidity and mortality risks as they age.[57-60] Sex-related differences in influenza vaccine effectiveness and immunogenicity have been observed in studies for both younger (18−64 years) and older (≥65 years) adults.[61-64] The unadjusted FDA sub-analysis of the HD relative vaccine efficacy trial[53] found potential differences in efficacy by sex for culture-confirmed influenza associated with protocol defined influenza-like

illness caused by viral types/subtypes antigenically similar to those contained in the vaccine. However, no significant difference in relative vaccine efficacy by sex was found for the primary endpoint (laboratory-confirmed influenza associated with protocol defined influenza-like illness caused by any viral types/subtypes).

The above-mentioned research suggests that the RVE of HD versus SD influenza vaccines could potentially be modified by age, sex, and factors related to the influenza season, such as severity of influenza circulation and differences between the vaccine and circulating influenza strains. This study aims mainly to investigate potential effect modification by age on the RVE of HD versus SD influenza vaccines for people ≥65 years. We hypothesized that the RVE of HD versus SD influenza vaccines may be higher among older vaccine recipients. We also investigated potential effect modification of age and sex on HD RVE.

The design of the study will be a retrospective cohort, including data from August 2012 to August 2018. The observation period includes six influenza seasons, with the start date of each influenza season defined as the first Sunday of August of that year.

The primary data source for this analysis will consist of Medicare administrative files, including specifically claims and enrollment records from the Centers for Medicare and Medicaid Services (CMS). Also, for this study, pharmacy data will be obtained mainly from the National Plan and Provider Enumeration System, the National Council for Prescription Drug Programs databases, and the Medicare Provider Enrollment, Chain, and Ownership System. Data on national respiratory specimen testing will be obtained from the National Respiratory and Enteric Virus Surveillance System (NREVSS). Data from the Minimum Data Set was used to identify nursing facilities.

The exposure for this study is inactivated influenza vaccine administered (HD or SD).

Influenza vaccinations are identified using Healthcare Common Procedure Coding System and Current Procedural Terminology codes for HD, trivalent SD, and quadrivalent SD influenza vaccinations. However, cell-cultured, recombinant, and adjuvanted SD influenza vaccines will be excluded from the SD vaccine cohort.

The primary outcome will be influenza hospital encounters, defined by inpatient hospitalizations or emergency department visits listing an ICD-9-CM influenza code (487.xx and 488.xx) from the 2012−13 to 2014−15 influenza seasons, or an ICD-10-CM influenza code (J09.xx, J10.xx, J11.xx, and J12.9) starting from the 2015−16 season. The secondary outcome, influenza inpatient hospitalization, will include only inpatient stays.

The study will include Medicare beneficiaries ≥65 years who received an inactivated influenza vaccine in a community pharmacy setting prior to January 31st of an influenza season. Beneficiaries were included for each season in which they received an influenza vaccination. We will exclude beneficiaries with more than one influenza vaccination type in a season.

For this study, we require continuous enrollment in fee-for-service Medicare Parts A (hospital insurance) and B (medical insurance) and no enrollment in Part C (private health insurance) for at least 183 days prior to vaccination to permit the identification of chronic medical conditions. Beneficiaries who entered Medicare due to disability or because of end stage renal disease prior to age 65 years, had a non-verifiable provider zip code on their index vaccination claim, had been in a nursing home facility at any time during the 183 days prior to index date, or received their vaccination at a pharmacy that did not administer the alternate dose within ±14 days of their vaccination date were excluded.

Each calendar week during the study period in each Department of Health and Human

Services (DHHS) region will be classified into high, medium, or low influenza activity periods as described in Shay *et al.*, 2017 using NREVSS data.[18] Data from high influenza activity periods is being used to perform analyses.

Follow-up begins on the 15th day after vaccination to permit the development of vaccine-specific immunity, and continued until one of the following occurred: the occurrence of a study endpoint as described above, disenrollment from Medicare Parts A or B, enrollment into a nursing home facility, the end of the influenza season, or death.

Data on demographics and potentially confounding medical conditions will be collected for each beneficiary during the 183 days prior to vaccination and included as covariates in the analyses. The standardized mean difference (SMD) was used to assess balance in baseline characteristics between the HD and SD cohorts, with a SMD of less than 0.10 denoting a negligible imbalance.

We will use a series of nested Poisson regression models to evaluate the effect of age on the RVE of HD versus SD influenza vaccines, and we are also using another series of nested Poisson models to investigate whether RVE varies by age and sex.

In our previous studies, we defined three age categories: 65−74, 75−84, and ≥85 years. However, defining age as a categorical variable assumes that vaccine effectiveness is constant within each age category and is different at category cut-off points. In reality, relative vaccine effectiveness could change smoothly by age. Therefore, in this study, age will be treated as a continuous variable with alternative functional specifications to explore possible non-linear relationships and make the most efficient use of our data[196]. Three different options for defining the continuous age variable are being used: 1) linear age, 2) cubic spline of age with three degrees of freedom, and 3) cubic spline of age with four degrees of freedom that places an internal knot

at the median.

We hypothesize that age modified the RVE of HD versus SD influenza vaccines among recipients ages ≥65 years. Data from seasons 2012–13 through 2017–18 are being used to conduct the primary analysis. We will start with a basic model with main effects of treatment (HD versus SD), age, sex, season, study covariates, and a season-treatment interaction term. We then build more complex models by sequentially adding the following interaction terms to the initial model: age-treatment, age-season, and age-season-treatment. RVE will be calculated from the rate ratio (RR) estimates comparing the HD and SD cohorts using the following formula: (1⬚RR)⬚100%. We are using measures of overall model fit, Akaike information criterion (AIC), the log-likelihood ratio (LLR) statistic, and graphs of predicted RVEs and incidence rates (IRs) to assess whether additional complexity yielded sufficient improvements in overall fit to justify the degrees of freedom used.

The secondary analysis will focus on investigating a possible age-sex effect on RVE. This new analysis will be performed separately for each season from 2012-13 to 2017-18. Similar to the primary analysis, we will start with a basic model with main effects of treatment (HD versus SD), age, sex, and study covariates, then build more complex models by sequentially adding age-treatment, age-sex, sex-treatment, and age-sex-treatment interaction terms.

The analyses will be conducted using R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) and SAS v. 9.4 (SAS Institute Inc., Cary, NC) with de-identified data collected for administrative purposes by the CMS.

Linking beneficiary surveys with Medicare claims using multiple imputation to evaluate and correct study cohort imbalances using data from our published real-world evidence analysis of the effectiveness of Zostavax vaccination among the U.S. elderly

As it has been indicated, the 21st Century Cures Act[11] directs the US regulators to

"develop a regulatory framework to evaluate how real world evidence (RWE) [13] can

potentially be used to support approval of new indications for approved drugs or to support

or satisfy post-approval study requirements"[25]. This is not without difficulties. In clinical trials,

the comparison groups (e.g. vaccine and placebo recipients) are usually randomized,

guaranteeing that subjects assigned to the test vaccine are not systematically different

from controls regarding measured and unmeasured variables. Thus, investigators can directly

obtain estimates of treatment effects. In RWE studies, the decision to vaccinate is not made at

random; it is instead made by parties such as the medical provider, patient, or insurance

company, for reasons that may be influenced by bias. Thus, the vaccinated and unvaccinated

groups are often not balanced with respect to potential confounders that could affect the

associations being studied. These imbalances, if not well controlled, generate bias which may

affect the direction and magnitude of the association being investigated. Using matching and

other techniques, investigators can control for potential measured confounders , but not for

unmeasured variables. As the magnitude and direction of the potential bias due to unmeasured

confounders cannot be estimated, it limits the use of RWE for regulatory decision-making.

Medicare claims and enrollment databases are a powerful source of RWE, Medicare provides

insurance to some 58.5 million beneficiaries in the United States, of whom 49.8 million are 65 years or older.[123] While Medicare databases include information on a vast array of demographics, health conditions, and services delivered, they do not contain comprehensive information on behavioral and impaired mobility measures. Estimates based on Medicare claims data may therefore be biased. One possible solution is to incorporate information from external sources to evaluate covariate balance and adjust for confounders unavailable in the database.

The Medicare Current Beneficiary Survey (MCBS) [124] is a continuing, multipurpose survey of a nationally representative sample of the Medicare population conducted by the Centers for Medicare and Medicaid Services (CMS) since 1991, with approximately 16,000 respondents yearly. Survey participants are selected each year from a stratified sample of the Medicare population based on age and disability status.[124,125] MCBS data can, therefore, be linked back to the Medicare claims database to provide additional beneficiary behavioral and impaired mobility information.[126]

In this study, we will pilot an approach to: (a) use MCBS data to assess the balance of covariates not available in the claims-based databases used among cohorts in our vaccine effectiveness (VE) studies and, (b) use multiple imputation techniques to evaluate the potential bias in our previous results by adjusting for a select set of MCBS covariates. Specifically, we will reanalyze our study of the effectiveness of the Herpes Zoster (HZ) live vaccine – Zostavax,[17] linking the study population to MCBS to obtain additional information regarding impaired mobility, education, and health seeking behavior. Since the MCBS population comprises only a small portion (0.1%-0.2%) of the Medicare population, we will treat beneficiaries who had not participated in the survey as observations with missing information (missing at random) and use a multiple imputation by chained equations (MICE) approach to impute variables identified as potential confounders.

CONCLUSIONS

In this thesis, we have discussed five vaccine effectiveness studies that have already significantly contributed to determine the extent to which real-world evidence studies can contribute to regulatory science.[150-153] These highly cited manuscripts were published in Lancet, CID and JID,[14-18] four of them were accompanied by journal editorials that highlighted our innovative use of claims data and analyses, and the fifth one was selected as the editor's choice for that issue.[150-153]

Here are the main conclusions from these studies:

(1) These studies have provided researchers with guidance for selecting cohorts with a low probability of including frail individuals, thus decreasing the risk of imbalances that could seriously undermine cohort comparability.

(2) They have contributed by defining claims algorithms for medical office visits that use creative claims combinations, and have demonstrated their validity by repeatedly obtaining results strikingly similar to those from randomized studies performed in similar populations during the same seasons,[48-51,55] thus showing that claims- based studies can reach sufficient outcome specificity for the study of effectiveness for regulatory purposes.

(3) These studies have also helped define high influenza circulation periods. Moreover, we were the first to use the national distribution of influenza antivirals in Medicare to define influenza circulation periods with a quality similar (or even better) to that from current surveillance, with the advantage of being available much faster and being cheaper than any existing system, creating a surveillance tool that is already been explored by us and others.[197,198]

(4) By obtaining effectiveness estimates for severe outcomes that were also very comparable to those obtained during clinical trials, and by obtaining estimates for very rare outcomes,

including death, these studies have also demonstrated the capacity of real-world evidence to provide data unavailable to most randomized studies. [5-7,9]

(5) Our studies have also shown the capacity of real-world evidence to identify significant effectiveness differences and interactions between drugs and vaccines even when the magnitude of the effect is small in magnitude. [5-7,9]

In summary, the successful studies presented here allow us to enter discussions with public health authorities regarding the value of using of real-world data for the systematic investigation of effectiveness against rare and severe outcomes, and for the evaluation of effectiveness of vaccines among special population and risk groups. The need to resolve potential limitations detected in our initial research motivated us to further develop our methods, particularly by using data external to the Medicare claims environment such as surveys that, once linked to individuals found in the claims environment, will allow us to obtain further information on frailty, education and behaviors that could influence the likelihood of becoming ill (frailty) or seeking care (education and other characteristics influencing health care seeking behavior). These efforts, that have already produced initial success, will allow us to both verify the potential for bias and, by using imputations, correct existing bias. Thus, we continue the study of age and sex interaction and vaccine-drug interactions; we are also continuing to creatively use surveys to both determine the cohort match and augment the CMS datasets to include covariates unmeasured in the claims such as level of education and frailty. We are also exploring multiple other approaches to identify and account for the effect of bias in claims studies. These studies, including those in development, are opening new areas in the exploration of the use of real-

world data and may soon become standard practice during the evaluation of new vaccines.

ANNEXES

Proof-of-concept study: Comparative effectiveness of High dose (HD) vs. Standard dose (SD) influenza vaccines against medical office visits and hospitalizations among Medicare beneficiaries ages 65 years and older during the 2012-13 season

Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis

Hector S Izurieta, Nicole Thadani*, David K Shay, Yun Lu, Aaron Maurer, Ivo M Foppa, Riley Franks, Douglas Pratt, Richard A Forshee,
Thomas MaCurdy, Chris Worrall, Andrew E Howery, Jeffrey Kelman*

Summary

Background A high-dose trivalent inactivated influenza vaccine was licensed in 2009 by the US Food and Drug Administration (FDA) on the basis of serological criteria. We sought to establish whether high-dose inactivated influenza vaccine was more effective for prevention of influenza-related visits and hospital admissions in US Medicare beneficiaries than was standard-dose inactivated influenza vaccine.

Methods In this retrospective cohort study, we identified Medicare beneficiaries aged 65 years and older who received high-dose or standard-dose inactivated influenza vaccines from community pharmacies that offered both vaccines during the 2012–13 influenza season. Outcomes were defined with billing codes on Medicare claims. The primary outcome was probable influenza infection, defined by receipt of a rapid influenza test followed by dispensing of the neuraminidase inhibitor oseltamivir. The secondary outcome was a hospital or emergency department visit, listing a Medicare billing code for influenza. We estimated relative vaccine effectiveness by comparing outcome rates in Medicare beneficiaries during periods of high influenza circulation. Univariate and multivariate Poisson regression models were used for analyses.

Findings Between Aug 1, 2012 and Jan 31, 2013, we studied 929730 recipients of high-dose vaccine and 1615545 recipients of standard-dose vaccine. Participants enrolled in each cohort were well balanced with respect to age and presence of underlying medical disorders. The high-dose vaccine (1·01 outcomes per 10000 person-weeks) was 22% (95% CI 15–29) more effective than the standard-dose vaccine (1·30 outcomes per 10000 person-weeks) for prevention of probable influenza infections (rapid influenza test followed by oseltamivir treatment) and 22% (95% CI 16–27%) more effective for prevention of influenza hospital admissions (0·86 outcomes per 10000 person-weeks in the high-dose cohort *vs* 1·10 outcomes per 10000 person-weeks in the standard-dose cohort).

Interpretation Our retrospective cohort study in US Medicare beneficiaries shows that, in people 65 years of age and older, high-dose inactivated influenza vaccine was significantly more effective than standard-dose vaccine in prevention of influenza-related medical encounters. Additionally, the large population in our study enabled us to show, for the first time, a significant reduction in influenza-related hospital admissions in high-dose compared to standard-dose vaccine recipients, an outcome not shown in randomised studies. These results provide important new information to be considered by policy makers recommending influenza vaccinations for elderly people.

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Introduction

Elderly people are at an increased risk of severe influenza-related complications compared with young people.[1,2] People aged 65 years and older account for more than 90% of all influenza deaths.[3] Despite this serious public health burden, only one large randomised placebo-controlled trial of the efficacy of an inactivated influenza vaccine in elderly people has been done.[4–6] That study[6] showed an efficacy of 58% (95% CI 26–77) for the prevention of symptomatic clinical illness associated with laboratory-confirmed influenza illness in participants aged 60 years and older; in those aged 60–69 years, vaccine efficacy was 59% (20 to 79), whereas in participants aged 70 years and older, it was 57% (−36 to 87). Thus, most information

about the effects of the influenza vaccine in people aged 65 years and older is based on observational studies. In these studies,[7–9] estimates of effectiveness of standard-dose inactivated influenza vaccines in the prevention of serious influenza-associated outcomes in people aged 65 years and older have varied widely, suggesting moderate to no effectiveness. Identification of ways to improve the clinical effects of influenza vaccination to reduce influenza disease and its complications in people aged 65 years and older is a public health priority. Researchers have been exploring new vaccines that might increase effectiveness in elderly people.[10]

In December, 2009, the US Food and Drug Administration (FDA) licensed an injectable inactivated

trivalent influenza vaccine (Fluzone High-Dose, Sanofi Pasteur, PA, USA), hereafter referred to as the high-dose vaccine. High-dose vaccines contain about four times more influenza haemagglutinin antigen than standard-dose influenza vaccines (60 µg *vs* 15 µg per strain).[11] The high-dose vaccine was approved by the

See **Online** for appendix

FDA for use in individuals aged 65 years and older, according to accelerated approval regulations.[12] These regulations are applicable to products for treatment or prevention of serious illnesses that provide meaningful therapeutic benefit compared with existing treatments. The data supporting effectiveness needed for licensure of high-dose vaccines came from immunogenicity studies showing that the high-dose vaccines elicited higher haemagglutination inhibition titres than standard-dose Fluzone in adults aged 65 years and older against influenza virus A strains H1N1 and H3N2, and non-inferior antibody titres for the B strain, included in the vaccine, compared with standard-dose Fluzone.[13] Results from a Sanofi-sponsored post-licensure randomised controlled trial[14] of high-dose versus standard-dose vaccine in about 30 000 participants aged 65 years and older showed superior efficacy of the high-dose vaccine for prevention of laboratory-confirmed influenza infections. However, despite the large number of participants enrolled, this study was not powered to characterise efficacy against serious influenza-related outcomes, including hospital admissions.

Additional data for the effectiveness of the high-dose vaccine are needed to obtain data for hospital admissions and other influenza-related outcomes of interest. To quantify the effectiveness of high-dose versus standard-dose vaccines against illness in the community setting and severe outcomes in adults aged 65 years and older, we did a retrospective cohort study in US adults aged 65 years and older using Medicare fee-for-service databases. Thus, unlike the published clinical randomised control trial,[14] we were able to estimate relative vaccine effectiveness by age subgroups for serious influenza illnesses resulting in hospital admission. We hypothesised, on the basis of immunogenicity data available at the time of vaccine licensure,[13] that the high-dose vaccine would be more effective than the standard-dose vaccine at preventing influenza-associated outcomes in US Medicare beneficiaries.

Methods

Study design and participants

In this retrospective cohort analysis, we used influenza vaccination and infection rates from administrative files for the population on the US Medicare programme. See appendix for the full study protocol.

Our study's base population was drawn from fee-for-service Medicare beneficiaries aged 65 years and older who had a Healthcare Common Procedure Coding System (HCPCS) or a Current Procedural Terminology (CPT) code for a high-dose influenza vaccination (CPT of 90662) or standard-dose vaccination (CPT of 90655–90661 or 90724; HCPCS of G0008 or Q2035-Q2038) between Aug 1, 2012, and Jan 31, 2013. Each beneficiary was enrolled in Medicare parts A and B for at least 6 months before vaccination to detect comorbidities, and each remained in the study population while still enrolled and

	High-dose cohort (n=929 730)	Standard-dose cohort (n=1 615 545)	Standardised mean difference
Sex			
Female participants	538 380 (57·91%)	959 072 (59·37%)	0·03
Male participants	391 350 (42·09%)	656 473 (40·63%)	0·03
Race			
White	867 552 (93·31%)	1 512 633 (93·63%)	0·01
Black	25 463 (2·74%)	41 714 (2·58%)	0·01
Other race/unknown	16 235 (1·75%)	27 571 (1·71%)	<0·01
Asian	12 973 (1·40%)	21 178 (1·31%)	0·01
Hispanic	6112 (0·66%)	10 328 (0·64%)	<0·01
Native North American	1395 (0·15%)	2121 (0·13%)	0·01
Dual enrolled	45 186 (4·86%)	79 750 (4·94%)	<0·01
Age (years)	75·74 (7·19)	75·35 (7·27)	0·05
65–74	461 260 (49·61%)	841 789 (52·11%)	0·05
75–85	340 728 (36·65%)	561 385 (34·75%)	0·04
85 and older	127 742 (13·74%)	212 371 (13·15%)	0·02
Region			
Region 1: CT, ME, MA, NH, RI, VT	38 557 (4·15%)	101 886 (6·31%)	0·09
Region 2: NJ, NY, PR, VI	53 732 (5·78%)	128 825 (7·97%)	0·09
Region 3: DE, DC, MD, PA, VA, WV	90 367 (9·72%)	132 085 (8·18%)	0·05
Region 4: AL, FL, GA, KY, MS, NC, SC, TN	250 165 (26·91%)	381 632 (23·62%)	0·08
Region 5: IL, IN, MI, MN, OH, WI	117 795 (12·67%)	297 026 (18·39%)	0·16*
Region 6: AR, LA, NM, OK, TX	103 532 (11·14%)	184 301 (11·41%)	0·01
Region 7: IA, KS, MO, NE	31 048 (3·34%)	80 014 (4·95%)	0·08
Region 8: CO, MT, ND, SD, UT, WY	44 257 (4·76%)	48 346 (2·99%)	0·09
Region 9: AZ, CA, HI, NV, AS, FS, GU, PU	137 678 (14·81%)	196 023 (12·13%)	0·08
Region 10: AK, ID, OR, WA	62 347 (6·71%)	65 056 (4·03%)	0·12*
Other	252 (0·03%)	351 (0·02%)	<0·01
At least one high-risk disorder	560 929 (60·33%)	958 625 (59·34%)	0·02
Asthma	35 276 (3·79%)	59 557 (3·69%)	0·01
Blood disorders	96 553 (10·39%)	162 313 (10·05%)	0·01
Chronic lung disease	128 606 (13·83%)	214 689 (13·29%)	0·02
Diabetes†	186 269 (20·03%)	322 258 (19·95%)	<0·01
Heart disease	302 605 (32·55)	508 973 (31·50%)	0·02
Kidney disorders	60 564 (6·51%)	100 047 (6·19%)	0·01
Liver disorders	16 418 (1·77%)	27 932 (1·73%)	<0·01
Neurological or neurodevelopmental conditions	99 777 (10·73%)	169 533 (10·49%)	0·01
Weakened immune system‡	106 803 (11·49%)	181 003 (11·20%)	0·01

Data are n (%) or mean (SD), unless otherwise specified. *Common characteristics between the high-dose and standard-dose cohorts with a standard mean difference of more than or equal to 0·10, suggesting a substantial difference in proportions between groups. †Diabetes was defined using the International Classification of Diseases, ninth revision, Clinical Modification and Healthcare Common Procedure codes.[23] ‡Weakened immune system was defined using the following Medicare condition categories: HIV/AIDS; metastatic cancer and acute leukaemia; lung or upper digestive or other severe cancer; lymphatic, head, neck, brain, or major cancer; breast, prostate, colorectal, or other cancer; and disorders of immunity

***Table 1*: Baseline characteristics of high-dose and standard-dose cohorts from 24 501 matched pharmacies**

alive. Each beneficiary was also enrolled in Medicare part D from Aug 1, 2012, throughout the high influenza season. Beneficiaries diagnosed with influenza before vaccination or recorded as having received both a high-dose and standard-dose influenza vaccination between Aug 1, 2012, and May 31, 2013, were excluded from the study. Beneficiaries who received standard-dose or high-dose vaccine at a community pharmacy that vaccinated at least one other beneficiary with the alternative influenza vaccine in the 2 weeks preceding or following the index vaccination were eligible for inclusion in the study. This restriction was designed to ensure that each participant had equal access to both vaccinations and was sufficiently healthy to enter a community pharmacy and request influenza vaccination. We believe that the request for vaccination at a community pharmacy implied a minimum amount of self-care ability in cohort members, which would decrease the bias associated with differences in frailty between recipients of each vaccine.[8] Additionally, this community pharmacy-based matching attempted to account for temporal and geographic factors possibly associated both with access to the high-dose vaccine and influenza disease exposure.

Procedures

For each beneficiary in the study, we linked Medicare enrolment and demographic data to claims from inpatient and community settings to track influenza vaccination trends, define outcomes, and establish population characteristics. We used the proportion of samples testing positive for influenza infection in samples submitted to laboratories collaborating with the National Respiratory and Enteric Virus Surveillance System (NREVSS).[15] This Centers for Disease Control and Prevention (CDC)-sponsored nationwide laboratory-based surveillance system monitors temporal and geographic patterns associated with the detection of influenza and other respiratory and enteric viruses. We used NREVSS data to define high, medium, and low influenza periods on the basis of previously published criteria.[16,17]

Outcomes

Our primary outcome was a probable episode of influenza-related illness defined by a community medical encounter with the provision of a rapid influenza diagnostic test coded with CPT 87804,[18] followed by a therapeutic dispensing of oseltamivir within a 2-day period (oseltamivir, 75 mg twice daily for 5 days).[19] Several outcomes attributed to one participant were included in the analysis because contraction of influenza more than once is possible during an influenza season. We did not include other influenza test types in our definition because delays in availability of test results would affect the prescription of influenza-specific antivirals by health-care providers.[20] The rapid influenza diagnostic test and oseltamivir treatment definition included only medical

encounters that occurred in a community setting because Medicare does not code prescriptions dispensed in hospital inpatient or emergency department outpatient claims, and thus, such data were not available to the investigators. In the Centers for Medicare and Medicaid Services (CMS), community setting refers to outcomes observed in a non-institutional setting or outpatient non-emergency department setting.

Our secondary outcome was a hospital inpatient admission or emergency department visit diagnosis of influenza, defined by International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) codes 487.xx or 488.xx. Diagnosis codes specific to influenza suggest a health-care provider's assessment that the Medicare beneficiary has an influenza-associated illness, which might not be confirmed by influenza testing. We used the influenza-associated outcome to capture emergency department visits or hospital admissions with influenza-like illness because of the unavailability of antiviral prescription or laboratory testing data that can be used to define influenza infection in the community setting.

Statistical analysis

To assess the comparability of the high-dose and standard-dose vaccine cohorts, we examined differences between baseline characteristics across cohorts using standardised mean differences, calculated as the difference in means or proportions of a variable divided by the pooled SD of the variable. A standardised mean difference of 0·1 or greater would suggest a substantial difference in means or proportions between groups.[21,22] The large numbers of enrolled participants means that small, clinically insignificant differences might have been statistically significant using standard p value cut-off points, such as $p=0.05$.
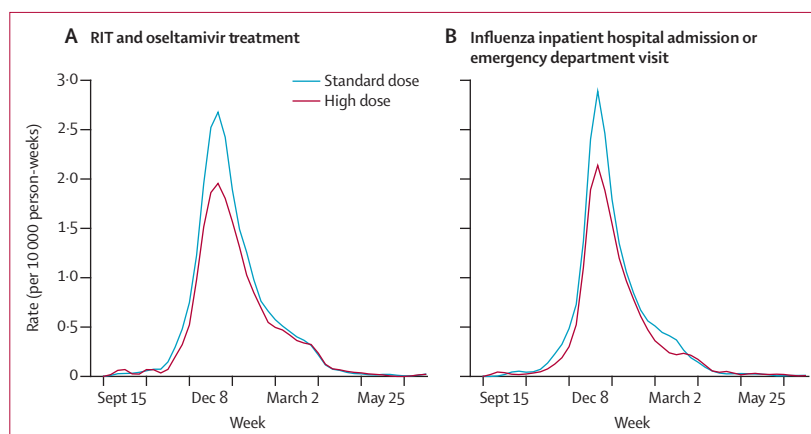
Figure 1: **Influenza outcome rates by vaccine type during the 2012–13 influenza season**
Each plot displays the rate of influenza per 10 000 person-weeks. Data was smoothed using a weighted average, placing a weight of 0·5 on the current week and a weight of 0·25 on the previous and following weeks. (A) Rapid influenza test followed by treatment with oseltamivir. (B) Inpatient hospital admissions or emergency department visits with an influenza International Classification of Diseases, ninth revision, Clinical Modification code. RIT=rapid influenza diagnostic test.
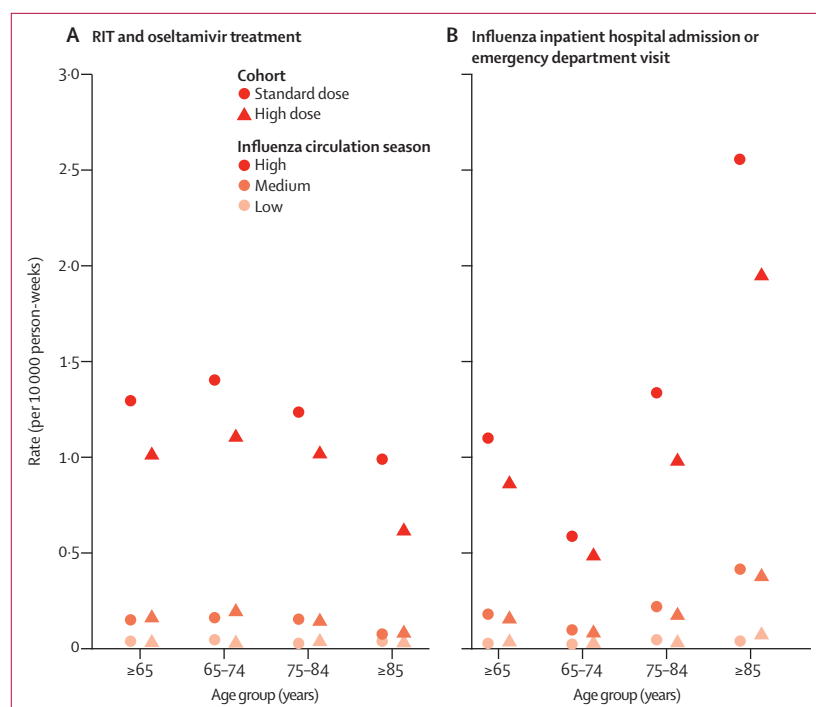
Figure 2: Influenza outcome rates in the 2012–13 influenza season
Each plot displays the rate of influenza per 10 000 person-weeks. (A) Community setting medical encounters including a rapid influenza test followed by treatment with oseltamivir. (B) Inpatient hospital admissions or emergency department visits with an influenza International Classification of Diseases, ninth revision, Clinical Modification code. Both graphs show the rates for the entire cohort (≥65 years) and for the cohort stratified into three age groups (65–74 years, 75–84 years, and ≥85 years). The rates are shown for three periods during the season—high, medium, and low circulation. RIT=rapid influenza diagnostic test.
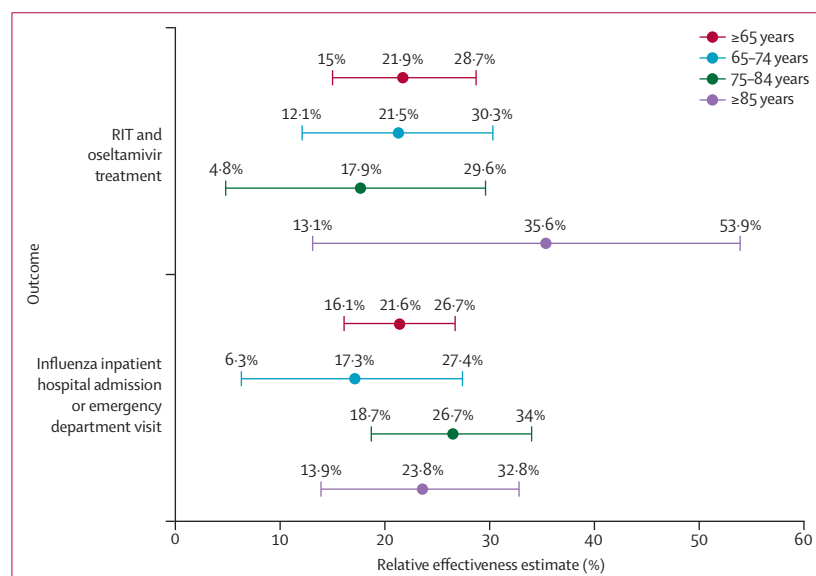
Figure 3: Relative vaccine effectiveness for different outcomes during the 2012–13 high influenza season
Shown are relative effectiveness and 95% CIs for two influenza outcomes. The top outcome is the measure of community medical encounters including a rapid influenza test followed by treatment with oseltamivir, and the bottom outcome is the measure of inpatient hospital admissions or emergency department visits with an International Classification of Diseases, ninth revision, Clinical Modification influenza code. For each outcome, we reported relative effectiveness for the entire cohort and for the cohort stratified into three age groups (65–74 years, 75–84 years, and ≥85 years). RIT=rapid influenza diagnostic test.

Outcome rates were calculated as the number of outcomes per person-time for both high-dose and standard-dose cohorts during the high-influenza period. Periods of influenza activity were classified as low, medium, or high based on CDC influenza virus surveillance data in the four US census regions. High periods of influenza activity included weeks when the proportion of respiratory samples that tested positive for influenza was at the 75th or greater percentile and low periods of influenza activity included the 55th percentile or lower from August, 2012, to August, 2013. We calculated the person-time denominator by summing the number of weeks that beneficiaries were enrolled for each region and period. We calculated the number of outcomes by week and region to establish the numerator.

Relative vaccine effectiveness (RVE) was estimated by the following equation: RVE=(1−rate high-dose recipients/rate standard-dose recipients)×100.

We accounted for potential confounders of the vaccine and outcome association by using multivariate Poisson regression models. The RVE estimates from the multivariate model were adjusted using the list of characteristics in table 1. All analyses were done using STATA version 13.

Role of the funding source
The US Food and Drug Administration made contributions to the design of the study, analysis of the data, interpretation of the results, and writing of the manuscript. The Assistant Secretary of Planning and Evaluation had no role in the design and conduct of the study, in the collection, analysis, and interpretation of the data, or in the preparation, review, or approval of the manuscript. NT had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author was responsible for the final decision to submit for publication.

Results
Between Aug 1, 2012 and Jan 31, 2013, 12 509 108 Medicare beneficiaries aged 65 years and older received influenza vaccinations. Of these beneficiaries, 2 437 077 (19%) received high-dose inactivated influenza vaccine, whereas 10 072 031 (81%) received standard-dose influenza vaccine. From these groups, we identified a cohort of 2 545 275 individuals who were vaccinated at 24 501 pharmacies that offered both vaccines during the 2 week periods. Overall, 929 730 (7·4%) beneficiaries received the high-dose vaccine and 1 615 545 (13%) received a standard-dose vaccine. The two groups were similar in age and underlying medical disorders, although we identified some differences in regional composition of the cohorts (table 1). We compared the high-dose and standard-dose groups by the presence of each of the 189 medical disorder categories designated for Medicare risk adjustment.[24] No standardised mean difference in the proportions of

beneficiaries with any of these disorders was greater than 0·2. Table 1 shows results for disorder categories grouped into classifications associated with increased risk of serious complications of influenza infection, as defined by CDC's Advisory Committee on Immunization Practices.[21,22] Health disorders remained well balanced when high-dose versus standard-dose vaccine recipients were stratified into three age groups (65–74 years, 75–84 years, 85 years and older), although differences by region persisted (data not shown). The correlation coefficient between influenza hospital admission claims and community claims for rapid influenza diagnostic tests followed by the dispensing of oseltamivir was 0·97.

During the high influenza season, the rapid influenza diagnostic test followed by oseltamivir treatment outcome occurred more frequently in the standard-dose recipients (1·30 outcomes per 10 000 person-weeks) than in the high-dose recipients (1·01 outcomes per 10 000 person-weeks), corresponding to a risk difference of 0·29 (95% CI 0·19–0·38; figure 1). We observed differences in outcomes between treatment groups in each age group (figure 2). Community outcomes were rare during periods of low influenza circulation, whereas we identified small differences in outcome during medium periods, and differences were most apparent during periods of high influenza circulation. Repeat outcomes were rare; we noted seven repeat community-based outcomes and no repeat influenza hospital admissions.

Receipt of the high-dose vaccine was correlated with a reduction in influenza inpatient hospital admissions and emergency department visits (0·86 outcomes per 10 000 person-weeks) relative to receipt of the standard dose vaccine (1·10 outcomes per 10 000 person-weeks; figure 2), corresponding to a risk difference of 0·24 (95% CI 0·17–0·30). The hospital admissions and emergency department outcome occurred more frequently in those aged 85 years and older than in younger age groups (figure 2).

In univariate analyses, the high-dose vaccine was more effective than the standard-dose vaccine in Medicare beneficiaries aged 65–74 years, 75–84 years, and 85 years and older (figure 3). For our primary outcome of the rapid influenza diagnostic tests followed by oseltamivir in the community setting, we identified a 22% (95% CI 15–29) reduction in rapid influenza diagnostic test followed by oseltamivir in the community setting high-dose vaccine group (1·01 outcomes per 10 000 person-weeks) compared with the standard-dose vaccine group (1·30 outcomes per 10 000 person-weeks) in all beneficiaries, and a 36% (95% CI 13–54) reduction in those aged 85 years and older (0·62 outcomes per 10 000 person-weeks in the high-dose cohort compared with 0·98 outcomes per 10 000 person-weeks in the standard-dose cohort). The difference in relative vaccine effectiveness between the overall and the 85 years and older groups was not statistically significant (p=0·11 for a two-sided test). In terms of the prevention of hospital

	RIT and oseltamivir treatment		Influenza inpatient hospital admissions or emergency department visit	
	Rate ratio	RVE (95% CI)	Rate ratio	RVE (95% CI)
Calculated rate ratio	0·781	21·9% (15·0–28·7)	0·784	21·6% (16·1–26·7)
Univariate Poisson model	0·782	21·8% (14·8–28·2)	0·783	21·7% (16·2–26·8)
Multivariate Poisson model	0·774	22·6% (15·7–29·0)	0·794	20·6% (14·9–24·8)

RIT=rapid influenza diagnostic test. RVE=relative vaccine effectiveness.

Table 2: Comparison of relative vaccine effectiveness between calculated rate ratio and adjusted and unadjusted Poisson models for the 2012–13 high influenza season

admission and emergency department visits, relative vaccine effectiveness in all beneficiaries was 22% (0·86 outcomes per 10 000 person-weeks in the high-dose cohort compared with 1·10 outcomes per 10,000 person weeks in the standard-dose cohort; 95% CI 16–27). The high-dose vaccine was more effective than the standard-dose vaccine for prevention of influenza-related outcomes in both hospital and emergency department and community settings for all age groups (figure 3). All effect estimates were consistent, whether derived from univariate or multivariate Poisson model regressions (table 2).

Discussion

During the 2012–13 influenza season, we identified that the high-dose influenza vaccine was 22% (95% CI 15–29) more effective at preventing influenza-associated illness treated in the community setting than standard-dose vaccine in a subset of US Medicare beneficiaries aged 65 years and older (panel). We identified a similar effect for influenza-associated hospital admissions and emergency department visits in this group. Our results are similar to the relative efficacy estimates reported in a completed, two-season, randomised controlled study of high-dose versus standard-dose Fluzone done by the manufacturer in more than 30 000 older adults.[14] In that study, the high-dose vaccine was 24% (95% CI 19–37) more effective at preventing reverse transcription PCR-confirmed influenza infections in adults aged 65 years and older than standard-dose vaccine.[13] In the community setting, the estimated relative effectiveness of the high-dose vaccine was higher in Medicare beneficiaries aged 85 years and older than in younger age groups, but this difference was not statistically significant.

A strength of our study is that its population base includes patients identified through Medicare claims data, or about 98% of the US population aged 65 years and older.[25] Medicare provides inpatient, emergency department, and community fee-for-service care for 37 million beneficiaries and prescription coverage for 23 million of these beneficiaries as of January, 2014.[26] In view of the representativeness of these data, we believe that CMS data sources have great potential for use in observational studies in elderly people. Another strength

Articles

Systematic review

Only a few studies of the efficacy, and none of the effectiveness, of the high-dose influenza vaccine have been published.[13,14] We did a systematic title-match PubMed review using the search terms "influenza vaccine effectiveness high dose" and "influenza vaccine efficacy high dose." Only one of the three studies[14] identified was relevant for comparison with the current study: Sanofi Pasteur's double-blind, randomised, active-controlled comparative effectiveness trial that included more than 31 000 participants.[14] That study reported that the high-dose vaccine was 24% (95% CI 19–37) more effective at preventing reverse transcription PCR-confirmed influenza infections in adults aged 65 years and older than the standard-dose vaccine.

Interpretation

Our study identified that the high-dose vaccine was more effective than the standard-dose vaccine to prevent influenza illness treated in both community and inpatient settings. Our frequency matching by community pharmacy resulted in a strong balance in observable potential confounders between the two groups. We had more than 2·5 million study participants after applying cohort restrictions, allowing us to undertake analyses by age into influenza hospital admissions, of particular interest to beneficiaries, providers, regulators, and public health officials. Therefore, our finding of a significantly higher relative effectiveness with the high-dose vaccine against influenza-associated illnesses, confirmed for all age groups analysed, adds important new information. In future studies, these methods might also be used to estimate the possible mortality benefits of newer influenza vaccines. Moreover, our successful use of new methods both for matching and for defining outcomes, in a system that provides coverage for almost all older US adults, opens the door for studies to estimate effectiveness against serious outcomes in specific risk groups in near-real time, for pandemic and other new vaccines.

of this study is the unusual comparability of beneficiaries in the high-dose and standard-dose vaccine groups, which underline the potential usefulness of studying Medicare beneficiaries who are vaccinated in a community pharmacy setting.

This study has several limitations. One potential limitation of the use of Medicare data is the unknown reliability of the ICD-9-CM codes used for the diagnosis of influenza in the community setting. Therefore, we developed an alternative definition for an influenza-related event, consisting of an influenza test followed by the prescription of oseltamivir (an antiviral used exclusively for influenza). Our use of only rapid influenza diagnostic test might have marginally decreased study power during the study period because only 75% of all influenza tests ordered were rapid influenza diagnostic tests. Our results are probably not generalisable to the whole US elderly population because we restricted the analysis to a subset of patients who received influenza vaccination in a community pharmacy setting. Another potential limitation in the use of our definition is that providers might find specific influenza test results most helpful at the beginning and end of influenza seasons and rely on symptoms and history to identify people with influenza infections during the peak of each season. Thus, we might have missed people with influenza, although we do not believe that the likelihood of influenza testing depended on whether a person received the high-dose or standard-dose vaccine.

Influenza-related hospital admissions might also be associated with secondary bacterial infections and with respiratory syncytial virus or other respiratory viral co-infections. Lower respiratory tract infections associated with these respiratory pathogens are difficult to distinguish and assigning a primary pathogen in patients with several infections is also difficult.[27–29] However, the near-perfect correlation between influenza hospital admission claims and community claims for rapid influenza diagnostic test followed by the dispensing of oseltamivir suggests that our hospital admission outcome during periods of high influenza circulation was specific for influenza-related events.

Another limitation of this study is that we did not have access to laboratory results and, therefore, could not define laboratory-confirmed outcomes. Instead, we developed what we believe is a specific outcome that combined a physician's order for a rapid influenza diagnostic test followed by the dispensing of an influenza-specific antiviral within the 2 days after the medical encounter. Because rapid influenza diagnostic test can provide a health-care provider with a result within 15 min after sample collection,[30] the test results can reasonably be expected to guide the decision to prescribe oseltamivir. Therefore, the combination of the rapid influenza diagnostic test and antivirals probably provides greater specificity than a physician diagnosis of influenza or a prescription of antivirals alone.[31,32]

As with all observational vaccine studies, vaccination was not randomly assigned and unmeasured confounders might bias our estimates of the relative effectiveness of high-dose vaccine.[33] However, restriction of the analysis to individuals who were vaccinated at a community pharmacy that offered both vaccines within a 2 week period seems to have yielded well balanced vaccine groups—at least in terms of a comparison of characteristics available and frequently used in pharmacoepidemiology studies (eg, the 189 medical disorder categories considered).[34] The balance we achieved was probably improved by the fact that Medicare beneficiaries do not pay for influenza vaccination in community pharmacy settings, and thus, people were not dissuaded from receiving the more expensive high-dose vaccine. Although the restrictions we used decreased the study sample size, we still had large numbers of participants in both cohorts (about 930 000 high-dose and 1·6 million standard-dose recipients), and were able to do analyses by age group and also for a serious outcome: influenza hospital admissions.

We plan to do similar analyses in upcoming influenza seasons and to do medical record reviews in an attempt to further validate the influenza-related outcomes for a subset of beneficiaries. Our ability to detect and statistically confirm differences in relative effectiveness would be expected to vary with the severity of influenza seasons and with the match between the vaccine and circulating influenza strains. Relative vaccine

effectiveness also might vary by influenza virus type and subtype, including new pandemic viruses. Because Medicare provides medical insurance coverage for almost all US adults aged 65 years and older, estimation of vaccine effectiveness for serious rare outcomes in specific risk groups is possible. Such assessments are usually not possible in randomised studies of comparative treatment or prevention modalities, even when tens of thousands of participants are randomly assigned in large, expensive studies. We plan to investigate the effectiveness of other vaccines administered to Medicare beneficiaries, and to do these assessments in near-real time[35] (eg, within 3 months of an event), as done for other FDA-CMS studies.[36–38]

References

1 Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA* 2004; **292:** 1333–40.

2 Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003; **289:** 179–86.

3 Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993-2008. *Clin Infect Dis* 2012; **54:** 1427–36.

4 Govaert TM, Dinant GJ, Aretz K, Masurel N, Sprenger MJ, Knottnerus JA. Adverse reactions to influenza vaccine in elderly people: randomised double blind placebo controlled trial. *BMJ* 1993; **307:** 988–90.

5 Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *JAMA* 1994; **272:** 1661–65.

6 Thijs C, Beyer WE, Govaert PME, Sprenger MJ, Dinant GJ, Knottnerus A. Mortality benefits of influenza vaccination in elderly people. *Lancet Infect Dis* 2008; **8:** 460–61.

7 Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of influenza vaccine in the community-dwelling elderly. *N Engl J Med* 2007; **357:** 1373–81.

8 Jackson LA, Nelson JC, Benson P, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *Int J Epidemiol* 2006; **35:** 345–52.

9 Cao W, Kim JH, Chirkova T, et al. Improving immunogenicity and effectiveness of influenza vaccine in older adults. *Expert Rev Vaccines* 2011; **10:** 1529–37.

10 McElhaney JE, Beran J, Devaster J-M, et al. AS03-adjuvanted versus non-adjuvanted inactivated trivalent influenza vaccine against seasonal influenza in elderly people: a phase 3 randomised trial. *Lancet Infect Dis* 2013; **13:** 485–96.

11 Centers for Disease Control and Prevention (CDC). Licensure of a high-dose inactivated influenza vaccine for persons aged >or=65 years (Fluzone High-Dose) and guidance for use—United States, 2010. *MMWR Morb Mortal Wkly Rep* 2010; **59:** 485–86.

12 Food and Drug Administration. Press Announcements. FDA approves a high dose seasonal influenza vaccine specifically intended for people ages 65 and older. Dec 13, 2009. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm195483.htm (accessed April 25, 2014).

13 Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis* 2009; **200:** 172–80.

14 DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med* 2014; **371:** 635–45.

15 Centers for Disease Control and Prevention. Overview of influenza surveillance in the United States. Oct 5, 2012. http://www.cdc.gov/flu/weekly/overview.htm (accesssed April 24, 2014).

16 Thompson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. *J Infect Dis* 2006; **1** (suppl 2): S82–91.

17 Brammer L, Budd A, Cox N. Seasonal and pandemic influenza surveillance considerations for constructing multicomponent systems. *Influenza Other Respir Viruses* 2009; **3:** 51–58.

18 Centers for Disease Control and Prevention. Rapid diagnostic testing for influenza: information for clinical laboratory directors. July 6th, 2013. http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm (accessed March 28, 2014).

19 Centers for Disease Control and Prevention. Influenza antiviral medications: summary for clinicians. March 21, 2014. http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm (accessed March 28, 2014).

20 Centers for Disease Control and Prevention. Guidance for clinicians on the use of RT-PCR and other molecular assays for diagnosis of influenza virus infection. July 9, 2013. http://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm (accessed March 28, 2014).

21 Mamdani M, Sykora K, Li P, et al. Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. *BMJ* 2005; **330:** 960–62.

22 Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009; **28:** 3083–107.

23 Graham DJ, Zhou EH, McKean S, et al. Cardiovascular and mortality risk in elderly Medicare beneficiaries treated with olmesartan versus other angiotensin receptor blockers. *Pharmacoepidemiol Drug Saf* 2014; **23:** 331–39.

24 Centers for Medicare and Medicaid Services. 2013 Model Software/ICD-9-CM Mappings. May 16, 2013. http://www.cms.gov/Medicare/Health-Plans/MedicareAdvtgSpecRateStats/Risk-Adjustors-Items/Risk2013.html?DLPage=1&DLSort=0&DLSortDir=descending (accessed April 24, 2014).

25 Wenger JB, Naumova EN. Seasonal synchronization of influenza in the United States older adult population. *PLoS One* 2010; **5:** e10187.

26 Centers for Medicare and Medicaid Services. 2014 CMS Statistics. Baltimore (Maryland): Centers for Medicare and Medicaid Services, 2014.

27 Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000; **342:** 232–39.

28 Skowronski DM, Janjua NZ, Sabaiduc S, et al. Influenza A/subtype and B/lineage effectiveness estimates for the 2011–2012 trivalent vaccine: cross-season and cross-lineage protection with unchanged vaccine. *J Infect Dis* 2014; **210:** 126–37.

29 Skowronski DM, Janjua NZ, De Serres G, et al. A sentinel platform to evaluate influenza vaccine effectiveness and new variant circulation, Canada 2010–2011 season. *Clin Infect Dis* 2012; **55:** 332–42.

30 Centers for Disease Control and Prevention. Rapid diagnostic testing for influenza: information for clinical laboratory directors, table 2. July 6, 2013. http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm#table2 (accessed March 28, 2014).

31 Tamiflu® [package insert]. Foster City, CA: Gilead Science, Inc.; 2008. http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM147992.pdf (accessed Feb 4, 2015).

32   Relenza® [package insert]. Research Triangle Park, NC: GlaxoSmithKline; 2013. https://www.gsksource.com/gskprm/htdocs/documents/RELENZA-PI.PDF (accessed Feb 4, 2015).

33   Simonsen L, Viboud C, Taylor RJ, Miller MA, Jackson L. Influenza vaccination and mortality benefits: new insights, new opportunities. *Vaccine* 2009; **27:** 6300–04.

34   Graham DJ, Ouellet-Hellstrom R, MaCurdy TE, et al. Risk of acute myocardial infarction, stroke, heart failure, and death in elderly Medicare patients treated with rosiglitazone or pioglitazone. *JAMA* 2010; **304:** 411–18.

35   Greene SK, Kulldorff M, Lewis EM, et al. Near real-time surveillance for influenza vaccine safety: proof-of-concept in the Vaccine Safety Datalink Project. *Am J Epidemiol* 2010; **171:** 177–88.

36   Burwen DR, Sandhu SK, MaCurdy TE, et al, and the Safety Surveillance Working Group. Surveillance for Guillain-Barré syndrome after influenza vaccination among the Medicare population, 2009–2010. *Am J Public Health* 2012; **102:** 1921–27.

37   Polakowski LL, Sandhu SK, Martin DB, et al. Chart-confirmed Guillain-Barre syndrome after 2009 H1N1 influenza vaccination among the Medicare population, 2009–2010. *Am J Epidemiol* 2013; **178:** 962–73.

38   Franks RR, Sandhu SK, Avagyan A, et al. Robustness properties of a sequential test for vaccine safety in the presence of misspecification. *Stat Anal Data Min* 2014; **7:** 368–75.

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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Comparative Influenza Vaccine Effectiveness Study Protocol

Background:

Understanding influenza vaccine effectiveness in the elderly is crucial to minimizing hospitalizations and death due to influenza. The elderly face a higher risk for severe influenza-related complications than other age groups, because immune systems often weaken with age.[1,2] The elderly also respond to vaccination with lower antibody titers to influenza hemagglutinin when compared with younger adults.[3] Researchers are investigating alternate formulations and higher doses of the influenza vaccine for improved vaccine effectiveness in the elderly.

The effectiveness of the standard-dose inactivated influenza vaccine among people ages 65 years and older is subject to controversy. Current study conclusions vary widely between very high estimates of effectiveness that suggest that the influenza vaccine reduces the risk of death from all causes by 50% and very low estimates that conclude the vaccine has no effectiveness.[4,5] Only one small (<2000 subjects) post-licensure clinical trial has been published, and its estimates of effectiveness depended upon serological diagnosis of influenza.[6] Recent research suggests that use of a serologic endpoint for influenza diagnosis tends to overestimate the effect of inactivated vaccines, because once antibody titers increase in response to the vaccine, they reach an "antibody ceiling" and cannot rise further in response to infection.[7]

On December 23, 2009 the Food and Drug Administration (FDA) licensed an injectable inactivated trivalent influenza vaccine (Fluzone High-Dose, Sanofi-Pasteur) that contains approximately four times the amount of influenza virus hemagglutinin antigen as compared to other inactivated influenza vaccines.[8] Fluzone High-Dose is licensed for use in the elderly and it has been available since the 2010-2011 influenza season, although its availability was initially limited. For licensure, efficacy of the vaccine was characterized by immunogenicity. Data from three studies among the elderly indicated that Fluzone High-Dose elicited higher hemagglutination inhibition titers against all three influenza virus strains included in the vaccine as compared to standard-dose Fluzone.[9,10,11] A recent two-season study conducted by Sanofi-Pasteur on the Fluzone High-Dose vaccine using a cohort of 30,000 older adults found that the High-Dose vaccine is 24·2 percent more effective in preventing influenza in older adults than the standard vaccine.[12] This study can be expanded upon by characterizing vaccine effectiveness in different age groups and in patients with different risk factors to understand the usefulness of the high-dose vaccine in the Medicare population.

Investigating influenza vaccine effectiveness is challenging. Vaccine effectiveness varies based on the adequacy of the antigenic match between the vaccine and the circulating influenza strain, the specific population vaccinated, the interval between vaccination and disease exposure, the age of vaccine administration, and the vaccinee's immune system, among other factors. Since influenza diagnostic tests are used infrequently, secondary infections such as bacterial pneumonia often cause influenza patient hospitalization. In addition, respiratory syncytial virus, other respiratory viruses, and other non-viral pathogens often cause lower respiratory tract infections in winter.[13] Therefore, identifying outcomes that can be used as surrogates for influenza-related complications is difficult. In addition, characteristics of the vaccinated population provide other complications in assessing the effectiveness of the influenza vaccine. Vaccine effectiveness is hard to assess for the very frail, since they are less likely to receive vaccines. In addition, vaccines are administered in a wide variety of settings, including nursing homes, hospitals, outpatient settings, and pharmacies. The patients that receive vaccination in these locations differ greatly in demographic and health characteristics.

In the United States, CMS is the primary medical insurance provider for a large majority of the elderly population through Medicare. CMS holds claims records for the medical care received by a large percentage of the 65 years and older population. These records have strong potential for use in a study of the high-dose influenza vaccine among the elderly. Since these records include a wide range of demographic and healthcare information, they can be used to determine high-dose vaccination field effectiveness in different age and risk groups. However, claims data has some limitations. Diagnoses on claims for respiratory illnesses are often imprecise since many conditions have similar symptoms. In addition, the vaccination status of individuals without vaccination claims in CMS is unknown, since they

may have been vaccinated outside of CMS or their claims may not have been submitted. Even with these limitations, CMS claims information is a viable tool for analyzing vaccine effectiveness in the elderly since the information is comprehensive, collected continuously, and covers a large percent of the population of interest.

This study uses CMS data to designate cohorts of study that focus on relatively homogenous populations in terms of health, socioeconomic status, and geographic region, with access to both the high-dose and seasonal-dose vaccine. Then, claims data is used to identify adverse outcomes related to influenza in vaccinated populations. These adverse outcomes are analyzed with consideration to the amount of influenza circulating at the time of event. With this information, this study can compare the effectiveness of the seasonal and high-dose vaccines in different phases of influenza circulation.

Methods:

Study Periods:

Protocols for this analysis were designed and refined using data from the 2010-2011 and 2011-2012 influenza seasons. For the 2012-2013 season these protocols will be implemented.

Data Sources:

Influenza vaccination and infection rates for this study were drawn from administrative files for the US Medicare population. For each beneficiary in the study, we linked Medicare enrollment and demographic data to claims from inpatient and community settings to track influenza vaccination trends, define outcomes, and determine population characteristics. The proportion of samples testing positive for influenza infection submitted to laboratories collaborating with the National Respiratory and Enteric Virus Surveillance System (NREVSS)[14] were used to define the high, medium, and low influenza seasons using previously published criteria.[15,16]

Study Population:

Our study's base population is drawn from Medicare beneficiaries aged 65 years and older who have a Healthcare Common Procedure Coding System (HCPCS) or Current Procedural Terminology (CPT) code for a high-dose influenza vaccination (CPT of 90662) or standard-dose vaccination (CPT of 90655-90661 or 90724; HCPCS of G0008, Q2035-Q2038) between August 1st, 2012 and January 31st, 2013. Each beneficiary must be enrolled in Medicare part A and B for a period of at least 6 months prior to vaccination through Medicare, and only remains in a study population while still enrolled and alive. Additionally, since our primary study outcome (defined under "Outcomes of Interest") includes receipt of an oseltamivir prescription, each beneficiary must also be enrolled in Medicare Part D from August 1st, 2012 throughout the high influenza season. No beneficiary who originally enrolled in Medicare due to disability is included, because these beneficiaries tend to be a sicker population than those who age into Medicare. Further, no beneficiary who is diagnosed with influenza prior to vaccination, or is recorded as having received both a high and seasonal dose influenza vaccination between August 1st, 2012 and May 31st, 2013 will be included.

The pharmacy-matched cohort is drawn from members of the base population who were vaccinated at a pharmacy. Vaccination at a pharmacy indicates that the beneficiary was able to enter the pharmacy to receive the shot, implying a basic level of mobility. In addition, each beneficiary in this cohort received their vaccination at a pharmacy which vaccinated another cohort member with the other dose within +/- two weeks. This restriction controls for temporal and geographic factors that may possibly affect high-dose vaccination rates and influenza disease exposure. We identify pharmacy locations by mapping national provider identifier (NPI) codes billed with each vaccine to pharmacy identifiers (NCPDPs).

Outcomes of Interest:

Our primary outcome of interest is a likely episode of influenza related illness defined by an outpatient medical encounter with the provision of a rapid influenza diagnostic test (RIT) coded with CPT 87804,[17] followed by a therapeutic dispensing of oseltamivir within a 2-day period (oseltamivir, 75 mg twice daily for 5 days, see Table 1 for list of NDCs).[18] This dosage did not include other influenza test types that take longer processing time and require more complex laboratory methods in our outcome measure because of the delay in availability of results to healthcare providers. This became necessary because we did not have access to results from the diagnostic test and, therefore, needed a test with immediately available results to support our assumption that the choice of an influenza-specific treatment following the test implied a positive laboratory result.[19] Multiple outcomes attributed to one participant are included in the analysis because it is possible to contract influenza more than once during an influenza season. The RIT and oseltamivir treatment definition includes only medical encounters that occur in a community setting because Medicare does not code prescriptions dispensed in hospital inpatient or emergency department outpatient claims, and thus such data is not available. In CMS, community setting refers to outcomes observed in a non-institutional setting or outpatient non-emergency department setting. We did not include any oseltamivir prescriptions dispensed to beneficiaries who received care in a nursing home facility, due to the possibility that these prescriptions were for prophylactic use.[18]

Our secondary outcome is a hospital inpatient admission or emergency department visit diagnosis of influenza, defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 487·0, 487·1, 487·8, 488·0. Diagnosis codes specific to influenza indicate a health care provider's assessment that the beneficiary suffers from an influenza-associated illness and may not be confirmed by influenza testing. We use the influenza-associated outcome to capture emergency department visits or hospitalizations with influenza-like illness because of the lack of availability of antiviral prescription or laboratory testing data as used to define influenza infection in the community setting.

Influenza Circulation:

To capture beneficiaries' exposure to influenza, the model requires a measure of influenza spread through the United States over the course of the influenza season. Influenza antiviral prescription rates in the Medicare part D 65 years and older population are used as an indicator of influenza spread in the model. To select this indicator, rates of antiviral claims over the influenza season by region were compared with CDC virologic surveillance of influenza. CDC surveillance tracks the number of viral tests administered weekly at collaborating laboratories, as well as the percentage that return a positive result. Trends in antiviral prescriptions correlate well with the number of positive influenza tests observed by CDC surveillance. In addition, since antiviral prescriptions are observed in an older population, they are more likely to represent the magnitude of influenza risk posed to the elderly. In the 2012-2013 season, when the 65 years and older population represented a higher proportion of influenza hospitalizations than any season for which the CDC has conducted such assessments, antiviral prescriptions indicated a higher magnitude of influenza circulation as compared to other seasons that was not apparent in CDC virologic surveillance.[20] We also used the rate of weekly virologic tests that return a positive result to define high (including and greater than 18% of tests, corresponding to the 75th percentile, return a positive result), low (including and less than 6·5% of tests, corresponding to the 55th percentile, return a positive result), and medium (remaining tests) influenza seasons.

Statistical Models:

We used univariate and multivariate Poisson regressions to model the weekly outcome rate of influenza infections in the high season. The covariates for the multivariate Poisson model (listed in Table 2) adjust for any factors that may influence influenza susceptibility between the two cohorts. Additionally, the model contains age covariates, so the impact of reduced immunity in the very elderly on vaccine effectiveness can be observed.

Further Analysis:

To account for the impact of age on vaccine effectiveness, the initial analysis will stratify the pharmacy-matched cohort into 65-74, 75-84, and 85+ age groupings. Later, we will incorporate age as a continuous variable in a model using splines to precisely characterize differential vaccine effectiveness by age group.

In subsequent analyses, this study will evaluate the significance of pharmacy effects on the model. Future studies will examine the full base population, as well as cohorts selected to examine vaccine effectiveness in frailer beneficiaries, such as those enrolled in home health or in skilled nursing facilities.

Table 1. List of NDCs used to define oseltamivir

NDC	Label Description
00004080085	Oseltamivir 75 mg gelcap
12280020310	Oseltamivir 75 mg gelcap
16590021310	Oseltamivir 75 mg gelcap
16590021320	Oseltamivir 75 mg gelcap
16590021330	Oseltamivir 75 mg gelcap
23490801600	Oseltamivir 75 mg gelcap
42254000110	Oseltamivir 75 mg gelcap
47463055710	Oseltamivir 75 mg gelcap
49999029810	Oseltamivir 75 mg gelcap
52959080110	Oseltamivir 75 mg gelcap
53002138701	Oseltamivir 75 mg gelcap
54569488800	Oseltamivir 75 mg gelcap
54868447600	Oseltamivir 75 mg gelcap
55045275901	Oseltamivir 75 mg gelcap
55048055710	Oseltamivir 75 mg gelcap
55887075510	Oseltamivir 75 mg gelcap
55887085110	Oseltamivir 75 mg gelcap
57866800201	Oseltamivir 75 mg gelcap
58016478901	Oseltamivir 75 mg gelcap
63874009810	Oseltamivir 75 mg gelcap
68030800201	Oseltamivir 75 mg gelcap

Table 2. List of covariates used in adjusted Poisson model.

Covariates	
Age	**Low Income Subsidy (LIS)**
65 to 74	*Not LIS*
75 to 84	*No Copay*
85 +	*Low Copay*
Gender	*High Copay*
Female	*15% Copay*
Male	
Race	**Medical Conditions**
White	*Diabetic*
Black	*At least one Inpatient Hospitalization*
Hispanic	*At Least One High Risk condition*
Asian	*Asthma Diagnosis*
Native	*Blood Disorder Diagnosis*
Unknown	*Chronic Lung Disease Diagnosis*
Regions	*Heart Disease Diagnosis*
1: CT, ME, MA, NH, RI, VT	*Kidney Disorder Diagnosis*
2: NJ, NY, PR, VI	*Liver Disorder Diagnosis*
3: DE, DC, MD, PA, VA, WV	*Neurological Disorder Diagnosis*
4: AL, FL, GA, KY, MS, NC, SC, TN	*Weakened Immune System Diagnosis*
5: IL, IN, MI, MN, OH, WI	
6: AR, LA, NM, OK, TX	
7: IA, KS, MO, NE	
8: CO, MT, ND, SD, UT, WY	
9: AZ, CA, HI, NV, AS, FS, GU, PU	
10: AK, ID, OR, WA	

References:

1.   Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA*. 2004; **292**(11): 1333–1340.
2.   Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the united states. *JAMA*. 2003; **289**(2): 179–186.
3.   Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine*. 2006; **24**:1159–1169.
4.   Nichol KL, Nordin JD, Nelson DB, et al. Effectiveness of Influenza Vaccine in the Community-Dwelling Elderly. *N. Engl. J. Med*. 2007; **357**(14): 1373–1381.
5.   Jackson LA, Nelson JC, Benson P, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *Int. J. Epidemiol*. 2006; **35**(2): 345–352.
6.   Govaert TE, Thijs CN, Masurel NN, et al. The efficacy of influenza vaccination in elderly individuals: A randomized double-blind placebo-controlled trial. *JAMA*. 1994; **272**(21): 1661–1665.
7.   Petrie JG, Ohmit SE, Johnson E, Cross RT, Monto AS. Efficacy Studies of Influenza Vaccines: Effect of End Points Used and Characteristics of Vaccine Failures. *J Infect Dis*. 2011; **203**(9):1309–1315.
8.   Centers for Disease Control and Prevention. Licensure of a High-Dose Inactivated Influenza Vaccine for Persons Aged ≥65 Years (Fluzone High-Dose) and Guidance for Use. *MMWR*. 2010; **59**(16): 485–486.
9.   Couch RB, Winokur P, Brady W, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. *Vaccine*. 2007; **35**(44): 7656–7663.
10.   Falsey AR, Treanor JJ, Tornieporth N, Cappelan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis*. 2009; **200**(2):172–180.
11.   Keitel WA, Atmar RL, Cate TR, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. *Arch Intern Med*. 2006; **166**(10):1121–1127.
12.   Diaz Granados CA, Dunning AJ, Kimmel M, et al. Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults, *N. Engl. J. Med*. 2014; **371**(7): 635–645.
13.   Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the Rates of Hospitalization for Respiratory Disease among Infants and Young Children. *N. Engl. J. Med*. 2000; **342**(4): 232–239.
14.   Centers for Disease Control and Prevention. Overview of Influenza Surveillance in the United States. October 5, 2012. Retrieved from http://www.cdc.gov/flu/weekly/overview.htm on April 24th, 2014.
15.   Thompson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. *J Infect Dis*. 2006; **1**(194):Suppl 2:S82–91.
16.   Brammer L, Budd A, Cox N. Seasonal and pandemic influenza surveillance considerations for constructing multicomponent systems. Influenza Other Respir Viruses. 2009; **3**(2):51–58.
17.   Centers for Disease Control and Prevention. Rapid diagnostic testing for influenza: information for clinical laboratory directors. July 6th, 2013. Retrieved from http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm on March 28th, 2014.
18.   Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. March 21st, 2014. Retrieved from http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm on March 28th, 2014.
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20.   Centers for Disease Control and Prevention. 2012-2013 Flu Season Drawing to a Close. March 29th, 2013. Retrieved from http://www.cdc.gov/flu/spotlights/2012-2013-flu-season-wrapup.htm on September 4th, 2013.

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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Comparative Influenza Vaccine Effectiveness Study Protocol

Background:

Understanding influenza vaccine effectiveness in the elderly is crucial to minimizing hospitalizations and death due to influenza. The elderly face a higher risk for severe influenza-related complications than other age groups, because immune systems often weaken with age.[1,2] The elderly also respond to vaccination with lower antibody titers to influenza hemagglutinin when compared with younger adults.[3] Researchers are investigating alternate formulations and higher doses of the influenza vaccine for improved vaccine effectiveness in the elderly.

The effectiveness of the standard-dose inactivated influenza vaccine among people ages 65 years and older is subject to controversy. Current study conclusions vary widely between very high estimates of effectiveness that suggest that the influenza vaccine reduces the risk of death from all causes by 50% and very low estimates that conclude the vaccine has no effectiveness.[4,5] Only one small (<2000 subjects) post-licensure clinical trial has been published, and its estimates of effectiveness depended upon serological diagnosis of influenza.[6] Recent research suggests that use of a serologic endpoint for influenza diagnosis tends to overestimate the effect of inactivated vaccines, because once antibody titers increase in response to the vaccine, they reach an "antibody ceiling" and cannot rise further in response to infection.[7]

On December 23, 2009 the Food and Drug Administration (FDA) licensed an injectable inactivated trivalent influenza vaccine (Fluzone High-Dose, Sanofi-Pasteur) that contains approximately four times the amount of influenza virus hemagglutinin antigen as compared to other inactivated influenza vaccines.[8] Fluzone High-Dose is licensed for use in the elderly and it has been available since the 2010-2011 influenza season, although its availability was initially limited. For licensure, efficacy of the vaccine was characterized by immunogenicity. Data from three studies among the elderly indicated that Fluzone High-Dose elicited higher hemagglutination inhibition titers against all three influenza virus strains included in the vaccine as compared to standard-dose Fluzone.[9,10,11] A recent two-season study conducted by Sanofi-Pasteur on the Fluzone High-Dose vaccine using a cohort of 30,000 older adults found that the High-Dose vaccine is 24·2 percent more effective in preventing influenza in older adults than the standard vaccine.[12] This study can be expanded upon by characterizing vaccine effectiveness in different age groups and in patients with different risk factors to understand the usefulness of the high-dose vaccine in the Medicare population.

Investigating influenza vaccine effectiveness is challenging. Vaccine effectiveness varies based on the adequacy of the antigenic match between the vaccine and the circulating influenza strain, the specific population vaccinated, the interval between vaccination and disease exposure, the age of vaccine administration, and the vaccinee's immune system, among other factors. Since influenza diagnostic tests are used infrequently, secondary infections such as bacterial pneumonia often cause influenza patient hospitalization. In addition, respiratory syncytial virus, other respiratory viruses, and other non-viral pathogens often cause lower respiratory tract infections in winter.[13] Therefore, identifying outcomes that can be used as surrogates for influenza-related complications is difficult. In addition, characteristics of the vaccinated population provide other complications in assessing the effectiveness of the influenza vaccine. Vaccine effectiveness is hard to assess for the very frail, since they are less likely to receive vaccines. In addition, vaccines are administered in a wide variety of settings, including nursing homes, hospitals, outpatient settings, and pharmacies. The patients that receive vaccination in these locations differ greatly in demographic and health characteristics.

In the United States, CMS is the primary medical insurance provider for a large majority of the elderly population through Medicare. CMS holds claims records for the medical care received by a large percentage of the 65 years and older population. These records have strong potential for use in a study of the high-dose influenza vaccine among the elderly. Since these records include a wide range of demographic and healthcare information, they can be used to determine high-dose vaccination field effectiveness in different age and risk groups. However, claims data has some limitations. Diagnoses on claims for respiratory illnesses are often imprecise since many conditions have similar symptoms. In addition, the vaccination status of individuals without vaccination claims in CMS is unknown, since they

may have been vaccinated outside of CMS or their claims may not have been submitted. Even with these limitations, CMS claims information is a viable tool for analyzing vaccine effectiveness in the elderly since the information is comprehensive, collected continuously, and covers a large percent of the population of interest.

This study uses CMS data to designate cohorts of study that focus on relatively homogenous populations in terms of health, socioeconomic status, and geographic region, with access to both the high-dose and seasonal-dose vaccine. Then, claims data is used to identify adverse outcomes related to influenza in vaccinated populations. These adverse outcomes are analyzed with consideration to the amount of influenza circulating at the time of event. With this information, this study can compare the effectiveness of the seasonal and high-dose vaccines in different phases of influenza circulation.

Methods:

Study Periods:

Protocols for this analysis were designed and refined using data from the 2010-2011 and 2011-2012 influenza seasons. For the 2012-2013 season these protocols will be implemented.

Data Sources:

Influenza vaccination and infection rates for this study were drawn from administrative files for the US Medicare population. For each beneficiary in the study, we linked Medicare enrollment and demographic data to claims from inpatient and community settings to track influenza vaccination trends, define outcomes, and determine population characteristics. The proportion of samples testing positive for influenza infection submitted to laboratories collaborating with the National Respiratory and Enteric Virus Surveillance System (NREVSS)[14] were used to define the high, medium, and low influenza seasons using previously published criteria.[15,16]

Study Population:

Our study's base population is drawn from Medicare beneficiaries aged 65 years and older who have a Healthcare Common Procedure Coding System (HCPCS) or Current Procedural Terminology (CPT) code for a high-dose influenza vaccination (CPT of 90662) or standard-dose vaccination (CPT of 90655-90661 or 90724; HCPCS of G0008, Q2035-Q2038) between August 1st, 2012 and January 31st, 2013. Each beneficiary must be enrolled in Medicare part A and B for a period of at least 6 months prior to vaccination through Medicare, and only remains in a study population while still enrolled and alive. Additionally, since our primary study outcome (defined under "Outcomes of Interest") includes receipt of an oseltamivir prescription, each beneficiary must also be enrolled in Medicare Part D from August 1st, 2012 throughout the high influenza season. No beneficiary who originally enrolled in Medicare due to disability is included, because these beneficiaries tend to be a sicker population than those who age into Medicare. Further, no beneficiary who is diagnosed with influenza prior to vaccination, or is recorded as having received both a high and seasonal dose influenza vaccination between August 1st, 2012 and May 31st, 2013 will be included.

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Outcomes of Interest:

Our primary outcome of interest is a likely episode of influenza related illness defined by an outpatient medical encounter with the provision of a rapid influenza diagnostic test (RIT) coded with CPT 87804,[17] followed by a therapeutic dispensing of oseltamivir within a 2-day period (oseltamivir, 75 mg twice daily for 5 days, see Table 1 for list of NDCs).[18] This dosage did not include other influenza test types that take longer processing time and require more complex laboratory methods in our outcome measure because of the delay in availability of results to healthcare providers. This became necessary because we did not have access to results from the diagnostic test and, therefore, needed a test with immediately available results to support our assumption that the choice of an influenza-specific treatment following the test implied a positive laboratory result.[19] Multiple outcomes attributed to one participant are included in the analysis because it is possible to contract influenza more than once during an influenza season. The RIT and oseltamivir treatment definition includes only medical encounters that occur in a community setting because Medicare does not code prescriptions dispensed in hospital inpatient or emergency department outpatient claims, and thus such data is not available. In CMS, community setting refers to outcomes observed in a non-institutional setting or outpatient non-emergency department setting. We did not include any oseltamivir prescriptions dispensed to beneficiaries who received care in a nursing home facility, due to the possibility that these prescriptions were for prophylactic use.[18]

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Statistical Models:

We used univariate and multivariate Poisson regressions to model the weekly outcome rate of influenza infections in the high season. The covariates for the multivariate Poisson model (listed in Table 2) adjust for any factors that may influence influenza susceptibility between the two cohorts. Additionally, the model contains age covariates, so the impact of reduced immunity in the very elderly on vaccine effectiveness can be observed.

Further Analysis:

To account for the impact of age on vaccine effectiveness, the initial analysis will stratify the pharmacy-matched cohort into 65-74, 75-84, and 85+ age groupings. Later, we will incorporate age as a continuous variable in a model using splines to precisely characterize differential vaccine effectiveness by age group.

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58016478901	Oseltamivir 75 mg gelcap
63874009810	Oseltamivir 75 mg gelcap
68030800201	Oseltamivir 75 mg gelcap

Table 2. List of covariates used in adjusted Poisson model.

Covariates	
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65 to 74	*Not LIS*
75 to 84	*No Copay*
85 +	*Low Copay*
Gender	*High Copay*
Female	*15% Copay*
Male	
Race	**Medical Conditions**
White	*Diabetic*
Black	*At least one Inpatient Hospitalization*
Hispanic	*At Least One High Risk condition*
Asian	*Asthma Diagnosis*
Native	*Blood Disorder Diagnosis*
Unknown	*Chronic Lung Disease Diagnosis*
Regions	*Heart Disease Diagnosis*
1: CT, ME, MA, NH, RI, VT	*Kidney Disorder Diagnosis*
2: NJ, NY, PR, VI	*Liver Disorder Diagnosis*
3: DE, DC, MD, PA, VA, WV	*Neurological Disorder Diagnosis*
4: AL, FL, GA, KY, MS, NC, SC, TN	*Weakened Immune System Diagnosis*
5: IL, IN, MI, MN, OH, WI	
6: AR, LA, NM, OK, TX	
7: IA, KS, MO, NE	
8: CO, MT, ND, SD, UT, WY	
9: AZ, CA, HI, NV, AS, FS, GU, PU	
10: AK, ID, OR, WA	

References:

1. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA*. 2004; **292**(11): 1333–1340.
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11. Keitel WA, Atmar RL, Cate TR, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. *Arch Intern Med*. 2006; **166**(10):1121–1127.
12. Diaz Granados CA, Dunning AJ, Kimmel M, et al. Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults, *N. Engl. J. Med*. 2014; **371**(7): 635–645.
13. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the Rates of Hospitalization for Respiratory Disease among Infants and Young Children. *N. Engl. J. Med*. 2000; **342**(4): 232–239.
14. Centers for Disease Control and Prevention. Overview of Influenza Surveillance in the United States. October 5, 2012. Retrieved from http://www.cdc.gov/flu/weekly/overview.htm on April 24th, 2014.
15. Thompson WW, Comanor L, Shay DK. Epidemiology of seasonal influenza: use of surveillance data and statistical models to estimate the burden of disease. *J Infect Dis*. 2006; **1**(194):Suppl 2:S82–91.
16. Brammer L, Budd A, Cox N. Seasonal and pandemic influenza surveillance considerations for constructing multicomponent systems. Influenza Other Respir Viruses. 2009; **3**(2):51–58.
17. Centers for Disease Control and Prevention. Rapid diagnostic testing for influenza: information for clinical laboratory directors. July 6th, 2013. Retrieved from http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm on March 28th, 2014.
18. Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians. March 21st, 2014. Retrieved from http://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm on March 28th, 2014.
19. Centers for Disease Control and Prevention. Guidance for clinicians on the use of RT-PCR and other molecular assays for diagnosis of influenza virus infection. July 9th, 2013. Retrieved from http://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm on March 28th, 2014.
20. Centers for Disease Control and Prevention. 2012-2013 Flu Season Drawing to a Close. March 29th, 2013. Retrieved from http://www.cdc.gov/flu/spotlights/2012-2013-flu-season-wrapup.htm on September 4th, 2013.

Journal editorials commenting the studies presented in this thesis

7   Writing Committee of the Second WHO Consultation on Clinical Aspects of Human Infection with Avian Influenza A (H5N1) Virus. Update on avian influenza A (H5N1) virus infection in humans. *N Engl J Med* 2008; **358:** 261–73.

8   Zhou B, Zhong N, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) infection. *N Engl J Med* 2007; **357:** 1450–51.

9   Kong LK, Zhou BP Successful treatment of avian influenza with convalescent plasma. *Hong Kong Med J* 2006; **12:** 489.

10   Herbreteau CH, Jacquot F, Rith S, et al. Specific polyclonal F(ab′)₂ neutralize a large panel of highly pathogenic avian influenza A viruses (H5N1) and control infection in mice. *Immunotherapy* 2014; **6:** 699–708.

11   Quiambao BP, Dytioco HZ, Dizon RM, Crisostomo ME, Laot TM, Teuwen DE. Rabies post-exposure prophylaxis in the Philippines: health status of patients having received purified equine F(ab′)₂ fragment rabies immunoglobulin (Favirab). *PLoS Negl Trop Dis* 2008; **2:** e243.

12   Hobson D, Curry RL, Beare AS, Ward-Gardner A. The role of serum haemagglutination-inhibiting antibody in protection against challenge infection with influenza A2 and B viruses. *J Hyg* 1972; **70:** 767–77.

Novel observational study designs with new influenza vaccines

In *The Lancet Infectious Diseases,* Hector Izurieta and colleagues[1] presented results of a cohort study in 929 730 older people (65 years and older) who received a high-dose influenza vaccine (high-dose Fluzone, Sanofi Pasteur, PA, USA, 60 µg per strain) and compared rates of influenza-related visits and hospital admissions with 1 615 545 older people who received a standard dose of the same vaccine (15 µg per strain). The high-dose vaccine seemed to be 22% more effective than the standard-dose vaccine. But how important is this study and finding, and what are its implications?

Most influenza-related deaths occur in older people and those with chronic comorbidities, such as pre-existing respiratory, cardiovascular, cerebrovascular, or renal disease, diabetes, cancer, and those with immuno-deficiencies.[2,3] Seasonal influenza vaccination has there-fore been recommended to be the mainstay of prevention in these vulnerable groups of people in most developed countries. However, vaccine uptake rates in older people have been disappointingly low in many countries despite strong recommendations.[4,5] One of the main reasons for this public health failure is that evidence for the clinical effects of vaccination in practice remains a matter of debate.[6–8] Much of the discussion pertains to the potential for selection of people for vaccination in non-randomised observational studies, which might have positively biased effect estimates from the lower true value in previous studies.

Randomisation is important to study causal vaccine effects because when properly done it removes bias. In older people, however, a single randomised placebo-controlled trial of influenza vaccination was done, which showed an effectiveness of 58% in reduction of symptoms of laboratory-confirmed influenza in the Netherlands.[9] Randomised placebo-controlled influenza vaccine trials in older people and other high-risk groups are usually thought to be unethical because many studies supporting the vaccine's benefit have already been done and immunisation is recommended worldwide.

Non-randomised (variations of) case-control or cohort vaccine effectiveness studies are suitable alter-natives to randomised controlled trials. Such designs have the advantages of timeliness, which is important in view of the annual changes in virology, reduction of costs, and increased feasibility, and most importantly, wider applicability to the target population. However, in non-randomised observational studies, the selection of vaccine recipients is affected by their risk profile, which might lead to confounding bias.[10] Advances have been made in developing alternative observational study designs to effectively control or quantify this bias. An elegant, novel approach is the test-negative case-control design.[11] A meta-analysis[11] presented in *The Lancet Infectious Diseases* showed vaccine effectiveness ranging from 46% to 58% in older people if the vaccine matched the viral strains; similar estimates were reported in the landmark randomised controlled trial. Alternatively, study designs with reference study periods during which influenza vaccination cannot have an effect, such as the pre-influenza or post-influenza season periods have been applied to quantify confounding by unmeasured variables.[12,13] Most of these studies reported reductions in mortality due to vaccination in older people.

Izurieta and colleagues are to be commended for their innovative approach in which comparison groups were selected from the same pharmacies and time periods.

Comment

The method is claimed to prevent bias by differential frailty status and temporal and geographical differences, which cannot be directly measured in most big healthcare databases. Importantly, a balance was achieved in the distribution of important potential measured confounders. Before this new design is accepted as unbiased, some comments need to be made. First, the accuracy of data for measured confounders with regards to either presence or severity of risk diseases remains unknown. When users of old treatments are compared with those of new treatments, potential channelling bias as a result of differential severity of disease might have occurred, which arises from concerns about vaccine safety or influenza risk. Second, univariate comparisons of distributions of each confounder across groups might have masked any potential differences in clusters of confounders, and third, unmeasured confounders such as smoking, functional status, alcohol drinking, or previous vaccine history could have been differentially distributed. Subject-matter scientific knowledge about determinants of choice for either treatment in the pharmacy is essential. Although probably unlikely in the study by Izurieta and colleagues, evidence for the absence of these biases might further support the validity of this novel design. Nonetheless, though their novel design is potentially valid for the comparison of new with old vaccines, its validity is questionable when vaccine recipients are compared with non-recipients who do not visit the pharmacy.

In view of the suboptimal effectiveness of around 50–60% of influenza vaccines,[9,11] the estimated 22% relative increase in vaccine effectiveness of the high-dose vaccine is certainly important, especially because this pertains to serious illness outcomes. Studies are warranted to examine potential safety issues and to model the cost-effectiveness to further support immunisation guideline developers.

Eelko Hak
Clinical Pharmacoepidemiology, University of Groningen, Groningen Research Institute of Pharmacy, Unit PharmacoEpidemiology and PharmacoEconomics, 9713 AV Groningen, Netherlands
e.hak@rug.nl

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1   Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. *Lancet Infect Dis* 2014; published online Feb 9. http://dx.doi.org/10.1016/S1473-3099(14)71087-4.
2   Fiore AE, Shay DK, Broder K, et al, Centers for Disease Control and Prevention, Advisory Committee on Immunization Practices. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2008. *MMWR Recomm Rep* 2008; **57:** 1–60.
3   Jansen AG, Sanders EA, Hoes AW, van Loon AM, Hak E. Influenza- and respiratory syncytial virus-associated mortality and hospitalisations. *Eur Respir J* 2007; **30:** 1158–66.
4   Reed C, Kim IK, Singleton JA, et al. Estimated influenza illnesses and hospitalizations averted by vaccination—United States, 2013–14 influenza season. *MMWR Morb Mortal Wkly Rep* 2014; 12; **63:** 1151–54.
5   Mereckiene J, Cotter S, Nicoll A, et al, VENICE Project Gatekeepers Group. Seasonal influenza immunisation in Europe. Overview of recommendations and vaccination coverage for three seasons: pre-pandemic (2008/09), pandemic (2009/10) and post-pandemic (2010/11). *Euro Surveill* 2014; **19:** 20780.
6   Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. *Lancet Infect Dis* 2007; **7:** 658–66.
7   Jefferson T, Di Pietrantonj C, Al-Ansary LA, Ferroni E, Thorning S, Thomas RE. Vaccines for preventing influenza in the elderly. *Cochrane Database Syst Rev* 2010; **2:** CD004876.
8   Beyer WE, McElhaney J, Smith DJ, Monto AS, Nguyen-Van-Tam JS, Osterhaus AD. Cochrane re-arranged: support for policies to vaccinate elderly people against influenza. *Vaccine* 2013; **31:** 6030–33.
9   Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *JAMA* 1994; **272:** 1661–65.
10   Groenwold RH, Hoes AW, Nichol KL, Hak E. Quantifying the potential role of unmeasured confounders: the example of influenza vaccination. *Int J Epidemiol* 2008; **37:** 1422–29.
11   Darvishian M, Bijlsma MJ, Hak E, van den Heuvel ER. Effectiveness of seasonal influenza vaccine in community-dwelling elderly people: a meta-analysis of test-negative design case-control studies. *Lancet Infect Dis* 2014; **14:** 1228–39.
12   Ortqvist A, Granath F, Askling J, Hedlund J. Influenza vaccination and mortality: prospective cohort study of the elderly in a large geographical area. *Eur Respir J* 2007; **30:** 414–22.
13   Groenwold RH, Hoes AW, Hak E. Impact of influenza vaccination on mortality risk among the elderly. *Eur Respir J* 2009; **34:** 56–62.

Ⓦ PCV13 in the USA: early successes and potential challenges

The clinical and economic burden of invasive pneumococcal disease (IPD) is substantial, with nearly 1 million deaths each year among children younger than 5 years.[1] The epidemiology of IPD is complicated by the existence of more than 90 distinct serotypes and the formidable ability of pneumococci to rapidly transform and evolve in response to changes in their environment.[2]

In the USA, within 3 years of the licensure of a seven-valent pneumococcal conjugate vaccine (PCV7) in 2000, the incidence of PCV7-serotype IPD was reduced by 94% and overall IPD by 75% among children targeted for immunisation.[3] Widespread use of PCV7 also conferred indirect protection to older adults, with one study suggesting that two cases of IPD among older adults

Moving Toward Improved Influenza Vaccines

Arnold S. Monto

Department of Epidemiology, University of Michigan School of Public Health, Ann Arbor

In 1943, a placebo-controlled trial of inactivated influenza vaccine (IIV) produced in fertile eggs was carried out among members of the Army Specialized Training Program at the University of Michigan [1]. The vaccine was approximately 70% efficacious in preventing laboratory-confirmed clinical influenza and the study also demonstrated that protection against infection was correlated with titers of hemagglutination-inhibiting (HAI) antibody. For the next 25 years, the US Military continued regularly to evaluate influenza vaccines, mainly in young adults. The trial designs varied, but the reported vaccine efficacy (VE) ranged from 70% to 90% [2]. Unlike the 1943 trial, many of the subsequent military studies relied exclusively on a serologic endpoint, comparing 4-fold rise in HAI antibody titers in the vaccinated with unvaccinated rather than identifying the infecting virus, at that time a laborious procedure. We now know that using this endpoint overestimates vaccine efficacy of IIV, as those with high HAI titers produced by vaccination are less likely to have a rise in titer when infected [3].

In contrast with the situation in the military, until relatively recently, vaccine use in the US general population was mainly confined to older adults and those with underlying conditions

[4]. This was based on the recognition that complications, including hospitalization and death, were more common in this population who actually had lower infection rates. Over a number of years, a variety of studies suggested that VE was much lower than 70%–90% in these older adults, and sometimes could not be demonstrated at all [5]. Many of the reports were anecdotal, and some involved nursing homes, so actual VE in those living independently was difficult to quantify. A study reviewing articles on HAI antibody vaccination response in older compared to younger adults as a way of predicting protection found that many factors made it hard to document actual differences [6]. A meta-analysis of studies with various clinical endpoints in older individuals concluded that, while heterogeneity did exist, in a subset, the VE was 56% in preventing respiratory illnesses [7]. However, that conclusion was challenged based on the nonspecific illness endpoints used.

The development and general use of the polymerase chain reaction (PCR) technique to identify actual influenza infection has now established a level playing field for various VE studies across ages. VE is rarely higher than 60%–70%, and sometimes lower. These findings came initially from placebo-controlled trials, mainly in younger adults where randomization is ethically possible [8–10]. Similar results have come recently from observational studies, using mainly the so-called test-negative design, comparing vaccination status in those with respiratory illnesses in the influenza season who test positive for influenza by PCR with those who test negative [11–13]. Because the studies are observational,

they can ethically involve individuals of all ages. There has not been a consistent drop-off in VE at age 60 or 65 years; often there are also variations by age in other groups. Factors such as the virus type or subtype involved and prior year vaccination may have a significant effect of VE. In particular, VE has been relatively high for A(H1N1) and type B, in the range of 60%, but much lower for A(H3N2) at all ages, even in years without major antigenic drift [14]. An issue in interpreting the results is that older individuals, especially the oldest of the old, are relatively underrepresented in these studies.

Various approaches over the years have attempted to improve vaccine performance overall. In the days when the military dominated research on influenza, adjuvanted vaccines were extensively evaluated, and clearly demonstrated higher antibody titers which were more broadly reactive. Adjuvants studied were water-in-oil including Freund's, and use was abandoned because of reactogenicity [15–17]. Later, the approach involving increasing the quantity of hemagglutinin (HA) in the vaccine began to be examined. A limitation was that the increased antibody response to increased HA content was far from linear, requiring much more than the 15 μg contained in the standard vaccine. The first studies were carried out in young adults and the HA content of each strain went up to 135 μg [18]. Significant increases were seen not only in serum antibody responses, but also in secretory antibody, known to correlate better with protection. Similar results were demonstrated in older adults, with antibody responses increasing 2-fold for a 9-fold increase in HA content [19].

Once the logistics of producing high-dose (HD) vaccine and other issues related to safety were overcome, the randomized controlled trial on the effect of the HA increase on antibody response in older individuals took place. The content of each of the 3 HD components was limited to 60 µg. In comparison with standard vaccine, the US Food and Drug Administration predefined superiority could be claimed for the A(H3N2) and A(H1N1) components but not for type B [20]. There was uncertainty on how much added protection against actual illness would result in older individuals with demonstrated increases in HA content until a trial with clinical outcomes could be conducted. Such a controlled trial is a major undertaking in terms of size especially when, as was ethically necessary, the comparator is not placebo but standard vaccine. It was carried out in 2 years, 2011–2012 and 2012–2013 and involved 31 989 participants. Relative efficacy against laboratory-confirmed clinical influenza of all types was 24.2% higher in recipients of the HD formulation than in those who received regular dose; absolute VE was impossible to determine since placebo could not be used [21]. Although point estimates suggested improved VE against all types and subtypes, statistical significance was achieved only for A(H3N2). In addition, secondary analyses suggested that the HD vaccine was more effective in preventing serious events possibly related to influenza, including hospitalization, but these events were relatively infrequent [22–23].

The only way to study infrequent outcomes is to use a much larger sample size. However, that can only be done using observational studies, in which there will be self-selection for vaccination. Then there is the question of the specificity of outcomes. Even with spreading use of PCR to identify influenza infections, the test is not regularly used enough, so unbiased identification of cases through this means alone is not possible. Rapid tests are more commonly used, but while

specific, most tests are not sensitive, making results difficult to interpret.

Shay et al, in this issue of *The Journal of Infectious Diseases*, used the Medicare database to access the required very large number of cases necessary to examine influenza-related mortality [24]. In addition to examining deaths following an *International Classification of Diseases* diagnosis of influenza, they also examined as secondary analyses all cases with such a diagnosis, as well as cases in which a rapid test for influenza with was ordered and oseltamivir treatment was dispensed. The latter methods were used, in part, to reproduce earlier findings from this group, which confirmed that this approach could replicate results from the randomized trial [25]. Because the study was observational, they controlled in the analysis for various factors such as frailty and socioeconomic status likely to confound the results. Well over a million recipients of the standard and of HD vaccine were studied in each of 2 years. In 2012–2013, the HD was 36.4% more effective in preventing death, but in 2013–2014 it was only 2.5% more effective, which was not statistically significant. This variation is not surprising and is actually in line with expectations. In 2013–2014 A(H1N1) predominated, but in 2012–2013 A(H3N2), known to cause higher mortality in the elderly, was most common, with some cases of type B. There is also the issue of basic differences in VE by subtype, using studies involving ambulatory visits as the benchmark. Overall, VE of standard vaccine in 2013–2014 in all age groups was approximately 54%, but in 2012–2013 it was only 39% for A(H3N2), leaving much room for improvement [26].

The demonstration that the HD vaccine has an enhanced effectiveness against influenza-associated mortality fits nicely with previous data that using this vaccine results in improved VE against uncomplicated illness and likely hospitalizations. This indicates that improvement in our 70-year-old influenza vaccines is possible, and to get

there more quickly we should not ignore older technologies while working on more dramatic advances. We know adjuvants result in better vaccine responses and we now have safer formulations than those used years ago in the military experiments Such an adjuvanted vaccine for older individuals is now available in the United States [27]. It has been shown in observational studies to reduce pneumonia and influenza hospitalizations by 25% compared to standard vaccine [28]. The biggest payoff of better vaccines in terms of reduced mortality will be in the elderly, but much of the vaccine in the United States is used at younger ages and improvement, especially of A(H3N2) vaccines, is needed for all age groups. The HD and adjuvanted approaches are welcome additions to our ability to counter effects of influenza and they should be further investigated and used. They should be viewed as not the end, but the beginning, of programs leading to vaccines of higher effectiveness, longer duration, and broader protection.

Note

References

1. Salk JE, Menke WJ, Francis T. A clinical, epidemiological and immunological evaluation of vaccination against epidemic influenza. Am J Epidemiol **1945**; 42:57–93.
2. Davenport FM. Protective efficacy of inactivated influenza vaccines, 1943–1969. Med J Aust **1973**; 33–8.
3. Petrie JG, Ohmit SE, Johnson E, Cross RT, Monto AS. Efficacy studies of influenza vaccines: effect of end points used and characteristics of vaccine failures. J Infect Dis **2011**; 203:1309–15.
4. Langmuir AD, Henderson DA, Serfling RE. The epidemiological basis for the control of influenza. Am J Public Health Nations Health **1964**; 54:563–71.
5. Strassburg MA, Greenland S, Sorvillo FJ, Lieb LE, Habel LA. Influenza in the elderly: report of an outbreak and a review of vaccine effectiveness reports. Vaccine **1986**; 4:38–44.
6. Beyer WE, Palache AM, Baljet M, Masurel N. Antibody in duction by influenza vaccines in the elderly: a review of the literature. Vaccine **1989**; 7:385–94.

7. Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of influenza vaccine in elderly persons. A meta-analysis and review of the literature. Ann Intern Med **1995**; 123:518–27.

8. Ohmit SE, Victor JC, Rotthoff JR, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. N Engl J Med **2006**; 355:2513–22.

9. Monto AS, Ohmit SE, Petrie JG, et al. Comparative efficacy of inactivated and live attenuated influenza vaccines. N Engl J Med **2009**; 361:1260–7.

10. Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infect Dis **2012**; 12:36–44.

11. Orenstein EW, De Serres G, Haber MJ, et al. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. Int J Epidemiol **2007**; 36:623–31.

12. Ohmit SE, Thompson MG, Petrie JG, et al. Influenza vaccine effectiveness in the 2011–2012 season: protection against each circulating virus and the effect of prior vaccination on estimates. Clin Infect Dis **2014**; 58:319–27.

13. Skowronski DM, Chambers C, Sabaiduc S, et al. A perfect storm: impact of genomic variation and serial vaccination on low influenza vaccine effectiveness during the 2014–2015 season. Clin Infect Dis **2016**; 63:21–32.

14. McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the united states during 2012–2013: variable protection by age and virus type. J Infect Dis **2015**; 211:1529–40.

15. Davenport FM, Hennessy AV, Bell JA. Immunologic advantages of emulsified influenza virus vaccines. Mil Med **1962**; 127:95–100.

16. Ujhazy V. Clinical trials of oil-adjuvant influenza vaccines, 1960–3. Report to the medical research council by its committee on influenza and other respiratory virus vaccines. Br Med J **1964**; 2:267–71.

17. Weibel RE, McLean A, Woodhour AF, Friedman A, Hilleman MR. Ten-year follow-up study for safety of adjuvant 65 influenza vaccine in man. Proc Soc Exp Biol Med **1973**; 143:1053–6.

18. Keitel WA, Couch RB, Cate TR, et al. High doses of purified influenza A virus hemagglutinin significantly augment serum and nasal secretion antibody responses in healthy young adults. J Clin Microbiol **1994**; 32:2468–73.

19. Keitel WA, Cate TR, Atmar RL, et al. Increasing doses of purified influenza virus hemagglutinin and subvirion vaccines enhance antibody responses in the elderly. Clin Diagn Lab Immunol **1996**; 3:507–10.

20. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis **2009**; 200:172–80.

21. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med **2014**; 371:635–45.

22. DiazGranados CA, Robertson CA, Talbot HK, Landolfi V, Dunning AJ, Greenberg DP. Prevention of serious events in adults 65 years of age or older: a comparison between high-dose and standard-dose inactivated influenza vaccines. Vaccine **2015**; 33:4988–93.

23. DiazGranados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V, Greenberg DP. Effect of previous-year vaccination on the efficacy, immunogenicity, and safety of high-dose inactivated influenza vaccine in older adults. Clin Infect Dis **2016**; 62:1092–9.

24. Shay DK, Chillarige Y, Kelman J, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines among us medicare beneficiaries in preventing post-influenza deaths during 2012–13 and 2013–14 -manuscript draft-.

25. Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in us residents aged 65 years and older from 2012 to 2013 using medicare data: a retrospective cohort analysis. Lancet Infect Dis **2015**; 15:293–300.

26. Gaglani M, Pruszynski J, Murthy K, et al. Influenza vaccine effectiveness against 2009 pandemic influenza A(H1N1) virus differed by vaccine type during 2013–2014 in the United States. J Infect Dis **2016**; 213:1546–56.

27. FLUAD [US package insert]. Holly Springs, NC: Seqirus, Inc. March **2016**. http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/VaccineSafety/UCM474387.pdf. Accessed 21 December 2016.

28. Mannino S, Villa M, Apolone G, et al. Effectiveness of adjuvanted influenza vaccination in elderly subjects in northern Italy. Am J Epidemiol **2012**; 176:527–33.

EDITORIAL COMMENTARY

Comparing Influenza Vaccine Types: The Path Toward Improved Influenza Vaccine Strategies

Brendan Flannery and Alicia M. Fry

Influenza Division, Centers for Disease Control and Prevention, Atlanta, Georgia

The 2017–2018 influenza season was a reminder that seasonal influenza can be associated with a large burden of severe disease and that adults aged ≥65 years are disproportionately affected; 660 000 hospitalizations and 68 000 deaths were estimated to be associated with influenza virus infection in this age group [1]. Older adults are a priority group for annual influenza vaccination. The 2017–2018 season, notable for the predominance of A(H3N2) viruses, also was a reminder that the H3N2 vaccine component is not as effective as other vaccine components. Vaccines reduced the risk of laboratory-confirmed influenza A and B–associated outpatient visits by 40%, but vaccine effectiveness (VE) estimates against A(H3N2) viruses were 24% [2]. Since 2004–2005, VE point estimates against A(H3N2) viruses have been lower than against 2009 pandemic influenza A(H1N1) virus (A[H1N1] pdm09) or influenza B viruses, and VE estimates against A(H3N2) viruses are usually lowest among older adults [2–4]. Thus, understanding why influenza vaccines are less effective against A(H3N2) viruses and identifying new strategies to improve VE are critical, especially during

A(H3N2)-predominant seasons, such as 2017–2018.

In this issue of *the Journal of Infectious Diseases*, Izurieta et al used data from Medicare beneficiaries aged ≥65 years to compare *International Classification of Diseases, 10th Revision* (ICD-10)–coded influenza-associated hospital visits among recipients of different influenza vaccines during the 2017–2018 influenza season [5]. The large population of Medicare recipients allowed the authors to compare not just 2 vaccine types, as reported previously [6, 7], but to compare multiple vaccine types during 1 influenza season. Comparisons among multiple vaccines aid understanding of current issues related to influenza vaccines and also offer insight into potential strategies to improve vaccine effectiveness.

For the 2018–2019 influenza season, there are 9 licensed vaccines recommended for people aged ≥65 years in the United States. The Advisory Committee on Immunization Practices indicates no preference for one type of influenza vaccine [8]. Most influenza vaccines contain vaccine viruses that are initially isolated and propagated in chicken eggs (ie, egg-based vaccines). Inactivated egg-based influenza vaccines are available in trivalent and quadrivalent formulations. Two vaccines designed to result in an enhanced immune responses are available for older adults [8]. High-dose vaccine is a trivalent inactivated egg-based vaccine with 4 times the antigen dose, compared with standard vaccines. A randomized clinical trial [9] during 2011–2012 and 2012–2013 and several observational studies [6, 7] reported a

higher relative effectiveness of high-dose as compared to standard-dose egg-based vaccines, although results from observational studies vary. An MF59-adjuvanted egg-based vaccine is also licensed for use in older adults [8]. One observational study reported a higher relative effectiveness of adjuvanted as compared to nonadjuvanted vaccines in this age group [10]. The effectiveness of high-dose and adjuvanted vaccines has not been compared previously. Finally, 2 licensed vaccines for older adults are not egg based: the cell-culture vaccine and a vaccine based on a recombinant influenza virus hemagglutinin (HA) protein that is produced in insect cells. In addition to several potential production advantages of non-egg based vaccines, the recent issues with A(H3N2) viruses have further increased interest in these vaccines.

Human influenza viruses grown in eggs may acquire mutations that facilitate propagation in eggs but inadvertently change antigenic properties of vaccine viruses; this is especially true for recent A(H3N2) viruses [11]. While these changes from egg propagation could result in less effective vaccines, the contribution of these changes toward lower VE estimates has not been quantified. Few studies are available to shed light on this issue. A randomized trial among adults aged ≥50 years during 2014–2015, an A(H3N2)-predominant season, reported a higher relative effectiveness of recombinant vaccine as compared to standard egg-based vaccines [12]. Unfortunately, there was too little use of the recombinant vaccine among Medicare beneficiaries to include this vaccine in the analysis

by Izurieta et al [5]. Until 2017–2018, the cell-culture vaccine used viruses initially isolated in eggs followed by propagation in a mammalian cell line. For the first time, in 2017–2018, the A(H3N2) vaccine virus in the cell-culture vaccine was completely cell derived from initial isolation through vaccine production [13]. The remaining 3 vaccine components of the 2017–2018 cell-culture vaccine were produced from egg-adapted A(H1N1) pdm09 and B viruses but, in future years, will also be completely cell derived. Since A(H3N2) viruses predominated during the 2017–2018 season, this was the first season that a completely cell-derived vaccine virus could be evaluated. Despite limited commercial uptake, the large Medicare population allowed evaluation of recipients of this vaccine by Izurieta et al [5].

For their primary outcome of ICD-10–coded influenza-associated hospital visits, Izurieta et al reported an 11% and 9% relative effectiveness among recipients of the cell-culture vaccine and high-dose egg-based vaccines as compared to standard egg-based trivalent or quadrivalent vaccines, respectively. In addition, they demonstrated no statistically significant relative effectiveness of cell-culture vaccine as compared to high-dose vaccine among beneficiaries during the 2017–2018 influenza season. The superior relative effectiveness of the cell-culture vaccine, with the same amount of HA antigen as the standard-dose egg-based comparator and one fourth as much H3N2 antigen as the high-dose vaccine, was likely due to the cell-derived A(H3N2) component. However, the small relative increase suggests that egg-adaptation changes do not entirely explain the lower VE reported for A(H3N2) viruses as compared to the other vaccine components, A(H1N1)pdm09 and B viruses. In addition, despite changes in the HA during egg propagation, high-dose vaccine offered superior effectiveness (similar to that of cell-culture vaccine) as compared to standard-dose egg-based vaccines. One wonders how a vaccine

with a higher dose and an absence of egg-adaptation changes would have compared in this study. Finally, cell-culture vaccine and high-dose egg-based vaccine had a 5%–7% higher relative effectiveness as compared to adjuvanted egg-based vaccine, which was 4% more effective than standard (ie, nonadjuvanted) egg-based vaccines. This suggests that adjuvant worked less well than an increased antigen dose at improving effectiveness against A(H3N2) viruses. In the future, we need to understand whether adjuvanted vaccines offer benefits against antigenically drifted viruses, as well as A(H1N1)pdm09 and B viruses, and, potentially, what role an adjuvanted cell-culture vaccine may have.

The measure used to compare vaccine types in the study by Izurieta el al is relative VE. In their cohort analysis, it represents the decrease in rates of ICD-10–coded influenza-associated hospitalization visits among beneficiaries who received a selected vaccine type as compared to those who received a comparator vaccine. It is analogous to the relative efficacy measured as the difference in attack rates in a clinical trial. An advantage of this approach is that it does not require an unvaccinated cohort. Medicare records may not capture all influenza vaccinations, leading to misclassification of some vaccinated individuals as unvaccinated. In addition, unvaccinated cohorts may introduce additional biases related to who gets vaccinated [6]. A disadvantage of this approach is that it does not permit estimation of the absolute VE for any vaccine; that is, the decrease in rates of outcomes in each vaccinated cohort as compared to an unvaccinated cohort. To put the relative effectiveness estimate in context, the authors derive estimates of absolute VE for each vaccine, based on several possible values for the 2017–2018 comparator vaccine. It is clear from this example that the relative effectiveness of cell-culture and high-dose vaccine resulted in modest improvements in protection against influenza-associated hospitalizations.

Since most postlicensure evaluations of different vaccine types will be observational studies, it is important to monitor and account for changes in the use of different vaccine types over time. In 2012–2013, 19% of vaccinated Medicare beneficiaries received high-dose vaccine, and 81% received trivalent standard-dose vaccine [6]. In 2017–2018, 63% received high-dose vaccine, and only 7% received trivalent standard-dose vaccine [5]. This may have played a role in the differences between the findings for hospital outcomes versus outpatient visit outcomes, as reported by Izurieta et al [5]. It is plausible that the small group of beneficiaries who received trivalent standard-dose vaccine in 2017–2018 may have differed from the majority of vaccinees in care-seeking behavior or likelihood of influenza testing in ways that affected influenza-related office visits differently than influenza-associated hospitalizations. In addition, commercial uptake will influence the ability to evaluate new vaccines and understand their role in vaccination strategies.

A limitation of using Medicare data is the absence of laboratory-confirmed influenza outcomes. Because A(H3N2) viruses predominated, we can only assume the cell-culture vaccine effects were related to the A(H3N2) vaccine virus. Therefore, replication of these findings with studies using laboratory-confirmed influenza virus infection outcomes will be needed to determine absolute and relative effectiveness of different influenza vaccines, by specific influenza virus types and subtypes. Several networks report annual absolute VE estimates against all vaccine viruses and by vaccine type in the United States [2]. Thus, evidence to inform future policy decisions will be dependent on multiple studies with different but complementary methods that can report annual results over several seasons, as well as statistical models to evaluate potential impact of changes in vaccine uptake. The lessons we learn from these studies will help improve influenza vaccines and vaccine strategies so that we

optimize the protection provided by seasonal influenza vaccines.

Notes

Disclaimer. The opinions in this editorial are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

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References

1. Centers for Disease Control and Prevention. Estimated influenza illnesses, medical visits, hospitalizations, and deaths in the United States—2017–2018 influenza season. https://www.cdc.gov/flu/about/burden/estimates.htm. Accessed 6 December 2018.
2. Flannery B, Chung JR, Ferdinands JM. Preliminary estimates of 2017–18 seasonal influenza vaccine effectiveness against laboratory-confirmed influenza from the US flu VE and HAIVEN networks. Atlanta, GA: Advisory Committee on Immunization Practices, **2018**.
3. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infect Dis **2016**; 16:942–51.
4. Rondy M, El Omeiri N, Thompson MG, Levêque A, Moren A, Sullivan SG. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: a systematic review and meta-analysis of test-negative design case-control studies. J Infect **2017**; 75:381–94.
5. Izurieta HS, Chillarige Y, Kelman J, et al. Relative effectiveness of cell-cultured and egg-based influenza vaccines among the U.S. elderly, 2017–18. J Infect Dis **2018. In this issue.**
6. Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. Lancet Infect Dis **2015**; 15:293–300.
7. Shay DK, Chillarige Y, Kelman J, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines among US medicare beneficiaries in preventing postinfluenza deaths during 2012–2013 and 2013–2014. J Infect Dis **2017**; 215:510–7.
8. Grohskopf LA, Sokolow LZ, Broder KR, Walter EB, Fry AM, Jernigan DB. Prevention and control of seasonal influenza with vaccines: recommendations of the advisory committee on immunization practices-United States, 2018-19 influenza season. MMWR Recomm Rep **2018**; 67:1–20.
9. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. N Engl J Med **2014**; 371:635–45.
10. Van Buynder PG, Konrad S, Van Buynder JL, et al. The comparative effectiveness of adjuvanted and unadjuvanted trivalent inactivated influenza vaccine (TIV) in the elderly. Vaccine **2013**; 31:6122–8.
11. Zost SJ, Parkhouse K, Gumina ME, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. Proc Natl Acad Sci U S A **2017**; 114:12578–83.
12. Dunkle LM, Izikson R, Patriarca P, et al.; PSC12 Study Team. Efficacy of recombinant influenza vaccine in adults 50 years of age or older. N Engl J Med **2017**; 376:2427–36.
13. Barr IG, Donis RO, Katz JM, et al. Cell culture-derived influenza vaccines in the severe 2017-2018 epidemic season: a step towards improved influenza vaccine effectiveness. NPJ Vaccines **2018**; 3:44.

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Herpes Zoster Vaccine and the Medicare Population

Steven Black

Center for Global Health, Cincinnati Children's Hospital, Ohio

(See Major Article by Izurieta et al on pages 785-93.)

The incidence of herpes zoster rises dramatically after 50 years of age, and reactivation of latent virus is associated with a vesicular rash and at times debilitating herpetic neuralgia [1]. This increased incidence is associated with a decrease in cellular immunity to herpes zoster virus in this age group. In 2006, a live attenuated vaccine (Zostavax, Merck) was licensed and approved for use in the United States to prevent herpes zoster in individuals aged ≥65 years after efficacy of 51% (95% confidence interval [CI], 44%–58%) was demonstrated in a large phase 3 clinical trial [2]. Since licensure, the vaccine has been used widely, but data on duration of protection, impact of age on effectiveness, and field effectiveness against various outcomes have not been widely studied. In this issue of *Clinical Infectious Diseases*, Izurieta and coauthors have conducted a pioneering study in 2 million individuals in the Medicare utilization database to extensively evaluate the effectiveness and durability of effectiveness induced by vaccination. This study is important because it provides useful information regarding the vaccine impact in seniors that can be used by physicians to set expectations for

patients receiving the vaccine, because of the information it provides to public health policy makers to facilitate decisions regarding this and other vaccines or vaccine regimens for herpes zoster and also because this study demonstrates the utility of the Medicare utilization databases for the evaluation of vaccine effectiveness when seniors are the target population.

Before discussing the results and their implications, it is important to note that there are important differences between the phase 3 prelicensure study and the results reported here. In the phase 3 trial, more than half of vaccine recipients were <70 years of age, whereas in the Izurieta study this number was only 11%[2]. While this has potential implications for interpreting the results, it is important to note that the level of impact of this age difference is likely small given that Izurieta found only a limited impact of age at vaccination upon observed efficacy. More relevant to viewing the results is the fact that the Medicare population includes people who might have been excluded from a phase 3 trial because of underlying conditions or a history of conditions such as cancer that could impact vaccine effectiveness. While one can argue as to which assessment represents a more accurate assessment of effectiveness, it is likely that the Medicare observations most accurately reflect the impact of the vaccine in the Medicare population and, as almost all individuals >65 years of age in the United States are enrolled in Medicare, that it reflects the true

effectiveness in seniors in the United States overall.

The primary analysis in this study a demonstrated a 33% (95% CI, 32%–35%) effectiveness against community zoster during the first 3 years following vaccination. This efficacy fell to 22% (95% CI, 20%–25%) after 4 or more years. This level of efficacy is significantly lower than the 51% efficacy observed in the phase 3 trial. Effectiveness for ophthalmic zoster was 31%, initially falling to 21% after ≥4 years. For postherpetic neuralgia, these values were 57% and 44%, respectively. Effectiveness against hospitalized zoster was higher at 74% within the first 3 years and 55% in the years following. While the higher impact and duration of protection against hospitalized zoster is important, this outcome is uncommon, with only 614 events observed in the Medicare study compared with 56 939 community zoster cases, 5282 ophthalmic zoster cases, and 2033 postherpetic neuralgia cases.

Given these results and the number of patients impacted, one can conservatively state that, especially for community zoster where the number of cases is high and for ophthalmic zoster where morbidity is high and incidence relatively high, that the protection provided by the current live attenuated zoster vaccine is suboptimal. While it is possible that additional "booster" doses of vaccine might provide higher or more durable protection, this has not been studied, so the potential impact is unknown. Likewise, the potential impact of the unlicensed herpes

zoster recombinant subunit vaccine on effectiveness and duration of protection on zoster, postherpetic neuralgia, and other complications awaits further study. Until other vaccine regimens and newer vaccines are evaluated, it makes sense to continue with the current vaccination regimen to prevent a less than optimal but significant number of cases of the more serious complications.

Finally, this study demonstrates the utility of large lined databases in the evaluation of vaccine effectiveness in the target population for a vaccine. While such studies are relatively common in the United Kingdom [3, 4] they have not been routinely performed in the United States. In the future, such studies should be considered for all newly introduced vaccines to assure that the assessments of vaccine impact from prelicensure trials and assumptions regarding duration of protection accurately predict the true vaccine effect.

Note

Potential conflicts of interest. The author is a part-time consultant for both Merck and GlaxoSmithKline vaccines. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Yawn BP, Saddier P, Wollan PC, Sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clinic Proc **2007**; 82:1341–49.
2. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med **2005**; 352:2271–84.
3. Trotter CL, Andrews NJ, Kaczmarski EB, Miller E, Ramsay ME. Effectiveness of meningococcal serogroup C conjugate vaccine 4 years after introduction. Lancet **2004**; 364:365–7.
4. Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine. Vaccine **2011**; 29:9127–31.

REFERENCES

1. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the Rates of Hospitalization for Respiratory Disease among Infants and Young Children. *New England Journal of Medicine.* 2000;342(4):232-239.

2. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the United States. *JAMA.* 2004;292(11):1333-1340.

3. Thompson WW, Shay DK, Weintraub E, et al. Mortality Associated With Influenza and Respiratory Syncytial Virus in the United States. *JAMA: The Journal of the American Medical Association.* 2003;289(2):179-186.

4. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993-2008. *Clin Infect Dis.* 2012;54(10):1427-1436.

5. Govaert Te TCNMNNSMWDGJKJA. The efficacy of influenza vaccination in elderly individuals: A randomized double-blind placebo-controlled trial. *JAMA: The Journal of the American Medical Association.* 1994;272(21):1661-1665.

6. (CDC) CfDCaP. Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths Averted by Vaccination in the United States. 2017; https://www.cdc.gov/flu/about/disease/2015- 16.htm. Accessed 04/30, 2018.

7. (CDC) CfDCaP. Influenza (flu) viruses. 2018.

8. (CDC) CfDCaP. Disease burden of influenza. 2018; https://www.cdc.gov/flu/about/disease/burden.htm. Accessed 03/07, 2018.

9. Nichol KL, Lind A, Margolis KL, et al. The effectiveness of vaccination against influenza in healthy, working adults. *N Engl J Med.* 1995;333(14):889-893.

10. Nichol KL, Nordin JD, Nelson DB, Mullooly JP, Hak E. Effectiveness of Influenza Vaccine in the Community-Dwelling Elderly. *New England Journal of Medicine.* 2007;357(14):1373-1381.

11. (FDA) FDA 21st Century Cures Act. 2016; https://www.fda.gov/RegulatoryInformation/LawsEnforcedbyFDA/SignificantAmendmentstothe FDCAct/21stCenturyCuresAct/default.htm. Accessed 04/05/2018, 2018.

12. The Lancet Infectious D. A better pathway to approval of 21st century cures? *Lancet Infect Dis.* 2017;17(2):117.

13. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-World Evidence - What Is It and What Can It Tell Us? *N Engl J Med.* 2016;375(23):2293-2297.

14. Izurieta HS, Chillarige Y, Kelman J, et al. Relative effectiveness of cell-cultured and egg-based influenza vaccines among the U.S. elderly, 2017-18. *J Infect Dis.* 2018.

15. Izurieta HS, Chillarige Y, Kelman JA, et al. Statin Use and Risks of Influenza-Related Outcomes Among Older Adults Receiving Standard-Dose or High-Dose Influenza Vaccines Through Medicare During 2010-2015. *Clin Infect Dis.* 2018;67(3):378-387.

16. Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. *Lancet Infect Dis.* 2015;15(3):293-300.

17. Izurieta HS, Wernecke M, Kelman J, et al. Effectiveness and Duration of Protection Provided by the Live-attenuated Herpes Zoster Vaccine in the Medicare Population Ages 65 Years and Older. *Clin Infect Dis.* 2017;64(6):785-793.

18. Shay DK, Chillarige Y, Kelman J, et al. Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccines Among US Medicare Beneficiaries in Preventing Postinfluenza Deaths During 2012-2013 and 2013-2014. *J Infect Dis.* 2017;215(4):510-517.

19. K M. Can randomised controlled trials be more efficient? 20016.

20. Jarow JP, LaVange L, Woodcock J. Multidimensional Evidence Generation and FDA Regulatory Decision Making: Defining and Using "Real-World" Data. *JAMA.* 2017;318(8):703-704.

21. Burwen DR, Sandhu SK, MaCurdy TE, et al. Surveillance for Guillain-Barre syndrome after influenza vaccination among the Medicare population, 2009-2010. *Am J Public Health.* 2012;102(10):1921-1927.

22. Burwen DR, Ball R, Bryan WW, et al. Evaluation of Guillain-Barre Syndrome among recipients of influenza vaccine in 2000 and 2001. *Am J Prev Med.* 2010;39(4):296-304.

23. Izurieta HS, Zuber P, Bonhoeffer J, et al. Roadmap for the international collaborative epidemiologic monitoring of safety and effectiveness of new high priority vaccines. *Vaccine.* 2013;31(35):3623-3627.

24. Izurieta HS, Moro PL, Chen RT. Hospital-based collaboration for epidemiological investigation of vaccine safety: A potential solution for low and middle-income countries? *Vaccine.* 2018;36(3):345-346.

25. (FDA) FaDA. Real-World Data and Evidence in Drug Development. 2017; https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm572939.pdf. Accessed 07/16/2018, 2018.

26. Platt R, Brown JS, Robb M, et al. The FDA Sentinel Initiative - An Evolving National Resource. *N Engl J Med.* 2018;379(22):2091-2093.

27. Platt R, Carnahan RM, Brown JS, et al. The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction. *Pharmacoepidemiol Drug Saf.* 2012;21 Suppl1:1-8.

28. Yih WK, Kulldorff M, Sandhu SK, et al. Prospective influenza vaccine safety surveillance using fresh data in the Sentinel System. *Pharmacoepidemiol Drug Saf.* 2016;25(5):481-492.

29. Dobardzic A, Izurieta H, Woo EJ, et al. Safety review of the purified chick embryo cell rabies vaccine: Data from the Vaccine Adverse Event Reporting System (VAERS), 1997-2005. *Vaccine.* 2007;25(21):4244-4251.

30. Dodd CN, Romio SA, Black S, et al. International collaboration to assess the risk of Guillain Barre Syndrome following Influenza A (H1N1) 2009 monovalent vaccines. *Vaccine.* 2013;31(40):4448-4458.

31. FDA. Food and Drug Administration. Press Announcements. FDA approves a high dose seasonal infl uenza vaccine specifically intended for people ages 65 and older. Dec 13, 2009.

32. FDA. Press Announcements. FDA approves a high dose seasonal influenza vaccine specifically intended for people ages 65 and older. Dec 13, 2009. 2009.

33. FDA. High dose Fluzone package insert. 2017; https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm3050 79.pdf. Accessed 02 22, 2018.

34. Finkelstein JB. Accelerated approval regulations may need overhaul, panel suggests. *J Natl Cancer Inst.* 2005;97(24):1802-1804.

35. Kraus VB, Simon LS, Katz JN, et al. Proposed study designs for approval based on a surrogate endpoint and a post-marketing confirmatory study under FDA's accelerated approval regulations for disease modifying osteoarthritis drugs. *Osteoarthritis Cartilage.* 2018.

36. Nash RR. The role of clinical equipoise and practical considerations in deciding whether to continue to provide a drug on an open-label extension study for an "unapproved indication". *Am J Bioeth.* 2014;14(4):59-60.

37. Booth CM, Tannock IF. Randomised controlled trials and population-based observational research: partners in the evolution of medical evidence. *Br J Cancer.* 2014;110(3):551-555.

38. Brammer TL, Izurieta HS, Fukuda K, et al. Surveillance for influenza--United States, 1994-95, 1995-96, and 1996-97 seasons. *MMWR CDC Surveill Summ.* 2000;49(3):13-28.

39.   Izurieta H. Influenza: basic epidemiological aspects for the development of vaccines. *Epidemiol Bull.* 2001;22(3):11-13.

40.   Goodwin K VC, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine.* 2006(24):1159-1169.

41.   Jackson LA, Nelson JC, Benson P, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *International Journal of Epidemiology.* 2006;35(2):345-352.

42.   Petrie JG, Ohmit SE, Johnson E, Cross RT, Monto AS. Efficacy Studies of Influenza Vaccines: Effect of End Points Used and Characteristics of Vaccine Failures. *Journal of Infectious Diseases.* 2011;203(9):1309-1315.

43.   (HHS)   DoHaHS.   Pandemic   influenza   plan: 2017   update.   2017; https://www.cdc.gov/flu/pandemic-resources/pdf/pan-flu-report-2017v2.pdf.   Accessed 05/04/2018, 2018.

44.   (CDC) CfDCap. Licensure of a High-Dose Inactivated Influenza Vaccine for Persons aged >= 65 years (Fluzone High-Dose) and Guidance for Use. In: States U, ed. Vol 59. Morbidity and Mortality Weekly Report2010:485-486.

45.   Couch RB WP, Brady R, et al. . Safety and immunogenicity of a high dosage trivalentinfluenza vaccine among elderly subjects. *Vaccine.* 2007(25):7656-7663.

46.   Falsey AR TJ, Tornieporth N, Cappelan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *Journal of Infectious Diseases.* 2009(200):172-180.

47.   Keitel WA AR, Cate TR, et al. . Safety ofhigh doses of influenza vaccine and effect on antibody responses in elderly persons. *Archives of Internal Medicine.* 2006(166):1121-1127.

48.   DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. *N Engl J Med.* 2014;371(7):635-645.

49.   Gravenstein S, Davidson HE, Taljaard M, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. *Lancet Respir Med.* 2017;5(9):738-746.

50.   DiazGranados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V, Greenberg DP. Efficacy and immunogenicity of high-dose influenza vaccine in older adults by age, comorbidities, and frailty. *Vaccine.* 2015;33(36):4565-4571.

51.   DiazGranados CA, Robertson CA, Talbot HK, Landolfi V, Dunning AJ, Greenberg DP. Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines. *Vaccine.* 2015;33(38):4988-4993.

52.   Nace DA, Lin CJ, Ross TM, Saracco S, Churilla RM, Zimmerman RK. Randomized, controlled trial of high-dose influenza vaccine among frail residents of long-term care facilities. *J Infect Dis.* 2015;211(12):1915-1924.

53.   Supplement to the Biologics License Application (sBLA) for Fluzone High-Dose, (2014).

54.   Richardson DM, Medvedeva EL, Roberts CB, Linkin DR. Comparative effectiveness of high-dose versus standard-dose influenza vaccination in community-dwelling veterans. *Clin Infect Dis.* 2015;61(2):171-176.

55.   Decker MD, DiazGranados CA, Chit A, Hosbach P, Robertson CA, Greenberg DP. Regarding Primary Care Patients Who Received Influenza Vaccine at Veteran Health Administration Medical Centers. *Clin Infect Dis.* 2015;61(8):1344-1345.

56.   Linkin DR, Richardson DM. Reply to Decker et al. *Clin Infect Dis.* 2015;61(8):1345.

57.   Fink AL, Klein SL. Sex and Gender Impact Immune Responses to Vaccines Among the Elderly. *Physiology (Bethesda, Md).* 2015;30(6):408-416.

58. Flanagan KL, Fink AL, Plebanski M, Klein SL. Sex and Gender Differences in the Outcomes of Vaccination over the Life Course. *Annual review of cell and developmental biology.* 2017;33:577-599.

59. Giefing-Kroll C, Berger P, Lepperdinger G, Grubeck-Loebenstein B. How sex and age affect immune responses, susceptibility to infections, and response to vaccination. *Aging cell.* 2015;14(3):309-321.

60. Short SE, Yang YC, Jenkins TM. Sex, gender, genetics, and health. *Am J Public Health.* 2013;103 Suppl 1:S93-101.

61. Engler RJ, Nelson MR, Klote MM, et al. Half- vs full-dose trivalent inactivated influenza vaccine (2004-2005): age, dose, and sex effects on immune responses. *Arch Intern Med.* 2008;168(22):2405-2414.

62. Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. *J Infect Dis.* 2009;200(2):172-180.

63. Furman D, Hejblum BP, Simon N, et al. Systems analysis of sex differences reveals an immunosuppressive role for testosterone in the response to influenza vaccination. *Proceedings of the National Academy of Sciences of the United States of America.* 2014;111(2):869-874.

64. Klein SL, Pekosz A. Sex-based biology and the rational design of influenza vaccination strategies. *J Infect Dis.* 2014;209 Suppl 3:S114-119.

65. DiazGranados CA, Dunning AJ, Jordanov E, Landolfi V, Denis M, Talbot HK. High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: safety, immunogenicity and relative efficacy during the 2009-2010 season. *Vaccine.* 2013;31(6):861-866.

66. DiazGranados CA, Dunning AJ, Robertson CA, Talbot HK, Landolfi V, Greenberg DP. Effect of Previous-Year Vaccination on the Efficacy, Immunogenicity, and Safety of High-Dose Inactivated Influenza Vaccine in Older Adults. *Clin Infect Dis.* 2016;62(9):1092-1099.

67. Cao W, Kim JH, Chirkova T, et al. Improving immunogenicity and effectiveness of influenza vaccine in older adults. *Expert Rev Vaccines.* 2011;10(11):1529-1537.

68. Louria DB, Blumenfeld HL, Ellis JT, Kilbourne ED, Rogers DE. Studies on influenza in the pandemic of 1957-1958. II. Pulmonary complications of influenza. *The Journal of clinical investigation.* 1959;38(1 Part 2):213-265.

69. Eickhoff TC, Sherman IL, Serfling RE. Observations on excess mortality associated with epidemic influenza. *Jama.* 1961;176:776-782.

70. McElhaney JE, Beran J, Devaster JM, et al. AS03-adjuvanted versus non-adjuvanted inactivated trivalent influenza vaccine against seasonal influenza in elderly people: a phase 3 randomised trial. *Lancet Infect Dis.* 2013;13(6):485-496.

71. Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *Jama.* 1994;272(21):1661-1665.

72. Couch RB, Winokur P, Brady R, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. *Vaccine.* 2007;25(44):7656-7663.

73. Keitel WA, Atmar RL, Cate TR, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. *Arch Intern Med.* 2006;166(10):1121-1127.

74. Afilalo J, Majdan AA, Eisenberg MJ. Intensive statin therapy in acute coronary syndromes and stable coronary heart disease: a comparative meta-analysis of randomised controlled trials. *Heart.* 2007;93(8):914-921.

75. Colhoun HM, Betteridge DJ, Durrington PN, et al. Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet.* 2004;364(9435):685-696.

76. Cheung BM, Lauder IJ, Lau CP, Kumana CR. Meta-analysis of large randomized controlled trials to evaluate the impact of statins on cardiovascular outcomes. *British journal of clinical pharmacology.* 2004;57(5):640-651.

77. Maron DJ, Fazio S, Linton MF. Current perspectives onstatins. *Circulation.* 2000;101(2):207-213.

78. Hebert PR, Gaziano JM, Chan KS, Hennekens CH. Cholesterol lowering with statin drugs, risk of stroke, and total mortality. An overview of randomized trials. *JAMA.* 1997;278(4):313-321.

79. Black S, Nicolay U, Del Giudice G, Rappuoli R. Influence of Statins on Influenza Vaccine Response in Elderly Individuals. *The Journal of Infectious Diseases.* 2016;213(8):1224-1228.

80. Omer SB, Phadke VK, Bednarczyk RA, Chamberlain AT, Brosseau JL, Orenstein WA. Impact of Statins on Influenza Vaccine Effectiveness Against Medically Attended Acute Respiratory Illness. *J Infect Dis.* 2016;213(8):1216-1223.

81. McLean HQ, Chow BDW, VanWormer JJ, King JP, Belongia EA. Effect of Statin Use on Influenza Vaccine Effectiveness. *The Journal of Infectious Diseases.* 2016;214(8):1150-1158.

82. Weitz-Schmidt G, Welzenbach K, Brinkmann V, et al. Statins selectively inhibit leukocyte function antigen-1 by binding to a novel regulatory integrin site. *Nat Med.* 2001;7(6):687-692.

83. Jain MK, Ridker PM. Anti-Inflammatory Effects of Statins: Clinical Evidence and Basic Mechanisms. *Nat Rev Drug Discov.* 2005;4(12):977-987.

84. Bu D-x, Griffin G, Lichtman AH. Mechanisms for the anti-inflammatory effects of statins. *Current Opinion in Lipidology.* 2011;22(3):165-170.

85. Bessler H, Salman H, Bergman M, Straussberg R, Djaldetti M. In vitro effect of statins oncytokine production and mitogen response of human peripheral blood mononuclear cells. *Clinical immunology (Orlando, Fla).* 2005;117(1):73-77.

86. Ghittoni R, Napolitani G, Benati D, et al. Simvastatin inhibits the MHC class II pathway of antigen presentation by impairing Ras superfamily GTPases. *European Journal of Immunology.* 2006;36(11):2885-2893.

87. Han KH, Ryu J, Hong KH, et al. HMG-CoA reductase inhibition reduces monocyte CC chemokine receptor 2 expression and monocyte chemoattractant protein-1-mediated monocyte recruitment in vivo. *Circulation.* 2005;111(11):1439-1447.

88. Mascitelli L, Goldstein MR. How Regulatory T-Cell Induction by Statins May ImpairInfluenza Vaccine Immunogenicity and Effectiveness. *J Infect Dis.* 2016;213(11):1857.

89. Fedson DS. Pandemic Influenza: A Potential Role for Statins in Treatment and Prophylaxis. *Clinical Infectious Diseases.* 2006;43(2):199-205.

90. Fedson DS. Treating influenza with statins and other immunomodulatory agents. *Antiviral research.* 2013;99(3):417-435.

91. Havers F, Bramley AM, Finelli L, et al. Statin Use and Hospital Length of Stay Among Adults Hospitalized With Community-acquired Pneumonia. *Clin Infect Dis.* 2016;62(12):1471-1478.

92. Laidler MR, Thomas A, Baumbach J, et al. Statin Treatment and Mortality: Propensity Score-Matched Analyses of 2007–2008 and 2009–2010 Laboratory-Confirmed Influenza Hospitalizations. *Open Forum Infectious Diseases.* 2015;2(1):ofv028.

93. Seo SH, Webby R, Webster RG. No apoptotic deaths and different levels of inductions of inflammatory cytokines in alveolar macrophages infected with influenza viruses. *Virology.* 2004;329(2):270-279.

94. Vandermeer ML, Thomas AR, Kamimoto L, et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study. *J Infect Dis.* 2012;205(1):13-19.

95. Peng J, Zhang D, Ma Y, Wang G, Guo Z, Lu J. Protective effect of fluvastatin on influenza virus infection. *Molecular medicine reports.* 2014;9(6):2221-2226.

96.   Fiscella K, Holt K, Meldrum S, Franks P. Disparities in preventive procedures: comparisons of self-report and Medicare claims data. *BMC Health Services Research.* 2006;6:122-122.

97.   Paules CI, Sullivan SG, Subbarao K, Fauci AS. Chasing Seasonal Influenza - The Need for a Universal Influenza Vaccine. *N Engl J Med.* 2018;378(1):7-9.

98.   Flannnery B CJ, for the US Flu VE Network and Ferdinands J, for the HAIVEN network. Preliminary estimates of 2017-18 seasonal influenza vaccine Effectiveness against laboratory-confirmed influenza from the U.S. Flu VE and HAIVEN networks. 2018; June 20, 2018 presentations to the Advisory Committee on Immunization Practices Available at: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2018-06/flu-02-Flannery-508.pdf. Accessed 08/22, 2019.

99.   Sullivan SG, Chilver MB, Carville KS, et al. Low interim influenza vaccine effectiveness, Australia, 1 May to 24 September 2017. *Euro Surveill.* 2017;22(43).

100.   Skowronski DM, Chambers C, De Serres G, et al. Early season co-circulation of influenza A(H3N2) and B(Yamagata): interim estimates of 2017/18 vaccine effectiveness, Canada, January 2018. *Euro Surveill.* 2018;23(5).

101.   Flannery B, Chung JR, Belongia EA, et al. Interim Estimates of 2017-18 Seasonal Influenza Vaccine Effectiveness - United States, February 2018. *MMWR Morbidity and mortality weekly report.* 2018;67(6):180-185.

102.   FDA. Flucelvax package insert. 2016; https://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM502 899.pdf. Accessed 02 22, 2018.

103.   FDA. Flublock Package Insert. 2017; https://www.fda.gov/downloads/biologicsbloodvaccines/vaccines/approvedproducts/ucm3360 20.pdf. Accessed 02 22, 2018.

104.   (WHO) WHO. Candidate vaccine viruses and potency testing reagents for development and production of vaccines for use in the northern hemisphere 2017-2018 influenza season. 2017; http://www.who.int/influenza/vaccines/virus/candidates_reagents/2017_18_north/en/. Accessed 03/21/2018, 2018.

105.   FDA. Fluad package insert. 2017; https://www.fda.gov/downloads/biologicsbloodvaccines/safetyavailability/vaccinesafety/ucm4 74387.pdf. Accessed 02 22, 2018.

106.   Pinchinat S, Cebrian-Cuenca AM, Bricout H, Johnson RW. Similar herpes zoster incidence across Europe: results from a systematic literature review. *BMC Infect Dis.* 2013;13:170.

107.   Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ open.* 2014;4(6):e004833.

108.   Tyring SK. Management of herpes zoster and postherpetic neuralgia. *Journal of the American Academy of Dermatology.* 2007;57(6 Suppl):S136-142.

109.   Kost RG, Straus SE. Postherpetic neuralgia--pathogenesis, treatment, and prevention. *N Engl J Med.* 1996;335(1):32-42.

110.   Edmunds WJ, Brisson M, Rose JD. The epidemiology of herpes zoster and potential cost-effectiveness of vaccination in England and Wales. *Vaccine.* 2001;19(23-24):3076-3090.

111.   Yawn BP, Wollan P, St. Sauver J. Comparing Shingles Incidence and Complication Rates From Medical Record Review and Administrative Database Estimates: How Close Are They? *Am J Epidemiol.* 2011;174(9):1054-1061.

112.   Oxman MN, Levin MJ, Johnson GR, et al. A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults. *New England Journal of Medicine.* 2005;352(22):2271-2284.

113.   Co. M. ZOSTAVAX (Zoster vaccine live): important information regarding storage and handling [package insert]. 2019;

http://www.merck.com/product/usa/pi_circulars/z/zostavax/zostavax_pi.pdf.
Accessed 01/20/2019, 2015.

114.   Donahue JG, Choo PW, Manson JE, Platt R. The incidence of herpes zoster. *Arch Intern Med.* 1995;155(15):1605-1609.

115.   Hales CM, Harpaz R, Bialek SR. Self-reported herpes zoster, pain, and health care seeking in the Health and Retirement Study: implications for interpretation of health care–based studies. *Annals of Epidemiology.*

116.   Jackson LA, Reynolds MA, Harpaz R. Hospitalizations to treat herpes zoster in older adults: causes and validated rates. *Clin Infect Dis.* 2008;47(6):754-759.

117.   Klompas M, Kulldorff M, Vilk Y, Bialek SR, Harpaz R. Herpes zoster and postherpetic neuralgia surveillance using structured electronic data. *Mayo Clinic proceedings.* 2011;86(12):1146-1153.

118.   Langan SM, Smeeth L, Margolis DJ, Thomas SL. Herpes zoster vaccine effectiveness against incident herpes zoster and post-herpetic neuralgia in an older US population: a cohort study. *PLoS medicine.* 2013;10(4):e1001420.

119.   Marin M, Yawn BP, Hales CM, et al. Herpes zoster vaccine effectiveness and manifestations of herpes zoster and associated pain by vaccination status. *Human vaccines & immunotherapeutics.* 2015;11(5):1157-1164.

120.   Mullooly JP, Riedlinger K, Chun C, Weinmann S, Houston H. Incidence of herpes zoster, 1997-2002. *Epidemiology and infection.* 2005;133(2):245-253.

121.   Tseng HF, Lewin B, Hales CM, et al. Zoster Vaccine and the Risk of Postherpetic Neuralgia in Patients Who Developed Herpes Zoster Despite Having Received the Zoster Vaccine. *J Infect Dis.* 2015;212(8):1222-1231.

122.   Tseng HF, Harpaz R, Luo Y, et al. Declining Effectiveness of Herpes Zoster Vaccine in Adults Aged >/=60 Years. *J Infect Dis.* 2016.

123.   CMS. CMS Fast Facts. 2018; https://www.cms.gov/fastfacts/.

124.   (CMS) CfMaMS. Medicare Current Beneficiary Survey (MCBS). 2018; https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS/index.html. Accessed 04/05/2018, 2018.

125.   CMS. Technical Documentation for the Medicare Current Beneficiary Survey 2013. 2013; https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/MCBS/Data-Tables-Items/2013CNP.html?DLPage=1&DLEntries=10&DLSort=0&DLSortDir=descending.

126.   Mann E. Linking the Medicare Current Beneficiary Survey (MCBS) to Identifiable Data. 2016; https://www.resdac.org/resconnect/articles/107.

127.   Pope GC, Kautter J, Ellis RP, et al. Risk adjustment of Medicare capitation payments using the CMS-HCC model. *Health care financing review.* 2004;25(4):119-141.

128.   Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Statistics in Medicine.* 2009:3083–3107.

129.   Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behavioral Research.* 2011;46(3):399-424.

130.   Xu S, Ross C, Raebel MA, Shetterly S, Blanchette C, Smith D. Use of stabilized inverse propensity scores as weights to directly estimate relative risk and its confidence intervals. *Value Health.* 2010;13(2):273-277.

131.   Lee BK, Lessler J, Stuart EA. Weight Trimming and Propensity Score Weighting. *PLOS One.* 2011.

132.   Funk MJ, Westreich D, Wiesen C, Sturmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. *Am J Epidemiol.* 2011;173(7):761-767.

133.   McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosting models. *Statistics in Medicine.* 2013:3388–3414.

134. Jackson ML, Chung JR, Jackson LA, et al. Influenza Vaccine Effectiveness in the United States during the 2015-2016 Season. *N Engl J Med.* 2017;377(6):534-543.

135. Appiah GD, Blanton L, D'Mello T, et al. Influenza activity - United States, 2014-15 season and composition of the 2015-16 influenza vaccine. *MMWR Morbidity and mortality weekly report.* 2015;64(21):583-590.

136. Fairman KA. Evaluating Medication Adherence: Which Measure Is Right for Your Program? *Journal of Managed Care Pharmacy.* 2000;6(6):499-506.

137. Potter CW, Oxford JS. DETERMINANTS OF IMMUNITY TO INFLUENZA INFECTION IN MAN. *British Medical Bulletin.* 1979;35(1):69-75.

138. Chang HY, Weiner JP, Richards TM, Bleich SN, Segal JB. Validating the adapted Diabetes Complications Severity Index in claims data. *The American journal of managed care.* 2012;18(11):721-726.

139. Mapel DW, Dutro MP, Marton JP, Woodruff K, Make B. Identifying and characterizing COPD patients in US managed care. A retrospective, cross-sectional analysis of administrative claims data. *BMC Health Serv Res.* 2011;11:43.

140. Stuart EA. Matching methods for causal inference: A review and a look forward. *Statistical science : a review journal of the Institute of Mathematical Statistics.* 2010;25(1):1-21.

141. Akaike H. A new look at the statistical model identification. *IEEE Transactions on Automatic Control.* 1974;19(6):716-723.

142. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. *A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines.* 2014;129(25 suppl 2):S1-S45.

143. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology (Cambridge, Mass).* 2010;21(3):383-388.

144. Tseng HF, Smith N, Harpaz R, Bialek SR, Sy LS, Jacobsen SJ. Herpes zoster vaccine in older adults and the risk of subsequent herpes zoster disease. *jama.* 2011;305(2):160-166.

145. Leung J, Harpaz R, Molinari NA, Jumaan A, Zhou F. Herpes zoster incidence among insured persons in the United States, 1993-2006: evaluation of impact of varicella vaccination. *Clin Infect Dis.* 2011;52(3):332-340.

146. Zhang J, Xie F, Delzell E, et al. Association between vaccination for herpes zoster and risk of herpes zoster infection among older patients with selected immune-mediated diseases. *jama.* 2012;308(1):43-49.

147. Rubin DB, Thomas N. Combining propensity score matching with additional adjustments for prognostic covariates. *Journal of the American Statistical Association.* 2000;95(450):573-585.

148. Bang H, Robins JM. Doubly robust estimation in missing data and causal inference models. *Biometrics.* 2005;61(4):962-973.

149. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. *Statistics in Medicine.* 2004;23(19):2937-2960.

150. Flannery B, Fry AM. Comparing influenza vaccine types: the path towards improved influenza vaccine strategies. *J Infect Dis.* 2018.

151. Black S. Herpes Zoster Vaccine and the Medicare Population. *Clin Infect Dis.* 2017;64(6):794-795.

152. Hak E. Novel observational study designs with new influenza vaccines. *Lancet Infect Dis.* 2015;15(3):253-254.

153. Monto AS. Moving Toward Improved Influenza Vaccines. *J Infect Dis.* 2017;215(4):500-502.

154. Bonmarin I, Belchior E, Bergounioux J, et al. Intensive care unit surveillance of influenza infection in France: the 2009/10 pandemic and the three subsequent seasons. *Euro Surveill.* 2015;20(46).

155.   Estimates of deaths associated with seasonal influenza --- United States, 1976-2007. *MMWR Morbidity and mortality weekly report.* 2010;59(33):1057-1062.

156.   Influenza activity--United States, 2012-13 season and composition of the 2013-14 influenza vaccine. *MMWR Morbidity and mortality weekly report.* 2013;62(23):473-479.

157.   Epperson S, Blanton L, Kniss K, et al. Influenza activity - United States, 2013-14 season and composition of the 2014-15 influenza vaccines. *MMWR Morbidity and mortality weekly report.* 2014;63(22):483-490.

158.   Barr IG, Russell C, Besselaar TG, et al. WHO recommendations for the viruses used in the 2013-2014 Northern Hemisphere influenza vaccine: Epidemiology, antigenic and genetic characteristics of influenza A(H1N1)pdm09, A(H3N2) and B influenza viruses collected from October 2012 to January 2013. *Vaccine.* 2014;32(37):4713-4725.

159.   Skowronski DM, Janjua NZ, De Serres G, et al. Low 2012-13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses. *PLoS One.* 2014;9(3):e92153.

160.   McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type. *J Infect Dis.* 2015;211(10):1529-1540.

161.   Lindegren ML, Griffin MR, Williams JV, et al. Antiviral treatment among older adults hospitalized with influenza, 2006-2012. *PLoS One.* 2015;10(3):e0121952.

162.   Williams LO, Kupka NJ, Schmaltz SP, Barrett S, Uyeki TM, Jernigan DB. Rapid influenza diagnostic test use and antiviral prescriptions in outpatient settings pre- and post-2009 H1N1 pandemic. *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology.* 2014;60(1):27-33.

163.   Garvin JH, Redd A, Bolton D, et al. Exploration of ICD-9-CM coding of chronic disease within the Elixhauser Comorbidity Measure in patients with chronic heart failure. *Perspectives in health information management / AHIMA, American Health Information Management Association.* 2013;10:1b.

164.   Jackson ML, Nelson JC, Jackson LA. Why do covariates defined by International Classification of Diseases codes fail to remove confounding in pharmacoepidemiologic studies among seniors? *Pharmacoepidemiol Drug Saf.* 2011;20(8):858-865.

165.   Psaty BM, Siscovick DS. Minimizing bias due to confounding by indication in comparative effectiveness research: the importance of restriction. *Jama.* 2010;304(8):897-898.

166.   McGrath LJ, Ellis AR, Brookhart MA. Controlling Time-Dependent Confounding by Health Status and Frailty: Restriction Versus Statistical Adjustment. *Am J Epidemiol.* 2015;182(1):17-25.

167.   Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. *Lancet Infect Dis.* 2016;16(8):942-951.

168.   DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults. *New England Journal of Medicine.* 2014;371(7):635-645.

169.   Representatives USHo. Testimony of Scott Gottlieb, Commisioner of Food and Drugs, Food and Drug Administration, before the Subcommittee on Oversight and Investigations, Committee on Energy and Commerce, U.S. House of Representatives: "Examining U.S. Public Health preparedness for and Response Efforts to Seasonal Influenza". . 2018; https://docs.house.gov/meetings/IF/IF02/20180308/106967/HHRG-115-IF02-Wstate-GottliebS-20180308.pdf. Accessed August 16, 2018.

170.   Zost SJ, Parkhouse K, Gumina ME, et al. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains.

Proceedings of the National Academy of Sciences of the United States of America. 2017;114(47):12578-12583.

171. Skowronski DM, Chambers C, Sabaiduc S, et al. A Perfect Storm: Impact of Genomic Variation and Serial Vaccination on Low Influenza Vaccine Effectiveness During the 2014-2015 Season. *Clin Infect Dis.* 2016;63(1):21-32.

172. (WHO) WHO. WHO Consultation and Information Meeting on the Composition of Influenza Virus Vaccines for Use in the 2018 Southern Hemisphere Influenza Season. 2017; http://www.who.int/influenza/vaccines/virus/recommendations/consultation201709/en/index 2.htm. Accessed 03/21/2018, 2018.

173. Gatherer D. Passage in egg culture is a major cause of apparent positive selection in influenza B hemagglutinin. *J Med Virol.* 2010;82(1):123-127.

174. (CDC) CfDCap. Weekly U.S. Influenza report: 2017-2018 Influenza Season Week 21 ending May 26, 2018. 2018; https://www.cdc.gov/flu/weekly/index.htm. Accessed June 4, 2018, 2018.

175. Saito T, Nakaya Y, Suzuki T, et al. Antigenic alteration of influenza B virus associated with loss of a glycosylation site due to host-cell adaptation. *J Med Virol.* 2004;74(2):336-343.

176. (CDC) CfDCaP. Rapid diagnostic testing for influenza: information for clinical laboratory directors, table 2. July 6th, 2013. 2014; http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm#table2. Accessed 05/28, 2014.

177. (FDA) FaDA. Tamiflu® [package insert]. Foster City, CA: Gilead Science, Inc. 2008; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&applno= 021087. Accessed February 21, 2018.

178. (FDA) FaDA. Relenza® [package insert]. Research Triangle Park, NC: GlaxoSmithKline. 2013; https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo= 021036. Accessed February 21, 2018.

179. Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ.* 2011;183(3):310-319.

180. Filion KB, Chateau D, Targownik LE, et al. Proton pump inhibitors and the risk of hospitalisation for community-acquired pneumonia: replicated cohort studies with meta-analysis. *Gut.* 2014;63(4):552-558.

181. Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA.* 2004;292(16):1955-1960.

182. Hermos JA, Young MM, Fonda JR, Gagnon DR, Fiore LD, Lawler EV. Risk of community-acquired pneumonia in veteran patients to whom proton pump inhibitors were dispensed. *Clin Infect Dis.* 2012;54(1):33-42.

183. Schmader KE, Levin MJ, Gnann JW, Jr., et al. Efficacy, safety, and tolerability of herpes zoster vaccine in persons aged 50-59 years. *Clin Infect Dis.* 2012;54(7):922-928.

184. Morrison VA, Johnson GR, Schmader KE, et al. Long-term persistence of zoster vaccine efficacy. *Clin Infect Dis.* 2015;60(6):900-909.

185. Jumaan AO, Yu O, Jackson LA, Bohlke K, Galil K, Seward JF. Incidence of herpes zoster, before and after varicella-vaccination-associated decreases in the incidence of varicella, 1992-2002. *J Infect Dis.* 2005;191(12):2002-2007.

186. Soni A, S.C. Hill. *Average Annual Health Care Use and Expenses for Shingles among the U.S. Civilian Noninstitutionalized Population, 2003–2005* Washington, DC: Agency for Healthcare Research and Quality;2007.

187. Bowsher D. The lifetime occurrence of Herpes zoster and prevalence of post-herpetic neuralgia: A retrospective survey in an elderly population. *European journal of pain (London, England).* 1999;3(4):335-342.

188. Lu PJ, Euler GL, Jumaan AO, Harpaz R. Herpes zoster vaccination among adults aged 60 years or older in the United States, 2007: uptake of the first new vaccine to target seniors. *Vaccine.* 2009;27(6):882-887.

189. Linet MS, Celentano DD, Stewart WF. Headache characteristics associated with physician consultation: a population-based survey. *Am J Prev Med.* 1991;7(1):40-46.

190. Marcus DA. Gender differences in chronic pain in a treatment-seeking population. *The journal of gender-specific medicine : JGSM : the official journal of the Partnership for Women's Health at Columbia.* 2003;6(4):19-24.

191. Mannion AF, Wieser S, Elfering A. Association between beliefs and care-seeking behavior for low back pain. *Spine.* 2013;38(12):1016-1025.

192. Williams WW, Lu PJ, O'Halloran A, et al. Surveillance of Vaccination Coverage Among Adult Populations - United States, 2014. *Morbidity and mortality weekly report Surveillance summaries (Washington, DC : 2002).* 2016;65(1):1-36.

193. Schwartz B, Orenstein WA. Prioritization of pandemic influenza vaccine: rationale and strategy for decision making. *Curr Top Microbiol Immunol.* 2009;333:495-507.

194. (CDC) CfDCaP. Seasonal Influenza Vaccine Supply for the U.S. 2017-2018 Influenza Season. 2017; https://www.cdc.gov/flu/about/qa/vaxsupply.htm. Accessed 04/27/2018,2018.

195. Eichelberger MC, Morens DM, Taubenberger JK. Neuraminidase as an influenza vaccine antigen: a low hanging fruit, ready for picking to improve vaccine effectiveness. *Curr Opin Immunol.* 2018;53:38-44.

196. Greenland S. Dose-response and trend analysis in epidemiology: alternatives to categorical analysis. *Epidemiology (Cambridge, Mass).* 1995;6(4):356-365.

197. Dahlgren FS, Shay DK, Izurieta HS, et al. Patterns of seasonal influenza activity in U.S. core based statistical areas, described using prescriptions of oseltamivir in Medicare claims data. *Epidemics.* 2018.

198. Dahlgren FS, Shay DK, Izurieta HS, et al. Evaluating oseltamivir prescriptions in Centers for Medicare and Medicaid Services medical claims records as an indicator of seasonal influenza in the United States. *Influenza Other Respir Viruses.* 2018;12(4):465-474.