Universidad Rey Juan Carlos

Departamento de Medicina Preventiva y Salud Pública e Inmunología y Microbiología Médicas

Facultad de Ciencias de la Salud

Development and Implementation of a European Network to Measure the Effectiveness of the Influenza Vaccine

TESIS DOCTORAL

Marta Valenciano Martínez-Orozco

Madrid 2011

Don José Luis del Barrio Fernández, Profesor de la Facultad de Ciencias de la Salud de la Universidad Rey Juan Carlos

CERTIFICA:

Que el proyecto de Tesis Doctoral titulado ***"*Development and implementation of a European network to measure the effectiveness of the influenza vaccine*",*** ha sido realizado bajo su dirección por la licenciada en Veterinaria Doña Marta Valenciano Martínez-Orozco, y reúne todos los requisitos científicos y formales para ser presentado y defendido ante el tribunal correspondiente.

Y para que así conste a todos los efectos, firmo el presente certificado

en Madrid a cuatro de noviembre de dos mil once.

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Centro Nacional de Epidemiología

Dña Amparo Larrauri Cámara, Investigadora Titular del Centro Nacional de Epidemiología del Instituto de Salud Carlos III.

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Que el proyecto de Tesis Doctoral titulado "***Development and implementation of a European network to measure the effectiveness of the influenza vaccine***", ha sido realizado bajo mi dirección por la licenciada en Veterinaria Doña Marta Valenciano Martínez-Orozco, y reúne todos los requisitos científicos y formales para ser presentado y defendido ante el tribunal correspondiente.

Y para que así conste a todos los efectos, firmo el presente certificado en Madrid a cuatro de noviembre de dos mil once.

Fdo. Amparo Larrauri Cámara, PhD

***A mi padre**, porque sin pretender ser ejemplo, con su inmensa humanidad y pasión por la Salud Pública, me hizo descubrir y amar esta profesión.*

***A mi madre**, siempre cerca, incluso cuando estuve muy lejos.*

***A Nico**, por la felicidad, por tu sonrisa, por nuestro futuro.*

Agradecimientos

Merci de tout cœur **Alain** pour être mon « grand-frère », mon coach, mon professeur, le meilleur superviseur, mon collègue.

Special thanks to **Esther** and **Bruno**: without your dedication, your "savoir faire" and your humour, the I-MOVE road would have been much more difficult and tedious.

Thanks to **all I-MOVE members** for your energy, professionalism and friendship.

Merci à tous mes **collègues d´EpiConcept**… c´est sympa et motivant d´être parmi vous. Vive la créativité.

Amparo, siempre es un placer trabajar contigo tanto en I-MOVE como en la preparación de la tesis. Mil gracias por animarme.

José Luis, gracias por haber aceptado el reto de dirigir esta tesis tan europea.

Merci **Anne** pour répondre toujours « présente ».

« Kiitos», thanks **Hanna** for finding in your busy schedule, time to read, comment, and for providing interesting inputs.

Y por supuesto, gracias a **mis hermanas Malena y Paloma**, a **mis cuñados Javier y Daniel**, a **mis sobrinos Nathalie, Javichu, Beto**: si he podido viajar durante años y pasar largas temporadas muy lejos es porque sé que estáis ahí, sois la raíz que me permite ir y venir sin perderme.

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LISTA DE ABREVIATURAS

AEM	Agencia Europea del Medicamento
CE	Comisión Europea
CIE	Código internacional de enfermedades
DTN	Diseño test negativo
ECDC	Centro Europeo para el Control de las Enfermedades
EEE	Espacio Económico Europeo
EEMM	Estados miembros
EISN	European Influenza Surveillance Network
EISS	European Influenza Surveillance Scheme
EV	Efectividad de la vacuna
UE	Unión Europea
HA	Hemaglutinina
I-MOVE	Influenza Monitoring Vaccine Effectiveness in Europe
NA	Neuranimidasa
OR	Odds Ratio
RT-PCR	Real Time Polymerase Chain Reaction
VENICE	Vaccine European New Integrated Collaboration Effort
OMS	Organización Mundial de la Salud

A) ANTECEDENTES

A.1. Generalidades sobre la gripe

La gripe es una enfermedad aguda de las vías respiratorias causada por el virus influenza. El virus influenza se transmite de persona a persona principalmente a través de gotículas y aerosoles expulsados al toser o estornudar. Se propaga rápidamente en forma de epidemias estacionales que, en el hemisferio norte tienen lugar entre noviembre y abril.

El virus de la gripe

El virus de la gripe es un virus ARN perteneciente a la familia *Orthomyxoviridae*. Tres tipos de virus de la gripe infectan a los seres humanos: A, B, C. Los serotipos A y B son los responsables de las epidemias de gripe anuales. Los virus de tipo A se clasifican en subtipos en función de la combinación de dos proteínas de la superficie viral la hemaglunina (HA) y la neuraminidasa (NA). Los virus de la gripe evolucionan constantemente sufriendo alteraciones en la estructura antigénica de las proteínas HA y NA. La deriva antigénica *(drift)* consiste en pequeños cambios antigénicos que ocurren con frecuencia y son los responsables del cambio de las cepas incluidas en las vacunas que son definidas por la Organización Mundial de la Salud (OMS) para cada temporada. Los virus de la gripe también sufren variaciones antigénicas más importantes denominadas saltos antigénicos *(shift*). Estos saltos antigénicos ocurren cuando se recombinan dos o más virus gripales de diferente origen, bien sea humano o bien animal, pudiendo dar lugar a un nuevo virus frente al que la población no tiene ninguna protección. Estos nuevos virus pueden originar pandemias.

Morbilidad, mortalidad por gripe

Por su sintomatología inespecífica y su variación entre temporadas, grupo de edades y países es difícil estimar con precisión la morbilidad y mortalidad por gripe. La OMS estima que durante las epidemias estacionales, la tasa de ataque de la enfermedad es entre 5% y 10% en adultos y entre 20% a 30% en niños y que la gripe produce anualmente en el mundo entre tres y cinco millones de casos graves y entre 250.000 y 500.000 muertes. La mayoría de los casos de gripe se recuperan en una o dos semanas sin necesidad de recibir

tratamiento médico. Sin embargo, la gripe puede provocar complicaciones tales como neumonía y muerte en ciertos grupos de población como niños pequeños, ancianos o personas con enfermedades crónicas. El Centro Europeo para el Control de las Enfermedades (ECDC) estima que la gripe estacional puede producir en Europa un exceso de 40.000 muertes en una temporada de gripe entre moderada y grave. Además de los costes directos derivados de la asistencia sanitaria, la gripe causa elevados costes indirectos derivados del absentismo laboral y de la pérdida de productividad.

A.2. Vigilancia de la gripe en Europa

En Europa se empezaron a establecer redes nacionales de vigilancia de gripe en 1950. En 1992, a través del proyecto CARE Telematics, se dieron los primeros pasos en el establecimiento de una red Europea de vigilancia de la gripe. Una vez finalizado el proyecto CARE, en 1995 se creó EISS (European Influenza Surveillance System) red que pasó a ser coordinada por el ECDC en 2008 denominándose EISN (European Influenza Surveillance Network). EISN integra datos clínicos, epidemiológicos y virológicos e incluye 33 redes de médicos centinela europeas.

La vigilancia de la gripe en Europa se basa en redes de médicos voluntarios de atención primaria (médicos centinela) que notifican casos de síndrome gripal o de infección respiratoria aguda al centro de coordinación de la vigilancia de la gripe en cada país. El número y tipo de médicos centinela y la proporción de población cubierta varían entre países. Generalmente, los médicos centinela representan entre el 1% y el 5% del total de médicos del país. Asimismo, dichos médicos centinela realizan frotis nasofaríngeos en una muestra de pacientes con síntomas gripales y envían las muestras al laboratorio de referencia correspondiente para confirmación virológica. El laboratorio nacional de referencia analiza una parte de la muestras para caracterizar genética y antigénicamente los virus circulantes. Además de frotis procedentes de los médicos centinela, los sistemas nacionales de vigilancia de gripe recogen información de muestras provenientes de otras fuentes (médicos no centinela, hospitales, residencias de ancianos, etc.). La información clínica, epidemiológica y virológica se notifica semanalmente a EISN durante la temporada de gripe. Uno de los objetivos de EISN es evaluar la efectividad de la vacuna antigripal.

A.3. Vacunación antigripal en Europa

Vacuna antigripal

La composición de la vacuna antigripal se revisa anualmente para adaptarla a las cepas de virus identificadas y tratar así de que los virus incluidos en la vacuna concuerden con las propiedades antigénicas de los virus circulantes. Dos veces al año, la OMS reúne a sus centros colaboradores y principales laboratorios de referencia para recomendar cuáles son los virus que deben incluirse en la vacuna de la temporada siguiente tanto en el hemisferio norte como en el hemisferio sur.

Las vacunas utilizadas actualmente en Europa para prevenir la gripe estacional son vacunas trivalentes e incluyen dos virus A y un virus B. En Europa existen principalmente tres tipos de vacunas, todas ellas inactivadas: vacunas de virus fraccionados, vacunas de subunidades y vacunas de virus enteros. Asimismo empiezan a estar disponibles vacunas vivas atenuadas intranasales que se utilizan principalmente en niños. En algunas vacunas se incluyen adyuvantes para mejorar la respuesta inmune.

Durante las pandemias, se elaboran vacunas específicas para la cepa pandémica. Las vacunas pandémicas están generalmente disponibles para la población después de cuatro o seis meses de haberse identificado el virus pandémico.

Grupos para los que se recomienda la vacunación en Europa

La estrategia de la vacunación antigripal anual se centra en reducir las complicaciones de la gripe, la mortalidad y las hospitalizaciones. En todos los países de la UE y EEE, la vacuna está indicada para las personas con riesgo elevado de padecer complicaciones (mayores de 59 o de 64 años dependiendo del país, con enfermedades crónicas, inmunodeprimidos) y para ciertos grupos profesionales. En seis países la vacuna se recomienda también en niños entre 6 meses y 18 años.

Coberturas de vacunación

Las encuestas del proyecto Europeo VENICE (Vaccine European New Integrated Collaboration Effort), revelan que la cobertura de vacunación antigripal se calcula de muy distintas formas en los distintos EEMM de la UE/EEE. Por ello es difícil comparar las

estimaciones entre países. Los resultados de la encuesta llevada a cabo por VENICE en 2009, indicaban que en 2007/2008 únicamente dos países, Reino Unido y los Países Bajos, habían logrado el objetivo fijado por la OMS para el año 2014 de alcanzar una cobertura de vacunación del 75% en la población mayor de 65 años. La proporción de personas vacunadas en este grupo de edad variaba entre el 1,1% en Estonia y el 82,6% en los Países Bajos. Seis EEMM pudieron estimar la cobertura vacunal en grupos de riesgo y en trabajadores sanitarios. En los grupos de riesgo la cobertura variaba entre el 32,9% en Hungría y el 71,7% y en los trabajadores sanitarios entre el 13,4% en el Reino Unido y el 89,4% en Rumanía.

A.4. Estudios de eficacia y efectividad de la vacuna antigripal

Definición eficacia

La eficacia de una vacuna se define como la disminución de la incidencia de la enfermedad en el grupo vacunado con respecto a la incidencia en los no vacunados. La eficacia de una vacuna suele evaluarse en ensayos clínicos controlados.

Definición efectividad

La efectividad de una vacuna mide el efecto de la vacuna en condiciones reales de administración. La efectividad de la vacuna depende de su eficacia, de las condiciones en las que se administra y de las características de la población. La efectividad de una vacuna se mide en estudios observacionales que por su naturaleza, están sujetos a sesgos.

A.5. Justificación del estudio

La vacunación anual es la intervención de elección para prevenir la gripe estacional y una de las intervenciones más valiosas en caso de gripe pandémica.

En respuesta a la evolución constante del virus de la gripe, la composición de las vacunas antigripales se reformula cada año. Por tanto, la efectividad de la vacuna (EV) antigripal no se puede establecer basándose en estimaciones de años anteriores. A nivel europeo, disponer de estimaciones anuales de la EV tan pronto como se inicia la temporada gripal y evaluar rutinariamente la EV a lo largo de la epidemia/pandemia es fundamental para:

- decidir las recomendaciones sobre el uso de la vacuna por grupos de edad y grupos de riesgo;
- implementar o reforzar otras intervenciones de salud pública (ej: utilización de antivirales) en segmentos de la población en los que la vacuna es menos efectiva;
- estimar con mayor precisión el impacto de las estrategias de vacunación en la carga de enfermedad para evaluar las campañas de vacunación;
- ayudar a la interpretación de los análisis virológicos que comparan la concordancia de las cepas vacunales y circulantes;
- estimular la investigación en el área de vacunas antigripales (mejora de la composición, utilización de adyuvantes, necesidad de dosis de recuerdo);
- validar la EV antigripal de nuevos modos de administración de la vacuna (ej: por vía intranasal, intradérmica);
- identificar a partir de qué momento la vacuna es efectiva (7, 14, 21 días después de la vacunación);
- comparar la EV antigripal de distintos tipos de vacunas (ej: adyuvada y no adyuvada);
- responder a los posibles informes de "fracasos" vacunales, especialmente durante las pandemias;
- disponer de datos para realizar una gestión adecuada del riesgo y un análisis de coste efectividad frente a posibles efectos adversos señalados.

En Europa, la vacuna antigripal está recomendada y accesible para los grupos de riesgo y por ello no sería ético realizar ensayos clínicos aleatorizados para estimar la EV antigripal. Por lo tanto, se pueden llevar a cabo únicamente estudios observacionales.

Para establecer un sistema que permitiera evaluar anualmente y en tiempo real la EV antigripal en los Estados miembros (EEMM) de la Unión Europea (UE) y del Espacio Económico Europeo (EEE) era necesario en primer lugar definir qué métodos observacionales podían ser utilizados. Un sistema cuyo objetivo fuera medir de forma rutinaria la EV antigripal, debía ser sencillo, sostenible y a la vez generar estimaciones científicamente robustas. Los métodos utilizados debían tener en cuenta la situación específica de cada Estado miembro en términos de recursos y fuentes de datos disponibles.

B) OBJETIVOS

Objetivo general

Desarrollar una red europea para evaluar anualmente la EV de la vacuna antigripal estacional y de la vacuna pandémica en la UE y en el EEE.

Objetivos específicos

1) Identificar y describir los estudios observacionales que permitan evaluar anualmente la EV antigripal estacional y pandémica en la UE y en el EEE;

2) Identificar los elementos metodológicos clave que deben tenerse en cuenta en los protocolos de estudios para evaluar la EV antigripal en tiempo real en los EEMM de la UE y del EEE;

3) Estimar la EV antigripal estacional y pandémica frente a síndrome gripal confirmado por laboratorio en las temporadas 2008/9, 2009/10 y 2010/11.

C) MÉTODOS

Con el fin de desarrollar una red europea para evaluar la EV antigripal, se estableció una red integrada por 18 Institutos de Salud Pública Europeos y EpiConcept, el centro de coordinación. La red se denominó I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe. Se definieron tres etapas para la puesta en marcha de dicha red. En la primera etapa (enero-septiembre 2008) se recogió toda la información necesaria que permitió desarrollar protocolos genéricos de estudios observacionales para evaluar la EV antigripal en Europa. La segunda fase, fue la fase piloto (temporada 2008/9) en la que se utilizaron dichos protocolos para llevar a cabo estudios en 7 países. En 2009/10 se inició la fase de implantación de I-MOVE con la evaluación de forma regular de la EV en Europa.

C.1. Encuesta Europea

Se llevó a cabo una encuesta en 29 EEMM de la UE y del EEE para identificar los estudios de EV antigripal que se habían realizado en Europa. Asimismo se recogió información en cada país del tipo de fuentes y de los datos existentes y necesarios para medir la EV antigripal (ej: identificación de casos de gripe confirmados por laboratorio, hospitalizados, muertes; documentación del estado vacunal; documentación de posibles factores de confusión). Para recoger la información se elaboró un cuestionario y se contactó con los expertos encargados de la vigilancia de la gripe en cada país (Anexo I). Los expertos podían elegir ser entrevistados (por teléfono o en persona) o completar ellos mismos el cuestionario y reenviarlo a los responsables de la encuesta.

Se completó la información recogida revisando los informes disponibles en las páginas web de EISS, VENICE (Vaccine European New Integrated Collaboration Effort) e Institutos de Salud Pública Europeos y los artículos sobre estudios de EV de la vacuna antigripal realizados en Europa.

C.2. Revisión de la literatura

Se identificaron aquellos artículos publicados hasta 2008 que describían los factores que afectan a la EV antigripal y los métodos utilizados para controlarlos. Se buscó en la base de datos Cochrane y se consultaron las revisiones Cochrane disponibles. Se consultaron también el informe "Health Technology Assessment: Systematic review and economic decision modelling for the prevention and treatment of influenza A and B" y una revisión reciente sobre EV antigripal realizada por Sanofi Pasteur. Se completó la lista de artículos con la bibliografía que aparecía en cada artículo y documento. Se revisaron asimismo artículos sobre aspectos metodológicos de la estimación de la EV antigripal.

C.3. Reuniones de expertos

Entre abril y junio de 2008, se organizaron cuatro reuniones con la participación de miembros del consorcio I-MOVE y expertos en gripe externos al consorcio (Anexo II). En la primera reunión en abril, se presentaron y discutieron los resultados de la encuesta Europea y de la revisión de la literatura. El grupo de expertos identificó los métodos observacionales más factibles para evaluar la EV antigripal en Europa e hizo recomendaciones sobre los elementos que deberían incluirse en los protocolos de estudio genéricos. En las reuniones subsiguientes, los representantes de los países interesados en llevar a cabo estudios durante la fase piloto definieron con más precisión los métodos comunes que iban a ser utilizados.

El grupo concluyó que durante la fase piloto 2008/9 se realizarían:

- dos estudios de cohorte prospectivos utilizando bases de datos clínicas informatizadas. Al menos una muestra de casos serían casos de gripe confirmados por el laboratorio;
- cinco estudios caso control para evaluar la EV antigripal frente a gripe confirmada por laboratorio. Los casos y los controles se identificarían a través de las redes centinela. Los datos de los cinco estudios se combinarían para contribuir a un estudio caso control multicéntrico;
- en los países que llevaran a cabo estudios de cohorte o caso control y que dispusieran de datos de cobertura de vacunación, se recomendaba estimar la EV antigripal utilizando asimismo el método de screening.

En esta tesis, se presentan los métodos, resultados y discuten los aspectos metodológicos de los estudios caso control multicéntricos llevados a cabo en 2008/9, 2009/10 y 2010/11.

C.4. Métodos estudio multicéntrico caso control

Métodos comunes utilizados en las tres temporadas (2008/9, 2009/10, 2010/11)

En cada una de las temporadas se llevó a cabo un estudio caso-control multicéntrico. En cada país incluido en el estudio los coordinadores nacionales invitaron a los médicos centinela a participar. La población de estudio se definió como aquellos pacientes que consultaran un médico centinela por síndrome gripal o enfermedad respiratoria aguda (Francia) en los ocho días posteriores a la fecha de inicio de síntomas. Según la temporada, los médicos centinela entrevistaron y obtuvieron frotis nasofaríngeos de todos o de una muestra de pacientes (ver párrafos métodos específicos para cada temporada).

Se definió un caso como un paciente con síndrome gripal y resultado de laboratorio (PCR o cultivo) positivo a cualquier tipo de virus de la gripe. Los controles se definieron como pacientes con síndrome gripal y resultado de laboratorio negativo a gripe (controles "test-negativo"). Se consideró vacunado a todo paciente con síndrome gripal que hubiera recibido la vacuna más de 14 días antes de la fecha de inicio de síntomas.

Los médicos centinela entrevistaron a los pacientes utilizando un cuestionario que incluía una lista de variables comunes para todos los países (Tabla 1). En cada país los cuestionarios de los médicos centinela se enviaron al equipo de coordinación nacional de I-MOVE. Los equipos de cada país grabaron y validaron los datos y enviaron las correspondientes bases de datos anonimizadas al equipo de coordinación del estudio multicéntrico. Dicho equipo verificó y realizó una segunda validación de los datos y agregó las bases de datos nacionales para crear una base común.

Se evaluó cualitativamente la heterogeneidad entre los datos de cada país comprobando si las definiciones de caso y de las variables comunes eran las mismas. Asimismo se evaluó la heterogeneidad cuantitativamente a través de la prueba Q y del índice I^2. La prueba Q de Cochran se basa en calcular la suma de las desviaciones cuadráticas entre el resultado individual de cada estudio y el resultado global, ponderadas por el peso con el que cada resultado interviene en el cálculo global. En la hipótesis de homogeneidad Q se distribuye como una Chi cuadrado con k-1 grados de libertad, siendo *k* el número de estudios. Por su parte, el índice I^2 describe el porcentaje de variación entre estudios que se atribuye a la

heterogeneidad y no al azar e indica la proporción de la variación entre estudios respecto de la variación total. Valores de I^2 de 25%, 50% y 75% indican una heterogeneidad baja, moderada o alta respectivamente.

Se estimó la EV antigripal cruda global, como 1 menos el odds ratio (OR) utilizando un modelo de efectos fijos e incluyendo el país de estudio como efecto fijo. Se calculó la EV antigripal ajustada utilizando un modelo de regresión logística que incorporaba todos los posibles factores de confusión.

En 2009/10 y 2010/11 se calculó primero la EV antigripal excluyendo todos los individuos con datos incompletos (análisis casos completo). En una segunda etapa, se estimaron los valores perdidos mediante imputación múltiple a través del sistema de ecuación en cadena en Stata. Se asumió que los valores perdidos seguían un mecanismo de perdida aleatoria (Missing at Random assumption).

Todos los análisis estadísticos se realizaron con el paquete estadístico Stata versión 10.1. StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP).

En función de los requerimientos de cada país, los pacientes incluidos en el estudio dieron su consentimiento oral o escrito.

Métodos temporada piloto, 2008/9

En la fase piloto, cinco países participaron en el estudio multicéntrico: Dinamarca, España, Hungría, Portugal y Rumanía. La población de estudio se restringió a las personas mayores: mayores de 59 años en Hungría y mayores de 64 años en los otro cuatro países. En Dinamarca, Hungría y Rumanía, los médicos centinela utilizaron por primera vez la definición europea de síndrome gripal: comienzo súbito de síntomas, presencia de al menos un síntoma general (fiebre, cefalea o malestar general) y presencia de al menos un síntoma respiratorio (tos, disnea o dolor de garganta). En España, se utilizó esta definición añadiendo un criterio adicional: “ausencia de otra sospecha diagnóstica”. En Portugal se mantuvo la definición de caso de la red centinela (gripe según criterio clínico del médico centinela). En todos los países se recogieron los signos clínicos para así poder reconstruir una definición de caso común. Los pacientes con síndrome gripal no eran elegibles para el estudio si residían en instituciones, sufrían demencia, no hablaban la lengua local o rechazaban participar en el

estudio. Los médicos centinela tomaron muestras de todos los pacientes con síndrome gripal pertenecientes al grupo de edad del estudio.

Con el fin de comprobar si la cobertura vacunal del grupo control "test negativo" era diferente a la de otros grupos control, se seleccionaron otros grupos control apareados al caso por tiempo y grupo de edad. En España, Hungría y Portugal se seleccionaron como controles una muestra aleatoria entre los pacientes que no habían desarrollado síndrome gripal desde el inicio de la temporada de gripe. En Dinamarca y Portugal los controles se seleccionaron aleatoriamente en la comunidad.

La EV se estratificó en dos grupos de edad: 65-74 años y > 74 años.

Métodos temporada pandémica 2009/10

En 2009/10 siete países participaron en el estudio multicéntrico: España, Francia, Hungría, Irlanda, Italia, Portugal y Rumanía. El estudio se inició en cada país dos semanas después del inicio de la campaña de vacunación de la vacuna pandémica. En cinco de los países, la población de estudio se definió como todos los pacientes con síndrome gripal o enfermedad respiratoria aguda (Francia) que acudieran a su médico en los ocho días siguientes al inicio los síntomas. En Hungría, la población se limitó a las personas mayores de 17 años y en Italia a la población a la que se le recomendaba la vacunación con la vacuna pandémica.

En España, Hungría, Italia, Portugal y Rumanía los médicos centinela seleccionaron sistemáticamente los pacientes a los que realizaban frotis nasofaríngeo. En Irlanda, cada médico centinela debía tomar muestras de cinco pacientes por semana. En Francia, cada médico centinela tenía asignado un grupo de edad y debía realizar un frotis al primer paciente de la semana de dicho grupo de edad que presentara enfermedad respiratoria aguda

Se definieron como casos todos los pacientes con un resultado positivo al virus pandémico A(H1N1)2009. Se excluyeron los pacientes positivos a virus A pero sin subtipo, los positivos a B y aquellos sin resultados de laboratorio.

Se midió la EV antigripal estacional 2009/10 y de la vacuna pandémica. La EV antigripal pandémica se comparó entre los grupos vacunados 8 días, entre 8 y 14 días y más de 14 días antes del inicio de síntomas.

Se estratificaron los resultados por grupo de edad (< 15, 15-64, > 64 años) y por presencia de enfermedades crónicas.

Métodos temporada 2010/11

En 2010/11 ocho países participaron en el estudio multicéntrico: España, Francia, Hungría, Irlanda, Italia, Polonia, Portugal y Rumanía. En siete países la población de estudio incluyó a todos los pacientes que consultaran por síndrome gripal o enfermedad respiratoria aguda (Francia) en los ocho días siguientes al inicio de síntomas. En Hungría la población de estudio se limitó a los pacientes mayores de 17 años. Los médicos centinela de Francia, Irlanda, Polonia, Portugal y España tomaron muestras de todos los pacientes con síndrome gripal (enfermedad respiratoria aguda en Francia) mayores de 64 años, en Hungría de todos los mayores de 59 años y en Italia seleccionaron sistemáticamente un paciente mayor de 64 años cada semana. Los pacientes de otros grupos de edad, se seleccionaron sistemáticamente en todos los países.

Por primera vez en 2010/11, en cinco estudios se recogió la variable "individuo perteneciente a grupo para el que la vacuna está recomendada". En los otros tres estudios, esta variable se definió en función de la información recogida en sus cuestionarios que permitía identificar los grupos para los que la vacuna estaba recomendada (información sobre grupo de edad, enfermedades crónicas, embarazo, profesión).

En un primer análisis se incluyó a toda la población y en un segundo únicamente a los grupos con recomendación de vacunación. Las estimaciones se estratificaron por grupos de edad ((< 15, 15-59, > 59) años y tipo de virus (virus A(H1N1) y B).

Para evaluar el efecto de la vacuna estacional 2010/11 y de la vacuna pandémica 2009/10, se definió una variable categórica con cuatro niveles:

- No vacunado con ninguna de las dos vacunas;
- Vacunado únicamente con la vacuna pandémica 2009/10;
- Vacunado únicamente con la vacuna estacional 2010/11;
- Vacunado con ambas vacunas.

Como en temporadas anteriores, se estimó la EV antigripal cruda global, utilizando un modelo de efectos fijos e incluyendo el país de estudio como efecto fijo. Posteriormente, se utilizó un modelo de efectos aleatorios para comparar los resultados obtenidos con ambos métodos. Debido al tamaño de la muestra, se incluyeron en los modelos únicamente los factores de confusión más importantes (grupo de edad, mes de inicio de síntomas, enfermedades

crónicas). El estudio irlandés no se pudo incluir en este análisis ya que no contaba con ningún caso vacunado.

D) DISCUSIÓN

El objetivo de este proyecto fue desarrollar una red europea para la evaluación de la efectividad de la vacuna antigripal estacional y pandémica en la UE/EEE. Esta red, I-MOVE, está ya establecida y ha permitido estimar la EV antigripal en tres temporadas consecutivas. En 2009, la red fue capaz de adaptar los estudios a la situación de pandemia. Centros de ocho EEMM colaboraron en los estudios de la fase piloto en la temporada 2008/9 y 11 EEMM en las temporadas 2009/10 y 2010/11. En cuanto a la comunicación, los miembros de la red intercambiaron información en tiempo real a través del sitio web de la red I-MOVE. Los resultados obtenidos a través de dicha red se han publicado en revistas con comité de revisión en cada una de las tres temporadas. I-MOVE permite obtener estimaciones de EV en una fase temprana de la temporada: durante la pandemia, los primeros resultados fueron comunicados a los EEMM de la UE, ECDC, CE, Agencia Europea del Medicamento (AEM) y OMS a comienzos de febrero de 2010. En febrero de 2011 se publicaron los primeros resultados de la vacuna estacional 2010/11 de tres centros de estudio de la red I-MOVE y del estudio multicéntrico de casos y controles. Los resultados de los estudios sobre la EV llevados a cabo a por la red I-MOVE han contribuido a orientar las políticas de salud pública en relación con la vacuna de la gripe tanto a nivel nacional como europeo. En concreto, durante la pandemia, se utilizaron los resultados de los estudios I-MOVE en los análisis riesgo-beneficio coordinados por la AEM en la UE y por la OMS a nivel global.

El hecho de que una red de investigación científica independiente realice los estudios de EV antigripal, aumenta la integridad de los resultados de I-MOVE e influye de forma positiva en cómo éstos son percibidos por los profesionales de la salud y por el público en general.

La red I-MOVE ha supuesto una plataforma única de intercambio de métodos para estimar la EV antigripal. Durante los seis talleres técnicos y las tres reuniones anuales celebrados organizados por la red I-MOVE (en los que se contó con la participación de colaboradores y expertos internacionales), las discusiones mantenidas en torno a los problemas epidemiológicos y logísticos han permitido mejorar las buenas prácticas científicas y reforzar la experiencia de la UE en el área a de EV antigripal. Asimismo, el establecimiento de la red ha contribuido a reforzar la vigilancia de la gripe en la UE. En la actualidad, la mayoría de los médicos de los sistemas centinela que participan en los estudios I-MOVE utilizan la misma

definición europea de caso de síndrome gripal y obtienen frotis de una muestra sistemática de aquellos pacientes que presentan síndrome gripal. Como los médicos que participan en la red I-MOVE también forman parte de los sistemas centinela nacionales, cualquier mejora y estandarización de los métodos que se logre en I-MOVE debería tener un efecto positivo en los sistemas de vigilancia de la gripe nacionales y europeos.

En la red participan 17 de los 30 EEMM de la UE/EEE. Sin embargo, ninguno de los países nórdicos realiza actualmente estudios de EV antigripal en el marco de la red I-MOVE. La integración de las estimaciones de EV antigripal de los países nórdicos en la red I-MOVE permitiría obtener una mayor representatividad de la efectividad de la vacuna de la gripe a nivel europeo.

Uno de los mayores retos para el futuro de I-MOVE es asegurar su financiación a largo plazo. El coste de los estudios I-MOVE es mucho menor que el coste de un ensayo clínico pero es más elevado que el coste de funcionamiento de las redes centinela. Una posibilidad es establecer un fondo europeo con financiación pública y privada, fijando mecanismos claros que aseguren la transparencia y la independencia de los investigadores y de los resultados.

D1. Diseños de estudio y aspectos metodológicos para medir la EV de forma rutinaria en la UE/EEE

Según la revisión de la literatura, los cálculos de la EV antigripal dependen de la especificidad de la variable resultado frente a la que se realicen las estimaciones, de la incidencia de gripe y de la concordancia entre las cepas vacunales y las cepas de gripe circulantes. Además, factores de confusión y modificadores del efecto afectan las estimaciones de EV antigripal. Los cálculos de la EV antigripal son más precisos cuando en los estudios se incluyen los resultados de gripe confirmada por laboratorio al menos en un subgrupo de los participantes en el estudio, cuando se documenta correctamente el estado vacunal y cuando se recoge información detallada que permita controlar la confusión o estratificarla en función del factor de confusión o modificador del efecto.

La red EISN es una red estable que cuenta con una larga experiencia en la detección y notificación de casos de gripe. Su componente de laboratorio permite obtener información para estimar la EV frente a gripe confirmada. Añadiendo algunas preguntas a los datos que son recopilados rutinariamente por los médicos que participan en las redes que integran EISN, se

puede obtener información sobre el estado vacunal y los posibles factores de confusión o modificadores del efecto. En consecuencia, la red EISN representa un marco sostenible sencillo y viable para llevar a cabo estudios que permitan obtener estimaciones tempranas de la EV de forma rutinaria. La elección del diseño de estudio para medir la EV en los EEMM de la UE dependerá de las fuentes de datos y de los recursos disponibles.

De acuerdo con los resultados de la revisión de la literatura, la encuesta europea y las reuniones de expertos, se desarrollaron unos protocolos genéricos que fueron adaptados por los EEMM para medir la EV antigripal en la UE. A partir de esos protocolos genéricos, los miembros de I-MOVE han llevado a cabo durante tres temporadas de gripe estudios de cohortes, de casos y controles y de screening.

Una de las principales limitaciones de la red I-MOVE es que sus estimaciones se basan en estudios observacionales y, por tanto, son propensas a verse afectadas por sesgos. Se intentó reducir esos sesgos utilizando un muestreo sistemático para seleccionar a los pacientes incluidos en los estudios y recogiendo la información que permitiera controlar los factores de confusión. La experiencia de las tres primeras temporadas demuestra que tanto los factores que actúan como factores de confusión como su magnitud varían en cada temporada. En consecuencia, incluso cuando en una temporada los posibles factores de confusión no afecten a la asociación entre la gripe y la vacunación, podrían actuar como tales factores de confusión en temporadas sucesivas. En definitiva, para controlar la confusión se debe continuar recogiendo el número mínimo de variables recomendadas.

Los datos de la red I-MOVE se recogen a través de una red de vigilancia y, por tanto, adolecen de una serie de limitaciones propias de los estudios basados en redes de vigilancia. Comparado con otros estudios observacionales en los que los investigadores son los responsables de recoger los datos y son remunerados por ello, en la red I-MOVE los médicos centinela participan en los estudios durante su ejercicio habitual: recopilan los datos de vigilancia de la gripe y, además, algunas otras variables que permiten documentar los posibles factores de confusión o factores modificadores del efecto. Para que sea aceptable, el formulario de recogida de datos debe ser sencillo. Aunque la calidad de los datos no es perfecta y respecto a algunas variables es incompleta, ha ido mejorando a lo largo de las tres temporadas. La ventaja de realizar los estudios dentro de redes de vigilancia ya existentes es que su sostenibilidad a largo plazo es mayor.

La red I-MOVE se basa en las redes centinela de atención primaria de ámbito nacional que participan en la red EISN y que notifican los síndromes gripales o las infecciones respiratorias agudas. Sin embargo, sería necesario verificar y cuantificar si una vacuna que es efectiva frente a un síndrome gripal o una infección respiratoria aguda también protege frente a las complicaciones de la gripe. En una situación de pandemia, si las autoridades sanitarias recomiendan no acudir al centro de salud cuando se presenta un síndrome gripal o una infección respiratoria aguda, los médicos de atención primaria podrían no ser una buena fuente para identificar los casos de gripe. Para evaluar mejor la efectividad de la vacuna de la gripe estacional y pandémica, se deberían incluir estimaciones de la EV antigripal frente a las formas graves de gripe. En la red I-MOVE, la EV antigripal frente a las formas clínicas graves se mide utilizando un diseño de cohorte en los centros de estudio que utilizan bases de datos informatizadas de atención primaria (Inglaterra, Escocia y Navarra). Dichas bases incluyen la identificación del paciente y su estado vacunal lo que permite conectarlas con las bases de datos hospitalarias pudiéndose estimar la efectividad frente a hospitalización. Las estimaciones de la EV antigripal frente a hospitalizaciones o muerte no confirmadas por laboratorio son propensas a verse afectadas por sesgos de indicación. Para reducir este efecto la EV debería ser calculada antes, durante y después de la temporada de la gripe. En los estudios de cohortes, las hospitalizaciones relacionadas con la gripe se definen de acuerdo con los Códigos Internacionales de Enfermedades (CIE) y la calidad del diagnóstico dependerá de la integridad, validez y precisión de los códigos CIE para identificar los casos de gripe en las personas hospitalizadas. Además, el tiempo de actualización de los códigos CIE en las bases de datos hospitalarias es largo y sólo puede disponerse de las estimaciones de la EV antigripal frente a hospitalizaciones cuando la temporada de gripe ya ha terminado. En la misma línea, no es frecuente disponer de la información sobre los fallecimientos en tiempo real. Con su estudio de cohortes, Navarra es actualmente el único centro de estudio de la red I-MOVE capaz de proporcionar estimaciones tempranas y reiteradas de la EV antigripal frente a hospitalizaciones por gripe confirmadas por laboratorio y frente a muertes. Por tanto, una de las limitaciones actuales de la red I-MOVE es que no proporciona estimaciones tempranas de la EV antigripal frente a las formas graves de gripe a nivel europeo. El principal obstáculo para obtener estimaciones de la EV antigripal basadas en hospitalizaciones confirmadas por laboratorio a nivel europeo es obtener un tamaño de muestra suficiente que permita obtener estimaciones precisas, ajustadas y estratificadas por los factores modificadores del efecto. La creación de una red hospitalaria europea con la participación de varios hospitales que utilicen

el mismo protocolo permitiría llevar a cabo un estudio multicéntrico con un tamaño de muestra suficiente para estimar con rapidez la EV antigripal frente a las formas clínicas graves de gripe. Como primer paso hacia la creación de dicha red hospitalaria, I-MOVE ha desarrollada un protocolo genérico de casos y controles para estimar la efectividad de la vacuna frente a hospitalizaciones por gripe confirmadas por laboratorio. En la temporada 2011/12, en base a este protocolo genérico, hospitales de varios EEMM de la UE (ej. Comunidad Autónoma Valenciana, Francia) realizan un estudio piloto multicéntrico con el fin de estimar la efectividad de la vacuna antigripal para prevenir hospitalizaciones por gripe confirmada por laboratorio.

Los estudios I-MOVE son elementos esenciales para evaluar el efecto protector de una vacuna estacional o pandémica en la población general. No obstante, sus resultados deberían ser interpretados en el contexto de otras evidencias, como el grado de concordancia virológica, la inmunogenicidad de la vacuna evaluada en estudios con animales y seres humanos, o la eficacia de la vacuna medida en ensayos clínicos aleatorizados. La evaluación y vigilancia de la EV antigripal seguirá siendo un reto metodológico y operativo importante y, en consecuencia, las decisiones que pretendan orientar las intervenciones deberán basarse en un conjunto de estudios que utilicen diferentes resultados, métodos e indicaciones.

D2. Estimaciones efectividad vacunal

En la temporada 2008/9, la concordancia entre la vacuna de la gripe estacional y las cepas circulantes predominantes fue buena. Las estimaciones de la EV antigripal específicas nacionales y la EV antigripal global sugirieron un efecto protector de la vacuna estacional 2008/9 en la población anciana, en una temporada con una buena concordancia entre la vacuna estacional y la cepa A(H3) que circulaba predominantemente en Europa. Debido a las limitaciones impuestas por el tamaño de la muestra, no se obtuvieron estimaciones según el tipo de virus de la gripe. Durante esta temporada piloto, se confirmó que los estudios de casos y controles negativos (controles con “test negativo”) basados en los médicos centinela era una forma viable de estimar a nivel europeo la EV antigripal estacional frente a síndromes gripales atendidos por médicos centinela y confirmados por laboratorio.

En la temporada 2009/10 se midió la efectividad de las vacunas pandémicas y estacionales de la temporada 2009/10. Los resultados indicaron que una dosis de las vacunas pandémicas utilizadas en los países participantes confirió una buena protección frente al

síndrome gripal por A(H1N1)2009 (65,5% al 100% según las distintas estratificaciones realizadas). La efectividad de la vacuna pandémica fue superior en personas menores de 65 años de edad y en personas que no tenían enfermedades crónicas. Además, las estimaciones puntuales indicaron una EV pandémica buena desde los ocho días después de la vacunación. Durante el período del estudio, la vacuna estacional de la temporada 2009/10 no pareció conferir protección frente a síndrome gripal confirmado como gripe A(H1N1)2009.

El principal problema encontrado durante la pandemia para estimar la EV antigripal fue la disponibilidad tardía de la vacuna pandémica. Durante las temporadas estacionales de gripe, las campañas de vacunación se realizan antes de que comience la temporada y, por tanto, el estado vacunal no es una variable que dependa del tiempo. Durante la pandemia, las campañas de vacunación pandémica comenzaron una vez iniciada la onda pandémica o después del pico de pandemia (Figura 8). El tiempo estaba por tanto asociado al estado vacunal y a la variable resultado (menor cobertura vacunal y mayor incidencia de gripe al inicio del estudio). La cobertura vacunal observada entre los controles aumentó con el tiempo. Cuando se dividió el período de estudio, la EV antigripal pandémica ajustada para las fases inicial y tardía fue superior a 68%. No fue posible efectuar otras estratificaciones, debido al pequeño número de casos.

Como consecuencia de la disponibilidad tardía de la vacuna, parte de la población había adquirido inmunidad natural frente a la gripe antes de comenzar los estudios. Si esta inmunidad natural fuera diferente entre los sujetos que después se vacunaron y los que no, este factor habría sesgado la EV antigripal en la pandemia. En concreto, si las personas vacunadas hubieran tenido un riesgo de infección más alto antes de la vacunación (ej., los niños) se podría haber sobreestimado la EV antigripal pandémica. También es posible que no se controlara totalmente este sesgo de indicación al ajustar en función de la edad y el momento del reclutamiento. Sólo un diseño de estudio de cohortes que incluya una estimación de la seroprevalencia al inicio del estudio podría ayudar a cuantificar este sesgo, que probablemente haya afectado a todos los estudios realizados durante la pandemia.

El estudio multicéntrico de casos y controles I-MOVE de la temporada 2010/11 basado en la participación de redes centinela de ocho EEMM de la UE aportó estimaciones de la EV global y estratificada. Los resultados indicaron una EV ajustada moderada frente a síndrome gripal confirmado como gripe (intervalo entre el 27,2% y el 77,2%). Las EV globales ajustadas

frente a A(H1N1) y gripe B no fueron sustancialmente diferentes de la estimación de la EV frente a todos los tipos de gripe.

De acuerdo con los datos publicados por la Red Comunitaria de Laboratorios de Referencia de la EISN para gripe humana en Europa, en la temporada 2010/11 se observó una buena concordancia entre la cepa de la vacuna y los virus A y B circulantes.

Si bien algunos estudios realizados en la temporada 2010/11 indicaban una mayor EV antigripal con el uso combinado de la vacuna estacional de la temporada 2010/11 y la vacuna pandémica 2009/10, no se obtuvo este resultado en el estudio multicéntrico de casos y controles I-MOVE. La EV antigripal ajustada frente a todos los tipos de gripe fue del 12% aproximadamente para la vacuna pandémica 2009/10, alrededor del 59% para la vacuna estacional de 2010/11 y del 44% cuando se administraron ambas vacunas.

La vacuna con una EV antigripal más alta fue la vacuna pandémica monovalente, mientras que las EV de la temporada 2008/9 y la temporada 2010/11 son similares a las observadas en temporadas interpandémicas. En estudios que utilizaron un diseño parecido con controles test negativo se obtuvieron estimaciones que variaron entre el 34% y el 92% en temporadas de buena concordancia vacunal. En un metanálisis publicado en 2011, la efectividad mediana de la vacuna pandémica frente a síndrome gripal confirmado como infección por A(H1N1)2009 fue de 69% (rango 60%-93%). La mayor EV de la vacuna pandémica podría explicarse por la excelente concordancia entre la cepa circulante del virus y la cepa de la vacuna, por la población vacunada relativamente más joven comparada con las temporadas estacionales o por la posible sobreestimación de la EV antigripal en la temporada 2009/10, como se comenta anteriormente. El amplio uso durante la pandemia de las vacunas adyuvadas por primera vez en Europa, podría haber contribuido también a esa elevada EV.

Los métodos, el tamaño de la muestra, la calidad de los datos y la rapidez de las estimaciones han ido mejorando a lo largo de las tres temporadas. En la primera temporada, no se pudo estimar la EV antigripal en función del tipo de virus de la gripe debido al pequeño tamaño de muestra. En la temporada 2009/10 la cepa pandémica fue altamente predominante (un virus B identificado en todos los frotis del estudio) y, por tanto, nuestras estimaciones de la EV antigripal fueron específicas para el virus A(H1N1)2009. En la temporada 2010/11, el tamaño de la muestra permitió estimar una EV en función del tipo/subtipo de virus de la gripe y del grupo de edad.

Limitaciones de las tres temporadas

Tamaño de la muestra

Durante las tres temporadas, una de las principales limitaciones de los estudios fue el pequeño tamaño de muestra que limitó la potencia estadística de alguno de los análisis estratificados. En la temporada 2008/9, en la que la población del estudio se limitó a los ancianos, la incidencia en este grupo de edad fue baja. Durante la temporada pandémica 2009/10, la cobertura vacunal fue baja, con un número bajo de casos vacunados. En 2010/11 la cobertura vacunal fue baja en los grupos de edad de 0-14 y 15-59 años (2,2% y 4,2%, respectivamente) y no fue posible obtener estimaciones globales precisas para estos grupos de edad. El tamaño de la muestra y el número de casos fue bajo en la población objetivo de la vacunación en los grupos de edad de 0-14 y 15-59 años y sólo hubo un caso vacunado de gripe B en el grupo de 15-59 años de edad. Cabría resaltar que, incluso cuando el tamaño de la muestra es bajo para algunos subanálisis, el número de pacientes reclutados y el número de médicos participantes aumentó a lo largo de las tres temporadas.

Identificación de la población diana de vacunación

En la temporada 2008/9 el estudio se limitó a la población anciana, por lo que todos los participantes formaban parte de la población diana de vacunación. Durante la pandemia la vacuna no se ofreció a todos los grupos diana al mismo tiempo (Anexo III). La mayoría de los centros de estudio no recogió la información necesaria para identificar a dichos grupos y no se pudieron restringir los análisis a grupos y periodos en los que los sujetos eran elegibles para la vacunación. En consecuencia, puede que se incluyeran sujetos para los cuales la vacunación no estaba indicada, o todavía no estaba indicada. De esta manera, se habría inflado el número de casos no vacunados en una fase inicial del estudio y sobreestimado la EV antigripal pandémica. En 2010/11 el análisis se pudo restringir a la población elegible para la vacunación. Las estimaciones globales de la EV antigripal en la población elegible fueron similares a las obtenidas en la población total. La variable “pertenecer a la población diana” no se recogió de forma homogénea en todos los centros del estudio y en algunos de ello no se dispuso de toda la información para identificar a todos los grupos elegibles para la vacunación (principalmente personas con profesiones para las que la vacunación estaba recomendada), lo que podría haber hecho que se excluyera parte de la población diana del análisis.

Tipo de vacunas

En los distintos países de la UE se usan diferentes vacunas antigripales (Tablas 10, 16). Aunque la mayoría de las vacunas estacionales no son adyuvadas, en algunos países se recomiendan vacunas adyuvadas para algunos grupos de riesgo. Durante la pandemia se usaron vacunas adyuvadas más frecuentemente que en otras temporadas. En las temporadas 2009/10 y 2010/11 se documentó el tipo comercial de vacuna, intentando realizar estimaciones en función de las características de la vacuna (adyuvada frente a no adyuvada). El tamaño limitado de la muestra para algunos tipos de vacunas y el hecho de que algunas de ellas se recomendaran para grupos diana específicos no identificables con los datos recogidos, impidió obtener estimaciones de la EV antigripal en función del tipo de vacuna.

En resumen, los resultados de las tres primeras temporadas indican que la vacuna de la gripe estacional no es de las vacunas más efectivas existentes. A pesar de ello y aunque no proporcionen una protección completa frente al síndrome gripal confirmado por laboratorio, las vacunas de la gripe se consideran la medida preventiva más efectiva disponible. Es necesario seguir trabajando para mejorar la efectividad de la vacuna, identificando métodos de producción alternativos, aumentando o ampliando la respuesta inmunitaria, mejorando la aceptabilidad de la vacunación y proporcionando o desarrollando vacunas específicas para cada población.

D3. Diseño test negativo

Durante las tres temporadas se llevó a cabo un estudio de casos y controles en el que los controles fueron pacientes con resultado de laboratorio negativo de gripe (diseño test-negativo). Este diseño test-negativo (DTN) se adapta bien a los estudios realizados en el marco de las redes centinela de vigilancia de gripe: los médicos centinela realizan rutinariamente frotis de los casos de síndrome gripal, y por tanto, seleccionar como controles aquellos con resultado negativo de gripe no representa ninguna tarea adicional. La tarea adicional para los médicos que participan en estudios DTN dependerá de la cantidad de información adicional que deban recoger de cada paciente incluido.

En el DTN los casos y los controles se seleccionan con independencia de su estado de caso o control. En los estudios de EV antigripal, los pacientes con síndrome gripal atendidos por el médico se incluyen en el estudio con independencia de su estado vacunal y se seleccionan antes de obtener la confirmación del laboratorio. Dado que ajustamos los casos en función del

tiempo (semana, mes) de inicio de síntomas del síndrome gripal, podemos asumir que los controles se seleccionan concomitantemente a los casos de gripe confirmados por el laboratorio, por lo que el DTN se aproxima a un diseño de de casos y control concurrente (o de densidad) en el que el efecto medido fuera una razón densidad de incidencias. EL DTN difiere del caso control concurrente en que en el DTN los pacientes que tuvieron gripe en esa temporada, antes del estudio, no son excluidos del grupo control (pacientes con síndrome gripal y test negativo). Sin embargo, estos sujetos ya no tienen riesgo de desarrollar la enfermedad y deberían, en teoría, ser excluidos del grupo control. En un estudio en Francia, se excluyeron del grupo control los sujetos con síndrome gripal previo. Sin embargo, con esta exclusión de casos anteriores de síndrome gripal se pueden excluir del grupo control a muchas personas cuyo síndrome gripal previo no es debido a una infección por virus de la gripe. Los resultados estarán sesgados si el estado vacunal de estos individuos difiere del de los controles test negativo incluidos.

Representatividad de los controles con test negativo

Como sucede en todo estudio de casos y controles, el grupo control (en nuestro caso, controles con test de gripe negativo) debería representar la exposición (cobertura de vacunación antigripal) de la población de la que surgen los casos. En nuestros estudios, la cuestión es definir cuál es la población de la que surgen los casos de síndrome gripal que acuden al médico y son confirmados como gripe. Durante la temporada piloto, para evaluar la representatividad de los controles con test negativo se comparó la cobertura vacunal entre distintos grupos control: controles con test negativo, pacientes que consultaban por motivos distintos de un síndrome gripal y controles comunitarios. La cobertura vacunal fue distinta según el grupo control y entre los países, sin un patrón específico definido. Este hecho indica que la población origen de los casos de gripe que acuden al médico de atención primaria puede ser específica de cada país. En general, la cobertura vacunal en la comunidad o en la zona de cobertura de cada médico fue menor que la cobertura vacunal de los pacientes de los médicos, lo que indica que los controles comunitarios no representan un buen grupo control para los casos de síndrome gripal atendidos por el médico y confirmados como gripe. Una selección aleatoria de los pacientes que acuden al médico por otros motivos distintos del síndrome gripal podría representar mejor a la población de la que surgen los casos. Sin embargo, la inclusión de este grupo control aumenta la carga de trabajo de los médicos que tienen que seleccionar y entrevistar a un grupo adicional de pacientes.

Factores de confusión en el DTN

Además de su viabilidad en el seno de las redes de vigilancia, otra ventaja del diseño con test negativo es que proporciona estimaciones de EV antigripal frente a un resultado específico y, por tanto, reduce la confusión existente. Para reducir aún más el efecto de los posibles factores de confusión, se ajustaron los análisis por la mayoría de los factores de confusión descritos como importantes en la literatura.

En la temporada 2008/9, las variables que modificaron el odds ratio en más del 5% cuando se introdujeron en el modelo de regresión logística fueron "vacunación antigripal en los últimos 2 años" (cambio del -13,5%) y "hospitalizaciones por enfermedades crónicas en los últimos 12 meses" (cambio del -9,2%). En la temporada 2009/10 esas variables fueron "grupo de edad" (cambio del -13,1%), "número de visitas al médico de atención primaria" (cambio del 5,3%), "mes de inicio de los síntomas" (cambio del 36,8%) y "vacunación antigripal estacional" 2009/10 (cambio del 5,7%). En la temporada 2010/11, las únicas covariables que modificaron el OR en más del 5% cuando se omitieron del modelo completo fueron grupo de edad (-10,7%) y semana de inicio (7,1%). En el grupo de elegibles para vacunación, el resultado fue parecido (grupo de edad, -11,5%, semana de inicio de síntomas, 8,0%).

Varios autores proponen que los controles de síndrome gripal con test negativo representan la población origen de los casos de gripe atendidos por los médicos centinela y que este diseño de estudio controla el factor de confusión de frecuentación de servicios de atención primaria. Esto significaría que la frecuentación de servicios de atención primaria es igual entre los pacientes con síndrome gripal con test positivo o con test negativo de gripe. A partir de la segunda temporada de I-MOVE se recogió información sobre el número de visitas al médico en el año anterior y, durante la pandemia, este fue uno de los principales factores de confusión. En consecuencia, el diseño con test negativo no controla totalmente dicho factor de confusión.

Igual que sucede en todos los estudios observacionales, no se puede descartar la presencia de factores de confusión residuales, aunque se haya intentado controlar al máximo los posibles factores de confusión.

Sesgo de selección en el DTN

En los estudios que utilizan un DTN el sesgo de selección se reduce ya que los médicos desconocen el estado de caso o control de los pacientes con síndrome gripal en el momento

del reclutamiento. Sin embargo, ello no impide el sesgo de selección que puede surgir si los médicos seleccionan a los pacientes a los que realizar un frotis en función del estado vacunal de los pacientes. Un estudio en Estados Unidos evaluó si este sesgo de selección estaba presente en los estudios de EV antigripal en niños, y llegó a la conclusión de que los médicos no realizaban frotis en función de sí el paciente estaba o no vacunado. En nuestros estudios multicéntricos de casos y controles el reclutamiento de los pacientes con síndrome gripal no se dejó al criterio de los médicos. En la temporada 2008/9 se obtuvieron frotis de todos las personas mayores de 59 o 64 años con síndrome gripal. En la temporada 2009/10 en cinco de los siete centros de estudio los médicos realizaron un muestreo sistemático para seleccionar a los pacientes con síndrome gripal a los que realizar un frotis. Los médicos irlandeses debían incluir cinco pacientes con síndrome gripal cada semana, sin aplicar un procedimiento de selección sistemático. No obstante, todos los médicos participantes de ese país reclutaron menos de cinco casos por semana, lo que indicaría que reclutaron a todos los pacientes que consultaron por un síndrome gripal. En Francia, cada médico reclutó a un grupo de edad específico para el estudio, de forma que los pacientes con síndrome gripal reclutados podrían no representar la distribución de edad de la población con síndrome gripal que consultaba a los médicos participantes y pudiendo así haber sesgado las estimaciones de la EV antigripal. No obstante, se comprobó que los casos de síndrome gripal reclutados por los médicos franceses tenían la misma distribución de edades que el conjunto de casos con síndrome gripal que les consultaron. En la temporada 2010/11 en siete de los ocho centros de estudio los médicos seleccionaron de manera sistemática a los pacientes de los que obtuvieron un frotis. En Francia, los médicos continuaron obteniendo frotis de un grupo de edad específico.

Error de clasificación en el DTN

En nuestros estudios, el tiempo transcurrido entre el inicio de síntomas y la obtención del frotis fue menor en los casos que en los controles. Este mismo dato se observó en un estudio en Wisconsin, Estados Unidos. Como la probabilidad de detectar la gripe disminuye con el tiempo transcurrido desde el inicio de síntomas hasta la toma de muestra respiratoria, se pudo haber clasificado erróneamente como controles a algunos casos de gripe con resultado negativo por laboratorio. Si los casos vacunados desarrollaron un cuadro más leve y consultaron más tarde, la cobertura vacunal en el grupo control se habría sobreestimado y por tanto también la EV antigripal. De igual modo, la EV antigripal se habría infraestimado si los casos no vacunados acudieron a su médico más tarde debido a su patrón

de utilización del sistema sanitario. Por otro lado, como los casos tienen menos probabilidades de haber sido vacunados, la cobertura vacunal de los controles disminuiría al clasificar erróneamente a los casos como controles, resultando en una EV antigripal más baja. La restricción del análisis a los casos de síndrome gripal estudiados en los cuatro días siguientes al inicio de los síntomas limita este posible error de clasificación. Además, en nuestros estudios, en más del 80% de los pacientes incluidos se obtuvieron los frotis en los tres días siguientes al inicio de los síntomas de síndrome gripal (80,7% en 2008/9, 94.0% en 2009/10, 91,7% en 2010/11).

D4. Estudio caso control multicéntrico

Durante las tres temporadas los centros de estudio utilizaron un protocolo y definiciones de casos muy parecidos, y un conjunto común de variables para realizar un estudio multicéntrico de casos y controles. En aquellos centros de estudio en los que no se utilizó la definición de caso de síndrome gripal de la UE, se recogieron los signos y síntomas que permitieron su reconstrucción.

Combinación de datos

Dada la excelente colaboración entre los centros participantes en el estudio y el centro coordinador, la combinación de los datos fue viable desde la fase piloto. Al combinar los datos de varios centros de estudio, el tamaño de muestra fue suficiente para obtener estimaciones precoces de la EV antigripal en febrero de 2010 y 2011. Comparada con las estimaciones por país, la agregación de datos permitió disponer de estimaciones más precisas de la EV antigripal y realizar algunos análisis de subgrupos.

Aunque los centros de estudio utilizaron el mismo protocolo, es posible que exista heterogeneidad entre los estudios. Dados los pequeños tamaños de la muestra en la mayoría de los estudios individuales, para el análisis agrupado se utilizó un modelo de efectos fijos en el que se acepta que el efecto de la exposición (la vacuna estacional o pandémica) y el efecto de las covariables son iguales en todos los estudios. Desconocemos si las diferencias en la circulación de virus gripales en los distintos países y en el patrón de utilización del sistema sanitario podrían modificar esta suposición. En 2008/9 y 2009/10 las pruebas de interacción entre el centro de estudio y las covariables no indicaban la presencia de heterogeneidad. No obstante, el pequeño tamaño de la muestra podría haber resultado en una potencia

insuficiente para detectar dicha heterogeneidad si existiese. La utilización de un modelo de efectos aleatorios para combinar los datos podría ser más apropiada para nuestro análisis, ya que tiene en cuenta la posible heterogeneidad entre los estudios. En la primera etapa de un modelo de efectos aleatorios se analizan los estudios de uno en uno para controlar mejor los factores de confusión específicos. En la segunda etapa, se combinan los odds ratios ajustados para cada estudio, utilizando un modelo lineal de efectos mixtos para obtener la estimación combinada. En 2010/11 se realizó a modo de análisis de sensibilidad un modelo de efectos aleatorios; debido a las limitaciones del tamaño de la muestra, sólo se pudieron incluir los factores de confusión más importantes. Las estimaciones de EV antigripal fueron muy parecidas a las obtenidas en el análisis combinado de una etapa, lo que indicaría que el modelo de una etapa era correcto. Si bien el análisis realizado con toda la población no demostró una heterogeneidad significativa, los resultados indicaron una heterogeneidad media entre los centros de estudio cuando el análisis se restringió al grupo de sujetos elegibles para vacunación. Al excluir uno de los centros (Italia), la heterogeneidad desapareció tanto globalmente como en todos los subgrupos y las estimaciones de la EV antigripal fueron más elevadas. Se investigó la existencia de posibles sesgos de información o de selección en Italia y no se pudo evidenciar ninguno. En consecuencia, se incluyó a Italia en las estimaciones de la EV antigripal, asumiendo que el modelo de efectos fijos era adecuado. De cara al futuro se intentará obtener un tamaño de la muestra más alto entre los grupos diana, para utilizar un modelo de efectos aleatorios ajustado por más covariables y así mejorar el proceso de validación de la idoneidad del modelo de efectos fijos.

Valores perdidos e imputaciones

En los estudios observacionales basados en datos de vigilancia, los valores perdidos son una de las mayores limitaciones. En nuestros estudios, los valores perdidos de algunas covariables estaban asociados al resultado y a la vacunación pandémica, y, por tanto, no pudimos asumir que nuestros valores perdidos pertenecían a la categoría de datos perdidos completamente al azar (Completely Missing At Random). Para reducir el posible sesgo asociado a los valores perdidos, desde la temporada 2009/10 se utilizó un método de imputaciones múltiples mediante un procedimiento de ecuaciones encadenadas en el que los valores se imputaron de acuerdo con las asociaciones observadas entre muchas otras variables (incluidos los factores de confusión) y el valor perdido. Pudimos utilizar un gran número de variables para la imputación, incluyendo algunas variables clave como la semana de inicio de

los síntomas, el resultado, el centro de estudio y la vacunación. Sin embargo, el objetivo de cara al futuro es disponer de datos más completos para todas esas variables. En 2010/11 la proporción de valores perdidos fue mucho menor.

E) CONCLUSIONES

1) Es posible obtener estimaciones de la EV antigripal de forma rutinaria y con datos tempranos en cada temporada de gripe en la UE.

2) I-MOVE contribuye a reforzar el intercambio de información entre los EEMM y a estandarizar los métodos de vigilancia.

3) I-MOVE es un ejemplo excelente de colaboración entre científicos, que permite mejorar los métodos de estimación de la efectividad de las vacunas antigripales utilizando redes de vigilancia de gripe.

4) El conocimiento científico y la experiencia en los aspectos prácticos, de gestión y logística obtenidos con esta red pueden servir de ejemplo para desarrollar métodos para medir la efectividad de otras vacunas como las vacunas contra el rotavirus, vacunas contra el neumococo, etc.

5) I-MOVE se basa en las redes de vigilancia de gripe centinela de Europa, que constituyen un marco excelente para realizar estudios observacionales de EV antigripal utilizando distintos diseños de estudio (cohortes, casos y controles o método screening).

6) Las redes de vigilancia centinela permiten medir la EV antigripal frente al síndrome gripal confirmado por laboratorio y, al añadir la recogida de algunas variables para controlar los factores de confusión positivos y negativos, se reducen algunas de las limitaciones de los estudios observacionales.

7) Los estudios I-MOVE utilizan métodos científicamente probados que proporcionan elementos esenciales para evaluar el efecto protector de la vacuna estacional y pandémica.

8) Los resultados de I-MOVE deben ser interpretados en el contexto de otras evidencias, como el grado de concordancia virológica y la inmunogenicidad de la vacuna evaluada en estudios con animales y seres humanos.

9) La elevada efectividad de la vacuna pandémica indica que, durante la pandemia, las vacunas pueden ser más eficaces, ya que la concordancia entre el virus pandémico y las vacunas pandémicas monovalentes es, probablemente, excelente. No obstante, el tiempo necesario desde la identificación del virus hasta tener disponible la vacuna pandémica para la población supone un reto.

10) La EV antigripal fue menor en las temporadas interpandémicas. Aunque las vacunas antigripales no proporcionen una protección completa frente al síndrome gripal confirmado por laboratorio, se consideran la medida preventiva más eficaz disponible para prevenir la gripe.

11) Comparado con otros estudios de casos y controles, el DTN es más simple, requiere menos recursos y por tanto es más adecuado para estimar la EV antigripal de manera continua y a lo largo de las diferentes temporadas de gripe.

12) Al igual que sucede con todos los estudios de casos y controles, el grupo control con test negativo debería representar la población que da origen a los casos. Se necesitan estudios para validar la representatividad de los controles con test negativo en cada uno de los centros de estudio de la red I-MOVE.

Recomendaciones

Recomendaciones para reforzar la red I-MOVE

Para reforzar la red I-MOVE, recomendamos:

- mejorar la representatividad de las estimaciones de la EV antigripal incluyendo en el futuro centros de estudio de países nórdicos de la UE y del EEE;
- estimar la EV antigripal frente a casos graves confirmados por laboratorio, desarrollando para ello una red de hospitales en Europa que lleve a cabo estudios multicéntricos;
- continuar acumulando experiencia en la evaluación de la efectividad de la vacuna antigripal, manteniendo el intercambio científico tanto entre expertos de la UE/EEE como entre expertos internacionales;
- integrar otras evidencias en los resultados de la red I-MOVE que permitan orientar mejor las decisiones de salud pública (datos virológicos, estudios de inmunogenicidad, efectos adversos, etc.);
- identificar un mecanismo de financiación a largo plazo para establecer un fondo europeo con aportaciones públicas y privadas, regido por reglas que aseguren la independencia científica de los investigadores y de los resultados.

Recomendaciones para reforzar la robustez de los resultados

Para seguir reforzando la robustez de los resultados de la red I-MOVE, recomendamos:

- continuar
  - realizando estudios con diferentes criterios de valoración, métodos y en diferentes centros de estudio,
  - incluyendo resultados de laboratorio con una selección sistemática de los pacientes de los que se obtiene un frotis,

  - recogiendo las variables necesarias para controlar los factores de confusión principales;

- aumentar el tamaño de la muestra en cada centro de estudio de casos y controles, para

  - disponer de estimaciones precisas de la EV antigripal en cada centro de estudio,

  - aumentar la precisión de las estimaciones de la EV antigripal en función del tipo y subtipo de gripe, grupo de edad y grupos de riesgo,

  - proporcionar la EV antigripal en función del tipo de vacuna,

  - utilizar un modelo de efectos aleatorios que integre mejor la variabilidad de cada centro de estudio en los resultados del estudio multicéntrico;

- mejorar la calidad de los datos

  - desarrollando un protocolo genérico para evaluar la calidad de los datos a nivel de cada centro de estudio,

  - reduciendo la proporción de datos perdidos mediante la formación de los médicos que participan en el estudio;

- recoger de forma estandarizada la información necesaria para identificar la población para la que está recomendada la vacunación antigripal, con el fin de medir la EV antigripal en esta población.

Recomendaciones para futuros proyectos de investigación

En cuanto a otros estudios e investigaciones necesarios, recomendamos:

- utilizar las bases de datos electrónicas de atención primaria, para evaluar la representatividad de los controles con test negativo comparando

  - la cobertura vacunal y la distribución de los factores de confusión de varios grupos control (por ejemplo, controles con test negativo, muestras aleatorias de pacientes de cada médico o muestras

aleatorias de pacientes que consultan por síntomas no relacionados con un síndrome gripal),

- las estimaciones de EV antigripal frente a gripe confirmada por laboratorio utilizando un diseño de cohorte y un diseño de casos y controles;

- controlar mejor las posibles diferencias en el patrón de utilización del sistema sanitario de los sujetos vacunados y no vacunados, describir las diferencias entre ambos grupos

  - utilizando las bases de datos electrónicas de atención primaria con información sobre la población vacunada y no vacunada, describir frecuentación de servicios de atención sanitaria en ambas poblaciones;

- cuantificar el sesgo potencial en la estimación de la EV antigripal frente a gripe confirmada por laboratorio introducido por una selección no sistemática de la muestra de pacientes con síndrome gripal de los que se obtiene un frotis

  - comparando en los centros de estudios que utilizan ambos procedimientos de selección, las EV antigripales obtenidas con una selección de la muestra de pacientes sistemática y no sistemática;

- a través de encuestas serológicas evaluar cómo influye en las estimaciones de EV antigripal la inmunidad adquirida mediante la infección natural o la administración de vacunas antigripales en temporadas anteriores;

- los grupos de investigación y los fabricantes de vacunas deberían identificar la forma de mejorar el efecto de la vacuna, por ejemplo mediante modificaciones de su composición, posología o procedimiento de administración, con objeto de aumentar el impacto de los programas de vacunación antigripal.

DEVELOPMENT AND IMPLEMENTATION OF A EUROPEAN NETWORK TO MEASURE THE EFFECTIVENESS OF THE INFLUENZA VACCINE

LIST OF ABBREVIATIONS

ARD	Acute Respiratory Disease
ARI	Acute Respiratory Infection
CVD	Cerebrovascular disease
EEA	European Economic Area
EC	European Commission
ECDC	European Centre for Disease Prevention and Control
EISN	European Influenza Surveillance Network
EISS	European Influenza Surveillance Scheme
EMA	European Medicines Agency
EU	European Union
GP	General Practitioners
HA	Haemaglutinin
ICD	International Classification of Diseases
ILI	Influenza-like illness
I-MOVE	Influenza Monitoring Vaccine Effectiveness in Europe
IRU	Incidence Rate in Unvaccinated
IRV	Incidence Rate in Vaccinated
ISO	International Organization for Standardization
IVE	Influenza Vaccine Effectiveness
MS	Member States
NA	Neuraminidase
OR	Odds Ratio
PIVE	Pandemic Influenza Vaccine Effectiveness
RCT	Randomised Controlled Trials
RT-PCR	Real Time Polymerase Chain Reaction
RR	Risk Ratio, Rate Ratio
SARI	Severe Acute Respiratory Infections
SD	Standard deviation
TND	Test Negative Design
UK	United Kingdom
USA	United States of America
VE	Vaccine Effectiveness
VENICE	Vaccine European New Integrated Collaboration Effort
WHO	World Health Organization

I) INTRODUCTION

1.1. Influenza

Influenza is an acute viral disease that presents generally with combination of symptoms like cough, runny nose, sore throat, fever, chills, cough, headache, muscle pain, and fatigue. In some cases, influenza can be more severe due to secondary bacteria infections producing pneumonia, bronchitis and even death. Those complications are more common in elderly or individuals with underlying chronic diseases. Influenza viruses are mainly transmitted by droplets and small-particle aerosols. Influenza causes annual epidemic and rare pandemics. In the Northern hemisphere, the epidemics occur generally between October and April.

Influenza virus

Influenza viruses are RNA virus belonging to the family *Orthomyxoviridae.* They are classified in three types (A, B and C) according to their core proteins. A and B types are responsible of the annual epidemics in the humans population. Influenza viruses A are further classified in subtypes based on the combination of two envelope glycoproteins having neuraminidase (NA) (N1-N9) or haemaglutinin (HA) (H1-H16) activity. Type B viruses are not divided in subtypes. Influenza viruses suffer continuous changes of the antigenic structure of the HA and NA proteins. Minor antigenic changes of circulating viruses occur frequently (antigenic drift). The antigenic drifts cause the annual epidemics, as the immune system does not recognise the virus. Reassortments of genetic material from different virus A subtypes can occur and produce major changes in the HA antigen (antigenic shift). Antigenic shifts are not rare but only occasionally lead to a viable, transmissible influenza A virus for which most of the population lacks immune protection. Those new viruses are pandemic strains. Type B viruses do not suffer antigenic shifts (1).

Two subtypes of influenza A (H1N1 and H3N2) have been circulating in human populations for three to four decades. Animal influenza subtypes can occasionally infect humans and cause high case fatality (e.g. avian H5N1 outbreaks).

Influenza burden

The morbidity and mortality due to influenza vary from season to season, among different age groups and among countries. Influenza causes non-specific symptoms and complications, cocirculates with other respiratory pathogens and therefore, it is difficult to quantify its burden. Influenza burden estimations vary depending on the outcome used: ILI consultations, hospitalisations, deaths. The World Health Organization (WHO) estimates the annual global seasonal influenza attack rate to be 5-10% in adults and 20-30% in children, resulting in between three to five million of cases of severe illness, and 250,000 and 500,000 deaths (1;2). In Europe, several studies have estimated the excess number of deaths due to influenza. In England and Wales 120,000 influenza associated-excess deaths would have occurred from 1968 to 1978 (3) and an average of 12,554 between 1989 and 1998 (4). The estimated influenza associated excess deaths were 910 in Norway from 1975 to 2004, 1,961 in Portugal in the 2008/9 season, 6,900 and 13,600 in Germany from 1990/91 to 2000/01 (5-7). Based on the 2008 European Union (EU) population (around 500 million), experts from the European Centre for Disease Prevention and Control (ECDC) suggest that seasonal influenza would result in 40,000 excess deaths in a moderate to severe season (8).

Influenza attack rates are higher among children than among adults. The highest bulk of the influenza related disease in children is experienced in the outpatient population resulting in high parental work absenteeism (9;10). The most common complication of influenza in children is acute otitis media (10-12). In a two year prospective cohort study in Finland, 39.7% of children < 3 years with a laboratory confirmed influenza developed acute otitis media (10). Children aged < 2 years are the increased risk of hospitalisation of children for influenza-attributable illnesses (10;11;13) but reported influenza mortality rates for children are low (< 1 per 100,000 person-years) (9).

In addition to the direct costs of medical care, influenza produces high indirect costs due mainly to work absenteeism and loss of work productivity. A study in US, France and Germany suggests that indirect costs of influenza can be 5-10 times higher than direct costs (14).

1.2. Influenza surveillance in Europe

In Europe, national influenza surveillance networks have been established since the 1950s based on sentinel practitioners networks. In 1992, the project Care Telematics was the first step towards the development of a European influenza surveillance network. Five European countries (Belgium, France, The Netherlands, Portugal and UK) established communication between national influenza surveillance networks (15). In 1995, the network decided to expand its activities and participating countries setting up the European Influenza Surveillance Scheme (EISS) (16). EISS participating countries shared clinical and virological influenza surveillance data. In 2008, the ECDC started to coordinate of the EU influenza surveillance network known since then as European Influenza Surveillance Network (EISN) (17). The EISN activities "*aim to contribute to reducing the burden of disease associated with influenza in Europe and include collection and exchange of timely information on influenza activity, contribution to the annual determination of the influenza vaccine content, provision of relevant information about influenza to health professionals and the general public and contribution to European influenza pandemic preparedness activities*"(17). EISN integrates 33 MS sentinel networks.

Sentinel practitioners include general practitioners (GPs), paediatricians or other physicians depending on the MS. They report cases of acute respiratory infections (ARI) or influenza like illness (ILI) to the national coordinating centre. The sentinel practitioners in each of the countries represent 1-5% of all the physicians (17). Sentinel physicians take nose and/or throat swabs from a sample of cases and send the specimens to the national or regional reference laboratories where they are tested for influenza virus and other respiratory viruses. National Reference Laboratories participating in EISN are evaluated periodically through external inter-laboratory quality control assessments. During the influenza season, EISN members report on a weekly basis clinical, epidemiological and virological information to EISN. One of the objectives of EISN is to evaluate the effectiveness of the influenza vaccine.

1.3. Influenza vaccination in Europe

Influenza vaccines

As described before, human influenza viruses are subject to permanent antigenic changes. The highest vaccine protection is observed when there is an identical antigenic match of the vaccine and epidemic virus HA and NA antigens. For this reason, vaccine strains are updated annually to optimise the antigenic match between vaccine and circulating virus strains. WHO issue recommendations for the strains to be included in the vaccine after two consultations held in February (for the Northern hemisphere) and September (for the Southern hemisphere). The recommendations are based on the information collected by the WHO Global Influenza Surveillance and Response System on circulating strains and related epidemiological data. The network includes 136 National Influenza Centres, six WHO Collaborating Centres for Reference and Research on Influenza, four Essential Regulatory Laboratories, and 11 WHO H5 Reference Laboratories (18). It takes several months to manufacture and distribute the vaccine. Consequently, if during this period the virus antigenic changes are important there will be poor match between vaccine and circulating strains.

Inactivated vaccines are available since the 1940s and most of them are administered via intramuscular injection. Live attenuated, cold-adapted influenza vaccines were developed in the 1960s and started to be used in the United States in 2003. The seasonal influenza vaccine is a trivalent vaccine that currently includes strains of the A subtypes H3N2 and H1N1 and one strain of B virus. In the EU/EEA there are predominantly three types of vaccines, all of them inactivated: split virus (virus disrupted by a detergent), subunit (HA and NA further purified by removal of other viral components) vaccine and whole virus vaccines (8). The European Medicines Agency (EMA) approved in 2011 an intranasal live attenuated vaccine recommended for children and adolescents from 24 months to 18 years. To increase the immunogenicity, some inactivated influenza vaccines include adjuvants or virosomes. The incorporation of adjuvants into vaccine formulations reduces the antigen amount needed for a successful immunisation and therefore allows increasing the vaccine supply. The estimated efficacy of seasonal vaccines to prevent laboratory-confirmed influenza ranges from 70-90% in healthy adults in seasons of good match between the vaccine and circulating strains (1;19-21). The only randomized control trial among community-dwelling persons aged $\geq$ 60 years reported a vaccine efficacy of 58% (95% CI: 26-77) (22).

In a pandemic situation, pandemic strain specific vaccines are produced and become available four to six months after begin of the vaccine development. For instance, during the last pandemic caused by the A(H1N1)2009 virus, the pandemic virus was identified in April 2009 but the first pandemic specific vaccines did not start to become available in Europe until end of September 2009. Based on the EMA scientific opinion, the European Commission (EC) granted marketing authorisation to five pandemic vaccines (four of them adjuvanted) for use in the EU MS (23). In some countries like France, Hungary and Romania, national regulation authorities provided a licence for additional vaccines.

Target groups for vaccination

In most EU/EEA countries, the immunisation strategy for preventing human seasonal influenza aims at avoiding severe influenza and its complications (1). This means focusing on the protection of vulnerable individuals and immunisation of risk groups rather than on achieving indirect protection through herd immunity (24). Some countries include vaccination of children to reduce the transmission in the community.

In May 2003, the World Health Assembly recommended vaccination for all people at high risk, defined as the elderly and persons with underlying diseases. Member States committed to attain a vaccination coverage of the elderly population of at least 50% by 2006 and 75% by 2010 (25).

In 2009, the European Council of Ministers recommended EU MS to achieve an influenza vaccination coverage of 75% in all at risk groups by the winter season of 2014/15. Risk groups were defined as individuals 65 years and older, and people with underlying medical conditions in the following categories: chronic respiratory and cardiovascular diseases; chronic metabolic disorders; chronic renal and hepatic diseases; immune system dysfunctions (congenital or acquired)(26).

A survey conducted in 2009 among 27 EU MS, Norway and Iceland indicated that all the 27 responding countries recommended seasonal vaccination to the older adult population and to individuals with underlying chronic disease. Twenty three countries recommended vaccination to health care workers (HCW) in hospitals and long-term facilities and 22 to HCW in out-patient clinics (27). Even though six countries recommended vaccination of children aged between six months and < 18 years (Latvia, Slovenia, Finland, Austria, Estonia, Slovakia)

Finland is currently the only country that has included influenza vaccine in the routine fully reimbursed childhood vaccination programme for children 6-35 months of age (28).

Angus et al. estimated that the proportion of the population in EU MS belonging to the two main risk groups (people aged 65 years and older and people with underlying chronic disease) ranged from 19% to 28% accounting in 2006, for 84 million persons aged 65 years or older and around 41 million younger persons living with chronic illness (24).

Vaccination coverage in EU/EEA

Monitoring of the vaccination coverage is a key component to evaluate a vaccination programmes. The ECDC funds the Vaccine European New Integrated Collaboration Effort (VENICE) project to monitor policies, practices and coverage in EU/EEA (http://venice.cineca.org). VENICE conducted two surveys (2008, 2009) to describe influenza vaccination policies and obtain vaccination coverage data in the EU/EEA MS (27;29).

VENICE surveys highlighted that the methods used for measuring influenza vaccine coverage in the EU vary between MS making comparisons difficult. The methods include population surveys (mail, face to face, telephone), vaccine sales data, vaccine registries, etc. In addition, the groups for which the vaccination coverage is measured differs across MS. Most MS monitor vaccination coverage among the elderly but only a few can measure vaccination coverage in other groups like individual with chronic diseases or health care workers.

The influenza vaccination coverage differs by age group, MS and along the seasons. The results of the VENICE/ECDC surveys indicated that in 2007/8 only two countries (UK and the Netherlands) had reached the WHO target of 75% coverage in the elderly. The vaccination coverage among the elderly varied from 1.1% in Estonia to 82.6% in the Netherlands (27).

Six countries could provide information on coverage for clinical risk groups and among health care workers. The range for the clinical risk groups varied from 32.9% in Hungary to 71.7% in the Netherlands and from 13.4% in the UK to 89.4% in Romania (27).

1.4. Influenza vaccine efficacy and effectiveness studies

Definition vaccine efficacy

Vaccine efficacy is defined as the reduction in the incidence of a disease among people who have received a vaccine compared to the incidence in unvaccinated people. The vaccine efficacy is generally estimated from Randomised Controlled Trials (RTC), in standardised and controlled vaccination conditions, usually using laboratory-confirmed cases. Since all the confounding factors are considered to be controlled by randomisation, the observed difference in incidences between vaccinated and unvaccinated is attributed to the vaccine. Properly conducted RCTs eliminate selection bias between vaccinated and unvaccinated groups. Trials to assess the vaccine efficacy can be provided in phase III or in phase IV (post-registration) of the vaccine development.

Three assumptions are made when measuring vaccine efficacy:

- the exposure to infection (e.g. the influenza virus) is equal among vaccinated and unvaccinated (random mixing);
- the vaccine is randomly allocated among subjects;
- vaccine efficacy estimates the optimal benefit, i.e., the direct effect at an individual level of immunisation in vaccinated subjects compared with non-vaccinated subjects (the comparison unit is the individual).

Definition vaccine effectiveness

Vaccine effectiveness studies measure the efficacy of a vaccine once in the field. VE studies measure the difference in incidence of disease in vaccinated versus unvaccinated individuals in the same population in which there is a vaccination programme. VE depends on several factors including the vaccine efficacy, the conditions under which the vaccine is used, the characteristics of the population, the vaccination coverage reached, the circulating agent (e.g. predominant influenza strain). The investigator neither controls the conditions of vaccination use (manufacturing, refrigeration, storage, administration techniques, compliance, etc.) nor the exposure to the vaccine.

Vaccine effectiveness is estimated from observational studies conducted in all or in a sample of a target population. The outcome of interest may or may not be based upon laboratory confirmation. In the case of influenza, using clinical case definitions assumes that effectiveness is measured against clinical respiratory illness caused by influenza viruses or from their consequences. As the vaccine is not allocated randomly, selection bias is a concern in such studies. Confounding factors are less likely to be controlled for. VE studies are performed in phase IV (post-registration) of the vaccine development.

VE measurement

Vaccine efficacy or effectiveness is defined as the percent reduction in incidence (risk or rate) among vaccinated individuals which is attributable to vaccination

$$\text{VE } \% = \frac{IRU - IRV}{IRU} \times 100 = (1 - RR) \times 100$$

where IRV is the incidence rate (or risk) in the subjects vaccinated and IRU is the incidence rate (or risk) in unvaccinated subjects (30). RR represents the rate ratio (or risk ratio). In situations where the RR cannot be measured directly, the RR can be estimated with the odds ratio (OR): VE =(1-OR) X 100.

1.5. Study justification

Influenza vaccination is part of the vaccination programmes conducted every year in EU MS. The vaccine is offered to a high number of individuals and, as any public health intervention, it is important to evaluate it in terms of its effectiveness. Because influenza viruses are constantly evolving, the influenza vaccine is the only vaccine reformulated each year. Therefore the influenza vaccine effectiveness (IVE) estimates from previous years cannot be used to estimate IVE in the subsequent years. Having annual IVE estimates at European level available as soon as possible after the start of a seasonal influenza epidemic or pandemic and monitoring it along the course of the epidemic or the pandemic is essential in order to:

- decide on recommendations for the use of the vaccine by specific age and risk groups;
- target complementary or alternative public health measures (e.g. antivirals) to

population segments in which the vaccine is less effective;

- estimate more precisely the impact of current vaccination strategies on the burden of disease with a view to supporting vaccination campaigns;
- provide some quantification to the current virological system of comparing antigenic matches of vaccine and circulating viruses;
- trigger further investigations on seasonal and pandemic vaccines (improving their composition, use of adjuvants, need for booster doses);
- validate IVE of new modes of administration (e.g. intra-nasal, intra-dermal);
- identify when the vaccine becomes effective (7, 14, 21 days after vaccination);
- compare IVE of various vaccine types (e.g. adjuvanted and non-adjuvanted);
- better manage and respond to reports of vaccine failures (especially during a pandemic);
- contribute to interpret influenza surveillance data;
- counterbalance the reports of adverse events following immunisation by providing a basis for adequate risk management and cost-effectiveness analysis.

The vaccine influenza is recommended and available for risk groups. Therefore clinical trials to estimate IVE in Europe would not be ethical and only observational studies could be considered. To develop a system to estimate IVE during an ongoing influenza season and allow monitoring it through consecutive seasons, it was necessary to define which observational study designs could be adopted in the MS of the EU and European Economic Area (EU/EEA). A system aimed at measuring IVE on a routine basis should be simple and sustainable while providing scientifically robust estimates. The methods needed to take into account the specific situation of each MS in terms of resources and available data.

II) AIM AND OBJECTIVES

2.1. Aim

To develop a European network to monitor seasonal and pandemic IVE in EU/EEA.

2.2 Objectives

1) To identify and describe the observational study designs adapted to measure IVE on a routine basis in EU / EEA.

2) To identify key methodological issues to be considered in the study protocols.

3) To estimate seasonal and pandemic influenza vaccine effectiveness against medically-attended Influenza-like illness (ILI) laboratory confirmed in the seasons 2008/9, 2009/10 and 2010/11.

III) METHODS

To develop a European network to monitor seasonal and pandemic IVE we set up in 2007 a consortium composed of 18 European Public Health Institutes and EpiConcept, the coordinating hub. The network was named I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe. We followed a three phases approach. In the first phase (January – September 2008), we collected all the information needed to develop generic protocols for observational studies to measure IVE in Europe. The second phase was the pilot season 2008/09 in which we tested the generic protocols. In 2009/10, pandemic season, we started to measure IVE in the EU and EEA.

3.1. European survey

We carried out a survey among EU/EEA Member States to identify, in each MS, observational IVE studies and available data sources that could be used for real-time IVE studies.

We contacted experts from 29 EU/EEA MS involved in influenza surveillance. The experts were the representatives of the institutions included in the I-MOVE consortium and, for MS not participating in the consortium, the epidemiologist focal point of the European Influenza Surveillance Scheme (EISS) or the gatekeeper of the VENICE project. The experts could choose either to provide information through a self-completed questionnaire (Annex I) or during a telephone or face-to-face interview. In addition, we reviewed available reports from EISS and VENICE, websites from European institutions involved in influenza surveillance and articles on IVE studies conducted in EU/EEA MS.

We collected data on IVE studies conducted in the MS, available data sources for case identification (identification of influenza cases, death registries, hospital registries, general practitioners' (GP) databases, other) and for documenting influenza vaccination status, as well as potential interest in conducting a pilot study during the season 2008/9.

3.2. Literature review

The objective of the literature review was to guide the development and piloting of observational study protocols for the rapid measurement of vaccine effectiveness in the context of seasonal and pandemic influenza in the EU/EEA. We did not conduct a systematic literature review but we aimed to identify relevant papers describing observational study designs used to estimate IVE, key factors affecting IVE estimates and methods to control them. We consulted available published reviews and meta-analysis on influenza vaccine effectiveness in various target populations. We first searched the Cochrane database and consulted Cochrane reviews on influenza vaccine effectiveness (31;32). Additionally, we reviewed the Health Technology Assessment report "Systematic review and economic decision modelling for the prevention and treatment of influenza A and B" (33). We also included a recent Sanofi Pasteur review (34). Based on these three documents, we built a first common list of articles. We completed this first list with the reference list of each selected article. The review included papers published until 2008.

From the abstracts, we selected studies reporting IVE estimates and methods used to compute them. We also included studies addressing methodological aspects of IVE estimates and certain studies addressing the methodology of VE measurements for other vaccines.

3.3. Expert meetings

From April to June 2008, we organised four workshops for experts participating in the consortium and additional invited influenza experts (Annex II).

The first workshop was held in April 2008. The aim was to present and discuss the results of the literature review and survey as described above and to consider the feasibility of the various observational methods to estimate real-time IVE at EU/EEA level. The participants included 25 experts from institutions participating in the consortium, four external influenza experts (London School of Hygiene and Tropical Medicine, Instituto de Salud Pública de Castellón, Sanofi Pasteur MSD, United States-Centers for Disease Control and Prevention Influenza division), four staff members from the ECDC Scientific Advice Unit and two EpiConcept epidemiologists.

The participants worked in three groups to discuss cohort studies, case-control studies, and screening method studies. For each study design, the groups made recommendations for the development of generic protocols for the pilot studies.

The second set of consultations was organised in June 2008 inviting the MS that were interested in conducting pilot studies in the season 2008/9. The objective was to further discuss methodological issues related to the two generic protocols for measuring IVE. Specific sessions were held for each study design.

The group agreed that, during the first season of the pilot phase, 2008/9, the following study designs were to be considered:

- Case-control studies based on influenza sentinel surveillance systems with laboratory-confirmed influenza-positive ILI as cases and influenza-negative ILI as controls. The data of the case-control studies could be pooled in a multicentre case-control study.

- Prospective cohort studies using computerised databases and providing IVE estimates for different periods (pre-/during/post-influenza season). At least a subset of the cases would be laboratory-confirmed.

- Countries conducting case-control and cohort studies and having available data on influenza vaccine coverage, could additionally provide estimates using the screening method.

In the season 2008/9 to apply and test the methods recommended, we conducted a pilot phase to estimate IVE using practitioners sentinel networks: two cohort, a multi-centre case control study with participation of five study sites and, two studies using the screening method.

In this thesis, we present the methods, results and discuss the methodological challenges of the multicentre case-control studies conducted in three consecutive seasons: 2008/9, 2009/10 and 2010/11.

3.4. Methods multicentre case-control study

Common methods multicentre case-control study 2008/9, 2009/10, 2010/11

To measure IVE against laboratory confirmed influenza in each of the seasons, we conducted multicentre-case-control studies. The studies were conducted within the context of EISN: sentinel primary care practitioners belonging to the National Sentinel Surveillance systems were invited to participate in the study. In Portugal and Italy, practitioners other than those participating in EISN, were also invited to participate.

The study population consisted of non-institutionalised patients consulting a participating practitioner for ILI or acute respiratory infection (ARI) (France) within eight days after symptom onset and with no contra-indication for influenza vaccination. The age groups and risk groups included in the study population varied from one season to another (see methods section of each season). Practitioners took nasal or throat swabs from all or a sample of ILI/ARI patients. The method to select the ILI patients to be swabbed varied between seasons (see methods section of each season).

Study sites progressively adopted the EU ILI case definition (35): four study sites in 2008/9, six study sites in 2009/10 and six study sites in 2010/11. In study sites not using the EU case definition, practitioners collected patients´ signs and symptoms that allowed identifying in the data analysis phase, those meeting EU case definition.

We defined a case of influenza as an ILI patient who was swabbed and tested positive for influenza using real-time polymerase chain reaction (RT-PCR) or culture. Controls were ILI patients swabbed and testing negative for influenza (test-negative controls).

We considered a person vaccinated if s/he had received a dose of the influenza vaccine of the corresponding season more than 14 days before date of onset of ILI symptoms.

The sentinel practitioners conducted face-to-face interviews with ILI patients using country-specific standardised questionnaires. They collected a set of pre-defined variables common to all study sites (Table 1). In some study sites, practitioners could complete the questionnaires electronically (Ireland, Italy). Practitioners sent completed questionnaires by mail or email to each of the national coordinators of the I-MOVE study.

The respective national or regional Influenza Reference Laboratory tested the nasal or throat swabs taken using RT-PCR techniques and/or culture. In each study site, all or a subset of influenza isolates were genetically characterised. Laboratory viral detection, typing, subtyping and variant analysis performed in each of the National Reference Laboratories are described elsewhere (17).

Each of the study teams at national level entered and validated data and sent anonymised databases of ILI cases recruited to the coordination team. The coordination team checked the data for inconsistencies, outliers and logical errors and created a common dataset. When important missing data or inconsistencies were identified, national coordinators contacted back the practitioners that verified the information on the medical records.

In each of the seasons, we compared the characteristics of cases and controls using Fisher's exact test or Mann-Whitney test as appropriate. We evaluated heterogeneity between studies qualitatively by assessing the standardisation of the case and covariate definitions.

We evaluated statistical heterogeneity using the Q-test and the I^2 index (36;37). The Q test results from summing the squared deviations of each study´s estimate from the overall pooled estimate, weighting each study´s contribution. P values are obtained by comparing Q statistic with a Chi square distribution with *k-1* degrees of freedom, being *k* the number of studies. The I^2 index describes the percentage of total variation across studies due to heterogeneity. An index of 0% indicates no heterogeneity, 25% low, 50% moderate and 75% high heterogeneity (38).

We estimated the pooled IVE as 1 minus the odds ratio (OR) (expressed as a percentage) using a one-stage method with the study site as fixed effect in the model. To estimate adjusted IVE, we used a logistic regression models including all potential confounding factors.

In 2009/10 and 2010/11, we first conducted the analysis excluding all individuals with missing values (complete case analysis). We then estimated missing data for vaccination status and covariates using the multiple multivariate imputation by chained equations procedure in Stata (39). We used missing at random assumptions. We used all predictors together to impute the missing values and independently analysed 20 copies of the data using 30 cycles of regression. Depending on the season, we stratified data by age group, chronic disease and influenza subtype.

METHODS

We conducted all statistical analysis using Stata version 10.1 (StataCorp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP).

I-MOVE national coordinators approached the appropriate ethical committees in their study site and according to country specific requirements; patients had to provide oral or written informed consent. In Hungary, Poland and Portugal, participants had to sign a written consent accepting the swab collection and the inclusion in the study. In France, Denmark, Italy, Ireland, Romania and Spain, the study was considered part of the existing influenza surveillance system and therefore, an oral consent was sufficient for inclusion of participants.

Pilot season 2008/9

Participating study sites

In the pilot season, five study sites participated in the multicentre case-control study: Denmark, Hungary, Portugal, Romania and Spain.

Study population

The study population was restricted to community dwelling elderly. Age groups included were 60 year olds and older in Hungary and 64 year olds in the other four study sites.

Definitions

For the first time, in Denmark, Hungary, and Romania sentinel practitioners used the EU ILI case definition. In Spain, the ILI EU case definition was used with an additional stated criterion "without any other suspected diagnosis". In Portugal, ILI was defined as in the routine sentinel surveillance, according to practitioners´ criteria. Practitioners collected clinical symptoms for all ILI cases. ILI patients were not eligible for the study if they were institutionalised, had evidence of dementia, did not speak the local language or refused participation.

Recruitment

Participating practitioners swabbed all community dwelling elderly individuals consulting for ILI.

Additional control groups

To check if vaccination coverage observed among ILI patients testing negative for influenza was different from that observed in other potential control groups, we measured vaccination coverage among systematic samples of patients from participating practitioners who had not had ILI since the beginning of the influenza season (non-ILI controls; up to two controls selected around the time of occurrence of a case) (Hungary, Portugal, Spain) and, in the community (Denmark, Portugal).

Analysis

We stratified results according to influenza strain and two age groups: 65-74 and >74 years.

Pandemic season 2009/10

Participating study sites

In 2009/10, seven study sites participated in the multicentre case-control study: France, Hungary, Ireland, Italy, Portugal, Romania, and Spain.

Study period

The study period started in each study site two weeks after the start of the pandemic vaccination campaign and finished the week that preceded two consecutive weeks in which none of the recruited patients tested positive for A(H1N1)2009.

Study population

In five out of the seven study sites, the study population consisted of all non-institutional patients consulting for ILI or ARI (France), having a nasal of throat swab taken within an interval of less than eight days of the onset of symptoms. In Hungary, the study population was restricted to patients aged more than 17 years. In Italy, the study population was restricted to patients belonging to the target group for pandemic vaccination.

Recruitment

In five of the seven study sites practitioners used a systematic random sample to select the patients to swab. In Ireland each participating practice was asked to take a nasal or throat swab from five patients presenting with ILI each week. In France, each practitioner had an age-group assigned and swabbed the first ARI patient of the week in the allocated age-group.

Definitions

During the pandemic season, we defined a case as an ILI patient swabbed who tested positive for A(H1N1)2009 influenza virus.

Analysis

We excluded individuals who tested positive for influenza A but had a non-typeable strain, those testing positive for other strains of influenza A or for influenza B, and those with missing information on laboratory results.

We measured the effectiveness of the seasonal vaccine 2009/10 and of the pandemic vaccine defining vaccinated all individuals who had received a dose of the vaccine more than 14 days

before the date of onset of ILI symptoms. For pandemic vaccination we also estimated the pandemic IVE among those vaccinated less than 8 days, those vaccinated between (and including) 8 and 14 days and those vaccinated more than 14 days before onset of symptoms compared to those never vaccinated.

We stratified the adjusted pandemic and seasonal IVE according to three age groups (< 15, 15-64, and 65+ years of age) and the adjusted pandemic IVE by presence of chronic disease.

Season 2010/11

Participating study sites

In 2010/11, eight study sites participated in the multicentre case-control study: France, Hungary, Ireland, Italy, Poland, Portugal, Romania and Spain.

Study population

The study population consisted of all non-institutionalised patients consulting a participating practitioner for ILI or acute respiratory illness (ARI) (France only) who had a nasal or throat swab taken less than eight days after symptom onset. In Hungary the study population was restricted to those older than 17 years.

Recruitment

Practitioners in France, Ireland, Poland Portugal, and Spain swabbed all ILI/ARI patients aged 65 and over, in Hungary they swabbed all ILI patients 60 and over and in Italy they systematically swabbed one ILI/ARI patient aged 65 and over per week. In all study sites practitioners systematically sampled ILI/ARI patients to swab among the other age groups, apart from Romania where practitioners swabbed all ILI patients in all age groups.

Data collected

For the first time in 2010/11, five study sites included the variable “belongs to the target group for vaccination” in their questionnaire. For the other three study sites, we defined it based on the variables (e.g. age group, chronic diseases, pregnancy, profession) included in the study site questionnaires that allowed target groups to be identified.

Analysis

In a first analysis, we included all study population and in a second one, we restricted it to the target groups for vaccination.

To assess the effects of the 2010/11 seasonal vaccine and the pandemic influenza vaccine 2009/10 we defined a four-level variable with the following categories:

- Not being vaccinated with any of the two vaccines;
- Being vaccinated only with the 2009/10 pandemic vaccine but not with the 2010/11 seasonal vaccine;
- Being vaccinated only with the seasonal 2010/11 vaccine;
- Being vaccinated with both vaccines

We stratified VE into three age groups (0-14, 15-59 and 60 years and above). Analyses were further restricted to the target group for vaccination. As a sensitivity analysis we carried out a two-stage pooled analysis (40) to compare against the 1-stage pooled results. Due to limitations in sample size we only included the potential most important confounders age groups (0-14, 15-59 and 60+ years), time (month of symptom onset), and chronic disease in the models as stable models could be fitted for each study site with these covariates. The Irish study site was excluded from this analysis, due to sparse data (no vaccinated cases).

METHODS

Table 1. Summary of methods used in the I-MOVE multicentre case-control study, seasons 2008/9, 2009/10, 2010/11

	Season 2008/9	Season 2009/10	Season 2010/11
Participating countries/study sites	De, Pt, Sp, Ro, Hu	Pt, Sp, Ro, Hu, It, Ire, Fr	Pt, Sp, Ro, Hu, It, Ire, Fr, Po
Study population	´≥ 65 yrs, 4 countries	All population, 4 study sites†	All population, 7 study sites
	Hu: >59 yrs	Hu: > 17 yrs	Hu: > 17 yrs
Influenza Like Illness case definition	EU, 4 study sites	EU, 6 study sites	EU, 7 study sites
	Pt: practitioners clinical criteria	It: WHO case definition	It: WHO case definition
Mode of selection of patients to swab	All	Systematic sampling, 6 study sites	All elderly, 7 study sites[¥]
			It: systematic sampling: 1 one individual > 64 yrs per week
		Ire: 5 ILI case/ GP / week	Other age groups: systematic sampling
Co-variables collected			
Age	YES	YES	YES
Sex	YES	YES	YES
Symptoms	YES	YES	YES
Date onset symptoms	YES	YES	YES
Date of swabbing	YES	YES	YES
Presence chronic diseases	YES	YES	YES
Hospitalisations for chronic disease iprevious 12 months	YES*	YES	YES
Smoking	YES	YES	YES
Functional status	YES	YES	YES
Influenza vaccination previous 3 seasons			Ro, Po
Influenza vaccination previous 2 seasons	YES	YES	Ire, Hu, It
Influenza vaccination previous season			Sp, Po, Fr
Date vaccination current season	YES	YES	YES
Seasonal vaccination current season	YES	YES	YES
Pandemic vaccination 2009/10		YES	YES

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	Season 2008/9	Season 2009/10	Season 2010/11
Vaccine brand		YES	YES
Number practitioner visits previous season		YES	YES
Pregnancy		YES	YES
Obesity		6 countries**	7 countries**
Antiviral use before swab collected		YES	7 countries†
Belonging to target population for vaccination			5 countries††

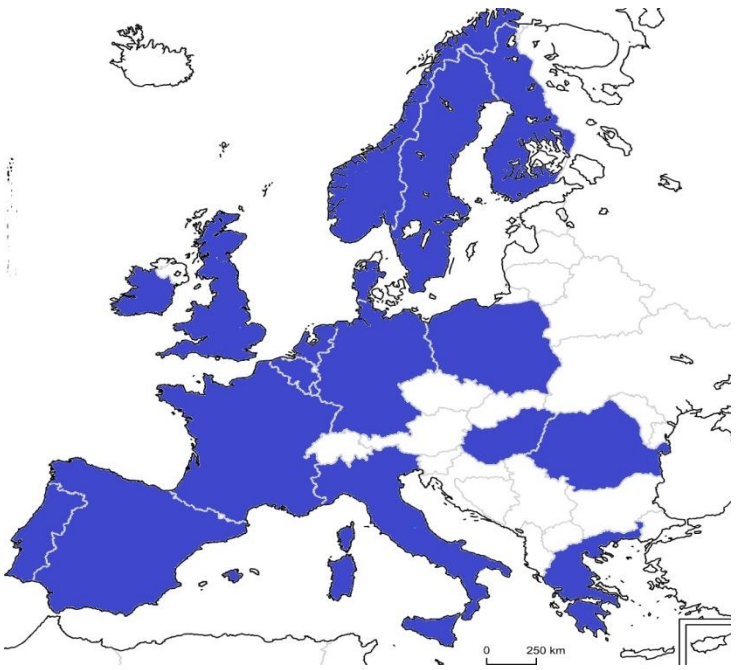
Denmark (De), France (Fr), Hungary (Hu), Italy (It), Ireland (Ire), Poland (Po), Portugal (Pt), Romania (Ro), Spain (Sp), EU (European Union);

* Hungary, Portugal: Any hospitalisation in previous 12 months;
** Varialbe " Obesity" not collected in France (2009/10, 2010/11) and Poland (2010/11);
† Variable "Antiviral use before swabbed" not collected in Spain in 2010/11
††Variable "Belonging to target population for vaccination!" not collected in France, Hungary, Italy

IV) RESULTS

In 2008, a European network was set up to monitor IVE in EU and EEA with the participation of 26 Institutions from 17 EU/EEA MS (Figure 1). From 2008/9 to 2010/11 fifteen study site teams conducted IVE studies with some of them using different study designs (Box 1). The I-MOVE network functioning is funded by ECDC and the IVE studies are co-funded by ECDC and by the study sites conducting them. EpiConcept in close collaboration with ECDC, coordinates I-MOVE activities. The network collaborates with non-EU teams conducting IVE studies in Canada, USA and Australia. Technical workshops are organised during the influenza season among I-MOVE study sites to discuss the preliminary results, to plan the final analysis and to define the publication strategy. Periodically, follow up videoconferences are organised among study sites. The whole network meets annually for three days at the end of the influenza season to share the IVE estimates, and to discuss practical and methodological issues related to the studies. An I-MOVE website is in place with three different levels of access: public, I-MOVE partners, I-MOVE study sites (41).

Figure 1. European Union and European Economic Area Member States participating in the I-MOVE network (2008-2011)



Box 1. List of study sites conducting influenza vaccine effectiveness studies as part of the I-MOVE network, influenza seasons 2008/9, 2009/10 and 2010/11

- **Multicentre case-control study including data from the case-control studies**
  - EpiConcept, (2008/9, 2009/10, 2010/11)
- **Case-control studies based on primary care sentinel networks**
  - Denmark, Statens Serum Institut (2008/9)
  - France, GROG network (2009/10, 2010/11)
  - Hungary, National Centre for Epidemiology (2008/9, 2009/10, 2010/11)
  - Ireland, Health Protection Surveillance Centre (2009/10, 2010/11)
  - Italy, Istituto Superiore di Sanità (2009/10, 2010/11)
  - Poland National Institute of Public Health – National Institute of Hygiene, (2010/11)
  - Portugal, Instituto Nacional de Saúde Dr Ricardo Jorge (2008/9, 2009/10, 2010/11)
  - Romania, National Institute of Research – Development for Microbiological and Immunology, Cantacuzino.
  - Spain, Instituto de Salud Carlos III (2008/9, 2009/10, 2010/11)
- **Cohort studies using primary care computerised databases**
  - England and Wales, Royal College of General Practitioners (2009/10, 2010/11)
  - Navarra, Instituto de Salud Pública de Navarra (2008/9, 2009/10, 2010/11)
  - Netherlands, Erasmus University (2009/10)
  - Scotland, Health Protection Scotland (2009/10, 2010/11)
  - UK study including Health Protection Scotland and the Royal College of General Practitioners (2008/9)
- **Case-control studies nested in the primary care computerised cohorts**
  - England and Wales, Royal College of General Practitioners (2008/9, 2009/10, 2010/11)
  - Navarra, Instituto de Salud Pública de Navarra (2008/9, 2009/10, 2010/11)
  - Netherlands, Erasmus University (2009/10)
  - Scotland, Health Protection Scotland (2008/9, 2009/10, 2010/11)
  - UK pooled case-control analysis, Health Protection Agency (2008/9, 2009/10, 2010/11)
- **Screening**
  - England and Wales, , Royal College of General Practitioners (2010/11)
  - Italy, Istituto Superiore di Sanità (2009/10, 2010/11)
  - Portugal, Instituto Nacional de Saúde Dr Ricardo Jorge (2008/9, 2009/10, 2010/11)
  - Scotland, Health Protection Scotland (2010/11)
  - Spain, Instituto de Salud Carlos III (2008/9, 2009/10, 2010/11)

4.1. Results European survey

We conducted the survey from January to March 2008. Among the 29 MS we contacted, 24 (83%) accepted to participate in the survey (Annex II). In four MS, we interviewed the experts face to face, in 12 by telephone and in eight MS the experts self-completed the questionnaire we sent them.

Of the 24 MS participating, ten had conducted IVE studies in the past. We identified 43 published articles reporting results of case-control studies (12 articles), of cohort studies (28 articles) and of studies using a screening method (three articles). In Table 2, we summarise additional details on the studies including data sources and study outcomes.

In most of these studies, the study population and data sources were identified through health delivery services. In the Czech Republic, Italy and Portugal, other data sources were used for IVE studies.

Computerised databases

Malta, Norway and Sweden had population registries including an individual unique identifier, which allowed linking existing databases (e.g. death registers, in-patient registers, vaccination registers if available). The linkage of the various databases was not immediate and an ethical or a personal protection approval was needed.

In Finland, France, Ireland, the Netherlands, Norway, and the United Kingdom (UK), various GP networks had computerised databases. Computerised GP databases were also available in some Autonomous Communities regions in Spain and in some counties in Sweden.

Computerised GP databases included essential elements needed to conduct IVE studies: information on various outcomes (ILI, ARI, death, hospitalisation, etc), vaccine status, and some confounding factors (e.g. co-morbidities).

IVE cohort studies based on computerised databases had been conducted before 2008 in the Netherlands, Spain, Sweden and the UK.

Sentinel surveillance

In all 24 responding MS, the main source to identify clinical cases of influenza on a real-time basis was the virological or epidemiological sentinel influenza surveillance system. Case definitions varied from MS to MS but most sentinel networks reported cases of ILI symptoms or ARI (42).

A subset of patients consulting the sentinel practitioners has laboratory tests for influenza. In most MS, practitioners used clinical criteria to select patients for whom he/she took specimens for laboratory testing. Thus, patients with laboratory tests were not a representative sample of all patients consulting a practitioner because of influenza symptoms. In Denmark and France, practitioners selected patients to sample in a systematic way. Following EISS recommendations, laboratory request forms included the patients´ vaccination status.

Sentinel surveillance systems were used to conduct case-control studies of IVE in Denmark, France, Germany, the Netherlands, and the UK (Table 2).

Hospitalisation discharge databases

In most MS, cases with severe clinical influenza outcome (hospitalisations, deaths) were not identified in real time. Hospitalisation discharge databases were available with delays varying from three months to two years. In France, hospitals reported on a daily basis to the Institut de Veille Sanitaire individual data from in-patients and out-patients consulting emergency rooms.

Various MS were developing real-time mortality monitoring (43). Mortality had not been used in Europe to estimate real-time IVE.

Influenza vaccination status

Sources to document influenza vaccination status included medical records, computerised medical records, immunisation registries, surveys, and pharmaceutical data (44). Vaccination registries allowing the extraction of real-time vaccination status were available at regional level in Finland, in some counties in Sweden and in some Autonomous regions in Spain. The quality of the data source used to document vaccination status will influence the IVE estimates. For instance, when case detection is based on GP practices, misclassification of vaccination status may occur if vaccinated individuals who did not receive the vaccine through their GP are considered as unvaccinated.

Table 2. Influenza vaccine effectiveness studies conducted in EU/EEA MS, by study design and country, I-MOVE literature review, 1971-2007

Country	Reference	Data source	Outcome
Cohort Studies			
Czech Republic	Chlíbek 2002 (45)	Mail questionnaire to volunteers	Influenza-like Illness
	Berran 2003 (46)	Medical records employees Skoda Auto factory	Influenza-like illness
Italy	Comeri 1995 (47)	Questionnaire to a sample of the	Clinical influenza
	Consonni 2004 (48)	Phone interviews, ambulatory	Influenza-like illness, ARI
	Pregliasco 2002 (49)	Interviews, medical records	ARI, hospitalisations
	Rizutto 2006 (50)	Interviews volunteers participants from Ministry of Health	Influenza-like illness
	Landi 2003, Landi 2006 (51;52)	Minimum Data Set for Home Care, Italian Silver Network Home Care, Project	Death (2003), hospitalisation (2006)
The Netherlands	Smits 2002 (53)	Computerised primary care	Low respiratory tract infection, otitis
	Tacken 2004 (54)	GP database (LINH)	Primary care contact rate during influenza epidemics
	Voordow 2003, 2006 (55;56)	GP database (Integrated Managed Care Information)	Influenza, pneumonia, deaths, LRTI, hospitalisation for pneumonia
Portugal	2006/7, 2007/8 (unpublished data)	Pharmacies, voluntary recruiters	Laboratory confirmed
Spain	Castilla, 2006 (57)	Sentinel GPs	Clinical influenza
	Gené Badía 1991 (58)	Records from 5 health centres,	Deaths, all hospitalisations,
	López Hernández 1994 (59)	Records from one health centre, hospital records, death register	Hospitalisations, deaths
	Salleras, 2006 (60)	Questionnaires in clinics	Acute febrile illness, Influenza-like illness, laboratory confirmed
	Vila-Córcoles 2007 (61)	GP electronic files, demographic	Deaths
Sweden	Christenson 2001, 2004, Orktvist 2007 (62-64)	Population register, vaccination database, discharge diagnosis database	Influenza hospitalisation, hospitalisation from pneumonia
UK	Fleming 1995 (65)	GP database	Death, death or severe respiratory illness, death or any respiratory illness without further specification
	Armstrong 2004 (66)	GPs, Office for National Statistics	Deaths attributable to influenza
	Mangtani 2004 (67)	General Practice Research Database	Hospitalisations respiratory disease, deaths respiratory disease
Cohort studies during outbreak investigations			
France	Aymard 1979 (68)	Geriatric hospital	Disease, death
Italy	Caminiti 1994 (69)	Medical charts, hospital records, death certificates	Influenza-like illness, hospitalisation for Influenza-like illness, hospitalisation for all respiratory illness, deaths from respiratory illness
UK	Arroyo 1984 (70)	One nursing home	Influenza-like illness, pneumonia,
	Mukerjee 1994 (71)	14 nursing homes	Upper respiratory tract infection
	Nicholls 2004 (72)	Self Complete questionnaire	Influenza-like illness

Country	Reference	Data source	Outcome
Case-control studies			
Denmark	Mazick 2006 (73)	GP surveillance network	Influenza-like illness, laboratory confirmed
France	Carrat 1998 (74)	GP practices	ARI, Influenza-like illness laboratory confirmed
	Lavallée 2002 (75)	Medical records of hospitalised cases, interviews	Hosp for ARI and hosp for brain infarction
Germany	Grau 2005 (76)	Hospital records, patients´ interviews	Hospitalisation from ischemic or hemorrhagic stroke / transient ischemic attack
	Uphoff 2006 (77)	Sentinel GPs Cases: Influenza-like illness flu positive Controls: Influenza-like illness flu negative	Influenza-like illness, laboratory confirmed
Italy	Crocetti 2001 (78)	Discharge diagnoses, mailed questionnaire, tel interviews	Hospitalisation from pneumonia or influenza
The Netherlands	Hak 2002 (79)	Administrative and medical databases from a health plan	GP visits for acute respiratory disease or cardiovascular disease
	RIVM 2006-2007 (not published)	Sentinel GPs. Cases: Influenza-like illness flu positive. Controls: Influenza-like illness flu negative	Influenza-like illness laboratory confirmed
Spain	Puig-Barberá 1997, 2004, 2007 (80-82)	Hospital emergency logs and records	Hospitalisation acute coronary syndrome, Hospitalisation cerebrovascular accident, hospitalisation pneumonia
UK	Ahmed 1995 (83)	Death certificates, GPs´records	Certified influenza death
	Jordan 2007 (84)	GP practice registries and hospital discharge registries	Hospitalisation for acute respiratory infection
UK (Scotland)	Health Protection Scotland, 2005-2006 and 2006-2007 (not published)	Sentinel GPs: Cases: Influenza-like illnesss. Controls: Influenza-like illness flu negative	Influenza-like illness ,laboratory confirmed
Screening			
France	Carrat 1998 (74)	Cases: reported by sentinel GPs. Vaccination coverage: national health survey	Influenza-like illness
	Legrand 2006 (85)	Cases: reported by sentinel GPs. Vaccination coverage: national health survey	Influenza-like illness
Germany	Uphoff 2006 (77)	Cases: reported by sentinel GPs. Vaccination coverage: national health survey	Influenza-like illness , laboratory confirmed
Spain	Instituto de Salud Carlos III (not published)	Cases: reported by sentinel GPs. Vaccination coverage: national health survey	Influenza-like illness

GP: General Practitioner
UK: United Kingdom
ARI: Acute Respiratory Infection
LRTI: Low Respiratory Tract Infection

4.2. Results literature review

Overall, we reviewed 284 scientific articles and of them selected 93 descriptive observational studies (34 cohort studies, 26 outbreak investigations, 31 case-control studies and two studies using the screening method). In addition, we consulted 23 articles focusing on methodological issues. The main factors affecting IVE described in the literature were the influenza virus circulation, the specificity of the outcome against which IVE is measured, the vaccination status ascertainment and the presence of confounding factors.

Virus circulation

One of the main factors affecting the effectiveness of the influenza vaccine is the relatedness of vaccine and circulating strains. When there is a good match between the vaccine and the circulating virus strains, the vaccine effectiveness is likely to be good. However, good effectiveness have been described in seasons of poor match and low in seasons with good match (86-89). Factors that can explain these results are possible cross-protection between strains even if not well matched, a different effect of the vaccine in certain populations, presence of confounding or variation in virus circulation by geographical areas and over the season. For instance, during a season in a certain region there could be co-circulation of two type A viruses, or a B virus may emerge and become dominant. Consequently the trivalent vaccine may not be well matched against all circulating viruses It is difficult to precisely define the overall degree of match given the heterogeneity of viral strains that co-circulate in a given year (86;90). Overall IVE against laboratory confirmed influenza does not provide information on the VE against each of the co-circulating strains and, sample size permitting, strain specific IVE should be calculated.

The incidence of influenza may have major variations from year to year and affects IVE estimates, especially when using non-specific outcomes. In seasons with mild activity, the estimated IVE is lower. If during the influenza season, there is a high circulation of viruses causing respiratory symptoms (e.g. respiratory syncytial virus), studies based on clinical outcomes will underestimate IVE. If the influenza incidence is low, studies with small sample sizes may not have enough power to have precise IVE estimates (73). In addition in seasons with very high incidence, if odds ratios are used to estimate IVE based on ILI outcomes, IVE would be overestimated.

Outcome

The specificity of the outcome is an important factor affecting the VE estimates (30;91). In the absence of a standard case definition for influenza, various clinical outcomes including different combination of signs and symptoms are used to measure IVE, each of them having different sensitivity, specificity and positive/negative predictive values (92-94).

The main clinical outcomes reported in the literature were hospitalisations for all or specific causes (e.g. pneumonia and influenza), deaths from all or specific causes (e.g. pneumonia and influenza), ILI, ARI and laboratory-confirmed cases of influenza.

IVE studies using non-specific clinical outcomes include as cases individuals with clinical symptoms and diseases unrelated to influenza. The influenza vaccine does not protect against the agents causing these other diseases and therefore, IVE is underestimated (92;93).

Laboratory confirmation offers the most specific outcome and should be favoured (95). It is usually based on RT-PCR and/or culture analysis performed on naso-pharyngeal swabs from patients consulting for ILI or ARI. The swabbing method and diagnostic tool may influence the specificity of the outcome. The likelihood to detect influenza in naso-pharyngeal swabs decreases with days after onset of illness. Due to the costs involved in laboratory testing, some authors have suggested to perform laboratory tests only in a small proportion of the study participants (validation set) (96).

Vaccination status ascertainment

Influenza vaccination status is key information in IVE studies. If study subjects are incorrectly classified as vaccinated or unvaccinated independently of their outcome, the magnitude of the measure of association (odds ratio, rate ratio, risk ratio) between influenza vaccination and study outcome will be reduced. When misclassification of the vaccination status is related to the outcome, the estimates will be biased resulting in an over- or underestimation of the IVE. Therefore, all efforts should be made to document type and date of vaccination correctly. If various vaccine doses are recommended, the number of doses should be collected to measure IVE for fully vaccinated or partially vaccinated individuals (e.g. children, some pandemic vaccines).

Various modes of vaccine status ascertainment were reported in the literature. They included insurance claims, medical records, vaccine registries, and interviews of cases or family carers. Cohort studies using computerised databases extracted vaccination status from the database (57;97). For case-control studies using ILI at GP office the ascertainment of the vaccination status of cases and

controls was done though medical records and patients interviews (43;89). In some studies, patients or family carers were interviewed as a source of vaccination information (82). Studies using the screening method estimated vaccine coverage through national surveys (85). The mode of vaccination ascertainment was not mentioned.

Confounding factors

In observational studies, vaccination is not allocated randomly. Some individual characteristics may be associated with vaccination while also representing risk factors for the occurrence of influenza related outcomes. Therefore they can act as confounding factors in IVE studies. In this context, negative and positive confounding factors have been identified.

Comparing the crude IVE estimates and the IVE estimates adjusted for confounding factors reported in the literature provided an overview of the magnitude of confounding in IVE studies. The difference observed in percentage between crude and adjusted IVE in case-control studies and cohort studies ranged from -220% to 21% (Figures 2 and 3).

The list of potential confounding factors reported in the literature was very long (Box 2).

The main confounding factors discussed in the literature were factors resulting either in an underestimation of the IVE (negative confounding) or in an overestimation of the IVE (positive confounding factors).

Negative confounding reflects that individuals at higher risk for influenza are more likely to be vaccinated than individuals at lower risk. Various studies suggest that, before vaccination, the group of individuals who will be vaccinated have a higher prevalence of risk factors for influenza related outcomes than non-vaccinated individuals (67;98). This corresponds to confounding by indication (99). The presence of confounding by indication underestimates the IVE.

Positive confounding is the consequence of healthy vaccinee effect or extreme frailty bias. Healthier individuals may be more health conscious and more motivated to accept vaccination. The better baseline health status of the vaccinated group may result in an overestimation of the IVE. Variables that have been used as indicators of health status include smoking history, physical exercise, socioeconomic status, education level and health seeking behaviour

Positive confounding can also be explained by critically ill patients not being offered (or refusing) to be vaccinated. Frail individuals with end stage conditions are less likely to be vaccinated. Some cohort studies may include a subpopulation of undervaccinated frail elderly people that results in an overestimation of the IVE. This bias may explain the high IVE observed in studies using all cause mortality as outcome (100;101).

Similarly, individuals with functional status limitations have an increased risk of death, are less likely to be vaccinated and, if vaccinated, less likely to respond to vaccination (100).

Different methods have been used to minimise the effect of the underlying differences between vaccinated and unvaccinated groups. Some authors have restricted the study population to homogeneous groups with respect to the potential confounding factor (65;98;102) or stratified VE according to risk groups (56;89;103).

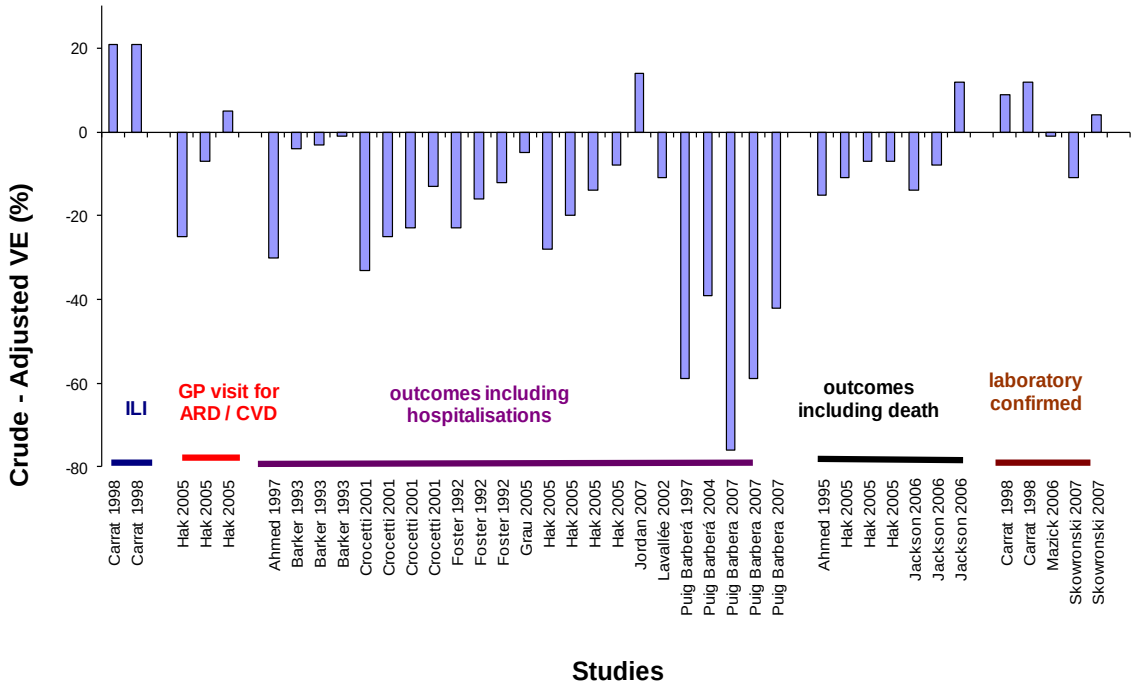
Most studies include the potential confounders as covariates in a multivariable model. Covariates can be extracted from medical records or collected through interviews. For models (e.g. logistic regression) and study designs (e.g. traditional case-control studies) that use odds ratios as a measure of association between outcome and vaccination, the outcome incidence should be low to properly estimate IVE.

Propensity scores estimate the probability of vaccination for each individual given his/her risk factor profile. Individuals are grouped on levels of propensity score or the propensity score may be included as a covariate in the regression model (61;99;104).

Sensitivity analysis attempts to quantify the error associated with unmeasured confounding factors. It consists in assessing how the IVE estimate varies with changes in the values of potential confounding factors (98).

Some authors claim that those methods are not enough to correct for the healthy vaccinee effect and frailty biases. They show positive IVE estimates during the pre-influenza season suggesting that positive residual confounding persists. They propose to eliminate positive confounding by developing multivariable variable models that result in a pre-influenza season IVE of zero percent. The same models can then be applied during the influenza season in an attempt to eliminate residual confounding (105).

Figure 2 Differences between crude and adjusted influenza vaccine effectiveness estimated in case-control studies, by study outcome, I-MOVE literature review, March 2008



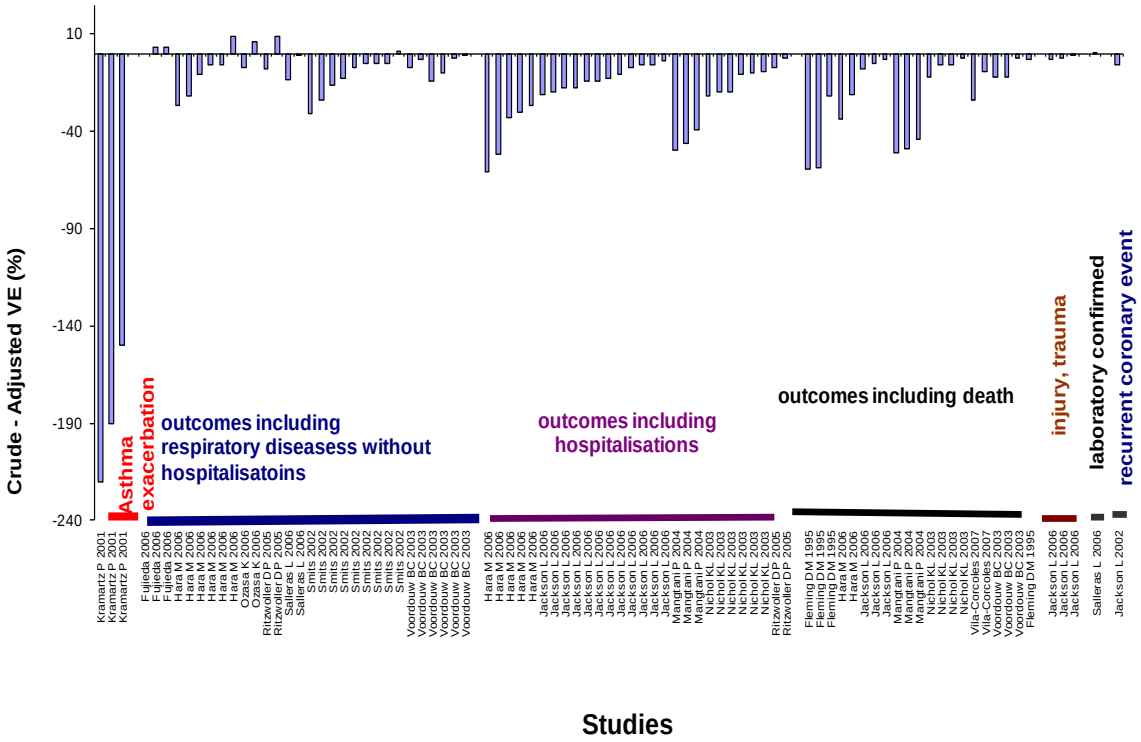
ARD: acute respiratory disease including acute bronchitis or exacerbations of chronic lung disease, influenza, pneumonia, and acute otitis media;

CVD: cerebrovascular disease including myocardial infarction, stroke, and heart failure;

GP, general practitioner;

ILI: Influenza-like illness

Figure 3. Difference between crude and adjusted influenza vaccine effectiveness in cohort studies, by study outcome, I-MOVE literature review, March 2008



Box 2. List o potential confounding factors in influenza vaccine effectiveness studies reported in the literature. I-MOVE literature review, March 2008

- Age
- Allergy to egg protein
- Asthma
- Diabetes mellitus and other endocrine diseases
- Disease severity
- Education level
- Functional status
- Former Influenza vaccination
- Former Pneumococcal vaccination
- Gender
- Health medical organisation
- Health-related behaviours
- Heart diseases
- House heating
- Immunosuppression including hematopoietic malignant diseases and steroid and immunosuppressive treatment
- Index case in the family or household
- Length of hospital stay
- Level of social interaction
- Lifestyle factors
- Living together with grandchildren
- Malignant disorders
- Marital status
- Medication prescribed and number of repeat prescriptions
- Musculoskeletal and connective tissue diseases
- Neurological diseases (including dementia, Parkinson´s disease and cerebrovascular diseases)
- Number of co-habitants
- Number of hospital admissions and out-patient visits
- Other pulmonary diseases
- Physical activity
- Place of residence: nursing and residential care homes; non institutional
- Pre-school attendance
- Preventive care practices
- Propensity score
- Renal diseases
- Smoking
- Socio-economic status
- Type of medical coverage
- Underlying chronic conditions
- Vaccination of caregiver
- Washing hands and gargling

4.3. Results expert meetings

Following the April 2008 workshop, the experts recommended to determine IVE in various population subgroups, to control for positive and negative confounding and to use laboratory-confirmed influenza as outcome. The group recommended measuring IVE in a homogenous population for a period of several years, using the same design each year.

In June 2008, the group agreed that, during the first season of the pilot phase, 2008/9, the following study designs were to be considered:

- Case-control studies based on influenza sentinel surveillance systems with laboratory-confirmed influenza-positive ILI as cases and influenza-negative ILI as controls.
- Prospective cohort studies using computerised databases and providing IVE estimates for different periods (pre-/during/post-influenza season). At least a subset of the cases would be laboratory-confirmed.

In addition, for countries willing to conduct a case-control or a cohort study and having within season influenza vaccination coverage estimates, they recommended to provide estimates using the screening method.

Based on these recommendations, we developed two generic protocols to estimate IVE: one for case-control studies and one on cohort studies using computerised databases (106;107). Those protocols were to be adapted to the situation of each MS.

4.4. Summary of recommended study designs to monitor IVE in EU/EAA MS

The survey, literature review, expert meetings and the 2008/9 pilot phase (see Results season 2008/9, pilot season) suggested that the sentinel practitioner networks existing In the EU / EEA could be a good framework to develop a simple and sustainable system to measure IVE on a routine basis. Sentinel practitioner networks can be used to identify cohorts of vaccinated and unvaccinated clients, to identify influenza cases and controls, to ascertain vaccination status and to document confounding factors. Cohort, case-control and screening method study designs could be used to estimate IVE within sentinel surveillance networks. Subjects included in studies based on sentinel practitioner networks reflect the health seeking

behaviour of the population and the practitioners' working practices. These may change during an influenza season or during the course of a pandemic. For instance, during the pandemic the health seeking behaviour may change due to the social alarm generated (i.e. individuals consulting with milder symptoms at the beginning) or to the recommendations issued (i.e. health authority recommendations of not visiting the practitioner unless developing severe symptoms). Therefore, the source population may vary between pandemic and non-pandemic years and within the same pandemic or influenza season. Ways to recognise and account for those changes have to be identified. As an example, documenting the number of GP visits in the previous 12 months may be used as an indicator of the study population health seeking behaviour in non-pandemic years.

Cohort studies

Sentinel practitioner networks with computerised medical records have been used to estimate IVE in various EU MS (56;57;64;65;67). Vaccinated and unvaccinated cohorts included in the databases are compared for various outcomes. Computerised cohort studies usually include large populations resulting in large sample sizes to conduct IVE studies.

If a unique identifier is used in different databases (e.g. GP medical records, vaccination, hospital, laboratory, deaths register) the databases can be linked and IVE for various outcomes measured. In some EU MS all national registers can be linked to constitute a national population cohort for VE studies (108). Database linkages need to be set up in accordance with the European Directive on the personal data confidentiality and safety (EU Data Protection Directive 1995). Access to and links between the various databases require the approval of an ethical and good practice body. If this is not anticipated, long delays in obtaining the authorisation to link the databases may occur making the study not suitable for obtaining rapid IVE estimates.

Underlying chronic conditions are ascertained using diagnosis codes included in the database (e.g. ICD9/10, International Classification for Primary Health Care). However some authors suggest that what matters for IVE estimates is the severity of the underlying condition rather than the condition itself (100;109). Because ICD codes do not discriminate severity properly within the same diagnosis group, attempts should be made to document severity of underlying chronic conditions. This may be done by collecting information on the number of recent

hospitalisations, all or specific to chronic conditions or by verifying the severity of the underlying condition in a sample of medical records.

The agreement between information included in the databases and the medical records should be measured. Electronic medical records are set up mainly for clinical purposes, not for conduction of epidemiological studies. Consequently, the validity of the diagnostic codes used to identify underlying conditions has been questioned in various studies (100). Important confounding factors such as smoking habits, functional status or severity of the chronic disease are often incomplete or even not documented (67;100).

Before using computerised databases to measure IVE, the validity of key variables should be assessed and monitored on a regular basis.

Particularly critical is the influenza outcome definition as it can affect the IVE estimates. It is recommended to include a specific outcome such as laboratory confirmed influenza in at least a sample of study participants with a clinical outcome (validation set) (96;110). The validation set is best selected using random or systematic sampling. Statistical methods for missing data are applied to the laboratory outcomes in the validation sample to correct estimates biased by including a non-specific clinical outcome.

To achieve acceptable external validity, the population included in the database should be representative of the general population. This may not always be the case. People with lower levels of access to care may not be included. If the reason for non-inclusion in the database is related to the occurrence of the outcome and to vaccination, it may represent an important confounding factor.

To assess the presence of positive confounding, it is recommended to measure IVE before and after the influenza season and compare it to the IVE estimated during the influenza period (100;109).

Case-control

In case-control studies based on sentinel practitioner networks, the vaccination status of influenza cases is compared to the vaccination status of a control group.

In such studies, cases should reflect the occurrence of the selected outcome and the vaccination status of such cases in the source population. For sentinel practitioner based

studies, the source population will be individuals likely to seek primary care if developing ILI or ARI symptoms.

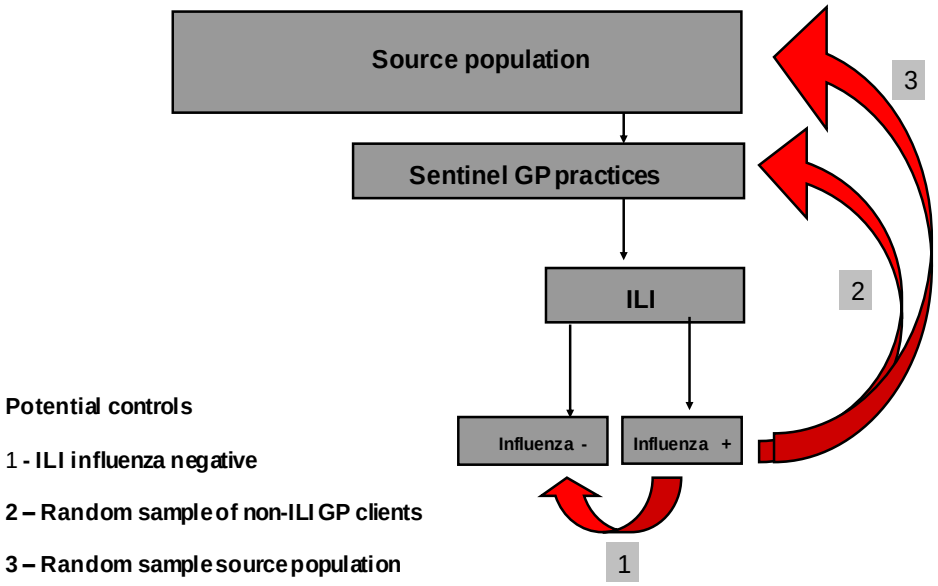
The representativeness of the cases should be assessed. Cases identified may be different from undetected cases in terms of disease severity, access to vaccination, access to health care, or distribution of potential confounding factors such as presence of chronic conditions. Health seeking behaviour for influenza may differ by age group.

To measure IVE against a specific outcome, cases should be laboratory confirmed. In sentinel practitioner networks, selection of patients to swab may not be systematic and changes over the season. For example, it is possible that during periods of high influenza activity, practitioners swab a lower proportion of patients to avoid overloading the laboratory. To avoid selection bias, practitioners should select patients to swab independently of their vaccination status and of other variables that are associated with both influenza vaccination and likelihood to seek medical attention for a respiratory illness (i.e. those with underlying clinical conditions). Ideally, practitioners should select randomly patients to swab.

A simple and acceptable sampling procedure should be identified (e.g. sampling the first case seen on a given weekday, assigning the selection of cases of a specific age group to each practitioner).

Controls are used to represent the vaccination coverage of the source population that gave rise to the cases. Several control groups can be selected, each of them represents a defined source population (Figure 4).

Figure 4. Sources of controls for case-control studies with influenza cases identified at practitioner level



Medically-attended influenza negative controls

Various studies use ILI patients consulting their GP, swabbed and testing negative for influenza as controls (test-negative controls) (77;89;111). The simplest option to estimate IVE using test-negative controls is to include all ILI patients swabbed by sentinel GPs participating in influenza surveillance networks: cases are ILI influenza positive and controls influenza negative (77;112;113). Vaccination status is usually documented in the patient's laboratory form. The limitation is that important confounding factors are not documented unless a specific questionnaire is added for all or a random selection of ILI patients. In that case, practitioners collect additional information on confounding factors from each ILI case swabbed. This can be achieved through patient interviews or through data extraction from computerised medical records.

Compared to other control groups, test-negative controls require less work for practitioners: in the framework of their routine influenza surveillance activities, practitioners already select, test, and interview ILI patients as a source of potential influenza cases. It is assumed that test-negative controls have similar health-care seeking behaviour than the population giving rise to the cases and thus represent the vaccination coverage of the source population (people likely to attend a GP practice if developing ILI)(111).

Random sample from GP practices

If controls are selected randomly from the practitioners' patient lists, two control groups can be used: any patient from the list (case-cohort design) or patients not yet having had ILI during the season (approximating a "density or concurrent case-control design") (114).

Another possibility would be to exclude, patients reporting ILI at the time of the selection (traditional case-control design) from the control group. In Denmark, a study estimated IVE using laboratory confirmed cases selected at the GP office and controls randomly selected from the GPs' patient list. They compared the IVE observed using a case cohort design (ILI cases could be included in the control group) and a traditional case-control design (controls excluding those with ILI). The traditional case-control design overestimated the IVE as a consequence of a high ILI attack rate (73). When the ILI attack rate is high, the case-cohort design should be favoured. In addition it is simpler for practitioners to select controls for case-cohort studies than for traditional or density case-control studies as ILI patients are selected independently of their ILI history.

Community controls

A random sample of controls can be selected in the community. However, in the pilot study we conducted in five EU MS the vaccination coverage in the community was lower than the vaccination coverage among GP patients (115). The results suggested that IVE may be underestimated when comparing cases at GP level to community controls.

Considerations on case-control studies to estimate IVE

Important issues should be considered when designing a case-control study to estimate IVE.

1/ The control group that best represents the vaccination coverage of the source population should be identified. This depends on the health-care seeking behaviour of the study population.

2/ The sample size should be large enough to provide IVE estimates by age-group and, if possible, for various influenza types. The sample needed depends on the influenza incidence, the vaccination coverage among the source population, the IVE to detect, the precision around the estimate and the desired power (Table 3). The number of practitioners needed for the study should be estimated based on the desired sample size.

3/ Patients to swab should be selected randomly. If the selection is done according to the practitioners' criteria, the potential bias introduced by this mode of selection should be assessed. If the proportion of patients swabbed changes along the season, ideally the IVE estimates should be corrected by including the sampling fraction by week in the analysis.

4/ A minimum set of confounding factors should be collected and IVE estimates adjusted for them (Table 4).

5/ To validate the data collected, a review of medical charts in a sub-set of patients is recommended.

Table 3. Sample size calculation for case-control studies: number of cases and control needed based on a ratio case control of 1, an alpha error of 0.05, a power of 80%, a detectable odds ratio ranging from 0.3 to 0.6 and a vaccination coverage among the source population ranging from 50% to 70%

Vaccination coverage in the source population (%)	Detectable OR	Number of cases	Number of controls
50 %	0.6	262	262
	0.5	148	148
	0.4	89	89
	0.3	56	56
60%	0.6	259	259
	0.5	144	144
	0.4	85	85
	0.3	52	52
70%	0.6	281	281
	0.5	153	153
	0.4	88	88
	0.3	52	52

*Note: the sample size should be respected for each population subgroup for which a stratified analysis is planned (e.g. for each age group stratum)

Table 4. Proposed minimum set of variables to document confounding factors in influenza vaccine effectiveness studies based on sentinel practitioners networks

Variables	Examples of how to document them
Presence of at least one underlying chronic disease for which the vaccine is recommended	List of underlying chronic diseases
Severity of the underlying chronic condition	Hospital admissions for the chronic disease(s) in the previous 12 months Prescriptions for the underlying disease
Smoking history	Never smoked, former smoker, current smoker
Previous influenza vaccination	Receipt of influenza vaccination in previous seasons
Functional status	Help needed for bathing or walking Barthel index
Health care seeking behaviour	Total number of visits to practitioners in the previous 12 months
Antiviral administration	Type of antiviral administered and date of administration

Screening

In some EU MS, influenza vaccination coverage in the community is available through vaccination registers or is estimated routinely through health surveys, vaccine sales, practitioners´ reports, health insurance data, etc (116). In this situation, the screening method is a simple method to estimate IVE by comparing the vaccination coverage among the ILI patients swabbed and positive to influenza to the vaccination coverage in a reference group (30;74;85;117). Bias may be introduced in the estimations if the cases and the reference group are drawn from different populations. For example, if the coverage in the reference group is lower than among practitioners' clients, IVE would be underestimated (118). However, if these potential biases are constant, the screening method conducted repeatedly every season or several times in the season, enables monitoring IVE over time and by comparing the estimates, identifying changes.

Delays in obtaining data on vaccination coverage data may not permit real-time measurement of IVE.

Specific surveys can be conducted to have real-time vaccination coverage (e.g. vaccination status of a sample of the GP patients in a specific period). This would be important in pandemic situations when vaccination coverage may change over time during the season.

The vaccination status of cases should be compared to the VC of the reference group measured in the period of occurrence of cases. For example, the VC of cases occurring during the peak of the epidemic should be compared to the VC in the reference group measured during peak. If possible, monthly VC estimates should be obtained to provide IVE estimates stratified by month.

The representativeness of the vaccination coverage in the reference group should be assessed and taken into account in the interpretation of the results. Variables to adjust for potential confounding factors are usually not available in the reference group. As a minimum, vaccination coverage should be available by age group to estimate influenza VE in each of the age groups. If possible, another key variable to be documented in the reference group and to adjust for it, is presence of chronic diseases (119).

Recommendations for selection of study design

The selection of the study design is a compromise between methodological constraints, availability and ease of access to the data sources and resources available (Figure 5).

Each study design has its advantages and limitations (Table 5). Minimum requirements should be included in the study design to have robust IVE estimates (Box 3).

RESULTS

The decision to select the study design will depend on the resources available and chosen. Each study design has its advantages and disadvantages.

Figure 5. Summary of main study designs for influenza vaccine effectiveness studies based on sentinel practitioners, according to data sources and resources available

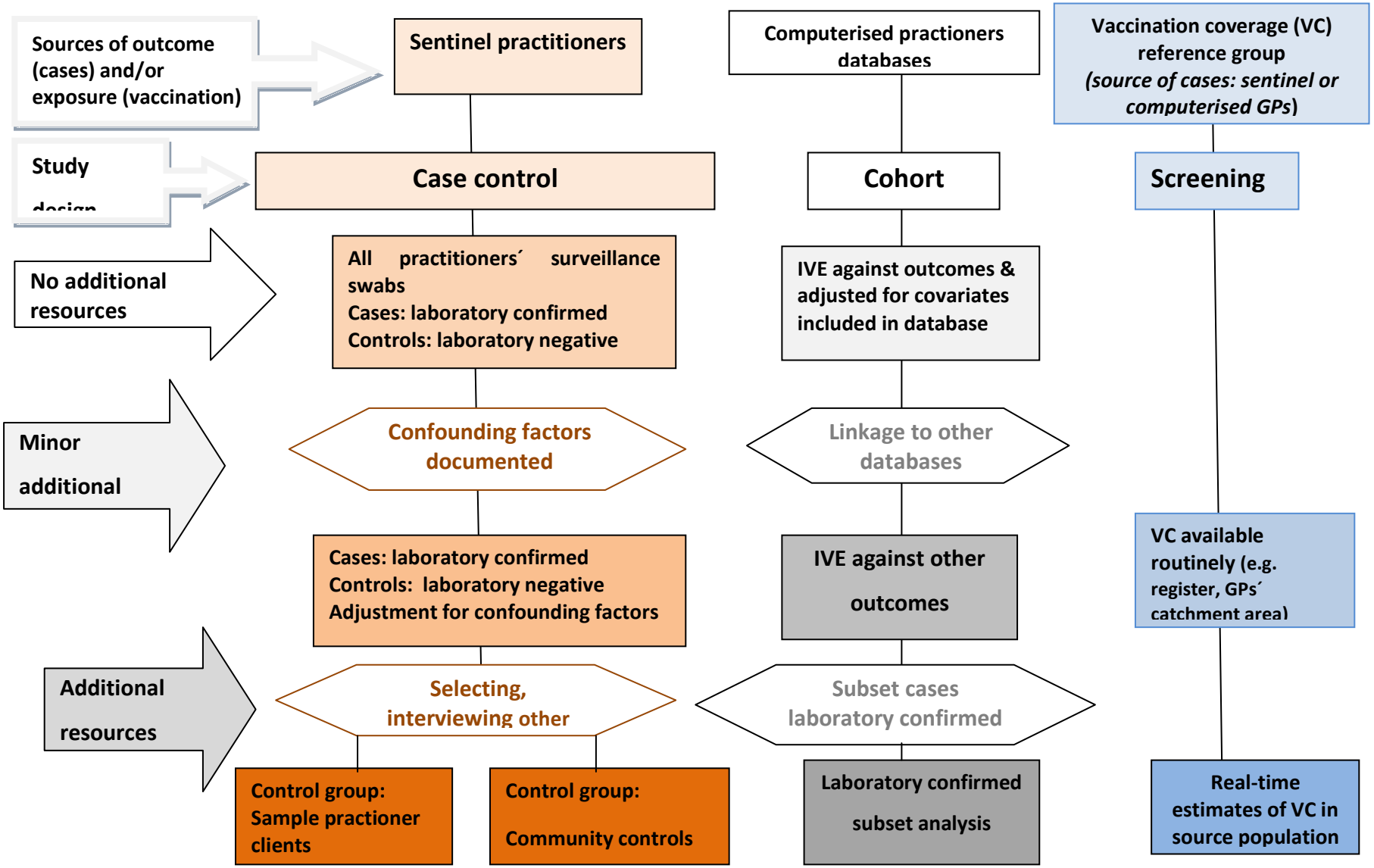


Table 5. Advantages and disadvantages of each study design to measure influenza vaccine effectiveness in studies based on sentinel practitioners networks

	Advantages	Disadvantages/issues to consider
Cohort extracted from practitioners databases	Based on existing computerised databases Large sample size Include various outcomes Possibility of person-time analysis Large amount of information on confounders Can adjust for healthy vaccinee effect Timeliness	Representativeness of the study population Validity of coding system If various databases linked, complexity of linkage Timeliness to obtain data for some outputs (e.g. hospitalisations)
Case-control studies based on sentinel GP networks	Test-negative controls: simple way to recruit cases and controls Possibility of documenting covariates directly through patient interviews Test-negative controls adjust for health seeking behaviour	Representativeness of control group used GPs´ workload Validity patients self-report Sample size
Screening	Simplicity Good timeliness if vaccination coverage data readily available	Limited confounding factors to adjust for Representativeness of reference group Delay in obtaining vaccination coverage data

Box 3. Proposed minimum requirements for influenza vaccine effectiveness studies based on sentinel practitioners networks

All study designs

Definition of specific objective(s) of the study detailing the outcome, target population

Inclusion of specific outcome (laboratory confirmation preferred)

Documentation of minimal list of confounding factors

Adequate sample size for subgroup analysis (age-group, influenza type)

Periodic validation of data sources (review of medical charts, vaccine registers, etc)

Database cohort

Assessment of the representativeness of the cohort population for external validity

Laboratory confirmation in at least a subset of the population

Estimation of IVE before, during and after the epidemic period to assess positive confounding

Case-control for (outcome laboratory confirmed influenza)

Random selection of patients to swab

Representativeness of control group to be assessed

Screening

Assess the representativeness of the reference group in which vaccination coverage is measured

Stratify estimates by age-group

4.5. Results season 2008/9, pilot season

Of the five countries participating in the multicentre case-control study during the pilot season, the epidemic started in Portugal at the end of 2008 (epidemiological week 49) and spread to the east of Europe (Hungary) in spring 2009 (week 4) (Figure 6).

In the five participating countries, the influenza vaccines used were trivalent inactivated influenza vaccine.

The number of practitioners enrolled in each of the study sites ranged from 40 in Denmark to 164 in Spain. Overall, 160 practitioners recruited at least one patient ranging from 21% in Portugal to 73% in Denmark (Table 6).

Figure 6. Influenza-like illness (ILI) incidence (cases per 100,000 population) reported by the national influenza sentinel surveillance in Denmark, Hungary, Portugal, Romania and, Spain, influenza season 2008/9

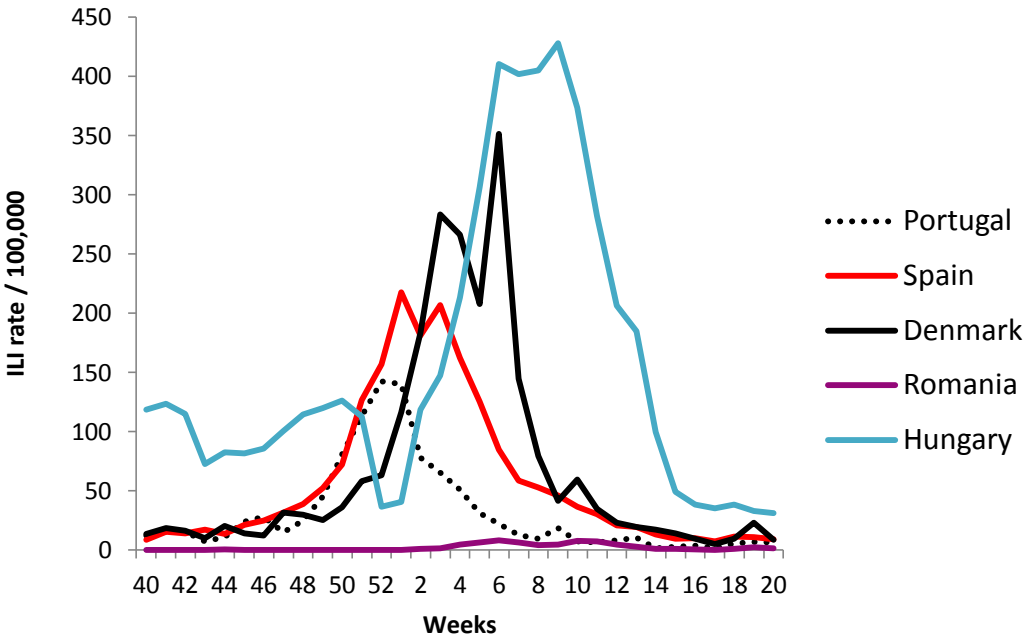


Table 6. Practitioner participation, influenza-like illness (ILI) patients, ILI patients positive to influenza, non ILI patients and community controls recruited by study site, I-MOVE multicentre case-control study, influenza season 2008/9

Study	Number of practitioners accepting to participate in the study	Number of practitioners recruiting at least one ILI * (%)	Number of ILI patients* recruited by practitioners	Number of ILI patients positive to influenza (%)	Number of non-Influenza-like illness practitioner patients	Number of community controls
Denmark	40	29 (72.5)	63	25 (39.7)	Not applicable	80
Hungary	50	27 (54.0)	144	45 (31.9)	89	Not applicable
Portugal	42	9 (21.4)	42	15 (35.7)	40	136
Romania	47	28 (59.6)	103	30 (29.1)	Not applicable	Not applicable
Spain	164	67 (40.1)	103	44 (42.7)	88	Not applicable
Total	343	160 (46.6)	455	159 (35.2)	217	216

*ILI patients meeting the EU case definition, swabbed < 8 days after onset of symptoms within the study period

RESULTS

Practitioners swabbed and interviewed 455 ILI patients. Among them, 159 (35%) were positive for influenza (from 29% in Romania to 43% in Spain). The completeness of the variables in the returned questionnaires varied from 85% to 100%.

Among 147 isolates typed before the restriction criteria were applied, 131 (89%) were influenza A and 16 (11%) B. Ninety-five of the A isolates were H3N2. All H3N2 strains genetically characterised were A/Brisbane/10/07 similar to the H3N2 vaccine component of the 2008/9 northern hemisphere vaccine. The B strain included in the 2008/9 vaccine did not match the circulating strain. Eight out of the 16 type B isolates were from cases enrolled in Hungary.

After applying the study restriction criteria, we included 138 cases and 189 test-negative controls in the analysis (Figure 7).

Among the 327 individuals included in the pooled analysis, 35 (10.7%) had at least a missing value for one of the variables collected. The variable with the highest proportion of missing values was presence of headache (13.7%) followed by hospitalisations in the previous 12 months (4.9%) (Table 7).

In Romania and Denmark, the proportion of ILI patients presenting with fever was higher among cases than among test-negative controls (Table 7). In Denmark, all of the cases and three quarters of the controls had a cough (p=0.02). In Romania, the proportion of ILI patients with pulmonary chronic disease was lower among cases than among controls (3% vs. 19%).

The mean delay between onset of symptoms and swab collection was shorter for cases than for test-negative controls in Portugal, Denmark and Romania (Table 8). In Spain and Portugal, the proportion of people having received influenza vaccines in at least one of the two previous seasons was lower among cases than among test-negative controls.

Vaccination coverage among controls varied according to country and control group; no specific pattern was identified (Table 9).

The country specific adjusted VE estimates ranged from 43.6% (95% CI: -119.8 - 85.6) in Hungary to 90.9% (95% CI: -42.6 - 99.4) in Denmark (Table 10).

Figure 7. Flowchart of data exclusion for pooled analysis, I-MOVE Multicentre case-control study, influenza season 2008/9

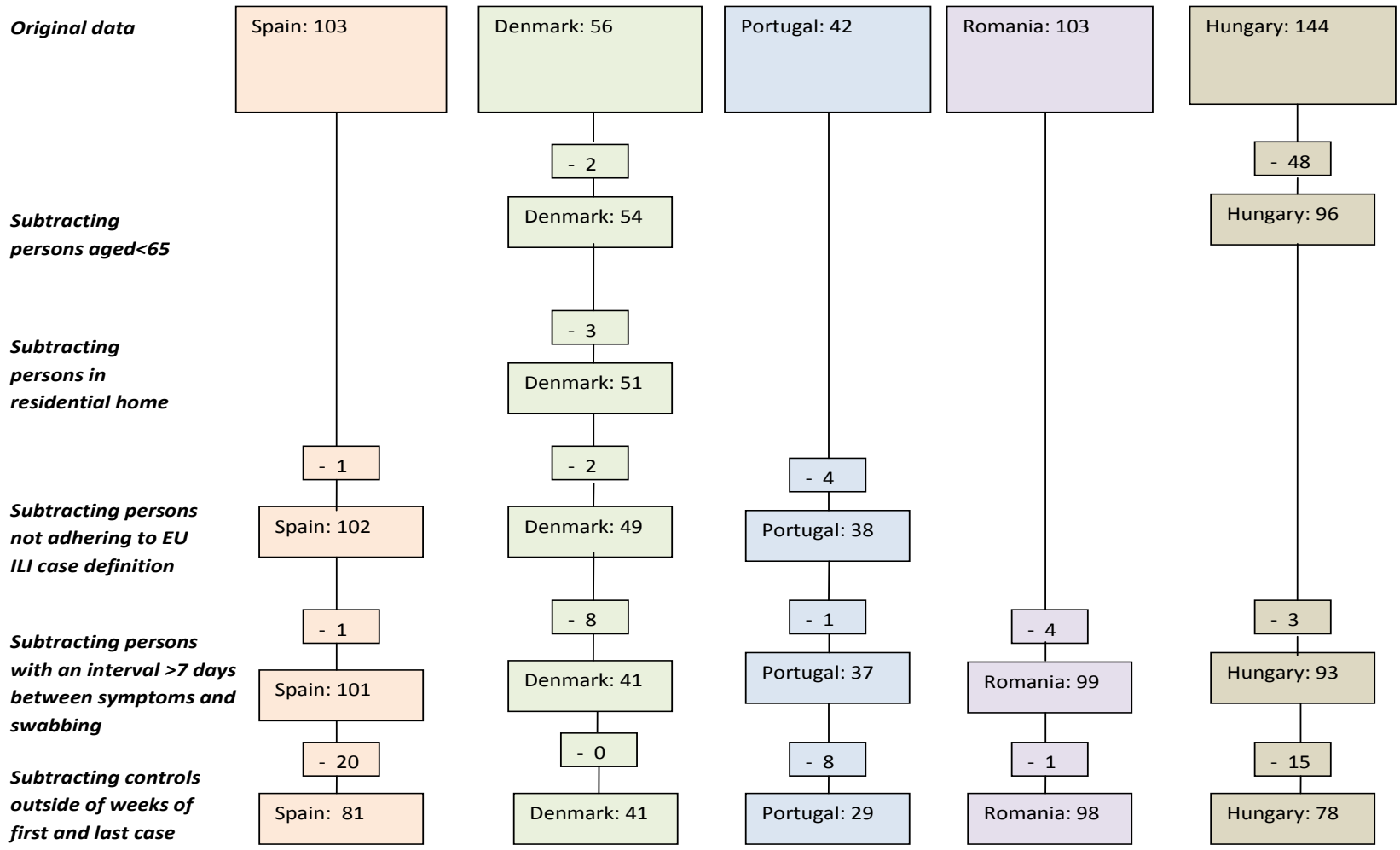


Table 7. Number and proportion of observations with missing values by variable, I-MOVE multicentre case-control study, seasons 2008/9, 2009/10, 2010/11

	2008/9 N*= 327		2009/10 N*=2902		2010/11 N*= 4410	
	Missing	**%**	**Missing**	**%**	**Missing**	**%**
Observations with no information for at least one variable	35	10.7	1400	48.2	1156	26.2
Variables						
Sex	0	0.0	19	0.7	19	0.4
Age group	0	0.0	7	0.24	0	0.0
Fever	8	2.4	27	0.9	14	0.3
Headache	45	13.7	59	2.0	54	1.2
Cough	2	0.6	24	0.8	10	0.2
Practitioners visits in previous 12 months	NA		799	36.9	789	17.9
Any chronic disease	11	3.4	577	19.9	64	1.5
Hospitalisations in previous 12 months	16	4.9	578	19.9	27	0.6
Smoking	10	3.1	349	12.0	482	10.9
Seasonal flu 2008/9	0	0.0	1055	36.4	2859	64.8
Seasonal flu 2009/10	NA		14	0.5	71	1.6
Seasonal vaccination for the 2010/11	NA		NA		20	0.5
Pandemic vaccination 2009/10	NA		67	2.3	68	1.5
Belonging to target group for vaccination	NA		NA		13	0.3

NA: not available (variable not collected for that season)

* Number of observations

RESULTS

Table 8. Characteristics of influenza cases and test-negative controls by study site, I-MOVE multicentre case-control study, influenza season 2008/9

Country	Characteristics	ILI patients		P value
		Influenza cases Number with characteristic / total (%)	Test-negative controls Number with characteristic / total (%)	
Portugal	Mean age	70	75	0.040*
	Any influenza vaccination in past 2 seasons	4/14 (28.6)	10/14 (71.4)	0.023**
	Interval from symptom onset to swab sample collection (mean in days)	1.5	2.33	0.030*
Spain	Any influenza vaccination in past 2 seasons	28/43 (65.1)	33/36 (91.7)	0.005**
Denmark	Interval from symptom onset to swab sample collection (mean in days)	3.05	4.25	0.0009*
	Fever	19/20 (95.0)	14/21 (66.7)	0.022**
	Cough	20/20 (100.0)	16/21 (76.2)	0.020**
Romania	Fever	30/30 (100.0)	57/68 (83.8)	0.019**
	Pulmonary chronic disease	1/30 (3.3)	13/68 (19.1)	0.040**
Hungary	Interval from symptom onset to swab sample collection (mean in days)	2.1	3.08	0.036*

* Mann-Whitney U test, ** Chi square

Table 9. Vaccination coverage (VC) for the seasonal 2008/9 influenza vaccine by control group and study site, I-MOVE multicentre case-control study, influenza season 2008/9

Study	VC (%) in ILI positive cases	VC (%) test-negative controls	VC (%) in non-ILI patients	VC (%) in community controls	VC (%) in participating practitioner´s catchment area
Denmark	55.0	71.4	Not applicable	49.0*	Not applicable
Hungary ***	41.9	48.7.0	42.7	Not applicable	38.5
Portugal	42.9	53.3	70.0	54.4**	Not applicable
Romania	46.7	67.6	Not applicable	Not applicable	86.9
Spain	61.4	89.2	80.7	Not applicable	65.3

ILI: Influenza-like illness

*Community controls randomly selected from the Danish population register

**Community controls sample selected for national telephone survey

*** Results apply to age 65 years and above, apart from Hungary where the study was carried out for 60 year-olds and older

Table 10. Study site specific and pooled crude and adjusted influenza vaccine effectiveness (IVE), I-MOVE multicentre case-control study, influenza season 2008/9

Study site vs pooled estimates		Crude analysis			Adjusted analysis			Variables used for adjustment
		N	IVE %	95% CI	N	IVE %	95% CI	
Study site specific estimates	Spain	81	80.8	36.0 - 94.2	76	82.9	30.6 - 95.8	age, sex, chronic disease, smoking, functional status
	Portugal	29	34.4	-184.3 - 84.9	28	82.3	-70.5 - 98.2	age, sex, chronic disease, smoking
	Denmark	41	51.1	-78.2 - 86.6	34	90.9	-43.0 - 99.4	age, sex, chronic disease, smoking, previous influenza vaccination
	Romania	98	58.2	-0.8 - 82.6	92	86.8	38.0 - 97.2	age, sex, chronic disease, smoking, previous influenza vaccination
	Hungary	78	28.6	-78.6 - 71.5	72	43.6	-119.8 - 85.6	age, sex, chronic disease, smoking, previous influenza vaccination
Pooled estimates	65+years	327	55.1	27.8-72.1	292	59.1	15.3 – 80.3	study, age, sex, chronic disease, smoking, previous influenza vaccination, functional status, previous hospitalisation
	65-74 years				196	65.4	15.6-85.8	study, sex, chronic disease, smoking, previous influenza flu vaccination, functional status, previous hospitalisation
	75+ years				96	59.6	-72.6 - 90.6	study, sex, chronic disease, smoking, previous influenza vaccination, functional status, previous hospitalisation
	A(H3) strain				259	56.4	-0.2 - 81.0	study, sex, chronic disease, smoking, previous influenza vaccination, functional status, previous hospitalisation

In terms of heterogeneity between study sites, two out of the five studies used a different ILI definition. Five study sites collected “number of hospitalisations”, “presence of chronic diseases” and, “functional status” differently. The Q test for heterogeneity was 2.87 (p = 0.579) and the I^2 index was 0%.

In the pooled analysis, the crude IVE was 55.1% (95% CI: 27.8-72.1). The IVE adjusted for study, age, sex, presence of chronic conditions, previous hospitalisations, smoking history, functional status, and previous influenza vaccination was 59.1% (95% CI: 15.3-80.3) (Table 10).

The adjusted IVE was 65.4% (95% CI: 15.6-85.8) in the 65-74 year-olds and 59.6% (95% CI: -72.6 - 90.6) in the age group of ≥75 years. The adjusted IVE against the A(H3) strain was 56.4% (95% CI: -0.2-81.0).

4.6. Results season 2009/10, pandemic season

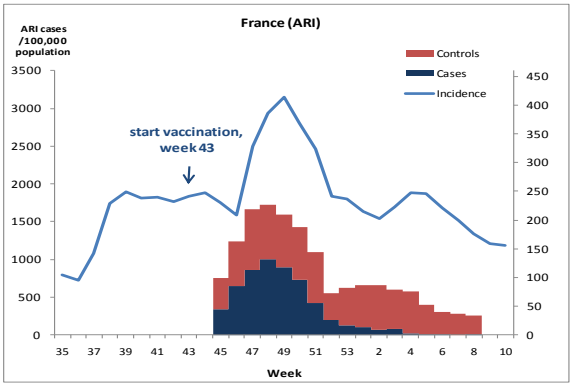
In the seven participating countries, influenza activity peaks were reached between week 43 (Ireland) and week 50 2009 (Hungary, Romania) (Figure 8).

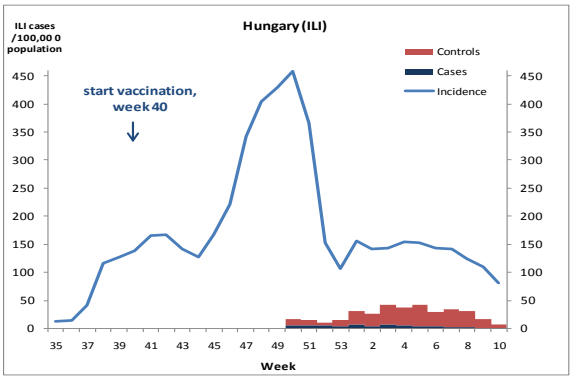
Of the six vaccines used at the seven study sites, three were adjuvanted (Table 11).

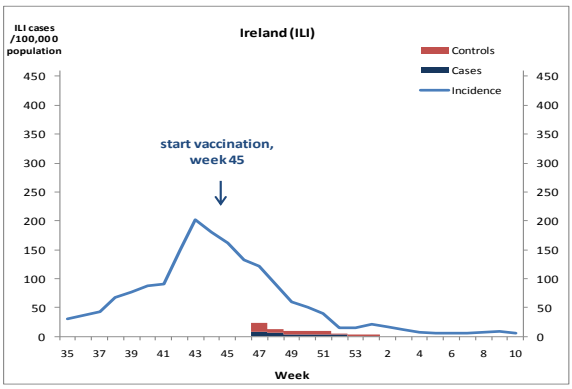
The first country to start the pandemic vaccination campaign was Hungary (week 40) and the last was Romania (week 48) (Figure 8).

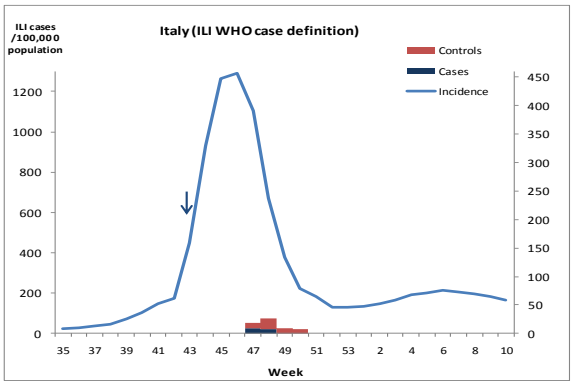
A total of 1,114 practitioners agreed to participate in the study. Within the study period, 699 of the practitioners recruited 2,926 patients who met the EU ILI case definition and who were swabbed less than eight days after symptom onset (Table 12). After excluding 17 individuals with non-subtypeable influenza A, one positive for influenza B, and six with missing information on laboratory results, a total of 2,902 ILI patients were included in the analysis (Figure 9). Among them, 918 (31.6%) were positive for A(H1N1)2009 (ranging from 15.2% in Hungary to 38.1% in France).

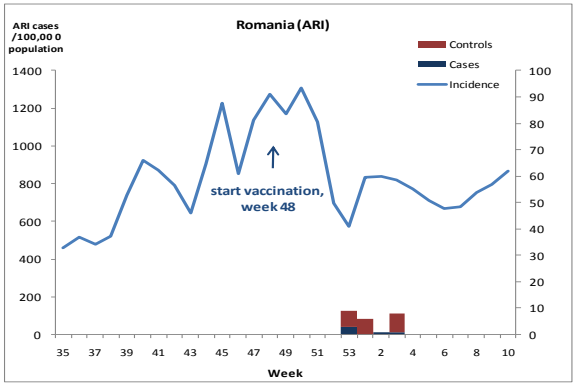
Figure 8. Influenza-like illness (ILI) incidence (ARI incidence in France) reported by the national influenza sentinel surveillance systems in France, Hungary, Ireland, Italy, Portugal, Romania, and Spain, influenza season 2010/11 and cases and controls recruited by week and study site, I-MOVE multicentre case-control study, influenza season 2009/10

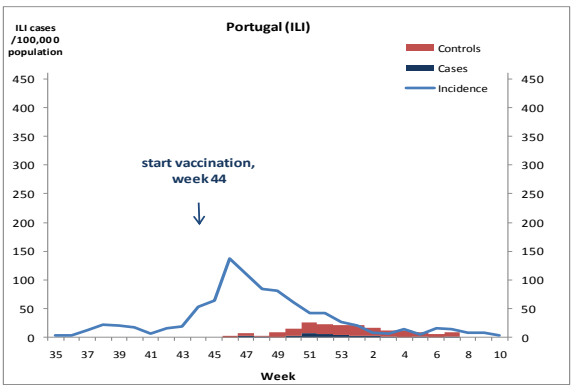












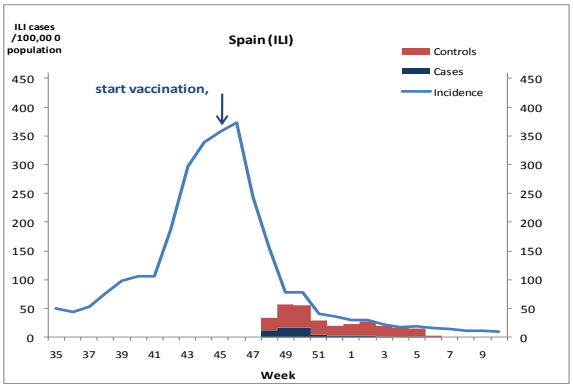


Table 11. Pandemic vaccines used by study site, I-MOVE multicentre case-control study, influenza season 2009/10

Vaccines	Adjuvant	Date Marketing authorisation, 2009	Countries						
			France	Hungary	Ireland	Italy	Portugal	Romania	Spain
Cevalpan (Baxter)	None	2 October	X		X				
Focetria (Novartis)	MF59	25 September	X			X			X
Pandemrix (GSK)	ASO3	25 September	X		X		X		X
Fluval P (Omninvest)	Aluminium phosphate	28 September		X					
Panenza (Sanofi Pasteur)	None	16 November	X						X
Cantgrip (Cantacuzino)	None	26 November						X	

RESULTS

Table 12. Practitioners´ participation, Influenza-like illness (ILI) patients recruited by case-control status, vaccination status, and study site, I-MOVE multicentre case-control study, influenza season 2009/10

Study site	Number of practitioners in the National sentinel system	Number of practitioners accepting to participate in the study	Number of practitioners recruiting at least one ILI * (%)	Number of ILI patients* recruited by practitioners	Inclusion period for the study†	Number of ILI patients included in the study positive for influenza A(H1N1)2009‡		Number of ILI patients included in the study negative for influenza A(H1N1)2009‡	
						Total	Vaccinated	Total	Vaccinated
France	550	550	429	1908	04 Nov 09 – 28 Feb 10	720	3	1172	63
Hungary	168	87	63	361	08 Dec 09 – 14 Mar 10	55	6	306	100
Ireland	137	48	19	77	17 Nov 09 – 10 Jan 10	29	1	48	2
Italy	1163+	47	21	69	03 Nov 09 – 13 Dec 09	18	0	44	0
Portugal	150	53	32	186	10 Nov 09 – 21 Feb 10	31	0	155	10
Romania	270	102	12	24	17 Dec 09– 31 Jan10	5	1	19	1
Spain	880	227	123	301	01 Dec 09 – 7 Feb 10	60	1	240	9
Total	3318	1114	699	2926		918	12	1984	185

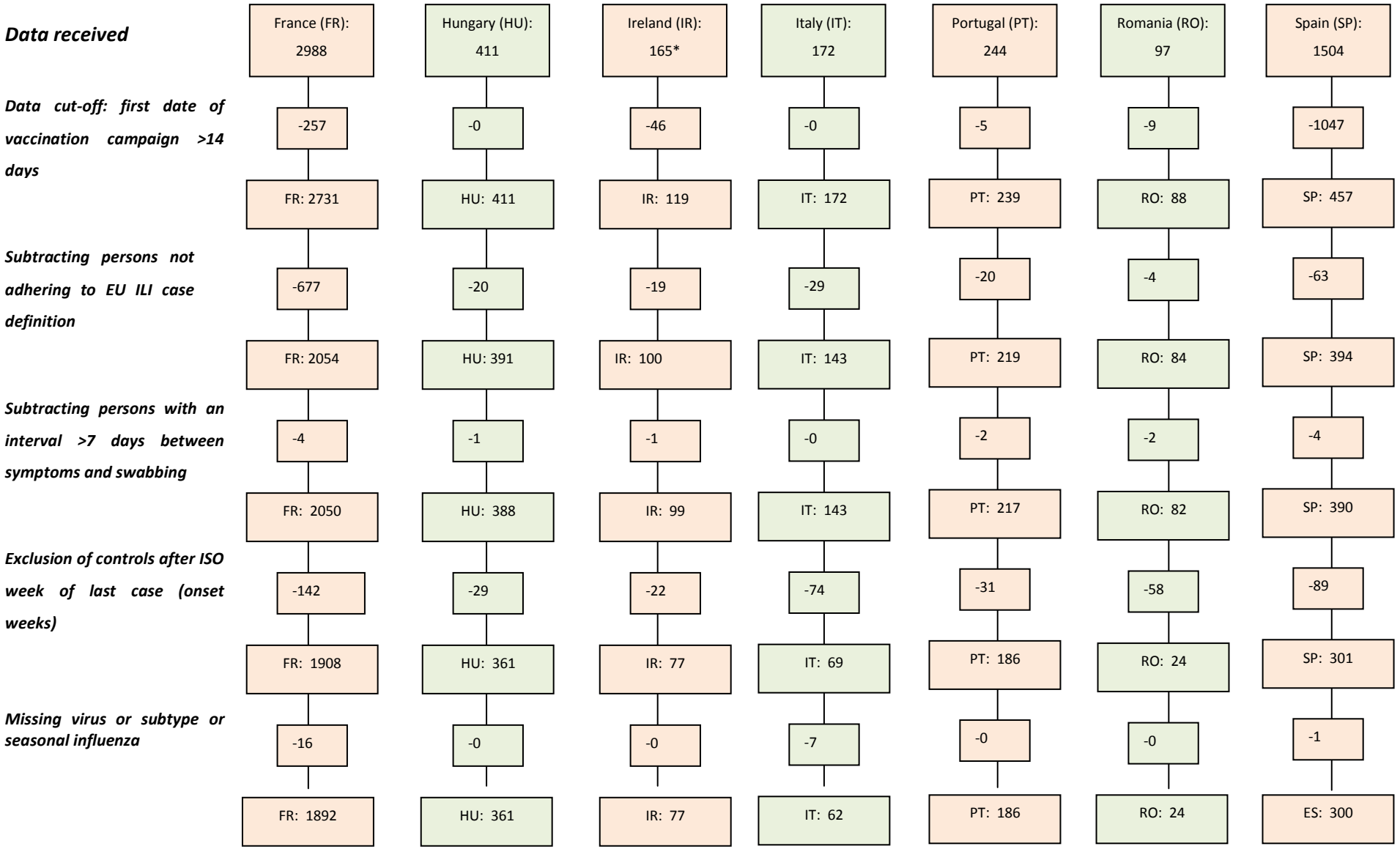
*ILI patients meeting the EU case definition, swabbed < 8 days after onset of symptoms within the study period

† For each study site, from 15 days after the start of the vaccination campaign up to the week that preceded two consecutive weeks in which none of the ILI patients recruited tested positive for influenza A(H1N1)2009 recruited. In Hungary, the start of the study period was the week of receiving the agreement from the Ethics Committee. Week number as defined by the International Standards Organization to ensure consistency across study sites (ISO weeks used).

‡ILI patients in the study after excluding those having tested positive previously to A(H1N1)2009, those positive to other influenza virus and those with missing information on laboratory results

+ Mean number of participating practitioners

Figure 9. Flowchart of data exclusion for pooled analysis, I-MOVE multicentre case-control study 2009/10



One hundred ninety seven individuals (6.9%) had received at least one dose of pandemic vaccine more than 14 days before the date of symptom onset (ranging from 0.0% in Italy to 29.4% in Hungary). Eleven of them had received two doses. Out of the 197 individuals vaccinated, vaccine brand was documented for 195. Among them, 155 (79.5%) had received an adjuvanted vaccine and 40 (20.5%) a non-adjuvanted vaccine

The median age was lower in cases (12 years) than in controls (27 years). The delay between onset of symptoms and swabbing was shorter in cases than in controls (Table 13). The proportion of individuals presenting with fever, headache or cough was higher among cases than among controls. Compared to cases, a higher proportion of controls had diabetes, heart disease and, were hospitalised at least once for their chronic disease in the previous 12 months. A higher proportion of controls were current or past smokers, vaccinated with the 2009/10 seasonal influenza vaccine and vaccinated against influenza in the previous two years. The median number of practitioner visits in the previous 12 months was three for cases (ranging from 0 to 22) and four for controls (ranging from 0 to 44) (Table 13).

A total of twelve A(H1N1)2009 cases were vaccinated with the pandemic vaccine more than 14 days before symptom onset. Two of these cases were under 15 years of age, three were 65 years of age or older and the remaining seven were aged 15 to 64 years. None of the cases had received two doses of the pandemic vaccine. In two of the seven studies there were no vaccinated individuals among the recruited cases (Table13).

In the complete case analysis, we included 1502 individuals (51.7% of the complete data). The highest proportion of missing values were for number of visits to a practitioner in the past 12 months (36.9 %) and influenza vaccination in the 2008/9 (36.4%) (Table 7).

Table 13. Characteristics of pandemic influenza A(H1N1)2009 cases and test-negative controls included, I-MOVE multicentre case-control study, influenza season 2009/10

Characteristics	Cases N=918	Test-negative controls N=1984	P value
Median age	12	27	<0.001*
Age group - nº/total nº. (%)			
0-4	180/917 (19.6)	520/1978 (26.3)	<0.001**
5-14	326/917 (35.6)	195/1978 (9.9)	
15-64	393/917 (42.9)	1069/1978 (54.0)	
≥ 65	18/917 (2.0)	194/1978 (9.8)	
Female sex - nº/total nº. (%)	485/912 (53.2)	1005/1971 (51.0)	0.279**
Symptoms - nº/total nº. (%)			
Fever	903/918 (98.4)	1842/1957 (94.1)	<0.001**
Headache	611/907 (67.4)	1194/1936 (61.7)	0.003
Cough	869/914 (95.1)	1718/1964 (87.5)	<0.001**
Sore throat	539/914 (59.0)	1340/1945 (68.9)	<0.001**
Days between onset of symptoms and swabbing – nº/total nº. (%)			
0	111/918 (12.1)	212/1984 (10.7)	<0.001**
1	512/918 (55.8)	987/1984 (49.7)	
2	201/918 (21.9)	454/1984 (22.9)	
3	70/918 (7.6)	181/1984 (9.1)	
4	17/918 (1.9)	77/1984 (3.9)	
5	6/918 (0.7)	36/1984 (1.8)	
6	1/918 (0.1)	21/1984 (1.1)	
7	0/918 (0.0)	16/1984 (0.8)	
Diabetes - nº/total nº. (%)	8/690 (1.2)	72/1670 (4.3)	<0.001**
Heart disease	20/ 688 (2.9)	198/1670 (11.9)	<0.001**
Any hospitalisation in the previous 12 months for chronic diseases - nº/total nº. (%)	5/680 (0.7)	37/1739 (2.3)	0.005**
Smoker - nº/total nº. (%)			
Current	35/814 (4.3)	176/1739 (10.1)	<0.001**
Former	80/814 (9.8)	244/1739 (14.0)	
Never	699/814 (85.9)	1319/1739 (75.8)	
Pandemic vaccination - nº/total nº. (%)	12/895 (1.3)	185/1940 (9.5)	<0.001**
Seasonal vaccination, 2009/10 - nº/total nº. (%)	56/913 (6.1)	240/1975 (12.2)	<0.001**
Any influenza vaccination in the previous two seasons - nº/total nº. (%)	56/516 (10.9)	213/1316 (16.2)	0.003**
Median number of practitioners visits in the previous 12 months	3	4	<0.001*

* Non parametric test of the median

**Two-sided Fisher's exact test

Pandemic vaccine effectiveness

In the pooled complete case analysis, the overall pandemic IVE adjusted for all potential confounding factors was 66.0%, 71.3% in those aged < 65 years and 70.2% in those with no chronic disease (Table 14).

In the pooled analysis with imputed data, we included all 2,902 individuals. The overall pandemic IVE adjusted for all potential confounding factors was 71.9%, 78.4% in those aged < 65 years and 72.9% in those with no chronic diseases (Table 14). Pandemic IVE were respectively 79.3% (95% CI: 4.7-95.9) in the early phase and 68.8% (95% CI: 35.8-84.8) in the late phase of the study.

An intermediate dataset included 2,073 records after dropping those with missing values in the variables that changed the odds ratio of being vaccinated by more than 5% in the complete-case or multiple imputation analysis (age group, number of practitioner visits in the previous 12 months, 2009/10 seasonal influenza vaccination and month of symptom onset). The pandemic IVE adjusted for these variables were 72.4% (95% CI: 44.1-86.4) overall, 80.1% (95% CI: 54.8-91.2) in those aged < 65 years and 73.4 (95% CI: 35.6-89.0) in those with no chronic disease.

In the complete case analysis taking into account different delays between date of vaccination and date of onset of ILI symptoms, the overall pandemic IVE was 66.0% for 8-14 days and 66.9% for more than 14 days (Table 15).

Vaccine effectiveness of the 2009/10 seasonal vaccine

A total of 296 individuals (10.2%) had received the 2009/10 seasonal vaccine more than 14 days before the date of symptom onset (Table 13). The seasonal IVE estimates adjusted for all potential confounding factors was 9.9% in the complete-case analysis and -1.5% in the multiple imputation analysis (Table 16).

Table 14. Pooled crude and adjusted pandemic vaccine effectiveness (PIVE), I-MOVE multicentre case-control study, influenza season 2009/10

		Included population	N	PIVE %	95% Confidence Interval
Complete case analysis *	**Crude‡**	All	1502	79.0	55.8-90.0
		< 65 years	1367	83.3	61.2-92.8
		15-64 years	912	76.6	44.7-90.1
		< 15 years	455	100	58.2-100.0∫∫
		No chronic disease	1190	81.5	53.0-92.7
	Adjusted model ∫	All	1502	66.0	23.9-84.8
		< 65 years	1367	71.3	29.1-88.4
		15-64 years	912	65.5	12.3-86.5
		< 15 years	455	100%	Not calculable∫∫∫
		No chronic disease	1190	70.2	19.4-89.0
Imputed data †	**Crude‡**	All	2902	82.8	68.6-90.6
		< 65 years	2688	86.9	73.9-93.4
		15-64 years	1463	80.6	57.2-91.2
		< 15 years	1218	94.2	75.6-98.6
		No chronic disease	2354	84.6	67.7-92.7
	Adjusted model ∫	All	2902	71.9	45.5-85.5
		< 65 years	2688	78.4	54.3-89.8
		15-64 years	1463	73.3	36.7-88.7
		<15years	1218	84.8	31.0-96.6
		No chronic disease	2354	72.9	39.7-87.8

* Excluding individuals with missing values

† Missing data imputed using imputation using chained equations

‡ Study site included in the model as fixed effect ∫ Model adjusted for 2009/10 seasonal influenza vaccination, any influenza vaccination in previous two seasons, presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, current smoker, age group, practitioner visits in previous 12 months (0, 1-4 and 5+ visits), month of symptom onset (note: in the 15-64 years stratum no adjustment for age group; in the "no chronic disease" stratum no adjustment for chronic disease or hospitalisations for chronic disease)

∫∫Exact logistic regression estimates with zero cases vaccinated

∫∫∫ If one of the cases would have been vaccinated, the estimated PIVE would be 85.2% (95% CI: – 30.0- 98.3)

Table 15. Pooled crude and adjusted pandemic vaccine effectiveness (PIVE), by categories based on delay between date of vaccination and date of onset of symptoms, complete case analysis, I-MOVE multicentre case-control study, influenza season 2009/10

	Included population	Definition of delay vaccination – onset of Influenza-like Illness symptoms	N	PIVE %	95% Confidence Interval
Crude*	All	< 8 days	1502	20.6	-157.9-75.5
		8-14 days		59.8	-85.3-91.3
		> 14 days		79.2	56.3-90.1
	< 65 years	< 8 days	1367	15.7	-18.1-74.7
		8-14 days		57.6	-97.6-90.9
		> 14 days		83.5	61.5-92.9
Adjusted model ‡	All	< 8 days	1502	18.8	-183.4-76.7
		8-14 days		66.0	-69.9-93.2
		> 14 days		66.9	26.0-85.2
	< 65 years	< 8 days	1367	15.5	-198.1-76.1
		8-14 days		66.6	-70.8-93.5
		> 14 days		72.0	30.8-88.7

Study site included in the model as fixed effect

‡ Model adjusted for 2009/10 seasonal influenza vaccination, any influenza vaccination in previous two seasons, presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, current smoker, age group, practitioner visits in previous 12 months (0, 1-4 and 5+ visits), month of symptom onset

Table 16. Pooled crude and adjusted 2009/10 seasonal influenza vaccine effectiveness (IVE), I-MOVE multicentre case-control study, influenza season 2009/10

		Included population	N	IVE %	95% Confidence Interval
Complete case analysis*	Crude‡	All	1502	47.5	21.3-65.0
		< 65 years	1367	47.0	14.0-67.4
	Adjusted model ∫	All	1502	9.9	-65.2-50.9
		< 65 years	1367	31.4	-34.4-65.0
Imputed data†	Crude‡	All	2902	40.6	18.6-56.7
		< 65 years	2688	25.6	-7.3-48.4
	Adjusted model ∫	All	2902	-1.5	-67.0-38.3
		< 65 years	2688	9.8	-57.2-48.3

* Excluding individuals with missing values

† Missing data imputed using imputation using chained equations

‡ Study site included in the model as fixed effect

∫ Model adjusted for 2009/10 pandemic influenza vaccination, any influenza vaccination in previous two seasons, presence of at least one chronic disease, sex, at list one hospitalisation for chronic disease in the previous 12 months, current smoker, age group, practitioner visits in previous 12 months (0, 1-4 and 5+ visits), month of symptoms onset

4.7. Results season 2010/11

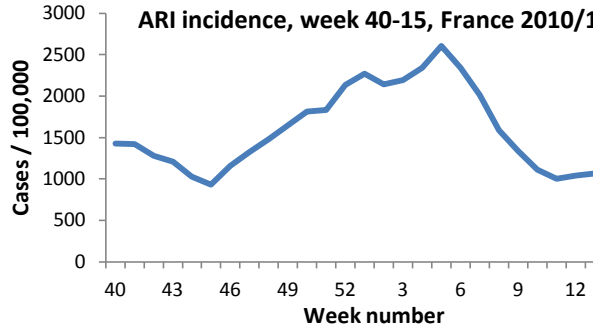
In the countries of the eight study sites, influenza activity peaked between week 52 (Portugal) and week 8 2011 (Romania) (Figure 10).

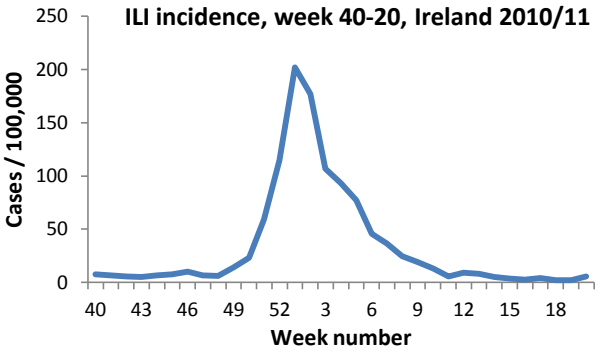
A total of 23 vaccines were used in the eight countries, six of them were adjuvanted (Table 17).

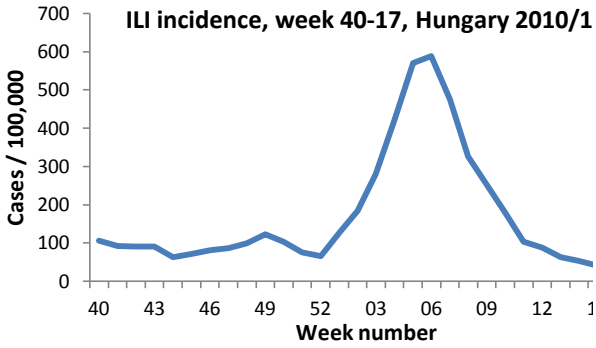
A total of 1,035 practitioners agreed to participate in the study; 765 of them (74.0%) recruited at least one ILI patient meeting the EU case definition and swabbed < 8 days after onset of symptoms within the study period (Table 18). We excluded two individuals with contraindications for vaccination, two individuals who had received antivirals prior to swabbing, 58 individuals without information on laboratory results, 12 individuals who received vaccination before begin of the country's national vaccination campaign, 660 individuals who did not adhere to the EU ILI case definition, 26 individuals who were swabbed more than seven days after symptom onset and 163 individuals that presented symptoms outside of the onset week of the first or last case (Figure 11).

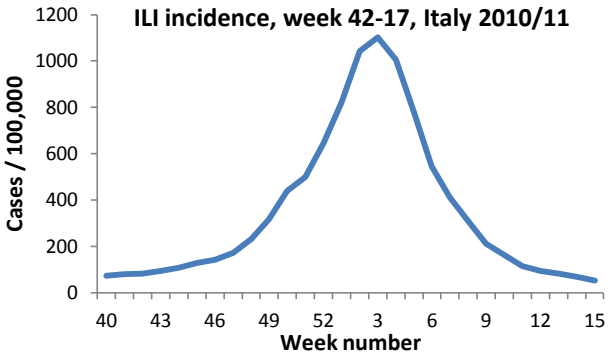
We included 4,410 ILI patients in the analysis: 2,019 cases and 2,391 controls. Among the cases, 1,179 (58.4%) were positive for influenza A(H1N1) virus, 40 (2.0%) for influenza A(H3N2) virus, 37 (1.8%) were positive for influenza A virus that could not be subtyped and 765 (37.9%) were positive for influenza B virus (Figure 12). Two of the cases presented a co-infection, one positive for influenza A(H1N1) and for influenza B virus and one positive for influenza A(H3N2) and influenza B virus.

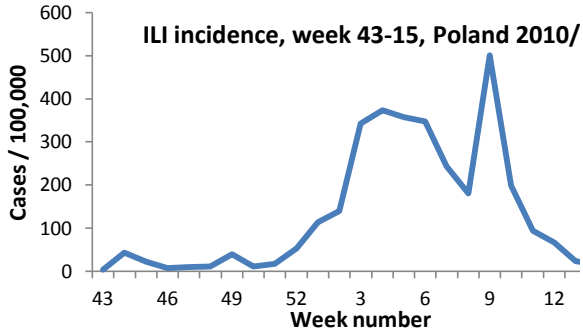
Figure 10. Influenza-like illness (ILI) incidence (ARI incidence in France) reported by the national influenza sentinel surveillance systems in France, Hungary, Ireland, Italy Poland, Portugal, Romania, and Spain, influenza season 2010/11

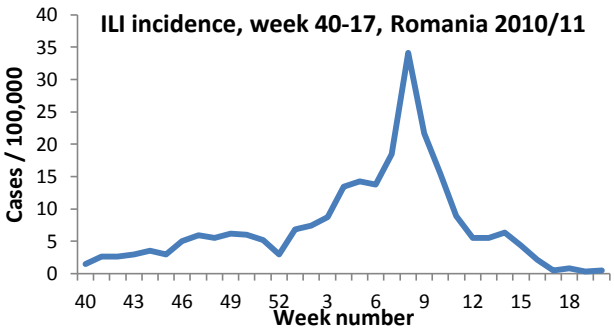


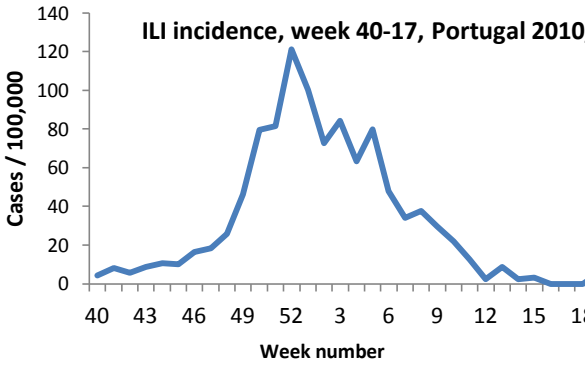


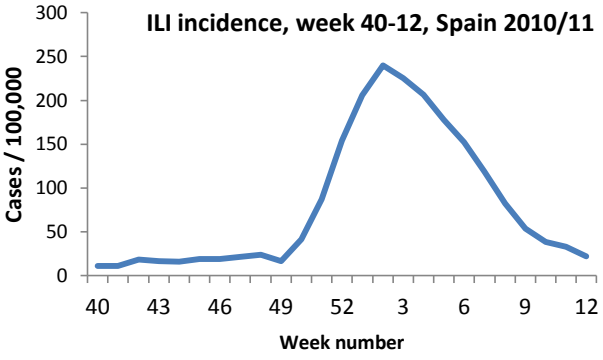












RESULTS

Table 17. Seasonal 2010/11 vaccines used by study site, I-MOVE multicentre case-control study, influenza season 2010/11

Vaccines	Adjuvant	Countries							
		France	Hungary	Ireland	Italy	Poland	Portugal	Romania	Spain
Fluval AB	Aluminium phosphate		X						
FLUAD	M59C.1				X*		X*		
Chiromas	M59C.1								X
GRIPGUARD	M59C.1	X *							
ISIFLU V	Virosomes				X				
Inflexal	Virosomes								X
ID flu (intradermal)			X		X**	X			
ISTIVAC							X		
ISTIVAC infantil (6-35 months)							X		
FLUARIX		X	X		X	X	X		X
Chiroflu							X		X
INTANZA 15 (> 60 years)							X		
Inactivated Split Virion				X					
INFLUVAC		X		X		X	X		
AGRIPAL		X			X	X			
IMMUGRIP		X							
VAXIGRIP		X				X			
MUTAGRIP		X							X
BERNA									X
Esteve									X
Leti									X
Gripavac									X
Cantacuzino (split)								X	

´* For individuals > 64 years ** For individuals > 17 years

Table 18. Practitioners´ participation, Influenza-like illness (ILI) patients recruited by case-control status, vaccination status, and study site, I-MOVE multicentre case-control study, influenza season 2010/11

Study site	Number of practitioners in the National sentinel system	Number of practitioners accepting to participate in the study	Number of practitioners recruiting at least one ILI *	Number of ILI patients* recruited by practitioners	Inclusion period for the study†	Number of ILI patients included in the study positive for influenza ‡		Number of ILI patients included in the study negative for influenza ‡	
						Total	Vaccinated	Total	Vaccinated
France	571	425	317	1186	wk 51, 2010 –wk 11, 2011	597	15	589	39
Hungary	1400	98	78	727	wk 50, 2010 –wk 13, 2011	119	4	608	52
Ireland	135	48	17	190	wk 48, 2010 –wk 9, 2011	106	0	84	6
Italy	1009+	38	27	415	wk 46, 2010 –wk 13, 2011	116	17	299	64
Poland	971	33	29	180	wk 48, 2010 –wk 14, 2011	98	6	81	10
Portugal	144	58	34	253	wk 45, 2010 –wk 11, 2011	144	6	109	19
Romania	270	89	66	255	wk 52, 2010 –wk 15, 2011	154	7	101	13
Spain	848	246	197	1205	wk 49, 2010 –wk 12, 2011	685	26	520	53
Total	5348	1035	765	4410		2019	81	2391	256

* ILI patients meeting the EU case definition, swabbed < 8 days after onset of symptoms within the study period

† For each study site, from 15 days after the start of the vaccination campaign up to the week that preceded two consecutive weeks in which none of the ILI patients recruited tested positive for influenza. (ISO weeks used).

‡ ILI patients in the study after applying exclusion criteria (contraindications for vaccine, antiviral use before swabbing, missing lab results) and excluding those not adhering to the EU ILI case definition, having a delay between symptom onset and swabbing of less than 8 days and presenting outside the study period).

+ Mean number of participating practitioners

Figure 11. Flowchart of data exclusion for pooled analysis, I-MOVE multicentre case-control study 2010/11

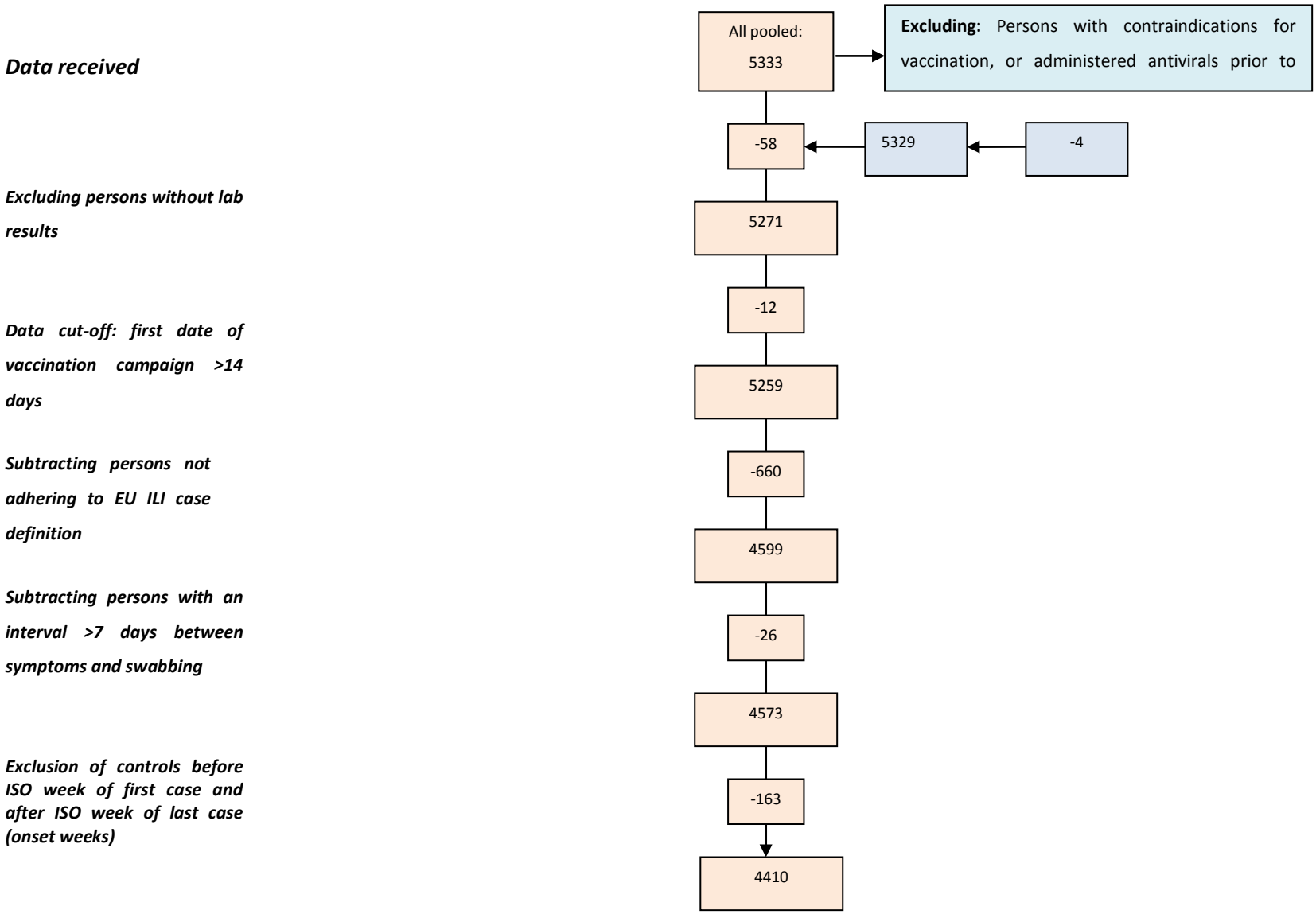
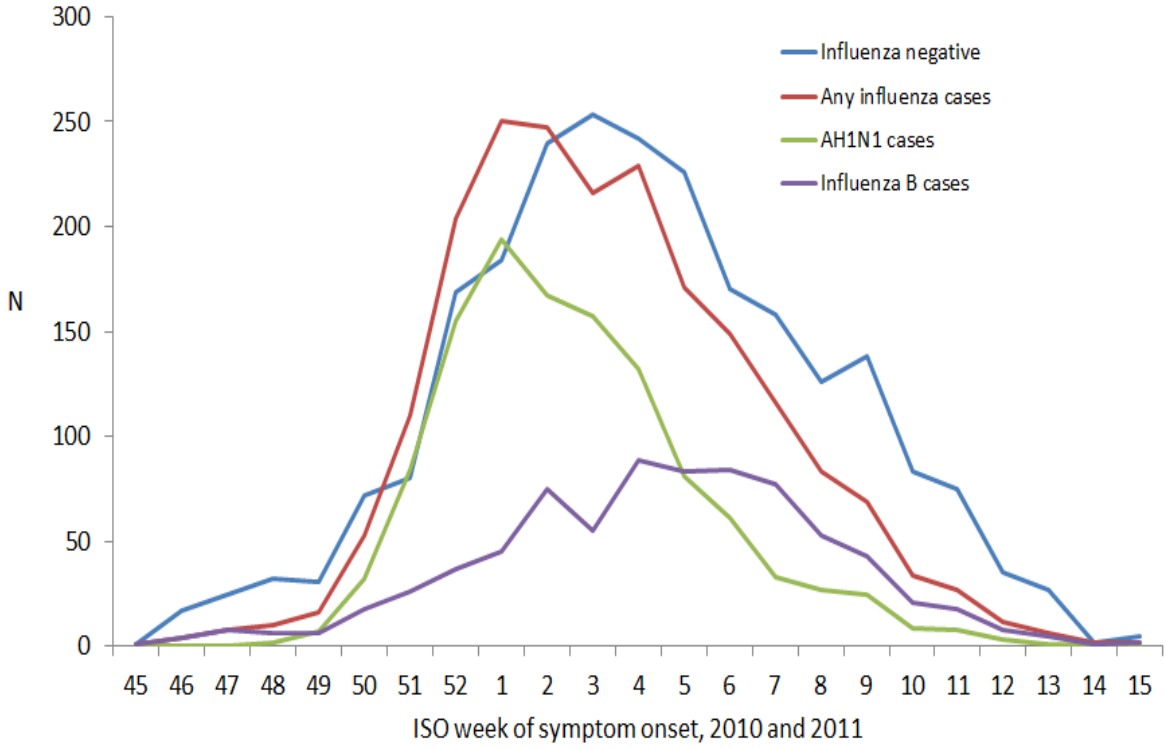


Figure 12. Influenza positive (N=2019), A(H1N1) positive (N=1179), B positive (N=765) and negative cases (N=2391) included, by week of symptom onset, I-MOVE multicentre case-control study, influenza season 2010/11



Among 4,390 individuals with information on vaccination status and vaccination date for seasonal vaccination in 2010/11, 337 (7.7%) were vaccinated (ranging from 3.2% in Ireland to 19.5% in Italy).

The median age was lower in cases (23 years, standard deviation (SD): 19.4 years) than in controls (32 years, SD: 22.7 years).

The delay between onset of symptoms and swabbing was slightly shorter in cases (mean: 1.7 days, range: 0-7 days) than in controls (mean: 1.8 days, range: 0-7 days). The proportion of individuals presenting with fever, headache, myalgia or cough was higher among cases than among controls, while the proportion of those presenting with shortness of breath or sore throat was higher among controls than among cases (Table 19). Compared with cases, a higher proportion of controls had diabetes, heart disease, any chronic disease or were hospitalised at least once for their chronic disease in the previous 12 months. A higher proportion of controls were current or past smokers, vaccinated with the 2009/10 seasonal influenza vaccine, vaccinated with the 2009/10 pandemic influenza vaccine and belonged to the target group for vaccination. The proportion of individuals visiting their practitioner more than once in the previous 12 months, was higher among controls (68.6%) than among cases (56.5%) (Table 19).

Table 19. Characteristics of influenza cases and test-negative controls included, I-MOVE multicentre case-control study, influenza season 2010/11

Characteristics	Cases N=2019	Test-negative controls N=2391	P value
Age group - nº/total nº. (%)			
0-4	269/2019 (13.3)	372/2391 (15.6)	<0.001**
5-14	503/2019 (24.9)	286/2391 (12.0)	
15-59	1117/2019 (55.3)	1394/2391 (58.3)	
60+	130/2019 (6.4)	339/2391 (14.2)	
Female sex - nº/total nº. (%)	1046/2012 (52.1)	1241/2383 (52.1)	1.000**
Symptoms - nº/total nº. (%)			
Fever	1964/2016 (97.5)	2246/2381 (94.3)	<0.001**
Headache	1446/1995 (72.5)	1562/2361 (66.2)	<0.001**
Myalgia	1487/1990 (74.7)	1659/2361 (70.3)	0.001**
Cough	1891/2018 (93.7)	2049/2382 (86.0)	<0.001**
Sore throat	1361/1993 (68.3)	1766/2376 (74.3)	<0.001**
Shortness of breath	208/1959 (10.6)	327/2349 (13.9)	0.001
Days between onset of symptoms and swabbing – nº/total nº. (%)			
0	138/2019 (6.8)	170/2391 (7.1)	0.002**
1	944/2019 (46.8)	1033/2391 (43.2)	
2	587/2019 (29.1)	650/2391 (27.2)	
3	219/2019 (10.8)	303/2391 (12.7)	
4	74/2019 (3.7)	116/2391 (4.9)	
5	39/2019 (2.0)	62/2391 (2.7)	
6	9/2019 (0.4)	32/2391 (1.3)	
7	9/2019 (0.4)	25/2391 (1.0)	
Diabetes - nº/total nº. (%)	30/1296 (2.3)	90/1715 (5.2)	<0.001**
Heart disease	62/ 1296 (4.8)	201/1715 (11.7)	<0.001**
Any reported chronic disease	219/1990 (11.0)	428/2356 (18.2)	<0.001**
Any hospitalisation in the previous 12 months for chronic diseases - nº/total nº. (%)	25/2012 (1.2)	56/2371 (2.4)	0.007**
Smoker - nº/total nº. (%)			
Current	165/1791 (9.2)	319/2137 (14.9)	<0.001**
Former	93/1791 (5.2)	201/2137 (9.4)	
Never	1534/1791 (85.6)	1617/2137 (75.7)	
Low functional status	9/1490 (0.6)	35/1853 (1.9)	0.001
Pandemic vaccination 2009/10 - nº/total nº. (%)	148/1994 (7.4)	300/2348 (12.8)	<0.001**
Seasonal vaccination, 2009/10 - nº/total nº. (%)	134/1990 (6.7)	341/2349 (14.5)	<0.001**
Number of visits to the practitioner in the previous 12 months			
0-1	695/1611 (43.1)	631/2010 (31.4)	<0.001**
2-4	482/1611 (29.9)	657/2010 (32.7)	
5+	434/1611 (27.0)	722/2010 (35.9)	
Belongs to target group for vaccination nº/total nº. (%)	381/2017 (18.9)	631/2380 (26.5)	<0.001**

* Non parametric test of the median **Two-sided Fisher's exact test

RESULTS

In the complete case dataset, the Q test (p=0.337) and the I^2 index (12.1%) testing for heterogeneity between seven study sites (Ireland excluded as no vaccinated cases) using models adjusted for age group, onset month and chronic disease suggested no statistical heterogeneity between study sites.

In the complete case analysis we included 3,254 individuals (73.8% of the complete data). A total of 1,271 of the 1,540 missing values (82.5%) were contained in two variables: practitioners visits in the previous 12 months, missing values in 789 (17.9%) records) and smoking, missing values in 482 (10.9%) records (Table 7). Excluding those two variables, the data were 95.4% complete.

The complete case crude IVE against all influenza was 65.5% (95% CI: 53.2-74.6) and adjusted IVE was 50.9% (95% CI: 25.2-67.7) (Table 20).

In the tables 20 to 23, we present the results of the complete case and imputed analysis but for simplification, in the text below, we only refer to the imputed analysis results. In the imputed analysis we included 4,410 individuals.

Crude imputed VE against any influenza was 64.2% (95% CI: 53.2-72.6) and the adjusted 51.9% (95% CI: 30.0 -66.9). The adjusted IVE against A(H1N1) was 55.4% (95% CI: 28.7-72.1) and against influenza B 49.8% (95% CI: 13.8-70.8) (Table 21).

The adjusted VE against all influenza by age group was 65.7% (95% CI: 15.4-86.1), 41.3% (95% CI: -2.6-66.4) and 59.9% (95% CI: 16.6-80.7) among those aged 0-14, 15-59 and 60+ years respectively (Table 21).

Adjusted VE against A(H1N1) was 77.2% (95% CI: 16.0-93.8), 27.2% (95% CI: -37.1-61.3) and 72.3 (95% CI: 26.4-89.6) in the 0-14, 15-59 and 60+ year old age groups (Table 22).

Adjusted VE against influenza B estimates in these age groups ranged between 63.8% for the 15-59 years and 55.5% for the age group 60+ years (Table 23).

When stratifying VE by pandemic 2009/10 vaccination status, the adjusted VE for those vaccinated only with the 2010/11 seasonal vaccine, was 60.9% (95% CI: 36.2-76.1), 10.3 % (95% CI: -20.5-33.2), for those vaccinated only in 2009/10 with the pandemic vaccine 2009/10 and 55.2% (95% CI: 22.0-74.3) for those vaccinated with both vaccines (Table 24).

The two-stage random effects pooled analysis IVE estimates against all influenza were very similar to the complete case fixed effects analysis adjusted for the same covariates (47.7% and 48.7% respectively (Table 25).

Table 20. Pooled crude and adjusted 2010/11 seasonal influenza vaccine effectiveness (IVE) against all influenza, influenza A(H1N1) and Influenza B, I-MOVE multicentre case-control study, influenza season 2010/11

Outcome			N	IVE %	95% Confidence Interval
All influenza	Crude‡	Complete case analysis †	3254	65.5	53.2-74.6
		Imputed data*	4410	64.2	53.2-72.6
	Adjusted model 1∫	Complete case analysis †	3254	50.9	25.2-67.7
		Imputed data*	4410	51.9	30.0-66.9
A(H1N1)	Crude‡	Complete case analysis †	2506	66.9	51.2-77.5
		Imputed data*	3344	67.9	54.6-77.3
	Adjusted model 1∫	Complete case analysis †	2506	50.9	16.8-71.0
		Imputed data*	3344	55.4	28.7-72.1
Influenza B	Crude‡	Complete case analysis †	2119	70.8	53.3-81.7
		Imputed data*	2944	65.8	49.4-76.9
	Adjusted model 1∫	Complete case analysis †	2119	55.7	16.8-76.4
		Imputed data*	2944	49.8	13.8-70.8

*Missing data imputed using imputation using chained equations

† excluding individuals with missing values

‡ Study site included in the model as fixed effect

∫ Model adjusted for 2009/10 seasonal and pandemic influenza vaccination, presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, current smoker, age group (10 year bands), practitioner visits in previous 12 months (0-1, 2-4 and 5+ visits), week of symptom onset

NB: For influenza B imputed analysis, we dropped week 14 (1 record) in order to do computation

Table 21. Pooled crude and adjusted 2010/11 seasonal influenza vaccine effectiveness (IVE) against all influenza by age group, I-MOVE multicentre case-control study, influenza season 2010/11

Age group			N	IVE %	95% Confidence Interval
0-14 years[1]	Crude‡	Complete case analysis †	892	60.6	2.4-84.1
		Imputed data*	1422	50.5	-4.2-76.5
	Adjusted model 1∫	Complete case analysis †	892	75.3	23.4-92.0
		Imputed data*	1422	65.7	15.4-86.1
15-59 years[2]	Crude‡	Complete case analysis †	1994	50.5	19.1-69.7
		Imputed data*	2509	56.5	31.2-72.6
	Adjusted model 1∫	Complete case analysis †	1994	33.2	-22.0-63.4
		Imputed data*	2509	41.3	-2.6-66.4
60+ years[3]	Crude‡	Complete case analysis †	348	55.0	21.1-74.3
		Imputed data*	464	55.2	29.0-71.7
	Adjusted model 1∫	Complete case analysis †	348	62.9	13.4-84.1
		Imputed data*	464	59.9	16.6-80.7

*Missing data imputed using imputation using chained equations
† excluding individuals with missing values
‡ Study site included in the model as fixed effect
∫ Model adjusted for 2009/10 seasonal and pandemic influenza vaccination, presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, current smoker, age group (10 year bands), practitioners visits in previous 12 months (0-1, 2-4 and 5+ visits), week of symptom onset

For certain analyses, data from some weeks had to be dropped due to only positive or negative outcomes during this week
[1] Week 13 14 dropped (8 records dropped)
[2] Week 14 dropped (2 records dropped)
[3] Weeks 46 and 14 dropped (5 records dropped)

Table 22. Pooled crude and adjusted 2010/11 seasonal influenza vaccine effectiveness (IVE) against influenza A(H1N1) by age group, I-MOVE multicentre case-control study, influenza season 2010/11

Age group			N	IVE %	95% Confidence Interval
0-14 years[1]	Crude‡	Complete case analysis †	557	75.8	-9.5-94.6
		Imputed data*	910	63.1	-10.6-87.7
	Adjusted model 1∫	Complete case analysis †	557	82.0	-14.6-97.2
		Imputed data*	910	77.2	16.0-93.8
15-59 years[2]	Crude‡	Complete case analysis †	1655	33.0	-17.1-61.7
		Imputed data*	2051	41.4	1.7-65.1
	Adjusted model 1∫	Complete case analysis †	1655	20.9	-57.2-60.2
		Imputed data*	2051	27.2	-37.1-61.3
60+ years[3]	Crude‡	Complete case analysis †	262	70.8	37.4-86.4
		Imputed data*	350	72.5	47.7-85.5
	Adjusted model 1∫	Complete case analysis †	262	75.5	25.0-92.0
		Imputed data*	350	72.3	26.4-89.6

*Missing data imputed using imputation using chained equations† excluding individuals with missing values

‡ Study site included in the model as fixed effect

∫ Model adjusted for 2009/10 seasonal and pandemic influenza vaccination, presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, current smoker, age group (10 year bands), practitioners visits in previous 12 months (0-1, 2-4 and 5+ visits), week of symptom onset.

For certain analyses, data from some weeks had to be dropped due to only positive or negative outcomes during this week

[1] Weeks 12, 13 and 14 dropped (8 records dropped)
[2] Week 14 dropped (1 record dropped)
[3] Weeks 48,49 and 10-14 dropped (28 records dropped

Table 23. Pooled crude and adjusted 2010/11 seasonal influenza vaccine effectiveness (VE) against influenza B by age group, I-MOVE multicentre case-control study, influenza season 2010/11

Age group			N	IVE %	95% Confidence Interval
0-14 years[1]	Crude‡	Complete case analysis †	673	54.1	-27.5-83.5
		Imputed data*	1067	45.5	-30.1-77.2
	Adjusted model 1∫	Complete case analysis †	673	77.4	18.6-93.7
		Imputed data*	1067	63.0	-6.3-87.1
15-59 years[2]	Crude‡	Complete case analysis †	1155	69.0	23.0-87.5
		Imputed data*	1502	74.6	38.4-89.6
	Adjusted model 1∫	Complete case analysis †	1155	52.5	-46.3-84.6
		Imputed data*	1502	63.8	-3.9-87.4
60+ years[3]	Crude‡	Complete case analysis †	201	52.7	-13.6-80.3
		Imputed data*	345	47.6	-1.6-72.9
	Adjusted model 1∫	Complete case analysis †	201	60.6	-78.0-91.3
		Imputed data*	345	55.5	-38.2-85.6

*Missing data imputed using imputation using chained equations

† excluding individuals with missing values

‡ Study site included in the model as fixed effect

∫ Model adjusted for 2009/10 seasonal and pandemic influenza vaccination, presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, current smoker, age group (10 year bands), practitioners visits in the previous 12 months (0-1, 2-4 and 5+ visits), week of symptom onset

For certain analyses, data from some weeks had to be dropped due to only positive or negative outcomes during this week

[1] Week 13 dropped (4 records dropped)

[2] Week 49 dropped (14 records dropped)

[3] Weeks 46 and 50 dropped (14 records dropped)

Table 24. Pooled crude and adjusted influenza vaccine effectiveness (IVE) according to pandemic 2009/10 and seasonal 2010/11 influenza vaccination status, I-MOVE, multicentre case-control study, 2010/11

	Vaccination status	IVE %	95% Confidence Interval
Crude* (imputed dataset)	Vaccinated with pandemic vaccine 2009/10 only	14.9	-10.9-34.6
	Vaccinated with seasonal vaccine 2010/11 only	67.6	54.0-77.1
	Vaccinated with both vaccines	59.6	39.5-73.1
Adjusted† (imputed dataset)	Vaccinated with pandemic vaccine 2009/10 only	11.8	-17.3-33.7
	Vaccinated with seasonal vaccine 2010/11 only	59.1	36.3-73.8
	Vaccinated with both vaccines	44.0	7.8-66.0

*Study site included in the model as fixed effect

† Model adjusted for 2009/10 seasonal influenza vaccination, presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, current smoker, age group (10 year bands), practitioners visits in previous 12 months (0-1, 2-4 and 5+ visits), week of symptom onset.

Table 25: 2010/11 seasonal influenza vaccine effectiveness (IVE) against all influenza using one-stage and two-stage pooled models, I-MOVE multicentre case-control study, 2010/11

All influenza		N	IVE %	95% Confidence Interval
Total population	Complete case one-stage fixed effect pooled analysis[1,2]	4141	48.7	29.7-62.6
	Two-stage random effects pooled analysis[2,3]	4129	47.7	25.3-63.4
Target group for vaccination	Complete case one-stage fixed effect pooled analysis[1,4]	903	52.8	30.8-67.8
	Two-stage random effects pooled analysis[4,5]	885	57.1	16.4-78.0

Records dropped where missing values present for either current seasonal vaccination, age, onset month or chronic condition. All models adjusted for age group, month of onset and presence of chronic conditions.

[1] Study site in model as fixed effect

[2] Ireland excluded as no vaccinated cases (N=190)

[3] Hungary: April dropped (9 records); Romania: December dropped (2 records); Portugal: November dropped (1 record)

[4] Ireland excluded as no vaccinated cases (N=46)

[5] Portugal: March dropped (5 records); Hungary: April and December dropped (13 records)

Analysis restricted to the groups targeted for the seasonal 2010/11 vaccine

Of the 4,410 ILI patients included in the study 1,012 (23.0%) belonged to a group targeted for the seasonal 2010/11 vaccination: 381 influenza cases and 631 controls. Among the cases, 227 (59.6%) were positive for influenza A(H1N1) virus, 9 (2.4%) for influenza A(H3) virus, 11 (2.9%) were positive for influenza A virus that could not be subtyped and 134 (35.2%) were positive for influenza B virus.

Among 1,002 individuals with information on vaccination status and vaccination date for seasonal vaccination in 2010/11, 281 (28.0%) were vaccinated (ranging from 11% in Poland to 43% in Italy).

The characteristics for which cases and controls differed were the same among the target group for vaccination as among all the ILI patients included in the study. The only exceptions were that in the target group there were no differences in the proportion of cases and controls presenting with myalgia or sore throat (Table 26).

In the complete case database (Ireland excluded as no vaccinated cases), the Q test ($p=0.045$) and the I^2 index (53.4%) testing for heterogeneity between the individual VE estimates of the seven study sites using models adjusted for age, onset month and chronic disease suggested medium statistical heterogeneity between study sites.

The adjusted imputed IVE against all influenza was 56.2% (95% CI: 34.3-70.7) and 54.0% (95% CI: 6.6 – 77.3) in the 15-59 year age group (Table 27).

Adjusted IVE against A(H1N1) was 58.9% (95% CI: 32.0-75.1), and 63.4% (95% CI: 31.0-80.6) against influenza B (Table 27).

The two-staged random effects pooled analysis IVE estimate against all influenza was 57.1% and the one-stage complete case fixed effects analysis adjusted for the same covariates was 52.8% (Table 25).

Table 26. Characteristics of influenza cases and test-negative controls among the target group for vaccination, I-MOVE multicentre case-control study, influenza season 2010/11

Characteristics	Cases N=381	Test-negative controls N=631	p value
Median age	39	58	<0.001*
Age group - nº/total nº. (%)			
0-4	15/381 (3.9)	23/631 (3.6)	<0.001**
5-14	72/381 (18.9)	39/631 (6.2)	
15-59	181/381 (47.5)	266/631 (42.2)	
60+	113/381 (29.7)	303/631 (48.0)	
Female sex - nº/total nº. (%)	200/381 (52.5)	338/631 (53.6)	0.845**
Symptoms - nº/total nº. (%)			
Fever	362/380 (95.3)	565/628 (90.0)	0.003**
Headache	298/380 (78.4)	436/624 (69.9)	0.003**
Cough	356/381 (93.4)	544/628 (86.6)	0.001**
Shortness of breath	69/372 (18.5)	151/621 (24.3)	0.040
Days between onset of symptoms and swabbing – nº/total nº. (%)			
0	28/381 (7.3)	28/631 (4.4)	0.007**
1	160/381 (42.0)	256/631 (40.6)	
2	127/381 (33.3)	173/631 (27.4)	
3	35/381 (9.2)	86/631 (13.6)	
4	10/381 (2.6)	40/631 (6.3)	
5	16/381 (4.3)	27/631 (4.5)	
6	2/381 (0.5)	11/631 (1.7)	
7	3/381 (0.8)	10/631 (1.6)	
Diabetes - nº/total nº. (%)	29/338 (8.6)	90/575 (15.7)	0.002**
Heart disease	58/338 (17.2)	196/575 (34.1)	<0.001**
Any reported chronic disease	209/352 (59.4)	423/604 (70.0)	0.001
Smoker - nº/total nº. (%)			
Current	40/357 (11.2)	78/590 (13.2)	0.002
Former	37/357 (10.4)	107/590 (18.1)	
Never	280/357 (78.4)	405/590 (68.6)	
Pandemic vaccination 2009/10 nº/total nº. (%)	55/379 (14.5)	148/615 (24.1)	<0.001**
Seasonal vaccination, 2009/10 - nº/total nº. (%)	77/372 (20.7)	247/619 (39.9)	<0.001**
Number of visits to the practitioner in the previous 12 months			
0-1	118/364 (32.4)	100/608 (16.4)	<0.001**
2-4	96/364 (26.4)	189/608 (31.1)	
5+	150/364 (41.2)	319/608 (52.5)	

* Non parametric test of the median
**Two-sided Fisher's exact test

Table 27. Pooled crude and adjusted 2010/11 seasonal vaccine effectiveness against all influenza (by age group), against influenza A(H1N1) and against influenza B, among target group for vaccination, I-MOVE multicentre case-control study, influenza season 2010/11

Outcome	Age group			N	VE %	95% Confidence Interval
All influenza	**All ages**[1]	Crude‡	Complete case analysis †	832	64.7	48.4-75.8
			Imputed data*	1004	63.2	48.4-73.7
		Adjusted model [1]∫	Complete case analysis †	832	56.0	30.7-72.0
			Imputed data*	1004	56.2	34.3-70.7
	15-59 years ^	Crude‡	Complete case analysis †	388	62.4	26.4-80.8
			Imputed data*	447	67.6	37.9-83.1
		Adjusted model∫	Complete case analysis †	388	41.3	-38.1-75.1
			Imputed data*	447	54.0	6.6-77.3
	60+ years^[,2]	Crude‡	Complete case analysis †	308	49.3	8.4-71.9
			Imputed data*	413	52.7	23.3-70.9
		Adjusted model∫	Complete case analysis †	308	54.3	-6.1-80.3
			Imputed data*	413	62.8	32.8-79.4
A(H1N1)	**All ages** [3]	Crude‡	Complete case analysis †	633	69.8	51.4-81.2
			Imputed data*	780	71.1	55.4-81.3
		Adjusted model 1∫	Complete case analysis †	633	57.4	25.3-75.8
			Imputed data*	780	58.9	32.0-75.1
Influenza B	**All ages**[4]	Crude‡	Complete case analysis †	578	69.1	43.6-83.0
			Imputed data*	705	62.2	37.4-77.2
		Adjusted model 1∫	Complete case analysis †	578	70.2	36.7-86.0
			Imputed data*	705	63.4	31.0-80.6

† excluding individuals with missing values ‡ Study site included in the model as fixed effect*Missing data imputed using imputation using chained equations

∫ Model adjusted for pandemic influenza vaccination, presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, current smoker, age group (10 year bands), practitioners visits in previous 12 months (0-1, 2-4 and 5+ visits), week of symptom onset

^ Onset month used for adjusting instead of onset week.

[1] weeks 45, 13 and 14 dropped (8 records), [2] April dropped (3 records), [3] November and April dropped (5 records), [4] weeks 45 and 13 dropped (7 records)

V) DISCUSSION

The aim of the project was to develop a European network to monitor seasonal and pandemic IVE in EU/EAA. The network is set up and has been able to estimate IVE in three consecutive seasons. In 2009, the network was able to timely adapt the studies to the pandemic situation. Eight study sites conducted studies in the pilot phase and 11 in 2009/10 2010/11. In terms of communication, members of the network exchange information on a real time basis through the I-MOVE website. I-MOVE results have been published in peer-reviewed journals in each of the three seasons (115;118;120-130). I-MOVE is able to give estimates early in the season: during the pandemic, we communicated the first results to EU MS, ECDC, EC, EMA and WHO in early February 2010. In February 2011, early results of the 2010/11 seasonal vaccine from three I-MOVE study sites and from the multicentre case-control study were published (118;121;123;126). Results of the IVE studies undertaken by I-MOVE have assisted in guiding public vaccination policy at national and European level. In particular during the 2009 pandemic the results contributed to the risk benefit analysis process coordinated in the EU by the EMA (131) and globally by WHO (132) by providing regular updates of vaccine effectiveness estimates. In addition, I-MOVE estimates were incorporated as a component of post-licensure surveillance for the 2009 pandemic vaccines (133).

I-MOVE studies are conducted by an independent scientific research network, which adds weight to the integrity of their results and to how they are perceived both professionally and by the public.

I-MOVE is a unique platform for exchanging views and experience on methods to estimate IVE. During six technical workshops and three annual I-MOVE meetings (with participation of partners and international experts) the discussions around the epidemiological and logistical challenges have allowed improvement of standard methods, respect of good scientific practices and have further expanded EU expertise on IVE. Moreover, the establishment of the network has contributed to strengthen influenza surveillance in EU. Currently most of sentinel practitioners conducting I-MOVE studies use the same ILI case definition and swab patients in a systematic way. As most practitioners participating in I-MOVE are part of the national sentinel surveillance systems, all the improvement and standardisation of methods

achieved, should have a positive impact in the national and European influenza surveillance systems. Those sentinel networks participating in I-MOVE, have increased the number of naso-pharyngeal swabs collected and therefore, more specimens are submitted to the WHO Global Influenza Surveillance Network and to EISN.

Seventeen out of the 30 EU/EEA MS participate in the network. However, none of the Nordic countries is currently conducting IVE studies within I-MOVE. Including in I-MOVE IVE estimates from Nordic countries would give a better picture of the effectiveness of the influenza vaccine at European level. Finland being the only EU MS integrating the influenza vaccine in their childhood immunisation programme, it would be interesting to have an I-MOVE study site in Finland to estimate IVE in children.

The major challenge for the future of I-MOVE is how to make the network sustainable. While the IVE studies conducted are much less expensive than trials, they increase the costs of the sentinel surveillance undertaken by the participating practitioners. I-MOVE studies require accurate virus testing and careful coordination to retain quality. What has yet to be resolved is how to attract co-sponsorship from industry and public sectors while retaining independence. Some manufactures and regulators have expressed during the I-MOVE annual meetings the interest of having results from such studies and their willingness to contribute to the funding. However, a way of combining monies in a share scheme has yet to be achieved. The recent agreement for sustaining WHO's essential influenza surveillance work may be an example of the way forward (134).

5.1. Study designs and methodological issues to measure IVE on a routine basis in EU/EEA

The literature review indicated that IVE estimates depend among others on the specificity of the selected outcome for influenza, the influenza circulating strains and its incidence, the match between the vaccine and co-circulating strains. In addition, IVE is modified and confounded by various factors. IVE estimates are more accurate when studies include laboratory confirmed influenza outcome in at least a validation subset of the study participants, document vaccination status and collect detailed information to control for confounding or to stratify by effect modifier. EISN is a stable network with a long experience in detecting and reporting influenza cases. Its laboratory component enables having a

laboratory confirmed outcome and adding some questions to the data routinely collected by practitioners offers the possibility to collect information on vaccination status and potential confounding or effect modifiers factors. Therefore, EISN represents a sustainable simple and feasible framework to provide early IVE estimates and to monitor them across seasons. At EU MS level, the choice of the study design to measure IVE will depend on the data sources and resources available.

According to the results of the literature review, the European survey and the expert meetings, we developed generic protocols that were adapted by MS to measure IVE in Europe (106;107;135). During the three seasons, based on these generic protocols, I-MOVE partners have conducted cohort and case-control studies and, studies using the screening method.

One of the main limitations of I-MOVE is that the estimates are based on observational studies and therefore prone to bias (30). We tried to minimise these bias by using systematic sampling for the laboratory confirmed outcome and by collecting information to control for confounding factors. The experience of the first three seasons shows that the factors acting as confounders and their magnitude vary between seasons. Therefore, even if in one season one of the potential confounding factors does not affect the association between influenza and vaccination, it may be a confounder in the following seasons. Thus, the minimum variables recommended to control for confounding should be kept.

I-MOVE data are collected within influenza surveillance networks and has consequently the limitations inherent to studies based on surveillance systems. Compared to other observational research studies in which investigators are in charge of collecting data and paid for it, in I-MOVE, sentinel physicians conduct the studies during their routine practice: they collect influenza surveillance data and in addition, some other variables to document potential confounding factors or effect modifiers. To be acceptable, the data collection form has to be simple. The data quality is not perfect, but the completeness has improved (Table 7). The advantage of conducting the studies within existing surveillance networks is that the long-term sustainability is higher.

I-MOVE is currently based on national primary care sentinel networks participating in EISN and reporting ILI or ARI. However, whether a vaccine effective against ILI or ARI also protects against influenza complications should be verified and quantified. In a pandemic situation, if

health authorities advise against visiting a general practitioner when experiencing ILI or ARI, primary care practitioners may not be a good source to identify influenza cases. To better assess the effectiveness of the seasonal and pandemic influenza vaccines, monitoring of IVE should include the effect on severe outcomes. In I-MOVE, IVE against clinical severe outcomes is measured in study sites using computerised practitioners databases linked to hospital databases (England, Scotland and Navarra). IVE estimates against non-laboratory confirmed hospitalisation or death are prone to indication bias and to minimise it IVE should be estimated before, during and after the influenza season (100;101;109;136). In the cohort studies, influenza related hospitalisations are defined according to ICD and the quality of the diagnosis depends upon the completeness, validity and accuracy of the ICD codes for identifying influenza cases in persons hospitalised. In addition, the delay in updating the ICD codes in the hospital databases is long and IVE estimates against hospitalisations are generally available once the influenza season is over. In the same line, real-time information on deaths is rare. The cohort study in Navarra is the only I-MOVE study site able to provide early and repeated estimates of IVE against death and hospitalisations with laboratory confirmed influenza. Therefore, one of the current limitations of I-MOVE is that it does not provide early estimates of IVE against severe outcomes at European level. The main challenge to have IVE estimates against hospitalisations with laboratory confirmed influenza at European level would be to attain a sufficient sample size enabling precise adjusted estimates and stratification by effect modifiers. A European hospital network with multiple sites using the same protocol, would allow conducting a multicentre study with a sufficient sample size to rapidly estimate IVE against severe influenza clinical outcomes. As a first step towards this multicentre study, the I-MOVE network has developed a generic protocol for IVE hospital case-control studies. From the 2011-12, hospitals in various EU MS (e.g. Valencia region in Spain, France) will implement studies based on this protocol and will provide pooled estimates against hospitalisations with laboratory confirmed influenza.

I-MOVE studies are essential elements to assess the protective effect of a seasonal or pandemic vaccine in the general population. However, their results should be interpreted in the context of other pieces of evidence such as the degree of virological matching, the vaccine immunogenicity evaluated in animal and human studies, the vaccine efficacy measured in RCTs trials. Measuring and monitoring IVE will remain a major methodological

and operational challenge. Consequently, decisions to guide interventions should be based on a set of studies using different outcomes, methods and settings.

5.2. Influenza vaccine effectiveness estimates

In the season 2008/9 the match between the seasonal influenza vaccine and the predominant circulating strains was good (137). The country specific and the pooled IVE estimates suggested a protective effect of the 2008/9 seasonal vaccine in the elderly population in a year with a good match between the seasonal vaccine and the A(H3) strain predominantly circulating in Europe. Due to sample size limitations, we could not provide estimates by influenza type. During this pilot season, we confirmed that test-negative case-control studies based on sentinel practitioners were a feasible way to estimate seasonal IVE against laboratory-confirmed medically- attended influenza in Europe.

In the season 2009/10, we estimated the effectiveness of the 2009/10 pandemic and seasonal vaccines. The pooled results suggested that one dose of the pandemic vaccines used in the participating countries conferred good protection against medically-attended A(H1N1)2009 ILI (65.5% to 100% according to various stratifications performed).The pandemic IVE was higher in persons aged < 65 years old and in those without any chronic disease. The highest pandemic IVE was in children < 15 years old, with no vaccinated cases among the 455 individuals included in the complete case analysis and an adjusted pandemic IVE of 84.8% (95%CI 31.0-96.6) in the imputed data. Furthermore, the point estimates suggested a good pandemic IVE as early as eight days after vaccination. During the study period, the 2009/10 seasonal vaccine seemed to have had no effect on A(H1N1)2009 illness.
The main challenge during the pandemic was the time of availability of the vaccine. During normal influenza seasons, the vaccinations campaigns are done before the season starts and therefore, vaccination status is not a time dependent variable. During the pandemic, the pandemic vaccination campaigns started during the pandemic wave or after the peak of the pandemic (Figure 8). Time was associated with vaccination status and outcome (lower vaccination coverage and higher influenza incidence at the beginning the study). The vaccine coverage observed among controls increased over time. When splitting the study period, the adjusted pandemic IVE for early and late phase were above 68%. Further stratification of time was not possible due to small numbers.

As a consequence of the late availability of the vaccine, part of the population had acquired natural immunity before the start of the studies. If this natural immunity differed between those who would later be vaccinated and those who would not, this would have biased the pandemic IVE. Particularly if vaccinated persons had had a higher risk of infection before vaccination (e.g. children) we may have overestimated the pandemic IVE. We may not have totally controlled for this indication bias by adjusting for age and time of recruitment. Only a cohort study design including a sero-prevalence component at start of the study can help quantifying this bias, which is likely to affect all studies conducted during the pandemic.

In the season 2010/11 the I-MOVE multicentre case-control study based on sentinel practitioner networks from eight EU countries provided overall and stratified IVE estimates. The pooled results suggested a moderate adjusted IVE against medically attended ILI confirmed as influenza (range from 27.2% to 77.2%). The overall adjusted VE against A(H1N1) and influenza B did not differ substantially from the VE estimate against all influenza.

According to data reported by the EISN Community Network of Reference Laboratories for Human influenza in Europe, in 2010/11 there was a good match between the vaccine strain and circulating A and B viruses (138). The adjusted point VE estimates against all influenza and against A(H1N1)2009 virus were lower in the 15-59 year olds than in the 0-14 and 60 and above age groups. Age-specific VE estimates against influenza B virus did not vary substantially.

While some studies conducted in the 2010/11 season suggested a higher effect of the combined use of 2010/11 seasonal and 2009/10 pandemic vaccines (121;126;127), this was not observed in the I-MOVE multicentre case-control study. Adjusted VE against all influenza was around 12% for the 2009/10 pandemic vaccine, around 59% for the 2010/11 seasonal influenza vaccine and 44% for both vaccines together.

The vaccine with the highest VE was the monovalent pandemic vaccine while the VE for the 2008/9 season and the 2010/11 seasons were similar to those observed in non-pandemic seasons. Studies using a similar test-negative design have reported VE for the seasonal vaccine ranging from 34% to 92% in seasons of good vaccine match (89;111-113;139). The high VE we found for the pandemic vaccine corroborates the good immunogenicity results observed in clinical studies conducted earlier (140-143) and, are in line with studies conducted in Europe, US and Canada measuring the pandemic influenza vaccine

effectiveness against laboratory confirmed outcome (122;141;144-149). A recent meta-analysis reported a median vaccine effectiveness for prevention of medically-attended laboratory confirmed A(H1N1)2009 infection of 69% (range 60%-93%)(150). The high pandemic IVE could be explained by the excellent match between the circulating virus strain and the vaccine strain, by the relatively younger population vaccinated as compared with normal seasons or by an overestimation of the VE in 2009/10 as discussed above. The extensive use during the pandemic of adjuvanted vaccines for the first time in Europe could have also contributed to these high pandemic IVE. As in the I-MOVE multicentre study, other studies also reported a protective effect of the pandemic vaccine already eight days after vaccination (122;145). It would be interesting to assess if this is also observed for the seasonal vaccine. However, in I-MOVE study sites, most of the population receives the seasonal vaccine well before the start of the epidemic: in the 2008/9 season none of the study participants were vaccinated less than 14 days before symptom onset and in 2010/11 only 13 of them (4.5%). Therefore, it was not possible to measure the effect of the seasonal vaccine shortly after vaccination.

The methods, sample size, data quality and timeliness of the results have improved along the seasons. In the first season we could not estimate IVE by influenza virus type. In 2009/10 the pandemic strain was highly predominant (one B virus identified among all the study swabs) and therefore, our IVE estimates were specific for A(H1N1)2009. In 2010/11, the sample size allowed estimating IVE by influenza subtype and by age-group.

Limitations three seasons

Sample size and statistical power

During the three seasons, one of the main limitations of the studies was the sample size that limited statistical power for some of the stratified analysis. In 2008/9 season in which the study population was restricted to elderly, the incidence among this age group was low (151). During the pandemic season 2009/10, the vaccination coverage was low resulting in low number of vaccinated cases. In 2010/11 the vaccination coverage was low in the 0-14 and 15-59 age groups (2.2% and 4.2% respectively) and precise overall estimates were not possible. Sample sizes and number of cases were low among the target groups for vaccination in the 0-14 and 15-59 age groups and there was only one vaccinated influenza B case among 15-59 year olds in this group. Even if the sample size is still low for some sub-

analysis, the number of participating primary care practitioners and the number of patients recruited have increased along the seasons: 343 primary care practitioners in 2008/9 compared to 1,035 in 2010/11 and 327 ILI cases recruited in 2008/9 compared to 4,410 in 2010/11. The main challenge to increase the power of our studies is the low influenza vaccination coverage in most EU MS, that is far behind from the targets set by WHO and the European Council (25-27;116).

Identification target population

In 2008/9, as we restricted our study to the elderly population, all participants belonged to the target population for vaccination. During the pandemic, target groups were not offered vaccination at the same time (Annex III). Most sites did not include the necessary information to identify those groups and we could not restrict our analysis to groups and periods at which individuals became eligible for vaccination. We might therefore have included individuals for whom vaccination was not (or not yet) indicated. Consequently, we might have inflated the number of cases unvaccinated at the early phase of the study and overestimated the pandemic IVE. In 2010/11, we could restrict the analysis to the target population for seasonal 2010/11 vaccine.

Overall IVE estimates in the target population were similar to the estimates in the whole population. One limitation of the analysis restricted to the target population for vaccination is that study sites did not collect the variable "belonging to the target population" homogeneously. In some study sites not all information to identify target group for vaccination was available (mainly lack of information on people with professions that are targeted for vaccination). This may have resulted in not including some of the target population sub-groups in the restricted analysis. If the vaccine effectiveness in those subgroups were different to the vaccine effectiveness in the other target population individuals, our estimates may not be representative for the whole target population.

Type of vaccines

Various influenza vaccines are used across and within EU MS (Tables 10, 16). Most seasonal vaccines used are non-adjuvanted but some countries also recommend adjuvanted vaccines for some risk groups. During the pandemic adjuvanted-vaccines were used more frequently than during the normal seasons. In 2009/10 and in 2010/11, we collected the vaccine brand in an attempt to give estimates by type of vaccine (adjuvanted vs non-adjuvanted). The

limited sample size for some of the vaccines and the fact that some of them were recommended for specific target groups that we could not identify with the data collected, impeded having estimates by type of vaccine.

In summary, the results of the three first seasons suggest that the seasonal influenza vaccine is not among the vaccines with highest effectiveness. Research is needed to improve the effectiveness of the vaccine by identifying alternate production methods, increase or broaden the immune response, improve acceptability and delivery or develop population-specific vaccines or regimens (152).

5.3. Test-negative design

During the three seasons we used a case-control study using as controls ILI patients testing negative for influenza (test-negative design). The test-negative design (TND) is adapted to studies conducted within sentinel surveillance networks: sentinel practitioners swab routinely ILI/ARI patients and complete a short questionnaire for each of them. Therefore, recruiting ILI/ARI patients testing negative for influenza as controls does not represent any additional task. The additional work for practitioners recruiting cases for an IVE TND study would depend on the amount of additional information collected for each patient.

In TND cases and controls are selected independently of their case-control status. In influenza VE studies, ILI patients are included in the study irrespective of their influenza status. They are selected on clinical ground before laboratory confirmation. Provided that we adjust for time (week, month) of ILI onset, we can assume that controls are selected concurrently to laboratory confirmed influenza cases which would indicate that the TND approaches a density case-control study design in which the effect measured would be an incidence density rate ratio (114). The TND differs from it since former influenza cases are not excluded from potential controls (ILI testing negative). These individuals are no longer at risk of disease and should theoretically be excluded from the potential controls. Attempts have been made to exclude individuals with an ILI since the beginning of the study from the control group (74). However this exclusion of former ILI cases leads to the exclusion from the potential controls of many people with a previous ILI other than influenza. If their vaccination status differs from that of included ILI patients that test negative, the results would be biased.

Representativeness of test-negative controls

As in all case-control studies, the control group (in our case, influenza test-negative controls) should represent the exposure (influenza vaccination coverage) of the population giving rise to the cases. The question in our studies is which is the source population of the MA-ILI influenza confirmed cases. During the pilot season, to assess the representativeness of test-negative controls, we compared the vaccine coverage between different control groups: test-negative controls, patients consulting for other reasons than ILI, community controls. The vaccine coverage differed by control group and between countries with no specific pattern. This suggested that the source population of influenza cases consulting a primary care practitioner might be country specific. In general, the vaccine coverage in the community or in the practitioners´ catchment area was lower than the vaccine coverage of practitioners´ clients indicating that community controls do not represent a good control group for MA-ILI influenza cases. A random selection of patients consulting a GP for other reasons than ILI may better represent the source population. However, including this control group adds workload for practitioners who have to select and interview an additional group of patients.

Confounding in TND

In addition to its feasibility within surveillance networks, another advantage of the TND is that it provides IVE against a specific outcome and therefore minimises the amount of the existing confounding (153;154). To further limit the effect of potential confounding factors, we adjusted for most of those described as important in the literature.

In the 2008/9 season, the variables that changed the OR by more than 5% when entering them in the logistic regression model were “previous flu vaccination in the past 2 years” (change of -13.5%) and “hospitalisations for chronic diseases in the past 12 months” (change of -9.2%). In the season 2009/10 those variables were “age group” (change of -13.1%), “number of GP visits” (change of 5.3%), “month of onset of symptoms” (change of 36.8%), “seasonal influenza vaccination” 2009/10 (change of 5.7%). In 2010/11, the control group had a poorer health status than cases. However for all outcomes used, in the multivariable analysis the only covariates that changed the OR by more than 5% when omitted from the

full model were age group (-10.7%) and onset week (7.1%). This was similar in the target group for vaccination (age group -11.5%, onset week 8.0%).

Various studies suggest that ILI test-negative controls represent the source population of influenza cases seen at practitioners offices and that the study design adjusts for propensity to seek care (111;112;155). This would mean that the propensity to seek care is equal between ILI patients who test positive and those testing negative for influenza. In the second I-MOVE season, we collected information on number of visits to the practitioner in the previous year and, during the pandemic, this was one of the main confounding factors. Therefore, the TND does not completely adjust for health-seeking behaviour.

As in all observational studies, even if in I-MOVE we do all efforts to control for confounding, we cannot rule out the presence of residual confounding.

Selection bias in TND

In studies using the TND selection bias is minimised as practitioners do not know the case or control status of the ILI patients at time of recruitment. This does not prevent the selection bias that can arise if practitioners were more likely to swab vaccinated or unvaccinated ILI patients. A study in the USA assessed the potential bias introduced by differential diagnostic testing in IVE studies among children and concluded that physician testing behaviour was not influenced by patient vaccination status (156). In our multicentre case-control studies, the recruitment of an ILI patient was not left to the decision of the practitioners. In the 2008/9 season, practitioners swabbed all elderly ILI patients. In 2009/10 five out of the seven sites practitioners used systematic sampling to recruit and swab ILI patients. In Ireland, according to the study-site procedures, practitioners had to include five ILI patients per week without applying a systematic selection procedure. However, all the participating practitioners in Ireland recruited less than five cases per week suggesting that they recruited all patients consulting for ILI. In France, each practitioner recruited a specific age group for the study. Thus, ILI patients recruited may not have represented the age distribution of the ILI population consulting participating practitioners. This could have biased the IVE estimates if IVE differed by age group. However, ILI cases recruited in the study by French participating practitioners had the exact same age distribution than all ILI cases

consulting them. In 2010/11 seven of eight studies used systematic sampling to select patients to swab. In France practitioners continued to swab a specific age group.

Misclassification in TND

We observed shorter delays between onset of symptom and swabbing in cases than in controls. This was also observed in a study in Wisconsin (111). As the probability of influenza detection decreases with time since onset (157;158), we may have misclassified as controls some influenza cases who tested negative. If vaccinated cases develop milder illness and consult later, the vaccination coverage in the control group will be inflated resulting in a higher IVE. Similarly, if unvaccinated cases tend to consult their practitioner later due to their health seeking behaviour, the IVE will be underestimated. On the other hand, since cases are less likely to be vaccinated, the vaccine coverage among controls will decrease by having cases misclassified as controls and the IVE will be underestimated. Restricting the analysis to ILI patients tested within four days of onset of symptom limits this potential misclassification. In addition, in our studies, most of the ILI patients were swabbed less than four days after onset of ILI symptoms (80.7% in 2008/9, 94.0% in 2009/10 and 91.7% in 2010/11).

5.4. Multicentre case-control study

In the three seasons, study sites used a very similar protocol, case definition and a common set of variables in order to conduct a multicentre case-control study. Study sites not using the EU ILI case definition, collected symptoms and signs to allow reconstructing it.

Pooling of data

Due to the excellent collaboration between the participating study sites and the coordination centre, the pooling of data was feasible from the pilot phase onwards. Using a multicentre case-control approach, the sample size was big enough in February of 2010 and 2011 to provide early estimates. Compared to country estimates, the pooling of data allowed having more precise IVE estimates and conducting some subgroup analysis.

Even if study sites shared the same protocol, heterogeneity between studies may exist. Given the small samples sizes in most of the individual studies, we used a one-stage pooling

model that assumes that the effect of the exposure (the seasonal or pandemic vaccine) and the effect of the covariates are the same in all the studies. We do not know if the difference in virus circulation in the various countries and a potential different health-seeking behaviour may violate this assumption. In 2008/9 and 2009/10 the tests for interaction between study and covariates did not suggest the presence of heterogeneity. However, the small sample size may have led to an insufficient power to detect heterogeneity. A two-stage random effect model for pooling might be more appropriate for our analysis as it takes into account the potential heterogeneity between studies (40). In the first-stage of a two stage-model, studies are analysed one at a time for a better control of study-specific confounders. In the second stage, individual study-specific adjusted log-odds ratios are combined using a linear mixed-effects model to provide a pooled estimate.

In 2010/11, as a sensitivity analysis, we carried out a two-stage pooled analysis but due to limitations in sample size, we only included the potential most important confounders. The IVE estimates were very similar to those of the one-stage pooled analysis suggesting that the one-stage model was appropriate. While analyses using the whole population showed no significant heterogeneity, the results suggested medium heterogeneity between study sites when restricting to the target group for vaccination. Upon exclusion of one country (Italy), heterogeneity was neither present overall nor in any subgroups and all IVE estimates were higher. Detailed investigation into information or selection bias between Italy and other study sites yielded no results. We therefore included Italy in the IVE estimates assuming that a one-stage model was still appropriate. In the future, a higher sample size will be sought among the target groups for vaccination in order to carry out a two-stage random effects pooled analysis adjusted for more covariates to further validate the appropriateness of the one-stage fixed effect pooled analysis in this population and overall.

Missing values / imputation

Missing values remain a limitation in observational studies based on surveillance data. In our studies, missing values for certain covariates were associated with the outcome and with the pandemic vaccination and therefore we could not assume that our missing values fell into the category of Completely Missing At Random (MCAR) (39). To reduce the potential bias associated with missing values, from the season 2009/10 we used a method of multiple imputation by chained equations procedure in which values are imputed

according to associations observed between many other variables (including confounders) and the missing variable. We were able to use a large number of variables for the imputation, including key variables such as week of symptom onset, outcome, study site, and vaccination variables. However, the objective in the future should be to have the most complete dataset for all variables. In 2010/11 the proportion of missing values was much lower than in the pandemic season (table 7).

VI) CONCLUSIONS

1) Estimating influenza vaccine effectiveness on a routine basis and having early within season estimates is feasible in the European Union.

2) I-MOVE contributes to strengthen information exchange between European member states and to standardise surveillance methods.

3) I-MOVE is an excellent example of collaboration between scientists that allows the improvement of methods to measure influenza vaccine effectiveness within influenza surveillance networks.

4) The scientific knowledge and experience in practical, managerial and logistical issues gained by the network, can be used to develop monitoring of the effectiveness of other vaccines like rotavirus vaccine, pneumococcal vaccine, etc.

5) I-MOVE is based on European sentinel surveillance networks that provide an excellent framework to conduct observational vaccine effectiveness studies using different study designs (cohort, case-control, and screening method).

6) Sentinel surveillance networks allow measuring influenza vaccine effectiveness against laboratory confirmed outcome and, by adding some variables to control for positive and negative confounding, the limitations inherent to observational studies are minimised.

7) The I-MOVE studies use scientifically sound methods providing essential elements to assess the protective effect of the seasonal and pandemic vaccine.

8) I-MOVE results should be interpreted in the context of other pieces of evidence such as the degree of virologic matching and the vaccine immunogenicity evaluated in animal and human studies.

9) The high effectiveness of the pandemic vaccine suggests that, during pandemics, the vaccines may be more effective due to the probable excellent match between the pandemic virus and the monovalent pandemic vaccines. However, the timeliness of availability of the pandemic vaccine in the population will always be a challenge.

10) Vaccine effectiveness was lower in non-pandemic seasons. Even if seasonal influenza vaccines do not provide a complete protection against medically-attended influenza-like illness laboratory confirmed, they are currently considered the most effective preventive measure available against influenza infections.

11) The test-negative design used in the multicentre study is a simple method, requires fewer resources than case-control studies using other controls, and therefore is adapted for monitoring IVE in the long term.

12) As in all case-control designs, the test-negative control group should represent the population giving rise to the cases. Further studies are needed to validate in each of the I-MOVE study sites, the representativeness of the test-negative controls.

Recommendations

Recommendations to strengthen the I-MOVE network

To strengthen the I-MOVE network, we recommend to:

- improve the representativeness of the IVE estimates by including study sites from Nordic EU/EEA countries;
- monitor IVE against severe outcomes laboratory confirmed by developing a European hospital network to conduct multicentre studies;
- continue building expertise in influenza vaccine effectiveness by maintaining the exchanges among EU/EEA experts and international experts;
- further integrate other pieces of evidence with I-MOVE results to better guide public health decisions (virological data, immunogenicity studies, adverse events, etc);
- identify a mechanism for establishing a public private co-sponsorship for influenza vaccine effectiveness studies that ensures the scientific independency of the investigators.

Recommendations to strengthen the robustness of the results

To continue strengthening the robustness of the I-MOVE results, we recommend to:

- continue
  - conducting studies using different outcomes, methods and settings,
  - including laboratory outcome selecting systematically patients to swab,
  - collecting the variables needed to control for main confounding factors;
- increase the sample size in each of the case-control study sites to
  - have precise IVE estimates by study site,
  - increase precision in the IVE estimates by influenza type and subtype, age group and risk groups,
  - provide IVE by type of vaccine,

  - take better into account each study site variability by pooling data from all study sites using a two-stage random effects model;
- improve data quality by
  - developing a generic protocol to assess data quality at study site level,
  - minimising the proportion of missing data through training of the practitioners participating in the study;
- collect in a standardised way the information needed to identify target population for influenza vaccination in order to have specific IVE estimates for the target population.

Recommendations for future research

In terms of additional studies needed and research, we recommend to

- using electronic primary care databases, assess representativeness of the test-negative controls by comparing
  - the vaccination coverage and distribution of confounding factors of various control groups (e.g. test-negative controls, random sample of practitioners patients, random sample of patients consulting for non-ILI related symptoms),
  - IVE estimates against laboratory confirmed outcome using a cohort and a case-control design;
- to better control for the potential difference in health seeking behaviour of vaccinated and unvaccinated individuals, describe differences in those two groups
  - within electronic primary care databases with information on the vaccinated and unvaccinated population, describe health seeking behaviours in those two populations;
- to quantify the potential bias introduced in IVE against laboratory outcomes by not using systematic swabbing
  - study sites having systematic and non-systematic sampling, can compare the IVE estimated using both sampling procedures;

- to evaluate the effect of natural or previous influenza vaccines immunity in IVE through serological surveys;
- research groups or vaccine manufacturers to identify ways to improve the effect of the vaccine including modifying the composition, the dosage, or the administration procedures to increase the impact of the vaccination policies.

VII) CONCLUSIONES EN ESPAÑOL

1) Es posible obtener estimaciones de la EV antigripal de forma rutinaria y con datos tempranos en cada temporada de gripe en la UE.

2) I-MOVE contribuye a reforzar el intercambio de información entre los EEMM y a estandarizar los métodos de vigilancia.

3) I-MOVE es un ejemplo excelente de colaboración entre científicos, que permite mejorar los métodos de estimación de la efectividad de las vacunas antigripales utilizando redes de vigilancia de gripe.

4) El conocimiento científico y la experiencia en los aspectos prácticos, de gestión y logística obtenidos con esta red pueden servir de ejemplo para desarrollar métodos para medir la efectividad de otras vacunas como las vacunas contra el rotavirus, vacunas contra el neumococo, etc.

5) I-MOVE se basa en las redes de vigilancia de gripe centinela de Europa, que constituyen un marco excelente para realizar estudios observacionales de EV antigripal utilizando distintos diseños de estudio (cohortes, casos y controles o método screening).

6) Las redes de vigilancia centinela permiten medir la EV antigripal frente al síndrome gripal confirmado por laboratorio y, al añadir la recogida de algunas variables para controlar los factores de confusión positivos y negativos, se reducen algunas de las limitaciones de los estudios observacionales.

7) Los estudios I-MOVE utilizan métodos científicamente probados que proporcionan elementos esenciales para evaluar el efecto protector de la vacuna estacional y pandémica.

8) Los resultados de I-MOVE deben ser interpretados en el contexto de otras evidencias, como el grado de concordancia virológica y la inmunogenicidad de la vacuna evaluada en estudios con animales y seres humanos.

9) La elevada efectividad de la vacuna pandémica indica que, durante la pandemia, las vacunas pueden ser más eficaces, ya que la concordancia entre el virus pandémico y las vacunas pandémicas monovalentes es, probablemente, excelente. No obstante, el tiempo necesario desde la identificación del virus hasta tener disponible la vacuna pandémica para la población supone un reto.

10) La EV antigripal fue menor en las temporadas interpandémicas. Aunque las vacunas antigripales no proporcionen una protección completa frente al síndrome gripal confirmado por laboratorio, se consideran la medida preventiva más eficaz disponible para prevenir la gripe.

11) Comparado con otros estudios de casos y controles, el DTN es más simple, requiere menos recursos y por tanto es más adecuado para estimar la EV antigripal de manera continua y a lo largo de las diferentes temporadas de gripe.

12) Al igual que sucede con todos los estudios de casos y controles, el grupo control con test negativo debería representar la población que da origen a los casos. Se necesitan estudios para validar la representatividad de los controles con test negativo en cada uno de los centros de estudio de la red I-MOVE.

Recomendaciones

Recomendaciones para reforzar la red I-MOVE

Para reforzar la red I-MOVE, recomendamos:

- mejorar la representatividad de las estimaciones de la EV antigripal incluyendo en el futuro centros de estudio de países nórdicos de la UE/EEE;
- estimar la EV antigripal frente a casos graves confirmados por laboratorio, desarrollando para ello una red de hospitales en Europa que lleve a cabo estudios multicéntricos;
- continuar acumulando experiencia en la evaluación de la efectividad de la vacuna antigripal, manteniendo el intercambio científico tanto entre expertos de la UE/EEE como entre expertos internacionales;
- integrar otras evidencias en los resultados de la red I-MOVE que permitan orientar mejor las decisiones de salud pública (datos virológicos, estudios de inmunogenicidad, efectos adversos, etc.);
- identificar un mecanismo de financiación a largo plazo para establecer un fondo europeo con aportaciones públicas y privadas, regido por reglas que aseguren la independencia científica de los investigadores y de los resultados.

Recomendaciones para reforzar la robustez de los resultados

Para seguir reforzando la robustez de los resultados de la red I-MOVE, recomendamos:

- continuar
    - realizando estudios con diferentes criterios de valoración, métodos y en diferentes centros de estudio,
    - incluyendo resultados de laboratorio con una selección sistemática de los pacientes de los que se obtiene un frotis,

- recogiendo las variables necesarias para controlar los factores de confusión principales;

- aumentar el tamaño de la muestra en cada centro de estudio de casos y controles, para
  - disponer de estimaciones precisas de la EV antigripal en cada centro de estudio,
  - aumentar la precisión de las estimaciones de la EV antigripal en función del tipo y subtipo de gripe, grupo de edad y grupos de riesgo,
  - proporcionar la EV antigripal en función del tipo de vacuna,
  - utilizar un modelo de efectos aleatorios que integre mejor la variabilidad de cada centro de estudio en los resultados del estudio multicéntrico;

- mejorar la calidad de los datos
  - desarrollando un protocolo genérico para evaluar la calidad de los datos a nivel de cada centro de estudio,
  - reduciendo la proporción de datos perdidos mediante la formación de los médicos que participan en el estudio;

- recoger de forma estandarizada la información necesaria para identificar la población para la que está recomendada la vacunación antigripal, con el fin de medir la EV antigripal en esta población.

Recomendaciones para futuros proyectos de investigación

En cuanto a otros estudios e investigaciones necesarios, recomendamos:

- utilizar las bases de datos electrónicas de atención primaria, para evaluar la representatividad de los controles con test negativo comparando
  - la cobertura vacunal y la distribución de los factores de confusión de varios grupos control (por ejemplo, controles con test

negativo, muestras aleatorias de pacientes de cada médico o muestras aleatorias de pacientes que consultan por síntomas no relacionados con un síndrome gripal),

- las estimaciones de EV antigripal frente a gripe confirmada por laboratorio utilizando un diseño de cohorte y un diseño de casos y controles;

- controlar mejor las posibles diferencias en el patrón de utilización del sistema sanitario de los sujetos vacunados y no vacunados, describir las diferencias entre ambos grupos
  - utilizando las bases de datos electrónicas de atención primaria con información sobre la población vacunada y no vacunada, describir la frecuentación de servicios de atención sanitaria en ambas poblaciones;

- cuantificar el sesgo potencial en la estimación de la EV antigripal frente a gripe confirmada por laboratorio introducido por una selección no sistemática de la muestra de pacientes con síndrome gripal de los que se obtiene un frotis
  - comparando en los centros de estudios que utilizan ambos procedimientos de selección, las EV antigripales obtenidas con una selección de la muestra de pacientes sistemática y no sistemática;

- a través de encuestas serológicas evaluar cómo influye en las estimaciones de EV antigripal la inmunidad adquirida mediante la infección natural o la administración de vacunas antigripales en temporadas anteriores;
- los grupos de investigación y los fabricantes de vacunas deberían identificar la forma de mejorar el efecto de la vacuna, por ejemplo mediante modificaciones de su composición, posología o procedimiento de administración, con objeto de aumentar el impacto de los programas de vacunación antigripal.

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Annex I: European Survey data collection

Survey:
Monitoring vaccine effectiveness during seasonal and pandemic influenza
in EU/EAA Member States
Data to be collected at country level

Member State name:

Date data collection:

I) Influenza Vaccine effectiveness studies

1.1. Studies already conducted in the country (up to 1998)

Identification of studies conducted and short description:

- Year
- Institution (Public Health Institute, University, etc)
- Study design
- Study population (age group, geographical area, risk group)
- Source of cohort/cases/controls
- Outcome(s)
- Vaccine ascertainment
- Data collected (confounding factors)
- Results

(ask for a copy of report/article if available)

1.2. Studies planned in the country

- Institution
- Study design
- Study population (age group, geographical area, risk group)
- Source of cohort/cases/controls
- Outcome(s)
- Vaccine ascertainment
- Data collected (confounding factors)

II) Influenza surveillance system

2.1. Sentinel surveillance system existing in the country:

- Validate information available at EISS (case definition, number of GPs, representativity, proportion of samples sent to lab, proportion of positive samples, surveillance period)
- Ask if the system has been evaluated recently

3.2. Other surveillance systems:

- Short description (case definition, data source, data collected)

(ask for a copy of reports/articles describing the systems if available)

III) Other potential sources for case identification (morbidity, mortality)

- Identify databases that could be used to estimate cases/numerator (e.g. population registries, GP databases, hospital databases, mortality registries, etc) and describe shortly.
  - Data sources and representativity
  - Data collected
  - Possibility to link various databases (unique identifier?)
  - Conditions of accessibility
  - Timeliness of information

(Ask if there are documents, webpages, articles describing them).

IV) Vaccination data (registries, surveys, etc)

- Validate the information recently collected by VENICE project.
  - Method to estimate Influenza vaccine coverage
  - Source of data: health medical records, survey, register
  - Population targeted (whole population, specific groups)
  - Timeliness of estimates (when are the estimates available? How often is the coverage estimated?)

Annex II: Lists of experts responding to the European survey and participating in the expert meetings (2008)

A) Experts responding to the European survey, January-March 2008

Austria
Reinhild Strauss
Michael Kunze
Livia Borsoi
Monika Redlberger
Theresa Popow-Kraupp

Belgium
Sophie Maes
Françoise Wuillaume

Czech Republic
Jan Kyncl

Denmark
Anne Mazick

Estonia
Olga Sadikova

Finland
Tuija Leino

France
Daniel Levy Bruhl
Isabelle Bonmarin
Sophie Vaux
Jean Marie Cohen
Anne Mosnier

Germany
Udo Buchholz
Helmut Uphoff

Greece
Helena Maltezou

Hungary
Ida Czumbel

Ireland
Joan O'donnell
Lisa Domegan

Italy
Caterina Rizzo
Fortunato Paolo Dancona

Latvia
Jurijs Perevoscikovs
Raina Nikiforova

Lithuania
Nerija Kupreviciene

Malta
Tanya Melillo
Gianfranco Spiteri

Norway
Preben Aavistland

The Netherlands
Fredericka Dijikstra
Marianne Van der Sande
Ioannis Karagiannis

Portugal
Helena Rebelo Andrade
Maria João Branco
Teresa Contreiras
Jose Marinho Falcão
Zilda Mendes
Baltazar Nunes

Romania
Viorel Alexandrescu
Claudiu Sbarcea

Slovakia
Margareta Sláciková

Lucia Hrivniaková
Judita Gabíková

Slovenia
Maja Socan
Margareta Sláciková
Lucia Hrivniaková
Judita Gabíková

Spain
Amparo Larrauri
Salvador de Mateo

Sweden
Annika Linde
Ake Ortqvist

United Kingdom
Alex Eliott
Douglas Fleming
Jim McMenamin (Scotland)
Richard Pebody
Jonathan Van Tam

B) Experts participating in the expert meetings, April-June 2008

Preben	Aavitsland	Norvegian Institute of Public Health, Oslo	Norway
Isabelle	Bonmarin	Institut de Veille Sanitaire, Paris	France
Udo	Buchholz	Robert Koch Institute, Berlin	Germany
Jesús	Castilla	Public Health Institute, Pamplona	Spain
Bruno	Ciancio	ECDC, Stockholm	Sweden
Jean-Marie	Cohen	Open Rome, Paris	France
Ida	Czumbel	National Center for Epidemiology	Hungary
Alex	Elliot	Birmingham Reserach Unit of the Royal College of General Practitioners, Birmingham	United Kingdom
Joanne	Enstone	Nottingham University, Nottingham	United Kingdom
José Marinho	Falcao	Instituto Nacional de Saude Dr Ricardo Jorge, Lisbon	Portugal
Douglas	Fleming	Birmingham Reserach Unit of the Royal College of General Practitioners, Birmingham	United Kingdom
Johan	Giesecke	ECDC, Stockholm	Sweden
Amparo	Larrauri	Instituto de Salud Carlos III, Madrid	Spain
Tuija	Leino	National Public Health Institute, Helsinki	Finland
Daniel	Levy-Bruhl	Institut de Veille Sanitaire, Paris	France
Annika	Linde	Smittskiddsinstitutet, Stockholm	Sweden
Helen	Maltezou	KEEL, National Institute of Health, Athens	Greece
Punam	Mangtani	London School of Hygiene & Trompical Medicine, London	United Kingdom
Anne	Mazick	Statens Serum Institut, Copenhagen	Denmark
Jim	McMenamin	Health Protection Scotland, Glasgow	United Kingdom
Anne	Mosnier	Open Rome, Paris	France
Alain	Moren	EpiConcept, Paris	France
Angus	Nicoll	ECDC, Stockholm	Sweden
Baltazar	Nunes	Instituto Nacional de Saude Dr Ricardo Jorge, Lisbon	Portugal
Joan	O'donnell	Health Protection Surveillance Centre, Dublin	Ireland
Ake	Ortqvist	Karolinska Intitute, Stockholm	Sweden
John	Paget	EISS, Amsterdam	The Netherlands
Richard	Pebody	Health Protection Agency, London	United Kingdom
Joan	Puig-Barberá	Centre Salut Publica Castello, Valencia	Spain
Caterina	Rizzo	Istituto Superiore di Sanitá, Rome	Italy
Camelia	Savulescu	Instituto de Salud Carlos III, Madrid	Spain
David K	Shay	CDC, Atlanta	USA
François	Simondon	SPMSD-EU, Lyon	France
Helmut	Uphoff	Centre for Health Protection, State of Hesse	Germany
Marta	Valenciano	EpiConcept, Paris	France
Marianne	Van der sande	Epidemiology and Surveillance, RIVM, Bilthoven	The Netherlands
Jonathan	Van tam	Nottingham University, Nottingham	United Kingdom
Todd	Weber	ECDC, Stockholm	Sweden
Françoise	Wuillaume	Scientific Institute of Public Health, Louis Pasteur, Brussels	Belgium

Annex III: Target groups for pandemic vaccination in I-MOVE study sites countries, 2009/10

Target groups for pandemic vaccination and date of start of the vaccination campaign by country study-site, I-MOVE multicentre case-control study, influenza season 2009/10.

Country	Target group for pandemic vaccination 2009/10	Date of start
France	Hospital health care workers	20/10/2009
	Primary care health care workers	02/11/2009
	High-risk people for seasonal influenza (6 months - 64 years) People with morbid obesity (6 months - 64 years) Professionals working with children under 3 years Other care professionals Household members of high-risk children under 6 months	12/11/2009
	Pregnant women (2nd and 3rd trimester) Non high-risk children 6-23 months	20/11/2009
	Secondary school children	25/11/2010
	Primary school children High-risk people for seasonal influenza > - 64 years	Early December
	Rest of the population, beginning with the youngest	15/12/2010
Hungary	People aged over 12 months with chronic underlying conditions that put them at risk for severe disease. Underlying conditions, considered to be risk factors: - Chronic lung diseases, including moderate or severe asthma - Severe obesity or those with impaired lung function due to neuromuscular diseases - Cardiovascular diseases, except for well-treated hypertension - Congenital or acquired immune deficiency (included HIV-positives, or those suffering from malignant tumour) - Chronic diseases of the liver or kidney - Chronic metabolic disorders, including diabetes mellitus Pregnant women Health Care Workers Institutionalised people People working in the central command and control structures, home security services and essential services, critical infrastructure	29/09/2009
	Healthy children from 12 months to 18 years of age attending to kindergarten or school People older than 18 living in a dormitory Workforce of the educational institutions Household contacts and caregivers of children younger than 12 months of age	02/11/2009

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Country	Target group for pandemic vaccination 2009/10	Date of start
Ireland	At-risk groups aged 6 months up to 65 years of age Pregnant women in the 2nd and 3rd trimester and up to 6 weeks post partum or in the 1st trimester with an additional risk factor Immunosuppressed individuals and household contacts of individuals with immunosuppression Residents of disability units regardless of whether they are in one of the medically at risk groups Individuals with significant physical or intellectual disability (including neurodevelopment conditions)	19/10/2009
	Health care staff Children aged 6 months – 5 years	09/11/2009
	Household contacts of children aged less than 6 months Children aged 5 – 18 years Adults aged 65 years and over	30/11/2009
	All other groups	01/02/2010
Italy	Health care personnel, personnel connected with essential services, Persons ≤65 with underlying conditions at high risk of severe or fatal complications due to influenza Pregnant women, Healthy children and adolescents aged between 2–18 years	Variable across regions, starting on 12/10/2009
	Healthy adults Elderly with chronic diseases	7/12/2009
Portugal	Essential services, pregnant women individuals with chronic diseases 6 months – 65 years Essential services; Pregnant women, in the 2nd and 3rd trimester ; Individuals with morbid obesity; Individuals with asthma 6 months-65 years; Individuals with chronic respiratory disease, neuromuscular disease and immunosuppression from all ages.	26/10/2009
	+ Priority to children between 6 months – 2 years and individuals with chronic diseases 6 months – 65 years	16/11/2009
	All children > 6 months – < 12 years.	17/12/2009
Romania	Health care workers Essential services School children over 16 years Students Teachers	26/11/2009
	All people aged over 16 years with priority to people with chronic diseases and pregnant women	16/12/2010
Spain	People over six months of age belonging to high risk groups including obesity and pregnant women a any time of pregnancy Essential civil services Care givers of high risk persons	16/11/010

Annex IV: Target groups for seasonal vaccination in I-MOVE study sites countries, 2010/11

Target groups for 2010/11 seasonal vaccination and date of start of the vaccination campaign by country study-site, I-MOVE multicentre case-control study, influenza season 2010/11.

Country	Target group for seasonal vaccination 2010/11	Date of start
France	People aged over 64 years Health care workers Children and teenagers taking salicylates People working in residential care and occupational groups who can transmit influenza to high-risk patients Household members of high-risk children under 6 months (People working in travel area (guides, airplane crews…) People living in a long term care facility	23/09/2010
	Pregnant women People with Body Mass Index $\geq$ 30	29/12/2010
Hungary	People aged over 64 years People aged over 12 months with chronic underlying conditions that put them at risk for severe disease. Underlying conditions, considered to be risk factors: lung disease, heart disease, diabetes and endocrine diseases, hematologic cancer, chronic hepatic disease, immunodeficiency and organ transplant, cancer, renal disease, obesity Health Care Workers	25/10/2009
Ireland	People aged over 64 years Those older than 6 months of age with chronic illness requiring medical follow-up (e.g. chronic respiratory disease including moderate or severe asthma, chronic heart) Immunosuppression due to disease or treatment, including asplenia or splenic dysfunction Children on long-term aspirin therapy Children with any condition (e.g. cognitive dysfunction, spinal cord injury, seizure disorder or other neuromuscular disorder) that can compromise respiratory function, especially those attending special schools/day centres People with Body Mass Index $\geq$ 40 Residents of nursing homes, old people's home and other long-stay facilities where rapid spread is likely to follow introduction of infection People likely to transmit influenza to a person at high risk for influenza complications (including household contacts and out-of-home care givers) Health Care Workers People who have close, regular contact with pigs, poultry or water fowl Pregnant women with chronic medical conditions requiring regular follow up or who are immunocompromised due to disease or treatment at any stage of pregnancy Pregnant women at any stage of pregnancy and up to six weeks post partum who are not in a medically at risk group and who have not already received pandemic (H1N1) 2009 vaccine.	06/10/2010

ANNEX IV

Country	Target group for seasonal vaccination 2010/11	Date of start
Italy	People aged over 64 years Health care personnel Essential services personnel (police, firemen, military corps, etc.) Pregnant women in their 2nd and 3rd trimester of pregnancy Women who delivered < 6 months before or person who takes care of the baby Individuals with at least one chronic underlying conditions in the age group 6 months-65 years Children aged >6 months attending day-care centres Children <18 years resident in long-term care facilities	01/10/2010
Poland	People aged over 55 years People with chronic disease Healthy children above 6month and below 18 years old	25/10/2010
Portugal	People aged over 64 years People with underlying chronic diseases	22/09/2010
Romania	People aged over 64 years Health Care workers Pregnant women Institutionalised persons People with underlying chronic diseases HIV infected persons	01/11/2010
Spain	People aged over 64 years or over 59 years (depending on the region) People over six months of age belonging to high risk groups including obesity and pregnant women at any time of pregnancy Essential civil services Care givers of high risk persons Health Care Workers	03/10/2010