Efficacité post autorisation de mise sur le marché de la vaccination antigrippale saisonnière contre l'hospitalisation avec une grippe confirmée virologiquement chez l'adulte en Europe

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Efficacité post autorisation de mise sur le marché de la vaccination antigrippale saisonnière contre l'hospitalisation avec une grippe confirmée virologiquement chez l'adulte en Europe

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RESUME

Efficacité post autorisation de mise sur le marché de la vaccination antigrippale saisonnière contre l'hospitalisation avec une grippe confirmée virologiquement chez l'adulte en Europe

Introduction

Les stratégies de vaccination contre la grippe saisonnière en Europe ont pour objectif de prévenir les cas sévères de grippe. La conduite d'essais cliniques parmi les groupes à risque de grippe sévère est à ce jour impossible pour des raisons éthiques. Le premier objectif de cette thèse était de mesurer en Europe, parmi les adultes, l'efficacité des vaccins (EV) saisonniers contre l'hospitalisation avec une grippe confirmée en laboratoire par (sous)type, groupe d'âge, co-morbidités et vaccinations anti-grippales passées. Le second objectif était de faire une revue et une méta-analyse des résultats publiés sur l'EV contre l'hospitalisation avec une grippe confirmée en laboratoire chez l'adulte dans le monde.

Méthode

En 2011, nous avons développé un protocole d'étude générique reposant sur un schéma d'étude cas-témoins de type « test-négatif » (TND). Ce protocole a été mis en œuvre entre 2011 et 2017 au cours de chaque saison grippale par un réseau d'hôpitaux localisés dans 12 pays européens. Un prélèvement naso-pharyngé était réalisé chez tous les patients adultes hospitalisés (uniquement âgés de 65 ans et plus en 2015-16 et 2016-17) avec des signes compatibles avec une infection respiratoire aigüe sévère. Une PCR spécifique par type et sous type de virus a été réalisée sur les échantillons prélevés. Nous avons comparé les cotes de la vaccination parmi les patients testant positifs et négatifs et calculé l'EV (1-rapport de cotes). A l'aide d'une régression logistique, nous avons ajusté les estimations d'EV sur la date de survenue des symptômes, le site d'étude, l'âge et les maladies chroniques sous-jacentes. Nous avons mesuré l'EV stratifiée par groupe d'âge, présence de certaines maladies sous-jacentes et vaccinations passées (au cours de deux saisons précédentes).
Pour la revue de littérature, nous avons inclus, après recherche sur Pubmed (01/2009 à 11/2016), les études mesurant l'EV à partir d'un schéma TND à l'hôpital. Nous avons effectué une méta-analyse en utilisant des modèles à effets aléatoires.

Résultats

Entre 2011-12 et 2016-17, nous avons recruté 3436 cas confirmés de grippe et 5969 témoins. Sur l'ensemble des saisons incluses, l'EV contre tous types de virus grippal confondus était de 26% (Intervalle de Confiance à 95% (IC95%):18;33) elle était de 40% chez les 18-64 ans, 25% chez les 65-79 ans et 23% chez les 80 ans et plus. Par saison, l'EV variait entre 15% (IC95%: -3;29) en 2016-17 et 44% (IC95%: 21;60) en 2013-14.
L'EV contre la grippe A(H1N1)pdm09 était 46% (IC95%: -3;72), 32% (IC95%:7;50) et 39% (IC95%:6;61) chez les patients âgés de 18-64, 65-79 et ≥80 ans respectivement. L'EV contre la grippe A(H3N2) était 28% (IC95%: -14;54), 24% (IC95%: 7;37) et 22% (IC95%: 6;35) chez les patients âgés de 18-64, 65-79 et ≥80 ans respectivement. L'EV contre la grippe B était 66% (IC95%: 19;86), 38% (IC95%: 11;57) et 46% (IC95%: 18;65) chez les patients âgés de 18-64, 65-79 et ≥80 ans respectivement.
L'EV n'était pas inférieure chez les patients atteints de maladies chroniques cardiaques ou respiratoires, de diabète ou de cancer.
Entre 2011 et 2016, parmi les patients âgés de 65 ans et plus non vaccinés au cours des deux saisons précédentes, l'EV de la saison en cours était 30% (IC95%:-35;64), 8% (IC95%:-94;56) et 33% (IC95%:-43;68) contre la grippe A(H1N1)pdm09, A(H3N2) et B respectivement. Parmi les patients vaccinés au cours des deux saisons précédentes, l'EV de la saison en cours était -1% (IC95%:-80;43), 37% (IC95%:7;57) et 43% (IC95%:1;68) contre la grippe A(H1N1)pdm09, A(H3N2) et B respectivement.
Dans la revue de la littérature, nous avons identifié 3411 publications, dont 30 répondaient à nos critères d'inclusion. Entre 2010-11 et 2014-15, l'EV combinée était de 41% (IC95%: 34; 48) contre tous types de virus (51% (IC95%: 44; 58) chez les 18 à 64 ans et 37% (IC95%: 30; 44) chez les ≥65 ans). Chez les personnes âgées de 65 ans et plus, l'EV contre A (H3N2) était 43% (IC95%: 33; 53) au cours des saisons où les souches

vaccinales et circulantes étaient antigéniquement similaires et 14% (IC95%: -3; 30) lorsqu'elles étaient antigéniquement distinctes.

Discussion

Nos résultats suggèrent une EV faible à modérée contre l'hospitalisation avec une grippe chez les les adultes en Europe. L'estimation de l'EV était particulièrement faible chez les personnes âgées au cours des saisons grippales dominées par les virus A(H3N2). Nos résultats suggèrent aussi que, peu importe l'historique récent de vaccinations, se faire vacciner procure un certain niveau de protection dans tous les cas sauf contre A(H1N1)pdm09 chez les patients vaccinés au cours des deux saisons précédentes.

Conclusion

La pérennisation et l'acccroissement de la taille des études multicentriques en Europe est essentielle pour étudier des questions telles que le rôle des vaccinations passées sur l'EV, l'EV selon les maladies chroniques, l'EV et l'impact des vaccins tétravalents et l'EV par type et marque de vaccin. Etant donné le faible niveau d'EV documenté dans ce travail, le renforcement et l'évaluation de modes de prévention complémentaires, tels que l'usage prophylactique d'antiviraux, la vaccination du personnel soignant et les approches non-pharmaceutiques (masque, hygiène des mains) devraient être une priorité.

SUMMARY

Post authorisation influenza vaccine effectiveness against influenza associated hospitalisation with laboratory confirmed influenza among adults in Europe

Introduction

Vaccination strategies against seasonal influenza in Europe aim at preventing severe cases of influenza. Clinical trials among groups at risk of severe flu are not authorised for ethical reasons. The first objective of this work was to measure influenza vaccine effectiveness (IVE) against laboratory confirmed hospitalised influenza among adults in Europe by (sub)type, age group, underlying conditions and previous vaccination status. The second objective was to compute summary estimates of published data on IVE against laboratory confirmed hospitalised influenza in adults.

Methods

In 2011, we developed a generic study protocol using a "test-negative" case-control study design (TND). Within a network of hospitals in 12 European countries, during each influenza season, hospital teams identified and swabbed adult patients hospitalised (only ≥65 years in 2015-16 and 2016-17) with signs compatible with a severe acute respiratory infection. Swabs were tested with RT-PCR for influenza type and subtype. We compared the odds of vaccination between positive and negative patients and calculated IVE (1-OR). Using logistic regression, IVE estimates were adjusted for date of symptoms onset, study site, age, and chronic underlying diseases. We measured IVE stratified by age group, presence of underlying conditions and previous vaccination status (over the past two seasons).
For the literature review, we did a Pubmed search (01/2009 to 11/2016) and included studies measuring IVE from hospital based TND studies. We calculated summary estimates of IVE using a meta-analysis and random-effect models.

Results

Between 2011-12 and 2016-17, we recruited 3436 cases of influenza and 5969 controls. Across all seasons, the pooled IVE against any influenza was 26% (95% Confidence Interval (95% CI): 18; 33), ranging from 15% (95% CI: -3; 29) in 2016-17 to 44% (95% CI: 21; 60) in 2013-14. We were able to provide estimates during the course of the influenza season (February) in 2015-16 and 2016-17. Overall, IVE against influenza A(H1N1) pdm09 was 46% (95% CI: -3;72), 32% (95% CI: 7;50) and 39% (95% CI: 6;61) in patients aged 18-64, 65-79 and ≥80 years respectively. IVE against influenza A(H3N2) was 28% (95% CI: -14;54), 24% (95% CI: 7;37) and 22% (95% CI: 6;35) in patients aged 18-64, 65-79 and ≥80 years respectively. IVE against influenza B was 66% (95% CI: 19;86), 38% (95% CI: 11;57) and 46% (95% CI: 18;65) in patients aged 18-64, 65-79 and ≥80 years respectively. IVE estimates remained stable in patients with underlying heart or lung disease and in those with diabetes or cancer.
Between 2011 and 2016, among patients aged ≥65 years unvaccinated in both previous two seasons, current seasonal IVE (pooled across seasons) was 30% (95%CI:-35;64), 8% (95%CI:-94;56) and 33% (95%CI:-43;68) against influenza A(H1N1)pdm09, A(H3N2) and B respectively. Among patients vaccinated in both previous seasons, current seasonal IVE (pooled across seasons) was -1% (95%CI:-80;43), 37% (95%CI:7;57) and 43% (95%CI:1;68) against influenza A(H1N1)pdm09, A(H3N2) and B respectively. In the literature review, we identified 3411 publications, 30 of which met our inclusion criteria. Overall IVE was 41% (95% CI: 34;48) against any influenza (51% (95%CI: 44;58) among patients aged 18 to 64 years and 37% (95% CI: 30;44) in those aged ≥65 years). Among persons aged ≥65 year, IVE against A(H3N2) was 43% (95%CI:33;53) in seasons when circulating and vaccine strains were antigenically similar and 14% (95%CI:-3;30) when strains were antigenically different.

Discussion

Our results suggest a low to moderate IVE against hospitalised influenza in adults in Europe. Our IVE estimates were particularly low in the elderly during influenza seasons dominated by A (H3N2) viruses. They also suggest that, regardless of patients' recent vaccination history, current seasonal vaccine conferred some protection to vaccinated patients against hospitalised influenza in all instances except against A(H1N1)pdm09 among patients vaccinated in the past two seasons.

Conclusion

Sustainable and larger multicentre studies in Europe are needed to measure the performance of influenza vaccines. They will help responding to questions such as the feasibility to measure IVE early in the season, the effect of repeated vaccinations, the effect of underlying chronic diseases on IVE, the IVE and impact of quadrivalent vaccines, and the conditions required to measure IVE by vaccine brand and type. Considering the low IVE we report in this work, evaluating complementary prevention options, such as prophylactic antiviral use, vaccination of health care workers and non-pharmaceutical interventions should be a priority.

RESUME COURT

Titre : Efficacité post autorisation de mise sur le marché de la vaccination antigrippale saisonnière contre l'hospitalisation avec une grippe confirmée virologiquement chez l'adulte en Europe

Mots clés : grippe, efficacité vaccinale, épidémiologie, adultes, cas-témoins

Notre objectif était de mesurer chez les adultes en Europe l'efficacité des vaccins (EV) anti-grippaux saisonniers contre l'hospitalisation avec une grippe confirmée en laboratoire. Nous avons coordonné une étude cas-témoins multicentrique dans 29 hôpitaux de 12 pays entre 2011 et 2017. Nous avons fait une analyse des données groupées lors de chaque saison grippale. Entre 2011-12 et 2016-17, nous avons recruté 3436 cas de grippe et 5969 témoins. L'EV tous virus confondus était de 26% ; elle était de 40% chez les 18-64 ans, 25% chez les 65-79 ans et 23% chez les 80 ans et plus. Par saison, l'EV variait entre 15% en 2016-17 et 44% en 2013-14. L'EV était particulièrement basse chez les seniors lors des saisons grippales dominées par le sous-type de grippe A(H3N2), atteignant 10% en 2011-12 et 2016-17 chez les personnes âgées de 80 ans et plus. Nos résultats suggèrent une EV faible à modérée contre la grippe hospitalisée chez l'adulte. Le renforcement et l'évaluation de modes de prévention complémentaires, tels que l'usage prophylactique d'antiviraux, la vaccination du personnel soignant et les approches non-pharmaceutiques (masque, hygiène des mains) devraient être une priorité.

SHORT SUMMARY

Title : Post authorisation influenza vaccine effectiveness against influenza associated hospitalisation with laboratory confirmed influenza among adults in Europe

Key words: influenza, vaccine effectiveness, epidemiology, adults, case-control

Our objective was to measure seasonal influenza vaccine effectiveness (IVE) against hospitalisation with laboratory-confirmed influenza in Europe among adults. Between 2011 and 2017, we coordinated a multicenter case-control study in 29 hospitals in 12 countries. We pooled and analysed the data after every season. Between 2011-12 and 2016-17, we recruited 3436 influenza cases and 5969 controls. Pooled across seasons, IVE against any influenza was 26%; 40% patients aged 18-64 yeas, 25% among those aged 65-79 years, and 23% among those aged ≥80 years. Season specific IVE ranged between 15% in 2016-17 and 44% in 2013-14. IVE was particularly low among elderly in seasons dominated by the A(H3N2) viruses; it was 10% in 2011-12 and 2016-17 in people aged ≥80 years. Our results suggest a low to moderate IVE against influenza hospitalisation in adults. Evaluating complementary prevention options, such as prophylactic antiviral use, vaccination of health care workers and non-pharmaceutical interventions should be a priority.

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SCIENTIFIC OUTPUT RELATED TO THE THESIS

Articles

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GLOSSARY

95%CI	95% confidence interval
ACIP	advisory committee on immunization practices
ARI	acute respirtaory infection
CDC	Centers for Disease Control and Prevention
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EMA	European medicines agency
EU	European Union
FDA	food and drug administration
GBS	Guillain Barre syndrome
GO	general practicioner
GSIRS	Global Influenza surveillance and response system
HA	haemagglutinin
ICU	intensive care unit
IIV	inactivated influenza vaccine
ILI	influenza-like illness
I-MOVE	influenza-monitoring of vaccine effectiveness
IVE	influenza vaccine effectiveness
NA	neuraminidase
NPI	non pharmaceutical intervention
OR	odds ratio
PAHO	Pan American Health Organization
QIV	quadrivalent inactivated vaccine
RCT	Randomised controlled trial
RNA	ribonucleic acid
RR	risk ratio
RT-PCR	reverse transcriptase Polymerase Chain Reaction
SARI	Severe acute respiratory infection
TIV	trivalent inactivated vaccine
TND	test-negative design
USA	United States of America
VAERS	Vaccine Adverse Event Reporting System
WHO	World health organization

RESUME SUBSTANTIEL

Introduction

La grippe est une maladie contagieuse causée par un virus à ARN de la famille des Orthomyxoviridiae (Myxovirus influenzae) dont l'expression épidémiologique dans la population suit un mode épidémique saisonnier. Les virus sont classés en quatre types (A, B, C) en fonction de leurs caractéristiques antigéniques. Seuls les virus A et B provoquent une infection symptomatique chez l'humain. Leur taux élevé de mutations, combiné à la pression sélective des anticorps, ont pour conséquences la survenue de glissements antigéniques fréquents à l'origine des épidémies annuelles de grippe. Depuis 2009, les virus A(H1N1)pdm09, A(H3N2), B Yamagata et B Victoria co-circulent en Europe.

Les virus grippaux se transmettent de personne à personne par contact direct, gouttelettes ou aérosols. Environ deux tiers des personnes infectées par la grippe développent des symptômes. La période d'incubation dure deux jours en moyenne et les symptômes de la grippe apparaissent généralement de façon soudaine. Ils sont caractérisés par des signes systémiques (fièvre, frissons, maux de tête, myalgies, malaise et anorexie) combinés à des signes respiratoires (toux, écoulements nasaux et maux de gorge).

Des complications pulmonaires peuvent apparaître et conduire à des formes sévères de grippe. Ces complications peuvent être causées par l'infection virale en tant que telle, une infection bactérienne secondaire ou une exacerbation de maladies chroniques sous-jacentes. Les personnes à risque de grippe sévère sont donc celles présentant des maladies chroniques sous-jacentes et celles dont le système immunitaire est susceptible de répondre de manière insuffisante à une infection virale ou à une infection bactérienne secondaire.

En Europe, la surveillance épidémiologique de la grippe repose sur la notification des cas présentant des syndromes grippaux par des réseaux de médecins généralistes volontaires (réseaux dits "sentinelles") et celle des admissions pour infection respiratoire aigüe sévère en soins intensifs par certains hôpitaux. Selon l'Organisation mondiale de la santé (OMS), les épidémies de grippe affectent 20 à 30% des enfants et 5 à 10% des adultes et causent entre trois et cinq millions d'hospitalisations et 250 000 à 500 000 décès chaque année dans le monde.

Les mesures préventives pour la grippe sont articulées autour de trois approches complémentaires: les interventions non pharmaceutiques visant à prévenir la transmission des virus, la vaccination antigrippale saisonnière et les antiviraux pour lutter contre les infections grippales.

Les premiers vaccins antigrippaux ont été autorisés en 1945 sur le marché américain. Depuis 1973, leur composition antigénique est revue chaque année sur la base de données de surveillance virologique et d'efficacité vaccinale. Les vaccins antigrippaux comportent traditionnellement trois composants antigéniques : A(H3N2), A(H1N1)pdm09 et un lignage B. Des vaccins tétravalents, comportant les deux lignages B sont disponibles depuis 2012. Quelle que soit leur valence, les vaccins antigrippaux sont soit inactivés, soit vivants atténués (recommandés seulement pour les enfants). Les vaccins inactivés peuvent contenir un adjuvant ou être à forte dose pour augmenter leur immunogénicité.

En Europe, les stratégies de vaccination antigrippales visent à réduire le nombre de cas sévères et de décès en ciblant les sujets à risque de développer des formes sévères de grippe. Dans la plupart des pays européens, la vaccination antigrippale est donc prise en charge pour les personnes âgées, les individus présentant certaines maladies chroniques sous-jacentes et les femmes enceintes. Au total, environ 125 millions d'Européens sont, chaque année, ciblés par la vaccination. D'autres stratégies vaccinales existent telles que la vaccination universelle aux Etats-Unis et dans certaines provinces canadiennes ou la vaccination pédiatrique en Angleterre.

L'OMS recommande aux Etats membres d'atteindre 75% de couverture vaccinale parmi les personnes âgées. En Europe, seule l'Ecosse a atteint cet objectif ; la couverture vaccinale médiane Européenne chez les personnes de 65 ans et plus était estimée à 45% en 2014-15, avec une tendance à la baisse sur la dernière décennie.

La sécurité des vaccins antigrippaux est considérée comme bonne. Leur performance est mesurée par un indicateur nommé l'efficacité vaccinale (EV). L'EV mesure le pourcentage de réduction de l'incidence (risque ou taux) de la maladie chez les vaccinés qui peut être attribuable à la vaccination.

L'EV pré-commercialisation est généralement mesurée au cours d'essais cliniques randomisés permettant de limiter au mieux les biais de sélection entre vaccinés et non vaccinés et de s'assurer que les différences observées sont attribuables exclusivement au vaccin. Dans le cas du vaccin contre la grippe et pour des raisons éthiques, ces essais cliniques ne peuvent être conduits que parmi la population pour laquelle le vaccin n'est pas recommandé.

Les données d'EV pré-commercialisation des vaccins contre la grippe montrent une protection de l'ordre de 60% chez les adultes sans maladies chroniques sous-jacentes. La vaccination annuelle des groupes à risque est recommandée depuis 1960 sans qu'aucune étude d'EV pré-marketing n'ait été effectuée dans cette population. Dans ce contexte, pour des raisons éthiques, seules des études d'EV post-commercialisation sont possibles parmi les groupes à risque ciblés par la vaccination.

Justification de l'étude et objectifs

Le suivi de l'EV des vaccins antigrippaux est essentiel pour évaluer et guider les stratégies de vaccination et de prévention. Ainsi, des données d'EV précises peuvent être utilisées dans des modèles de coût-efficacité pour décider de mettre en œuvre ou de maintenir des programmes vaccinaux. L'EV par (sous)type de grippe peut aussi permettre de mettre en évidence des (sous)-types de grippe contre lesquels le vaccin marche plus ou moins bien, d'identifier des groupes de population à risque accru d'échec vaccinal ou encore de promouvoir des modes de prévention alternatifs en cas d'indication précoce de faible EV en cours de saison. Les chiffres d'EV peuvent aussi guider les politiques vaccinales vers l'adoption, ou non, de nouveaux vaccins, tels que les vaccins tétravalents ou ceux avec adjuvants, ou de mieux comprendre des problématiques telles que l'effet des vaccinations répétées sur l'EV.

Le premier objectif de ce travail était alors de mesurer l'efficacité du vaccin antigrippal contre la grippe hospitalisée confirmée en laboratoire chez l'adulte en Europe. Pour répondre à cet objectif, nous avons mis en place un réseau européen d'hôpitaux dans lesquels les équipes d'étude ont adapté un protocole générique. Avec ce réseau, nous avons aussi tâché de répondre à des questions complémentaires. Pour chaque (sous)type de grippe, nous avons cherché à mesurer l'EV stratifiée par groupe d'âge, parmi la population visée par les programmes de vaccination, parmi les patients atteints de maladies sous-jacentes spécifiques (diabète, cancer, maladies cardiaques ou pulmonaires), par marque de vaccin et selon les vaccinations antérieures.

Le second objectif était de faire une revue et un résumé quantitatif des données publiées d'EV contre la grippe hospitalisée confirmée en laboratoire chez l'adulte. Pour répondre à cet objectif, nous avons mené, en collaboration avec des collègues de l'OMS, le centre collaborateur référence de l'OMS de Melbourne et le CDC américain, une revue systématique des résultats publiés dans la littérature et une méta-analyse.

Mesure de l'efficacité du vaccin antigrippal contre la grippe hospitalisée confirmée en laboratoire chez l'adulte en Europe

En 2011, nous avons développé un protocole d'étude générique reposant sur un schéma d'étude cas-témoins de type « test-négatif » (TND). Nous avons conduit une étude pilote en 2011-12, dans 21 hôpitaux localisés dans quatre sites d'étude (France, Italie, et les régions espagnoles de Navarre et Valence), co-financés par des fonds publics, EpiConcept et des laboratoires pharmaceutiques. Ce réseau, InNHOVE, a duré jusqu'en 2013-14. En 2014, EpiConcept et le réseau I-MOVE+ (une vingtaine d'instituts publics européens), ont remporté un appel d'offres Horizon 2020 de la commission européenne permettant de financer pendant trois saisons un réseau de 25 hôpitaux dans onze pays. En 2015, nous avons initié ce réseau ciblant exclusivement les personnes âgées de 65 ans et plus et nous rapportons ici les résultats de 2015-16 et 2016-17.

Dans les hôpitaux participants, durant chaque saison grippale, les équipes ont identifié et réalisé des prélèvements naso-pharyngés les patients hospitalisés pour un motif potentiellement lié à la grippe (syndrome respiratoire, troubles cardiovasculaires, détérioration de l'état de santé général ou fonctionnel) et ayant des signes compatibles avec une infection respiratoire aigüe sévère depuis moins de huit jours. Ils ont effectué une PCR spécifique par type et sous type de grippe sur les échantillons prélevés. Nous avons comparé les cotes de la vaccination parmi les patients ayant des résultats de PCR positifs et négatifs et calculé l'EV (1-rapport de cotes). A l'aide d'une régression logistique, nous avons ajusté les estimations d'EV sur la date de survenue des symptômes, le site d'étude, l'âge et les maladies chroniques sous-jacentes. Nous avons mesuré l'EV stratifiée par groupe d'âge, la présence de certaines maladies sous-jacentes et les vaccinations antérieures (au cours de deux saisons précédentes).

Résultats

Entre 2011-12 et 2016-17, nous avons recruté 3436 cas de grippe et 5969 témoins. Parmi les cas confirmés, 63% étaient infectés par des virus A(H3N2), 22% par A(H1N1)pdm09, 2% par des virus A non sous-typés et 13% par des virus B. Au cours des saisons 2011-12 et 2016-17 les virus circulants étaient presque exclusivement A(H3N2). Pour les autres saisons, nous avons observé une co-circulation des trois types de virus en 2012-13, de virus A(H1N1)pdm09 et A(H3N2) en 2013-14 et de virus A(H1N1)pdm09 et B en 2015-16.

Sur l'ensemble des saisons incluses, l'EV contre tous types de virus et tous âges confondus était de 26% (Intervalle de Confiance à 95% (IC95%):18;33). Elle était de 40% (95%CI: 15;58), 25% (95%CI: 13;36) et 23% (95%CI: 10;34) chez les 18-64 (inclus de 2011 à 2014 seulement), 65-79 et ≥80 ans respectivement.

Grippe A(H1N1)pdm09

Sur l'ensemble des saisons, l'EV contre la grippe A(H1N1)pdm09 était de 46% (IC95%: -3; 72), 32% (IC95%: 7; 50) et 39% (IC95%: 6; 61) chez les 18-64, 65-79 et ≥80 ans respectivement.

Les souches vaccinales et circulantes de virus A(H1N1)pdm09 sont restées stables et antigéniquement similaires au cours de notre période d'étude. En cohérence avec de nombreuses publications, nous avons observé une proportion des cas de A(H1N1)pdm09 plus élevée parmi les adultes jeunes par rapport aux personnes âgées. Nos résultats suggèrent aussi une EV contre A(H1N1)pdm09 légèrement supérieure chez les 18-64 ans par rapport aux sujets plus âgés. Les infections naturelles récentes, renforçant la réponse immunitaire à la vaccination saisonnière chez les 18-64 ans et la sénescence immunitaire chez les personnes âgées (dégradation des capacités immunitaires liée au vieillissement de l'organisme), peuvent expliquer en partie ces différences d'EV par groupe d'âge.

Grippe A(H3N2)

L'EV contre la grippe A(H3N2) était de 28% (IC95%: -14; 54), 24% (IC95%: 7; 37) et 22% (IC95%: 6; 35) chez les 18-64, 65-79 et ≥80 ans respectivement. L'EV contre la grippe A (H3N2) parmi les patients de moins de

65 ans variait entre 8% (IC95%: -145; 65) en 2013-14 et 47% (IC95%: -1; 72) en 2011-2012. Parmi les patients âgés de 65 à 79 ans, l'EV contre A(H3N2) était inférieure à 30% trois saisons sur quatre. Enfin, parmi les patients âgés de 80 ans et plus, l'EV contre A(H3N2) était particulièrement basse (8%) en 2011-12 et 2016-17.
Nos résultats suggèrent une EV faible contre les cas hospitalisés de grippe A(H3N2). Le vaccin semble particulièrement peu performant chez les personnes âgées au cours des épidémies où les virus A(H3N2) prédominent.

Grippe B
L'EV contre la grippe B était de 66% (IC95%: 19; 86), 38% (IC95%: 11; 57) et 46% (IC95%: 18; 65) chez les 18-64, 65-79 et ≥80 ans respectivement. Parmi les patients âgés de 65 ans et plus (les 18-64 ans n'étant pas inclus en 2015-16), nous avons mesuré des EV contre la grippe B plus élevées en 2015-16, lorsque les lignages circulants et vaccinaux étaient différents, par rapport à 2012-2013, lorsque les lignages circulants et vaccinaux étaient identiques.

En résumé, nos résultats suggèrent une EV modérée à faible, en particulier chez les personnes âgées, contre la grippe hospitalisée confirmée en laboratoire. L'EV était particulièrement basse contre la grippe A(H3N2). Nos résultats suggèrent aussi la présence de protection croisée entre les lignages de grippe B. Nous avons pu fournir des estimations anticipées d'EV à nos partenaires en 2015-16 et les publier dans une revue scientifique en 2016-17.

Efficacité en fonction des vaccinations antérieures
A partir des données de 2011 à 2014 et celles de 2015-16, nous avons mesuré l'EV pour la saison en cours en fonction des vaccinations reçues au cours des deux années antérieures chez les 65 ans et plus. Au cours de cette période, nous disposions de 5295 patients, dont 465 cas d'A(H1N1)pdm09, 642 cas d'A(H3N2), 278 cas de grippe B et 3910 témoins.
Parmi les patients non vaccinés au cours des deux saisons précédentes, l'EV de la saison en cours était de 30% (IC95%:-35;64), 8% (IC95%:-94;56) et 33% (IC95%:-43;68) contre la grippe A(H1N1)pdm09, A(H3N2) et B respectivement. Parmi les patients vaccinés les deux saisons antérieures, l'EV de la saison en cours était -1% (IC95%:-80;43), 37% (IC95%:7;57) et 43% (IC95%:1;68) contre la grippe A(H1N1)pdm09, A(H3N2) et B respectivement.
Nos résultats suggèrent qu'indépendamment des vaccinations antérieures récentes des patients, le vaccin de la saison en cours apporte une protection contre la grippe hospitalisée A(H3N2) et B. Ils suggèrent également que le vaccin de la saison en cours apportait une protection modérée contre la grippe A(H1N1)pdm09 parmi les patients qui n'étaient pas vaccinés auparavant mais était inefficace parmi les patients vaccinés les deux saisons antérieures.

Efficacité par marque de vaccins
A partir des données groupées des saisons 2013-14, 2015-16 et 2016-17 nous avons mesuré l'EV par marque de vaccins. Pour chaque marque de vaccin, nous avons restreint l'analyse aux pays et saisons au cours desquelles au moins un patient inclus avait reçu le produit. Pour chaque marque de vaccin, nous avons utilisé la régression logistique pour mesurer l'EV ajustée contre toutes grippes puis contre A(H1N1)pdm09 et A(H3N2) parmi les personnes âgées de 65 ans et plus.
Nous disposions de données pour 1828 cas et 3309 témoins. Au cours des trois saisons, 2767/5137 (54%) patients étaient vaccinés. Parmi eux, 37% avaient reçu Influvac, 38% avaient reçu Vaxigrip, 15% avaient reçu des vaccins d'autres marques et la marque vaccinale était manquante pour les 10% restants de patients vaccinés. Sur l'ensemble de la période d'étude, l'EV d'Influvac contre toutes grippes confondues était de 19% (IC95%: 2; 33) chez les personnes âgées de 65 ans et plus, variant entre -74% (IC95%: -486; 48) en 2013-14 et 26% (IC95%:-5; 48) en 2015-16. L'EV d'Influvac était de 20% (IC95%: -21; 48) contre les virus A(H1N1)pdm09 et 18% (IC95%: -3; 35) contre les virus A(H3N2). Sur l'ensemble de la période d'étude, l'EV de Vaxigrip contre toutes grippes confondues était de 29% (95% CI: 13; 43) chez les personnes âgées de 65 ans et plus, variant entre -1% (IC95%: -37; 25) en 2016-17 et 47% (IC95%: 19 ; 66)

en 2013-14. L'EV de Vaxigrip était de 50% (IC95%: 26; 66) contre les virus A(H1N1)pdm09 et 14% (IC95%: -10; 34) contre les virus A(H3N2).
L'estimation ponctuelle d'EV de Vaxigrip contre toutes grippes confondues était légèrement supérieure à celle d'Influvac, mais les intervalles de confiance se chevauchaient largement. À l'heure actuelle, la mesure de l'EV contre la grippe hospitalisée est impossible pour la grande majorité des marques de vaccin en raison des petites parts de marché pour la majorité des marques et des petites tailles d'échantillon qui en découlent. Bien que nous ayons pu calculer les estimations d'EV pour deux marques de vaccins, nos résultats sont imprécis et ne tiennent pas compte de facteurs susceptibles d'affecter ces estimations, comme les vaccinations antérieures par exemple. Enfin, il est pour l'instant impossible de comparer l'EV entre ces deux marques de vaccins puisqu'ils étaient utilisés dans différents pays et dans des proportions différentes selon les saisons. Compte tenu des variations d'EV, pour un vaccin donné, en fonction des saisons et des pays, les différences observées ne peuvent être imputées à la performance des vaccins. Enfin, en raison d'une trop faible taille d'échantillon, nous n'avons pas pu calculer d'EV pour les vaccins avec adjuvant. Dans un contexte de faible EV parmi les personnes âgées, ces estimations seraient importantes.

Revue de la littérature et méta-analyse

Pour la revue de littérature, nous avons inclus, après recherche sur Pubmed (01/2009 à 11/2016), les études mesurant l'EV à partir d'un schéma TND à l'hôpital. Deux auteurs ont sélectionné, de façon indépendante, les articles répondant aux critères d'inclusion. Nous avons effectué une méta-analyse en utilisant des modèles à effets aléatoires.
Nous avons identifié 3411 publications, dont 30 répondaient à nos critères d'inclusion. Entre 2010-2011 et 2014-15, l'EV saisonière groupée était de 41% (IC95%: 34; 48) contre toutes grippes confondues (51% (IC95%: 44; 58) chez les personnes de 18 à 64 ans et 37% (IC95%: 30; 44) chez les ≥65 ans). L'EV était de 48% (IC à 95%: 37; 59), 37% (IC95%: 28; 46) et 38% (IC95%: 23; 53) contre les virus A(H1N1)pdm09, A(H3N2) et B, respectivement. L'EV contre A(H3N2) était de 52% (IC95%: 39; 66) au cours des saisons où les souches vaccinales et circulantes étaient antigéniquement similaires (59% (IC95%: 38; 80) chez les 18-64 ans et 43% (95 % CI: 33; 53) chez les ≥ 65 ans) et 29% (IC95%: 13; 44) lorsqu'elles étaient antigéniquement distinctes (46% (IC95%: 30; 61) chez les 18-64 ans ans et 14% (IC95%: -3; 30) chez les ≥65 ans).
Les vaccins contre la grippe fournissent une protection modérée contre les hospitalisations associées à la grippe chez les adultes. Leur performance est particulièrement faible chez les personnes âgées au cours des saisons où les souches de virus A(H3N2) circulantes et vaccinales sont antigéniquement distinctes. Cette information, combinée au suivi en temps réel de l'évolution des distances antigéniques entre les virus circulants d'A(H3N2) et la souche vaccinale, pourraient faciliter la promotion précoce de mesures de prévention alternatives.

Discussion

Limites

Erreurs systématiques

Biais de sélection

La population d'étude initiale de ce projet incluait la population adulte dans les pays participants.
Nous avons, à la suite des premières années de cette étude, restreint notre population d'étude aux adultes ciblés par la vaccination antigrippale et plus susceptibles que la population générale de développer des fomes sévères de grippe.
Certains auteurs remettent en cause le schéma TND pour la mesure de l'EV à l'hôpital. Ils craignent qu'avec un recrutement fondé sur des signes cliniques on inclut un grand nombre de patients hospitalisés pour une exacerbation de maladies chroniques cardiopulmonaires sous-jacentes sans lien avec une infection respiratoire. Ce type de biais pourrait conduire à une sur-représentation de ce profil de patients parmi les témoins. Dans le cas où ces patients seraient plus vaccinés que la population source des cas, on surestimerait l'EV. Pour prendre en compte ce biais potentiel, nous avons systématiquement conduit des

analyses de sensibilités restreintes aux patients sans maladies chroniques cardiopulmonaires et ajusté nos estimations sur la présence et la sévérité de maladies chroniques.

Biais d'information

La qualité des données était élevée dans notre étude avec moins de 3% de données manquantes pour la vaccination ou pour les résultats de laboratoires et moins de 5% de données manquantes pour les variables de confusion.

Les biais de mémorisation sur le statut vaccinal étaient probablement minimes dans notre étude puisque cette information était collectée indépendamment des résultats de laboratoire des patients.

Un long délai entre l'apparition des symptômes et le prélèvement des patients pourrait conduire à la présence de faux négatifs si les patients ont éliminé le virus avant le prélèvement. Sur les cinq saisons incluses dans ce travail, la même proportion de témoins (64%) et de cas (66%, p = 0,43) ont été prélevés dans les quatre jours suivant l'apparition des symptômes, ce qui suggère que les erreurs de classification dues à des prélèvements tardifs devaient être rares.

Facteurs de confusion

Le recueil de données détaillées sur les antécédents médicaux des patients et la sévérité des maladies chroniques nous a permis une recherche approfondie de facteurs de confusion potentiels dans la mesure de l'EV. De façon globale et à chaque saison, nous avons mesuré des degrés de confusion très faibles dans nos estimations. Nous ne pouvons cependant pas exclure la présence de facteurs de confusion non identifiés que nous n'aurions pas recueillis.

Erreurs aléatoires

Malgré l'augmentation des tailles d'échantillon et une couverture vaccinale de 50% parmi les témoins, nos estimations d'EV demeurent imprécises. Les estimations ponctuelles d'EV dans les sous-groupes de population ou par marques / types de vaccins ont été reportées avec des intervalles de confiance très larges. À l'avenir, augmenter la taille d'échantillon sera essentiel pour identifier avec une meilleure précision des groupes spécifiques à haut risque d'EV faible ou des vaccins plus ou moins performants.

Analyses groupées

Nous reportons actuellement, en résultat principal, des estimations issues d'analyses groupées en considérant le site d'étude comme un ayant un effet fixe. Pouvoir l'intégrer dans un modèle à deux niveaux avec un effet aléatoire permettrait de prendre en compte les différences éventuelles d'EV réelle, mais aussi de facteurs de confusion, entre les sites d'étude. Pour ce faire, il est essentiel d'augmenter la taille d'échantillon par site.

Résumés des observations

A partir des résultats de notre travail, des données d'EV annuelles contre l'hospitalisation avec une grippe sont désormais disponibles et peuvent alimenter les analyses coût-efficacité et potentiellement les stratégies de vaccination.

Nos résultats suggèrent une EV faible à modérée contre l'hospitalisation associée à la grippe, notamment chez les personnes âgées, parmi lesquelles la morbidité sévère et la mortalité, en particulier lors des saisons dominées par les virus A(H3N2), sont préoccupantes. Des vaccins plus immunogènes (à forte dose ou avec adjuvants) existent et la conduite d'essais cliniques comparatifs chez les personnes âgées pourraient permettre de mesurer leurs performances relatives contre les grippes sévères. La mesure de l'efficacité et de l'impact d'approches de prévention alternatives chez les personnes âgées est aussi nécessaire. Il sera notamment intéressant de suivre l'approche anglaise de protection indirecte des personnes âgées grâce à la vaccination des enfants. Des essais randomisés pour mesurer l'effet de la vaccination des soignants sur le risque de grippe sévère chez les personnes âgées seraient également pertinents. Dans la situation actuelle et avant de disposer de ces données, il serait utile, notamment en cas d'épidémies à virus A(H3N2), de promouvoir plus activement l'usage prophylactique d'antiviraux chez les personnes âgées tout en surveillant l'émergence de résistance. La mesure et la communication de l'EV

en temps réel pourrait permettre de mieux guider ces actions de santé publique en cours de saison. Enfin, les interventions non pharmaceutiques (hygiène, port du masque, isolement, etc.) et l'évaluation de leurs effets devraient être mises en œuvre quel que soit le (sous-)type de grippe circulant et l'EV.
La conduite de méta-analyses est nécessaire pour fournir des données solides afin de décider en faveur ou non de l'utilisation du vaccin tétravalent chez l'adulte. Compte tenu du manque actuel de concordance entre les lignages de virus B sélectionnés dans le vaccin et ceux circulants, il serait intéressant de discuter de l'alternance systématique des lignages Yamagata et Victoria dans le vaccin.

Il serait important de conduire de grandes études prospectives de cohorte pour déterminer le rôle des vaccinations répétées sur l'EV car cela pourrait conduire à réviser les stratégies de sélection des souches vaccinales ou les intervalles de temps entre les vaccinations successives. Cependant, de telles études sont très coûteuses et nécessiteraient plusieurs années d'observation pour atteindre des résultats concluants.

Malgré son efficacité faible à modérée contre les formes sévères de grippe, la vaccination saisonnière reste une mesure de prévention collective utile et pertinente contre la grippe. La combinaison de son utilisation avec des antiviraux et des approches non pharmaceutiques permet de réduire le nombre de cas notamment hospitalisés et mortels. Alors qu'on assiste à une diminution de la couverture vaccinale et une méfiance grandissante vis-à-vis de la vaccination, les campagnes de marketing social et de communication visant à promouvoir le vaccin contre la grippe devraient fournir des messages clairs et présenter de façon transparente les résultats d'études indépendantes. Pour promouvoir son utilisation, communiquer, auprès du grand public, sur le nombre de cas (hospitalisés) et de décès évités, aurait certainement un impact positif plus fort.

Les réseaux InNHOVE et I-MOVE + ont permis de montrer que les études multicentriques pour mesurer l'EV contre l'hospitalisation avec une grippe confirmée en laboratoire étaient réalisables en Europe. Ces études hospitalières font maintenant partie intégrante de l'évaluation de nos politiques de santé publique.

1 BACKGROUND

1.1 Influenza viruses

Seasonal influenza is an acute respiratory infection caused by three RNA viruses of the family Orthomyxoviridiae (Myxoviruse influenzae A, B, C and D), whose epidemiological pattern follows a seasonal epidemic mode. Influenza viruses A and B cause symptomatic infection in humans (6).

Among influenza A viruses, which are the most frequent and virulent, different subtypes are distinguished by their haemagglutinin (HA) and neuraminidase (NA) surface antigens (7). The high frequency of genetic drifts and shifts of these viruses contributes to the high variability of HA (H1 to H17) and NA (N1 to N9). Humans are generally infected with subtypes H1, H2 or H3 and N1 or N2. Antigenic drifts are antigenic variations resulting from the accumulation of point mutations in HA and NA genes. These drifts are driven by antibody-mediated selective pressure and a high rate of mutations due to the absence of proofreading activity by the viral polymerase that transcribes the influenza genome (8). The antigenic drifts allow the virus to escape immunity induced by vaccination and previous exposure but they do not alter the overall antigenic structure of the virus for which partial immunity is conserved in the short term. Antigenic drifts are responsible for annual epidemics.

Antigenic shifts are radical changes in the hemagglutinin structure resulting from re-assortments occurring between animal and human subtypes leading to the replacement of one type of hemagglutinin with another (9). It leads to novel virus strains, against which a large proportion of the population does not have immunity (10). Four influenza pandemics occurred in the past century; the most recent one was caused by the H1N1 swine influenza in 2009.

The influenza B virus infects almost exclusively the human and is therefore not subject to genetic re-assortments (7). It mutates at a 2 to 3 times lower rate than influenza A (11). It is genetically less diverse, allowing the acquisition of some immunity, however insufficient to confer long-term protection. Two lineages of influenza B, "Victoria" and "Yamagata" co-circulate among human beings (10).

Influenza A and B are antigenically distinct and do not exhibit cross-protections. Currently, the pandemic A(H1N1)pdm09 virus co-circulate with A(H3N2) and B viruses (12). During influenza epidemics, influenza B incidence often increases after a peak of influenza A activity (7).

1.2 Influenza transmission

Influenza activity is seasonal and is peaking during the coldest months of the year (November-February in Northern hemisphere and May-October in Southern hemisphere) (13). A typical influenza season peaks within 2-3 weeks and lasts 5-6 weeks (14). The median seasonal influenza epidemic reproductive number is 1.28 (15) and the attack rate of laboratory confirmed influenza infection varies between 3.5% among adults and 15.2% among children (16).

During an epidemic season, influenza viruses are transmitted from human to human through direct contact, droplets or aerosols (17,18). Contact transmission occurs when there is transfer of microorganisms to upper respiratory tract either directly or via a contaminated object or person. The virus remains infectious for a short time on the hands but can remain infectious on non-porous surfaces in the environment for up to 48 h. When an infected individual sneezes or coughs, pathogen-containing particles ranging from 0.1 µm to 100 µm are expelled (19). Fine particles (aerosols) and droplet nuclei, generated

from the rapid desiccation of larger droplets, remain suspended in the air for long periods of time and can infect individuals some distance away from (different rooms/wards) the source patient. These aerosols can reach the upper and the lower respiratory tracts (10,18). Larger droplets generated from the respiratory tract can be propelled to a distance of less than 1m on the upper respiratory tract (e.g. mouth and nose through the air)). The relative importance of each route of transmission remains under debate (17,18).

1.3 Clinical presentation

Approximately two third of people infected with influenza will develop symptoms (1). The incubation period averages two days (range 1-4 days) (20). Viral shedding starts before symptoms onset (21), peaks in the first 1-2 days of clinical illness and decreases to undetectable levels after a week, in correlation with the severity of clinical symptoms (22). Immunocompromised individuals shed the virus for a longer period of time, averaging 19 days (19). Influenza symptoms typically appear suddenly. They are characterized by systemic features, including fever, chills, headache, myalgia, malaise, and anorexia, combined with respiratory symptoms, including non-productive cough, nasal discharge, and sore throat (10,25,26). The World Health Organization (WHO) defines an influenza like illness (ILI) as an acute respiratory infection with measured fever of ≥ 38 C°, cough with onset within the last 10 days (27). Monto et al. reviewed large datasets of antivirals clinical trials to determine that a combination of cough and fever within 48 hours of onset were the best predictors (positive predictive value=79%) for laboratory confirmation of influenza among adults and adolescent (28).

1.3.1 Pulmonary complications

Pulmonary complications may occur as a direct consequence of influenza infection, after secondary bacterial infection or through the exacerbation of chronic conditions. Primary viral pneumonia occurs more often among patients with underlying cardiopulmonary diseases and is characterised by a rapid respiratory decompensation and a case fatality of 6% to 29% during seasonal influenza (29,30). Secondary bacterial infections often start after near resolution of the influenza infection by the recurrence of fever and respiratory symptoms, including pulmonary consolidation (31). The most common pathogens responsible for secondary bacterial infections are *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Haemophilus influenza* (32). There are also been reports of secondary bacterial infections with unusual pathogens such as Aspergillus sp., *Chlamydia pneumoniae*, B-hemolytic streptococci, and *Legionella pneumophila* (33–35). Synergetic interaction between bacteria and influenza viruses was mostly studied for *Streptococcus pneumoniae*. Bacterial infections may be eased by influenza viruses through different mechanisms: influenza viruses alter the lungs in a way that predisposes to adherence, invasion, and induction of disease by bacteria; they may damage the epithelium and facilitate the access of bacteria to receptors; and they affect the host immune response by decreasing their ability to clear bacteria and by amplifying the inflammatory cascade (36). Data from autopsy tissue samples of 100 US deaths with laboratory-confirmed 2009 H1N1 virus infection suggested that more than a quarter of them had suffered from bacterial co-infections (37). Combinations of primary influenza-associated and secondary bacterial pneumonia can also occur (12).
Influenza viruses account for 25% of the pathogens responsible for exacerbation of chronic lung diseases (38), such as asthma, chronic obstructive pulmonary disease, and bronchitis (12). This probably implies the stimulation of inflammatory mediators, such as interleukins, cytokines, and modifications in the ratio of T-cell subsets leading to increased sensitivity to allergens (39).

1.3.2 Non pulmonary complications

In addition to pulmonary complications, influenza infections may affect several other organ systems. Myosistis and rhabdomyolysis, which can lead to renal failure or ambulatory difficulties during 4-6 weeks have been reported (40). Neurological complications associated with influenza infections usually involve the central nervous system and may include encephalitis/encephalopathy, Reye's syndrome, acute necrotising encephalopathy, and myelitis as well as autoimmune conditions, such as Guillain-Barre's syndrome (41). Influenza frequently exacerbates underlying cardiac conditions such as congestive heart failure and ischemic heart disease (42) and may induce pericarditis and myocarditis (12). Ison et al. described transient electrocardiographic changes, early in the course of the disease, in over 50% of ambulatory influenza adults (43).

1.3.3 Individuals at-risk for influenza complications

Consequently, individuals at risk of developing severe influenza are those whose immune system is likely to sub-optimally respond to viral or secondary bacterial infection (44). Patients with underlying cardiovascular or pulmonary diseases may also suffer from an exacerbation of these conditions due to influenza infection (45,46). Elderly populations, defined as those aged 65 years and above, and, more specifically, elderly with underlying cardiac and pulmonary conditions have been described as having increased risk for hospitalisation due to influenza infection (47). Patients with cancer treated with chemotherapy (48) and diabetic patients are more vulnerable to influenza infection due to their impaired immune response (49) that could also affect host response to vaccination (75,76).

1.4 Surveillance of influenza

In Europe, the priority objectives of influenza programmes, according to the European Center for Disease Prevention and Control (ECDC), are to decrease morbidity and mortality due to seasonal influenza through increased use of immunisation, appropriate use of antivirals, and better use of personal health measures. Influenza programmes also aim to improve preparedness for a pandemic and to stimulate research programmes to obtain scientific evidence for the mitigation of influenza in Europe (52). Surveillance data should also allow describing influenza incidence and burden, signaling the start and end of influenza season, and identifying at-risk groups in order to adapt prevention strategies if needed. Clinical surveillance allows monitoring the severity of the flu and susceptibility to antivirals in order to adapt treatment strategies accordingly. Epidemiological data can be used to measure the post-marketing effectiveness of influenza vaccine (IVE) to inform health professionals and population on the performance of the vaccine. Finally, virological surveillance and IVE data facilitate the selection of candidate strains to be included in the vaccine (52).

In the European Union (EU), cases of influenza-like illness (ILI) or acute respiratory infections (ARI) are reported by physicians members of sentinel networks to national or regional coordination centers. These physicians account for 1-5% of all doctors of a given area. They cover a population supposed to be representative of the general population for a range of parameters including age, sex or socio-economic status (53). Each week they report all patients with ILI or ARI to their coordinating center. They perform a nasopharyngeal swab from a sample of these patients and send the specimens to the national or regional laboratory that conducts tests to detect influenza and other respiratory viruses. Physicians' notification allows monitoring the ILI/ARI incidence at European level. Laboratory data are used for virological surveillance. All of these data are compiled in a weekly influenza surveillance bulletin available to

everyone on the ECDC website (54). Data collected from reporting physicians, combined with virological data, are used to measure IVE.

Surveillance of severe cases of influenza is based on notification by hospitals of patients admitted with laboratory-confirmed influenza. Most hospitals focus on intensive care units (ICU) admissions. This surveillance aims to provide, in real time, data on severity of the influenza cases compared to previous seasons, to identify specific medical conditions associated with severe forms of influenza, to highlight effective interventions in the prevention of severe cases of influenza and to contribute to the detection of emerging respiratory pathogens (55).

The EuroMOMO project monitors, in real-time, all-cause mortality in Europe (56). The FluMOMO project aims to quantitatively assess the impact of influenza on mortality (57).

1.5 Burden of influenza

Surveillance data allows us to estimate the burden of influenza disease. The WHO estimates that, each year, seasonal influenza epidemics globally affect 20-30% of children and 5-10% of adults (6) and that they cause three to five million severe (hospitalised) cases and 250,000 to 500,000 deaths worldwide (58). In 2007, a European pilot study measuring the impact of seven infectious diseases in terms of the number of years of life lost placed influenza in third place (59). Several studies have suggested that influenza was the main cause of excess winter mortality in patients with ischemic heart disease, pneumonia, diabetes or cardiac arrest (60–62).

The mean annual incidence of influenza related hospitalisations among elderly ranges between 136 and 309 episodes per 100,000 persons in the United States and England (63–65) and the case fatality among hospitalised cases of influenza is estimated to be 7% (66). More than 90% of seasonal influenza-related deaths occur in patients aged 65 years and over (67) and case-fatality increases with the number of underlying diseases (68). Finally, as a result of the aging of the population, the overall number of influenza related hospitalisations and deaths tends to increase (67).

Pregnant women also have an increased risk of severe or fatal episodes of influenza. Influenza infection can lead to complications such as stillbirths, neonatal deaths, premature deliveries, and low birthweights (69).

1.6 Prevention options

Preventive approaches for influenza viruses are articulated around three pillars: non pharmaceutical actions to stop the spread of viruses, influenza vaccines and antiviral drugs to address influenza infections. These three approaches complement each other.

1.6.1 Non pharmaceutical interventions (NPIs)

According to the US Centers for Disease Control and Prevention (US-CDC), NPIs can be classified as personal, environmental or community based (70). Personal NPIs include mouth/nose covering when sneezing and coughing, hand washing and self-quarantine when symptomatic. Environmental NPIs aim at limiting indirect transmission through surface cleaning. Community-based NPIs include health education, social distancing and restriction on public gatherings. A recent systematic review of evidence about the use of NPIs to reduce influenza transmission in adults highlighted the limited amount of data currently

available (71). The authors found studies providing robust evidence of the effectiveness of hand washing and oral hygiene (such as gargling, which could reduce the oral load of influenza virus) (72).

1.6.2 Antivirals

Neuraminidase-inhibitors oseltamivir and zanamivir are antiviral drugs targeting influenza A and B viruses. Antivirals can be used as a postexposure or preexposure chemoprophylaxis for influenza.

In the post-exposure chemoprophylaxis approach, neuraminidase inhibitors are offered to individuals who were in contact with a suspected case of influenza in the past 48 hours. Individuals at increased risk of severe forms of influenza and unvaccinated healthcare workers are the main targets for this approach (73). Oseltamivir and zanamivir efficacy against influenza illness among individuals sharing a household with an influenza laboratory-confirmed person ranges between 69% and 89% (74).

In the pre-exposure chemoprophylaxis approach, individuals are given antivirals during influenza activity in the community. RCTs among healthy adults have demonstrated over 80% efficacy against laboratory confirmed influenza for oseltamivir and zanamivir (75,76) and observational studies have found high effectiveness of pre-exposure use of these antivirals among patients in institutional settings (74). This high effectiveness of antivirals to prevent influenza comes with some constraints. To be efficacious, the pre-exposure chemoprophylaxis must be administered throughout the entire period of virus circulation. Long-term use of neuraminidase-inhibitors may be associated with an increased risk of adverse events (77) and development of antivirals-resistant strains of viruses. To maximize its effectiveness, antiviral medication must be taken every day, leading to concerns about compliance and supply capacity (74).

In this context, prevention against influenza through vaccination remains the most recommended approach.

1.6.3 Vaccination

The first commercial influenza vaccines were approved for the use in the USA in 1945 (78). Most of the current seasonal influenza vaccines contain two strains of influenza A and one strain of influenza B. Since 1973 (and since 1998 for Southern hemisphere) (7), antigenic composition of these vaccines is reviewed twice a year (one for each hemisphere) and is based on the distribution of circulating influenza viruses as interpreted by the WHO Global Influenza Surveillance and Response System (GSIRS) (79,80). Each year, within six months production periods, about 450 million doses are produced and marketed in more than 190 countries (81,82). For the Northern hemisphere vaccines, vaccine composition is decided in February and the vaccines are available in October.

There are two types of influenza vaccines available (**Table 1**): an inactivated (killed) preparation administered as an injection and a live attenuated influenza virus vaccine normally delivered intranasally. Inactivated influenza vaccines (IIV), some of which contain adjuvants for greater immunogenicity, are recommended for populations at risk. IIV may be of three types: whole virus vaccines, split virus vaccines, and subunit vaccines. In split virus vaccines, the virus has been disrupted by a detergent in order to reduce vaccine reactogenicity. In subunit vaccines, hemagglutinin and neuraminidase, the two glycoproteins of the influenza virus membrane have been further purified by removal of other viral components (83). Oil-in-water adjuvants, such as MF59 and AS03, improve immune response to IIV, particularly among children and persons older than 60 years (84,85). Several of these vaccines are delivered, mainly to elderly, in Europe. For live attenuated influenza vaccines (LAIV), authorized since 2003, a temperature-sensitive variant vaccine virus strain is used, that replicates well in the nasopharynx but poorly in the lower

respiratory tract. They are only indicated for healthy persons and mostly used in children. There is little evidence of their effectiveness in the elderly (86). These live attenuated vaccines will not be studied in this work.

The inclusion of both lineages of influenza B virus has recently led to the development of a quadrivalent influenza vaccine (QIV), for which applications for European marketing authorization are currently being studied (87).

Current vaccine prices vary across EU countries. In Nordic countries, TIV negociated price averages 3-4€ while they are sold 6-8€ over the counter (in pharmacies). No organised programmes have introduced QIV and its price over the counter is approximately 12€. LAIV cost approximately 20€ and adjuvanted vaccines are sold around 25€ per dose in the USA (personal communication by Kari Johansen, ECDC).

Table 1: Types of seasonal influenza vaccines available for use globally as of 2016.

Vaccine type	Dose	Route	Age indications
Inactivated influenza virus (IIV) vaccines			
Trivalent, egg-based (adjuvanted or unadjuvanted)	Standard	Intramuscular	≥6 months
Trivalent, egg-based	High	Intramuscular	≥65 years
Trivalent, cell culture-based	Standard	Intramuscular	≥18 years
Trivalent, recombinant hemagglutinin influenza vaccine	Standard	Intramuscular	≥18 years
Quadrivalent, egg-based (unadjuvanted)	Standard	Intramuscular	≥6 months
Quadrivalent, cell culture-based (unadjuvanted)	Standard	Intramuscular	≥4 years
Quadrivalent, egg-based	Standard	Intradermal	18–64 years
Live-attenuated influenza virus (LAIV) vaccines			
Quadrivalent since 2013-14 (previously trivalent)	Standard	Intranasal	2–49 years

1.7 Vaccination strategies

1.7.1 Current vaccination strategies in Europe

Every year, vaccination activities are organised before the beginning of the influenza season (taking into account the average two weeks that an individual needs to mount an adequate immunological response (88)). It usually starts with largely advertised vaccination campaigns.

Following WHO recommendations (89), European member states recommend and subsidise vaccination for the population at risk of developing severe forms of influenza (90). This strategy has been assessed as

cost effective (79,91) and primarily aims at reducing the number of cases of severe influenza by targeting the population at high risk of hospitalisation or death (79,92–94). People with a high risk of infection, who can act as a bridge between the general population and at-risk groups, such as caregivers in nursing homes, are also targeted by vaccination (95). According to WHO recommendations, groups at increased risk of severe disease include pregnant women, children under 5 years of age, the elderly and individuals with underlying conditions such as HIV/AIDS, asthma, chronic cardiac or pulmonary disease (79). These generic recommendations are then adapted in each country and the target age groups specified. In 2006, the proportion of the European population aged 65 years and over was estimated at 16.9%, while an estimated 8.3% of the population had at least one underlying disease. In total, 125 million people were targeted by seasonal influenza vaccination (96).

1.7.2 Other vaccination strategies

Other strategies for seasonal influenza vaccination are being implemented across the world. Since 2010, the USA promote annual vaccination of all persons aged 6 months and older (91). Previous experiences of universal vaccination, such as in the Canadian province of Ontario since 2000, had proven to be cost-effective. While the Ontario programme of universal vaccination cost approximately twice as much as the targeted programme, local researchers estimated a decrease in the number of influenza cases by 61%, influenza specific mortality by 28%, and the health care services cost by 52% (97).

Since 2013, England and Wales have introduced a publicly funded pediatric vaccination programme using LAIV. This decision was, among others, based on modelling studies concluding on the role of key infection spreaders played by children (98,99). This program is still scaling up.

Current vaccination strategies options discussed at the European level include indirect effect through vaccination of children (as in England and wales), use of broader vaccines (quadrivalent inactivated vaccines (QIV), adjuvanted or high-dose vaccines) or a combination of vaccination with use of antivirals and close monitoring of resistance development.

1.7.3 Vaccine coverage in Europe

Monitoring vaccination coverage is an essential component of the evaluation of influenza vaccination campaigns. The VENICE project conducted surveys in 2008 and 2009 to measure vaccine coverage in the 27 participating countries. Methods used by countries included the use of administrative data (vaccination registry, census), data shared by vaccine producers (sales of vaccines) and surveys conducted by telephone, mail or face-to-face (100).

Vaccine coverage among the elderly varied between 1% in Estonia and 76% in Scotland in 2014-15 and tended to decrease over time (101). In general, countries in which the cost of vaccination was subsidised had higher vaccine coverage in those over 64 years (100). Among those targeted by vaccination due to underlying chronic diseases, vaccine coverage was reported by eight countries and ranged from 21% to 72%.

Despite European member states' and the World Health Organization's (WHO) recommendations to annually vaccinate elderly (89), influenza vaccine coverage among elderly remains below the 75% target in most European countries (102). In France, the seasonal influenza vaccine coverage among elderly has been constantly decreasing in the past decade, dropping from 65% in 2008-09 to 48% in 2015-16 (103).

1.7.4 Vaccine safety

The Vaccine Adverse Event Reporting System (VAERS), which is the US national vaccine safety surveillance program co-sponsored by the CDC and the Food and Drug Administration (FDA), reported, as most common adverse events, injection-site reactions, pain, fever, myalgia, and headache (91). The most common severe adverse event after TIV injection in adults reported to VAERS was Guillain-Barré Syndrome (GBS)(104). Authors from a recent meta-analysis concluded that there was a small (RR=1.22; 95% CI, 1.01-1.48) but statistically significant association between seasonal influenza vaccines and GBS (105). The CDC considers that the potential benefits of influenza vaccination in preventing serious illness, hospitalisation, and death substantially outweigh these estimates of risk for vaccine-associated GBS (91). Sustainable safety surveillance is particularly relevant in a context of introduction of new vaccine types (LAIV, adjuvanted, quadrivalent vaccines) and in preparation for the next pandemic vaccines. In 2009-10, an association between pandemic vaccine Pandemrix and narcolepsy was identified in various European countries, including Finland, France and Ireland (106–108).

1.8 Measure of vaccine efficacy/effectiveness and product approval by European Medical Agency

1.8.1 Vaccine efficacy / effectiveness

In vaccinology, we usually measure the effect of the vaccine among vaccinated individuals. However, a vaccination programme may also reduce the risk of a disease in the entire population, including unvaccinated individuals. To measure the risk reduction in the entire population (overall effect), we compare the risks in a population with a vaccination programme (including vaccinated and unvaccinated individuals) and a population without a vaccination programme (**Figure 1**).

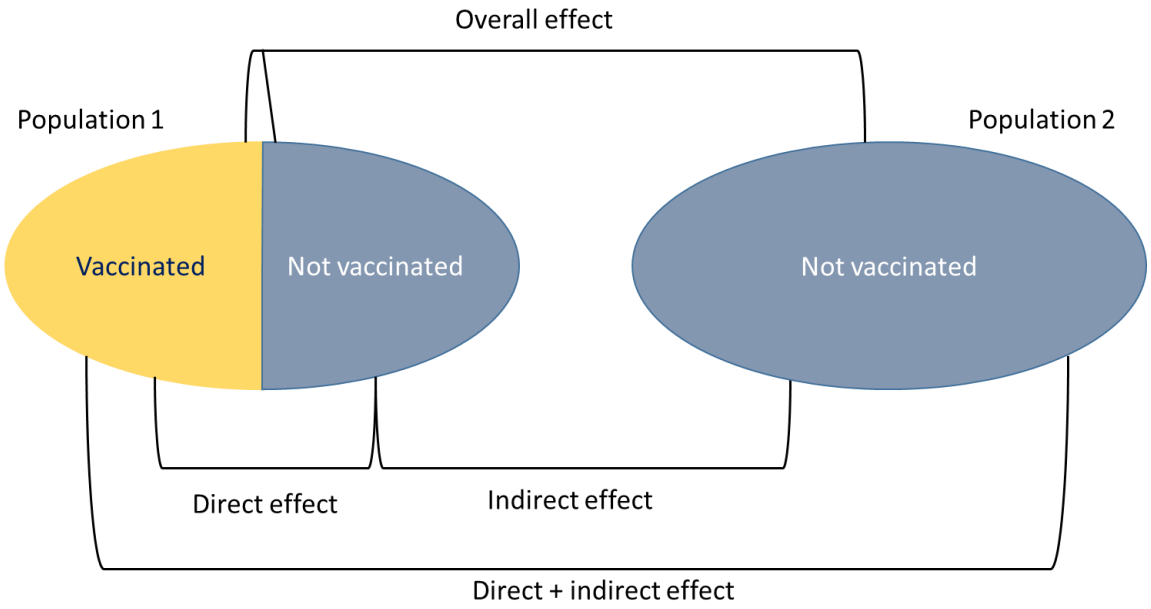

Figure 1: Types of effects in vaccinology, adapted from Halloran et al. (109)

This is usually done by comparing the incidence of a disease in a given population before and after the introduction of a vaccination programme (110). To measure the overall effect (also called impact) of the influenza vaccination programme, we would need to use a place where seasonal influenza vaccine has not yet been introduced. Even if we were to find such a place, natural differences in annual incidence of influenza are such that we would not be able to attribute a risk reduction to the sole effect of the vaccine programme. We can also measure the effect of a vaccine programme on the unvaccinated population by computing the risk reduction between a group of unvaccinated individuals in a population with and without a vaccine programme. By doing do, we will measure the indirect effect, also called herd immunity, which reflects the effect that vaccinating part of the population has on the virus circulation among the unvaccinated population. Finally, we can compute the sum of the direct and the indirect effect (known as the total effect (111)) by measuring the risk reduction between vaccinated individuals from a population with a vaccination programme and unvaccinated individuals from a population with no vaccination programme. Measuring the indirect and the total effect of seasonal influenza present the same limitations as to measure the overall effect.

In this context, we will focus on measuring the effect of the vaccine on vaccinated individuals. This effect, called the direct effect (or vaccine efficacy or effectiveness), is the measure of the percentage of reduction in the incidence (risk or rate) of a given disease in vaccinated individuals that may be due to vaccination. We calculate it as the percentage of incidence reduction between those who received a vaccine and those who did not, in a population with a vaccination programme (Figure).

Its calculation is made according to the following formula:

$$VE\% = (1 - RR) \times 100 \ = (1 - \frac{IV}{IU}) \times 100$$

Where IU is the incidence rate in the unvaccinated and IV in the vaccinated. RR represents the rate ratio (or risk ratio). When risks cannot be measured directly, it is possible to approach the RR by measuring the odds ratio (OR). In this case, VE = (1-OR) x 100.

In the scientific community, there is a general consensus to define vaccine efficacy as the pre-marketing measure of the vaccine performance, obtained through clinical trials (112). Post-marketing measures of vaccine performance are referred as vaccine effectiveness.

1.8.2 Vaccine efficacy

Pre-marketing vaccine efficacy is generally measured in RCT using laboratory confirmation as the endpoint. Properly conducted RCT should reduce, as much as possible, selection bias between vaccinated and unvaccinated so as to ensure that the differences observed are attributable exclusively to the vaccine. These RCT are also based on the assumption that exposure to the virus is the same between vaccinated and unvaccinated.

Pre-marketing efficacy data for influenza vaccines show a 60% protection in adults without chronic underlying disease (86). This protection rises to 70-90% against laboratory confirmed clinical disease in healthy adults when the vaccine antigens correspond to the viruses in circulation (91).

Annual vaccination of risk groups has been recommended since 1960 in the United States without any vaccine efficacy studies in this population (2,3). As these recommendations have been relayed at the international level, the conduct of clinical trials in these risk groups has become impossible for ethical reasons. Only post-marketing effectiveness studies can be conducted among the groups targeted by

vaccination. The level of evidence of influenza vaccine effectiveness among populations targeted by vaccination is considered low (95) based on recent literature reviews (113).

1.8.3 Marketing authorization

Considering the short time lag for vaccine production and marketing, it is impossible to conduct yearly clinical trials to measure pre-marketing vaccine efficacy. Consequently, each year new TIV are authorised based on immunogenicity data (114). The haemagglutination inhibition reaction is used as an immune correlate of the protection conferred by the vaccine for the delivery of its marketing authorization (114,115). This reaction indirectly measures the ability of the antibodies produced by the vaccine uptake to inhibit the hemagglutinating capabilities of the virus. The titer of these antibodies is the equivalent of the last dilution inhibiting haemagglutination. A titer greater than or equal to 40 is commonly considered as protective by the European and American drug regulatory agencies. Although there is a relationship between the level of clinical protection against influenza and the titer in healthy adults (116), protection reflects complex immune responses that cannot be summarized as a single measure (117). The development of correlates of protection against severe influenza in a context where the vaccination strategies are aimed at preventing these events represents a major stake (118).

1.8.4 Post-marketing vaccine effectiveness

Post-marketing vaccine effectiveness measures the direct effect of a vaccine once it is put on the market. It quantifies the difference in the incidence of a disease between vaccinated and unvaccinated individuals belonging to the same population in which there is a vaccination program. Post-marketing effectiveness is thus influenced by the pre-marketing efficacy of the vaccine, the conditions of use of the vaccine, the characteristics of the population and the circulating agent (influenza strain). Investigators cannot control vaccine use conditions (manufacture, refrigeration, storage, administration, compliance with protocols, etc.) or the exposure of patients to vaccines. Post-marketing vaccine effectiveness is measured by observational population-based studies.

1.9 Study justification

1.9.1 How can IVE guide public health actions

Considering the absence of pre-marketing data, the high burden of seasonal influenza illness and the expenses engaged in annual influenza vaccination, monitoring vaccine safety and performances are essential to evaluate and guide influenza vaccination and prevention strategies.

Vaccine performance is commonly measured by computing IVE, which measures the percentage risk reduction of influenza illness among vaccinated individuals compared to those unvaccinated. IVE estimates by type/subtype, vaccine type or brand, population subgroup or history of vaccination may also guide public health policies.

1.9.1.1 IVE against any influenza

IVE may be used to derive a number of cases / deaths averted by a vaccination programme (119). These figures are often easier than IVE estimates to communicate to the general population.

In recent years, there has been an increase in the use of influenza vaccine among middle-income countries targeting high-risk groups (120) and policy makers in low- and middle-income countries are increasingly assessing whether and how to implement new influenza immunization programmes. By 2014, 59% of the

194 WHO member states had a national influenza immunization policy in place (121). IVE data is needed to feed cost-effectiveness analysis to support countries considering implementing an influenza vaccination programme. This is especially relevant in a context of recent questioning regarding influenza vaccine performance. Furthermore, this data is sensible in light of the increasingly wider range of vaccines offered and the need to prioritize resources for the immunization programs.

1.9.1.2 IVE against severe influenza

Seasonal vaccination strategies in Europe are aimed to reduce severe outcomes by targeting those at-risk of developing severe forms of illness. Measuring IVE against severe outcome is hence relevant to evaluate and guide vaccination strategies. Currently, cost-effectiveness analysis rely on estimates of IVE against mild outcome, assuming that IVE against hospitalised outcome is the same (122,123). Considering the cost of inpatients compared with outpatients, integrating IVE against hospitalised outcome in cost effectiveness analysis would be relevant. In a recent cost-effectiveness analysis, Newall et al. concluded that evidence to establish the disease burden and vaccine efficacy in the elderly (particularly against severe outcome) was needed (124).

Across five seasons of a European based primary care study measuring IVE, less than 15% of influenza cases were aged 60 years and above (125), and about 20% of patients had underlying chronic conditions (126–128), making the computation of precise estimates in these subgroups difficult. Hospital based studies may capture better than primary care based studies influenza cases from the population targeted by seasonal vaccination.

During the 2009 A(H1N1) pandemic, adults aged <65 years were at higher risk for hospitalised influenza compared with elderly (129). Having a system in place to measure IVE against severe outcome would be relevant in case of pandemic as it would enable public health authorities to target the use of complementary approaches to subgroups of the population where the vaccine does not perform well.

1.9.1.3 IVE by subtype/lineage

1.9.1.3.1 (Sub)type specific performance

While IVE against overall influenza is useful for cost effectiveness studies, it is hard-to-interpret since vaccines perform differently according to the viruses circulating (130). Repeated evidence of suboptimal effectiveness of seasonal influenza vaccines against specific influenza subtype(s) or lineage(s) may help promoting alternative prevention measures early in the season if virological data show that this/ese subtype(s) or lineage(s) are predominantly circulating. Such measures would be of particular relevance in the case of the circulation of a (sub-)type known to be associated with excess hospital admissions and mortality.

1.9.1.3.2 Cross lineage protection and need for a quadrivalent vaccine

Two lineages of B viruses co-circulate among human. In TIV, only one lineage is included. Current questions are raised about the need to introduce a QIV on the European market. Arguments from pro-quadrivalent vaccines include the inability to predict which influenza B lineage will circulate (131) and the low cross-lineage protection that the TIV currently provides (132).

Providing TIV IVE against unmatched B viruses, together with data on burden of influenza B (and in particular unmatched B viruses) could help feeding cost effectiveness models to decide whether introducing QIV should be recommended.

Understanding previous effect of seasonal vaccination against influenza B may also help vaccine lineage selection. Among possible lineage selection strategies, the yearly alternative approach proposes to

alternate one Yamagata and one Victoria strain, assuming a one-year residual protection against the other lineage (133).

1.9.1.4 Early IVE estimates

Early estimation and communication of poor vaccine performance may help promoting the use of antivirals by health professionals, among at-risk individuals (even vaccinated) in particular. Other prevention measures may be promoted, such as hand washing, isolation or mask wearing.

Within-season virus drifts are common in influenza viruses, leading to imperfect match between circulating viruses and vaccine contained components. Several clades may be co-circulating and be potential candidates for the next season vaccine. Measuring IVE against each of these clades and showing differences in clade specific IVE may help the GSIRS chose between several available strains for vaccine content.

1.9.1.5 IVE estimates by specific groups (age/comorbidities)

Seasonal influenza vaccination is recommended to the population at-risk of developing severe forms of illness. Evidence of the effectiveness of influenza vaccination in preventing severe clinical outcomes was recently described as low or very low among elderly (134), and among patients with cancer (135), diabetes mellitus (136), lung diseases (137)(138), or cardiovascular diseases (139). IVE estimates in these subgroups are important. Results showing that vaccines provide substantial protection to these patients would give arguments to health professionals to propose seasonal vaccination to patients. On the other hand, suboptimal IVE in specific subgroups of population at increased risk of developing severe forms of illness may lead to testing alternative strategies (e.g. targeting their relatives).

It can also be used to recommend or evaluate vaccination strategies as part of cost effectiveness studies. In a 2010 Cochrane review on IVE among elderly, Jefferson et al. reported estimates that were consistently below those usually quoted for economic modelling or decision making (134).

1.9.1.6 IVE by brand or type of vaccine

Authorizations to deliver an influenza vaccine product on the market were traditionally based on haemagglutination-inhibiting antibody titers in healthy population (115). While these immunogenicity data are thought to be valid for healthy adults (116), the development of correlates of protection suited to vulnerable populations is still to be achieved (118). In 2015, the EMA started requesting the manufacturing companies to provide product-specific IVE.

On the other hand, in a survey that we performed among 19 EU/EEA member states, 17 countries reported that they purchased more or all subsidised vaccine products through national or regional tenders. The main criteria for product selection is currently its price. Product specific IVE would allow health authorities to also base their choice on vaccine performance.

Vaccine type specific IVE may also be used to provide or revise recommendations in case of suboptimal performance of specific vaccine type/products. They may also be used to feed cost effectiveness analysis and evaluate recommendations.

1.9.1.7 Effect of repeated vaccination

Results of recent studies have questioned the effect of repeated influenza vaccinations on current season IVE (140–143). Several immunological hypotheses have been suggested to explain the potential effect of previous influenza vaccination, or natural infection, on IVE.

According to the infection block hypothesis, heterosubtypic immunity can be acquired following natural infection. This cross-protective immunity would be sufficient to temporarily block other influenza infections. If verified for influenza in humans, this would mean that vaccination, by avoiding natural infection, could prevent the acquisition of this natural infection protection and therefore represent a risk factor for future influenza infections (144).
Smith et al. (142) have developed what is known as the antigenic distance hypothesis. They suggest that antigenic distances between the first and second vaccines, and between the first vaccine and the epidemic strain, significantly affect attack rates in repeat vaccinees. When the antigenic distance between previous and current seasons vaccine strains is small, but the antigenic distance between previous season vaccine and current season circulating strain is high, negative interference may be expected. Antibodies produced by the immune response to previous season vaccine may cross-react with current season vaccine, avoiding current season to induce an immune response. Such negative interference is not expected when antigenic distance between consecutive vaccines is high. Finally, positive interference is expected when previous vaccine and current circulating strains are antigenically similar (142).
The original antigenic sin hypothesis was first described by Francis et al. when they observed that humans produced minimal antibody response to the current infecting viruses but instead produced higher titer antibody against influenza viruses they encountered as children (145). Protection against influenza mainly relies on antibody responses targeted against HA and NA. Regular antigenic drifts alter these sites and lead to antigenically related viruses with shared common antigenic epitopes and unique strain-specific epitopes (146). The antigenic sin approach proposes a model where there is a competition between antigen-specific memory and naïve B cells for common epitopes. Exposures to dominant antigens of first-(in time) infecting viruses, when seen later as secondary antigens (similar but distinct antigen) reinforce antibody response to the original strains at the expense of responses to newer strains (147). In the context of influenza, annual vaccination may induce original antigenic sin (now also called original antigenic virtue), by enhancing the immune response to new influenza infection by a virus antigenically related to the vaccine component.
The few epidemiological studies describing the effect of repeated vaccinations, have mainly focused on primary care based studies with non-severe outcomes (140,141,148,149). Further understanding the role of repeated vaccinations on seasonal IVE in elderly is important to better interpret current seasonal IVE, guide new vaccine development and, eventually, inform vaccination strategies (150).

1.9.2 fInfluenza Vaccine effectiveness studies in Europe (before this project)

1.9.2.1 I-MOVE

While seasonal influenza vaccines were first delivered in the USA in 1945 (78), monitoring of their effectiveness started in 2003-04 in the USA (151). In order to annually monitor IVE, a number of countries or regional platforms of primary or secondary health care units have emerged across the world, including the European I-MOVE network (152), US Flu VE Network (153), the Canadian Sentinel Practitioner Surveillance Network (SPSN) (154) and the Australian FluCAN vaccine effectiveness surveillance (155).

In Europe as part of the project "Surveillance of the IVE against seasonal influenza and pandemic influenza in the EU", a network of study sites has been set up in EU Member States to measure the seasonal and pandemic IVE against influenza. Since 2008, this network, called I-MOVE (Influenza Monitoring Vaccine Effectiveness), is conducting IVE studies within existing surveillance systems based on networks of primary care practitioners (152,156–159).

Primary care based studies were logically first implemented as they rely on pre-existing surveillance systems consisting of sentinel networks of general practitioners (GP). In these networks, GP systematically swab a proportion of patients visiting with ILI symptoms. The specimens are then tested using RT-PCR tests and results are sent, together with basic information on the patients, to the regional or national surveillance teams. Reporting of vaccination status by the GPs is facilitated by the fact that they are the vaccine providers in most countries. Using a TND approach (further detailed later in this report) is very cost-effective to measure IVE. TND studies consist in comparing the odds of vaccination between ILI patients testing positive and ILI patients testing negative for influenza. However, these studies based on primary care settings do not allow to measure IVE against severe forms of influenza illnesses.

1.9.2.2 IVE against hospitalised influenza

Surveillance of severe cases of influenza in Europe relies on a systematic swabbing and testing of patients admitted to hospital or ICU with a severe acute respiratory infection (SARI), at the regional or national level. In 2014, the ECDC presented an evaluation of severe influenza surveillance and concluded that there was a very high heterogeneity of systems in place (160). Relying on such heterogeneous systems to apply a TND approach and compute IVE against laboratory confirmed hospitalised influenza would be challenging. If countries using hospitalisation as an outcome do not collect information on ICU admission, we will end with a mix of outcomes that would lead to results difficult to interpret. Seasonal influenza related ICU admissions are uncommon and, using that as an outcome, would most likely lead to imprecise results. Furthermore, obtaining the vaccination status for patients admitted to hospital in routine is difficult as it requires contacting the patients' GP.

In this context, measuring IVE against laboratory confirmed hospitalised influenza required setting up a network of hospitals able to apply a generic protocol to include and swab patients based on the same criteria.

2 HYPOTHESES AND OBJECTIVES

2.1 Hypotheses

Based on the context described above and the experience from primary care based IVE studies, we have made the following hypotheses:

- Building a network of hospitals using a common generic protocol will allow us to measure IVE against hospitalisation with laboratory confirmed influenza with good precision.
- Obtaining large sample size will allow us to conduct stratified analyses to identify groups of patients among whom the IVE is lower (e.g. age groups, specific underlying conditions).
- Repeating the study every season and measuring (sub)type specific analyses will lead to identifying (sub)types against which the IVE is lower.
- Collecting data on previous years vaccine status will allow us to explore the effect of repeated vaccination on IVE.
- Gathering IVE estimates against influenza hospitalisation globally will allow us to obtain more precise summary estimates and identify trends in influenza vaccine performances.

2.2 Objectives

Given the background, hypotheses and methodological issues outlined above, this thesis addresses two main objectives.

The first objective was to measure influenza vaccine effectiveness against hospitalisation with laboratory confirmed influenza among adults in Europe. To address this objective, we set up a European network of hospitals in which study teams adapted a generic protocol. Through this network we aimed at addressing a number of secondary objectives. For each influenza (sub)type, we aimed at measuring IVE stratified by age group, among the population targeted by the vaccination programmes, among patients with specific chronic conditions (including diabetes, cancer, underlying cardiac or lung diseases), by vaccine brand and according to previous vaccination status.

The second objective was to compute summary estimates of published data on IVE against hospitalisation with laboratory confirmed influenza in adults globally. To address this objective, we conducted, in collaboration with colleagues from WHO-PAHO, Melbourne WHO Collaborating Centre for Reference and Research on Influenza and US-CDC, a systematic review of published results and a meta-analysis.

3 MEASURE OF SEASONAL INFLUENZA VACCINE EFFECTIVENESSS AGAINST HOSPITALISATION WITH INFLUENZA IN EUROPE

3.1 IVE against hospitalised laboratory outcome: potential study designs

Potential study designs to measure IVE include cohort studies, case-control studies and the so-called "screening" method.

Whatever the study design, the study population may be defined as all persons living in the community who may be admitted at a hospital for a severe form of influenza. Hospitalised influenza could be defined as an influenza associated hospitalisation (patients staying in hospital for at least 24 hours). The primary endpoint can be defined as influenza laboratory-confirmed by RT-PCR methods.

A person can be considered to have been vaccinated against influenza if she/he had received at least one dose of the seasonal influenza vaccine at least 14 days before the onset of ILI/SARI symptoms (patients vaccinated less than 14 days before the onset of ILI may be considered as unvaccinated or excluded).

3.1.1 Cohort studies

3.1.1.1 Principle

In cohort studies, the incidence rate of laboratory-confirmed influenza in hospitalised patients in a vaccinated population is compared to the laboratory-confirmed influenza incidence rate in hospitalised patients in a non-vaccinated population. The measure of effect is calculated on the basis of a risk ratio.

The vaccinated population includes all individuals in the study population who have been vaccinated with a seasonal influenza vaccine for more than 14 days. The unvaccinated population includes all individuals in the study population who have not (yet) received a seasonal influenza vaccine for more than 14 days.

3.1.1.2 Sources of information

To define our cohorts, data on the vaccination status of the entire source population are needed. Electronic vaccination registers are the most appropriate source of information for this type of study design.

The identification of hospitalised cases of influenza takes place within the participating hospitals and are based on a positive laboratory RT-PCR results.

Clinical data and access to care, which may act as a confounding or modifying effect in the IVE estimation also need to be available for the entire source population. The most appropriate sources of information would then be electronic primary and secondary care medical records.

3.1.1.3 Calculation of the IVE

For cohort studies, the risk of laboratory-confirmed hospitalised influenza in individuals vaccinated and not vaccinated is compared using a risk or a rate ratio. IVE is calculated using the formula IVE = 1 - RR (expressed as a percentage).

Formula for cohort studies:

$$VE\% = (1 - RR) \times 100 \ = (1 - \frac{IV}{IU}) \times 100$$

Where:

IVE: Influenza vaccine effectiveness
RR: Risk or rate ratio
IV: Influenza incidence in vaccinated population
IU: Influenza incidence in unvaccinated population

3.1.1.4 Potential settings

In Europe, cohort studies to measure IVE against laboratory confirmed influenza may be conducted in countries or regions equipped with electronic registries and healthcare databases. To be suited for this study, routine swabbing of patients admitted with ILI or SARI symptoms must be in place in participating hospitals.

In 2014, the only place in Europe where such conditions were combined was the Spanish region of Navarra (640,000 inhabitants). Navarra has a fully computerized health data management system. In addition to drug prescription data (including vaccination), this system contains data on medical diagnostics in primary and secondary health care, as well as laboratory data.

In this region, hospital medical staff routinely swab patients admitted with ILI symptoms for influenza laboratory test. Data on the diagnosis of ILI and laboratory test results are entered into the regional database, which contains a list of underlying diseases and vaccination status for each patient. Using this database, it is thus possible to define cohorts of vaccinated and non-vaccinated persons each year and to estimate and compare the incidence rate of laboratory-confirmed hospitalised influenza among these two cohorts. However, considering the low incidence of the outcome and the relatively small population size of Navarra, limitations in terms of statistical power are likely to occur.

3.1.2 Screening method

3.1.2.1 Principle

Vaccine coverage among the population covered by a given hospital area are obtained (if possible by age group and groups at risk for severe influenza) and compared to the vaccination coverage among confirmed cases of hospitalised influenza. If there is no definition of the area served by the hospital, the reference population used for immunization coverage must be defined.

3.1.2.2 Source of information

For the screening method, data sources may include:

To estimate vaccination coverage among severe cases:
- Patient Medical Records
- Interview with patient or family
- Interview with the general practitioner of patients
- Vaccination register
- Laboratory

To estimate vaccination coverage in the reference population:
- Vaccination registers

- Insurance data
- Immunization coverage survey data

3.1.2.3 Calculation of the IVE

For studies using the screening method, the OR of vaccination in cases vs the reference population is calculated.

$$\text{IVE} = 1 - \text{OR} = 1 - \frac{PCaV\ (1-PPV)}{PPV\ (1-PCaV\ )} = \frac{PPV\ -PCaV}{PPV\ (1-PCaV\ )}$$

With:

IVE= Influenza Vaccine Effectiveness
OR: Odds Ratio
PCaV: Proportion of cases vaccinated
PPV: Proportion of the reference population vaccinated

3.1.2.4 Potential Study Sites

Surveillance of severe cases of influenza is based on the notification of patients admitted to the ICU with laboratory-confirmed influenza (55). The objective of this monitoring is to provide real-time data on the severity of the influenza epidemic. The collection of the vaccination status of confirmed severe cases of influenza is performed routinely in some countries (including France) and in the region of Navarre in particular. Applying the screening method would therefore be possible in these locations.

The screening methods is a cost and time effective approach to measure IVE as it does not require detailed data collection on non-cases, unlike TND studies. However, screening method studies are fully dependent on accurate and valid data on vaccine coverage in the source population. In order to adjust for potential confounding inherent to IVE studies, we would need to obtain vaccine coverage by numerous subcategories of the population including by detailed age groups and specific chronic conditions. In its latest Field Guide for the Evaluation of Influenza Vaccine Effectiveness, WHO recommends against the use of screening method designs to estimate IVE (161). We decided not to use this approach in this work.

3.1.3 Case-control studies

3.1.3.1 Principle

In case control studies, we derive IVE from the comparison of the odds of vaccination among cases and controls (OR). Cases may be defined as patients hospitalised with laboratory confirmed influenza. In order for the OR to approximate the RR, the control group needs to have experienced the same exposure of interest (influenza vaccination) as the population giving rise to the cases. Hospitalised cases of influenza are likely to be patients at-risk for severe influenza. They are therefore more likely than the general population to have underlying conditions and therefore to be vaccinated. In this context, we need to target similar profile of patients when recruiting controls.

In the last decade, a growing number of study teams has been using a specific type of case control study called test-negative design (TND) studies. First developed to measure IVE against medically attended outcomes (162), the TND (163,164) has been increasingly used for hospital based studies. In this approach, investigators enroll patients based on clinical criteria and measure the IVE derived from the relative

difference between the odds of vaccination among patients testing positive and those testing negative for influenza viruses.

By doing so, we hope to recruit patients at increased risk for severe forms of respiratory illnesses and therefore to include a control group representative from the source population of cases.

3.1.3.2 Source of information

In hospitals, data can be collected using a standardized form of data collection. The sources of information may include:
- Patient Medical Records
- Interview with patient or family
- Interview with the general practitioner of patients
- Vaccination registry
- Laboratory

3.1.3.3 Calculation of the IVE

For case-control studies, the Odds Ratio (OR) of vaccination among cases and controls are calculated. IVE is calculated using the formula IVE = 1 - OR (expressed as a percentage).

Formula for case-control studies:

$$\mathrm{IVE} = 1 - OR = 1 - \frac{PCaV \ / \ (1 - PCaV)}{P\mathrm{Co}V \ / \ (1 - P\mathrm{Co}V)}$$

Where:

IVE: Influenza Vaccine Effectiveness
OR: Odds ratio
PCaV: Proportion of cases vaccinated
PCoV: Proportion of controls vaccinated

3.1.3.4 Potential Study Sites

EpiConcept developed and shared a generic study protocol to measure IVE against laboratory-confirmed hospitalised influenza according to the negative test design. The adaptation of this protocol to a large number of hospitals in Europe aimed to allow the pooling of the data collected and the constitution of a sample of sufficient size to accurately estimate IVE.

3.2 Setting up a network of hospitals in Europe

In 2010, the ECDC requested EpiConcept to "define activities to be conducted in order to set up a network of hospitals in EU/EEA that is suitable for conducting influenza vaccine effectiveness and potentially other influenza related studies". This request resulted in the organisation of an expert meeting with potential partners at ECDC and the decision to write a generic protocol for hospital based studies.

3.2.1.1 InNHOVE network – 2011 to 2014

In 2011, in a context of reduced public funding for IVE studies, EpiConcept decided to set up a network of study sites able to start hospital based IVE studies based on the generic protocol for the season 2011-12. Four study sites embarked in this network. Sanofi Pasteur provided a grant to complete public funding for the French site (7 hospitals) and half of the Valencia region site (9 hospitals), where SPMSD contributed for the other half. GSK provided a grant to one hospital in Rome and Navarra was exclusively publicly funded. The coordination, the pooling of the data and its analysis was co-funded by the three manufacturers and EpiConcept and taken care of by EpiConcept. In 2012-13 and 2013-14, two publicly funded Lithuanian hospitals joined the European network (Table 2).

At the end of the 2013-14 season, in a context of changes of the EMA obligations towards the vaccine producers in Europe, GSK and Sanofi Pasteur cut their funding to the European network. To remain free from any conflict of interest, EpiConcept decided not to embark in an IVE study funded by a single vaccine producer.

3.2.1.2 I-MOVE+ network – 2015 onwards

In 2014, EpiConcept responded to a Horizon 2020 call for tender from the European Commission. We built a consortium with 20 public institutes and proposed to build a European plateform to measure and compare effectiveness and impact of influenza vaccines and vaccination strategies in the elderly. We included 25 hospitals from eleven countries in the hospital network for IVE. Our successful bid allowed us to sustain independent funding for the I-MOVE+ network for three seasons. This funding had to be used to measure IVE among elderly only.

Table 2: Study site and number of hospitals included by season, InNHOVE and I-MOVE + projects, 2011-2017

	Number of hospitals by season				
Study site	2011-12	2012-13	2013-14	2015-16	2016-17
Croatia				1	1
Finland				2	1
France	7	5	6	3	4
Hungary				2	2
Italy - InNHOVE	1	2	2		
Italy - I-MOVE+				3	3
Lithuania		2		2	2
Navarra, Spain	4	4	4	3	3
Netherlands				1	3
Poland				3	3
Portugal				2	2
Spain				2	2
Romania				3	3
Valencia, Spain	9	5			
TOTAL	**21**	**18**	**12**	**27**	**29**

3.3 Generic protocol

We developed and shared a generic protocol detailing the study design, population and period as well as proposing options for study conduction.

We conducted a multicentre hospital-based TND case-control study in several European countries.
The study population consisted of all community-dwelling individuals, aged 18 years and above in 2011-14 and 65 years and above in 2015-17, hospitalised with symptoms compatible with influenza like illness (ILI) /severe acute respiratory infection (SARI) to one of the participating hospitals/services, with no contra-indication for influenza vaccination and who had not yet been tested positive for influenza during the current season.
In each study site, the study period started at least 15 days after the seasonal influenza vaccine of the corresponding season became available. The study lasted from the start to the end of the influenza season, according to local influenza activity.

3.3.1 Outcome

The outcome of interest was laboratory-confirmed influenza in patients hospitalised with an ILI/SARI. More specifically, they were influenza A(H1N1)pdm09, influenza A(H3N2) or influenza B.

3.3.2 Definitions

3.3.2.1 ILI/SARI patient

In 2011-14, we used the term ILI to define the symptoms presentation. We changed for SARI in 2015. The ILI and SARI case definitions remained essentially identical: a hospitalised person with at least one systemic sign (fever or feverishness, malaise, headache, myalgia) and at least one respiratory sign (cough, sore throat or shortness of breath) at admission or within 48 hours after admission. The symptoms should not have started (or clearly worsened, if chronic) more than 7 days before swabbing.
We will refer as SARI patients in the rest of this document.

3.3.2.2 Hospitalised patient

A hospitalised patient was defined as a patient who has been admitted in one of the participating hospitals during the study period, and has not been discharged home or home-equivalent before 24h.
An influenza case was defined as a patient hospitalised with ILI/SARI with a respiratory sample positive for influenza. A control was defined as a patient hospitalised with ILI/SARI with a respiratory sample negative for influenza.

3.3.3 Patients identification – Algorithm for patients inclusion

Study teams actively screened patients admitted for potentially influenza-related conditions (**Table 3**).
For hospitals with electronic patient records and/or diagnosis codes commonly displayed, SARI related ICD codes were sought. Patients admitted with any of the ICD codes listed in **Table 3** were approached; those meeting the SARI case definition and the inclusion criteria were proposed to be part of the study and to sign an informed consent (**Figure 2**).

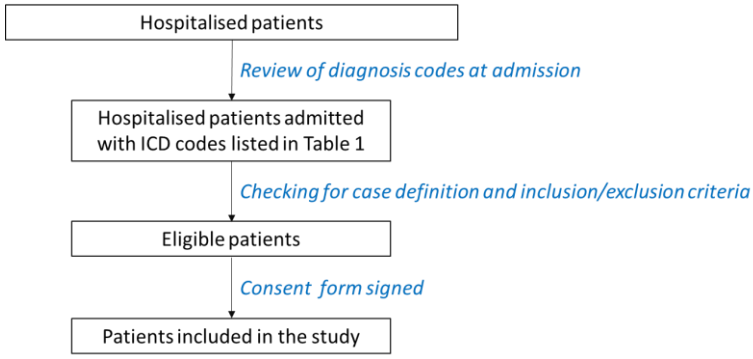

Figure 2: Proposed inclusion algorithm for hospitals/services relying on common use of ICD codes, IMOVE+ hospital based IVE studies

For hospitals where ICD codes at admission were not systematically collected or accessible, a systematic screening of all patients admitted was organised. This was typically either by sensitisation of the medical staff at the beginning of the influenza season. Patients meeting the SARI case definition and the inclusion criteria were proposed to be part of the study and to sign an informed consent (**Figure 3**).

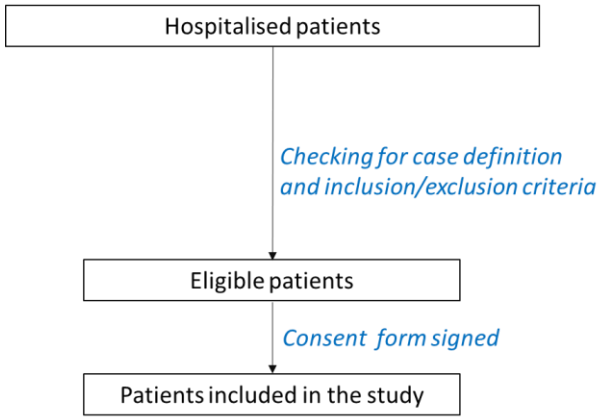

Figure 3: Proposed inclusion algorithm for hospitals/services systematic screening of all admitted patients, IMOVE+ hospital based IVE studies

Table 3: List of diagnosis codes for which patients must be screened for onset of SARI symptom that started within the past seven days, IMOVE+ hospital based IVE studies

Category	Morbidity	ICD-9	ICD-10
Influenza like illness	Cough	786.2	R05
	Difficulty breathing	786.05	R06
	Sore throat	784.1	R07.0
	Dysphagia	787.20	R13
	Fever	780.6	R50.9
	Headache	784.0	R51
	Myalgia	729.1	M79.1
	Fatigue/malaise	780.79	R53.1, R53.81, R53.83
Cardiovascular diagnosis	Acute myocardial infarction or acute coronary syndrome	410-411, 413-414	I20-23, I24-25
	Heart failure	428 to 429.0	I50, I51
Respiratory diagnosis	Emphysema	492	J43.9
	Chronic obstructive pulmonary disease	496	J44.9
	Asthma	493	J45
	Myalgia	729.1	M79.1
	Dyspnoea/respiratory abnormality	786.0	R06.0
	Respiratory abnormality	786.00	R06.9
	Shortness of breath	786.05	R06.02
	Other respiratory abnormalities	786.09	R06.00, R06.09, R06.3 R06.89
Infections	Pneumonia and influenza	480-488.1	J09-J18
	Other acute lower respiratory infections	466, 519.8	J20-J22
	Viral infection, unspecified	790.8	B34.9
	Bacterial infection, unspecified	041.9	A49.9
	Bronchitis	490, 491	J40, 41
Inflammation	SIRS non infectious without acute organ dysfunction	995.93	R65.10
	SIRS non infectious with acute organ dysfunction	995.94	R65.11
Diagnoses related to deterioration of general condition or functional status	General physical deterioration, lethargy, tiredness	780.79	R53.1, R53.81, R53.83
	Anorexia	783.0	R63.0
	Feeding difficulties	783.3	R63.3
	Abnormal weight loss	783.21	R63.4
	Other symptoms and signs concerning food and fluid intake	783.9	R63.8
	Desorientation/Altered mental status	780.97	R41.0
	Dizziness and giddiness	780.4	R42
	Infective delirium	293.0, 293.1	F05
	Coma	780.01	R40.2
	Transient alteration of awareness	780.02	R40.4
	Other alteration of consciousness (Somnolence, stupor)	780.09	R40.0, R40.1
	Febrile convulsions (simple), unspecified	780.31	R56.00
	Complex febrile convulsions	780.32	R56.01

Exclusion criteria:

The patient was not enrolled in the study if she or he:

- had a contraindication for influenza vaccine
- was hospitalised < 48 hours prior to SARI onset (to avoid including nosocomial infections among patient with consecutive hospital admissions)
- had his/her SARI onset ≥ 48 hours after admission at the hospital (to avoid including nosocomial infections)
- was unwilling to participate or unable to communicate and give consent (the consent could also be given by her/his legal representative, or by specific consent procedures, acceptable according to the local ethical review process)
- was institutionalised at the time of symptoms onset (living in a residence for people who require continual nursing care and have difficulty with the required activities of daily living).

Note: a patient can be selected several times as long as he/she does not have a previous laboratory confirmed influenza

3.3.4 Laboratory testing

Study nurses or physicians collected respiratory specimens from all eligible patients. Influenza laboratory confirmation was done using RT-PCR.

3.3.5 Definition of vaccination status

An individual was considered as vaccinated against influenza if he/she had received at least one dose of the influenza vaccine more than 14 days before ILI/SARI symptoms onset. An individual was considered as unvaccinated if he/she did not receive influenza vaccine in the current season or if he/she was vaccinated ≤14 days before SARI symptoms onset.

3.3.6 Data collected

We collected information on a broad range of potential confounding factors.

3.3.6.1.1 Underlying chronic diseases

We collected information related to chronic conditions and classified them according to **Table 4**.

The severity of the underlying conditions was measured by the number of hospital admissions due to underlying conditions in the 12 months prior to inclusion in the study.

Smoking history was collected and coded as follows: never-smoker, former smoker (stopped smoking at least one year before inclusion in the study), current smoker.

Vaccination against influenza in the last two seasons and vaccination against pneumococcal diseases were collected.

Frailty may be associated with both vaccination and the risk to develop severe symptoms in case of influenza infection. We captured the presence of functional impairment using a question related to the ability of patients to do a range of daily activities without assistance (based on the Barthel index questionnaire (165).

The use of antivirals prior to swabbing may lead to misclassification biases. We ran sensitivity analyses excluding patients who were administered antivirals prior to swabbing. We documented whether the patients

received any antiviral treatment in the two weeks preceding the symptoms onset and the type (curative or preventive) of antivirals received.

Source of information

The vaccination status was collected using vaccine registries in Spain (including Navarra and Valencia), Portugal and Finland. In other study sites, the teams would interview the patients and collect vaccine brand and vaccination dates by calling the pharmacists or the GPs. In the Netherlands, patients were the unique source of information for the vaccination status.

Underlying conditions and other potential confounding factors were collected through interview and hospital databases (or medical records) in all study sites. The Finnish and Navarra teams also gathered clinical information from a primary care database.

Table 4: ICD-9 and ICD-10 codes for chronic diseases

Category	ICD-9	ICD-10	Underlying conditions included
Anaemia	280–285	D50-64	Nutritional anemias, Hemolytic anemias, Aplastic and other anemias and other bone marrow failure syndromes
Chronic liver disease	571	K70, K72-74, K754, K769	Alcoholic liver disease, Hepatic failure, Chronic hepatitis, Fibrosis and cirrhosis of liver, Other inflammatory liver diseases
Cardiovascular diseases	093, 112.81, 130.3, 391, 393–398, 402, 404, 410–429, 745, 746, 747.1, 747.49, 759.82, 785.2-3	A52.01, B37.6, B58.81, I05-9, I11, I13, I20-25, I26.09, I26.9, I27, I30-51, I97.0-1, R00.1, T81.718A, T81.72XA, T82.817A, T82.818A, Q20-24, Q25.1-2, Q26.0-1, Q26.8, Q87.4, R01.1-2	Syphilitic aneurysm of aorta, Candidal endocarditis, Toxoplasma myocarditis, Chronic rheumatic heart diseases, Ischemic heart diseases, Hypertensive heart and chronic kidney disease, pulmonary embolism with acute cor pulmonale, pulmonary heart diseases, diseases of pulmonary vessels, Other forms of heart disease (including Nonrheumatic valve disorders, pericarditis, endocarditis, myocarditis, cariomyophathy, heart failure, block, cardiac arrhythmias, heart failure), Complication of other artery / vein following a procedure, Embolism of cardiac/vascular prosthetic devices, implants and grafts, congenital malformations of cardiac chambers and connections or heart, Coarctation or atresia of aorta, Congenital malformations of great veins, Marfan's syndrome, Cardiac murmur
Diabetes	250	E10-11	Type 1 and Type 2 diabetes mellitus
Obesity	27800, 278.01, 278.03	E66.01, E66.2, E66.9	Obesity
Immunodeficiency or organ transplant	042, 279, V08, V42	B20, D80-84, D89.8-9, Z21, Z94	HIV, immunity deficiency, organ or tissue replaced by transplant
Renal disease	274.1, 408, 580–591, 593.71–593.73, 593.9	M10.30, N00-19, N20.0, N28.9	Gout due to renal impairment, Glomerular diseases, Renal tubulo-interstitial diseases, Acute kidney failure and chronic kidney disease, Calculus of kidney, Disorder of kidney and ureter, unspecified
Dementia	290, 294, 331	F01, F03, F05, G30, G31, G91, G94	Vascular dementia, other dementia, Delirium due to known physiological condition, Alzheimer's disease, Other degenerative diseases of nervous system
Stroke	348, 438	G93, I67.83, I69	Brain disorders, Posterior reversible encephalopathy syndrome, Sequelae of cerebrovascular disease

Rheumatologic diseases	446, 710, 714	M30-34, M35.0, M35.5, M35.8-9, M05-06, M08, M12.00	Polyarteritis nodosa and related conditions, Other necrotizing vasculopathies, Systemic lupus erythematosus (SLE), Dermatopolymyositis, Systemic sclerosis, Sicca syndrome, Multifocal fibrosclerosis, other systemic involvement of connective tissue, Rheumatoid arthritis with rheumatoid factor, Other rheumatoid arthritis, Juvenile arthritis, Chronic postrheumatic arthropathy
Cancer	140–208	C00-96	Malignant neoplasms and neuroendocrine tumours
Lung disease	011, 490–511, 512.8, 513–517, 518.3, 518.8, 519.9, 714.81	A15, J40-47, J60-94, J96, J99, J182, M34.81, M05.10	Respiratory tuberculosis, Bronchitis, not specified as acute or chronic, Chronic bronchitis, Emphysema, Other chronic obstructive pulmonary disease, Asthma, Bronchiectasis, Hypersensitivity pneumonitis due to organic dust, Pneumoconiosis, Airway disease due to specific organic dust, Hypersensitivity pneumonitis due to organic dust, Respiratory conditions due to inhalation of chemicals, gases, fumes and vapor, Pneumonitis due to solids and liquids, Respiratory conditions due to other external agents, Acute respiratory distress syndrome, Pulmonary edema, Pulmonary eosinophilia, not elsewhere classified, Other interstitial pulmonary diseases, Abscess of lung and mediastinum, Pyothorax, Pleural effusion, Pneumothorax and air leak, Other pleural conditions, Intraoperative and postprocedural complications and disorders of respiratory system, not elsewhere classified, Other diseases of the respiratory system, Hypostatic pneumonia, unspecified

3.3.7 Sample size

The minimum sample size was estimated for each study in order to obtain precise IVE estimates. Assuming a vaccination coverage of 50% among the source population and a proportion of positive for Influenza of 30% among swabbed SARI patients, we needed at least 155 influenza cases and 361 controls to be able to detect an OR of 0.4 (= VE of 60%) with a power of 80% and a precision of 20% (**Table 5**).

Table 5: Number of cases and controls to recruit to estimate IVE with a 20% absolute precision according to different vaccine coverage and IVE, I-MOVE+ hospital based IVE studies

Absolute precision	Alpha	Power	Proportion of cases among SARI patients	Vaccine coverage in the source population	Detectable VE(1-OR)	Number of cases	Number of controls	Total SARI patients included
0.2	0.05	0.8	0.3	0.15	0.7	358	835	1193
0.2	0.05	0.8	0.3	0.15	0.6	458	1069	1527
0.2	0.05	0.8	0.3	0.15	0.5	569	1329	1898
0.2	0.05	0.8	0.3	0.15	0.4	692	1615	2307
0.2	0.05	0.8	0.3	0.15	0.3	826	1927	2753
0.2	0.05	0.8	0.3	0.3	0.7	176	410	586
0.2	0.05	0.8	0.3	0.3	0.6	235	548	783
0.2	0.05	0.8	0.3	0.3	0.5	303	706	1009
0.2	0.05	0.8	0.3	0.3	0.4	380	887	1267
0.2	0.05	0.8	0.3	0.3	0.3	467	1089	1556
0.2	0.05	0.8	0.3	0.5	0.7	108	252	360
0.2	0.05	0.8	0.3	0.5	0.6	155	361	516
0.2	0.05	0.8	0.3	0.5	0.5	211	492	703
0.2	0.05	0.8	0.3	0.5	0.4	278	648	926
0.2	0.05	0.8	0.3	0.5	0.3	355	829	1184

3.3.8 Data management

3.3.8.1 Data entry and validation

For hospitals using electronic medical records, if paper questionnaires were used, we recommended study site coordinators to select a sample of them to be checked against the medical records and against the study database.

Web-based data collection methods or paper-based methods were used. Data entry will include checks to minimise data entry errors. Double data entry was recommended unless medical electronic records were used.

Laboratory information were reported to the study site coordinator using the reporting procedures existing in each study site for influenza surveillance.

For the multi-centre pooled analysis, study sites sent an anonymised database to the coordinating team. EpiConcept provided the option of web-based data collection methods, if so desired by the countries. Overall, three countries used this option (France, Romania and Croatia).

3.3.8.2 Management of database for pooled analysis

EpiConcept conducted the pooled analysis. Each individual study database was sent to the coordinating team study database using a secure protocol (Figure 4). All personal identifier information such as names, addresses, day of birth and medical registration codes were deleted before data transmission to the coordinating team, where all individual data was pooled.
A country (or study) identifier was included in each record (e.g. ES for Spain, IT for the Italy), a hospital code was included (e.g. a unique number), and each record was given a unique number. This number was also included in the study team's database and was used by the coordinating team and the study teams during pooling, so that records could be traced back by local team whilst maintaining anonymity at the data analysis level, if needed. Tracing back was performed by the study teams, not by the coordinating team. Study databases could be sent in any format.

3.3.8.3 Data cleaning

Standardised data coding procedures were shared with the study sites.
At the study site level, inconsistency checks were included in the electronic questionnaires to avoid inconsistencies in the data entry or run afterwards. Once detected, inconsistencies were checked against the questionnaires or queried with the hospitals.
At the pooled level, summary and frequency tables and graphic displays of appropriate variables were used to find illegal, implausible or missing values within the dataset. Checks for inconsistencies were carried out (e.g. date of respiratory specimen collection before date of onset of symptoms). Any improbable, illegal or missing values was reported to the study site in question. Any subsequent changes to the data was fully documented and stored separately from the crude database, to ensure reproducibility and transparency of data management. A study-site specific flowchart of exclusions and restrictions as well as a descriptive table of the data were shared with each of the study sites for validation. Variables were recoded and new variables were generated. The recoded data was stored separately from the crude data and recoding was documented.

3.3.8.4 Missing data

Any missing data will be described. If more than 5% of exposure or outcome data and/or more than 10% of adjustment variable is missing, and variables that are considered good predictors of the missing data are available, multiple imputation methods at study level will be used to replace missing values. A sensitivity analysis will be carried out comparing results from the complete case analysis (where records with missing data will be dropped) and the full set analysis (with imputed data).

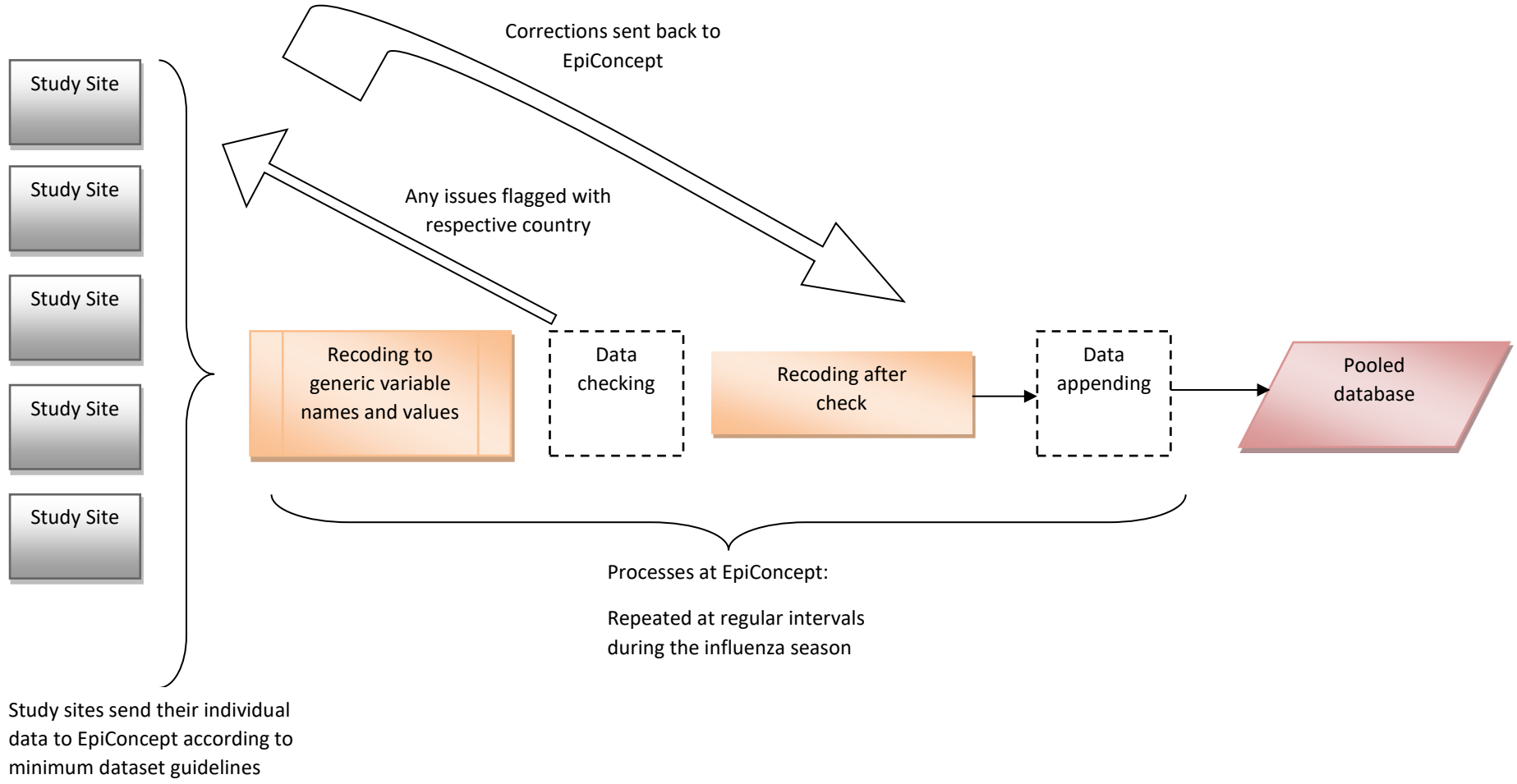

Figure 4: Data flow for pooled database, I- MOVE+ hospital based IVE studies

3.3.9 Data Analysis

The analysis was carried out first for each individual study site. In a second step, a pooled analysis was conducted.

3.3.9.1 Individual study analysis

3.3.9.1.1 Descriptive analysis

The proportion of eligible hospitalised cases and controls who accepted to participate in the study was calculated. Reasons for no participation was documented. Study participants were described by baseline characteristics. Baseline characteristics of cases and controls were compared using the chi-square test, Fisher's exact test, t-test or the Mann-Whitney test (depending on the nature of the variable and the sample size).

Continuous variables in the I-MOVE+ datasets included age, time of onset of symptoms, GP visits and hospitalisations in the past 12 months. The two latest variables were used as categorical variables in our analyses. We modelled age and time using restricted cubic splines with 3 or 4 knots depending on the sample size.

3.3.9.1.2 Measure of effect

Vaccine effectiveness was computed as VE = 1 – OR (expressed as percentage). An exact 95% confidence interval was computed around the point estimate.

3.3.9.1.3 Stratified analysis

The analysis was stratified according to:

- age groups 18-64, 65-79 years, 80+ years
- absence, presence of underlying conditions
- specific chronic conditions (e.g. respiratory, cardiovascular diseases)
- time: early influenza season, peak, late influenza season
- vaccine type (subunit vs split virion)
- previous seasons' vaccination

The analyses were conducted using A(H3N2), A(H1N1)pdm09 and B viruses as outcome.

Effect modification was assessed first comparing the OR across the strata of the potential effect modifiers. Confounding was assessed by comparing crude and adjusted OR for each potential confounder.

3.3.9.1.4 Multivariable analysis

A multivariable logistic regression analysis was conducted to control for negative and positive confounding. Odds ratios and standard errors were obtained. Variables were tested for multicollinearity. Interactions were tested using the likelihood ratio test or Wald's test and were included in the model if significant at the 5% level. Factors other than statistical significance (prevalence of exposure, magnitude of OR) were also be used as criteria for inclusion of a variable or an interaction term. When possible, a variable for age and for onset time were always included in the model.

3.3.9.2 Pooled analysis

For the pooled data, interim analyses were conducted in different periods according to the available sample size.

The timing to conduct each interim analysis depended on the time needed to reach the appropriate sample size. This depended mainly on the incidence of hospitalisation, influenza incidence, vaccination coverage and the number of participating hospitals/services per hospital.

3.3.9.2.1 Descriptive analysis

The main characteristics of each study were summarised individually, including:

- Number of hospitals participating and catchment population
- Beginning of the study
- Beginning of influenza period, peak, end
- Beginning of vaccination campaigns for seasonal vaccine
- Vaccines used
- Number of patients screened
- Number of patients excluded per reasons for exclusion

3.3.9.2.2 Identifying heterogeneity, testing for heterogeneity

Qualitative heterogeneity

Study-specific crude and adjusted ORs and their confidence intervals were plotted in separate forest plots. Following the core protocol minimises heterogeneity between studies. However adherence to the protocol and study design and study quality characteristics were checked through site visits. Other study site characteristics were assessed where feasible, such as types of circulating virus, information on health care use, organisation of the vaccination campaign. Then a qualitative decision took place if one or more studies were substantially different from the other and should be excluded from the pooled analysis.

Statistical heterogeneity

Statistical heterogeneity between studies was tested using Q-test and the I^2 index (see boxes for formulae below). The Q statistic follows a Chi^2 distribution (with k-1 degrees of freedom). The Q-test reports presence or absence of heterogeneity, while the I^2 index (based on the Q-statistic) quantifies the extent of the heterogeneity. According to the Higgens and Thompson classification, an I^2 index of around 25% indicates low, 50% indicates medium and 75% indicated high heterogeneity between studies.

$$Q = \sum w_i \ (\log(OR_i) - \log(OR_F))^2$$

Where:

$$w_i = 1/v_i$$

v_i is the inverse variance of the estimated log odds ratio of study i

$$\log(OR_F) = \frac{\sum w_i \times \log(OR_i)}{\sum w_i}$$

$$I^2 = \frac{Q-(k-1)}{Q} \times 100\% \quad \text{for } Q > (k-1)$$

$$I^2 = 0 \quad \text{for } Q \leq (k-1)$$

3.3.9.2.3 Two-stage pooled analysis approach

When adequate sample size by study was achieved to obtain an adjusted OR, then a 2-stage approach to pooled analysis was undertaken.

Study-specific adjusted ORs and standard errors for the effect of current influenza vaccination obtained from the individual studies, were combined in a model that incorporates random effects of the studies, to account for unmeasured country- and study-specific factors that differ between studies.

The study-specific exposure-disease effects (ORs) were then weighted by the inverse of their marginal variances. The marginal variance is the sum of the individual study-specific variances and the variance of the random study effects (τ2). This gave the pooled odds ratio and standard error.

$$\log(OR_R) = \frac{\sum w_i * \times \log(ORi)}{\sum w_i *}$$

$$wi* = \frac{1}{vi + \tau^2}$$

The study specific ORs and their confidence intervals, along with the pooled odds ratio were presented graphically in a forest plot.

3.3.9.2.4 One-stage pooled analysis approach

When sample sizes were too small to measure vaccine effectiveness controlling for all potential confounders for each individual study site, a 1-stage pooled approach was used for analysis. A one-stage pooled analysis approach was almost systematically used when doing stratified analyses.

Individual study data were pooled into one dataset and analysed as a 1-stage model with study site as a fixed effect. In this analysis, we assume not only that the underlying true exposure effect is the same in all studies, but also that the association of all covariates with the outcome is the same in all studies.

3.3.9.2.5 Stratified analysis

The same analysis process was carried out for the following strata:

- age groups 65-79 years, 80+ years
- absence, presence of at least one, presence of more than on high-risk condition
- specific chronic conditions (e.g. respiratory, cardiovascular diseases)
- time: early influenza season, peak, late influenza season
- vaccine type (adjuvanted vs non adjuvanted)
- previous vaccination

3.3.9.3 Specific analyses

3.3.9.3.1 Effect of previous vaccination on IVE

In a stratified analysis based on the data pooled across seasons and using unvaccinated in the current season as a reference, we compared VE measured in the current season between individuals who were vaccinated in the past season and those who were not vaccinated in the past season. Due to low sample size, we excluded patients vaccinated in only one of the two previous seasons from this analysis.

Using patients unvaccinated in current and the two previous seasons as the reference, we conducted an indicator analysis. We computed the effectiveness of being vaccinated in current season only, in previous season but not current (regardless of penultimate season vaccine status), and in current and both previous seasons for each season and overall. Due to low sample size, we excluded patients vaccinated in the penultimate season only, those vaccinated in the penultimate and current seasons only and those vaccinated in the previous and current seasons only.

We conducted sensitivity analyses restricted to patients for whom the vaccination status ascertainment was based on vaccination registers.

3.3.9.3.2 IVE by vaccine type or brand

We grouped the vaccine brands in split virion, subunit or adjuvanted vaccines. To compute vaccine type specific effectiveness, we restricted our analyses to countries with at least one patient vaccinated with a specific type.

3.4 Critical appraisal of the use of TND to measure IVE against hospitalised influenza infection

In the recent years, an increasing number of studies measuring IVE against medically attended and hospitalised laboratory confirmed influenza have used the test-negative design (TND) approach (166). In TND studies, investigators recruit patients based on clinical criteria and classify them as influenza cases or controls based on laboratory results. TND studies to measure IVE were initially developed to use existing sentinel influenza surveillance systems. The first TND study measuring IVE was published in Canada in 2005 (162). This study design is widely used and accepted (164,166–169) to measure IVE against medically attended influenza at GP level.

GP based TND studies are assumed to correct for an important source of bias when measuring IVE: the care-seeking behavior (168). This type of bias is important when measuring IVE against a mild clinical endpoint, such as medically attended influenza. Considering a correlation between the propensity of seeking medical care and being vaccinated, we assume that recruiting cases and controls seeking care for similar clinical pictures will lead to a homogenous sample in terms of propensity to be vaccinated. Differential health seeking behaviour between vaccinated and unvaccinated individuals is likely to be marginal with hospital end-point in industrialised countries if we assume that any individual with a SARI would be hospitalised.

For hospital based TND studies, clinical inclusion criteria include a combination of symptoms that are usually leading to a SARI clinical picture (170). Patients included in TND studies may therefore include influenza positive patients, patients infected with a non-influenza respiratory virus and patients with acute exacerbation of chronic cardiopulmonary affection.

A number of methodological papers that we discuss below have questioned the validity of the TND to measure IVE in various contexts and upon different hypotheses. These articles suggest that IVE estimates may be biased using the TND if a number of conditions are not fulfilled.

To discuss the validity of the TND to measure IVE against hospitalised laboratory confirmed influenza in Europe, we reported each point raised by these methodological papers and confronted them with our protocol. Of note, some of these characteristics apply not only to TND but to all studies measuring IVE.

3.4.1 Definition of the study population

3.4.1.1 Rates of contact with infectious individuals among vaccinated and unvaccinated

To attribute the difference in disease incidence to the sole influenza vaccine, rates of exposure to the virus should be the same between vaccinated and unvaccinated individuals (168). Institutionalised patients are likely to be more vaccinated than the rest of the population. Because they live in a closed setting with a very high vaccine coverage, we also assume that they have less chance to be in contact with infected individuals. Including them in the analysis would likely lead to overestimating the vaccine coverage among controls and therefore the IVE. Hospitalised patients would be in a similar scenario as institutionalised patients. Therefore, we excluded from our study individuals who were institutionalised at the time of symptoms onset (living in a residence for people who require continual nursing care and have difficulty with the required activities of daily living), as well as individuals

hospitalised < 48 hours prior to SARI onset or those with SARI onset ≥ 48 hours after admission at the hospital (to avoid including nosocomial infections).

3.4.1.2 Censoring of influenza positive patients

A methodological paper on TND suggested that patients testing negative (first) and positive (second) at two consecutive points in time should be counted twice (171). Under the assumption of an effective vaccine, these patients would likely be less vaccinated than the control group. If we assume these individuals are still susceptible, excluding after a first inclusion would lead to overestimating the vaccine coverage among cases and underestimating the IVE. In our study protocol, we specified that a patient could be selected several times as long as he/she did not have a previous laboratory confirmed influenza.

3.4.2 Definition of the study period

3.4.2.1 At-risk period

Including patients who seek care when influenza is not circulating would bias the results (168). To overcome this bias, our recruitment period was defined based on the definition of the influenza season for each study site. Our study period was then refined according to each influenza (sub)type IVE analysis as starting on the week of the first confirmed case and ending on the week of the last confirmed case.

3.4.3 Case definition

3.4.3.1 Specificity and sensitivity of the outcome

Methodological papers ague that IVE would be underestimated if laboratory tests used are not both highly sensitive and specific (171,172). Indeed, under the assumption of a vaccine providing some protection (OR away from 1), misclassifying patients as cases or controls would lead to a dilution of the effect and, consequently it would pull IVE estimates towards 0 (OR towards 1). In our study, all specimens were tested using RT-PCR, which is a highly sensitive and specific test for influenza (173). Loss of sensitivity leading to false negatives could occur if nasopharyngeal swabs were not done properly. However, all laboratories involved in our studies used internal controls to check for the presence of cellular material on the swabs before validating a result.

3.4.4 Control group

3.4.4.1 Incidence of non-influenza SARI-like illness among vaccinated and unvaccinated

The principle of a control group is that it mirrors the vaccination experienced by the source population from where cases emerge. In our study, we assume that influenza vaccine coverage among non-influenza SARI patients should be the same as in the population from where influenza cases emerge. If the incidence of non-influenza SARI was different between vaccinated and unvaccinated this condition may be violated. Several papers compared the incidence of non-influenza SARI between vaccinated and not vaccinated out- and inpatients, finding no evidence of differences (174,175). In hospital based TND studies where other respiratory viruses were tested for, a large proportion of influenza negative patients were “pan negative” (70 to 85%) (174,176). While we cannot exclude that some of these patients had a SARI due to pathogens that were tested for, it is likely that a proportion of them were recruited due to an exacerbation of chronic conditions. A recent paper suggested that if

SARI cases due to an exacerbation of an underlying cardiopulmonary disease were not excluded from the study, IVE against hospitalised influenza could be biased (177). Such a bias would lead to recruiting a higher proportion of patients with cardiopulmonary disease in the study compared to the source population giving rise to hospitalised influenza cases. If individuals with cardiopulmonary disease were more likely than the source population to be vaccinated, such a bias would result in an overrepresentation of vaccinated patients in the control group and, ultimately, an overestimation of the IVE. To overcome this selection bias, a good documentation of cardiopulmonary disease is necessary to properly adjust the IVE estimates for cardiopulmonary disease. Furthermore, in our study, we ran sensitivity analyses excluding patients with cardiopulmonary disease from our population.

3.4.4.2 Impact of vaccination on virus shedding

If vaccination shortens the duration or intensity of viral shedding, we may expect a higher proportion of false negative influenza results among vaccinated than unvaccinated individuals. This would result in an overrepresentation of vaccinated among controls and therefore an overestimation of the IVE. Comparing the number of days between onset and swabbing between vaccinated and unvaccinated cases is important to discuss this point. Comparing IVE obtained between various categories of delays since swabbing allowed us to assess this potential bias.

3.4.5 Data analysis

3.4.5.1 Proper adjustment for calendar time

Because influenza circulation and vaccine uptake are both time-dependent and TND is a density case control study, IVE should be adjusted for patients' date of SARI symptoms (178). In our study, all pooled estimates and all study-site specific estimates with large enough sample size were adjusted on date of SARI onset (as a restricted cubic spline or as week of onset).

Hospital based TND studies, if conducted according to an appropriate study protocol, may fulfill the criteria needed to provide unbiased estimates. Careful documentations of underlying conditions, high quality laboratory testing and proper adjustment of the estimates are critical to obtain these results.

3.5 Results

3.5.1 Influenza Vaccine effectiveness by season, (sub)type and risk group

From 2011-12 to 2016-17, a total of 9,692 hospitalised patients, including 3,102 influenza cases (32%), were included in InNHOVE/I-MOVE+ networks hospitals. Annual recruitment ranged between 1,066 patients in 2013-14 and 2,644 patients in 2016-17 (**Table 6**) and there were between 23% and 42% of influenza cases among patients included (**Table 7**).

Table 6: Patients recruited by study site and season, InNHOVE/I-MOVE+ hospital network, Europe, 2011-17

Study site	2011-12	2012-13	2013-14	2015-16	2016-17	Total
Spain	0	0	0	411	910	1321
Finland	0	0	0	111	70	181
France	174	428	380	160	315	1457
Croatia	0	0	0	46	47	93
Hungary	0	0	0	42	40	82
Italy	26	84	238	276	210	834
Lithuania	0	183	0	79	135	397
Navarra, Spain	46	93	448	372	529	1488
Netherlands	0	0	0	27	108	135
Poland	0	0	0	35	0	35
Portugal	0	0	0	51	80	131
Romania	0	0	0	168	200	368
Valencia, Spain	1678	1492	0	0	0	3170
Total	**1924**	**2280**	**1066**	**1778**	**2644**	**9692**

Among confirmed cases, 63% were infected with A(H3N2) viruses, 22% with A(H1N1)pdm09, 2% with non-subtyped A viruses and 13% with B viruses (**Table 7**).

We observed that (sub)type distribution varied by age group (**Table 8**). When restricting to the three seasons when the entire adult population was included, the proportion of A(H1N1)pdm09 viruses among cases was the highest among patients aged 18-64 years (38%) and the lowest in those aged 80 years and above (8%). On the other hand, the proportion of A(H3N2) decreased by decreasing age (from 72% in the ≥80 years to 39% in the 18-64 years). When we included the two extra-seasons restricted to the population aged 65 years and above, we could see a difference between the age groups 65-79 years and 80 years and above. We observed a higher proportion of A(H1N1)pdm09 in the younger age group and higher proportion of A(H3N2) in the older age group. The proportion of influenza B viruses remained stable across the age groups.

Table 7: Influenza (sub)types and cases and controls by season among hospitalised cases, InNHOVE/I-MOVE+ hospital network, Europe, 2011-17

	Influenza (sub)type N (% of confirmed cases)						Influenza cases and controls N (% of all included patients)	
Season	A(H1N1)pdm09	A(H3N2)	A unsubtyped	B	A/B coinfection	A(H1)/A(H3) coinfection	Any influenza	Controls
2011-12	8 (1)	595 (96)	6 (1)	11 (2)			**620 (32)**	**1304 (68)**
2012-13	165 (32)	78 (15)	2 (<1)	274 (52)	2 (<1)	1 (<1)	**522 (23)**	**1758 (77)**
2013-14	145 (43)	176 (53)	11 (3)	2 (1)		1 (<1)	**335 (31)**	**731 (69)**
2015-16	351 (67)	41 (8)	23 (4)	101 (19)	5 (1)		**521 (29)**	**1257 (71)**
2016-17	9 (1)	1064 (96)	18 (2)	13 (1)			**1104 (42)**	**1540 (58)**
Total	**678 (22)**	**1954 (63)**	**60 (2)**	**401 (13)**	**7 (<1)**	**2 (<1)**	**3102 (32)**	**6590 (68)**

Table 8: Influenza (sub)types by age group and season among hospitalised cases, InNHOVE/I-MOVE+ hospital network, Europe, 2011-17

Season	Influenza (sub)type N (% of confirmed cases)						Influenza cases and controls N (% of all included patients)	
	A(H1N1)pdm09	A(H3N2)	A unsubtyped	B	A/B coinfection	A(H1)/A(H3) coinfection	Any influenza	Controls
18-64 years								
2011-12	5 (4)	122 (91)	2 (1)	5 (4)	0	0	**134 (28)**	**339 (72)**
2012-13	109 (44)	34 (14)	2 (1)	102 (41)	2 (1)	1 (<1)	**250 (31)**	**551 (69)**
2013-14	90 (61)	52 (35)	4 (3)	1 (1)	0	0	**147 (37)**	**250 (63)**
Pooled from 2011 to 2014	**204 (38)**	**208 (39)**	**8 (2)**	**108 (20)**	**2 (<1)**	**1 (<1)**	**531 (32)**	**1140 (68)**
65-79 years								
2011-12	1 (<1)	230 (97)	3 (1)	2 (1)	0	0	**236 (34)**	**466 (66)**
2012-13	42 (27)	22 (14)	0 (0)	92 (59)	0	0	**156 (21)**	**577 (79)**
2013-14	36 (37)	58 (60)	2 (2)	0 (0)	0	1 (1)	**97 (26)**	**273 (74)**
2015-16	232 (68)	25 (7)	13 (4)	69 (20)	4 (1)	0	**343 (33)**	**696 (67)**
2016-17	5 (1)	455 (95)	9 (2)	8 (2)	0	0	**477 (38)**	**771 (62)**
Pooled from 2011 to 2014	**79 (16)**	**310 (63)**	**5 (1)**	**94 (19)**	**0 (0)**	**1 (<1)**	**489 (27)**	**1316 (73)**
Pooled from 2011 to 2017	**316 (24)**	**790 (60)**	**27 (2)**	**171 (13)**	**4 (<1)**	**1 (<1)**	**1309 (32)**	**2783 (68)**
80 years and above								
2011-12	2 (1)	243 (97)	1 (<1)	4 (2)	0	0	**250 (33)**	**499 (67)**
2012-13	14 (12)	22 (19)	0 (0)	80 (69)	0	0	**116 (16)**	**630 (84)**
2013-14	19 (21)	66 (73)	5 (5)	1 (1)	0	0	**91 (30)**	**208 (70)**
2015-16	119 (67)	16 (9)	10 (6)	32 (18)	1 (1)	0	**178 (24)**	**561 (76)**
2016-17	4 (1)	609 (97)	9 (1)	5 (1)	0	0	**627 (45)**	**769 (55)**
Pooled from 2011 to 2014	**35 (8)**	**331 (72)**	**6 (1)**	**85 (19)**	**0 (0)**	**0 (0)**	**457 (25)**	**1337 (75)**
Pooled from 2011 to 2017	**158 (13)**	**956 (76)**	**25 (2)**	**122 (10)**	**1 (<1)**	**0 (0)**	**1262 (32)**	**2667 (68)**

IVE against all Influenza

Overall, IVE against any influenza hospitalisation among adults pooled across the five seasons was 26% (95%CI: 18;33), ranging from 15% (95%CI: -3;29) in 2016-17 to 44% (95%CI: 21;60) in 2013-14. Pooled across the seasons from 2011 to 2014, IVE was 40% (95%CI: 15;58) among the 18-64 years. IVE against any influenza was 25% (95%CI: 13;36) and 23% (95%CI: 10;34) among the 65-79 years and 80 years old and above respectively. For both older age groups, IVE were the lowest in 2011-12 and 2016-17, which were the two only seasons predominated by A(H3N2) viruses circulation (**Table 9**).

IVE against influenza A(H1N1)pdm09

Pooled across 2012-13 and 2013-14, IVE against A(H1N1)pdm09 was 46% (95%CI: -3;72) among patients aged 18-64 years. Among 65-79 years old, IVE against A(H1N1)pdm09 ranged between 30% in 2015-16 and 44% in 2012-13. Among patients aged 80 years and above, there was a great variability in season specific IVE estimates against A(H1N1)pdm09, ranging between -172% (95%CI: -1171;42) in 2012-13 and 53% (95%CI: 6;61) in 2015-16 (**Table 10**).

IVE against influenza A(H3N2)

Pooled across all seasons, IVE against A(H3N2) was below 30% in all age groups. Season specific IVE against influenza A(H3N2) among patients aged under 65 years ranged between 8% (95%CI: -145;65) in 2013-14 and 47% (95%CI: -1;72) in 2011-12. Among patients aged 65-79 years, IVE against A(H3N2) was below 30% in three out of four seasons. Among patients aged 80 years and above, IVE against A(H3N2) was 22% (95%CI: 6;35) overall and it was the lowest at 8% in 2011-12 and 2016-17 (**Table 10**).

IVE against influenza B

Pooled across available seasons, IVE against influenza B was 66% (95%CI: 19;86) among adults aged 18-64 year (measured in a single season (2012-13)), 38% (95%CI: 11;57) among patients aged 65-79 years and 46% (95%CI: 18;65) among patients aged 80 years and above. Among patients aged 65 years and above, we observed higher point estimates in 2015-16, when there was a mismatch between lineages included in the vaccine and those circulating, compared to 2012-13, when the circulating lineage was included in the vaccine (**Table 10**).

Overall, our results suggest that influenza vaccination decreases the risk of hospitalisation with laboratory confirmed influenza by 40% among 16-64 years adults and by 25% among those aged 65 years and above. IVE varied greatly by subtype. In each age group, we observed that IVE was lowest against influenza A(H3N2) and the highest against influenza B. IVE against A(H3N2) was particularly low among elderly in seasons when it was predominantly circulating (2011-12 and 2016-17). Finally, our results on IVE against influenza B may suggest some cross-lineage protection.

We were able, at the end of every season, to report and publish estimates of IVE by (sub)type and for various age and risk groups. The following chapters present more detailed results from annual publications from InNHOVE and I-MOVE+ networks.

Table 9: Vaccine effectiveness against any laboratory confirmed influenza by age group and season, InNHOVE/I-MOVE+ hospital network, Europe, 2011-17*

Season	All age groups			18-64 years			65-79 years			80 years and above		
	Vaccinated /total cases	Vaccinated /total controls	IVE (95% CI)	Vaccinated/ total cases	Vaccinated /total controls	IVE (95% CI)	Vaccinated /total cases	Vaccinated /total controls	IVE (95% CI)	Vaccinated /total cases	Vaccinated /total controls	IVE (95% CI)
2011-12	332/578	743/1196	23 (3;39)	26/95	90/232	44 (-5;70)	137/234	291/465	26 (-7;49)	169/249	362/499	10 (-31;38)
2012-13	146/349	887/1525	37 (18;52)	18/101	118/338	49 (4;72)	65/139	347/567	30 (-8;54)	63/109	422/620	38 (2;61)
2013-14	112/262	325/592	44 (21;60)	18/80	40/129	27 (-61;66)	42/93	141/266	34 (-12;62)	52/89	144/197	50 (11;72)
2015-16	203/492	624/1162	36 (16;50)				126/322	310/662	29 (1;49)	77/170	314/500	43 (12;64)
2016-17	554/1073	857/1494	15 (-3;29)				181/467	369/753	21 (-3;40)	373/606	488/741	10 (-16;31)
Pooled	**1347/2754**	**3436/5969**	**26 (18;33)**	**62/276**	**248/699**	**40 (15;58)**	**551/1255**	**1458/2713**	**25 (13;36)**	**734/1223**	**1730/2557**	**23 (10;34)**

*All IVE estimates were adjusted for study site, month of onset, age, lung disease, cardiac disease, diabetes, obesity, renal disease, cancer and hospitalisation in the past 12 months

Table 10: (Sub)type specific influenza vaccine effectiveness by age group and season, InNHOVE/I-MOVE+ hospital network, Europe, 2011-17

	18-64 years			65-79 years			80 years and above		
Season	Vaccinated/ total cases	Vaccinated/total controls	IVE (95% CI)	Vaccinated/total cases	Vaccinated/ total controls	IVE (95% CI)	Vaccinated/total cases	Vaccinated/total controls	IVE (95% CI)
Influenza A(H1N1)pdm09									
2012-13	9/60	105/312	42 (−31;74)	18/42	276/462	44 (-11;72)	12/14	412/609	-172 (-1,171;42)
2013-14	8/48	36/100	61 (-2;85)	15/37	102/181	39 (-32;72)	13/19	102/145	20 (-148;74)
2015-16				83/220	248/511	30 (-6;53)	48/114	253/400	53 (18;73)
Pooled	**16/85**	**149/418**	**46 (-3;72)**	**115/296**	**688/1241**	**32 (7;50)**	**73/147**	**758/1138**	**39 (6;61)**
Influenza A(H3N2)									
2011-12*	23/87	90/232	47 (-1;72)	135/229	291/465	25 (-9;48)	165/242	362/499	8 (-35;37)
2012-13	3/14	39/129	26 (-216;83)	7/22	91/159	52 (-34;83)	10/22	147/194	74 (30;90)
2013-14	9/32	36/125	8 (-145;65)	29/59	134/260	26 (-36;59)	38/66	146/200	55 (15;76)
2016-17				172/445	367/743	22 (-3;40)	368/588	487/733	8 (-18;29)
Pooled	**35/128**	**171/480**	**28 (-14;54)**	**341/747**	**888/1629**	**24 (7;37)**	**579/914**	**1136/1612**	**22 (6;35)**
Influenza B									
2012-13	7/60	91/286	66 (19;86)	40/92	288/473	28 (-19;57)	41/80	348/520	45 (7;67)
2015-16				31/73	280/558	47 (6;70)	18/33	300/445	54 (-4;80)
Pooled	**7/60**	**91/286**	**66 (19;86)**	**71/165**	**568/1031**	**38 (11;57)**	**59/113**	**648/965**	**46 (18;65)**

*Difference with article's estimates are due to different restriction in terms of maximum delay between symptoms onset and swabbing delay (4 days in the article, 7 days in this table)

Influenza H1N1:

- 2012-13 and 2013-14: Adjusted for study site, month of onset, age and presence of chronic conditions (except >=80 years adjusted for study site and onset month in 2012-13)
- 15-16 and total : adjusted for study site, month of onset, age, lung disease, cardiac disease, diabetes, obesity, renal disease, cancer and hospitalisation in the past 12 months

Influenza H3N2:

- 2011-12 and 16-17 and total : adjusted for study site, month of onset, age, lung disease, cardiac disease, diabetes, obesity, renal disease, cancer and hospitalisation in the past 12 months
- 2012-13 and 2013-14: Adjusted for study site, month of onset, age and presence of chronic conditions (except <65 adjusted for study site and onset month in 2012-13

Influenza B: Adjusted for study site, month of onset, age and presence of chronic conditions

3.5.1.1 Results from 2011-12 season

In 2011-12, we piloted our multicentre study in three study sites (France, Italy and the Spanish regions of Navarra and Valencia). The season was late (starting on the last week of 2011) and marked by a great predominance of A(H3N2) viruses, that were antigenically distant from the vaccine component. We included 21 hospitals. Our study population included adults admitted for illnesses potentially related to influenza and who had an onset of ILI symptoms in the past seven days. Our study objective was to assess the feasibility of measuring seasonal IVE against hospitalisation with laboratory confirmed influenza through a network of hospitals in Europe.

Overall, we receirved 9,397 patients' records. Of them, 1,895 eligible patients were swabbed within seven days after illness onset, including 593 A(H3N2) cases and 1302 negative controls. Less than 0.5% of patients had missing vaccination status. To decrease the risk of including false negatives, we restricted our analysis to the 375 cases (63%) and 770 controls (59%) swabbed within 4 days. More than 90% of included patients belonged to the targeted groups for vaccination and more than 75% of recruited patients were aged 65 years or above. We measured a low IVE against A(H3N2) at 25% (95%CI: -2;45) overall and 29% (95%CI: 3;48) when restricting to target population.

In our manuscript, we discussed the source population of our control group. We compared the vaccine coverage between our control group (60% overall and 64% among those targeted by vaccination), the general adult population (23%) and the population targeted by the vaccination (59% in Navarra, 49% in France). We suggested that hospital based study results are likely to be less biased if confined to the population targeted by influenza vaccination.

Furthermore, during this pilot season, a high proportion of records received were dropped due to patients being recruited outside the study period. This was due to study teams getting used to the recruitment approaches before the start of the influenza season.

Our study showed that measuring IVE against laboratory confirmed influenza hospitalisation with high quality data was feasible in Europe. Our results suggested that the 2012-13 season IVE was low against A(H3N2) viruses.

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2011–12 Seasonal Influenza Vaccines Effectiveness against Confirmed A(H3N2) Influenza Hospitalisation: Pooled Analysis from a European Network of Hospitals. A Pilot Study

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Abstract

Background: Influenza vaccination strategies aim at protecting high-risk population from severe outcomes. Estimating the effectiveness of seasonal vaccines against influenza related hospitalisation is important to guide these strategies. Large sample size is needed to have precise estimate of influenza vaccine effectiveness (IVE) against severe outcomes. We assessed the feasibility of measuring seasonal IVE against hospitalisation with laboratory confirmed influenza through a network of 21 hospitals in the European Union.

Methods: We conducted a multicentre study in France (seven hospitals), Italy (one hospital), and Navarra (four hospitals) and Valencia (nine hospitals) regions in Spain. All ≥18 years hospitalised patients presenting an influenza-like illness within seven days were swabbed. Cases were patients RT-PCR positive for influenza A (H3N2); controls were patients negative for any influenza virus. Using logistic regression with study site as a fixed effect we calculated IVE adjusted for potential confounders. We restricted the analyses to those swabbed within four days.

Results: We included, 375 A(H3N2) cases and 770 controls. The overall adjusted IVE was 24.9% (95%CI−1.8;44.6). Among the target group for vaccination (N = 1058) the adjusted IVE was 28.8% (95%CI:2.8;47.9); it was respectively 36.8% (95%CI:−48.8; 73.1), 42.6% (95%CI:−16.5;71.7), 17.8%(95%CI:−40.8; 52.1) and 37.5% (95%CI:−22.8;68.2) in the age groups 18–64, 65–74, 75–84 and more than 84 years.

Discussion: Estimation of IVE based on the pooling of data obtained through a European network of hospitals was feasible. Our results suggest a low IVE against hospitalised confirmed influenza in 2011–12. The low IVE may be explained by a poor immune response in the high-risk population, imperfect match between vaccine and circulating strain or waning immunity due to a late season. Increased sample size within this network would allow more precise estimates and stratification of the IVE by time since vaccination and vaccine types or brands.

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Competing Interests: The following study sites received funding from vaccine producers to perform the study: Valencia and France from Sanofi Pasteur and Sanofi Pasteur MSD, Italy from GlaxoSmithKline. The pooled analysis was co-funded by the Sanofi Pasteur, Sanofi Pasteur MSD, GlaxoSmithKline and EpiConcept. The funders had no role in the pooled study design, data collection and analysis, decision to publish, or preparation of the manuscript. Also, be assured that the authors' declared conflicts of interest do not alter their adherence to all the PLOS ONE policies on sharing data and materials.

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Introduction

Worldwide, influenza annual epidemics result in three to five million cases of severe illness and an estimated 250,000 to 500,000 deaths [1]. The average annual rate of influenza-associated hospitalisations was estimated to be between 136 and 309 per 100,000 persons in those aged 65 years and older in the US and England [2–4]. As a consequence of the ageing of the population,

the overall influenza-related hospitalisation rate tends to increase with time [5]. In Europe, influenza ranks third in terms of number of years of life lost due to mortality from infectious diseases [6].

Measuring influenza vaccine effectiveness (IVE) against severe outcome among at-risk individuals is necessary to guide vaccination strategies. Yet, weak evidence supports their effectiveness in preventing influenza-related morbidity in elderly [7,8]. Yearly measures of IVE among the most susceptible population may help evaluating the benefit of vaccination programs. Results can also catalyse the research on the development of more immunogenic vaccines for elderly people, the use of larger doses of antigens or the use of antiviral in a more aggressive manner for treatment and prophylaxis. These IVE measures could also lead to recommendations aiming at indirectly protecting elderly people through increased vaccination of transmitter populations or changing the recommendations for the use of the vaccines in terms of timing and targeted population.

With the project "Monitoring vaccine effectiveness during seasonal and pandemic influenza in Europe" (named I-MOVE), the European Centre for Disease Prevention and Control (ECDC) developed a network of study centres in European Union member states measuring seasonal and pandemic influenza vaccine effectiveness against laboratory confirmed medically attended influenza like illness (ILI) during the seasons 2008–2009 through 2012–13[9–14]. Beside the Navarra electronic cohort study [15], the I-MOVE network does not allow measuring IVE against severe outcomes.

To measure IVE against severe outcome and to broadly capture a population belonging to the target group for vaccination, laboratory confirmed influenza hospitalisation appeared as an appropriate outcome [7].

In January 2010 the ECDC organised a meeting with potential partners to set up a multicentre hospital based study in EU. This resulted in developing a generic study protocol [16]. In 2011, we launched a pilot study in Spain, France and Italy to estimate the IVE against laboratory confirmed influenza hospitalisation. Sources of funding of study sites and coordination included public and private sectors.

The objective of this project was to assess the feasibility of measuring seasonal IVE against hospitalisation with laboratory-confirmed influenza through a network of hospitals in Europe.

Materials and Methods

We conducted a multicentre case control study using the test-negative design [17] in 21 hospitals located in France (seven hospitals), Italy (one hospital), and Spain, in Valencia (nine hospitals) and Navarra (four hospitals). Study sites adapted the generic study protocol to the local settings. In each study site, the study period lasted from the week of the first laboratory confirmed case of A(H3N2) influenza until the week of the last laboratory confirmed case of A(H3N2) influenza.

The protocol was approved by the competent Authorities of each country/provinces. The Ethical Principles for Medical Research Involving Human Participants of the World Medical Association and the Declaration of Helsinki (World Medical Association, Inc. Available at: http://www.wma.net/en/30publications/10policies/b3/index.html) were adhered to. According to country specific requirements for ethical approval, all participants (or their legal tutor) provided written consent for recruitment to the study.

The following ethics committees/institutional review boards gave their approval:

- the "Ile de France IV" Ethics Committee ("Comité de Protection des Personnes Ile-de-France IV"), Paris, France
- the Ethical Committee of the Catholic University of Rome, Italy
- the Navarre Ethical Committee for Medical Research, Spain
- the Public Health CSISP Research Ethics Committee of Valencia, Spain.

Study Population

The study population corresponded to all non institutionalised adults (18 years or older) hospitalised for at least 24 hours in one of the participating hospitals, with no contra-indication for influenza vaccination and onset of influenza-like-illness (ILI) within seven days prior to naso-pharyngeal swabbing. We defined ILI as the presence of at least one systemic symptom (fever, malaise, headache or myalgia) and at least one respiratory symptom (cough, sore throat or shortness of breath). Patients were screened for presence of ILI within the past seven days. In 16 hospitals, this screening applied to patients admitted at the emergency department for a range of pre-defined chief complaints (Table 1). In the other five hospitals, all patients admitted in the participating services were screened.

Patients who had previously tested positive for influenza virus in the 2011/12 season or had received antiviral treatment between the symptom onset and the swabbing were excluded from the study.

All eligible patients who agreed to participated were swabbed and interviewed.

Data Collection

The swabbing was performed by the hospital physicians in all study sites but Valencia where it was under the responsibility of dedicated study nurses. Data collected included demographics, information on the ILI episode (dates of symptom onset, hospitalisation, laboratory testing and swabbing and treatment), presence of chronic diseases, number of hospital admissions in the past 12 months, number of GP consultations in the previous three months, smoking status, vaccination against influenza in 2011–12 and in the last two seasons and for those aged 65 years and older functional status before onset using the Barthel score [18]. Individuals belonged to the target group for vaccination if they corresponded to the country specific recommendations for vaccination [19–21]. Patients were considered vaccinated if they had received a dose of the 2011–12 seasonal vaccine more than 14 days before the date of onset of ILI symptoms. They were considered as unvaccinated if they had received no vaccine or if the vaccine was given less than 15 days before the onset of ILI symptoms.

Data sources included hospital medical records, interview with patient, patient's family and patient's physician, vaccination registries and laboratory databases. Vaccination status was ascertained using registries in Valencia and Navarra, interview with patients in France and interview with patients and with their physician in Italy.

Laboratory Confirmation

Influenza laboratory confirmation was done through reverse transcription polymerase chain reaction (RT-PCR) on nasopharyngeal swabs. Isolates underwent a molecular analysis for currently circulating influenza A viruses (subtypes H3 and H1), A(H1N1)pdm09 and influenza B. In view of the dominance of Influenza H3N2 during the 2011–12 season [22], we restricted the

Table 1. Participating services, screening procedure and number of patients screened and included per study site, hospital based Influenza VE study, EU, 2011–12.

Participating hospitals	Participating service(s)	Screening filter	Weekly average number of admissions	Reported number of patients screened	Number of patients included in the analysis	Proportion of patients included among those screened	Patients swabbed within 4 days (% of patients included)
France							
Cochin hospital, Paris	Pneumology, internal medecine	None	33	74	35	47.3%	25 (71,4%)
Bichat hospital, Paris	Pneumology, internal medecine, infectious diseases, gerontology	None	105	76	40	52.6%	28 (70,0%)
Clermont-Ferrand hospital	Intensive care, infectious diseases	None	23	83	14	16.9%	5 (35,7%)
St Eloi hospital, Montpellier	Infectious diseases department internal medicine	Respiratory syndroms	35	196	16	8.2%	8 (50,0%)
St Etienne hospital	Emercency Ward, Pneumoology, Infectious diseases	None	NA	38	9	23.7%	7 (77,8%)
Limoges hospital	Emercency Ward	Respiratory syndroms	64	118	26	22.0%	18 (69,2%)
Rennes hospital	Infectious diseases, pneumology	None	48	62	18	29.0%	9 (50,0%)
Total - France			**308**	**647**	**158**	**24.4%**	**100 (63,3%)**
Navarre							
Hospital de Navarra	All	Respiratory syndroms	344	64	15	23.4%	11 (73,3%)
Hospital Virgen del Camino			439	180	24	13.3%	17 (70,8%)
Hospital García Orcoyen de Estella			94	5	4	80.0%	4 (100,0%)
Hospital Reina Sofía de Tudela			158	9	1	11.1%	0 (0,0%)
Total - Navarre			**1035**	**258**	**44**	**17.1%**	**32 (72,7%)**
Valencia							
Hospital de la Plana	Emercency Ward	Respiratory and cardio vascular syndroms	204	667	157	23.5%	100 (63,7%)
Hospital Arnau de Vilanova			211	1 009	179	17.7%	100 (55,9%)
Hospital Pesset			397	1 482	256	17.3%	159 (62,1%)
Hospital San Juan de Alicante			261	733	133	18.1%	88 (66,2%)
Hospital general de Elda			273	981	244	24.9%	181 (74,2%)
Hospital general de Castellon			324	1 222	226	18.5%	130 (57,5%)
Hospital de La Fe			520	787	105	13.3%	62 (59,0%)
Hospital de Xativa			165	423	161	38.1%	65 (40,4%)
Hospital General de Alicante			415	828	207	25.0%	112 (54,1%)
Total - Valencia			**2 770**	**8 132**	**1 668**	**20.5%**	**997 (59,8%)**
Italy (one hospital)							
Catholic University hospital	Emercency Ward	Respiratory syndroms	**630**	**360***	**25**	**6.9%**	**16 (64,0%)**

*Based on weekly average number of patients admitted with respiratory syndromes.

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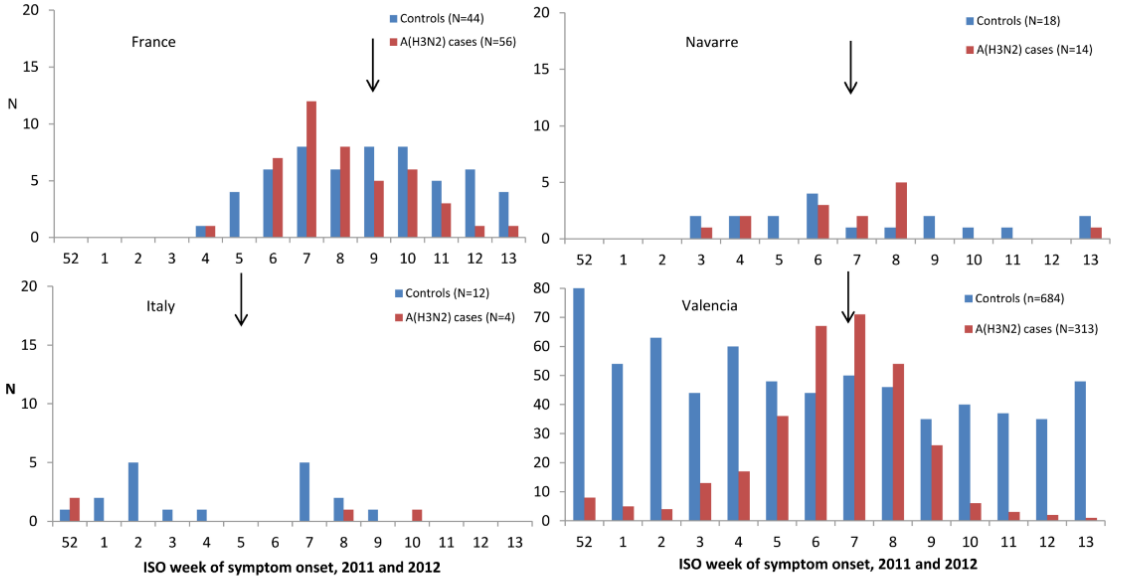

Figure 1. Number of ILI patients positive for influenza A(H3N2) and negative for any influenza by week of symptom onset, hospital based study, and week of peak of influenza activities (pointed by the arrow) in the region. By study site, 2011–12.
doi:10.1371/journal.pone.0059681.g001

case definition to those patients with a nasopharyngeal sample positive for influenza A(H3N2). Controls were patients with negative samples for any influenza virus.

Data Management and Analysis

Study sites transmitted anonymised datasets to EpiConcept, the pooled analysis coordinator, through a secured web based system. We ran a complete case analysis, excluding records for which outcome, exposure or confounding variables were missing.

To minimise potential misclassification, we restricted our analysis to those patients swabbed within four days after onset of ILI symptoms. We then ran a sensitivity analysis on all patients swabbed within seven days.

Baseline characteristics of cases and controls were compared using the chi-square test, Fisher's exact test, t-test or the Mann-Whitney test (depending on the nature of the variable and the sample size).

We assessed qualitative heterogeneity of the studies through site visits to document the recruitment approaches and the strategies set up to ensure the systematic screening and inclusion of ILI patients. We collected information on the vaccines used in the areas covered by the study sites.

We aimed at testing statistical heterogeneity between studies using Cochran's Q-test and the I^2 index [23]. We estimated the pooled IVE as 1- the odds ratio (OR)x100, using a one-stage method with study site as a fixed effect in the model. To estimate adjusted IVE, we used a logistic regression model including potential confounding factors: time of symptom onset (by pair of onset weeks), age group (four categories), gender, number of GP visits in the previous three months (more than one vs. one or less), hospitalisation in the previous 12 months, presence of chronic conditions, presence of lung disease and presence of cardiovascular disease.

We stratified IVE in four age groups (18–64, 65–74, 75–84 and 85 years and above) and we confined the analysis to the patients belonging to the target group for vaccination.

We conducted all statistical analysis using Stata version 11 *(StataCorp. 2009. Stata Statistical Software: Release 11. College Station, TX: StataCorp LP).*

Results

Overall, 9,397 patients were screened in the various hospitals (Table 1). Valencia screened (N = 8,132) and recruited (N = 1,668) the largest number of patients included in this analysis Overall, 8,497 records were received in the pooled database. Of these records, 1,264 were outside the study period, 2,131 were younger than 18 years old or had no age information, 2,171 did not meet the ILI case definition and 986 had been swabbed more than seven days after their symptoms onset. We excluded 10 records because of missing information (vaccination status (6), hospitalisation in the previous year (3) and cardiovascular disease (1)). Eleven patients tested positive for Influenza B, eight for Influenza A(H1N1) and the subtyping was inconclusive for six specimens of Influenza A. These 25 patients were excluded from the analysis. The proportion of patients included among those screened ranged from 6.9% in Italy to 24.4% in France (Table 1). Overall, 1,895 patients swabbed within seven days after illness onset were eligible, including 593 A(H3N2) cases and 1302 negative controls. We restricted our analysis to the 375 cases (63.2%) and 770 controls (59.1%) swabbed within 4 days.

Based on influenza activities reported through GP sentinel network, the influenza season was earlier in Spain and Italy compared to France [24–27]. The inclusions per study site followed the same pattern (Figure 1). In the pooled data, inclusion of cases was highest between the weeks 6 and 8 (Figure 2).

The 2011–12 seasonal influenza vaccination coverage was 54.9% among cases and 59.7% among controls (p = 0.126). The

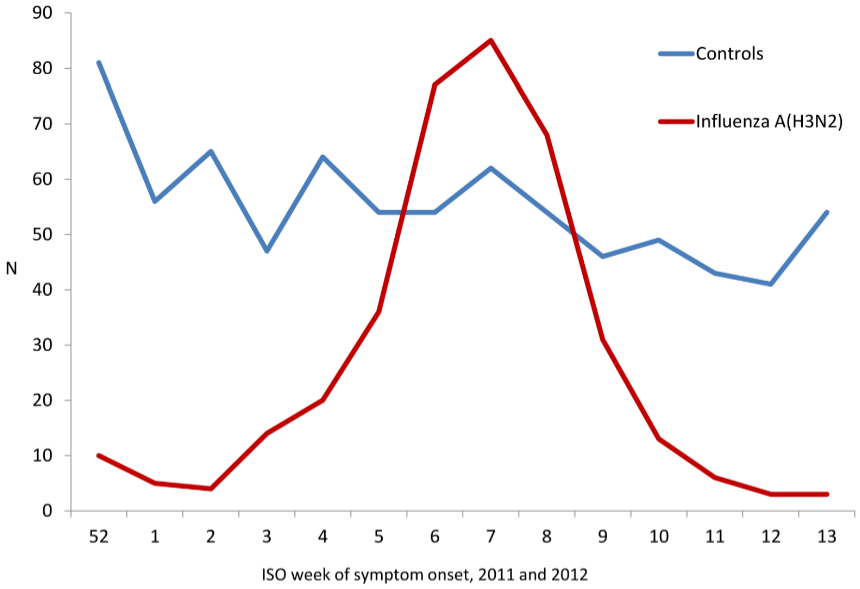

Figure 2. Number of ILI patients positive for influenza A(H3N2) (N = 375) and negative for any influenza (N = 770) by week of symptom onset, hospital based IVE studies, EU – 2011–12.
doi:10.1371/journal.pone.0059681.g002

age distribution was not statistically different between cases and controls (p = 0.148) (Table 2). Respectively 93.1% of proportion of cases and 92.1% of controls belonged to the target group for vaccination (p = 0.635). Compared to controls, a larger proportion of cases had cough and fever (p<0.001). The proportion of patients hospitalised in the previous year was 33.9% among cases and 37.4% among controls (p = 0.266). Among the 814 patients aged over 65 years for whom the Barthel score was assessed, a higher proportion of controls than cases had a low functional status (p = 0.023) (Table 2).

Site visits and protocol review ensured a homogeneous implementation of the protocol within the participating hospitals. All hospitals systematically included all patients with ILI. In Valencia, dedicated study nurses screened patients for ILI and swabbed them. Elsewhere, clinicians swabbed the patients. Due to low number of sites and small sample size, the statistical heterogeneity could not be assessed.

The overall crude IVE (N = 1145) was 23.1% (95% CI: −1.5; 41.8). The adjusted IVE was 24.9% (95% CI: −1.8; 44.6). Among those aged less than 65 years (N = 271), the adjusted IVE was 16.0% (95% CI: −73.0; 59.2).

Among the target group for vaccination (N = 1058) the adjusted IVE was 28.8% (95% CI: 2.8; 47.9). The adjusted IVE were respectively 36.8% (95% CI: −48.3; 73.1), 42.6%(95% CI: −16.5; 71.7), 17.8% (95% CI: −40.8; 52.1) and 37.5% (95% CI: −22.8; 68.2) in the age groups 18–64, 65–74, 75–84 and more than 84 years (Table 3).

When we included patients swabbed 5 to 7 days after ILI onset, the overall adjusted IVE (N = 1895) was 17.5% (95% CI: −4.4; 34.7) and 20.7% (95% CI: −0.6; 37.6) among the target group for vaccination (N = 1754).

Discussion

The results of our 2011–12 pilot multicentre hospital based influenza study suggest a low IVE against laboratory confirmed A(H3N2) Influenza. The IVE point estimate was 24.9% overall and ranged between 17.8% in the 75–84 years and 42.6% in the 65–74 years.

The 21 hospitals followed a common core protocol, allowing for pooling data sets. The systematic inclusion of ILI patients and the access to medical records ensured the collection of a good quality data. We had very few missing values (0.5%) and were able to perform a complete case analysis. We used RT-PCR confirmation allowing measuring IVE against a very specific outcome [28]. The absolute difference between crude and adjusted IVE varied from 1.6% (among all targeted population) to 7.3% (among the less than 65 years targeted by the vaccination) suggesting little confounding from the variables included in our study.

Ninety two percent of the ILI patients belonged to the target groups for vaccination. Estimating effectiveness against laboratory confirmed influenza in this population is particularly relevant since no efficacy measures are available [7].

Some biases may limit the interpretation of our study. High risk groups are more likely to be vaccinated and to develop a severe form of influenza. This may overestimate the number of vaccinated cases seen at the hospital and underestimate IVE. People with a healthy lifestyle are more likely to accept/request vaccination and less likely to be severely sick. This would overestimate IVE. However, while this bias is likely to happen for mild outcomes, it is unlikely to affect the IVE estimate in a hospital setting. Extremely frail people are less likely to be offered vaccination but more likely to develop a severe form of the disease. This would overestimate IVE [29]. We collected detailed information on severity of chronic conditions and functional status. This allowed us to correct for this potential confounding.

Table 2. Characteristics of A(H3N2) influenza cases (N = 375) and test-negative controls (N = 770) swabbed less than five days after ILI symptoms onset included in the study, hospital based Influenza VE study, EU, 2011–12.

	Cases	Controls	
	N *(%)*	N *(%)*	p-value‡
Age group			
18–64 years	80 *(21.3)*	191 *(24.8)*	0.148
65–74 years	69 *(18.4)*	153 *(19.9)*	
75–84 years	145 *(38.7)*	245 *(31.8)*	
85 years+	81 *(21.6)*	181 *(23.5)*	
Sex = Male	213 *(56.8)*	432 (56.1)	0.849
Belongs to target group for vaccination	349 *(93.1)*	709 *(92.1)*	0.635
Symptoms			
Fever	333 *(88.8)*	616 (80.0)	<0.001
Malaise or headache	278 *(74.1)*	570 *(74.0)*	1.000
Myalgia	74 *(19.8)*	124 *(16.1)*	0.134
Cough	342 *(91.2)*	643 *(83.5)*	<0.001
Sore throat	113 *(30.1)*	223 *(29.0)*	0.588
Shortness of breath	319 *(85.1)*	680 *(88.3)*	0.274
Sudden onset	238 *(64.3)*	495 *(64.5)*	0.947
At least one chronic condition	315 *(84.0)*	657 *(85.3)*	0.598
More than one chronic condition	187 *(49.9)*	427 *(55.5)*	0.077
Chronic conditions			
Diabetes	108 *(28.8)*	216 *(28.1)*	0.834
Heart disease	167 *(44.5)*	362 *(47.0)*	0.449
Lung disease	172 *(45.9)*	384 *(49.9)*	0.620
Immunocompromised	18 *(4.8)*	38 *(4.9)*	1.000
Obese	86 *(22.9)*	228 *(29.6)*	0.020
More than one GP visit in previous 3 months	191 *(50.9)*	426 *(55.3)*	0.165
At least one hospitalisation in previous 12 months	127 *(33.9)*	288 *(37.4)*	0.266
Low functional status (among >65 years)*	50 *(16.9)*	137 *(23.7)*	0.023
Number of days between onset of symptoms and swabbing			
0–2 days	105 *(28.0)*	295 *(38.3)*	<0.001
3–4 days	270 *(72.0)*	475 *(61.7)*	
2011–12 seasonal flu vaccination	206 *(54.9)*	460 *(59.7)*	0.126
2010–11 seasonal flu vaccination	240 *(64.0)*	509 *(66.1)*	0.508

*N = 814 (one record with missing information).
‡Two-sided Fisher's exact test.
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However, we cannot exclude that residual confounding still biases our results.

Over a third of patients included in this study were swabbed between five and seven days after onset of symptoms. Although hospitalised patients were described as shedding influenza virus for longer periods [30], the likelihood of misclassifying patients' outcome increases with time. To reduce the chance for misclassification bias, we restricted our analysis to those swabbed within four days. We are confident that, by adopting this approach, we limited the presence of false negatives in our study population. In the sensitivity analysis including all patients swabbed within seven days, the IVE was lower suggesting the presence of misclassification biases. In the future, further studies investigating the duration of shedding of seasonal influenza viruses among high risk population would help setting up cut-offs to reduce misclassification biases.

The sources of information included medical records consultation and results of very specific laboratory tests, minimising information biases. Vaccination status ascertainment relied on registries in the Spanish studies, patients' interview in France and Italy, with confirmation of information by the practitioner in Italy. At the time of interview, patients did not know if they had confirmed influenza. This limited differential recall of vaccination status between cases and controls.

The source population giving rise to the cases can be defined as individuals likely to be hospitalised in case of severe ILI. Considering the good access to hospital care in France, Spain and Italy, the source population can be defined as the general population. Recruiting controls in the community would be logistically challenging as a very large sample size would be needed to adjust for the numerous potential confounders. Recruiting controls among those hospitalised for ILI testing negative for

Table 3. Pooled crude and adjusted Influenza vaccine effectiveness against influenza A(H3N2) in target group for vaccination swabbed less than five days after ILI symptoms onset (N = 1058), by age group, EU, 2011–12.

				Percent vaccinated (%)			
Population	**Model used**	**N**	**Number of cases**	**cases**	**controls**	**IVE (%)**	**95% CI**
All target population[a]	Crude*	1058	349	57.6	63.5	30.4	6.6; 48.1
	Adjusted					28.8	2.8; 47.9
Age group[b]							
18–64 years‡	Crude*	160	54	31.5	40.6	44.1	−23.2; 74.6
	Adjusted					36.8	−48.3; 73.1
65–74 years¥	Crude*	205	69	52.2	58.8	37.9	−20.3; 67.9
	Adjusted					42.6	−16.5; 71.7
75–84 years±	Crude*	389	145	66.9	72.1	23.4	−28.1; 54.3
	Adjusted					17.8	−40.8; 52.1
85 years and olderΩ	Crude*	244	80	63.8	73.2	39.6	−15.9; 68.5
	Adjusted					37.5	−22.8; 68.2

*Adjusted for study site and week of onset.
[a]Adjusted for study site, week of symptoms onset, age group (four categories), gender, GP visit in the previous three months, hospitalisation in the previous year, presence of chronic condition, presence of lung diseases and presence of cardiovascular disease.
[b]Adjusted for study site, week of symptoms onset, gender, GP visit in the previous three months, hospitalisation in the previous year, presence of chronic condition, presence of lung diseases and presence of cardiovascular disease.
‡24 controls dropped due to no cases in this age group, targeted by the vaccination, on the 7th pair of weeks.
¥16 controls dropped due to no cases in this age group on the 7th pair of weeks. 1 control dropped due to no cases in Italy.
±1 control dropped due to no cases in Italy.
Ω17 controls dropped due to no cases in this age group on the 7th pair of weeks. 1 case dropped due to no controls in Italy.
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influenza has the advantage of being resource saving as it does not require extra sampling. However, test negative controls may not be representing the vaccination coverage in the general population. In our analysis, vaccination coverage among controls was 59.7% and 63.5% among those belonging to the target group for vaccination. A population based study estimated the vaccination coverage in France to be 23% in the general population aged 15 years and older in 2011–12 [31]. During this season, the vaccine coverage was 59% among non institutionalised targeted population in Navarre [26] and 49% among targeted population in France [31]. The observed vaccine coverage in our control groups is close to the coverage reported among the target group for influenza vaccination. Furthermore, 92.1% of the controls belonged to the target group for vaccination. Selection biases are certainly minimised in our analysis confined to the target group for vaccination.

Sample size varied across study sites, ranging from 25 patients in Italy to 1668 in Valencia region. The performance of a one-stage pooled analysis also assumes that the IVE and confounding are similar in all studies. Considering the broad range of vaccines used across sites (18 vaccine brand names) and potential differences in health care use, we can expect IVE and confounding effects to vary across study sites. If so, a two-stage model and larger sample sizes in each study site are needed.

Considering the lack of power to assess statistical heterogeneity across study sites [23], qualitative heterogeneity assessment is of great relevance in this analysis. We conducted site visits and documented the protocol implementation within each hospital to assure systematic recruitment processes and provide recommendations if needed. The four sites had a different research status impacting on patients' recruitment. In Navarra region, health data are computerised and a systematic swabbing of ILI patients is implemented in the hospitals. France and Italy implemented this pilot protocol as non-interventional studies. Swabbing had to be part of the usual patient management and was the responsibility of clinicians. As a consequence most Italian and French hospitals had difficulties to comply with an exhaustive swabbing of ILI patients. In Valencia, one study nurse was hired in each hospital and was in charge of the recruitment and the swabbing of all patients with ILI in the past seven days. This active surveillance and swabbing of eligible patients, conducted independently from the routine case management, seems crucial to ensure a systematic inclusion of all hospitalised ILI patients from the source population and reach large sample size.

Our study suggests a low VE against laboratory confirmed influenza A(H3N2) hospitalisation in the 2011–12 season. Our estimates are lower than the previously published results from IVE against GP attended influenza [10,26,32] among vaccination target groups this season. Our study population was older and more likely to have at least one chronic condition compared to GP based populations. Lower effectiveness and efficacy of influenza vaccines among the elderly can be explained by a lower immune response [26,27]. These observations, underline the need of developing more immunogenic vaccine formulations for the elderly.

In 2011–12, the influenza A(H3) virus circulating has moved genetically and antigenically away from seasonal vaccine viruses [33,34]. In addition, the 2011–12 season occurred very late compared to previous seasons. The time lag between the vaccination campaigns and the beginning of the epidemics was longer than usual. Protection against vaccine strains begins within two weeks of immunisation, peaks at 4–6 weeks and then wanes [35]. A waned protection could partially explain this low VE, as discussed in recently published papers [36–38]. Bigger sample sizes are needed to measure IVE against hospitalised Influenza according to time since vaccination.

This study allowed the collection of good quality data. Patients belonging to the target group for vaccination are an appropriate study population to guide influenza vaccination strategies in Europe. To compute more precise IVE and be able to estimate specific IVE by vaccine type and mode of administration, increasing the samples within hospitals are needed to better assess the quantitative validity of the pooling of data. Maintaining harmonised practices across study sites through a continuous and strong coordination will ensure the qualitative validity of the pooling. Our pilot study suggests that a multicentre hospital based study is feasible and needed in EU to measure IVE against hospitalised influenza. A large hospital study network in EU could allow for studying VE against various vaccine preventable diseases while optimising the high cost of such a network.

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3.5.1.2 Results from 2012-13 season

The 2012-13 season was characterised by a co-circulation of influenza A(H1N1)pdm09, A(H3N2) and B viruses, which good levels of antigenic match between circulating strains and vaccine components. We included 18 hospitals from France, Italy, Spain (Navarra and Valencia regions and Lithuania). We restricted our analysis to patients belonging to target groups for vaccination. Our study objective was to measure the 2012-13 seasonal IVE against hospitalisation with influenza A(H1N1)pdm09, A(H3N2) and B among the adult population targeted for vaccination in four EU countries.

We included 1,972 patients; 116 influenza A(H1N1)pdm09, 58 A(H3N2) and 232 influenza B cases. Adjusted IVE was 21% (95%CI: -25;51; n=1,628), 62% (95% CI: 27;80; n=557) and 43% (95% CI: 21;59; n=1,526) against influenza A(H1N1) pdm09, A(H3N2) and B respectively.

Overall, adjusted IVE was low against A(H1N1)pdm09 and it was moderate against influenza A(H3N2) and B. Our results suggested some effects of previous seasons' vaccination on the IVE. We observed some residual protection from 2011-12 season vaccine against A(H1N1)pdm09. Our results also suggested some negative interference for A(H3N2) and B and positive for A(H1N1)pdm09. We discussed these results in the context of various immunological hypothesis and a low sample making any conclusion impossible.

2012/13 influenza vaccine effectiveness against hospitalised influenza A(H1N1)pdm09, A(H3N2) and B: estimates from a European network of hospitals

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While influenza vaccines aim to decrease the incidence of severe influenza among high-risk groups, evidence of influenza vaccine effectiveness (IVE) among the influenza vaccine target population is sparse. We conducted a multicentre test-negative case–control study to estimate IVE against hospitalised laboratory-confirmed influenza in the target population in 18 hospitals in France, Italy, Lithuania and the Navarre and Valencia regions in Spain. All hospitalised patients aged ≥18 years, belonging to the target population presenting with influenza-like illness symptom onset within seven days were swabbed. Patients positive by reverse transcription polymerase chain reaction for influenza virus were cases and those negative were controls. Using logistic regression, we calculated IVE for each influenza virus subtype and adjusted it for month of symptom onset, study site, age and chronic conditions. Of the 1,972 patients included, 116 were positive for influenza A(H1N1)pdm09, 58 for A(H3N2) and 232 for influenza B. Adjusted IVE was 21.3% (95% confidence interval (CI): -25.2 to 50.6; n=1,628), 61.8% (95% CI: 26.8 to 80.0; n=557) and 43.1% (95% CI: 21.2 to 58.9; n=1,526) against influenza A(H1N1)pdm09, A(H3N2) and B respectively. Our results suggest that the 2012/13 IVE was moderate against influenza A(H3N2) and B and low against influenza A(H1N1)pdm09.

Background

Antigenic drifts of influenza viruses expose the population to new but related influenza variants on a regular basis [1]. On the basis of a yearly revised composition of seasonal influenza vaccines, the World Health Organization (WHO) considers annual Influenza vaccination as the most efficient measure against influenza [2]. Every year, the seasonal influenza vaccine licensure is obtained based on immunogenicity data [3]. While these immunogenicity data are thought to be valid for healthy adults [4], the development of correlates of protection suited to vulnerable populations is still to be achieved [5].

The population targeted for influenza vaccination in Europe includes those at increased risk of exposure to influenza virus as well as of developing severe disease, especially disease resulting in hospitalisation or death [6]. Target groups for vaccination usually include adults over 59 or 64 years of age and people of any age with certain underlying medical conditions [7,8]. Measuring influenza vaccine effectiveness (IVE) in each influenza season is important for the following reasons: to identify vaccines types and brands with low IVE; to decide on alternative preventive strategies if early estimates of IVE are low (e.g. preventive use of antivirals among vulnerable individuals); and to help decide on the next season's vaccine content. Repeated evidence of suboptimal IVE among the population targeted for annual

Table 1

Generic protocol adaptations in each study site, hospital-based influenza vaccine effectiveness study, four European countries, 2012/13

Protocol adaptation	France	Italy	Lithuania	Spain	
				Navarre	Valencia
Additonal staff for the study	Yes	Yes	No	No	Yes
Services	Emergency ward	Emergency ward internal medicine unit	Emergency ward Infectious disease hospital	All	Emergency ward
Vaccine status ascertainment	Patient	Patient or GP	Patient or GP	Register	Register and oral
Ascertainment of type of vaccine used	Ecological data	Individual data	Ecological data	Individual data	Individual data
Exclusion based on place of residence	No	No	No	Yes	Yes
Inclusion of patients unable to sign the consent form	Yes	Yes	No	Yes	Yes
Type of respiratory specimen	Nasal	Nasal and pharyngeal	One pharyngeal and two nasal	Nasal and pharyngeal	Nasal and pharyngeal
Data entry validation	Coordination team	Coordination team	Coordination team	Coordination team	Double entry for laboratory results Weekly quality checks
Study periods[a]					
Influenza A(H1N1)pdm09	Week 1, 2013	Week 2, 2013	Week 52, 2012	Week 7, 2013	Week 47, 2012
	Week 10, 2013	Week 8, 2013	Week 9, 2013	Week 11, 2013	Week 15, 2013
Influenza A(H3N2)	Week 52, 2012	Week 3, 2013	Week 3, 2013	Week 4, 2013	Week 9, 2013
	Week 14, 2013	Week 6, 2013	Week 13, 2013	Week 13, 2013	Week 12, 2013
Influenza B	Week 50, 2012	Week 5, 2013	Week 4, 2013	Week 50, 2012	Week 51, 2012
	Week 13, 2013	Week 9, 2013	Week 15, 2013	Week 11, 2013	Week 15, 2013

GP: general practitioner.

[a] The International Organization for Standardization's week numbers were used, to ensure consistency across study sites.

influenza vaccination would also further advocate the need for vaccines that are more effective in this population. Moreover, there are ongoing scientific debates about the effect of repeated vaccination on the immunological response induced by the seasonal influenza vaccine [9-11] and further evidence is needed.

In 2011, we launched a pilot study to estimate the IVE against laboratory-confirmed influenza hospitalisation using a network of hospitals in the European Union (EU) [12]. During the 2012/13 influenza season, co-circulation of influenza A(H1N1)pdm09, A(H3N2) and B/Victoria- and B/Yamagata-lineage viruses was reported in Europe [13]. The objective of the study presented here was to measure the 2012/13 seasonal IVE against hospitalisation with subtype-specific laboratory-confirmed influenza in a hospital network in four EU countries: France, Italy, Lithuania and Spain.

Methods

We conducted a case–control study using the test-negative design [14] in 18 hospitals located in five study sites: France (five hospitals), Italy (two), Lithuania (two), and the Navarre (four) and Valencia (five) regions in Spain. Each study site adapted a generic protocol [15] to the local context (Table 1).

Study population

The study population was all community-dwelling adults (18 years of age or older), belonging to the target groups for vaccination as defined locally [16-20], admitted to one of the participating hospitals with no contraindication for influenza vaccination. Patients were excluded if they had previously tested positive for influenza virus in the 2012/13 season or resided outside the hospital catchment area (for the 11 hospitals with known catchment area).

Study teams actively screened all patients admitted for potentially influenza-related conditions. These conditions included the following: acute myocardial infarction or acute coronary syndrome; heart failure; pneumonia and influenza; chronic pulmonary obstructive disease; myalgia; altered consciousness, convulsions, febrile-convulsions; respiratory abnormality; shortness of breath; respiratory or chest symptoms; acute cerebrovascular disease; sepsis; and systemic inflammatory response syndrome. Among them, study teams invited patients with an onset of influenza-like

Table 2

Definition of the categories of chronic conditions according to the variables collected, hospital-based influenza vaccine effectiveness study, four European countries, 2012/13

Categories of chronic conditions	Chronic conditions	Study sites that collected the information
Cardiovascular disease	Cardiovascular disease[a]	FR, IT, LT, VA
	Heart disease	FR, IT, LT, NV, VA
	Stroke	FR, IT, LT, NV
	Transient ischemic attack	IT
	Peripheral arterial disease	IT, VA
Respiratory disease	Lung diseases[a]	FR, IT, LT, NV
	Asthma	IT, VA, LT
	Chronic obstructive pulmonary disease	IT, LT
	Emphysema	IT, LT
	Mucoviscidosis	FR, IT, LT
	Bronchitis	VA, LT
Metabolic and endocrine disorders	Diabetes	FR, IT, NV, VA
	Nutritional deficiency	FR, IT, LT
	Endocrine disease	FR, IT, LT, VA
Haematological disease or cancer	Haematological cancer	FR, IT, LT, NV
	Anaemia/spleen condition	FR, IT, LT, VA
	Drepanocytosis	FR, IT
	Cancer	FR, IT, LT, NV, VA
Immunodeficiency	Immunodeficiency	FR, IT, LT, NV, VA
	Rheumatological disease	FR, IT, LT, NV
Hepatic disease		FR, IT, LT, NV, VA
Renal disease		FR, IT, LT, NV, VA
Obesity[b]		FR, IT, LT, NV, VA
Neuromuscular disorder		FR, IT
Dementia		FR, IT, LT, NV, VA

FR: France; IT: Italy; LT: Lithuania; NV: Navarre, Spain; VA: Valencia, Spain.

[a] May include the conditions from the same category listed below.
[b] Defined as body mass index ≥30 kg/m².

illness (ILI) symptoms (one systemic and one respiratory symptom) within the past seven days to participate. Those accepting to participate were swabbed and tested for influenza. Reverse transcription polymerase chain reaction (RT-PCR) was used to detect influenza viruses and to classify them as influenza A(H3N2), influenza A(H1N1)pdm2009 or influenza B. Patients positive for influenza were classified as cases of a given influenza type/subtype and those testing negative were controls.

We defined the study period as at least 15 days after the beginning of each site-specific seasonal influenza vaccination campaign until the end of the influenza season as declared by local influenza surveillance systems. For each of the influenza type/subtype analyses, we excluded the controls with onset of symptoms before the week of the first laboratory-confirmed case or after the week of the last laboratory-confirmed case. We used the International Organization for Standardization's week numbers [21] to ensure consistency across study sites.

We considered patients as vaccinated against seasonal influenza if they had received at least one dose of the 2012/13 influenza vaccine more than 14 days before onset of ILI symptoms. Patients not vaccinated or vaccinated less than 15 days before ILI onset were considered as unvaccinated.

Data collection

We collected data on the ILI episode, demographics, chronic diseases (Table 2), number of hospitalisations in the previous 12 months, number of consultations at the general practitioner (GP) in the previous three months, smoking status, vaccination against influenza in 2012/13 and 2011/12 and, for those aged 65 years and over, functional status before ILI onset using the Barthel score [22]. The data were gathered from hospital medical records, face-to-face interviews with the patient and/or patient's family and laboratory databases. The vaccination status was obtained from vaccination registers in two study sites, interview with the patients and/or patient's family in two sites and contact with the patient's physician in one site.

Table 3

Number of records received by the pooled analysis coordinator and included in the pooled analysis by study site, hospital-based influenza vaccine effectiveness study, four European countries, 2012/13

Type of record	Number of records per study site					
	France[a]	Italy	Lithuania[b]	Navarre, Spain	Valencia, Spain	Total
Eligible records	433	84	184	93	1,535	**2,329**
Non-target groups for vaccination	78	14	96	18	102	**308**
Missing laboratory results	2	0	0	0	43	**45**
Unknown vaccination status	3	0	1	0	0	**4**
Total records used for the analyses	350	70	87	75	1,390	**1,972**
Influenza A(H1N1)pdm09						
Cases	20	10	20	9	57	**116**
Controls	213	39	24	24	1,213	**1,513**
Influenza A(H3N2)						
Cases	38	4	9	2	5	**58**
Controls	229	24	29	33	204	**519**
Influenza B						
Cases	62	13	25	17	115	**232**
Controls	219	31	28	45	971	**1,294**

[a] In France, one specimen of influenza A virus could not be subtyped.

[b] In Lithuania, one patient was coinfected with A(H3N2) and A(H1N1)pdm09 viruses.

Data analysis

Study sites transmitted anonymised datasets to the pooled analysis coordinator, through a password-secured web-based platform. We ran a complete case analysis, excluding records for which laboratory results, vaccination status or potential confounding variables were missing.

To test for heterogeneity between study sites, we used Cochran's Q-test and the I^2 index [23]. The Q-test provides a p value that indicates the presence or not of heterogeneity. The I^2 index quantifies the proportion of the variance attributable to differences between study sites. It is common to consider that I^2 around 25%, 50% and 75% indicate low, medium and high heterogeneity, respectively.

We conducted separate analyses for each type/subtype of influenza. We estimated the pooled IVE as 1 minus the odds ratio (OR) (expressed as a percentage) of being vaccinated in cases versus controls, using a one-stage method with study site as fixed effect in the model [24].

We assessed the presence of effect modification by comparing the time- and study site-adjusted OR (assuming that the test-negative design case–control study is a density case–control study implying adjustment for the time of symptom onset) across strata of characteristics using the homogeneity test. We considered a variable as a confounder when the percentage change between the unadjusted and adjusted OR was greater than 15%.

We conducted a multivariable logistic regression analysis. In addition to study site and month of symptom onset, we adjusted the models for the covariates identified as potential confounders in the stratified analysis as well as the presence of at least one underlying condition and the age that we modelled as a restricted cubic spline with four knots [25]. The likelihood ratio test was used to decide on the final models. We conducted stratified analyses by age group (less than 65 years, 65–79 years and 80 years and above).

To study the effect of previous influenza vaccination on laboratory-confirmed influenza, we conducted a stratified analysis using four vaccination status categories: vaccination in none of the seasons (2011/12 and 2012/13), 2012/13 vaccination only, 2011/12 vaccination only and vaccination in both seasons and computed and compared IVE for each of these categories using vaccination in none of the seasons as a reference.

We carried out sensitivity analyses excluding the weeks when less than 10% of the patients included were positive for influenza, excluding patients who received antivirals between the onset of symptoms and swabbing and by restricting the analysis to patients swabbed within four days of symptoms onset. To avoid the inclusion of patients with acute manifestation of chronic respiratory illnesses rather than respiratory infection, we restricted our analysis to patients with no underlying respiratory conditions.

We ran all analyses with Stata v12 (Stata Corp LP, College Station, TX, United States).

Table 4

Characteristics of influenza A(H1N1)pdm09 (n=116), influenza A(H3N2) (n=58) and influenza B (n=232) cases and corresponding test-negative controls included in the study, hospital-based influenza vaccine effectiveness study, four European countries[a], 2012/13 (n=1,972)

Charactertistic	A(H1N1)pdm09		A(H3N2)		B	
	Controls[b] (n=1,513)	Cases (n=116)	Controls[c] (n=519)	Cases (n=58)	Controls[d] (n=1,294)	Cases (n=232)
	Number (%)[e]	Number (%)[e]	Number (%)[e]	Number (%)[e]	Number (%)[e]	Number (%)[e]
Median age in years	77.0	63.0*	75.0	73.0	77.0	75.2
Age group in years						
18–64	339 (22.4)	60 (51.7)*	146 (28.1)	14 (24.1)	301 (23.3)	60 (25.9)
65–79	563 (37.2)	42 (36.2)*	175 (33.7)	22 (37.9)	473 (36.6)	92 (39.7)
80–103	611 (40.4)	14 (12.1)*	198 (38.2)	22 (37.9)	520 (40.2)	80 (34.5)
Sex						
Male	851 (56.2)	67 (57.8)	294 (56.6)	24 (41.4)*	718 (55.5)	108 (46.6)*
Vaccine status						
2012/13 seasonal influenza vaccination	866 (57.2)	39 (33.6)*	296 (57.0)	20 (34.5)*	734 (56.7)	88 (37.9)*
2011/12 seasonal influenza vaccination	835 (55.3)	37 (31.9)*	296 (57.5)	25 (44.6)	702 (54.5)	102 (44.5)*
Presence of comorbidities						
Metabolic and endocrine disorders	546 (36.1)	41 (35.3)	195 (37.6)	24 (41.4)	462 (35.7)	72 (31.0)
Cardiovascular disease	768 (50.8)	49 (42.2)	247 (47.6)	26 (44.8)	636 (49.1)	103 (44.6)
Renal disease	198 (13.1)	9 (7.8)	84 (16.2)	8 (13.8)	165 (12.8)	27 (11.7)
Respiratory disease	750 (49.6)	50 (43.5)	243 (46.8)	25 (43.1)	634 (49.0)	80 (34.6)*
Neuromuscular disorder	82 (5.6)	7 (8.0)	27 (5.9)	3 (6.4)	70 (5.7)	7 (3.7)
Hepatic disease	65 (4.3)	2 (1.7)	14 (2.7)	0 (0.0)	57 (4.4)	8 (3.5)
Immunodeficiency	102 (6.7)	8 (6.9)	40 (7.7)	5 (8.6)	87 (6.7)	16 (6.9)
Haematological disease or cancer	321 (21.7)	16 (14.5)	96 (19.2)	12 (21.8)	279 (21.6)	30 (13.0)*
Any chronic condition (of all chronic conditions collected in the study site)	1,404 (92.8)	106 (91.4)	473 (91.1)	52 (89.7)	1,195 (92.3)	192 (82.8)*
More than one chronic condition	1,013 (67.0)	62 (53.4)*	340 (65.5)	37 (63.8)	853 (65.9)	113 (48.7)*
Obesity[f]	423 (28.1)	26 (22.6)	127 (24.7)	10 (17.9)	359 (27.9)	54 (23.5)
Pregnancy	10 (0.7)	1 (1.3)	7 (2.0)	0 (0.0)	11 (1.0)	8 (4.7)*
Low functional status[g] (among patients ≥65 years)	232 (19.8)	9 (16.1)	5 (14.8)	4 (9.1)	187 (18.9)	34 (19.8)
Other potential confounders						
More than one GP visit in previous 3 months	738 (49.1)	46 (39.7)	261 (51.3)	26 (46.4)	649 (50.7)	109 (48.0)
Hospitalisations in previous 12 months	582 (38.5)	32 (27.6)*	205 (39.6)	22 (37.9)	502 (38.8)	70 (30.2)*
Smoker status						
Current	277 (18.3)	39 (33.6)*	108 (20.8)	13 (22.4)	243 (18.8)	32 (13.9)*
Former	580 (38.3)	35 (30.2)*	173 (33.4)	16 (27.6)	485 (37.5)	58 (25.1)*
Never	656 (43.4)	42 (36.2)*	237 (45.8)	29 (50.0)	565 (43.7)	141 (61.0)*
Potential for misclassification						
Swabbing delay<4 days	745 (49.2)	69 (59.5)*	233 (44.9)	24 (41.4)	621 (48.0)	90 (38.8)*
Antiviral treatment before swabbing	18 (1.2)	12 (10.4)*	17 (3.3)	5 (8.6)	18 (1.4)	17 (7.3)*

GP: general practitioner.

* p value for difference between cases and controls<0.05.

[a] France, Italy, Lithuania and Spain (Navarre and Valencia regions).

[b] Comparisons were made with controls recruited between the week of the first case of influenza A(H1N1)pdm09 and the week of the last case of influenza A(H1N1)pdm09 (1,513 controls).

[c] Comparisons were made with controls recruited between the week of the first case of influenza A(H3N2) and the week of the last case of influenza A(H3N2) (519 controls).

[d] Comparisons were made with controls recruited between the week of the first case of influenza B and the week of the last case of influenza B (1,294 controls).

[e] Unless otherwise indicated.

[f] Defined as body mass index ≥30 kg/m².

[g] Determined using the Barthel score [22].

Table 5

Influenza vaccine effectiveness against influenza A(H1N1)pdm09, A(H3N2) and B, adjusted for various covariables by age group, hospital-based influenza vaccine effectiveness study, four European countries[a], 2012/13

Groups assessed	A(H1N1)pdm09	A(H3N2)	B
All target groups			
Number of cases and controls	1,628	577	1,526
Number of cases; number of vaccinated cases	116; 39	58; 20	232; 88
Number of controls; number of vaccinated controls	1,512; 865	519; 296	1,294; 734
Variables used for adjustment of vaccine effectiveness	Percentage influenza vaccine effectiveness (95% CI)		
Study site	47.0 (18.8 to 65.4)	54.4 (16.1 to 75.2)	46.5 (27.7 to 60.4)
Study site and month of symptom onset	45.7 (16.4 to 64.8)	53.0 (13.2 to 74.5)	44.3 (24.3 to 59.0)
Study site, month of symptom onset and age	20.9 (−25.3 to 50.1)	61.9 (27.2 to 80.1)	46.9 (26.8 to 61.5)
Study site, month of symptom onset, age and presence of chronic conditions	21.3 (−25.2 to 50.6)	61.8 (26.8 to 80.0)	43.1 (21.2 to 58.9)
Patients aged 18–64 years belonging to target groups			
Number of cases and controls	372[b]	143[c]	346[d]
Number of cases; number of vaccinated cases	60; 9	14; 3	60; 7
Number of controls; number of vaccinated controls	312; 105	129; 39	286; 91
Variables used for adjustment of vaccine effectiveness	Percentage influenza vaccine effectiveness (95% CI)		
Study site and month of onset	42.5 (−28.3 to 74.3)	26.1 (−215.9 to 82.7)	68.4 (25.7 to 86.6)
Study site, month of onset and presence of chronic conditions	41.8 (−30.7 to 74.1)	NA[c]	66.0 (19.3 to 85.7)
Patients aged 65–79 years			
Number of cases and controls	504[e]	181[f]	565
Number of cases; number of vaccinated cases	42; 18	22; 7	92; 40
Number of controls; number of vaccinated controls	462; 276	159; 91	473; 287
Variables used for adjustment of vaccine effectiveness	Percentage influenza vaccine effectiveness (95% CI)		
Study site and month of onset	44.2 (−9.0 to 71.4)	55.7 (−22.8 to 84.0)	37.3 (−2.1 to 61.5)
Study site, month of onset and presence of chronic conditions	43.8 (−10.7 to 71.5)	52.4 (−33.9 to 83.1)	28.2 (−18.9 to 56.6)
Patients aged 80–103 years			
Number of cases and controls	623[g]	216[h]	600
Number of cases; number of vaccinated cases	14; 12	22; 10	80; 41
Number of controls; number of vaccinated controls	609; 412	194; 147	520; 348
Variables used for adjustment of vaccine effectiveness	Percentage influenza vaccine effectiveness (95% CI)		
Study site and month of symptom onset	−171.7 (−1,170.7 to 41.9)	73.8 (30.0 to 90.2)	46.4 (9.6 to 68.2)
Study site, month of symptom onset and presence of chronic conditions	NA[g]	73.8 (29.9 to 90.2)	44.8 (6.7 to 67.4)

CI: confidence interval; NA: not applicable.

[a] France, Italy, Lithuania and Spain (Navarre and Valencia regions).

[b] A total of 27 controls dropped because no cases in November among patients less than 65 years.

[c] A total of 17 controls dropped because no cases in December and April and in Italy among patients less than 65 years. No adjustment for chronic disease because all A(H3N2) cases aged less than 65 years had chronic conditions.

[d] A total of 15 controls dropped because no cases in April among patients less than 65 years.

[e] A total of 101 controls dropped because no cases in December among patients aged 65–79 years.

[f] A total of 16 controls dropped because no cases in December and in Navarre, Spain, among patients aged 65–79 years.

[g] Two controls dropped because no cases in Lithuania among patients aged 80 years and over. No adjustment for chronic disease because all A(H1N1)pdm09 cases aged 80 years and over had chronic conditions.

[h] Four controls dropped because no cases in April among patients aged 80 years and over.

Results

Overall, 2,329 eligible patients, of whom 2,021 belonged to the target groups for influenza vaccination, were recruited in the 18 study hospitals (Table 3). A total of 45 (2.2%) and four (0.2%) patients were excluded due to missing laboratory results and missing vaccination status, respectively. We included a total of 1,972 patients in the analysis: 1,390 from Valencia (177 cases), 350 from France (121 cases), 87 from Lithuania (53 cases), 75 from Navarre (28 cases) and 70 from Italy (27 cases).

Influenza A(H3N2), A(H1N1)pdm09 and B co-circulated in all study sites (Table 1). The study site having included patients for the longest period of time was Valencia (week 47, 2012 to 15, 2013) and for the shortest period was in Italy (week 2–8, 2013). The period of

Table 6

Crude and adjusted vaccine effectiveness against influenza A(H1N1)pdm09 (n=1,625), A(H3N2) (n=571) and B (n=1,518) by vaccination status, hospital-based influenza vaccine effectiveness study, four European countries[a], 2012/13

Influenza type	Number of cases	Number of controls	Crude VE[b] (95% CI)	Adjusted VE[c] (95% CI)
A(H1N1)pdm09 (n=1,625)				
No vaccination in 2012/13 and 2011/12	71	539	–	–
2012/13 vaccination only	8	135	26.2 (–62.9 to 66.6)	6.2 (–110.4 to 58.2)
2011/12 vaccination only	6	108	39.8 (–47.1 to 75.4)	26.6 (–81.6 to 70.3)
2011/12 and 2012/13 vaccinations	31	727	52.8 (24.3 to 70.6)	27.9 (–20.5 to 56.9)
A(H3N2) (n=571)				
No vaccination in 2012/13 and 2011/12	30	183	–	–
2012/13 vaccination only	1	36	65.3 (–176.6 to 95.7)	68.3 (–157.2 to 96.1)
2011/12 vaccination only	6	40	5.1 (–156.4 to 64.9)	12.3 (–140.7 to 68.1)
2011/12 and 2012/13 vaccinations	19	256	49.2 (1.7 to 73.8)	59.6 (18.5 to 80.0)
B (n=1,518)				
No vaccination in 2012/13 and 2011/12	121	478	–	–
2012/13 vaccination only	6	109	69.5 (27.6 to 87.2)	68.3 (24.5 to 86.7)
2011/12 vaccination only	21	82	0.4 (–73.1 to 42.7)	–5.6 (–84.5 to 39.6)
2011/12 and 2012/13 vaccinations	81	620	39.3 (15.5 to 56.3)	37.3 (10.7 to 56.0)

CI: confidence interval; VE: vaccine effectiveness.

[a] France, Italy, Lithuania and Spain (Navarre and Valencia regions).
[b] Adjustment for study site and month of symptom onset.
[c] Adjustment for study site, month of symptom onset, age and comorbidities.

recruitment was the longest for A(H1N1)pdm2009 (21 weeks) and the shortest for A(H3N2) (15 weeks).

Of the 1,972 patients included in the pooled analysis, 116 patients tested positive for influenza A(H1N1) pdm09, 58 for A(H3N2) and 232 for influenza B. Two patients were coinfected with types A and B and one patient was coinfected with A(H3N2) and A(H1N1) pdm09. One specimen of influenza A could not be subtyped.

Influenza A(H1N1)pdm09 cases were younger (63 vs 77 years, p<0.05) than controls. A lower proportion of A(H1N1)pdm09 cases had more than one underlying condition (53.4% vs 67.0%, p<0.05), had been hospitalised in the previous year (27.6% vs 38.5%, p<0.05) and a higher proportion were current smokers (33.6% vs 18.3%, p<0.05) compared with controls (Table 4).

Influenza A(H3N2) cases and controls were similar for all characteristics except for the proportion of male patients (41.4% vs 56.6%, p<0.05).

Compared with controls, a lower proportion of influenza B cases had underlying conditions (82.8% vs 92.3%, p<0.05), had been hospitalised in the previous year (30.2% vs 38.8%, p<0.05) and were smokers (13.9% vs 18.8% of current smokers, p<0.05).

The 2012/13 vaccine coverage was 57.2% among all controls (all influenza-negative patients included in the study), 33.6% among A(H1N1)pdm09, 34.5% among A(H3N2) and 37.9% among influenza B cases (Table 4).

The p values associated with the Q-test and the I^2 index using models adjusted for age, month of symptom onset and chronic condition, testing for heterogeneity between study sites, were respectively 0.19 and 40.0% for A(H3N2), 0.10 and 48.3% for A(H1N1)pdm09 and 0.08 and 56.2% for influenza B.

The overall adjusted A(H1N1)pdm09 IVE was 21.3% (95% confidence interval (CI): –25.2 to 50.6; n=1,628); 41.8% (95% CI: –30.7 to 74.1; n=372) among the 18–64 year-old patients and 43.8% (95% CI: –10.7 to 71.5; n=504) among those aged 65–79 years. Among patients aged 80 years and older, there were 14 A(H1N1)pdm09 cases, including 12 vaccine failures (Table 5). Restricted to those aged less than 80 years-old, the adjusted IVE was 35.2% (95% CI: –9.1 to 61.5; n=1,004). Adjusted IVE against A(H1N1)pdm09 was 6.2% (95% CI: –110.4 to 58.2; n=753) among patients vaccinated in the 2012/13 season only, 26.6% (95% CI: –81.6 to 70.3; n=724) for those vaccinated in 2011/12 and 27.9% (95% CI: –20.5 to 56.9; n=1,368) for those vaccinated in both seasons (Table 6).

Table 7

Adjusted[a] vaccine effectiveness against influenza A(H3N2), influenza A(H1N1)pdm09 and B viruses according to various restrictions, hospital-based influenza vaccine effectiveness study, four European countries[b], 2012/13

Restriction	A(H1N1)pdm09		A(H3N2)		B	
	Total number/ number of cases	Adjusted VE (95% CI)	Total number/ number of cases	Adjusted VE (95% CI)	Total number/ number of cases	Adjusted VE (95% CI)
No restriction	1,628/116	21.3 (−25.2 to 50.6)	577/58	61.8 (26.8 to 80.0)	1,526/232	43.1 (21.2 to 58.9)
No antiviral treatment started between symptom onset and swabbing	1,598/104	18.6 (−30.7 to 49.3)	555/53	59.4 (21.7 to 79.0)	1,491/215	40.5 (17.3 to 57.2)
Swabbing delay≤4 days	1,147/88	14.9 (−47.1 to 50.8)	359/36	60.4 (10.0 to 82.5)	1,037/151	45.3 (18.8 to 63.2)
Weeks when ratio controls to cases was<9:1	1,019/109	29.8 (−15.1 to 57.2)	542/56	62.7 (27.5 to 80.8)	1,142/221	44.3 (21.6 to 60.4)
Patients with no chronic respiratory conditions	829/66	38.9 (−20.3 to 69.0)	304/33	57.8 (−4.3 to 82.9)	812/152	50.7 (24.1 to 68.0)

CI: confidence interval: VE: vaccine effectiveness.

[a] Adjustment for study site, month of symptom onset, presence of any chronic condition and age.

[b] France, Italy, Lithuania and Spain (Navarre and Valencia regions).

The overall adjusted IVE against A(H3N2) was 61.8% (95% CI: 26.8 to 80.0; n=577) (Table 5). The adjusted IVE was 52.4% (95% CI: −33.9 to 83.1; n=181) among 65–79 years patients and 73.8% (95% CI: 29.9 to 90.2; n=216) among those 80 years and older. Among patients aged less than 65 years, all cases had chronic conditions. In this age group, the IVE adjusted for month of symptom onset and study site was 26.1% (95% CI: −215.9 to 82.7; n=143). Adjusted IVE was 68.3% (95% CI: −157.2 to 96.1; n=250) among patients vaccinated in 2012/13 only and 59.6% (95% CI: 18.5 to 80.0; n=488) among patients vaccinated in 2011/12 and 2012/13 (Table 6).

The overall adjusted IVE against influenza B was 43.1% (95% CI: 21.2 to 58.9; n=1,526), 28.2% (95% CI: −18.9 to 56.6; n=565) among patients aged 65–79 years and 66.0% (95% CI: 19.3 to 85.7; n=346) among those younger than 65 years (Table 5). Adjusted IVE against influenza B was 68.3% (95% CI: 24.5 to 86.7; n=714) among patients vaccinated in 2012/13 only and 37.3% (95% CI: 10.7 to 56.0; n=1,300) in those vaccinated in both seasons (Table 6).

There were few changes in the IVE when conducting the sensitivity analyses (Table 7). The IVE against A(H1N1) pdm09 was higher when restricted to patients with no chronic respiratory conditions (38.9% (95% CI: −20.3 to 69.0) vs 21.3% (95% CI: −25.2 to 50.6)).

Discussion

Our results suggest that in the population targeted for the influenza vaccination, the 2012/13 IVE for laboratory-confirmed hospitalised influenza was 21.3% against A(H1N1)pdm09, 61.8% against A(H3N2) and 43.1% against B.

The adaptation of a generic protocol by 18 European hospitals enabled us to pool data and obtain a sample of 1,972 hospitalised ILI patients targeted for influenza vaccination. In a season with co-circulation of the three viruses, this large sample size allowed us to compute type-/subtype-specific estimates of IVE against hospitalised influenza and to further attempt to stratify by age group. However, stratified analyses led to estimates with broad confidence intervals. Consequently, some results of the stratified analyses can only be used to generate hypotheses.

The test-negative design has been mainly discussed and validated for GP-based studies [26,27]. It is assumed that by restricting the study population to patients consulting for ILI, the health-seeking behaviour confounding effect (associated with propensity to get vaccinated and to go to the GP in case of influenza) is controlled for. Since in our study sites all people needing hospitalisation are likely to be hospitalised, we believe that confounding due to health-seeking behaviour is minimised.

In hospital-based studies, several outcomes could be used. If we were to measure IVE against influenza confirmed-severe acute respiratory infection (SARI), we would need to make sure that for both cases and controls a respiratory infection was the cause of admission. We have chosen a broader case definition and a more sensitive inclusion criteria to cover a larger part of the influenza disease burden. As a consequence, some of the ILI in the seven days before admission may correspond to an exacerbation of underlying respiratory conditions. This could lead to an overestimation of the

IVE. Restricting our analysis to patients with no underlying respiratory conditions provides similar results and does not support this hypothesis. Furthermore, we adjusted for the presence and number of previous hospitalisations for underlying conditions.

The inclusion of patients swabbed more than four days after symptoms onset or after antiviral treatment had started could have led to misclassification biases if viral clearance occurred before swabbing. However, analyses confined to patients swabbed within four days of symptom onset and to patients who did not receive antiviral treatment did not change the results.

Studies using the test-negative design may underestimate the IVE when the ratio of controls to cases is high, especially if the laboratory tests have low specificity [28]. In our study, all cases were confirmed by RT-PCR, which has high specificity [29]. In the analyses restricted to weeks when the control to case ratio was lower than 9:1 resulted in very similar IVE estimates.

The data quality was high with only 49/2,021 records with missing outcomes or exposures in the database. We believe that ascertainment of vaccination status through patient interviews in two of the five study sites has not introduced differential information bias as data were collected before laboratory testing.

Due to the small sample size in some study sites, the test of heterogeneity may have had no power to detect heterogeneity even if differences exist between study sites. Different IVE across study sites could be due to variations in circulating strains, different vaccines by study site or different measured and unmeasured confounding factors. Further typing of circulating strains would be valuable to discuss site-specific IVE with regard to the level of matching between vaccine and locally circulating strains. Different access to vaccination according to age and underlying condition and to hospitalisation [30] could partly explain variations in IVE across study sites. Finally, the presence of random errors cannot be ruled out due to low sample size by study site. A larger sample size would be needed to carry out a two-stage pooled analysis [24].

Our results suggest that, in people belonging to target groups for vaccination, the 2012/13 IVE varied by subtype and age group. However, we cannot exclude the possibility that the variability of IVE results by age group mainly reflects sample size limitations. Small stratum-specific sample sizes (and very small number of cases) lead to unstable results and do not allow for biological interpretation of age-specific results. Our results would suggest that IVE against A(H3N2) was higher among older age groups. This observation would be in contradiction to the principles of immune senescence. In addition to the sample-size limitations, and as discussed above, we cannot exclude a selection bias for our controls, which we adjusted for. However we used the same control group for the three subtypes and age-specific results vary by subtype. We consider that it is unlikely that confounding factors would differ by subtype.

When looking at the effect of repeated vaccination (over two consecutive seasons), similar patterns were observed for influenza A(H3N2) and B. The highest point estimate IVE was in patients vaccinated in 2012/13 only, the lowest in those vaccinated in 2011/12 only and intermediate among those vaccinated both seasons. Such findings are consistent with recent reports from the Unites States and Australia [9,10,31]. The 2011/12 vaccine included an A/Perth/16/2009(H3N2)-like virus and a B/Brisbane/60/2008-like virus, while the 2012/13 vaccine included an A/Victoria/361/2011(H3N2)-like virus and a B/Wisconsin/1/2010-like (Yamagata lineage). On the basis of European virological surveillance data [13], the main circulating strains during the 2012/13 season were an A/Victoria/361/2011(H3N2) (with some A/Texas/50/2012 circulation reported) and B/Wisconsin/1/2010-like (with some B/Estonia and B/Massachusets/2/2012 circulation reported). These data support the absence of protection by the 2011/12 seasonal vaccine on the 2012/13 circulating strains as they were not matched.

Some authors have discussed the hypothesis of attenuated immunological responses as a result of repeated vaccination. From a school-based study, Davies et al. [32] suggested that a natural infection in season 1 produces antibodies that have a larger potential to form high post-vaccination titres in season 2 than vaccine-induced antibodies. Smith et al. [33] hypothesised that large antigenic distances between vaccines in seasons 1 and 2, and between vaccine in season 1 and epidemic strain in season 2, significantly increase the risk of infection among repeated vaccinees compared with those receiving the vaccine in season 2 only. Considering the antigenic differences between the 2011/12 vaccine and the 2012/13 circulating strains, this hypothesis could explain our results, suggesting a higher IVE against influenza A(H3N2) and B among patients vaccinated in 2012/13 only compared with those vaccinated in 2011/12 and 2012/13. Further studies, including a longer history of vaccine uptake and natural infections would be of great value to better understand the effect of repeated vaccination on the immunological response to a new influenza seasonal vaccine and the level of clinical protection conferred to individuals.

Our results suggest a low IVE against A(H1N1)pdm09, especially among the elderly [34]. A total of 14 cases of influenza A(H1N1)pdm09 occurred among patients older than 80 years. While the majority of these cases (n=12) were vaccinated patients, small numbers make the IVE estimates hard to interpret in that age group. The IVE was similar for those vaccinated in 2011/12 only or in both seasons. There was no effect for those vaccinated in 2012/13 only. The recommended A/California/7/2009(H1N1)pdm09-like virus strain

was the same for the 2011/12 and 2012/13 vaccines and matched the 2012/13 circulating strains (some A/California/06/2009 also reported). Long-lasting immune response induced by trivalent inactivated vaccines was previously described [35] and some recent results suggest that frequent previous vaccinations may be effective for the current influenza season [11]. The absence of protection among patients vaccinated in 2012/13 only is difficult to understand and interpret; it may reflect the presence of associated (and unmeasured) negative confounders for which repeated vaccination may be a surrogate. In addition, other studies [36-38] suggest a decreasing effect in the season difficult to reconcile with a long-term effect between seasons. Considering the small sample size in some of the vaccination groups in our study, we cannot exclude the possibility that this observation is due to chance.

Increasing the number of study sites in this network would allow a sufficient sample size to be reached early enough in the season to prompt the use of alternative prevention measures if a low IVE against hospitalised cases is observed among the target group. Early estimates of IVE against hospitalised influenza are also a useful complement to guide the decision-making of WHO experts regarding the composition of the next season's vaccines. A larger sample size and good documentation of vaccine brands used would allow the computing of brand-specific IVE. To further study the effect of previous seasonal vaccination will require documenting past vaccination over several seasons. In addition, ways to measure past natural immunity may also be needed to better understand the complex immunity of influenza natural infection and vaccination.

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Conflict of interest

No conflict of interest. Sanofi Pasteur, GlaxoSmithKline, Sanofi Pasteur MSD supported the study. They had no role in study design, data collection, pooled analysis and publication.

Authors' contributions

Marc Rondy was involved in the original methodological design of the study (generic protocol). He coordinated the European hospital IVE network, undertook the statistical analysis on which the research article is based and led the writing of the research article. Alain Moren initiated the original methodological design of the study. He coordinated the European hospital IVE network and contributed to the writing of the research article. Odile Launay, Joan Puig-Barberà, Giedre Gefenaite, Jesús Castilla, Katleen de Gaetano Donati, Florence Galtier, Eelko Hak, Marcela Guevara and Simona Costanzo were responsible for the coordination of the study at the local level. They were in charge of the data collection and management. They read, contributed and approved the manuscript final version. The European hospital IVE network contributors were in charge of supervising the study at the hospital level and collected the data published in this research article.

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* Authors' correction

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3.5.1.3 Results from 2013-14 season

In 2013-14, there was a co-circulation of A(H3N2) and A(H1N1)pdm09 viruses and vaccine and circulating strains were antigenically similar. The network included three study sites (France, Italy, and Navarra) and twelve hospitals. Our study objective was to measure the 2013-14 seasonal IVE against hospitalisation with A(H1N1)pdm09 and A(H3N2) influenza among the adult population targeted for vaccination in three EU countries

We included 104 A(H1N1)pdm09 cases, 157 A(H3N2) cases and 585 controls. We observed a lower proportion of elderly among A(H1N1)pdm09 cases than among A(H3N2) cases. IVE was 43% (95%CI: 6;65) against A(H1N1)pdm09 (61% (95%CI: -2;85), 39% (95%CI: -32;72) and 20% (95%CI:-148;74) among patients aged 18–64, 65–79 and ≥80 years respectively). IVE against A(H3N2) was 38% (95%CI: 8;58) (8% (95%CI: -145;65), 26% (95%CI: -36;59) and 55% (95%CI: 15;76) among patients aged 18–64, 65–79 and ≥80 years respectively).

Our results suggested a moderate IVE against hospitalised influenza. They also suggested differences in age-group specific IVE.

We discussed the possible link between lower incidence of A(H1N1)pdm09 among elderly and poorer vaccine performance among them. Lower influenza incidence in elderly has been previously observed and is likely due to their former exposure to A(H1N1) viruses the 1950's. On the other hand, recent natural infection may play a booster role on the immunological response to seasonal vaccination. Therefore, we suggested that younger age group, by getting infected with A(H1N1)pdm09 at a higher rate than elderly, respond better to vaccine against that strain.

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Moderate influenza vaccine effectiveness against hospitalisation with A(H3N2) and A(H1N1) influenza in 2013–14: Results from the InNHOVE network

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ABSTRACT

We conducted a multicentre test negative case control study to estimate the 2013–14 influenza vaccine effectiveness (IVE) against hospitalised laboratory confirmed influenza in 12 hospitals in France, Italy and Spain. We included all ≥18 years hospitalised patients targeted by local influenza vaccination campaign reporting an influenza-like illness within 7 days before admission. We defined as cases patients RT-PCR positive for influenza and as controls those negative for all influenza virus. We used a logistic regression to calculate IVE adjusted for country, month of onset, chronic diseases and age. We included 104 A(H1N1) pdm09, 157 A(H3N2) cases and 585 controls. The adjusted IVE was 42.8% (95%CI: 6.3;65;0) against A(H1N1) pdm09. It was respectively 61.4% (95%CI: −1.9;85.4), 39.4% (95%CI: −32.2;72.2) and 19.7% (95%CI:-148.1;74.0) among patients aged 18–64, 65–79 and ≥80 years. The adjusted IVE against A(H3N2) was 38.1% (95%CI: 8.3;58.2) overall. It was respectively 7.8% (95%CI: −145.3;65.4), 25.6% (95%CI: −36.0;59.2) and 55.2% (95%CI: 15.4;76.3) among patients aged 18–64, 65–79 and ≥80 years. These results suggest a moderate and age varying effectiveness of the 2013–14 influenza vaccine to prevent hospitalised laboratory-confirmed influenza. While vaccination remains the most effective prevention measure, developing more immunogenic influenza vaccines is needed to prevent severe outcomes among target groups.

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Introduction

European immunisation strategies recommend yearly influenza vaccination of the population at risk for severe outcome.[1] Measuring and reporting influenza vaccine effectiveness (IVE) against hospitalised outcome within the targeted population is critical to evaluate and adapt these strategies.

In a review published in 2011,[2] Michiels et al. qualified as "moderate to poor" the evidences regarding IVE in these target groups. Among elderly, for whom a reduced capacity to produce antibodies leads to an impaired immune response (also known as immune-senescence),[3,4] the evidence gathered in a 2010 Cochrane review suggested a modest IVE of the trivalent inactivated vaccines (TIV).[5]

Reporting of IVE among subgroups for which the vaccine may have suboptimal effectiveness may help promoting the development of more immunogenic vaccine products or alternative approaches (e.g. prophylactic antiviral use) for these patients.

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In 2011, we set up InNHOVE, a European Network of Hospitals for measuring IVE. The use of a common generic protocol, study site visits and meetings of network partners ensured common practices across hospitals and the possibility to pool data. A pilot phase conducted in 2011–12 reinforced the homogeneity in implementing protocols across study sites.[6]

In the European Union, the 2013–14 season was marked by a dominant circulation of A(H1)pdm09 A/California/7/2009 (H1N1)-like and A/Texas/50/2012 (H3N2)-like viruses and a sporadic circulation of influenza B viruses.[7] The objective of this study was to measure the 2013/14 seasonal IVE against hospitalisation with laboratory-confirmed A(H1N1)pdm09 and A(H3N2) influenza among the adult population targeted for vaccination in 3 EU countries.

Results

Of the 962 eligible patients, we excluded 8 patients due to missing laboratory results and 11 due to missing vaccination status (Fig. 1). We included a total of 157 A(H3N2) and 104 A(H1N1)pdm09 cases. For the A(H3N2) analysis we excluded 220 controls with dates of onset outside the study period and included 585 controls. Similarly, after excluding 357 controls for the A(H1N1)pdm09 analysis, we ended up with 426 controls.

Patients' inclusion started on week 50, 2013 in Spain, on week 1, 2014 in France and on week 3, 2014 in Italy. A(H1N1)pdm09 and A(H3N2) cases were reported throughout the season in France and Spain (Table 1; Fig. 2). We excluded Italy from the A(H1N1)pdm09 analysis as only 2 cases were reported.

All recorded vaccines were TIV. In Navarra, Spain, one brand of unadjuvanted vaccine was exclusively distributed. In France, 5 brands of unadjuvanted vaccines were recorded. In Italy, 3 brands, including one adjuvanted vaccine, were reported.

A(H1N1)pmd09 cases were younger than controls (median age 65.2 vs 75.6 years). A lower proportion of cases than controls had chronic diseases (81.7 vs 91.8%), had been hospitalised in the past 12 months (31.7 vs 41.7%) and had never smoked (39.0 vs 53.5%). The 2013–14 vaccine coverage was 34.6% among A(H1N1)pdm09 cases and 56.3% among controls (Table 2).

A(H3N2) cases were of similar age as controls and had comparable chronic diseases. They were less likely than controls to be obese (8.4 vs 19.1%) and to have been hospitalised in the past 12 months (29.9 vs 42.2%). The 2013–14 vaccine coverage was 48.4% among A(H3N2) cases and 54.0% among controls (Table 2).

Adjusted for study site, month of onset, age and presence of chronic conditions, the IVE against A(H1N1)pdm09 were respectively 42.0% (95%CI: −25.8;73.3) and 43.8% (95%CI: −6.3;70.3) in France and Spain. The p-value and I^2 index testing for heterogeneity between these IVE estimates were

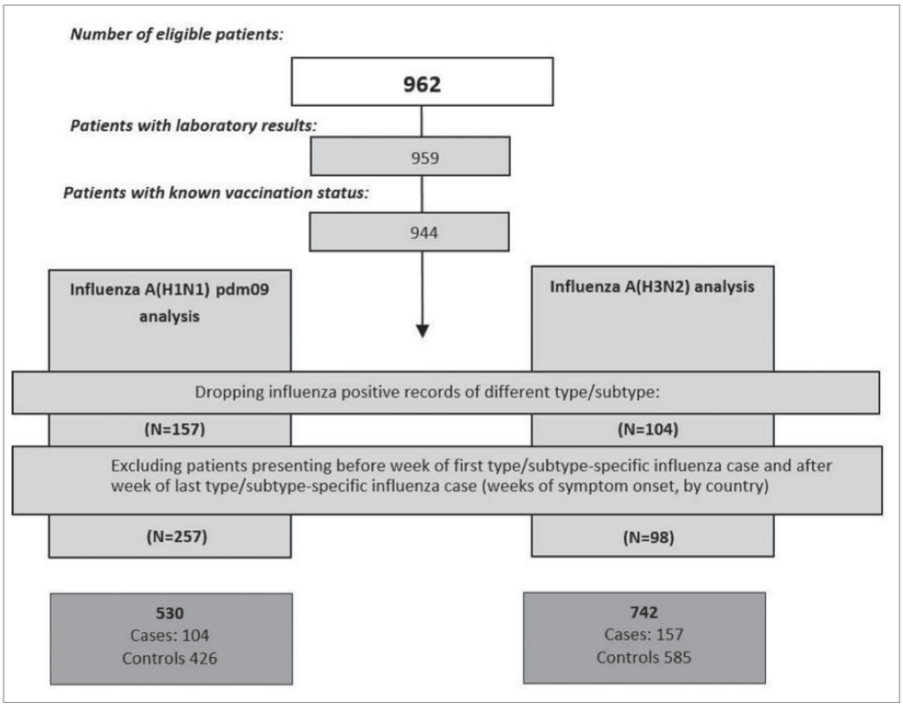

Figure 1. Flowchart of data exclusion for pooled analysis, InNHOVE multicentre study, France, Italy, Spain, 2013-14

Table 1. Study period, inclusions of laboratory confirmed influenza and test negative controls by vaccination status and study site, InNHOVE multicentre study, France, Italy, Spain, 2013–14.

					Number of cases and controls included after restriction*			
		Study period			A(H1N1)pdm09 analysis		A(H3N2) analysis	
Study site	Number of hospitals involved	A(H1N1)pm09	A(H3N2)	Number of eligible patients	Controls	Cases	Controls	Cases
France	6	W 1–13, 2014	W 2–11, 2014	315	217	40	188	32
Italy[‡]	2	NA	W 3–10, 2014	266	NA	NA	188	20
Navarra	4	W 50, 2013 - W 8, 2014	W 50, 2013 - W 8, 2014	381	209	64	209	105
Overall	12			962	426	104	585	157

‡<10 cases of A(H1N1)pdm09 included. Italy exclued from A(H1N1)pdm09 analysis

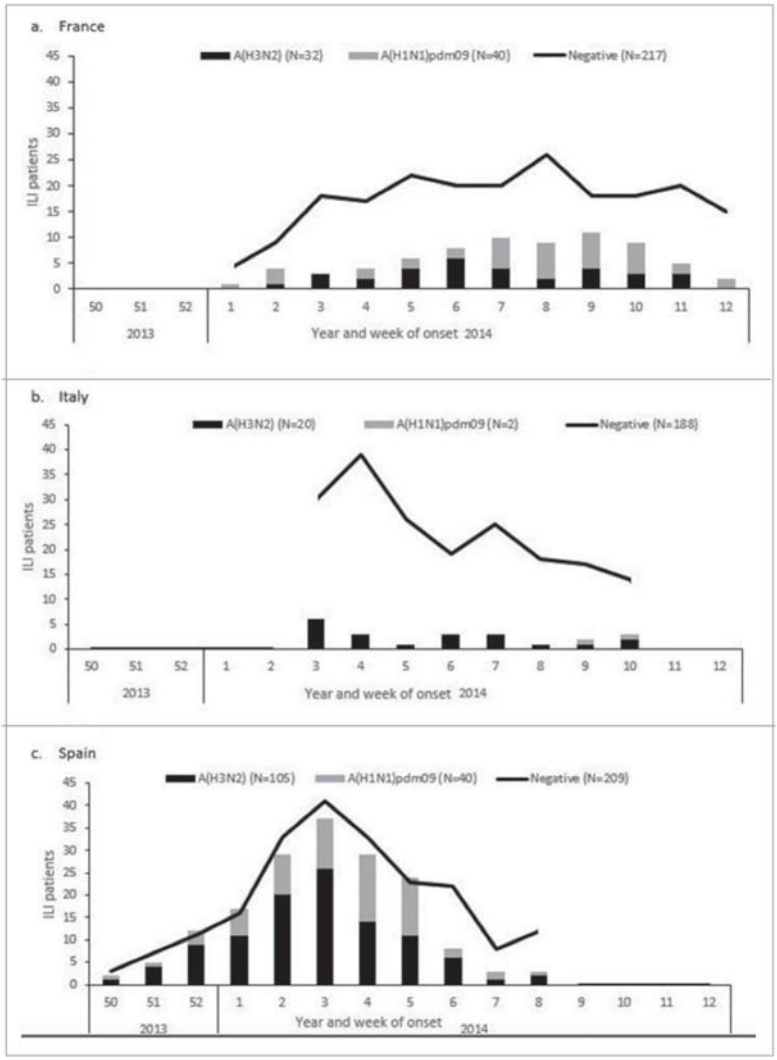

Figure 2. Number of ILI patients positive for influenza A(H3N2), positive for influenza A(H1N1)pdm09 and negative for any influenza by week of symptom onset, InNHOVE multicentre study, France, Italy, Spain. By study site, 2013-14

Table 2. Characteristics of Influenza A(H1N1)pdm09 (n=104), Influenza A (H3N2) (n=157) and test-negative controls, InNHOVE multicentre study, France, Italy, Spain, 2013–14.

	Influenza A(H1N1)pdm09				Influenza A(H3N2)			
	Cases (n=104)		Controls (n=426)		Cases (n=157)		Controls (n=585)	
	N	%	N	%	N	%	N	%
Median age	65.2	75.6*	77.5	75.4				
Age group								
18–64	48	(46.2)	100	(23.5)*	32	(20.4)	125	(21.4)
65–79	37	(35.6)	181	(42.5)	59	(37.6)	260	(44.4)
80–104	19	(18.3)	145	(34.0)	66	(42.0)	200	(34.2)
Sex = Male	57	(54.8)	221	(51.9)	72	(45.9)	310	(53.0)
Vaccine status								
2013–14 seasonal influenza vaccine**	36	(34.6)	240	(56.3)*	76	(48.4)	316	(54.0)
2012–13 seasonal influenza vaccine	39	(38.6)	250	(59.5)*	86	(54.8)	338	(58.5)
Presence of comorbidities								
Any chronic disease	85	(81.7)	391	(91.8)*	135	(86.0)	522	(89.2)
More than one chronic condition	58	(55.8)	286	(67.1)*	88	(56.1)	373	(63.8)
Diabetes, endocrine diseases or nutritional deficiency	33	(31.7)	164	(38.5)	57	(36.3)	209	(35.7)
Cardiac disease	36	(34.6)	193	(45.6)*	59	(38.1)	247	(42.4)
Renal diseases	13	(12.5)	61	(14.4)	28	(17.9)	87	(14.9)
Respiratory diseases	32	(30.8)	187	(43.9)*	64	(40.8)	244	(41.7)
Neurological diseases	8	(7.7)	67	(15.7)*	23	(14.7)	99	(16.9)
Cirrhosis	0	(0.0)	18	(4.2)*	6	(3.8)	22	(3.8)
Immunocompetency disorders	16	(15.5)	65	(15.3)	13	(8.3)	73	(12.5)
Hematological diseases	20	(19.2)	105	(24.6)	34	(21.8)	121	(20.7)
Obesity	15	(15.2)	73	(17.8)	13	(8.4)	109	(19.1)*
Pregnant	4	(4.9)	5	(1.6)	1	(0.8)	5	(1.3)
Low functional status¥	9	(16.1)	91	(27.9)	43	(34.4)	123	(26.7)
Other potential confounders								
More than one GP visits in previous 3 months	61	(62.2)	258	(64.5)	95	(62.9)	292	(52.8)*
Any hospitalisations in previous 12 months?	33	(31.7)	203	(47.7)*	47	(29.9)	247	(42.2)*
Smoking status								
Current	43	(43.0)	90	(21.5)*	30	(19.4)	110	(19.0)*
Former	18	(18.0)	105	(25.1)	32	(20.6)	183	(31.6)
Never	39	(39.0)	224	(53.5)	93	(60.0)	287	(49.5)
Days symptoms onset - swabbing <4 days	49	(47.1)	236	(55.4)	73	(46.5)	285	(48.7)

*($p<0.05$)
**Vaccination received at least 15 days prior to ILI onset
¥Barthel index ≤60

respectively 0.999 and 0.0%. The adjusted IVE against A (H3N2) were respectively 31.8% (95%CI: −52.5;69.5), −30.9% (95%CI: −282.3;55.2) and 49.5% (95%CI: 16.6;69.8) in France, Italy and Spain; the p-value associated with the Q-test and the I^2 index were respectively 0.216 and 34.8% (Table 3).

The pooled adjusted IVE against A(H1N1)pdm09 was 42.8% (95%CI: 6.3;65.0). The adjusted age-group specific IVE was respectively 61.4% (95%CI: −1.9;85.4), 39.4% (95%CI: −32.2;72.2) and 19.7% (95%CI:-148.1;74.0) among patients aged 18–64, 65–79 and 80 years and above (Table 4).

The pooled adjusted IVE against A(H3N2) was 38.1% (95%CI: 8.3;58.2). The adjusted age-group specific IVE was respectively 7.8% (95%CI: −145.3;65.4), 25.6% (95%CI: −36.0;59.2) and 55.2% (95%CI: 15.4;76.3) among patients aged 18–64, 65–79 and 80 years and above (Table 4).

Discussion

Our results suggest that the 2013–14 influenza vaccines provided a moderate protection against hospitalisation with laboratory confirmed A(H1N1)pdm09 (42.8%) and A(H3N2) (38.1%) influenza among adults targeted by the vaccination program. Our data also suggest different IVE by age-group. The highest IVE point estimate was among those aged < 65 years for A(H1N1)pdm09 and those aged > 80 for A (H3N2).

We used a test-negative case control design to recruit our patients. This approach, widely used and validated among GP based IVE studies, assumes that, by recruiting patients presenting with the same syndrome, we are likely to minimise selection biases[16–18]. In our study, A(H3N2) cases were of similar age as controls but tended to have less chronic diseases (non-significant differences). A(H1N1) pdm09 cases were younger and had significantly less chronic diseases than controls. A higher proportion of controls with comorbidities could lead to an overestimation of the VE if the presence of comorbidities was associated with higher vaccine uptake. Our estimates were adjusted for presence of chronic diseases, age, time and study sites and stratified by age-group. Adjusting for chronic diseases had little effect on the IVE estimates, even within each age group. Adjusting on specific categories of comorbidities or hospitalisation for chronic conditions in the previous year had a marginal effect on the IVE estimates. However, some stratified analyses led to small sample size, increasing variability and limiting interpretation of positive and negative confounding. Furthermore, we cannot exclude that residual confounding biases our results.

Table 3. Crude and age adjusted Influenza vaccine effectiveness against influenza A(H1N1)pdm09 and influenza A(H3N2) by study site, InNHOVE multicentre study, France, Italy, Spain, 2013–14.

Subtype assessed	France	Navarra	Italy
A(H1N1)pdm09			
Number of cases; vaccinated cases	12/40	24/64	
Number of controls; vaccinated controls	107/217	133/209	
Variable used for adjustement of vaccine effectivess			
study sites and month of symptoms onset (place/time)	56.1 (8.9;78.8)	64.9 (37.0;80.4)	
place/time and age*	47.2 (-12.4;75.2)	45.7 (-2.3;71.2)	
place/time, age* and presence of ≥1 comorbidity	42.0 (-25.8;73.3)	43.8 (-6.3;70.3)	
Q-test p-value†	0.999		
I^2index†	0.0%		
A(H3N2)			
Number of cases; vaccinated cases	13/32	53/105	10/20
Number of controls; vaccinated controls	92/188	133/209	91/188
Variable used for adjustement of vaccine effectivess			
study sites and month of symptoms onset (place/time)	28.5 (-53.2;66.6)	42.2 (6.4;64.3)	-6.2 (-169.3;58.1)
place/time and age*	35.8 (-41.0;70.8)	49.8 (16.6;69.8)	-27.9 (-270.0;55.8)
place/time, age* and presence of ≥1 comorbidity	31.8 (-52.5;69.5)	49.5 (16.6;69.8)	-30.9 (-282.3;55.2)
Q-test p-value†	0.216		
I^2 index	34.8%		

*age modeled as a cubic spline
†values for comparison of the adjusted IVE estimates

Vaccination status was missing in 1.6% of eligible patients. While its ascertainment was based on a registry in Navarra, we relied on patients, pharmacist and/or GP memory in France and Italy. We cannot exclude some misclassification. However, as all patients presenting at the hospitals had similar signs and as the vaccination was ascertained prior to the laboratory results, there is no reason to expect a differential misclassification bias between cases and controls.

European virological surveillance data suggested that A (H1N1)pm09 and A(H3N2) circulating and vaccine viruses

Table 4. Crude and age adjusted Influenza vaccine effectiveness against influenza A(H1N1)pdm09 and influenza A(H3N2), overall and by age group, InNHOVE multicentre study, France, Italy, Spain, 2013–14.

Group assessed	A(H1N1)pdm09	A(H3N2)
All target groups		
Number of cases; vaccinated cases	36/104	76/157
Number of controls; vaccinated controls	240/426	316/585
Variable used for adjustement of vaccine effectivess		
study sites and month of symptoms onset (place/time)	62.1 (40.2;76.0)	32.9 (2.6;53.8)
place/time and age*	45.7 (11.6;66.7)	38.6 (9.0;58.5)
place/time, age* and presence of ≥1 comorbidity	42.8 (6.3;65;0)	38.1 (8.3;58.2)
place/time, age* and presence of ≥2 comorbidities	43.5 (7.5;65.5)	37.4 (7.1;57.8)
place/time, age* and hospitalisation in the past 12 months	42.0 (4.8;64.7)	38.2 (8.4;58.3)
place/time, age* and presence of respiratory conditions	42.4 (5.3;65.0)	38.8 (9.3;58.7)
place/time, age* and presence of cardiac conditions†	45.8 (11.8;66.7)	38.2 (8.0;58.4)
<65 years		
Number of cases; vaccinated cases	8/48	9/32
Number of controls; vaccinated controls	36/100	36/125
Variable used for adjustement of vaccine effectivess		
study sites and month of symptoms onset	68.4 (21.5;87.3)	21.7 (-103.7;69.9)
place/time and age*	67.6 (19.1;87.0)	4.8 (-153.9;64.3)
place/time, age* and presence of ≥1 comorbidity	61.4 (-1.9;85.4)	7.8 (-145.3;65.4)
65–79 years		
Number of cases; vaccinated cases	15/37	29/59
Number of controls; vaccinated controls	102/181	134/260
Variable used for adjustement of vaccine effectivess		
study sites and month of symptoms onset	46.3 (-11.2;74.1)	22.0 (-40.9;56.9)
place/time and age*	39.6 (-31.4;72.2)	25.1 (-36.3;58.9)
place/time, age* and presence of ≥1 comorbidity	39.4 (-32.2;72.2)	25.6 (-36.0;59.2)
80 years and older		
Number of cases; vaccinated cases	13/19	38/66
Number of controls; vaccinated controls	102/145	146/200
Variable used for adjustement of vaccine effectivess		
study sites and month of symptoms onset	18.5 (-139.2;72.2)	52.4 (11.7;74.4)
place/time and age*	6.8 (-180.1;69.0)	55.4 (16.1;76.3)
place/time, age* and presence of ≥1 comorbidity	19.7 (-148.1;74.0)	55.2 (15.4;76.3)

*age modeled as a cubic spline
†3 controls and 2 A(H3N2) with excluded due to missing information on cardiac conditions

were antigenically similar in the 2013–14 season.[11] For A (H3N2), while the French national laboratory reported no significant mutation,[12] the region of Navarra, Spain, reported some genetic differences between the circulating and vaccine viruses.[13] Of particular interest was the L157S mutation, located in the HA1 antigenic site B near the receptor binding site, observed in 16/17 patients. This site is located close to 4 of the 7 positions (positions 145, 155, 156, 158, 159, 189 and 193) associated with all majors H3 antigenic change since 1968.[14] The L157 mutation observed as part of the virological surveillance scheme, if present in the patients included in the study and if affecting antigenicity, could partially explain the moderate IVE against A(H3N2) we observed this season. A representative virus characterization from the patients included in the various study sites of our multicenter study would be of great value to better interpret vaccines performances against given subtypes as well as IVE differences between study sites.

The age-group specific IVE results need to be read in the light of the small sample size in the various age groups, particularly among the A(H1N1)pdm09 cases aged ≥80 years and the A (H3N2) cases aged less than 65 years. The confidence intervals surrounding the IVE were very large in these 2 groups. The proportion of patients aged 65 and above was lower among A (H1N1)pdm09 cases compared to controls and A(H3N2) cases. This may reflect the lower incidence of A(H1N1)pdm09 influenza among the older age group compatible with a former exposure to A(H1N1) virus.[15,16] Recent past natural infections may play a booster role on the immunological response to seasonal vaccination.[17,18] Immune senescence[4] and a lower incidence of A(H1N1)pdm09 among elderly since the 2009 pandemic could partially explain the lower IVE against this subtype observed among patients. The higher IVE against A(H3N2) among elderly would require further investigation as it is in contradiction with the principles of immune senescence. We cannot exclude that variability due to small sample size, or biases due to unmeasured confounding, lead to this unexpectedly high estimate. Larger age group specific sample size would be needed to measure and compare IVE estimates between age groups with more precision. A better documentation of past natural infections and vaccinations would be useful to understand these differences, if any. Furthermore, larger sample size would be required to investigate the effect of repeated vaccination as only few patients have changing vaccination status over time.

This season, the InNHOVE network included a total of 12 hospitals. The recruitment approaches ensured a systematic inclusion of patients hospitalised for influenza related conditions and presenting with an ILI onset in the past 7 days. We did not find statistically significant difference between study site specific estimates of IVE against A(H1N1)pdm09 and A (H3N2). However, small study site specific sample size made it difficult to observe a statistically significant heterogeneity. While French and Spanish specific IVE estimates against A (H1N1)pdm09 were close, large differences could be observed between study sites for A(H3N2) analyses. Although access to care is high in the 3 participating regions, different access to vaccination and to hospitalization in case of severe ILI across study sites cannot be excluded. If not taken into account when adjusting on the age and the presence of chronic conditions, residual confounding of a different magnitude across study sites could partially explain the observed differences. If these differences in estimates were to reflect true differences in IVE across study sites, possible explanations could be the use of distinct vaccine types and brands or the circulation of different viruses across study sites. Our sample size was too small to provide product specific IVE estimates with interpretable confidence intervals. In the future, we suggest that each study site select a systematic sample of viruses for genetic and antigenic characterization. This would allow for a better interpretation of differences in IVE between study sites.

While seasonal vaccination remains the most effective prevention measure against influenza,[19] our study suggests that developing more immunogenic influenza vaccines is needed to prevent severe outcomes among those targeted by the vaccination. The InNHOVE project represents a good example of a European network of hospitals working according to the same generic protocol, allowing pooling data together. Encouraging this initiative and further increasing this network is the best way to compute strain, age groups and product specific estimates.

Material and methods

We conducted a multicentre case control study using a test-negative design in 12 hospitals located in France (6 hospitals), Italy (2 hospitals), and Spain (4 hospitals in Navarra region). Study sites adapted the generic study protocol to their local settings.[20]

The competent authorities of each country/region approved the protocol. All study sites complied with "The Ethical Principles for Medical Research Involving Human Participants of the World Medical Association and the Declaration of Helsinki" (World Medical Association, Inc. Available at: www.wma.net/en/30publications/10policies/b3/index.html). According to country specific requirements for ethical approval, all participants (or their legal tutor) provided written consent for recruitment into the study.

The "Ile de France IV" Ethical Committee ("Comité de Protection des Personnes Ile-de-France IV," Paris, France), the Ethical Committee of the Catholic University of Rome, Italy and the Navarra Ethical Committee for Medical Research, Spain gave their approval to conduct the study.

Study population

The study population included all community-dwelling adults (≥18 years) belonging to the target group for influenza vaccination, with no contra-indication for vaccination, likely to be hospitalized in one of the participating hospitals in case of influenza related illness.

Individuals were considered to belong to target group for vaccination if they had at least one of the medical conditions or the age required to fall into this group according to the country specific recommendations for vaccination.[21-23]

Study period

In each study site, the study period lasted from the week of the first laboratory confirmed case of influenza to the week of the last laboratory confirmed case of influenza followed by 2 weeks

without a case. We defined separately the study period for A (H1N1)pdm09 and A(H3N2).

Patient inclusion

Study teams approached all patients admitted for at least 24 hours in one of the participating hospitals with influenza related conditions. These conditions included acute myocardial infarction or acute coronary syndrome; heart failure; pneumonia and influenza; chronic pulmonary obstructive disease; myalgia; altered consciousness, convulsions, febrile-convulsions; dyspnoea/respiratory abnormality; respiratory abnormality; shortness of breath; respiratory abnormality necrotising enterocolitis; respiratory symptoms/chest symptoms; acute cerebrovascular disease; sepsis; systemic inflammatory response syndrome.

The influenza-like-illness (ILI) case definition included the presence of at least one of the following systemic symptoms: fever or feverishness, malaise, headache, myalgia; and at least one of the following respiratory symptoms: cough, sore throat, shortness of breath. Study teams proposed to those reporting an ILI onset in the past 7 days and no later than 48 hours after admission to undergo a nasopharyngeal swab, to be interviewed and included in the study.

Data collection

Study teams collected data on demographics, chronic diseases and their severity (using as proxy the number of hospital admissions due to chronic diseases in the past 12 months), number of GP consultations in the previous 3 months (to adjust for health seeking behavior), smoking status, vaccination against influenza in the last 2 seasons (including vaccine brand for the 2013–14 season) and functional status before onset using the Barthel index[24] through patient/family interview and from medical records. Patients with a Barthel index below or equal to 60 were considered as having a low functional status.

We defined an individual as vaccinated against seasonal influenza if he/she had received at least one dose of influenza vaccine more than 14 days before ILI symptoms onset. Patients not vaccinated or vaccinated less than 15 days prior to ILI onset were considered unvaccinated. The Spanish study team documented patients' vaccination status using vaccination registers. The French and Italian sites collected that information through interview with the patient/family and call to general practitioners (GPs) or pharmacists to check the information.

Reverse transcription polymerase chain reaction (RT-PCR) was used to detect influenza viruses and to classify positive patients as cases of influenza A(H3N2) or A(H1N1)pdm2009. Laboratory tests were centralised within each study site.

Case definition

We defined cases as hospitalised ILI patients belonging to the study population and testing positive for A(H1N1)pdm09 or A (H3N2). Controls were hospitalised ILI patients belonging to the study population and testing negative for all influenza virus.

Data analysis

Study sites sent anonymised datasets to the pooled analysis coordinator through a secured web based platform (Voozanoo^{TM}).

To avoid introducing too much variability, for each influenza A subtype, we excluded from the pooled analysis study sites with less than 10 cases (arbitrary set threshold).

We assessed heterogeneity across study sites using the significance of the Cochran Q-test and the I^2 index that quantifies the proportion of the variance attributable to differences between study sites.[25]

We conducted a separate analysis for each type/subtype of influenza. We estimated the pooled IVE as 1 minus the odds ratio (OR) of being vaccinated in cases versus controls, using a one-stage method with study site as a fixed effect in the model.[26] We used a multivariable logistic regression model to compute IVE adjusted for month of onset, study site and age modeled as restricted cubic spline with 4 knots. We further calculated IVE adjusted for the presence of any or specific chronic conditions. We measured stratified IVE by age group (< 65, 65–79; 80 years and above) adjusting for all the potential confounding factors.

Disclosure of potential conflicts of interest

No conflict of interest. GlaxoSmithKline and Sanofi Pasteur MSD financially supported the study. They had no role in study design, data collection, pooled analysis, and publication.

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3.5.1.4 Results from 2015-16 season

In 2015-16, there was a co-circulation of A(H1N1)pdm09 and B viruses, with also a few cases of influenza A(H3N2), although not enough to measure IVE against A(H3N2). While the vaccine was well matched against A(H1N1)pdm09, the vaccine and main circulating B lineages were different. The 2015-16 season was the first season for the I-MOVE+ network. We included twelve study sites in eleven European countries and 27 hospitals. We included in our study patients aged 65 years and above admitted for illnesses potentially related to influenza and who had an onset of SARI symptoms in the past seven days. Our study objective was to measure the 2015-16 seasonal IVE against hospitalisation with influenza A(H1N1)pdm09 and influenza B among elderly in Europe by risk groups and for specific vaccine types.

We included 355 influenza A(H1N1)pdm09 cases, 110 influenza B cases, and 1274 controls. More than 90% of our study participants had at least one underlying chronic conditions. Among controls, 61% had a heart diseases, 45% had a lung disease, 29% were diabetic and 27% had a cancer. Overall, adjusted IVE against influenza A(H1N1)pdm09 was 42% (95%CI:22 to 57). It was 59% (95%CI:23 to 78), 48% (95%CI:5 to 71), 43% (95%CI:8 to 65) and 39% (95%CI:7 to 60) in patients with diabetes mellitus, cancer, lung and heart disease respectively. Adjusted IVE against influenza B was 52% (95%CI:24 to 70). It was 62% (95%CI:5 to 85), 60% (95%CI:18 to 80) and 36% (95%CI:-23 to 67) in patients with diabetes mellitus, lung and heart disease respectively.

On the top of the 1-stage model analysis, we reported results from the 2-stage analysis, where we computed a weighted average of study site specific IVE. This allowed us to use different adjustment variables by study site and therefore control for study site specific confounding.

We measured a moderate IVE against influenza A(H1N1)pdm09 (42%) and influenza B (52%) and we did not observe any drop in IVE estimates in patients with specific underlying conditions. The 52% IVE against influenza B, despite the lineage mismatch between vaccine and circulating strains and considering the fact that vaccinated patients had all received TIV, suggested some cross-lineage protection conferred by the vaccine.

Research article

2015/16 seasonal vaccine effectiveness against hospitalisation with influenza A(H1N1)pdm09 and B among elderly people in Europe: results from the I-MOVE+ project

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We conducted a multicentre test-negative case–control study in 27 hospitals of 11 European countries to measure 2015/16 influenza vaccine effectiveness (IVE) against hospitalised influenza A(H1N1)pdm09 and B among people aged ≥ 65 years. Patients swabbed within 7 days after onset of symptoms compatible with severe acute respiratory infection were included. Information on demographics, vaccination and underlying conditions was collected. Using logistic regression, we measured IVE adjusted for potential confounders. We included 355 influenza A(H1N1)pdm09 cases, 110 influenza B cases, and 1,274 controls. Adjusted IVE against influenza A(H1N1)pdm09 was 42% (95% confidence interval (CI): 22 to 57). It was 59% (95% CI: 23 to 78), 48% (95% CI: 5 to 71), 43% (95% CI: 8 to 65) and 39% (95% CI: 7 to 60) in patients with diabetes mellitus, cancer, lung and heart disease, respectively. Adjusted IVE against influenza B was 52% (95% CI: 24 to 70). It was 62% (95% CI: 5 to 85), 60% (95% CI: 18 to 80) and 36% (95% CI: -23 to 67) in patients with diabetes mellitus, lung and heart disease, respectively. 2015/16 IVE estimates against hospitalised influenza in elderly people was moderate against influenza A(H1N1)pdm09 and B, including among those with diabetes mellitus, cancer, lung or heart diseases.

Background

Elderly populations, defined as those aged 65 years and above, and, more specifically, elderly people with underlying conditions, are at increased risk for hospitalisation due to influenza [1]. Influenza may also increase the severity of underlying chronic lung diseases, probably through inflammatory processes [2]. Viral pneumonia due to influenza seems to predispose to myocardial infarction, and congestive heart failures are more common during influenza seasons [3]. Patients with cancer treated with chemotherapy [4] and diabetic patients are more vulnerable to influenza. Their impaired immune response [5] could also affect host response to vaccination [6,7]. Evidence of

Figure 1

Location of the hospitals participating in the I-MOVE+ study, Europe, influenza season 2015/16 (n = 27 hospitals)

I MOVE+: Integrated Monitoring of Vaccines in Europe plus.

Each dot represents one location and there may be more than one hospital in one location.

the effectiveness of influenza vaccination in preventing severe clinical outcomes was recently described as low or very low among elderly people [8], and among patients with cancer [9], diabetes mellitus [10], lung diseases [11] [12], or cardiovascular diseases [13].

Despite the Council of the European Union and the World Health Organization's (WHO) recommendations to annually vaccinate elderly people [14,15], influenza vaccine coverage among elderly people remains below the 75% target in most European countries [16].

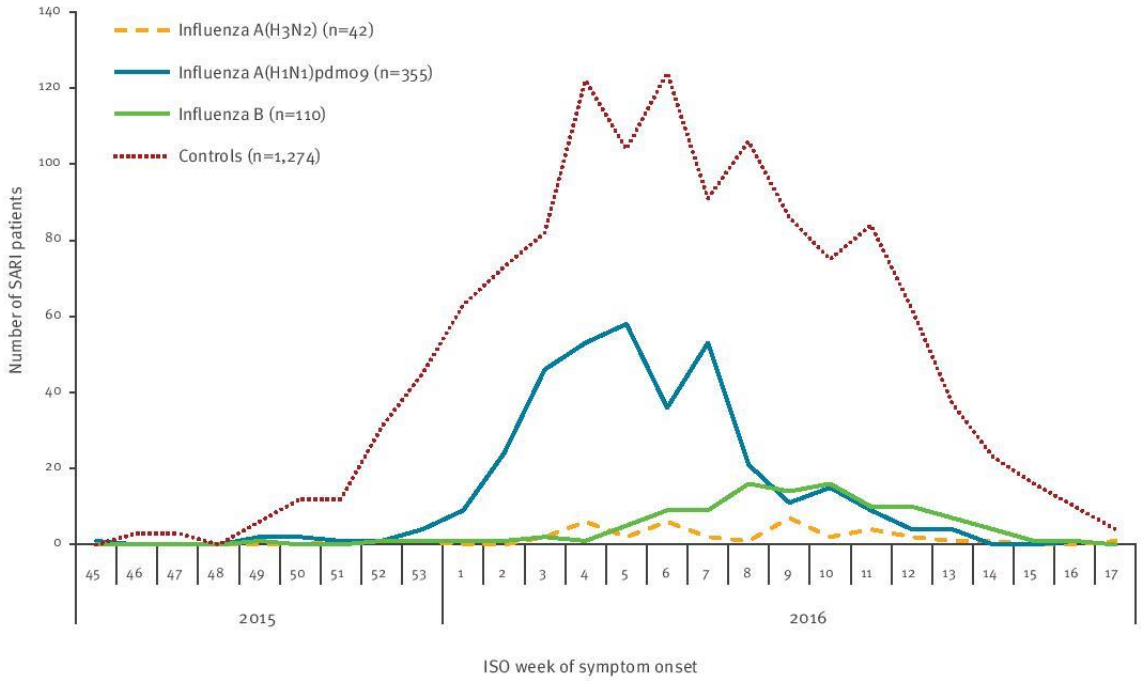
In this context, post-marketing studies to estimate the influenza vaccine effectiveness (IVE) among elderly people are needed to inform about vaccination benefits for vaccinees, detect subgroups in which the vaccine performs less well and identify vaccine types that perform best. In 2015, to address this issue, the Integrated Monitoring of Vaccines in Europe plus (IMOVE+) consortium initiated a network of hospitals across Europe to measure IVE against laboratory-confirmed hospitalised influenza among elderly people.

The WHO recommended to include in the 2015/16 trivalent influenza vaccine for the northern hemisphere an A/California/7/2009 (H1N1)pdm09-like virus, an A/Switzerland/9715293/2013 (H3N2)-like virus and a B/Phuket/3073/2013-like virus (Yamagata lineage) [17].

In the 2015/16 influenza season in Europe, influenza A(H1N1)pdm09 and influenza B (mainly Victoria lineage) viruses predominated [18]. We conducted a multicentre hospital-based test-negative design (TND) case–control study to measure the 2015/16 seasonal IVE against hospitalisation with influenza A(H1N1)pdm09 and influenza B among elderly people in Europe, by risk groups and for specific vaccine types.

FIGURE 2

Cases of severe acute respiratory infection with influenza A(H3N2), A(H1N1)pdm09, and B, and negative controls, I-MOVE+ study, Europe, influenza season 2015/16 (n = 504 casesa; n = 1,274 controls)



I-MOVE+: Integrated Monitoring of Vaccines in Europe plus; ISO: International Organisation for Standardisation; SARI: severe acute respiratory infection.

[a] Including two influenza A(H1N1)pdm09 and B co-infections and one influenza A(H3N2) and B co-infection.

Methods

Study sites and design

We set up a European network of 27 hospitals in 11 countries (Croatia, Finland, France, Hungary, Italy, Lithuania, the Netherlands, Poland, Portugal, Romania and Spain) (Figure 1), organised in 12 study sites (in Spain, Navarre region hospitals had their own coordination centre). Each study site adapted a generic protocol to their local setting [19,20]. Monitoring visits were organised to ensure the study was done similarly across hospitals. We conducted a multicentre TND case–control study.

Study period

In each study site, the study period started at least two weeks after the beginning of the vaccination campaign in the respective countries and lasted from the week of the first detection of a laboratory-confirmed case of influenza to the week of the last laboratory-confirmed case of influenza. We defined different study periods for influenza A(H1N1)pdm09 and B.

Study population

Our study population included all community dwelling patients aged 65 years and above who had no contraindication for influenza vaccination or previous laboratory-confirmed influenza in the season and agreed to participate. In the participating services of each hospital, patients admitted for clinical conditions that could be related to influenza were screened for eligibility. Study physicians, nurses or collaborating medical staff asked patients about onset of symptoms compatible with the definition of a severe acute respiratory infection (SARI) in the previous 7 days.

We defined a SARI case as a hospitalised patient with at least one systemic (fever or feverishness, malaise, headache, myalgia or deterioration of general or functional condition) and at least one respiratory sign or symptom (cough, sore throat or shortness of breath) at admission, or within 48 hours after admission.

Data collection

The hospital study teams swabbed patients meeting the SARI case definition. Specimens were tested by

Table 1

Vaccine types used and source of information for vaccination status by study site, I-MOVE + study, Europe, influenza season, 2015/16

Study site	Number of hospitals	Vaccines used	Data sources	
			Source of information for vaccination status	Source of information for underlying conditions
Croatia	1	Inactivated subunit	I	I; H
Finland	2	Inactivated split	R; I; GP	I; GP; H
France	3	Inactivated subunit; inactivated split	I; P	I; H
Hungary	2	Adjuvanted	I; GP	I; H
Italy	3	Inactivated subunit; inactivated split; adjuvanted	I; GP	I; H
Lithuania	2	Inactivated subunit	I; GP	I; H
Navarre	3	Inactivated split	R	I; GP; H
The Netherlands	1	Inactivated subunit; inactivated split	I	I; H
Poland	3	Unknown	I; GP	I; H
Portugal	2	Inactivated subunit; inactivated split	R; I; GP	I; H
Romania	3	Inactivated subunit	I; GP	I; H
Spain	2	Inactivated subunit; inactivated split	R; I; GP	I; H

GP: general practitioner/primary care database; H: hospital database/medical charts; I: interview with patient; I-MOVE+: Integrated Monitoring of Vaccines in Europe plus; P: pharmacist; R: register

RT-PCR and patients classified as influenza A(H1N1) pdm09 cases, influenza B cases, other influenza cases or controls if their specimens tested negative for any influenza virus.

The hospital study teams collected information on patients' age and sex, influenza vaccination status including date and brand of the 2015/16 vaccine and the status in two previous seasons and underlying conditions listed for clinical risk groups recommended for influenza vaccination [21]. The underlying conditions included diabetes mellitus, obesity (defined as body mass index ≥ 30 kg/m2), cardiovascular conditions (such as congenital heart disease, congestive heart failure and coronary artery disease), lung diseases (such as chronic obstructive pulmonary disease, cystic fibrosis, asthma), renal and rheumatologic diseases, cancer, stroke, dementia and cirrhosis. Information on number of hospitalisations for underlying conditions in the previous 12 months, number of general practitioners (GP) visits in the previous three months, smoking status and functional impairment (based on Barthel index score [22]) was also collected.

Information on demographics and underlying conditions were collected from interviews with patients (or their relatives) and hospital and/or primary care databases. In study sites with no vaccination register, vaccination status was collected through interview with patients. For patients vaccinated or unable to provide their vaccination status, study sites called patients' GP or pharmacists to retrieve vaccination status, date and brand (Table 1).

We defined patients as vaccinated with the 2015/16 influenza vaccine if they had been vaccinated at least 14 days before symptoms onset. Otherwise, they were considered as unvaccinated.

Data analysis

We computed the IVE as (1 minus the odds ratio (OR) of vaccination between cases and controls) x 100. We performed a pooled one-stage analysis using the study site as a fixed effect and estimated IVE stratified on the presence of underlying conditions. All IVE estimates were adjusted for study site, date of SARI symptom onset and age modelled as restricted cubic splines with four knots (initial model). To adjust for additional potential confounders (sex, each group of underlying conditions, hospitalisation in the past year, more than one GP visit in the past 3 months, functional impairment, current smoking), we performed a multivariable analysis using an onward step by step modelling and analysing them as dichotomous variables. Patients with missing covariates were excluded from the analyses adjusted for these covariates. We retained in the model (full model) all covariates that changed the IVE estimate by 10% of more (relative change).

We grouped the vaccine brands in split virion, subunit or adjuvanted vaccines. To compute vaccine type-specific effectiveness, we restricted our analyses to

Table 2

Characteristics of influenza A(H1N1)pdm09 and influenza B hospitalised cases and corresponding test-negative controls included in the I-MOVE+ study, Europe, influenza season 2015/16

	Influenza A(H1N1)pdm09				Influenza B			
	Cases (n = 355)		Controls (n = 976)		Cases (n = 110)		Controls (n = 1,015)	
	n	%	n	%	n	%	n	%
Median age in years (range)	76 (65–95)	–	78 (65–101)	–	76 (65–94)	–	78 (65–101)	–
Aged 65–79 years	235/355	66.2	535/976	54.8[a]	76/110	69.1	566/1,015	55.8[a]
Sex = male	194/351	55.3	512/975	52.5	57/110	51.8	520/1,014	51.3
2015/16 seasonal influenza vaccination	138/355	38.9	543/976	55.6[a]	50/110	45.5	588/1,015	57.9[a]
2014/15 seasonal influenza vaccination	136/347	39.2	537/958	56.1[a]	53/109	48.6	589/998	59.0[a]
Type of vaccine								
Not vaccinated	217/353	61.5	433/970	44.6[a]	60/110	54.5	427/1012	42.2[a]
Inactivated subunit	77/353	21.8	209/970	21.5	20/110	18.2	207/1012	20.5
Inactivated split virion	59/353	16.7	312/970	32.2	30/110	27.3	332/1012	32.8
Adjuvanted	0/353	0.0	16/970	1.6	0/110	0.0	46/1012	4.5
Underlying conditions								
Diabetes	99/347	28.5	277/954	29.0	31/104	29.8	284/992	28.6
Heart disease	215/351	61.3	590/967	61.0	63/107	58.9	631/1,006	62.7
Lung disease	141/351	40.2	438/965	45.4	46/108	42.6	484/996	48.6
Immunodeficiency	7/343	2.0	34/942	3.6	10/106	9.4	32/986	3.2[a]
Cancer	93/350	26.6	263/963	27.3	19/105	18.1	280/1,001	28.0[a]
Nutritional deficiency	16/239	6.7	65/723	9.0	9/84	10.7	51/753	6.8
Renal disease	54/349	15.5	221/960	23.0[a]	20/106	18.9	236/996	23.7
Dementia or stroke	46/346	13.3	160/956	16.7	17/104	16.3	156/991	15.7
Rheumatologic disease	15/246	6.1	80/737	10.9[a]	11/87	12.6	83/757	11.0
Obesity[b]	43/349	12.3	139/951	14.6	5/104	4.8	123/985	12.5[a]
Any underlying condition	325/350	92.9	908/976	93.0	99/110	90.0	955/1,015	94.1
≥ 2 underlying conditions	244/347	70.3	719/964	74.6	72/108	66.7	752/1,006	74.8
Functional impairment[c]	116/347	33.4	347/948	36.6	20/109	18.3	359/988	36.3[a]
Hospitalisation in past 12 months	152/345	44.1	446/960	46.5	39/108	36.1	475/989	48.0[a]
Current smoking	79/340	23.2	183/901	20.3	36/102	35.3	210/927	22.7[a]
Study sites								
Croatia	16/355	4.5	15/976	1.5	5/110	4.5	3/1,015	0.3
Finland	18/355	5.1	57/976	5.8	3/110	2.7	35/1,015	3.4
France	11/355	3.1	124/976	12.7	26/110	23.6	124/1,015	12.2
Hungary	0/355	0.0	0/976	0.0	1/110	0.9	5/1,015	0.5
Italy	3/355	0.8	102/976	10.5	10/110	9.1	249/1,015	24.5
Lithuania	17/355	4.8	41/976	4.2	3/110	2.7	31/1,015	3.1
Navarra	87/355	24.5	240/976	24.6	27/110	24.5	230/1,015	22.7
The Netherlands	5/355	1.4	12/976	1.2	3/110	2.7	6/1,015	0.6
Poland	17/355	4.8)	14/976	1.4	6/110	5.5	9/1,015	0.9
Portugal	14/355	3.9	35/976	3.6	1/110	0.9	1/1,015	0.1
Romania	58/355	16.3	101/976	10.3	2/110	1.8	70/1,015	6.9
Spain	109/355	30.7	235/976	24.1	23/110	20.9	252/1,015	24.8
Potential for misclassification								
Antivirals before swabbing	36/353	10.2	32/972	3.3[a]	7/107	7.5	27/1,012	2.7[a]
Swabbing within 3 days of onset	216/355	60.8	518/976	53.1[a]	54/110	49.1	585/1,015	57.6

I MOVE+: Integrated Monitoring of Vaccines in Europe plus.

[a] Indicates a significant difference (p value < 0.05) between cases and controls.

[b] Defined as body-mass index ≥ 30 kg/m2.

[c] Defined as Barthel score < 100 [22].

Table 3

Pooled adjusted seasonal influenza vaccine effectiveness against hospitalised influenza A(H1N1)pdm09 overall among elderly people, by risk groups and vaccine type, I-MOVE + study, Europe, influenza season, 2015/16

Analyses	Model used for adjustment[a]	Vaccinated /cases	Vaccinated /controls	Adjusted IVE	95% CI
Overall					
	Initial	138/355	543/976	42.4	22.0 to 57.4
	Full	131/336	509/923	39.4	16.6 to 55.9
By risk groups					
At least one underlying condition	Initial	130/317	499/892	35.7	11.4 to 53.3
	Initial plus severity			35.6	11.2 to 53.3
Diabetes mellitus					
No	Initial	98/242	370/674	33.9	4.6 to 54.2
Yes	Initial	33/96	150/266	58.5	22.8 to 77.7
	Initial plus severity			58.5	22.7 to 77.8
Heart disease					
No	Initial	54/131	207/372	37.3	-1.2 to 61.1
Yes	Initial	80/211	321/581	38.4	6.5 to 59.5
	Initial plus severity			39.0	7.3 to 59.9
Lung disease					
No	Initial	61/203	250/515	39.7	8.0 to 60.4
Yes	Initial	72/139	276/434	42.4	7.2 to 64.3
	Initial plus severity			42.8	7.8 to 64.5
Cancer					
No	Initial	93/252	375/691	35.7	6.7 to 55.7
Yes	Initial	41/90	150/256	47.7	4.8 to 71.3
	Initial plus severity			47.8	4.8 to 71.4
Vaccine type					
Inactivated subunit	Initial	77/224	209/538	28.1	-8.6 to 52.4
Inactivated split virion	Initial	59/178	312/588	54.7	30.7 to 70.4
Sensitivity analyses					
Two-stage model	two-stage[b]	132/329	527/932	49.0	13.5 to 70.0
Restricted to patients swabbed within 3 days	Initial	85/216	313/518	49.1	23.8 to 66.0
Restricted to patients not receiving antivirals before swabbing	Initial	126/317	531/940	42.2	20.8 to 57.8

CI: confidence interval; I MOVE+: Integrated Monitoring of Vaccines in Europe plus; IVE: influenza vaccine effectiveness.

[a] Initial: one-stage model adjusted for study site, date of symptom onset and age (modelled as restricted cubic splines). Full: one-stage model adjusted for study site, date of symptom onset, age (modelled as restricted cubic splines), lung, heart, renal disease, diabetes mellitus, cancer, obesity (body-mass index ≥ 30 kg/m²) and hospitalisation for underlying conditions in past year. Severity: hospitalisations for underlying conditions in the previous year.

[b] Poland and Hungary were excluded because there were no vaccinated controls in Poland and no cases in Hungary.

countries with at least one patient vaccinated with a specific type.

We also computed a pooled IVE with a two-stage model, adjusting study site-specific IVE for study site-specific confounders (same as listed above) when sample size allowed. We quantified the heterogeneity between site estimates using the I-square [23].

To minimise the inclusion of false influenza-negatives in the control group, we carried out sensitivity analyses by restricting population to (i) patients swabbed up to three days after symptom onset and (ii) patients not treated with antivirals until the day before swabbing.

Results

A total of 2,077 patients meeting the inclusion criteria were recruited in the study. We excluded 472 controls (23%) recruited outside of the study period and 65 patients (4%) with missing information on vaccination status. We included 1,274 controls and 528 cases, of which 353 (67%) were influenza A(H1N1)pdm09 positive, 105 (20%) were influenza B-positive, 41 (8%) were influenza A(H3N2)-positive, 24 (5%) were influenza A (non-subtyped)-positive, two (<1%) were co-infected by influenza A(H1N1)pdm09 and B, one (<1%) was co-infected by influenza A(H3N2) and B and two (<1%) were co-infected by influenza A (non-subtyped) and B. Of the 52 cases of influenza B with a known lineage, 47

Table 4

Study site specific and two-stage[a] pooled seasonal vaccine effectiveness against hospitalised influenza A(H1N1)pdm09 among elderly people, I- MOVE+ study, Europe, influenza season 2015/16 (n = 1,261)

Study site	Inclusion period	Variables used for adjustment[b]	Vaccinated /cases	Vaccinated /controls	Adjusted IVE	95% CI	I-square
Croatia	2016w5–2016w13	Date	4/16	1/15	-122.0	−4,314.5 to 88.8	–
Finland	2015w50–2016w7	Date	5/18	38/57	85.0	43.7 to 96.0	–
France	2016w4–2016w14	Date	3/11	84/124	83.7	32.2 to 96.1	–
Italy	2016w5–2016w11	Date	2/3	47/102	-152.2	−3,081.1 to 80.0	–
Lithuania	2016w2–2016w10	Date	1/17	7/41	66.8	−210.4 to 96.4	–
Navarra	2015w46–2016w13	Date	46/87	169/240	45.9	5.3 to 69.1	–
The Netherlands	2015w50–2016w7	Date	1/5	10/12	94.8	6.9 to 99.7	–
Portugal	2015w51–2016w8	Date, cancer, obesity	3/14	14/35	11.9	−372.7 to 83.6	–
Romania	2016w3–2016w14	Date, cancer, renal disease	4/58	6/100	-22.6	−490.3 to 74.6	–
Spain	2016w1–2016w14	Date, age, heart disease, dependency	63/100	151/206	22.5	−39.6 to 56.9	–
two-stage pooled	–	–	–	–	49.0	13.5 to 70.0	36.2%

CI: confidence interval; I MOVE+: Integrated Monitoring of Vaccines in Europe plus; IVE: influenza vaccine effectiveness; w: week (International Organisation for Standardisation (ISO) week).

[a] Poland and Hungary were excluded from the two-stage analyses because there were no vaccinated controls in Poland and no cases in Hungary.

[b] Date of symptom onset and age modelled as restricted cubic spline with four knots.

(90%) were Victoria and 5 (10%) were Yamagata. The 42 cases positive for influenza A(H3N2) did not allow us to compute IVE against this subtype.

The maximum number of influenza A(H1N1)pdm09 cases were recruited in weeks 5 to 8 of 2016 and the maximum number of influenza B and A(H3N2) cases in week 10 (Figure 2).

Overall, 216/528 cases (41%) and 694/1,274 controls (54%) had received trivalent inactivated vaccines. Among those vaccinated, 51 (6%) received adjuvanted vaccines, 338 (37%) inactivated subunit vaccines,513 (56%) inactivated split virion vaccines and the information on vaccine type was missing for 8 (1%) vaccinated patients. Age and time adjusted IVE against any influenza was 39% (95 % confidence interval (CI): 22 to 53).

Vaccine effectiveness against hospitalised influenza A(H1N1)pdm09

We included in this analysis 355 cases of influenza A(H1N1)pdm09, of whom 138 (39%) were vaccinated, and 976 controls, of whom 543 (56%) vaccinated. The median age of A(H1N1)pdm09 cases and controls was 76 (Interquartile range (IQR) = 12 years) and 78 (IQR = 12 years) years respectively (p = 0.001). The proportion of patients with underlying conditions was similar among cases and controls except for renal (16% among cases vs 23% among controls, p = 0.003) and rheumatologic diseases (6% among cases vs 11% among controls, p = 0.033). Ten percent of A(H1N1)pdm09 cases and 3% of controls had received antivirals before swabbing (p < 0.001) and 61% of cases vs 53% of controls were swabbed within 3 days after symptoms onset (p = 0.013) (Table 2).

One-stage pooled IVE against A(H1N1)pdm09 adjusted for onset time and age was 42% (95% CI: 22 to 57) and 39% (95% CI: 17 to 56) when further adjusted for a range of underlying conditions and hospitalisation in the previous year (Table 3). IVE against A(H1N1)pdm09 was 59% (95% CI: 23 to 78), 48% (95% CI: 5 to 71), 43% (95% CI: 8 to 65) and 39% (95% CI: 7 to 60) in patients with diabetes mellitus (n = 362), cancer (n = 346), lung (n = 573) and heart disease (n = 792), respectively (Table 3).

IVE against A(H1N1)pdm09 was 28% (95% CI: −9 to 52) for inactivated subunit vaccines (n = 762) and 55% (95% CI: 31 to 70) for inactivated split virion vaccines (n = 716).

Study site specific IVE ranged between −152% (95% CI: −3,081 to 80) in Italy (n = 105) and 95% (95% CI: 7 to 100) in the Netherlands (n = 17) (Table 4). The statistical heterogeneity between study site specific IVE estimates was moderate (I2 = 36%). The two-stage pooled analysis (n = 1,261) included Croatia, Finland, France, Italy, Lithuania, Navarre, the Netherlands, Portugal, Romania and Spain. IVE was 49% (95% CI: 14 to 70). In sensitivity analyses, IVE against influenza A(H1N1) pdm09 was 42% (95% CI: 21 to 58) when restricting to patients not having received antiviral treatment (n = 1,257) and 49% (95% CI: 24 to 66) among patients

Table 5

Pooled adjusted seasonal vaccine effectiveness against hospitalised influenza B among elderly people overall and by risk groups, I-MOVE+study, Europe, influenza season 2015/16

	Model used for adjustment[a]	Vaccinated /cases	Vaccinated /controls	Adjusted IVE	95% CI
Overall					
Overall	Initial	50/110	588/1,015	51.8	23.7 to 69.5
Overall	Full	46/101	544/948	47.0	13.1 to 67.7
By risk groups					
At least one underlying condition	Initial	47/97	536/929	50.2	18.7 to 69.4
	Initial plus severity			49.4	17.5 to 69.0
Diabetes mellitus					
No	Initial	33/72	404/696	40.9	−7.1 to 67.4
Yes	Initial	13/30	152/272	62.1	5.8 to 84.7
	Initial plus severity			62.0	5.3 to 84.8
Heart disease					
No	Initial	16/44	211/368	66.5	27.6 to 84.5
Yes	Initial	32/61	354/614	36.3	−22.2 to 66.8
	Initial plus severity			36.1	−22.9 to 66.7
Lung disease					
No	Initial	27/61	258/502	32.8	−28.6 to 64.8
Yes	Initial	22/45	305/475	60.5	19.2 to 80.6
	Initial plus severity			59.9	18.2 to 80.4
Vaccine type					
Inactivated subunit	Initial	20/61	207/542	49.0	13.5 to 70.0
Inactivated split virion	Initial	30/74	332/652	54.1	18.9 to 74.0
Sensitivity analyses					
two-stage model	two-stage[b]	48/86	551/858	47.0	11.9 to 68.2
Restricted to patients swabbed within 3 days	Initial	31/54	358/585	25.0	−50.5 to 62.6
Restricted to patients not receiving antivirals before swabbing	Initial	46/99	577/985	52.3	22.8 to 70.5

CI: confidence interval; I MOVE+: Integrated Monitoring of Vaccines in Europe plus; IVE: influenza vaccine effectiveness.

[a] Initial: one-stage model adjusted for study site, date of onset and age (modelled as restricted cubic splines). Full: one-stage model adjusted for study site, date of symptom onset, age (modelled as restricted cubic splines), lung, heart, renal disease, diabetes mellitus, cancer, obesity and hospitalisation in the previous year Severity: hospitalisations for underlying conditions in the previous year.

[b] Croatia, Hungary, Italy, Lithuania, the Netherlands, Poland, Portugal and Romania were excluded from the two-stage analyses because there were no vaccinated controls and/or cases, respectively.

swabbed within 3 days of symptoms onset (n=734) (Table 3).

Vaccine effectiveness against hospitalised influenza B

We included in this analysis 110 cases of influenza B, of whom 50 (46%) were vaccinated and 1,015 controls, of whom 588 (58%) vaccinated. The median age of cases and controls were 76 (IQR: 12 years) and 78 years (IQR: 12 years) respectively (p=0.056). A lower proportion of cases than controls had cancer (18% vs 28%, p=0.037), a functional impairment (18% vs 36%, p<0.001), and had been hospitalised in the previous 12 months (36% vs 48%, p=0.02). The proportion of current smokers was higher among influenza B cases than among controls (35% vs 23%, p=0.007) (Table 2).

One stage pooled IVE against influenza B adjusted for symptom onset time and age was 52% (95% CI: 24 to 70) and 47% (95% CI: 13 to 68) when further adjusted for a range of underlying conditions and hospitalisation in the previous year (Table 5). IVE was 62% (95% CI: 5 to 85), 60% (95% CI: 18 to 80) and 36% (95% CI: −23 to 67) in patients with diabetes mellitus (n=302), lung (n=520) and heart disease (n=675), respectively.

IVE against influenza B was 49% (95% CI: 14 to 70) for inactivated subunit vaccines (n=603) and 54% (95% CI: 19 to 74) for inactivated split virion vaccines (n=726).

Study site specific IVE ranged between 18% (95% CI: −106 to 67) in Finland (n=38) and 76% (95% CI: −24 to 95) in Italy (n=259) (Table 6). There was no statistical heterogeneity between study site specific IVE

Table 6

Study site-specific and two-stage[a] pooled seasonal vaccine effectiveness against hospitalised influenza B among elderly people, I- MOVE+ study, Europe, influenza season 2015/16

Study site	Inclusion period	Variables used for adjustment[b]	Vaccinated /cases	Vaccinated /controls	Adjusted IVE	95% CI	I-square
Finland	2016w8–2016w15	Date	2/3	22/35	23.3	-1,785.9 to 96.9	–
France	2016w4–2016w14	Date, age, functional impairment	17/26	87/120	18.1	-105.6 to 67.4	–
Italy	2016w1–2016w12	Date	2/10	121/249	75.5	-23.7 to 95.1	–
Navarre	2015w53–2016w17	Date	17/27	165/230	59.4	-2.5 to 83.9	–
Spain	2016w2–2016w16	Date, lung disease, dependency	11/20	159/220	44.3	-48.9 to 79.1	–
two-stage pooled (n=944)	–	–	–	–	47.0	11.9 to 68.2	0.0%

CI: confidence interval; I MOVE+: Integrated Monitoring of Vaccines in Europe plus; IVE: influenza vaccine effectiveness; w: week (International Organisation for Standardisation (ISO) week).

[a] Croatia, Hungary, Italy, Lithuania, the Netherlands, Poland, Portugal and Romania were excluded from the two-stage analyses because there were no vaccinated controls and/or cases.

[b] Date of onset and age modelled as restricted cubic spline with four knots.

estimates ($I2=0\%$). The two-stage pooled analysis (n=944) included Finland, France, Italy, Navarre and Spain. IVE was 47% (95% CI: 12 to 68). In sensitivity analyses, IVE against influenza B was 52% (95% CI: 23 to 71) when restricting to patients not having received antiviral treatment (n=1,084) and 25% (95%CI: −51 to 63) among patients swabbed within 3 days of symptoms onset (n=639).

Discussion

Our results suggest that the seasonal IVE against hospitalised influenza among elderly people was moderate during the 2015/16 influenza season in Europe for influenza: 39% overall, 42% against influenza A(H1N1) pdm09 and 52% against influenza B . These estimates did not vary between categories of underlying conditions.

Data from European virological surveillance reported that most of the characterised influenza A(H1N1)pdm09 viruses belonged to the emerging subclade 6B.1, defined by haemagglutinin amino acid substitutions S162N and I216T [18]. Despite these genetic evolutions, A(H1N1)pdm09 viruses were considered antigenically similar to the northern hemisphere vaccine component A/California/7/2009. IVE estimates against hospitalised A(H1N1)pdm09 was consistent with the results we reported in 2012/13 and 2013/14 among hospitalised elderly people [24,25].

In 2015/16, the circulating influenza B Victoria lineage was distinct from the Yamagata vaccine component [26] and there was no quadrivalent vaccine used in our study population. IVE against influenza B was close to what we reported, using the same generic protocol, in 2012/13 (66% in the 65–79 year-olds and 44% in the 80 year-olds and older) in a season with co-circulation of B Victoria and Yamagata lineages and a Yamagata vaccine component [24,27]. These results suggest some cross-lineage protection and they are in line with previously reported data in GP-based studies [28,29] and a meta-analysis of eight randomised controlled trials with mismatched B viruses resulting in a VE of 52% (95% CI: 19 to 72) among healthy adults [30]. Further studies are needed to increase the understanding of mechanisms of cross-lineage protection for influenza B and better guide policy makers in terms of recommendations for using trivalent or tetravalent seasonal vaccines.

We observed higher point estimates of IVE for the inactivated split virion vaccines compared with inactivated subunit vaccines, although the 95% CIs of the point estimates were widely overlapping. The completeness of data on vaccine type was high (1% of missing vaccine type among those vaccinated), thus these results, concurring with published data [31-33], could be due to differences in T-cell responses conferred by the two vaccine types [34]. However, they should be interpreted with caution as they may be due to random variation. Further evidence, and pooling of several years of data would be required to obtain precise vaccine type specific effectiveness. Higher adjuvant vaccine coverage would be needed to compute adjuvant vaccine specific IVE. This would be useful information to adapt influenza vaccination strategies among elderly people.

Recent reviews underlined the need for further evidence of seasonal IVE against laboratory-confirmed influenza in elderly people and patients with underlying conditions [8-13]. We were able to collect high quality data from 1,802 elderly patients hospitalised with SARI, making our study one of the largest hospital-based studies on IVE. The large number of participants,

and a vaccine coverage close to 50%, enabled us to compute IVE against type/subtype-specific influenza among patients with specific underlying conditions. Our results suggest that, in 2015/16, the seasonal influenza vaccine provided protection against hospitalised influenza A(H1N1)pdm09 and B in the elderly with diabetes mellitus, heart and lung disease. We were unable to refine the underlying conditions categories further. To better guide vaccine recommendations, IVE among patients receiving specific treatment (e.g. statins [35,36], chemotherapy [9,37]) or with more specific conditions (e.g. asthma, chronic obstructive pulmonary disease) would be needed. A larger sample size would be required for such studies.

We collected information related to access to care, health conditions and smoking status. Recruited cases and controls were similar. We adjusted our estimates for study site, onset week and age. Further adjustment for potential confounders (underlying lung, heart, renal disease, diabetes mellitus, cancer, obesity and hospitalisations in the past year) did not change the estimates. However, as in any observational study, we cannot exclude unmeasured confounding leading to over- or under-estimation of the IVE.

The contribution to the pooled dataset was different between study sites. The two Spanish sites recruited 44% of the patients. The viruses circulating and vaccines used in Spain were similar to the other countries. Consequently we do not expect the over-representation of Spanish sites to have biased our overall estimates. Variations in the number of recruited individuals may be explained by differences in local influenza activity or number and size of participating hospitals/services. We believe that access to hospitalisation in case of severe influenza is similar across participating European countries. A common generic protocol and the monitoring of its implementation through on-site visits contributed to ensuring comparability of patients recruited and data collected across study sites. We measured low statistical heterogeneity based on I-square values. However, small number of estimates and large study-specific CIs may hinder adequate quantitative assessment of heterogeneity between studies [38]. True differences between study site specific IVE could be related to different vaccines used during this season or different immunological profiles of recruited patients including their past vaccination histories [39]. Larger study site-specific sample sizes are required to ensure that the differences in IVE across study sites are not due to chance. Currently, multicentre studies are necessary to obtain precise IVE estimates.

A recent publication by Foppa et al. suggested that measuring IVE against laboratory-confirmed influenza SARI hospitalisation using the TND was subject to biases if the test-negative controls were hospitalised because of an exacerbation of underlying lung disease unrelated to a respiratory infection [40]. In our study, cases and controls had similar prevalence of underlying lung disease. Underlying lung disease did not appear to confound IVE estimates, even when combined with a proxy of its severity (hospitalisation because of underlying conditions in the past 12 months). Cohort and TND-based IVE estimates against laboratory-confirmed hospitalised influenza in Navarre repeatedly showed similar estimates, reassuring on the appropriateness of TND at hospital level [41].

Several studies suggest that past influenza vaccinations may decrease or enhance current vaccine effectiveness depending on previous and current vaccine and circulating strains as well as past exposure to the virus [24,32,42-44]. A large proportion of our vaccinated population had been vaccinated in the previous season(s) but the very small number of patients with varying repeated vaccination status over the years did not allow us to measure the effect of previous vaccinations. To understand the effect of repeated vaccinations on IVE, large cohorts of individuals with different vaccination patterns and symptomatic (and asymptomatic) influenza infection status over the years would be needed.

Conclusion

Our multicentre test-negative case–control study estimated that in 2015/16 the seasonal influenza vaccination prevented approximately half of the cases of hospitalisation with laboratory-confirmed influenza among vaccinated elderly people. Our results suggest that vaccination provided similar protection to elderly patients with underlying diabetes mellitus, cancer, lung and heart diseases. Because vaccination remains the most effective preventive measure against severe influenza among elderly people, increasing the vaccine coverage in this group should be a priority. This pilot season of the hospital-based I-MOVE+project proved that obtaining precise estimates of IVE against a severe influenza outcome among elderly people was feasible. Enlarging our network and its sample size will enable us to better guide vaccination strategies against severe influenza cases by comparing the performance of different vaccine types and identifying risk groups for poor response to vaccination.

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Conflict of interest

None declared.

Authors' contributions

Marc Rondy was involved in the original methodological design of the study (generic protocol). He coordinated the European hospital IVE network, undertook the statistical analysis on which the research article is based and led the writing of the research article.

Marta Valenciano initiated the original methodological design of the study. She coordinated the European hospital

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The I-MOVE+ hospital working group contributors contributed to developing the study site specific protocol. They were in charge of supervising the study at the hospital level and collect the data published in this research article. They read, contributed and approved the manuscript final version.

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3.5.1.5 Results from 2016-17

In 2016-17, the influenza season in Europe was characterised by its early start (week 46, 2016) and a great predominance of A(H3N2) viruses. Overall, 90% of strains reported to the ECDC where influenza A, and 99% of them where A(H3N2) viruses. There were early indications of high hospitalisation rate and mortality, especially among elderly. Using the I-MOVE+ hospital network, we measured the 2016-17 seasonal IVE against hospitalisation with A(H3N2) influenza among persons aged 65 years and above in the European Union.

Hospital teams recruited and sent records from 2,917 patients. Of them 88 patients presented an exclusion criteria and 137 were recruited outside the study period. Among eligible patients, we excluded 41 patients due to missing laboratory data, 18 patients due to missing vaccination status and 19 patients vaccinated <15 days before symptoms onset. We included 1,073 A(H3N2) cases and 1,541 controls between week 47, 2016 and week 14, 2017. The vast majority of vaccinated patients had been vaccinated before the study start. Adjusted IVE was 17% (95% CI: 1 ; 31) overall; 25% (95% CI: 2 ; 43) among 65–79-year-olds and 13% (95% CI: −15 ; 30).

Our results suggest a low IVE against hospitalised influenza A(H3N2) among elderly, and in particular among patients aged 80 years and above. The A(H3N2) virus component included in the 2017-18 vaccine will remain the same. Close monitoring of virological surveillance data will be required to prompt early intervention among elderly in the 2017-18 season. Indeed, low IVE may be expected in case of circulation of A(H3N2) viruses, especially if these viruses are antigenically distinct from A/Hong Kong/4801/2014(H3N2)-like viruses. Alternative measures, such as non-pharmaceutical prevention approaches and prophylactic use of antivirals for elderly should then be promoted among health professionals.

Low 2016/17 season vaccine effectiveness against hospitalised influenza A(H3N2) among elderly: awareness warranted for 2017/18 season

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In a multicentre European hospital study we measured influenza vaccine effectiveness (IVE) against A(H3N2) in 2016/17. Adjusted IVE was 17% (95% confidence interval (CI): 1 to 31) overall; 25% (95% CI: 2 to 43) among 65–79-year-olds and 13% (95% CI: −15 to 30) among those ≥ 80 years. As the A(H3N2) vaccine component has not changed for 2017/18, physicians and public health experts should be aware that IVE could be low where A(H3N2) viruses predominate.

In 2016/17, the influenza season in Europe was characterised by an early start (week 46, 2016) and a predominance of A(H3N2) viruses. Overall, 89% of strains reported to the European Centre for Disease Prevention and Control (ECDC) were A(H3N2) viruses [1]. High hospitalisation rates and case fatality ratios were reported among persons aged 65 years and above [2]. The I-MOVE+ (Integrated Monitoring of Vaccines in Europe plus) hospital network early estimates, suggested a low 2016/17 seasonal influenza vaccine effectiveness (IVE) against hospitalisation with influenza A(H3N2) among persons aged 65 years and above in the European Union (EU) [3].

Since the A(H3N2) vaccine component has not changed in 2017/18, we present the final 2016/17 season IVE against hospitalisation with influenza A(H3N2) among persons aged 65 years and above in Europe, to inform on the level of IVE that can be expected against A(H3N2) in the upcoming 2017/18 season.

Study design

We conducted a multicentre hospital-based test-negative design (TND) case-control study in 27 hospitals from 10 countries (Croatia, Finland, France, Hungary, Italy, Lithuania, the Netherlands, Portugal, Romania and Spain) according to a generic protocol adapted to each local setting [4]. The detailed methods are described elsewhere [5]. In brief, hospital teams identified and swabbed patients aged 65 years and above,

Table 1

Characteristics of influenza A(H3N2) hospitalised cases (n = 1,073) and test-negative controls (n = 1,541), I-MOVE + study, Europe, influenza season 2016/17

	Influenza A(H3N2) cases (n = 1,073)		Controls (n = 1,541)	
Median age in years (range)	81 (65–102)		80 (65–102)	
Characteristic	n/N[a]	%	n/N[a]	%
Aged 65–69 years	457/1,073	42.6	770/1,541	50.0
Sex = male	516/1,072	48.1	815/1,535	53.1
2016/17 seasonal influenza vaccination	556/1,073	51.8	894/1,541	58.0
2015/16 seasonal influenza vaccination	578/1,054	54.8	896/1,525	58.8
Current and previous vaccination status				
2016/17 seasonal vaccine only	46/1,054	4.4	99/1,525	6.5
2015/16 seasonal vaccine only	73/1,054	6.9	112/1,525	7.3
2015/16 and 2016/17 seasonal vaccines	505/1,054	47.9	784/1,525	51.4
Type of 2016/17 vaccine				
Not vaccinated	517/1,007	48.2	647/1,421	42.0
Inactivated subunit egg	243/1,007	22.6	431/1,421	28.0
Inactivated split virion egg	229/1,007	21.3	321/1,421	20.8
Adjuvanted	18/1,007	1.7	22/1,421	1.4
Underlying conditions				
Diabetes mellitus	325/1,072	30.3	473/1,540	30.7
Heart disease	710/1,070	66.4	1,032/1,541	67.0
Lung disease	392/1,069	36.7	672/1,534	43.8
Cancer	201/1,069	18.8	369/1,533	24.1
Renal disease	223/1,071	20.8	319/1,539	20.7
Stroke	125/879	14.2	176/1,287	13.7
Rheumatologic disease	157/1,070	14.7	341/1,539	22.2
Obesity[b]	124/1,062	11.7	154/1,527	10.1
Any underlying condition	996/1,063	93.7	1,456/1,531	95.1
At least two underlying conditions	776/1,025	75.7	1,206/1,491	80.9
Functional impairment	399/1,066	37.4	588/1,529	38.5
Hospitalisations in past 12 months	353/1,063	33.2	668/1,526	43.8
Current smoker	182/901	20.2	318/1,220	26.1
Potential for misclassification				
Antivirals received before swabbing	177/1,069	16.0	90/1,535	5.8
Swabbing within 3 days of symptom onset	653/1,073	58.7	876/1,541	56.2
Study sites				
Croatia	31/1,073	2.9	13/1,541	0.8
Finland	20/1,073	1.9	50/1,541	3.2
France	119/1,073	11.1	209/1,541	13.6
Hungary	8/1,073	0.7	19/1,541	1.2
Italy	73/1,073	6.8	136/1,541	8.8
Lithuania	67/1,073	6.2	58/1,541	3.8
Navarre, Spain	242/1,073	22.6	290/1,541	18.8
The Netherlands	40/1,073	3.7	63/1,541	4.1
Portugal	49/1,073	4.6	29/1,541	1.9
Romania	90/1,073	8.4	103/1,541	6.7
Spain[c]	334/1,073	31.1	571/1,541	37.1

I MOVE+: Integrated Monitoring of Vaccines in Europe plus.

[a] N represents the total number of cases or controls with available information.

[b] Defined as body mass index ≥ 30 kg/m².

[c] Excluding Navarre.

Table 2

Seasonal influenza vaccine effectiveness against influenza influenza A(H3N2) overall and stratified by patient characteristics, I-MOVE+ study, Europe, influenza season 2016/17

Population and patient characteristics	Vaccinated /cases	%	Vaccinated /controls	%	Adjusted IVE	95% CI
Aged 65 years and above - age/time[a]	556/1,073	52	894/1,541	58	17	1 to 31
Aged 65 years and above - full model[a]	544/1,041	52	868/1,494	58	14	−3 to 29
Aged 65–79 years - age/time[a]	175/457	38	382/770	50	25	2 to 43
Aged 80 years and above - age/time[a]	381/616	62	512/771	66	13	−12 to 32
According to underlying diseases						
Diabetes mellitus	183/320	57	295/468	63	22	−8 to 44
Heart disease	378/703	54	622/1,024	61	19	−1 to 35
Lung disease	209/386	54	440/668	66	35	14 to 51
Cancer	105/198	53	227/362	63	21	−19 to 47
At least two underlying chronic diseases	414/767	54	732/1,196	61	17	−2 to 33
According to previous vaccination						
Not vaccinated in 2015/16	46/473	10	99/623	16	39	−3 to 59
Vaccinated in 2015/16	502/572	88	776/887	87	−2	−44 to 28
Sensitivity analyses						
Swabbed within 3 days	502/872	58	333/629	53	8	−16 to 28
No antivirals before swabbing	867/1,446	60	509/904	56	14	−3 to 29

I MOVE+: Integrated Monitoring of Vaccines in Europe plus.

[a] Variables used for adjustment:

-age/time: adjusted for study site, age and onset date (modelled as a restricted cubic spline with 3 and 4 knots respectively);

-full model: adjusted for study site, onset date, age (modelled as a restricted cubic spline with 3 and 4 knots respectively), lung diseases, heart diseases, diabetes, obesity, renal diseases, cancer and hospitalisation in the past 12 months;

-other estimates were adjusted for study site, onset date, age (modelled as a restricted cubic spline with 3 and 4 knots respectively) and hospitalisation in the past 12 months.

hospitalised with signs compatible with a severe acute respiratory infection (SARI) defined as at least one systemic and one respiratory sign or symptom. Swabs were tested with reverse-transcriptase polymerase chain reaction (RT-PCR) for influenza A(H3N2), A(H1N1) pdm09 and B. We compared the odds of vaccination between patients positive for influenza A(H3N2) virus and those negative for any influenza virus. We calculated IVE as (1-odds ratio (OR)).

We measured IVE stratified by age group (65–79 year-olds and ≥ 80 year-olds), presence of underlying conditions (diabetes mellitus, cancer, heart or lung disease, and presence of at least two underlying chronic diseases) and 2015/16 seasonal influenza vaccination status. In a one-stage approach, using logistic regression with the study site as a fixed effect, we adjusted IVE estimates for date of symptoms onset, age (as cubic splines) and individual underlying conditions. Using patients unvaccinated in both 2015/16 and 2016/17 seasons as a reference, we computed the effectiveness of being vaccinated in 2015/16 season only, in 2016/17 season only and in both seasons.

Vaccine effectiveness against influenza A(H3N2) in 2016/17

We included 1,073 influenza A(H3N2) cases, nine A(H1N1)pdm09 cases, 13 cases of influenza B and 1,541 controls between week 47, 2016 and week 14, 2017. Due to the small number of cases, we were not able to measure IVE against influenza A(H1N1)pdm09 and B. We excluded these 22 records from all analyses.

The median age of A(H3N2) cases was 81 years (range: 65–102 years) while that of controls was 80 (range: 65–102 years). Ninety-four percent of cases and 95% of controls had at least one underlying condition ($p = 0.14$). Controls were more likely than cases to have underlying lung disease (44 vs 37%, $p < 0.05$), rheumatologic disease (22 vs 15%, $p < 0.05$) and cancer (24 vs 19%, $p < 0.05$), to have been hospitalised in the past 12 months (44 vs 33%, $p < 0.05$) and to be current smokers (26 vs 20%, $p < 0.05$) (Table 1).

The one-stage pooled adjusted IVE was 17% (95% confidence interval (CI): 1 to 31) overall; 25% (95% CI: 2 to 43) among patients aged 65–79 years and 10% (95 %CI: −15 to 30) among those aged 80 years and above. Among patients with specific underlying conditions, IVE ranged between 19% (95% CI: −1 to 35) among patients with heart disease and 35% (95% CI: 14 to 51) among patients with lung disease (Table 2).

The 2016/17 seasonal IVE was −2% (95% CI: −44 to 28) among patients who had received 2015/16 seasonal influenza vaccine and 39% (95 %CI: −3 to 59) among patients not vaccinated in 2015/16 (Table 2). Taking as a reference patients unvaccinated in 2015/16 and

Table 3

Seasonal influenza vaccine effectiveness against influenza A(H3N2) by vaccine uptake in 2015/16, 2016/17 and in both seasons, I-MOVE+study, Europe, influenza season 2016/17

Vaccine uptake in 2015/16 and 2016/17 influenza seasons	Cases	Controls	IVE	95% CI
Not vaccinated	427	524	Reference	
2016/17 only	46	99	38	9 to 58
2015/16 only	70	111	19	−15 to 42
Vaccinated in both seasons	502	776	15	−3 to 30

CI: confidence interval; I-MOVE+: Integrated Monitoring of Vaccines in Europe plus; IVE: influenza vaccine effectiveness.

[a] Adjusted for study site, age and onset date (modelled as a restricted cubic spline with 3 and 4 knots, respectively).

The A(H3N2) vaccine components were A/Switzerland/2013 (3C.3a) in the 2015/16 seasonal vaccine and A/Hong Kong/2014 (3c.2a) in the 2016/17 seasonal vaccine.

2016/17, IVE for those vaccinated in 2015/16 only was 19% (95% CI: −15 to 42) and IVE when vaccinated both in 2015/16 and 2016/17 was 15% (95 %CI: −3 to 30) (Table 3).

Discussion

In the 2016/17 influenza season, A(H3N2) viruses largely predominated. IVE against hospitalisation with influenza A(H3N2) virus infection among persons aged 65 years and above was low at 17%. The IVE point estimate was even lower (10%) among patients aged 80 years and above. IVE was similar among patients with heart disease, diabetes mellitus and cancer. The IVE point estimate was higher among patients with lung disease. While 95% CIs were largely overlapping, the 2016/17 IVE point estimate was lower (IVE: −2%) among patients vaccinated also in 2015/16 than among those unvaccinated in 2015/16 (IVE: 39%).

Low IVE against influenza A(H3N2) among persons aged 65 years and above has been previously observed in hospital settings [6-8]. A recent meta-analysis measured that the pooled IVE against hospitalisation with influenza A(H3N2) in seasons when circulating and vaccine strains were antigenically different was 14% (95% CI: −3 to 30) among persons aged 65 years and above [9]. It was 43% (95% CI: 33 to 53) in seasons when circulating and vaccine A(H3N2) strains were antigenically similar; 48% (95% CI: 37 to 59) against influenza A(H1N1)pdm09 and 38% (95% CI: 25 to 53) against influenza B [9].

Based on specimens received from week 40/2016 to week 5/2017, available antigenic data from the World Health Organization (WHO) European Region indicated that most circulating viruses that could be analysed were considered as antigenically similar to the 2016/17 vaccine component [10]. Consequently, European data supported the WHO recommendation to maintain the same vaccine component A/Hong Kong/4801/2014 (clade 3C.2a) for influenza A(H3N2) in the 2017/18 season vaccine for the northern hemisphere [11]. However, one third of viruses isolated during the above-mentioned period could not be assigned to an antigenic reporting category, reflecting technical challenges or antigenic changes in circulating viruses. Genetic data from Europe centralised at the ECDC suggested that circulating A(H3N2) viruses had undergone considerable genetic diversification during the above-mentioned period, with the emergence of subclusters within clade 3C.2a and subclade 3C.2a1 [10].

In September 2017, WHO updated the A(H3N2) component to A/Singapore/INFIMH-16-0019/2016 (subclade 3C.2a1) in the 2018 seasonal vaccine for the southern hemisphere [12]. The latest WHO update on 2 October 2017, reported that influenza A(H3N2) viruses were still predominating worldwide in September 2017. Further genetic information was not provided at this stage [13]. Our results taking patients unvaccinated in both 2015/16 and 2016/17 seasons as a reference suggested that influenza vaccination in 2015/16 and/or 2016/17 reduced the risk of influenza-associated hospitalisation among vaccinated patients. Our stratified results suggested that 2015/16 vaccination modified the 2016/17 IVE. Although too imprecise to be conclusive, our results could suggest that patients vaccinated in both seasons benefited from a residual protection from the 2015/16 vaccine, with no additional effect of the 2016/17 vaccine uptake.

Conclusion

Our results suggest a low IVE against hospitalised influenza A(H3N2) among persons aged 65 years and above, particularly among patients aged 80 years and above. They also suggest a modifying effect of 2015/16 influenza vaccination on 2016/17 IVE. The A(H3N2) virus component included in the 2017/18 vaccine will remain the same as in the 2016/17 season. The latest WHO influenza surveillance report suggests that influenza A(H3N2) viruses were predominating worldwide in August 2017. Low IVE may be expected during the 2017/18 season in case of predominant circulation of A(H3N2) viruses. However, IVE against influenza A(H1N1)pdm09 and B are usually reported to be higher. Close monitoring of virological surveillance data will be required to prompt early promotion of complementary measures such as the use of antivirals or non-pharmaceutical interventions.

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Conflict of interest

None declared.

Authors' contributions

Marc Rondy was involved in the original methodological design of the study (generic protocol). He coordinated the European hospital IVE network, undertook the statistical analysis on which the research article is based and led the writing of the research article.

Alain Moren initiated the original methodological design of the study. He coordinated the European hospital IVE network and contributed to the writing of the research article.

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The I-MOVE+ hospital working group contributors contributed to developing the study site specific protocol. They were in charge of supervising the study at the hospital level and collect the data published in this research article. They read, contributed to and approved the final version of the manuscript.

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3.5.2 Early estimation of influenza vaccine effectiveness

We were able to provide early estimates in 2015-16 and 2016-17. In 2015-16, due to late season and issues regarding timely access to some important confounding variables in some study sites, we decided not to make our estimates publicly available but we sent them to our partners.

In 2016-17, the influenza season was characterised by an early start and early indications of high influenza-related hospitalisation rates and excess mortality, especially among elderly. We were able to publish early estimates together with the results from the primary health care based network.

3.5.2.1 2015-16 influenza vaccine effectiveness interim results: I-MOVE + hospital multicentre case-control study (as published on the I-MOVE + restricted website)

We present here the 2015-16 interim results (week 46, 2015 to week 8, 2016). We measured influenza VE against hospitalised laboratory confirmed influenza in the age group 65 years and above. We used a test-negative design as described in the I-MOVE+ generic protocol.

The 2015-16 season started late in the participating countries. Some study sites are still consolidating their data on underlying conditions and access to health care. We present results adjusted by week of onset, and age and for those with information on comorbities, VE further adjusted by the presence of at least two comorbidities. The sample size for this interim analysis was limited resulting in low precision (**Table 11** and **Table 12**). The results should be interpreted with caution. The final estimates will be available at the end of the influenza season.

Table 11: Influenza vaccine effectiveness against hospitalised laboratory confirmed influenza by influenza type/suptype among patients aged 65 years and above. I-MOVE+ multicentre case control study, interim results influenza season 2015-16 (week 46/2015-week 8/2016), all eligible patients included

Influenza type	N	Cases; vaccinated	Controls; vaccinated	VE* adjusted by study site only (CI**)	VE* adjusted by study site and onset time (CI**)	VE* adjusted by study site, onset time and age (CI**)
Any influenza	748	235;96	513;260	44.3 (19.1;61.6)	44.0 (18.2;61.7)	41.2 (13.6;60.0)
Influenza A	727	217;87	510;262	46.6 (21.0;64.0)	45.9 (19.4;63.7)	43.1 (14.6;62.1)
Influenza A(H1N1)pdm09	581	182;73	399;225	52.6 (27.7;69.0)	52.6 (27.0;69.2)	50.5 (23.2;68.1)

* VE: Vaccine effectiveness / ** CI: Confidence Interval

Table 12: Influenza vaccine effectiveness against hospitalised laboratory confirmed influenza by influenza type/suptype among patients aged 65 years and above. I-MOVE+ multicentre case control study, interim results influenza season 2015-16 (week 46/2015-week 8/2016), patients with information about underlying conditions

Influenza type	Patients with information about underlying conditions N	cases; vaccinated	Controls; vaccinated	VE* adjusted by study site, onset time and age (CI**)	VE* adjusted by study site, onset time, age and comorbidities[ŧ](CI**)
Any influenza	627	201;86	426;205	27.5 (-11.1;52.8)	26.1 (-13.5;51.9)
Influenza A	606	187;80	419;204	26.5 (-15.3;53.1)	25.3 (-17.3;52.4)
Influenza A(H1N1)pdm09	463	155;68	308;167	33.0 (-9.5;59.0)	31.3 (-12.6;58.0)

* VE: Vaccine effectiveness /

** CI: Confidence Interval

ŧat least two underlying conditions vs less than two

3.5.2.2 2016-17 influenza vaccine effectiveness interim results: I-MOVE + hospital multicentre case-control study

RAPID COMMUNICATIONS

Early 2016/17 vaccine effectiveness estimates against influenza A(H3N2): I-MOVE multicentre case control studies at primary care and hospital levels in Europe

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We measured early 2016/17 season influenza vaccine effectiveness (IVE) against influenza A(H3N2) in Europe using multicentre case control studies at primary care and hospital levels. IVE at primary care level was 44.1%, 46.9% and 23.4% among 0–14, 15–64 and ≥65 year-olds, and 25.7% in the influenza vaccination target group. At hospital level, IVE was 2.5%, 7.9% and 2.4% among ≥65, 65–79 and ≥80 year-olds. As in previous seasons, we observed suboptimal IVE against influenza A(H3N2).

The 2016/17 influenza season in Europe is marked by the predominant circulation of influenza A(H3N2) viruses [1], with significant pressure on hospitals, mostly due to patients aged 65 years and older developing severe disease [1]. Many European countries have reported excess all-cause mortality [2]. Initial estimates based on Swedish and Finnish electronic databases suggest low influenza vaccine effectiveness (IVE) among older adults [3,4]. We measured early IVE at primary care and hospital levels against laboratory-confirmed influenza A(H3N2) in Europe.

Primary care and hospital-based multicentre case control studies in Europe to measure influenza vaccine effectiveness

We conducted separate multicentre primary care and hospital-based case–control studies and analyses using the test-negative design (TND). We have described the methods in detail previously [5-7].

In the primary care study, comprising 893 practitioners (including general practitioners and paediatricians) in 12 countries, we included a systematic sample of all community-dwelling patients presenting to their practitioner with influenza-like illness (ILI), as defined by the European Union ILI case definition (*sudden onset* of symptoms and at least one of the following systemic symptoms: fever or feverishness, malaise, headache, myalgia, and at least one of the following respiratory symptoms: cough, sore throat, shortness of breath). In the hospital study, comprising 27 hospitals from 11 countries, we included community-dwelling patients aged 65 years and older admitted to hospital for influenza-related clinical conditions with symptoms compatible with severe acute respiratory infection (SARI). Each study site adapted a generic protocol to their local setting [8,9].

At each study site, the study period commenced more than 14 days after the start of the vaccination campaign and lasted from the week of the first influenza case to the date of sending data for the interim analysis at the end of January 2017.

A case of confirmed influenza was an ILI (primary care) or SARI (hospital) patient who was swabbed and tested positive for influenza A(H3N2) virus using real-time RT-PCR. Controls were ILI (primary care) or SARI (hospital) patients who tested negative for any influenza virus using RT-PCR.

We excluded patients with contraindications for influenza vaccination, SARI patients discharged from a previous hospital stay within 48 hours of symptom onset (hospital), those with a previous laboratory-confirmed influenza in the season, those refusing to participate or unable to consent, those who had received antiviral drugs before swabbing (primary care), those swabbed more than 7 days after symptom onset, patients with missing laboratory results and any patients positive to any influenza virus other than influenza A(H3N2).

Practitioners and hospital teams collected clinical and epidemiological information including date of symptom onset and date of swabbing, 2016/17 seasonal

TABLE 1A

Influenza A(H3N2) cases and controls included in the 2016/17 season influenza vaccine effectiveness analysis, I-MOVE/I-MOVE+ multicentre case control studies (primary care (n = 5,023) and hospital (n = 635) levels) Europe, influenza season 2016/17

Variables	Primary care level						Hospital level					
	Number of A(H3N2) n = 2,250			Number of controls n = 2,773			Number of A(H3N2) n = 267			Number of controls n = 368		
	n	Total	%	n	Total	%	n	Total	%	n	Total	%
Median age (years)	29			28			79			80		
Age groups (years)												
0–4	276	2,242	12.3	723	2,766	26.1	NA			NA		
5–14	508	2,242	22.7	336	2,766	12.1	NA			NA		
15–64	1,177	2,242	52.5	1,438	2,766	52.0	NA			NA		
65–79	234	2,242	10.4	214	2,766	7.7	138	267	51.7	185	368	50.3
≥ 80	47	2,242	2.1	55	2,766	2.0	129	267	48.3	183	368	49.7
Missing	8			7			0			0		
Sex												
Female	1,126	2,237	50.3	1,407	2,758	51.0	141	267	52.8	190	368	51.6
Missing	13			15			0			0		
Chronic conditions												
At least one chronic condition	451	2,237	20.2	542	2,743	19.8	237	255	92.9	321	344	93.3
Missing	13			30			12			24		
At least one hospitalisation in the previous 12 months for chronic conditions	26	2,196	1.2	57	2,686	2.1	66	247	26.7	146	334	43.7
Missing	54			87			20			34		
Target group for vaccination												
Belongs to a target group for vaccination	616	2,241	27.5	706	2,755	25.6	267	267	100.0	368	368	100.0
Missing	9			18			0			0		
Swab delay												
Swabbed within 3 days of symptom onset	2,024	2,250	90.0	2,291	2,773	82.6	154	267	57.7	212	368	57.6
Vaccination status												
Seasonal flu vaccination 16–17	231	2,250	10.3	301	2,773	10.9	108	267	40.4	191	368	51.9
Seasonal flu vaccination 15–16	223	2,196	10.2	316	2,665	11.9	117	252	46.4	199	362	55.0
Missing	54			108			15			6		
Previous and current season influenza vaccination												
Not vaccinated in any season	1,929	2,196	87.8	2,284	2,665	85.7	128	252	50.8	147	362	40.6
Current season vaccination only	44	2,196	2.0	65	2,665	2.4	7	252	2.8	16	362	4.4
Previous season vaccination only	43	2,196	2.0	95	2,665	3.6	20	252	7.9	28	362	7.7
Current and previous season vaccination	180	2,196	8.2	221	2,665	8.3	97	252	38.5	171	362	47.2
Missing	54			108			15			6		
Type of vaccine												
Not vaccinated	2019	2,215	91.2	2,472	2,725	90.7	159	261	60.9	177	359	49.3
Inactivated subunit egg	97	2,215	4.4	108	2,725	4.0	65	261	24.9	101	359	28.1
Inactivated split virion egg	71	2,215	3.2	118	2,725	4.3	32	261	12.3	74	359	20.6
Adjuvanted	18	2,215	0.8	21	2,725	0.8	5	261	1.9	7	359	1.9
Quadrivalent vaccine	10	2,215	0.5	6	2,725	0.2	0	261	0.0	0	359	0.0
Missing vaccine type	35			48			6			9		
Month of onset												
October 2016	4	2,250	0.2	84	2,773	3.0	0	267	0.0	0	368	0.0
November 2016	154	2,250	6.8	759	2,773	27.4	3	267	1.1	6	368	1.6
December 2016	1,199	2,250	53.3	1,194	2,773	43.1	174	267	65.2	236	368	64.1
January 2017	893	2,250	39.7	736	2,773	26.5	90	267	33.7	126	368	34.2

NA: Not applicable.

Table 1B

Influenza A(H3N2) cases and controls included in the 2016/17 season influenza vaccine effectiveness analysis, I-MOVE/I-MOVE+ multicentre case control studies (primary care (n = 5,023) and hospital (n = 635) levels) Europe, influenza season 2016/17

Variables	Primary care level						Hospital level					
	Number of A(H3N2) n = 2,250			Number of controls n = 2,773			Number of A(H3N2) n = 267			Number of controls n = 368		
	n	Total	%	n	Total	%	n	Total	%	n	Total	%
Study sites												
Croatia	13	2,250	0.6	13	2,773	0.5	NA			NA		
Finland	NA			NA			14	267	5.2	17	368	4.6
France	584	2,250	26.0	609	2,773	22.0	35	267	13.1	116	368	31.5
Germany	28	2,250	12.8	873	2,773	31.5	NA			NA		
Hungary	39	2,250	1.7	84	2,773	3.0	NA			NA		
Ireland	135	2,250	6.0	113	2,773	4.1	NA			NA		
Italy	411	2,250	18.3	367	2,773	13.2	37	267	13.9	58)	368	15.8
Lithuania	NA			NA			30	267	11.2	18	368	4.9
Navarra	NA			NA			20	267	7.5	34	368	9.2
The Netherlands	47	2,250	2.1	142	2,773	5.1	6	267	2.2	19	368	5.2
Poland	9	2,250	0.4	33	2,773	1.2	NA			NA		
Portugal	156	2,250	6.9	80	2,773	2.9	36	267	13.5	14	368	3.8
Romania	27	2,250	1.2	9	2,773	0.3	60	267	22.5	37	368	10.1
Spain	474	2,250	21.1	303	2,773	10.9	29	267	10.9	55	368	14.9
Sweden	66	2,250	2.9	147	2,773	5.3	NA			NA		

NA: Not applicable.

vaccination status, date of vaccination and vaccine product administered, 2015/16 seasonal vaccination status, sex, age, presence of chronic conditions, whether the patient belonged to a target group for influenza vaccination (primary care) and number of hospitalisations for chronic conditions in the past 12 months.

We defined individuals as vaccinated if they had received at least one dose of the 2016/17 influenza vaccine at least 15 days before ILI/SARI symptom onset. We excluded individuals vaccinated less than 15 days before symptom onset and individuals with unknown vaccination date.

At primary care level, nine study sites (France, Germany, Hungary, Ireland, the Netherlands, Portugal, Romania, Spain and Sweden) participated in a substudy using an in-depth laboratory protocol, and randomly selected positive influenza A(H3N2) specimens for genetic sequencing.

We pooled individual patient data in each study and computed the pooled IVE as ((1–OR of vaccination between cases and controls) × 100) using logistic regression with study site as a fixed effect. We conducted a complete case analysis excluding patients with missing values for any of the variables in the model. All IVE estimates were adjusted for study site, calendar time of onset and age (where sample size allowed). Further potential confounding factors included sex, underlying chronic conditions and hospitalisations in the past year.

We stratified IVE by age group. We measured IVE among the target groups for influenza vaccination at primary care level, defined as older adults (aged over 54, 59 or 64 years depending on study site), individuals with chronic conditions and other groups for whom the vaccine was recommended in a given country (e.g. pregnant women, healthcare workers and other professional groups, depending on the study site).

Influenza vaccine effectiveness in primary care

In the primary care analysis, we included 2,250 cases of influenza A(H3N2) and 2,773 negative controls.

The 2016/17 seasonal influenza vaccine coverage was 10.3% among influenza A(H3N2) cases and 10.9% among controls. Compared with cases, a greater proportion of controls belonged to the age group of 0–4-year-olds (26.1% vs 12.3%) and a lower proportion belonged to the age group of 5–14-year-olds (12.1% vs 22.7%) (Table 1).

Nine study sites sequenced 204 randomly selected specimens out of 1,817 (11.2%) (Table 2). Of these, 156 (76.5%) belonged to the 3C.2a1 clade A/Bolzano/7/2016, 46 (22.5%) to A/Hong Kong/4801/2014 (3C.2a) and two (1.0%) to A/Switzerland/9715293/2013 (3C.3a).

Table 2

Influenza A(H3N2) viruses characterised by clade, amino acid substitutions and study site, at nine participating laboratories, I-MOVE/I-MOVE+ primary care multicentre case control study, Europe, influenza season 2016/17 (n = 1,817)

Characterised viruses (clade)	Germany n = 289		France n = 584		Hungary n = 39		Ireland n = 135		The Netherlands n = 47		Portugal n = 156		Romania n = 27		Spain n = 474		Sweden n = 66		Total n = 1,817	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
A/HongKong/4801/2014 (3C.2a)	10		6		3		0		8		8		4		3		4		46	
N121K + S144K	3	30	6	100	3	100	0		1	12	8	100	4	100	3	100	3	75	31	67
A/Bolzano/7/2016 (3C.2a1)	33		19		3		5		20		23		8		36		9		156	
N171K + N121K + I140M	10	30	0		0		0		7	35	2	9	4	50	8	22	3	33	34	22
N171K + N121K + T135K	2	6	0		2	67	0		3	15	0		0		1	3	3	33	11	7
N171K + N121K + K92R + H311Q	8	24	0		1	33	1	20	4	20	4	17	0		10	28	0		28	18
N171K + R142G	7	21	3	16	0		3	60	3	15	17	74	0		1	3	1	11	35	22
A/Switzerland/9715293/2013 (3C.3a)	0		0		0		2		0		0		0		0		0		2	
Total sequenced/total A(H3N2)	**43**	**15**	**25**	**4**	**6**	**15**	**7**	**5**	**28**	**60**	**31**	**20**	**12**	**44**	**39**	**8**	**13**	**20**	**204**	**11**

Table 3

Pooled adjusted seasonal vaccine effectiveness against laboratory-confirmed influenza A(H3N2) by age group and target group for vaccination, I-MOVE/I-MOVE+ multicentre case control studies (primary care (n = 4,937) and hospital (n = 635)), influenza season 2016/17

Analyses	Adjustment / stratification	Cases			Controls			Adjusted VE	95% CI
		All	Vaccinated	%	All	Vaccinated	%		
Primary care									
All ages	Adjusted by study site only	2,216	229	10	2,721	297	11	10.9	−8.3 to 26.6
	Adjusted by calendar time and study site	2,216	229	10	2,721	297	11	27.9	11.9 to 41.1
	Adjusted by calendar time, age and study site	2,216	229	10	2,721	297	11	38.4	22.2 to 51.3
	Fully adjusted: calendar time, age, study site, presence of chronic conditions, sex	2,216	229	10	2,721	297	11	38.0	21.3 to 51.2
By age group (years)[a]	0–14	773	20	3	1,043	27	3	44.1	−12.3 to 72.2
	15–64	1,164	69	6	1,410	126	9	46.9	25.2 to 62.3
	≥ 65	278	140	50	268	144	54	23.4	−15.4 to 49.1
Target group for vaccination[a]	All ages	606	201	33	698	235	34	25.7	1.5 to 43.9
Hospital									
≥ 65 years	Adjusted by study site only	267	108	40	368	191	52	−0.7	−46.8 to 30.9
	Adjusted by calendar time and study site	267	108	40	368	191	52	3	−42.2 to 33.8
	Adjusted by calendar time, age and study site	267	108	40	368	191	52	2.5	−43.6 to 33.8
	Fully adjusted: time, age, study site, sex, chronic condition (lung, heart, renal disease, diabetes, cancer, obesity) and hospitalisation in the past year	240	95	40	316	162	51	2.0	−51.7 to 36.8
By age group (years)[b]	65–79	130	38	29	165	70	42	7.9	−67.3 to 49.3
	≥80	115	59	51	167	102	61	2.4	−81.3 to 47.5

CI: confidence interval; VE: vaccine effectiveness at hospital level.

[a] Adjusted by study site, age, calendar time, presence of chronic conditions and sex.

[b] Adjusted by calendar time, age and study site.

Among the 156 viruses of the 3C.2a1 clade, further genetic groups have emerged in 108 (69.2%) (Table 2). These include 34 viruses in group 1 (22%), harbouring the I140M substitution located in the antigenic site A of the haemagglutinin, in addition to changes in amino acid positions 171 and 121, both located in the antigenic site D. Eleven viruses belonged to group 2 (7%), carrying the T135K mutation located in the antigenic site A and resulting in the loss of a glycosylation site, in addition to the already mentioned changes in positions 171 and 121. Twenty-eight viruses belonged to genetic group 3 (18%), carrying the K92R and H311Q substitutions located in the antigenic sites E and C, respectively, in addition to changes in positions 171 and 121. Finally, 35 viruses belonged to group 4 (22%), carrying the R142G mutation located in the antigenic site A and the N171K substitution. Thirty-one viruses (67%) belonging to the 3C.2a clade (A/HongKong/4801/2014) carried the substitutions N121K and S144K, the latter located in the antigenic site position A.

Adjusted IVE against influenza A(H3N2) across all age groups was 38.0% (95% CI: 21.3 to 51.2). It was 44.1% (95% CI: −12.3 to 72.2), 46.9% (95% CI: 25.2 to 62.3) and 23.4% (95% CI: −15.4 to 49.1) in 0–14, 15–64 and ≥ 65 year-olds, respectively. The IVE in the target group for vaccination was 25.7% (95% CI: 1.5 to 43.9) (Table 3).

Influenza vaccine effectiveness at hospital level

In the hospital study, we included 267 cases of influenza A(H3N2) and 368 negative controls.

The 2016/17 seasonal influenza vaccine coverage was 40.4% among influenza A(H3N2) cases and 51.9% among controls. A higher proportion of controls were vaccinated with inactivated split-virion vaccine group (20.6% vs 12.3%). A higher proportion of controls had been hospitalised for chronic conditions in the past twelve months (43.7% vs 26.7%) (Table 1).

Adjusted IVE against influenza A(H3N2) among those aged 65 years and older was 2.5% (95% CI: −43.6 to 33.8), it was 7.9% (95% CI: −67.3 to 49.3) among those aged 65 to 79 years and 2.4% (95% CI: −81.3 to 47.5) among those aged 80 years and older (Table 3).

Discussion

In primary care, early estimates suggest moderate IVE against influenza A(H3N2) among 0–64-year-olds and low IVE in the target group for influenza vaccination. Among those aged 65 years and older, IVE was low at both primary care and hospital level, however precision was low.

Viruses of the 3C.2a1 clade (A/Bolzano/7/2016) predominated in the study sites participating in the laboratory protocol. Compared to the vaccine virus A/HongKong/4801/2014, they had the N171K substitution and in addition, most of them had the N121K substitution. This clade appears to be antigenically similar to the A(H3N2) vaccine component. However, our sequencing results suggest that this cluster is continuing to evolve: 70% of sequenced viruses had further mutations, forming clusters defined by new HA1 amino acid substitutions in antigenic sites, including antigenic site A. We did not measure IVE against A/Bolzano/7/2016 viruses, as estimates were not robust because of the small sample size.

The 2016/17 early primary care IVE estimate among all ages was 38% (95% CI: 21.3 to 51.2), similar to the early estimates from the Canadian Sentinel Practitioner Surveillance [10] and comparable to early estimates against influenza A(H3N2) in previous seasons: 43% (95% CI: -0.4 to 67.7) in 2011/12 and 41.9% (95% CI: −67.1 to 79.8) in 2012/13 [11,12]. This season, we reached better precision thanks to a larger sample size. The IVE estimates among those aged 65 years and older and target groups for vaccination were low and, despite low precision, reinforce the risk assessment from the European Centre for Disease Prevention and Control (ECDC), which suggests to consider administering antiviral drugs to populations vulnerable to severe influenza irrespective of vaccination status, in line with national and international recommendations [1].

These early results are included in the Global Influenza Vaccine Effectiveness (GIVE) report to contribute to the World Health Organization consultation and information meeting on the composition of influenza virus vaccines for use in the 2017/18 northern hemisphere influenza season [13].

Conclusion

The early season estimates presented here corroborate the suboptimal performance of inactivated influenza vaccine against influenza A(H3N2) that the I-MOVE team and others have reported in the previous post-2009 pandemic seasons [14,15].

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Conflict of interest

None declared.

Authors' contributions

Esther Kissling: coordination I-MOVE/I-MOVE+ primary care network, study design, analysis of primary care data, interpretation of results, manuscript writing

Marc Rondy: coordination I-MOVE+ hospital network, study design, analysis of hospital data, interpretation of results, manuscript writing

Both authors contributed equally to the study and manuscript.

I-MOVE/I-MOVE+ study team:

Primary care and hospital sites at national/regional level: data collection, data validation, results interpretation, review of manuscript. Laboratories: virological analysis, genetic characterisation, interpretation of results.

Francisco Pozo: coordinated the I-MOVE/I-MOVE+ virological analysis of the primary care study.

Alain Moren, Marta Valenciano: study design, coordination of I-MOVE/I-MOVE+ network, interpretation of results, contribution to manuscript writing.

Kari Johansen, Pasi Penttinen: study design, interpretation of results, review of manuscript.

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3.5.3 Vaccine effectiveness by previous vaccination status

Using data collected as part of the InNHOVE and I-MOVE+ networks, we measured the effect of the two previous seasons' vaccination on current season IVE. To do so, we compared IVE measured in the current season between individuals who were vaccinated in the past season and those who were not vaccinated in the past season.

Using patients unvaccinated in current and the two previous seasons as the reference, we also conducted an indicator analysis. We computed the effectiveness of being vaccinated in current season only, in previous season but not current (regardless of penultimate season vaccine status), and in current and both previous seasons for each season and overall.

Our results suggest that, regardless of patients' recent vaccination history, current seasonal vaccine conferred protection to vaccinated patients against hospitalised influenza A(H3N2) and B in all instances. They also suggest that current seasonal vaccine was effective against A(H1N1)pdm09 among patients not previously vaccinated but ineffective among patients vaccinated in both the previous two seasons. Taking as a reference patients unvaccinated in the past two and the current season, the highest IVE point estimate was systematically observed among patients vaccinated all three seasons.

The detailed methods and results are presented in the next below published in *Vaccine*.

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Repeated seasonal influenza vaccination among elderly in Europe: Effects on laboratory confirmed hospitalised influenza

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ABSTRACT

In Europe, annual influenza vaccination is recommended to elderly. From 2011 to 2014 and in 2015–16, we conducted a multicentre test negative case control study in hospitals of 11 European countries to measure influenza vaccine effectiveness (IVE) against laboratory confirmed hospitalised influenza among people aged ≥65 years. We pooled four seasons data to measure IVE by past exposures to influenza vaccination.

We swabbed patients admitted for clinical conditions related to influenza with onset of severe acute respiratory infection ≤7 days before admission. Cases were patients RT-PCR positive for influenza virus and controls those negative for any influenza virus. We documented seasonal vaccination status for the current season and the two previous seasons.

We recruited 5295 patients over the four seasons, including 465A(H1N1)pdm09, 642A(H3N2), 278 B case-patients and 3910 controls. Among patients unvaccinated in both previous two seasons, current seasonal IVE (pooled across seasons) was 30% (95%CI: −35 to 64), 8% (95%CI: −94 to 56) and 33% (95%CI: −43 to 68) against influenza A(H1N1)pdm09, A(H3N2) and B respectively. Among patients vaccinated in both previous seasons, current seasonal IVE (pooled across seasons) was −1% (95%CI: −80 to 43), 37% (95%CI: 7–57) and 43% (95%CI: 1–68) against influenza A(H1N1)pdm09, A(H3N2) and B respectively.

Our results suggest that, regardless of patients' recent vaccination history, current seasonal vaccine conferred some protection to vaccinated patients against hospitalisation with influenza A(H3N2) and B. Vaccination of patients already vaccinated in both the past two seasons did not seem to be effective against A(H1N1)pdm09. To better understand the effect of repeated vaccination, engaging in large cohort studies documenting exposures to vaccine and natural infection is needed.

1. Background

The World Health Organization (WHO) strategy for seasonal influenza vaccination aims at reducing death and hospitalisation among individuals at risk of severe influenza [1]. In Europe, annual vaccination is recommended to individuals with specific underlying conditions and elderly [2]. Despite WHO recommendation to reach 75% coverage in elderly by 2010, uptake among Europeans aged 65 years and above was below 50% in 2014 [3]. Results of recent studies question the effect of repeated influenza vaccinations on influenza vaccine effectiveness (IVE) [4–7].

Immunologists suggest that past natural influenza infections may enhance immune response to new variant influenza viruses [8] and that genetic distances between consecutive vaccine components and circulating strains may affect IVE [6]. Previous seasons' vaccination may provide some residual protection but may also modify current seasonal IVE [4,5,9]. The few epidemiological studies describing the effect of repeated vaccinations, have mainly focused on primary care based studies with non-severe outcomes [4,5,9,10]. Further understanding the role of repeated vaccinations on seasonal IVE in elderly is important to better interpret current seasonal IVE, guide new vaccine development and, eventually, inform vaccination strategies [11].

We have set up two European networks of hospitals (InNHOVE 2011–14 & I-MOVE plus since 2015) allowing to measure seasonal IVE against laboratory confirmed hospitalised influenza among elderly [12–14]. The same generic protocol was used across seasons [15,16].

We pooled four seasons data to measure, among patients aged 65 years and above, the IVE against hospitalisations associated with influenza A(H3N2), A(H1N1)pdm09 and B infections according to past exposures to influenza vaccination.

2. Methods

We conducted a multicentre hospital-based case-control study using the test-negative design (TND) [17]. We included between three and twelve study sites per season in the analysis.

The study population consisted of all community-dwelling individuals aged 65 years and above admitted as inpatients with influenza related illness, and who had no contra-indication for influenza vaccination or previous laboratory confirmed influenza in the season.

We defined specific study periods for each influenza season, study site and influenza (sub)type as lasting from the week of the first to the week of the last laboratory confirmed case of a given (sub)type of influenza.

We included hospitalised patients who had in the past seven days at least one systemic (fever or feverishness, malaise, headache, myalgia) and at least one respiratory symptoms (cough, sore throat or shortness of breath).

In the participating services of each hospital, patients admitted for clinical conditions that could be related to influenza were screened for eligibility. The study teams swabbed patients meeting the inclusion criteria. Specimens were tested by RT-PCR and patients classified as influenza A(H1N1)pdm09, A(H3N2), B cases or controls if their specimens tested negative for all influenza viruses.

We documented seasonal vaccination status for the current season (defined as the season when the patients were included in the study and therefore tested positive or negative for influenza) and the two previous seasons. We defined patients as vaccinated if they had been vaccinated at least 14 days before symptoms onset. Otherwise, they were considered as unvaccinated.

Hospital study teams collected patients' demographic characteristics, date of current seasonal vaccination, underlying conditions (diabetes mellitus, obesity, cardiovascular, lung diseases, and cancer), number of hospitalisations for underlying diseases in the past 12 months and smoking status. Underlying conditions were collected through interviews with patients (or their relatives) and hospital and/or primary care databases. In Finland, Spain (including Valencia and Navarra) and Portugal, vaccination status was retrieved from vaccination registers. In study sites with no vaccination register, study teams collected vaccination status for current and past seasons through patients' interview. For patients vaccinated or unable to provide their vaccination status, study teams

Table 1
List of vaccine recommended components and predominant circulating strains in Europe (2011–14, 2015–16)

Season	Vaccine strains		Main Circulating strain
	Penultimate season	Previous season	Current season	
Season 11–12	A/Brisbane/59/2007 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/Perth/16/2009(H3N2)-like
	A/Brisbane/10/2007 (H3N2)-like	A/Perth/16/2009(H3N2)-like	A/Perth/16/2009(H3N2)-like	
	B/Brisbane/60/2008-like (Victoria lineage)	B/Brisbane/60/2008-like (Victoria lineage)	B/Brisbane/60/2008-like (Victoria lineage)	
Season 12–13	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like
	A/Perth/16/2009(H3N2)-like	A/Perth/16/2009(H3N2)-like	A/Victoria/361/2011(H3N2)-like MUTATION IN EGG_ADAPTED	A/Victoria/361/2011(H3N2)
	B/Brisbane/60/2008-like (Victoria)	B/Brisbane/60/2008-like (Victoria)	B/Wisconsin/61/2010-like (Yamagata)	B/Massachusetts/2/2012-like (Yamagata)
Season 13–14	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like
	A/Perth/16/2009(H3N2)-like	A/Victoria/361/2011(H3N2)-like MUTATION IN EGG_ADAPTED	A/Texas/50/2012(H3N2)-like	A/Texas/50/2012(H3N2)-like
	B/Brisbane/60/2008-like (Victoria lineage)	B/Wisconsin/61/2010-like (Yamagata)	B/Massachusetts/2/2012-like (Yamagata)	
Season 15–16	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like	A/California/7/2009 (H1N1)-like
	A/Texas/50/2012(H3N2)-like	A/Texas/50/2012(H3N2)-like	A/Switzerland/9715293/2013 (H3N2)-like	
	B/Massachusetts/2/2012-like (Yamagata)	B/Massachusetts/2/2012-like (Yamagata)	B/Phuket/3073/2013-like (Yamagata)	B/Brisbane/60/2008-like (Victoria)

Sources: http://www.who.int/influenza/vaccines/virus/recommendations/2016_17_north/en/; http://ecdc.europa.eu/en/publications/surveillance_reports/influenza/Pages/influenza_virus_characterisation.aspx.

called patients' GP or pharmacists or searched for vaccination passes to retrieve vaccination status and date of uptake.

For each season, we pooled data from participating hospitals. Using the odds ratio (OR) of being vaccinated between cases and controls we computed the VE as (1 − OR) x 100%. We performed a logistic regression to adjust IVE estimates for potential confounders. We used the one in ten rule of predictor degrees of freedom to events to determine the number covariates to include in analyses with low sample sizes in order to avoid overfitting the model [18,19]. We used a one-stage method with study site as a fixed effect. Due to low sample and inherent risks for overfitting, and based on previously published data [12–14], we apriori decided on adjustment variables. When sample size allowed, we further adjusted IVE estimates for month of symptoms onset, age (modelled as a restricted cubic spline with four knots) and presence of chronic conditions. We pooled data from seasons with circulation of the same (sub)type specific influenza and computed pooled IVE further adjusting on the season.

In a stratified analysis based on the data pooled across seasons and using unvaccinated in the current season as a reference, we compared VE measured in the current season between individuals who were vaccinated in the past season and those who were not vaccinated in the past season. Due to low sample size, we excluded patients vaccinated in only one of the two previous seasons from this analysis.

Using patients unvaccinated in current and the two previous seasons as the reference, we conducted an indicator analysis. We computed the effectiveness of being vaccinated in current season only, in previous season but not current (regardless of penultimate season vaccine status), and in current and both previous seasons for each season and overall. Due to low sample size, we excluded patients vaccinated in the penultimate season only, those vaccinated in the penultimate and current seasons only and those vaccinated in the previous and current seasons only.

We conducted sensitivity analyses restricted to patients for whom the vaccination status ascertainment was based on vaccination registers.

3. Results

We included 21 hospitals in 2011–12, 18 in 2012–13, 12 in 2013–14 and 25 in 2015–16. The 5295 patients recruited over the four seasons included 465A(H1N1)pdm09, 642A(H3N2), 278 B case-patients and 3910 controls (Table 2) for whom current vaccination status was available. Previous vaccination information was missing for 116 (8.2%) cases and 255 (6.5%) controls.

We included seasons 2012–13, 2013–14 and 2015–16 for A (H1N1)pdm09 analyses, seasons 2011–12, 2012–13 and 2013–14 for A(H3N2) and seasons 2012–13 and 2015–16 for influenza B analyses (Table 1).

3.1. Influenza A(H1N1)pdm09

Vaccine and circulating A(H1N1)pdm09 viruses remained stable across the study period (Table 1).

The median age was 76 years among A(H1N1)pdm09 cases and 79 years among controls ($p < 0.01$). A higher proportion of controls than cases had respiratory chronic conditions (47% vs 40%, $p < 0.01$) and were obese (21% vs 13%, $p < 0.01$). A higher proportion of A (H1N1)pdm09 cases than controls had cancer (25% vs 18%, $p < 0.01$) (Table 2).

Season specific IVE against A(H1N1)pdm09 virus ranged between 15% (95%CI: −51 to 52) in 2012–13 and 41% (95%CI: 20–57) in 2015–16. Pooled across 2012–13, 2013–14 and 2015–16, IVE against A(H1N1)pdm09 virus was 38% (95%CI: 21–51) (Table 3).

Table 2
Characteristics for influenza A(H1N1)pdm09, A(H3N2) and influenza B, and controls included in the study, InNHOVE 2011–14 and I-MOVE + 2015–16.

	A(H1N1)pdm09					A(H3N2)					B				
	Cases		Controls			Cases		Controls			Cases		Controls		
	(N = 465)	%	(N = 2462)	%	p-value	(N = 642)	%	(N = 1798)	%	p-value	(N = 278)	%	(N = 1996)	%	p-value
Median age	75.6		79.0		0.000	80.0		79.7		0.550	77.0		79.0		0.025
Sex = Male	0,557484	55.7	1353/2461	55.0	0.799	348/642	54.2	991/1798	55.1	0.712	136/278	48.9	1074/1995	53.8	0.140
Vaccine status															
Current season influenza vaccination	196/465	42.2	1493/2462	60.6	0.000	385/642	60.0	1186/1798	66.0	0.007	130/278	46.8	1216/1996	60.9	0.000
Previous two and current season vaccination															
None	200/423	47.3	669/2346	28.5	0.000	121/591	20.5	300/1671	18.0	0.332	95/255	37.3	556/1922	28.9	0.000
Current season only	15/423	3.5	95/2346	4.0		12/591	2.0	38/1671	2.3		9/255	3.5	78/1922	4.1	
Current and previous seasons	12/423	2.8	101/2346	4.3		36/591	6.1	92/1671	5.5		8/255	3.1	69/1922	3.6	
Current and penultimate seasons	8/423	1.9	80/2346	3.4		12/591	2.0	41/1671	2.5		1/255	0.4	63/1922	3.3	
All three seasons	153/423	36.2	1170/2346	49.9		321/591	54.3	1004/1671	60.1		111/255	43.5	970/1922	50.5	
Penultimate and previous seasons	18/423	4.3	135/2346	5.8		52/591	8.8	112/1671	6.7		20/255	7.8	110/1922	5.7	
Previous season only	8/423	1.9	32/2346	1.4		17/591	2.9	37/1671	2.2		2/255	0.8	28/1922	1.5	
Penultimate season only	9/423	2.1	64/2346	2.7		20/591	3.4	47/1671	2.8		9/255	3.5	48/1922	2.5	
Unknown vaccination status	*42*		*116*			*51*		*127*			*23*		*74*		
Presence of comorbidities															
Diabetes	135/455	29.7	759/2431	31.2	0.544	211/637	33.1	578/1786	32.4	0.730	75/257	29.2	595/1963	30.3	0.773
Cardiac disease	266/461	57.7	1422/2451	58.0	0.918	322/640	50.3	966/1795	53.8	0.128	148/275	53.8	1174/1987	59.1	0.103
Respiratory diseases	185/461	40.1	1152/2448	47.1	0.007	294/641	45.9	844/1795	47.0	0.645	104/276	37.7	971/1977	49.1	0.000
Cancer	114/460	24.8	437/2449	17.8	0.001	116/289	40.1	327/1071	30.5	0.002	30/273	11.0	362/1982	18.3	0.003
Obesity	59/458	12.9	511/2421	21.1	0.000	134/638	21.0	442/1783	24.8	0.058	49/272	18.0	401/1962	20.4	0.376
Any chronic disease	425/460	92.4	2279/2462	92.6	0.923	549/642	85.5	1605/1797	89.3	0.012	237/278	85.3	1861/1996	93.2	0.000
More than one chronic condition	313/457	68.5	1741/2451	71.0	0.288	370/642	57.6	1148/1798	63.8	0.006	158/276	57.2	1417/1988	71.3	0.000
Hospitalisations in previous 12 months	196/455	43.1	1044/2446	42.7	0.877	206/640	32.2	691/1797	38.5	0.005	89/276	32.2	857/1969	43.5	0.000
Current smoking	108/449	24.1	357/2386	15.0	0.000	81/640	12.7	193/1793	10.8	0.191	49/270	18.1	319/1910	16.7	0.544
Antivirals treatment prior to swabbing	42/463	9.1	45/2457	1.8	0.000	9/631	1.4	16/1782	0.9	0.452	19/275	6.9	36/1993	1.8	0.000
Delays symptoms onset – swabbing < 4 days	272/465	58.5	1298/2462	52.7	0.023	258/642	40.2	805/1798	44.8	0.046	127/278	45.7	1079/1996	54.1	0.010

Table 3
Adjusted vaccine effectiveness against influenza A(H1N1)pdm09, A(H3N2) and B by season, among patients aged 65 years and older, InNHOVE 2011–14 and I-MOVE + 2015–16.*

Influenza type/subtype	Season	Number of hospitals	N	Cases	Vaccinated cases	Controls	Vaccinated controls	IVE	95%CI
A(H1N1)pdm09	**Pooled**[a]		**2927**	**465**	**196**	**2462**	**1493**	**37.6**	**(20.6 to 50.9)**
	12–13[b]	18	1230	56	30	1174	755	15.1	(-51.2 to 52.3)
	13–14[c]	12	382	56	28	326	204	34.1	(-22.2 to 64.5)
	15–16[d]	25	1315	353	138	962	534	41.2	(20.3 to 56.7)
A(H3N2)	**Pooled**[e]		**2440**	**642**	**385**	**1798**	**1186**	**28.9**	**(13.2 to 41.7)**
	11–12[f]	21	1438	473	301	965	654	13.6	(-11.9 to 33.3)
	12–13[g]	18	417	44	17	373	252	62.5	(23.1 to 81.7)
	13–14[h]	12	585	125	67	460	280	40.3	(7.9 to 61.3)
B	**Pooled**[i]		**2274**	**278**	**130**	**1996**	**1216**	**44.3**	**(26.2 to 58.0)**
	12–13[j]	18	1165	172	81	993	636	38.0	(11.1 to 56.8)
	15–16[k]	25	1109	106	49	1003	580	50.5	(21.3 to 68.9)

List of study sites included in the analysis:
[a] ES FI FR HR IT LT NA NL PL PT RO VA.
[b] FR IT LT NA VA.
[c] FR NA.
[d] ES FI FR HR IT LT NA NL PL PT RO.
[e] FR IT LT NA VA.
[f] FR IT NA VA.
[g] FR IT LT NA VA.
[h] FR IT NA.
[i] ES FI FR HR HU IT LT NA NL PL PT RO VA.
[j] FR IT LT NA VA.
[k] ES FI FR HR HU IT LT NA NL PL PT RO.
* Adjusted for study site, date of onset, age, presence of at least one chronic condition and season.

Table 4
Influenza vaccine effectiveness for current season stratified by two previous seasons vaccination status by influenza (sub)type and season, InNHOVE, 2011–14 and I-MOVE + 2015–16.*

Type subtype	Seasons included	Among those not vaccinated in either of the two previous seasons				Among those vaccinated in both previous two seasons			
		Cases (vaccinated)	Controls (vaccinated)	VE	95%CI	Cases (vaccinated)	Controls (vaccinated)	VE	95%CI
A(H1N1)pdm09[1]	2012–13, 2013–14 and 2015–16	212 (14)	764 (95)	30	(−35 to 64)	171 (153)	1305 (1170)	−1	(−80 to 43)
A(H3N2)[2]	2011–12, 2012–13 and 2013–14	133 (12)	338 (38)	8	(−94 to 56)	373 (321)	1116 (1004)	37	(7 to 57)
B[3]	2012–13 and 2015–16	104 (9)	634 (78)	33	(−43 to 68)	131 (111)	1080 (970)	43	(1 to 68)

* Adjusted for study site, month of onset, age, presence of chronic conditions and season.
[1] Missing vaccination status for 42 influenza A(H1N1)pdm09 cases and 116 controls. Missing information on chronic conditions for 3 influenza A(H1N1)pdm09 cases.
[2] Missing vaccination status for 51 influenza A(H3N2) cases and 127 controls. Missing information on chronic conditions for 1 control.
[3] Missing vaccination status for 23 influenza B cases and 74 controls.

In the stratified analysis, current season IVE (pooled across seasons) was 30% (95%CI: −35 to 64) among those not vaccinated in either of the two previous seasons and −1% (95%CI: −80 to 43) among those vaccinated in both previous two seasons (Table 4).

In the indicator analysis, using patients never vaccinated in the three seasons as the reference, pooled season IVE when vaccinated in the three seasons was 39% (95%CI: 19–54). Among those unvaccinated in the current season but vaccinated in the previous season, IVE was 30% (95%CI: −8 to 55) (Table 5).

3.2. Influenza A(H3N2)

Vaccine components, as recommended by WHO, were antigenically similar to circulating strains in all A(H3N2) seasons included in this analysis (table 1). In 2012–13, mutations in the egg-adapted A(H3N2) vaccine strain led to a vaccine strain antigenically distinct from the circulating one [20].

A(H3N2) case-patients had the same median age (80 years, p = 0.55) and sex ratio (p = 0.71) as their respective controls. A total of 85% of cases and 89% of controls had at least one underlying condition (p = 0.01) and 32% of cases and 38% of controls (p < 0.01) had been hospitalised for chronic conditions in the past 12 months (Table 2).

Season specific IVE against A(H3N2) virus ranged between 14% (95%CI: −12 to 33) in 2011–12 and 63% (95%CI: 23–82) in 2012–13. Pooled across 2011–12, 2012–13 and 2013–14, IVE against A (H3N2) virus was 29% (95%CI: 13–42) (Table 3).

In the stratified analysis, current season IVE (pooled across seasons) was 8% (95%CI: −94 to 56) among those not vaccinated in either of the two previous seasons and 37% (95%CI: 7–57) among those vaccinated in both previous two seasons (Table 4).

In the indicator analysis, using patients never vaccinated in the three seasons as the reference, pooled season IVE when vaccinated in the three seasons was 39% (95%CI: 19–53). Among those unvaccinated in the current season but vaccinated in the previous season, IVE was 14% (95%CI: −23 to 40) overall. It was 25% (95%CI: −22 to 53) in 2011–12 and 9% (95%CI: −80 to 54) in 2013–14 (Table 5).

3.3. Influenza B

In 2012–13, vaccine and circulating lineages were Yamagata while vaccines contained Victoria in the two previous seasons. In 2015–16, the current and two previous seasonal vaccines contained a Yamagata component while the main circulating viruses were Victoria (Table 1).

Table 5
Previous, current and combined seasonal influenza vaccine effectiveness (VE) by influenza (sub)type and season, InNHOVE 2011–14 and I-MOVE + 2015–16.[*]

Season	Vaccine uptake in the current and past two seasons	Influenza A(H1N1)pdm09				Influenza A(H3N2)				Influenza B			
		Cases	Controls	IVE	95% CI	Cases	Controls	IVE	95% CI	Cases	Controls	IVE	95% CI
Season 11–12	None					68	96	Reference					
	Current only					6	10	21	(−162 to 76)				
	Previous season and not current					64	113	25	(−22 to 53)				
	All					255	559	37	(7 to 57)				
Season 12–13	None	18	291	Reference		15	82	Ref		52	257	Reference	
	Current only	4	57	−30[*]	(−304 to 58)	1	14	NA		4	44	43	(−72 to 81)
	Previous season and not current	6	121	23[*]	(−100 to 71)	5	31	NA		22	92	−31	(−137 to 28)
	All	24	591	34[*]	(−24 to 65)	14	207	NA		69	504	27	(−12 to 52)
Season 13–14	None	19	83	Reference		38	122	Reference					
	Current only	0	8	NA		5	14	−20	(−284 to 63)				
	Previous season and not current	8	36	12[*]	(−123 to 65)	20	52	9	(−80 to 54)				
	All	23	170	45[*]	(−8 to 72)	52	238	48	(12 to 69)				
Season 15–16	None	161	295	Reference						43	299	Reference	
	Current only	10	30	38	(−40 to 72)					5	34	−12	(−227 to 61)
	Previous season and not current	21	74	44	(−1 to 68)					9	94	23	(−76 to 66)
	All	106	409	45	(20 to 62)					42	466	50	(16 to 71)
Overall	None	198	669	Reference		121	300	Reference		95	556	Reference	
	Current only	14	95	30	(−33 to 63)	12	38	15	(−78 to 60)	9	78	29	(−49 to 67)
	Previous season and not current	35	231	30	(−8 to 55)	89	196	14	(−23 to 40)	31	186	−4	(−66 to 35)
	All	153	1170	39	(19 to 54)	321	1004	39	(19 to 53)	111	970	37	(12 to 54)

NA: not applicable (sample size too small to adjust IVE on study site).
[*] Adjusted for study site, month of onset, age, presence of chronic conditions and season unless otherwise specified.
[*] Adjusted for study site.

The median age was 77 years for Influenza B cases and 79 years for controls (p = 0.02). A higher proportion of controls than cases had respiratory chronic conditions (49% vs 38%, p < 0.01), cancer (18% vs 11%, p < 0.01) and were hospitalised for chronic conditions in the past twelve months (44% vs 32%, p < 0.01) (Table 2).

Season specific IVE against influenza B virus was 38% (95%CI: 11–57) in 2012–13 and 51% (95%CI: 21–69) in 2015–16. Pooled across 2012–13 and 2015–16, IVE against B virus was 44% (95% CI: 26–58) (table 3).

In the stratified analysis, current season IVE (pooled across seasons) was 33% (95%CI: −43 to 68) among those not vaccinated in either of the two previous seasons and 43% (95%CI: 1–68) among those vaccinated in both previous two seasons (Table 4).

In the indicator analysis, using patients never vaccinated in the three seasons as the reference, pooled season IVE when vaccinated in the three seasons was 37% (95%CI: 12–54). Among those unvaccinated in the current season but vaccinated in the previous season, IVE was −4% (95%CI: −66 to 35) overall; −31% (95%CI: −137 to 28) in 2012–13 and 23% (95%CI: −76 to 66) in 2015–16 (Table 5).

In sensitivity analyses restricted to patients for whom vaccine status was ascertained using registries, point estimates were close to the original analysis point estimates in most instances. In the indicator analysis, point estimates sometimes derived from the original analysis but confidence intervals in both analyses largely overlapped (Supplementary Tables 1 and 2).

4. Discussion

Our results suggest that, regardless of patients' recent vaccination history, current seasonal vaccine conferred protection to vaccinated patients against hospitalisation associated with influenza infections in all instances except against A(H1N1)pdm09 among patients vaccinated in both the previous two seasons. Taking as a reference patients unvaccinated in the past two and the current season, the highest IVE point estimate was systematically observed among patients vaccinated in all three (current and two previous) seasons.

As in previously published studies [5,9,13], we used patients never vaccinated in three seasons as reference to measure the effect conferred by various vaccination patterns in the three seasons. This also allowed us to discuss the residual effect of previous vaccination, alone or combined with vaccination in the current season. Using a stratified analysis with patients unvaccinated in the current season as reference, we measured how much former vaccination modified the effectiveness of current vaccination. This allowed us to discuss the protection conferred by the current season vaccine, provided recent vaccine history.

Limitations need to be discussed before further interpreting our results.

High risk groups may be more likely to be vaccinated and to develop a severe form of influenza, leading to chances for underestimation of IVE. In our study, adjustment on underlying chronic conditions or hospitalisation for chronic conditions in the previous year did not change the IVE estimates. However, unmeasured confounding cannot be excluded. Previous seasons' vaccination status was missing for less than 10% of patients. Vaccination status ascertainment relied on patients' and physicians' interviews for 32% of recruited patients; otherwise vaccination status was ascertained based on vaccine registries. Recall bias on vaccination status (previous and current vaccinations) could affect IVE estimates if differential between cases and controls. We believe that differential recall bias is not present in our study as vaccination status was collected independently from the patients' laboratory results. Furthermore, the results were similar when restricting to patients with vaccination status extracted from vaccination registers.

The literature suggests that elderly have consistent vaccination habits over time. Having been vaccinated in the past seasons was reported as a strong predictor of current vaccination status [21–23]. This led, in our study, to small number of patients with changing vaccination status. Despite pooling seasons we still had low precision estimates of current IVE according to past seasons vaccination. We cannot exclude that the observed differences are due to random errors. Due to small sample size, we could not interpret season specific results. The role of previous vaccination on current IVE may vary by season as genetic distance between previous and current vaccine strains as well as with the circulating strains change. Prior vaccination may negatively interfere with current vaccine when antigenic distance between vaccine and circulating strains is large but distance between consecutive vaccine components is small [6]. Enlarging the number of participating hospitals will allow measuring seasonal effect of previous vaccination on current IVE with more precise estimates.

Our study population was elderly population in the EU. They are offered annual vaccination for free [24] and have a higher probability than younger adults of having been exposed to influenza viruses in the past. Effects of previous vaccination and/or infection on IVE may be of different magnitude according to birth cohorts. Epidemiological inputs into these theories would require setting up longitudinal studies with prospective collection of vaccination status and natural infection.

Keeping in mind the above limitations, our results suggest some residual effects from previous year vaccination against A(H1N1)pdm09 virus, a very limited effect against A(H3N2) virus and no effect against influenza B virus. Residual protection against A(H1N1)pdm09 virus was previously suggested [25] and may be explained by some antigenic stability of A(H1N1)pdm09 viruses over time [26]. These results are also consistent with findings suggesting stable within-season IVE against A(H1N1)pdm09 [27] and decreasing IVE against A(H3N2) and B viruses. On the other hand, recent findings from McLean et al. measuring IVE against primary health care endpoints among adults suggested some residual protections against influenza A(H3N2) and B viruses [9]. Diminished immune response to influenza vaccination in elderly compared with younger age group [28] could lead to shorter duration of protection among older adults and explain the discrepancy between McLean's and our results. The small number of seasons included in this analysis may also explain differences observed with McLean et al. We included only two influenza B seasons with different patterns in terms of consecutive circulating and vaccine lineages and we could rely only on surveillance data to interpret lineages circulation. Lineage characterisation at the individual level would ease the interpretation of our results. Understanding previous effect of seasonal vaccination against influenza B may help vaccine lineage selection. Among possible lineage selection strategies, the yearly alternative approach proposes to alternate one Yamagata and one Victoria strain, assuming a one-year residual protection against the other lineage [31].

Stratified analyses suggested some interference from previous vaccinations on current season IVE against A(H1N1)pdm09 (negative effect) and against A(H3N2) (positive effect) but very limited effect against influenza B viruses. We observed that current season IVE against A(H1N1)pdm09 viruses was close to null among patients vaccinated in both previous two seasons and 30% among patients not vaccinated in either of the two previous seasons. This observation, potentially explained by residual protection from previous vaccination, is in line with a recently published study concluding that current influenza vaccination or several prior doses are needed to have a high protective effect against A(H1N1)pdm09 viruses [32]. Despite largely overlapping confidence intervals, our stratified analysis suggested that patients previously vaccinated had a higher current seasonal IVE (37% when vaccinated in both previous seasons) against A(H3N2) viruses compared with patients unvaccinated in the previous seasons (8%). Although antibody titers are poor surrogates for vaccine protection [33], such positive effect has been previously suggested for A(H3N2) viruses based on comparison of sero-responses to different vaccination patterns [34]. Most studies measuring VE against medically-attended influenza A(H3N2) in adults reported negative effect of repeated vaccination against A(H3N2) viruses. Authors of these studies hypothesised that this negative effect could be due to either the original antigenic sin [9,35] or antigenic distance hypothesis [5]. None of the A(H3N2) seasons included in our analysis met the criteria to fulfill the antigenic distance hypothesis. Furthermore, these differences between our results and published studies may reflect random errors due to small numbers or differences in the outcomes and study populations.

5. Conclusion

To our knowledge, this work is the largest hospital based IVE study presenting the effects of repeated vaccination. Our results suggest that, regardless of patients' recent vaccination history, current seasonal vaccine conferred protection to vaccinated patients against hospitalised influenza in all instances except against A(H1N1)pdm09 viruses among patients vaccinated in the past two seasons. Meanwhile, working on a different, long lasting and more efficient influenza vaccine is urgent. Engaging in longitudinal studies, prospectively collecting exposure to both influenza vaccination and influenza infection, is needed to understand potential interferences between consecutive vaccinations. Acquiring such knowledge is crucial at a time when universal influenza vaccination is being recommended in an increasing number of countries.

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Potential conflicts of interest

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Authors' contribution

Marc Rondy was involved in the original methodological design of the study (generic protocol). He coordinated the European hospital IVE network, undertook the statistical analysis on which the research article is based and led the writing of the research article. Alain Moren initiated the original methodological design of the study. He coordinated the European hospital IVE network and contributed to the writing of the research article.

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The InNHOVE/I-MOVE + working group contributors contributed to developing the study site specific protocol. They were in charge of supervising the study at the hospital level and collect the data published in this research article. They read, contributed and approved the manuscript final version.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2017.06.088.

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3.5.4 Vaccine effectiveness by vaccine brand

3.5.4.1 Background

Over twenty different influenza seasonal vaccine products are available on the European market. Since 2015, the EMA request from the vaccine producers to provide product specific IVE estimates (190). In the meantime, most European countries chose the vaccine(s) that they subsidise for delivery to targeted population through national or regional tenders. At the moment, vaccine price is the most important driver to attribute the tender. Precise measures of brand specific IVE could help countries/regions to make better informed decision when choosing the product to subsidise. We used the data from InNHOVE-I-MOVE+ to investigate the feasibility to measure brand specific IVE.

3.5.4.2 Methods

We used data from 2013-14, 2015-16 and 2016-17 seasons, when completeness of vaccine brand was high. For each product specific analysis, we included only countries/seasons where at least one patient had received the product. Using logistic regression and pooling the three seasons together, we measured brand specific IVE against any influenza, A(H3N2) and A(H1N1)pdm09 among the elderly and by age group (65-79 and 80 years and above), adjusted for onset month, age and presence of underlying conditions.

3.5.4.3 Results

Over the three seasons, 2767/5137 (54%) patients were vaccinated. Among them, 37% had received Influvac, 38% had received Vaxigrip, 15% had received vaccines from other brand and the vaccine brand was missing for the remaining 10% of vaccinated patients (**Table 13**).

Table 13: Patients vaccinated by vaccine brand, InNOHVE/I-MOVE+, Europe, 2013-14 and 2015-17

Vaccine brand	N (%)
Missing	283 (10%)
Begripal	1 (0%)
Opthaflu	2 (0%)
3Fluart	14 (1%)
Immugrip	23 (1%)
Fluad	80 (3%)
Fluarix	112 (4%)
Intanza	174 (6%)
Influvac	1029 (37%)
Vaxigrip	1049 (38%)
Total	**2767**

We present here IVE for Influvac and Vaxigrip only. France and the Netherlands were the two only countries to use both vaccines every season they participated in the study. Navarra region exclusively used Vaxigrip and Spanish patients represented the majority of Influvac vaccinees in 2015-16 and 2016-17 (**Table 14**).

Table 14: Patients vaccinated by brand by season and by study site, InNOHVE/I-MOVE+, Europe, 2013-14 and 2015-17

Study site	Vaccine brand			
	Influvac N (%)	Vaxigrip N (%)	Other brand N (%)	Unknown N (%)
Season 2013-14 :				
FR	13 (12)	47 (42)	6 (5)	46 (41)
IT	0 (0)	9 (9)	44 (46)	42 (44)
NA	0 (0)	183 (100)	0 (0)	0 (0)
Total	**13 (3)**	**239 (61)**	**50 (13)**	**88 (23)**
Season 2015-16 :				
ES	244 (88)	0 (0)	33 (12)	0 (0)
FI	0 (0)	7 (10)	61 (90)	0 (0)
FR	46 (45)	47 (46)	7 (7)	3 (3)
HR	10 (100)	0 (0)	0 (0)	0 (0)
HU	0 (0)	0 (0)	4 (100)	0 (0)
IT	3 (2)	1 (1)	128 (97)	0 (0)
LT	11 (100)	0 (0)	0 (0)	0 (0)
NA	0 (0)	254 (100)	1 (0)	0 (0)
NL	5 (26)	14 (74)	0 (0)	0 (0)
PL	0 (0)	0 (0)	0 (0)	1 (100)
PT	5 (28)	8 (44)	1 (6)	4 (22)
RO	12 (100)	0 (0)	0 (0)	0 (0)
Total	**336 (37)**	**331 (36)**	**235 (26)**	**8 (1)**
Season 2016-17 :				
ES	432 (72)	0 (0)	1 (0)	165 (28)
FI	42 (100)	0 (0)	0 (0)	0 (0)
FR	96 (48)	85 (42)	14 (7)	7 (3)
HR	6 (86)	1 (14)	0 (0)	0 (0)
HU	0 (0)	0 (0)	10 (100)	0 (0)
IT	1 (1)	0 (0)	95 (90)	10 (9)
LT	21 (91)	2 (9)	0 (0)	0 (0)
NA	0 (0)	346 (100)	1 (0)	0 (0)
NL	46 (52)	42 (48)	0 (0)	0 (0)
PT	25 (83)	0 (0)	0 (0)	5 (17)
RO	11 (79)	3 (21)	0 (0)	0 (0)
Total	**680 (46)**	**479 (33)**	**121 (8)**	**187 (13)**

Median age of vaccinated controls was 78 years for Influvac and 81 years for Vaxigrip. Compared with controls vaccinated with Vaxigrip, those who received Influvac more often had heart and lung diseases, and were less often diabetic (**Table 15**).

Table 15: Characteristics of vaccinated controls by vaccine brands for Influvac (N=667) and Vaxigrip (N=675)

Caharacteristics	Vaccination status			p-value (difference between Influvac and Vaxigrip)
	Unvaccinated N(%)	Influvac N(%)	Vaxigrip N(%)	
Median age	76	78	81	
Male	688 (48)	388 (59)	369 (55)	0,043
Chronic conditions				
Diabetes	406 (29)	177 (27)	253 (37)	0,000
Heart disease	782 (63)	467(70)	382(57)	0,000
Lung disease	520 (37)	367 (56)	296 (44)	0,000
Cancer	329 (23)	171 (26)	184 (27)	0,611
Obesity	214 (15)	58 (9)	75 (11)	0,144
At least one chronic condition	1311 (93)	631 (95)	637 (94)	0,852
At least two chronic conditions	1014 (74)	535 (81)	516 (77)	0,050
Hospitalisations in previous year	594 (42)	312 (47)	304 (45)	0,522
Current smoker	239 (19)	217 (38)	93 (15)	0,000

Overall, influvac VE against any influenza was 19% (95%CI: 2;33) among patients aged 65 years and above, ranging from -74% (95%CI: -486;48) in 2013-14 to 26% (95%CI: -5;48) in 2015-16. It was 18% (95%CI:-3;35) against A(H3N2) viruses and 20% (95%CI: -21;48) against A(H1N1)pdm09 viruses (**Table 16**).

Overall, Vaxigrip VE against any influenza was 29% (95%CI: 13;43) among elderly, ranging from -1% (95%CI: -37;25) in 2016-17 to 47% (95%CI: 19;66) in 2013-14. It was 14% (95%CI:-10;34) against A(H3N2) viruses and 50% (95%CI: 26;66) against A(H1N1)pdm09 viruses (**Table 16**).

Table 16: IVE against (sub)type specific influenza by season for Vaxigrip and Influenza vaccines, InNOHVE/I-MOVE+, Europe, 2013-14 and 2015-17

Influenza (sub)types and season(s)	Vaccine brand	Vaccinated /total cases	Vaccinated /total controls	VE (95%CI)
Among patients aged 65 years and above				
Any influenza - all seasons	Influvac	358/1010	660/1704	19 (2;33)
	Vaxigrip	372/848	673/1471	29 (13;43)
A(H3N2) - all seasons	Influvac	251/678	587/1393	18 (-3;35)
	Vaxigrip	269/595	603/1195	14 (-10;34)
A(H1N1)pdm09 - all seasons	Influvac	78/231	214/603	20 (-21;48)
	Vaxigrip	72/172	382/705	50 (26;66)
Any influenza - 2013-14	Influvac*	5/35	8/143	-74 (-486;48)
	Vaxigrip	75/164	164/352	47 (19;66)
Any influenza - 2015-16	Influvac	107/320	225/640	26 (-5;48)
	Vaxigrip	86/197	244/540	52 (28;68)
Any influenza - 2016-17	Influvac	246/655	427/921	22 (1;38)
	Vaxigrip	211/487	265/579	-1 (-37;25)

All estimates (otherwise mentioned) were adjusted for study sites, onset month, season, age (restricted cubic spline) and chronic conditions (at least two chronic conditions).

*adjusted for study sites and season only

3.5.4.4 Discussion

Overall, Vaxigrip VE point estimates were slightly higher than Influvac VE point estimates but confidence intervals were largely overlapping. Season specific IVE point estimates by brand varied greatly, reflecting small sample size and questioning our ability to properly measure brand specific estimates.

Currently, measuring brand specific IVE against laboratory confirmed hospitalised influenza is impossible for the vast majority of brands due to small brand specific market share and, consequently small sample size. While we were able to compute IVE estimates for two vaccine brands, we ended up with imprecise results and could not take into account factors that could affect these estimates, such as history of previous vaccination (191) and duration of protection in the season. Finally, we could not compare IVE between these two vaccine brands since they were used in different countries and in different proportions according to the seasons. Considering IVE changes, for a given vaccine, across seasons and countries due to differences in circulating viruses, observed differences could not be imputed to vaccines performance. Finally, due to insufficient sample size, we were unable to compute IVE for adjuvanted vaccines. In a context of low TIV IVE in this age group, such estimates would be an important information to guide vaccination strategies among them.

4 IVE AGAINST HOSPITALISED LABORATORY OUTCOME: LITERATURE REVIEW AND META-ANALYSIS

4.1 Need for summary estimates and project start

Influenza vaccines have been used for decades in high-income countries and in recent years there have been significant increases in their use in middle-income countries. Annual monitoring of IVE is necessary because of the continuous evolution of influenza viruses and to guide complementary public health measures. Great progress has been made in the annual estimation of IVE, which has been enabled by the use of TND studies. TND capitalizes on existing surveillance networks, thus avoiding the costs associated with establishing special studies to monitor IVE. IVE studies have mainly focused on mild influenza illnesses identified in primary care patient populations. The results of such studies were summarised by Belongia et al. in April 2016 (130), which suggested that IVE ranged from 33% against A(H3N2) to 67% against A(H1N1)pdm09. Studies that measure IVE against severe influenza illnesses have been less frequent. However, they may be of greater interest to policy makers—both in countries with established programmes and in those considering introducing a programme—given that influenza vaccination programmes tend to target those at higher risk of severe outcome, including hospitalisation. Due to the lower incidence of influenza associated hospitalisation compared with primary care endpoints, these studies often report IVE with lower precision. In order to have precise estimates to rely on, there was a need for summary estimates of published IVE against hospitalised outcomes.

In June 2016, following an annual meeting where worldwide experts meet to discuss IVE results, we initiated a collaboration with colleagues from WHO-PAHO, Melbourne WHO Collaborating Centre for Reference and Research on Influenza and US-CDC. We agreed on a study protocol and, with the WHO-PAHO colleague, jointly reviewed published articles using web-based collaborative systems (Google docs and spreadsheets). Our Melbourne WHO colleague supported us in the meta-analysis approach and the US-CDC colleague assisted us in the interpretation of the data. We wrote and submitted a manuscript describing this project.

Our study provides the first global summary estimates of IVE against hospitalisation with laboratory-confirmed influenza. We included 30 studies reporting IVE from TND among hospitalised patients. These results show that seasonal vaccines prevent 41% of hospitalised influenza cases among vaccinated adults and that the IVE is lower among persons aged 65 years and older compared to those aged 18-64 years. Although not statistically significant, IVE summary estimates were higher against A(H1N1)pdm09 compared with A(H3N2) and B viruses. We assessed IVE against A(H3N2) by antigenic match and noted particularly low IVE in seasons predominated by variant A(H3N2) viruses, and this was statistically significant for the elderly.

We concluded that influenza seasonal vaccines provided moderate protection against severe forms of influenza illnesses. While most countries recommend vaccination to elderly, these vaccines appear to be less effective in this age group. Seasonal vaccines provide very limited protection to elderly in seasons where vaccine component and circulating A(H3N2) viruses are antigenically variant. Real-time monitoring of antigenic drift during influenza A(H3N2) epidemics may facilitate the early implementation of alternative prevention measures, such as prophylactic use of antivirals.

4.2 Effectiveness of influenza vaccines in preventing severe influenza illness among adults: a systematic review and meta-analysis of test-negative design case-control studies (Published in *Journal of Infection)*

Running title: Influenza vaccine effectiveness against adult hospitalizations.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Abstract

Objectives

Summary evidence of influenza vaccine effectiveness (IVE) against hospitalized influenza is lacking. We conducted a meta-analysis of studies reporting IVE against laboratory-confirmed hospitalized influenza among adults.

Methods

We searched Pubmed (January 2009 to November 2016) for studies that used test-negative design (TND) to enrol patients hospitalised with influenza-associated conditions. Two independent authors selected relevant articles. We calculated pooled IVE against any and (sub)type specific influenza among all adults, and stratified by age group (18-64 and 65 years and above) using random-effects models.

Results

We identified 3,411 publications and 30 met our inclusion criteria. Between 2010-11 and 2014-15, the pooled seasonal IVE was 41% (95%CI:34;48) for any influenza (51% (95%CI:44;58) among people aged 18-64y and 37% (95%CI:30;44) among ≥65 years). IVE was 48% (95%CI:37;59), 37% (95%CI:24;50) and 38% (95%CI:23;53) against influenza A(H1N1)pdm09, A(H3N2) and B, respectively.

Among persons aged ≥65 year, IVE against A(H3N2) was 43% (95%CI:33;53) in seasons when circulating and vaccine strains were antigenically similar and 14% (95%CI:-3;30) when A(H3N2) variant viruses predominated.

Conclusions

Influenza vaccines provided moderate protection against influenza-associated hospitalizations among adults. They seemed to provide low protection among elderly in seasons where vaccine and circulating A(H3N2) strains were antigenically variant.

Funding

None

Keywords: Influenza, vaccine effectiveness, hospitalization, adults, systematic review, meta-analysis.

Background

Each year, seasonal influenza epidemics affect 20-30% of children and 5-10% of adults globally (1) and that they cause three to five million severe (hospitalised) cases and 250,000 to 500,000 deaths worldwide (2). Pulmonary complications, as a direct consequence of influenza infection, after secondary bacterial infection or through the exacerbation of chronic conditions (3), and neuromuscular or cardiac complications (4) may cause severe forms of influenza. Consequently, individuals at risk of developing severe influenza are those whose immune system is likely to sub-optimally respond to viral or secondary bacterial infection (5) and patients who may suffer from an exacerbation of these conditions due to influenza infection (6,7). The mean annual incidence of influenza related hospitalizations among persons 65 years and older typically ranges between 136 and 309 episodes per 100,000 persons in the United States, and England (8–11) and the case fatality among hospitalized patients is estimated to be 7% (12).

Vaccination is the primary means of preventing influenza illnesses and reducing their burden. The World Health Organization (WHO) recommends annual vaccination to individuals at increased risk of severe influenza illness, including adults with chronic medical conditions and persons 65 years and older (1). Most middle and high income countries provide vaccination through routine immunization programs targeting these groups (13,14). While a goal of reaching 75% vaccination coverage among persons 65 years and older by 2010 was set during the 2003 World Health Assembly (15), few regions have reached this target. In Europe, vaccine uptake was below 50% in this group in 2014 (16). Vaccine delivery in developed countries currently faces various challenges, including a decrease in populations' trust in vaccine effectiveness (17) (18).

As recommendations to annually vaccinate high risk groups have been adopted internationally, conducting clinical trials to determine vaccine efficacy has become impossible for ethical reasons. To monitor the IVE, post-marketing (Phase IV) studies have been conducted using observational data. Such studies have historically built on existing outpatient-based sentinel surveillance networks, with a focus on the prevention of medically attended influenza like illnesses (ILI). More recently, a growing number of health authorities and research teams have set up hospital-based studies to measure IVE in preventing hospitalized influenza-associated outcomes (19–21). First developed to measure IVE against medically attended outcomes (22), the test-negative design (TND) (23,24) has become increasingly popular for use in hospital based studies. In this approach, investigators enroll patients based on clinical criteria and measure the IVE derived from the relative difference between the odds of vaccination among patients testing positive and those testing negative for influenza viruses. Because influenza-associated hospitalization is a rare outcome, these studies have mostly reported IVE estimates with broad confidence intervals and limited conclusive evidence about the effectiveness of vaccines against influenza-associated hospitalization. Providing robust evidence of influenza vaccine effectiveness (IVE) in preventing severe influenza illness is important to inform current vaccination strategies. While there have been published reports of meta-analyses of studies reporting IVE against medically attended influenza (25,26) or against hospitalised outcomes in high risk groups (27), there is a gap regarding meta-analyses of IVE focusing on severe outcomes associated with influenza viruses among adults. To provide precise estimates of IVE against laboratory-confirmed influenza-associated hospitalizations, we reviewed published results and summarized IVE estimates by adult age groups (18–64 years, ≥65 years of age), influenza subtype/lineage and influenza season.

Methods

We conducted a systematic review and meta-analysis of extracted IVE estimates.

Search strategy and selection criteria

Two review authors (M.R. & N.E.) used the following search terms on Pubmed: ("influenza" OR "flu") AND ("vaccine" OR "vaccinat*") AND ("hospital" OR "hospitali*" OR "patient" OR "inpatient"). They independently extracted, selected and reviewed articles.

A preliminary review of the literature showed very scarce data prior to 2009. To enable the computation of season-specific IVE meta-estimates, we restricted the search to studies measuring IVE from 2009 onwards. Studies published in English, French, Spanish or Portuguese were considered. The review was initially conducted on 02/06/2016 and was updated on 11/11/2016. The references of retrieved articles were also screened. Titles identified through the initial search were screened independently by two review authors (M.R. & N.E.). Abstracts of title based selected articles were reviewed and the full text of those considered relevant was retrieved and reviewed. Pandemic monovalent, and seasonal trivalent and quadrivalent influenza virus vaccines were considered.

In this meta-analysis, we included original analyses of IVE against hospitalized laboratory confirmed influenza among adults. After applying these criteria and classifying studies by study design, we observed that most published studies (39/50) used a TND approach. In order to reduce qualitative heterogeneity among studies included in this meta-analysis, we restricted studies to those using a TND. We included studies with any method of vaccination status ascertainment and used any laboratory techniques for case confirmation, including rapid diagnostic tests. We did not assess the risk of bias of the included studies since no risk-of-bias tools are suitable to TND studies.

Exclusion

We excluded duplicate reports, studies reporting secondary analyses of previously-published IVE data and interim reports superseded by a final report. We also excluded reports where IVE estimates were calculated using all ages (children and adults), unless their authors could provide us with adult-specific results. We excluded site-specific estimates for studies included in multicenter projects. We reported only season-specific IVE and excluded multiple-season pooled estimates. To ensure comparability between results, and due the very limited number of TND studies providing such estimates, we excluded studies restricted to intensive care unit (ICU) admissions associated influenza.

We excluded estimates reporting IVE for the 2009-10 seasonal influenza vaccines containing the A/Brisbane/59/2007-like seasonal A(H1N1) virus against A(H1N1)pdm09 (A/California/7/2009-like viruses), because the seasonal influenza vaccine was not expected to provide protection against the pandemic virus.

Data collection

We used a structured electronic collection tool to screen and extract quantitative data from the studies reviewed and used a semi-formatted form to compile qualitative information. For each article, one review author extracted the information and another one checked the extracted data. Disagreement were solved through discussion between the two authors. We collected information about the country, influenza season, study population, age group, vaccine type, laboratory test used, data sources, clinical criteria to include patients in the study and maximum number of days between onset and specimen collection. For each age group and outcome [any influenza, A(H1N1)pdm09, A(H3N2) and B], we collected IVE estimates, their 95% confidence interval (95%CI) and the list of co-variates used in the multivariable analysis. Similar to a previous review (25), for each study reporting IVE against A(H3N2), we retrieved the authors' conclusion about the antigenic similarity between vaccine and circulating strains. When no conclusion was provided by the authors, we looked at the WHO

recommendation for compositions of the influenza vaccine; if the A(H3N2) component was updated in the following season, we assumed that the vaccine component and circulating strains during the prior season were not antigenically optimally similar and we categorized them as "variant" in this review.

Data analyses

We defined IVE as 100% × (1 –ratio of odds of vaccination among influenza cases versus that among test-negative controls). We assessed heterogeneity among studies using the χ^2-based Q test (Cochran's Q) and I^2 statistic (28) and we pooled study specific data to calculate summary estimates. We computed meta-estimates using random-effect models, assuming IVE would not be fixed across study sites and seasons because of different levels of antigenic match between vaccine components and circulating strains. We used inverse variances that incorporated an estimate of the between-study variance to calculate the weights for the model (28,29). We computed pooled pandemic IVE for all adult ages against monovalent A(H1N1)pdm09 vaccines in 2009-10. We computed summary seasonal IVE by age group (all ages ≥18 years, 18–64 years and ≥65 years) against any influenza viruses, and separately for influenza A(H1N1)pdm09, A(H3N2) and B viruses, pooling estimates of the 2010-11 and subsequent seasons. We computed season specific summary estimates for all adult ages against any type of influenza virus, grouping each southern hemisphere season with the following northern hemisphere season. We calculated summary estimates of IVE against A(H3N2) by adult age group and antigenic similarity.

In sensitivity analyses, we computed summary estimates by age group and (sub)type of influenza viruses restricting our data to studies using a clearly stated set of clinical criteria [e.g., ILI or severe acute respiratory infection (SARI)] to enroll patients, and to studies using exclusively RT-PCR for laboratory testing.

When authors did not report age group specific IVE (18-64 years, ≥65 years) but did provide IVE estimates for smaller breakdowns of these age groups (for example 18-49 years and 50-64 years), we computed a study specific age group IVE meta-estimates and their 95%CI using fixed effects models.

We assessed the possibility of publication bias by plotting the log of studies' variability (standard error of the OR) against the log of the size of the reported effect (OR) (30). The symmetry of the resulting 'funnel plots' was assessed both visually, and formally with the Egger's test (31). We did all analyses with STATA version 14.2.

Role of the funding source

There was no funding source for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 3,411 unduplicated publications, of which we selected 407 for abstract review and further selected 93 for full-text review. We extracted data from 50 articles and included 30 of them in our IVE meta-analysis (21,32–60) (Figure 1, Table sup 1, Table sup 2). Nineteen studies were conducted in the Northern hemisphere and included studies covering seasons 2009-10 through 2015-16 (Table 1). In 22/30 articles, a clear set of clinical criteria was used to select patients to swab. In the remaining eight articles, the selection of patients to swab was left to the discretion of the clinician. A maximum allowed number of days between onset of clinical illness and swabbing to enroll patients was mentioned in 21/30 reports. All 27 studies reporting seasonal IVE presented estimates adjusted for

age and presence of comorbidities and 13/27 further adjusted for calendar time. The three studies reporting pandemic IVE adjusted for calendar time and 2/3 further adjusted for age; none of them adjusted for comorbidities (Table sup 1).

Overall, we compiled 116 IVE estimates, including 59 estimates against any influenza, 18 against influenza A(H1N1)pdm09, 28 against A(H3N2) and 11 against B viruses (Table sup 3).

Estimates against any type of influenza

Twenty-four studies through six seasons reported seasonal IVE estimates against any type of influenza virus among adults of all ages, with IVE point estimates ranging from -65% to 59% (Figure 2). Heterogeneity was moderate at I2=48%, and the pooled IVE estimate for all ages was 41% (95%CI: 34;48).

For adults younger than 65 years of age, IVE point estimates ranged from -67% to 61%, I^2 was 0%, and the pooled IVE estimate was 51% (95%CI: 44;58). For adults aged ≥65 years, IVE ranged from -25% to 58%, I^2 was 26% and the pooled IVE estimate was statistically lower at 37% (95%CI: 30;44) (Table 2).

Pooled season-specific seasonal IVE estimates against any influenza viruses in all adults ranged between 31% in 2011-12 and 2014-15 and 53% in 2013-14. Summary monovalent pandemic IVE against influenza A(H1N1)pdm09 hospitalization in 2009-10 was 72% (95%CI: 22;100) (Table 3).

Seasonal vaccine effectiveness against influenza A(H1N1)pdm09 viruses

Seven TND studies through four seasons reported seasonal IVE against hospitalized A(H1N1)pdm09 among adults of all ages. The pooled IVE estimate was 48% (95%CI: 37;59) (Figure 3). Heterogeneity was low at I2=28%. For adults <65 years of age, the summary IVE against influenza A(H1N1)pdm09 viruses was 55% (95%CI: 34;76) with I2=0%. For adults ≥65 years of age, summary IVE was 54% (95%CI: 26;82) with I2=64% (Table 2).

Seasonal vaccine effectiveness against influenza A(H3N2) viruses

Based on nine reported estimates through four seasons, the pooled IVE against A(H3N2) influenza viruses among adults of all ages was 37% (95%CI: 24;50) (Figure 4). Heterogeneity was moderate at I2=56%. For adults <65 years of age, the summary IVE against influenza A(H3N2) viruses was 50% (95%CI: 38;62) with low heterogeneity (I2=0%) and for persons 65 years and older, summary IVE was 33% (95%CI: 21;45) with low heterogeneity between estimates (I2=33%) (Table 2).

Information regarding antigenic similarity between vaccine and circulating strains was mentioned in all studies reporting IVE against A(H3N2) except one (46), for which we assumed similarity based on the fact that there had been no change in the A(H3N2) vaccine component in the subsequent season. When restricting to seasons with antigenically similar vaccine and circulating strains, pooled IVE against A(H3N2) was 52% (95%CI: 39;66) among all adults, 59% (95%CI: 38;80) among those aged <65 years and 43% (95%CI: 33; 53) among persons 65 years and older (Table 4). In seasons with reported A(H3N2) variant viruses, pooled IVE against A(H3N2) was 29% (95%CI: 13;44), 46% (95%CI: 30;61) and 14% (95%CI: -3;30) among all age adults, adults <65 years and persons 65 years and older. Of note, the pooled IVE among persons 65 years and older of 43% against A(H3N2) during seasons with similar vaccine and circulating strains was statistically higher than the IVE of 14% during seasons with variant A(H3N2) viruses (with 95% CI that did not overlap).

Seasonal vaccine effectiveness against influenza B viruses

Based on five reported estimates through four seasons, with I^2=0% heterogeneity, the pooled IVE estimate against influenza B viruses among adults of all ages was 38% (95%CI: 23;53) (Figure 5). For adults aged <65 years, the summary IVE against influenza B was 45% (95%CI: 8;81; I2=0%) and for persons 65 years and older, summary IVE was 31% (95%CI: 11;51; I2=0%) (Table 2).

Sensitivity analysis

Sensitivity analyses, whereby we excluded data from studies not using clear clinical criteria for patients' inclusion or those not exclusively using RT-PCR for laboratory testing, resulted in similar summary estimates (Tab sup 4, Table sup 5). Of note, the gap in IVE against any influenza hospitalization between adults aged <65 years (52%, 95%CI: 44; 59) and adults aged ≥65 years was wider (32%, 95%CI: 21;43) when limited to studies using clear clinical criteria.

Publication bias assessment

The funnel plots for IVE against any influenza were symmetrical around a single peak (Figure 6). There was no statistically significant difference between the results in small and large studies (Egger's test, p=0.475, p=0.252 and p=0.606 among adults all ages, 18-64 years and 65 years and older respectively). Similar results were obtained for (sub)types specific estimates (data not shown).

Discussion

Our meta-analysis estimated at 41% (95%CI: 34;48) the overall seasonal IVE against hospitalizations associated with laboratory confirmed influenza virus infections among adults, with (sub)type IVE of 48% (95%CI :37;59) against influenza A(H1N1)pdm09, 37% (95%CI: 24;50) against influenza A(H3N2) and 38% (95%CI: 23;53) against influenza B viruses. Monovalent pandemic vaccine yielded to the highest pooled IVE at 72% (95%CI: 22;100). Our results suggested that IVE was significantly higher among adults aged less than 65 years compared to those aged 65 years or older (51% vs. 37%, respectively). In seasons with antigenic dissimilarity between A(H3N2) vaccine and circulating strains, IVE against hospitalized influenza A(H3N2) was close to null among elderly at 14% (95%CI: -3;30).

Our estimates were in line with the recently published meta-estimates of IVE against medically attended influenza illnesses (25). Compared to influenza illnesses in outpatient settings, we found slightly lower IVE estimates against influenza A(H1N1)pdm09 and B virus hospitalizations. In contrast, our IVE point estimates against A(H3N2) virus hospitalizations were a few percentage points higher than the findings from outpatient settings (25). These comparisons are also in line with a recent meta-analysis comparing outpatient and inpatient based IVE estimates within the same season and population, which concluded that IVE for outpatient and inpatient influenza were consistent most of the time (61).

Although prior reviews have noted lower influenza vaccine immunogenicity among older adults (62) and lower IVE point estimates among persons 65 years and older compared to adults aged <65 year (25), this is the first review to document with sufficient precision that IVE against influenza hospitalization is significantly lower for the elderly. This gap in vaccine protection was especially notable against A(H3N2) hospitalizations.

Our results suggest that IVE against A(H3N2) was particularly low in seasons predominated by variant A(H3N2) viruses. Lower IVE point estimates during seasons predominated by variant A(H3N2) viruses were noted for all adults, but the difference was only statistically significant among persons 65 years and older (43% vs. 14% in antigenically similar vs. variant seasons). The reasons why a poorly matched

A(H3N2) vaccine component would provide less protection to older adults is unclear, but may include a narrower and more specific immune response to influenza vaccines (62–64) and possibly age-cohort specific differences in A(H3N2) virus exposure history (65).

Our meta-analysis of published IVE against hospitalizations associated with influenza virus infections presented several limitations. Firstly, we solely searched the Pubmed database to identify relevant studies, which captures the journals that influenza TND studies are published in.Comparison of databases suggests Pubmed offers optimal frequency and timely updates (66). Furthermore, using funnel plots and the Egger's test, we observed no evidence of publication biases (30,31). The limited number of observations made the computation of subtype specific estimates by season difficult. While our overall estimates are useful evidence for public health decision makers, they do not reflect inter-seasonal variability of IVE. Suboptimal IVE may be due to mismatch between WHO-recommended and circulating strains but also to manufacturing processes, as described for the A(H3N2) vaccine component (e.g., (67)). We were not able to collect and compute influenza B lineage-specific IVE, though primary care based published studies suggest the existence of influenza B cross-lineage protection (68,69).

We observed low to moderate heterogeneity (I^2 ranging between 0 and 64%) across IVE estimates included in the various meta-estimates. However, the small number of estimates and the large study-specific confidence intervals may hinder proper quantitative assessment of heterogeneity between studies (70). Following Greenland's recommendations on the validation of meta-analysis approaches (71), we compared our results with values obtained using a fixed-model approach and found very small differences in IVE point estimates (data not shown).

Excluding IVE estimates focused only on intensive care unit (ICU) outcomes, and including only TND based studies in our estimates, we tried to limit potential qualitative heterogeneity across study methods. However, we did not apply restrictions to other methodological features, such as symptom eligibility criteria, vaccination status ascertainment, laboratory tests and specimen collection procedures, inclusion criteria based on the number of days between illness onset and specimen collection. A systematic review of TND IVE studies (72) concluded that the most common variation in their practices was the analytical approach. Similarly, we noted considerable variability in the variables used to adjust IVE estimates across the studies in this review; however, all studies adjusted for age and presence of comorbidities, which are the most consistently included covariates in IVE TND studies (72). We believe that differences in other adjustment variables reflect local settings' specificities. Indeed, variations in viruses' circulation and access to vaccines across study sites are likely to lead to different confounding factors when measuring IVE (73).

In 8/30 articles, patients' inclusion was based on the physicians' diagnosis rather than on a clear set of signs and symptoms. Such an inclusion approach could have led to a selection bias if the decision to include/exclude a patient was based on his/her vaccination status. One study in France comparing ad-hoc and systematic sampling of ILI patients by general practitioners showed a higher propensity of the physicians to select influenza positive cases and vaccinated patients (74). Although clinician testing has not been shown consistently to be associated with vaccination status (75), such a bias, if present in the hospital based studies would lead to underestimating the IVE. However, we found similar results when we restricted our analysis to studies using clearly defined sets of clinical criteria.

To reduce qualitative heterogeneity between studies included in the meta-analysis, we restricted our analyses to articles reporting results from TND studies. Other study designs may be used to measure IVE against laboratory confirmed hospitalised influenza. Cohort studies are scarce as they usually rely on vaccine registries to allow defining cohorts of vaccinated and unvaccinated individuals and require

a systematic swabbing of SARI patients in all hospitals covering the source population (76). In the screening method (77–80), the odds of vaccination among cases is compared with the odds of vaccination in a reference population (based on administrative data). However, it is usually difficult to obtain vaccine coverage stratified on all potential confounders, which may bias IVE estimates. Consequently, WHO recommends against its use to measure IVE (73). In case control studies, controls must have experienced the same exposure of interest (here, influenza vaccination) as the population giving rise to the cases. The source population of hospitalised influenza cases may be defined as those at increased risk of SARI. In this context, non-influenza SARI patients may represent an appropriate group of controls and the TND a suitable study design to measure IVE. A recent modeling-based article suggested that measuring IVE against hospitalized influenza among inpatients was subject to biases if recruited test negative controls were included in the study because patients with exacerbation of underlying cardiopulmonary (CP) disease would be over-sampled (81). Such a bias would lead to recruiting a higher proportion of patients with CP in the study compared to the source population giving rise to hospitalized cases. If the population with CP were more likely to be vaccinated than the source population, such a bias would result in an overrepresentation of vaccinated patients in the control group and, ultimately, an overestimation of the IVE. In our meta-analysis, the presence of underlying conditions was controlled for in all studies reporting seasonal IVE. Furthermore, published observational studies conducted in Navarra (Spain) reported similar IVE estimates against influenza hospitalizations using cohort and TND designs (76).

Our review could not examine the possible role of prior vaccination history in modifying current season IVE against severe outcomes, which has been suggested by an increasing number of publications (82,83). Repeat influenza vaccination over multiple years has been associated with decreased clinical IVE against influenza A(H3N2) and B viruses associated medical visits (84). Given that documenting current year influenza vaccination status is especially challenging in hospital settings (32,33), it is not surprising the effect of prior vaccination on IVE was reported in very few articles (36,41,58). Nonetheless, research that considers the possible modification of current season IVE by prior vaccination history among hospitalized patients is needed, especially when consecutive identical vaccine components are followed by an antigenically distinct circulating strain. This can result in a blunting of IVE as described by Smith et al. (85) and observed in 2014-15 (86,87).

Due to the limited number of TND studies reporting very severe outcomes (45,52,88), we could not compute pooled IVE against ICU admission associated with laboratory confirmed influenza. Castilla et al. (88) reported a higher IVE against ICU compared to hospitalized influenza and concluded that vaccination lowered the severity of hospitalized cases of influenza. For the same reason of paucity of published data, we could not explore the effects of more potent vaccines. Adjuvanted vaccines may induce a more rapid and broader immune response (89) and an observational study suggested a reduction by 25% of the risk of hospitalization for influenza or pneumonia with adjuvanted versus non-adjuvanted trivalent inactivated vaccines (90). Increasing the size and the number of studies using ICU admissions and deaths associated with laboratory confirmed influenza as outcomes as well as more potent influenza vaccines would be useful to further guide influenza vaccination policies.

Conclusion

In conclusion, our review of the published literature suggests that among vaccinated individuals influenza vaccines may prevent nearly half of the laboratory confirmed hospitalizations associated with influenza viruses. We observed lower IVE among persons 65 years and older compared to adults aged 18–64 years. We also noted poor performance of the seasonal influenza vaccines against influenza A(H3N2) viruses among the elderly in seasons characterized by a mismatch between vaccine and circulating strains. Real-time monitoring of antigenic drift during influenza A(H3N2) epidemics may facilitate the early implementation of alternative prevention measures, such as prophylactic use of antivirals, among the elderly.

Despite the lower effectiveness of influenza vaccines compared to other vaccines of the expanded programs on immunization, seasonal vaccination remains the best and safest public health measure to reduce morbidity and mortality due to influenza. Improving communication about IVE against severe influenza could increase influenza vaccine uptake and sustain investments in the vaccines. Larger studies providing insight into the effectiveness of different vaccine types (e.g., adjuvanted/unadjuvanted, high-dose/standard dose) in preventing severe influenza illness over various seasons could better target vaccination strategies, especially among high risk populations. Developing more immunogenic vaccines should however remain a public health priority.

Contributors

MR and NEO designed the study. MR and NEO screened and abstracted publications. MR and SS analysed data. MR, NEO, and MT interpreted the results. MR wrote the manuscript, with editorial contributions from NEO, AM, AL, MT and SS. All authors reviewed the manuscript for accuracy and scientific content.

Declaration of interests

All authors declare no competing interests.

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Figures

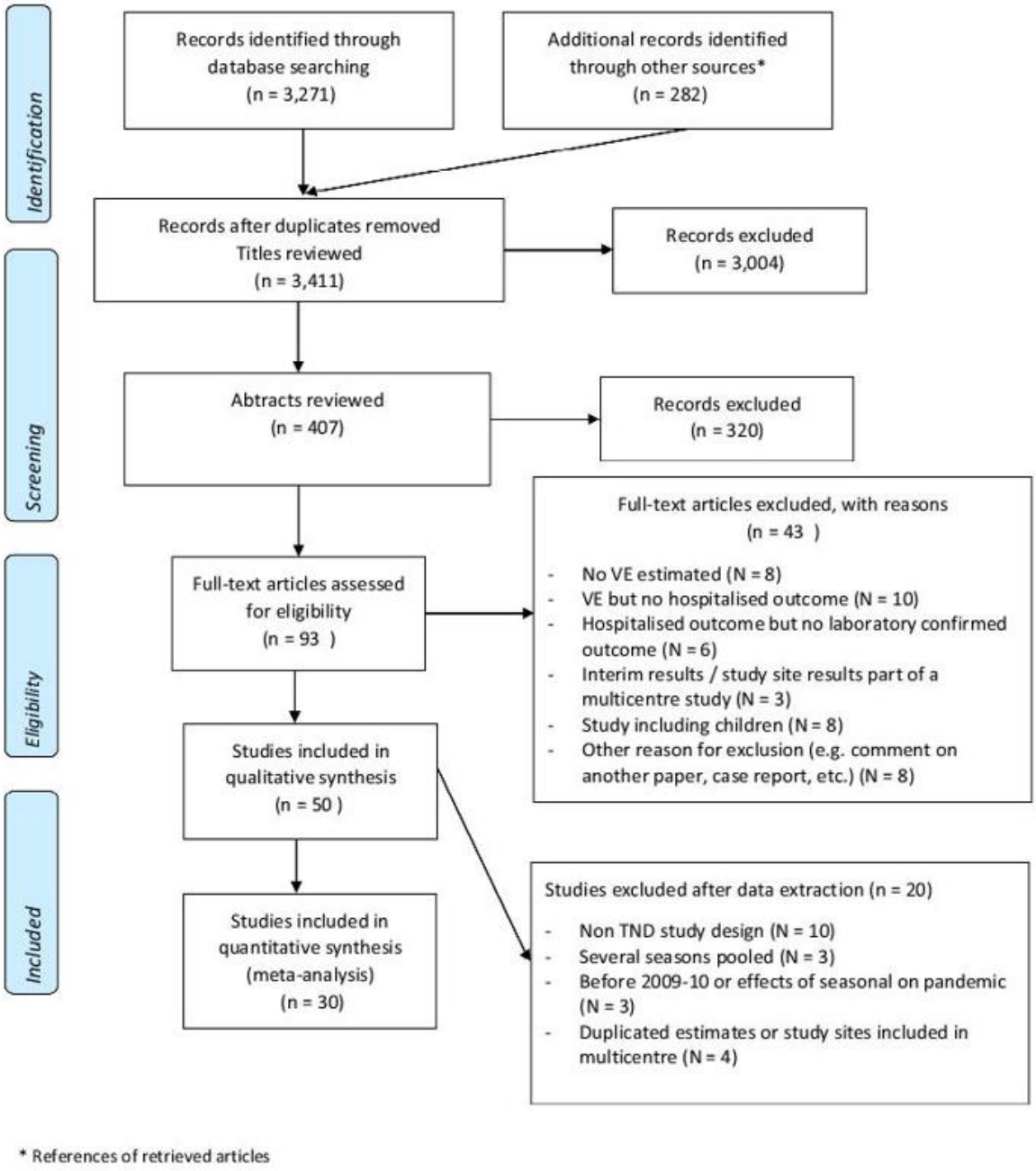


Figure 1. Flow chart for selection of studies.

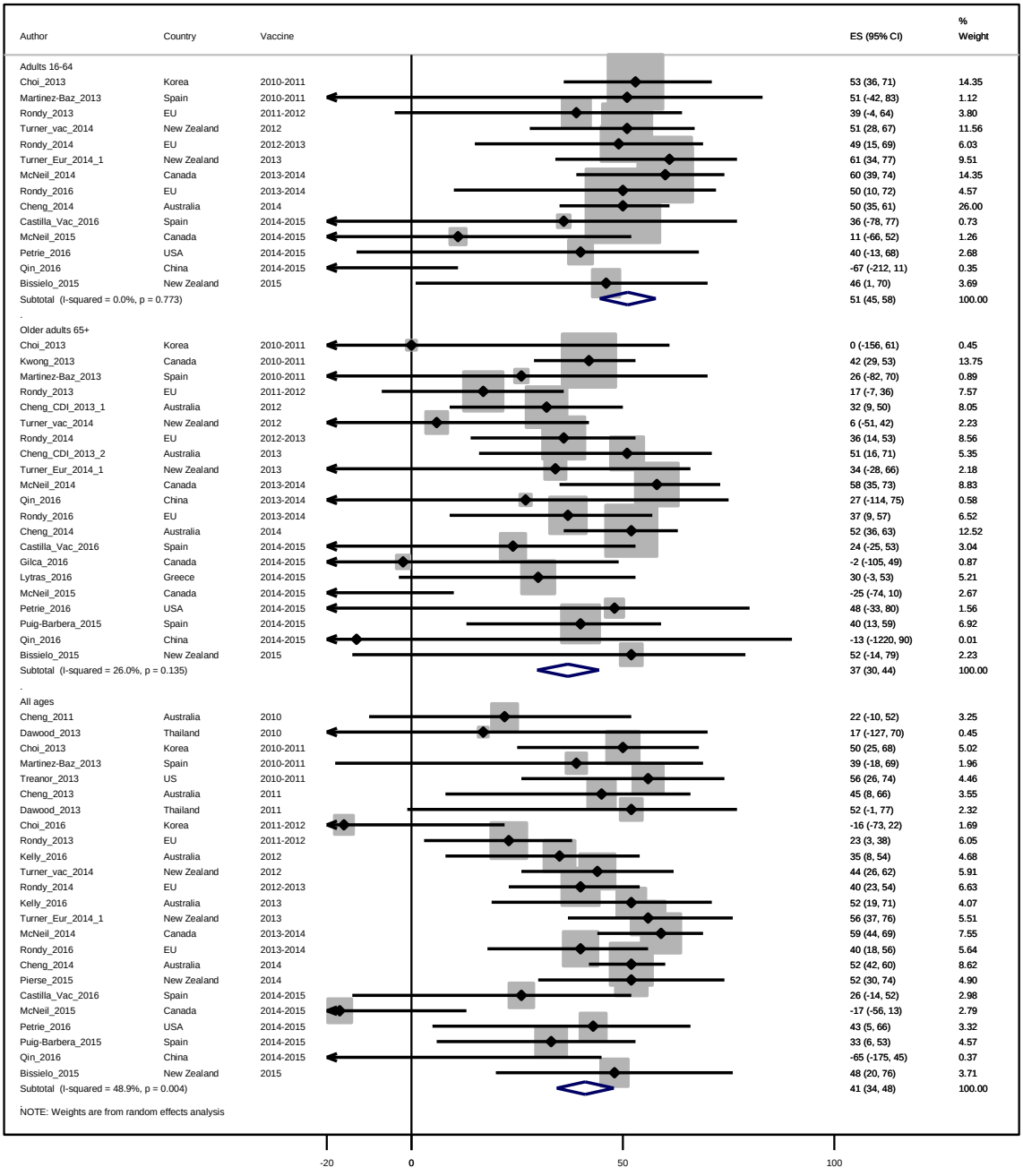


Figure 2: Study specific and pooled seasonal influenza vaccine effectiveness against any influenza by age group

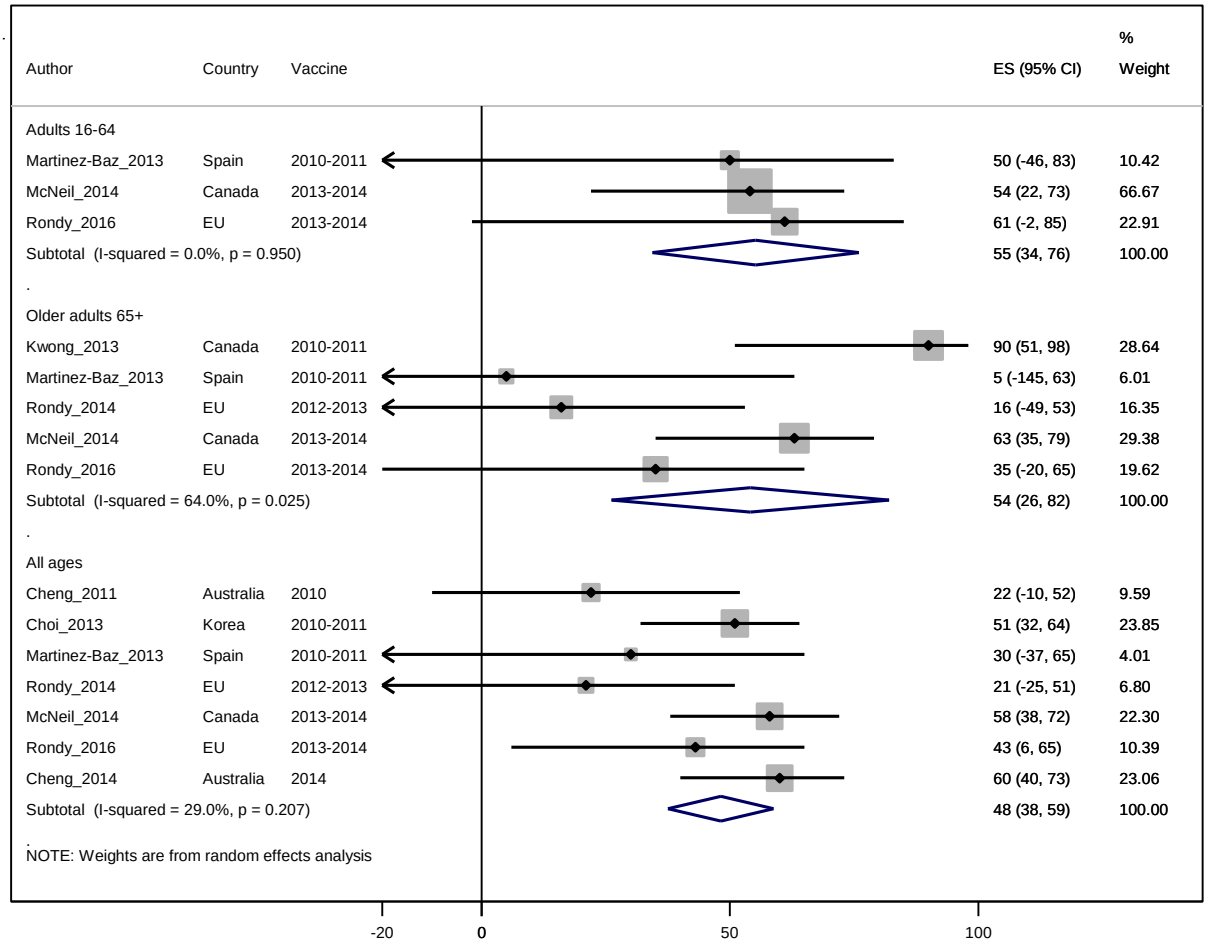


Figure 3: Study specific and pooled seasonal influenza vaccine effectiveness against influenza A(H1N1)pdm09 by age group

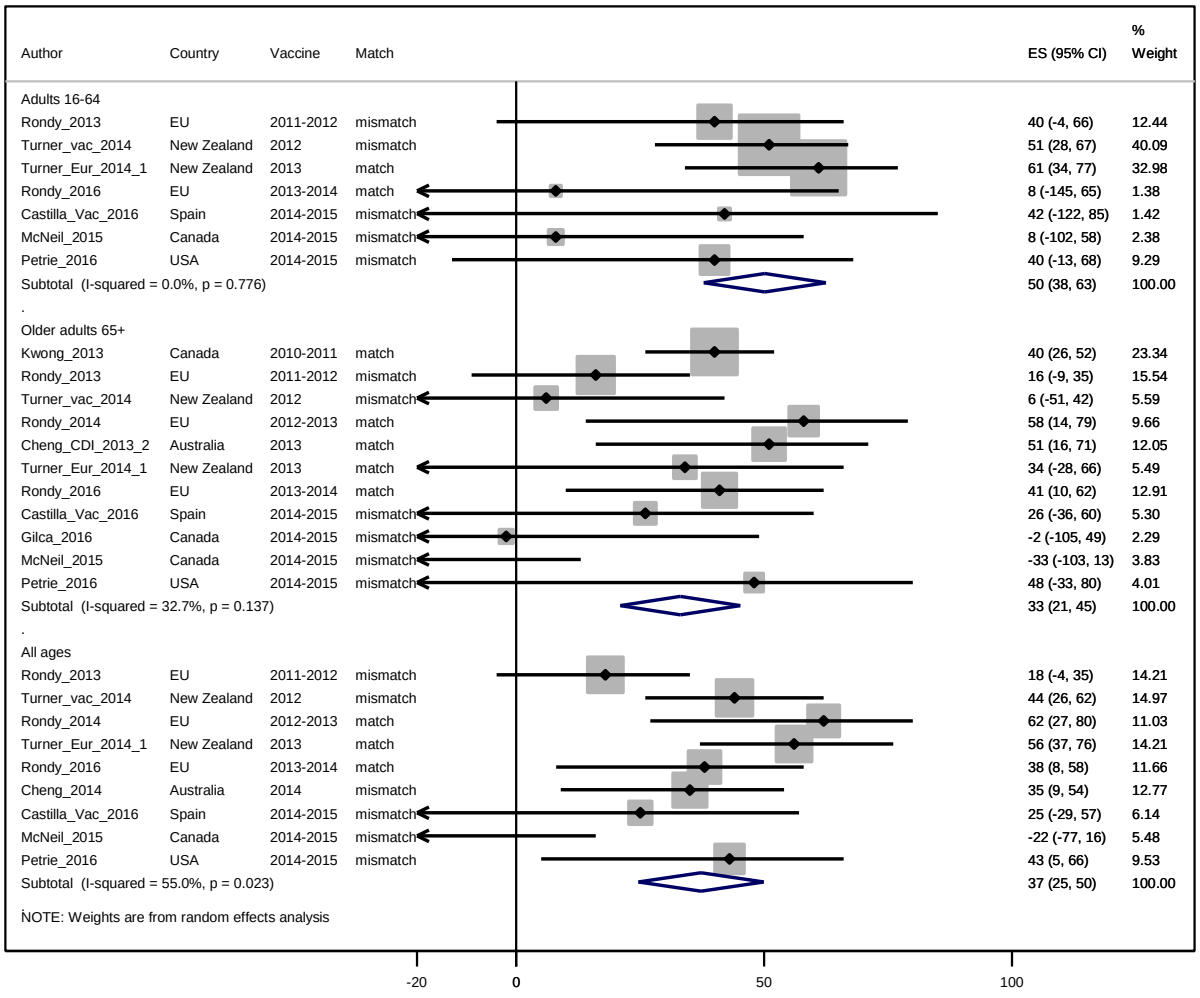


Figure 4: Study specific and pooled seasonal influenza vaccine effectiveness against influenza A(H3N2) by age group

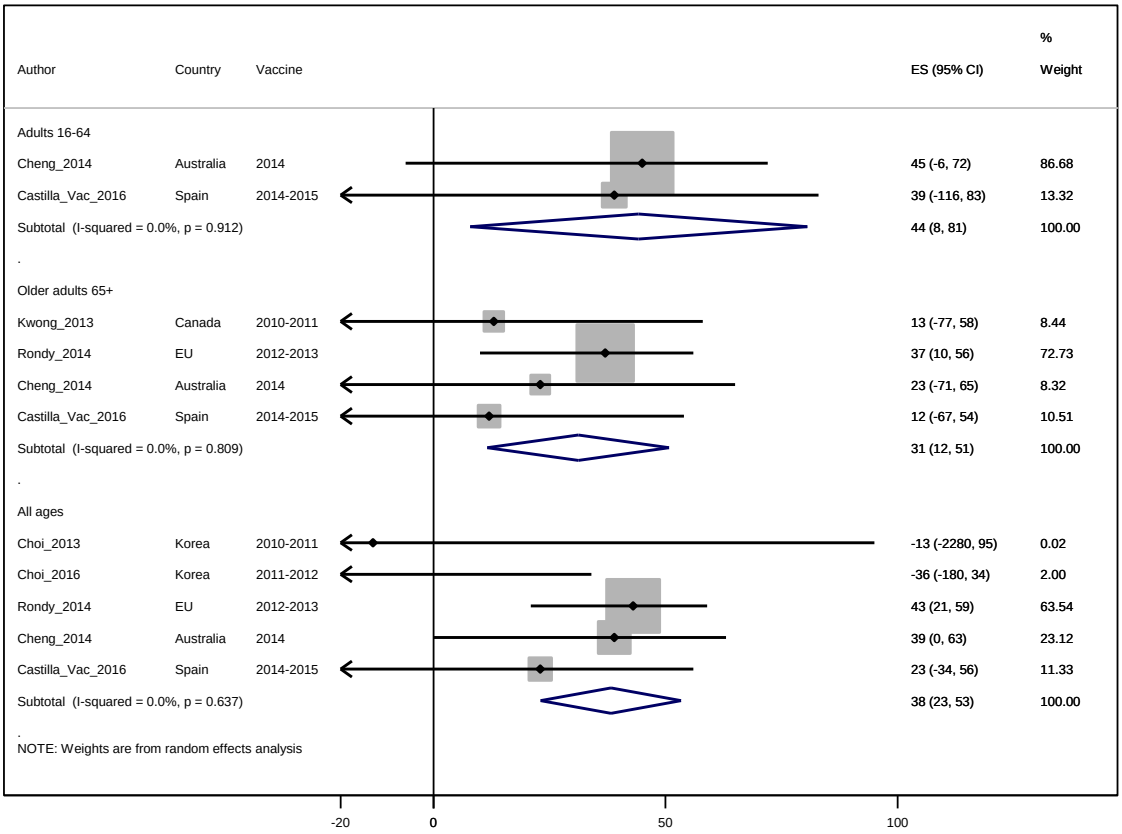
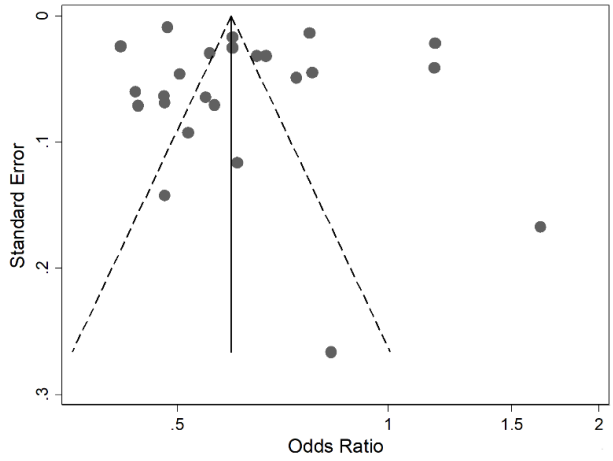
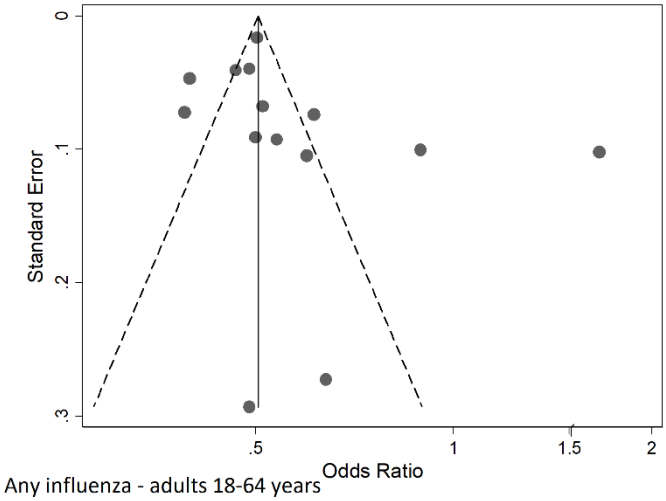


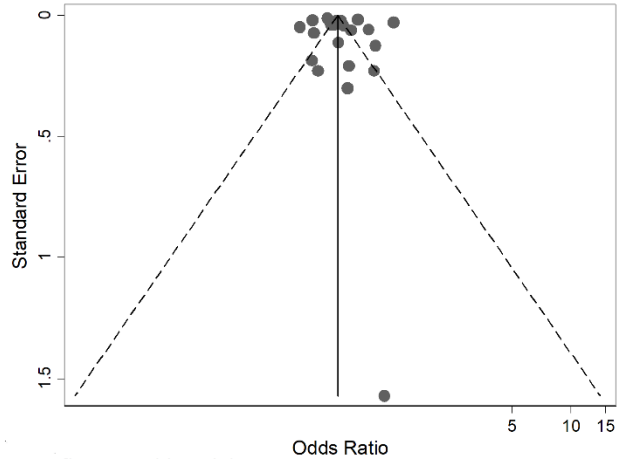
Figure 5: Study specific and pooled seasonal influenza vaccine effectiveness against influenza B by age group



Any influenza - all ages



Any influenza - adults 18-64 years



Any influenza - older adults 65+

Figure 6 : funnel plots of effect size of individual studies included in the meta-analysis of influenza vaccine effectiveness against any influenza among adults all ages, 18-64 years and 65 years and older. Points correspond to OR from individual studies, diagonal lines show the expected 95% confidence intervals around the summary estimate. Odds ratios are plotted on a logarithmic scale

Table 1: Characteristics of the 30 studies included in this review reporting influenza vaccine effectiveness estimates against laboratory confirmed hospitalized influenza, 2008-2016

Characteristics of selected published studies		N
Number of unique studies		30
Hemisphere	North	19
	South	11
By country income (World bank classification)[ϯ]	Upper-middle-income economies	2
	High income economies	28
Continent	Europe	11
	North America	6
	Oceania	10
	Asia	3
Influenza season	2009/10	3
	2010/11	6
	2011/12	4
	2012/13	3
	2013/14	4
	2014/15	9
	2015/16	1
Vaccine type	Seasonal trivalent vaccine	27
	Pandemic monovalent	3

* Southern hemisphere seasons were grouped with the following northern hemisphere season

ϯ Source of information: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups

Table 2: Pooled seasonal vaccine effectiveness (VE) against influenza hospitalizations by type and subtype of influenza virus and by age group

	Pooled VE (%)	95%CI	Number of VE estimates	p-value for heterogeneity	I^2
Any influenza					
All adults	41	34;48	24	0,005	48
Under 65 years	51	44;58	14	0,762	0
65 years and above	37	30;44	21	0,137	26
A(H1N1)pdm09					
All adults	48	37;59	7	0,212	28
Under 65 years	55	34;76	3	0,948	0
65 years and above	54	26;82	5	0,026	64
A(H3N2)					
All adults	37	24;50	9	0,021	56
Under 65 years	50	38;62	7	0,775	0
65 years and above	33	21;45	11	0,137	33
B					
All adults	38	23;53	5	0,640	0
Under 65 years	45	8;81	2	0,907	0
65 years and above	31	11;51	4	0,812	0

Table 3: Pooled vaccine effectiveness (VE) against influenza A(H3N2) hospitalizations among all adults by antigenic similarity between circulating and vaccine strains

	Age group	Pooled VE* (%)	95%CI	number of VE estimates	p-value for heterogeneity	I^2
	All	52	39;66	3	0,387	0
Similar	16-64 years	59	38;80	2	0,332	0
	65 years and above	43	33;53	5	0,829	0
	All	29	13;44	6	0,082	49
Variant	16-64 years	46	30;61	5	0,857	0
	65 years and above	14	-3;30	6	0,486	0

* and 95% confidence interval in parentheses.

Table 4. Pooled vaccine effectiveness (VE) against influenza hospitalizations among adults by season

	Vaccine type	Pooled VE* (%)	95%CI	number of VE estimates	p-value for heterogeneity
Any influenza					
2009-10	pandemic	72	22;100	3	0,286
2010-11	seasonal	43	34;52	6	0,613
2011-12	seasonal	31	12;49	5	0,143
2012-13	seasonal	39	29;48	4	0,824
2013-14	seasonal	53	45;61	6	0,704
2014-15	seasonal	31	15;47	9	0,003

* and 95% confidence interval in parentheses.

Note: Supplementary material is in Annex 1

5 DISCUSSION

5.1 Current limitations

Throughout the season's specific interpretation of our results, we have identified a number of limitations inherent to our European multicentre hospital based TND study that we aim to discuss in this chapter.

5.1.1 Systematic errors

5.1.1.1 Selection biases

The source population giving rise to the cases included in our study can be defined as the adults likely to be hospitalised in case of SARI. In theory, any adult may develop a severe form of respiratory infection and end up hospitalised in the EU. However, there is a general and international consensus to define adults at higher risk to develop severe influenza as those with specific chronic diseases, those aged 65 years and above and pregnant women (192). Overall, the vaccine coverage among our control group was 54% and 94% of the patients recruited in our study belonged to the target group for vaccination. Based on the latest VENICE report, the EU median seasonal vaccine coverage among elderly was 45% and it was 50% among individuals with chronic medical conditions (101). Vaccine coverage estimates from the general adult population are scarce but a population based survey estimated that vaccination coverage in France was 23% in the general population aged 15 years and older in 2011–12 (193). Vaccine coverage in our control group seems therefore much closer to the vaccine coverage in the targeted population than in the general population. To reduce selection biases, we restricted our study population to the population targeted by seasonal influenza vaccination.

As discussed in chapter 3.4.4.1, we may be over-representing patients with lung diseases by recruiting SARI cases that are not due to infectious pathogens but instead the result of an exacerbation of underlying lung conditions. Since these patients are more likely to be vaccinated and more likely to be hospitalised as controls, such bias would overestimate the IVE. In our study, we ran sensitivity analyses excluding patients with cardiopulmonary disease. Results were similar in most instances. In order to further discuss this issue, we ran simulations in which we used various changing ratio of cases/controls among patients with chronic diseases. These simulations show that, while the crude OR decreases with an increasing proportion of controls with chronic conditions, the adjusted OR remained identical.

In the future, it could be interesting to test patients for other respiratory viruses or bacteria and restrict the control group to those testing positive for a respiratory pathogen. We are currently assessing the study sites who could provide such information.

5.1.1.2 Information biases

Data quality was high in our study with less than 3% of missing exposure or outcome variables and under 5% of missing information for confounding variables.

5.1.1.2.1 Exposure

Vaccination status ascertainment relied on patients' and physicians' interviews for 35% of patients included our study. For the rest of the patients included, vaccination status was ascertained based on vaccine registries in Finland, Portugal and Spain (including Navarra and Valencia).

Recall bias on vaccination status (previous and current vaccinations) could affect IVE estimates if differential between cases and controls. We believe that differential recall bias is unlikely to be present in our study since vaccination status was collected independently from the patients' laboratory results.

5.1.1.2.2 Outcome

Long delay between symptoms onset and swabbing could lead to false negative if the patients cleared the virus before swabbing. Misclassification bias (having cases in the control group) would bring IVE estimates closer to zero. To reduce the risk of misclassification, we included in our study only patients swabbed within seven days of symptoms onset. In 2011-12, we reported results from patients swabbed within four days as main results since we observed a higher point estimate among them. In the subsequent seasons, we reported, as main results, IVE among patients swabbed within seven days and as a sensitivity analysis IVE among patients swabbed within four days. Results were similar. Over the five seasons included in this work, the same proportion of controls (64%) and cases (66%, p=0.43) were swabbed within four days, suggesting that misclassifications due to delayed swabbing were minimal. The proportion of vaccinated and unvaccinated cases swabbed within four days was also similar (67 vas 65%, p=0.49) suggesting that vaccination was unlikely decreasing the duration of virus shedding among cases.

Starting in 2012-13, we observed the inclusion of a large number of Lithuanian patients having received antivirals prior to their swabbing. Prior to that observation, we had decided that patients who had received antivirals before swabbing should be excluded due to risk of false negatives among them. However, we noticed that the proportion of patients having received antivirals was higher among cases than controls. We concluded that antivirals were unlikely to lead to a high proportion of false negatives and decided to not exclude these patients from the main analysis, but rather to conduct sensitivity analyses excluding them. We did not observe systematic differences in IVE between patients with and without antiviral treatment.

5.1.1.3 Confounding

High risk groups are more likely to be vaccinated and to develop a severe form of influenza. This may overestimate the number of vaccinated cases seen at the hospital and underestimate IVE.
People with a healthy lifestyle are more likely to accept/request vaccination and less likely to be severely sick. This would overestimate IVE. However, while this bias is likely to occur for mild outcomes, it is unlikely to affect the IVE estimate in a hospital setting.
Extremely frail people are less likely to be offered vaccination but more likely to develop a severe form of the disease (194). We collected detailed information on chronic conditions, their severity (approximated using the number of hospitalisations in the past twelve months) and functional status. This allowed us to search for potential confounding related to chronic conditions. Overall and for each season specific analysis, we measured very little confounding in our data. Cases and controls were similar for most characteristics and adjusted models gave results that were very similar to crude estimates. However, we cannot exclude the presence of unmeasured confounding biasing our results in an unpredictable way.

5.1.2 Random error

Despite increasingly large sample size and a 50% vaccine coverage among controls, our IVE estimations remained imprecise. IVE point estimates within population sub-groups or for vaccine brands/types were reported with large confidence intervals. To overcome the issue of small sample size, we pooled several seasons' data sets. However, doing so, we assumed that differences between population

subgroups or vaccine brands/types remained the same across seasons and influenza (sub)types. In the future, increasing the sample size would be critical to identify specific high-risk groups or better performing vaccines with more precision.

5.1.3 Limitation related to the data pooling

The performance of a one-stage pooled analysis also assumes that the IVE and confounding are the same in all study sites. This is a strong hypothesis that is unlikely to be met. Indeed, considering the broad range of vaccines used across study sites, differences in circulating viruses and potential differences in access to vaccination and health care use, we can expect IVE and confounding effects to vary across study sites. Since the 2013-14 season, we were able to report study site specific and 2-stage model analyses. While we sometimes observed differences in study site specific confounding, 2-stage model IVE estimates were systematically very close to results from the one-stage analysis.

We quantified the heterogeneity between study site specific IVE estimates with the I^2 value and observed low to high heterogeneity between IVE estimates. Study site specific estimates were mostly imprecise and 95%CI around them overlapped in most instances. Observed differences may therefore be explained by random variations.

However, true differences between study site specific IVE may exist and be due to differences in vaccines used, circulating viruses or population immunological background. As we characterise a higher proportion of specimens and become able to measure clade specific IVE at the GP level, we realise that IVE may vary by clade. Considering the high mutation rate of influenza viruses, geographical IVE differences may be partially explained by viral heterogeneity (187). Systematising the characterisation of specimens among confirmed cases could help us interpret differences between study site specific IVE.

5.2 Summary of evidences / Responses at this stage

5.2.1 Vaccine effectiveness against any influenza

In our networks of hospitals we measured that IVE against any influenza among adults was 26% when pooled across all available seasons; it was 40% among adults aged 18-64 years, 25% among those aged 65-79 years and 23% among patients aged 80 years and above. Season specific IVE estimates ranged between 10% among the 80 years and above in 2011-12 and 2016-17 and 50% in that same age group in 2014-15.
In our meta-analysis of estimates published in the literature, we measured an overall IVE of 41% against any influenza-associated hospitalisation in adults; 51% among the 18-64 years adults and 37% among persons aged 65 years and older.

These works provides the first repeated and precise estimates of IVE against hospital-associated influenza infection, especially among elderly. Our results suggest that the IVE was moderate to low against severe outcome. Most cost-effectiveness studies that have led to implementing annual influenza vaccination strategies have relied on much higher IVE hypotheses (195,196). Published work on cost-effectiveness of influenza vaccination in elderly in Australia suggested that the existing vaccination programme (targeting elderly aged 65 years and above) was likely to be cost-effective as long as the IVE (no outcome specified) would be above 30% (124). Putting our results in perspective with this finding, European vaccination programmes (similar to Australian programme) would not be cost-effective among elderly during A(H3N2) seasons. Our EU IVE estimates may be used in cost-effectiveness studies to evaluate current influenza vaccination strategies or to decide on which immunisation programmes to prioritise in countries that have not yet implemented annual influenza vaccination. Revising these cost-effectiveness analyses using our estimates would be useful to properly measure the cost-benefit ratio (in euros per quality-adjusted life year (QALY) gained) of these programmes.

This overall low performance of the vaccine against severe outcome among the elderly should stimulate further evaluation of the use of alternative approaches to prevent influenza infection in this population. Hand washing has proven to be effective in reducing influenza transmission (197) and hydroalcoolic solutions were associated with a 40% decreased risk of infection in a school-based study (198). Evaluating the effect of these harmless prevention measures among elderly would be useful to provide a rationale to promote them more aggressively during influenza epidemics. Furthermore, non-pharmaceutical approaches are not specific to influenza, and have the ability to prevent other infectious diseases. Despite their effectiveness in preventing influenza (75,76), prophylactic use of antivirals remain low in most western European countries, even as a treatment (<9% among medically-attended ILI patients aged ≥65 years in 2015-16 in France (199)). Understanding the reasons for their underuse among GPs and in health care facilities could help promoting them. However, their continuous use throughout a season would probably be difficult to support logistically and financially and could lead to antiviral resistance. A more realistic prophylactic use of antivirals could target individuals at-risk of severe outcome when they are at increased risk of contact with influenza viruses. Such interventions could be rolled out in health care settings or households where influenza cases have been detected.

Our low estimates should also be used to urge public health authorities and vaccine manufacturers to develop more immunogenic vaccines. Adjuvanted and high-dose vaccines are currently available on

the European market but robust data of superior post-marketing IVE of these products against severe outcome are scarce. Conducting large comparative studies may be necessary to inform public health authorities in the future.

Despite these low estimates, seasonal vaccination remains the most effective realistic prevention approach among elderly and high risk groups. A vaccine effectiveness of 30% still reduces by almost a third the risk of severe influenza among vaccinated individuals. Based on a 35% IVE against influenza-attributable death, Bonmarin et al. estimated that on average, 2,000 deaths were avoided each year through influenza vaccination in France (119).

5.2.2 (Sub)type specific vaccine effectiveness

Over the past six influenza seasons, data from ECDC sentinel surveillance indicates that influenza A viruses have predominated in five of them (Annex 2, supplementary table 1). Overall, 71% of viruses reported with type information were influenza A viruses; among them, two third were A(H3N2) viruses. Among influenza B viruses, where lineages were less often reported compared with subtype among influenza A viruses, there was an equal distribution of Victoria and Yamagata viruses.

Between 2011 and 2017, while influenza A(H1N1)pdm09 and B viruses systematically co-circulated with another (sub)type of influenza, two seasons (2011-12 and 2016-17) were marked by a quasi-exclusive circulation of A(H3N2) viruses. Both these two A(H3N2) seasons were associated with an excess mortality among the elderly (200,201). Influenza B viruses circulated mainly in three seasons and were matched with the vaccine lineage in two seasons (2012-13 and 2014-15).

In our study, 63% of confirmed cases were infected with A(H3N2) viruses, 22% with A(H1N1)pdm09, 2% with non-subtyped A viruses and 13% with B viruses. We observed large differences in age group specific virus (sub)type distribution. The proportion of A(H1N1)pdm09 viruses decreased with increasing age while the proportion of A(H3N2) viruses was higher among older age groups. Lower incidence of influenza A(H1N1)pdm09 among elderly compared with younger age groups has been previously described (202) and may be attributed to priming by previous natural infection in this age group. Indeed, exposure to a 1918-like H1N1, that circulated until 1930, may have contributed to the induction of a cross-reactive antibody response to A(H1N1)pdm09 (203). This priming may also affect the severity of the influenza A(H1N1)pdm09 illness, which was reported to be milder among elderly (204). The age distribution of GP attended cases of influenza A(H3N2) usually also suggest a lower proportion of elderly compared with the general population (205). However, the older age groups are over-represented among A(H3N2) hospitalised cases (206).

5.2.2.1 IVE against influenza A(H1N1)pdm09

A(H1N1)pdm09 circulating and vaccine strains have remained stable over our study period. Higher incidence and severity of A(H1N1)pdm09 have been consistently reported among younger age group (203,207). We found a higher IVE (46%) among adults aged 18-65 years old compared with older age groups (32% among patients aged 65-79 years and 39% among ≥80 years). Recent natural infections, playing a booster role on the immunological response to seasonal vaccination among younger age groups (208) and immune senescence among the elderly (209) may partially explain the observed differences in age group specific IVE against A(H1N1)pdm09 viruses.

We also observed a residual protective effect of previous vaccination on the risk of hospitalised A(H1N1)pdm09 influenza, most likely explained by its antigenic stability over time (210,211). New vaccination among patients who had received doses of vaccines in both the two previous seasons was not effective, as if the level of protection conferred by vaccination against A(H1N1)pdm09 was plateauing after a certain number of doses received. Longer term observation of the effect of repeated vaccination against A(H1N1)pdm09 would be useful to understand this mechanism.

5.2.2.2 IVE against influenza A(H3N2)

The majority of cases recruited were infected by A(H3N2) viruses, which circulated in 4/5 seasons covered by our network. Two seasons (2011-12 and 2016-17) were strongly dominated by A(H3N2) viruses and both seasons were associated with high mortality and poor IVE in elderly. Our network was disrupted during the 2014-15 season, which was also dominated by A(H3N2) viruses in the northern hemisphere and a vaccine performance close to null against primary and secondary care outcomes (127,141,183,185,191). Our meta-analysis suggested a particularly low IVE in seasons dominated by A(H3N2) viruses antigenically distinct from the vaccine strains, especially among the elderly. Published studies suggest that A(H3N2) epidemics are associated with higher severe morbidity and mortality than A(H1N1) and B viruses epidemics (212,213). The relative excess mortality associated with A(H3N2) viruses was found to be higher among older adults compared with younger age groups (214,215).

Early indication of A(H3N2) virus circulation through virological surveillance should lead public health authorities to start promoting alternative preventive options, especially among elderly.

5.2.2.3 IVE against influenza B

Based on data from European sentinel surveillance at primary care level, 29% of cases reported between 2011 and 2017 were caused by influenza B. Half of influenza B cases for which a lineage was reported were of a different lineage than the one included in the vaccine, suggesting that the choice of lineage to include in the vaccine is not performing well (Annex 2, supplementary table 2). Based on this data, about 15% of influenza cases were due to unmatched influenza B viruses.

In our hospital network, influenza B cases accounted for 13% of the total number of cases included and were reported in 2012-13 and 2015-16. IVE against influenza B was higher than IVE against A(H3N2) and A(H1N1)pdm09 in all age groups; it was 66%, 38% and 46% among patients aged 18-64, 65-79 and 80 years and above respectively. Due to low proportion of B viruses characterised, data from InNHOVE/I-MOVE+ did not allow us to compute lineage specific IVE. However, our results from 2015-16, when data from European virological surveillance indicated a vast majority of unmatched circulating viruses (216), suggested a good level of cross lineage protection. Cross protection has been suggested by other studies, especially reporting IVE against medically attended influenza (217,218).

To justify the need to introduce the QIV in influenza vaccine programmes, Ambrose et al. relied on vaccine efficacy results of 22% to 52% against unmatched lineages and 78% against vaccine matched lineages (131,219,220). Considering the extreme situation of a low (22%) and high (78%) IVE against unmatched and matched lineage respectively, and the proportion of unmatched lineages out of all viruses (15%) observed through ECDC sentinel surveillance, we can approximate the additional proportion of cases prevented by the QIV compared to the TIV among vaccinated patients. Assuming the same protection of both vaccine types against A(H3N2), A(H1N1)pdm09 and matched B viruses, the additional proportion of prevented cases (due to unmatched B viruses) would be 11.7% (0.78x0.15) for QIV and 3.3% (0.22x0.15) for TIV. Based on these optimistic hypotheses, we could expect an extra 8.4% of influenza cases prevented by the QIV among vaccinated individuals. However, our data suggest only 13% of hospitalised cases due to any influenza B viruses (30% of which occurred in a season when unmatched viruses circulated) and IVE point estimates against influenza B were higher in the unmatched compared to the matched season.

We observed a relatively low burden of unmatched influenza B viruses in secondary care and we observed cross-protection conferred by the TIV. Our data remains scarce; gathering more evidence to assess the potential benefits of introducing QIV among adults to prevent severe influenza would be needed. Moreover, considering the observed low concordance between vaccine and circulating strains, and assuming some residual protection from previous year vaccine (149) (not observed at the hospital level), a systematic alternation of Yamagata and Victoria lineage in the vaccine would seem reasonable (133).

5.2.3 Early VE estimates

Our networks were able to provide early estimates of IVE in 2015-16 and 2016-17, and to publish them in 2016-17. In 2016-17, our article was published on 16 February in Eurosurveillance (187). By that time, based on our data, 97% of hospitalised cases of influenza had already occurred, making the usefulness of such publication arguable. To timely inform public health decisions, we need to increase the timeliness our data collection, transfer and analysis and try to get closer to real-time estimation of IVE. We have developed a web-based questionnaire to collect data at the hospital level. At the moment, this solution is used by three study sites only. We are currently assessing the possibility to implement this web-based application in other study sites. This option would increase the timeliness of the data transfer and cleaning steps. However, some study sites retrieve periodically information from registries. As long as no automatic transfer of this data from the registers to a web-based platform exist, we will not be able to have a real-time estimation of IVE.

In 2016-17, early risk assessment published on ECDC website reported first indications of low IVE among elderly, based on Finnish and Swedish electronic databases (181). Early estimates suggesting low vaccine performance could be used to promote alternative prevention options. To standardise the response of health authorities to indications of low vaccine performance, developing a frame of actions according to different levels of IVE would be interesting. Such a document could, for instance, indicate the threshold to reach before issuing recommendations regarding the prophylactic use of antivirals in population at-risk of severe outcome. Rationales to establish these thresholds would most likely rely on cost-effectiveness analysis combining data on the effectiveness of vaccines, antivirals and NPIs.

Early estimates may also be useful for the GSIRS to choose between several available strains for vaccine content. In seasons when several clades of a given subtype co-circulate, the GSIRS could decide to recommend the strain against which the vaccine performs best. Virological surveillance at the

European level currently relies on convenient selection of strains to characterise. It is common for reference laboratories to characterise atypical cases, including severe and/or vaccinated cases. Relying on this selection approach to measure IVE would lead to biased estimates. In order to avoid this, in 2016 the partners of the I-MOVE+ GP network agreed on a common protocol for specimen selection and characterization of a random sample of specimens. It relies on a systematic selection approach, with variable sampling fractions throughout the season. The objective is to characterise a large number of specimens early in the season to be able to compute clade-specific IVE before the strain selection committee. Due to financial reason, systematic specimen characterization is not yet implemented at the hospital level.

5.2.4 VE estimates by specific groups (age/comorbidities)

We were able to measure IVE against influenza hospitalisation in elderly patients with underlying chronic lung and cardiac diseases as well as in patients with cancer and diabetes. We could not identify any type of underlying conditions associated with particularly low IVE. Our estimates remain imprecise but, to date, such data was lacking (134–139,221) and questions were raised about influenza vaccine performance among patients with disease-associated immunosuppression (due to the disease itself or due to treatment)(49–51). Furthermore, several studies suggested that vaccines were safe in patients with immunosuppressive treatment, including cancer patients (221). In this context, and keeping in mind that influenza vaccination remains the most effective prevention measure against seasonal influenza, our results will help specialist physicians to offer influenza vaccination to their patients. Further data collection on treatment and analysis of their effect on IVE would be interesting. Of particular interest is the use of statins as a modifier of IVE.

Statins are a class of drugs primary used to lower cholesterol levels by inhibiting the enzyme HMG-CoA reductase. Published studies suggest that statins may reduce severity of laboratory confirmed influenza on the one hand and decrease IVE on the other hand. Statins induce suppression of T-cell activation (222) and have immunomodulatory anti-inflammatory effects (223). In a prospective study among hospitalised patients with laboratory confirmed influenza, Vandermeer et al. observed a 41% reduction in case fatality within 30 days of positive influenza test among statin users compared to non-statin users (224). Some researchers suggest that statin could be used as a treatment for influenza in case of shortage of antivirals, as during the 2009 pandemic (225). On the other hand, recent papers have suggested that statin's immunomodulatory effects could negatively interfere with seasonal influenza vaccine (226–228), especially against A(H3N2) viruses. In a recent study, McLean et al. observed a protective effect of either statin use only or vaccine uptake only against medically attended influenza (228). However, they found that the risk of medically attended influenza was the highest among vaccinated statin users. In stratified analyses, McLean et al. suggested that statins were more likely to decrease IVE among patients vaccinated in the previous influenza seasons and that non-synthetic statins decreased further the IVE compared to synthetic statins. Further documentation and understanding of the interaction between statins and influenza vaccination is needed to decide whether statins users should be recommended influenza vaccination. The public health impact of such decision may be worth considering since more than one billion individuals are currently treated with statins worldwide (229). Our hospital network would certainly be an interesting setting to collect information about statin use and investigate the effect of statin on IVE. However, standardising the collection of treatment data in terms of brand name, duration and posology will be challenging. We will aim at piloting such data collection in volunteering study sites in 2017-18.

In our study and in the meta-analysis, we reported lower IVE among elderly compared to younger adults. Considering their increased risk of severe outcome, lower vaccine performance is worrying. One way forward could be to vaccinate those responding best to vaccination in order to indirectly protect the elderly. In a recent meta-analysis, Thomas et al. concluded that current data from studies looking at the effect of HCW's vaccination on influenza incidence among nursing home residents were not conclusive (230). Authors stressed the need for high quality randomised control trials to estimate the effectiveness of HCW's vaccination against laboratory confirmed influenza among residents. Promoting such vaccination strategies should anyway rely on the individual protection conferred by the vaccine to the vaccinees rather than on their indirect effect among elderly. In England and Wales, in 2013, a cost effectiveness study concluded that targeting children in addition to older adults was the most effective way to reduce overall influenza morbidity and mortality (231). These conclusions were mostly driven by the role of influenza spreader played by children. Vaccinating them would therefore indirectly protect the rest of the population. School vaccination programme were consecutively launched, targeting children 2-17 years with LAIV. This approach will need to be evaluated and could represent an interesting option for other countries. However, dispensing additional vaccines to children in order to protect the elderly might be challenging in countries facing increasing vaccine hesitancy (150).

5.2.5 VE by brand or type of vaccine

We were able to compute brand-specific IVE for the two vaccine brands with the largest market shares in Europe. We ended up with imprecise results and could not take into account factors that could affect these estimates, such as history of previous vaccination (191). Furthermore, we could not compare IVE estimates between the products since they were provided in different study sites and seasons.

At the moment, the EMA has not given specific requirements in terms of outcome to be used for IVE estimates or precisions required around IVE estimates. Such information would be crucial to further assess the feasibility of measuring brand specific IVE. In the hospital setting, to measure an IVE of 30% with an absolute precision of 10% and a vaccine coverage of 25% (assuming a market share of 50% and a vaccine coverage of 50%), we would need to include 1,897 cases and 4,426 controls for a specific brand IVE estimate. At the moment, no hospital network can achieve such high sample size. Furthermore, most vaccines have much lower market share. Finally, while GP networks lead to higher sample size, they recruit a population with low vaccine coverage and a low proportion of elderly. It is therefore crucial that EMA clarifies their expectations and provide means for research networks to achieve their goals.

Product or type specific IVE are important to guide public health actions. In the USA, in June 2014, the advisory committee for immunization practices (ACIP) published a preferential recommendation for the use of LAIV, over the IIV, for children aged 2-8 years (232). However, several TND studies reported that 2013-14 LAIV VE was significantly lower than IIV VE among children and adolescent (233,234). These studies reported low LAIV VE, especially against A(H1N1)pdm09. MedImmune post-licensure study reported that LAIV VE was similar to IIV against influenza B-Yamagata, but low against A(H1N1)pdm09 (235). MedImmune replaced the A(H1N1) component for the 2015-16 season but results from 2015-16 LAIV VE were very low against A(H1N1)pdm09 and B/Yamagata. Based on this evidence, the US ACIP recommended LAIV not to be used in 2016-17 (236). This was the first example of the use of post-marketing results to de-recommend an influenza vaccine product. While differences between vaccine types (LAIV and IIV) effectiveness were statistically significant, they relied on observational studies that were not designed to compare two products. It raises questions about what

level of evidence is needed to make preferential recommendations, de-recommend a product or to re-recommend a product. Regulatory agencies, such as the EMA (or the FDA) should provide clear guidance to make informed decision in terms of product specific recommendations.

Adjuvanted vaccines are designed to induce an enhanced immunological response from the host. They could provide an interesting solution to the poor vaccine performance currently observed among the elderly. In the meantime high-dose influenza vaccine was found to reduce more the risk of laboratory confirmed influenza compared with standard dose vaccine in a RCT among elderly (237). Evidence of the superiority of these vaccines in preventing severe outcome should however be tested through unbiased studies. RCTs, comparing non-adjuvanted, adjuvanted and high dose inactivated vaccines would be relevant.

5.2.6 Effect of repeated vaccination

Our results, based on four influenza seasons, suggest that, regardless of patients' recent vaccination history, current seasonal vaccine confers some protection to vaccinated patients against hospitalised influenza A(H3N2) and B in all instances. They also suggest a residual effect of previous vaccination on influenza A(H1N1)pdm09 and the absence of added protection from current vaccination against that subtype among those previously vaccinated.

Current studies provide limited evidence on the effect of repeated vaccination on the IVE. A first challenge relates to the limited statistically power due to small sample size in groups of individuals with changing vaccination status. Most individuals engage in the same pattern of vaccination (or non-vaccination) every year (238–240). Reasons for individuals to vaccinate for the first time, interrupt vaccination habits or continue to vaccinate may be linked to their risk of disease. For instance, influenza illness may stimulate individuals to be vaccinated for the first time. Natural immunity acquired from this natural infection will likely decrease their risk of disease the next year and artificially inflate the measure of vaccine performance. The cohort effect associated with different vaccination pattern (e.g. first vaccinees naturally younger than repeated vaccinees) will involve different past exposures to natural infections and affect the influenza antibody landscape (241). Adjusting our IVE estimates on age might not be enough to take into account these different pre-disposition to influenza infection (242). Using TND studies, it is difficult to retrieve reliable information on past vaccinations prior to two seasons ago and we have no information about previous natural infections.

Better understanding the immunological effects of annual vaccination is needed to interpret IVE data and, ultimately, guide public health policies. According to the widely accepted antigenic distance hypothesis (142), previous vaccination may alter the response to current season vaccination. However, this model currently takes into account a single prior season while studies suggest that multiple prior vaccinations may act differently than a single prior vaccination on IVE (149). Better defining the antigenic closeness between successive vaccine strains to expect a negative interference of previous on current vaccine performance could help WHO in selecting vaccine component and the public health authorities to forecast poor IVE according to the vaccine components and viruses circulating in the early course of an influenza season.

Understanding these interactions is crucial in a context of universal vaccination, where adults may receive up to 60-70 doses of influenza vaccination in their life. Further research in that direction may inform optimal strategies for vaccine strain selection and/or vaccination intervals in different age group or population sub-groups. Multi-season cohort studies measuring the cumulative risk of laboratory confirmed clinical influenza according to different vaccination patterns are needed to address these issues. To be ethical, such studies should be conducted in population groups among

whom influenza vaccination is not recommended. To be unbiased, vaccination patterns should be randomly allocated to account for differences in pre-study exposure to infection and vaccination.

6 CONCLUSION

Based on our work, repeated and precise measures of IVE against hospitalised outcome may now be used to revise cost-effectiveness analysis and potentially, vaccination strategies.

Our results indicate a low IVE against influenza associated hospitalisation among elderly, who remain the population with the highest severe morbidity and mortality, especially in A(H3N2) seasons. More immunogenic vaccines exist and RCTs should be considered, among elderly, to determine their relative performance. It would be informative and ethical to conduct comparative vaccine efficacy studies between non adjuvanted TIV, adjuvanted TIV and high dose vaccines among elderly and take as an endpoint hospitalisation with laboratory confirmed influenza. Measuring the effectiveness and impact of alternative prevention approaches among them is needed. It will be interesting to follow the English approach of indirect protection of the elderly through children vaccination. RCTs to measure the effect of vaccinating health care workers on the risk of influenza related severe laboratory confirmed outcome in elderly would also be relevant. Finally, in the current situation and before gathering these evidences, it would be useful to more aggressively promote the use of antivirals in case of A(H3N2) epidemics while monitoring resistance to antivirals among elderly. Computing real-time IVE could help guiding these within-season public health actions. In the meantime, promoting the use of non-pharmaceutical approaches, and evaluate their effect, should be undertaken whatever the circulating (sub)type.

Further meta-analyses are needed to provide strong evidence for or against the use of QIV to protect adults from hospitalised influenza outcome. Considering the challenges to select the right lineage to include in the vaccine, engaging in systematic alternation of Yamagata and Victoria lineage in the vaccine should be discussed.

Engaging in large prospective cohort studies to determine the role of repeated vaccination on the IVE is crucial as it could lead to revising the strategies for vaccine strain selection or time intervals between vaccinations. However, such studies are expensive and would require several years of observation to reach conclusive results.

Despite the low IVE, seasonal vaccination remains the most effective realistic prevention approach among elderly and high-risk population. Combining its use with antivirals and non-pharmaceutical approaches will most likely lead to reducing the number of mild, hospitalised and fatal cases. In a context of decreasing vaccine coverage and distrust towards vaccines in general, communication campaigns to promote influenza vaccine should deliver clear messages and transparently report results from independent studies. To promote its use, communication could focus on the number of averted (hospitalised) cases and deaths rather than on IVE, which is a difficult concept to understand by the general population.

The InNHOVE and I-MOVE+ networks have succeeded in showing that multicentre studies to measure IVE against laboratory confirmed hospitalised influenza were feasible. Scientists from this network are motivated and value the contribution of this study to the general knowledge and understanding of influenza vaccination. Regardless of the future of our funding options for the European network, there

are good reasons to believe that hospital based IVE studies have become necessary to evaluate our public health policies.

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ANNEX 1: SUPPLEMENTARY MATERIAL – META-ANALYSIS ARTICLE

Table sup 1: Study characteristics of articles included in the meta-analysis

Digital object identifier (DOI)	Author and year of publication	Journal	Country	Vaccine type	Influenza season(s)	Diagnosis test used	Max delay symptoms onset - swabbing	Clinical inclusion criteria	Study population	Adult age group included
10.1016/j.vaccine.2010.09.042	Puig-Barbera_2010	Vaccine	Valencia, Spain	monovalent pandemic	2009-2010	RT-PCR	75% of swabs collected within 7 days	ILI	All	18 years and above
10.1093/infdis/jiq014	Andrews_2011	JID	England	monovalent pandemic	2009-2010	RT-PCR	>80% of swabs taken within 7 days	ILI	target group for vaccination	25 years and above
10.1186/1471-2334-12-127	Hellenbrand_2012	BMC Inf Dis	Germany	monovalent pandemic	2009-2010	RT-PCR and Haemagglutination inhibition (HI)	7 days	ARI	Community dwelling	Under 65 years

10.1016/j.vaccine.2011.07.087	Cheng_2011	Vaccine	Australia	TIV	2010	RT-PCR	no limit	Suspected influenza (as defined by clinicians)	All	18 years and above
10.1093/cid/cis574	Treanor_2013	CID	US	TIV	2010-2011	RT-PCR	7 days	ARI	Community dwelling	18 years and above
10.1186/1471-2458-13-191	Martinez-Baz_2013	BMC Pub Health	Spain	TIV	2010-2011	RT-PCR	7 days	ILI	Community dwelling	18 years and above
10.1371/journal.pone.0068760	Cheng_2013	PlosOne	Australia	TIV	2011	RT-PCR	no limit	Suspected influenza (as defined by clinicians)	All	18 years and above
10.1111/irv.12233	Dawood_2013	IORV	Thailand	TIV	2011	RT-PCR	no limit	ARI	All	50 years and above

10.5694/mja15.01017	Kelly_2016	MJA	Australia	TIV	2011, 2012 and 2013	RT-PCR	7 days	Suspected influenza (as defined by clinicians)	All	18 years and above
10.1371/journal.pone.0059681	Rondy_2013	PlosOne	EU	TIV	2011-2012	RT-PCR	7 days	ILI	Community dwelling target group	18 years and above
10.1128/CVI.00009-13	Choi_2013	CVI	Korea	TIV	2010-2011	rapid antigen test (RAT), PCR test, or influenza virus culture	2 days	ILI	All	18 years and above
10.1093/cid/cit404	Kwong_2013	CID	Canada	TIV	2010-2011	RT-PCR	no limit	Suspected influenza (as defined by clinicians)	Community dwelling	65 years and above
10.1016/j.vaccine.2014.04.013	Turner_vac_2014	Vaccine	New Zealand	TIV	2012	RT-PCR or viral culture	7 days	SARI	All	18 years and above

PMID*: 24890961	Cheng_CDI_2013_1	Comm Dis Intell	Australia	TIV	2012	RT-PCR	no limit	Suspected influenza (as defined by clinicians)	All	18 years and above
10.2807/1560-7917.ES2015.20.2.21011	Rondy_2014	Eurosurveillance	EU	TIV	2012-2013	RT-PCR	7 days	ILI	Target group	18 years and above
10.2807/1560-7917.ES2014.19.34.20884	Turner_Eur_2014_1	Eurosurveillance	New Zealand	TIV	2013	RT-PCR	7 days	SARI	All	18 years and above
PMID*: 25222208	Cheng_CDI_2013_2	Comm Dis Intell	Australia	TIV	2013	RT-PCR	no limit	Suspected influenza (as defined by clinicians)	All	18 years and above
10.2807/1560-7917.ES2014.19.9.20729	McNeil_2014	Eurosurveillance	Canada	TIV	2013-2014	RT-PCR or viral culture	7 days	Any respiratory infection or diagnosis, or any respiratory or influenza-like symptom	All	16 years and older

10.1080/21645515.2015.1126013	Rondy_2016	Hum Vacc and Imm	EU	TIV	2013-2014	RT-PCR	7 days	ILI	Target group	18 years and above
10.1016/j.vaccine.2015.10.016	Cheng_2014	Vaccine	Australia	TIV	2014	RT-PCR	7 days	Suspected influenza (as defined by clinicians)	All	16 years and older
10.1016/j.vaccine.2015.11.073	Pierse_2015	Vaccine	New Zealand	TIV	2014	RT-PCR or viral culture	7 days	SARI	All	18 years and above
10.2807/1560-7917.ES2015.20.5.21024	McNeil_2015	Eurosurveillance	Canada	TIV	2014-2015	RT-PCR or viral culture	7 days	Any respiratory infection or diagnosis, or any respiratory or influenza-like symptom	All	16 years and older
10.2807/1560-7917.ES2015.20.8.21044	Puig-Barbera_2015	Eurosurveillance	Spain	TIV	2014-2015	RT-PCR	7 days	ILI	All	18 years and above

10.1371/journal.pone.0098716	Choi_2016	Plos One	Korea	TIV	2011-2012	rapid antigen test (RAT), PCR test, or influenza virus culture	2 days	ILI	All	18 years and above
10.1371/journal.pone.0132195	Gilca_2016	Plos One	Canada	TIV	2014-2015	RT-PCR	7 days	cough, sore throat, or fever/feverishness of unknown etiology	All	65 years and above
10.1016/j.vaccine.2016.01.054	Castilla_Vac_2016	Vaccine	Spain	TIV	2014-2015	RT-PCR	7 days	ILI	all	18 years and above
10.1016/j.vaccine.2016.03.068	Qin_2016	Vaccine	China	TIV	2014-2015	RT-PCR	7 days	ILI	All	18 years and above
10.1002/jmv.24551	Lytras_2016	J Med Virology	Greece	TIV	2014-2015	RT-PCR	>90% taken up to 10 days after onset	Suspected influenza (as defined by clinicians)	All	18 years and above

10.1093/cid/ciw432	Petrie_2016	CID	USA	TIV	2014-2015	RT-PCR	10 days	ARI	All	18 years and above
10.2807/1560-7917.ES.2016.21.1.30101	Bissielo_2015	Eurosurveillance	New Zealand	TIV	2015	RT-PCR or viral culture	7 days	SARI	All	18 years and above

Table sup 2: List of articles excluded after full review and reason for exclusion

Digital object identifier (DOI)	Author and year of publication	Year	Country	Reason for exclusion
10.1371/journal.pmed.1000258	Skowronski_2010	Plos Medicine	Canada	non TND study design
10.1371/journal.pone.0010722	Johns_2010	PlosOne	USA	Before 2009-10 or effects of seasonal on pandemic
10.1093/infdis/jiq076	Talbot_2011	JID	USA	Several seasons pooled
https://doi.org/10.1016/j.vaccine.2011.01.046	Pebody_2011	Vaccine	England	Before 2009-10 or effects of seasonal on pandemic
10.1186/1471-2334-11-196	Steens_2011	BMC Inf Dis	Germany	non TND study design
https://doi.org/10.1016/j.vaccine.2011.11.024	Castilla_2011	Vaccine	Navarre, Spain	Duplicated estimates or study sites included in multicentre
https://doi.org/10.1016/j.vaccine.2011.11.033	Amour_2012	Vaccine	France	Before 2009-10 or effects of seasonal on pandemic
	Bonmarin_2012	Eurosurveillance	France	non TND study design
https://doi.org/10.1016/j.vaccine.2012.06.090	Dominguez_2012	Vaccine	Spain	non TND study design
https://doi.org/10.1016/j.vaccine.2012.07.006	Puig-Barbera_2012	Vaccine	Valencia, Spain	non TND study design (case-case study design)
	Castilla_Eur_2013	Eurosurveillance	Spain	Duplicated estimates or study sites included in multicentre
https://doi.org/10.1093/cid/cit194	Castilla_CID_2013	CID	Spain	non TND study design
10.4161/hv.23090	Dominguez_2013	Hum Vacc Immuno	Spain	non TND study design
	Thomas_2013	EpidemiolInfect	UK	non TND study design
	Widgren_2013	Eurosurveillance	Sweden	non TND study design
10.1186/s12879-015-0882-3	Remschmidt_2015	BMC Inf Dis	Germany	non TND study design
10.1080/21645515.2015.1038002	Martinez-Baz_2015	Hum Vacc and Imm	Spain	Duplicated estimates or study sites included in multicentre
10.1001/jama.2015.12160	Grijalva_2016	JAMA	USA	Several seasons pooled
10.1016/j.vaccine.2016.02.037	Talbot_2016	Vaccine	USA	Several seasons pooled
	Castilla_Eur_2016	Eurosurveillance	Spain	Duplicated estimates or study sites included in multicentre

Table sup 3: List of estimates included in the meta-analysis

Type or subtype	Age group	Vaccine type	Author and year of publication	Country	Antigenic Similarity between A(H3N2) vaccine and circulating strains	Hemisphere	Influenza season	VE	95%CI	Meta estimate*
ALL	16-64	TIV	Martinez-Baz_2013	Spain		North	2010-2011	51	(-42;83)	
ALL	16-64	TIV	Choi_2013	Korea		North	2010-2011	53	(36;71)	yes
ALL	16-64	TIV	Rondy_2013	EU		North	2011-2012	39	(-4;64)	
ALL	16-64	TIV	Rondy_2014	EU		North	2012-2013	49	(15;69)	
ALL	16-64	TIV	Turner_vac_2014	New Zealand		South	2012	51	(28;67)	
ALL	16-64	TIV	McNeil_2014	Canada		North	2013-2014	60	(39;74)	
ALL	16-64	TIV	Turner_Eur_2014_1	New Zealand		South	2013	61	(34;77)	
ALL	16-64	TIV	Rondy_2016	EU		North	2013-2014	50	(10;72)	
ALL	16-64	TIV	Castilla_Vac_2016	Spain		North	2014-2015	36	(-78;77)	
ALL	16-64	TIV	McNeil_2015	Canada		North	2014-2015	11	(-66;52)	
ALL	16-64	TIV	Cheng_2014	Australia		South	2014	50	(35;61)	
ALL	16-64	TIV	Qin_2016	China		North	2014-2015	-67	(-212;11)	
ALL	16-64	TIV	Petrie_2016	USA		North	2014-2015	40	(-13;68)	
ALL	16-64	TIV	Bissielo_2015	New Zealand		South	2015	46	(1;70)	
ALL	65+	TIV	Martinez-Baz_2013	Spain		North	2010-2011	26	(-82;70)	
ALL	65+	TIV	Kwong_2013	Canada		North	2010-2011	42	(29;53)	
ALL	65+	TIV	Choi_2013	Korea		North	2010-2011	0	(-156;61)	
ALL	65+	TIV	Rondy_2013	EU		North	2011-2012	17	(-7;36)	
ALL	65+	TIV	Rondy_2014	EU		North	2012-2013	36	(14;53)	
ALL	65+	TIV	Turner_vac_2014	New Zealand		South	2012	6	(-51;42)	
ALL	65+	TIV	Cheng_CDI_2013_1	Australia		South	2012	32	(9;50)	
ALL	65+	TIV	Turner_Eur_2014_1	New Zealand		South	2013	34	(-28;66)	
ALL	65+	TIV	Cheng_CDI_2013_2	Australia		South	2013	51	(16;71)	
ALL	65+	TIV	McNeil_2014	Canada		North	2013-2014	58	(35;73)	
ALL	65+	TIV	Qin_2016	China		North	2013-2014	27	(-114;75)	
ALL	65+	TIV	Rondy_2016	EU		North	2013-2014	37	(9;57)	
ALL	65+	TIV	Petrie_2016	USA		North	2014-2015	48	(-33;80)	

ALL	65+	TIV	McNeil_2015	Canada	North	2014-2015	-25	(-74;10)	
ALL	65+	TIV	Gilca_2016	Canada	North	2014-2015	-2	(-105;49)	
ALL	65+	TIV	Lytras_2016	Greece	North	2014-2015	30	(-3;53)	
ALL	65+	TIV	Puig-Barbera_2015	Spain	North	2014-2015	40	(13;59)	
ALL	65+	TIV	Cheng_2014	Australia	South	2014	52	(36;63)	
ALL	65+	TIV	Castilla_Vac_2016	Spain	North	2014-2015	24	(-25;53)	
ALL	65+	TIV	Qin_2016	China	North	2014-2015	-13	(-1220;90)	
ALL	65+	TIV	Bissielo_2015	New Zealand	South	2015	52	(-14;79)	
ALL	all	TIV	Dawood_2013	Thailand	South	2010	17	(-127;70)	
ALL	all	TIV	Choi_2013	Korea	North	2010-2011	50	(25;68)	
ALL	all	TIV	Martinez-Baz_2013	Spain	North	2010-2011	39	(-18;69)	
ALL	all	TIV	Treanor_2013	US	North	2010-2011	56	(26;74)	
ALL	all	TIV	Cheng_2011	Australia	South	2010	22	(-10;52)	
ALL	all	TIV	Rondy_2013	EU	North	2011-2012	23	(3;38)	
ALL	all	TIV	Choi_2016	Korea	North	2011-2012	-16	(-73;22)	
ALL	all	TIV	Cheng_2013	Australia	South	2011	45	(8;66)	
ALL	all	TIV	Dawood_2013	Thailand	South	2011	52	(-1;77)	
ALL	all	TIV	Rondy_2014	EU	North	2012-2013	40	(23;54)	
ALL	all	TIV	Turner_vac_2014	New Zealand	South	2012	44	(26;62)	yes
ALL	all	TIV	Kelly_2016	Australia	South	2012	35	(8;54)	
ALL	all	TIV	McNeil_2014	Canada	North	2013-2014	59	(44;69)	
ALL	all	TIV	Turner_Eur_2014_1	New Zealand	South	2013	56	(37;76)	yes
ALL	all	TIV	Kelly_2016	Australia	South	2013	52	(19;71)	
ALL	all	TIV	Rondy_2016	EU	North	2013-2014	40	(18;56)	
ALL	all	TIV	Qin_2016	China	North	2014-2015	-65	(-175;45)	yes
ALL	all	TIV	McNeil_2015	Canada	North	2014-2015	-17	(-56;13)	
ALL	all	TIV	Castilla_Vac_2016	Spain	North	2014-2015	26	(-14;52)	
ALL	all	TIV	Pierse_2015	New Zealand	South	2014	52	(30;74)	yes
ALL	all	TIV	Petrie_2016	USA	North	2014-2015	43	(5;66)	
ALL	all	TIV	Cheng_2014	Australia	South	2014	52	(42;60)	
ALL	all	TIV	Puig-Barbera_2015	Spain	North	2014-2015	33	(6;53)	
ALL	all	TIV	Bissielo_2015	New Zealand	South	2015	48	(20;76)	yes
A(H1N1)pdm09	16-64	pandemic	Hellenbrand_2012	Germany	North	2009-2010	50	(-380;100)	
A(H1N1)pdm09	16-64	TIV	Martinez-Baz_2013	Spain	North	2010-2011	50	(-46;83)	
A(H1N1)pdm09	16-64	TIV	Rondy_2016	EU	North	2013-2014	61	(-2;85)	

A(H1N1)pdm09	16-64	TIV	McNeil_2014	Canada		North	2013-2014	54	(22;73)
A(H1N1)pdm09	65+	TIV	Martinez-Baz_2013	Spain		North	2010-2011	5	(-145;63)
A(H1N1)pdm09	65+	TIV	Kwong_2013	Canada		North	2010-2011	90	(51;98)
A(H1N1)pdm09	65+	TIV	Rondy_2014	EU		North	2012-2013	16	(-49;53)
A(H1N1)pdm09	65+	TIV	Rondy_2016	EU		North	2013-2014	35	(-20;65)
A(H1N1)pdm09	65+	TIV	McNeil_2014	Canada		North	2013-2014	63	(35;79)
A(H1N1)pdm09	all	pandemic	Andrews_2011	England		North	2009-2010	1	(-156;62)
A(H1N1)pdm09	all	pandemic	Puig-Barbera_2010	Valencia, Spain		North	2009-2010	90	(48;100)
A(H1N1)pdm09	all	TIV	Cheng_2011	Australia		South	2010	22	(-10;52)
A(H1N1)pdm09	all	TIV	Martinez-Baz_2013	Spain		North	2010-2011	30	(-37;65)
A(H1N1)pdm09	all	TIV	Choi_2013	Korea		North	2010-2011	51	(32;64)
A(H1N1)pdm09	all	TIV	Rondy_2014	EU		North	2012-2013	21	(-25;51)
A(H1N1)pdm09	all	TIV	Rondy_2016	EU		North	2013-2014	43	(6;65)
A(H1N1)pdm09	all	TIV	McNeil_2014	Canada		North	2013-2014	58	(38;72)
A(H1N1)pdm09	all	TIV	Cheng_2014	Australia		South	2014	60	(40;73)
A(H3N2)	16-64	TIV	Rondy_2013	EU	Variant	North	2011-2012	40	(-4;66)
A(H3N2)	16-64	TIV	Turner_vac_2014	New Zealand	Variant	South	2012	51	(28;67)
A(H3N2)	16-64	TIV	Turner_Eur_2014_1	New Zealand	Similar	South	2013	61	(34;77)
A(H3N2)	16-64	TIV	Rondy_2016	EU	Similar	North	2013-2014	8	(-145;65)
A(H3N2)	16-64	TIV	Petrie_2016	USA	Variant	North	2014-2015	40	(-13;68)
A(H3N2)	16-64	TIV	Castilla_Vac_2016	Spain	Variant	North	2014-2015	42	(-122;85)
A(H3N2)	16-64	TIV	McNeil_2015	Canada	Variant	North	2014-2015	8	(-102;58)
A(H3N2)	65+	TIV	Kwong_2013	Canada	Similar	North	2010-2011	40	(26;52)
A(H3N2)	65+	TIV	Rondy_2013	EU	Variant	North	2011-2012	16	(-9;35)
A(H3N2)	65+	TIV	Rondy_2014	EU	Similar	North	2012-2013	58	(14;79)
A(H3N2)	65+	TIV	Turner_vac_2014	New Zealand	Variant	South	2012	6	(-51;42)
A(H3N2)	65+	TIV	Cheng_CDI_2013_2	Australia	Similar	South	2013	51	(16;71)
A(H3N2)	65+	TIV	Rondy_2016	EU	Similar	North	2013-2014	41	(10;62)
A(H3N2)	65+	TIV	Turner_Eur_2014_1	New Zealand	Similar	South	2013	34	(-28;66)
A(H3N2)	65+	TIV	Petrie_2016	USA	Variant	North	2014-2015	48	(-33;80)
A(H3N2)	65+	TIV	Castilla_Vac_2016	Spain	Variant	North	2014-2015	26	(-36;60)
A(H3N2)	65+	TIV	Gilca_2016	Canada	Variant	North	2014-2015	-2	(-105;49)
A(H3N2)	65+	TIV	McNeil_2015	Canada	Variant	North	2014-2015	-33	(-103;13)
A(H3N2)	all	TIV	Rondy_2013	EU	Variant	North	2011-2012	18	(-4;35)
A(H3N2)	all	TIV	Rondy_2014	EU	Similar	North	2012-2013	62	(27;80)

A(H3N2)	all	TIV	Turner_vac_2014	New Zealand	Variant	South	2012	44	(26;62)	yes
A(H3N2)	all	TIV	Turner_Eur_2014_1	New Zealand	Similar	South	2013	56	(37;76)	yes
A(H3N2)	all	TIV	Rondy_2016	EU	Similar	North	2013-2014	38	(8;58)	
A(H3N2)	all	TIV	Castilla_Vac_2016	Spain	Variant	North	2014-2015	25	(-29;57)	
A(H3N2)	all	TIV	McNeil_2015	Canada	Variant	North	2014-2015	-22	(-77;16)	
A(H3N2)	all	TIV	Cheng_2014	Australia	Variant	South	2014	35	(9;54)	
A(H3N2)	all	TIV	Petrie_2016	USA	Variant	North	2014-2015	43	(5;66)	
B	16-64	TIV	Castilla_Vac_2016	Spain		North	2014-2015	39	(-116;83)	
B	16-64	TIV	Cheng_2014	Australia		South	2014	45	(-6;72)	
B	65+	TIV	Kwong_2013	Canada		North	2010-2011	13	(-77;58)	
B	65+	TIV	Rondy_2014	EU		North	2012-2013	37	(10;56)	
B	65+	TIV	Castilla_Vac_2016	Spain		North	2014-2015	12	(-67;54)	
B	65+	TIV	Cheng_2014	Australia		South	2014	23	(-71;65)	
B	all	TIV	Choi_2013	Korea		North	2010-2011	-13	(-2280;95)	
B	all	TIV	Choi_2016	Korea		North	2011-2012	-36	(-180;34)	
B	all	TIV	Rondy_2014	EU		North	2012-2013	43	(21;59)	
B	all	TIV	Cheng_2014	Australia		South	2014	39	(0;63)	
B	all	TIV	Castilla_Vac_2016	Spain		North	2014-2015	23	(-34;56)	

*Study specific age group IVE meta-estimates computed based on smaller age group breakdown estimates

Table sup 4: Pooled seasonal vaccine effectiveness (VE) against influenza hospitalizations by type and subtype of influenza virus and by age group, restricted to studies using clear clinical criteria for patients inclusion

	Pooled VE (%)	95%CI	number of VE estimates	p-value for heterogeneity	I^2
Any influenza					
All adults	39	31;48	19	0.003	54
Under 65 years	52	44;59	13	0.697	0
65 years and above	32	21;43	16	0.148	27
A(H1N1)pdm09					
All adults	49	39;60	5	0.425	0
Under 65 years	55	34;76	3	0.948	0
65 years and above	44	19;69	4	0.240	29
A(H3N2)					
All adults	37	23;52	8	0.012	61
Under 65 years	50	38;62	7	0.775	0
65 years and above	27	11;43	9	0.169	31
B					
All adults	38	21;55	4	0.471	0
Under 65 years	ONLY ONE ESTIMATE				
65 years and above	34	12;55	2	0.451	0

Table sup 5: Pooled seasonal vaccine effectiveness (VE) against influenza hospitalizations by type and subtype of influenza virus and by age group, restricted to studies using exclusively RT-PCR for laboratory testing

	Pooled VE* (%)	95%CI	number of VE estimates	p-value for heterogeneity	I^2
Any influenza					
All adults	43	38;49	20	0,343	9
Under 65 years	50	42;57	11	0,811	0
65 years and above	37	30;44	16	0.688	0
A(H1N1)pdm09					
All adults	40	22;58	5	0.134	43
Under 65 years	58	22;94	2	0.774	0
65 years and above	25	-6;57	3	0.788	0
A(H3N2)					
All adults	41	30;51	8	0.127	38
Under 65 years	51	39;64	6	0.830	0
65 years and above	31	18;44	8	0.398	4
B					
All adults	40	25;55	3	0.721	0
Under 65 years	45	8;81	2	0.907	0
65 years and above	33	12;53	3	0.720	0

* and 95% confidence interval in parentheses.

ANNEX 2: INFLUENZA CASES REPORTED TO THE ECDC BY SENTINEL SYSTEMS, EU/EEA, 2011-17

Supplementary table 1: Influenza cases reported to the ECDC by sentinel systems, by season, virus type and subtype/lineage, EU/EEA, 2011-17*

	2011-12			2012-13			2013-14			2014-15			2015-16			2016-17			All seasons (2011-17)		
	N	%	% among known subtype / lineage	N	%	% among known subtype / lineage	N	%	% among known subtype / lineage	N	%	% among known subtype / lineage	N	%	% among known subtype / lineage	N	%	% among known subtype / lineage	N	%	% among known subtype / lineage
Influenza A	8462	**89%**		7177	**47%**		6924	**98%**		10618	**67%**		10496	**56%**		16240	**89%**		**59917**	**71%**	
A(H1N1)pdm09	117	2%	1%	3976	62%	42%	3458	53%	53%	2308	23%	20%	8665	86%	61%	187	1%	1%	**18711**	34%	29%
A(H3N2)	7682	98%	96%	2413	38%	26%	3021	47%	46%	7659	77%	68%	1365	14%	10%	13574	99%	93%	**35714**	66%	56%
Influenza B±	1011	**11%**		8209	**53%**		176	**2%**		5231	**33%**		8144	44%		1961	**11%**		**24732**	**29%**	
Victoria	113	60%	1%	286	10%	3%	11	15%	0%	31	2%	0%	3974	96%	28%	386	45%	3%	**4801**	50%	7%
Yamagata	74	40%	1%	2713	90%	29%	61	85%	1%	1319	98%	12%	145	4%	1%	481	55%	3%	**4793**	50%	7%
Total	9473			15386			7100			15849			18640			18201			**84649**		

Supplementary table 2: Cases of matched and unmatched influenza B reported to the ECDC by sentinel systems, by season, EU/EEA, 2011-17*

	Vacccine strain	Matched viruses	Unmatched viruses
2011-12	Victoria	113 (60%)	74 (40%)
2012-13	Yamagata	2713 (90%)	286 (10%)
2013-14	Yamagata	61 (85%)	11 (15%)
2014-15	Yamagata	1319 (98%)	31 (2%)
2015-16	Yamagata	145 (4%)	3974 (96%)
2016-17	Victoria	386 (45%)	481 (55%)
Pooled		**4737 (49%)**	**4857 (51%)**

*sources:
http://ecdc.europa.eu/en/publications/Publications/Influenza-Europe-2011-2012-surveillance-report.pdf
http://ecdc.europa.eu/en/publications/Publications/influenza-fortnightly-surveillance-overview-24-may-2013.pdf
http://ecdc.europa.eu/en/publications/Publications/Influenza-2013-14-season-report.pdf
Flu News Europe - Week 20/2015 from http://flunewseurope.org/Archives, visited on 24/06/2017
Flu News Europe - Week 20/2016 from http://flunewseurope.org/Archives, visited on 24/06/2017
Flu News Europe - Week 20/2017 from http://flunewseurope.org/Archives, visited on 24/06/2017
± In red, lineage included in the seasonal vaccine

ANNEX 3: LIST OF PUBLISHED ARTICLES DURING THE THESIS NOT LINKED TO THE THESIS

International Ebola Response Team, Agua-Agum J, Ariyarajah A, Aylward B, Bawo L, Bilivogui P, et al. Exposure Patterns Driving Ebola Transmission in West Africa: A Retrospective Observational Study. PLoS Med. 2016 Nov;13(11):e1002170.

Rondy M, Issifou D, Ibrahim AS, Maman Z, Kadade G, Omou H, Fati S, Kissling E, Meyer S, Ronveaux O. Vaccine Effectiveness of Polysaccharide Vaccines Against Clinical Meningitis - Niamey, Niger, June 2015. PLoS Curr. 2016;8. PMCID: PMC4846038

Luquero FJ, **Rondy** M, Boncy J, Munger A, Mekaoui H, Rymshaw E, et al. Mortality rates during cholera epidemic, Haiti, 2010–2011. Emerg Infect Dis. 2016 Mar

Rico A, Brody D, Coronado F, **Rondy** M, Fiebig L, Carcelen A, et al. Epidemiology of epidemic Ebola virus disease in Conakry and surrounding prefectures, Guinea, 2014–2015. Emerg Infect Dis. 2016 Feb

Dixon MG, Taylor M, Dee J, Hakim A, Cantey P, Lim T, Bah H, Camara SM, Ndongmo C, Togba M, Touré LY, Bilivogui P, Sylla M, Kinzer M, Coronado F, Tongren JE, Swaminathan M, Mandigny L, Diallo B, Seyler T, **Rondy** M, Rodier G, Perea WA, Dahl B. Contact Tracing Activities during the Ebola Virus Disease Epidemic in Kindia and Faranah, Guinea, 2014. EID Nov 15; 21(11