Evaluation of seasonal influenza vaccine effectiveness using national and regional test-negative design surveillance studies: Quantitative evidence reviews

By

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Abstract

Background: Early-season (interim) rather than end-season (final) seasonal influenza vaccine (SIV) effectiveness estimates from surveillance studies are utilised for decision-making regarding SIV components. Despite, concordance between these estimates is underexplored. Further, SIV effectiveness suggestively varies across geographical regions, population characteristics, vaccine antigenic similarity with circulating virus strains (VAS), and study methods, but the evidence has largely conflicted. This thesis aimed to address these gaps in knowledge.

Methods: Systematic evidence reviews with meta-analyses and a mixed methods study, adhering to standard guidelines. Included published full-text articles of SIV effectiveness against laboratory-confirmed (RT-PCR/culture) influenza from test-negative design (TND) studies in outpatients after the 2009/10 influenza pandemic, with patients vaccinated against influenza ≥14days before symptom onset and symptom onset ≤7days. Multivariable logistic regression was used to assess determinants of a substantial difference (≥10%) between paired adjusted point interim/final estimates. Pooled adjusted final estimates against A(H1N1)pdm09, A(H3N2), and influenza B were calculated using an inverse variance, random-effects model. The chi-square statistic ($\chi 2$) was used to assess the statistical significance of the difference between estimates.

Results: There were 68 pairs of interim/final estimates, with no statistically significant difference between almost all. Inconsistent statistical model in estimations, and interim estimation before influenza circulation peak increased the odds of having a substantial difference between paired estimates. Point pooled estimates were higher in the Southern compared with Northern hemispheres, with statistically significant difference between almost all pooled

estimates (76 articles). Pooled estimates decreased with increasing age in the Northern hemisphere, and were almost entirely statistically significantly higher with vaccine antigenically similar compared with dissimilar to circulating virus strains. Pooled estimates were higher with self-reported vaccination compared with from medical records, almost entirely higher with respiratory specimen collection ≤7days compared with ≤4days of symptom onset, and higher with adjustment for age but not medical conditions compared with adjustment for both (70 articles); however, mostly non-statistically significant.

Conclusions: Interim SIV effectiveness estimates seem sufficient for SIV composition decision-making. Variations in final estimates across geographical regions and age groups, and according to VAS and study methods necessitate consideration of these factors when designing, evaluating or comparing TND studies of SIV effectiveness.

Preface

This thesis is comprised of original research designed and conducted by the PhD candidate, George Ndubuisi Okoli. The thesis has six chapters. Chapter 1 is an introduction, made up of nine sections, namely; Seasonal influenza epidemiology, Influenza prevention, Influenza treatment, Seasonal influenza vaccination and vaccine effectiveness, Test-negative design for seasonal influenza vaccine effectiveness estimation, Alternative methods for estimating influenza vaccine effectiveness, Problem statement, Thesis hypotheses, and Thesis objectives. Chapter 2 focuses on the common methods across the included studies and is made up of seven sections, namely; Literature search strategy, Study eligibility criteria, Citation screening and literature selection, Data extraction, Study quality assessment, Data synthesis, and Knowledge dissemination. Chapters 3, 4 and 5 are for the three studies that comprise this thesis. Chapter 3 focuses on the assessment of interim seasonal influenza vaccine effectiveness estimates as proxy for final estimates. Chapter 4 focuses on the assessment of variations in seasonal influenza vaccine effectiveness across geographical regions, age groups, and levels of the vaccine antigenic similarity with circulating virus strains. Chapter 5 focuses on the assessment of variations in seasonal influenza vaccine effectiveness due to study characteristics. Chapter 6 is the discussion, and is made up of seven sections, namely; Summary of the key findings, Interpretation of findings, Study limitations, Study merits, Implications of the findings for policy, planning and practice, Recommendations for future research, and Conclusions. These chapters are followed by appendices and references.

Conflict of interests: I (George Ndubuisi Okoli) have no competing interests to declare.

Disclaimers: This thesis was completed using data from published primary studies obtained through a systematic search of various bibliographic databases and relevant websites, including literature and organisational websites. All data generated or analysed during the studies that comprise the thesis are included in the published articles and their supplementary information files. The results and conclusions are those of the candidate and principal investigator, George Ndubuisi Okoli, and the co-authors, and no official endorsement of the University of Manitoba.

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Dedication

To the Glory of the Almighty God, and in loving memory of my wonderful parents, Francis (my Papa) and Regina (my Mama).

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List of abbreviations

- **CDC**: Centers for Disease Control and Prevention
- **CI**: Confidence interval
- **DAG**: Directed acyclic graph
- **Embase**: Excerpta Medica database
- **GISRS**: Global Influenza Surveillance and Response System
- **I-MOVE**: Influenza Monitoring Vaccine Effectiveness in Europe
- **LAIV**: Live attenuated influenza vaccine
- **MEDLINE**: Medical Literature Analysis and Retrieval System Online
- **MS**: Microsoft
- **NACI**: National Advisory Committee on Immunization
- **OR**: Odds ratio
- **PRESS**: Peer Review of Electronic Search Strategies
- **PHE**: Public Health England
- **PRISMA**: Preferred Reporting Items for Systematic Reviews and Meta-analysis
- **PROSPERO**: International prospective register of systematic reviews
- **PubMed**: Public/Publisher MEDLINE
- **RNA**: Ribonucleic acid
- **RT-PCR**: Reverse-Transcription Polymerase Chain Reaction
- **SCOPUS**: An abstract and citation database of peer-reviewed literature
- **SIV**: Seasonal influenza vaccine
- **STATA**: Statistics and data (a statistical software for data science)
- **TND**: Test-Negative Design

- **UK**: United Kingdom
- **USA**: United States of America
- **VAS**: Vaccine antigenic similarity with circulating virus strains
- **VE**: Vaccine Effectiveness
- **WHO**: World Health Organization

Contributions of Authors

This is a sandwich thesis (grouped manuscript thesis). The thesis consists of a collection of published articles in high-impact academic journals. The PhD candidate, George Ndubuisi Okoli conceptualised and executed all the studies under the supervision of Dr Salaheddin Mahmud, and wrote the thesis under the supervision of Dr Mahmud and the support of the advisory committee; Dr Silvia Alessi-Severini (co-Advisor), Dr Paul Van Caeseele, and Dr I fan Kuo. George Ndubuisi Okoli was solely responsible for data acquisition, the statistical analyses, and interpretations of the results, and takes full responsibility for the accuracy of this thesis. All authors listed on the manuscripts contributed to the interpretation of the results and drafting of the manuscripts, and approved the final manuscripts for submission to academic journals for publication.

Chapter 1. Introduction

Seasonal influenza epidemiology

Influenza, commonly referred to as the flu, is an infectious disease of the respiratory system. This disease is caused by certain members of the Orthomyxoviridae virus family; the Alphainfluenzavirus (influenza A virus), the Betainfluenzavirus (influenza B virus), and the Gammainfluenzavirus (influenza C virus), all of which are ribonucleic acid (RNA) viruses; that is, they have RNA as genetic material.[1-4] These viruses are the only of the Orthomyxoviridae virus family known to cause infections in humans.[5-8] They are spread from person to person mostly through respiratory droplets or aerosols released into the air when an infected person coughs, sneezes or talks near a susceptible person or if a susceptible person touches any surfaces with droplets containing the viruses and then touches their nose, month or eyes with the contaminated hand.[9-13]

While the time frame is not the same for every person who is exposed to and infected with influenza, influenza incubation period; that is, the time from exposure until appearance of symptoms averages two days, but ranges from one to four days.[14] However, a systematic review suggested a lower incubation period of 1.4 days (95% confidence interval: 1.3 days to 1.5 days) although the authors cautioned that estimates from the included studies were poorly referenced, inconsistent and based on limited data.[15] The mean serial interval for influenza transmission; that is, the time from illness onset in a primary case to illness onset in a successive secondary case directly linked with the primary case is estimated to be two to four days.[16-18] With infection, the influenza virus reproduces in the body of an infected person and the duration of influenza virus shedding (expulsion of virus progeny) in immunocompetent persons averages about five days,[14] although virus shedding could continue for more days especially in the very young (<5 year-

olds),[19] older adults (≥65 year-olds),[20] the immunocompromised, and persons with certain chronic conditions.[20-24]

Whereas the influenza C virus causes a very mild infection and is rarely implicated in influenza epidemics,[21,25] the influenza A and influenza B viruses are clinically more important and are responsible for seasonal outbreaks of influenza epidemics among humans,[26,27] occurring mostly during the winter seasons in both the Northern and Southern hemispheres of the world.[28] This is because of small genetic variations that occur in the influenza A and influenza B viruses over time (antigenic drift), allowing them to keep changing and circulating among humans.[9,29,30] Further, the influenza B and influenza C viruses primarily infect humans whereas the influenza A virus, in addition to infecting humans, also infects other animals, including birds, pigs, horses and cats.[31-34] This creates the opportunity for two or more different strains of the influenza A virus to combine (reassortment) and suddenly form a new virus subtype (antigenic sift),[30,35] with the potential to cause a pandemic (globally spread epidemics) especially if a highly replicative, easy-spreading and high disease-causing resultant novel subtype emerges, for which the general population would have little or no immunity.[5,36]

The virulence (ability to cause disease) of the influenza viruses depends on factors including the molecular structures on the surface of the viruses known as the antigen. Influenza antigens are surface proteins on the viruses that are recognizable by the human immune system and are capable of triggering an immune response (antibody production).[37,38] These surface proteins are the hemagglutinin and the neuraminidase proteins,[39-42] with 18 hemagglutinin and 11 neuraminidase subtypes (H1 through to H18, and N1 through to N11, respectively) known thus far. The influenza A virus subtypes are named based on these two surface proteins;[2,43,44] for example, the H1N1 and H3N2 influenza A subtypes that commonly circulate among humans.

However, the influenza B viruses do not have subtypes but rather classified into lineages known as the B/Yamagata and B/Victoria.[45,46]

Influenza A and influenza B infections could be asymptomatic or mildly symptomatic, presenting with slight fever and some respiratory symptoms, and infected persons usually recover within a few days without needing medical attention.[47] However, some infections could lead to severe illness, sometimes with complications, necessitating hospitalisation and occasionally leading to death, especially among higher-risk persons such as the very young, older adults, pregnant women, and persons with certain chronic medical conditions like diabetes, cancers, and immunodeficiency.[48,49] While the disease burden attributable to seasonal influenza is significant,[49,50] the estimates often focus on the burden resulting from respiratory infection alone despite additional hidden burden from broader consequences of the disease such as exacerbation of underlying chronic medical conditions and functional decline. As such, the disease burden of influenza is much more significant.

Although methodologically difficult to measure, estimates by the World Health Organization (WHO) suggest that there are three to five million cases of severe influenza illness every year globally, with an associated 290,000 to 650,000 deaths.[51] An estimated 9 million to 41 million illnesses, 140,000 to 710,000 associated hospitalisations and 12,000 to 52,000 related deaths are attributable to influenza in the United States of America (USA) alone every year between 2010 and 2020,[52] with an estimated economic burden of US$5.8 billion every year, which accounts for about 65% of the burden due to all vaccine preventable diseases in the USA.[53] In Canada, an estimated 10% to 20% of the population is infected each influenza season, with over 12,000 associated hospitalisations and an estimated 3,500 deaths.[54] On average, a hospitalisation due to influenza in Canada costs almost CAD$15,000.[55] Further, it is estimated

that 1.5 million workdays are lost every year due to influenza in Canada, with an associated healthcare and lost productivity costs of around CAD$1billion.[56] Even so, influenza is ranked among the top ten leading causes of death in Canada.[57]

Influenza prevention

Good hygiene practices, including cleaning and disinfection of surfaces, frequent washing of hands with soap and water, and adequate ventilation of rooms are common strategies to limit influenza infection. However, vaccination remains one of the most successful public health strategies, for not only influenza prevention, but also for achieving herd immunity in order to protect unvaccinated persons,[58,59] and to mitigate the impact of infection if a person becomes infected.[60,61] Reductions in mortality and morbidity attributable to vaccine preventable diseases demonstrate the effectiveness of vaccines.[62] Nevertheless, whereas some vaccines confer life-long protection, vaccines like the seasonal influenza vaccine (SIV) provide short-lived protection. This is due to the evolution occurring in circulating influenza viruses, which often leads to poor antigenic matching between previous season's influenza vaccine virus strains and current season circulating influenza virus strains, and as a result, reformulation of influenza vaccine is necessary every influenza season, in an attempt to match vaccine virus strains with circulating virus strains for better protection.[9,29,30] Estimates suggest that it takes 10 days to 14 days for an adequate response to the SIV by the immune system for the vaccine to be able to confer the expected protection.[63]

Various SIV types are available. These include the live attenuated influenza vaccine (LAIV), a vaccine created by weakening the influenza viruses, but still keeping them viable;[64,65] and the inactivated influenza vaccine, a vaccine that consists of influenza virus particles or viruses that have been grown in culture and then killed to destroy their disease-producing

capacity.[66] Whereas the LAIV is administered nasally by spraying, the inactivated influenza vaccine is an intramuscularly injected vaccine. Depending on the method of production, these vaccines could be egg-grown (vaccine viruses grown in chicken eggs),[67,68] cell culture-based (vaccine viruses grown in cultured cells of mammalian origin),[69,70] and recombinant (vaccine produced using a type of technology known as the recombinant technology).[71-73] Further, depending on the strength of the vaccines, particularly for the inactivated type, the vaccines could be of standard dose, high dose (contains four times the amount of antigen in a standard dose vaccine),[74,75] or adjuvanted (made with certain ingredients that help to elicit a stronger response by the immune system of the body).[71,76,77] Furthermore, depending on the number of viruses covered in the vaccines (vaccine valency), the vaccines could be trivalent (contains the influenza A virus subtypes (H1N1 and H3N2) and one influenza B virus strain),[78] or quadrivalent (contains the influenza A virus subtypes and two influenza B virus strains (the B/Yamagata and B/Victoria)).[79] While the LAIV usually contains three live influenza viruses (H1N1, H3N2, and one influenza B virus strain) and is approved for use only among healthy non-pregnant persons and persons two years to 49 years old,[80,81] the inactivated vaccine may contain three or four influenza virus strains and is approved for use among persons at least six months old,[82] although there are age-specific recommendations for some of the vaccine types such as the high dose, adjuvanted and recombinant, recommended for use mostly among older adults.[71]

Influenza treatment

In many seasonal influenza outbreak scenarios, SIV insufficiency (shortages), unaffordability (financial and storage constraints in some countries), and the urgency of the need for a health intervention may make vaccine prevention to seem suboptimal. In such scenarios, the use of

antiviral drugs where readily available may gain more importance and may therefore take somewhat precedence over vaccination although as a strategy for prevention of influenza, the need for a healthy person to take an antiviral drug daily for a substantially long period makes efficiency of antiviral drug use for this purpose questionable. However, for already infected persons, in addition to antiviral drugs ameliorating the impact of infection, they may reduce viral shedding, thus reducing infectivity and making onward transmission from these persons less likely.[83,84]

Until recently, two main classes of antiviral drugs, the influenza M2 proton channel inhibitors; amantadine and its methyl derivative, rimantadine, and the influenza virus neuraminidase inhibitors (NAIs); oseltamivir, zanamivir, laninamivir, and peramivir have been available for mostly treatment of influenza although may also be used for prevention.[85] While amantadine, rimantadine and oseltamivir are orally administered and swallowed drugs, zanamivir and laninamivir are orally and nasally inhaled drugs, respectively. On the other hand, peramivir is a solely injectable drug and mostly used for emergency treatment of severe influenza in tertiary settings.[86] While amantadine and rimantadine are cheaper than the NAIs,[87] they have substantial issues of toxicity,[88] are only known to be effective against influenza A,[89] but have issues of resistance in some subtypes of this influenza virus such as the H1N1, H3N2 and H5N1.[85,90] Consequently, these drugs are no longer recommended for influenza prevention/treatment, leaving only the NAIs as the antiviral drugs of choice for prevention and treatment of influenza, although the evidence on these drugs points to potentially emerging resistance especially to oseltamivir and zanamivir, particularly among the very young and the immunocompromised.[91,92]

The NAIs work by selectively inhibiting neuraminidase, one of the surface proteins on both influenza A and influenza B viruses that enables these viruses to be released from the host cells, and as such, the drugs prevent release of newly formed influenza A and influenza B virus particles from the cell surface.[85] In 2018, a new class of antiviral drug, the endonuclease inhibitor, baloxavir marboxil was approved for treatment of influenza in the USA.[93,94] This orally administered and swallowed antiviral drug works by inhibiting the endonuclease activity of the polymerase acidic protein, an influenza virus-specific enzyme in the viral RNA polymerase complex required for viral gene transcription.[94] Thus, the drug inhibits influenza virus replication. The efficacy/effectiveness of the NAIs for influenza prevention,[95-98] and reduction in the risk of influenza-associated complications such as pneumonia and respiratory failure, [99,100] and mortality,[101] are established. The efficacy/effectiveness of baloxavir marboxil are also established.[102,103] Nevertheless, evidence suggests that vaccination is more cost-effective than treatment against influenza especially among healthy persons,[104-106] and therefore, vaccination remains the strategy of choice against influenza.

Seasonal influenza vaccination and vaccine effectiveness

Many countries have implemented seasonal influenza vaccination programmes, with the aim of reducing the impact of seasonal influenza outbreaks especially among those population subgroups that are most at risk of influenza-related complications and hospitalisations.[48,49] To optimise the effectiveness of the vaccination programmes, assessment of SIV efficacy and monitoring of SIV effectiveness are highly necessary. However, SIV efficacy/effectiveness has been elusive and a focus of debate due to a host of factors, including that influenza outbreak virus strains differ by place and time, vaccine strains differ by season and region, and population characteristics are naturally dynamic and differ demographically, with varying proportions of

populations having pre-existing antibody titres against influenza from previous infections and vaccinations.[107] Therefore, even a well-designed, appropriately-conducted and large randomised controlled trial (RCT) of SIV efficacy would simply provide a place/time/season/participants-specific observation of SIV efficacy.[107] Moreover, due to practical and ethical constraints, RCTs of SIV efficacy are not feasible. Regulatory approvals for SIV are often predicated on the findings of small immunogenicity clinical trials that do not necessarily correlate with vaccine effectiveness in real life.[82,108] In addition, monitoring of SIV effectiveness post-licensure is typically using observational studies, with no consensus on which method of estimation of the vaccine effectiveness constitutes a pragmatic gold standard. For these reasons, the measurement of efficacy and effectiveness of SIVs remain controversial.

Compared with a cohort study design, the traditional case-control study design had been a common observational study design used for assessing SIV effectiveness due to its cost-effectiveness and easier and faster implementation.[109-111] As the name implies, a case-control study is always a retrospectively-conducted study considering that the study outcome (the cases) is known at the start of the study and the exposures are then investigated retrospectively. However, one of the major problems with this study design is the identification of appropriate controls for the cases; that is, identification of persons that represent the exposure distribution in the same population from which the cases derive, in order to limit selection bias and subsequent invalid estimations of the vaccine effectiveness.[112] Even so, definition of cases may differ between studies, which presents further difficulties for when comparing estimates of SIV effectiveness. For example, some studies may use laboratory confirmation of influenza for case definition whereas others may use presentation with acute respiratory symptoms. Even among

those that use laboratory confirmation of influenza for case definition, laboratory tests may differ, further complicating comparisons of SIV effectiveness estimates between studies.

Different approaches to identifying controls in case-control studies of SIV effectiveness are evident from the literature.[113] Following the identification of persons presenting with symptom set suggestive of an acute respiratory illness (ARI) or an influenza-like illness (ILI) symptom set in outpatient or in-patient settings and/or laboratory confirmation of influenza (cases), the controls may be identified from either the general study population, from persons presenting with symptoms unrelated to influenza, or from persons diagnosed with other similar acute respiratory diseases. Controls may also be identified by using propensity score matching of each case to one or more controls that share certain important characteristics with the cases, particularly those characteristics that may be associated with being infected with influenza and receipt of influenza vaccination; i.e., potential confounders.[114] However, these approaches pose a high risk of selection bias, which may affect the validity of SIV effectiveness estimates derived using them. Nevertheless, irrespective of approach, confounding factors still must be taken into account, for example, using statistical adjustment.

Test-negative design for seasonal influenza vaccine effectiveness estimation

To address the problem of identification of appropriate controls for cases in estimation of SIV effectiveness, in 2005, Skowronski and colleagues from British Columbia, Canada proposed a unique study design, the test-negative design (TND),[115] although earlier vaccine effectiveness estimation studies had utilised a methodologically similar approach; for example, in assessing the effectiveness of the pneumococcal vaccine.[116-118] Since then, the use of the TND in estimation of SIV effectiveness has been gaining attention and the design is increasingly embedded in influenza surveillance studies in many jurisdictions, globally.[119,120] In this study

design, cases are persons presenting with ARI symptom set or symptom set suggestive of ILI in clinical outpatient or in-patient settings, mostly depending on severity,[113] and their respiratory specimen (nasopharyngeal or throat secretions) testing positive for influenza; ideally, with laboratory confirmation using the reverse-transcription polymerase chain reaction (RT-PCR) or viral culture since these tests are highly specific and are considered the gold standards for influenza confirmation.[121,122] The non-cases (controls) are persons also presenting with ARI symptom set or symptom set suggestive of ILI, but testing negative for influenza using the same laboratory confirmatory test as the cases to ensure consistency and appropriate comparisons between cases and non-cases. Influenza vaccination status of the persons testing positive and of those testing negative for influenza are then determined; ideally, from medical records to limit recall and social desirability biases associated with self-reported vaccination.[123,124] The odds of vaccination in each group is determined and the confounder-adjusted odds ratio calculated. SIV effectiveness is then estimated as, one minus the adjusted odds ratio, multiplied by 100%.

The TND has often been referred in the literature to as a type of case-control study design perhaps because comparison is made between cases and non-cases (the controls).[107,125,126] However, unlike in a case-control study in which sampling of participants is conditional on their influenza status, recruitment of persons into the TND study is not guided by influenza status, as persons are first recruited into a study before their influenza status is ascertained.[119] As such, it may be improper to view the study design as a case-control type.[120] The design has also been referred to as a variant of a cohort study because the study participants are a clearly defined group of people who share a common clinical definition of ARI or ILI for eligibility for participation, and those who do not meet the definition are ignored.[127] However, a control group is defined and compared with the cases in the TND, which negates the thought of the study

design being of a traditional cohort type. On the other hand, by limiting study participation to a group of people who share a common clinical definition of ARI or ILI in the TND study of SIV effectiveness estimation and then establishing cases and non-cases based on laboratory confirmation of influenza, such an approach may even be viewed to be more of a nested case-control or case-cohort study types although generally still not informed by influenza status. That said, the TND is a uniquely defined study design and therefore, it may be more appropriate to treat it as a separate study design irrespective of similarities with case-control and cohort study types, as this will help limit confusion. This idea has also been previously suggested.[119]

Nevertheless, the validity of the TND for estimation of SIV effectiveness is not well established. Despite this fact, the low-cost nature of the study design when compared with the cohort or the traditional case-control study designs, and the perceived simplicity of its implementation have led to a wide-spread use of the TND, raising concerns of the possibility of some researchers not having a grounded understanding of the epidemiological principles that underpin the study design and therefore, the potential for invalid estimations with improper implementation of the design.[107,120,125] First, the validity of the TND is based on the assumption that SIV has no effect on other acute respiratory diseases that may present similar to influenza.[125] The reason being avoidance of cross-protection and, as such, the validity of the TND is also based on the assumption that the risk of infections by non-SIV-targeted pathogens resulting in an ARI or ILI does not vary by influenza vaccination status.[113] This core assumption of the TND for SIV effectiveness estimation was validated by De Serres and colleagues, with the conclusion that, if met, estimates from appropriately conducted TND were accurate and precise when compared with the gold standard of classic per-protocol RCT analysis.[125] Modelling studies have also suggested that the TND could produce estimates comparable with those of case-control and

cohort studies; however, if only a highly specific diagnostic test is used for testing.[128,129] Further, the TND assumes that SIV confers total protection to the vaccinated persons, but whether this is truly so is difficult to establish and therefore, this assumption is not easily validated and guaranteed in TND studies of SIV effectiveness.[130] Moreover, the potential biases that SIV effectiveness estimations are prone to also need to be determined within the context of the circulating influenza viruses and influenza season, the characteristics of study participants, and key methodological steps such as, study participants recruitment; for example, whether patients were recruited consecutively or systematically at physician's discretion, study setting, respiratory specimen collection and testing, and how confounders are dealt with; for example, confounder adjustments in data analysis.

There is the need for a cautious approach to study participants recruitment, with a clearly defined symptom set for ARI or ILI and giving all persons who present with the symptom set equal opportunity to participate (consecutive recruitment), as this will minimise biased sampling compared with if patients were to be included at physicians' discretion (systematic recruitment) considering that physicians are more likely to request laboratory testing for the more severe persons compared with for those presenting with milder symptoms, and for persons who did not receive SIV compared with those who received vaccine. A systematic recruitment at physicians' discretion would likely lead to a false increase in the proportion of the non-vaccinated among the cases, resulting in overestimation of vaccine effectiveness. Even so, definition for ARI or ILI must not only be clear but should be applied consistently across all presenting persons; otherwise, a biased sampling of the presenting persons could also arise. Consistency is also vital in diagnostic testing of study participants and the use of the RT-PCR or viral culture is advocated to minimise misclassification bias and invalid estimations of SIV effectiveness.[131] Modelling

studies have shown that using influenza diagnostic tests with low sensitivity and specificity; for example, the rapid influenza diagnostic test (RIDT) lead to underestimation of SIV effectiveness in comparison to using RT-PCR or viral culture.[128,129] Further, potential confounders that have been considered in TND studies of SIV effectiveness across the literature, include age, sex, chronic diseases and other high-risk status, calendar time, prior SIV receipt and prior influenza infection.[113,132] While age and chronic disease status have been found to be associated with receipt of SIV,[133,134] as well as with increased susceptibility to influenza,[135-137] and therefore may be regarded to be strongly established confounders of SIV effectiveness, the plausible associations between sex and receipt of SIV and increased susceptibility to influenza are largely debatable; therefore, sex in particular may not be a strongly established confounder of SIV effectiveness and, as such, is often omitted in SIV effectiveness studies.[132] Evidence from a modelling study demonstrated confounding that could arise if a study fails to adjust for calendar time, suggesting that calendar time may be strongly associated with receipt of SIV and being infected with influenza.[119] This may be true considering that seasonal influenza vaccination and influenza virus circulation are both seasonal. Despite that prior exposure to an influenza virus (whether via vaccination or natural infection) is believed to induce immunity that may protect against infections by the virus and may confer cross protection against antigenically similar virus strains,[138] prior SIV receipt and influenza infection are often not adjusted for in many studies; thus, suggesting residual confounding in SIV effectiveness estimates from such studies.[120] Furthermore, it has been argued that adjusting for disease severity in TND studies of SIV effectiveness is necessary considering that an important factor relating to seeking care for an ARI or ILI may be the severity of the illness and that influenza severity is expected to be associated

with vaccination status, which makes it likely that the unvaccinated would develop more severe infection if infected and are therefore the more likely persons to seek care.[139]

Variations in the methodological approaches to TND are evident from the literature. A large systematic review found that, of 253 published TND studies of influenza vaccine effectiveness up to October 2018, 45% were conducted in outpatient settings, and 57%, 19%, 3.5% and 1.6% utilised ILI, ARI, severe respiratory illness, and febrile respiratory illness and pneumonia, respectively, for study participants recruitment.[113] The review also found that while in 99% of studies cases and non-cases were determined alike as previously described, confounder adjustment varied across studies, with adjustments for age in 83% of the studies and for calendar time in 71%, but the proportion that adjusted for comorbidities and sex were not clear from the review reporting. However, even when age is adjusted, adjusting for age as a categorical rather than a continuous variable as observed in some of the reviewed studies might have led to residual confounding due to age, the importance of which matters in SIV effectiveness when small changes in age may correspond to substantial differences in immunological competence, as the authors of the review argued.[113]

Strengths in test-negative design study of seasonal influenza vaccine effectiveness

One major tenet of study participation in the TND study of SIV effectiveness is a person seeking medical attention because of an ARI or ILI and gets invited and agrees to participate in a study. When viewed from a case-control study perspective therefore, the TND study of SIV effectiveness satisfies the major principle that underpins the validity of a case-control study since cases and controls derive from the same treatment-seeking population and, controls are only distinguishable from cases based on laboratory confirmation of influenza.[107,125,127] As such, this is an inherent strength in the TND and, in selecting a group of persons seeking medical care for a

specific set of clinical symptoms, similarity between cases and non-cases is optimised, thus minimizing selection bias.

Evidence from cohort studies of SIV effectiveness among older adults has shown that observed benefits of influenza vaccination among this important subpopulation are often mostly due to the high uptake of vaccination among relatively healthy healthcare-seeking persons who are often mostly recruited in studies compared with unhealthy persons who may have the less capability, capacity and likelihood to seek medical care, and are therefore less likely to be included in studies.[140] Seasonal influenza vaccination is voluntary and therefore vaccination is likely influenced by healthcare-seeking behaviour of persons; that is, the propensity of a person to seek medical care, and also a person's preventive health behaviour is likely associated with them being infected with influenza.[141] Whether vaccinated against influenza or not, a person might still be infected with influenza, but may or may not develop symptoms. Symptomatic persons would likely seek medical care; however, potentially depending on symptom severity and their healthcare-seeking behaviour. Even so, whether vaccinated or not against influenza, some persons may develop an ARI or ILI, but still test negative for influenza. It is therefore important that persons have equal chance of being recruited into a study evaluating influenza vaccine effectiveness irrespective of their influenza status. Consequently, by selecting only persons who have sought medical care for an ARI or ILI, the TND is believed to minimise confounding by healthcare-seeking behaviour.[3] The principle that underpins this concept is detailed in the literature,[120,141] and demonstrated by studies.[142] Nevertheless, confounding by healthcare-seeking behaviour could persist under the TND if significant variation in symptom severity gives rise to differential healthcare-seeking behaviour with respect to influenza vaccination status of persons and their health care seeking for symptoms.[130]

Sullivan and colleagues argued that the non-cases in cohort and the traditional case-control studies often do not have their respiratory specimen tested for influenza and that without laboratory-confirmation of influenza status, some of these persons influenza status might in fact be misclassified.[120] Therefore, by including only laboratory-tested persons for influenza, the TND study of SIV effectiveness potentially minimises misclassification of influenza status; that is, wrongly identifying a person who has influenza as a non-case and vice versa. Any residual misclassifications may then likely be due to laboratory sample contamination or documentation error. Nevertheless, laboratory testing of persons does not necessarily guarantee avoidance of misclassification of influenza status since not all infected persons shed enough viruses to enable laboratory detection.[143] Moreover, considering that influenza viral shedding often precedes ARI or ILI symptom onset by about 24 hours and could last up to 5 days,[21] it is reasonably possible that persons presenting with ARI or ILI 4 days or more following symptom onset may no longer be shedding virus and laboratory test may therefore present with a false negative result.[120] It is mostly for this reason that some influenza surveillance studies may limit participation in TND studies of SIV effectiveness to only persons presenting within 4 days of ARI or ILI symptom onset although even so, there may still be issues with recall bias considering self-declaration of symptom onset. Moreover, there is also the issue of poor specimen collection technic and quality of the collected sample,[144] which may mean that a respiratory specimen may not be of good enough quality for laboratory testing and as such, potentially compromising optimal laboratory testing. To address these issues, there is the suggestion to use respiratory specimen that tested positive for another respiratory virus in determining non-cases, as this may mean that the respiratory specimen is of sufficient quality to enable identification of a viral pathogen.[145]

Further, unlike the retrospective cohort study type and the traditional case-control studies in which influenza vaccination status may be determined after influenza status ascertainment and vaccination status may therefore be subject to differential recall between influenza cases and non-cases, the TND may avoid differential recall bias of influenza vaccination status because case status is unknown at study participants' recruitment. Moreover, case status is also not a prerequisite to recruitment into the TND study of SIV effectiveness. However in a TND study of SIV effectiveness, it is possible that influenza case ascertainment could be made prior to or after the determination of influenza vaccination status. Therefore, to reduce the likelihood of differential recall of vaccination status by influenza status when vaccination status is self-reported in such a scenario, blinding of study participants to their influenza status following laboratory testing may be necessary until after the determination of their influenza vaccination status.

Generally, relative to the cohort and traditional case-control study types, the TND for SIV effectiveness estimation is less susceptible to confounding by healthcare-seeking behaviour and to influenza status misclassification bias, and is seen to be a convenient, practically easier and mostly a more cost-efficient study design.[125] The usefulness of this study design has been demonstrated in the relatively quick and methodologically-consistent assessments of SIV effectiveness at different points during the influenza season across influenza surveillance networks.[146-148]

Limitations of test-negative design study of seasonal influenza vaccine effectiveness

Notwithstanding the advantages of the TND over the traditional case-control and cohort study designs for SIV effectiveness estimation, the TND has some limitations much in common with these study designs. The use of the TND without understanding the principles that underpin the

study design and knowledge of the principles of epidemiology could produce invalid vaccine effectiveness estimations and flawed results interpretations.[107]

As previously mentioned, the method of enrolment of study participants may present biased sampling if systematic; for example, if at the discretion of the clinician and the clinician decides based on their knowledge of a person's influenza vaccination status, perceived severity of symptoms or expectation of a likely positive test if persons are unvaccinated.[149] While it may be difficult to ascertain the extent or direction of bias as a result of such enrolment method,[107] in such a scenario of testing being at the discretion of the clinician, the proportion of the unvaccinated among cases would likely be increased, potentially resulting in vaccine effectiveness overestimation. Testing and giving all persons seeking medical care equal opportunity to participate (consecutive sampling) in a TND study of SIV effectiveness may likely mitigate the bias.

Self-reported vaccination has been established to be prone to recall and social desirability biases.[123,124] These biases are therefore inherent in TND studies that utilise self-report to determine vaccination status. If handled inappropriately; for example, if participants become aware of their influenza status prior to ascertainment of their vaccination status, it may result in differential recall by influenza status and, in such a scenario, may bias SIV effectiveness estimations. Further, considering its potentially limited accuracy, self-report may increase the potential for misclassification of covariates, which also could alter the estimates of vaccine effectiveness. Even when influenza vaccination status is determined from medical records or registries, data for some persons may be missing or incomplete, and even if complete, these data sources are still prone to documentation errors; thus, may lead to erroneous SIV effectiveness estimations. Further, considering that it takes approximately 14 days for the immune system to

adequately respond to SIV to be able to confer the expected protection,[63] only persons vaccinated in a season at least 14 days prior to ARI or ILI symptom onset are considered to have been vaccinated in a TND study. Self-reporting of this information is also subject to recall and social desirability biases, which could increase the likelihood of misclassification of vaccination status, and a differential misclassification between the cases and the non-cases, may lead to underestimation or overestimation of vaccine effectiveness. In addition, symptom onset in a TND study of SIV effectiveness can only be self-reported and therefore is subject to these biases, further increasing the potential for biased estimation of the vaccine effectiveness although almost all forms of vaccine effectiveness estimation will have this problem.

An often overlooked limitation of the TND study of SIV effectiveness is the potential for misclassification of influenza status if a gold standard diagnostic test is not utilised, as is common in a country like Japan, where RIDT mostly using ImunoAce Flu is frequently employed in clinical practice due to its efficiency and ease of use by clinicians.[107] Due to lower sensitivity and specificity of this test type when compared with the gold standard tests, the RIDT tend to underestimate SIV effectiveness.[128,129] It is therefore highly necessary that influenza status is established using a gold standard test. Use of a consistent test across clinics that are part of an influenza surveillance network may also be necessary considering that all data from a network may contribute to estimating a total vaccine effectiveness from within a surveillance network. Further, symptom onset in the TND study of SIV effectiveness is usually limited to not more than 7 days prior to presentation at a clinic to increase the likelihood of still ongoing viral shedding. It is reasonably possible that persons presenting 4 days or more following symptom onset may no longer be shedding sufficiently detectable virus and therefore, irrespective of the

laboratory test type, may present with a false negative result,[120] thus, increasing the potential for unreliable estimation of SIV effectiveness.

When applied retrospectively to influenza surveillance or administrative healthcare data, the advantage of the TND in optimizing similarity between cases and non-cases might be limited if study definition of ARI or ILI symptom set is misapplied, and even so, it is not always clear from administrative databases if persons actually met the participation criteria.[113] To avoid this potential limitation, it has been argued that prospectively conducted TND may be the more robust application of the study design.[113]

SIV effectiveness should be the same irrespective of whether one seeks care for an ARI or ILI or not,[119] and in a TND study, it is assumed that the distribution of ARI or ILI that are unrelated to influenza does not vary by influenza vaccination status or healthcare-seeking behaviour.[119] In investigating this assumption, Haber and colleagues demonstrated that if influenza vaccination does not affect the probability of developing an ARI unrelated to influenza, then, SIV effectiveness estimates from TND studies are unbiased even if the vaccinated and unvaccinated persons have different probabilities of seeking healthcare against ARI, as long as the ratio of the probabilities is the same for influenza and non-influenza associated illnesses.[150] Shi and colleagues showed how vaccine effectiveness estimates could be biased as a result of this assumption not holding.[151] Nevertheless, establishing these principles may be difficult and therefore, SIV effectiveness estimates from TND may actually not be entirely accurate and perhaps also not always generalisable to the source population from which the study samples derive.

Considering that SIV uptake,[140] and influenza virus circulation are both seasonal,[28,152-154] estimates of SIV effectiveness from TND would likely be biased if persons with an ARI or ILI

are recruited outside of influenza circulation period. As Jackson and Nelson highlighted,[119] such a practice has been likened to the immortal time bias in prospective cohort studies,[155,156] since study participants are unlikely to be infected with influenza. As Jackson and Nelson also highlighted, the magnitude and direction of bias in SIV effectiveness estimation in such a scenario will likely depend on the rate of vaccine uptake in the study population.[119] Since SIV uptake is seasonal, it correlates with calendar time. Likewise, incidence of influenza and ARI or ILI are seasonal and therefore correlate with calendar time. As such, TND studies of SIV effectiveness must adjust for calendar time, not only to minimise confounding due to calendar time, but also to aid investigation of the effect of time on persistence or waning of SIV-induced immunity especially among important subpopulations like the very young and older adults.[113,130] However, Chua and colleagues found that, of the 253 publications on TND studies of influenza vaccine effectiveness included in their systematic review, 71% controlled for calendar time while 1% conducted time-stratified analyses, 13% matched cases and non-cases by calendar time, and 11% restricted participants' recruitment to influenza epidemic periods.[113]

Just like with all observational study types, the TND study of SIV effectiveness is subject to residual confounding, including confounding due to unmeasured/unknown and therefore unadjusted factors.[120] In addition, simulation studies have demonstrated that biases may arise in vaccine effectiveness estimations from TND if SIV uptake affects the likelihood of non-influenza ARI or ILI,[151] and healthcare-seeking between infected and uninfected persons.[139]

Alternative methods for estimating influenza vaccine effectiveness

In addition to the traditional case-control and cohort study types, and the TND which currently is the most widely utilised method for estimating SIV effectiveness, another available approach to SIV effectiveness estimation is the screening method.[157,158] This method has previously been

used for evaluation of the effectiveness of various vaccines, including the pneumococcal,[159] pertussis,[160] mumps,[161] *Haemophilus influenzae* type b,[162] and pandemic influenza vaccines,[163] in addition to the SIV.[164,165] In the screening method, instead of identifying one or more non-cases for every established case as would be the case in a case-control study for example, the entire population at risk or a random sample of the population judged to be a good representation of the population at risk becomes the reference (comparator) population. The screening method requires three parameters for vaccine effectiveness estimation; namely, the number of cases, vaccine uptake proportion among the cases, and vaccine uptake proportion in the reference population.[159] Estimation of vaccine effectiveness is by comparing vaccine uptake among cases with vaccine uptake in the reference population, and vaccine effectiveness calculation is by subtracting vaccine uptake proportion among cases from vaccine uptake proportion in the reference population and then dividing this by vaccine uptake proportion in the reference population multiplied by one minus vaccine uptake proportion among cases, and the result multiplied by 100%.[157,166]

The screening method is purported to be a potentially less resource-intensive method for estimating vaccine effectiveness and judged to be a more economical and rapid method.[158,166] Compared with other observational study methods, the screening method has an important advantage of being useful in providing an early indication of SIV effectiveness.[167] It has also been suggested to be a first step "screening" to vaccine effectiveness evaluation to determine if further and more extensive evaluations are required, and to monitor changes in vaccine effectiveness over time, assuming that any biases remain constant.[166] However, vaccine effectiveness estimated using this method could be inaccurate if the needed parameters for the estimation are drawn from different populations and, it has been argued that this method should

not be relied upon for precise vaccine effectiveness estimations since it serves more purpose as vaccine effectiveness "screening".[166] Compared with the TND, it has been suggested that vaccine effectiveness estimations using the screening method are more prone to selection bias and confounding, and that care must be taken to stratify the data by possible confounders and, if necessary, that restricted analysis may need to be conducted.[158]

Problem statement

The Global Influenza Surveillance and Response System (GISRS) unit of the WHO is responsible for providing recommendations on SIV influenza strain composition each influenza season based on several factors, including pathogenicity of circulating strains.[168] This requires robust influenza surveillance and assessment of SIV effectiveness in regions of the world.[169] The GISRS committee meets twice a year for the recommendations; in February for the Northern hemisphere and in September for the Southern hemisphere. Decisions on the appropriate vaccine strains must be made within a short period to allow sufficient time for vaccine development and production prior to the following season. As such, the WHO utilises early-season (interim) SIV effectiveness estimates while influenza viruses are still in circulation, rather than the end-season (final) estimates.[170]

In recent years, several national and regional SIV effectiveness surveillance networks; for example, the I-MOVE: Influenza – Monitoring Vaccine Effectiveness in Europe,[171] have sought to provide timely (interim and final) SIV effectiveness estimates often using similar TND methods. Estimates from these surveillance networks often suggest that SIV effectiveness may vary depending on geographical region, population characteristics, level of influenza vaccine antigenic similarity with circulating virus strains (VAS), and study methods. However, the

evidence has been largely conflicting, and little is known regarding concordance between interim and final SIV effectiveness estimates from these surveillance studies.[172]

Compared with effect estimates from primary studies, effect estimates from systematic reviews with meta-analysis are more robust and are therefore relied upon for evidence-based decision-making.[173] In view of the accumulating data from influenza surveillance networks and similar surveillance studies, pooled analysis of the evidence on SIV effectiveness and assessment of agreement between interim and final SIV effectiveness estimates from these networks/studies are needed.

Thesis hypotheses

While individual SIV effectiveness estimations via different methods are suggestive, it is hypothesised that as a generality, the following may be demonstrated using SIV effectiveness estimates from TND studies spanning multiple influenza seasons:

1. Interim SIV effectiveness estimates as used by the WHO for decision-making regarding SIV development is an accurate proxy for the final estimates.
2. Pooled SIV effectiveness estimates vary across geographical regions, age groups, and by level of VAS.
3. Pooled SIV effectiveness estimates vary depending on the method of confirmation of vaccination status, timing of respiratory specimen swab collection relative to symptom onset, and set of covariates included in adjusted analysis for SIV effectiveness estimations.

Thesis objectives

1. To assess for concordance between interim and final SIV effectiveness estimates.

   Research questions

   - Do paired interim and final SIV effectiveness estimates differ statistically?

     - Does this vary by influenza type/subtype (influenza A subtypes; A(H1N1)pdm09 and A(H3N2), and influenza B)?

2. To assess for variability in pooled final SIV effectiveness estimates across geographical regions, age groups, and levels of VAS.

   Research questions

   - Does SIV effectiveness differ across geographical regions?
   - Does SIV effectiveness differ across age groups?
   - Does SIV effectiveness differ across levels of VAS?

     - Do these vary by influenza type/subtype?

3. To assess for variability in pooled final SIV effectiveness estimates across methods of confirmation of vaccination status, timing of respiratory specimen swab collection relative to symptom onset, and by covariates adjustments in data analysis.

   Research questions

   - Does SIV effectiveness differ according to the method of confirmation of vaccination status?
   - Does SIV effectiveness differ according to the timing of respiratory specimen

swab collection relative to symptom onset?

- Does SIV effectiveness differ according to covariate adjustments in data analysis?
    - Do these vary by influenza type/subtype?

Chapter 2. Methods

This thesis comprises one mixed-methods study and two comprehensive systematic reviews and meta-analyses. Prior to conducting the studies, the PhD candidate registered a systematic review protocol based on which the studies were conducted in the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42017064595). The systematic reviews were conducted following the Cochrane Handbook for Systematic Reviews of Interventions guidelines,[174] and in adherence to the Methodological Expectations of the Cochrane Intervention Reviews (MECIR) guidelines.[175] The findings were reported following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[176]

Literature search strategy

A fully-trained systematic review methodologist (the PhD candidate) also trained in knowledge synthesis literature searching, designed a literature search strategy in MEDLINE (Ovid) **(Appendix 1)**. The search strategy was reviewed by a knowledge synthesis librarian using the Peer Review of Electronic Search Strategies (PRESS) checklist.[177] The PhD candidate adapted the revised MEDLINE search strategy for Embase (Ovid), PubMed, Scopus (Elsevier), and Web of Science bibliographic databases. The PhD candidate also searched Google Scholar, website of various influenza vaccine manufacturers (GlaxoSmithKline, Sanofi Pasteur, ID Biomedical Corporation of Quebec, Seqirus, Protein Sciences, MedImmune) and websites of the International Federation of Pharmaceutical Manufacturers Associations (IFPMA), the WHO, the Centers for Disease Control and Prevention (CDC), the Canadian Influenza Sentinel Practitioner Surveillance Network (SPSN), the I-MOVE, and www.flu-gov for literature. All retrieved

literature citations following the searches were imported and de-duplicated in EndNote citation management software (version X6).

Study eligibility criteria

The de-duplicated literature citations were imported into Microsoft (MS) Access 2016 database (Microsoft Corporation, Redmond, WA, USA) designed by the PhD candidate specifically for citation sifting. Only full-text articles were included, irrespective of language of publication. The population/intervention/comparator/outcomes/study type (PICOS) framework (eligibility criteria) that informed the reviews were as follows:

- **Population**: Outpatients attending primary care clinics or day clinics in hospitals (i.e., excluding patients seen in emergency departments and those admitted), six months old or older, irrespective of health status, who have been vaccinated at least 14 days before symptom onset, and whose respiratory specimens were collected within 7 days of ARI or ILI symptom onset.
- **Intervention**: Seasonal influenza vaccination irrespective of vaccine type.
- **Comparator**: No seasonal influenza vaccination.
- **Outcomes**: Laboratory-confirmed influenza based on a reverse-transcription polymerase chain reaction (RT-PCR) assay or viral culture of a respiratory specimen.
- **Study type**: TND study of SIV effectiveness after the 2009/10 influenza pandemic.

Unpublished studies, studies other than the TND type, studies that evaluated just ARI or ILI without evaluating laboratory-confirmed influenza and studies that only evaluated vaccine effectiveness against pandemic and/or avian influenza types were excluded. Studies that evaluated vaccine effectiveness against hospitalisation, non-community-based studies such as

studies conducted in schools, personal care homes, military barracks, prisons etc., studies conducted only in special subpopulations such as persons suffering from a chronic disease(s), and studies that did not include a comparison with an unvaccinated group were also excluded.

Citation screening and literature selection

The PhD candidate screened the de-duplicated citations in the specially designed MS Access database for eligibility using a two-stage sifting approach to assess the title/abstract and full-text articles of relevant citations. As per good practice, another systematic reviewer independently screened the de-duplicated citations for eligibility in the same specially designed MS Access database using the same two-stage sifting approach to assess the title/abstract and full-text articles of relevant citations. The number of ineligible citations at the title/abstract screening stage and both the number and reasons for exclusion at the full-text article screening stage were documented. Any disagreements between the PhD candidate and the systematic reviewer were resolved through discussion or involvement of a third reviewer (the PhD candidate's Advisor).

Data extraction

The PhD candidate developed a data extraction spreadsheet using MS Excel 2016 (Microsoft Corporation, Redmond, WA, USA) and piloted on a small selection of studies (n=10). The PhD candidate extracted data from the included studies in the MS Excel spreadsheet, and, as per good practice, another systematic reviewer checked the extracted data for errors. Disagreements between the PhD candidate and the systematic reviewer were resolved through discussion or involvement of a third reviewer (the PhD candidate's Advisor). The following data were extracted:

- Basic study information such as the last name of the first author and an article publication year, country, region, number of participating clinical practices, funding information, year of study.
- Details relevant to study population such as outpatient type (clinic or hospital), participants' enrolment (whether consecutive or systematic), number of participants, average age or age range of participants, gender distribution, and health status.
- Influenza surveillance information such as the influenza season, influenza confirmatory test type, number of days from symptom onset to swab collection for testing, the circulating virus strain(s), the dominant strain and vaccine match with circulating strain(s). Information regarding the dominant strain and vaccine match with circulating strains were extracted from national influenza surveillance sources if not reported in a publication.
- Intervention and comparator information such as influenza vaccine type if reported.
- Outcome details such as all influenza, influenza A subtypes: A(H1N1)pdm09 and A(H3N2), or influenza B.
- Results for each specified outcome, including covariate adjustments, multivariable adjusted vaccine effectiveness estimates, with associated 95% confidence intervals (CI), and whether interim or final vaccine effectiveness estimates.
- Details relevant to study quality assessments.

In addition, pairing of interim SIV effectiveness study with the associated final SIV effectiveness study was conducted using Microsoft Excel 2016. The PhD candidate examined each interim study against the final studies and created matched pairs of interim/final studies based on the jurisdiction of study (study country and region), influenza season, reported vaccine effectiveness;

that is, against which influenza type/subtype, and study authors. The PhD candidate assessed whether there was inconsistency in statistical models; that is, if models did not adjust for exactly the same covariates between an interim vaccine effectiveness estimation and the matched final vaccine effectiveness estimation. The PhD candidate also ascertained the stage of seasonal influenza epidemic during which an interim vaccine effectiveness estimation was made based on the report in studies, and, where not reported, this was determined by examining the reported epidemic graph (curve) in the matched final vaccine effectiveness study. As per good practice, another systematic reviewer independently checked the matched pairs, assessed inconsistency in the statistical model and ascertained the epidemic stage of interim vaccine effectiveness assessment for errors. Disagreements between the PhD candidate and the systematic reviewer were resolved through discussion or involvement of a third reviewer (the PhD candidate's Advisor).

Further, the PhD candidate determined levels of VAS using reports from the WHO national influenza centres and region/country-specific centres for disease control. For example, for studies from the USA, summary reports from the CDC on each influenza season were utilised. For studies from the United Kingdom (UK), reports by Public Health England (PHE) on surveillance of influenza were utilised. For Canada, the National Advisory Committee on Immunization (NACI) statements on SIV for each influenza season were utilised. For Australia, the Australian Influenza Surveillance report for each influenza season was utilised. The WHO reports on influenza for the Northern and Southern hemispheres for each influenza season were also utilised where necessary, for collaboration of country-specific surveillance information. As per good practice, another systematic reviewer independently checked the determined level of

VAS for errors. Disagreements between the PhD candidate and the systematic reviewer were resolved through discussion or involvement of a third reviewer (the PhD candidate's Advisor).

Study quality assessment

Detailed study quality assessment was not anticipated considering the unavailability of a quality assessment tool for TND studies. However, in view of the strict inclusion criteria limiting the included studies to those conducted in outpatient settings on patients with laboratory-confirmed influenza, vaccinated against influenza at least 14 days before symptom onset, and whose respiratory specimens were collected within 7 days of symptom onset, quality assessment was improvised by examining other relevant study characteristics that could introduce bias. These included the method of study participants' enrolment, the method of vaccination confirmation, and inclusion of age and/or medical conditions, among other covariates in the logistic regression model for vaccine effectiveness estimation. The PhD candidate examined these other relevant study characteristics and, as per good practice, another systematic reviewer independently checked the assessments for errors. Disagreements between the PhD candidate and the systematic reviewer were resolved through discussion or involvement of a third reviewer (the PhD candidate's Advisor).

Data synthesis

Data synthesis was conducted by the PhD candidate according to the framework recommended by the University of York Centre for Review and Dissemination.[178] This framework includes the development of a theory of how an intervention works, why and for whom, the development of a preliminary synthesis of findings of included studies, the exploration of relationships within and between studies, and assessment of the robustness of the synthesis. Important characteristics and

outcome measures in included studies and the study quality assessments were synthesised narratively and in a tabular form.

Knowledge dissemination

Three abstracts from this thesis were presented at the International Society for Pharmacoepidemiology (ISPE) annual conference in Philadelphia, USA, in August 2019. Two abstracts from the thesis were presented (including an oral presentation) at the OPTIONS X for the control of influenza (the only global scientific meeting with a dedicated focus on influenza) in Singapore, in August/September 2019. Further, one abstract from the thesis was accepted for presentation and published as part of the 19th International Congress on Infectious Diseases (ICID) in Kuala Lumpur, Malaysia, in 2020 (the conference was however cancelled due to the COVID-19 pandemic). Manuscripts from the three studies presented in this thesis are published in high-impact journals.

Chapter 3. Interim seasonal influenza vaccine effectiveness estimates as proxy for final estimates: analysis of systematically identified matched pairs of interim/final estimates from test-negative design studies in outpatient settings from 2010/11 to 2018/19

Preface

The previous chapter (Chapter 2) details the common methods across the three studies included in this thesis, the first of which is the study reported in this present chapter. The WHO provides recommendations on SIV influenza strain composition each influenza season. The recommendations are made within a short period to allow sufficient time for the vaccine development and production before season commencement. As a result, interim (early-season) rather than final (end-season) SIV effectiveness estimates from surveillance studies are utilised for this purpose. Despite, the concordance between these estimates has been underexplored and there is a paucity of knowledge around the topic. This chapter presents a published study that explored this problem.

Publication citation

Okoli GN, Abdulwahid T, Racovitan F, Righolt CH, Mahmud SM. Interim seasonal influenza vaccine effectiveness estimates as proxy for final estimates: Analysis of systematically identified matched pairs of interim/final estimates from test-negative design studies in outpatient settings from 2010/11 to 2018/19. *Expert Review of Vaccines*. 2021 May; 20(5):585-599.

[**Note**: The manuscript presented herein is the accepted author version prior to copy editing]

Abstract

Objectives: Limited time for seasonal influenza vaccine development means that the World Health Organization must consider interim (early-season) rather than final (end-season) vaccine effectiveness (VE) estimates in deciding influenza vaccine composition for the next influenza season. We assessed agreement between interim and final adjusted VE estimates, and factors that may determine a substantial difference (≥10%) between point estimates.

Methods: This was a mixed methods study. We systematically searched, identified and matched interim/final VE studies of test-negative design (TND) type in outpatient settings after the 2009/10 influenza pandemic. The chi-square statistic ($\chi 2$) was used to assess the statistical significance of the difference between paired interim/final VE estimates. We calculated the difference between point estimates and used multivariable logistic regression to assess factors that may determine a substantial difference.

Results: We identified 68 interim/final VE pairs. There was no statistically significant difference between almost all compared pairs. An inconsistent statistical model for interim/final VE estimation and interim VE estimation before the influenza epidemic peak increased the odds of having a substantial difference between estimates.

Conclusions: Interim seasonal influenza VE appears to be sufficient for influenza vaccine composition decision-making. Consistency in interim/final VE estimation, and interim VE estimation during/after epidemic peak may increase agreement between the VE estimates.

Introduction

Vaccination remains the most practical and effective public health strategy for mitigating the impact of seasonal influenza epidemics. However, influenza viruses continuously change (antigenic drift)[1] and, as a result, influenza vaccine developed for a season may not be protective against influenza viruses in subsequent seasons. Influenza vaccine therefore has to be re-formulated each season, with the potential for mismatch between the virus strains contained in re-formulated vaccine and those in circulation. Observational studies are used to monitor influenza vaccine effectiveness (VE) because ethical and practicality considerations preclude the use of randomised controlled trials for this purpose. In particular, studies employing test-negative design (TND) are now the mainstay for influenza VE assessment,[2,3] and are published increasingly earlier during an influenza season (interim VE estimation).

The Global Influenza Surveillance and Response System (GISRS) unit of the World Health Organization (WHO) is responsible for providing global recommendations on the influenza vaccine strain composition each season based on several factors, including circulating strains' pathogenicity, speed and extent of spread, and current VE against the virus strains. This assessment requires robust global surveillance data collection from national influenza centres, laboratory testing of many influenza virus samples and assessment of influenza vaccine performance in many jurisdictions.[4] There is a short period within which decisions have to be made to allow sufficient time for vaccine development and production for the following season. Vaccine composition for the coming season is usually decided in February for the Northern hemisphere and in September for the Southern hemisphere.[5] The WHO decision-making relies on interim (early-season) VE estimates, while influenza viruses are still in circulation.

Agreement of interim VE estimates with final VE estimates would help optimise the accuracy and precision of the WHO influenza vaccine component recommendations and, conversely, the effectiveness of seasonal influenza vaccination programmes. Sullivan and colleagues reported a high agreement of interim and final VE estimates for influenza seasons 2007 to 2012 in Australia.[6] Belongia and colleagues also reported similar finding for 2007/08 influenza season in Wisconsin, United States of America (USA),[7] and, in Spain, Jimenez-Jorge and colleagues found that interim and final VE estimates from influenza seasons 2010 to 2014 showed greater agreement for all populations and influenza subtypes.[8] To our knowledge, there is currently one published global systematic review on this topic.[9] The review found similarities between interim and final VE estimates. However, due to a paucity of data the influence of important factors, such as inconsistency in statistical model used in estimating interim and paired final VE could not be assessed. Since the publication of the review in 2016, a lot more data have been published, providing the opportunity to further explore this important topic as there remains a huge gap in knowledge.

We systematically searched, identified, matched, summarised and analysed data on interim and final VE estimates from published TND studies in outpatient settings after the 2009/10 influenza pandemic, adhering to the Cochrane Handbook for Systematic Reviews of Interventions guidelines,[10] and we reported our findings following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[11]

Methods

The study methods are partly described in Chapter 2. In summary, this was a mixed methods study that comprised a systematic search and review of published literature to identify paired interim and final adjusted VE estimates studies from different jurisdictions, and an observational study of the systematically identified pairs of interim and final adjusted VE estimates. Literature was searched from January 2011, initially, in April 2017 and the search was subsequently updated in February 2020.

Data analysis

VE was represented as a percentage, calculated as one minus the adjusted ratio of the odds of vaccination among confirmed influenza cases, to the odds of vaccination among non-cases, multiplied by 100%. Paired interim and final VE estimates against all influenza, A(H1N1)pdm09, A(H3N2), and influenza B were depicted graphically using forest plots. The chi-square statistic ($\chi 2$) was used to assess the statistical significance (p-value) of the difference between paired interim and final VE estimates.[12] We calculated the difference between paired interim and final VE point estimates, and with reference to previous literature,[6,7] we considered ≥10% difference to be substantial. However, as a sensitivity analysis, we examined ≥5% and ≥20% difference, and underestimation/overestimation of the final estimate compared with the interim estimate. Furthermore, we considered difference between interim and final VE point estimates as a continuous outcome.

We categorised inconsistency in the statistical model as 0 = "no inconsistency" and 1 = "inconsistency". The stage of seasonal influenza epidemic during which interim VE estimation was made was categorised as 0 = "pre-peak" and 1 = "peak/post-peak". We considered the stage of the seasonal influenza epidemic to be a proxy for the relative population size of the interim

estimates since it is expected that pre-peak periods will have fewer influenza and influenza-like cases compared with peak periods. To inform appropriate covariate selection and to avoid unnecessary covariate adjustments,[13] we developed causal diagrams (directed acyclic graphs) in DAGitty, a web-based platform for creating and analysing causal diagrams (http://www.dagitty.net/). The code for the resulting diagram is presented as **Appendix 2**. Using multivariable logistic regression models, we calculated adjusted odds ratios (aOR) and 95% CIs of having a substantial difference between paired interim and final VE point estimates by assessing the impact of inconsistency in statistical model, epidemic stage during which interim VE estimation was made, and study region (geographical hemisphere). We also calculated aOR of having ≥5% and ≥20% difference between paired interim and final VE point estimates, and underestimation/overestimation of final VE point estimate with respect to the paired interim VE point estimate. Using a multivariable linear regression model, we calculated adjusted regression coefficients (aβ) and 95% CIs for the difference between paired interim and final VE point estimates. All statistical analyses were implemented in STATA (version 13; StataCorp LP, Texas, USA).

Results

From a total of 11,931 retrieved unique citations, we matched 68 pairs of interim/final VE estimates from 53 articles that met our inclusion criteria (**Figure 1**).[6,8.14-64] The main characteristics of the studies are detailed in **Table 1** and summarised statistically in **Table 2**.

Figure 1: Modified PRISMA flowchart of the selection of the included articles (for study 1).

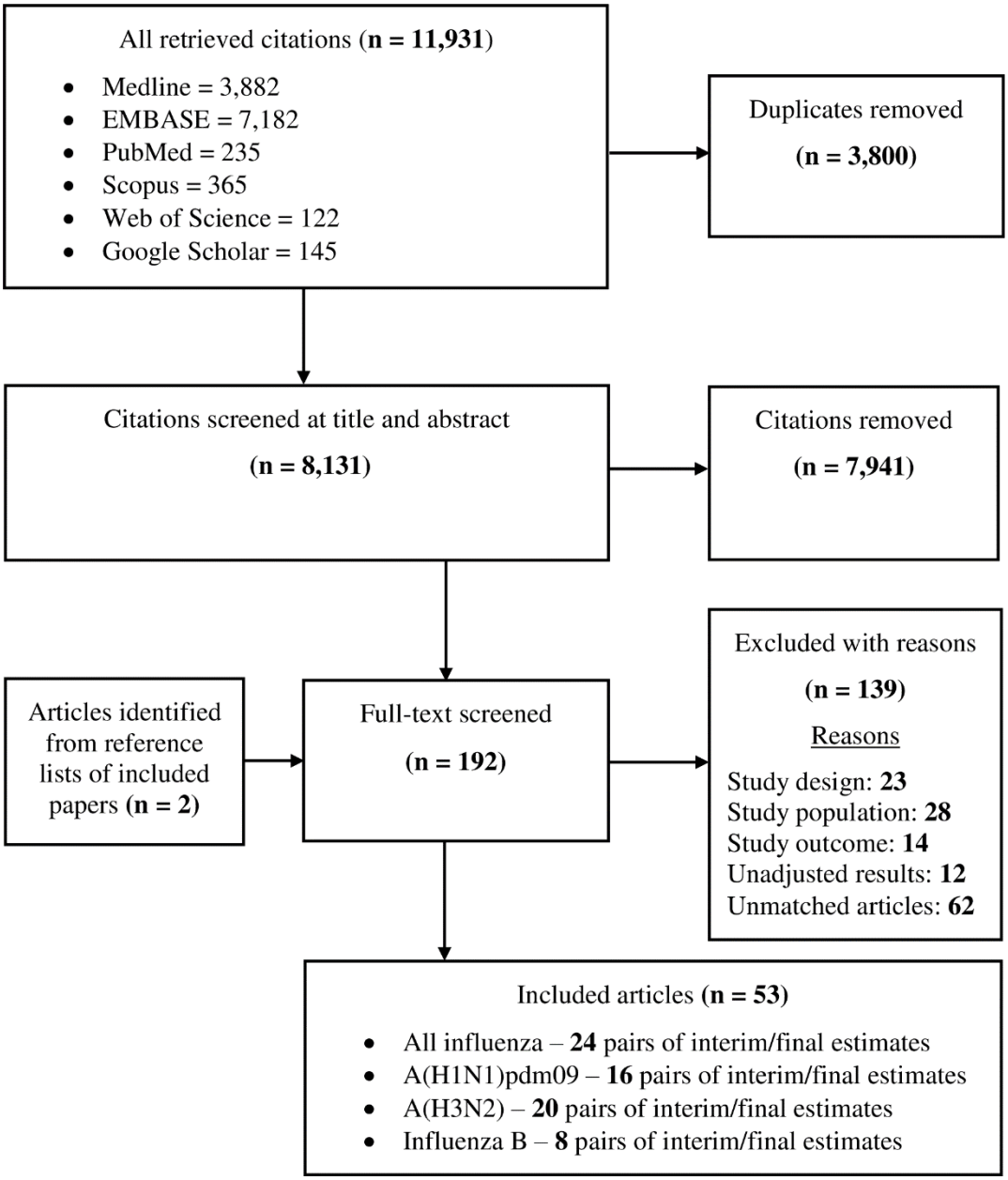


Table 1: Summary of the main characteristics of the included studies (for study 1).

Study	Country	Region	Season	Report type	Epidemic stage	Study population size	No. of variables in model	Model included age, period, and risk status	No. of weeks	Model change
All influenza										
Sullivan 2013[6]	Australia	Victoria	2010	Final	Post-peak	425	2	Age, Period	27	No
				Interim	Peak	378			19	
Kissling 2011[14]	Europe	8 countries	2010/11	Final	Post-peak	3,254	8	Yes	NA	No
Kissling 2011[15]		7 countries		Interim	Pre-peak	1,390				
Jimenez-Jorge 2012[19]	Spain	8 regions	2010/11	Final	Post-peak	1,293	4	Age, Period	15	No
Savulescu 2011[17]				Interim	Peak	1,061			9	
Sullivan 2013[6]	Australia	Victoria	2011	Final	Post-peak	588	2	Age, Period	27	No
				Interim	Peak	530			19	
Jimenez-Jorge 2013[23]	Spain	7 regions	2011/12	Final	Post-peak	378	3	Age, Period	19	No
Jimenez-Jorge 2012[18]				Interim	Peak	197			8	
Jimenez-Jorge 2015[8]	Spain	17 regions	2011/12	Final	Post-peak	1,446	3	Yes	19	No
				Interim		NR			8	
Sullivan 2013[6]	Australia	Victoria	2012	Final	Post-peak	678	2	Age, Period	27	No
				Interim		627			19	
Skowronski 2014[32]	Canada	5 provinces	2012/13	Final	Post-peak	1,501	5	Yes	27	No
Skowronski 2013[26]				Interim	Peak	739			13	
McLean 2015[36]	USA	5 States	2012/13	Final	Post-peak	6,452	4	Yes	18	Yes
Jackson 2013[22]				Interim	Pre-peak	2,697	5	Age	7	
Martinez-Baz 2015[35]	Spain	Navarra	2012/13	Final	Post-peak	522	5	Yes	22	Yes
Castilla 2013[21]				Interim	Pre-peak	206			13	
Jimenez-Jorge 2015[8]	Spain	17 regions	2012/13	Final	Post-peak	1,432	3	Yes	19	No
				Interim		NR			9	
Jimenez-Jorge 2015[8]	Spain	17 regions	2013/14	Final	Post-peak	NR	3	Yes	19	Yes
Jimenez-Jorge 2014[29]		6 regions		Interim	Peak	601	9		7	
Skowronski 2015[40]	Canada	5 provinces	2013/14	Final	Post-peak	1,700	5	Yes	27	No
Skowronski 2014[31]				Interim	Pre-peak	792			13	
Pebody 2015[37]	UK	National	2014/15	Final	Post-peak	2,931	5	Age, Period	26	No
Pebody 2015[38]				Interim	Peak	2,278			16	
Pierse 2016[46]	New Zealand	Auckland	2014	Final	Post-peak	1,154	10	Age, High-risk	27	Yes
Turner 2014[33]				Interim	Peak	919	2	Age, Period	18	
Skowronski 2016[48]	Canada	4 provinces	2014/15	Final	Post-peak	1,930	6	Yes	26	No
Skowronski 2015[39]		5 provinces		Interim	Pre-peak	861			11	

Study	Country	Region	Season	Report type	Epidemic stage	Study population size	No. of variables in model	Model included age, period, and risk status	No. of weeks	Model change
Zimmerman 2016[49]	USA	5 States	2014/15	Final	Post-peak	9,311	9	Yes	22	Yes
Flannery 2015[34]				Interim	Peak	2,321	6	Age	8	
Redlberger-Fritz 2016[47]	Austria	NR	2014/15	Final	Post-peak	815	3	Time	29	Yes
				Interim	Pre-peak	567	2	Age	21	
Pebody 2016[44]	UK	National	2015/16	Final	Post-peak	3,824	5	Age, Period	30	No
Pebody 2016[45]				Interim	Pre-peak	1,550			16	
Flannery 2019[57]	USA	5 States	2016/17	Final	Post-peak	7,083	4	Yes	20	Yes
Flannery 2017[50]				Interim	Peak	3,144	7	Age	10	
Martinez-Baz 2019[59]	Spain	Navarra	2017/18	Final	Post-peak	604	4	Yes	21	Yes
Castilla 2018[52]				Interim	Pre-peak	460	5		9	
Pebody 2019[60]	UK	National	2017/18	Final	Post-peak	3,080	6	Yes	30	Yes
Rondy 2018[55]				Interim	Pre-peak	1,331	5	Age	15	
Rolfes 2019[61]	USA	5 States	2017/18	Final	Post-peak	8,436	4	Yes	21	Yes
Flannery 2018[53]				Interim	Peak	4,562	7	Age	13	
Flannery 2020[64]	USA	5 states	2018/19	Final	Post-peak	4,018	7	Age, Period	23	Yes
Doyle 2019[56]				Interim	Pre-peak	3,254			10	
A(H1N1)pdm09										
Kissling 2011[14]	Europe	8 countries	2010/11	Final	Post-peak	2,506	8	Yes	NA	No
Kissling 2011[15]		7 countries		Interim	Pre-peak	1,158				
Jimenez-Jorge 2012[19]	Spain	8 regions	2010/11	Final	Post-peak	1,165	3	Age, Period	15	No
Savulescu 2011[17]				Interim	Peak	983			9	
Pebody 2013[25]	UK	National	2010/11	Final	Post-peak	7,758	4	Age, Period	28	No
Pebody 2011[16]		3 regions		Interim	Pre-peak	3,480			19	
Andrews 2014[28]	UK	National	2012/13	Final	Post-peak	3,286	4	Age, Period	29	No
				Interim	Pre-peak	2,435			17	
Kissling 2014[30]	Europe	7 countries	2012/13	Final	Post-peak	3,196	4	Yes	NA	Yes
Valenciano 2013[27]		5 countries		Interim	Pre-peak	602				
Jimenez-Jorge 2015[8]	Spain	17 regions	2013/14	Final	Post-peak	747	3	Yes	19	Yes
Jimenez-Jorge 2014[29]		6 regions		Interim	Peak	413	9		7	
Skowronski 2015[40]	Canada	5 provinces	2013/14	Final	Post-peak	1,452	5	Yes	27	No
Skowronski 2014[31]				Interim	Pre-peak	639			13	
Pierse 2016[46]	New Zealand	Auckland	2014	Final	Post-peak	477	10	Age, High-risk	27	Yes
Turner 2014[33]				Interim	Peak	384	2	Age, Period	18	
Redlberger-Fritz 2016[47]	Austria	NR	2014/15	Final	Post-peak	431	3	Time	29	Yes
				Interim	Pre-peak	301	2	Age	21	

Study	Country	Region	Season	Report type	Epidemic stage	Study population size	No. of variables in model	Model included age, period, and risk status	No. of weeks	Model change
Pebody 2016[44]	UK	National	2015/16	Final	Post-peak	3,841	5	Age, Period	30	No
Pebody 2016[45]				Interim	Pre-peak	1,548			16	
Kissling 2018[54]	Europe	12 countries	2015/16	Final	Post-peak	6,823	5	Yes	NA	Yes
Kissling 2016[43]		10 countries		Interim	Pre-peak	1,933	Unclear	Unclear		
Skowronski 2017[51]	Canada	4 provinces	2015/16	Final	Post-peak	1,522	6	Yes	17	Yes
Chambers 2016[41]				Interim	Pre-peak	931	5			
Rolfes 2019[61]	USA	5 States	2017/18	Final	Post-peak	8,436	4	Yes	21	Yes
Flannery 2018[53]				Interim	Peak	3,058	7	Age, High-risk	13	
Kissling 2019[58]	Europe	11 countries	2017/18	Final	Post-peak	7,175	4	Age, Period	NA	No
				Interim	Pre-peak	2,009				
Skowronski 2019[63]	Canada	4 regions	2018/19	Final	Post-peak	3,034	4	Age, Period	26	No
Skowronski 2019[62]				Interim	Pre-peak	1,442			10	
Flannery 2020[64]	USA	5 states	2018/19	Final	Post-peak	8,574	7	Age, Period	23	No
Doyle 2019[56]				Interim	Pre-peak	3,082			10	
A(H3N2)										
Kissling 2013[24]	Europe	8 countries	2011/12	Final	Post-peak	1,033	7	Yes	NA	Yes
Kissling 2012[20]				Interim	Pre-peak	521	6			
Jimenez-Jorge 2013[23]	Spain	7 regions	2011/12	Final	Post-peak	342	3	Age	19	No
				Interim	Peak	190			8	
Jimenez-Jorge 2015[8]	Spain	17 regions	2011/12	Final	Post-peak	1,348	3	Age	19	No
				Interim		NR			8	
Skowronski 2014[32]	Canada	5 provinces	2012/13	Final	Post-peak	1,244	5	Yes	27	No
Skowronski 2013[26]				Interim	Peak	671			13	
Kissling 2014[30]	Europe	7 countries	2012/13	Final	Post-peak	3,012	4	Yes	NA	No
Valenciano 2013[27]		5 countries		Interim	Pre-peak	688				
Andrews 2014[28]	UK	National	2012/13	Final	Post-peak	2,310	4	Age, Period	29	No
				Interim	Pre-peak	1,534			17	
McLean 2015[36]	USA	5 States	2012/13	Final	Post-peak	5,437	4	Yes	18	Yes
Jackson 2013[22]				Interim	Pre-peak	2,128	5	Age	7	
Jimenez-Jorge 2015[8]	Spain	17 regions	2013/14	Final	Post-peak	762	3	Yes	19	Yes
Jimenez-Jorge 2014[29]		6 regions		Interim	Peak	417	9		7	
Pebody 2015[37]	UK	All regions	2014/15	Final	Post-peak	2,658	5	Age, Period	26	No
Pebody 2015[38]				Interim	Peak	1,273			16	
Skowronski 2016[48]	Canada	4 provinces	2014/15	Final	Post-peak	1,685	6	Yes	26	No
Skowronski 2015[39]		5 provinces		Interim	Pre-peak	830			11	

Study	Country	Region	Season	Report type	Epidemic stage	Study population size	No. of variables in model	Model included age, period, and risk status	No. of weeks	Model change
Redlberger-Fritz 2016[47]	Austria	NR	2014/15	Final	Post-peak	629	3	Age, Period	29	Yes
				Interim	Pre-peak	462	2	Age	21	
Gherasim 2016a[42]	Spain	SISS	2014/15	Final	Post-peak	2,838	5	Yes	19	Yes
				Interim	Pre-peak	1,532	4	Age, High-risk	10	
Gherasim 2016b[42]	Spain	cycEVA	2014/15	Final	Post-peak	878	5	Yes	19	Yes
				Interim	Pre-peak	429	4	Age, High-risk	10	
Zimmerman 2016[49]	USA	5 States	2014/15	Final	Post-peak	8,895	9	Yes	22	Yes
Flannery 2015[34]				Interim	Peak	2,212	6	Age	8	
Flannery 2019[57]	USA	5 States	2016/17	Final	Post-peak	6,382	4	Yes	20	Yes
Flannery 2017[50]				Interim	Peak	3,144	7	Age	10	
Kissling 2019[58]	Europe	11 countries	2016/17	Final	Post-peak	10591	4	Age, Period	NA	No
				Interim	Pre-peak	3,541				
Rolfes 2019[61]	USA	5 States	2017/18	Final	Post-peak	7,147	4	Yes	21	Yes
Flannery 2018[53]				Interim	Peak	3,993	7	Age	13	
Kissling 2019[58]	Europe	11 countries	2017/18	Final	Post-peak	5,607	4	Age, Period	NA	No
				Interim	Pre-peak	1,413				
Pebody 2019[60]	UK	National	2017/18	Final	Post-peak	3,080	6	Yes	30	No
				Interim	Pre-peak	1071			15	
Flannery 2020[64]	USA	5 states	2018/19	Final	Post-peak	8,599	7	Age	23	Yes
Doyle 2019[56]				Interim	Pre-peak	2,890			10	
Influenza B										
Kissling 2014[30]	Europe	7 countries	2012/13	Final	Post-peak	6,425	4	Yes	NA	Yes
Valenciano 2013[27]		5 countries		Interim	Pre-peak	681				
Andrews 2014[28]	UK	National	2012/13	Final	Post-peak	3,286	4	Age, Period	29	No
				Interim	Pre-peak	2,435			17	
Jimenez-Jorge 2015[8]	Spain	17 regions	2012/13	Final	Post-peak	947	3	Yes	19	No
				Interim		NR			9	
Redlberger-Fritz 2016[47]	Austria	NR	2014/15	Final	Post-peak	439	3	Age, Period	29	Yes
				Interim	Pre-peak	262	2	Age	21	
Gherasim 2016[42]	Spain	17 regions	2014/15	Final	Post-peak	798	5	Yes	19	Yes
				Interim	Pre-peak	322	4	Age, High-risk	10	
Flannery 2019[57]	USA	5 States	2016/17	Final	Post-peak	5,688	4	Yes	20	Yes
Flannery 2017[50]				Interim	Peak	3,144	7	Age	10	
Rolfes 2019[61]	USA	5 States	2017/18	Final	Post-peak	8,436	4	Yes	21	Yes

Flannery 2018[53]				Interim	Peak	3,173	7	Age	13	
Pebody 2019[60]	UK	5 regions	2017/18	Final	Post-peak	2,534	6	Yes	30	No
				Interim	Pre-peak	1,122			15	

USA = United States of America; UK = United Kingdom; NR = not reported; NA = not applicable; No = no model change; Yes = model change; SISS = Spanish Influenza Surveillance System; cycEVA = case-control study for measuring influenza vaccine effectiveness in Spain

Table 2: Number (%) of paired interim/final VE estimates across levels of assessed variables and ≥10% difference between interim and final VE point estimates.

	≥10% difference	
	Yes	**No**
	(N=35)	(N=33)
Inconsistency in statistical model		
Consistent model	11 (31.4%)	24 (72.7%)
Inconsistent model	24 (68.6%)	9 (27.3%)
Epidemic stage during interim VE estimation		
Pre-peak	25 (71.4%)	14 (42.4%)
Peak/Post-peak	10 (28.6%)	19 (57.6%)
Proportion of interim VE patient population		
Within one-third	5 (14.3%)	3 (9.1%)
Between one-third and two-thirds	20 (57.1%)	20 (60.6%)
More than two-thirds	9 (25.7%)	6 (18.2%)
Unknown	1 (2.9%)	4 (12.1%)
Geographical region		
Northern	33 (94.3%)	30 (90.9%)
Southern	2 (5.7%)	3 (9.1%)
Country		
Australia	0 (0.0%)	3 (9.1%)
Austria	4 (11.4%)	0 (0.0%)
Canada	2 (5.7%)	6 (18.2%)
Europe (I-MOVE)	8 (22.9%)	2 (6.1%)
New Zealand	2 (5.7%)	0 (0.0%)
Spain	8 (22.9%)	8 (24.2%)
UK	6 (17.1%)	5 (15.2%)
USA	5 (14.3%)	9 (27.3%)
Influenza type/subtypes		
All influenza	12 (34.3%)	12 (36.4%)
A(H1N1)pdm09	7 (20.0%)	9 (27.3%)
A(H3N2)	12 (34.3%)	8 (24.2%)
Influenza B	4 (11.4%)	4 (12.1%)
Influenza season		
2010/11	3 (8.6%)	3 (9.1%)
2011/12	1 (2.9%)	5 (15.2%)
2012/13	4 (11.4%)	10 (30.3%)
2013/14	2 (5.7%)	3 (9.1%)
2014/15	13 (37.1%)	2 (6.1%)
2015/16	3 (8.6%)	1 (3.0%)
2016/17	3 (8.6%)	1 (3.0%)
2017/18	4 (11.4%)	6 (18.2%)
2018/19	2 (5.7%)	2 (6.1%)

VE = vaccine effectiveness; UK = United Kingdom; USA = United States of America; i-MOVE = Influenza-Monitoring Vaccine Effectiveness in Europe

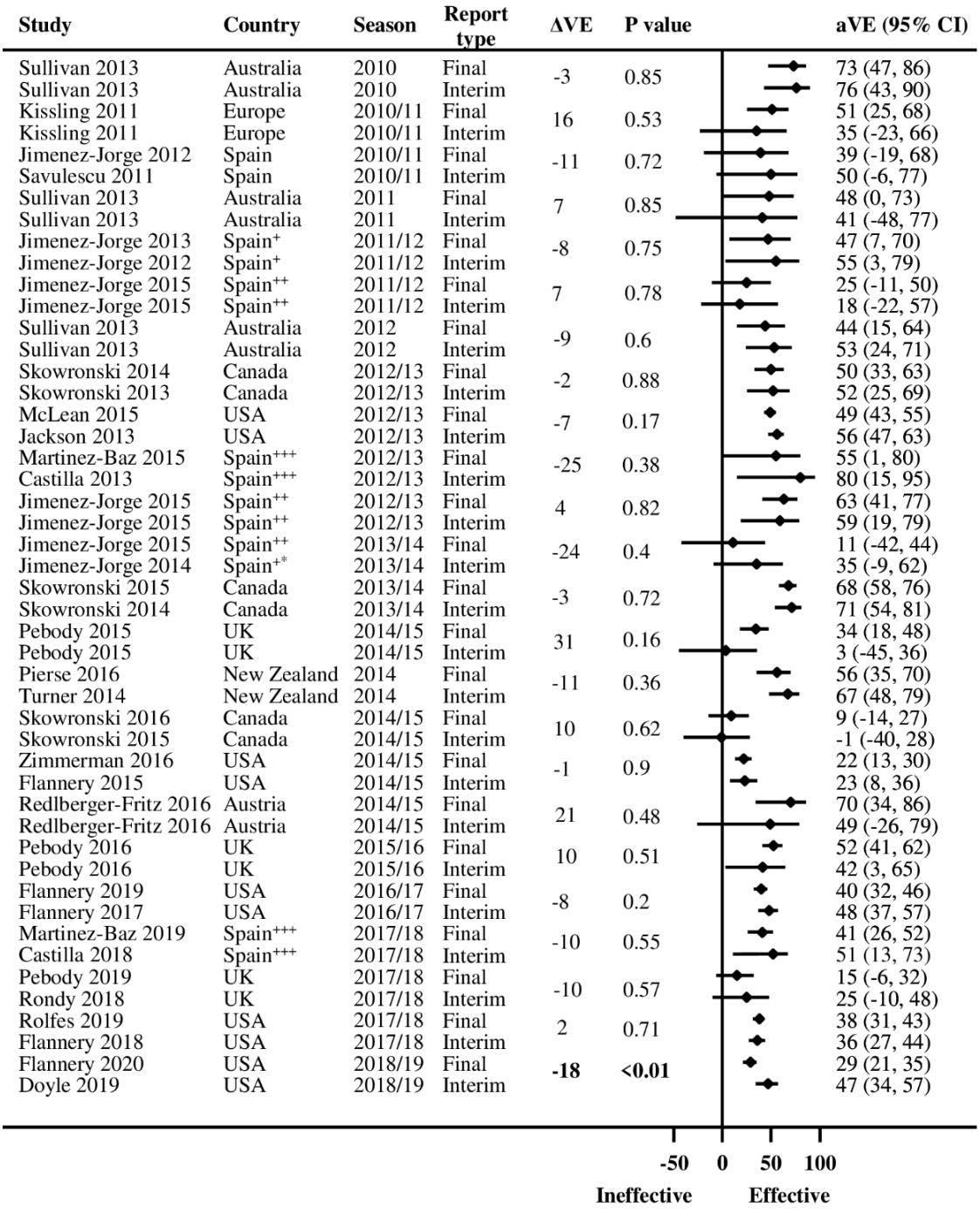
Of the matched 68 pairs of estimates, 24 pairs were for all influenza, 16 pairs for A(H1N1)pdm09, 20 pairs for A(H3N2), and eight pairs for influenza B. Overall, Australia contributed three pairs of VE estimates; Austria four pairs; Canada eight pairs; the European Influenza - Monitoring Vaccine Effectiveness (I-MOVE) network ten pairs; New Zealand two pairs; Spain 16 pairs; United Kingdom (UK) eleven pairs and the USA 14 pairs. Where reported, difference between paired interim and final VE study durations ranged from zero to 16 weeks. Overall, inconsistency in statistical model was identified in about 49% (33/68) of the paired VE estimates. Among these, a substantial difference between point estimates was observed in about 73% (24/33) of the pairs whereas this was observed in only about 31% (11/35) of the pairs with consistent statistical model. Across pairs of final and interim VE estimates, a higher proportion of the final point estimates was lower than the interim point estimates: all influenza (62.5%), A(H1N1)pdm09 (75%), A(H3N2) (75%), and influenza B (50%). However, lower final point VE estimates were observed in higher proportions of compared VE pairs with inconsistency in statistical model, except for A(H1N1)pdm09 which had similar proportions between VE pairs with and without inconsistency in statistical model. Further summary statistics are detailed as **Appendix 3**, **Appendix 4** and **Appendix 5**, respectively, for ≥5% and ≥20% difference between interim and final VE point estimates and for underestimation versus overestimation.

Comparison between interim and final VE estimates.

The difference between interim and final VE point estimates ranged from -25% to 31% for all influenza (**Figure 2**), -28% to 16% for A(H1N1)pdm09 (**Figure 3**), -35% to 55% for A(H3N2) (**Figure 4**), and -36% to 21% for influenza B (**Figure 5**), with only one statistically significant difference: -18% ($p<0.01$) for all influenza in 2018/19 influenza season in the USA; -28%

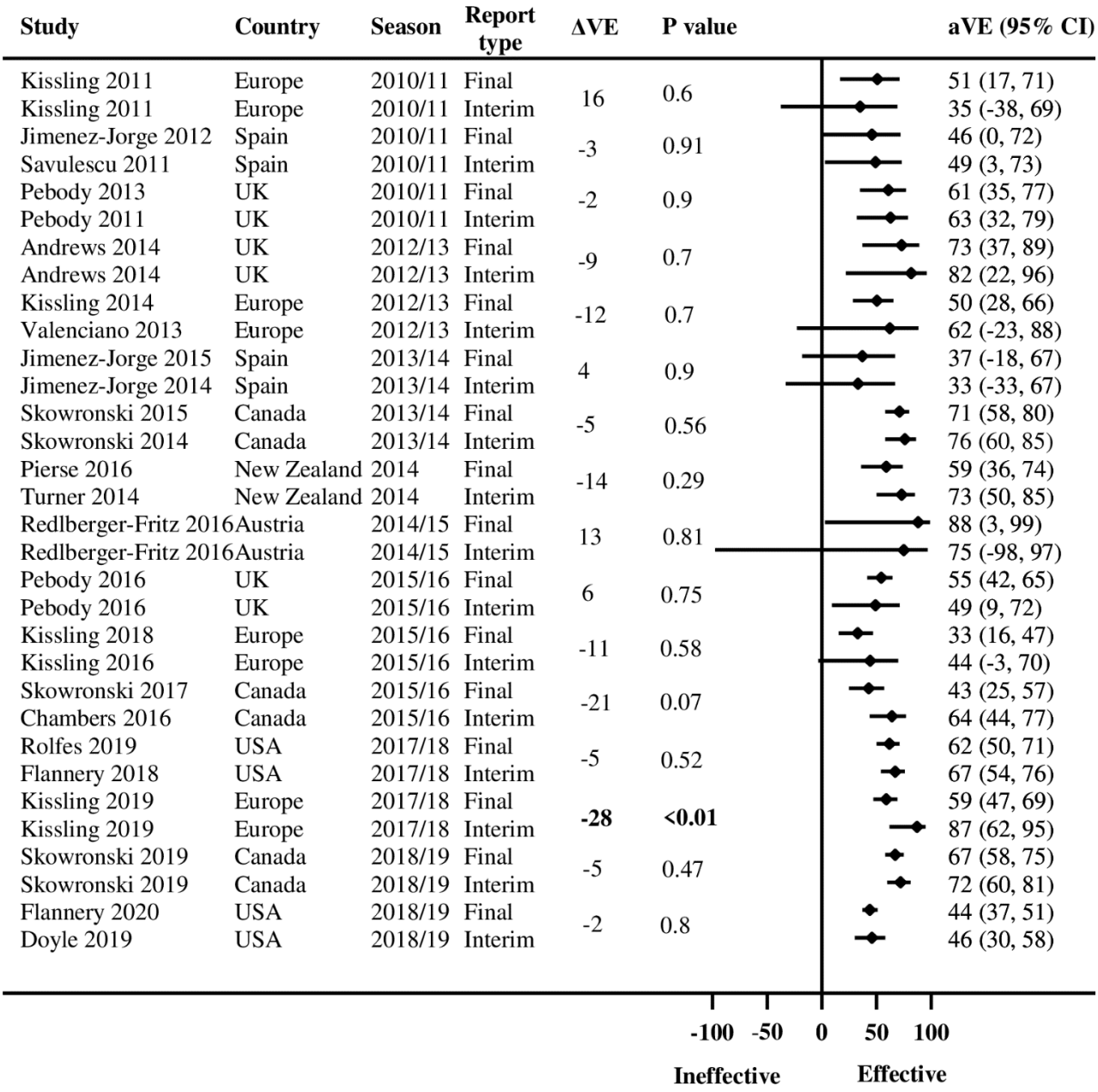
($p<0.01$) for A(H1N1)pdm09 in 2017/18 from the I-MOVE; -35% ($p<0.01$) for A(H3N2) in 2018/19 in the USA, and -20% ($p=0.02$) for influenza B in 2016/17 in the USA.

Figure 2: Forest plot of paired interim and final VE estimates against all influenza (24 pairs).



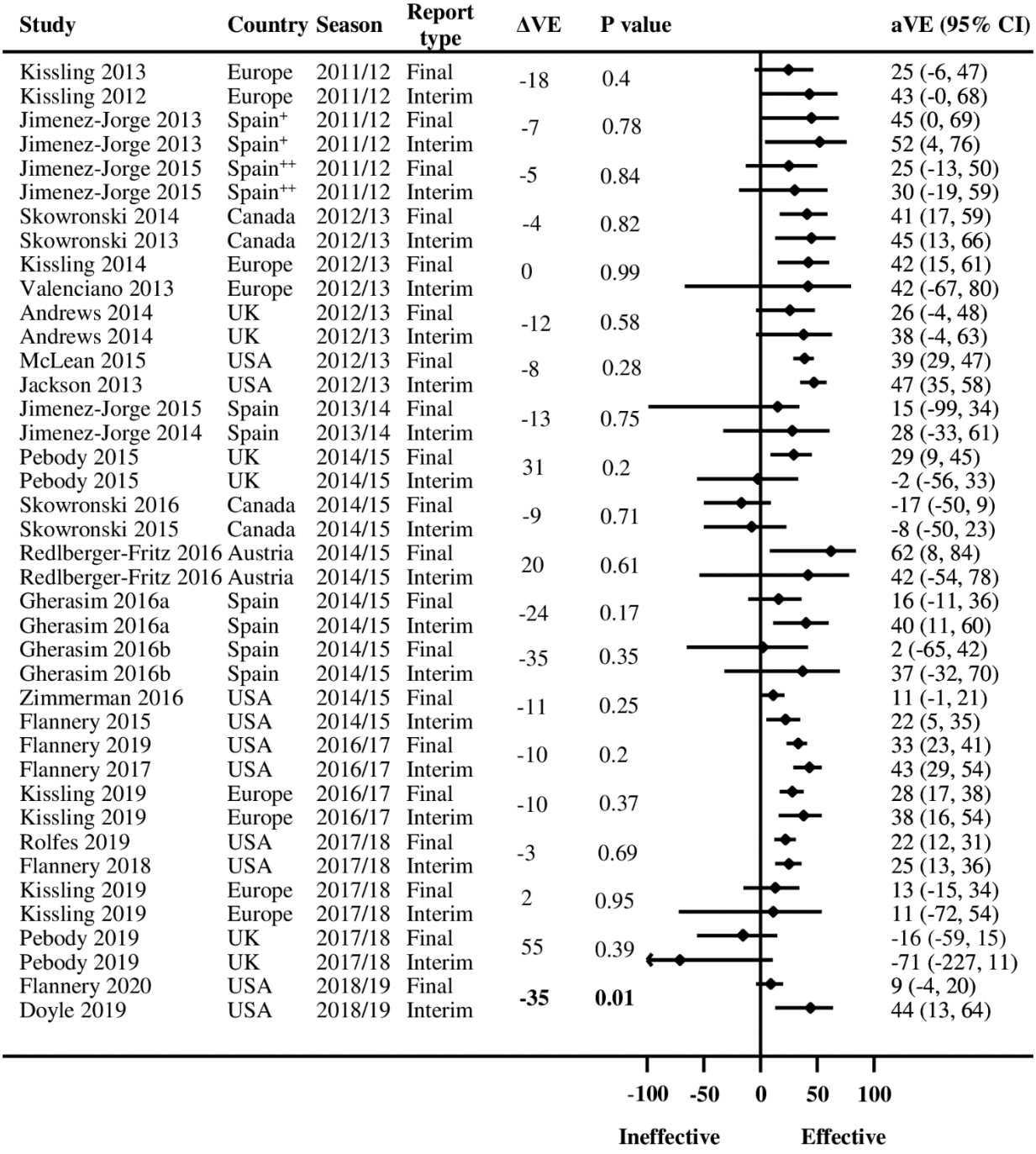
ΔVE = change in interim and final vaccine effectiveness point estimates; aVE = adjusted vaccine effectiveness; + = study covered 7 regions; ++ = study covered 17 regions; +++ = study covered 1 region; +* = study covered 6 regions; Bold P value = statistically significant; CI = confidence interval; UK = United Kingdom; USA = United States of America

Figure 3: Forest plot of paired interim and final VE estimates against A(H1N1)pdm09 (16 pairs).



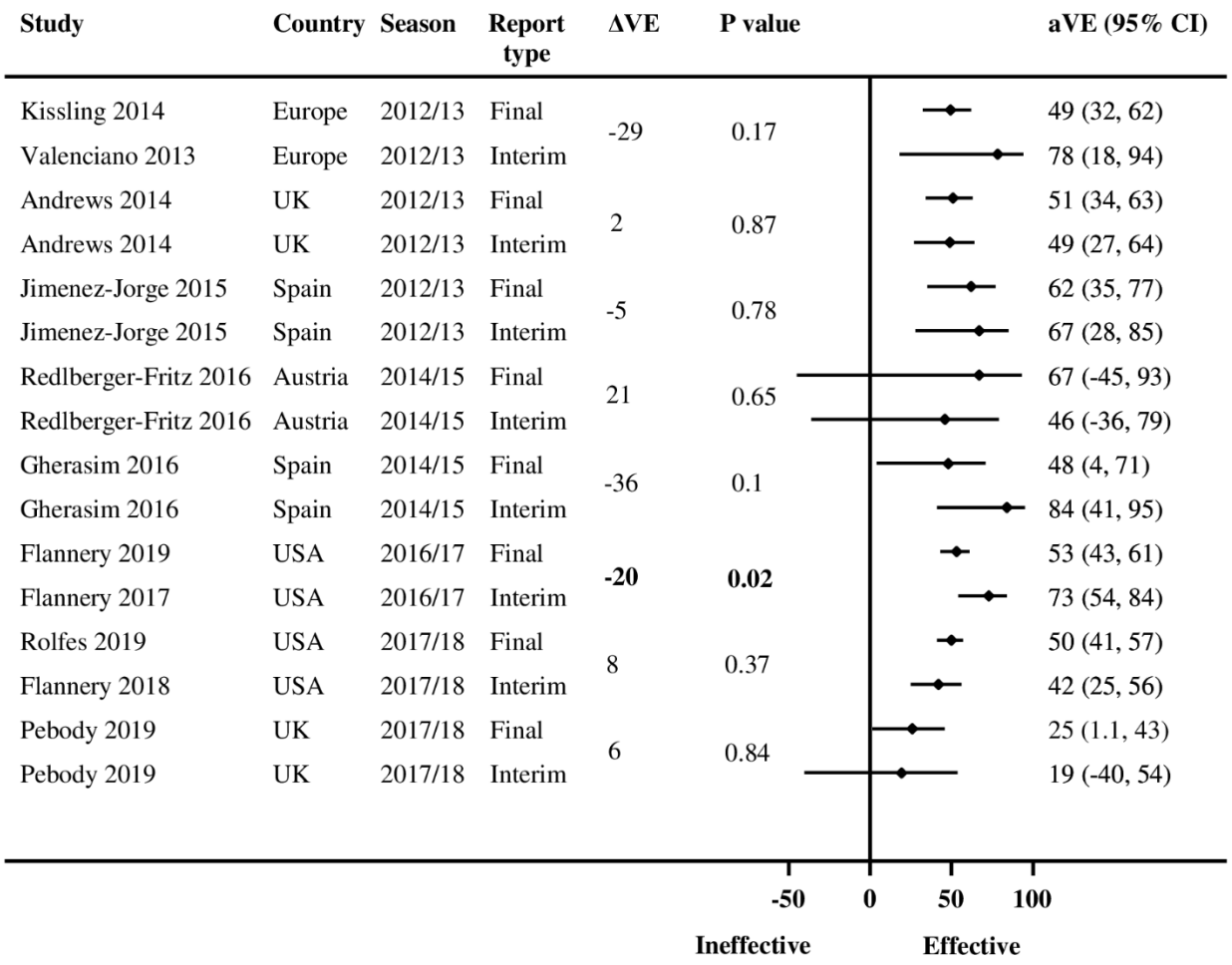
ΔVE = change in interim and final vaccine effectiveness point estimates; aVE = adjusted vaccine effectiveness; Bold P value = statistically significant; CI = confidence interval; UK = United Kingdom; USA = United States of America

Figure 4: Forest plot of paired interim and final VE estimates against A(H3N2) (20 pairs).



ΔVE = change in interim and final vaccine effectiveness point estimates; aVE = adjusted vaccine effectiveness; + = study covered 7 regions; ++ = study covered 17 regions; Bold P value = statistically significant; CI = confidence interval; UK = United Kingdom; USA = United States of America

Figure 5: Forest plot of paired interim and final VE estimates against influenza B (8 pairs).



ΔVE = change in interim and final vaccine effectiveness point estimates; aVE = adjusted vaccine effectiveness; Bold P value = statistically significant; CI = confidence interval; UK = United Kingdom; USA = United States of America

Logistic regression of ≥10% difference (substantial difference) between paired interim and final VE point estimates.

In the unadjusted analysis, inconsistency in statistical model was associated with a substantial difference, but epidemic stage of interim VE estimation and geographical region both showed no association (**Table 3**). In the adjusted analysis, inconsistency in statistical model and epidemic stage of interim VE estimation were associated with a substantial difference. Inconsistency in statistical model increased the odds of having a substantial difference [aOR 5.8 (2.0 – 16.5); p=0.001] whereas interim VE estimation at peak/post-peak of epidemic decreased the odds [0.2 (0.04 – 0.7); p=0.017] (**Table 3**). When stratified by epidemic stage of interim VE estimation, the influence of inconsistency in statistical model was stronger, with an associated higher increased odds of having a substantial difference when interim VE estimation was conducted pre-peak of epidemic [12.7 (2.3 – 71.0); p=0.004], albeit with a wide confidence interval. No association was found for inconsistency in statistical model when interim VE estimation was conducted at peak/post-peak of epidemic (**Table 3**). Epidemic stage of interim VE estimation was not associated with a substantial difference with consistency in statistical model. There was a paucity of data to assess the association with inconsistency in statistical model or to perform subgroup analysis by influenza subtype/type and season.

Table 3: Logistic regression model of ≥10% difference between paired interim and final VE point estimates (N = 68).

Variables	Overall (n = 68)		Pre-peak of epidemic (n=39)	Peak/post-peak of epidemic (n=29)	Consistent model (n=35)	Inconsistent model (n=33)
	OR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Inconsistency in statistical model (Yes or No)[a]	**5.8 (2.0 – 16.6)**	**5.8 (2.0 – 16.5)**	**12.7 (2.3 – 71.0)**	4.2 (0.8 – 22.0)	–	–
Epidemic stage of interim VE estimation (Pre- or peak/post-peak)[b]	0.3 (0.1 – 0.8)	**0.2 (0.04 – 0.7)**	–	–	0.5 (0.1 – 4.7)	NA
Region (Hemisphere)[c]	0.6 (0.1 – 3.9)	0.6 (0.1 – 3.9)	1.0	1.3 (0.2 – 9.7)	1.0	1.0

VE = vaccine effectiveness; OR = crude odds ratio; aOR = adjusted odds ratio; CI = confidence interval; a = adjusted for region; b = adjusted for season; c = no adjustment needed; NA = not applicable; Bold results = statistically significant.

Linear regression of difference between interim and final VE point estimates.

In the unadjusted analysis, inconsistency in statistical model predicted the difference, but epidemic stage of interim VE estimation and geographical region did not (**Table 4**). In the adjusted analysis, inconsistency in statistical model predicted the difference [aβ -11.8 (-19.1 to -4.5); p=0.002; F (2, 65) = 5.25: inconsistency in statistical model accounting for 11.2% of the explained variability in the difference], but epidemic stage of interim VE estimation and geographical region did not (**Table 4**). Inconsistency in statistical model also predicted the

difference in both strata of epidemic stage of interim VE estimation: pre-peak [-13.7 (-25.0 to -2.4); p=0.019; F (1, 37) = 6.0: inconsistency in statistical model accounting for 11.6% of the explained variability in the difference] and peak/post-peak [-9.4 (-18.2 to -0.6); P=0.036; F (2, 26) = 2.66: inconsistency in statistical model accounting for 10.6% of the explained variability in difference].

Table 4: Linear regression model of difference between paired interim and final VE point estimates.

Variables	**Overall (n = 68)**		**Pre-peak (n=39)**	**Peak/post-peak (n=29)**	**Consistent model (n=35)**	**Inconsistent model (n=33)**
	β (95% CI)	aβ (95% CI)	aβ (95% CI)	aβ (95% CI)	aβ (95% CI)	aβ (95% CI)
Inconsistency in statistical model (Yes or No)[a]	**-11.7 (-19.0 – -4.5)**	**-11.8 (-19.1 – -4.5)**	**-13.7 (-25.0 – -2.4)**	**-9.4 (-18.2 – -0.6)**	–	–
Epidemic stage of interim VE estimation (Pre- or peak/post-peak)[b]	1.9 (-5.9 – 9.8)	1.8 (-7.1 – 10.6)	–	–	2.3 (-12.1 – 16.6)	-0.6 (-17.2 – 16.0)
Region (Hemisphere)[c]	-2.2 (-17.2 – 12.8)	-2.2 (-17.2 – 12.8)	0.0	-3.8 (-16.2 – 8.5)	-3.7 (-22.1 – 14.6)	-2.7 (-25.7 – 20.4)

VE = vaccine effectiveness; β = crude regression coefficient; aβ = adjusted regression coefficient; CI = confidence interval; a = adjusted for region; b = adjustment for season; c = no adjustment needed; Bold results = statistically significant.

Logistic regression of ≥5% and ≥20% difference between paired interim and final VE point estimates, and underestimation/overestimation of final compared with interim VE point estimates.

In the unadjusted as well as the adjusted analyses, inconsistency in statistical model, epidemic stage of interim VE estimation and geographical region were not statistically significantly associated with a ≥5% difference (**Appendix 6**), or with underestimation/overestimation of final VE point estimates (**Appendix 7**). Inconsistency in statistical model was, however, found to be associated with a ≥20% difference in the unadjusted as well as the adjusted analyses (**Appendix 6**), with an increased odds of having a ≥20% difference when statistical model is inconsistent [aOR 4.4 (1.2 – 15.8); p=0.02]. When stratified by epidemic stage of interim VE estimation, the influence of inconsistency in statistical model was stronger for when interim VE estimation was conducted pre-peak of epidemic [10.0 (1.8 – 55.6); p=0.009], albeit with a wide confidence interval.

Discussion

In this systematic review involving 68 pairs of interim/final seasonal influenza VE estimates from TND studies conducted after the 2009/10 influenza pandemic, we assessed the agreement of paired interim and final seasonal influenza VE estimates, and the influence of certain important factors on a substantial difference (≥10%) between the paired VE point estimates. We found no significant difference between almost all compared pairs of interim and final VE estimates. We found that inconsistency in statistical model used for interim and final VE estimations, and influenza epidemic stage during which interim VE estimation was calculated, may both be associated with a substantial difference between interim and final VE point estimates. We also found that inconsistency in statistical models may predict the difference between interim and final VE point estimates. Final VE estimates were observed to be generally lower than interim VE estimates. However, a higher proportion of the lower final VE estimates were observed among VE pairs with inconsistent statistical models. Compared with A(H1N1)pdm09, a higher proportion of the lower final VE estimates was also observed among VE pairs against A(H3N2) whereas the lowest proportion was observed for influenza B. VE may also be waning as influenza season progresses. This, perhaps, may be a residual reason for the observed differences in VE. However, our review was not set up to examine this and studies did not report on time since vaccination to enable such assessment.

VE estimate pairs assessed in this review were from North America, Europe and Oceania. There were none from Asia and Africa. As such, our findings may not be generalisable. There is also the need for a cautious interpretation of our multivariable regression analyses considering that the number of contributing VE comparisons may not be large enough to enable robust detection of the associations that we examined, and that the effect of some important factors may

not have been accounted for in our model due to a lack of data. The main difference between some of the paired VE estimates was in the specification of statistical model for VE estimation. Study periods also differed across jurisdictions in terms of influenza season commencement and end dates, and the number of weeks covered in the interim and final VE estimations. Severity of epidemics was also variable. In addition, there were underlying differences in the health systems especially with regard to seasonal influenza vaccination policy, vaccine access and surveillance systems. Conversely, there were variations in the proportions of vaccinated study participants, confirmed influenza cases, and the overall study population sizes. Nevertheless, in all studies, irrespective of study jurisdiction, study participants were vaccinated at least 14 days before symptom onset, respiratory specimen swab collected within seven days of symptom onset, and influenza confirmed using either RT-PCR or viral culture, but more predominantly, RT-PCR.

Just as we found in this review, Jimenez-Jorge and colleagues also concluded that interim estimates from TND studies were good proxy for the final VE estimates in 2010 to 2014 influenza seasons in Spain, and that interim and final estimates showed greater agreement within all population and for all influenza subtypes.[8] They also observed that interim estimates were higher compared to final estimates. A study conducted in Australia by Sullivan and colleagues using data from TND studies in influenza seasons 2007 to 2012 reported that late season interim estimates reliably predicted final estimates in Victoria, Australia and, just as we found, also reported that interim VE estimates after epidemic peak may be more reliable.[6] Our findings are also similar to those of the only available global systematic review on the topic (Leung et al.).[9] The review concluded that interim and final VE estimates were similar enough to support the WHO's use of interim estimates as proxy for final estimates in vaccine composition decision-making. Using a stepwise linear regression model and a ≥10% difference between interim and

final VE point estimates as substantial difference just as we did, the review found that, among other factors, sample size and stage of seasonal influenza epidemic during which interim estimate was made may influence having a substantial difference. However, there was not enough sample size to be able to assess the impact of some of these factors in a multivariable adjusted regression model and the influence of inconsistency in statistical model could also not be examined. Our review, however, involves more than twice the evidence in Leung et al.: 68 VE pairs vs. 33 pairs, representing 24 pairs vs. 12 pairs for all influenza, 16 pairs vs. 10 pairs for A(H1N1)pdm09, 20 pairs vs. 7 pairs for A(H3N2), and 8 pairs vs. 4 pairs for influenza B. Leung et al. also included data for a few hospitalised patients whereas we limited to outpatients. In addition, a few VE estimates prior to the 2010/11 influenza season were included in the review whereas we limited to VE estimates after the 2009/10 influenza pandemic so as to focus on the seasons when A(H1N1)pdm09 was in circulation.

Our review provides more knowledge that could help optimise the effectiveness of global influenza vaccination programmes, and adds to the evidence base on the need for standardizing influenza VE evaluations across jurisdictions. In view of the difficulties in using final VE estimates for policy decisions due to time constraints, our findings support the WHO GISRS's use of interim VE estimates as a proxy for final estimates in vaccine composition decision-making. Our findings also reveal the need for consistency in the methods used for VE evaluations within and across jurisdictions, and suggest that application of a uniform statistical modelling approach to global seasonal influenza VE estimations may indeed lead to more reliable VE estimates, for better informed global decision-making. That said, it is worth recognizing that surveillance data collection capabilities vary across jurisdictions. However, at minimum, there is the need to establish, a priori, a minimum set of variables to be included in

statistical models for VE estimations. Furthermore, our review reveals a lack of publications of influenza VE estimates from some regions of the world. In particular, while there are published interim or final VE estimates from many regions, these estimates do not have matching interim or final estimates for comparison. This reduced the paired VE estimates that could have been included in this review for more precise results. For those final VE studies without a matched interim VE study, it may be possible to conduct interim VE estimation retrospectively, by limiting the data to a certain earlier date in the season. This could help increase the number of matched interim/final VE pairs for comparison.

Due to a paucity of data, we could not explore any interactions between important factors and we could also not conduct subgroup analysis by influenza subtype/type and season as planned a priori, despite the likelihood that there may be variability in the effect of some of the factors across levels of other factors. However, the evidence from our models suggests it is unlikely that influenza subtypes/type and season may be associated with having a substantial difference between interim and final VE point estimates. We could also not compare early and mid-season interim estimates separately against final estimates. Such a comparison would have been helpful as a proxy for assessing the potential impact of study population size. Limiting our review to influenza seasons after the 2009/10 influenza pandemic may have limited the number of relevant studies for inclusion, but it enabled concentration on studies conducted from when influenza vaccination became increasingly publicly funded in many jurisdictions.

These limitations notwithstanding, our review has many merits, including utilization of a comprehensive search strategy, and having been conducted/reported in full compliance with known guidelines.

Conclusions

Substantial agreement appears to exist between interim and final seasonal influenza VE estimates. This suggests adequacy of interim estimates for use in seasonal vaccine composition and public health policy decision-making while influenza viruses are still in circulation. However, there is a need for consistency in statistical modelling of interim and final VE estimations as this could increase agreement between interim and final VE estimates. Interim VE estimation during/after epidemic peak may also increase agreement between interim and final VE estimates.

Declarations

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References

1. Boni MF. Vaccination and antigenic drift in influenza. *Vaccine*. 2008 Jul; 18;26:C8-C14.
2. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine*. 2013 Apr 19; 31(17):2165-2168.
3. Sullivan SG, Tchetgen Tchetgen EJ, Cowling BJ. Theoretical Basis of the Test-Negative Study Design for Assessment of Influenza Vaccine Effectiveness. *Am J Epidemiol*. 2016 Sep 1; 184(5):345-353.
4. World Health Organization. A description of the process of seasonal and H5N1 influenza vaccine virus selection and development. Geneva: The World Health Organization; 2007.
5. World Health Organization. Recommended composition of influenza virus vaccines for use in the 2019- 2020 northern hemisphere influenza season. Geneva: The World Health Organization; 2019.
6. Sullivan SG, Kelly H. Late season interim estimates of influenza vaccine effectiveness reliably predict end of season estimates in Victoria, Australia, 2007 to 2012. *Euro Surveill*. 2013 Oct 10; 18(41):5-11.
7. Belongia EA, Kieke BA, Donahue JG, et al. Influenza vaccine effectiveness in Wisconsin during the 2007-08 season: comparison of interim and final results. *Vaccine*. 2011 Sep 2; 29(38):6558-6563.
8. Jimenez-Jorge S, Pozo F, Larrauri A, et al. Interim influenza vaccine effectiveness: A good proxy for final estimates in Spain in the seasons 2010-2014. *Vaccine*. 2015 Jun 26; 33(29):3276-3280.

9. Leung VK, Cowling BJ, Feng S, et al. Concordance of interim and final estimates of influenza vaccine effectiveness: a systematic review. *Euro Surveill*. 2016 Apr 21; 21(16):16.
10. Cumpston M, Li T, Page MJ, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. *Cochrane Database Syst Rev*. 2019 Oct 3; 10:ED000142.
11. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009 Jul 21; 6(7):e1000097.
12. McHugh ML. The chi-square test of independence. *Biochem Med (Zagreb)*. 2013; 23(2):143-149.
13. Schisterman EF, Cole SR, Platt RW. Overadjustment bias and unnecessary adjustment in epidemiologic studies. *Epidemiology*. 2009 Jul; 20(4):488-495.
14. Kissling E, Valenciano M, Cohen JM, et al. I-MOVE multi-centre case control study 2010-11: overall and stratified estimates of influenza vaccine effectiveness in Europe. *PLoS One*. 2011; 6(11):e27622.
15. Kissling E, Valenciano M, I-MOVE case–control studies team. Early estimates of seasonal influenza vaccine effectiveness in Europe, 2010/11: I-MOVE, a multicenter case–control study. *Euro Surveill*. 2011; 16(11):pii=19818.
16. Pebody R, Hardelid P, Fleming DM, et al. Effectiveness of seasonal 2010/11 and pandemic influenza A(H1N1)2009 vaccines in preventing influenza infection in the United Kingdom: mid-season analysis 2010/11. *Euro Surveill*. 2011 Feb 10; 16(6):8-13.

17. Savulescu C, Jimenez-Jorge S, de Mateo S, et al. Effectiveness of the 2010/11 seasonal trivalent influenza vaccine in Spain: preliminary results of a case-control study. *Euro Surveill*. 2011 Mar 17; 16(11):5-10.
18. Jimenez-Jorge S, de Mateo S, Pozo F, et al. Early estimates of the effectiveness of the 2011/12 influenza vaccine in the population targeted for vaccination in Spain, 25 December 2011 to 19 February 2012. *Euro Surveill*. 2012-1 Mar 22; 17(12):8-13.
19. Jimenez-Jorge S, Savulescu C, Pozo F, et al. Effectiveness of the 2010-11 seasonal trivalent influenza vaccine in Spain: cycEVA study. *Vaccine*. 2012-2 May 21; 30(24):3595-3602.
20. Kissling E, Valenciano M, I-MOVE case–control studies team. Early estimates of seasonal influenza vaccine effectiveness in Europe among target groups for vaccination: results from the I-MOVE multicenter case–control study, 2011/12. *Euro Surveill*. 2012; 17(15):20146.
21. Castilla J, Martinez-Baz I, Martinez-Artola V, et al. Early estimates of influenza vaccine effectiveness in Navarre, Spain: 2012/13 mid-season analysis. *Euro Surveill*. 2013 Feb 14; 18(7):6-11.
22. Jackson L, Jackson ML, Phillips CH, et al. Interim Adjusted Estimates of Seasonal Influenza Vaccine Effectiveness - United States, February 2013. *Mmwr-Morbid Mortal W*. 2013 Feb 22; 62(7):119-123.
23. Jimenez-Jorge S, de Mateo S, Delgado-Sanz C, et al. Effectiveness of influenza vaccine against laboratory-confirmed influenza, in the late 2011-2012 season in Spain, among population targeted for vaccination. *BMC Infect Dis*. 2013 Sep 22; 13:441.

24. Kissling E, Larrauri A, Oroszi B, et al. Low and decreasing vaccine effectiveness against influenza A(H3) in 2011/12 among vaccination target groups in Europe: results from the I-MOVE multicenter case–control study. *Euro Surveill*. 2013; 18(5):20390.
25. Pebody RG, Andrews N, Fleming DM, et al. Age-specific vaccine effectiveness of seasonal 2010/2011 and pandemic influenza A(H1N1) 2009 vaccines in preventing influenza in the United Kingdom. *Epidemiol Infect*. 2013 Mar; 141(3):620-630.
26. Skowronski DM, Janjua NZ, De Serres G, et al. Interim estimates of influenza vaccine effectiveness in 2012/13 from Canada's sentinel surveillance network, January 2013. *Euro Surveill*. 2013 Jan 31; 18(5):7-16.
27. Valenciano M, Kissling E, Team I-MC-CS. Early estimates of seasonal influenza vaccine effectiveness in Europe: results from the I-move multicentre case-control study, 2012/13. *Euro Surveill*. 2013 Feb 14; 18(7):12-17.
28. Andrews N, McMenamin J, Durnall H, et al. Effectiveness of trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2012/13 end of season results. *Euro Surveill*. 2014 Jul 10; 19(27):5-13.
29. Jimenez-Jorge S, Pozo F, de Mateo S, et al. Influenza vaccine effectiveness in Spain 2013/14: subtype-specific early estimates using the cycEVA study. *Euro Surveill*. 2014 Mar 6; 19(9):7-15.
30. Kissling E, Valenciano M, Buchholz U, et al. Influenza vaccine effectiveness estimates in Europe in a season with three influenza type/subtypes circulating: the I-MOVE multicentre case-control study, influenza season 2012/13. *Euro Surveill*. 2014 Feb 13; 19(6):22-33.

31. Skowronski DM, Chambers C, Sabaiduc S, et al. Interim estimates of 2013/14 vaccine effectiveness against influenza A(H1N1) pdm09 from Canada's sentinel surveillance network, January 2014. *Euro Surveill*. 2014 Feb 6; 19(5):4-17.
32. Skowronski DM, Janjua NZ, De Serres G, et al. Low 2012-13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses. *PLoS One*. 2014; 9(3):e92153.
33. Turner N, Pierse N, Huang QS, et al. Interim estimates of the effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2014. *Euro Surveill*. 2014 Oct 23; 19(42):19-24.
34. Flannery B, Clippard J, Zimmerman RK, et al. Early Estimates of Seasonal Influenza Vaccine Effectiveness - United States, January 2015. *Mmwr-Morbid Mortal W*. 2015 Jan 16; 64(1):10-15.
35. Martinez-Baz I, Navascues A, Pozo F, et al. Influenza vaccine effectiveness in preventing inpatient and outpatient cases in a season dominated by vaccine-matched influenza B virus. *Hum Vaccin Immunother*. 2015; 11(7):1626-1633.
36. McLean HQ, Thompson MG, Sundaram ME, et al. Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type. *J Infect Dis*. 2015 May 15; 211(10):1529-1540.
37. Pebody R, Warburton F, Andrews N, et al. Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results. *Euro Surveill*. 2015; 20(36).

38. Pebody RG, Warburton F, Ellis J, et al. Low effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 mid-season results. *Euro Surveill*. 2015 Feb 5; 20(5):6-12.
39. Skowronski DM, Chambers C, Sabaiduc S, et al. Interim estimates of 2014/15 vaccine effectiveness against influenza A(H3N2) from Canada's Sentinel Physician Surveillance Network, January 2015. *Euro Surveill*. 2015 Jan 29; 20(4):7-24.
40. Skowronski DM, Chambers C, Sabaiduc S, et al. Integrated Sentinel Surveillance Linking Genetic, Antigenic, and Epidemiologic Monitoring of Influenza Vaccine-Virus Relatedness and Effectiveness During the 2013-2014 Influenza Season. *J Infect Dis*. 2015 Sep 1; 212(5):726-739.
41. Chambers C, Skowronski DM, Sabaiduc S, et al. Interim estimates of 2015/16 vaccine effectiveness against influenza A(H1N1)pdm09, Canada, February 2016. *Euro Surveill*. 2016; 21(11):30168.
42. Gherasim A, Pozo F, de Mateo S, et al. Waning protection of influenza vaccine against mild laboratory confirmed influenza A(H3N2) and B in Spain, season 2014-15. *Vaccine*. 2016 Apr 29; 34(20):2371-7.
43. Kissling E, Valenciano M. Early influenza vaccine effectiveness results 2015-16: I-MOVE multicentre case-control study. *Euro Surveill*. 2016; 21(6).
44. Pebody R, Warburton F, Ellis J, et al. Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results. *Euro Surveill*. 2016 Sep 22; 21(38).

45. Pebody R, Warburton F, Ellis J, et al. Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 mid-season results. *Euro Surveill*. 2016 Mar 31; 21(13):31-38.
46. Pierse N, Kelly H, Thompson MG, et al. Influenza vaccine effectiveness for hospital and community patients using control groups with and without non-influenza respiratory viruses detected, Auckland, New Zealand 2014. *Vaccine*. 2016 Jan 20; 34(4):503-509.
47. Redlberger-Fritz M, Kundi M, Popow-Kraupp T. Detailed Report on 2014/15 Influenza Virus Characteristics, and Estimates on Influenza Virus Vaccine Effectiveness from Austria's Sentinel Physician Surveillance Network. *PLoS One*. 2016; 11(3):e0149916.
48. Skowronski DM, Chambers C, Sabaiduc S, et al. A Perfect Storm: Impact of Genomic Variation and Serial Vaccination on Low Influenza Vaccine Effectiveness During the 2014-2015 Season. *Clin Infect Dis*. 2016 Jul 1; 63(1):21-32.
49. Zimmerman RK, Nowalk MP, Chung J, et al. 2014-2015 Influenza Vaccine Effectiveness in the United States by Vaccine Type. *Clin Infect Dis*. 2016 Dec 15; 63(12):1564-1573.
50. Flannery B, Chung JR, Thaker SN, et al. Interim Estimates of 2016-17 Seasonal Influenza Vaccine Effectiveness - United States, February 2017. *Mmwr-Morbid Mortal W*. 2017 Feb 17; 66(6):167-171.
51. Skowronski DM, Chambers C, Sabaiduc S, et al. Beyond Antigenic Match: Possible Agent-Host and Immuno-epidemiological Influences on Influenza Vaccine Effectiveness During the 2015-2016 Season in Canada. *J Infect Dis*. 2017 Dec 19; 216(12):1487-1500.
52. Castilla J, Navascues A, Casado I, et al. Interim effectiveness of trivalent influenza vaccine in a season dominated by lineage mismatched influenza B, northern Spain, 2017/18. *Euro Surveill*. 2018 Feb 15; 23(7):2-7.

53. Flannery B, Chung JR, Belongia EA, et al. Interim Estimates of 2017-18 Seasonal Influenza Vaccine Effectiveness - United States, February 2018. *Mmwr-Morbid Mortal W*. 2018 Feb 16; 67(6):180-185.

54. Kissling E, Valenciano M, Pozo F, et al. 2015/16 I-MOVE/I-MOVE+ multicentre case-control study in Europe: Moderate vaccine effectiveness estimates against influenza A(H1N1)pdm09 and low estimates against lineage-mismatched influenza B among children. *Influenza Other Respir Viruses*. 2018 Jul; 12(4):423-437.

55. Rondy M, Kissling E, Emborg HD, et al. Interim 2017/18 influenza seasonal vaccine effectiveness: combined results from five European studies. *Euro Surveill*. 2018 Mar; 23(9).

56. Doyle JD, Chung JR, Kim SS, et al. Interim Estimates of 2018-19 Seasonal Influenza Vaccine Effectiveness - United States, February 2019. *Mmwr-Morbid Mortal W*. 2019 Feb 15; 68(6):135-139.

57. Flannery B, Chung JR, Monto AS, et al. Influenza Vaccine Effectiveness in the United States During the 2016-2017 Season. *Clin Infect Dis*. 2019 May 17; 68(11):1798-1806.

58. Kissling E, Pozo F, Buda S, et al. Effectiveness of influenza vaccine against influenza A in Europe in seasons of different A(H1N1)pdm09 and the same A(H3N2) vaccine components (2016-17 and 2017-18). *Vaccine X*. 2019 Dec 10; 3:100042.

59. Martinez-Baz I, Navascues A, Casado I, et al. Remaining Effect of Influenza Vaccines Received in Prior Seasons. *J Infect Dis*. 2019 Aug 30; 220(7):1136-1140.

60. Pebody R, Djennad A, Ellis J, et al. End of season influenza vaccine effectiveness in adults and children in the United Kingdom in 2017/18. *Euro Surveill*. 2019 Aug; 24(31).

61. Rolfes MA, Flannery B, Chung JR, et al. Effects of Influenza Vaccination in the United States During the 2017-2018 Influenza Season. *Clin Infect Dis*. 2019 Nov 13; 69(11):1845-1853.
62. Skowronski DM, Leir S, Sabaiduc S, et al. Interim estimates of 2018/19 vaccine effectiveness against influenza A(H1N1)pdm09, Canada, January 2019. *Euro Surveill*. 2019 Jan; 24(4).
63. Skowronski DM, Sabaiduc S, Leir S, et al. Paradoxical clade- and age-specific vaccine effectiveness during the 2018/19 influenza A(H3N2) epidemic in Canada: potential imprint-regulated effect of vaccine (I-REV). *Euro Surveill*. 2019 Nov; 24(46).
64. Flannery B, Kondor RJG, Chung JR, et al. Spread of Antigenically Drifted Influenza A(H3N2) Viruses and Vaccine Effectiveness in the United States During the 2018-2019 Season. *J Infect Dis*. 2020 Jan 1; 221(1):8-15.

Chapter 4. Variable seasonal influenza vaccine effectiveness across geographical regions, age groups and levels of vaccine antigenic similarity with circulating virus strains: A systematic review and meta-analysis of the evidence from test-negative design studies after the 2009/10 influenza pandemic

Preface

The previous chapter (Chapter 3) explored concordance between interim and final SIV effectiveness estimates considering that interim rather than final estimates inform decision-making regarding SIV composition each influenza season. Following development, production and deployment of SIV, the effectiveness of the vaccine is evaluated via various influenza surveillance networks. SIV effectiveness estimates from these surveillance networks often suggest that the vaccine effectiveness may vary depending on geographical region, study population characteristics such as age, and the level of VAS. However, the evidence has largely conflicted. This chapter presents a published study that explored this problem.

Publication citation

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Abstract

Background: We examined the influence of some factors on seasonal influenza vaccine effectiveness (VE) from test-negative design (TND) studies.

Methods: We systematically searched for full-text publications of VE against laboratory-confirmed influenza from TND studies in outpatient settings after the 2009/10 influenza pandemic. Two reviewers independently selected studies for inclusion, and conducted data extracted from the included studies. We calculated pooled adjusted VE across geographical regions, age groups and levels of vaccine antigenic similarity with circulating virus strains, using an inverse variance, random-effects model.

Results: We included 76 full-text articles from 11,931 citations. VE estimates against A(H1N1)pdm09, A(H3N2), influenza B, and all influenza were homogenous and point pooled VE higher in the Southern hemisphere compared with the Northern hemisphere. The difference in pooled VE between the Southern and Northern hemispheres was statistically significant for A(H3N2), influenza B, and all influenza. A consistent pattern was observed in pooled VE across both hemispheres and continents, with the highest point pooled VE being against A(H1N1)pdm09, followed by influenza B, and lowest against A(H3N2). A nearly consistent pattern was observed in pooled VE across age groups in the Northern hemisphere, with pooled VE mostly decreasing with age. Point pooled VE against A(H3N2), influenza B, and all influenza were statistically significantly higher when vaccine was antigenically similar to circulating virus strains compared with when antigenically dissimilar. Similar pattern was observed in the Northern hemisphere, but there was a lack of data from the Southern hemisphere.

Conclusions: Consistent patterns appear to exist in seasonal influenza VE across regions, age groups, and levels of vaccine antigenic similarity with circulating virus strains, with best vaccine performance against A(H1N1)pdm09 and worst against A(H3N2). The evidence highlights the need to consider geographical location, age, and vaccine antigenic similarity with circulating virus strains when designing and evaluating influenza VE studies.

Introduction

Seasonal influenza is characterised by epidemics occurring from around April to September in the Southern hemisphere, and from around October to March in the Northern hemisphere. Vaccination has been an effective strategy for influenza prevention. However, following widespread mitigation measures during the coronavirus disease 2019 (COVID-19) pandemic such as social/physical distancing, influenza activities appeared to be less in the United States of America (USA) and in various countries in the Southern hemisphere,[1] although historical data from the USA generally suggests that influenza circulation has been low during the COVID-19 pandemic. It may however mean that a combination of these strategies may be as effective as vaccination. Nevertheless, in terms of practicality of strategies for influenza prevention, vaccination remains the most practical of the strategies and is very effective.

Continuous changes that occur in influenza viruses over time (antigenic drift),[2] however, mean that influenza vaccines have to be re-formulated each influenza season, and can be mismatched with the virus strains in circulation.[3] Similarly, seasonal influenza vaccine effectiveness (VE) may differ across geographical regions depending on the circulating strains. Characteristics of vaccine recipients, such as age, may also impact VE.[4] As such, influenza VE is evaluated each influenza season to assess vaccine performance and forecast the virus strains that are likely to be in circulation in the immediate subsequent season; then, this knowledge is used to inform vaccine development,[3] vaccination policy and public health planning.

Due to feasibility and ethical considerations, observational studies are used instead of randomised controlled trials to assess influenza VE. The test-negative design (TND) has become an increasingly popular observational study design for estimating influenza VE.[5] In TND, individuals presenting with acute respiratory or influenza-like illness are tested for influenza;

those who test positive become the cases and those who test negative become the controls.[6] VE is then calculated as one minus the adjusted ratio of the odds of vaccination in those that tested positive, to the odds of vaccination in those that tested negative, multiplied by 100. It is suggested that the TND helps to reduce biases due to differential healthcare-seeking behaviour between vaccinated and unvaccinated persons, and differential misclassification of influenza infection status.[5] However, the TND may fail to correct for differential healthcare-seeking behaviour among vaccinated and unvaccinated individuals if stringent methods for study participants' enrolment and influenza testing are not applied.[7]

We undertook a systematic review and meta-analysis to identify, critically appraise and summarise the findings of published TND studies that examined seasonal influenza VE in outpatient (primary care) settings after the 2009/10 influenza pandemic.

Methods

This was a large systematic review and meta-analysis. The methods are partly described in Chapter 2. In summary, literature was searched from January 2011; initially, in April 2017 and the search was subsequently updated in February 2020. To avoid duplication of data, I-MOVE studies were excluded, leaving only country-specific data from Europe. Further, all studies from the USA, Spain, and Australia (countries with more than one published article for a season) were examined to ensure that there was no overlap or duplication of data (**Appendix 8**).

Data analysis

Relevant study characteristics were synthesised in tabular form. Reported VE estimates and associated 95% CI were pooled using inverse variance, random effects models implemented in STATA (version 13; StataCorp LP, Texas, USA). Statistical heterogeneity between pooled VE

was assessed and quantified using the I-squared statistic (I^2).[8] Where necessary, study variation (excess heterogeneity) was explored using random effects meta-regression.[9] The chi-square statistic ($\chi 2$) was used to assess the statistical significance (p value) of the difference between compared pooled VE estimates.[10] Where appropriate, publication bias was assessed visually using funnel plots and, statistically, using Egger's regression test.[11] Subgroup analyses were conducted by study region, age group (under 5 years, 5–17 years, 18–49 years, 50–64 years, and ≥65 years), and vaccine antigenic similarity with circulating virus strains.

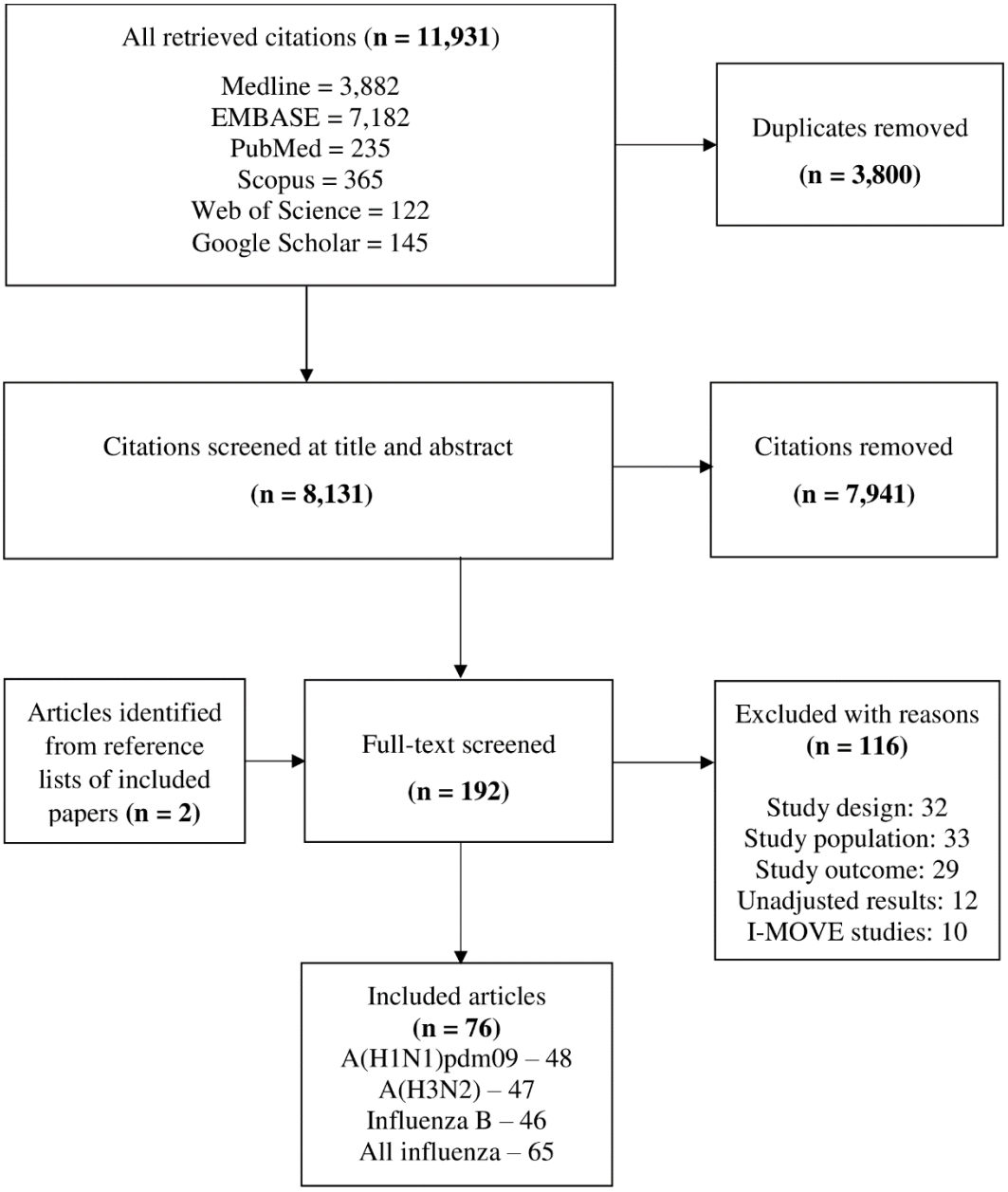
Study region was divided into global hemispheres (Northern and Southern) since different influenza vaccine composition is recommended each season for the hemispheres. Region was further divided into continents to explore differences between pooled VE from more homogenous regions. VE estimates reported for particular age groups were summarised according to age category as previously defined above, excluding VE reports for any overlapping age group or any that did not fit well into any of the a priori determined age categories. The specific age ranges included in each of the a priori determined age categories for pooled VE by age is detailed in **Appendix 9**.

Results

Descriptive analysis

From a total 11,931 identified citations, 76 full-text articles met our eligibility criteria for inclusion (**Fig. 6**).[12-87]

Figure 6: Modified PRISMA flowchart of the selection of the included articles (for study 2).



I-MOVE = Influenza Monitoring Vaccine Effectiveness

These articles comprised 13 articles from Spain,[15-17,29,30,34-37,43-45,68] 12 articles from the USA,[13,20,26-28,33,48,51,62,67,80,87] ten articles from Australia,[14,23,24,38-40,64,65,77,78] eight articles from the UK,[12,52-58] seven articles from Canada,[68-75] four articles from China,[42,83,85] three articles from Germany,[22,32,49] two articles each from Israel,[76,86] Japan,[19,79] Netherlands,[21,81] Romania,[60,61] and South Africa,[46,47] and one article each from Austria,[63] Croatia,[25] France,[82] Hong Kong,[18] Italy,[66] New Zealand,[59] Portugal,[50] Taiwan,[41] and Turkey[31]. Geographical mapping of these articles is represented graphically as **Appendix 10** and the main characteristics of the studies reported by the articles are summarised in **Table 5**. Overall, 63 articles were for studies conducted in the Northern hemisphere (8 Asia; 36 Europe; 19 North America) while 13 articles were for studies conducted in the Southern hemisphere (11 Oceania; 2 Africa). Of those that clearly reported study sample size, the range was from 197 to 10,496 participants. 48 articles reported VE against A(H1N1)pdm09, 47 articles against A(H3N2), 46 articles against influenza B, and 65 articles against all influenza. Our improvised quality assessment of the studies based on the three potentially relevant study characteristics is presented in **Appendix 11**.

Table 5: Summary of the main characteristics of the included studies (for study 2).

Article	Country	Influenza season	Respiratory specimen (Diagnostic test)	Number of participants	Dominant influenza type	VE assessed
Andrews 2014[12]	UK	2012/13	Not reported (Polymerase Chain Reaction [PCR])	3,286	Influenza B	A(H1N1)pdm09, A(H3N2), Influenza B
Bateman 2013[13]	USA	2010/11	Nasal and oropharyngeal swab (PCR)	1,549	A(H3N2)	A(H1N1)pdm09, A(H3N2)
Carville 2015[14]	Australia	2013	Nose or throat swab (PCR)	262	Influenza B	A(H1N1)pdm09, Influenza B, All influenza
Castilla 2013[15]	Spain	2011/12	Nasopharyngeal and pharyngeal swabs (PCR)	588	A(H3N2)	All influenza
Castilla 2016[16]	Spain	2014/15	Nasopharyngeal and pharyngeal (PCR)	660	A(H3N2) & Influenza B	A(H3N2), Influenza B, All influenza
Castilla 2020[17]	Spain	2018/19	Nasopharyngeal and pharyngeal swabs (PCR)	552	A(H1N1)pdm09 & A(H3N2)	A(H1N1)pdm09, A(H3N2), All influenza
Chan 2019[18]	Hong Kong	2017/18	Not reported (PCR)	919	Influenza B	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Chon 2019[19]	Japan	2015/16	Nasopharyngeal specimen (PCR)	713	A(H1N1)pdm09	Influenza B, All influenza
Cowling 2016[20]	USA	2010/11 2011/12 2012/13	Nasopharyngeal, oropharyngeal or nasal swab (PCR)	4,208: 2010/11 2,164: 2011/12 4,278: 2012/13	2010/11: A(H1N1)pdm09 2011/12: A(H3N2) 2012/13: A(H3N2) & influenza B	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Darvishian 2017[21]	Netherlands	2010/11 2011/12 2012/13	Throat swab and nose swab (PCR)	Not reported	2010/11: Influenza B 2011/12: A(H3N2) 2012/13: Influenza B 2013/14: A(H3N2)	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Englund 2013[22]	Germany	2010/11	Nasal or pharyngeal swabs or nasopharyngeal aspirates (PCR)	1,866	A(H1N1)pdm09	A(H1N1)pdm09, Influenza B, All influenza

Fielding 2012[23]	Australia	2011	Nose and/or throat swab (PCR)	529	A(H1N1)pdm09 & Influenza B	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Fielding 2016[24]	Australia	2015	Nose/throat swabs (PCR)	2,443	Influenza B	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Filipovic 2015[25]	Croatia	2010/11	Not reported (PCR)	495	A(H1N1)pdm09	A(H1N1)pdm09, All influenza
Flannery 2019[26]	USA	2016/17	Nasal and throat swabs (PCR)	7,083	A(H3N2)	A(H3N2), Influenza B, All influenza
Flannery 2020[27]	USA	2018/19	Combined nasal and oropharyngeal swab specimens (nasal swab specimens only for children aged <2 years) (PCR)	10,012	A(H1N1)pdm09	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Gaglani 2016[28]	USA	2013/14	Combined nose and throat swab specimens (nose swab specimen were only obtained from children aged <2 years) (PCR)	5,637	A(H1N1)pdm09	A(H1N1)pdm09
Gherasim 2016[29]	Spain	2014/15	Not reported (PCR)	5,044	A(H3N2)	A(H3N2), Influenza B
Gherasim 2017[30]	Spain	2015/16	Not reported (PCR & Culture)	661	Influenza B	A(H1N1)pdm09, Influenza B
Hekimoglu 2018[31]	Turkey	2014/15	Nasal, nasopharyngeal, throat (PCR)	2,561	Influenza B	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Helmeke 2015[32]	Germany	2012/13	Throat or nasopharyngeal swab (PCR)	834	Influenza B	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Jackson 2017[33]	USA	2015/16	Nasal/oropharyngeal swab (PCR)	6,879	A(H1N1)pdm09	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Jimenez-Jorge 2012[34]	Spain	2010/11	Not reported (PCR)	1,369	A(H1N1)pdm09	A(H1N1)pdm09, Influenza B, All influenza
Jimenez-Jorge 2013[35]	Spain	2011/12	Not reported (PCR & Culture)	378	A(H3N2)	A(H3N2), All influenza

Jimenez-Jorge 2015[36]	Spain	2010/11 2011/12 2012/13	Nasal or nasopharyngeal (PCR & Culture)	2010/11: 3,180 & 1,369; 2011/12: 3,484 & 1,446; 2012/13: 3,357 & 1,432	2010/11: A(H1N1)pdm09 2011/12: A(H3N2) 2012/13: Influenza B	A(H1N1)pdm09, A(H3N2), Influenza B
Jimenez-Jorge 2015[37]	Spain	2010/11 2011/12 2012/13 2013/14	Nasal or nasopharyngeal (PCR & Culture)		2010/11: A(H1N1)pdm09 2011/12: A(H3N2) 2012/13: Influenza B 2013/14: A(H1N1)pdm09	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Kelly 2013[38]	Australia	2010 2011	Combined nose and throat swab specimens (nose swab specimen were only obtained from children aged <2 years) (PCR)	309 (2010) 398 (2011)	2010: A(H1N1)pdm09 2011: A(H3N2)	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Kelly 2016[39]	Australia	2011 2012 2013	Not reported (PCR)	642 (2011) 684 (2012) 354 (2013)	Not reported	All influenza
Levy 2014[40]	Australia	2010 2011 2012	Two nose and one throat swab (PCR)	448 (2010) 351 (2011) 1,361 (2012)	2010, 2011: A(H1N1)pdm09 2012: A(H3N2)	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Lo 2013[41]	Taiwan	2011/12	Throat or nasal swabs (PCR & Culture)	918	Influenza B	Influenza B, All influenza
Ma 2017[42]	China	2014/15	Oral pharyngeal swab (PCR)	9,297	A(H3N2)	A(H3N2), Influenza B, All influenza
Martínez-Baz 2013[43]	Spain	2010/11	Nasopharyngeal swabbing (PCR)	530	A(H1N1)pdm09	All influenza
Martinez-Baz 2015[44]	Spain	2012/13	Nasopharyngeal and pharyngeal swabs (PCR)	522	Influenza B	Influenza B, All influenza
Martinez-Baz 2019[45]	Spain	2017/18	Nasopharyngeal and pharyngeal swab (PCR)	604	A(H3N2)	All influenza
McAnerney 2015[46]	South Africa	2010 2011 2012 2013	Nasopharyngeal swab (PCR)	5,344	2010: Influenza B 2011: A(H1N1)pdm09	All influenza

					2012: A(H3N2) 2013: A(H1N1)pdm09	
McAnerney 2017[47]	South Africa	2015	Throat and/or nasal swabs (PCR)	899	A(H1N1)pdm09	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
McLean 2015[48]	USA	2012/13	Nasal and throat specimens (for children age <2 years, only nasal specimens were obtained) (PCR)	6,452	A(H3N2)	A(H3N2)pdm09, All influenza
Mohl 2018[49]	Germany	2012/13 2013/14 2014/15 2015/16	Not reported (PCR)	Varied	2012/13: Influenza B 2013/14, 2014/15: A(H3N2) 2015/16: Influenza B	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Nunes 2014[50]	Portugal	2012/13	Nasopharyngeal swab or a combined nasopharyngeal and oropharyngeal swab (PCR & Culture)	335	A(H1N1)pdm09	All influenza
Ohmit 2014[51]	USA	2011/12	Throat swab and nasal swab (or nasal swab only in patients aged <2 years) (PCR)	4,771	A(H3N2)	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Pebody 2013[52]	UK	2010/11	Mouth swab (PCR)	7,121	A(H1N1)pdm09	A(H1N1)pdm09, Influenza B
Pebody 2013[53]	UK	2011/12	Not reported (PCR)	3,560	A(H3N2)	A(H3N2)
Pebody 2015[54]	UK	2014/15	Not reported (PCR)	2,931	A(H3N2)	A(H3N2), Influenza B, All influenza
Pebody 2016[55]	UK	2015/16	Not reported (PCR)	3,841	A(H1N1)pdm09	A(H1N1)pdm09, Influenza B, All influenza
Pebody 2017[56]	UK	2016/17	Not reported (PCR)	2,881	A(H3N2)	A(H3N2), Influenza B, All influenza
Pebody 2019[57]	UK	2017/18	Not reported (PCR)	3,080	A(H3N2) & Influenza B	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza

Pebody 2020[58]	UK	2018/19	Combined throat and nose swabs (PCR)	2,326	A(H1N1)pdm09	A(H1N1)pdm09, A(H3N2), All influenza
Pierse 2016[59]	New Zealand	2014	Nasopharyngeal or throat swab (PCR)	1,154	A(H1N1)pdm09	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Pitigoi 2012[60]	Romania	2010/11	Not reported (PCR)	255	A(H1N1)pdm09 & Influenza B	A(H1N1)pdm09, Influenza B, All influenza
Pitigoi 2015[61]	Romania	2012/13	Not reported (PCR)	197	Influenza B	A(H1N1)pdm09, All influenza
Powell 2019[62]	USA	2017/18	Not reported (PCR)	3,595	A(H1N1)pdm09 & A(H3N2)	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Redlberger-Fritz 2016[63]	Austria	2014/15	Nasopharyngeal swabs (PCR)	815	A(H3N2)	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Regan 2019[64]	Australia	2012-2015	Not reported (PCR)	2012: 1,498 2013: 1,140 2014: 1,982 2015: 2,650	2012: A(H3N2) 2013: A(H3N2) 2014: A(H1N1)pdm09 2015: Influenza B	A(H1N1)pdm09, All influenza (2013/14), A(H3N2), Influenza B
Regan 2019[65]	Australia	2016	Nasal/throat swabs (PCR)	1,085	A(H1N1)pdm09 & A(H3N2)	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Rizzo 2016[66]	Italy	2014/15	Nasal or throat swab (PCR)	1,193	A(H1N1)pdm09 & A(H3N2)	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Rolfes 2019[67]	USA	2017/18	Nasal and throat swab (PCR)	8,436	A(H3N2)	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Savulescu 2014[68]	Spain	2010/11	Not reported (PCR & Culture)	5,057	A(H1N1)pdm09 & Influenza B	A(H1N1)pdm09, Influenza B
Skowronski 2012[69]	Canada	2010/11	Nasal/nasopharyngeal specimen (PCR)	1,718	A(H3N2)	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Skowronski 2014[70]	Canada	2011/12	Nasal/nasopharyngeal swabs (PCR)	1,507	Influenza B	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Skowronski 2014[71]	Canada	2012/13	Nasal or nasopharyngeal swabs (PCR)	1,501	A(H3N2)	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Skowronski 2015[72]	Canada	2013/14	Nasal/nasopharyngeal specimens (PCR)	1,700	A(H1N1)pdm09	A(H1N1)pdm09, All influenza

Skowronski 2016[73]	Canada	2014/15	Nasal/nasopharyngeal specimens (PCR)	1,930	A(H3N2)	A(H3N2), Influenza B, All influenza
Skowronski 2017[74]	Canada	2015/16	Nasal/nasopharyngeal swab (PCR)	2,008	A(H1N1)pdm09	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Skowronski 2019[75]	Canada	2018/19	Nasal/nasopharyngeal swab (PCR)	1,993 (H3N2)	A(H3N2)	A(H1N1)pdm09, A(H3N2)
Stein 2018[76]	Israel	2016/17	Nasal-throat swab (PCR)	1,088	A(H3N2)	A(H3N2)
Sullivan 2013[77]	Australia	2010 2011 2012	Not reported (PCR)	420 (2010) 630 (2011) 678 (2012)	2010: A(H1N1)pdm09 2011: Influenza B 2012: A(H3N2)	All influenza
Sullivan 2014[78]	Australia	2012	Nasal and throat specimens (PCR)	600	A(H3N2)	A(H3N2), All influenza
Suzuki 2014[79]	Japan	2011/12	Nasopharyngeal swab (PCR)	309	A(H3N2)	All influenza
Treanor 2012[80]	USA	2010/11	Nasal and throat swabs (children aged <2 years provided nasal swabs only) (PCR)	4,757	A(H1N1)pdm09	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Van Doorn 2017[81]	Netherlands	2010/11 2011/12 2012/13 2013/14	Nose and throat swabs (PCR & Culture)	Unclear	2010/11: A(H1N1)pdm09 2011/12, 2012/13, 2013/14: A(H3N2)	All influenza
Vilcu 2018[82]	France	2014/15 2015/16	Nasopharyngeal specimen (PCR)	2014/15: 1,428 2015/16: 3,447	2014/15: A(H3N2) 2015/16: Influenza B	A(H1N1)pdm09, A(H3N2), Influenza B, All influenza
Wang 2016[83]	China	2011/12	Nasopharyngeal specimen (PCR)	668	Not reported	All influenza
Wu 2018[84]	China	2016/17	Pharyngeal swab (PCR)	10,496	A(H3N2)	A(H1N1)pdm09, A(H3N2), All influenza
Yang 2014[85]	China	2012/13	Pharyngeal swabs (Culture)	1,998	A(H1N1)pdm09	A(H1N1)pdm09, A(H3N2), All influenza
Yaron-Yakoby 2018[86]	Israel	2014/15	Nose and throat swabs (PCR)	1,005 (2014/15)	2014/15: A(H3N2);	A(H3N2), All influenza in 2014/15; A(H1N1)pdm09,

				1,658 (2015/16)	2015/16: A(H1N1)pdm09 & Influenza B	Influenza B, All influenza in 2015/16
Zimmerman 2016[87]	USA	2014/15	Nasal and throat swabs (children aged <2 years provided nasal swabs only) (PCR)	9,311	A(H3N2)	A(H3N2), All influenza

Meta-regression

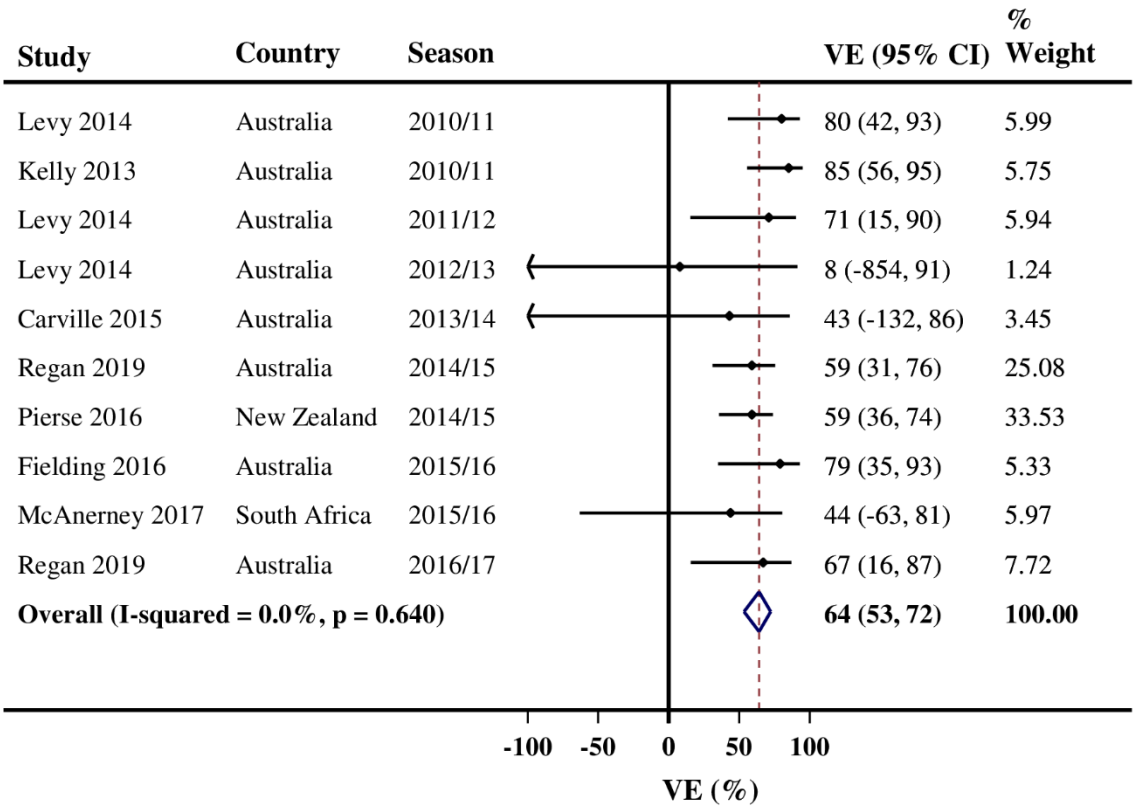
Study region (both hemisphere and continent), influenza season, method of vaccination confirmation, method of study participants' enrolment, and vaccine antigenic similarity with circulating virus strains could not explain any observed heterogeneity in the overall pooled VE against A(H1N1)pdm09. On the contrary, observed heterogeneity in pooled VE against A(H3N2) and against all influenza were both found to be possibly explained by study region (hemisphere [p=0.04 and p<0.01] and continent [p<0.01 and p=0.02]), influenza season (p=0.03 and p=0.04), and vaccine antigenic similarity with circulating virus strains (p<0.001). Study region (continent [p<0.01]) and vaccine antigenic similarity with circulating virus strains (p<0.001) were also found to be possible explanations for observed heterogeneity in pooled VE against influenza B.

Pooled adjusted VE by geographical region

VE estimates were more homogenous and point pooled VE higher in the Southern hemisphere compared with the Northern hemispheres; 64% (53–72%; I^2=0%) compared with 56% (51–60%; I^2=46.4%) for A(H1N1)pdm09 ([**Figure 7**] and [**Figure 8**]), 42% (31–51%; I^2=0%) compared with 22% (15–29%; I^2=66.9%) for A(H3N2) ([**Figure 9**] and [**Figure 10**]), 56% (45–64%; I^2=2.6%) compared with 42% (34–49%; I^2=71.3%) for influenza B ([**Figure 11**] and [**Figure**

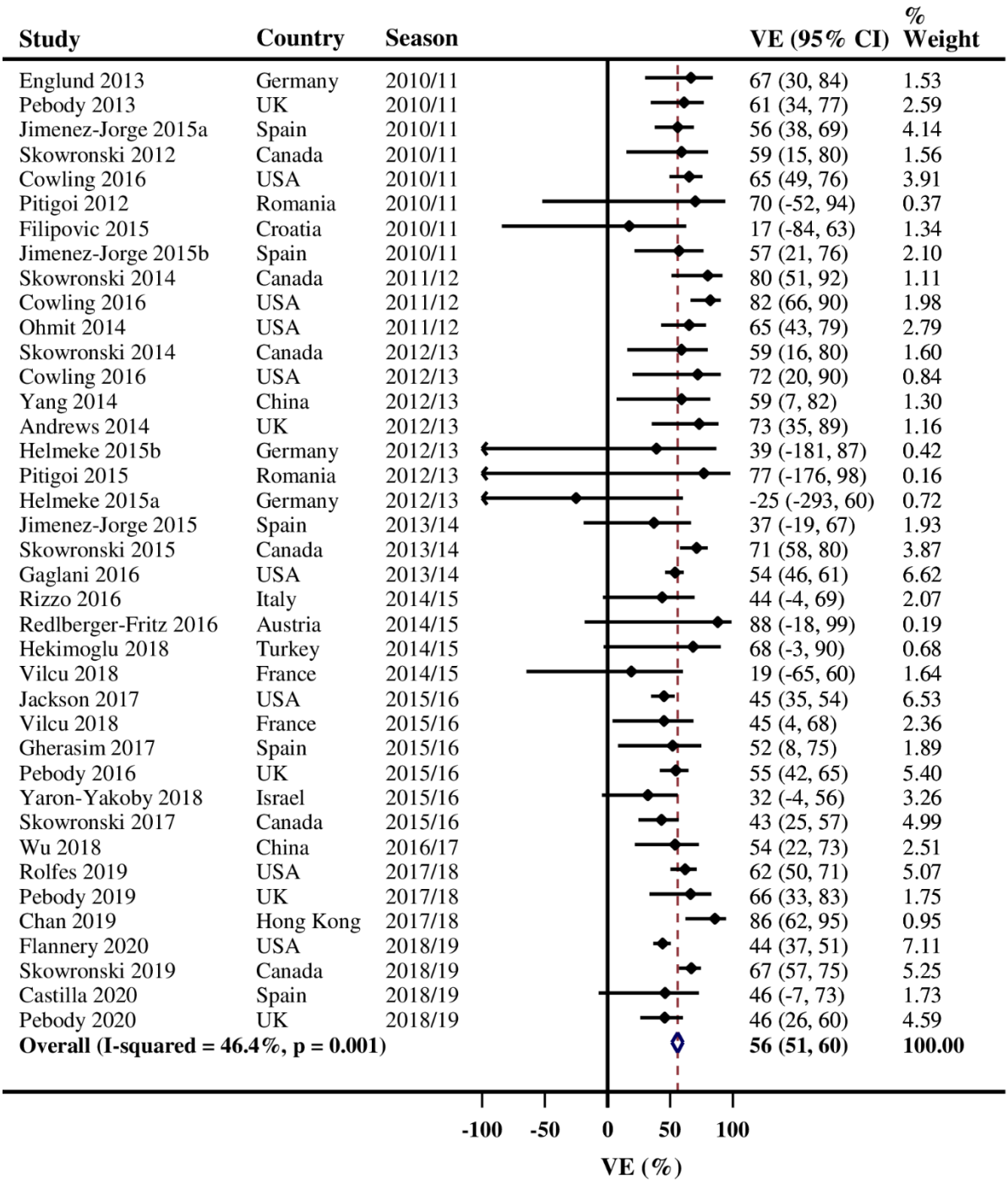
12]), and 54% (48–59%; I^2=0%) compared with 37% (32–42%; I^2=79.8%) for all influenza ([**Appendix 12**] and [**Appendix 13**]).

Figure 7: Forest plot of adjusted VE against A(H1N1)pdm09 (all participants: Southern hemisphere).



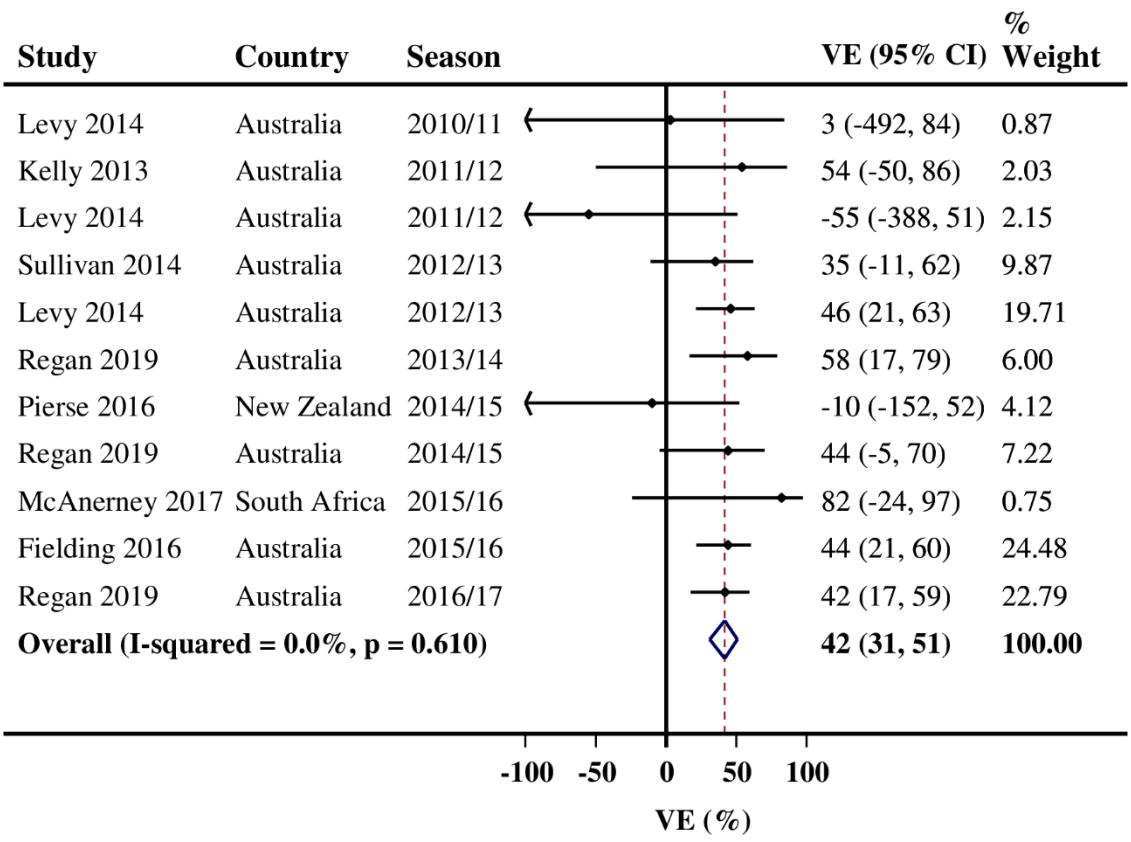
VE = vaccine effectiveness; CI = confidence interval

Figure 8: Forest plot of adjusted VE against A(H1N1)pdm09 (all participants: Northern hemisphere).



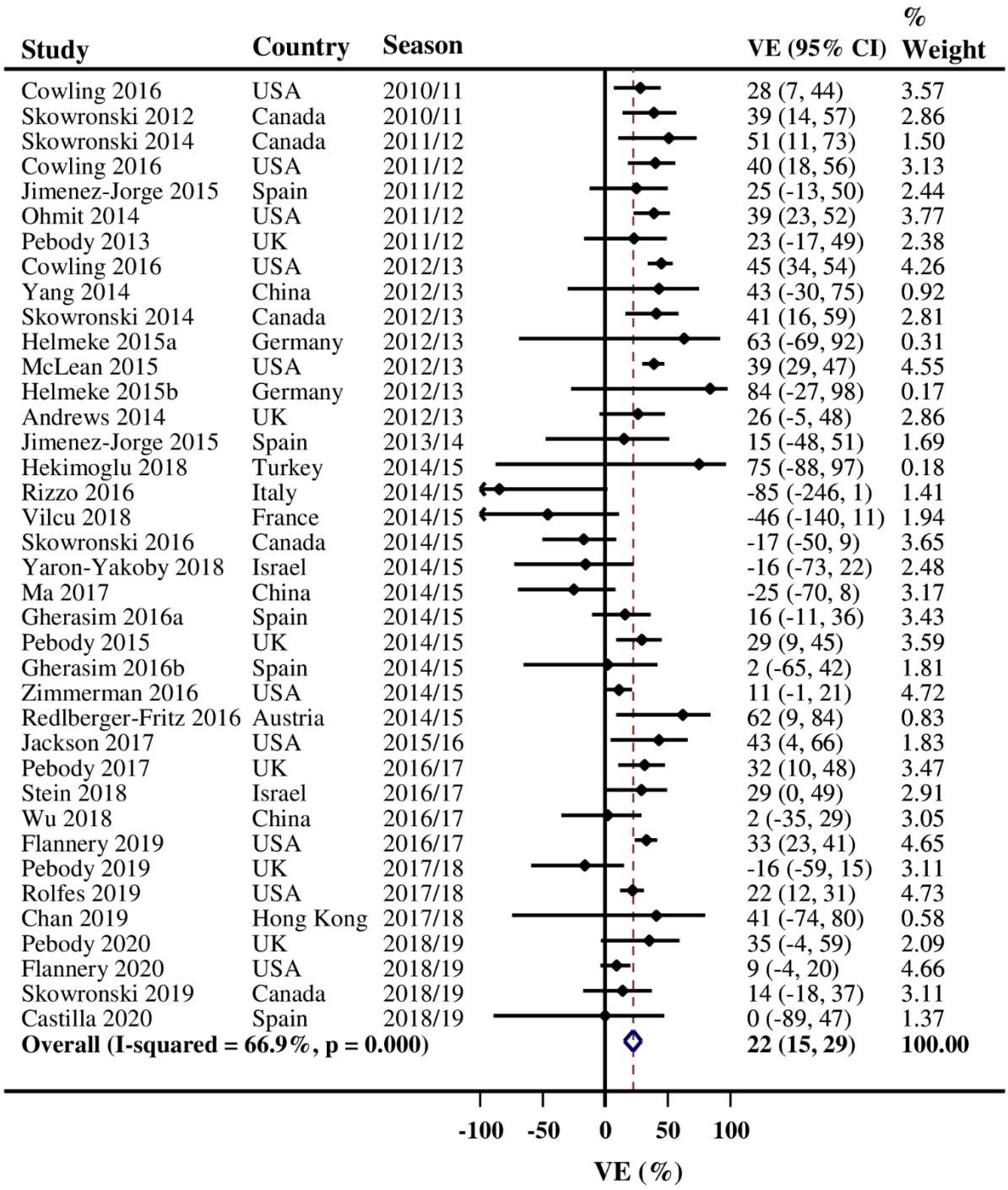
VE = vaccine effectiveness; CI = confidence interval

Figure 9: Forest plot of adjusted VE against A(H3N2) (all participants: Southern hemisphere).



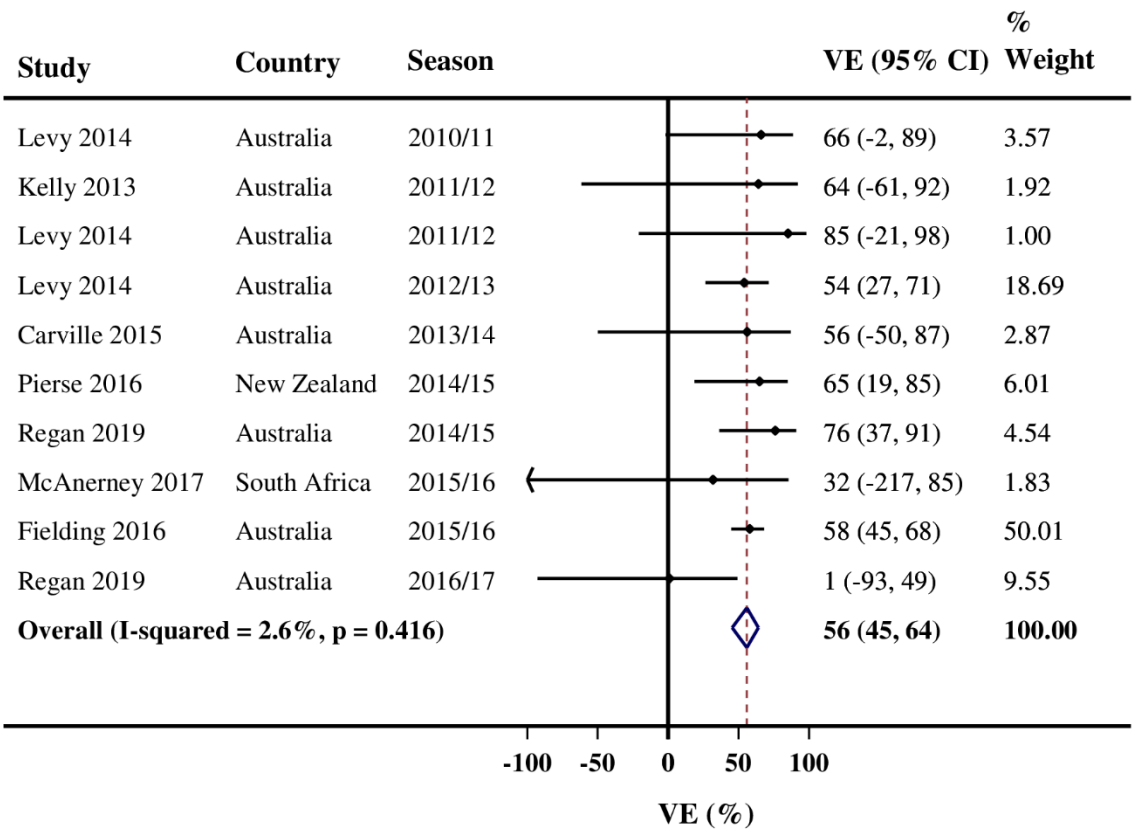
VE = vaccine effectiveness; CI = confidence interval

Figure 10: Forest plot of adjusted VE against A(H3N2) (all participants: Northern hemisphere).



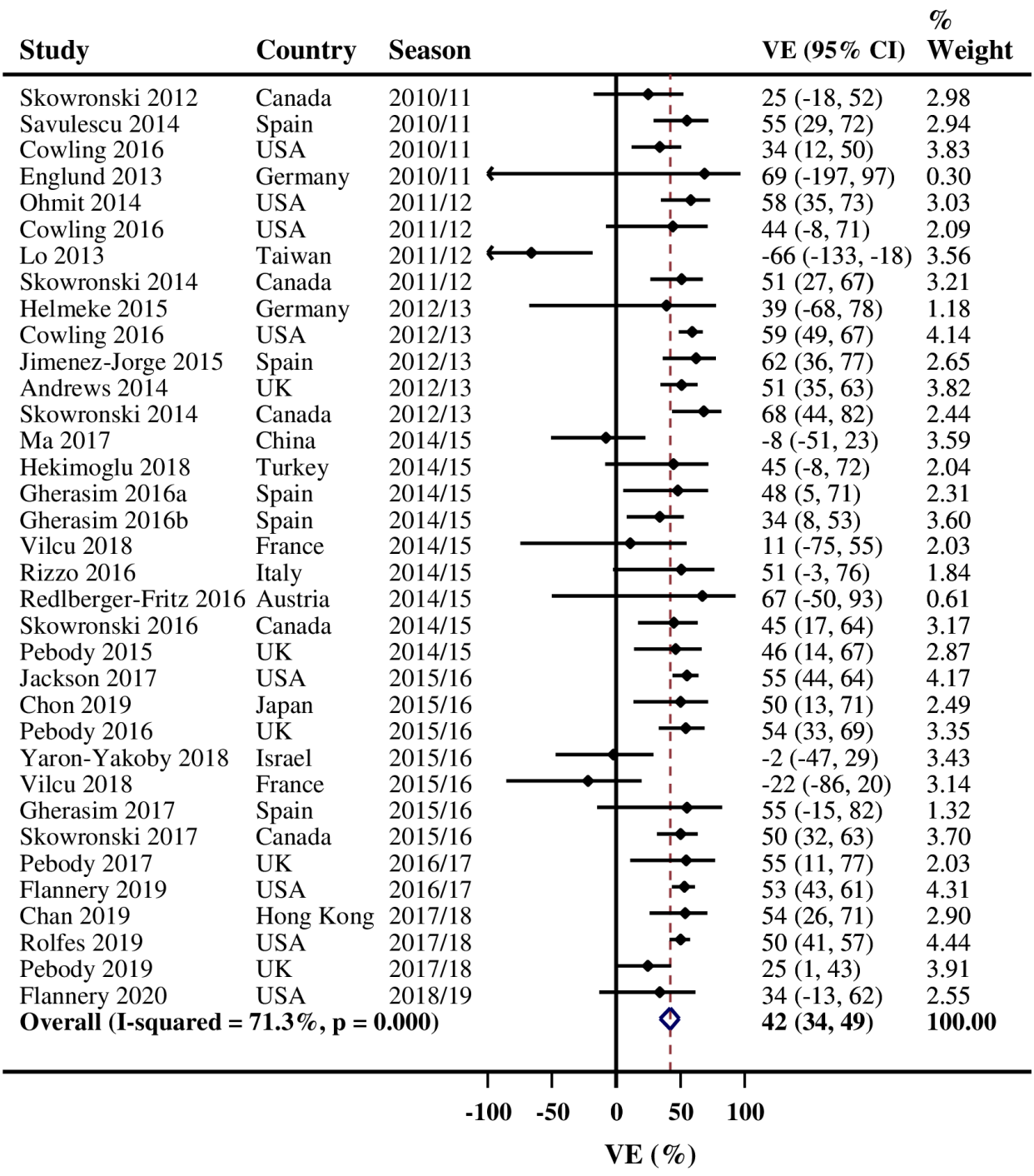
VE = vaccine effectiveness; CI = confidence interval

Figure 11: Forest plot of adjusted VE against influenza B (all participants: Southern hemisphere).



VE = vaccine effectiveness; CI = confidence interval

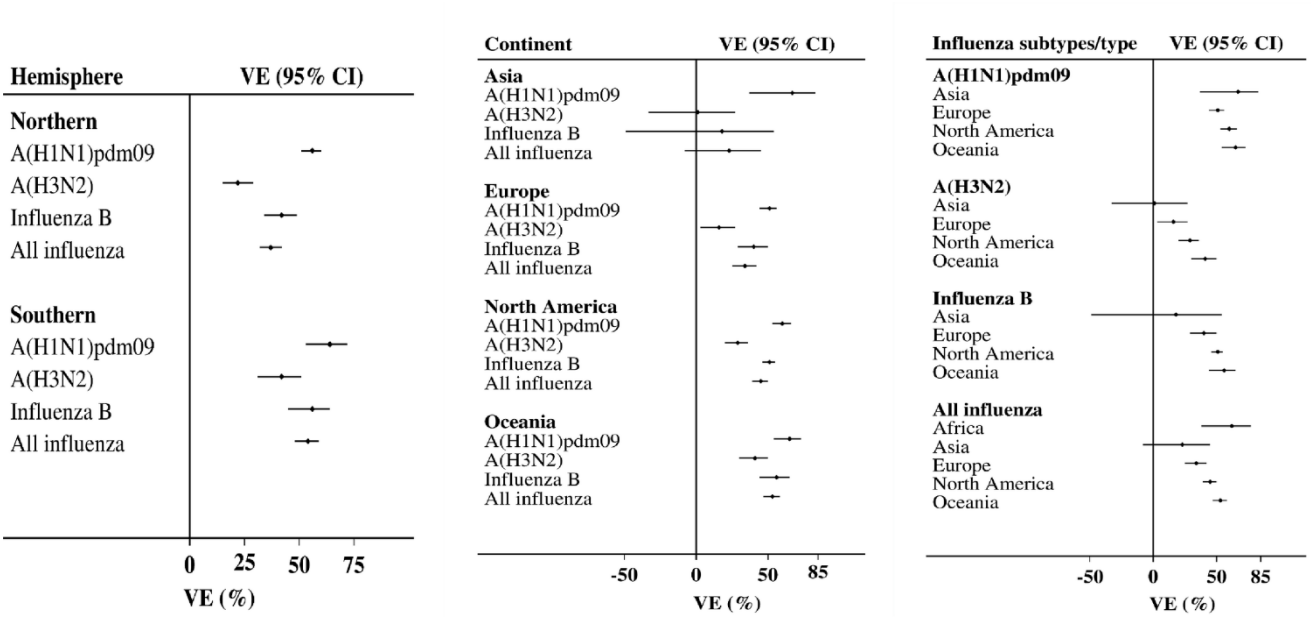
Figure 12: Forest plot of adjusted VE against influenza B (all participants: Northern hemisphere).



VE = vaccine effectiveness; CI = confidence interval

The difference between compared pooled VE pairs was statistically significant for A(H3N2) (p=0.001), influenza B (p=0.023) and all influenza (p=<0.001), but not for A(H1N1)pdm09 (p=0.14). A consistent pattern was observed in pooled VE across hemispheres and continents, with the highest point pooled VE being against A(H1N1)pdm09, followed by against influenza B, and lowest against A(H3N2) (**Figure 13**).

Figure 13: Forest plot of all pooled adjusted VE for all participants across hemispheres and continents.



VE = vaccine effectiveness; CI = confidence interval

In almost all pooled VE against the influenza subtypes/type, point pooled VE increased in the same order: from Asia, to Europe, North America, and Oceania although the point pooled VE against A(H1N1)pdm09 was highest for Asia; however, with the widest CI and least lower CI (**Figure 13**). The point pooled VE against other strains for Asia were smaller than those for other continents, but with wider CIs and the results were not statistically significant. Within each hemisphere, the difference between pooled VE against A(H1N1)pdm09, A(H3N2) and influenza

B was statistically significant in both the Southern hemisphere ($p=0.007$) and Northern hemisphere ($p<0.001$). Similarly, the difference was statistically significant within continents: Asia ($p=0.002$), Europe ($p<0.001$), North America ($p<0.001$), and Oceania ($p=0.003$). The results are summarised in **Table 6**.

Table 6: Pooled adjusted VE for all study participants irrespective of age (for study 2).

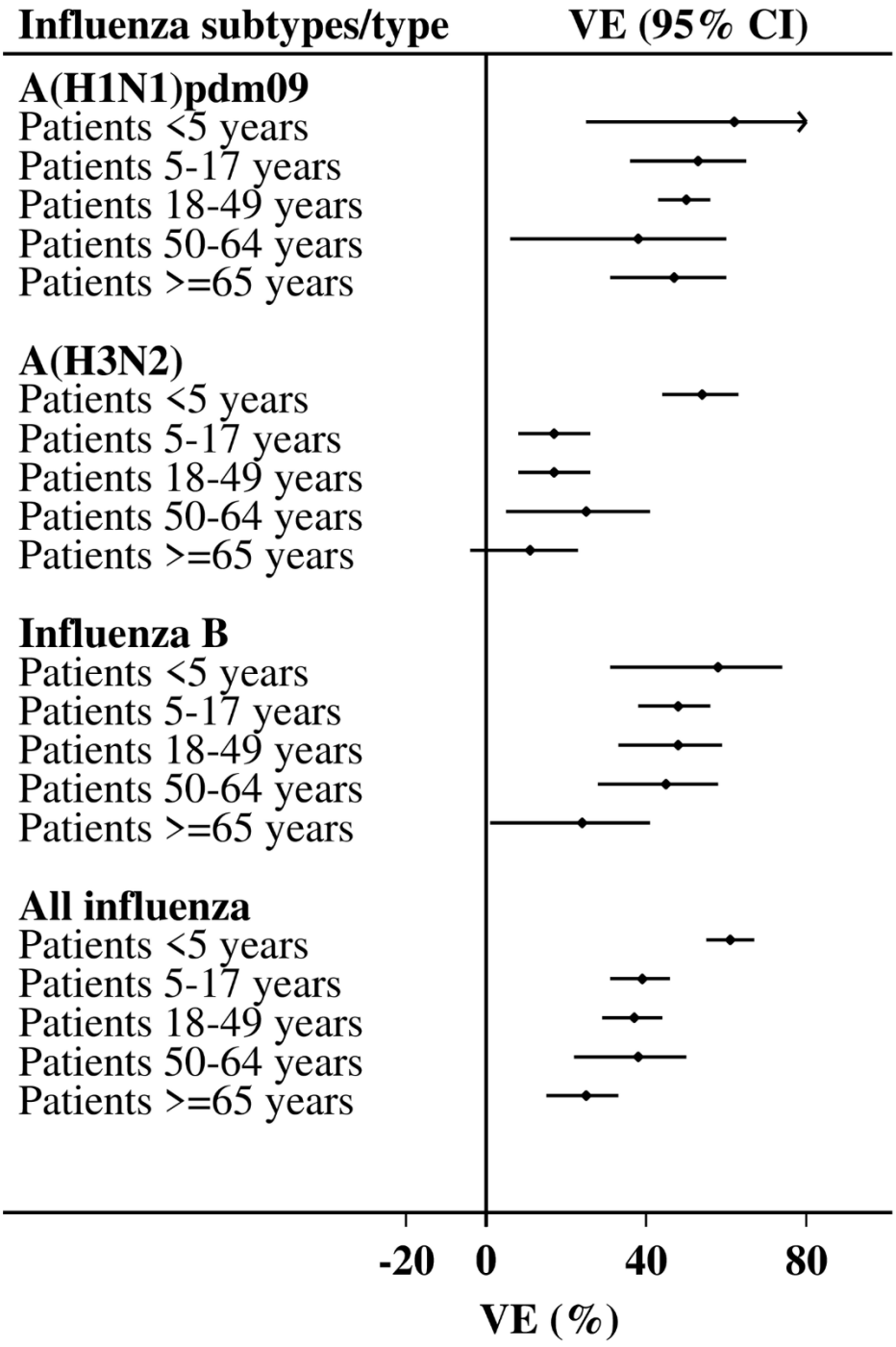
Influenza type/subtypes and analysed subgroups	No. of studies	Pooled VE for all seasons (95% CI)	I-squared statistic (%)	Publication bias (Egger's test p-value)
A(H1N1)pdm09				
Northern hemisphere	39	56 (51-60)	46.4	0.03
Southern hemisphere	11	64 (53-72)	0.0	0.54
Africa	1	44 (-63-81)	NA	NA
Asia	3	67 (37-83)	54.2	NA
Europe	22	51 (44-56)	0.0	0.66
North America	14	60 (53-66)	71.9	<0.01
Oceania	10	65 (54-73)	0.0	0.40
Antigenically similar vaccine	45	57 (53-61)	44.9	<0.01
Antigenically partially similar vaccine	5	42 (-4-68)	0.0	NA
Antigenically dissimilar vaccine	0	-	-	-
A(H3N2)				
Northern hemisphere	38	22 (15-29)	66.9	0.83
Southern hemisphere	11	42 (31-51)	0.0	0.59
Africa	1	82 (-24-97)	NA	NA
Asia	4	1 (-33-27)	34.8	NA
Europe	19	16 (3-27)	45.6	0.59
North America	15	29 (20-36)	77.4	0.25
Oceania	10	41 (30-50)	0.0	0.17
Antigenically similar vaccine	24	36 (31-41)	18.9	0.67
Antigenically partially similar vaccine	11	22 (14-30)	27.2	0.12
Antigenically dissimilar vaccine	14	1 (-15-14)	46.8	0.95
Influenza B				
Northern hemisphere	36	42 (34-49)	71.3	0.59
Southern hemisphere	10	56 (45-64)	2.6	0.70
Africa	1	32 (-217-85)	NA	NA
Asia	4	18 (-49-54)	88.1	NA
Europe	19	40 (29-50)	50.3	0.27
North America	13	51 (46-55)	20.2	0.46
Oceania	9	56 (44-65)	10.4	NA
Antigenically similar vaccine	27	51 (47-55)	25.2	0.66
Antigenically partially similar vaccine	10	39 (20-54)	39.2	0.23
Antigenically dissimilar vaccine	9	20 (-9-41)	73.1	N/A
All influenza				
Northern hemisphere	58	37 (32-42)	79.8	0.92
Southern hemisphere	18	54 (48-59)	0.0	0.11
Africa	5	62 (38-77)	39.4	N/A
Asia	7	23 (-8-45)	83.4	N/A
Europe	34	34 (25-42)	65.7	0.42
North America	17	45 (39-50)	86.0	0.05
Oceania	13	53 (47-58)	0.0	0.19
Antigenically similar vaccine	46	49 (45-53)	61.5	0.01
Antigenically partially similar vaccine	26	27 (20-34)	43.4	0.53
Antigenically dissimilar vaccine	4	-9 (-28-8)	30.4	N/A

VE = vaccine effectiveness; CI = confidence interval; NA = not applicable

Pooled adjusted VE by age group

There was a lack of data from the Southern hemisphere to enable comparison with the Northern hemisphere across age groups except for pooled VE against all influenza in the <5 years old and ≥65 years old age groups (**Appendix 14**). A statistically significantly higher pooled VE against all influenza was observed among ≥65 years old in the Southern hemisphere 52% (25–70%; I^2=7.3%) compared with the Northern hemisphere 25% (15–33%; I^2=0%) (p=0.03) whereas the opposite was observed in the <5 years old age group: 7% (-199–71%; I^2=0%) in the Southern hemisphere versus 61% (55–67%; I^2=0%) in the Northern hemisphere (p=0.43). However, the CI in the Southern hemisphere was markedly wide and the difference between the Southern and Northern hemispheres was not statistically significant. A nearly consistent pattern was observed in pooled VE against A(H1N1)pdm09, A(H3N2), influenza B, and all influenza across all age groups in the Northern hemisphere, with point pooled VE mostly decreasing with age (**Figure 14**).

Figure 14: Forest plot of all pooled adjusted VE across age groups in the Northern hemisphere.

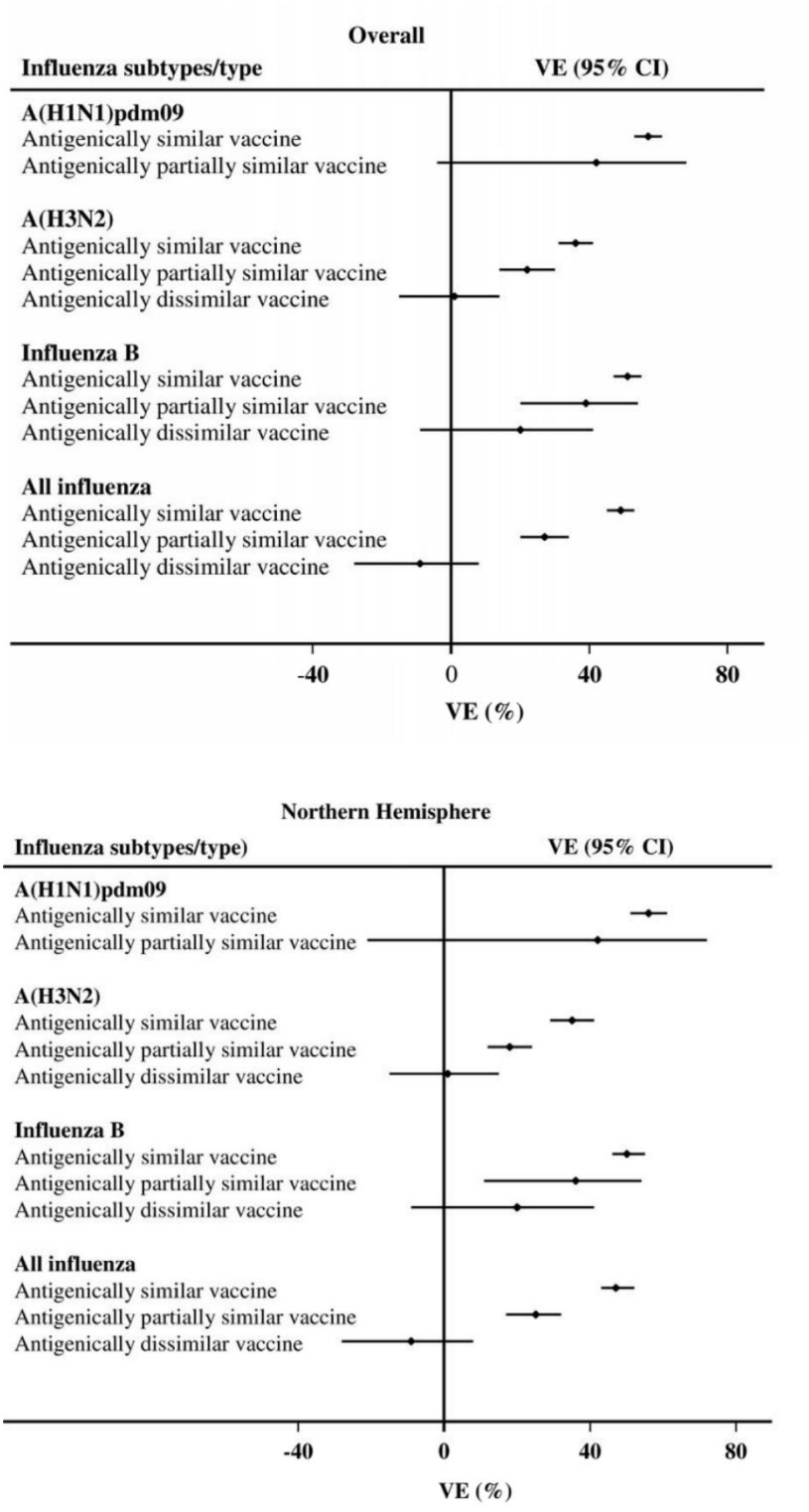


VE = vaccine effectiveness; CI = confidence interval

Pooled adjusted VE by vaccine antigenic similarity with circulating virus strains

Overall, point pooled VE against A(H3N2), influenza B, and all influenza were higher with antigenically similar compared with antigenically dissimilar vaccines: 36% (31–41%; I^2=18.9%) compared with 1% (-15–14%; I^2=46.8%) for A(H3N2); 51% (47–55%; I^2=25.2%) compared with 20% (-9–41%; I^2=73.1%) for influenza B; and 49% (45–53%; I^2=61.5%) compared with -9% (-28–8%; I^2=30.4%) for all influenza. The difference between these compared pooled VE pairs was statistically significant for A(H3N2) (p<0.001), influenza B (p=0.016), and all influenza (p<0.001), with a consistent pattern observed (**Figure 15**). The same observation was made with regard to the Northern hemisphere: p<0.001 for A(H3N2), P=0.02 for influenza B, and p<0.001 for all influenza. There was a paucity of data from the Southern hemisphere and there was no antigenically dissimilar vaccine against A(H1N1)pdm09. However, point pooled VE against A(H1N1)pdm09 was higher with antigenically similar vaccine compared with antigenically partially similar vaccine (**Table 6**). Most of these observations were also made within some age groups (**Appendix 14**).

Figure 15: Forest plot of pooled adjusted VE across levels of vaccine antigenic similarity with circulating virus strains – overall, and the Northern hemisphere.



VE = vaccine effectiveness; CI = confidence interval

Discussion

In this systematic review and meta-analysis of VE against laboratory-confirmed seasonal influenza from TND studies conducted in outpatient settings after the 2009/10 influenza pandemic, substantial variability was found in VE across geographical regions, age groups, and levels of vaccine antigenic similarity with circulating virus strains. In the analysis involving all study participants (not age restricted), VE estimates against A(H1N1)pdm09, A(H3N2), influenza B, and all influenza were homogenous in the Southern hemisphere and point pooled VE higher in the Southern hemisphere compared with the Northern hemisphere. Vaccine performed best against A(H1N1)pdm09 and worst against A(H3N2) in all regions. Point pooled VE against almost all influenza subtypes/type increased in the same order: from Asia, to Europe, North America, and Oceania. Point pooled VE against almost all influenza subtypes/type declined with age in the Northern hemisphere; there was a lack of data from the Southern hemisphere. VE was significantly higher with vaccine antigenically similar compared with antigenically dissimilar to circulating virus strains.

Compared with the Northern hemisphere, significantly fewer studies contributed to the analysis for the Southern hemisphere. These studies were mostly from Australia, whereas studies for the Northern hemisphere were from diverse countries. Methods of study participant enrolment differed across the included studies, with participants consecutively recruited in 45% of studies and systematically recruited in 55% of studies. Method of confirmation of influenza vaccination status also differed across studies; however, a majority was through medical record (70%) while 14% was self-reported, 13% mixed, and 3% unknown. There were also differences across studies in the type of respiratory specimen collected, although specimen swab time in all the studies was within 7 days of symptom onset. Influenza testing was largely by RT-PCR.

Although studies were restricted to outpatient settings, it was not clear to what extent study populations differed by comorbidity status. There were variations in logistic regression models. In addition to other covariates adjusted for, about 53% of studies adjusted for both age and comorbidity, 43% for age but not comorbidity, 3% for comorbidity but not age, and about 1% adjusted for neither age nor comorbidity. Furthermore, sample size differed significantly across the studies. These differences may have contributed to the heterogeneity observed in some of the pooled analyses. Nevertheless, our review contributes significantly to the evidence base and highlights patterns that may exist in VE across regions, age groups, and levels of vaccine antigenic similarity with circulating virus strains.

When compared with A(H1N1)pdm09 and influenza B, point pooled VE against A(H3N2) was lowest in all regions and in almost all age groups. It was markedly lower among ≥65 years old in the Northern hemisphere (11%), compared with point pooled VE against A(H1N1)pdm09 (47%) and influenza B (24%) among the same age group. On the other hand, among <5 years old in the Northern hemisphere, point pooled VE was substantially higher against A(H3N2) (54%), A(H1N1)pdm09 (62%), and influenza B (58%). Point pooled VE against A(H1N1)pdm09, A(H3N2) and influenza B were also substantially higher among other age groups in the Northern hemisphere when compared with ≥65 years old; thus, suggesting an age-related immune response effect.

Influenza viruses may undergo changes when incubated in eggs during the production of vaccine viruses. However, while this is particularly problematic for influenza B lineages, the B/Victoria and B/Yamagata, as well as for A(H3N2), the changes that occur in A(H3N2) result in more mutations.[71] These egg-adapted changes may alter antigenic integrity of vaccine viruses and reduce the effectiveness of vaccine against the circulating virus strains based upon which

vaccine strains were determined.[71] This means that, between the time of recommendation of seasonal vaccine virus strains by the WHO and the production of vaccines, the A(H3N2) component of vaccine in particular may undergo significant changes that could reduce the effectiveness of the developed vaccines against this influenza subtype. Secondly, compared with A(H1N1)pdm09 and influenza B, more antigenic drift has been reported in A(H3N2) during some seasons, with associated increased morbidity and fatality, and this may partly explain the observed low pooled VE against A(H3N2).[88-90] Flannery (2016) found that VE against A(H3N2) was almost zero for an antigenically drifted genetic group of viruses, and 44% against a genetic group that were antigenically similar to the seasonal vaccine strains.[91] Furthermore, it was observed that vaccine performed very poorly in the 2014/15 influenza season, during which there was widespread circulation of A(H3N2) viruses antigenically dissimilar from the A/Texas/50/2012 that was covered in the season's vaccine.

Our findings are similar to those of Belongia (2016), a systematic review and meta-analysis of 56 studies which found substantial variation in VE across influenza A(H1N1)pdm09, A(H3N2) and influenza B, and substantially low VE against A(H3N2).[92] While we did not aim to update or to replicate the study, our methods were considerably similar. However, influenza seasons prior to the 2009/10 influenza pandemic were included in the review, whereas we included only studies after the 2009/10 influenza pandemic, to allow us to focus on studies conducted from when universal public funding of influenza vaccination increased in most of the Western jurisdictions. Belongia and colleagues included data from hospitalised patients in some of the pooled analyses, whereas we limited our analyses strictly to outpatient settings since VE tends to differ between inpatient and outpatient populations.[39,93] However, a study found no differences in VE estimates between both patient populations; albeit, with a small sample size.[94]

Furthermore, the review included interim VE data that has not yet been superseded by final estimates, whereas we included only final VE estimates to ensure that data from throughout each influenza season were considered, and to enable an easier update of, and comparison with, our findings in the future. Belongia and colleagues also included only studies that reported age-stratified or age-adjusted VE estimates, whereas we included all multivariable-adjusted VE estimates and then provided additional information regarding covariate adjustments in studies. Two other systematic reviews also examined seasonal influenza VE from TND studies; one was limited to community-dwelling elderly individuals and employed individual participant data meta-analysis,[95] while the other assessed severe influenza illness prevention with vaccination among hospitalised adults.[96] Although the reviewed populations were significantly different from ours, our findings regarding VE were quite similar.

Although we evaluated influenza surveillance studies of TND type in outpatient settings after the 2009/10 influenza pandemic, it should be noted that some eligible studies conducted during this specified period may not have been published at the time of our literature search, and therefore not included in this review. Due to inadequacy of data, we could not thoroughly examine VE in all age groups and, therefore, could not compare age groups between regions. There were also differences in the categorization of age groups across studies, further limiting data for age group analysis. We could also not compare VE by vaccine type although we are aware that the vaccine types are very different and that VE is not equivalent for all vaccine types. Studies did not report prior seasonal influenza vaccinations so we could not assess the impact on the assessed VE, despite growing evidence to suggest that vaccine effectiveness may be influenced by prior vaccinations.[97,98] Furthermore, it was not possible to account for laboratory variability in antigenic characterization assays, and it was not also possible to assess the impact

of social desirability reporting and recall biases in studies with self-reported vaccination. Within and across regional studies, it was not possible to assess the impact of vaccination policies and programmes.

Notwithstanding the aforementioned limitations, our review has many merits including having been conducted in full compliance with the Cochrane Handbook for Systematic Reviews of Interventions guidelines and reported in accordance with the PRISMA guidelines. Our literature search strategy was comprehensive, and was reviewed by a knowledge synthesis librarian using the PRESS checklist.

Conclusions

Consistent patterns appear to exist in seasonal influenza VE across geographical regions, age groups, and levels of vaccine antigenic similarity with circulating viruses, with vaccine performing best against A(H1N1)pdm09 and worst against A(H3N2). Likewise, vaccine appears to perform best when antigenically similar with circulating virus strains, and VE appears to reduce with age. The evidence highlights the importance of considering geographical location, age, and vaccine antigenic similarity with circulating viruses when designing and evaluating influenza VE studies.

Declarations

S.M.M has received unrestricted research grants from GlaxoSmithKline, Merck, Sanofi Pasteur, Pfizer and Roche-Assurex for unrelated studies, and fees as an advisory board member for Sanofi Pasteur. The other authors declare that they have no conflicts of interest.

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References

1. Olsen SJ, Azziz-Baumgartner E, Budd AP, et al. Decreased influenza activity during the COVID-19 pandemic — United States, Australia, Chile, and South Africa, 2020. *MMWR Morb Mortal Wkly Rep* 2020;69:1305-1
2. Boni MF. Vaccination and antigenic drift in influenza. *Vaccine*. 2008;26:C8-C14.
3. Barr IG, McCauley J, Cox N, et al. Epidemiological, antigenic and genetic characteristics of seasonal influenza A(H1N1), A(H3N2) and B influenza viruses: Basis for the WHO recommendation on the composition of influenza vaccines for use in the 2009-2010 Northern Hemisphere season. *Vaccine*. 2010;28(5):1156-1167.
4. Lorenzo MMG, Fenton MJ. Immunobiology of Influenza Vaccines. *Chest*. 2013;143(2):502-510.
5. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine*. 2013;31(17):2165-2168.
6. Sullivan SG, Tchetgen EJT, Cowling BJ. Theoretical Basis of the Test-Negative Study Design for Assessment of Influenza Vaccine Effectiveness. *Am J Epidemiol*. 2016;184(5):345-353.
7. Lewnard JA, Tedijanto C, Cowling BJ, Lipsitch M. Measurement of Vaccine Direct Effects Under the Test-Negative Design. *Am J Epidemiol*. 2018;187(12):2686-2697.
8. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21(11):1539-1558.
9. Huizenga HM, Visser I, Dolan CV. Testing overall and moderator effects in random effects meta-regression. *Brit J Math Stat Psy*. 2011;64(1):1-19.
10. McHugh ML. The Chi-square test of independence. *Biochem Medica*. 2013;23(2):143-149.
11. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ*. 2001;323(7304):101-105.
12. Andrews N, McMenamin J, Durnall H, et al. Effectiveness of trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2012/13 end of season results. *Euro Surveill*. 2014;19(27):20851.

13. Bateman AC, Kieke BA, Irving SA, Meece JK, Shay DK, Belongia EA. Effectiveness of monovalent 2009 pandemic influenza A virus subtype H1N1 and 2010-2011 trivalent inactivated influenza vaccines in Wisconsin during the 2010-2011 influenza season. *Journal of Infectious Diseases*. 2013;207(8):1262-1269.
14. Carville KS, Grant KA, Sullivan SG, et al. Understanding influenza vaccine protection in the community: An assessment of the 2013 influenza season in Victoria, Australia. *Vaccine*. 2015;33(2):341-345.
15. Castilla J, Martínez-Baz I, Martínez-Artola V, et al. Decline in influenza vaccine effectiveness with time after vaccination, Navarre, Spain, season 2011/12. *Euro Surveill*. 2013;18(5):20388.
16. Castilla J, Navascues A, Fernandez-Alonso M, et al. Effectiveness of subunit influenza vaccination in the 2014-2015 season and residual effect of split vaccination in previous seasons. *Vaccine*. 2016;34(11):1350-1357.
17. Castilla J, Portillo ME, Casado I, et al. Effectiveness of the current and prior influenza vaccinations in Northern Spain, 2018-2019. *Vaccine*. 2020;38(8):1925-1932.
18. Chan YWD, Wong ML, Au KW, Chuang SK. Seasonal influenza vaccine effectiveness at primary care level, Hong Kong SAR, 2017/2018 winter. *Hum Vacc Immunother*. 2019;15(1):97-101.
19. Chon I, Saito R, Hibino A, et al. Effectiveness of the quadrivalent inactivated influenza vaccine in Japan during the 2015-2016 season: A test-negative case-control study comparing the results by real time PCR, virus isolation. *Vaccine X*. 2019;1:100011.
20. Cowling BJ, Feng S, Finelli L, Steffens A, Fowlkes A. Assessment of influenza vaccine effectiveness in a sentinel surveillance network 2010-13, United States. *Vaccine*. 2016;34(1):61-66.
21. Darvishian M, Dijkstra F, Van Doorn E, et al. Influenza vaccine effectiveness in the Netherlands from 2003/2004 through 2013/2014: The importance of circulating influenza virus types and subtypes. *PLoS ONE*. 2017;12(1):e0169528.
22. Englund H, Campe H, Hautmann W. Effectiveness of trivalent and monovalent influenza vaccines against laboratory-confirmed influenza infection in persons with medically attended influenza-like illness in Bavaria, Germany, 2010/2011 season. *Epidemiol Infect*. 2013;141(9):1807-1815.

23. Fielding JE, Grant KA, Tran T, Kelly HA. Moderate influenza vaccine effectiveness in Victoria, Australia, 2011. *Euro Surveill*. 2012;17(11):20115.
24. Fielding JE, Levy A, Chilver MB, et al. Effectiveness of seasonal influenza vaccine in Australia, 2015: An epidemiological, antigenic and phylogenetic assessment. *Vaccine*. 2016;34(41):4905-4912.
25. Filipovic SK, Gjenero-Margan I, Kissling E, Kaic B, Cvitkovic A. Influenza vaccine effectiveness estimates in Croatia in 2010-2011: a season with predominant circulation of A(H1N1)pdm09 influenza virus. *Epidemiology and Infection*. 2015;143(12):2596-2603.
26. Flannery B, Chung JR, Monto AS, et al. Influenza Vaccine Effectiveness in the United States During the 2016-2017 Season. *Clin Infect Dis*. 2019;68(11):1798-1806.
27. Flannery B, Kondor RJG, Chung JR, et al. Spread of Antigenically Drifted Influenza A(H3N2) Viruses and Vaccine Effectiveness in the United States During the 2018-2019 Season. *J Infect Dis*. 2020;221(1):8-15.
28. Gaglani M, Pruszynski J, Murthy K, et al. Influenza Vaccine Effectiveness Against 2009 Pandemic Influenza A(H1N1) Virus Differed by Vaccine Type During 2013–2014 in the United States. *Journal of Infectious Diseases*. 2016;213:1546-1556.
29. Gherasim A, Pozo F, de Mateo S, et al. Waning protection of influenza vaccine against mild laboratory confirmed influenza A(H3N2) and B in Spain, season 2014-15. *Vaccine*. 2016;34(20):2371-2377.
30. Gherasim A, Martinez-Baz I, Castilla J, Pozo F, Larrauri A, Grp cW. Effect of previous and current vaccination against influenza A(H1N1) pdm09, A(H3N2), and B during the post-pandemic period 2010-2016 in Spain. *PloS ONE*. 2017;12(6): e0179160.
31. Hekimoglu CH, Emek M, Avci E, Topal S, Demiroz M, Ergor G. Seasonal Influenza Vaccine Effectiveness in Preventing Laboratory Confirmed Influenza in 2014-2015 Season in Turkey: A Test-Negative Case Control Study. *Balk Med J*. 2018;35(1):77-83.
32. Helmeke C, Gräfe L, Irmscher HM, Gottschalk C, Karagiannis I, Oppermann H. Effectiveness of the 2012/13 trivalent live and inactivated influenza vaccines in children and adolescents in Saxony-Anhalt, Germany: A test-negative case-control study. *PLoS ONE*. 2015;10(4):e0122910.
33. Jackson ML, Chung JR, Jackson LA, et al. Influenza Vaccine Effectiveness in the United States during the 2015-2016 Season. *New Engl J Med*. 2017;377(6):534-543.

34. Jimenez-Jorge S, Savulescu C, Pozo F, et al. Effectiveness of the 2010-11 seasonal trivalent influenza vaccine in Spain: cycEVA study. *Vaccine*. 2012;30(24):3595-3602.
35. Jimenez-Jorge S, de Mateo S, Delgado-Sanz C, et al. Effectiveness of influenza vaccine against laboratory-confirmed influenza, in the late 2011-2012 season in Spain, among population targeted for vaccination. *BMC infectious diseases*. 2013;13:441.
36. Jimenez-Jorge S, de Mateo S, Delgado-Sanz C, et al. Estimating influenza vaccine effectiveness in Spain using sentinel surveillance data. *Euro Surveill*. 2015;20(28):21187.
37. Jimenez-Jorge S, Pozo F, Larrauri A. Interim influenza vaccine effectiveness: A good proxy for final estimates in Spain in the seasons 2010-2014. *Vaccine*. 2015;33(29):3276-3280.
38. Kelly HA, Sullivan SG, Grant KA, Fielding JE. Moderate influenza vaccine effectiveness with variable effectiveness by match between circulating and vaccine strains in Australian adults aged 20-64years, 2007-2011. *Influenza Other Resp*. 2013;7(5):729-737.
39. Kelly HA, Lane C, Cheng AC. Influenza vaccine effectiveness in general practice and in hospital patients in Victoria, 2011-2013. *Medical Journal of Australia*. 2016;204(2):76.
40. Levy A, Sullivan SG, Tempone SS, et al. Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012. *Vaccine*. 2014;32(47):6312-6318.
41. Lo YC, Chuang JH, Kuo HW, et al. Surveillance and Vaccine Effectiveness of an Influenza Epidemic Predominated by Vaccine-Mismatched Influenza B/Yamagata-Lineage Viruses in Taiwan, 2011-12 Season. *PLoS ONE*. 2013;8(3):e58222.
42. Ma CN, Pan Y, Zhang L, et al. Influenza vaccine effectiveness against medically attended influenza illness in Beijing, China, 2014/15 season. *Hum Vacc Immunother*. 2017;13(10):2379-2384.
43. Martínez-Baz I, Martínez-Artola V, Reina G, et al. Effectiveness of the trivalent influenza vaccine in Navarre, Spain, 2010-2011: A population-based test-negative case-control study. *BMC Public Health*. 2013;13(1):191.
44. Martinez-Baz I, Navascues A, Pozo F, et al. Influenza vaccine effectiveness in preventing inpatient and outpatient cases in a season dominated by vaccine-matched influenza B virus. *Human Vaccines and Immunotherapeutics*. 2015;11(7):1626-1633.

45. Martinez-Baz I, Navascues A, Casado I, Aguinaga A, Ezpeleta C, Castilla J. Remaining Effect of Influenza Vaccines Received in Prior Seasons. *J Infect Dis*. 2019;220(7):1136-1140.
46. McAnerney JM, Walaza S, Cohen AL, et al. Effectiveness and knowledge, attitudes and practices of seasonal influenza vaccine in primary healthcare settings in South Africa, 2010-2013. *Influenza Other Resp*. 2015;9(3):143-150.
47. McAnerney JM, Walaza S, Tempia S, et al. Estimating vaccine effectiveness in preventing laboratory-confirmed influenza in outpatient settings in South Africa, 2015. *Influenza Other Resp*. 2017;11(2):177-181.
48. McLean HQ, Thompson MG, Sundaram ME, et al. Influenza Vaccine Effectiveness in the United States During 2012–2013: Variable Protection by Age and Virus Type. *Journal of Infectious Diseases*. 2015;211(10):1529-1540.
49. Mohl A, Grafe L, Helmeke C, et al. Estimating vaccine effectiveness against laboratory-confirmed influenza among children and adolescents in Lower Saxony and Saxony-Anhalt, 2012-2016. *Epidemiology and Infection*. 2018;146(1):78-88.
50. Nunes B, Machado A, Guiomar R, et al. Estimates of 2012/13 influenza vaccine effectiveness using the case test-negative control design with different influenza negative control groups. *Vaccine*. 2014;32(35):4443-4449.
51. Ohmit SE, Thompson MG, Petrie JG, et al. Influenza vaccine effectiveness in the 2011-2012 season: Protection against each circulating virus and the effect of prior vaccination on estimates. *Clinical Infectious Diseases*. 2014;58(3):319-327.
52. Pebody R, Andrews N, Fleming D, et al. Age-specific vaccine effectiveness of seasonal 2010/2011 and pandemic influenza A (H1N1) 2009 vaccines in preventing influenza in the United Kingdom. *Epidemiology and infection*. 2013;141(03):620-630.
53. Pebody RG, Andrews N, McMenamin J, et al. Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: Evidence of waning intra-seasonal protection. *Euro Surveill*. 2013;18(5):pii=20389.
54. Pebody R, Warburton F, Andrews N, et al. Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results. *Euro Surveill*. 2015;20(36).

55. Pebody R, Warburton F, Ellis J, et al. Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-ofseason results. *Euro Surveill*. 2016;21(38):pii=30348.
56. Pebody R, Warburton F, Ellis J, et al. End-of-season influenza vaccine effectiveness in adults and children, United Kingdom, 2016/17. *Euro Surveill*. 2017;22(44):10-22.
57. Pebody R, Djennad A, Ellis J, et al. End of season influenza vaccine effectiveness in adults and children in the United Kingdom in 2017/18. *Euro Surveill*. 2019;24(31):23-39.
58. Pebody RG, Whitaker H, Ellis J, et al. End of season influenza vaccine effectiveness in primary care in adults and children in the United Kingdom in 2018/19. *Vaccine*. 2020;38(3):489-497.
59. Pierse N, Kelly H, Thompson MG, et al. Influenza vaccine effectiveness for hospital and community patients using control groups with and without non-influenza respiratory viruses detected, Auckland, New Zealand 2014. *Vaccine*. 2016;34(4):503-509.
60. Pitigoi D, Ivanciuc AE, Necula G, Lupulescu E, Alexandrescu V, Savulescu C. Influenza vaccine effectiveness to prevent medically attended laboratory confirmed influenza during season 2010-2011 in Romania: a case control study. *Rev Romana Med Lab*. 2012;20(2):127-134.
61. Pitigoi D, Necula G, Alexandrescu V, et al. Circulating influenza viruses and the effectiveness of seasonal influenza vaccine in Romania, season 2012-2013/Virusurile gripale circulante și eficacitatea vaccinului gripal sezonier în România, în sezonul 2012-2013. *Romanian Review of Laboratory Medicine*. 2015;23(1):9-20.
62. Powell L, Begue RE. Estimate of the Effectiveness of Influenza Vaccine among Children for the 2017-2018 Season. *J Invest Med*. 2019;67(2):598-598.
63. Redlberger-Fritz M, Kundi M, Popow-Kraupp T. Detailed report on 2014/15 influenza virus characteristics, and estimates on influenza virus vaccine effectiveness from Austria's sentinel physician surveillance network. *PLoS ONE*. 2016;11(3): e0149916.
64. Regan AK, Gibbs R, Bloomfield L, Effler PV. Estimating influenza vaccine effectiveness using data routinely available in electronic primary care records. *Vaccine*. 2019;37(5):755-762.

65. Regan AK, Fielding JE, Chilver MB, et al. Intraseason decline in influenza vaccine effectiveness during the 2016 southern hemisphere influenza season: A test-negative design study and phylogenetic assessment. *Vaccine*. 2019;37(19):2634-2641.
66. Rizzo C, Bella A, Alfonsi V, et al. Influenza vaccine effectiveness in Italy: Age, subtype-specific and vaccine type estimates 2014/15 season. *Vaccine*. 2016;34(27):3102-3108.
67. Rolfes MA, Flannery B, Chung JR, et al. Effects of Influenza Vaccination in the United States During the 2017-2018 Influenza Season. *Clinical Infectious Diseases*. 2019;69(11):1845-1853.
68. Savulescu C, Jiménez-Jorge S, Delgado-Sanz C, et al. Higher vaccine effectiveness in seasons with predominant circulation of seasonal influenza A(H1N1) than in A(H3N2) seasons: Test-negative case-control studies using surveillance data, Spain, 2003-2011. *Vaccine*. 2014;32(35):4404-4411.
69. Skowronski DM, Janjua NZ, De Serres G, et al. A sentinel platform to evaluate influenza vaccine effectiveness and new variant circulation, Canada 2010-2011 season. *Clinical Infectious Diseases*. 2012;55(3):332-342.
70. Skowronski DM, Janjua NZ, Sabaiduc S, et al. Influenza A/subtype and B/lineage effectiveness estimates for the 2011-2012 trivalent vaccine: Cross-season and cross-lineage protection with unchanged vaccine. *Journal of Infectious Diseases*. 2014;210(1):126-137.
71. Skowronski DM, Janjua NZ, De Serres G, et al. Low 2012–13 Influenza Vaccine Effectiveness Associated with Mutation in the Egg-Adapted H3N2 Vaccine Strain Not Antigenic Drift in Circulating Viruses. *PLoS ONE*. 2014;9(3):e92153.
72. Skowronski DM, Chambers C, Sabaiduc S, et al. Integrated Sentinel Surveillance Linking Genetic, Antigenic, and Epidemiologic Monitoring of Influenza Vaccine-Virus Relatedness and Effectiveness During the 2013-2014 Influenza Season. *Journal of Infectious Diseases*. 2015;212(5):726-739.
73. Skowronski DM, Chambers C, Sabaiduc S, et al. A Perfect Storm: Impact of Genomic Variation and Serial Vaccination on Low Influenza Vaccine Effectiveness During the 2014–2015 Season. *Clinical Infectious Diseases*. 2016;63(1):21-32.
74. Skowronski DM, Chambers C, Sabaiduc S, et al. Beyond Antigenic Match: Possible Agent-Host and Immuno-epidemiological Influences on Influenza Vaccine Effectiveness

During the 2015-2016 Season in Canada. *Journal of Infectious Diseases*. 2017;216(12):1487-1500.

75. Skowronski DM, Sabaiduc S, Leir S, et al. Paradoxical clade- and age-specific vaccine effectiveness during the 2018/19 influenza A(H3N2) epidemic in Canada: potential imprint-regulated effect of vaccine (I-REV). *Euro Surveill*. 2019;24(46):39-50.
76. Stein Y, Mandelboim M, Sefty H, et al. Seasonal Influenza Vaccine Effectiveness in Preventing Laboratory-Confirmed Influenza in Primary Care in Israel, 2016-2017 Season: Insights Into Novel Age-Specific Analysis. *Clinical Infectious Diseases*. 2018;66(9):1383-1391.
77. Sullivan SG, Kelly H. Late season interim estimates of influenza vaccine effectiveness reliably predict end of season estimates in Victoria, Australia, 2007 to 2012. *Euro Surveill*. 2013;18(41):20605.
78. Sullivan SG, Komadina N, Grant K, Jelley L, Papadakis G, Kelly H. Influenza vaccine effectiveness during the 2012 influenza season in Victoria, Australia: Influences of waning immunity and vaccine match. *Journal of Medical Virology*. 2014;86(6):1017-1025.
79. Suzuki M, Minh LN, Yoshimine H, et al. Vaccine effectiveness against medically attended laboratory-confirmed influenza in Japan, 2011-2012 season. *PLoS ONE*. 2014;9(2):e88813.
80. Treanor JJ, Talbot HK, Ohmit SE, et al. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. *Clinical Infectious Diseases*. 2012;55(7):951-959.
81. Van Doorn E, Darvishian M, Dijkstra F, et al. Influenza Vaccine Effectiveness Estimates in the Dutch Population from 2003 to 2014: The Test-Negative Design Case-Control Study with Different Control Groups. *Vaccine*. 2017;35(21):2831-2839.
82. Vilcu AM, Souty C, Enouf V, et al. Estimation of seasonal influenza vaccine effectiveness using data collected in primary care in France: comparison of the test-negative design and the screening method. *Clin Microbiol Infec*. 2018;24(4):431.e5-431.e12.
83. Wang Y, Zhang T, Chen L, et al. Seasonal influenza vaccine effectiveness against medically attended influenza illness among children aged 6–59 months, October 2011–

September 2012: A matched test-negative case–control study in Suzhou, China. *Vaccine*. 2016;34(21):2460-2465.

84. Wu SS, Pan Y, Zhang XX, et al. Influenza vaccine effectiveness in preventing laboratory-confirmed influenza in outpatient settings: A test-negative case-control study in Beijing, China, 2016/17 season. *Vaccine*. 2018;36(38):5774-5780.
85. Yang P, Thompson MG, Ma C, et al. Influenza vaccine effectiveness against medically-attended influenza illness during the 2012-2013 season in Beijing, China. *Vaccine*. 2014;32(41):5285-5289.
86. Yaron-Yakoby H, Sefty H, Pando R, et al. Effectiveness of influenza vaccine in preventing medically-attended influenza virus infection in primary care, Israel, influenza seasons 2014/15 and 2015/16. *Euro Surveill*. 2018;23(7):27-37.
87. Zimmerman RK, Nowalk MP, Chung J, et al. 2014–2015 Influenza Vaccine Effectiveness in the United States by Vaccine Type. *Clinical Infectious Diseases*. 2016;63(12):1564-1573.
88. Tewawong N, Prachayangprecha S, Vichiwattana P, et al. Assessing Antigenic Drift of Seasonal Influenza A(H3N2) and A(H1N1)pdm09 Viruses. *PloS ONE*. 2015;10(10):0139958
89. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *J. Am Med Assoc*. 2003;289(2):179-186.
90. Allen JD, Ross TM. H3N2 influenza viruses in humans: Viral mechanisms, evolution, and evaluation. *Hum Vacc Immunother*. 2018;14(8):1840-1847.
91. Flannery B, Zimmerman RK, Gubareva LV, et al. Enhanced Genetic Characterization of Influenza A(H3N2) Viruses and Vaccine Effectiveness by Genetic Group, 2014-2015. *Journal of Infectious Diseases*. 2016;214(7):1010-1019.
92. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. *Lancet Infect Dis*. 2016;16(8):942-951.
93. Castilla J, Godoy P, Domínguez A, et al. Influenza vaccine effectiveness in preventing outpatient, inpatient, and severe cases of laboratory-confirmed influenza, *Clinical Infect Dis*. 2013;57(2):167-175.

94. Feng S, Cowling BJ, Sullivan SG. Influenza vaccine effectiveness by test-negative design – Comparison of inpatient and outpatient settings. *Vaccine*. 2016;34(14):1672-1679.
95. Darvishian M, Bijlsma MJ, Flak E, van den Heuvel ER. Effectiveness of seasonal influenza vaccine in community-dwelling elderly people: a meta-analysis of test-negative design case-control studies. *Lancet Infect Dis.* 2014;14(12):1228-1239.
96. Rondy M, El Omeiri N, Thompson MG, Leveque A, Moren A, Sullivan SG. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: A systematic review and meta-analysis of test-negative design case-control studies. *J Infection*. 2017;75(5):381-394.
97. Sullivan SG, Kelly H. Stratified Estimates of Influenza Vaccine Effectiveness by Prior Vaccination: Caution Required. *Clinical Infectious Diseases*. 2013;57(3):474-476.
98. McLean HQ, Thompson MG, Sundaram ME, et al. Impact of Repeated Vaccination on Vaccine Effectiveness Against Influenza A(H3N2) and B During 8 Seasons. *Clinical Infectious Diseases*. 2014;59(10):1375-1385.

Chapter 5. Variations in seasonal influenza vaccine effectiveness due to study characteristics: A systematic review and meta-analysis of test-negative design studies

Preface

The previous chapter (Chapter 4) explored variability in SIV effectiveness across geographical regions, study population characteristics such as age, and the level of VAS. SIV effectiveness estimates from influenza surveillance networks also suggestively vary depending on the methods of estimation; for example, source of vaccination information, respiratory specimen swab time relative to symptom onset, and covariate adjustments. However, the evidence has largely conflicted. This chapter presents a published study that explored this problem.

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Abstract

Background: Study characteristics influence vaccine effectiveness (VE) estimation. We examined the influence of some of these on seasonal influenza VE estimates from test-negative design (TND) studies.

Methods: We systematically searched bibliographic databases and websites for full-text publications of TND studies on VE against laboratory-confirmed seasonal influenza in outpatients after the 2009 pandemic influenza. We followed the Cochrane Handbook for Systematic Reviews of Interventions guidelines. We examined influence of source of vaccination information, respiratory specimen swab time, and covariate adjustment on VE. We calculated pooled adjusted VE against A(H1N1)pdm09 and A(H3N2) influenza subtypes, influenza B, and all influenza, using an inverse variance, random-effects model.

Results: We included 70 full-text articles. Pooled VE against A(H1N1)pdm09 and A(H3N2) influenza subtypes, influenza B, and all influenza was higher for studies that used self-reported vaccination than for those that used medical records. Pooled VE was higher with respiratory specimen collection ≤7 days vs. ≤4 days of symptom onset, but the opposite was observed for A(H1N1)pdm09. Pooled VE was higher for studies that adjusted for age but not for medical conditions compared with those that adjusted for both. There was however a lack of statistical significance in almost all differences in pooled VE between compared groups.

Conclusions: The available evidence is not strong enough to conclude that influenza VE from TND studies varies by source of vaccination information, respiratory specimen swab time, and adjustment for age/medical conditions. The evidence is, however, indicative that these factors ought to be considered while designing or evaluating TND studies of influenza VE.

Introduction

Vaccination is the most effective prevention for seasonal influenza. Observational studies, rather than randomised controlled trials, are used to examine seasonal influenza vaccine effectiveness (VE) due to feasibility and ethical considerations. Continuous changes that occur in influenza viruses (antigenic drift)[1] mean that influenza vaccines have to be re-formulated every influenza season and that vaccine virus strains may be mismatched with circulating virus strains. Influenza VE studies are conducted each season in many jurisdictions worldwide to assess vaccine performance and to inform subsequent influenza season vaccine development.

Studies on influenza VE often have differences in their design. Studies approach participants' recruitment differently and influenza vaccination status may be determined by either self-report or medical record ascertained. Clinic presentation and timing of respiratory specimen swab collection differ across study participants. The characteristics of study participants, such as age and health status, also vary and may impact VE.[2] Adjustment in analysis of VE varies across studies, and adjustment for specific potential confounders such as age and medical conditions may lead to differences in VE estimations. Due to these variations and other factors, influenza VE estimates vary between jurisdictions.

The test-negative design (TND), an observational study design type, is an increasingly popular design for estimating influenza VE.[3, 4] In a TND study, patients presenting with influenza-like symptoms are tested for influenza. Those with a positive test result become the cases and those with a negative test result become the controls. Influenza VE (represented as a percentage) is calculated as one minus the adjusted ratio of the odds of vaccination in those with positive test results, to the odds of vaccination in those with negative test results, multiplied by 100. The TND has been credited with reducing biases due to differential healthcare-seeking

behaviour between vaccinated and unvaccinated individuals, and differential misclassification of influenza infection status.[3] However, if stringent methods for study participants' enrolment and influenza testing are not applied, the TND may fail to correct for differential healthcare-seeking behaviour among the vaccinated and the unvaccinated individuals.[5]

We systematically identified, critically appraised, and summarised the findings of published TND studies that examined seasonal influenza VE in primary care settings since the 2009 pandemic influenza. We conducted a systematic review and meta-analysis following the Cochrane Handbook for Systematic Reviews of Interventions guidelines,[6] and we reported our findings following the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.[7]

Methods

This was a systematic literature review with meta-analysis. The methods are partly described in Chapter 2. Literature was searched from January 2011; initially, in April 2017 and the search was subsequently updated in July 2018. Corresponding authors of regional influenza surveillance studies were contacted to check if any relevant publications were missed. The outcomes of interest were adjusted influenza VE against the A(H1N1)pdm09, A(H3N2), influenza B, and all influenza.

Data analysis

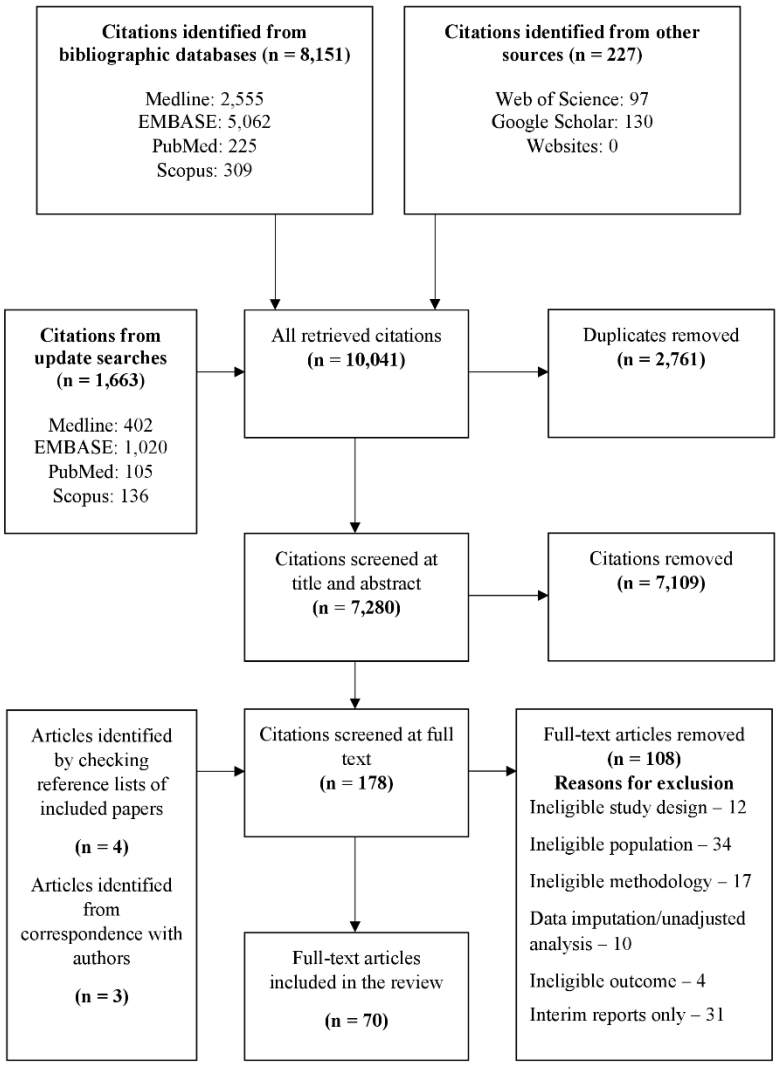
The main study characteristics were synthesised in tabular form and the reported multivariable adjusted influenza VE estimates and their associated 95% CIs were pooled using inverse variance, random effects models implemented in STATA (version 13; StataCorp LP, Texas, USA). Heterogeneity between the pooled adjusted VE estimates was assessed and quantified

statistically using the I-squared statistic (I^2).[8] Chi-square statistic (χ^2) was used to assess the statistical significance (p-value) of the difference between two groups of pooled adjusted results. Publication bias was assessed (where appropriate) visually using funnel plots, and, statistically, using the Egger's regression test.[9] Subgroup analysis was conducted according to the source of participants' influenza vaccination status, respiratory specimen swab time, and whether studies included age or age and medical conditions in their multivariable adjustment models. The subgroup analyses were conducted for all patients, and for each of under 5 years, 5 to 17 years, 18 to 49 years, 50 to 64 years, and ≥65 years age groups. Only results for age groups that clearly fall within these predefined age groups without overlapping with another age group were included.

Results

From a total of 10,041 identified citations, 70 full-text articles met our eligibility criteria (**Figure 16**).[10-79]

Figure 16: Modified PRISMA flowchart of the selection of the included articles (for study 3).



The main characteristics of these articles are summarised in **Table 7**. There were 11 articles each from the USA and Spain, eight articles from Australia, seven articles from the I-MOVE group (involving multiple European countries), and six articles each from the United Kingdom and Canada. There were three articles from China, and two articles each from Germany, Israel, Netherlands, Romania, and South Africa. One article each was from Austria, Croatia, Italy, Japan, New Zealand, Portugal, Taiwan, and Turkey. The sample size from the studies in these articles ranged from 197 to 11,430 participants. All the studies were funded by non-industry sources, and one study received funding from both industry and non-industry sources.

Table 7: Summary of the main characteristics of the included studies (for study 3).

Study	Country	Influenza season (Study period)	Respiratory specimen (Diagnostic test)	Number of participants	Circulating Influenza type(s)	Dominant Influenza type	VE outcomes assessed
Kissling et al. (2011)[10]	Europe	2010/11	Nasal or throat swab (PCR & Culture)	3,254	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza A(H1N1)pdm09 Influenza B
Jimenez – Jorge et al. (2012)[11]	Spain	2010/11	Not reported (PCR)	1,369	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza A(H1N1)pdm09 Influenza B
Fielding et al. (2012)[12]	Australia	2011	Nose and/or throat swab (PCR)	529	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09 – first half, A(H3N2) – mid to latter season, Influenza B – throughout	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Treanor et al. (2012)[13]	USA	2010/11	Nasal and throat swabs (children aged <2 years provided nasal swabs only) (PCR)	4,757	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza A(H1N1)pdm09 A(H3N2) Influenza A Influenza B
Skowronski et al. (2012)[14]	Canada	2010/11	Nasal/nasopharyngeal specimen (PCR)	1,718	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	All influenza A(H1N1)pdm09 A(H3N2) Influenza A Influenza B
Pitigoi et al. (2012)[15]	Romania	2010/11	Not reported (PCR)	255	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09 & Influenza B	All influenza A(H1N1)pdm09 Influenza B
Castilla et al. (2013)[16]	Spain	2011/12	Nasopharyngeal and pharyngeal swabs (PCR)	588	A(H3N2), Influenza B	A(H3N2)	All influenza
Kelly et al. (2013)[17]	Australia	2010 & 2011	Combined nose and throat swab specimens (nose swab specimen were only obtained from children aged <2 years) (PCR)	309 (2010) 398 (2011)	A(H1N1)pdm09, A(H3N2), Influenza B	2010 A(H1N1)pdm09, 2011 A(H3N2)	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Sullivan et al. (2013)[18]	Australia	2010, 2011 & 2012	Not reported (PCR)	420 (2010) 630 (2011) 678 (2012)	A(H1N1)pdm09, A(H3N2), Influenza B	2010 A(H1N1)pdm09, 2011 Influenza B, 2012 A(H3N2)	All influenza
Martínez – Baz et al. (2013)[19]	Spain	2010/11	Nasopharyngeal swabbing (PCR)	530	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza

Kissling et al. (2013)[20]	Europe	2011/12	Nasopharyngeal swab (PCR & Culture)	4,362	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	A(H3N2)
Jimenez – Jorge et al. (2013)[21]	Spain	2011/12	Not reported (PCR & Culture)	378	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	All influenza A(H3N2)
Pebody et al. (2013)[22]	UK	2011/12	Respiratory samples (PCR)	3,560	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	A(H3N2)
Bateman et al. (2013)[23]	USA	2010/11	Nasal and oropharyngeal swab (PCR)	1,549	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	A(H1N1)pdm09 A(H3N2) Influenza A
Englund et al. (2013)[24]	Germany	2010/11	Nasal or pharyngeal swabs or nasopharyngeal aspirates (PCR)	1,866	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza A(H1N1)pdm09 Influenza B
Lo et al. (2013)[25]	Taiwan	2011/12	Throat or nasal swabs (PCR & Culture)	918	A(H1N1)pdm09, A(H3N2), Influenza B	Influenza B	All influenza Influenza A Influenza B
Pebody et al. (2013)[26]	UK	2010/11	Mouth swab (PCR)	7121	A(H1N1)pdm09, Influenza B	A(HINI)pdm09	A(H1N1)pdm09 Influenza B
Sullivan et al. (2014)[27]	Australia	2012	Nasal and throat samples (PCR)	600	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	All influenza A(H3N2)
Levy et al. (2014)[28]	Australia	2010 to 2012	Two nose and one throat swab (PCR)	448 (2010) 351 (2011) 1,361 (2012)	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09 in 2010 & 2011, A(H3N2) in 2012	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Ohmit et al. (2014)[29]	USA	2011/12	Throat swab and nasal swab (or nasal swab only in patients aged <2 years) (PCR)	4,771	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	All influenza A(H1N1)pdm09 A(H3N2) Influenza A Influenza B
Kissling et al. (2014)[30]	Europe	2012/13	Nasopharyngeal swab (PCR & Culture)	6,609	A(H1N1)pdm09, A(H3N2), Influenza B	Influenza B	A(H1N1)pdm09 A(H3N2) Influenza B
Suzuki et al. (2014)[31]	Japan	2011/12	Nasopharyngeal swab (PCR)	309	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	All influenza Influenza A
Skowronski et al. (2014)[32]	Canada	2011/12	Nasal/nasopharyngeal swabs (PCR)	1,507	A(H1N1)pdm09, A(H3N2), Influenza B	Influenza B	All influenza A(H1N1)pdm09 A(H3N2) Influenza A Influenza B
Savulescu et al. (2014)[33]	Spain	2010/11	Not reported (PCR & Culture)	5,057	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09 & Influenza B	A(H1N1)pdm09 Influenza B

Nunes et al. (2014)[34]	Portugal	2012/13	Nasopharyngeal swab or a combined nasopharyngeal and oropharyngeal swab (PCR & Culture)	335	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza
Skowronski et al. (2014)[35]	Canada	2012/13	Nasal or nasopharyngeal swabs (PCR)	1,501	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	All influenza A(H1N1)pdm09 A(H3N2) Influenza A Influenza B
Yang et al. (2014)[36]	China	2012/13	Pharyngeal swabs (Culture)	1,998	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza A(H1N1)pdm09 A(H3N2)
Andrews et al. (2014)[37]	UK	2012/13	Not reported (PCR)	3,286	A(H1N1)pdm09, A(H3N2), Influenza B	Influenza B	A(H1N1)pdm09 A(H3N2) Influenza A Influenza B
McAnerney et al. (2015)[38]	South Africa	2010 to 2013	Nasopharyngeal swab (PCR)	5,344	A(H1N1)pdm09, A(H3N2), Influenza B	2010 – Influenza B, 2011 – A(H1N1)pdm09, 2012 – A(H3N2), 2013 – A(H1N1)pdm09	All influenza
Pitigoi et al. (2015)[39]	Romania	2012/13	Not reported (PCR)	197	A(H1N1)pdm09, A(H3N2), Influenza B	Influenza B	All influenza A(H1N1)pdm09
Valenciano et al. (2015)[40]	Europe	2013/14	Nasopharyngeal swab (PCR)	3,020	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	A(H1N1)pdm09
Helmeke et al. (2015)[41]	Germany	2012/13	Throat or nasopharyngeal swab (PCR)	834	A(H1N1)pdm09, A(H3N2), Influenza B	Influenza B	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Carville et al. (2015)[42]	Australia	2013	Nose or throat swab (PCR)	262	A(H1N1)pdm09, A(H3N2), Influenza B	Influenza A & B	All influenza A(H1N1)pdm09 Influenza B
Chen et al. (2015)[43]	USA	2010/11 & 2011/12	One nasal and one throat swab (PCR)	927	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza
McLean et al. (2015)[44]	USA	2012/13	Nasal and throat specimens (for children age <2 years, only nasal specimens) (PCR)	6,452	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	All influenza A(H3N2)

Jimenez – Jorge et al. (2015)[45]	Spain	2010/11, 2011/12 & 2012/13	Nasal or nasopharyngeal (PCR & Culture)	2010/11 (3,180:SISS, 1,369:cycEVA) 2011/12 (3,484:SISS, 1,446:cycEVA) 2012/13 (3,357:SISS, 1,432:cycEVA)	A(H1N1)pdm09, A(H3N2), Influenza B	2010/11 A(H1N1)pdm09, 2011/12 A(H3N2), 2012/13 Influenza B	A(H1N1)pdm09 A(H3N2) Influenza B
Jimenez – Jorge et al. (2015)[46]	Spain	2010/11, 2011/12, 2012/13 & 2013/14	Nasal or nasopharyngeal (PCR & Culture)	(cycEVA)	A(H1N1)pdm09, A(H3N2), Influenza B	2010/11 A(H1N1)pdm09, 2011/12 A(H3N2), 2012/13 Influenza B, 2013/14 A(H3N2) & A(H1N1)pdm09	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Kurecic – Filipovic et al. (2015)[47]	Croatia	2010/11	Not reported (PCR)	495	A(H1N1)pdm09, Influenza B	A(H1N1)pdm09	All influenza A(H1N1)pdm09
Martinez – Baz et al. (2015)[48]	Spain	2012/13	Nasopharyngeal and pharyngeal swabs (PCR)	522	A(H1N1)pdm09, A(H3N2), Influenza B	Influenza B	All influenza Influenza B
Skowronski et al. (2015)[49]	Canada	2013/14	Nasal/nasopharyngeal specimens (PCR)	1,700	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza A(H1N1)pdm09
Pebody et al. (2015)[50]	UK	2014/15	Not reported (PCR)	2,931	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	All influenza A(H3N2) Influenza A Influenza B
Gherasim et al. (2016)[51]	Spain	2014/15	Not reported (PCR)	5,044	A(H3N2), Influenza B	A(H3N2)	A(H3N2) Influenza B
Fielding et al. (2016)[52]	Australia	2015	Nose/throat swabs (PCR)	2,443	A(H1N1)pdm09, A(H3N2), Influenza B	Influenza B	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Pebody et al. (2016)[53]	UK	2015/16	Respiratory samples (PCR)	3,841	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza A(H1N1)pdm09 Influenza B
Rizzo et al. (2016)[54]	Italy	2014/15	Nasal or throat swab (PCR)	1,193	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09 & A(H3N2)	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Castilla et al. (2016)[55]	Spain	2014/15	Double swabs, nasopharyngeal and pharyngeal (PCR)	660	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2) & Influenza B	All influenza A(H3N2) Influenza B

Redlberger – Fritz et al. (2016)[56]	Austria	2014/15	Nasopharyngeal swabs (PCR)	815	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Thompson et al. (2016)[57]	USA	2011/12 & 2012/13	Nasal and throat specimens (or nasal specimens only for children aged <2 years) (PCR)	1,441 (2011/12) 1,327 (2012/13)	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2) in both seasons	All influenza A(H3N2) Influenza B
Pierse et al. (2016)[58]	New Zealand	2014	Nasopharyngeal or throat swab (PCR)	1,154	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)	All influenza A(H1N1)pdm09 A(H3N2) Influenza A Influenza B
Van Doorn et al. (2017)[59]	Netherlands	2010/11, 2011/12, 2012/13 & 2013/14	Nose and throat swabs (PCR & Culture)	Unclear	A(H1N1)pdm09, A(H3N2), Influenza B	2010/11 A(H1N1)pdm09, 2011/12, 2012/13 & 2013/14 A(H3N2)	All influenza
Kelly et al. (2016)[60]	Australia	2011, 2012 & 2013	Not reported (PCR)	642 (2011) 684 (2012) 354 (2013)	A(H1N1)pdm09, A(H3N2), Influenza B	Not reported	All influenza
Wang et al. (2016)[61]	China	2011/12	Nasopharyngeal specimen (PCR)	668	Not reported	Not reported	All influenza
Cowling et al. (2016)[62]	USA	2010/11, 2011/12 & 2012/13	Nasopharyngeal, oropharyngeal or nasal swab (PCR)	4,208-2010/11 2,164-2011/12 4,278-2012/13	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09, A(H3N2) & influenza B in 2010/11, A(H3N2) in 2011/12, A(H3N2) & influenza B in 2012/13	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Skowronski et al. (2016)[63]	Canada	2014/15	Nasal/nasopharyngeal specimens	1,930	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	All influenza A(H3N2) Influenza B
Zimmerman et al. (2016)[64]	USA	2014/15	Nasal and throat swabs (children aged <2 years provided nasal swabs only) (PCR)	9,311	A(H3N2), Influenza B	A(H3N2)	All influenza A(H3N2)
Gaglani et al. (2016)[65]	USA	2013/14	Combined nose and throat swab specimens (nose swab specimen were only obtained from children aged <2 years) (PCR)	5,637	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	A(H1N1)pdm09

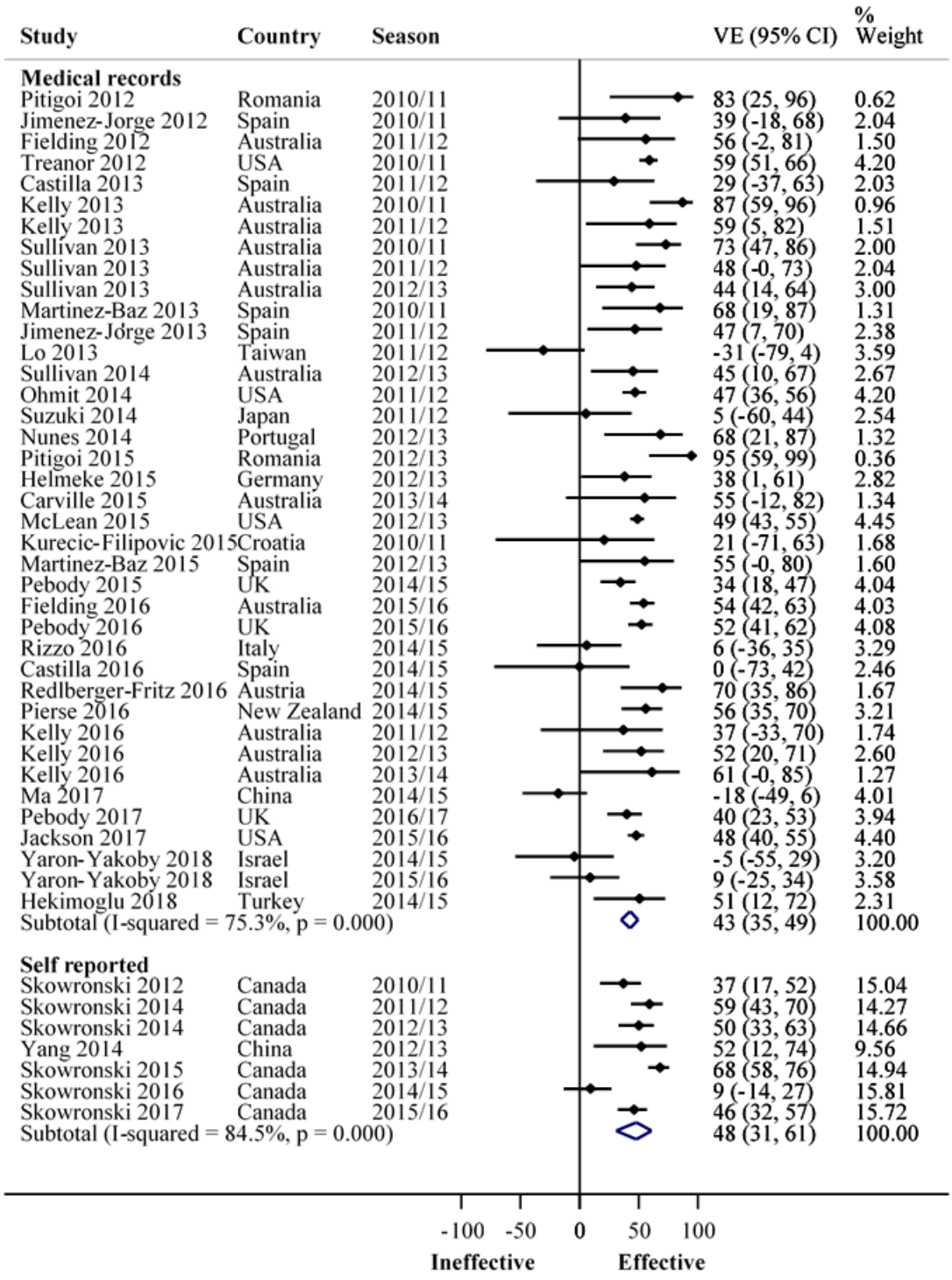
Valenciano et al. (2016)[66]	Europe	2014/15	Nasopharyngeal specimens (PCR)	6,524	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	A(H1N1)pdm09 A(H3N2) Influenza B
McAnerney et al. (2017)[67]	South Africa	2015	Throat and/or nasal swabs (PCR)	899	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Darvishian et al. (2017)[68]	Netherlands	2010/11, 2011/12 & 2012/13	Throat swab and nose swab (PCR)	Not reported	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2) in 2011/12, Influenza B in 2012/13, A(H3N2) in 2013/14, Influenza B in 2010/11	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Ma et al. (2017)[69]	China	2014/15	Oral pharyngeal swab (PCR)	9,297	A(H3N2), Influenza B	A(H3N2)	All influenza A(H3N2) Influenza B
Pebody et al. (2017)[70]	UK	2016/17	Not reported (PCR)	2,881	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2)	All influenza Influenza A A(H3N2) Influenza B
Skowronski et al. (2017)[71]	Canada	2015/16	Nasal/nasopharyngeal swab (PCR)	2,008	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza Influenza A A(H1N1)pdm09 A(H3N2) Influenza B
Jackson et al. (2017)[72]	USA	2015/16	Nasal/oropharyngeal swab (PCR)	6,879	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Gherasim et al. (2017)[73]	Spain	2015/16	Not reported (PCR & Culture)	661	A(H1N1)pdm09, Influenza B	Influenza B	A(H1N1)pdm09 Influenza B
Stein et al. (2018)[74]	Israel	2016/17	Nasal-throat swab (PCR)	1,088	A(H1N1)pdm09, A(H3N2)A, Influenza B	A(H3N2)	A(H3N2)
Yaron-Yakoby et al. (2018)[75]	Israel	2014/15	Nose and throat swabs (PCR)	1,005 (2014/15) 1,658 (2015/16)	A(H1N1)pdm09, A(H3N2), Influenza B	A(H3N2) in 2014/15, A(H1N1)pdm09 & Influenza B in 2015/16	All influenza and A(H3N2) in 2014/15 All influenza, A(H1N1)pdm09 and Influenza B in 2015/16
Poehling et al. (2018)[76]	USA	2015/16	Nasal swab (PCR)	1,012	A(H1N1)pdm09, Influenza B	A(H1N1)pdm09	All influenza A(H1N1)pdm09 Influenza B
Valenciano et al. (2018)[77]	Europe	2011/12 – 2016/17	Nasopharyngeal swab (PCR)	Not clear	A(H1N1)pdm09, Influenza B (2015/16) A(H3N2) (2016/17)	A(H3N2)	A(H1N1)pdm09 A(H3N2) Influenza B

Hekimoglu et al. (2018)[78]	Turkey	2014/15	Nasal, nasopharyngeal, throat, nasal plus throat, nasopharyngeal plus throat, nasal plus nasopharyngeal (PCR)	2,561	A(H1N1)pdm09, A(H3N2), Influenza B	Influenza B	All influenza A(H1N1)pdm09 A(H3N2) Influenza B
Kissling et al. (2018)[79]	Europe	2015/16	Nasopharyngeal or combined nasopharyngeal & oropharyngeal specimens (PCR)	11,430	A(H1N1)pdm09, A(H3N2), Influenza B	A(H1N1)pdm09 & Influenza B	A(H1N1)pdm09 Influenza B

Pooled adjusted VE by method of confirmation of vaccination status

Although not statistically significant, we observed a 10% higher pooled VE against A(H1N1)pdm09 (p=0.191), 7% against A(H3N2) (p=0.626), and 5% against both influenza B (p=0.529) and all influenza (p=0.554) (**Figure 17**), for self-reported vaccination compared with medical records vaccination confirmation (**Table 8**). Almost all of the studies with self-reported vaccination were, however, from one research group in Canada. More of the studies with self-reported vaccination compared with those with medical records vaccination confirmation adjusted for both age and medical conditions. 0% (for A(H1N1)pdm09), 20% (for A(H3N2), and influenza B) and 14% (for all influenza) of the studies with self-reported vaccination were from seasons in which vaccine virus strains were antigenically dissimilar to the circulating strains. In contrast, 8.3% (for A(H1N1)pdm09), 30.8% (for A(H3N2)), 23.1% (for influenza B) and 16% (for all influenza) of the studies with medical records vaccination confirmation were from seasons in which vaccine virus strains were antigenically dissimilar. Similar observations were made against A(H1N1)pdm09 in 18 to 49 year-olds and against all influenza in ≥65 year-olds (**Appendix 15**).

Figure 17: Forest plot of adjusted VE against all influenza by confirmation of vaccination status.



VE = vaccine effectiveness; CI = confidence interval

Table 8: Pooled adjusted VE for all study participants irrespective of age (for study 3).

Influenza types and subtypes Analysed subgroups	Number of studies	Pooled VE across all seasons (95% CI)	I-squared statistic (%)	Publication bias (Egger's test p-value)
A(H1N1)pdm09				
Vaccination status: Medical records	24	52 (45-58)	32.7	0.031
Vaccination status: Self-reported	6	62 (46-73)	55.0	N/A
Respiratory specimen swab: ≤7 days	39	54 (49-58)	39.5	0.022
Respiratory specimen swab: ≤4 days	7	59 (47-69)	0.0	N/A
Adjusted age	26	57 (51-63)	32.1	0.034
Adjusted age & medical conditions	20	53 (46-59)	43.6	0.148
A(H3N2)				
Vaccination status: Medical records	26	25 (15-34)	55.0	0.988
Vaccination status: Self-reported	5	32 (-0-53)	76.9	N/A
Respiratory specimen swab: ≤7 days	35	28 (22-34)	57.5	0.301
Respiratory specimen swab: ≤4 days	8	18 (-26-47)	63.3	N/A
Adjusted age	23	34 (28-40)	11.5	0.794
Adjusted age & medical conditions	20	21 (10-30)	70.5	0.997
Influenza B				
Vaccination status: Medical records	26	43 (31-52)	70.3	0.701
Vaccination status: Self-reported	5	48 (36-59)	28.2	N/A
Respiratory specimen swab: ≤7 days	33	48 (43-53)	28.2	0.974
Respiratory specimen swab: ≤4 days	10	38 (4-60)	77.5	0.070
Adjusted age	22	50 (44-56)	26.5	0.893
Adjusted age & medical conditions	21	40 (27-51)	70.7	0.252
All influenza				
Vaccination status: Medical records	39	43 (35-49)	75.3	0.807
Vaccination status: Self-reported	7	48 (31-61)	84.5	N/A
Respiratory specimen swab: ≤7 days	56	46 (41-51)	70.6	0.152
Respiratory specimen swab: ≤4 days	12	38 (15-55)	77.3	0.009
Adjusted age	32	47 (42-52)	56.5	0.477

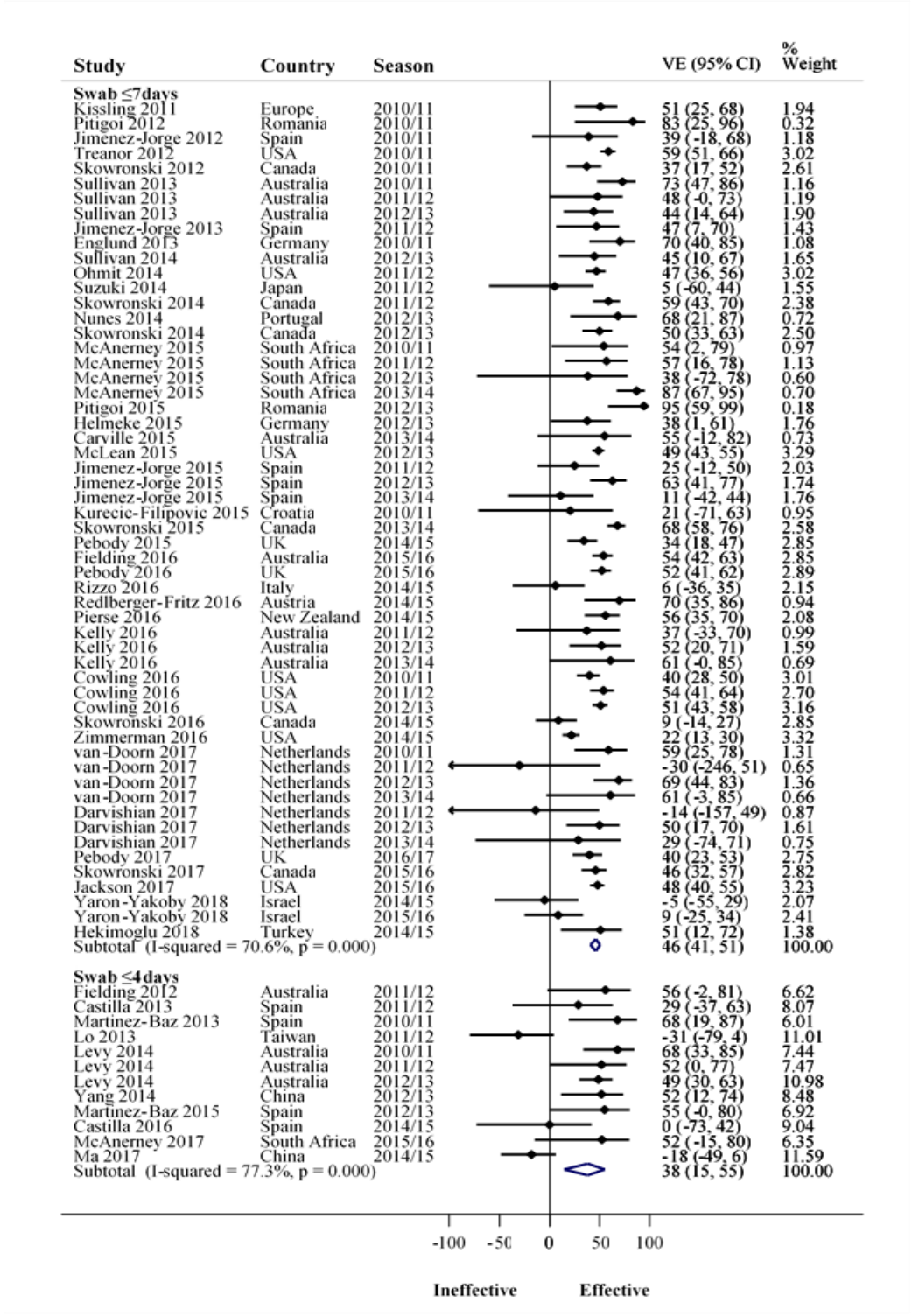
Adjusted age & medical conditions	37	43 (34-51)	79.8	0.184

VE = vaccine effectiveness; CI = confidence interval; N/A = not applicable

Pooled adjusted VE by timing of respiratory specimen swab collection

Despite a lack of statistical significance, we observed a 10% higher pooled adjusted VE against A(H3N2) (p=0.596) and influenza B (p=0.491), and 8% against all influenza (p=0.447) (**Figure 18**), for swab collection ≤7 days compared with ≤4 days of symptom onset (**Table 8**). In contrast, a 5% higher pooled adjusted VE was observed against the A(H1N1)pdm09 (p=0.410) for swab collection ≤4 days compared with swab collection ≤7 days of symptom onset. There was no meaningful difference between studies with swab collection ≤7 days and ≤4 days with regards to adjustment for both age and medical conditions in their analyses. 15% (for influenza B) and 18.5% (for all influenza) of the studies with swab collection ≤7 days were, however, from seasons in which vaccine virus strains were antigenically dissimilar to the circulating strains. In contrast, 22.2% (for influenza B) and 27.3% (for all influenza) of the studies with swab collection ≤4 days were from seasons in which vaccine virus strains were antigenically dissimilar. Similarly, 5% (for A(H1N1)pdm09) of the studies with swab collection ≤7 days were from seasons in which vaccine strains were antigenically dissimilar whereas 0% of the studies with swab collection ≤4 days were from seasons in which vaccine strains were antigenically dissimilar. Evidence was conflicting across age groups (**Appendix 15**).

Figure 18: Forest plot of adjusted VE against all influenza by timing of respiratory specimen swab collection.

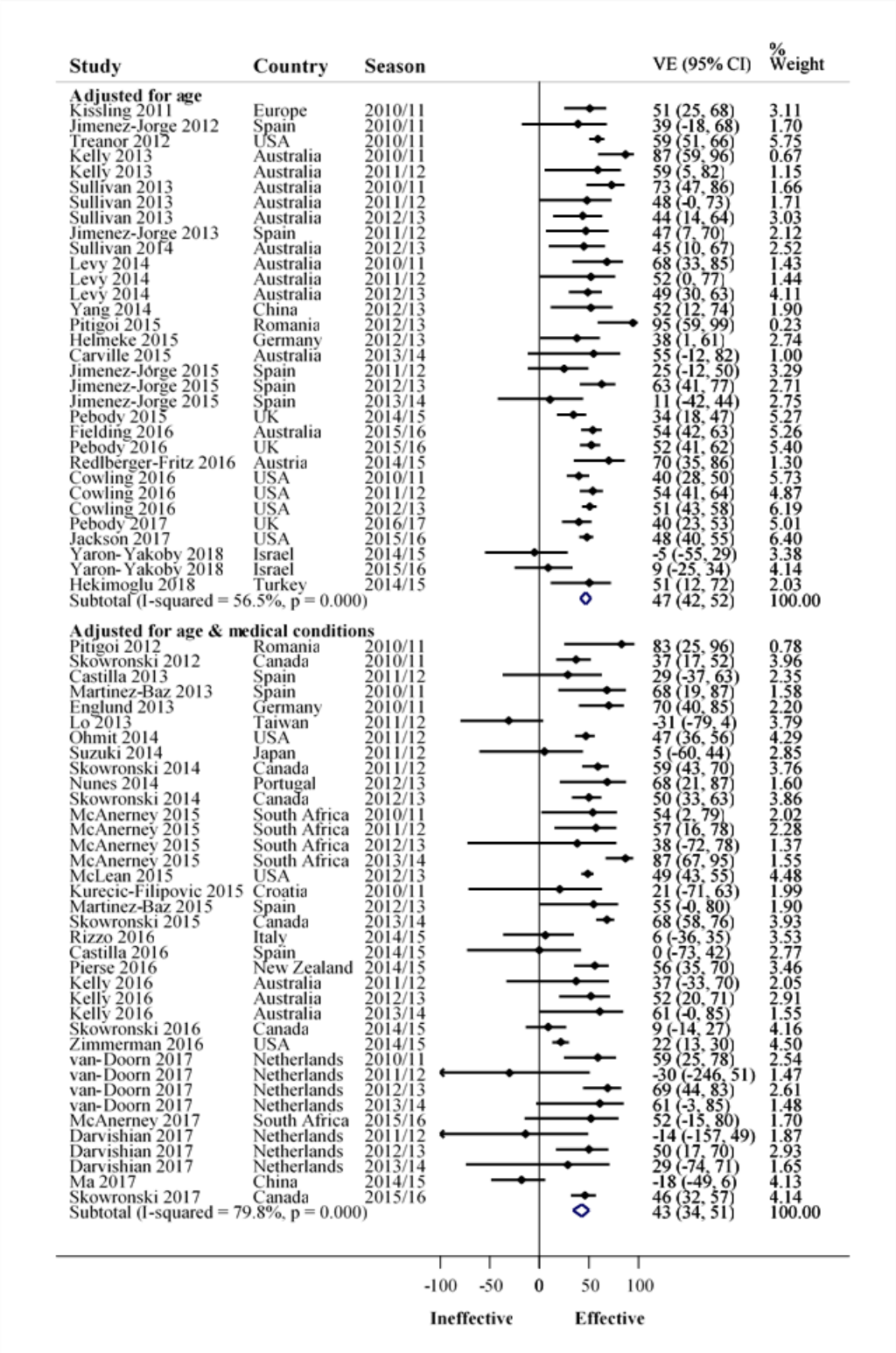


VE = vaccine effectiveness; CI = confidence interval

Pooled adjusted VE by covariate adjustment

Notwithstanding a lack of statistical significance apart from for A(H3N2), we observed a 4% higher pooled adjusted VE against the A(H1N1)pdm09 (p=0.375), 13% against the A(H3N2) (p=0.029), 10% against influenza B (p=0.144), and 4% against all influenza (p=0.427) (**Figure 19**), for studies that included age among the adjusted covariates compared with those that included both age and medical conditions (**Table 8**). 3.8% (for A(H1N1)pdm09), 13% (for A(H3N2)), 13.6% (for influenza B) and 6.7% (for all influenza) of the studies that included age but not medical conditions were, however, from seasons in which vaccine virus strains were antigenically dissimilar to the circulating strains. In contrast, 5.3% (for A(H1N1)pdm09), 36.8% (for A(H3N2)), 20% (for influenza B) and 30.6% (for all influenza) of the studies that included age and medical conditions among the adjusted covariates were from seasons in which vaccine virus strains were antigenically dissimilar. Evidence was conflicting across age groups (**Appendix 15**).

Figure 19: Forest plot of adjusted VE against all influenza by covariate adjustment.



VE = vaccine effectiveness; CI = confidence interval

Discussion

Despite a lack of statistical significance, we observed differences in pooled adjusted influenza VE between sources of influenza vaccination confirmation, respiratory specimen swab timing, and adjustments for two key confounders in study analysis. In our analysis of all study participants (irrespective of age), small differences were found between self-reported and medical record-confirmed influenza vaccinations, with higher pooled VE observed for self-reported vaccination contrary to our expectation. However, almost all of the studies for self-reported vaccination were conducted in Canada and by the same group of researchers. We found substantial differences between respiratory specimen swab time of ≤7 days and ≤4 days, with higher pooled VE observed for swab time of ≤7 days. We also found substantial differences between studies that adjusted for age, and those that adjusted for both age and medical conditions, with higher pooled VE observed for studies that adjusted for age. The above findings differed across age groups.

Studies have found that exposure misclassification can lead to significant bias in VE estimation.[80, 81] Self-reported vaccination is susceptible to recall and social desirability (individuals wanting to present a vaccine compliant image) biases, with the potential for vaccination status misclassification. Smedt and colleagues showed in their simulation study that decreased exposure sensitivity and specificity underestimate true VE when misclassification of exposure (vaccination status) is non-differential, but that, when misclassification is differential, the bias could go in either direction, with the estimated VE deviating largely from the true VE. Compared with vaccination confirmation from medical records, self-reported vaccination usually has a higher sensitivity across various populations,[82, 83] but a lower specificity in some population subgroups.[84, 85] Compared with whites, Hispanics were 2.7 times more likely to claim

receipt of vaccination (self-report) and, compared with younger individuals, self-reported influenza vaccination in the elderly had low specificity.[83] The observed higher pooled adjusted VE for self-reported compared with medical record-confirmed influenza vaccination status in this review, although not expected, may be due to differential misclassification of vaccination status, which Smedt and colleagues showed could either inflate or underestimate the true VE. This becomes more plausible considering that the studies with self-reported vaccination were almost all from Canada and from the same research group. Study centre influence such as characteristics of the study participants, participants' recruitment strategy, and influenza testing may also explain our finding.

Influenza incubation averages two days (ranging from one to four days).[86] To maximise influenza virus detection from respiratory specimens, it is advocated that, ideally, swabs be collected <4 days from influenza-like symptom onset. The longer swab collection is from symptom onset, the less the likelihood of detecting influenza and the greater the potential for false negative testing. Accurate reporting of symptom onset is therefore important since a good TND study is predicated on patient symptom onset of ≤7 days. It will also help minimise outcome misclassification bias. False negative testing among the vaccinated leads to VE overestimation while false negative testing among the unvaccinated leads to VE being underestimated. The observed higher pooled adjusted VE for swab collection of ≤7 days compared with ≤4 days in this review may therefore be due to a higher proportion of false negatives among the ≤7 days swab collection group, although this is not confirmable. Additionally, studies that included ≤4 days swab collection possibly used more stringent swab collection criteria, resulting in reduced precision of VE estimation.

Seasonal influenza VE can vary from person to person. Various individual factors impact the VE,[87] and two main factors (age and medical conditions) are known to play an important role in determining the likelihood that a vaccine will protect a person against influenza and to what extent. Age-dependent patterns in influenza vaccine protection have been reported from season to season, implicating the potential effect of age-related immune response in seasonal influenza VE.[88] For example, VE in the elderly population is reduced because of lower seroconversion rates which arise due to poorer immunological response to vaccination.[89] How well an individual responds to a vaccine may also be determined by the underlying health conditions.[90] The observed higher pooled adjusted VE for studies that included age but not medical conditions compared with those that included both age and medical conditions among adjusted covariates in studies are in line with expectations since adjusting for both age and medical conditions is likely to diminish VE compared with adjusting for age.

It is widely known that antigenic drift can markedly reduce seasonal influenza VE. For example, Flannery (2016) found that VE against A(H3N2) was almost zero for an antigenically drifted genetic group of A(H3N2) viruses, and 44% against a genetic group of A(H3N2) that were antigenically similar to the seasonal vaccine strains.[91] This may explain the observed higher pooled adjusted VE in the compared subgroups with lower proportions of studies in which the seasonal influenza vaccine was antigenically dissimilar to the circulating virus strains. Variations in study design, sample size, vaccine type, and the demographic and temporal patterns underlying VE estimates from the included studies may also explain the variations observed in the pooled adjusted VE between compared groups. This, together with vaccine antigenic similarity with the circulating virus strains, may explain the high heterogeneity in many of the pooled adjusted VE. Where there were adequate numbers of studies for exploration of

heterogeneity using meta-regression, the available covariates tended to be highly collinear thus limiting the usefulness of meta-regression. Secondly, it was impossible to disentangle the effects of vaccine type nor the underlying patient-level variations as the analysis was conducted at study-level and these were not clearly reported in studies.

To our knowledge, our review is the first to evaluate differences in VE due to source of influenza vaccination status, respiratory specimen swab time, and confounder adjustments in statistical models for analysis. Irving et al. (2009) evaluated influenza vaccination status determined by self-report and by a real-time vaccination registry, and found that the sensitivity and specificity of self-reported influenza vaccination compared with vaccination registry records were 95% and 90%, respectively, and that self-reported vaccination status was a sensitive and somewhat specific indicator of actual vaccine status, with misclassification being more common among young people.[82] However, the study did not compare influenza VE from these two sources of vaccination. No reviews seem to have compared seasonal influenza VE by respiratory specimen swab time, and inclusion of main confounders in statistical models for analysis as we have done.

Our decision to include only influenza seasons after the 2009 pandemic influenza may have limited the number of potentially relevant TND studies for this review. However, it allowed us to focus on studies conducted from when public funding of influenza vaccination increased in most Western jurisdictions. It should be noted that some eligible studies conducted during this stated period may not have been published by the time we conducted our literature search, and therefore not included in this review. Despite growing evidence to suggest that VE may be influenced by prior vaccinations,[92, 93] the included studies did not report whether the study participants received previous season's influenza vaccination; hence, we could not assess the

impact on VE estimates in our analyses. Furthermore, due to insufficient data, we could not examine VE against all outcomes for our subgroup analyses and for all age groups. We could also not separate individual study participants' effects from study centre effects (for example, effectiveness of vaccine policies and programmes, participant recruitment strategy, and slight differences in symptom definitions), since the studies were conducted in different jurisdictions with potentially unique jurisdictional characteristics. Finally, we could not assess the reliability of reported estimates from the included studies because we could not ascertain if the studies met all of the assumptions that well-conducted TND studies are expected to meet to ensure that effect size estimates from the studies are not biased.[5] Although many of the studies adjusted for age or age and medical conditions, there were differences in the other covariates adjusted for in the studies. This may have contributed to the high heterogeneity observed in some of our pooled VE estimates.

Our review has many merits. We developed and registered a detailed protocol in PROSPERO prior to the execution of our search strategy, and we fully complied with the Cochrane Handbook for Systematic Reviews of Interventions guidelines throughout the review. We utilised the expertise of a methodologist trained in evidence synthesis literature searching to develop a comprehensive search strategy for the review and this was subsequently reviewed by a professional knowledge synthesis librarian using the PRESS checklist. We searched appropriate bibliographic databases for literature, and properly screened retrieved citations (against the eligibility), following the standards specified in the Cochrane Handbook for Systematic Reviews of Interventions. Where necessary, we requested additional data from the corresponding authors of the included studies, to ensure completeness of the analysed data. We included only studies in which influenza testing was conducted using the gold-standard tests (PCR or viral culture).

Furthermore, we examined variations in seasonal influenza VE across all clinically relevant age groups (<5 years, 5 to <18 years, 18 to 49 years, 50 to 64 years, and ≥65 years). We conducted the review to the highest expected standards, and have reported in accordance with the PRISMA guidelines.

Conclusions

The available evidence from TND studies conducted after the 2009 pandemic influenza is not strong enough to conclude that influenza VE varies by source of vaccination status, respiratory specimen swab time, or adjustment for age/medical conditions. However, the evidence is indicative that these factors should be considered while designing or evaluating influenza VE from this study type. There is the need for researchers to ensure that age and medical conditions are both adjusted for in influenza VE estimations from TND studies, while uniformity in covariate adjustments across studies would help reduce heterogeneity and increase precision of pooled VE.

Declarations

S.M.M has received unrestricted research grants from GlaxoSmithKline, Merck, Sanofi Pasteur, Pfizer and Roche-Assurex for unrelated studies, and fees as an advisory board member for Sanofi Pasteur. The other authors declare that they have no conflicts of interest.

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References

1. Boni MF. Vaccination and antigenic drift in influenza. *Vaccine* 2008; 26: C8-C14.
2. Lorenzo MMG and Fenton MJ. Immunobiology of Influenza Vaccines. *Chest* 2013; 143: 502-510.
3. Jackson ML and Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine* 2013; 31: 2165-2168.
4. Sullivan SG, Tchetgen EJT and Cowling BJ. Theoretical Basis of the Test-Negative Study Design for Assessment of Influenza Vaccine Effectiveness. *Am J Epidemiol* 2016; 184: 345-353.
5. Lewnard JA, Tedijanto C, Cowling BJ, et al. Measurement of Vaccine Direct Effects Under the Test-Negative Design. *Am J Epidemiol* 2018; 187: 2686-2697.
6. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane Collaboration, 2019.
7. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Int J Surg* 2010; 8: 336-341.
8. Higgins JP and Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; 21: 1539-1558.
9. Sterne JA, Egger M and Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001; 323: 101-105.
10. Kissling E, Valenciano M, Cohen JM, et al. I-MOVE Multi-Centre Case Control Study 2010-11: Overall and Stratified Estimates of Influenza Vaccine Effectiveness in Europe. *Plos One* 2011; 6:e27622.
11. Jimenez-Jorge S, Savulescu C, Pozo F, et al. Effectiveness of the 2010-11 seasonal trivalent influenza vaccine in Spain: cycEVA study. *Vaccine* 2012; 30: 3595-3602.
12. Fielding JE, Grant KA, Tran T, et al. Moderate influenza vaccine effectiveness in Victoria, Australia, 2011. *Euro Surveill.* 2012; 17:20115.
13. Treanor JJ, Talbot HK, Ohmit SE, et al. Effectiveness of seasonal influenza vaccines in the United States during a season with circulation of all three vaccine strains. *Clinical Infectious Diseases* 2012; 55: 951-959.

14. Skowronski DM, Janjua NZ, De Serres G, et al. A sentinel platform to evaluate influenza vaccine effectiveness and new variant circulation, Canada 2010-2011 season. *Clin Infect Dis* 2012; 55: 332-342.
15. Pitigoi D, Ivanciuc AE, Necula G, et al. Influenza vaccine effectiveness to prevent medically attended laboratory confirmed influenza during season 2010-2011 in Romania: a case control study. *Rev Romana Med Lab* 2012; 20: 127-134.
16. Castilla J, Martínez-Baz I, Martínez-Artola V, et al. Decline in influenza vaccine effectiveness with time after vaccination, Navarre, Spain, season 2011/12. *Euro Surveill.* 2013; 18:20388.
17. Kelly HA, Sullivan SG, Grant KA, et al. Moderate influenza vaccine effectiveness with variable effectiveness by match between circulating and vaccine strains in Australian adults aged 20-64years, 2007-2011. *Influenza and other Respiratory Viruses* 2013; 7: 729-737.
18. Sullivan SG and Kelly H. Late season interim estimates of influenza vaccine effectiveness reliably predict end of season estimates in Victoria, Australia, 2007 to 2012. *Euro Surveill.* 2013; 18:20605.
19. Martínez-Baz I, Martínez-Artola V, Reina G, et al. Effectiveness of the trivalent influenza vaccine in Navarre, Spain, 2010-2011: A population-based test-negative case-control study. *BMC Public Health* 2013; 13:191.
20. Kissling E, Valenciano M, Larrauri A, et al. Low and decreasing vaccine effectiveness against influenza A(H3) in 2011/12 among vaccination target groups in Europe: Results from the I-MOVE multicentre case-control study. *Euro Surveill.* 2013; 18:20390.
21. Jimenez-Jorge S, de Mateo S, Delgado-Sanz C, et al. Effectiveness of influenza vaccine against laboratory-confirmed influenza, in the late 2011-2012 season in Spain, among population targeted for vaccination. *BMC infectious diseases* 2013; 13:441.
22. Pebody RG, Andrews N, McMenamin J, et al. Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: Evidence of waning intra-seasonal protection. *Euro Surveill.* 2013; 18:20389.
23. Bateman AC, Kieke BA, Irving SA, et al. Effectiveness of monovalent 2009 pandemic influenza A virus subtype H1N1 and 2010-2011 trivalent inactivated influenza vaccines

in Wisconsin during the 2010-2011 influenza season. *Journal of Infectious Diseases* 2013; 207:1262-1269.

24. Englund H, Campe H and Hautmann W. Effectiveness of trivalent and monovalent influenza vaccines against laboratory-confirmed influenza infection in persons with medically attended influenza-like illness in Bavaria, Germany, 2010/2011 season. *Epidemiol Infect* 2013; 141: 1807-1815.
25. Lo YC, Chuang JH, Kuo HW, et al. Surveillance and Vaccine Effectiveness of an Influenza Epidemic Predominated by Vaccine-Mismatched Influenza B/Yamagata-Lineage Viruses in Taiwan, 2011-12 Season. *PLoS ONE* 2013; 8:e58222.
26. Pebody R, Andrews N, Fleming D, et al. Age-specific vaccine effectiveness of seasonal 2010/2011 and pandemic influenza A (H1N1) 2009 vaccines in preventing influenza in the United Kingdom. *Epidemiology and infection* 2013; 141:620-630.
27. Sullivan SG, Komadina N, Grant K, et al. Influenza vaccine effectiveness during the 2012 influenza season in Victoria, Australia: Influences of waning immunity and vaccine match. *Journal of Medical Virology* 2014; 86:1017-1025.
28. Levy A, Sullivan SG, Tempone SS, et al. Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012. *Vaccine* 2014; 32 6312-6318.
29. Ohmit SE, Thompson MG, Petrie JG, et al. Influenza vaccine effectiveness in the 2011-2012 season: Protection against each circulating virus and the effect of prior vaccination on estimates. *Clinical Infectious Diseases* 2014; 58:319-327.
30. Kissling E, Valenciano M, Buchholz U, et al. Influenza vaccine effectiveness estimates in Europe in a season with three influenza type/subtypes circulating: The I-MOVE multicentre case-control study, influenza season 2012/13. *Euro Surveill.* 2014; 19:20701.
31. Suzuki M, Minh LN, Yoshimine H, et al. Vaccine effectiveness against medically attended laboratory-confirmed influenza in Japan, 2011-2012 season. *PLoS ONE* 2014; 9:e88813.
32. Skowronski DM, Janjua NZ, Sabaiduc S, et al. Influenza A/subtype and B/lineage effectiveness estimates for the 2011-2012 trivalent vaccine: Cross-season and cross-lineage protection with unchanged vaccine. *Journal of Infectious Diseases* 2014; 210: 126-137.

33. Savulescu C, Jiménez-Jorge S, Delgado-Sanz C, et al. Higher vaccine effectiveness in seasons with predominant circulation of seasonal influenza A(H1N1) than in A(H3N2) seasons: Test-negative case-control studies using surveillance data, Spain, 2003-2011. *Vaccine* 2014; 32:4404-4411.
34. Nunes B, Machado A, Guiomar R, et al. Estimates of 2012/13 influenza vaccine effectiveness using the case test-negative control design with different influenza negative control groups. *Vaccine* 2014; 32:4443-4449.
35. Skowronski DM, Janjua NZ, De Serres G, et al. Low 2012–13 Influenza Vaccine Effectiveness Associated with Mutation in the Egg-Adapted H3N2 Vaccine Strain Not Antigenic Drift in Circulating Viruses. *PLoS ONE* 2014; 9:e92153.
36. Yang P, Thompson MG, Ma C, et al. Influenza vaccine effectiveness against medically-attended influenza illness during the 2012-2013 season in Beijing, China. *Vaccine* 2014; 32:5285-5289.
37. Andrews N, McMenamin J, Durnall H, et al. Effectiveness of trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2012/13 end of season results. *Euro Surveill.* 2014; 19:20851.
38. McAnerney JM, Walaza S, Cohen AL, et al. Effectiveness and knowledge, attitudes and practices of seasonal influenza vaccine in primary healthcare settings in South Africa, 2010-2013. *Influenza and other Respiratory Viruses* 2015; 9:143-150.
39. Pitigoi D, Necula G, Alexandrescu V, et al. Circulating influenza viruses and the effectiveness of seasonal influenza vaccine in Romania, season 2012-2013/Virusurile gripale circulante și eficacitatea vaccinului gripal sezonier în România, în sezonul 2012-2013. *Romanian Review of Laboratory Medicine* 2015; 23:9-20.
40. Valenciano M, Kissling E, Reuss A, et al. The European I-MOVE Multicentre 2013-2014 Case-Control Study. Homogeneous moderate influenza vaccine effectiveness against A(H1N1)pdm09 and heterogenous results by country against A(H3N2). *Vaccine* 2015; 33:2813-2822.
41. Helmeke C, Gräfe L, Irmscher HM, et al. Effectiveness of the 2012/13 trivalent live and inactivated influenza vaccines in children and adolescents in Saxony-Anhalt, Germany: A test-negative case-control study. *PLoS ONE* 2015; 10:e0122910.

42. Carville KS, Grant KA, Sullivan SG, et al. Understanding influenza vaccine protection in the community: An assessment of the 2013 influenza season in Victoria, Australia. *Vaccine* 2015; 33:341-345.
43. Chen Q, Griffin MR, Nian H, et al. Influenza vaccine prevents medically attended influenza-associated acute respiratory illness in adults aged ≥ 50 Years. *Journal of Infectious Diseases* 2015; 211:1045-1050.
44. McLean HQ, Thompson MG, Sundaram ME, et al. Influenza Vaccine Effectiveness in the United States During 2012–2013: Variable Protection by Age and Virus Type. *Journal of Infectious Diseases* 2015; 211:1529-1540.
45. Jimenez-Jorge S, de Mateo S, Delgado-Sanz C, et al. Estimating influenza vaccine effectiveness in Spain using sentinel surveillance data. *Euro Surveill.* 2015; 20:21187.
46. Jimenez-Jorge S, Pozo F and Larrauri A. Interim influenza vaccine effectiveness: A good proxy for final estimates in Spain in the seasons 2010-2014. *Vaccine* 2015; 33:3276-3280.
47. Filipovic SK, Gjenero-Margan I, Kissling E, et al. Influenza vaccine effectiveness estimates in Croatia in 2010-2011: a season with predominant circulation of A(H1N1)pdm09 influenza virus. *Epidemiology and Infection* 2015; 143:2596-2603.
48. Martinez-Baz I, Navascues A, Pozo F, et al. Influenza vaccine effectiveness in preventing inpatient and outpatient cases in a season dominated by vaccine-matched influenza B virus. *Human Vaccines and Immunotherapeutics* 2015; 11:1626-1633.
49. Skowronski DM, Chambers C, Sabaiduc S, et al. Integrated Sentinel Surveillance Linking Genetic, Antigenic, and Epidemiologic Monitoring of Influenza Vaccine-Virus Relatedness and Effectiveness During the 2013-2014 Influenza Season. *Journal of Infectious Diseases* 2015; 212:726-739.
50. Pebody R, Warburton F, Andrews N, et al. Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results. *Euro Surveill.* 2015; 20.
51. Gherasim A, Pozo F, de Mateo S, et al. Waning protection of influenza vaccine against mild laboratory confirmed influenza A(H3N2) and B in Spain, season 2014-15. *Vaccine* 2016; 34:2371-2377.

52. Fielding JE, Levy A, Chilver MB, et al. Effectiveness of seasonal influenza vaccine in Australia, 2015: An epidemiological, antigenic and phylogenetic assessment. *Vaccine* 2016; 34:4905-4912.
53. Pebody R, Warburton F, Ellis J, et al. Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-ofseason results. *Euro Surveill.* 2016; 21:30348.
54. Rizzo C, Bella A, Alfonsi V, et al. Influenza vaccine effectiveness in Italy: Age, subtype-specific and vaccine type estimates 2014/15 season. *Vaccine* 2016; 34:3102-3108.
55. Castilla J, Navascues A, Fernandez-Alonso M, et al. Effectiveness of subunit influenza vaccination in the 2014-2015 season and residual effect of split vaccination in previous seasons. *Vaccine* 2016; 34:1350-1357.
56. Redlberger-Fritz M, Kundi M and Popow-Kraupp T. Detailed report on 2014/15 influenza virus characteristics, and estimates on influenza virus vaccine effectiveness from Austria's sentinel physician surveillance network. *PLoS ONE* 2016; 11:e0149916.
57. Thompson MG, Clippard J, Petrie JG, et al. Influenza vaccine effectiveness for fully and partially vaccinated children 6 months to 8 years old during 2011-2012 and 2012-2013: The importance of two priming doses. *Pediatric Infectious Disease Journal* 2016; 35:299-308.
58. Pierse N, Kelly H, Thompson MG, et al. Influenza vaccine effectiveness for hospital and community patients using control groups with and without non-influenza respiratory viruses detected, Auckland, New Zealand 2014. *Vaccine* 2016; 34:503-509.
59. Van Doorn E, Darvishian M, Dijkstra F, et al. Influenza Vaccine Effectiveness Estimates in the Dutch Population from 2003 to 2014: The Test-Negative Design Case-Control Study with Different Control Groups. *Vaccine* 2017; 35:2831-2839.
60. Kelly HA, Lane C and Cheng AC. Influenza vaccine effectiveness in general practice and in hospital patients in Victoria, 2011e2013. *Medical Journal of Australia* 2016; 204: 76.e71-76.
61. Wang Y, Zhang T, Chen L, et al. Seasonal influenza vaccine effectiveness against medically attended influenza illness among children aged 6–59 months, October 2011–September 2012: A matched test-negative case–control study in Suzhou, China. *Vaccine* 2016; 34:2460-2465.

62. Cowling BJ, Feng S, Finelli L, et al. Assessment of influenza vaccine effectiveness in a sentinel surveillance network 2010-13, United States. *Vaccine* 2016; 34:61-66.
63. Skowronski DM, Chambers C, Sabaiduc S, et al. A Perfect Storm: Impact of Genomic Variation and Serial Vaccination on Low Influenza Vaccine Effectiveness During the 2014–2015 Season. *Clinical Infectious Diseases* 2016; 63:21-32.
64. Zimmerman RK, Nowalk MP, Chung J, et al. 2014–2015 Influenza Vaccine Effectiveness in the United States by Vaccine Type. *Clinical Infectious Diseases* 2016; 63:1564-1573.
65. Gaglani M, Pruszynski J, Murthy K, et al. Influenza Vaccine Effectiveness Against 2009 Pandemic Influenza A(H1N1) Virus Differed by Vaccine Type During 2013–2014 in the United States. *Journal of Infectious Diseases* 2016; 213:1546-1556.
66. Valenciano M, Kissling E, Reuss A, et al. Vaccine effectiveness in preventing laboratory-confirmed influenza in primary care patients in a season of co-circulation of influenza A(H1N1)pdm09, B and drifted A(H3N2), I-MOVE Multicentre Case–Control Study, Europe 2014/15. *Euro Surveill.* 2016; 21:pii=30139.
67. McAnerney JM, Walaza S, Tempia S, et al. Estimating vaccine effectiveness in preventing laboratory-confirmed influenza in outpatient settings in South Africa, 2015. *Influenza and other Respiratory Viruses* 2017; 11:177-181.
68. Darvishian M, Dijkstra F, Van Doorn E, et al. Influenza vaccine effectiveness in the Netherlands from 2003/2004 through 2013/2014: The importance of circulating influenza virus types and subtypes. *PLoS ONE* 2017; 12:e0169528.
69. Ma CN, Pan Y, Zhang L, et al. Influenza vaccine effectiveness against medically attended influenza illness in Beijing, China, 2014/15 season. *Hum Vacc Immunother* 2017; 13:2379-2384.
70. Pebody R, Warburton F, Ellis J, et al. End-of-season influenza vaccine effectiveness in adults and children, United Kingdom, 2016/17. *Euro Surveill.* 2017; 22:10-22.
71. Skowronski DM, Chambers C, Sabaiduc S, et al. Beyond Antigenic Match: Possible Agent-Host and Immuno-epidemiological Influences on Influenza Vaccine Effectiveness During the 2015-2016 Season in Canada. *Journal of Infectious Diseases* 2017; 216:1487-1500.

72. Jackson ML, Chung JR, Jackson LA, et al. Influenza Vaccine Effectiveness in the United States during the 2015-2016 Season. *New Engl J Med* 2017; 377:534-543.
73. Gherasim A, Martinez-Baz I, Castilla J, et al. Effect of previous and current vaccination against influenza A(H1N1)pdm09, A(H3N2), and B during the post-pandemic period 2010-2016 in Spain. *PloS ONE* 2017; 12:e0179160.
74. Stein Y, Mandelboim M, Sefty H, et al. Seasonal Influenza Vaccine Effectiveness in Preventing Laboratory-Confirmed Influenza in Primary Care in Israel, 2016-2017 Season: Insights Into Novel Age-Specific Analysis. *Clinical Infectious Diseases* 2018; 66:1383-1391.
75. Yaron-Yakoby H, Sefty H, Pando R, et al. Effectiveness of influenza vaccine in preventing medically-attended influenza virus infection in primary care, Israel, influenza seasons 2014/15 and 2015/16. *Euro Surveill.* 2018; 23:27-37.
76. Poehling KA, Caspard H, Peters TR, et al. 2015-2016 Vaccine Effectiveness of Live Attenuated and Inactivated Influenza Vaccines in Children in the United States. *Clinical Infectious Diseases* 2018; 66:665-672.
77. Valenciano M, Kissling E, larrauri A, et al. Exploring the effect of previous inactivated influenza vaccination on seasonal influenza vaccine effectiveness against medically attended influenza: Results of the European I-MOVE multicentre test-negative case-control study, 2011/2012-2016/2017. *Influenza & Other Respiratory Viruses* 2018; 12:567-581.
78. Hekimoglu CH, Emek M, Avci E, et al. Seasonal Influenza Vaccine Effectiveness in Preventing Laboratory Confirmed Influenza in 2014-2015 Season in Turkey: A Test-Negative Case Control Study. *Balk Med J* 2018; 35:77-83.
79. Kissling E, Valenciano M, Pozo F, et al. 2015/16 I-MOVE/I-MOVE plus multicentre case-control study in Europe: Moderate vaccine effectiveness estimates against influenza A(H1N1)pdm09 and low estimates against lineage-mismatched influenza B among children. *Influenza and Other Respiratory Viruses* 2018; 12:423-437.
80. De Smedt T, E M, D M, et al. Bias due to differential and non-differential disease- And exposure misclassification in studies of vaccine effectiveness. *PLoS ONE* 2018; 13:e0199180.

81. Jackson ML, Phillips CH, Benoit J, et al. The impact of selection bias on vaccine effectiveness estimates from test-negative studies. *Vaccine* 2018; 36:751-757.
82. Irving S, J D, D S, et al. Evaluation of self-reported and registry-based influenza vaccination status in a Wisconsin cohort. *Vaccine* 2009; 27:6546-6549.
83. Rolnick S, E P, J N, et al. Self-report compared to electronic medical record across eight adult vaccines: Do results vary by demographic factors? *Vaccine* 2013; 31:3928-3935.
84. Jackson ML. Use of self-reported vaccination status can bias vaccine effectiveness estimates from test-negative studies. *Vaccines* 2019; 1:100003.
85. Zimmerman R, M R, J J, et al. Sensitivity and specificity of patient self-report of influenza and pneumococcal polysaccharide vaccinations among elderly outpatients in diverse patient care strata. *Vaccine* 2003; 21:1486-1491.
86. Carrat F, E V, N F, et al. Time lines of infection and disease in human influenza: A review of volunteer challenge studies. *Am J Epidemiol* 2008; 167:775-785.
87. Dhakal S, S K, NameId Dhakal SORCIDho, et al. Host Factors Impact Vaccine Efficacy: Implications for Seasonal and Universal Influenza Vaccine Programs. *J Virol* 2019; 93:e00797-19.
88. Lewnard J, S C, Email Lewnard J, et al. Immune history and influenza vaccine effectiveness. *Vaccines* 2018; 6:28.
89. Wilhelm M. Influenza in older patients: a call to action and recent updates for vaccinations. *Am J Manag Care* 2018; 24:15-24.
90. Zhao L, Stirling R and Young K. Should individuals use influenza vaccine effectiveness studies to inform their decision to get vaccinated? *Canadian Communicable Disease Report* 2019; 45:156-158.
91. Flannery B, Zimmerman RK, Gubareva LV, et al. Enhanced Genetic Characterization of Influenza A(H3N2) Viruses and Vaccine Effectiveness by Genetic Group, 2014-2015. *J Infect Dis* 2016; 214:1010-1019.
92. Sullivan SG and Kelly H. Stratified Estimates of Influenza Vaccine Effectiveness by Prior Vaccination: Caution Required. *Clinical Infectious Diseases* 2013; 57:474-476.
93. McLean HQ, Thompson MG, Sundaram ME, et al. Impact of Repeated Vaccination on Vaccine Effectiveness Against Influenza A(H3N2) and B During 8 Seasons. *Clinical Infectious Diseases* 2014; 59:1375-1385.

Chapter 6. Discussion

Summary of key findings

Generally, there was no statistically significant difference between paired interim and final SIV effectiveness estimates. An inconsistent statistical model for interim and final SIV effectiveness estimations, and interim estimation before influenza circulation peak increased the odds of having a substantial difference between point interim and final estimates. Point pooled SIV effectiveness estimates against A(H1N1)pdm09, A(H3N2), and influenza B were higher in the Southern compared with Northern hemispheres, with SIV performing best (highest effectiveness estimate) against A(H1N1)pdm09 and worst (lowest effectiveness estimate) against A(H3N2) in both hemispheres and across continents. Overall, point pooled SIV effectiveness estimate increased from Asia, to Europe, North America, and Oceania, and declined with age in the Northern hemisphere. There were significantly higher pooled SIV effectiveness estimates with vaccine antigenically similar compared with dissimilar to circulating virus strains. SIV effectiveness seemingly varied by source of vaccination information (self-reported compared with medical records), respiratory specimen swab time relative to symptom onset (≤7 days compared with ≤4 days), and inclusion of age/medical conditions (inclusion of only age compared with both age and medical conditions) among adjusted covariates.

Interpretation of findings

Interim estimates of SIV effectiveness are timely. They therefore provide early insights into SIV effectiveness while influenza is still circulating and help to guide SIV virus strain selection. However, their validity and reliability are usually questionable,[172] whereas final estimates have advantages in terms of having a larger study sample size, more data for important covariates, with potentially being post peak of influenza circulation, all of which increase precision and reliability of the estimates. Evidence from this thesis (Chapter 3) with respect to the observed concordance between paired interim and final SIV effectiveness estimates may be due to the largely comparable sample sizes between most of the interim and matched final estimates. However, the stage of the epidemic during which interim estimation was made influenced having a substantial difference between the interim and final point estimates. A previous study reported similar observations although the analysed data was limited.[172] This thesis involved a far larger (more than twice) sample size of matched pairs of interim and final estimates compared with the previous study: overall, 68 pairs compared with 33 pairs, representing 24 pairs compared with 12 pairs for all influenza, 16 pairs compared with ten pairs for A(H1N1)pdm09, 20 pairs compared with seven pairs for A(H3N2), and eight pairs compared with four pairs for influenza B. In addition, this thesis attempted to address potential methodological issues with the previous study; for example, only the data from outpatients were included in this thesis whereas the previous study appeared to have included data for both outpatients and hospitalised patients, despite that the WHO decision-making regarding SIV composition is mostly predicated on influenza surveillance and SIV effectiveness in the community. Moreover, potential differences may exist in patient characteristics and SIV effectiveness between outpatients and hospitalised patients. While the aim was not to assess agreement with any previous studies, an observational study in

Australia using data from TND studies of SIV effectiveness from 2007 to 2012 influenza seasons also found that interim estimates reliably predicted final estimates and that interim estimates after epidemic peak may be more reliable for comparison with final estimates.[179] In addition, an observational study from Spain also found that interim SIV effectiveness estimates from TND studies were good proxy for the final estimates during the 2010 to 2014 influenza seasons, with agreement within all assessed subpopulations and for all influenza subtypes.[148] Further, just as observed in this thesis, the study also found that interim estimates were higher compared with the final estimates.

The final estimates were generally lower than the interim estimates, with the largest proportion of the lower final estimates observed for the A(H3N2), which evidence suggests is the most drifted and antigenically mismatched of all human influenza virus subtypes/strains, and the lowest proportion observed for influenza B, which evidence also suggests that, relative to influenza A, undergoes seasonal antigenic drifting and mutation at far lower rate and therefore, mostly better matched with SIVs.[180-183] SIV effectiveness has been reported to diminish with time after vaccination, suggesting that the vaccine effectiveness reduces as the influenza season progresses.[184-187] A study from the USA concluded that the effectiveness of inactivated influenza vaccines diminishes within 180 days following 14 days after the vaccination,[187] and another study also from the USA, suggested that the maximum SIV effectiveness is observed shortly after vaccination and that this is then followed by an absolute decline in effectiveness of about 8% to 9% per month post vaccination, although this estimate was for hospitalised adults.[184] Among several mechanisms that have been postulated as plausible explanations for this observed decline in SIV effectiveness over time are effects of host factors (immune response) and changes in the circulating influenza strains,[188,189] including antigenic drift of the influenza viruses and

suggested “leaky vaccine effect”; that is, that vaccine potentially provides partial protection of all vaccinees rather than complete protection as in some vaccines.[185] However, inconsistent findings have also been reported,[190,191] and it has been suggested that, in addition to circulating influenza virus strains and study population characteristics, the observed discrepancies might be due to differences in influenza season, climatic conditions (temperate/tropical) and study methodology.[187] While this topic has been largely debated, it is more likely that SIV effectiveness declines over time, considering that hemagglutination-inhibiting antibody titres associated with clinical protection against influenza virus infection have been found to decline over time,[192] and that the protection conferred by the SIV is generally known to be short-lived.

The seasonal influenza epidemic typically occurs from November to April in the Northern hemisphere and from June to October in the Southern hemisphere, and SIV composition is usually different for the Northern and Southern hemispheres.[28,193] As such, estimates of seasonal influenza infection and SIV effectiveness may differ between the hemispheres, not just because of differences in geographical and environmental factors, but among other potential reasons, may also be due to differences in population characteristics and variations in circulating influenza virus strains. Investigating SIV effectiveness between the Northern and Southern hemispheres is therefore important because temporal and geographical variability in influenza epidemiology can affect SIV effectiveness.[194,195] While the temperate regions of the Northern and Southern hemispheres typically have distinct influenza seasonality patterns,[196] seasonal influenza circulation is less well defined in the tropics and subtropics, with almost year-round influenza activity and several influenza circulation peaks.[194,197] This has several implications for SIV effectiveness, as determining the optimal time for influenza vaccination is important for the effectiveness of influenza vaccination programmes in this region.

A study found that 25% and 39% of SIV recommendations, respectively, for the Northern and Southern hemispheres countries, were out of phase with peak influenza circulation in their corresponding hemisphere; thus, indicating that routine seasonal influenza vaccination efforts need tailoring to local (at least, country-specific) patterns of influenza circulation rather than being treated based on a country's hemispheric position.[198] These findings may partly explain the higher point pooled SIV effectiveness estimates against both subtypes of influenza A, the A(H1N1)pdm09 and A(H3N2), and against influenza B in the Southern compared with the Northern hemispheres as observed from this thesis (Chapter 4), considering that significantly fewer studies contributed to the analysis for the Southern hemisphere compared with the Northern hemisphere, and that these studies were mostly from one country, Australia, which uniquely has both tropical and temperate climates. This may also partially explain the observed highest overall point pooled SIV effectiveness estimate within Oceania continent, as overall point pooled SIV effectiveness was found to increase from Asia, to Europe, North America, and Oceania.

Similar to the observations from a smaller (included 56 studies) systematic review and meta-analysis by Belongia and colleagues, which, although included hospitalised patients and data from influenza seasons during and before the 2009/10 influenza pandemic, and a few interim SIV effectiveness data,[199] SIV was observed to perform best (highest effectiveness estimate) against A(H1N1)pdm09 and worst (lowest effectiveness estimate) against A(H3N2) in both hemispheres and across continents. Accurate matching of SIV virus strains with circulating influenza virus strains is one of the keys to SIV effectiveness and therefore, influenza seasons with mismatch between vaccine and circulating virus strains may be more prone to higher influenza-related population morbidity and mortality due to poor vaccine performance as the

2014/2015 influenza season demonstrated, especially in the Northern hemisphere.[76,200] When compared with A(H1N1)pdm09 and influenza B, the A(H3N2) has been found to undergo more antigenic drifting,[201,202] which may partly explain the observed lowest pooled SIV effectiveness against this subtype. Even so, for egg-grown SIV viruses, during incubation and production of the vaccine viruses, influenza viruses may undergo small mutations that alter the antigenic determinants of the virus, and while this is a particular problem for the influenza B lineages as well as for A(H3N2), the changes that occur in A(H3N2) often result in more mutations of the virus and therefore, these egg-adapted changes may alter antigenic integrity of the virus; thus, reducing vaccine effectiveness against the circulating virus strain based upon which SIV strains were determined.[203] A study reported almost no SIV effectiveness against an antigenically drifted genetic group of A(H3N2), but a fairly substantial 44% vaccine effectiveness against a genetic group that were antigenically similar to the SIV strains; thus, elucidating the detrimental effect of antigenic drifting of the A(H3N2) on SIV effectiveness against the subtype.[204] This is further supported by the observed very low SIV effectiveness during the 2014/15 influenza season, with widespread circulation of A(H3N2) viruses that were antigenically dissimilar from the A/Texas/50/2012 virus strain component of the SIVs.[205-207] These explanations may also be responsible for the considerably higher pooled SIV effectiveness estimates that were observed with antigenically similar compared with dissimilar SIV with circulating virus strains.

While much attention is often given to seasonal influenza virus-related factors that may affect vaccine responses and therefore, vaccine effectiveness, host-related factors are as important and should always be explored. Accumulating evidence suggest that host-related factors such as age, sex, chronic conditions, and immune history modify SIV effectiveness. Certain protective immune functions decline with age (immunosenescence), thus, increasing

susceptibility of older adults to infectious diseases and suboptimal protective immune responses to vaccination.[208,209] It is mostly for this reason that enhanced SIVs such as adjuvanted and the high-dose SIVs have been developed in an attempt to enhance immunological response to vaccination for improved SIV effectiveness, particularly among older adults because the effectiveness of the traditional SIV can be suboptimal in this subpopulation.[76] While a paucity of data did not allow for a full assessment of variability in SIV effectiveness across age groups as planned a priori, point pooled SIV effectiveness estimate was observed to decline with increasing age in the Northern hemisphere; highest among the very young and lowest among older adults, in line with the expectation. When compared with A(H1N1)pdm09 and influenza B, similar to the observations by Belongia and colleagues,[199] point pooled SIV effectiveness against A(H3N2) was lowest in almost all age groups and geographical regions, most likely due to the more antigenic drifting of the A(H3N2). Nevertheless, the lowest vaccine effectiveness against A(H3N2) was observed among older adults, suggesting an age-related immune response effect and the potential impact of chronic medical conditions on immune response,[210] considering that the prevalence of many chronic diseases increases with age.[211-213] Further, while it has been suggested that repeated SIV may reduce vaccine effectiveness,[214-216] the effects of previous season influenza vaccination versus immunosenescence were difficult to distinguish due to a lack of data, despite that older adults have the highest vaccination rates and are therefore more prone to repeat seasonal influenza vaccination.

Despite a lack of statistical significance, pooled SIV effectiveness estimates with self-reported seasonal influenza vaccination status differed from those with vaccination status derived from medical records (Chapter 5), with higher pooled estimates observed for self-reported vaccination contrary to the expectation. However, the data for self-reported vaccination were

almost entirely from one research group in Canada. Irrespective of approach, there are potential limitations to determination of seasonal influenza vaccination status in any observational study. Individuals could simply be asked directly or via questionnaire if they (or those in their care; for e.g., children) have been vaccinated, when they were, and perhaps, the type of SIV that they received, especially if in a region where different vaccine types are available. However, recall of seasonal influenza vaccination by individuals and of those in their care, can be inaccurate,[123,217-219] and it is difficult and, arguably, impossible to determine via self-reported vaccination, the SIV type that an individual may have received.[220] In addition, individuals may feel compelled to conform to societal expectation, and as such, self-reported vaccination may be subject to social desirability bias, and therefore, potentially inflated.[124,221] Even if reported correctly, self-reported vaccination status still requires documentation and is therefore prone to documentation errors and potential misclassification of vaccination status.[220] On the other hand, determination of vaccination status of individuals could be via paper-based or electronic medical records, or registries, and where available, electronic registries are highly useful; however, not perfect, as it may be difficult to match individuals to their vaccination record and data entry errors can occur and lead to misclassification of vaccination status.[220,222] As such, registry vaccination records may have high specificity, but variable sensitivity depending on the quality controls.[220] When compared with vaccination confirmation from medical records or registries, self-reported vaccination is described as having a higher sensitivity in some populations,[223,224] but a lower specificity in others.[225,226] For example, when compared with Whites, it was found that Hispanics had 2.7 times more likelihood of claiming self-reported vaccination, and when compared with younger persons, self-reported influenza vaccination in the elderly had low specificity.[223] Further, a simulation study demonstrated that decreased exposure sensitivity and specificity

underestimated true vaccine effectiveness when misclassification of vaccination status is non-differential, but that, when misclassification is differential, the bias could go in either direction, with the estimated vaccine effectiveness deviating largely from the true estimate.[227] The observed higher pooled SIV effectiveness estimates with self-reported vaccination status may be due to differential misclassification of vaccination status although considering that the studies were mostly from the same research group in Canada, factors such as study population characteristics and methodological approaches unique to the research group such as patients recruitment and swabbing techniques may also explain the observed results. Notwithstanding that exposure misclassification can lead to unreliable vaccine effectiveness estimation, it was not possible to assess misclassification of vaccination status between influenza cases and non-cases across the included individual studies considering that this thesis was a secondary analysis of data from primary studies, and therefore, the potential influence of misclassification of vaccination status on the pooled estimates could not be determined.

Although not statistically significant, pooled SIV effectiveness was observed to be higher with swab time of ≤7 days compared with swab time of ≤4 days. However, there are no published similar evidence summaries to compare this finding with. Nevertheless, to maximise detection of influenza virus from respiratory specimens considering the short incubation period for the virus,[14] ideally, respiratory specimen collection needs to be within 4 days of ARI or ILI symptom onset although due to practical reasons, up to 7 days may be more feasible. As previously mentioned, influenza viral shedding could last up to 5 days,[21] and it is possible that persons presenting >4 days following symptom onset may no longer be shedding virus and laboratory tests may therefore present with false negative results.[120] This may explain the observed higher pooled SIV effectiveness with swab time of ≤7 days since the longer swab

collection from symptom onset, the less likelihood it is to detect the influenza virus from respiratory specimens and therefore, the increased likelihood of false negative testing; thus, potentially increasing misclassification of cases. Even though influenza confirmation was based on the gold standards across all included studies, swabbing techniques differed across the studies, and this may likely have an influence on the observed results although it is difficult to explain exactly how. While false negatives among vaccinated persons would likely overestimate SIV effectiveness and false negatives among unvaccinated person likely to underestimation SIV effectiveness, it was not possible to assess these across the included individual studies, and therefore, the potential influence of misclassification of cases on the pooled estimates could not be ascertained and taken into consideration.

In addition to determining vaccination status and assessing vaccine effectiveness in observational studies of SIV effectiveness, data on other covariates are collected for potential stratification of the vaccine effectiveness estimates based on subpopulations of interest; for example, the very young, older adults and those with or without a chronic condition, or to control for potential confounders via matching at study design phase or adjustments during data analysis. Confounding as a result of differences in influenza risk between vaccinated and unvaccinated persons can greatly bias estimates of SIV effectiveness[150,220,228]. Evidence has shown that SIV effectiveness varies between persons due to certain individual factors,[188] and age and chronic medical conditions are established strong determinants of receipt of SIV,[133,229] and SIV effectiveness,[230] and are therefore potential confounders of SIV effectiveness.[231] Although not statistically significant, pooled SIV effectiveness estimates from studies that adjusted for age were observed to differ from those that adjusted for both age and medical conditions, with higher pooled SIV effectiveness estimates observed for those that adjusted for age but not medical

conditions. While acknowledging that statistical adjustments are usually limited to known and measured confounders and therefore residual confounding will certainly persist in observational outcome studies, the finding underscores the potential effect of residual confounding, as not adjusting for a measured or an unknown and therefore unmeasured confounder poses the threat of residual confounding in any assessments of associations, potentially resulting to unreliable effect estimations.[232] Simulation studies have shown that residual confounding could bias results of associations between exposures and outcomes;[233,234] and, as observed, adjusting for both age and medical conditions as should be, likely diminished SIV effectiveness when compared with adjusting for age alone, which potentially exaggerated the magnitude of the effect.

The evidence from this thesis further demonstrated a paucity of matched interim and final SIV effectiveness estimations from national influenza surveillance studies, especially from Africa and Asia, and as such, the study sample size (number of paired estimates) was relatively small and may not be large enough to power the test of the associations that were conducted, resulting in wide confidence intervals (poor precisions) of the effect estimates. The evidence may therefore be weak. Moreover, the findings may not be generalisable considering that the evidence was only from Europe, North America and Oceania, and even so, with underlying differences in the health systems across the regions, including in influenza vaccination policies and programmes, SIV access, and influenza surveillance systems. The most prominent methodological differences between the matched pairs of estimates were in the specification of the statistical model for SIV effectiveness estimation, with different durations for interim and final estimations. Arguably, statistical models used for calculating both interim and final estimates should be the same and decided a priori as this would enable focusing on potential epidemiological causes of any significant differences that may be observed between interim and

final estimates such as the change in virus circulation and waning of vaccine effectiveness, rather than focusing on heterogeneity in the estimates as a result of differences in methodological approaches. However, a paucity of data on some important confounders earlier on during the influenza season may be an impediment and may therefore make such an optimal approach less feasible. Nevertheless, at minimum, there is the need for a priori establishment of a minimum set of variables to inform statistical models for any interim and matched final SIV effectiveness estimations.

Study limitations

Study selection

While the focus was on TND studies of SIV effectiveness among patients vaccinated ≥14 days before symptom onset and symptom onset ≤7 days in outpatient settings after the 2009/10 influenza pandemic, some potentially eligible TND studies conducted during this specified period may not have been published at the time of literature search, and therefore, would not have been retrieved from the searched bibliographic databases. As such, there is the possibility that all potentially eligible studies may not have contributed to the studies in this thesis. In addition, literature inclusion was limited to published studies, which may mean exclusion of unpublished studies that could have been eligible. Nevertheless, if at all any eligible studies were missed, particularly, those that eventually made publication, the numbers are very likely small and exclusion of a small number of studies is unlikely to have changed the conclusions reached in this thesis, considering the large body of the included evidence. Although the pooled estimates may be biased if excluded unpublished data differ systematically from the included published data, it has been suggested that this occurs only in a minority of systematic reviews,[235] especially those with a small body of evidence. Moreover, inclusion of unpublished data needs very careful considerations since the methodologies in the studies that may have produced such data have not been peer-reviewed and vetted; thus, they present the potential for bias. That said, there was almost entirely no evidence of publication bias, including in the subgroup analyses, indicating that patterns of findings from any excluded studies may not have differed from those of the included studies. In addition, influenza viruses continuously evolve, causing seasonal epidemics, and therefore, SIV effectiveness is assessed regularly, meaning that SIV effectiveness data will

continue to accumulate, allowing periodic updates on the studies that make up this thesis, and future assessments of whether the conclusions as reached in the studies remain.

Gathering of the evidence

Data extraction was not conducted separately by at least two systematic reviewers as the Cochrane Handbook for Systematic Reviews of Interventions guidelines recommend;[174] rather, one systematic reviewer (the PhD candidate) extracted all data and a second systematic reviewer checked the extracted data for errors. Studies have found substantial errors in extracted data for evidence reviews when carried out by one systematic reviewer,[236,237] and that data extraction independently by two systematic reviewers resulted in fewer errors compared with data extraction by one systematic reviewer and then checked by a second systematic reviewer.[238] Further, it is plausible that any potentially relevant data mistakenly omitted by one reviewer may not be identified by a second reviewer, if both reviewers did not conduct data extraction separately. Nevertheless, as the Cochrane guidelines also recommend, the first reviewer who conducted data extraction (the PhD candidate) is a trained and experienced knowledge synthesis methodologist in addition to having medical training and a good understanding of the topics of the reviews, and the second reviewer was well-informed about the reviews' objectives and methodologies, was trained in knowledge synthesis, and also has medical training, with a good understanding of the topics of the reviews.[174] Moreover, both reviewers first piloted the data extraction sheet separately before the data extraction process and, following data extraction and checking of the extracted data, discussed and resolved any disagreements or sought involvement of a third reviewer who is a content expert on the reviews' topics (the PhD candidate's Advisor). The extracted data were therefore more likely less prone to errors.

Quality assessment

Despite the recommendation by the Cochrane Handbook for Systematic Reviews of Interventions guidelines,[174] detailed study quality assessments were not possible in any of the reviews due to the fact that a quality assessment tool for TND studies was not available. This meant that the quality of the evidence was not considered in making conclusions from the findings from the reviews. Nevertheless, the parsimonious eligibility criteria for study inclusion based mostly on high quality TND study methodology limited inclusion of studies with poor methodologies and therefore of poor quality although efforts were still made to develop an improvised study quality assessment tool based on a few other identified important methodological elements. This enabled depiction of a few deficiencies in the methodologies of the included studies; however, without an overall quality assessment of the studies considering that the improvised quality assessment tool was not validated and therefore not judged appropriate for study quality assessment irrespective of how well the tool may have performed.

Determination of covariates

Determination of the stage of influenza circulation during which interim SIV effectiveness estimation was made was using reports in studies or epidemic curve reported in the studies of final SIV effectiveness estimation. This approach may not have been perfect considering that this measure was only based on the number of presenting cases at clinics; rather than the actual virus circulation, meaning that infected persons who did not present at clinics were not counted. It is however difficult to determine any error that may have arisen due to this approach and how it may have impacted the findings. Nevertheless, measuring the actual virus circulation is mostly theoretical and the approach adopted in this thesis is an acceptable proxy for determining influenza circulation peak and has been utilised by a previous similar study.[172] The determination

of SIV antigenic similarity with circulating virus strains may also not be perfect considering that circulating influenza viruses may change during the influenza season; hence, presenting immense difficulties to making this important epidemiological determination. Nevertheless, even if not perfect, reports from the WHO national influenza centres and from region/country-specific centres for disease control were cautiously utilised for this purpose, and these reports included assessments on how well the recommended SIV compared with the circulating influenza virus strains in various geographical areas. As such, this approach to determining SIV antigenic similarity is sensible and appropriate. Further, there is no published evidence on a validated substantial difference between interim and final SIV effectiveness estimates. Therefore, a 10% difference was relied upon as being substantial in view of the 10% difference often considered as a "rule of thumb" for identifying the presence of confounding in epidemiological research, and with reference to previous literature.

Misclassification of exposures and outcome

Whereas influenza case determination across the included studies was solely laboratory-confirmed using the gold standard tests and, as such, the less likelihood of wrong case ascertainment, case ascertainment was still prone to misclassification due to documentation errors. Considering that the studies in this thesis were secondary analyses of data from primary studies, it was not possible to determine whether any such misclassifications existed in the included studies and whether they would have been differential or non-differential between the vaccinated and the non-vaccinated persons. There was also the possibility of misclassification of influenza vaccination status especially considering that it was not very clear from some studies if information regarding influenza vaccination for the entire study participants was from medical records or that some were self-reported. If vaccination status was determined from medical

records, misclassification could have occurred due to documentation errors. However, for the reasons previously mentioned, it was also not possible to determine whether any such misclassification existed in the included studies and whether they would have been differential or non-differential between influenza cases and non-cases. Nevertheless, even if any misclassifications were non-differential, bias towards the null may not necessarily result in underestimations of SIV effectiveness in any such studies.[239] Further, the accuracy and completeness of the immunization registries and health databases utilised across studies could not be ascertained and therefore, the likelihood of documentation errors across the registries/databases could not be determined. In addition, vaccination status misclassification bias could also not be ruled out in the studies that utilised self-reported influenza vaccination, considering social desirability reporting and recall biases inherent in self-reported vaccinations, which could easily lead to misclassification of vaccination status.[123,124] Although the focus was on only studies with participants presenting in outpatient settings within 7 days of symptom onset, symptom onset was possibly also prone to recall and social desirability biases considering that some individuals may not have even noticed or remembered exactly when symptom(s) were first noticed, or may have reported very recent symptom onset to portray an immediate healthcare-seeking attitude.

Data analysis

Limiting study inclusion to TND studies after the 2009/10 influenza pandemic may have limited the number of paired interim/final estimates and the number of studies that contributed to the pooled estimates, but it enabled concentration on studies conducted from when influenza vaccination became increasingly publicly funded in many jurisdictions. Moreover, following the

2009/10 pandemic, the influenza A virus strain, the A(H1N1)pdm09 remained in circulation every season thereafter, and therefore, limiting to studies after the pandemic enabled assessment of vaccine effectiveness against this influenza A virus strain. Adequacy of study sample size is important as inadequacy and therefore a low statistical power (the ability to detect a true effect if there was one) can increase the probability that a statistically significant result may actually be a false positive, and even if a true positive, that the effect size may actually be exaggerated from the actual value.[240,241] Despite this fact, sample size was not calculated for the study of the determinants of a substantial difference between interim and final SIV effectiveness estimates and, as such, it was not certain that the analyses had enough statistical power.[242] Nevertheless, even if sample size was calculated, the number of paired interim/final SIV effectiveness estimates for the study was purely dependent on the available published evidence and therefore, nothing could have been done regarding the sample size. As Price, Carville and Sullivan noted, the precision of SIV effectiveness estimates depends on study sample size and the distribution of patient characteristics within levels of vaccination and influenza status, whereas the accuracy of SIV effectiveness estimates depends on the method by which the patients in the study are sampled.[243] While sample size considerations have been advocated and various approaches suggested for SIV effectiveness and cost-effectiveness estimations,[220,244,245] sample size calculations were poorly conducted and reported across the included SIV effectiveness studies, and as such, it was not possible to determine the adequacy of the various study samples and how such may have impacted the precision of the SIV effectiveness estimates from the studies. In addition, the accuracy of SIV effectiveness estimates were not explored although study participants' sampling methods were determined and presented in tabular form as part of study

quality assessment; however, without pooled analysis of SIV effectiveness estimates for each sampling method because of perceived uncertainties in the determination.

There were differences in the set of covariates that were adjusted for in the included studies although a majority adjusted for age and/or medical conditions. This may have contributed to the high heterogeneity observed in some of the pooled vaccine effectiveness estimates. Due to a paucity of data, comparison of early- and mid-season interim SIV effectiveness estimates separately against final estimates was not possible despite that such a comparison would have been insightful and would have also helped as a proxy for assessing the potential impact of study population size as a determinant of a substantial difference between interim and final SIV effectiveness estimates. A paucity of data also meant that exploration of potential interactions between important determinants and, subgroup analysis by influenza subtype/type, and season were not possible despite being planned a priori. There were differences in the categorization of age groups across studies, thus limiting data for age group analysis. A thorough examination of SIV effectiveness across all established age groups was therefore not possible. SIV effectiveness could not be determined and compared between vaccine types because vaccine effectiveness was hardly reported by vaccine type across studies despite that the SIV types are different and that vaccine effectiveness is not equivalent for all vaccine types. Studies did not report prior seasonal influenza vaccinations so it was not possible to assess the impact on SIV effectiveness, despite growing evidence to suggest that SIV effectiveness may be influenced by prior seasonal influenza vaccinations.[246,247] While adjustments were made for potential confounders as appropriately determined using a DAG, some established predictors of a substantial difference between interim and final SIV effectiveness estimates were not available in the dataset and therefore not considered in the models even if suggested by the DAG. This posed

the potential for residual confounding in the analyses. Even so, any unknown and therefore not measured determinant of a significant difference may have also confounded the analyses.

Study merits

These limitations notwithstanding, there are some merits in this thesis. As per the expected standards, the literature search strategies for the studies were developed appropriately and peer-reviewed by a knowledge synthesis librarian using the PRESS checklist,[177] and literature search was detailed. This approach strengthened identification of potentially relevant literature for inclusion. Moreover, no language limitation was applied to the literature search and study selection, and as such, the reviews were comprehensive. Known guidelines and standards were followed in the conduct and reporting of the studies, with important subgroup analyses conducted. The findings provide useful insights and an evidence-base that could aid public health decision-making and practice regarding influenza prevention and control.

Implications of the findings for policy, planning and practice

Influenza viruses continuously undergo small mutations that alter the antigenic determinants of the viruses, necessitating vaccine redevelopment and redeployment each influenza season,[30,35] and constant influenza infection surveillance, vaccine effectiveness estimations, and vaccination programme assessments. As such, conceptual public health objectives such as disease elimination or eradication may never be possible with influenza even though some scientists have loftier ambitions and believe that the threat of influenza could be eradicated.[248] For now, public health interventions must focus on influenza prevention/control and reductions in influenza-associated hospitalisations and mortalities.[249-251] Concordance between interim and final SIV effectiveness estimates, and variations in SIV effectiveness have several implications for global influenza policy, SIV development, influenza surveillance practices and approaches to SIV effectiveness assessment.

This thesis suggests concordance between interim and final SIV effectiveness estimates; thus, providing evidence of potential sufficiency of interim SIV effectiveness estimates for SIV composition decision-making by the WHO. The thesis also provides a strong evidence base for variability in SIV effectiveness across geographical regions, age groups, and levels of VAS, and some evidence in support of potential variability in SIV effectiveness due to source of influenza vaccination status, respiratory specimen swab timing relative to symptom onset, and covariate adjustments in SIV effectiveness estimations. However, methodological approaches to SIV effectiveness assessment differed considerably across the surveillance studies from difference jurisdictions, suggesting the need for a global policy with clear recommendations on influenza surveillance planning and practices to support uniformity in SIV effectiveness assessments across jurisdictions. There is therefore the need for the GISRS unit of the WHO to recommend a

uniform approach to influenza surveillance and SIV effectiveness assessments, and to strictly require SIV assessments according to SIV type; at least, across the WHO Collaborating Centres for Reference and Research on Influenza, considering that SIV recommendations differ between the Northern and Southern hemispheres and vaccine type may differ across jurisdictions.[28] Moreover, influenza surveillance and SIV effectiveness estimates from the WHO centres inform SIV composition decision-making globally. Perhaps, success in developing an effective, safe and acceptable universal influenza vaccine might help navigate around this issue.[248,252,253]

Standardization of methodological approaches in TND studies of SIV effectiveness estimation, for example, of study participants recruitment and respiratory specimen swab collection and timing, could help increase the robustness and accuracy of estimates.[243] There is also the need for a standardized grouping of age in analyses and reporting of vaccine effectiveness by socioeconomic and health statuses, as this would provide more insights and help in comparisons of vaccine effectiveness estimates across studies.

Recommendations for future research

This thesis addresses important gaps in knowledge by demonstrating that interim SIV effectiveness estimates seem sufficient for SIV composition decision-making by the WHO and providing useful insights that aid understanding of the variability in SIV effectiveness across geographical regions, age groups, levels of VAS, and some study methods. The thesis also reveals some weaknesses and missing information in the evidence base, elucidating some unanswered questions to guide future research.

Although interim SIV effectiveness estimates seemed sufficient for SIV composition decision-making, the evidence base was somewhat limited and, as such, future reassessment with additional evidence may be needed for a stronger and more robust evidence base. An outstanding question that could not be addressed by this thesis due to a lack of data is concordance between early-season and end-season SIV effectiveness estimates by SIV type, and variations in SIV effectiveness also by SIV type. This is highly necessary since effectiveness may not be equivalent for the SIV types.[254]

Non-uniformity in some key methodological approaches and analyses across the studies included in the reviews also limited very important assessments of variations in vaccine effectiveness; for example, non-uniformity in categorizations for age and respiratory specimen swab time, and sets of covariates adjustments, which meant the exclusion and therefore loss of vital data that could have aided some of the analyses. These outstanding deficiencies and limitations in the evidence base call for standardization of SIV effectiveness estimation, which would inform the much-needed consensus to guide future research for a more robust evidence base. Further, the observed paucity of studies on SIV effectiveness from the Southern

hemisphere calls for more influenza research in countries from this region, as this would provide more insights that could aid influenza prevention and control in the region.

Conclusions

Evidence from TND studies of SIV effectiveness in outpatients after the 2009/10 influenza pandemic is indicative that interim SIV effectiveness estimates are likely sufficient for SIV composition decision-making by the WHO. While the evidence is strongly indicative of variability in SIV effectiveness across geographical regions, age groups, and levels of VAS, the evidence for variability in SIV effectiveness across sources of vaccination status determination, respiratory specimen swab timing relative to symptom onset, and covariates adjustments in effectiveness estimations is weak. However, it is suggestive that these factors ought to be considered when designing, evaluating or comparing data from TND studies. Consistent patterns appeared to exist in vaccine effectiveness within and across geographical regions, age groups, and levels of VAS, with the best vaccine performance against A(H1N1)pdm09 and when antigenically similar to circulating virus strains, and the worst vaccine performance against A(H3N2) and when antigenically dissimilar, with vaccine effectiveness generally reduced with age. A uniform methodological approach to assessing SIV effectiveness is needed to enable more appropriate comparisons of estimates and for a stronger evidence base.

Appendices

Group A: Supplementary information for Chapter 2

Appendix 1: The literature search strategy for Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily <1946 to Search date>.

No.	**Searches**
1	persons.mp. or Persons/
2	patients.mp. or Patients/
3	(infant* or child* or paediatr* or pediatr* or preschool or juvenile* or adolescen* or young* or student* or adult* or elder* or old* or geriatr* or person* or subject* or individual* or patient* or people or boy* or girl* or male* or female* or men or women or health* or ill* or risk).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
4	1 or 2 or 3
5	influenza vaccine.mp. or Influenza Vaccines/
6	(seasonal or flu-vaccine* or influenza-vaccine* or (flu and vaccine*) or (influenza and vaccine*) or trivalent or quadrivalent or inactivated or (life and attenuated*) or adjuvant* or recombinant or IIV or RIV or LAIV or Fluzone or Flulaval or Fluarix or Afluria or Flucelvax or Fluvirin or Fluad or Flublok or FluMist or Fluenz* or Focetria or Foclivia or IDflu or Intanza or Daronrix or Prepandrix or Aflunov or intradermal).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
7	5 or 6
8	(unvaccin* or (no and vaccin*) or (no and influenza and vaccin*) or (no and flu and vaccin*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
9	polymerase chain reaction.mp. or Polymerase Chain Reaction/
10	(influenza or flu or infect* or H1N1 or H3N2 or (influenza and A) or (influenza and B)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
11	9 or 10
12	4 and 7 and 8 and 11
13	interim estimate*.mp.
14	12 or 13
15	limit 14 to (humans and yr="2011 – Current")

Appendix 2: Code for the directed acyclic graphs in DAGitty (http://www.dagitty.net/).

```
dag {
"A-Drift" [pos="-0.652,-1.688"]
"Change-VE" [outcome,pos="1.400,1.621"]
"Epi-Stage" [pos="0.991,-0.777"]
"Flu-type" [pos="-1.447,-0.907"]
"Interim-Proportion" [pos="-1.471,1.015"]
"Model-C" [exposure,pos="-2.200,1.597"]
"Sample-Size" [pos="-0.536,0.900"]
Region [pos="-2.203,-1.182"]
Season [pos="-1.878,0.141"]
Severity [pos="0.216,-0.994"]
"A-Drift" -> "Change-VE"
"A-Drift" -> Severity
"Epi-Stage" -> "Change-VE"
"Epi-Stage" -> "Interim-Proportion"
"Epi-Stage" -> "Sample-Size"
"Flu-type" -> "A-Drift"
"Flu-type" -> "Change-VE"
"Flu-type" -> Severity
"Interim-Proportion" -> "Change-VE"
"Model-C" -> "Change-VE"
"Sample-Size" -> "Change-VE"
"Sample-Size" -> "Interim-Proportion"
Region -> "A-Drift"
Region -> "Change-VE"
Region -> "Flu-type"
Region -> "Model-C"
Season -> "A-Drift"
Season -> "Change-VE"
Season -> "Epi-Stage"
Season -> "Flu-type"
Season -> Severity
Severity -> "Change-VE"
Severity -> "Sample-Size"
}
```

Group B: Supplementary information for Chapter 3

Appendix 3: Number (%) of paired interim/final adjusted VE estimates across levels of assessed variables and ≥5% difference between interim and final adjusted VE point estimates.

	≥5% difference	
	Yes	**No**
	(N=53)	(N=15)
Inconsistency in statistical model		
Consistent model	24 (45.3%)	11 (73.3%)
Inconsistent model	29 (54.7%)	4 (26.7%)
Epidemic stage during interim VE estimation		
Pre-peak	33 (62.3%)	6 (40.0%)
Peak/Post-peak	20 (37.7%)	9 (60.0%)
Proportion of interim VE patient population		
Within one-third	5 (9.4%)	3 (20.0%)
Between one-third and two-thirds	32 (60.4%)	8 (53.3%)
More than two-thirds	12 (22.6%)	3 (20.0%)
Unknown	4 (7.5%)	1 (6.7%)
Geographical region		
Northern	49 (92.5%)	14 (93.3%)
Southern	4 (7.5%)	1 (6.7%)
Country		
Australia	2 (3.8%)	1 (6.7%)
Austria	4 (7.5%)	0 (0.0%)
Canada	5 (9.4%)	3 (20.0%)
Europe (I-MOVE)	8 (15.1%)	2 (13.3%)
New Zealand	2 (3.8%)	0 (0.0%)
Spain	13 (24.5%)	3 (20.0%)
UK	9 (17.0%)	2 (13.3%)
USA	10 (18.9%)	4 (26.7%)
Influenza type/subtypes		
All influenza	18 (34.0%)	6 (40.0%)
A(H1N1)pdm09	12 (22.6%)	4 (26.7%)
A(H3N2)	16 (30.2%)	4 (26.7%)
Influenza B	7 (13.2%)	1 (6.7%)
Influenza season		
2010/11	3 (5.7%)	3 (20.0%)
2011/12	6 (11.3%)	0 (0.0%)
2012/13	9 (17.0%)	5 (33.3%)
2013/14	3 (5.7%)	2 (13.3%)
2014/15	14 (26.4%)	1 (6.7%)
2015/16	4 (7.5%)	0 (0.0%)
2016/17	4 (7.5%)	0 (0.0%)
2017/18	7 (13.2%)	3 (20.0%)
2018/19	3 (5.7%)	1 (6.7%)

VE = vaccine effectiveness; UK = United Kingdom; USA = United States of America; i-MOVE = Influenza-Monitoring Vaccine Effectiveness in Europe

Appendix 4: Number (%) of paired interim/final adjusted VE estimates across levels of assessed variables and ≥20% difference between interim and final adjusted VE point estimates.

	≥20% difference	
	Yes	**No**
	(N=16)	(N=52)
Inconsistency in statistical model		
Consistent model	4 (25.0%)	31 (59.6%)
Inconsistent model	12 (75.0%)	21 (40.4%)
Epidemic stage during interim VE estimation		
Pre-peak	12 (75.0%)	27 (51.9%)
Peak/Post-peak	4 (25.0%)	25 (48.1%)
Proportion of interim VE patient population		
Within one-third	2 (12.5%)	6 (11.5%)
Between one-third and two-thirds	10 (62.5%)	30 (57.7%)
More than two-thirds	3 (18.8%)	12 (23.1%)
Unknown	1 (6.3%)	4 (7.7%)
Geographical region		
Northern	16 (100.0%)	47 (90.4%)
Southern	0 (0.0%)	5 (9.6%)
Country		
Australia	0 (0.0%)	3 (5.8%)
Austria	3 (18.8%)	1 (1.9%)
Canada	1 (6.3%)	7 (13.5%)
Europe (I-MOVE)	2 (12.5%)	8 (15.4%)
New Zealand	0 (0.0%)	2 (3.8%)
Spain	5 (31.3%)	11 (21.2%)
UK	3 (18.8%)	8 (15.4%)
USA	2 (12.5%)	12 (23.1%)
Influenza type/subtypes		
All influenza	4 (25.0%)	20 (38.5%)
A(H1N1)pdm09	2 (12.5%)	14 (26.9%)
A(H3N2)	6 (37.5%)	14 (26.9%)
Influenza B	4 (25.0%)	4 (7.7%)
Influenza season		
2010/11	0 (0.0%)	6 (11.5%)
2011/12	0 (0.0%)	6 (11.5%)
2012/13	2 (12.5%)	12 (23.1%)
2013/14	1 (6.3%)	4 (7.7%)
2014/15	8 (50.0%)	7 (13.5%)
2015/16	1 (6.3%)	3 (5.8%)
2016/17	1 (6.3%)	3 (5.8%)
2017/18	2 (12.5%)	8 (15.4%)
2018/19	1 (6.3%)	3 (5.8%)

VE = vaccine effectiveness; UK = United Kingdom; USA = United States of America; i-MOVE = Influenza-Monitoring Vaccine Effectiveness in Europe

Appendix 5: Number (%) of paired interim/final adjusted VE estimates by levels of assessed variables and estimation of adjusted VE (underestimation versus overestimation).

	Underestimation of VE	
	Yes	**No**
	(N=22)	(N=46)
Inconsistency in statistical model		
Consistent model	15 (68.2%)	20 (43.5%)
Inconsistent model	7 (31.8%)	26 (56.5%)
Epidemic stage during interim VE estimation		
Pre-peak	14 (63.6%)	25 (54.3%)
Peak/Post-peak	8 (36.4%)	21 (45.7%)
Proportion of interim VE patient population		
Within one-third	2 (9.1%)	6 (13.0%)
Between one-third and two-thirds	12 (54.5%)	28 (60.9%)
More than two-thirds	6 (27.3%)	9 (19.6%)
Unknown	2 (9.1%)	3 (6.5%)
Geographical region		
Northern	21 (95.5%)	42 (91.3%)
Southern	1 (4.5%)	4 (8.7%)
Country		
Australia	1 (4.5%)	2 (4.3%)
Austria	4 (18.2%)	0 (0.0%)
Canada	1 (4.5%)	7 (15.2%)
Europe (I-MOVE)	4 (18.2%)	6 (13.0%)
New Zealand	0 (0.0%)	2 (4.3%)
Spain	3 (13.6%)	13 (28.3%)
UK	7 (31.8%)	4 (8.7%)
USA	2 (9.1%)	12 (26.1%)
Influenza type/subtypes		
All influenza	9 (40.9%)	15 (32.6%)
A(H1N1)pdm09	4 (18.2%)	12 (26.1%)
A(H3N2)	5 (22.7%)	15 (32.6%)
Influenza B	4 (18.2%)	4 (8.7%)
Influenza season		
2010/11	2 (9.1%)	4 (8.7%)
2011/12	2 (9.1%)	4 (8.7%)
2012/13	3 (13.6%)	11 (23.9%)
2013/14	1 (4.5%)	4 (8.7%)
2014/15	7 (31.8%)	8 (17.4%)
2015/16	2 (9.1%)	2 (4.3%)
2016/17	0 (0.0%)	4 (8.7%)
2017/18	5 (22.7%)	5 (10.9%)
2018/19	0 (0.0%)	4 (8.7%)

VE = vaccine effectiveness; UK = United Kingdom; USA = United States of America; i-MOVE = Influenza-Monitoring Vaccine Effectiveness in Europe

Appendix 6: Logistic regression model of ≥5% and ≥20% difference between paired interim and final adjusted VE point estimates (N = 68).

Variables	**ΔVE ≥5%**		**ΔVE ≥20%**	
	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Inconsistency in statistical model (Yes or No)[a]	3.3 (0.9 – 11.8)	3.3 (0.9 – 11.9)	**4.4 (1.3 – 15.6)**	**4.4 (1.2 – 15.8)**
Epidemic stage of interim VE estimation (Pre- or peak/post-peak)[b]	0.4 (0.1 – 1.3)	0.2 (0.1 – 1.0)	0.4 (0.1 – 1.3)	0.3 (0.1 – 1.5)
Region (Hemisphere)[c]	1.1 (0.1 – 11.1)	1.1 (0.1 – 11.1)	1.0	1.0

VE = vaccine effectiveness; ΔVE = change in vaccine effectiveness; OR = crude odds ratio; aOR = adjusted odds ratio; CI = confidence interval; a = adjusted for region; b = adjusted for season; c = no adjustment needed; NA = not applicable; Bold results = statistically significant.

Appendix 7: Logistic regression model of underestimation and overestimation of final adjusted VE with respect to the paired interim adjusted VE (N = 68).

Variables	Underestimation of final VE		Overestimation of final VE	
	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
Inconsistency in statistical model (Yes or No)[a]	0.4 (0.1 – 1.0)	0.4 (0.1 – 1.0)	2.8 (1.0 – 8.1)	2.9 (1.0 – 8.4)
Epidemic stage of interim VE estimation (Pre- or peak/post-peak)[b]	0.7 (0.2 – 1.9)	0.7 (0.2 – 2.2)	1.5 (0.5 – 4.2)	1.5 (0.5 – 5.0)
Region (Hemisphere)[c]	0.5 (0.1 – 4.8)	0.5 (0.1 – 4.8)	2.0 (0.2 – 19.0)	2.0 (0.2 – 19.0)

VE = vaccine effectiveness; OR = crude odds ratio; aOR = adjusted odds ratio; CI = confidence interval; a = adjusted for region; b = adjusted for season; c = no adjustment needed; NA = not applicable; Bold results = statistically significant.

Group C: Supplementary information for Chapter 4

Appendix 8: Information guiding de-duplication of results from countries with more than one result for an influenza season.

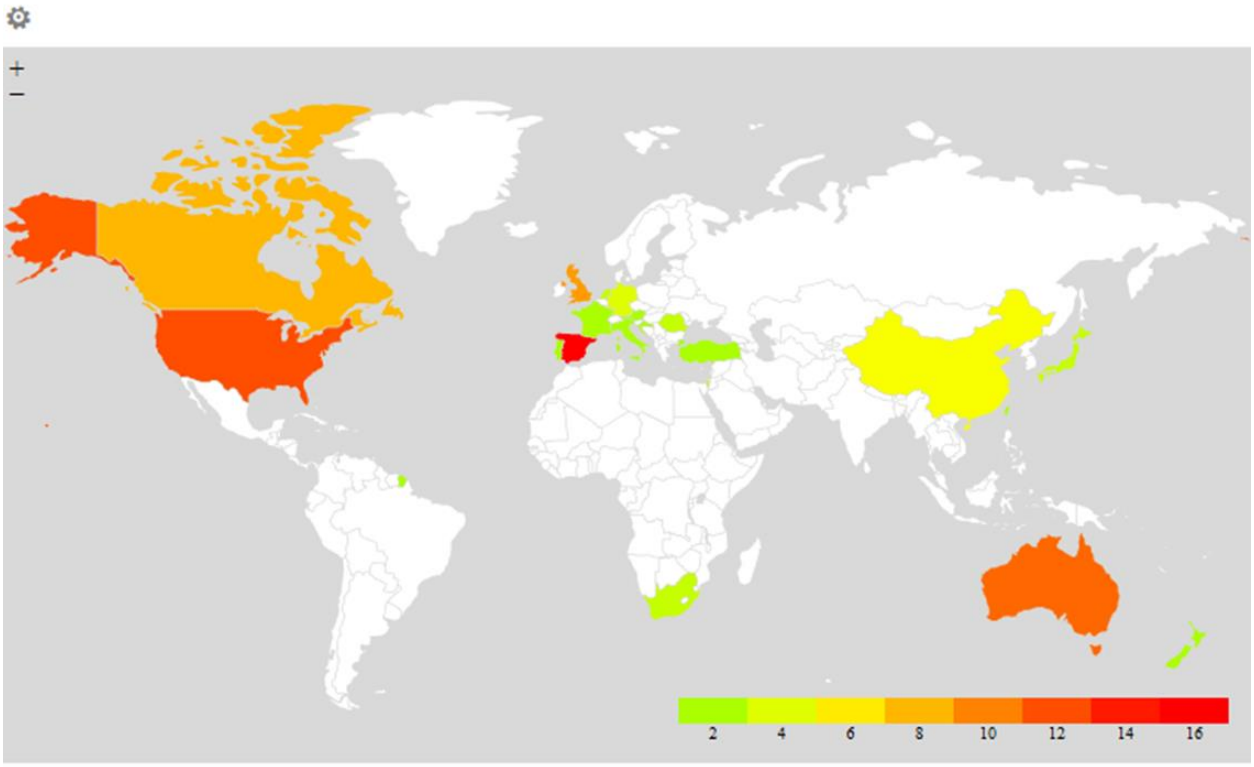
USA									
Public health jurisdictions from which data were collected	Cowling 2016		McLean 2015	Ohmit 2014		Treanor 2012	Bateman 2013		
	Florida; Iowa; Minnesota; North Dakota; Oregon; Wisconsin; New York City; New Jersey; Virginia; Los Angeles; Philadelphia; Utah; Texas. N = 13		Wisconsin Michigan (Ann Arbor & Detroit) Texas (Temple-Belton) Washington (Seattle) Pennsylvania (Pittsburgh) (N = 5)	Wisconsin Michigan (Ann Arbor & Detroit) Texas (Temple-Belton) Washington (Seattle) Pennsylvania (Pittsburgh) (N = 5)		Wisconsin Michigan (Ann Arbor & Detroit) New York (Rochester) Tennessee (Nashville) N = 4	Wisconsin. N = 1		
Spain									
Public health jurisdictions from which data were collected	Jimenez-Jorge 2012	Jimenez-Jorge 2013	Jimenez-Jorge 2015	Martinez-Baz 2015	Jimenez-Jorge 2015a&b	Savulescu 2014	Castilla 2013	Gherasin 2014a&b	Martinez-Baz 2013
	Eight of the 17 sentinel regions N = 8	Seven of the 17 sentinel regions N = 7	All 17 sentinel regions N = 17	Region of Navarra N = 1	All 17 sentinel regions N = 17	All 17 sentinel regions N = 17	Region of Navarra N = 1	Six of the 17 sentinel regions N = 6	Region of Navarra N = 1
Australia									
Public health jurisdictions from which data were collected	Regan 2019	Carville 2015	Kelly 2016	Sullivan 2014	Levy 2014	Kelly 2013	Sullivan 2013	Fielding 2016	Fielding 2012
	ASPREN, SPNWA & VicSPIN in 2016; Western Australia in 2012,13,14 & 15	Victoria	Victoria	ASPREN	Western Australia	Metropolitan Melbourne and regional Victoria	Victoria	ASPREN, SPNWA & VicSPIN	Victoria

ASPREN = Australian Sentinel Practices Research Network; SPNWA = Sentinel Practitioners Network of Western Australia; VicSPIN = Victorian Sentinel Practice Influenza Network

Appendix 9: The specific age ranges included in each of the a priori determined age categories for pooled adjusted VE by age.

Age group	**Consists of results reported for:**
Patients under 5 years	6–35months; 6months–4 years; 2–4 years; <5 years
Patients 5 to 17 years	5–14 years; 5–17 years; 6–17 years; 7–17 years; 9–17 years
Patients 18 to 49 years	18–44 years; 18–49 years; 20–49 years
Patients 50 to 64 years	50–64 years; 55–64 years
Patients 65 years or more	>64 years; ≥65 years

Appendix 10: Geographical mapping of the included articles.

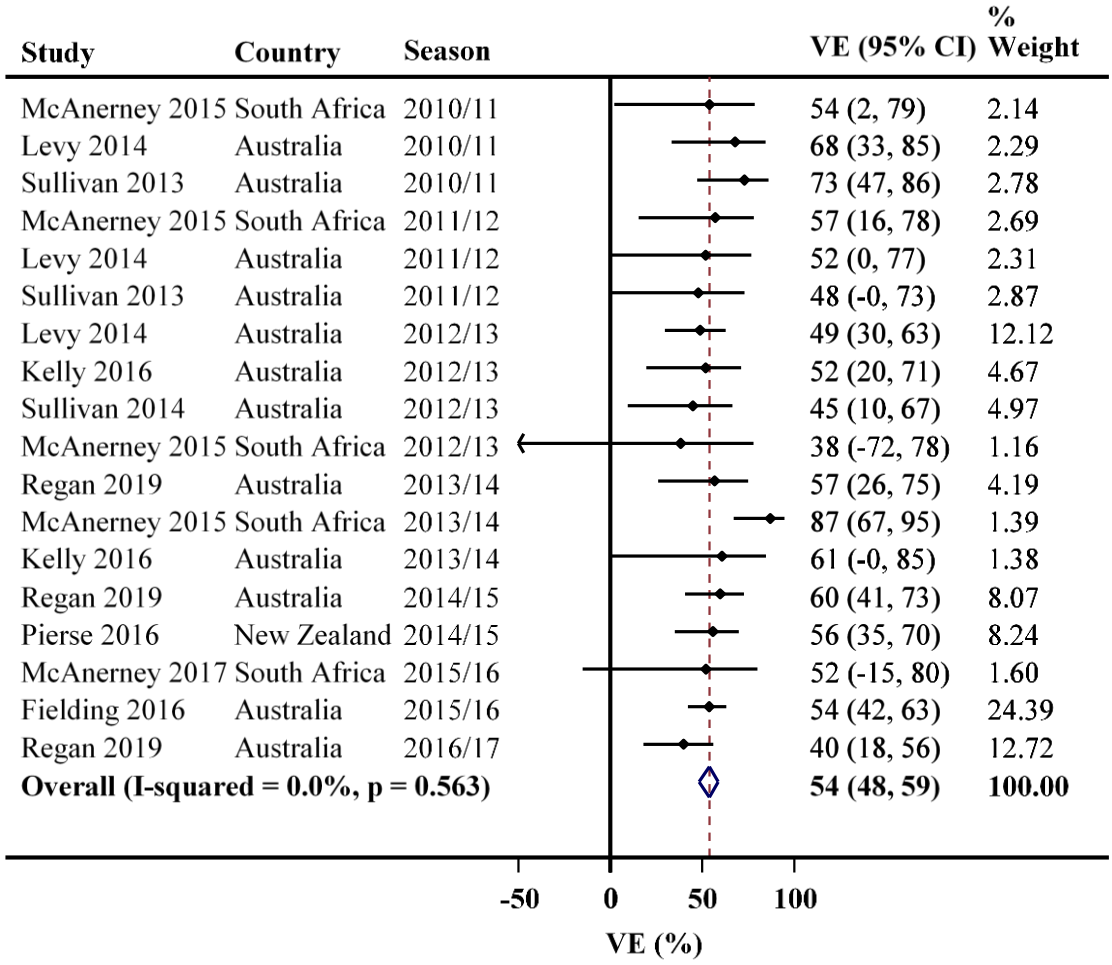


Appendix 11: Improvised quality assessment of the included studies based on three potentially relevant study characteristics.

Published article	Country	Patient recruitment	Influenza vaccination confirmation	Whether age and/or comorbidity among covariates adjusted in logistic regression analysis
Andrews 2014	UK	Systematic	Medical records	Age
Bateman 2013	USA	Consecutive	Medical records	Yes
Carville 2015	Australia	Systematic	Medical records	Age
Castilla 2013	Spain	Consecutive	Medical records	Yes
Castilla 2016	Spain	Consecutive	Medical records	Yes
Castilla 2020	Spain	Consecutive	Medical records	Yes
Chan 2019	Hong Kong	Consecutive	Self-reported	Yes
Chon 2019	Japan	Consecutive	Not specified	Age
Cowling 2016	USA	Systematic	Mixed methods	Age
Darvishian 2017	Netherlands	Systematic	Mixed methods	Yes
Englund 2013	Germany	Systematic	Mixed methods	Yes
Fielding 2012	Australia	Systematic	Medical records	Comorbidity
Fielding 2016	Australia	Systematic	Medical records	Age
Flannery 2019	USA	Consecutive	Mixed methods	Yes
Flannery 2020	USA	Consecutive	Mixed methods	Age
Gaglani 2016	USA	Consecutive	Mixed methods	Yes
Gherasim 2016	Spain	Systematic	Medical records	Yes
Gherasim 2017	Spain	Systematic	Medical records	Yes
Hekimoglu 2018	Turkey	Consecutive	Medical records	Age
Helmeke 2015	Germany	Systematic	Medical records	Age
Jackson 2017	USA	Consecutive	Medical records	Age
Jimenez-Jorge 2012	Spain	Systematic	Medical records	Age
Jimenez-Jorge 2013	Spain	Systematic	Medical records	Age
Jimenez-Jorge 2015	Spain	Systematic	Medical records	Age
Jimenez-Jorge 2015	Spain	Systematic	Medical records	Age
Kelly 2013	Australia	Consecutive	Medical records	Age
Kelly 2016	Australia	Systematic	Medical records	Yes
Kurecic-Filipovic 2015	Croatia	Systematic	Medical records	Yes
Levy 2014	Australia	Systematic	Medical records	Age
Lo 2013	Taiwan	Systematic	Medical records	Yes
Ma 2017	China	Systematic	Medical records	Yes
Martínez-Baz 2013	Spain	Consecutive	Medical records	Yes
Martinez-Baz 2015	Spain	Consecutive	Medical records	Yes
Martinez-Baz 2019	Spain	Consecutive	Medical records	Yes
McAnerney 2015	South Africa	Systematic	Mixed methods	Yes
McAnerney 2017	South Africa	Systematic	Mixed methods	Yes
McLean 2015	USA	Consecutive	Medical records	Yes
Mohl 2018	Germany	Systematic	Medical records	Age
Nunes 2014	Portugal	Systematic	Medical records	Yes
Ohmit 2014	USA	Consecutive	Medical records	Yes
Pebody 2013	UK	Systematic	Medical records	Age

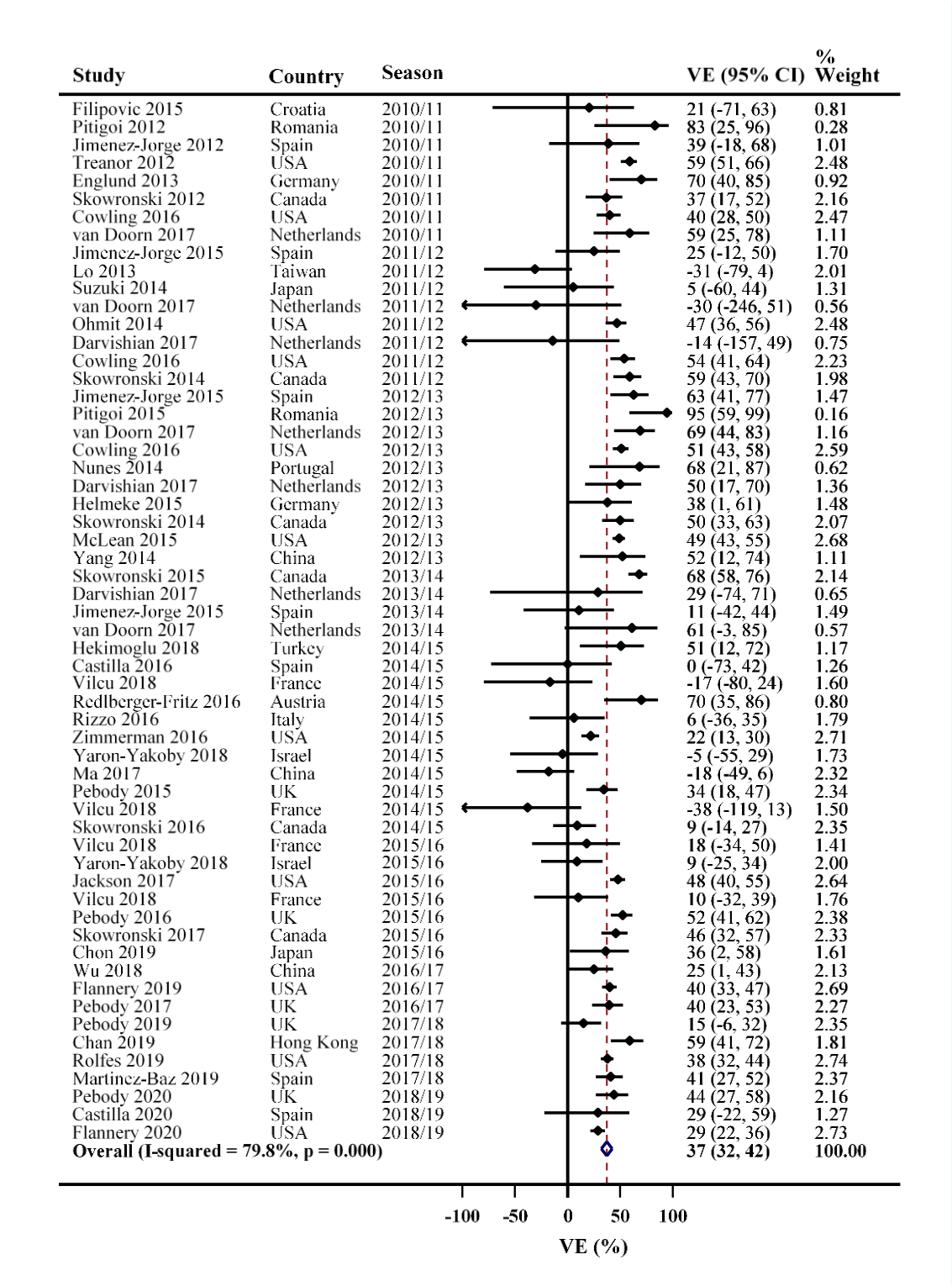
Pebody 2013	UK	Systematic	Medical records	Age
Pebody 2015	UK	Systematic	Medical records	Age
Pebody 2016	UK	Systematic	Medical records	Age
Pebody 2017	UK	Systematic	Medical records	Age
Pebody 2019	UK	Systematic	Medical records	No
Pebody 2020	UK	Systematic	Medical records	Yes
Pierse 2016	New Zealand	Consecutive	Medical records	Yes
Pitigoi 2012	Romania	Consecutive	Medical records	Yes
Pitigoi 2015	Romania	Consecutive	Medical records	Age
Powell 2019	USA	Consecutive	Medical records	Comorbidity
Redlberger-Fritz 2016	Austria	Consecutive	Medical records	Age
Regan 2019	Australia	Systematic	Medical records	Age
Regan 2019	Australia	Systematic	Medical records	Age
Rizzo 2016	Italy	Systematic	Medical records	Yes
Rolfes 2019	USA	Consecutive	Self-reported	Age
Savulescu 2014	Spain	Systematic	Mixed methods	Age
Skowronski 2012	Canada	Consecutive	Self-reported	Yes
Skowronski 2014	Canada	Consecutive	Self-reported	Yes
Skowronski 2014	Canada	Consecutive	Self-reported	Yes
Skowronski 2015	Canada	Consecutive	Self-reported	Yes
Skowronski 2016	Canada	Consecutive	Self-reported	Yes
Skowronski 2017	Canada	Consecutive	Self-reported	Yes
Skowronski 2019	Canada	Consecutive	Self-reported	Yes
Stein 2018	Israel	Systematic	Medical records	Yes
Sullivan 2013	Australia	Systematic	Medical records	Age
Sullivan 2014	Australia	Consecutive	Medical records	Age
Suzuki 2014	Japan	Consecutive	Medical records	Yes
Treanor 2012	USA	Consecutive	Medical records	Age
Vilcu 2018	France	Systematic	Self-reported	Age
Wang 2016	China	Systematic	Medical records	Yes
Wu 2018	China	Systematic	Medical records	Yes
Yang 2014	China	Systematic	Self-reported	Age
Yaron-Yakoby 2018	Israel	Systematic	Medical records	Age
Zimmerman 2016	USA	Consecutive	Mixed methods	Yes
Van Doorn 2017	Netherlands	Systematic	Not specified	Yes

Appendix 12: Forest plot of adjusted VE against all influenza for the Southern hemisphere



VE = vaccine effectiveness; CI = confidence interval

Appendix 13: Forest plot of adjusted VE against all influenza for the Northern hemisphere



VE = vaccine effectiveness; CI = confidence interval

Appendix 14: Pooled adjusted VE by age group (for study 2).

Influenza type/subtypes and analysed subgroups	No. of studies	Pooled VE for all seasons (95% CI)	I-squared statistic (%)	Publication bias (Egger's test p-value)
<5 years old				
A(H1N1)pdm09				
Northern hemisphere	7	62 (25-81)	71.9	NA
Southern hemisphere	0	-	-	-
A(H3N2)				
Northern hemisphere	7	54 (44-63)	0.0	NA
Southern hemisphere	0	-	-	-
Europe	2	47 (-8-74)	NA	NA
North America	5	55 (44-64)	0.0	NA
Antigenically similar vaccine	3	55 (42-66)	0.0	NA
Antigenically partially similar vaccine	4	53 (35-66)	0.0	NA
Influenza B				
Northern hemisphere	4	58 (31-74)	69.1	NA
Southern hemisphere	0	-	-	-
All influenza				
Northern hemisphere	6	61 (55-67)	0.0	NA
Southern hemisphere	2	7 (-199-71)	NA	NA
5–17 years old				
A(*H1N1)pdm09*				
Northern hemisphere	10	53 (36-65)	37.4	0.15
Southern hemisphere	0	-	-	-
Europe	3	63 (-24-89)	71.2	NA
North America	7	51 (35-62)	18.0	NA
Antigenically similar vaccine	9	51 (33-64)	38.4	NA
Antigenically partially similar vaccine	1	73 (23-91)	NA	NA
A(H3N2)				
Northern hemisphere	13	17 (8-26)	0.0	0.26
Southern hemisphere	0	-	-	-
Europe	4	21 (-29-51)	46.9	NA
North America	9	17 (7-26)	0.0	NA
Antigenically similar vaccine	6	23 (10-35)	0.0	NA
Antigenically partially similar vaccine	5	19 (-9-39)	36.7	5
Antigenically dissimilar vaccine	2	3 (-25-25)	NA	NA
Influenza B				
Northern hemisphere	9	48 (38-56)	17.3	NA
Southern hemisphere	0	-	-	-
Europe	4	57 (38-70)	1.7	NA
North America	5	45 (33-55)	21.0	NA
Antigenically similar vaccine	7	48 (37-58)	28.3	NA
Antigenically partially similar vaccine	1	36 (-16-64)	NA	NA
Antigenically dissimilar vaccine	1	64 (20-83)	NA	NA
All influenza				
Northern hemisphere	16	39 (31-46)	47.0	0.18
Southern hemisphere	0	-	-	-
Europe	5	42 (22-57)	30.2	NA
North America	11	38 (29-46)	54.6	0.13
Antigenically similar vaccine	12	43 (37-49)	14.8	0.04
Antigenically partially similar vaccine	4	17 (2-30)	0.0	NA

18–49 years old				
A(H1N1)pdm09				
Northern hemisphere	10	50 (43-56)	0.0	0.00
Southern hemisphere	0	-	-	-
Europe	1	60 (36-75)	NA	NA
North America	9	49 (42-55)	0.0	NA
A(H3N2)				
Northern hemisphere	13	17 (8-26)	23.9	0.35
Southern hemisphere	0	-	-	-
Europe	2	27 (-12-52)	NA	NA
North America	11	17 (7-26)	34.2	0.38
Antigenically similar vaccine	8	25 (14-34)	8.6	NA
Antigenically partially similar vaccine	4	12 (-2-24)	0.0	NA
Antigenically dissimilar vaccine	1	-3 (-29-18)	NA	NA
Influenza B				
Northern hemisphere	9	48 (33-59)	47.1	NA
Southern hemisphere	0	-	-	-
Europe	2	44 (8-66)	NA	NA
North America	7	48 (30-62)	60.0	NA
Antigenically similar vaccine	7	48 (29-61)	60.0	NA
Antigenically partially similar vaccine	1	51 (3-75)	NA	NA
Antigenically dissimilar vaccine	1	40 (-51-76)	NA	NA
All influenza				
Northern hemisphere	14	37 (29-44)	63.2	0.04
Southern hemisphere	0	-	-	-
Europe	1	55 (34-70)	NA	NA
North America	13	35 (27-42)	61.5	0.08
Antigenically similar vaccine	12	40 (33-46)	47.8	0.08
Antigenically partially similar vaccine	2	18 (1-32)	NA	NA
50–64 years old				
A(H1N1)pdm09				
Northern hemisphere	4	38 (6-60)	79.7	NA
Southern hemisphere	0	-	-	-
A(H3N2)				
Northern hemisphere	6	25 (5-41)	64.5	NA
Southern hemisphere	0	-	-	-
Antigenically similar vaccine	2	42 (17-59)	NA	NA
Antigenically partially similar vaccine	3	9 (-26-34)	42.6	NA
Antigenically dissimilar vaccine	1	18 (-13-40)	NA	NA
Influenza B				
Northern hemisphere	2	45 (28-58)	NA	NA
Southern hemisphere	0	-	-	-
All influenza				
Northern hemisphere	7	38 (22-50)	78.3	NA
Southern hemisphere	0	-	-	-
Antigenically similar vaccine	5	44 (26-57)	78.5	NA
Antigenically partially similar vaccine	2	19 (3-33)	NA	NA
≥65 years old				
A(H1N1)pdm09				
Northern hemisphere	9	47 (31-60)	13.2	NA
Southern hemisphere	0	-	-	-
Europe	3	50 (12-72)	10.0	NA
North America	6	47 (25-62)	27.8	NA

A(H3N2)				
Northern hemisphere	14	11 (-4-23)	0.0	0.35
Southern hemisphere	2	49 (1-73)	NA	NA
Europe	7	-16 (-60-16)	0.0	NA
North America	7	17 (1-31)	0.0	NA
Oceania	2	49 (1-73)	NA	NA
Antigenically similar vaccine	6	11 (-19-34)	19.4	NA
Antigenically partially similar vaccine	6	20 (-12-42)	32.4	NA
Antigenically dissimilar vaccine	4	7 (-25-31)	0.0	NA
Influenza B				
Northern hemisphere	11	24 (1-41)	0.0	0.60
Southern hemisphere	1	64 (19-84)	NA	NA
Europe	7	30 (-6-53)	15.5	NA
North America	4	17 (-18-42)	0.0	NA
Oceania	1	64 (19-84)	NA	NA
Antigenically similar vaccine	8	29 (2-48)	19.3	NA
Antigenically partially similar vaccine	1	19 (-161-75)	NA	NA
Antigenically dissimilar vaccine	3	29 (-89-73)	36.4	NA
All influenza				
Northern hemisphere	19	25 (15-33)	0.0	0.06
Southern hemisphere	5	52 (25-70)	7.3	NA
Asia	1	71 (-167-97)	NA	NA
Europe	8	21 (-7-41)	28.4	NA
North America	10	27 (16-36)	0.0	0.02
Oceania	5	52 (25-70)	7.3	NA
Antigenically similar vaccine	17	33 (22-42)	13.9	0.03
Antigenically partially similar vaccine	6	17 (-5-34)	0.0	NA
Antigenically dissimilar vaccine	1	20 (-48-57)	NA	NA

VE = vaccine effectiveness; CI = confidence interval; NA = not applicable

Group D: Supplementary information for Chapter 5

Appendix 15: Pooled adjusted VE by age group (for study 3).

Age group Influenza type/subtype Analysed subgroups	Number of studies	Pooled VE across all seasons (95% CI)	I-squared statistic (%)	Publication bias (Egger test p-value)
<5 years old				
A(H1N1)pdm09				
Respiratory specimen swab: ≤7 days	5	54 (-7-80)	71.2	N/A
Adjusted age	2	78 (-54-97)	75.8	N/A
Adjusted age & medical conditions	3	34 (-136-81)	77.6	N/A
A(*H3N2)*				
Vaccination status: Medical records	2	47 (-8-74)	0.0	N/A
Respiratory specimen swab: ≤7 days	5	54 (42-64)	0.0	N/A
Adjusted age	4	56 (43-66)	0.0	N/A
Adjusted age & medical conditions	1	39 (-36-73)	N/A	N/A
All influenza				
Vaccination status: Medical records	2	67 (40-81)	0.0	N/A
Respiratory specimen swab: ≤7 days	3	58 (49-66)	3.5	N/A
Respiratory specimen swab: ≤4 days	2	7 (-199-71)	0.0	N/A
Adjusted age	5	57 (48-65)	0.2	N/A
5–17 years old				
A(H1N1)pdm09				
Vaccination status: Medical records	1	63 (23-82)	N/A	N/A
Respiratory specimen swab: ≤7 days	6	54 (38-65)	0.0	N/A
Adjusted age	3	52 (29-67)	0.0	N/A
Adjusted age & medical conditions	3	56 (31-72)	0.0	N/A
A(*H3N2)*				
Vaccination status: Medical records	2	46 (-28-77)	65.4	N/A
Respiratory specimen swab: ≤7 days	6	19 (4-31)	0.0	N/A
Adjusted age	3	18 (-2-34)	0.0	N/A
Adjusted age & medical conditions	3	27 (-11-52)	57.7	N/A

Influenza B				
Vaccination status: Medical records	4	56 (35-70)	6.1	N/A
Respiratory specimen swab: ≤7 days	6	50 (36-61)	23.8	N/A
Adjusted age	6	50 (36-61)	23.8	N/A
All influenza				
Vaccination status: Medical records	10	51 (41-59)	0.0	0.290
Respiratory specimen swab: ≤7 days	14	46 (38-53)	24.9	0.144
Adjusted age	6	48 (36-58)	42.7	N/A
Adjusted age & medical conditions	5	43 (27-56)	36.2	N/A
18–49 years old				
A(H1N1)pdm09				
Vaccination status: Medical records	4	48 (38-57)	0.0	N/A
Vaccination status: Self-reported	3	66 (39-82)	0.0	N/A
Respiratory specimen swab: ≤7 days	11	52 (46-58)	0.0	0.050
Adjusted age	6	49 (40-57)	0.0	N/A
Adjusted age & medical conditions	3	55 (45-63)	0.0	N/A
A(*H3N2)*				
Vaccination status: Medical records	3	32 (17-45)	0.0	N/A
Vaccination status: Self-reported	3	32 (4-51)	0.0	N/A
Respiratory specimen swab: ≤7 days	10	22 (9-33)	32.9	0.596
Adjusted age	4	23 (2-39)	25.6	N/A
Adjusted age & medical conditions	4	20 (-11-42)	61.7	N/A
Influenza B				
Vaccination status: Medical records	5	60 (44-72)	32.9	N/A
Vaccination status: Self-reported	3	50 (21-69)	0.0	N/A
Respiratory specimen swab: ≤7 days	10	49 (32-62)	55.2	0.917
Adjusted age	7	49 (25-65)	68.4	N/A
Adjusted age & medical conditions	1	51 (3-75)	N/A	N/A
All influenza				
Vaccination status: Medical records	6	48 (41-54)	10.4	N/A

Vaccination status: Self-reported	3	45 (29-58)	0.0	N/A
Respiratory specimen swab: ≤7 days	13	42 (33-50)	63.3	0.135
Adjusted age	7	46 (37-54)	46.2	N/A
Adjusted age & medical conditions	4	36 (15-52)	76.9	N/A
50–64 years old				
A(H1N1)pdm09				
Vaccination status: Medical records	3	10 (-15-29)	0.0	N/A
Respiratory specimen swab: ≤7 days	5	38 (1-61)	85.5	N/A
Adjusted age	3	10 (-15-29)	0.0	N/A
Adjusted age & medical conditions	2	64 (54-72)	0.0	N/A
A(*H3N2)*				
Vaccination status: Medical records	1	52 (34-65)	N/A	N/A
Respiratory specimen swab: ≤7 days	2	37 (-6-63)	81.3	N/A
Adjusted age & medical conditions	2	37 (-6-63)	81.3	N/A
Influenza B				
Vaccination status: Medical records	3	42 (12-62)	20.6	N/A
Respiratory specimen swab: ≤7 days	3	42 (12-62)	20.6	N/A
Adjusted age	3	42 (12-62)	20.6	N/A
All influenza				
Vaccination status: Medical records	5	40 (12-59)	82.3	N/A
Respiratory specimen swab: ≤7 days	6	37 (14-54)	80.3	N/A
Adjusted age	3	23 (4-38)	16.0	N/A
Adjusted age & medical conditions	3	50 (16-71)	86.8	N/A
≥65 years old				
A(H1N1)pdm09				
Vaccination status: Medical records	6	49 (24-66)	48.1	N/A
Vaccination status: Self-reported	2	49 (4-73)	0.0	N/A
Respiratory specimen swab: ≤7 days	10	51 (38-62)	18.1	0.492
Adjusted age	4	63 (47-74)	0.0	N/A
Adjusted age & medical conditions	5	46 (23-62)	33.0	N/A

A(*H3N2)*				
Vaccination status: Medical records	8	-4 (-37-21)	11.8	N/A
Vaccination status: Self-reported	1	17 (-64-58)	N/A	N/A
Respiratory specimen swab: ≤7 days	10	4 (-18-22)	0.0	0.169
Adjusted age	4	5 (-55-42)	31.2	N/A
Adjusted age & medical conditions	4	8 (-20-30)	0.0	N/A
Influenza B				
Vaccination status: Medical records	10	23 (-17-49)	37.2	0.358
Vaccination status: Self-reported	2	15 (-77-59)	0.0	N/A
Respiratory specimen swab: ≤7 days	12	23 (-9-45)	23.9	0.308
Adjusted age	8	14 (-43-49)	45.3	N/A
Adjusted age & medical conditions	2	15 (-77-59)	0.0	N/A
All influenza				
Vaccination status: Medical records	11	31 (17-43)	0.0	0.710
Vaccination status: Self-reported	3	38 (9-58)	0.0	N/A
Respiratory specimen swab: ≤7 days	15	32 (21-42)	0.0	0.930
Respiratory specimen swab: ≤4 days	2	58 (9-81)	0.0	N/A
Adjusted age	9	37 (22-50)	0.0	0.904
Adjusted age & medical conditions	7	32 (17-45)	0.0	N/A

VE = vaccine effectiveness; CI = confidence interval; N/A = not applicable

References

1. Payne S. Family Orthomyxoviridae. *Viruses: From Understanding to Investigation.* 2017:197-208.
2. Bouvier NM, Palese P. The biology of influenza viruses. *Vaccine.* 2008;26:D49-D53.
3. Skelton RM, Huber VC. Comparing Influenza Virus Biology for Understanding Influenza D Virus. *Viruses-Basel.* 2022;14(5):1036.
4. Herz C, Stavnezer E, Krug R, Gurney T, Jr. Influenza virus, an RNA virus, synthesizes its messenger RNA in the nucleus of infected cells. *Cell.* 1981;26(3 Pt 1):391-400.
5. Kumar B, Asha K, Khanna M, Ronsard L, Meseko CA, Sanicas M. The emerging influenza virus threat: status and new prospects for its therapy and control. *Arch Virol.* 2018;163(4):831-844.
6. Briese T, Chowdhary R, Travassos da Rosa A, et al. Upolu virus and Aransas Bay virus, two presumptive bunyaviruses, are novel members of the family Orthomyxoviridae. *J Virol.* 2014;88(10):5298-5309.
7. Tang JW, Shetty N, Lam TT, Hon KL. Emerging, novel, and known influenza virus infections in humans. *Infect Dis Clin North Am.* 2010;24(3):603-617.
8. Wong SS, Yuen KY. Avian influenza virus infections in humans. *Chest.* 2006;129(1):156-168.
9. Santibanez S, Fiore AE, Merlin TL, Redd S. A Primer on Strategies for Prevention and Control of Seasonal and Pandemic Influenza. *Am J Public Health.* 2009;99:S216-S224.
10. Leung NHL. Transmissibility and transmission of respiratory viruses. *Nat Rev Microbiol.* 2021;19(8):528-545.
11. Brankston G, Gitterman L, Hirji Z, Lemieux C, Gardam M. Transmission of influenza A in human beings. *Lancet Infect Dis.* 2007;7(4):257-265.
12. Killingley B, Nguyen-Van-Tam J. Routes of influenza transmission. *Influenza Other Respir Viruses.* 2013;7 Suppl 2:42-51.
13. Cowling BJ, Ip DKM, Fang VJ, et al. Aerosol transmission is an important mode of influenza A virus spread. *Nat Commun.* 2013;4:1935.
14. Carrat F, Vergu E, Ferguson NM, et al. Time lines of infection and disease in human influenza: A review of volunteer challenge studies. *Am J Epidemiol.* 2008;167(7):775-785.

15. Lessler J, Reich NG, Brookmeyer R, Perl TM, Nelson KE, Cummings DAT. Incubation periods of acute respiratory viral infections: a systematic review. *Lancet Infect Dis.* 2009;9(5):291-300.
16. Donnelly CA, Finelli L, Cauchemez S, et al. Serial Intervals and the Temporal Distribution of Secondary Infections within Households of 2009 Pandemic Influenza A (H1N1): Implications for Influenza Control Recommendations. *Clin Infect Dis.* 2011;52:S123-S130.
17. Cowling BJ, Fang VJ, Riley S, Peiris JSM, Leung GM. Estimation of the Serial Interval of Influenza. *Epidemiology.* 2009;20(3):344-347.
18. Vink MA, Bootsma MCJ, Wallinga J. Serial Intervals of Respiratory Infectious Diseases: A Systematic Review and Analysis. *Am J Epidemiol.* 2014;180(9):865-875.
19. Ng S, Lopez R, Kuan G, et al. The Timeline of Influenza Virus Shedding in Children and Adults in a Household Transmission Study of Influenza in Managua, Nicaragua. *Pediatr Infect Dis J.* 2016;35(5):583-586.
20. Lee N, Chan PKS, Hui DSC, et al. Viral Loads and Duration of Viral Shedding in Adult Patients Hospitalized with Influenza. *J Infect Dis.* 2009;200(4):492-500.
21. Moghadami M. A Narrative Review of Influenza: A Seasonal and Pandemic Disease. *Iran J Med Sci.* 2017;42(1):2-13.
22. Maier HE, Lopez R, Sanchez L, et al. Obesity Increases the Duration of Influenza A Virus Shedding in Adults. *J Infect Dis.* 2018;218(9):1378-1382.
23. Leekha S, Zitterkopf NL, Espy MJ, Smith TF, Thompson RL, Sampathkumar P. Duration of influenza a virus shedding in hospitalized patients and implications for infection control. *Infect Cont Hosp Ep.* 2007;28(9):1071-1076.
24. Memoli MJ, Athota R, Reed S, et al. The Natural History of Influenza Infection in the Severely Immunocompromised vs Nonimmunocompromised Hosts. *Clin Infect Dis.* 2014;58(2):214-224.
25. Taubenberger JK, Morens DM. The pathology of influenza virus infections. *Annu Rev Pathol-Mech.* 2008;3:499-522.
26. Poon LLM, Song T, Rosenfeld R, et al. Quantifying influenza virus diversity and transmission in humans. *Nat Genet.* 2016;48(2):195-200.

27. Mosnier A, Caini S, Daviaud I, et al. Clinical Characteristics Are Similar across Type A and B Influenza Virus Infections. *Plos One.* 2015;10(9):e0136186.
28. Cox N. Influenza seasonality: timing and formulation of vaccines. *B World Health Organ.* 2014;92(5):311-311.
29. Yewdell JW. Antigenic drift: Understanding COVID-19. *Immunity.* 2021;54(12):2681-2687.
30. Treanor J. Influenza vaccine--outmaneuvering antigenic shift and drift. *N Engl J Med.* 2004;350(3):218-220.
31. Taubenberger JK, Kash JC. Influenza virus evolution, host adaptation, and pandemic formation. *Cell Host Microbe.* 2010;7(6):440-451.
32. Borland S, Gracieux P, Jones M, Mallet F, Yugueros-Marcos J. Influenza A Virus Infection in Cats and Dogs: A Literature Review in the Light of the "One Health" Concept. *Front Public Health.* 2020;8:83.
33. Wahlgren J. Influenza A viruses: an ecology review. *Infect Ecol Epidemiol.* 2011;1:10.3402/iee.v3401i3400.6004.
34. Frymus T, Belak S, Egberink H, et al. Influenza Virus Infections in Cats. *Viruses-Basel.* 2021;13(8):1435.
35. Kim H, Webster RG, Webby RJ. Influenza Virus: Dealing with a Drifting and Shifting Pathogen. *Viral Immunol.* 2018;31(2):174-183.
36. Hause BM, Collin EA, Liu R, et al. Characterization of a novel influenza virus in cattle and Swine: proposal for a new genus in the Orthomyxoviridae family. *mBio.* 2014;5(2):e00031-00014.
37. Schild GC. The influenza virus: Antigenic composition and immune response. *Postgrad Med J.* 1979;55(640):87-97.
38. Watanabe H, Mackenzie JS. The Detection of Influenza-a Virus-Antigens in Cultured-Cells by Enzyme-Linked Immunosorbent-Assay. *Archives of Virology.* 1981;67(1):31-43.
39. Kosik I, Yewdell JW. Influenza Hemagglutinin and Neuraminidase: Yin-Yang Proteins Coevolving to Thwart Immunity. *Viruses-Basel.* 2019;11(4):346.
40. McAuley JL, Gilbertson BP, Trifkovic S, Brown LE, McKimm-Breschkin JL. Influenza Virus Neuraminidase Structure and Functions. *Front Microbiol.* 2019;10:39.

41. Amaro RE, Ieong PU, Huber G, et al. A Computational Assay that Explores the Hemagglutinin/Neuraminidase Functional Balance Reveals the Neuraminidase Secondary Site as a Novel Anti-Influenza Target. *Acs Central Sci.* 2018;4(11):1570-1577.
42. Das K, Aramini JM, Ma LC, Krug RM, Arnold E. Structures of influenza A proteins and insights into antiviral drug targets. *Nat Struct Mol Biol.* 2010;17(5):530-538.
43. A Revision of the System of Nomenclature for Influenza-Viruses - a Who Memorandum. *B World Health Organ.* 1980;58(4):585-591.
44. Hinshaw VS, Webster RG, Rodriguez RJ. Influenza-a Viruses - Combinations of Hemagglutinin and Neuraminidase Subtypes Isolated from Animals and Other Sources. *Archives of Virology.* 1979;62(4):281-290.
45. Xu CL, Chan KH, Tsang TK, et al. Comparative Epidemiology of Influenza B Yamagata- and Victoria-Lineage Viruses in Households. *Am J Epidemiol.* 2015;182(8):705-713.
46. Caini S, Kusznierz G, Garate VV, et al. The epidemiological signature of influenza B virus and its B/Victoria and B/Yamagata lineages in the 21st century. *Plos One.* 2019;14(9):e0222381.
47. Patrozou E, Mermel LA. Does Influenza Transmission Occur from Asymptomatic Infection or Prior to Symptom Onset? *Public Health Rep.* 2009;124(2):193-196.
48. Young K, Gemmill I, Harrison R. Summary of the NACI Seasonal Influenza Vaccine Statement for 2020-2021. *Can Commun Dis Rep.* 2020;46(5):132-137.
49. Troeger CE, Blacker BF, Khalil IA, et al. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: an analysis for the Global Burden of Disease Study 2017. *Lancet Resp Med.* 2019;7(1):69-89.
50. Iuliano AD, Roguski KM, Chang HH. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet.* 2018;391(10127):1285-1300.
51. World Health Organization. Influenza (Seasonal). The World Health Organization. https://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal). Accessed August 15, 2022.
52. Centers for Disease Control and Prevention. Disease burden of influenza. National Center for Immunization and Respiratory Diseases (NCIRD).

https://www.cdc.gov/flu/about/disease/burden.htm. Published 2022. Accessed August 15, 2022.

53. Ozawa S, Portnoy A, Getaneh H, et al. Modeling The Economic Burden Of Adult Vaccine-Preventable Diseases In The United States. *Health Aff (Millwood).* 2016;35(11):2124-2132.
54. Schanzer DL, Sevenhuysen C, Winchester B, Mersereau T. Estimating influenza deaths in Canada, 1992-2009. *Plos One.* 2013;8(11):e80481.
55. Ng C, Ye L, Noorduyn SG, et al. Resource utilization and cost of influenza requiring hospitalization in Canadian adults: A study from the serious outcomes surveillance network of the Canadian Immunization Research Network. *Influenza Other Respir Viruses.* 2018;12(2):232-240.
56. Canadian Healthcare Influenza Immunization Network. Influenza Fact Sheet: True or False Quiz Answer Sheet. Immunize Canada. https://www.immunize.ca/sites/default/files/resources/1841e.pdf. Accessed January 2, 2023.
57. Government of Canada. Flu (influenza): For health professionals. Government of Canada. https://www.canada.ca/en/public-health/services/diseases/flu-influenza/health-professionals.html. Published 2022. Accessed July 16, 2022.
58. Anderson RM, May RM. Vaccination and Herd-Immunity to Infectious-Diseases. *Nature.* 1985;318(6044):323-329.
59. Brisson M, Edmunds WJ. Economic evaluation of vaccination programs: The impact of herd-immunity. *Med Decis Making.* 2003;23(1):76-82.
60. Tessmer A, Welte T, Schmidt-Ott R, et al. Influenza vaccination is associated with reduced severity of community-acquired pneumonia. *Eur Respir J.* 2011;38(1):147-153.
61. Godoy P, Romero A, Soldevila N, et al. Influenza vaccine effectiveness in reducing severe outcomes over six influenza seasons, a case-case analysis, Spain, 2010/11 to 2015/16. *Eurosurveillance.* 2018;23(43):13-21.
62. Andre FE, Booy R, Bock HL, et al. Vaccination greatly reduces disease, disability, death and inequity worldwide. *Bull World Health Organ.* 2008;86(2):140-146.
63. European Centre for Disease Prevention and Control. Seasonal influenza vaccines: Timing of influenza vaccination. ECDC. https://www.ecdc.europa.eu/en/seasonal-

influenza/prevention-and-control/vaccines/timing. Published 2022. Accessed August 15, 2022.

64. Carter NJ, Curran MP. Live Attenuated Influenza Vaccine (FluMist (R); Fluenz (TM)) A Review of its Use in the Prevention of Seasonal Influenza in Children and Adults. *Drugs.* 2011;71(12):1591-1622.
65. Harper SA, Fukuda K, Cox NJ, Bridges CB. Using Live, Attenuated Influenza Vaccine for Prevention and Control of Influenza. *MMWR.* 2003;52(RR13):1-8.
66. Lamontagne JR, Noble GR, Quinnan GV, et al. Summary of Clinical-Trials of Inactivated Influenza Vaccine - 1978. *Rev Infect Dis.* 1983;5(4):723-736.
67. Boerner LK. The Flu Shot and the Egg. *Acs Central Sci.* 2020;6(2):89-92.
68. Rajaram S, Wojcik R, Moore C, et al. The impact of candidate influenza virus and egg-based manufacture on vaccine effectiveness: Literature review and expert consensus. *Vaccine.* 2020;38(38):6047-6056.
69. Manini I, Domnich A, Amicizia D, et al. Flucelvax (Optaflu) for seasonal influenza. *Expert Rev Vaccines.* 2015;14(6):789-804.
70. Doroshenko A, Halperin SA. Trivalent MDCK cell culture-derived influenza vaccine Optaflu (R) (Novartis Vaccines). *Expert Rev Vaccines.* 2009;8(6):679-688.
71. Centers for Disease Control and Prevention. Different Types of Flu Vaccines. National Center for Immunization and Respiratory Diseases (NCIRD). https://www.cdc.gov/flu/prevent/different-flu-vaccines.htm. Published 2021. Accessed August 15, 2022.
72. Sedova ES, Shcherbinin DN, Migunov AI, et al. Recombinant Influenza Vaccines. *Acta Naturae.* 2012;4(4):17-27.
73. Cox MMJ, Patriarca PA, Treanor J. FluBlok, a recombinant hemagglutinin influenza vaccine. *Influenza Other Resp.* 2008;2(6):211-219.
74. Robertson CA, DiazGranados CA, Decker MD, Chit A, Mercer M, Greenberg DP. Fluzone (R) High-Dose Influenza Vaccine. *Expert Rev Vaccines.* 2016;15(12):1495-1505.
75. Diaco M, Chang LJ, Seet B, et al. Introductory paper: High-dose influenza vaccine Preface. *Vaccine.* 2021;39:A1-A5.

76. Tregoning JS, Russell RF, Kinnear E. Adjuvanted influenza vaccines. *Hum Vacc Immunother.* 2018;14(3):550-564.
77. Podda A. The adjuvanted influenza vaccines with novel adjuvants: experience with the MF59-adjuvanted vaccine. *Vaccine.* 2001;19(17-19):2673-2680.
78. Baxter D. Evaluating the case for trivalent or quadrivalent influenza vaccines. *Hum Vacc Immunother.* 2016;12(10):2712-2717.
79. Gresset-Bourgeois V, Leventhal PS, Pepin S, et al. Quadrivalent inactivated influenza vaccine (VaxigripTetra (TM)). *Expert Rev Vaccines.* 2018;17(1):1-11.
80. European Medicines Agency. MedImmune. Fluenz® intranasal live attenuated influenza vaccine: EU summary of product characteristics. In. Amsterdam, The Netherlands.
81. U. S. Food & Drug Administration. MedImmune LLC. FluMist® intranasal live attentuated influenza vaccine: US prescribing information. In. Silver Spring, MD, USA.
82. Weir JP, Gruber MF. An overview of the regulation of influenza vaccines in the United States. *Influenza Other Respir Viruses.* 2016;10(5):354-360.
83. Ng S, Cowling BJ, Fang VJ, et al. Effects of Oseltamivir Treatment on Duration of Clinical Illness and Viral Shedding and Household Transmission of Influenza Virus. *Clin Infect Dis.* 2010;50(5):707-714.
84. Fry AM, Goswami D, Nahar K, et al. Efficacy of oseltamivir treatment started within 5 days of symptom onset to reduce influenza illness duration and virus shedding in an urban setting in Bangladesh: a randomised placebo-controlled trial. *Lancet Infect Dis.* 2014;14(2):109-118.
85. McKimm-Breschkin JL. Influenza neuraminidase inhibitors: antiviral action and mechanisms of resistance. *Influenza Other Resp.* 2013;7:25-36.
86. Wester A, Shetty AK. Peramivir injection in the treatment of acute influenza: a review of the literature. *Infect Drug Resist.* 2016;9:201-214.
87. Smith KJ, Roberts MS. Cost-effectiveness of newer treatment strategies for influenza. *Am J Med.* 2002;113(4):300-307.
88. Moscona A. Drug therapy - Neuraminidase inhibitors for influenza. *New Engl J Med.* 2005;353(13):1363-1373.
89. Ison MG. Antiviral Treatments. *Clin Chest Med.* 2017;38(1):139-153.

90. Belshe RB, Burk B, Newman F, Cerruti RL, Sim IS. Resistance of Influenza-a Virus to Amantadine and Rimantadine - Results of One Decade of Surveillance. *J Infect Dis.* 1989;159(3):430-435.
91. Lee N, Hurt AC. Neuraminidase inhibitor resistance in influenza: a clinical perspective. *Curr Opin Infect Dis.* 2018;31(6):520-526.
92. Nitsch-Osuch A, Brydak LB. Influenza viruses resistant to neuraminidase inhibitors. *Acta Biochim Pol.* 2014;61(3):505-508.
93. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. *New Engl J Med.* 2018;379(10):913-923.
94. Heo YA. Baloxavir: First Global Approval. *Drugs.* 2018;78(6):693-697.
95. Okoli GN, Otete HE, Beck CR, Nguyen-Van-Tam JS. Use of Neuraminidase Inhibitors for Rapid Containment of Influenza: A Systematic Review and Meta-Analysis of Individual and Household Transmission Studies. *Plos One.* 2014;9(12):e113633.
96. Jefferson T, Jones MA, Doshi P, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Db Syst Rev.* 2014;2014(4):CD008965.
97. Heneghan CJ, Onakpoya I, Jones MA, et al. Neuraminidase inhibitors for influenza: a systematic review and meta-analysis of regulatory and mortality data. *Health Technol Asses.* 2016;20(42):1-242.
98. Higashiguchi M, Matsumoto T, Fujii T. A meta-analysis of laninamivir octanoate for treatment and prophylaxis of influenza. *Antivir Ther.* 2018;23(2):157-165.
99. Louie JK, Yang S, Samuel MC, Uyeki TM, Schechter R. Neuraminidase inhibitors for critically ill children with influenza. *Pediatrics.* 2013;132(6):e1539-1545.
100. Louie JK, Yang S, Acosta M, et al. Treatment with neuraminidase inhibitors for critically ill patients with influenza A (H1N1)pdm09. *Clin Infect Dis.* 2012;55(9):1198-1204.
101. Muthuri SG, Venkatesan S, Myles PR, et al. Effectiveness of neuraminidase inhibitors in reducing mortality in patients admitted to hospital with influenza A H1N1pdm09 virus infection: a meta-analysis of individual participant data. *Lancet Respir Med.* 2014;2(5):395-404.

102. Kuo YC, Lai CC, Wang YH, Chen CH, Wang CY. Clinical efficacy and safety of baloxavir marboxil in the treatment of influenza: A systematic review and meta-analysis of randomized controlled trials. *J Microbiol Immunol.* 2021;54(5):865-875.
103. Ikematsu H, Hayden FG, Kawaguchi K, et al. Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts. *New Engl J Med.* 2020;383(4):309-320.
104. Rothberg MB, Rose DN. Vaccination versus treatment of influenza in working adults: a cost-effectiveness analysis. *Am J Med.* 2005;118(1):68-77.
105. Muennig PA, Khan K. Cost-effectiveness of vaccination versus treatment of influenza in healthy adolescents and adults. *Clin Infect Dis.* 2001;33(11):1879-1885.
106. Yang KC, Hung HF, Chen MK, et al. Cost-effectiveness analysis of universal influenza vaccination: Application of the susceptible-infectious-complication-recovery model. *Int J Infect Dis.* 2018;73:102-108.
107. Fukushima W, Hirota Y. Basic principles of test-negative design in evaluating influenza vaccine effectiveness. *Vaccine.* 2017;35(36):4796-4800.
108. Domnich A, Manini I, Panatto D, Calabro GE, Montomoli E. Immunogenicity Measures of Influenza Vaccines: A Study of 1164 Registered Clinical Trials. *Vaccines-Basel.* 2020;8(2):325.
109. Song JW, Chung KC. Observational Studies: Cohort and Case-Control Studies. *Plast Reconstr Surg.* 2010;126(6):2234-2242.
110. Setia MS. Methodology Series Module 2: Case-control Studies. *Indian J Dermatol.* 2016;61(2):146-151.
111. Lewallen S, Courtright P. Epidemiology in practice: case-control studies. *Community Eye Health.* 1998;11(28):57-58.
112. Hayden GF, Kramer MS, Horwitz RI. The case-control study. A practical review for the clinician. *JAMA.* 1982;247(3):326-331.
113. Chua H, Feng S, Lewnard JA, et al. The use of test-negative controls to monitor vaccine effectiveness: a systematic review of methodology. *Epidemiology.* 2020;31(1):43–64.
114. Okoli GN, Sanders RD, Myles P. Demystifying propensity scores. *Brit J Anaesth.* 2014;112(1):13-15.

115. Effectiveness of vaccine against medical consultation due to laboratory-confirmed influenza: results from a sentinel physician pilot project in British Columbia, 2004-2005. *Can Commun Dis Rep.* 2005;31(18):181-191.

116. Benin AL, O'Brien KL, Watt JP, et al. Effectiveness of the 23-valent polysaccharide vaccine against invasive pneumococcal disease in Navajo adults. *J Infect Dis.* 2003;188(1):81-89.

117. Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Pneumococcal polysaccharide vaccine efficacy. An evaluation of current recommendations. *JAMA.* 1993;270(15):1826-1831.

118. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med.* 1991;325(21):1453-1460.

119. Jackson ML, Nelson JC. The test-negative design for estimating influenza vaccine effectiveness. *Vaccine.* 2013;31(17):2165-2168.

120. Sullivan SG, Tchetgen Tchetgen EJ, Cowling BJ. Theoretical Basis of the Test-Negative Study Design for Assessment of Influenza Vaccine Effectiveness. *Am J Epidemiol.* 2016;184(5):345-353.

121. Jeremiah Bella J, Selvarangan R. Evaluation of the Alere i Influenza A&B Nucleic Acid Amplification Test by Use of Respiratory Specimens Collected in Viral Transport Medium. *J Clin Microbiol.* 2014;52(11):3992–3995.

122. Vemula SV, Zhao J, Liu J, Wang X, Biswas S, Hewlett I. Current Approaches for Diagnosis of Influenza Virus Infections in Humans. *Viruses.* 2016;8(4):96.

123. Schmier JK, Halpern MT. Patient recall and recall bias of health state and health status. *Expert Rev Pharmacoecon Outcomes Res.* 2004;4(2):159-163.

124. Latkin CA, Edwards C, Davey-Rothwell MA, Tobin KE. The relationship between social desirability bias and self-reports of health, substance use, and social network factors among urban substance users in Baltimore, Maryland. *Addict Behav.* 2017;73:133-136.

125. De Serres G, Skowronski DM, Wu XW, Ambrose CS. The test-negative design: validity, accuracy and precision of vaccine efficacy estimates compared to the gold standard of randomised placebo-controlled clinical trials. *Euro Surveill.* 2013;18(37):20585.

126. Vandenbroucke JP, Pearce N. Test-Negative Designs Differences and Commonalities with Other Case-Control Studies with "Other Patient" Controls. *Epidemiology.* 2019;30(6):838-844.
127. Wacholder S, McLaughlin JK, Silverman DT, Mandel JS. Selection of controls in case-control studies. I. Principles. *Am J Epidemiol.* 1992;135(9):1019-1028.
128. Jackson ML, Rothman KJ. Effects of imperfect test sensitivity and specificity on observational studies of influenza vaccine effectiveness. *Vaccine.* 2015;33(11):1313-1316.
129. Orenstein EW, De Serres G, Haber AJ, et al. Methodologic issues regarding the use of three observational study designs to assess influenza vaccine effectiveness. *Int J Epidemiol.* 2007;36(3):623-631.
130. Lewnard JA, Tedijanto C, Cowling BJ, Lipsitch M. Measurement of Vaccine Direct Effects Under the Test-Negative Design. *Am J Epidemiol.* 2018;187(12):2686-2697.
131. Ferdinands JM, Shay DK. Magnitude of Potential Biases in a Simulated Case-Control Study of the Effectiveness of Influenza Vaccination. *Clin Infect Dis.* 2012;54(1):25-32.
132. Sullivan SG, Feng S, Cowling BJ. Potential of the test-negative design for measuring influenza vaccine effectiveness: a systematic review. *Expert Rev Vaccines.* 2014;13(12):1571-1591.
133. Okoli GN, Lam OLT, Racovitan F, et al. Seasonal influenza vaccination in older people: A systematic review and meta-analysis of the determining factors. *Plos One.* 2020;15(6):e0234702.
134. Yeung MPS, Lam FLY, Coker R. Factors associated with the uptake of seasonal influenza vaccination in adults: a systematic review. *J Public Health-Uk.* 2016;38(4):746-753.
135. Keilich SR, Bartley JM, Haynes L. Diminished immune responses with aging predispose older adults to common and uncommon influenza complications. *Cell Immunol.* 2019;345:103992.
136. Hernandez-Vargas EA, Wilk E, Canini L, et al. Effects of Aging on Influenza Virus Infection Dynamics. *Journal of Virology.* 2014;88(8):4123-4131.
137. Walker TA, Waite B, Thompson MG, et al. Risk of Severe Influenza Among Adults With Chronic Medical Conditions. *J Infect Dis.* 2020;221(2):183-190.

138. Hancock K, Veguilla V, Lu XH, et al. Cross-Reactive Antibody Responses to the 2009 Pandemic H1N1 Influenza Virus. *New Engl J Med.* 2009;361(20):1945-1952.
139. Foppa IM, Haber M, Ferdinands JM, Shay DK. The case test-negative design for studies of the effectiveness of influenza vaccine. *Vaccine.* 2013;31(30):3104-3109.
140. Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *Int J Epidemiol.* 2006;35(2):337-344.
141. Ozasa K, Fukushima W. Commentary: Test-Negative Design Reduces Confounding by Healthcare-Seeking Attitude in Case-Control Studies. *J Epidemiol.* 2019;29(8):279-281.
142. Zhang L, Wei MW, Jin PF, Li JX, Zhu FC. An evaluation of a test-negative design for EV-71 vaccine from a randomized controlled trial. *Hum Vacc Immunother.* 2021;17(7):2101-2106.
143. Lau LLH, Cowling BJ, Fang VJ, et al. Viral Shedding and Clinical Illness in Naturally Acquired Influenza Virus Infections. *J Infect Dis.* 2010;201(10):1509-1516.
144. Landry ML. Diagnostic tests for influenza infection. *Curr Opin Pediatr.* 2011;23(1):91-97.
145. Levy A, Sullivan SG, Tempone SS, et al. Influenza vaccine effectiveness estimates for Western Australia during a period of vaccine and virus strain stability, 2010 to 2012. *Vaccine.* 2014;32(47):6312-6318.
146. Skowronski DM, Zou M, Sabaiduc S, et al. Interim estimates of 2019/20 vaccine effectiveness during early-season co-circulation of influenza A and B viruses, Canada, February 2020. *Eurosurveillance.* 2020;25(7):2-8.
147. McMenamin J, Andrews N, Robertson C, et al. Effectiveness of seasonal 2012/13 vaccine in preventing laboratory-confirmed influenza infection in primary care in the United Kingdom: mid-season analysis 2012/13. *Eurosurveillance.* 2013;18(5):2-6.
148. Jimenez-Jorge S, Pozo F, Larrauri A, Team cS. Interim influenza vaccine effectiveness: A good proxy for final estimates in Spain in the seasons 2010-2014. *Vaccine.* 2015;33(29):3276-3280.
149. Coleman LA, Kieke B, Irving S, et al. Comparison of influenza vaccine effectiveness using different methods of case detection: Clinician-ordered rapid antigen tests vs. active

surveillance and testing with real-time reverse-transcriptase polymerase chain reaction (rRT-PCR). *Vaccine.* 2011;29(3):387-390.

150. Haber M, An Q, Foppa IM, Shay DK, Ferdinands JM, Orenstein WA. A probability model for evaluating the bias and precision of influenza vaccine effectiveness estimates from case-control studies. *Epidemiol Infect.* 2015;143(7):1417-1426.
151. Shi M, An Q, Ainslie KEC, Haber M, Orenstein WA. A comparison of the test-negative and the traditional case-control study designs for estimation of influenza vaccine effectiveness under nonrandom vaccination. *Bmc Infect Dis.* 2017;17(1):757.
152. Zanobini P, Bonaccorsi G, Lorini C, et al. Global patterns of seasonal influenza activity, duration of activity and virus (sub)type circulation from 2010 to 2020. *Influenza Other Resp.* 2022;16(4):696-706.
153. Saha S, Davis WW. The need for a One Health approach for influenza surveillance. *Lancet Glob Health.* 2022;10(8):e1078-e1079.
154. Yu H, Alonso WJ, Feng L, et al. Characterization of regional influenza seasonality patterns in China and implications for vaccination strategies: spatio-temporal modeling of surveillance data. *PLoS Med.* 2013;10(11):e1001552.
155. Suissa S. Immortal time bias in observational studies of drug effects. *Pharmacoepidemiol Drug Saf.* 2007;16(3):241-249.
156. Matok I, Azoulay L, Yin H, Suissa S. Immortal time bias in observational studies of drug effects in pregnancy. *Birth Defects Res A Clin Mol Teratol.* 2014;100(9):658-662.
157. Hatton P. The Use of the Screening Technique as a Method of Rapidly Estimating Vaccine Efficacy. *Public Health.* 1990;104(1):21-25.
158. Farrington CP. Estimation of Vaccine Effectiveness Using the Screening Method. *Int J Epidemiol.* 1993;22(4):742-746.
159. Cohen AL, Taylor T, Farley MM, et al. An Assessment of the Screening Method to Evaluate Vaccine Effectiveness: The Case of 7-Valent Pneumococcal Conjugate Vaccine in the United States. *Plos One.* 2012;7(8):e41785.
160. Guris D, Strebel PM, Tachdjian R, Bardenheier B, Wharton M, Hadler SC. Effectiveness of the pertussis vaccination program as determined by use of the screening method: United States, 1992-1994. *J Infect Dis.* 1997;176(2):456-463.

161. Cohen C, White JM, Savage EJ, et al. Vaccine effectiveness estimates, 2004-2005 mumps outbreak, England. *Emerg Infect Dis.* 2007;13(1):12-17.
162. Ramsay ME, McVernon J, Andrews NJ, Heath PT, Slack MP. Estimating Haemophilus influenzae type b vaccine effectiveness in England and Wales by use of the screening method. *J Infect Dis.* 2003;188(4):481-485.
163. Seyler T, Bella A, Puzelli S, Donatelli I, Rizzo C, Grp SMW. Estimating pandemic vaccine effectiveness in two Italian regions using the screening method, 2009-2010. *Vaccine.* 2012;30(2):109-111.
164. Falchi A, Souty C, Grisoni ML, et al. Field seasonal influenza vaccine effectiveness Evaluation of the screening method using different sources of data during the 2010/2011 French influenza season. *Hum Vacc Immunother.* 2013;9(11):2453-2459.
165. Thomas HL, Andrews N, Green HK, et al. Estimating vaccine effectiveness against severe influenza in England and Scotland 2011/2012: applying the screening method to data from intensive care surveillance systems. *Epidemiol Infect.* 2014;142(1):126-133.
166. Orenstein WA, Bernier RH, Dondero TJ, et al. Field-Evaluation of Vaccine Efficacy. *B World Health Organ.* 1985;63(6):1055-1068.
167. Minodier L, Blanchon T, Souty C, et al. Influenza vaccine effectiveness: best practice and current limitations of the screening method and their implications for the clinic. *Expert Rev Vaccines.* 2014;13(8):1039-1048.
168. World Health Organization. Global Influenza Surveillance and Response System (GISRS). The WHO. https://www.who.int/initiatives/global-influenza-surveillance-and-response-system. Accessed September 1, 2022.
169. World Health Organization. *A description of the process of seasonal and H5N1 influenza vaccine virus selection and development.* Geneva: The World Health Organization;2007.
170. World Health Organization. *Recommended composition of influenza virus vaccines for use in the 2019- 2020 northern hemisphere influenza season.* Geneva: World Health Organization;2019.
171. Valenciano M, Ciancio BC, Team I-MS. I-MOVE: a European network to measure the effectiveness of influenza vaccines. *Eurosurveillance.* 2012;17(39):11-21.

172. Leung VK, Cowling BJ, Feng S, Sullivan SG. Concordance of interim and final estimates of influenza vaccine effectiveness: a systematic review. *Eurosurveillance.* 2016;21(16):35-50.
173. Haidich AB. Meta-analysis in medical research. *Hippokratia.* 2010;14(Suppl 1):29-37.
174. Higgins JPT, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). In: The Cochrane Collaboration; 2022: www.training.cochrane.org/handbook. Accessed August 17, 2022.
175. Higgins J, Lasserson T, Chandler J, et al. Methodological Expectations of Cochrane Intervention Reviews (MECIR): Standards for the conduct and reporting of new Cochrane Intervention Reviews, reporting of protocols and the planning, conduct and reporting of updates. 2022. https://community.cochrane.org/sites/default/files/uploads/MECIR%20Version%20February%202022.pdf. Accessed August 17, 2022.
176. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71.
177. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. *Journal of Clinical Epidemiology.* 2016;75:40-46.
178. Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. In: York: University of York; 2008.
179. Sullivan SG, Kelly H. Late season interim estimates of influenza vaccine effectiveness reliably predict end of season estimates in Victoria, Australia, 2007 to 2012. *Eurosurveillance.* 2013;18(41):5-11.
180. Scorza FB, Tsyetnitsky V, Donnelly JJ. Universal influenza vaccines: Shifting to better vaccines. *Vaccine.* 2016;34(26):2926-2933.
181. Valesano AL, Fitzsimmons WJ, McCrone JT, et al. Influenza B Viruses Exhibit Lower Within-Host Diversity than Influenza A Viruses in Human Hosts. *Journal of Virology.* 2020;94(5):e01710-01719.
182. Petrova VN, Russell CA. The evolution of seasonal influenza viruses. *Nat Rev Microbiol.* 2018;16(1):47-60.

183. Air GM, Gibbs AJ, Laver WG, Webster RG. Evolutionary changes in influenza B are not primarily governed by antibody selection. *Proc Natl Acad Sci U S A.* 1990;87(10):3884-3888.

184. Ferdinands JM, Gaglani M, Martin ET, et al. Waning Vaccine Effectiveness Against Influenza-Associated Hospitalizations Among Adults, 2015-2016 to 2018-2019, United States Hospitalized Adult Influenza Vaccine Effectiveness Network. *Clin Infect Dis.* 2021;73(4):726-729.

185. Tokars JI, Patel MM, Foppa IM, Reed C, Fry AM, Ferdinands JM. Waning of Measured Influenza Vaccine Effectiveness Over Time: The Potential Contribution of Leaky Vaccine Effect. *Clin Infect Dis.* 2020;71(10):E633-E641.

186. Ray GT, Lewis N, Klein NP, et al. Intraseason Waning of Influenza Vaccine Effectiveness. *Clin Infect Dis.* 2019;68(10):1623-1630.

187. Hu WP, Sjoberg PA, Fries AC, DeMarcus LS, Robbins AS. Waning Vaccine Protection against Influenza among Department of Defense Adult Beneficiaries in the United States, 2016-2017 through 2019-2020 Influenza Seasons. *Vaccines-Basel.* 2022;10(6):888.

188. Dhakal S, Klein SL. Host Factors Impact Vaccine Efficacy: Implications for Seasonal and Universal Influenza Vaccine Programs. *Journal of Virology.* 2019;93(21):e00797-00719.

189. Belongia EA, Sundaram ME, McClure DL, Meece JK, Ferdinands J, VanWormer JJ. Waning vaccine protection against influenza A (H3N2) illness in children and older adults during a single season. *Vaccine.* 2015;33(1):246-251.

190. Kissling E, Nunes B, Robertson C, et al. I-MOVE multicentre case-control study 2010/11 to 2014/15: Is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination? *Eurosurveillance.* 2016;21(16):13-24.

191. Radin JM, Hawksworth AW, Myers CA, Ricketts MN, Hansen EA, Brice GT. Influenza vaccine effectiveness: Maintained protection throughout the duration of influenza seasons 2010-2011 through 2013-2014. *Vaccine.* 2016;34(33):3907-3912.

192. Coudeville L, Bailleux F, Riche B, Megas F, Andre P, Ecochard R. Relationship between haemagglutination-inhibiting antibody titres and clinical protection against influenza: development and application of a bayesian random-effects model. *Bmc Med Res Methodol.* 2010;10:18.

193. European Centre for Disease Prevention and Control (ECDC). Factsheet about seasonal influenza 2019. 2019. https://www.ecdc.europa.eu/en/seasonalinfluenza/facts/factsheet.
194. Bloom-Feshbach K, Alonso WJ, Charu V, et al. Latitudinal Variations in Seasonal Activity of Influenza and Respiratory Syncytial Virus (RSV): A Global Comparative Review. *Plos One.* 2013;8(2):e54445.
195. Caini S, Andrade W, Badur S, et al. Temporal Patterns of Influenza A and B in Tropical and Temperate Countries: What Are the Lessons for Influenza Vaccination? *Plos One.* 2016;11(3):e0152310.
196. Hirve S, Newman LP, Paget J, et al. Influenza Seasonality in the Tropics and Subtropics - When to Vaccinate? *Plos One.* 2016;11(4):e0153003.
197. Moura FEA. Influenza in the tropics. *Curr Opin Infect Dis.* 2010;23(5):415-420.
198. Alonso WJ, Yu C, Viboud C, et al. A global map of hemispheric influenza vaccine recommendations based on local patterns of viral circulation. *Sci Rep-Uk.* 2015;5:17214.
199. Belongia EA, Simpson MD, King JP, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. *Lancet Infect Dis.* 2016;16(8):942-951.
200. Centers for Disease Control and Prevention. Summary of the 2014-2015 Influenza Season. https://www.cdc.gov/flu/pastseasons/1415season.htm#print. Accessed December 4, 2022.
201. Allen JD, Ross TM. H3N2 influenza viruses in humans: Viral mechanisms, evolution, and evaluation. *Hum Vacc Immunother.* 2018;14(8):1840-1847.
202. Tewawong N, Prachayangprecha S, Vichiwattana P, et al. Assessing Antigenic Drift of Seasonal Influenza A(H3N2) and A(H1N1)pdm09 Viruses. *Plos One.* 2015;10(10):e0139958.
203. Skowronski DM, Janjua NZ, De Serres G, et al. Low 2012-13 influenza vaccine effectiveness associated with mutation in the egg-adapted H3N2 vaccine strain not antigenic drift in circulating viruses. *Plos One.* 2014;9(3):e92153.
204. Flannery B, Zimmerman RK, Gubareva LV, et al. Enhanced Genetic Characterization of Influenza A(H3N2) Viruses and Vaccine Effectiveness by Genetic Group, 2014-2015. *J Infect Dis.* 2016;214(7):1010-1019.

205. Seki Y, Oonishi H, Onose A, Sugaya N. [Effectiveness of Influenza Vaccine in Adults Using A Test-negative, Case-control Design -2013/2014 and 2014/2015 Seasons-]. *Kansenshogaku Zasshi.* 2016;90(4):486-492.
206. Paules CI, Sullivan SG, Subbarao K, Fauci AS. Chasing Seasonal Influenza - The Need for a Universal Influenza Vaccine. *N Engl J Med.* 2018;378(1):7-9.
207. Tan MP, Tan WS, Mohamed Alitheen NB, Yap WB. M2e-Based Influenza Vaccines with Nucleoprotein: A Review. *Vaccines (Basel).* 2021;9(7):739.
208. Aw D, Silva AB, Palmer DB. Immunosenescence: emerging challenges for an ageing population. *Immunology.* 2007;120(4):435-446.
209. Goronzy JJ, Weyand CM. Understanding immunosenescence to improve responses to vaccines. *Nat Immunol.* 2013;14(5):428-436.
210. Castrucci MR. Factors affecting immune responses to the influenza vaccine. *Hum Vacc Immunother.* 2018;14(3):637-646.
211. Boutayeb A. The double burden of communicable and non-communicable diseases in developing countries. *T Roy Soc Trop Med H.* 2006;100(3):191-199.
212. Raina P, Gilsing A, Mayhew AJ, Sohel N, van den Heuvel E, Griffith LE. Individual and population level impact of chronic conditions on functional disability in older adults. *Plos One.* 2020;15(2):e0229160.
213. Wolff JL, Starfield B, Anderson G. Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. *Arch Intern Med.* 2002;162(20):2269-2276.
214. Kwong JC, Chung H, Jung JK, et al. The impact of repeated vaccination using 10-year vaccination history on protection against influenza in older adults: a test-negative design study across the 2010/11 to 2015/16 influenza seasons in Ontario, Canada. *Euro Surveill.* 2020;25(1):1900245.
215. Sugishita Y, Nakayama T, Sugawara T, Ohkusa Y. Negative effect on immune response of repeated influenza vaccination and waning effectiveness in interseason for elderly people. *Vaccine.* 2020;38(21):3759-3765.
216. Okoli GN, Racovitan F, Abdulwahid T, et al. Decline in Seasonal Influenza Vaccine Effectiveness With Vaccination Program Maturation: A Systematic Review and Meta-analysis. *Open Forum Infect Dis.* 2021;8(3):ofab069.

217. Jimenez-Garcia R, Hernandez-Barrera V, Rodriguez-Rieiro C, et al. Comparison of self-report influenza vaccination coverage with data from a population based computerized vaccination registry and factors associated with discordance. *Vaccine.* 2014;32(35):4386-4392.
218. Mangtani P, Shah A, Roberts JA. Validation of influenza and pneumococcal vaccine status in adults based on self-report. *Epidemiol Infect.* 2007;135(1):139-143.
219. Brown C, Clayton-Boswell H, Chaves SS, et al. Validity of parental report of influenza vaccination in young children seeking medical care. *Vaccine.* 2011;29(51):9488-9492.
220. World Health Organization. Evaluation of influenza vaccine effectiveness: a guide to the design and interpretation of observational studies. In: Geneva, Switzerland: World Health Organization; 2017. Accessed November 30, 2022.
221. Vesely S, Klockner CA. Social Desirability in Environmental Psychology Research: Three Meta-Analyses. *Front Psychol.* 2020;11:1395.
222. Fu CX, He Q, Li ZT, et al. Seasonal influenza vaccine effectiveness among children, 2010-2012. *Influenza Other Resp.* 2013;7(6):1168-1174.
223. Rolnick SJ, Parker ED, Nordin JD, et al. Self-report compared to electronic medical record across eight adult vaccines: Do results vary by demographic factors? *Vaccine.* 2013;31(37):3928-3935.
224. Irving SA, Donahue JG, Shay DK, Ellis-Coyle TL, Belongia EA. Evaluation of self-reported and registry-based influenza vaccination status in a Wisconsin cohort. *Vaccine.* 2009;27(47):6546-6549.
225. Zimmerman RK, Raymund M, Janosky JE, Nowalk MP, Fine MJ. Sensitivity and specificity of patient self-report of influenza and pneumococcal polysaccharide vaccinations among elderly outpatients in diverse patient care strata. *Vaccine.* 2003;21(13-14):1486-1491.
226. Jackson ML. Use of self-reported vaccination status can bias vaccine effectiveness estimates from test-negative studies. *Vaccine-X.* 2019;1:100003.
227. De Smedt T, Merrall E, Macina D, Perez-Vilar S, Andrews N, Bollaerts K. Bias due to differential and non-differential disease- and exposure misclassification in studies of vaccine effectiveness. *Plos One.* 2018;13(6):e0199180.

228. Ainslie KEC, Haber M, Orenstein WA. Challenges in estimating influenza vaccine effectiveness. *Expert Rev Vaccines.* 2019;18(6):615-628.
229. Roller-Wirnsberger R, Lindner S, Kolosovski L, et al. The role of health determinants in the influenza vaccination uptake among older adults (65+): a scope review. *Aging Clin Exp Res.* 2021;33(8):2123-2132.
230. Centers for Disease Control and Prevention. How Flu Vaccine Effectiveness and Efficacy are Measured. Centers for Disease Control and Prevention, National Center for Immunization and Respiratory Diseases (NCIRD). https://www.cdc.gov/flu/vaccines-work/effectivenessqa.htm#print. Accessed December 6, 2022.
231. Darvishian M, van den Heuvel ER, Bissielo A, et al. Effectiveness of seasonal influenza vaccination in community-dwelling elderly people: an individual participant data meta-analysis of test-negative design case-control studies. *Lancet Resp Med.* 2017;5(3):200-211.
232. Sox HC, Goodman SN. The methods of comparative effectiveness research. *Annu Rev Public Health.* 2012;33:425-445.
233. Fewell Z, Davey Smith G, Sterne JA. The impact of residual and unmeasured confounding in epidemiologic studies: a simulation study. *Am J Epidemiol.* 2007;166(6):646-655.
234. Liang W, Zhao Y, Lee AH. An investigation of the significance of residual confounding effect. *Biomed Res Int.* 2014;2014:658056.
235. Schmucker CM, Blümle A, Schell LK, et al. Systematic review finds that study data not published in full text articles have unclear impact on meta-analyses results in medical research. *Plos One.* 2017;12(4):e0176210.
236. Gotzsche PC, Hrobjartsson A, Maric K, Tendal B. Data extraction errors in meta-analyses that use standardized mean differences. *Jama-J Am Med Assoc.* 2007;298(4):430-437.
237. Jones AP, Remmington T, Williamson PR, Ashby D, Smyth RL. High prevalence but low impact of data extraction and reporting errors were found in Cochrane systematic reviews. *Journal of Clinical Epidemiology.* 2005;58(7):741-742.

238. Buscemi N, Harding L, Vandermeer B, Tjosvold L, Klassen TP. Single data extraction generated more errors than double data extraction in systematic reviews. *Journal of Clinical Epidemiology.* 2006;59(7):697-703.
239. Jurek AM, Greenland S, Maldonado G, Church TR. Proper interpretation of non-differential misclassification effects: expectations vs observations. *Int J Epidemiol.* 2005;34(3):680-687.
240. Ioannidis JPA. Why most discovered true associations are inflated. *Epidemiology.* 2008;19(5):640-648.
241. Button KS, Ioannidis JPA, Mokrysz C, et al. Power failure: why small sample size undermines the reliability of neuroscience. *Nat Rev Neurosci.* 2013;14(5):365-376.
242. Noordzij M, Tripepi G, Dekker FW, Zoccali C, Tanck MW, Jager KJ. Sample size calculations: basic principles and common pitfalls. *Nephrol Dial Transpl.* 2010;25(5):1388-1393.
243. Price OH, Carville KS, Sullivan SG. Right sizing for vaccine effectiveness studies: how many is enough for reliable estimation? *Commun Dis Intell.* 2019;43.
244. Chung JR, Flannery B, Kim SS, et al. Sample size considerations for mid-season estimates from a large influenza vaccine effectiveness network in the United States. *Vaccine.* 2021;39(25):3324-3328.
245. Byrnes GB. A Markov model for sample size calculation and inference in vaccine cost-effectiveness studies. *Stat Med.* 2002;21(21):3249-3260.
246. McLean HQ, Thompson MG, Sundaram ME, et al. Impact of Repeated Vaccination on Vaccine Effectiveness Against Influenza A(H3N2) and B During 8 Seasons. *Clin Infect Dis.* 2014;59(10):1375-1385.
247. Ohmit SE, Thompson MG, Petrie JG, et al. Influenza Vaccine Effectiveness in the 2011-2012 Season: Protection Against Each Circulating Virus and the Effect of Prior Vaccination on Estimates. *Clin Infect Dis.* 2014;58(3):319-327.
248. Krammer F, Garcia-Sastre A, Paleseu P. Is It Possible to Develop a "Universal" Influenza Virus Vaccine? Potential Target Antigens and Critical Aspects for a Universal Influenza Vaccine. *Csh Perspect Biol.* 2018;10(7):a028845.

249. Restivo V, Costantino C, Bono S, et al. Influenza vaccine effectiveness among high-risk groups: A systematic literature review and meta-analysis of case-control and cohort studies. *Hum Vacc Immunother.* 2018;14(3):724-735.

250. Uyeki TM, Hui DS, Zambon M, Wentworth DE, Monto AS. Influenza. *Lancet.* 2022;400(10353):693-706.

251. Yedlapati SH, Khan SU, Talluri S, et al. Effects of Influenza Vaccine on Mortality and Cardiovascular Outcomes in Patients With Cardiovascular Disease: A Systematic Review and Meta-Analysis. *J Am Heart Assoc.* 2021;10(6):e019636.

252. Larkin HD. New "Universal" Flu Vaccine Candidate Enters Clinical Trial. *Jama-J Am Med Assoc.* 2022;328(6):518-518.

253. Nachbagauer R, Feser J, Naficy A, et al. A chimeric hemagglutinin-based universal influenza virus vaccine approach induces broad and long-lasting immunity in a randomized, placebo-controlled phase I trial. *Nat Med.* 2021;27(1):106-114.

254. Flannery B, Fry AM. Comparing Influenza Vaccine Types: The Path Toward Improved Influenza Vaccine Strategies. *J Infect Dis.* 2019;220(8):1237-1239.