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Review

Exploring indirect protection associated with influenza immunization – A systematic review of the literature

Lindsay Friedman [a,*], Ariane Renaud [a], Delaney Hines [a], Anne Winter [a], Shelly Bolotin [a,b], Jennie Johnstone [a,b,c,d], Jeffrey C. Kwong [a,b,e,f,g], Allison J. McGeer [b,c,d], Natasha S. Crowcroft [a,b,c,e], Bryna F. Warshawsky [a,h]

[a] Public Health Ontario, 480 University Avenue, Suite 300, Toronto, Ontario M5G 1V2, Canada
[b] Dalla Lana School of Public Health, University of Toronto, 155 College Street, Toronto, Ontario M5T 3M7, Canada
[c] Department of Laboratory Medicine and Pathobiology, University of Toronto, 1 King's College Circle, Toronto, Ontario M5S 1A8, Canada
[d] Department of Microbiology, Mount Sinai Hospital, 600 University Avenue, Toronto, Ontario M5G 1X5, Canada
[e] ICES, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5, Canada
[f] Department of Family and Community Medicine, University of Toronto, 500 University Avenue, 5th floor, Toronto, Ontario M5G 1V7, Canada
[g] Toronto Western Family Health Team, Toronto Western Hospital, 399 Bathurst Street, Toronto, Ontario M5T 2S8, Canada
[h] Department of Epidemiology and Biostatistics, Schulich School of Medicine and Dentistry, Western University, 1151 Richmond Street, London, Ontario N6A 5C1, Canada

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ABSTRACT

Background: Influenza causes significant annual morbidity and mortality, particularly in older adults, for whom influenza vaccine effectiveness (VE) is also lower. Immunizing one group (e.g., children) against influenza may indirectly protect another group (e.g., older adults) against influenza and its complications.
Methods: We updated previous systematic reviews on indirect protection against influenza by searching MEDLINE and EMBASE for relevant human studies published until January 4, 2017. We abstracted and critically appraised English language publications that reported or provided information to calculate indirect VE against influenza, as a percentage, in non-institutional settings.

We developed a term called 'estimated actual protection' to explore the relationship between indirect protection and the product of direct VE and relative vaccine coverage. We calculated estimated actual protection for a subset of studies that reported coverage and indirect VE for: laboratory-confirmed influenza; outpatient care for respiratory illness; influenza-associated emergency visits; or influenza-associated hospitalizations. We ran linear mixed models to compare estimated actual protection against indirect VE for the four outcomes, and graphed the data.
Results: Of 2320 unique records identified, we abstracted and appraised 26 articles describing 24 studies. The majority of included studies reported at least one outcome suggesting that immunizing one group reduced influenza-related outcomes in another group. Critical appraisal of the abstracted studies identified recurring methodological weaknesses, such as lack of laboratory-confirmed influenza.

Our exploratory analyses of 18 studies indicated a positive but not statistically significant relationship between estimated actual protection and indirect protection for each of the four outcomes.
Conclusions: Our systematic review and exploratory analyses suggest influenza immunization provides some level of indirect protection. However, our critical appraisal highlights the need for a standardized and consistently applied approach to measuring indirect protection against influenza to fill existing knowledge gaps. Additionally, the concept of estimated actual protection requires validation.

Abbreviations: VE, vaccine effectiveness; ARI, acute respiratory illness; MAARI, medically attended acute respiratory illness; ILI, influenza-like illness; P&I, pneumonia and influenza; Δ, delta; PCR, polymerase chain reaction; ED, emergency department; RCT, randomized controlled trial; US, United States; UK, United Kingdom; R, reproductive number; Ic, herd immunity threshold; IQR, interquartile range.

* Corresponding author.
E-mail addresses: lindsay.friedman@oahpp.ca (L. Friedman), shelly.bolotin@oahpp.ca (S. Bolotin), jennie.johnstone@oahpp.ca (J. Johnstone), jeff.kwong@utoronto.ca (J.C. Kwong), allison.mcgeer@sinaihealthsystem.ca (A.J. McGeer), natasha.crowcroft@utoronto.ca (N.S. Crowcroft), bryna.warshawsky@oahpp.ca (B.F. Warshawsky).

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Contents

1. Background

Influenza causes significant annual morbidity and mortality, particularly among groups at high risk for influenza complications (e.g., older adults, individuals with chronic medical conditions) [1], for whom influenza vaccines may also be less effective compared to the general population [2]. As a result, immunization strategies that prioritize high-risk groups may have limited impact at the population level, since these groups typically mount poor immunologic responses to influenza vaccines [3,4], and play a minor role in influenza transmission.

This review focuses on indirect protection against influenza and influenza-related complications, that is, protecting one group (e.g., older adults) against influenza infection and complications by immunizing another group (often school-age children, because they disproportionately contribute to the spread of influenza [5,6]). By reducing an individual's chances of influenza infection (direct protection) the influenza vaccine also decreases transmission to others (indirect protection). At sufficiently high levels of coverage, influenza transmission in the community as a whole may decrease or cease, in what is referred to as 'herd immunity', 'herd effect', 'herd protection', or more recently, 'community protection' [7–9].

Quantifying direct and indirect effects of influenza immunization is challenging since a number of factors impact direct vaccine effectiveness (VE) against circulating strains and therefore also impact indirect VE. In addition, comparing effects across studies is complicated by heterogeneity in study designs, settings, and measured outcomes.

The aim of our systematic review is to: (1) update and broaden previously published reviews of studies that measure indirect protection against influenza [10,11]; and (2) use a novel approach to explore the relationship between direct VE, vaccine coverage, and indirect protection.

2. Definitions: Nomenclature used throughout the review

2.1. Group nomenclature

Intervention community: Community or communities that implement an intervention, in this case an influenza immunization program targeting a specific cohort (e.g., school children).

Comparison community: Community or communities, usually similar to the intervention community, except that the intervention (e.g., influenza immunization program targeting school children) has not been implemented.

Target group: The specific cohort (e.g., school children) targeted for the influenza immunization program in the intervention community.

Target comparison group: A cohort that, although similar to the target group (e.g., school children), differs in that their community has not implemented an influenza immunization program targeting this group. While individual members of the target comparison group may or may not be immunized against influenza, vaccine coverage is generally lower than in the target group.

Indirect group: A cohort in the intervention community that is not targeted by the intervention (e.g., older adults), but may indirectly benefit from immunization of the target group.

Indirect comparison group: A cohort in the comparison community that is similar to the indirect group (e.g., older adults) except it is not exposed to an immunized target group.

2.2. Vaccine effectiveness & protection

Direct vaccine effectiveness (VE) and direct protection: The intervention's effect, measured in members of the target group immunized through the influenza immunization program. Direct VE is estimated by comparing an outcome in the immunized members of the target group to the target comparison group, who are a proxy for what would have happened without the influenza immunization program [12]; it is calculated using the formula: Direct VE = [1 – (Odds or risk of outcome in immunized members of the target group/Odds or risk of outcome in the target comparison group)]*100%. We use 'direct protection' to describe the vaccine's impact on those who received it.

Indirect vaccine effectiveness (VE) and indirect protection: The intervention's effect measured in those who live in the intervention community but are not targeted for the influenza immunization program (indirect group) [12]. To estimate indirect VE, an outcome is compared between the indirect group and the indirect comparison group; it is calculated using the following equation: Indirect VE = [1 – (Odds or risk of outcome in the indirect group/Odds or risk of outcome in the indirect comparison group)]*100%. We use 'indirect protection' to describe the impact of the influenza immunization program on the indirect group as a result of protection in the target group.

Estimated actual protection: A concept developed for this systematic review, it is the product of how well the vaccine works (direct VE) and the difference between the numbers of people immunized in the target and target comparison groups (called 'delta (Δ)' coverage). Estimated actual protection is calculated using the formula: Estimated actual protection = [Direct VE $\times$ Δ coverage]*100%, where Δ coverage accounts for the possibility that, though not targeted for immunization, target comparison group members may receive an influenza vaccine.

3. Methods

3.1. Search strategy

This systematic review is based on a literature search initially conducted on December 1, 2015. We later expanded the study's scope and updated the original MEDLINE and EMBASE search to include literature published up to January 4, 2017. The search strategy included combinations of terms relating to influenza, immunization, herd immunity, and disease transmission in human populations (Appendix 1). We hand-searched reference lists of relevant articles to identify studies not captured in our database search. We registered the study protocol with PROSPERO (Centre for Reviews and Dissemination, 2011) (registration ID: CRD42017059572).

3.2. Screening & study selection

Two reviewers (LF, AR/DH) screened abstracts and/or titles for evidence of indirect protection against influenza. Titles/abstracts advanced to full-text review when both reviewers agreed upon an abstract's relevance, the abstract provided insufficient information to determine relevance, or the abstract could not be retrieved.

Reviewers assessed full-texts against the inclusion and exclusion criteria to determine eligibility. We included all observational studies and randomized-controlled trials (RCTs) that measured indirect VE against influenza-related outcomes and reported indirect VE as a percentage (%), or provided sufficient data to calculate indirect VE using the formula, VE = [1 –(Relative risk or odds ratio)]*100%.

We excluded: animal, modelling, and cost-effectiveness studies; research on nosocomial influenza transmission or healthcare worker immunization; research on relative effectiveness of two influenza vaccines; studies that did not report or permit the calculation of indirect VE as a percentage; commentaries, reviews, letters, conference abstracts, news bulletins; and non-English publications. A third author (AW or BFW) adjudicated whenever the reviewers could not reach consensus.

3.3. Outcomes of interest

We examined indirect VE for the following outcomes: (1) laboratory-confirmed influenza infections in outpatient settings; (2) outpatient care for acute respiratory illness (ARI), which included clinically diagnosed influenza-like illness (ILI) or medically attended acute respiratory infection (MAARI), administrative or surveillance records based medical visits containing influenza-related diagnostic codes, and self-reported ILI/respiratory medical visits; (3) influenza-associated emergency department (ED) visits; (4) influenza-associated hospitalizations; (5) self-reported respiratory/febrile illnesses without physician diagnosis or medical visit; (6) mortality attributable to pneumonia and influenza (P&I); and (7) school or work absenteeism.

We included direct VE estimates for outcomes measured in *immunized* members of the target group compared with measures from the target comparison group, whereas we did not include estimates based on measurements from a target group that included both immunized and unimmunized members, as this does not reflect a 'true' direct effect. However, it should be noted that even direct VE estimates based only on immunized members of the target group inherently include some impact of indirect protection as well—a result of immunized individuals interacting with one another [13].

We report estimates of indirect VE based on the comparison of outcomes between the indirect group and indirect comparison group.

3.4. Data abstraction and synthesis

Two reviewers independently abstracted data from included articles using standardized tables for study characteristics, key outcomes, and critical appraisal. For studies that reported outcomes for multiple age-groups or influenza subtypes, we aggregated outcomes whenever possible to create a single estimate. We report outcomes by influenza season for multi-year studies.

3.5. Critical appraisal

We used modified Critical Appraisal Skills Programme (CASP) appraisal tools developed for RCTs [14] or cohort studies [15] to critically appraise abstracted articles. Additionally, we developed a framework based on common themes highlighted by the CASP,

which we used to summarize each study's strengths and weaknesses/limitations.

3.6. Exploratory analyses

As study heterogeneity made conducting meta-analyses unsuitable, we used an exploratory approach to quantitatively assess key drivers of indirect effect: direct VE and the difference in vaccine coverage between the target and target comparison groups (Δ coverage), which accounts for the possibility that, though not targeted for immunization, target comparison group members may receive an influenza vaccine.

Inclusion criteria for exploratory analyses stipulated that articles report target group vaccine coverage *and* indirect VE for any of the following: laboratory-confirmed influenza in outpatient settings, outpatient care for ARI, influenza-associated ED visits, and/or influenza-associated hospitalizations. We excluded mortality, self-reported illness without physician diagnosis/medical visit, and absenteeism from the exploratory analyses because we had too few data points to analyse, or because most studies already included outcomes that are more specific for influenza.

We developed 'estimated actual protection' to represent the product of direct VE and Δ coverage. We calculated Δ coverage for each study, multiplied it by direct VE, and then graphed the relationship between estimated actual protection (x-axis) and indirect protection (y-axis) for each of the four outcomes in R (Version 3.4.0, R Foundation for Statistical Computing, Vienna, Austria). For each outcome, we ran linear mixed models using the *lmer* function to account for the group effect of clustering by study, and fitted a trend line with an estimated slope and p-value. We set the significance level to $p < 0.05$.

For studies that provided multiple coverage values (e.g., coverage reported for multiple age-groups) we computed median coverage, which we then used to calculate Δ coverage. We established assumptions (below) for studies that met exploratory analysis inclusion criteria but did not provide all the data required to calculate estimated actual protection.

3.6.1. Assumptions about vaccine coverage in the target comparison group

All studies that did not provide target comparison coverage data were conducted either in the United States (US) or the United Kingdom (UK) and assessed interventions targeting children. We applied coverage estimates corresponding to the country, influenza season and age-group in question. For US-based studies, we used coverage estimates based on annual US survey data, reported for 5- to 12-year olds and 13- to 17-year olds [16]. For studies that targeted 5- to 11-year olds or elementary school students, we applied 5- to 12-year old age group data. For studies that targeted the 5- to 17-year-old age group, we calculated a weighted mean of coverage values for the two age groups (5- to 12-year olds and 13- to 17-year olds) based on the distribution of these age groups in the study.

As proxies for target comparison group coverage in UK-based studies, we used immunization data from Public Health England's annual influenza immunization reports for the seasons studied (2013/14 and 2014/15) [16,18]. Only data for high-risk children aged 5- to 16-years are available in reports from these years, since no other paediatric group had been routinely offered influenza vaccine at the time; we used these data as numerators. For the denominators, we obtained mid-year population estimates for the corresponding age group from the Office for National Statistics online Population Estimates Analysis Tool [19].

3.6.2. Assumptions about direct VE for studies that did not provide direct VE data

For multi-year studies that reported aggregated indirect VE for all study seasons but not aggregated direct VE, we assigned a direct VE of 50% – based on pooled VEs from systematic reviews [20–22] – to use in the calculation of estimated actual protection. For single-season indirect VEs reported without corresponding direct VEs, we classified study seasons as 'matched' or 'mismatched' based on author classifications of circulating strain-vaccine match when noted in the article itself, or obtained season- and country-specific vaccine match information from other included studies when authors did not note vaccine match.

Next, we estimated direct VEs for matched and mismatched seasons between 2004/05 and 2015/16 (years for which data were available) using annual influenza VE data published for the US [23], Canada [24], and the UK or Europe [25–34]. We arranged estimates in ascending order, divided the list into quartiles — where the first quartile (Q1) represented the bottom 25% of VEs and the fourth quartile (Q4) represented the top 25% of VEs — and then calculated median direct VE for Q1 (VE = 21%) and Q4 (VE = 67%). Taking a more conservative approach, we rounded median Q1 and Q4 values down to the nearest ten, assigning direct VE values as follows: match = 60%; and mismatch = 20%. These values are conservative compared to some other aggregated estimates of matched and mismatched VEs [19,22,35].

4. Results

4.1. Characteristics of selected studies

We identified 2320 unique records by systematically searching databases and hand-searching reference lists (Fig. 1). Of these, we abstracted 26 articles representing 24 studies (Monto et al. [35,37] and Loeb et al. [37,39] each published two papers per study) (Tables 1A–1C). Studies included non-randomized designs based in communities or cohorts (n = 16) [35,37,40–53], schools (n = 2) [53,55] or households (n = 1) [56]; RCTs (n = 3) [57–59], and cluster-randomized (n = 1) [37,39] or partially cluster-randomized designs (n = 1) [60], conducted in Canada (n = 1) [37,39], US (n = 17) [35,37,40–42,46–48,50–56,59–61], UK (n = 2) [42,44], Japan (n = 1) [45], Italy (n = 2) [56,58], or Russia (n = 1) [49].

In 23 studies, influenza immunization programs targeted children [35–47,61], whereas only the study by Taksler et al. [48] focused on influenza vaccine coverage in adults aged 18–64 years. From here on, 'target group' refers to children, unless otherwise specified.

Eighteen studies [38–44,46–54,56,60,61] also satisfied inclusion criteria for exploratory analyses. We excluded three studies [35,37,45,55] that did not measure at least one of four specified outcomes, and three household studies [57–59] whose design precluded calculation of population-level Δ coverage.

4.2. Study outcomes

Studies typically measured multiple outcomes of interest (e.g., laboratory-confirmed influenza and outpatient care for ARI) and some used multiple methods or definitions to measure a single outcome (e.g., influenza confirmed by polymerase chain reaction (PCR) and culture) (Appendix 2). Findings often varied in magnitude and significance between and within studies (Fig. 2). We applied the term 'positive' to outcomes with indirect VE > 0%, 'neutral' to outcomes suggestive of no difference (i.e., indirect VE = 0%) and 'negative' to represent outcomes with an indirect VE < 0%

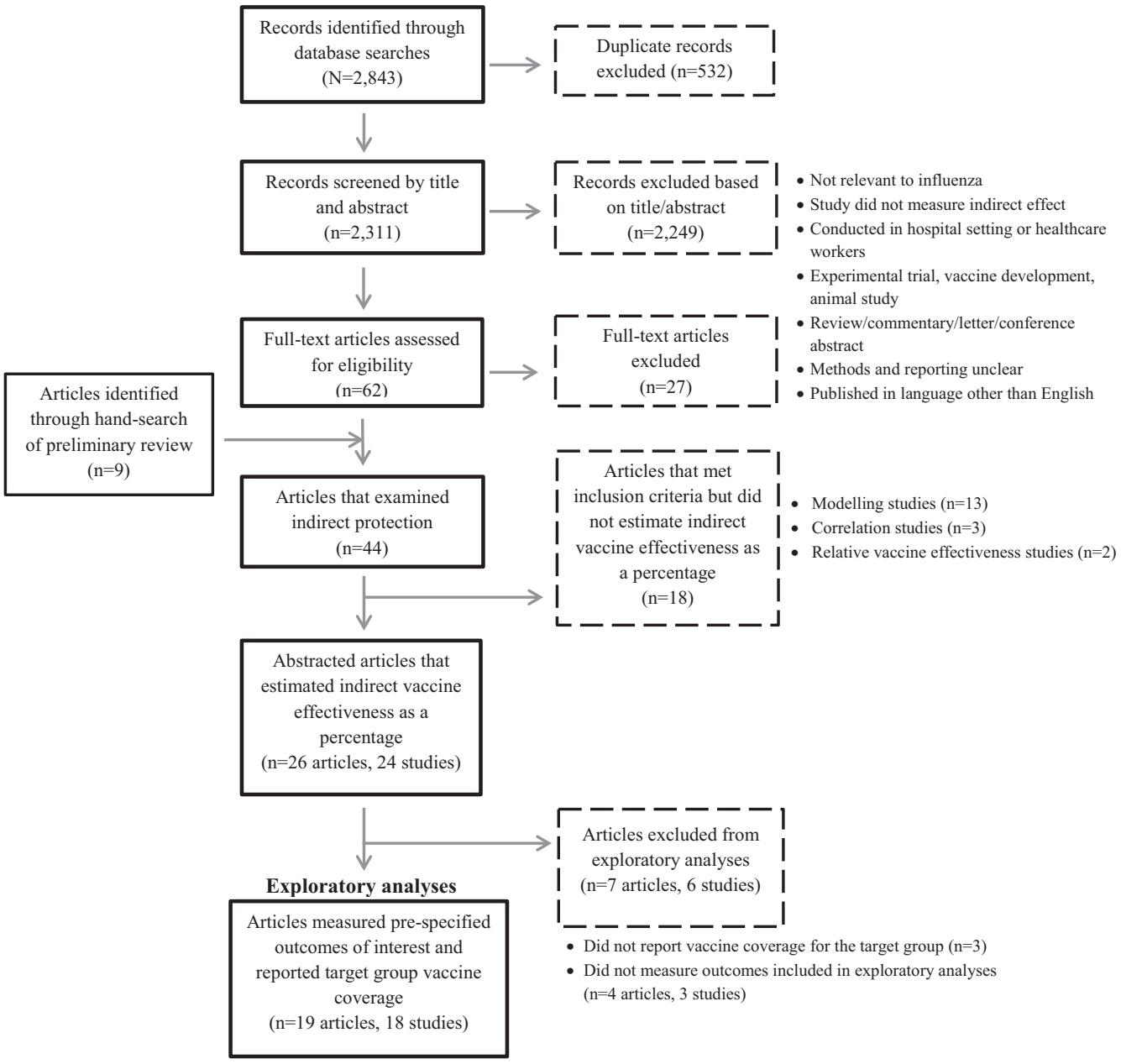

Fig. 1. PRISMA flow diagram.

(negative value). In the main-text, we focus on the four outcomes included in both the review and exploratory analyses; findings for the remaining three outcome categories are in Appendix 3.

4.2.1. Laboratory-confirmed influenza in outpatient settings

Seven articles [38–40,43,43,46,54], describing six studies, used PCR (n = 5 studies) [37,39,43,43,46,54], culture (n = 1) [40], and serology (n = 1) [39] to confirm influenza in outpatient settings. Target group vaccine coverage ranged between 34.3% [54] and 83.0% [37,39], with an estimated median of 54.7%.

Five studies [38–40,43,43,54] reported at least one positive measure of indirect protection against laboratory-confirmed influenza. Of these, only Loeb et al. [37,39] and Pannaraj et al. [54] reported statistically significant outcomes. However, Pannaraj et al. [54] reported information on statistical significance for only one of four intervention schools included in the study. Glezen et al. [40] and Poehling et al. [46] provided no information regarding statistical significance of laboratory-tested outcomes.

We included all six studies (representing seven articles) in the exploratory analysis of laboratory-confirmed influenza. Three studies reported both coverage in the target comparison group and direct VE [38–40,46]. For the remaining studies, we used vaccine coverage estimates as a proxy for target comparison group coverage in two studies [42,44] and circulating strain-vaccine match estimates as a proxy for direct VE in three studies [42,44,54]. For the four studies that reported coverage in the target group and target comparison group, Δ coverage ranged from 13.5% [46] to approximately 83.0% [37,39]. We observed a positive but not statistically significant relationship between estimated actual protection and indirect protection for laboratory-confirmed outcomes (slope = 0.96, p = 0.15) (Fig. 3).

4.2.2. Outpatient care for acute respiratory illness

Twelve studies measured outpatient care for ARI, which included physician-diagnosed ILI (n = 1 study) [49], medical encounters with ARI diagnostic codes (n = 7) [40–44,48,50], or

Table 1
(A–C) Study characteristics.

Table 1A. Characteristics of community-based studies

Study	Location, year/ Study design	Intervention/ Comparator	Direct/Indirect	Key outcomes	How measured
Monto et al., [36]±	Michigan, USA, 1968/69	**Intervention:** Tecumseh ran a school-based immunization program offering monovalent (Hong Kong influenza A) vaccine	**Direct:** Immunized target age students (5–14 years) attending school in the intervention community (n = 409) versus target age students attending school in the comparison community	Respiratory illness in the target age group (5- to 14- year olds)	Collected data using two distinct, self-reported surveillance programs operating within each community. The authors provided respiratory illness data for immunized and unimmunized students in the target group.
	Non-randomized, community-based trial	**Comparator:** Adrian did not offer a school-based immunization program	**Indirect:** Unimmunized target age students (5–14 years) attending school in the intervention community (N = 55) versus target age students attending school in the comparison community		
Monto et al., [37]±	Michigan, USA, 1968/69	**Intervention:** Tecumseh ran a school-based immunization program offering monovalent (Hong Kong influenza A) vaccine	**Direct:** Students enrolled in intervention community schools (n = 3,159 immunized) versus comparison community schools	Age-specific weekly mean rates of respiratory illness	Used two distinct, self-reported surveillance programs operating within each community to collect data on respiratory illness for each age group
	Non-randomized, community-based trial	**Comparator:** Adrian did not offer a school-based immunization program	**Indirect:** Pre-school-aged children and adults whose households participated in the intervention versus the comparison community surveillance program		
Piedra et al., [41]	Central Texas, USA, 1998/99 to 2000/01	**Intervention:** Two communities, Temple and Belton, offered CAIV-T to age-eligible children	**Direct:** Age-eligible (1.5–18 years) SWHP members living in intervention (N = 13,339*) versus age-eligible members (N = 15, 457*) living in control communities	MAARI incidence rates among adults ≥35 years of age	Estimated age-specific MAARI incidence rates using ICD-9-CM coded MAARI visits/medical encounters in SWHP administrative database
	Open-label, non-randomized, community-based trial	**Comparator:** Three communities – Waco, College Station, Bryan - did not offer CAIV-T to age-eligible children	**Indirect:** Non-age-eligible SWHP members (N = 36,600*) living in intervention versus comparison communities (N= 37,868*)		
Ghendon et al., [49]	Moscow, Russia, 2001/02	**Intervention:** Two communities, Mytishci and Orekhovo-Zuevo, ran mass influenza immunization programs targeting kindergarten and school children	**Direct:** Target age children (3- to 17-year olds) residing in intervention (n = 28,309) versus control (N = 60,946) communities	ILI among children	Physician-diagnosed ILI (based on World Health Organization case definition: sudden onset of fever of>38 C and cough or sore throat)
	Non-randomized, community-based trial	**Comparator:** Two communities, Naro-Fominsk and Odintsovo, did not run mass influenza immunization programs targeting school children	**Indirect:** Unimmunized, non-institutionalized older adults residing in intervention (N = 82,050) versus control (N = 76,401) communities	ILI and potentially influenza-associated morbidities among older adults	Physician-diagnosed illness (district physicians using specific forms made diagnoses)
Piedra et al., [42]	Central Texas, USA, 2003/04	**Intervention:** Two communities, Temple and Belton, offered children LAIV (or IIV-T)	**Direct:** Immunized age-eligible SWHP members (5- to- 18 year olds) residing in the intervention (n = 2,034*) versus unimmunized age-eligible SWHP members in control communities (N =8,970*)	Age-specific MAARI rates	ICD-9-CM codes for MAARI visits in the SWHP administrative database

Table 1 (*continued*)

Table 1A. Characteristics of community-based studies

Study	Location, year/ Study design	Intervention/ Comparator	Direct/Indirect	Key outcomes	How measured
	Open-label, non-randomized, community-based trial	**Comparator:** Three control communities –Waco, College Station, Bryan – did not offer LAIV	**Indirect:** Non-age eligible (<5 years or ≥18 years) SWHP members residing in intervention (*N* = 53,117*) versus control communities (*N* = 41,595*)		
Poehling et al., [46]	Tennessee, USA, 2006/07	**Intervention:** Knox County ran school-based LAIV programs	**Direct:** Immunized children (6 months to <13 years) seeking outpatient care at the children's hospital in the intervention county (*n* = 157) versus unimmunized children seeking outpatient care at the children's hospital in the comparison county (*N* = 275)	Outpatient burden of laboratory-confirmed influenza (proportion of samples that tested positive for influenza virus)	Information gathered through parent questionnaires, review of patient charts, nasal and throat swabs of children presenting with respiratory or febrile symptoms to confirm influenza infection
	Non-randomized community-based trial	**Comparator:** Davidson County did not run school-based LAIV programs	**Indirect:** Infants (< 6 months) and unimmunized children (<13 years) seeking outpatient care at the children's hospital in the intervention (*N* = 258) versus the comparison county (*N* = 341)		
Talbot et al., [49]	Tennessee, USA, 2006/07	**Intervention:** Knox County ran school-based LAIV programs	**Direct:** School-age children residing in the intervention county (*N* = 60,784, *n* = 29,408*) versus the comparison county	Laboratory-confirmed influenza among hospitalized older adults (≥50years)	Eligibility based on hospital discharge database (ICD-9 codes for acute respiratory illness (ARI) or non-localizing fever) and patient medical charts Nasal and throat swabs tested by PCR; influenza positive samples underwent viral culture
	Non-randomized community-based trial	**Comparator:** Davidson County did not run school-based LAIV programs	**Indirect:** Adults ≥50 years admitted to a surveillance hospital with acute respiratory illness or non-localizing fever in the intervention (*N* = 345) versus comparison county (*N* = 187)		
Glezen et al., [40]	Texas, USA, 2007/08	**Intervention:** 25 elementary schools across seven independent school districts in Bell County offered school-based LAIV (or TIV) or community catch-up clinics	**Direct:** Target age SWHP members (5- to 11- year olds) residing in the intervention (*N* = 10,418) versus comparison communities	Age-specific MAARI rates	SWHP administrative database (patient information and ICD-9 codes for MAARI)
	Non-randomized, open-label community trial	**Comparator:** Elementary schools in Waco and Bryan-College Station did not run school-based immunization programs	**Indirect:** Non-target age SWHP members residing in intervention versus control communities	Proportion of influenza-positive cultures (5011 years)	Cultured throat swab specimens from patients presenting with febrile acute respiratory illness (surveillance)
Grijalva et al., [53]	Tennessee, USA, 2005/06 to 2006/07	**Intervention:** Knox County ran a school-based immunization program offering LAIV to students	**Direct:** Target age students (5- to 17- year olds) residing in the intervention county (*n* =24,198 in year 1, *n* = 29,408 in year 2) versus comparison (*N* = 71,751*) counties	Rates of ED visits for MAARI attributable to influenza (overall excess & age-specific excess MAARI)	Electronic hospital discharge database containing ICD-9-CM diagnostic codes for MAARI
	Retrospective cohort study	**Comparator:** Eight surrounding counties without school-based LAIV programs, along with data from five pre-intervention seasons in Knox County	**Indirect:** Non-target age groups residing in the intervention versus comparison counties	Hospitalization rates for MAARI attributable to influenza (overall excess & age-specific excess MAARI)	

(*continued on next page*)

Table 1 (*continued*)

Table 1A. Characteristics of community-based studies

Study	Location, year/ Study design	Intervention/ Comparator	Direct/Indirect	Key outcomes	How measured
Hull et al.,[50]	Tennessee (TN), USA, 2005 to 2007 & Minnesota (MN), USA, 2006/07	**Interventions:** Knox County, TN offered LAIV to school children. Lyon, Mower, Stearns, MN offered LAIV to school children	**Direct:** Children attending school in the intervention (n = 24,198 in year 1; n = 29,408 in year 2) versus comparison county in TN. Children attending school in the intervention (n = 15,812) versus comparison counties in MN	Age-adjusted MAARI rates among older adults	Medicare administrative data, identified based on ICD-9 codes for MAARI and P&I
	Retrospective, non-randomized cohort study	**Comparators:** Davidson, TN did not offer LAIV to school children. Blue Earth, Crow Wing, Douglas, MN did not offer LAIV to school children	**Indirect:** Medicare recipients (≥65 years) residing in intervention versus comparison counties in TN or MN	Age-adjusted P&I hospitalization rates among older adults	
King et al., [61]	Maryland, USA, 2005/06 to 2007/08	Between two and 24 counties offered mass influenza immunization programs targeting school-age children each year of the study. The authors	**Direct:** Target age children (5- to 11- year olds) residing in counties with mass influenza immunization programs for school-age children	County-specific MAARI-related ED visits	Electronic records containing ICD-9-CM diagnostic codes for MAARI-related ED visits
	Retrospective non-randomized, community-based intervention trial	assessed the effect of increasing vaccine coverage in the target group on rates of influenza-associated outcomes during intense influenza outbreak periods in counties with mass influenza immunization programs	**Indirect:** Non-target age residents of counties with mass influenza immunization programs for school-age children	County-specific MAARI-related hospitalizations County-specific P&I mortality (≥50 years) (modelled)	Electronic records containing ICD-9-CM diagnostic codes for MAARI-related hospitalization Administrative data for P&I related deaths
Loeb et al., [38]±	Alberta, Saskatchewan, Manitoba, Canada, 2008/09	**Intervention:** 22 Hutterite colonies randomized to the IIV group	**Direct:** Healthy influenza-immunized children (3- to 15-year olds) residing in intervention (N = 593, n = 502 received IIV) versus hepatitis A immunized children from control colonies (N = 528, n = 445 received Hep A vaccine)	Laboratory-confirmed influenza	PCR testing of respiratory samples from participants with ≥2 ILI symptoms
	Cluster randomized trial	**Comparator:** 24 Hutterite colonies randomized to the hepatitis A vaccine control group	**Indirect:** Unimmunized study participants residing in intervention (N = 1,271) versus control colonies (N = 1,055)		
Loeb et al., [39]±	Alberta, Saskatchewan, Manitoba, Canada, 2008/09	**Intervention:** 22 Hutterite colonies randomized to the IIV group	**Direct:** Healthy influenza-immunized children (3- to 15- year olds) residing in intervention (N = 593, n = 502 received IIV) versus hepatitis A immunized children from control colonies (N = 528, n = 445 received Hep A vaccine)	PCR-confirmed influenza (infection-confirmed symptomatic illness)	PCR testing of respiratory samples from participants reporting ≥2 ILI symptoms
	Cluster randomized trial	**Comparator:** 24 Hutterite colonies randomized to the hepatitis A control group	**Indirect:** Unimmunized study participants residing in intervention (N = 1,271) versus control colonies (N = 1,055)	Serology-confirmed influenza among all unimmunized participants	All unimmunized participants (symptomatic and asymptomatic) underwent serological testing to identify those with evidence of influenza infection (infection = ≥4-fold increase in antibody titres against influenza)

Table 1 (*continued*)

Table 1A. Characteristics of community-based studies

Study	Location, year/ Study design	Intervention/ Comparator	Direct/Indirect	Key outcomes	How measured
Charu et al., [45]	Japan, 1977/78 to 2005/06 Retrospective, non-randomized cohort study (historical re-analysis)	**Intervention:** Mandatory schoolchildren immunization program (1977– 1994) **Comparator:** Post-mandatory schoolchildren immunization program (1995 – 2006)	**Direct:** School children during versus after the mandatory immunization program **Indirect:** Older adults during versus after the period of mandatory schoolchildren immunization	Adjusted protective effectiveness against excess P&I mortality rates	Monthly ICD-8,-9,-10 codes for P&I deaths obtained from ministry records, 1977 to 2006
McBean et al., [51]	Tennessee, USA, 2005/06 to 2007/08 Non-randomized community-based trial	**Intervention:** Knox County ran school-based LAIV programs **Comparator:** Eight counties, surrounding Knox, did not run school-based LAIV programs	**Direct:** Children attending school in the intervention county versus control counties **Indirect:** Older adult (≥66 years) Medicare beneficiaries residing in the intervention county versus control counties	Age-adjusted P&I hospitalizations (whole cohort, unimmunized)	Medicare files containing ICD-9 diagnostic codes for P&I
Pebody et al., [43]	England, UK, 2013/14 Retrospective non-randomized community-based trial	**Intervention:** Seven English pilot areas offered LAIV programs targeting school children **Comparator:** Non-pilot areas in England did not offer LAIV immunization programs targeting school children	**Direct:** Target age children (4- to 11- year olds) residing in pilot areas (n = 104,792 immunized) versus non-pilot areas **Indirect:** Non-target age-groups (<4 years and ≥12 years) residing within the seven pilot areas versus the non-pilot areas	Swab positivity (proportion of influenza positive swabs) Primary care consultation rates ED admissions coded as respiratory Laboratory-confirmed influenza hospitalization	Various sources of national surveillance data collected from primary and secondary care
Tran et al., [52]	Florida, USA, 2011/12 to 2012/2013 Retrospective non-randomized community-based trial	**Intervention:** Alachua County ran school-located influenza vaccine (SLIV) LAIV programs **Comparator:** All counties in Florida, excluding Alachua (i.e. non-Alachua counties) did not offer SLIV programs	**Direct:** All children (5- to 17- year olds) attending school in the intervention county (N = 10,490 in year 1, N = 11,188 in year 2) versus comparison counties **Indirect:** Non-school age residents of the intervention versus comparison counties	Age-specific ILI associated emergency or urgent care visits	Routine surveillance (electronic database)
Pebody et al., [44]	England, UK, 2014/15 Retrospective non-randomized community-based trial	**Intervention:** Six pilot areas offered school-based LAIV to primary students; four areas offered school-based LAIV to primary and a cohort of secondary students **Comparator:** Non-pilot areas in England which did not participate in the school-based LAIV program	**Direct:** Target age students (5- to 10- year olds and 11- to 16-year olds) residing in combined primary and secondary school program pilot areas (n = 381,969 immunized) versus non-pilot areas. Note: although the direct group comprised students ages 5–16 years, those >13 years were not eligible for LAIV **Indirect:** Non-target age individuals (<5 years and ≥17 years) residing in combined primary and secondary school program areas versus non-pilot areas	Swab positivity (proportion of influenza positive swabs) Primary care consultation rates for ILI ED admissions coded as respiratory Laboratory-confirmed influenza hospitalization Laboratory-confirmed influenza ICU admission	Various sources of national surveillance data collected from primary and secondary care

(*continued on next page*)

Table 1 (*continued*)

Table 1A. Characteristics of community-based studies

Study	Location, year/ Study design	Intervention/ Comparator	Direct/Indirect	Key outcomes	How measured
Taklser et al., [48]	313 urban counties throughout the USA, 2002/03 to 2009/10	**Intervention:** Counties with influenza vaccine coverage ≥16% among younger adults (18–64 years). Based on county-wide vaccine coverage, counties fell into one of the following categories: 16% to 20%, 21% to 25%, 26% to 30%, ≥31%	**Direct:** Adults (18- to 64- year olds) (*N* = 520,229) residing in urban counties with coverage ≥16% versus adults residing in urban counties with coverage ≤15%	Primary diagnosis of Influenza	ICD-9 codes in Medicare claims (outpatient, inpatient, carrier claims)
	Retrospective, non-randomized cohort study	**Comparator:** Counties with vaccine coverage ≤15% among younger adults (18–64 years)	**Indirect:** Older adult (≥65 years) Medicare beneficiaries (*N* = 3,317,709) (immunized, unimmunized and total) residing in urban counties with coverage ≥16% among younger adults versus older adults residing in urban counties with coverage ≤15% among younger adults	Hospitalization for influenza	

Table 1B. Characteristics of household studies

Study	Location, year/ Study design	Intervention/ Comparator	Direct/Indirect	Key outcomes	How measured
Hurwitz et al., [60]	San Diego, California, USA, 1996/97	**Intervention:** Children recruited from 10 Navy-affiliated daycares, randomized into the intervention group (two doses of IIV)	**Direct:** Target age (2- to 5- year olds) daycare attendees immunized with IIV (*n* = 60) versus age-matched control children immunized against hepatitis A (*n* = 67)	Respiratory illness and febrile respiratory illnesses among household contacts	Self-report of symptoms on a standardized study questionnaire (telephone interviews)
	Single blind, Randomized controlled trial	**Comparator:** Children recruited from the same 10 Navy-affiliated daycares, randomized into the placebo control group (two doses of hepatitis A vaccine)	**Indirect:** Household contacts of daycare attendees immunized against influenza (*N* = 162) versus hepatitis A (*N* = 166)	Respiratory-related morbidities among unimmunized 5 to 17 year-old household contacts	
Esposito et al., [58]	Milan, Italy, 2000/01	**Intervention:** Children with recurrent respiratory tract infections attending an infectious disease clinic, randomized to receive two doses of intranasal TIV vaccine	**Direct:** Eligible children (6 months to 14 years), immunized against influenza (*n* = 64) versus placebo control group (*n* = 63)	Various indicators of respiratory and febrile-related morbidity among study children and their household contacts	Physical examination, follow-up phone calls, follow-up medical appointments
	Double-blind, randomized, placebo controlled trial	**Comparator:** Children with recurrent respiratory tract infections attending the same infectious disease clinic as the intervention group, randomized to receive two doses of placebo (saline) control	**Indirect:** Household contacts of influenza immunized children (*N* = 176) versus placebo control children (*N* = 173)		
Principi et al., [59]	Italy, 2001/02	**Intervention:** Children randomized to receive the virosomal influenza vaccine	**Direct:** Healthy children ages 6 months to 5 years of age immunized against influenza (*n* = 202) versus unimmunized control group children (*n* = 101)	Various indicators of respiratory and febrile-related morbidity among study children and their household contacts	* Data modified from Esposito et al 2002 Standardized questionnaire (biweekly telephone interview, monthly medical visits)
	Randomized controlled trial	**Comparator:** Children randomized into the placebo-free control group	**Indirect:** Household contacts of influenza immunized children (*N* = 728) versus unimmunized control group children (*N* = 370)		

Table 1 (*continued*)

Table 1B. Characteristics of household studies

Study	Location, year/ Study design	Intervention/ Comparator	Direct/Indirect	Key outcomes	How measured
King et al., [57]	Carroll County, Maryland, USA, 2003/04	**Intervention:** One Carroll County public elementary school offered LAIV to healthy students	**Direct:** Elementary school students ≥ 5 years attending the target school (N = 460; n = 185) versus the control schools (N = 1,158)	Self-reported fever or respiratory illness-related medical care utilization by household members	Anonymous, self-administered questionnaires
	Open-label, non-randomized, non-blinded, controlled, community intervention pilot study	**Comparator:** Two Carroll County schools, similar to the intervention school, did not offer their students LAIV	**Indirect:** Participating households with a child attending the target school (N = 157) versus control schools (N = 452)	Self-reported work/school absenteeism Overall student absenteeism	Administrative data
King et al., [61]	Maryland, Texas, Minnesota, Washington state, USA, 2004/05	**Intervention:** 11 intervention schools, located across four US states, offered students LAIV	**Direct:** Healthy elementary school students (≥ 5 years) attending intervention (N = 5,840; n = 2,717) versus control schools (N = 9,451)	Self-reported episodes of 'any fever or ILI' or 'fever plus cough or sore throat' during peak week Self-reported health care use (outpatient or ED visits)	Household questionnaire/ parent survey
	Open-label, un-blinded, controlled, partially randomized community intervention study	**Comparator:** 17 schools, located across four US states did not offer its students LAIV	**Indirect:** Participating households with an child attending an intervention school (N = 3,022) versus households with a child attending a control school (N = 5,488)	Self-reported paid workdays missed (ILI or to care for sick child) School absenteeism	School administrative data

Table 1C. Characteristics of school-based studies

Study	Location, year/ Study design	Intervention/ Comparator	Direct/Indirect	Key outcomes	How measured
Graitcer et al., [56]	Maine, USA, 2009 Non-randomized, school-based trial	The study categorized 93 participating schools from four counties in Maine, based on levels of student A (H1N1) 2009 pandemic virus vaccine coverage, from low (10th percentile) to high (90th percentile) and compared high versus low coverage schools	**Direct:** Students attending high versus low coverage schools **Indirect:** Unimmunized students attending high versus low coverage schools	Student absenteeism	Schools submitted student vaccination registries and electronic daily absenteeism records
Pannaraj et al., [55]	Los Angeles County, California,USA, 2010/11	**Intervention:** Four elementary schools in two Los Angeles County school districts held LAIV immunization clinics	**Direct:** Immunized children (kindergarten to grade 6) attending intervention schools (n = 813) versus students attending control schools (N = 2,087)	PCR-confirmed influenza incidence among unimmunized children only and among all students	Swabs collected from children meeting ILI case definition and analysed by PCR
	Non-randomized, Uncontrolled school-based intervention	**Comparator:** Four elementary schools (paired with the four intervention schools) in two Los Angeles County school districts did not hold school-based immunization clinics	**Indirect:** Unimmunized children attending intervention (N = 1,555) versus control schools (N = 2,087)		

Notes:
n refers to the specified number of immunized or unimmunized individuals in a group whereas N represents the entire community/cohort (not only those included in the study). Typically, no direct VE is reported where only N is provided.
Abbreviations: VE – vaccine effectiveness; MAARI – medically attended acute respiratory illness; ILI – influenza-like illness; P&I – pneumonia and influenza; LAIV – live-attenuated influenza vaccine; IIV/TIV – inactivated influenza vaccine/trivalent inactivated influenza vaccine; CAIV-T –cold adapted influenza vaccine (live), trivalent; SWHP – Scott & White Health Plan; PCR – polymerase chain reaction; ED – emergency department.
* Denotes estimated or approximate sample size.
± Denotes multiple publications based on a single study.

self-reported household medical visits (n = 4) [56–58,60]. Ten studies reported coverage in the target group, with values between approximately 20.0% [41] and 75.8% [40], and median coverage of 43.0%.

Six [39,41,44,48–50] of eight community-based studies reported at least one positive, statistically significant measure of indirect protection against ARI outpatient care. One of these studies, where adults aged <64 years comprised the target group (Taksler et al. [48]), found significant indirect protection against influenza among unimmunized older adults (≥65 years) living in counties with >25% target group vaccine coverage, but not in counties with target group coverage ≤25%. The remaining two studies [41,43] reported non-statistically significant findings that varied by age-group.

At the household-level (n = 4 studies), two studies [56,58] found contacts of immunized children reported significantly fewer respiratory-related medical visits than contacts of control children. Another two studies [55,60] found adult household contacts of children attending intervention schools (the children may or may not be immunized) reported fewer respiratory or fever-related physician visits than adult household contacts of control group children, though only one study [56] reported statistically significant findings.

Ten studies met inclusion criteria for the exploratory analysis of outpatient care for ARI [40–44,48–50,56,60]. One study [42] provided both direct VE and target comparison group vaccine coverage; we used vaccine coverage proxies for target comparison group data in three studies [42,44,50] and circulating strain-vaccine match as a proxy for direct VE in nine studies [39,41,43,43,48–50,56,60]. Seven studies reported coverage for both the target group and target comparison group, with Δ coverage ranging from 5.3% [48] to 64.7% [49]. We found a positive but not statistically significant relationship between estimated actual protection and indirect protection against outpatient care for ARI (slope = 1.1, p = 0.18) (Fig. 4).

4.2.3. Influenza-associated ED visits

Seven studies examined influenza-associated ED visits in intervention communities or schools [42,44,52,52,56,60,61]. Across studies, mean target group vaccine coverage ranged between 24.5% [61] and 56.8% [44], with an estimated median of 46.0%.

Five community-based studies used administrative or surveillance data to identify ED visits with influenza-related codes [42,44,52,52,61]. Of these, two multi-year studies reported findings that varied by season and/or age-group: King et al. (2010) [61] reported significant indirect protection from MAARI-related ED visits in two of four non-targeted age-groups— children <4 years of age, and adults aged 19–49 years— while Tran et al. [52] found lower rates of ILI-associated ED visits (significance depended on age-group and study season) for the intervention county compared to the rest of the state. Two single-year studies [42,44], and one study that aggregated data from two seasons [53], reported positive but not statistically significant indirect VEs.

Two studies measured indirect protection against self-reported influenza-associated ED visits among household contacts of children attending intervention schools [55,60]. King et al. [56] and King et al. [60] reported non-statistically significant negative indirect protection and non-statistically significant positive indirect protection, respectively, against self-reported ED visits.

All seven studies measuring influenza-associated ED visits satisfied inclusion criteria for the exploratory analysis. We used vaccine coverage proxies for target comparison group data in three studies [42,44,53] and circulating strain-vaccine match as a proxy for direct VE in all seven studies. King et al. [61] assessed outcomes based on a 20%-point increase in coverage, so for this study, we set Δ coverage to 20%. Three studies reported vaccine coverage for both the target group and target comparison group [51,56,60], wherein Δ coverage ranged from approximately 22.5% [52] to 35.0% [60]. We found a positive but not statistically significant relationship between estimated actual protection and indirect protection (slope = 1.2, p = 0.15) (Fig. 5).

4.2.4. Influenza-associated hospitalization

Nine studies [42,44,47,47,50,50,53,60,61] measured indirect protection against influenza-associated hospital admissions. One of these studies [48] measured indirect protection associated with adult immunization. All nine studies provided target group vaccine coverage, which ranged from a mean of 24.5% [61] to 56.8% [44], with 45.0% estimated median coverage.

Three studies measured laboratory-confirmed influenza in hospital patients [47] or patients admitted for laboratory-confirmed influenza [42,44]. All three studies reported positive indirect protection, though only Talbot et al. [47] found statistically significant indirect protection, specifically among hospitalized patients aged 50–64 years, but not among the older age-group or entire study cohort. One study of self-reported hospitalization found significant negative indirect VE against ILI-related inpatient care in adults [56].

Five administrative records-based studies of influenza-associated hospitalizations also described variable findings [47,50,50,53,61]. Three studies [47,51,53] consistently reported positive indirect protection among non-target age-groups residing in the intervention communities, though only McBean et al. [51] and Taksler et al. [48], found any statistically significant outcomes; significance varied by year or immunization status of the indirect group. King et al. [61] primarily reported non-statistically significant, negative indirect VE across age-groups and study years, whereas Hull et al. [50] reported indirect VEs that varied by study year and location.

We included nine studies in the exploratory analysis of influenza-related hospitalizations [42,44,47,47,50,50,53,60,61]. We used vaccine coverage proxies for target comparison group data in five studies [42,44,50,50,53] and circulating strain-vaccine match as a proxy for direct VE in all nine studies. As before, we set Δ coverage to 20% in King et al. [61]. In studies that provided an estimate for vaccine coverage of both the target group and target comparison group (n = 3) [46,48,60], Δ coverage ranged from approximately 5.3% [48] to 36.0% [47]. We found a positive but not statistically significant association between estimated actual protection and hospitalization (slope = 1.2, p = 0.13) (Fig. 6).

4.3. Critical appraisal

We display the outcomes of the critical appraisal, using modified CASPs (Appendix 4), in Tables 2A and 2B. The most common weaknesses/limitations included study design (n = 20 studies) [35,37,40–56,61], single-season study (n = 16) [36–40,42–44,46,46,49,54–60], non-laboratory-confirmed influenza (n = 17)[35,37,41,41,45,48–53,55–60], and study population details not provided and/or unknown comparability of intervention and control groups (n = 20) [35,37,40–47,49–58,61].

5. Discussion

5.1. Systematic review

We aimed to update and extend previously published systematic reviews of indirect protection against influenza [10,11] by broadening eligibility criteria to include more study designs, all age-groups, and a greater range of outcomes. Though studies

Outcome Reported in *n* studies	Number of studies reporting positive indirect protection		Number of studies reporting no difference or omitting information about significance	Number of studies reporting negative indirect protection	
	Significant	Non-significant		Non-significant	Significant
Laboratory-confirmed (n=6)	**2**[37,38,53]	**2**[42,43]	**5**[39,42,43,45,53]	**1**[44]	
Outpatient care (n=12)	**9**[39,40,43,47-49,55-57]	**5** [41-43,47,59]		**3**[39,41,49]	
Emergency department (n=7)	**2**[51,60]	**6**[42,43,51,52,59,60]	**1**[60]	**2**[55,60]	
Hospitalization (n=9)	**4**[46,47,49,50]	**8**[42,43,46,47,49,50,52,60]		**3**[46,49,60]	**2**[59,60]
Self-reported illness (n=5)	**4**[56-59]	**1**[58]	**2**[35,36,58]	**1**[58]	
Mortality (n=2)	**1**[44]	**1**[60]		**1**[60]	
Absenteeism (n=6)	**5**[55-59]		**3**[55,56,60]		
Total	**27**	**23**	**11**	**11**	**2**

Figure key

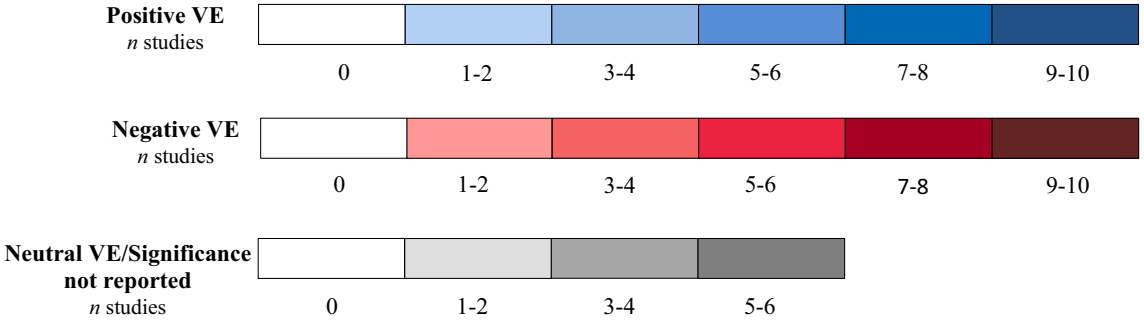

Fig. 2. Summary of findings.

included in our review seldom reported exclusively positive and significant findings, most studies reported at least one finding suggesting that immunizing one group reduced influenza-related outcomes in another group.

Our findings are consistent with other systematic reviews and meta-analyses. Mertz et al. [10] calculated the odds of influenza-related outcomes in contacts of immunized individuals compared to contacts of unimmunized individuals. The authors reported an overall positive, non-statistically significant herd effect in seven RCTs and a positive, statistically significant effect in four observational studies. Yin et al. [11] reported that immunizing children indirectly protected against certain influenza-related outcomes (e.g., laboratory-confirmed influenza) in specific settings (e.g., small, isolated communities). However, limited data, low-quality evidence, and heterogeneity restricted the formation of strong conclusions about indirect protection from influenza.

Compared to other pathogens, influenza is not a particularly infectious organism; a systematic review of basic and/or effective

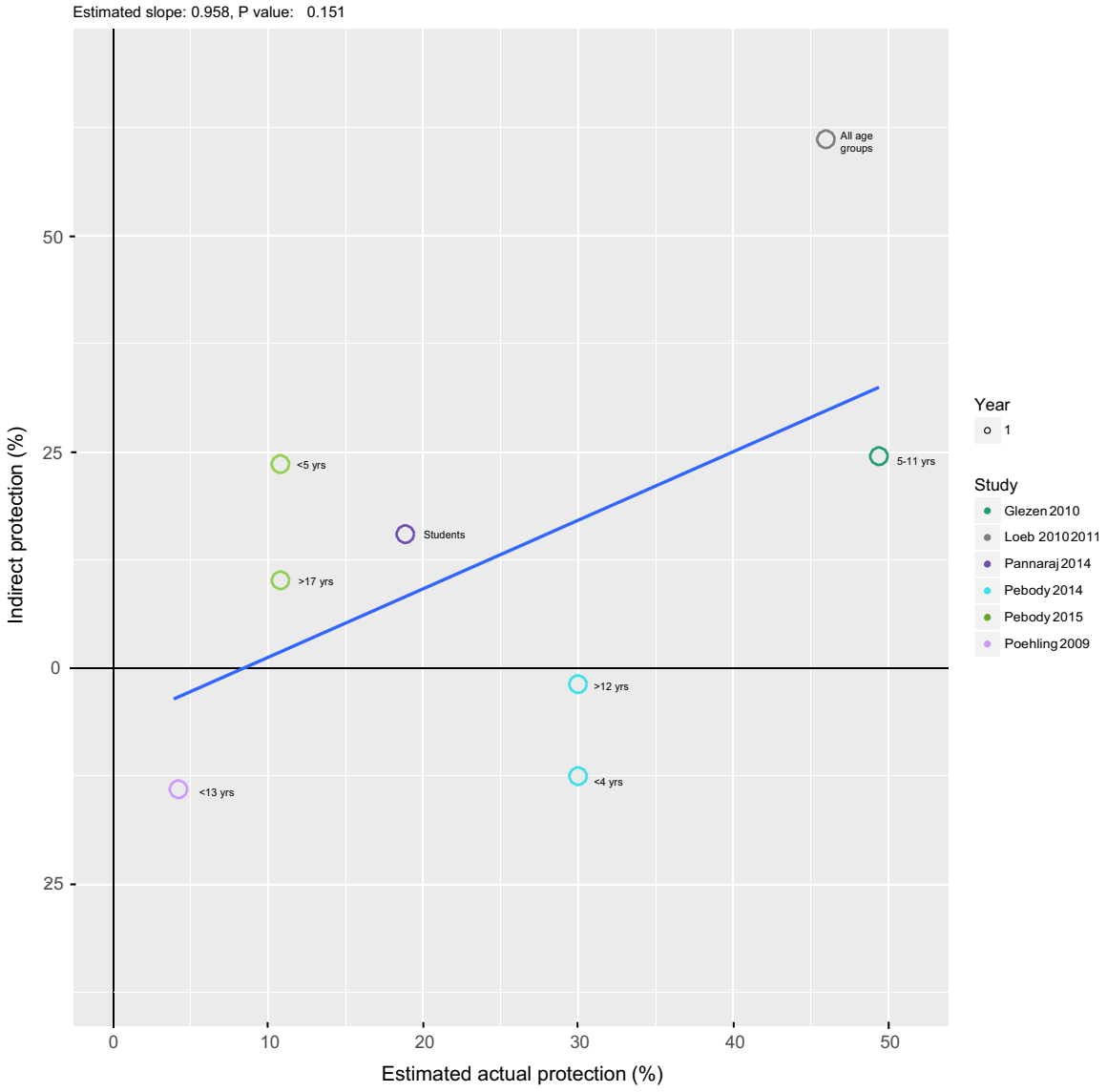

Fig. 3. Exploratory analysis: Laboratory-confirmed influenza in outpatient settings. Colours are used to differentiate between studies, and shapes differentiate between seasons for multi-year studies. Each data point represents one influenza season and one age-group, or an aggregate of age-groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

reproductive numbers (R) estimated that median R for seasonal influenza in community settings is 1.28 (interquartile range (IQR): 1.19–1.37) [62], indicating that, on average, one influenza-infected person typically infects 1.28 other people, though this number varies by setting, environmental conditions, and population characteristics (e.g., proportion susceptible). R-values for pandemic viruses are generally higher; the 2009 A/H1N1 pandemic had a median R-value of 1.46 (IQR: 1.30–1.70) [62].

Using an R-value of 1.28 to calculate herd immunity threshold [$I_c = 1-(1/R)$] [7,8,63] suggests that, theoretically, in a community with seasonal influenza immunity > 22% (surpassing the threshold value) transmission should be interrupted. Given that influenza vaccines are, on average, 50% effective [63,65], herd immunity threshold estimates based on influenza vaccine coverage must account for less-than-perfect VE— a calculation referred to as critical coverage [critical vaccine coverage = I_c/VE] [66]. With 50% VE, ≥44% of the population would need an influenza vaccine to achieve herd immunity. However, estimates from the National Influenza Immunization Coverage Survey indicate that Canadian seasonal influenza coverage levels are below critical coverage [67]. Only 23.9% of Canadian children (6 months to 17 years) and 35.8% of adults (≥18 years) reported receiving the seasonal influenza vaccine in 2016/17; critical coverage for the 2016/17 influenza season would have been 48.9%, using a median R of 1.28 and that season's 45% VE [24] [critical coverage = 0.22/0.45].

Besides coverage, factors that impact direct VE (e.g., vaccine-strain match, intra-seasonal waning, vaccine types and manufacturing processes, previous immune and vaccination status, age) may affect the persistence of influenza transmission in immunized communities. In addition, other factors (e.g., non-homogeneous distribution of vaccinated individuals, contact patterns, living conditions, demographic characteristics) also impact influenza transmission in communities. These other factors may explain why transmission may not be interrupted even when coverage exceeds the critical coverage threshold.

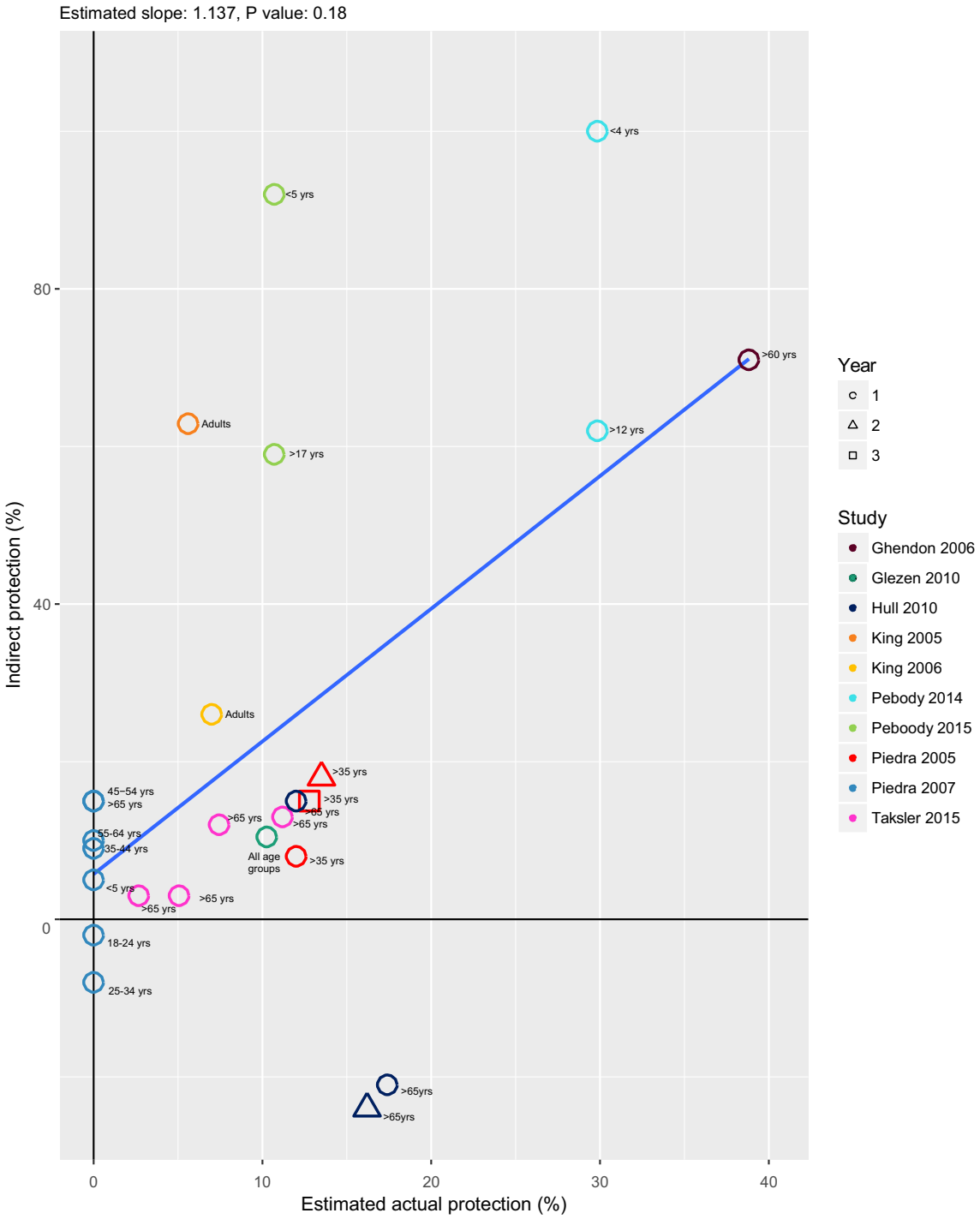

Fig. 4. Exploratory analysis: Outpatient care for acute respiratory illnesses. Colours are used to differentiate between studies, and shapes differentiate between seasons for multi-year studies. Each data point represents one influenza season and one age-group, or an aggregate of age-groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

5.2. Exploratory analyses

We used a novel approach to quantitatively explore key drivers of indirect effect: vaccine coverage of the group targeted for immunization in the intervention community relative to a non-targeted group in the comparison community, and direct VE. We introduced the term 'estimated actual protection', which recognizes that only a portion of the target group receives the vaccine, and only a proportion of those who receive the vaccine mount an effective immune response; vaccine recipients who mount an effective immune response are those expected to be 'actually protected' against influenza. This is the first time, to our knowledge, that this synthesis measure has been assessed against indirect protection.

We graphically displayed the combined effect of direct VE and coverage on indirect protection to find a positive but non-statistically significant linear relationship between estimated actual protection and indirect protection for each of the four outcomes. It is not surprising that the exploratory analyses produced non-statistically significant results given the array of reported positive/neutral/negative findings and the inclusion of non-laboratory-

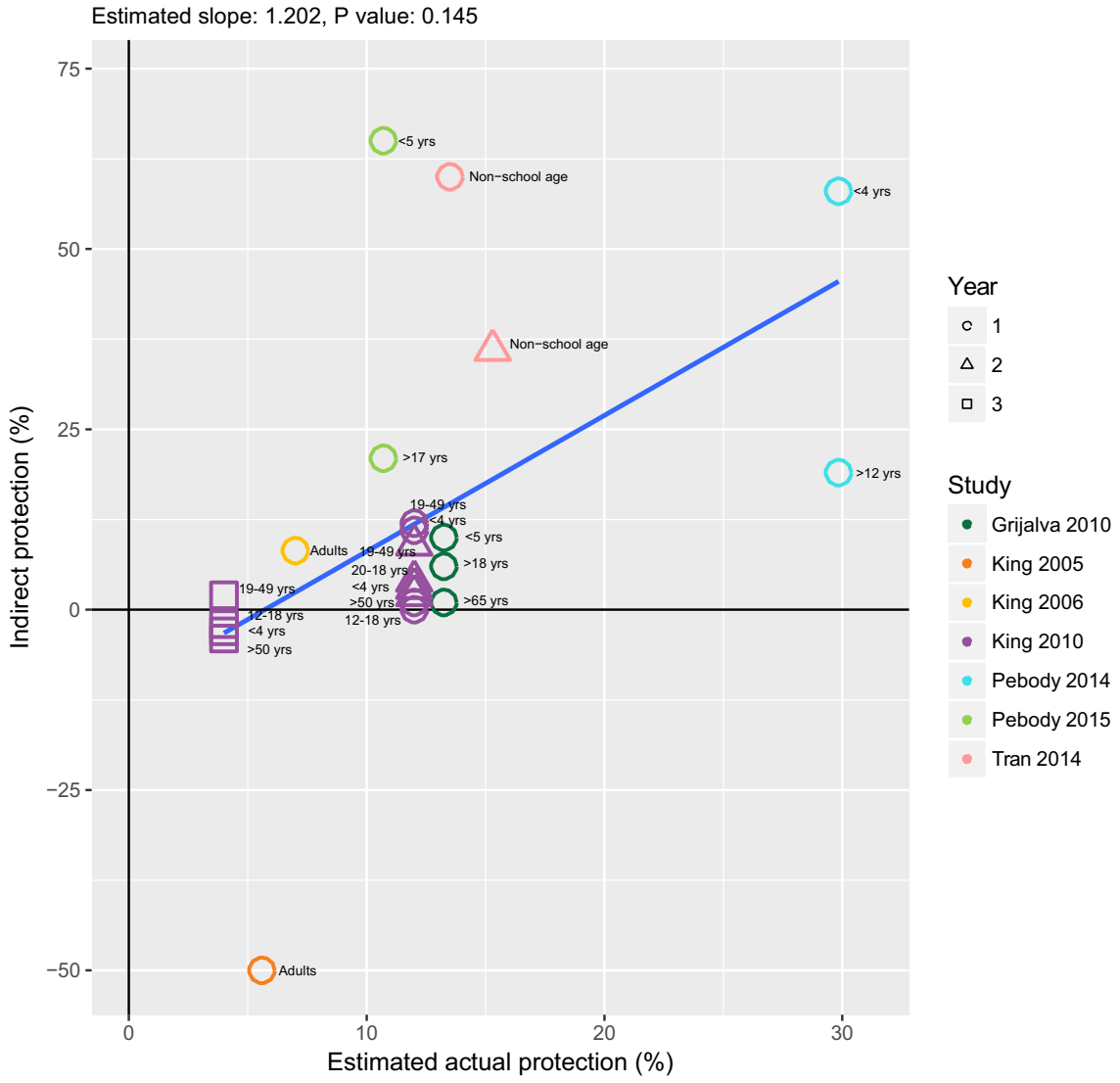

Fig. 5. Exploratory analysis: Influenza-associated emergency department visits. Colours are used to differentiate between studies, and shapes differentiate between seasons for multi-year studies. Each data point represents one influenza season and one age-group, or an aggregate of age-groups.

confirmed outcomes, which likely counted both influenza and respiratory infections due to non-influenza pathogens, thereby diluting the ability to demonstrate an indirect effect from the influenza vaccine. Further research is required to validate this novel approach.

5.3. Strengths & limitations

5.3.1. Systematic review

Our literature search captured studies published until January 4, 2017, thereby updating Mertz et al.'s [10] March 2014 search and Yin et al.'s [11] August 2016 search. Our review is further distinguished from earlier efforts by using broadened eligibility criteria. Unlike Yin et al. [11], who only included studies that immunized children, we placed no age restrictions on target groups. Unlike Mertz et al. [10], who limited their review to RCTs and observational studies, we included all study designs. We ultimately included four studies [45,48,53,55] in our systematic review that were not included by either Mertz et al. or Yin et al.

Similar to the reviews by Yin et al. and Mertz et al. [10,11], the primary research studies on which this review is based have a number of methodological limitations, including a preponderance of observational designs and frequent non-reporting of vaccine coverage for the groups used to assess indirect protection (which might have enhanced or masked an indirect effect). Additionally, we compared estimates of indirect VE from studies that differed substantially in terms of study location, time period/influenza season, vaccine used, data source and populations of interest. Due to this data heterogeneity, we did not meta-analyse the data as other authors have done [10,11]. Further limitations of our review are that we did not attempt to adjust VE estimates by influenza virus type or subtype, though it has been demonstrated that VE is higher for influenza A/H1N1 and influenza B than for A/H3N2 [65]; and we did not assess primary studies for the presence of publication bias. Though not all included studies reported positive, significant results, we recognize that studies with significant findings are more likely to be published and that this publication bias may have skewed our findings towards demonstrating indirect protection.

5.3.2. Exploratory analyses

The strength of our systematic review is the novel, exploratory approach we used to study indirect protection. We introduced estimated actual protection, and by integrating vaccine

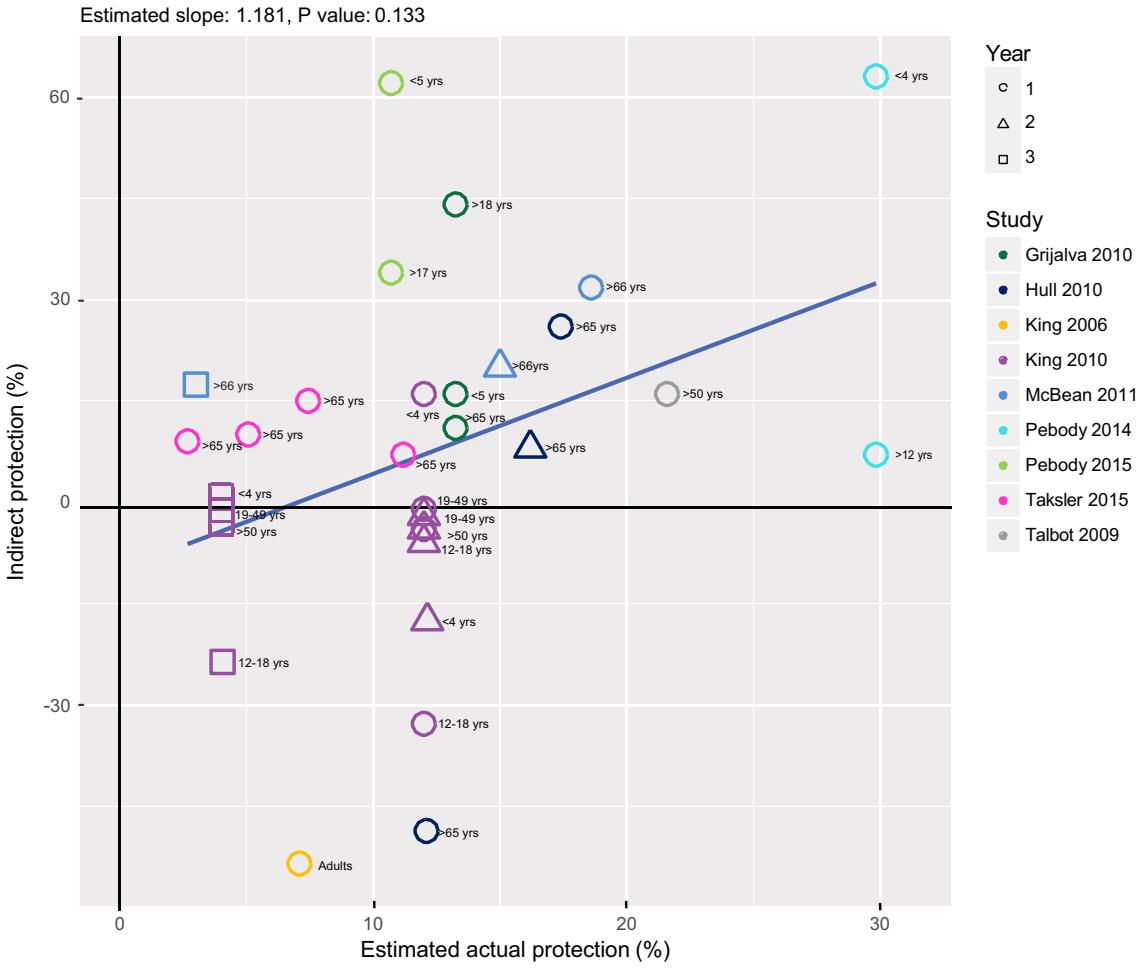

Fig. 6. Exploratory analysis: Influenza-associated hospitalization. Colours are used to differentiate between studies, and shapes differentiate between seasons for multi-year studies. Each data point represents one influenza season and one age-group, or an aggregate of age-groups. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

coverage into our exploratory analyses, we directly addressed the impact of coverage on indirect VE, which is not addressed in previous reviews. We supplemented data not reported by the study authors with published data from credible sources. For supplemented data, we aimed to use conservative estimates and to be specific in terms of age-group, influenza season, as well as country. However, we used country-level coverage data to estimate vaccine coverage in the target comparison group because state- or county-specific data corresponding to the necessary age-groups and study seasons are not readily available to the public. For studies that provided coverage by age group, we calculated a median or mean value in order to use in our estimated actual protection calculation.

Notably, we did not test the validity of the assumptions by varying the estimates in sensitivity analyses. Additional weaknesses of the exploratory analyses include: displaying data points from studies that differed in terms of designs, populations, influenza seasons, or vaccine used together in graphs, based on the fact that they measured similar influenza-related outcomes; using mean or median coverage to calculate Δ coverage for studies that reported multiple coverage values could have conceivably introduced uncertainty or imprecision into the calculation of estimated actual protection; and our focus on Δ coverage rather than absolute coverage in the target group may have limited our ability to assess indirect protection associated with the absolute magnitude of coverage in the study population.

6. Conclusion

This work updates previous systematic reviews [10,11]. Many included studies reported at least one outcome suggesting that immunizing one group (primarily school-age children) reduced influenza-related outcomes in another group. Our exploratory analyses suggest a positive, though not statistically significant, linear relationship between estimated actual protection and indirect VE. The concept of estimated actual protection requires additional study and validation.

Our findings emphasize the need for large-scale, sufficiently powered studies measuring laboratory-confirmed influenza in comparable study populations over multiple influenza seasons to fill existing knowledge gaps. A more standardized and consistently applied approach to measuring influenza indirect VE and protection, including addressing the features outlined in the critical appraisals of the articles in this review, will reduce heterogeneity between studies, thereby facilitating comparison of outcomes across studies and the pooling of outcomes in meta-analyses.

Table 2A
Strengths and weakness/limitations of reviewed community-based studies.

Study citation	Study design						Study population	Reported			
	RCT or cluster-randomized	Multi-year study	Multiple intervention sites	Lab-confirmed outcomes	Measured direct VE in immunized target group	Funding: No conflict of interest	Comparable vs. non-comparable or unclear	Sample sizes, all groups	p-values or 95% CIs, all outcomes	Data to calculate Δ coverage	Vaccine match, seasonal details
Community-based studies											
Monto [36]	X	X	X	X	X	NR	X	X	X	X	✓
Monto [37]	X	X	X	X	X	✓	X	X	X	X	X
Piedra [41]	X	✓	✓	X	NR	X	X	✓	✓	✓	✓
Ghendon [49]	X	X	✓	X	X	✓	X	✓	✓	✓	✓
Piedra [42]	X	X	✓	X	✓	X	X	✓	X	✓	✓
Poehling [46]	X	X	X	✓	X	X	X	✓	X	✓	✓
Talbot [47]	X	X	X	✓	NR	X	X	X	✓	✓	✓
Glezen [40]	X	X	✓	✓	✓	X	X	✓	X	✓	✓
Grijalva [53]	X	✓	X	X	NR	X	X	X	✓	X	X
Hull [50]	X	✓*	✓*	X	✓	NR	X	X	✓	X	✓
King [61]	X	✓	✓	X	NR	X	X	X	✓	✓	✓
Loeb [38]	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	✓
Charu [45]	X	✓	✓	X	NR	✓	X	X	✓	✓	N/A
Loeb [39]	✓	X	✓	✓	✓	✓	✓	✓	✓	✓	✓
McBean [51]	X	✓	X	X	X	X	X	X	✓	X	X
Tran [52]	X	✓	X	X	X	✓	X	X	✓	✓	✓
Pebody [43]	X	X	✓	✓	X	✓	X	X	✓	X	X
Pebody [44]	X	X	✓	✓	X	✓	X	X	✓	X	✓
Taksler [48]	X	✓	✓	X	X	✓	✓†	✓†	✓	✓	✓

Abbreviations: VE – vaccine effectiveness; CI – confidence interval; RCT – randomized controlled trial; NR – not reported; N/A – not applicable.
✓ = strength (satisfied indicator of strength); **X** = weakness (did not satisfy indicator of strength); NR = authors did not report the information needed to assess the strength/weakness indicator.
Legend:
*Hull et al., report on two separate studies, one that included two study years but only one intervention community; the other included multiple communities but covered only one season.
†Reported in the supplementary material.
N/A – Charu et al. covered 29 influenza seasons.

Table 2B
Strengths and weakness/limitations of reviewed household- and school-based studies.

Study citation	Study design						Study populations	Reported			
	RCT or cluster-randomized	Multi-year study	Multiple intervention sites	Laboratory-confirmed outcomes	Measured direct VE in immunized target group	Funding: No conflict of interest reported	Comparable vs. non-comparable or unclear	Sample sizes, all groups	p-values or 95% CIs, all outcomes	Data to calculate Δ coverage	Vaccine match, seasonal details
Household studies											
Hurwitz [59]	✓	X	✓	X	NR	✓	✓	✓	✓	X	X
Esposito [57]	✓	X	✓	X	✓	✓	X	✓	✓	X	X
Principi [58]	✓	X	✓	X	✓	✓	X	✓	✓	X	X
King [56]	X	X	X	X	X	X	X	✓	✓	✓	✓
King [60]	X	X	✓	X	X	X	✓	✓	✓	✓	✓
School-based studies											
Graitcer [55]	X	X	✓	X	X	✓	X	X	X	✓	X
Pannaraj [54]	X	X	✓	✓	X	✓	X	✓	X	✓	X

Abbreviations: VE – vaccine effectiveness; CI – confidence interval; RCT – randomized controlled trial; NR – not reported.
✓ = strength (satisfied indicator of strength); **X** = weakness (did not satisfy indicator of strength); NR = authors did not report the information needed to assess the strength/weakness indicator.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

AJM reports research funds from GSK and Sanofi-Pasteur. All other authors have no conflicts to disclose.

ICMJE criteria

All authors attest they meet the ICMJE criteria for authorship.

Authors' contributions

BFW and AW carried out a preliminary literature summary, which inspired this review; BFW, AW, and SB conceived the idea for this systematic review and its design. JJ, JCK, AJM, and NSC

served on the advisory committee, contributed to protocol development and offered expert advice at all stages of the review. AW finalized the review protocol and registered the protocol with PROSPERO; AR/DH and LF screened abstracts/titles and full-text articles; AR and LF abstracted data and critically appraised the included articles. LF drafted the original manuscript with help from AR, AW, and BFW. All authors reviewed various iterations this manuscript and provided thoughtful feedback.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [AJM reports research funds from GSK and Sanofi-Pasteur. All other authors have no conflicts to disclose.].

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.09.086.

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