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Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies

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Abstract

Objective: Animal and *in vitro* studies suggest viral acute respiratory infection (VARI) can predispose to pneumococcal infection. These findings suggest that prevention of VARI can yield additional benefits for the control of pneumococcal disease (PD). In population-based studies, however, the evidence is not in accordance, possibly due to a variety of methodological challenges and problems in these studies. We aimed to summarise and critically review the methods and results from these studies in order to inform future studies.

Methods: We conducted a systematic review of population-based studies that analysed the association between preceding seasonal VARI and subsequent PD. We searched MEDLINE, Embase and Global Health databases using tailored search strategies.

Results: A total of 26 studies were included. After critically reviewing the methodologies and findings, 13 of the 26 included studies did not control for seasonal factors shared by both VARI and PD. This, in turn, could lead to an overestimation of the association between the two illnesses. The remaining 13 studies that controlled for seasonal factors suggested that influenza and/or RSV infections were likely to be associated with the subsequent occurrence of PD (influenza: 11/13 studies; RSV: 4/5 studies). However, these studies were unable to conduct individual patient data-based analyses. Nevertheless, the included studies suggested that the association between seasonal VARI and subsequent PD were related to additional factors such as virus type and subtype, age group, comorbidity status, presentation of PD and pneumococcal serotype.

Conclusions: Population-based studies do not give consistent support for an association between preceding seasonal VARI and subsequent PD incidence. The main methodological challenges of existing studies include the failure to utilize individual patient data, control for seasonal factors of VARI and PD, or include other factors related to the association (e.g. virus, age, comorbidity and pneumococcal serotype).

Strengths and limitations of this study

- This is the first review that critically reviewed the methods and the findings of population-based studies that reported an association between VARI and PD.
- Results of studies summarised according to study design and methods
- No meta-analysis was conducted due to a variety of study designs, data sources and analytical methods in the studies so a narrative summary of the methods and results is provided.
- The review is presented in a manner that would be accessible to a general audience so no detailed statistical techniques are discussed.

Introduction

Both viral acute respiratory infection (VARI) and pneumococcal disease (PD) account for a substantial disease burden worldwide, especially in young children.[1 2 2] The association of viral acute respiratory infection (VARI) and subsequent pneumococcal disease (PD) was not well recognised until the catastrophic 1918 influenza pandemic, which resulted in an estimated 40-50 million deaths;[3] it has been suggested that pneumococcus may have been a major cause the deaths.[4] Most recently, it was observed that the incidence of PD was higher during 2009 influenza H1N1 pandemic period than the same period in pre-pandemic[5-9] and post-pandemic years.[6 8 9]

During inter-pandemic periods, the associations of seasonal influenza and other seasonal respiratory viruses such as respiratory syncytial virus (RSV), human metapneumovirus (hMPV) and parainfluenza (PIV) with PD incidence are poorly understood and remain unclear. In animal and in-vitro studies, it has been suggested that viral respiratory infection could predispose to pneumococcal infection and might facilitate pneumococcal transmission; in turn, this co-infection could induce a lethal synergism that is much more severe than infection with either pathogen alone (a brief summary of findings displayed in **Supplementary Table S1**). However, these studies are all relatively small-scale studies and may be subject to publication bias favouring reporting of positive findings. In population-based studies, the findings were inconsistent. These studies differed substantially in study design, data sources and methods, making it difficult to compare and interpret the results across the studies. We conducted a systematic review of population-based studies on the association of preceding VARI on the occurrence of PD to summarise the methodology and results, critically review the findings and present recommendations for future studies.

Methods

Search Strategy and Selection Criteria

We searched MEDLINE, Embase and Global Health databases using tailored search strategies (details in **Supplementary Text S1**, PRISMA flowchart in **Figure 1**). We restricted the search to studies published between 1 January 1990 and 27 April 2017. We included population-based studies with

clinically diagnosed PD cases (see below for detailed definition). In terms of VARI exposure, we accepted the following studies: (1) those with laboratory confirmed viral infections; (2) those with an ICD code for influenza and/or RSV infection; (3) those with case definition of influenza-like illness (ILI) and bronchiolitis. We excluded animal studies and theoretical studies where no population data were applied. We focused our review on the association of seasonal VARI and PD and thus excluded studies that reported pandemic influenza cases only. No language restrictions were applied. The reference lists of eligible studies were also checked to identify additional studies for inclusion. The protocol for this systematic review was registered on PROSPERO (registration number: CRD42017064760).

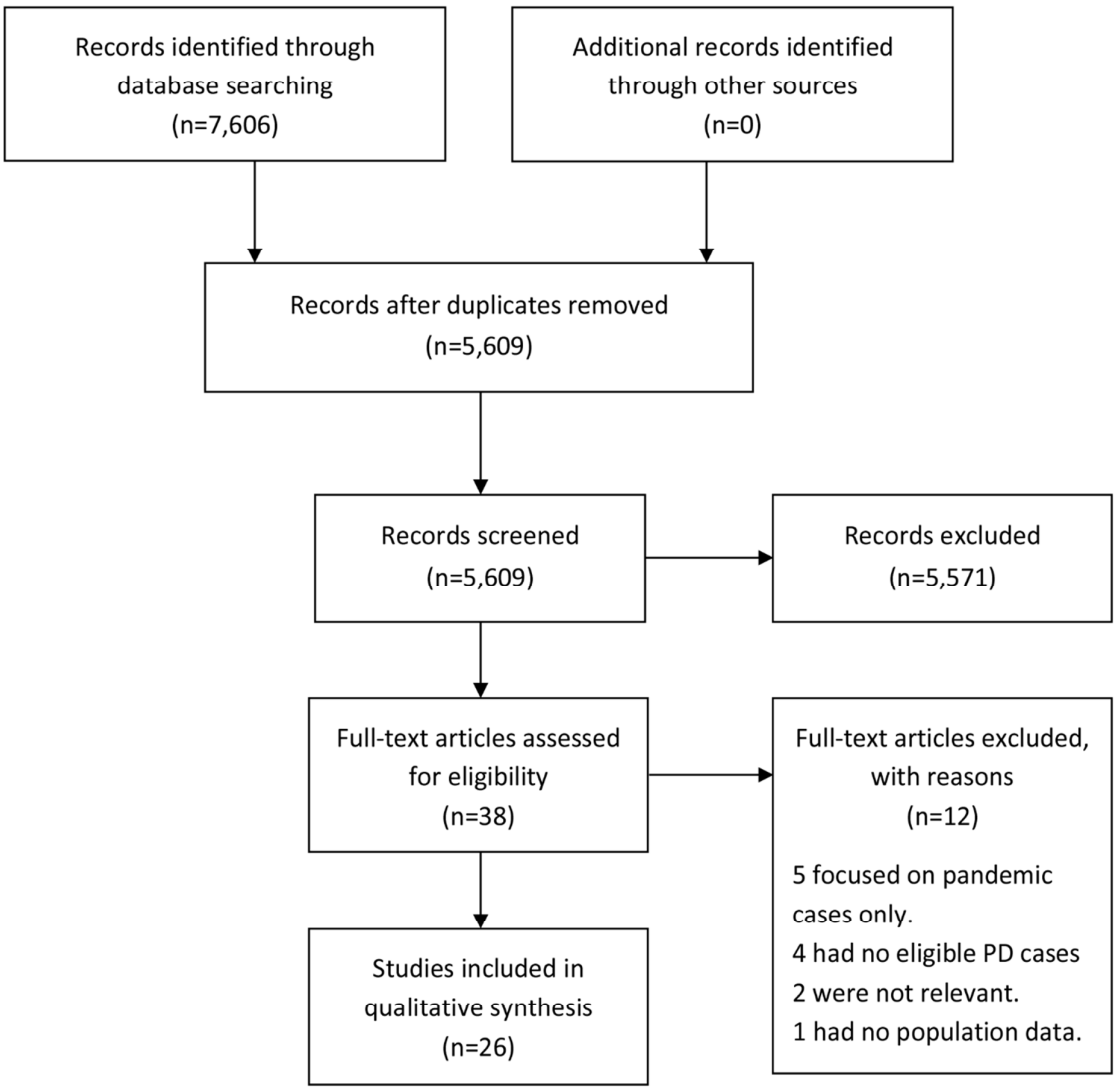

Figure 1. PRISMA flow diagram of the literature search. PD: pneumococcal disease.

Definitions

We defined PD as any disease caused by *Streptococcus pneumoniae* (pneumococcus). Since this definition contains a broad range of diseases and symptoms, including some that are trivial to our review, we adopted a narrower definition. This narrowed definition includes invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP). We defined IPD as detection of pneumococcus in typical sterile sites (e.g. blood, pleural and cerebrospinal fluid). A detailed category of PD for our review is displayed in **Figure 2**. Additionally, we used the term "non-pneumonic invasive pneumococcal disease (npIPD)", which referred to all IPD without diagnosis of pneumonia, in order to differentiate from non-invasive pneumococcal pneumonia. We defined VARI as a respiratory tract

infection with laboratory-confirmed viral aetiology. We defined ILI as a symptomatic cough and fever ≥38°C with onset within 7 days.

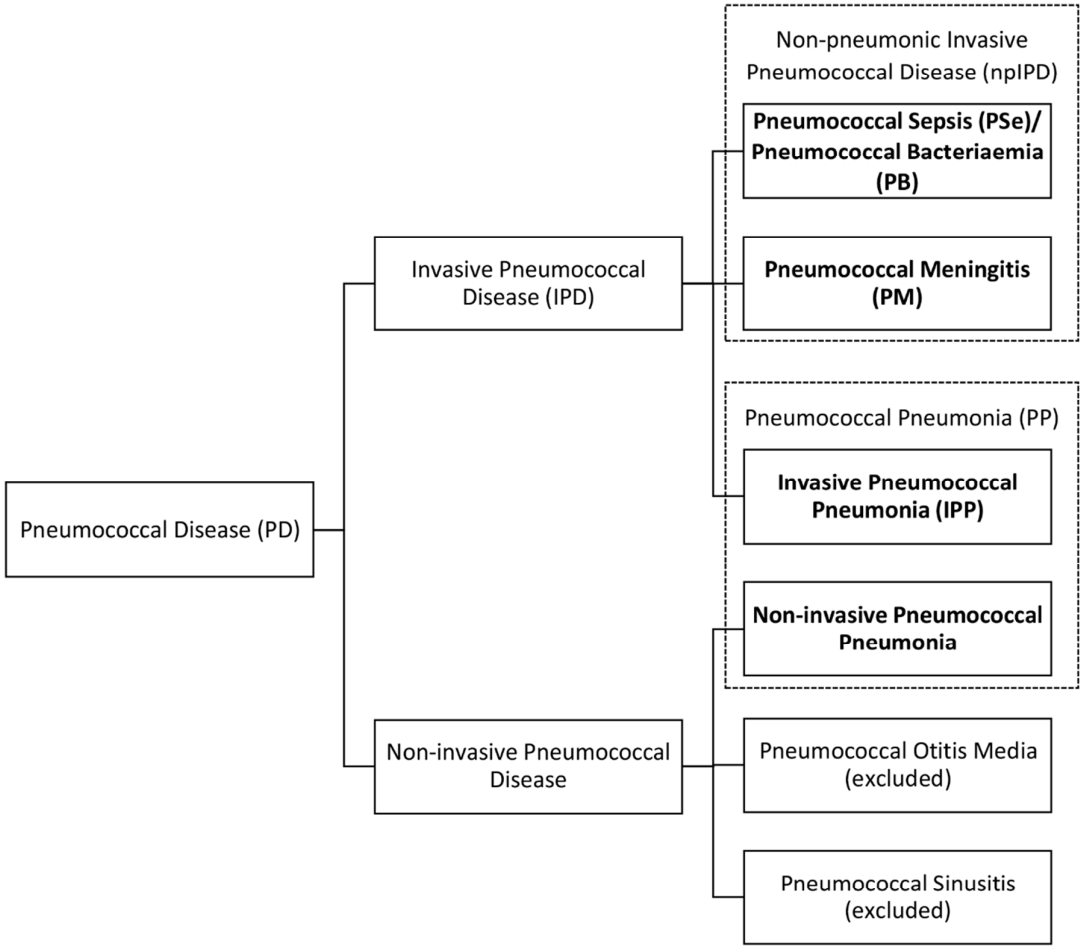

Figure 2. Category of pneumococcal disease in the present review.

Data Extraction

We used a standardised data extraction template to extract relevant data from the eligible full-text studies, including study design, data source, methods, results and conclusion. The principle summary measures of the association between VARI and PD include correlation coefficients, risk ratios, rate ratios and odds ratios. In addition, we determined the number of tests conducted in each study, so a Bonferroni correction could be applied where applicable; only the tests dealing with the association between VARI and pneumococcal infection were included as part of the correction. YL and MP independently extracted the data. HN or HC arbitrated any disagreement with the extraction.

Results

A total of 26 studies were eligible and included in the review. We summarised the studies and displayed the results according to study design and methods.

Individual Patient Data Based Studies

Individual patient data based studies during the inter-pandemic period are sparse. Only three studies were included (**Table 1**). The reported results consistently supported the role of preceding VARI on occurrence of PD. However, none of these three studies attempted to control the seasonal factors of VARI and PD that could confound the association.

Table 1. Summary of individual patient data based studies.

Study	Study Period	Population	VARI	PD (n of cases)	Methods	Main findings
Edwards et al. 2011[10]	2005–2009	all ages Northern Territory, Australia	IFV	IPD (n=346)	Using data from Notifiable Diseases System, the relative risk of IPD in ≤4w after IFV compared with background risk was calculated.	RR=112.5 [48.9–224.8]
O'Brien et al. 2000[11]	1995–1996	<18y Iowa, US	ILI IFV A	Severe PP (n=13)	Case-control design: case from children with severe PP, 3 controls per case selected from friends of cases or from the same primary case practice, matched with age (within 1y of the case). ILI history (7–28d) investigated by telephone interview and IFV A convalescent serology collected.	OR (ILI history)=12.4 [1.7-306], OR (IFV A convalescent serology)=3.7 [1.0–18.1]
Stensballe et al. 2008[12]	1996–2003	all ages Denmark	RSV non-RSV	IPD (n=7,787)	Prospective cohort study: two exposure groups were RSV and non-RSV respiratory infection hospitalisations within 30d	RR for RSV=7.1 [3.6–14.3], RR for non-RSV=4.5 [2.0–10.0]

Abbreviations: d, day(s); IFV, influenza virus; ILI, influenza-like illness; IPD, invasive pneumococcal disease; OR, odds ratio; PD, pneumococcal disease; PP, pneumococcal pneumonia; RR, relative risk; RSV, respiratory syncytial virus; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Ecological Studies

In our review, twenty-three of 26 studies were ecological studies. Additionally, the study by Stensballe et al.[12] analysed data at both population and individual level. Since such ecological studies often utilized multiple analytical methods, we reported the results below according to the study methodology used to allow for more appropriate comparisons.

Correlation analyses with no control for seasonal patterns

Table 2 shows a summary of 11 studies using correlation analyses. Since all studies conducted multiple tests in analysing the correlation (e.g. across age groups, viruses and lag time between VARI and PD), Bonferroni method was applied to adjust the significance level. The correlation between PD and influenza or RSV was significant in all five studies that analysed population data of all ages (correlation coefficient r: 0.40–0.71 for influenza at no time lag, 0.47–0.77 for RSV at no time lag). However, such correlation can never suggest a causal role of VARI on subsequent PD. The shared seasonal risk factors (e.g. temperature, rainfall and length of sunshine) of VARI and PD can confound the effects, leading to falsely high correlation coefficients while no causal effect exists. Of the 11 studies displayed, seven studies did not perform any further analysis to control for seasonal patterns, and subsequently it is difficult to interpret the findings from these studies.

Table 2. Summary of ecological studies utilising correlation analysis.

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Correlation Method	Correlation Coefficients (time lag)
Ampofo et al. 2008[13]	2001–2007	<18y Utah, US	IFV RSV PIV ADV hMPV	IPD (n=435)	Hospitalisation and lab data, fortnightly	Pearson	<u><18y</u>, IPD coded by ICD-9 IFV: **0.23** (0), **0.24** (2w), **0.18** (4w); RSV: **0.31a** (0), **0.35a** (2w), **0.34a** (4w); PIV: 0.03 (0), −0.01 (2w), −0.03 (4w); ADV: 0.01 (0), −0.05 (2w), −0.08 (4w); hMPV: **0.31a** (0), **0.39a** (2w), **0.37a** (4w) (similar results for culture-confirmed IPD)
Burgos et al. 2015[14]	1996–2012	≥18y Barcelona, Spain	IFV	IPD (n=1,150)	Hospitalisation and surveillance lab data, monthly	Spearman	<u>≥18y</u> IFV: **0.65a** (0), **0.45a** (1m)
Ciruela et al. 2016[15]	2006–2012	all ages Catalonia, Spain	IFV RSV ADV	IPD (n=8,044)	Microbiological reporting system, monthly	Spearman	<u>All ages</u> IFV: **0.71a** (0), **0.64a** (1m); RSV: **0.77a** (0), **0.80a** (1m); ADV: **0.61a** (0), **0.39a** (1m) (similar results for age-stratified analysis of IFV and RSV; results of ADV were only significant among <5y with no lag)
Jansen et al. 2008[16]	1997–2003	all ages Netherlands	IFV RSV	IPD (n=7,266; PM+PB)	Weekly Sentinel System, weekly	Spearman	<u>0–4y</u>, <u>5–17y</u>, <u>≥18y</u> IFV-PB: **0.24b**, **0.21b**, **0.62b** IFV-PM: **0.23b**, **0.14b**, **0.39b** RSV-PB: **0.29b**, **0.12b**, **0.59b** RSV-PM: **0.36b**, —, **0.44b**

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Correlation Method	Correlation Coefficients (time lag)
Kim et al. 1996[17]	1990–1993	all ages Houston, TX, US	IFV RSV ADV PIV non-IFV	IPD (n=480)	Hospitalisation and surveillance lab data, fortnightly	Pearson	≥18y IFV: **0.46a** (0), **0.35** (4w) RSV: **0.56a** (0), **0.54a** (4w) ADV: **0.25** (0), **0.29** (4w) non-IFV: **0.38a** (0), **0.35** (4w) <18y IFV: 0.08 (0), **0.23** (4w), **0.47a** (8w) RSV: 0.13 (0), **0.28** (4w), **0.32** (8w) ADV: **0.31** (0), **0.55a** (4w), **0.24** (8w) non-IFV: **0.24** (0), **0.39a** (4w), **0.21** (8w)
Murdoch et al. 2009[18]	1995–2006	all ages Christchurch, New Zealand	IFV RSV ADV PIV	IPD (n=737)	Surveillance data, monthly	Spearman	All ages IFV A: **0.44a** (0), **0.37a** (1m) IFV B: **0.23** (0), 0.13 (1m) RSV: **0.52a** (0), **0.47a** (1m) ADV: **0.27a** (0), **0.33a** (1m) PIV 1/2: **0.24** (0), **0.31a** (1m) PIV 3: **0.34a** (0), **0.17** (1m) (correlations were stronger in 5–65y and >65y)
Nicoli et al. 2013[19]	1996–2009	all ages England and Wales, UK	IFV RSV	IPD (n=71,333)	Surveillance data, weekly	Pearson and Spearman	All ages, Pearson IFV: **0.54a** RSV: **0.47a** All ages, Spearman IFV: **0.67a** RSV: **0.63a** (correlations were stronger in 15–64y and ≥65y than 0–4y and 5–14y)

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Correlation Method	Correlation Coefficients (time lag)
Peltola et al. 2011[20]	1995–2007	<5y Finland	RV EV RSV IFV PIV ADV	IPD (about 90 cases per year)	National Infectious Disease Register + 3 studies + virus database, fortnightly	Pearson	<5y RV: **0.28**, **0.25**, 0.31, **0.23a** (from 4 studies) EV: **0.17** RSV: 0.05 IFV: −0.03 IFV A: −0.08 PIV: 0.02 ADV: -0.05
Stensballe et al. 2008[12]	1996–2003	all ages Denmark	RSV non-RSV	IPD (n=7,787)	Population Based Registries Cohort, monthly	Pearson	All ages RSV: **0.55a** non-RSV: **0.65a** <2y RSV: 0.08
Talbot et al. 2005[21]	1995–2002	all ages Tennessee, US	IFV RSV	IPD (n=4,147)	Surveillance data, weekly	Pearson	All ages RSV: **0.56a** (0), **0.60a** (1w), **0.59a** (2w), **0.57a** (3w), **0.55a** (4w) IFV: **0.40a** (0), **0.41a** (1w), **0.34a** (2w), **0.33a** (3w), **0.26a** (4w) (correlations were stronger in ≥18y than <18y)

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Correlation Method	Correlation Coefficients (time lag)
Watson et al. 2006[22]	2000 (May–Oct)	all ages New South Wales, Australia	IFV RSV PIV	IPD (n=681)	Surveillance data, weekly	Pearson	<u><18y</u> IFV: not significant RSV: **0.58a** PIV: **–0.40** <u>≥18y</u> IFV: not significant RSV: not significant PIV: not significant RSV or IFV: **0.48**

Time lag indicates the time difference between preceding VARI and subsequent PD incidence.

Abbreviations: ADV, adenovirus; EV, enterovirus; IFV, influenza virus; IPD, invasive pneumococcal disease; m, month(s); MPV, metapneumovirus; PB, pneumococcal bacteraemia; PD, pneumococcal disease; PIV, parainfluenza virus; PM, pneumococcal meningitis; RSV, respiratory syncytial virus; RV, rhinovirus; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Correlation coefficients **in bold** were statistically significant (P<0.05); correlation coefficients ending with “a” were statistically significant after Bonferroni adjustment (P< 0.05/number of relevant tests) or when the Bonferroni correction was deemed unnecessary; correlation coefficients ending with “b” did not have enough information to apply the Bonferroni correction.

Analyses controlling for seasonal patterns

Table 3 shows the summary of 13 studies that controlled for seasonal patterns. Where required, we applied the Bonferroni correction to account for multiple tests. Results were inconsistent among the studies. In all-age population studies, preceding influenza infection was likely to be associated with IPD (11 of 13 studies reported an association). According to two studies that displayed age-stratified results,[18 19] the association between influenza and IPD was more likely to exist among older people than among young children. In terms of preceding RSV infection, four out of five studies observed an association of RSV with PD incidence. Specifically, one study[15] found the association between RSV and IPD only existed among children <5 years. Studies reporting other viruses such as ADV and PIV were sparse (two and one studies, respectively). Five studies that analysed two or more viruses demonstrated that the association differed by the type of the virus. Moreover, the association could differ among virus subtypes (e.g. influenza A *vs* influenza B[23] and PIV 1/2 *vs* PIV 3[18]). Notably, there are other factors that could influence the strength of the associations reported in these studies. For instance, the association could vary by presentation of PD (invasive pneumococcal pneumonia, IPP vs npIPD[24-26] and PP vs pneumococcal sepsis, PSe[27]). Preceding VARI was more likely to be associated with the occurrence of pneumonia than other clinical presentations. Additionally, the results from studies in Denmark, where comorbidity status and pneumococcal serotype were available, demonstrated that influenza had a greater influence on the incidence of low-invasiveness serotypes than medium- or high- invasiveness among the low comorbidity group; among the high comorbidity group, the pattern was reversed.[26 28]

156 **Table 3. Summary of ecological studies controlling for seasonal patterns.**

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Allard et al. 2012[29]	1997–2008	all ages Montreal, Canada	IFV (case)	IPD (n=2,920)	Notification data and sentinel surveillance data, weekly	Negative binomial regression	long-term trends and seasonal trends of IPD	<u>All ages</u> IFV A: 1.01 (0), 1.00 (1w), 1.00 (2w), 0.99 (3w), 1.00 (4w), 1.00 (5w) IFV B: 1.01 (0), 1.01 (1w), 1.00 (2w), 1.01 (3w), 0.99 (4w), 1.01 (5w)	
Burgos et al. 2015[14]	1996–2012	≥18y Barcelona, Spain	IFV (IR per 1,000)	IPD (n=1,150)	Hospitalisation and surveillance lab data, monthly	Negative binomial regression	temperature	<u>≥18y</u> IFV: **1.23a** [1.03–1.47]	
Ciruela et al. 2016[15]	2006–2012	all ages Catalonia, Spain	IFV RSV ADV (IR per 100,000)	IPD (n=8,044)	Microbiological reporting system, monthly	Negative binomial regression	temperature >17°C	<u>All ages</u> IFV: **1.26b** [1.03–1.54] (0), 1.09 [0.87–1.36] (1m) RSV: 1.15 [0.89–1.48] (0), **1.81b** [1.36–2.41] (1m) ADV: 1.58 [0.88–2.74] (0), 1.32 [0.68–2.42] (1m) <u><5y</u> IFV: 1.16 [0.90–1.50] (0), 1.06 [0.80–1.42] (1m) RSV: 1.41 [1.00–1.97] (0), **2.57b** [1.78–3.71] (1m) ADV: **2.47b** [1.38–4.53] (0), 1.00 [0.59–1.68] (1m) (not significant in 5–64y or ≥65y)	

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Grabowska et al. 2006[30]	1994–2004	all ages Sweden	IFV (binary)	IPD (n=11,637)	Surveillance data, weekly	Negative binomial regression	yearly trends and seasonal trends of IPD	All ages IFV: 1.03 [0.93–1.15] (0), 1.11 [1.00–1.23] (1w), 1.11 [0.99–1.22] (2w), **1.14** [1.02–1.26] (3w), **1.12** [1.01–1.23] (4w)	All ages **6%** [1–12%] (3w)
Kuster et al. 2011[23]	1995–2009	all ages Toronto/ Peel area, Canada	IFV (100 cases)	IPD (n=6,191)	Population-based surveillance, weekly	Negative binomial regression	multi-year trends and seasonal trends of IPD, relative humidity, temperature, UV index	All ages IFV A&B: **1.09a** [1.05–1.14] (1w), **0.93** [0.89–0.98] (3w) IFV A: identical to IFV A&B IFV B: not significant	
Murdoch et al. 2009[18]	1995–2006	all ages Christchurch, New Zealand	IFV RSV ADV PIV (binary)	IPD (n=737)	Surveillance data, monthly	Negative binomial regression	average daily temperature <10°C, PM10 >50µg/m^3, days with rainfall >10, mean daily 9 am humidity >75%, mean daily sunshine >6h	All ages IFV: **1.38** [1.02–1.85] (0), 1.20 [0.91–1.58] (1m) RSV: 1.15 [0.87–1.52] (0), 0.90 [0.68–1.18] (1m) PIV 1/2: 1.04 [0.82–1.30] (0), 1.04 [0.84–1.29] (1m) PIV 3 outside IFV season: **1.64a** [1.18–2.30] (0), **1.49** [1.07–2.08] (1m) ADV: 0.97 [0.78–1.20] (0), **1.26** [1.02–1.54] (1m) (similar in 5–65y, >65y; not significant in <5y)	

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Nicoli et al. 2013[19]	1996–2009	all ages England and Wales, UK	IFV RSV (case)	IPD (n=71,333)	Surveillance data, weekly	Negative binomial regression	weekly temperature or monthly hours of sunshine (separately in models; results were similar)		All ages, 0–4y, 5–14y, 15–64y, ≥65y controlling for temperature, multiplicative model IFV: **5.6%b** [0.2–23.8%] , −0.4% [−1.8–0.0%], **2.9%** [0.0–13.6%], **1.8%** [0.1–7.4%], **3.2%b** [0.0–14.7%] RSV: **2.9%b** [0.1–14.2%], **1.4%** [0.0–6.9%], **5.9%b** [0.0–27.6%], **14.5%b** [0.0–52.7%], **7.9%b** [0.0–27.4%] (no significant results in time lag analyses)
Walter et al. 2010[24]	1995–2006	all ages US	IFV (positive percentage)	IPD (IPP, npIPD; n=21,239)	Surveillance data, weekly	Negative binomial regression	seasonal trends and linear trends of IPP		Northeast, all ages IFV-IPP: **4.9%** [4.5–5.3%] (1w) South, all ages IFV-IPP: **5.4%b** [5.0–5.9%] (1w) West, all ages IFV-IPP: **5.2%** [4.8–6.0%] (1w) (not significant for IFV-npIPD)
Weinberger et al. 2014[25]	1996–2012	<7y Navajo/White Mountain Apache population, US	Bronchiolitis (IR, as a proxy for RSV) IFV (IR)	IPD (IPP, npIPD; n=496)	4 community-based studies, monthly	Poisson regression	pneumococcal carriage prevalence, seasonal trends of IPD, PCV periods		<7y Bronchiolitis-PP: **15.5%b** [1.8–26.1%] Bronchiolitis-npIPD: 8.0% [−4.8–19.3%] (not significant for IFV)

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Weinberger et al. 2013[28]	1977–2007	≥40y Denmark	ILI (case, as a proxy for IFV)	IPP (n=8,308)	Surveillance data + nationwide general practice reports, weekly	Poisson regression	seasonal trends of IPP, dummy variable for week 1,2,3,51,52 and its interaction with ILI		≥40y, low comorbidity and low serotype invasiveness ILI: **17.9%a** [13.6–21.9%] (1w) ≥40y, low comorbidity and high serotype invasiveness ILI: **6.7%a** [3.8–11.7%] (1w) ≥40y, medium/high comorbidity and low serotype invasiveness ILI: 1.3% [−1.6–5.4%] (1w) ≥40y, medium/high comorbidity and high serotype invasiveness ILI: **8.9%a** [6.6–11.8%] (1w)

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Weinberger et al. 2014[26]	1977–2007	all ages Denmark	ILI (case, as a proxy for IFV)	IPD (IPP, npIPD; n=13,882)	Surveillance data + nationwide general practice reports, weekly	Poisson regression	seasonal trends of IPD, dummy variable for week 1,2,3,51,52 and its interaction with ILI		15–39y, low comorbidity ILI-IPD: **9.9%a** [6.0–13.0%] (1w) ILI-IPP: **11.2%a** [6.5–14.8%] (1w) ILI-npIPD: 6.6% [−1.2–14.3%] (1w) 15–39y, medium/high comorbidity ILI-IPD: 0.3% [−8.4–9.7%] (1w) ILI-IPP: 5.4% [−5.0–18.7%] (1w) ILI-npIPD: −6.6% [−25.7–7.6%] (1w) ≥40y, low comorbidity ILI-IPD: **7.6%a** [5.1–11.6%] (1w) ILI-IPP: **7.8%a** [5.8–11.7%] (1w) ILI-npIPD: **6.9%a** [1.8–12.8%] (1w) ≥40y, medium/high comorbidity ILI-IPD: **6.2%a** [4.3–9.3%] (1w) ILI-IPP: **6.5%a** [4.4–10.1%] (1w) ILI-npIPD: **5.3%a** [2.5–8.9%] (1w)

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Weinberger et al. 2015[27]	1992–2009	<2y 36 states in US	IFV RSV (IR)	PD (PP, PSe; n=17,404)	State inpatient databases, weekly	Poisson regression	seasonal trends of PD, PCV periods, IFV or RSV, state	0–2m, 3–11m, 0–11m, 12–23m RSV-PP: **1.42b** [1.30–1.55], **1.24b** [1.17–1.33], **1.23b** [1.19–1.30], **1.12b** [1.09–1.18]	0–2m, 3–11m, 0–11m, 12–23m IFV-PP: 2.1% [−4.5–1.4%], **2.2%a** [0.1–3.4%], 0.6% [−0.9–1.4%], **3.2%a** [1.7–4.7%] RSV-PP:**35.7%a** [27.9–42.7%], **20.0%a** [14.7–24.8%], **20.3%a** [17.4–25.1%], **10.1%a** [7.6–13.9%] IFV-PSe: 0.7% [−1.1–2.2%], **−2.7%a** [−3.7—1.7%], −0.6% [−1.4–0.3%], **1.9%a** [1.1–2.6%] RSV-PSe: **15.0%a** [13.1–17.1%], 0.1% [−4.9–5.0%], **7.2%a** [5.3–9.0%], **3.8%a** [2.5–5.2%]
Zhou et al. 2012[31]	1994–2005	all ages Atlanta, US	IFV RSV (positive percentage)	IPP (n=5,683)	Surveillance data, weekly	Negative binomial regression (comparison between models with and without IFV and RSV)	temperature, sunshine, precipitation	p values for the likelihood ratio test were <0.05 for 5 of 11 influenza seasons: 1994–95, 1996–97, 1998–99, 2003–04, 2004–05; after Bonferroni adjustment association was significant for 3 of 11 influenza seasons: 1996–97, 2003–04, 2004–05.	

Time lag indicates the time difference between VARI and subsequent PD incidence.

Abbreviations: ADV, adenovirus; AP, attributable percentage; CI, confidence interval; IFV, influenza virus; h, hour(s); ILI, influenza-like illness; IPD, invasive pneumococcal disease; IPP, invasive pneumococcal pneumonia; IR, incidence rate; npIPD, non-pneumonic invasive pneumococcal disease; PCV,

pneumococcal conjugate vaccine; PD, pneumococcal disease; PIV, parainfluenza virus; PP, pneumococcal pneumonia; PSe, pneumococcal sepsis; RR, relative risk; RSV, respiratory syncytial virus; UV index, clear-sky ultraviolet index; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Relative risk or attributable percentage **in bold** were statistically significant (P<0.05); relative risk or attributable percentage ending with "a" were statistically significant after Bonferroni adjustment (P<0.05/number of relevant tests) or when the Bonferroni correction was deemed unnecessary, those ending with "b" did not have enough information to apply the Bonferroni correction.

Studies utilising other analyses

Five ecological studies utilised other analytical methods (**Table 4**). While four of five studies supported the association between preceding VARI and PD, these studies did not control for the seasonal factors of VARI and PD.

Table 4. Summary of ecological studies utilising other methods.

Study	Study Period	Population	VARI	PD (n of cases)	Methods	Main findings
Dangor et al. 2014[32]	2005–2008	<15y Soweto, South Africa	IFV	IPD (n=636)	X-11 seasonal adjustment method to obtain peak timing. Peak timing was compared using time series graph.	IFV peaked in May–Jul, followed by IPD (Aug–Oct).
Kuster et al. 2011[23]	1995–2009	all ages Toronto/ Peel area, Canada	IFV	IPD (n=6,191)	Spearman correlation for phase and amplitude terms between influenza and IPD; Granger methods to test whether influenza predicted IPD; Case-crossover analysis to evaluate short-term associations.	IFV enhanced short-term risk of IPD (1w lag), but seasonal waveforms were not correlated.
Opatowski et al. 2013[33]	2001–2004	all ages France	VARI (only available during winter season)	PM (n=1,383)	Weekly PM was modelled using a generalised estimating equations approach; a mathematic model of pneumococcal colonisation and meningitis infection was built.	Model simulations suggested a combined impact of VARI on pneumococcal transmissibility and pathogenicity.
Shrestha et al. 2013[34]	1989–2009	Illinois, US	IFV	PP (n not known)	SIRS compartmental model of pneumococcal transmission using influenza incidence as a covariate.	a transient (~1w) but strong increase (~ 100 fold) in the risk of PP after infection with IFV.

Study	Study Period	Population	VARI	PD (n of cases)	Methods	Main findings
Toschke et al. 2008[35]	1997–2003	<16y Germany	IFV A	IPD (n=1,474)	Time series analysis using Farrington algorithm; multivariate time series analysis using "3h algorithm".	Influenza A season did not affect IPD season (*P*=0.49); influenza A peak did not precede IPD peak.

Abbreviations: IFV, influenza virus; IPD, invasive pneumococcal disease; PD, pneumococcal disease; PM, pneumococcal meningitis; PP, pneumococcal pneumonia; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Discussion

In our review, we summarised population-based studies that evaluated the association of seasonal VARI and subsequent PD. To our knowledge, this is the first review that summarises the methodology and findings of existing epidemiological studies on this topic.

We found that reported associations between VARI and subsequent PD were inconsistent among the 26 included studies. Only three studies[10-12] analysed the association using individual patient data. These studies did not account for the shared risk factors between VARI and PD that influenced their seasonality, such as temperature, length of sunshine and amount of rainfall, substantially limiting the inferences that can be made from these data. In ecological studies, only 13 of the 23 ecological studies accounted for seasonal patterns. In these studies, we found that influenza and/or RSV infections were likely to be associated with the subsequent occurrence of PD. For influenza, the association was stronger among younger populations compared to older adults[18 19] while the pattern was reversed for RSV.[15] Data from multiple studies suggested that virus type (five studies) and subtype (two studies), comorbidity status (two studies) and pneumococcal serotype invasiveness (one study) could influence the association. However, the 13 ecological studies had various population characteristics (e.g. age, comorbidity, immunity status), PD datasets, VARI datasets and

analytical methods. As such, heterogeneity among the studies, along with their ecological nature, limits the amount of valid inferences that can be made from the data (as summarised above).

Nevertheless, these studies provide important clues for the potential factors related to the association between VARI and subsequent PD, and thus could help with the conception and design of future studies. Ideally, in order to understand whether a particular preceding VARI can predispose an individual to PD, a prospective cohort study that monitors each individual for VARI and pneumococcal infection would be utilised, allowing analyses at both individual and population levels. However, such a design would not be feasible or affordable as inter alia pneumococcal infections are rare. Alternatively, utilisation of large-scale routine health data and reliable data linkage (through unique individual identifiers) from sources such as surveillance data and hospitalisation datasets may be feasible in many industrialised countries. An example of such data linkage in our review is the study by Stensballe and colleagues[12] that linked information from four Danish population-based registries. While the authors conducted individual-level analysis, the results were based on cases tested for both the presence of respiratory viruses and pneumococcal infection. The true number of VARI-associated PD cases is likely to be significantly higher due to incomplete testing of cases; the untested viral-pneumococcal cases could represent a crucial source of selection bias. Community-based active surveillance can likely address the issue of missing cases but such surveillance would be labour intensive to conduct. Another option is a case-control study, which is affordable and practical, but not without its limitations. In addition to challenges in designing such studies, defining the history of VARI is likely to be inaccurate since the timing of viral serology may be less accurate.[20] In the case-control study by O'Brien and colleagues,[11] the authors used influenza-strain specific convalescent serology as evidence for preceding influenza infection. The authors also conducted telephone interviews to investigate ILI history but they did not mention whether interviewers and interviewees were blind to case or control status. Moreover, the value of this case-control study is limited by its very small sample size (n case = 13).

Compared with individual patient data based studies, ecological studies are more feasible, and thus the most common study design included in our review (23/26). However, the results should be interpreted at a population level and cannot be generalised to the individual level. Since ecological studies used data aggregated into broad categories, the potential biases introduced by the aggregation should be taken into account. For instance, while 14 out of 23 ecological studies used weekly data, others used fortnightly or monthly data. This may lead to misclassification as the time window of the association of VARI on PD susceptibility can be as short as one week.[36 37] Moreover, data from different sources in ecological studies should represent the same population.

Apart from the study design, one further challenge of analysing the association is accounting for the influence of seasonal factors of VARI and PD. Both VARI and PD have similar seasonal patterns, and thus are likely to correlate as indicated by the correlation results from ecological studies. The increased risk of PD during an epidemic season could be caused by VARI or by seasonal risk factors or by both. In the present review, ten ecological studies and all three individual patient data based studies did not attempt to control for seasonal confounders, likely leading to biased estimations of the association. For example, the study by Edwards and colleagues[10] reported a relative risk as high as 112.5 when not adjusting any seasonal factors. One way to address this problem in such studies would be to match the individuals with the onset timing of pneumococcal infection, keeping the risk of PD comparable between VARI cases and non-VARI cases.

Our review suggests that the association of VARI and subsequent PD could vary by virus type[15 18 19 25 28] and even by subtype[18 23]. Studies using combinations of viral infections such as all virus, influenza + RSV, non-influenza, or non-RSV could give biased estimations of the association. However, it is not always practical to analyse the association by virus type. In ecological studies, different types of viruses might co-circulate and thus be highly correlated in incidence, making it difficult to determine the role for each virus. In terms of PD, most studies used IPD as the outcome of interest. However, studies that categorised IPD into IPP and npIPD found that the association was more pronounced in IPP than in npIPD.[24-26] A similar finding, that the association was stronger in PP than PSe, was

reported in another study.[27] These results suggest VARI is more likely to be associated with pneumonic pneumococcal infections than non-pneumonic infections. In our review, we excluded studies using information other than clinical diagnosis as a proxy for PD (e.g. prescription data and carriage data). Pneumococcal carriage could have a fundamental role in the transmission and incidence of PD.[38] In a study analysing the impact of pneumococcal carriage and viral activity, Weinberger and colleagues[25] found npIPD was associated with carriage prevalence, whereas IPP was associated with bronchiolitis (as a proxy for RSV). The authors also proposed that preceding VARI increased susceptibility but did not enhance transmission (indicated by carriage prevalence) in children. However, more studies are needed to confirm these findings.

The association could also vary by population characteristics. According to two studies that displayed age-stratified results,[18 19] the association of influenza and subsequent IPD was more likely to exist among older people than among young children. Studies by Weinberger et al.[26 28] gauged the association in different comorbidity and pneumococcal serotype groups among Denmark populations. The results showed that influenza had a stronger impact on the incidence of low-invasiveness serotypes than medium- or high- invasiveness ones in the low comorbidity group, while the pattern reversed in the high comorbidity group. Another study that analysed clinical records of 919 patients with PP found that infrequently colonising pneumococcal serotypes were more likely to cause PP after preceding VARI, particularly in patients with immunodeficiency or chronic lung diseases.[39] These findings suggest the need for future studies to analyse the association by age group, pneumococcal serotype and comorbidity status. Moreover, the recent introduction of pneumococcal vaccines has brought changes in the incidence of serotype-specific PD,[40] making the association of VARI and PD more complicated to understand. As a result, future studies should consider the possible serotype-specific influence that pneumococcal vaccines have on both individual immunity and herd immunity when analysing the association.

In addition to the factors discussed above, additional factors may influence the estimates of the association. The first is the change over time in the methodology of data collection, including

changes in test method or diagnosis, clinical practice and health-seeking behaviour. The second is the possible delay in measurement, which happened most often in passive hospital-based studies. Thirdly, for ecological studies using aggregated data, “holiday spikes” could occur due to more social gatherings;[41] besides, weekends and holidays might influence timely tests or diagnosis as well as the health-seeking behaviour of patients.

We found many studies tended to conduct multiple statistical tests using different subgroups and time periods (e.g. age group, virus, time lag between VARI and PD) without specifying the primary study question a priori or making proper statistical adjustments to account for multiple testing. This could give rise to an increased risk of reporting false positive results. In this review, we applied Bonferroni corrections to adjust for the multiple tests where deemed necessary. Since the Bonferroni method is conservative and we are unable to adjust for studies where *P* values were not given, the adjustment in our review is intended for readers’ reference and as caveats for future studies.

Given the substantial burden of VARI across the world,[1] even a modest association between VARI and subsequent PD could lead to a substantial burden of disease in terms of VARI-related PD cases. If proper anti-bacterial interventions could be applied to those with higher risk of PD due to a preceding VARI, subsequent pneumococcal infections could be prevented. The interventions would be more effective / better targeted if we could estimate the risk (i.e. the strength of association) according to timing of infection by week/month of a year, age, comorbidity status, virus type and status of immunity. In turn, understanding the association between VARI and subsequent pneumococcal infection can help evaluate the full impact of viral vaccine programs.

In conclusion, the role of seasonal VARI on subsequent PD incidence remains controversial in population-based studies. Nevertheless, these studies provide valuable information and can help with the conception of future well-designed studies. Future work could explore the association by timing of infection, age, comorbidity status, virus type, pneumococcal serotype and presentation, and thus would identify potentially susceptible populations with VARI for preventive interventions.

Supplementary Materials

Table S1. Summary of findings from animal and in vitro studies.

Text S1. Search strategy

File S1. PRISMA checklist

File S2. Protocol registered in PROSPERO

Contributors: HN and HC conceived the study. YL did the literature search and reviewed the articles. YL and MP extracted and analysed the data independently with oversight from HN and HC. YL drafted the manuscript. MP, HN and HC critically reviewed the manuscript. All authors read and approved the final draft of the manuscript.

Competing interests: none declared.

Data sharing statement: Data extraction sheets are available in the Edinburgh DataShare repository, http://dx.doi.org/10.7488/ds/2047.

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REFERENCES

1. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2013;2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet 2016;388(10053):1459-544.
2. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet 2009;374(9693):893-902.
3. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev 2006;19(3):571-82.
4. Chien Y-W, Klugman KP, Morens DM. Bacterial Pathogens and Death during the 1918 Influenza Pandemic. N Engl J Med 2009;361(26):2582-83.
5. Fleming-Dutra KE, Taylor T, Link-Gelles R, et al. Effect of the 2009 influenza A(H1N1) pandemic on invasive pneumococcal pneumonia. J Infect Dis 2013;207(7):1135-43.
6. Launes C, Garcia-Garcia JJ, Trivino M, et al. Respiratory viruses, such as 2009 H1N1 influenza virus, could trigger temporal trends in serotypes causing pneumococcal disease. Clin Microbiol Infect 2014;20(12):O1088-90.

7. Nelson GE, Gershman KA, Swerdlow DL, et al. Invasive pneumococcal disease and pandemic (H1N1) 2009, Denver, Colorado, USA. Emerg Infect Dis 2012;18(2):208-16.
8. Pedro-Botet ML, Burgos J, Lujan M, et al. Impact of the 2009 influenza A H1N1 pandemic on invasive pneumococcal disease in adults. Scand J Infect Dis 2014;46(3):185-92.
9. Weinberger DM, Simonsen L, Jordan R, et al. Impact of the 2009 influenza pandemic on pneumococcal pneumonia hospitalizations in the United States. J Infect Dis 2012;205(3):458-65.
10. Edwards LJ, Markey PG, Cook HM, et al. The relationship between influenza and invasive pneumococcal disease in the Northern Territory, 2005-2009. Med J Aust 2011;194(4):207.
11. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. Clin Infect Dis 2000;30(5):784-9.
12. Stensballe LG, Hjuler T, Andersen A, et al. Hospitalization for respiratory syncytial virus infection and invasive pneumococcal disease in Danish children aged <2 years: a population-based cohort study. Clin Infect Dis 2008;46(8):1165-71.
13. Ampofo K, Bender J, Sheng X, et al. Seasonal invasive pneumococcal disease in children: role of preceding respiratory viral infection. Pediatrics 2008;122(2):229-37.
14. Burgos J, Larrosa MN, Martinez A, et al. Impact of influenza season and environmental factors on the clinical presentation and outcome of invasive pneumococcal disease. Eur J Clin Microbiol Infect Dis 2015;34(1):177-86.
15. Ciruela P, Broner S, Izquierdo C, et al. Invasive pneumococcal disease rates linked to meteorological factors and respiratory virus circulation (Catalonia, 2006-2012). BMC Public Health 2016;16(400).
16. Jansen AG, Sanders EA, A VDE, et al. Invasive pneumococcal and meningococcal disease: association with influenza virus and respiratory syncytial virus activity? Epidemiol Infect 2008;136(11):1448-54.
17. Kim PE, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses. Clin Infect Dis 1996;22(1):100-6.
18. Murdoch DR, Jennings LC. Association of respiratory virus activity and environmental factors with the incidence of invasive pneumococcal disease. J Infect 2009;58(1):37-46.
19. Nicoli EJ, Trotter CL, Turner KM, et al. Influenza and RSV make a modest contribution to invasive pneumococcal disease incidence in the UK. J Infect 2013;66(6):512-20.
20. Peltola V, Heikkinen T, Ruuskanen O, et al. Temporal association between rhinovirus circulation in the community and invasive pneumococcal disease in children. Pediatr Infect Dis J 2011;30(6):456-61.

21. Talbot TR, Poehling KA, Hartert TV, et al. Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation. Am J Med 2005;118(3):285-91.

22. Watson M, Gilmour R, Menzies R, et al. The association of respiratory viruses, temperature, and other climatic parameters with the incidence of invasive pneumococcal disease in Sydney, Australia. Clin Infect Dis 2006;42(2):211-5.

23. Kuster SP, Tuite AR, Kwong JC, et al. Evaluation of coseasonality of influenza and invasive pneumococcal disease: results from prospective surveillance. PLoS Med 2011;8(6):e1001042.

24. Walter ND, Taylor TH, Shay DK, et al. Influenza circulation and the burden of invasive pneumococcal pneumonia during a non-pandemic period in the United States. Clin Infect Dis 2010;50(2):175-83.

25. Weinberger DM, Grant LR, Steiner CA, et al. Seasonal drivers of pneumococcal disease incidence: impact of bacterial carriage and viral activity.[Erratum appears in Clin Infect Dis. 2014 Mar;58(6):908]. Clin Infect Dis 2014;58(2):188-94.

26. Weinberger DM, Harboe ZB, Viboud C, et al. Pneumococcal disease seasonality: incidence, severity and the role of influenza activity. Eur Respir J 2014;43(3):833-41.

27. Weinberger DM, Klugman KP, Steiner CA, et al. Association between respiratory syncytial virus activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. PLoS Med 2015;12(1):e1001776.

28. Weinberger DM, Harboe ZB, Viboud C, et al. Serotype-specific effect of influenza on adult invasive pneumococcal pneumonia. J Infect Dis 2013;208(8):1274-80.

29. Allard R, Couillard M, Pilon P, et al. Invasive bacterial infections following influenza: a time-series analysis in Montreal, Canada, 1996-2008. Influenza other respi 2012;6(4):268-75.

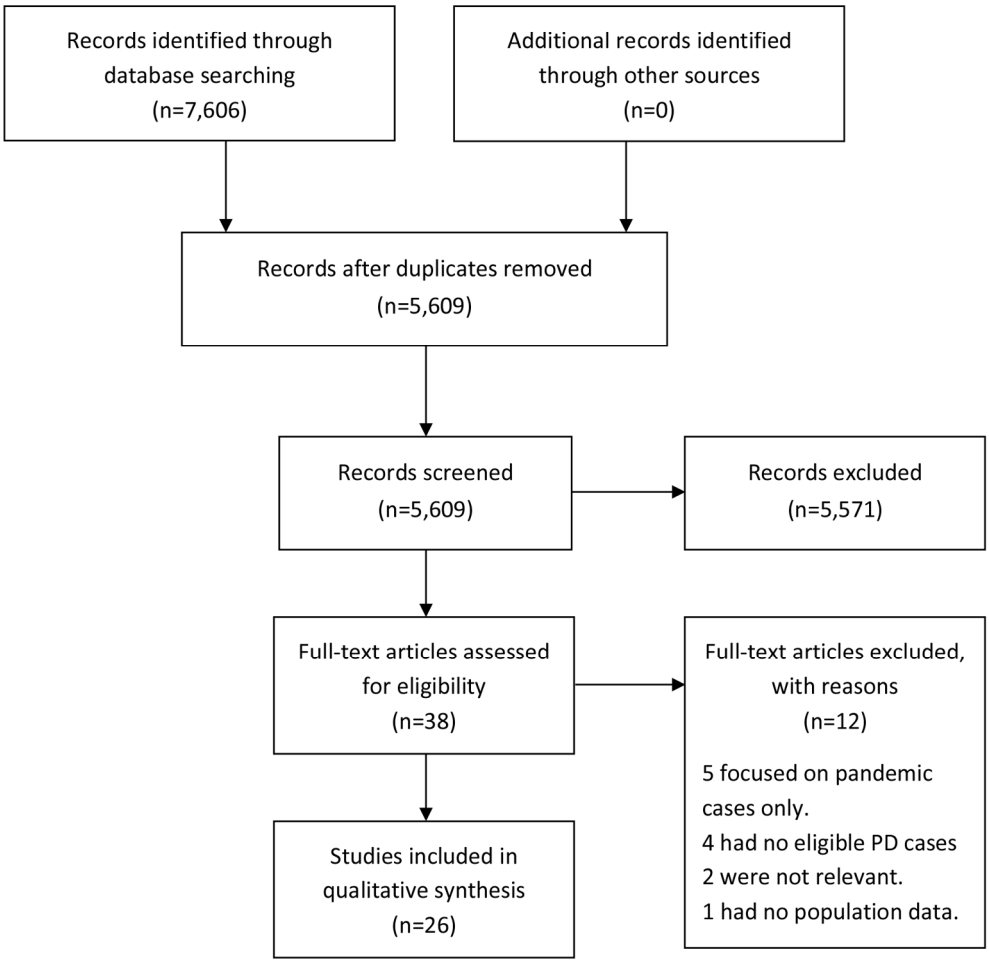
30. Grabowska K, Hogberg L, Penttinen P, et al. Occurrence of invasive pneumococcal disease and number of excess cases due to influenza. BMC Infect Dis 2006;6:58.

31. Zhou H, Haber M, Ray S, et al. Invasive pneumococcal pneumonia and respiratory virus co-infections. Emerg Infect Dis 2012;18(2):294-7.

32. Dangor Z, Izu A, Moore DP, et al. Temporal association in hospitalizations for tuberculosis, invasive pneumococcal disease and influenza virus illness in South African children. PLoS ONE 2014;9(3):e91464.

33. Opatowski L, Varon E, Dupont C, et al. Assessing pneumococcal meningitis association with viral respiratory infections and antibiotics: insights from statistical and mathematical models. Proc Biol Sci 2013;280(1764):20130519.

34. Shrestha S, Foxman B, Weinberger DM, et al. Identifying the interaction between influenza and pneumococcal pneumonia using incidence data. Sci Transl Med 2013;5(191):191ra84.
35. Toschke AM, Arenz S, von Kries R, et al. No temporal association between influenza outbreaks and invasive pneumococcal infections. Arch Dis Child 2008;93(3):218-20.
36. McCullers JA, Rehg JE. Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor. J Infect Dis 2002;186(3):341-50.
37. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection. Nat Med 2008;14(5):558-64.
38. Simell B, Auranen K, Käyhty H, et al. The fundamental link between pneumococcal carriage and disease. Expert Rev Vaccines 2012;11(7):841-55.
39. Song JY, Nahm MH, Cheong HJ, et al. Impact of preceding flu-like illness on the serotype distribution of pneumococcal pneumonia. PLoS ONE 2014;9(4):e93477.
40. Shiri T, Datta S, Madan J, et al. Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis. The Lancet Global Health 2017;5(1):e51-e59.
41. Walter ND, Taylor THJ, Dowell SF, et al. Holiday Spikes in Pneumococcal Disease among Older Adults. N Engl J Med 2009;361(26):2584-85.



PRISMA flow diagram of the literature search. PD: pneumococcal disease.

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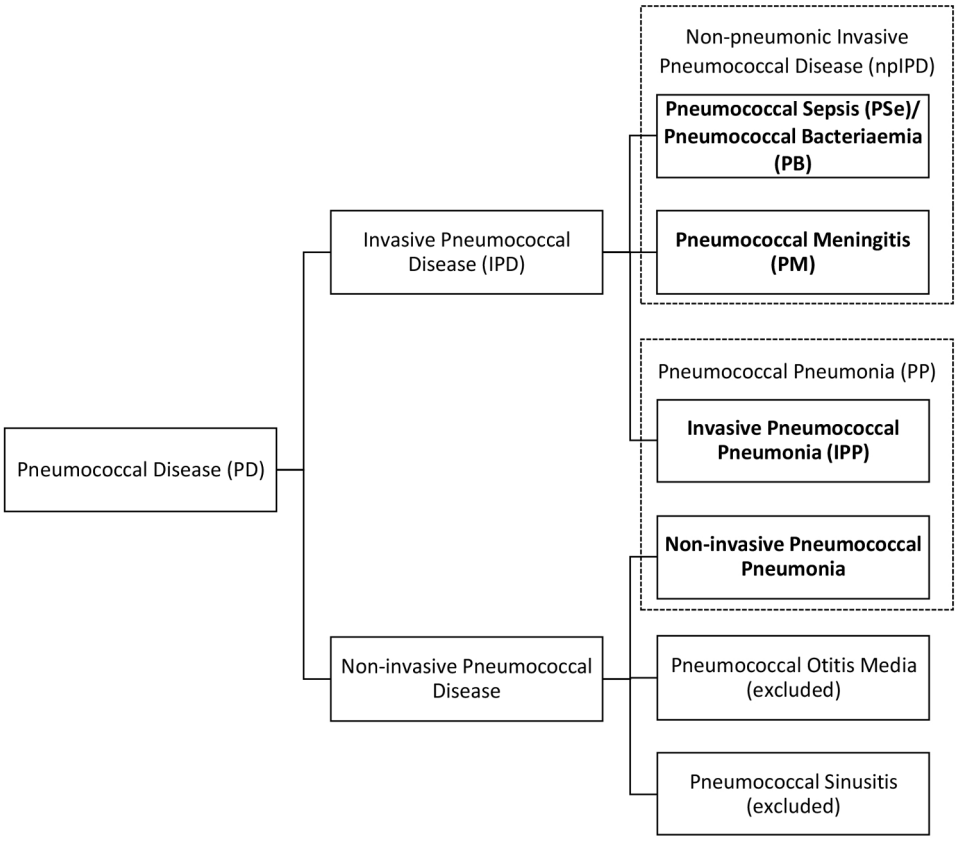

Category of pneumococcal disease in the present review.

167x157mm (300 x 300 DPI)

Table S1. Summary of findings from animal and in vitro studies.

Study	Material	Exposure	Main findings
Diavatopoulos et al. 2010[1]	Mice (n=~10 per group)	influenza A + pneumococcus (3d later)	On day 3 of pneumococcus challenge, pneumococcus numbers increased in the nasopharynx (50-fold, P=0.0002) and the lungs (300-fold, P=0.0005) in influenza A group, compared with mock-treated group; transmission of pneumococcus between littermates was dependent on infection with influenza A.
Hament et al. 2004[2]	Monolayers of human nasopharyngeal cells and pneumocyte type II cells	RSV + pneumococcus	After RSV infection of the monolayers, an increased adherence (2–10 fold) was observed among all serotypes compared with uninfected monolayers.
Hament et al. 2005[3]	Mice (n=7 per group)	RSV + pneumococcus (0 or 4d later)	At 24h of pneumococcus challenge, mice infected with RSV 0 or 4d before pneumococcus challenge had higher levels of bacteremia than control group.
Kukavica-Ibrulj et al. 2009[4]	Mice (n=18 per group)	hMPV/ influenza A + pneumococcus (5d later)	Pneumococcus numbers on day 7 of pneumococcus challenge: 5×10^2 CFU/lung in mock infection, 10^7 CFU/lung in hMPV group and 10^8 CFU/lung in influenza A group.

Study	Material	Exposure	Main findings
LeVine et al. 2001[5]	Mice (n=3 per group)	influenza A + pneumococcus (7d later)	Lungs of influenza-exposed mice demonstrated greater colony counts 24h and 48h following pneumococcus challenge.
Ludewick et al. 2011[6]	Mice (n=18 per group)	hMPV/ influenza A + pneumococcus (14d later)	Only mice infected with influenza A demonstrated an 8% weight loss 72h following pneumococcus challenge while hMPV group and mock group did not.
McCullers et al. 2002[7]	Mice (n=20 per group)	influenza A + pneumococcus (0 or 7d later)	60% of mice died 2–11d after pneumococcus challenge in influenza A group compared with 15% in mock group; reversal of the order of challenge led to protection from influenza; challenge of influenza and pneumococcus on the same day led to 100% mortality.
McCullers et al. 2010[8]	Ferrets (n=5 per group) and Mice (n=~5 per group)	influenza A + pneumococcus (7d later)	Prior influenza infection enhanced pneumococcal transmission and disease; the influenza-mediated effects were pneumococcal strain dependent.
Sharma-Chawla et al. 2016[9]	Mice (n=3–5 per group)	influenza A + pneumococcus T4, 19F or 7F (7d later)	Pneumococcal coinfection during the acute phase of influenza A infection increased degree of pneumonia and mortality for all tested pneumococcal strains. However, the incidence and kinetics of systemic dissemination remained strain dependent.

Study	Material	Exposure	Main findings
Smith et al. 2014[10]	Human ciliated respiratory epithelial cells and mice (n=10 per group)	RSV + pneumococcus	Following incubation with RSV, pneumococcus demonstrated a significant increase in the inflammatory response and bacterial adherence to human ciliated epithelial cultures and increased virulence in mice model.
Stark et al. 2006[11]	Mice (n>12 per group)	RSV + pneumococcus (7d later)	Pneumococcus numbers at 24h of pneumococcus challenge: 7.45×10^5 CFU/lung in RSV group, 5.9×10^3 CFU/lung in mock group.

The number in brackets in the column Material refers to the number of animals observed under each experiment condition; number of animals used in transmission models (used by some studies) were not displayed.

Abbreviations: CFU, colony-forming units; d, day(s); h, hour(s); hMPV, human metapneumovirus; RSV, respiratory syncytial virus.

Reference

1. Diavatopoulos DA, Short KR, Price JT, et al. Influenza A virus facilitates Streptococcus pneumoniae transmission and disease. Faseb J 2010;24(6):1789-98.

2. Hament J-M, Aerts PC, Fleer A, et al. Enhanced Adherence of Streptococcus pneumoniae to Human Epithelial Cells Infected with Respiratory Syncytial Virus. Pediatr Res 2004;55(6):972-78.

3. Hament JM, Aerts PC, Fleer A, et al. Direct binding of respiratory syncytial virus to pneumococci: a phenomenon that enhances both pneumococcal adherence to human epithelial cells and pneumococcal invasiveness in a murine model. Pediatr Res 2005;58(6):1198-203.

4. Kukavica-Ibrulj I, Hamelin ME, Prince GA, et al. Infection with human metapneumovirus predisposes mice to severe pneumococcal pneumonia. J Virol 2009;83(3):1341-9.

5. LeVine AM, Koeningsknecht V, Stark JM. Decreased pulmonary clearance of S. pneumoniae following influenza A infection in mice. J Virol Methods 2001;94(1-2):173-86.

6. Ludewick HP, Aerts L, Hamelin ME, et al. Long-term impairment of Streptococcus pneumoniae lung clearance is observed after initial infection with influenza A virus but not human metapneumovirus in mice. J Gen Virol 2011;92(Pt 7):1662-5.

7. McCullers JA, Rehg JE. Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor. J Infect Dis 2002;186(3):341-50.

8. McCullers JA, McAuley JL, Browall S, et al. Influenza enhances susceptibility to natural acquisition of and disease due to Streptococcus pneumoniae in ferrets. J Infect Dis 2010;202(8):1287-95.

9. Sharma-Chawla N, Sender V, Kershaw O, et al. Influenza A virus infection predisposes hosts to secondary infection with different Streptococcus pneumoniae serotypes with similar outcome but serotype-specific manifestation. Infection and Immunity 2016;84(12):3445-57.

10. Smith CM, Sandrini S, Datta S, et al. Respiratory syncytial virus increases the virulence of Streptococcus pneumoniae by binding to penicillin binding protein 1a. A new paradigm in respiratory infection. Am J Respir Crit Care Med 2014;190(2):196-207.

11. Stark JM, Stark MA, Colasurdo GN, et al. Decreased bacterial clearance from the lungs of mice following primary respiratory syncytial virus infection. J Med Virol 2006;78(6):829-38.

Text S1. Search strategy

Medline

1. Meningitis, Pneumococcal/ or Pneumonia, Pneumococcal/ or exp Pneumococcal Infections/ or pneumococc*.mp.

2. exp Streptococcus pneumoniae/ or Streptococcus pneumoniae.mp.

3. virus.mp. or exp Viruses/

4. exp Virus Diseases/ or virus disease*.mp.

5. correlat*.mp.

6. associat*.mp.

7. interact*.mp.

8. relat*.mp.

9. 1 or 2

10. 3 or 4

11. 5 or 6 or 7 or 8

12. 9 and 10 and 11

13. limit 12 to yr="1990 -Current"

1664 results by 27 Apr 2017

EMbase

1. exp pneumococcal infection/ or pneumococc*.mp.

2. Streptococcus pneumoniae.mp. or exp Streptococcus pneumoniae/

3. exp virus/ or virus*.mp.

4. exp virus infection/ or virus infection*.mp. or virus disease*.mp.

5. exp correlational study/ or exp correlation analysis/ or correlat*.mp.

6. associat*.mp.

7. interact*.mp.

8. relat*.mp.

9. 1 or 2

10. 3 or 4

11. 5 or 6 or 7 or 8

12. 9 and 10 and 11

13. limit 12 to yr="1990 -Current"

4778 results by 27 Apr 2017.

Global Health

1. Streptococcus pneumoniae.mp. or exp Streptococcus pneumoniae/

2. pneumococc*.mp.

3. virus*.mp. or viruses/

4. virus disease*.mp. or viral diseases.sh. or virus infection*.mp.

5. exp correlation/ or correlation analysis/ or correlat*.mp.

6. associat*.mp.

7. interact*.mp.

8. relat*.mp.

9. 1 or 2

10. 3 or 4

11. 5 or 6 or 7 or 8

12. 9 and 10 and 11

13. limit 12 to yr="1990 -Current"

1164 results by 27 Apr 2017

UNIVERSITY of York
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NHS
National Institute for Health Research

PROSPERO International prospective register of systematic reviews

Review title and timescale

1 Review title

Give the working title of the review. This must be in English. Ideally it should state succinctly the interventions or exposures being reviewed and the associated health or social problem being addressed in the review.

Association of seasonal viral acute respiratory infection (VARI) with pneumococcal disease (PD): a systematic review of population-based studies

2 Original language title

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3 Anticipated or actual start date

Give the date when the systematic review commenced, or is expected to commence.

07/12/2016

4 Anticipated completion date

Give the date by which the review is expected to be completed.

31/05/2017

5 Stage of review at time of this submission

Indicate the stage of progress of the review by ticking the relevant boxes. Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. This field should be updated when any amendments are made to a published record.

The review has not yet started ×

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	Yes	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

Review team details

6 Named contact

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

You Li

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9 Named contact phone number

Enter the telephone number for the named contact, including international dialing code.

+44 (0)7871 566188

10 Organisational affiliation of the review

Full title of the organisational affiliations for this review, and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

The University of Edinburgh

Website address:
www.ed.ac.uk

11 Review team members and their organisational affiliations
Give the title, first name and last name of all members of the team working directly on the review. Give the organisational affiliations of each member of the review team.

Title	First name	Last name	Affiliation
Mr	You	Li	The University of Edinburgh
Ms	Meagan	Peterson	The University of Edinburgh
Professor	Harish	Nair	The University of Edinburgh
Professor	Harry	Campbell	The University of Edinburgh

12 Funding sources/sponsors
Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Any unique identification numbers assigned to the review by the individuals or bodies listed should be included.
None

13 Conflicts of interest
List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.
Are there any actual or potential conflicts of interest?
None known

14 Collaborators
Give the name, affiliation and role of any individuals or organisations who are working on the review but who are not listed as review team members.

Title	First name	Last name	Organisation details

Review methods

15 Review question(s)
State the question(s) to be addressed / review objectives. Please complete a separate box for each question.
What methods have been used in population-based studies analysing the association between VARI and subsequent PD?

What results have been reported in population-based studies analysing the association between VARI and subsequent PD?

16 Searches
Give details of the sources to be searched, and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.
We searched three bibliographic databases (MEDLINE, Embase and Global Health) for primary research studies published between 1 January 1990 and 27 April 2017. No restrictions were placed on the language of publication.

17 URL to search strategy
If you have one, give the link to your search strategy here. Alternatively you can e-mail this to PROSPERO and we will store and link to it.

I give permission for this file to be made publicly available
Yes

18 Condition or domain being studied
Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Viral acute respiratory infection; pneumococcal disease.

19 Participants/population
Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.
Population-based studies involving people with viral acute respiratory infection and pneumococcal disease. Specifically, the following participants were considered: (1) Those with laboratory confirmed viral infections; (2) Those with ICD code for influenza and RSV infection; (3) Those with a case definition of an influenza-like illness (ILI) and bronchiolitis.

20 Intervention(s), exposure(s)
Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
Population-based studies involving people with viral acute respiratory infection and pneumococcal disease.

21 Comparator(s)/control
Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group).
Not applicable.

22 Types of study to be included
Give details of the study designs to be included in the review. If there are no restrictions on the types of study design eligible for inclusion, this should be stated.
There were no restrictions imposed on the types of study design eligible for inclusion. We included population-based studies involving clinically diagnosed PD cases, and specifically, we accepted the following studies: (1) Those involving laboratory confirmed viral infections; (2) Those involving an ICD code for influenza and RSV infection; (3) Those involving case definitions of an influenza-like illness (ILI) and bronchiolitis. We excluded animal studies and theoretical studies in which no population data was applied. We focused our review on the association of seasonal VARI with PD, and thus excluded studies that reported influenza pandemic cases only.

23 Context
Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24 Primary outcome(s)
Give the most important outcomes.
The association between VARI and subsequent PD.

Give information on timing and effect measures, as appropriate.

25 Secondary outcomes
List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
Factors that could affect the association between VARI and subsequent PD.

Give information on timing and effect measures, as appropriate.

26 Data extraction (selection and coding)
Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

27 Risk of bias (quality) assessment
State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.
Risk of bias will be assessed by evaluating the power of the studies, the measures taken to control for confounders, and any multiple tests made without reasonable correction or justification. Bias is expected to have little impact on the review because it is intended to provide a summary of all relevant studies, and no quantitative analysis will be conducted.

28 Strategy for data synthesis
Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where appropriate a brief outline of analytic approach should be given.

A descriptive synthesis is planned. A summary of both the methods and the results of eligible studies will be provided.

29 Analysis of subgroups or subsets
Give any planned exploration of subgroups or subsets within the review. 'None planned' is a valid response if no subgroup analyses are planned.
None planned.

Review general information

30 Type and method of review
Select the type of review and the review method from the drop down list.
Systematic review

31 Language
Select the language(s) in which the review is being written and will be made available, from the drop down list. Use the control key to select more than one language.
English

Will a summary/abstract be made available in English?
Yes

32 Country
Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved. Use the control key to select more than one country.
Scotland

33 Other registration details
Give the name of any organisation where the systematic review title or protocol is registered together with any unique identification number assigned. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here.

34 Reference and/or URL for published protocol
Give the citation for the published protocol, if there is one.
Give the link to the published protocol, if there is one. This may be to an external site or to a protocol deposited with CRD in pdf format.

I give permission for this file to be made publicly available
Yes

35 Dissemination plans
Give brief details of plans for communicating essential messages from the review to the appropriate audiences.
Do you intend to publish the review on completion?
Yes

36 Keywords
Give words or phrases that best describe the review. (One word per box, create a new box for each term)

37 Details of any existing review of the same topic by the same authors
Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38 Current review status
Review status should be updated when the review is completed and when it is published.
Ongoing

39 Any additional information
Provide any further information the review team consider relevant to the registration of the review.

40 Details of final report/publication(s)

This field should be left empty until details of the completed review are available.
Give the full citation for the final report or publication of the systematic review.
Give the URL where available.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Text S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	4-6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-23
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8-23
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-23
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	27
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	27
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	27
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	NA

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies

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Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases
Keywords:	respiratory tract infection, pneumococcal infection, viral acute respiratory infection, pneumococcal disease

Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies

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Abstract

Objective: Animal and *in vitro* studies suggest viral acute respiratory infection (VARI) can predispose to pneumococcal infection. These findings suggest that prevention of VARI can yield additional benefits for the control of pneumococcal disease (PD). In population-based studies, however, the evidence is not in accordance, possibly due to a variety of methodological challenges and problems in these studies. We aimed to summarise and critically review the methods and results from these studies in order to inform future studies.

Methods: We conducted a systematic review of population-based studies that analysed the association between preceding seasonal VARI and subsequent PD. We searched MEDLINE, Embase and Global Health databases using tailored search strategies.

Results: A total of 28 studies were included. After critically reviewing the methodologies and findings, 11 studies did not control for seasonal factors shared by VARI and PD. This, in turn, could lead to an overestimation of the association between the two illnesses. One case-control study was limited by its small sample size (n case=13). The remaining 16 studies that controlled for seasonal factors suggested that influenza and/or RSV infections were likely to be associated with the subsequent occurrence of PD (influenza: 12/14 studies; RSV: 4/5 studies). However, these 16 studies were unable to conduct individual patient data based analyses. Nevertheless, these studies suggested the association between VARI and subsequent PD was related to additional factors such as virus type and subtype, age group, comorbidity status, presentation of PD and pneumococcal serotype.

Conclusions: Population-based studies do not give consistent support for an association between preceding seasonal VARI and subsequent PD incidence. The main methodological challenges of existing studies include the failure to utilise individual patient data, control for seasonal factors of VARI and PD, or include other factors related to the association (e.g. virus, age, comorbidity and pneumococcal serotype).

Strengths and limitations of this study

- This is the first review that critically reviewed the methods and findings of population-based studies that reported an association between VARI and PD.
- Results of studies summarised according to study design and methods.
- No meta-analysis was conducted due to a variety of study designs, data sources and analytical methods in the studies so a narrative summary of the methods and results is provided.

Introduction

Both viral acute respiratory infection (VARI) and pneumococcal disease (PD) account for a substantial disease burden worldwide, especially in young children and the elderly.[1-3] The association of viral acute respiratory infection (VARI) and subsequent pneumococcal disease (PD) was not well recognised until the catastrophic 1918 influenza pandemic, which resulted in an estimated 40–50 million deaths;[4] it has been suggested that pneumococcus may have been a major cause of death.[5] Most recently, it was observed that the incidence of PD was higher during 2009 influenza H1N1 pandemic period than the same period in pre-pandemic[6-10] and post-pandemic years.[7 9 10]

During inter-pandemic periods, the associations of seasonal influenza and other seasonal respiratory viruses such as respiratory syncytial virus (RSV), human metapneumovirus (hMPV) and parainfluenza virus (PIV) with PD incidence are poorly understood and remain unclear. In animal and in-vitro studies, it has been suggested that viral respiratory infection could predispose to pneumococcal infection and might facilitate pneumococcal transmission; in turn, this co-infection could induce a lethal synergism that is much more severe than infection with either pathogen alone (a brief summary of findings displayed in **Supplementary Table S1**). However, these studies are all relatively small-scale studies and may be subject to publication bias favouring reporting of positive findings. In population-based studies, the findings were inconsistent. These studies differed substantially in study design, data sources and methods, making it difficult to compare and interpret the results across the studies. We conducted a systematic review of population-based studies on the association of preceding VARI on the occurrence of PD to summarise the methodology and results, critically review the findings and present recommendations for future studies.

Methods

Search Strategy and Selection Criteria

We searched MEDLINE, Embase and Global Health databases using tailored search strategies (search strategies in **Supplementary Text S1**, PRISMA flowchart in **Figure 1**). We restricted the search to studies published between 1 January 1990 and 31 Dec 2017. We included population-based studies

with clinically diagnosed PD cases (see below for detailed definition). In terms of VARI exposure, we accepted the following studies: (1) those with laboratory confirmed viral infections; (2) those with an ICD code for influenza and/or RSV infection; (3) those with case definition of influenza-like illness (ILI) and bronchiolitis as proxies for influenza and RSV, respectively. We excluded animal studies and theoretical studies where no population data were applied. We focused our review on the association of seasonal VARI and PD and thus excluded studies that reported pandemic influenza cases only. No language restrictions were applied. The reference lists of eligible studies were also checked to identify additional studies for inclusion. For all included studies, quality assessment was conducted using tailored Critical Appraisal Skills Programme (CASP) checklists for case-control studies and cohort studies (**Supplementary File S1**). The review was conducted and reported according to the PRISMA guidelines (**Supplementary File S2**). The protocol for this systematic review was registered on PROSPERO (registration number: CRD42017064760; **Supplementary File S3**).

Figure 1. PRISMA flow diagram of the literature search. PD: pneumococcal disease.

Definition of PD

We defined PD as any disease caused by *Streptococcus pneumoniae* (pneumococcus). Since this definition contains a broad range of diseases and symptoms, including some that are trivial to our review, we adopted a narrower definition. This narrowed definition includes invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP). We defined IPD as detection of pneumococcus in typical sterile sites (e.g. blood, pleural and cerebrospinal fluid). A detailed category of PD for our review is displayed in **Figure 2**. Additionally, we used the term “non-pneumonic invasive pneumococcal disease (npIPD)”, which referred to all IPD without diagnosis of pneumonia, in order to differentiate from non-invasive and invasive pneumococcal pneumonia.

Figure 2. Category of pneumococcal disease in the present review.

Definition of VARI

We defined VARI as a respiratory tract infection with viral aetiology. ILI was viewed as a proxy for influenza infection in the present review. We defined ILI as a symptomatic cough and fever ≥38°C with onset within 7 days.

Data Extraction

We used a standardised data extraction template to extract relevant data from the eligible full-text studies, including study design, data source, methods, results and conclusion. The principle summary measures of the association between VARI and PD include correlation coefficients, risk ratios, rate ratios, odds ratios and attributable percentage of PD to VARI. YL and MP independently extracted the data. HN or HC arbitrated any disagreement with the extraction.

Data Analysis

Since it was expected that methodology would differ substantially between studies and a quantitative meta-analysis would not be appropriate, a narrative synthesis was conducted. Studies were summarised according to methodology to allow for more appropriate comparisons of the results.

In addition, because of the concern of multiple testing, we determined the number of tests conducted in each study, so a Bonferroni correction could be applied where applicable; only the tests relevant to the association between VARI and pneumococcal infection were included as part of the correction. The Bonferroni-adjusted significance level was calculated as 0.05 divided by the number of relevant statistical tests within a study.

Results

A total of 28 studies[11-38] were eligible and included in the review. We noticed a variety of study designs, exposures and outcomes of interest and analytical methods in these studies (summarised in **Table S2**). Due to the variety, we summarised the studies and displayed the results according to study design and methods.

Individual Patient Data Based Studies

Individual patient data based studies during the inter-pandemic period are sparse. Only three studies[17 25 29] were identified (**Table 1**), including two cohort studies[17 29] and one small case-control study by O'Brien et al[25]. The reported results consistently supported the role of preceding VARI on occurrence of PD. However, the two cohort studies did not attempt to control the seasonal risk factors of VARI and PD that could potentially bias the estimated effect size.

Table 1. Summary of individual patient data based studies.

Study	Study Period	Population	VARI	PD (n of cases)	Methods	Main findings
Edwards et al. 2011[17]	2005–2009	all ages Northern Territory, Australia	IFV	IPD (n=346)	Using data from Notifiable Diseases System, relative risk of IPD calculated in ≤4w after IFV compared with background risk	RR=112.5 [48.9–224.8]
O'Brien et al. 2000[25]	1995–1996	<18y Iowa, US	ILI IFV A	Severe PP (n=13)	Case-control design: case from children with severe PP, 3 controls per case selected, from friends of cases or from the same primary care practice, matched by age (within 1y of the case). ILI history (7–28d within admission) investigated by telephone interview and IFV A convalescent serology collected.	OR (ILI history)=12.4 [1.7-306], OR (IFV A convalescent serology)=3.7 [1.0–18.1]
Stensballe et al. 2008[29]	1996–2003	all ages Denmark	RSV non-RSV	IPD (n=7,787)	Prospective cohort study: two exposure groups, RSV and non-RSV respiratory infection hospitalisations within 30d	RR for RSV=7.1 [3.6–14.3], RR for non-RSV=4.5 [2.0–10.0]

Abbreviations: d, day(s); IFV, influenza virus; ILI, influenza-like illness; IPD, invasive pneumococcal disease; OR, odds ratio; PD, pneumococcal disease; PP, pneumococcal pneumonia; RR, relative risk; RSV, respiratory syncytial virus; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Ecological Studies

In our review, 25[11-16 18-24 26-28 30-38] of the 28 studies were ecological studies. 16[11 13 14 16 18 19 22-24 26 32 34-38] out of the 25 ecological studies controlled for seasonal patterns of VARI and PD (**Table S2**). Additionally, the study by Stensballe et al.[29] analysed data at both population and individual level but did not control for the seasonal patterns.

Correlation analyses with no control for seasonal patterns

Table 2 shows a summary of 11 studies[12-14 20 21 23 24 27 29 30 33] using correlation analyses without controlling for seasonal patterns of VARI and PD. Since all studies conducted multiple tests in analysing the correlation (e.g. across age groups, viruses and lag time between VARI and PD),

Bonferroni method was applied to adjust the significance level. The correlation between PD and influenza or RSV was statistically significant in all five studies [14 23 24 29 30] that analysed population data of all ages (correlation coefficient r: 0.40–0.71 for influenza at no time lag, 0.47–0.77 for RSV at no time lag).

Table 2. Summary of ecological studies utilising correlation analysis.

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Correlation Method	Correlation Coefficients (time lag)
Ampofo et al. 2008[12]	2001–2007	<18y Utah, US	IFV RSV PIV ADV hMPV	IPD (n=435)	Hospitalisation and lab data, fortnightly	Pearson	<u><18y</u>, IPD coded by ICD-9 IFV: **0.23c** (0), **0.24c** (2w), **0.18c** (4w); RSV: **0.31a** (0), **0.35a** (2w), **0.34a** (4w); PIV: 0.03 (0), −0.01 (2w), −0.03 (4w); ADV: 0.01 (0), −0.05 (2w), −0.08 (4w); hMPV: **0.31a** (0), **0.39a** (2w), **0.37a** (4w) (similar results for culture-confirmed IPD)
Burgos et al. 2015[13]	1996–2012	≥18y Barcelona, Spain	IFV	IPD (n=1,150)	Hospitalisation and surveillance lab data, monthly	Spearman	<u>≥18y</u> IFV: **0.65a** (0), **0.45a** (1m)
Ciruela et al. 2016[14]	2006–2012	all ages Catalonia, Spain	IFV RSV ADV	IPD (n=8,044)	Microbiological reporting system, monthly	Spearman	<u>All ages</u> IFV: **0.71a** (0), **0.64a** (1m); RSV: **0.77a** (0), **0.80a** (1m); ADV: **0.61a** (0), **0.39a** (1m) (similar results for age-stratified analysis of IFV and RSV; results of ADV were only significant among <5y with no lag)
Jansen et al. 2008[20]	1997–2003	all ages Netherlands	IFV RSV	IPD (n=7,266; PM+PB)	Weekly Sentinel System, weekly	Spearman	<u>0–4y</u>, <u>5–17y</u>, <u>≥18y</u> IFV-PB: **0.24b**, **0.21b**, **0.62b** IFV-PM: **0.23b**, **0.14b**, **0.39b** RSV-PB: **0.29b**, **0.12b**, **0.59b** RSV-PM: **0.36b**, —, **0.44b**

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Correlation Method	Correlation Coefficients (time lag)
Kim et al. 1996[21]	1990–1993	all ages Houston, TX, US	IFV RSV ADV PIV non-IFV	IPD (n=480)	Hospitalisation and surveillance lab data, fortnightly	Pearson	≥18y IFV: **0.46a** (0), **0.35c** (4w) RSV: **0.56a** (0), **0.54a** (4w) ADV: **0.25c** (0), **0.29c** (4w) non-IFV: **0.38a** (0), **0.35c** (4w) <18y IFV: 0.08 (0), **0.23c** (4w), **0.47a** (8w) RSV: 0.13 (0), **0.28c** (4w), **0.32c** (8w) ADV: **0.31c** (0), **0.55a** (4w), **0.24c** (8w) non-IFV: **0.24c** (0), **0.39a** (4w), **0.21c** (8w)
Murdoch et al. 2009[23]	1995–2006	all ages Christchurch, New Zealand	IFV RSV ADV PIV	IPD (n=737)	Surveillance data, monthly	Spearman	All ages IFV A: **0.44a** (0), **0.37a** (1m) IFV B: **0.23c** (0), 0.13 (1m) RSV: **0.52a** (0), **0.47a** (1m) ADV: **0.27a** (0), **0.33a** (1m) PIV 1/2: **0.24c** (0), **0.31a** (1m) PIV 3: **0.34a** (0), **0.17c** (1m) (correlations were stronger in 5–65y and >65y)
Nicoli et al. 2013[24]	1996–2009	all ages England and Wales, UK	IFV RSV	IPD (n=71,333)	Surveillance data, weekly	Pearson and Spearman	All ages, Pearson IFV: **0.54a** RSV: **0.47a** All ages, Spearman IFV: **0.67a** RSV: **0.63a** (correlations were stronger in 15–64y and ≥65y than 0–4y and 5–14y)

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Correlation Method	Correlation Coefficients (time lag)
Peltola et al. 2011[27]	1995–2007	<5y Finland	RV EV RSV IFV PIV ADV	IPD (about 90 cases per year)	National Infectious Disease Register + 3 studies + virus database, fortnightly	Pearson	<u>≤5y</u> RV: **0.28c**, **0.25c**, 0.31, **0.23a** (from 4 studies) EV: **0.17c** RSV: 0.05 IFV: −0.03 IFV A: −0.08 PIV: 0.02 ADV: -0.05
Stensballe et al. 2008[29]	1996–2003	all ages Denmark	RSV non-RSV	IPD (n=7,787)	Population Based Registries Cohort, monthly	Pearson	<u>All ages</u> RSV: **0.55a** non-RSV: **0.65a** <u>≤2y</u> RSV: 0.08
Talbot et al. 2005[30]	1995–2002	all ages Tennessee, US	IFV RSV	IPD (n=4,147)	Surveillance data, weekly	Pearson	<u>All ages</u> RSV: **0.56a** (0), **0.60a** (1w), **0.59a** (2w), **0.57a** (3w), **0.55a** (4w) IFV: **0.40a** (0), **0.41a** (1w), **0.34a** (2w), **0.33a** (3w), **0.26a** (4w) (correlations were stronger in ≥18y than <18y)

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Correlation Method	Correlation Coefficients (time lag)
Watson et al. 2006[33]	2000 (May–Oct)	all ages New South Wales, Australia	IFV RSV PIV	IPD (n=681)	Surveillance data, weekly	Pearson	<u>≤18y</u> IFV: not significant RSV: **0.58a** PIV: **–0.40c** <u>≥18y</u> IFV: not significant RSV: not significant PIV: not significant RSV or IFV: **0.48c**

Time lag indicates the time difference between preceding VARI and subsequent PD incidence.

Abbreviations: ADV, adenovirus; EV, enterovirus; IFV, influenza virus; IPD, invasive pneumococcal disease; m, month(s); MPV, metapneumovirus; PB, pneumococcal bacteraemia; PD, pneumococcal disease; PIV, parainfluenza virus; PM, pneumococcal meningitis; RSV, respiratory syncytial virus; RV, rhinovirus; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Correlation coefficients **in bold** were statistically significant as originally reported in the study (P<0.05); correlation coefficients ending with “a” were statistically significant after Bonferroni adjustment (P< 0.05/number of relevant tests) or when the Bonferroni correction was deemed unnecessary; correlation coefficients ending with “b” did not have enough information to apply the Bonferroni correction; correlation coefficients ending with “c” were not statistically significant after Bonferroni adjustment.

Regression analyses controlling for seasonal patterns

Table 3 shows the summary of the 15 studies[11 13 14 16 18 22-24 26 32 34-38] that controlled for seasonal patterns by regression analysis. Results were inconsistent among the studies. In all-age population studies, preceding influenza infection was likely to be associated with IPD (12 studies[13 14 16 18 22-24 32 35-38] reported an association and two studies[11 34] reported no association). According to two studies[23 24] that reported age-stratified results, the association between influenza and IPD was more likely to exist among older people than among young children. In terms of preceding RSV infection, four[14 24 34 37] out of five studies[14 23 24 34 37] observed an association of RSV with PD incidence. Specifically, one study[14] found the association between RSV and IPD only existed among children <5 years. Studies reporting other viruses such as ADV and PIV were sparse (two[14 23] and one[23] studies, respectively). Five studies[14 23 24 34 37] that reported two or more viruses demonstrated that the association differed by the type of virus. Moreover, the association could differ among virus subtypes (e.g. influenza A *vs* influenza B[22] and PIV 1/2 *vs* PIV 3[23]). Notably, there are other factors that could influence the strength of the associations reported in these studies. For instance, the association could vary by presentation of PD (invasive pneumococcal pneumonia, IPP vs npIPD[32 34 36] and PP vs pneumococcal sepsis, PSe[37]); preceding VARI was more likely to be associated with the occurrence of pneumonia than other clinical presentations. Additionally, the results from studies in Denmark, where comorbidity status and pneumococcal serotype were available, demonstrated that influenza had a greater influence on the incidence of low-invasiveness serotypes than medium- or high- invasiveness among the low comorbidity group; among the high comorbidity group, the pattern was reversed.[35 36]

166 **Table 3. Summary of ecological studies controlling for seasonal patterns.**

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Allard et al. 2012[11]	1997–2008	all ages Montreal, Canada	IFV (case)	IPD (n=2,920)	Notification data and sentinel surveillance data, weekly	Negative binomial regression	long-term trends and seasonal trends of IPD	<u>All ages</u> IFV A: 1.01 (0), 1.00 (1w), 1.00 (2w), 0.99 (3w), 1.00 (4w), 1.00 (5w) IFV B: 1.01 (0), 1.01 (1w), 1.00 (2w), 1.01 (3w), 0.99 (4w), 1.01 (5w)	
Burgos et al. 2015[13]	1996–2012	≥18y Barcelona, Spain	IFV (IR per 1,000)	IPD (n=1,150)	Hospitalisation and surveillance lab data, monthly	Negative binomial regression	temperature	<u>≥18y</u> IFV: **1.23a** [1.03–1.47]	
Ciruela et al. 2016[14]	2006–2012	all ages Catalonia, Spain	IFV RSV ADV (IR per 100,000)	IPD (n=8,044)	Microbiological reporting system, monthly	Negative binomial regression	temperature >17°C	<u>All ages</u> IFV: **1.26b** [1.03–1.54] (0), 1.09 [0.87–1.36] (1m) RSV: 1.15 [0.89–1.48] (0), **1.81b** [1.36–2.41] (1m) ADV: 1.58 [0.88–2.74] (0), 1.32 [0.68–2.42] (1m) <u>≤5y</u> IFV: 1.16 [0.90–1.50] (0), 1.06 [0.80–1.42] (1m) RSV: 1.41 [1.00–1.97] (0), **2.57b** [1.78–3.71] (1m) ADV: **2.47b** [1.38–4.53] (0), 1.00 [0.59–1.68] (1m) (not significant in 5–64y or ≥65y)	

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Domenech de Cellès et al. 2017[16]	2000–2014	all ages France	ILI (as a proxy for IFV)	IPD (n=64,542)	National surveillance system, weekly	Mixed-effect linear regression	seasonal trends of IPD		All ages ILI: median 4.9% across all study years (1w)
Grabowska et al. 2006[18]	1994–2004	all ages Sweden	IFV (binary)	IPD (n=11,637)	Surveillance data, weekly	Negative binomial regression	yearly trends and seasonal trends of IPD	All ages IFV: 1.03 [0.93–1.15] (0), 1.11 [1.00–1.23] (1w), 1.11 [0.99–1.22] (2w), **1.14c** [1.02–1.26] (3w), **1.12c** [1.01–1.23] (4w)	All ages **6%c** [1–12%] (3w)
Kuster et al. 2011[22]	1995–2009	all ages Toronto/ Peel area, Canada	IFV (100 cases)	IPD (n=6,191)	Population-based surveillance, weekly	Negative binomial regression	multi-year trends and seasonal trends of IPD, relative humidity, temperature, UV index	All ages IFV A&B: **1.09a** [1.05–1.14] (1w), **0.93c** [0.89–0.98] (3w) IFV A: identical to IFV A&B IFV B: not significant	
Murdoch et al. 2009[23]	1995–2006	all ages Christchurch, New Zealand	IFV RSV ADV PIV (binary)	IPD (n=737)	Surveillance data, monthly	Negative binomial regression	average daily temperature <10°C, PM10 >50µg/m^3, days with rainfall >10, mean daily 9 am humidity >75%, mean daily sunshine >6h	All ages IFV: **1.38c** [1.02–1.85] (0), 1.20 [0.91–1.58] (1m) RSV: 1.15 [0.87–1.52] (0), 0.90 [0.68–1.18] (1m) PIV 1/2: 1.04 [0.82–1.30] (0), 1.04 [0.84–1.29] (1m) PIV 3 outside IFV season: **1.64a** [1.18–2.30] (0), **1.49c** [1.07–2.08] (1m) ADV: 0.97 [0.78–1.20] (0), **1.26c** [1.02–1.54] (1m) (similar in 5–65y, >65y; not significant in <5y)	

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Nicoli et al. 2013[24]	1996–2009	all ages England and Wales, UK	IFV RSV (case)	IPD (n=71,333)	Surveillance data, weekly	Negative binomial regression	weekly temperature or monthly hours of sunshine (separately in models; results were similar)		All ages, 0–4y, 5–14y, 15–64y, ≥65y controlling for temperature, multiplicative model IFV: **5.6%b** [0.2–23.8%] , −0.4% [−1.8–0.0%], **2.9%c** [0.0–13.6%], **1.8%c** [0.1–7.4%], **3.2%b** [0.0–14.7%] RSV: **2.9%b** [0.1–14.2%], **1.4%c** [0.0–6.9%], **5.9%b** [0.0–27.6%], **14.5%b** [0.0–52.7%], **7.9%b** [0.0–27.4%] (no significant results in time lag analyses)
Opatowski et al. 2013[26]	2001–2004	all ages France	VARI (IR)	PM (n=1,383)	Surveillance data, weekly	Poisson regression using generalised estimating equations approach	seasonal trends of PM	All ages regression parameter: **19.4c** **23.1a** (1w) **23.9a** (2w)	
Walter et al. 2010[32]	1995–2006	all ages US	IFV (positive percentage)	IPD (IPP, npIPD; n=21,239)	Surveillance data, weekly	Negative binomial regression	seasonal trends and linear trends of IPP		Northeast, all ages IFV-IPP: **4.9%c** [4.5–5.3%] (1w) South, all ages IFV-IPP: **5.4%b** [5.0–5.9%] (1w) West, all ages IFV-IPP: **5.2%c** [4.8–6.0%] (1w) (not significant for IFV-npIPD)

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Weinberger et al. 2014[34]	1996–2012	<7y Navajo/White Mountain Apache population, US	Bronchiolitis (IR, as a proxy for RSV) IFV (IR)	IPD (IPP, npIPD; n=496)	4 community-based studies, monthly	Poisson regression	pneumococcal carriage prevalence, seasonal trends of IPD, PCV periods		<7y Bronchiolitis-PP: **15.5%b** [1.8–26.1%] Bronchiolitis-npIPD: 8.0% [−4.8–19.3%] (not significant for IFV)
Weinberger et al. 2013[35]	1977–2007	≥40y Denmark	ILI (case, as a proxy for IFV)	IPP (n=8,308)	Surveillance data + nationwide general practice reports, weekly	Poisson regression	seasonal trends of IPP, dummy variable for week 1,2,3,51,52 and its interaction with ILI		≥40y, low comorbidity and low serotype invasiveness ILI: **17.9%a** [13.6–21.9%] (1w) ≥40y, low comorbidity and high serotype invasiveness ILI: **6.7%a** [3.8–11.7%] (1w) ≥40y, medium/high comorbidity and low serotype invasiveness ILI: 1.3% [−1.6–5.4%] (1w) ≥40y, medium/high comorbidity and high serotype invasiveness ILI: **8.9%a** [6.6–11.8%] (1w)

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Weinberger et al. 2014[36]	1977–2007	all ages Denmark	ILI (case, as a proxy for IFV)	IPD (IPP, npIPD; n=13,882)	Surveillance data + nationwide general practice reports, weekly	Poisson regression	seasonal trends of IPD, dummy variable for week 1,2,3,51,52 and its interaction with ILI		15–39y, low comorbidity ILI-IPD: **9.9%a** [6.0–13.0%] (1w) ILI-IPP: **11.2%a** [6.5–14.8%] (1w) ILI-npIPD: 6.6% [−1.2–14.3%] (1w) 15–39y, medium/high comorbidity ILI-IPD: 0.3% [−8.4–9.7%] (1w) ILI-IPP: 5.4% [−5.0–18.7%] (1w) ILI-npIPD: −6.6% [−25.7–7.6%] (1w) ≥40y, low comorbidity ILI-IPD: **7.6%a** [5.1–11.6%] (1w) ILI-IPP: **7.8%a** [5.8–11.7%] (1w) ILI-npIPD: **6.9%a** [1.8–12.8%] (1w) ≥40y, medium/high comorbidity ILI-IPD: **6.2%a** [4.3–9.3%] (1w) ILI-IPP: **6.5%a** [4.4–10.1%] (1w) ILI-npIPD: **5.3%a** [2.5–8.9%] (1w)

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Weinberger et al. 2015[37]	1992–2009	<2y 36 states in US	IFV RSV (IR)	PD (PP, PSe; n=17,404)	State inpatient databases, weekly	Poisson regression	seasonal trends of PD, PCV periods, IFV or RSV, state	0–2m, 3–11m, 0–11m, 12–23m RSV-PP: **1.42b** [1.30–1.55], **1.24b** [1.17–1.33], **1.23b** [1.19–1.30], **1.12b** [1.09–1.18]	0–2m, 3–11m, 0–11m, 12–23m IFV-PP: 2.1% [−4.5–1.4%], **2.2%a** [0.1–3.4%], 0.6% [−0.9–1.4%], **3.2%a** [1.7–4.7%] RSV-PP:**35.7%a** [27.9–42.7%], **20.0%a** [14.7–24.8%], **20.3%a** [17.4–25.1%], **10.1%a** [7.6–13.9%] IFV-PSe: 0.7% [−1.1–2.2%], **−2.7%a** [−3.7—1.7%], −0.6% [−1.4–0.3%], **1.9%a** [1.1–2.6%] RSV-PSe: **15.0%a** [13.1–17.1%], 0.1% [−4.9–5.0%], **7.2%a** [5.3–9.0%], **3.8%a** [2.5–5.2%]
Zhou et al. 2012[38]	1994–2005	all ages Atlanta, US	IFV RSV (positive percentage)	IPP (n=5,683)	Surveillance data, weekly	Negative binomial regression (comparison between models with and without IFV and RSV)	temperature, sunshine, precipitation	p values for the likelihood ratio test were <0.05 for 5 of 11 influenza seasons: 1994–95, 1996–97, 1998–99, 2003–04, 2004–05; after Bonferroni adjustment association was significant for 3 of 11 influenza seasons: 1996–97, 2003–04, 2004–05.	

Time lag indicates the time difference between VARI and subsequent PD incidence.

Abbreviations: ADV, adenovirus; AP, attributable percentage; CI, confidence interval; IFV, influenza virus; h, hour(s); ILI, influenza-like illness; IPD, invasive pneumococcal disease; IPP, invasive pneumococcal pneumonia; IR, incidence rate; npIPD, non-pneumonic invasive pneumococcal disease; PCV,

pneumococcal conjugate vaccine; PD, pneumococcal disease; PIV, parainfluenza virus; PP, pneumococcal pneumonia; PSe, pneumococcal sepsis; RR, relative risk; RSV, respiratory syncytial virus; UV index, clear-sky ultraviolet index; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Relative risk or attributable percentage **in bold** were statistically significant as originally reported in the study (P<0.05); relative risk or attributable percentage ending with “a” were statistically significant after Bonferroni adjustment (P<0.05/number of relevant tests) or when the Bonferroni correction was deemed unnecessary, those ending with “b” did not have enough information to apply the Bonferroni correction; relative risk or attributable percentage ending with “c” were not statistically significant after Bonferroni adjustment.

Studies utilising other analyses

Seven ecological studies[15 16 19 22 26 28 31] utilised other analytical methods (**Table 4**). Except for studies by Hendriks et al.[19] and Toschke et al.[31], all studies reported an association between VARI and PD.

Table 4. Summary of ecological studies utilising other methods.

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Methods	Main findings
Dangor et al. 2014[15]	2005–2008	<15y Soweto, South Africa	IFV	IPD (n=636)	Hospitalisation and surveillance laboratory data, monthly	X-11 seasonal adjustment method to retain seasonal components. Peak timing compared by time series graph.	IFV peak in May–Jul, followed by IPD (Aug–Oct); no correlation analysis results reported
Domenech de Cellès et al. 2017[16]	2000–2014	all ages France	ILI (as a proxy for IFV)	IPD (n=64,542)	National surveillance system, weekly	Correlation analysis of waveforms of ILI and IPD	Correlation of peak timing of ILI and IPD peak 2: 0.42 [0.04-0.66]; correlation of total cases of ILI and IPD: 0.31 [0.03-0.56]
Hendriks et al. 2017[19]	2004–2014	all ages Netherlands	ILI (as a proxy for IFV)	IPD (n=6,572)	Surveillance data, weekly	cross-correlations of the time series model (SARIMA) residuals	no significant cross-correlations observed

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Methods	Main findings
Kuster et al. 2011[22]	1995–2009	all ages Toronto/ Peel area, Canada	IFV	IPD (n=6,191)	Population-based surveillance, weekly	Spearman correlation for phase and amplitude between IFV and IPD; Granger methods to test whether influenza predicted IPD; Case-crossover analysis to evaluate short-term associations	Phase and amplitude between IFV and IPD not correlated; Granger test of IFV causing IPD: *P*<0.001; case-crossover OR: 1.10[1.02–1.18] at 1w lag
Opatowski et al. 2013[26]	2001–2004	all ages France	VARI	PM (n=1,383)	Surveillance data, weekly	Mathematic model of pneumococcus transmission, to estimate the interaction parameters between VARI and PM	Factor of VARI on pneumococcus acquisition or transmissibility: 8.7[4.6–14.4]; factor of VARI on pathogenicity: 92[28–361]
Shrestha et al. 2013[28]	1989–2009	all ages Illinois, US	IFV	PP (n not known)	Hospital data, weekly (Dataset I from 1989 to 1997, dataset II from 2000 to 2013)	Mathematic model of pneumococcus transmission, to estimate the interaction parameters between VARI and PP	Factor of IFV on PP susceptibility: dataset I 115[70–200], dataset II 85[30–160]

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Methods	Main findings
Toschke et al. 2008[31]	1997–2003	<16y Germany	IFV A	IPD (n=1,474)	Surveillance data, monthly	Multivariate time series analysis using "3h algorithm", which fit an autoregressive Poisson or negative binomial model to time series	IFV A season did not affect IPD season (*P*=0.49); IFV A peak did not precede IPD peak

Abbreviations: IFV, influenza virus; IPD, invasive pneumococcal disease; PD, pneumococcal disease; PM, pneumococcal meningitis; PP, pneumococcal pneumonia; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Discussion

In our review, we summarised population-based studies that evaluated the association of seasonal VARI and subsequent PD. To our knowledge, this is the first review that summarises the methodology and findings of existing epidemiological studies on this topic.

We found that reported associations between VARI and subsequent PD were inconsistent among the 28 included studies. Only three studies[17 25 29] analysed the association using individual patient data. The two cohort studies[17 29] did not account for the shared risk factors between VARI and PD that influenced their seasonality, substantially limiting the inferences that can be made from these data while the case-control study[25] was limited by its small sample size (n case=13). In ecological studies, only 16[11 13 14 16 18 19 22-24 26 32 34-38] of the 25[11-16 18-24 26-28 30-38] ecological studies accounted for seasonal patterns. In these studies, we found that influenza and/or RSV infections were likely to be associated with the subsequent occurrence of PD. For influenza, the association was stronger among younger populations compared to older adults[23 24] while the pattern was reversed for RSV.[14] Data from multiple studies suggested that virus type (five studies[14 23 24 34 37]) and subtype (two studies[22 23]),

comorbidity status (two studies[35 36]) and pneumococcal serotype invasiveness (one study[35]) could influence the association. However, these 16 ecological studies had various population characteristics (e.g. age, comorbidity, immunity status), PD datasets, VARI datasets and analytical methods. As such, heterogeneity among the studies, along with their ecological nature, limits the amount of valid inferences that can be made from the data (as summarised above).

Nevertheless, these studies provide important clues for the potential factors related to the association between VARI and subsequent PD, and thus could help with the conception and design of future studies. Ideally, in order to understand whether a particular preceding VARI can predispose an individual to PD, a prospective cohort study that monitors each individual for VARI and pneumococcal infection would be utilised, allowing analyses at both individual and population levels. However, such a design would not be feasible or affordable as inter alia pneumococcal infections are rare. Alternatively, utilisation of large-scale routine health data and reliable data linkage (through unique individual identifiers) from sources such as surveillance data and hospitalisation datasets may be feasible in many industrialised countries. An example of such data linkage in our review is the study by Stensballe and colleagues[29] that linked information from four Danish population-based registries. While the authors conducted individual-level analysis, the results were based on cases tested for both the presence of respiratory viruses and pneumococcal infection. The true number of VARI-associated PD cases is likely to be significantly higher due to incomplete testing of cases; the untested viral-pneumococcal cases could represent a crucial source of selection bias. Community-based active surveillance can likely address the issue of missing cases but such surveillance would be labour intensive and less cost-effective to conduct. Another option is a case-control study, which is affordable and practical, but not without its limitations. In addition to challenges in designing such studies, defining the history of VARI is likely to be inaccurate since the timing of viral serology may be less accurate (information bias).[27] In the case-control study by O'Brien and colleagues,[25] the authors used influenza-strain specific convalescent serology as evidence for preceding influenza infection. The authors also conducted telephone interviews to investigate ILI history but they did not

mention whether interviewers and interviewees were blind to case or control status. Moreover, the value of this case-control study is limited by its very small sample size (n case = 13).

Compared with individual patient data based studies, ecological studies are more feasible, and thus the most common study design included in our review (25/28). However, there are some caveats when interpreting results from ecological studies. First, causality can never be inferred from such studies. Second, the results should be interpreted at a population level and cannot be generalised to the individual level. Since ecological studies used data aggregated into broad categories, the potential biases introduced by the aggregation should be taken into account. For instance, while 16 out of 25 ecological studies used weekly data, others used fortnightly or monthly data. This may lead to misclassification as the time window of the association of VARI on PD susceptibility can be as short as one week.[39 40] Moreover, data from different sources in ecological studies should represent the same population.

Apart from the study design, one further challenge of analysing the association is accounting for the influence of seasonal factors of VARI and PD (confounding). Both VARI and PD have similar seasonal patterns, and thus are likely to correlate as indicated by the correlation results from ecological studies. The increased risk of PD during an epidemic season could be caused by VARI or by seasonal risk factors or by both. In the present review, 11 studies[12 15 17 20 21 27-31 33] did not attempt to control for seasonal confounders, likely leading to biased estimations of the association. For example, the study by Edwards and colleagues[17] reported a relative risk as high as 112.5 when not adjusting any seasonal factors. One way to address this problem in such studies would be to match the individuals with the onset timing of pneumococcal infection, keeping the risk of PD comparable between VARI cases and non-VARI cases; for ecological studies, regression analysis adding seasonal terms or climatic factors (such as temperature and humidity), or cross-correlation analysis of time series controlling for seasonal patterns could be considered.

Our review suggests that the association of VARI and subsequent PD could vary by virus type[14 23 24 34 35] and even by subtype[22 23]. Studies using combinations of viral infections such as all virus, influenza

+ RSV, non-influenza, or non-RSV could give biased estimations of the association. However, it is not always practical to analyse the association by virus type. In ecological studies, different types of viruses might co-circulate and thus be highly correlated in incidence, making it difficult to determine the role for each virus. In terms of PD, most studies used IPD as the outcome of interest. However, studies that categorised IPD into IPP and npIPD found that the association was more pronounced in IPP than in npIPD.[32 34 36] A similar finding, that the association was stronger in PP than PSe, was reported in another study.[37] These results suggest VARI is more likely to be associated with pneumonic pneumococcal infections than non-pneumonic infections. In our review, we excluded studies using information other than clinical diagnosis as a proxy for PD (e.g. prescription data and carriage data). Pneumococcal carriage could have a fundamental role in the transmission and incidence of PD.[41] In a study analysing the impact of pneumococcal carriage and viral activity, Weinberger and colleagues[34] found npIPD was associated with carriage prevalence, whereas IPP was associated with bronchiolitis (as a proxy for RSV). The authors also proposed that preceding VARI increased susceptibility but did not enhance transmission (indicated by carriage prevalence) in children. However, more studies are needed to confirm these findings.

The association could also vary by population characteristics. According to two studies that displayed age-stratified results,[23 24] the association of influenza and subsequent IPD was more likely to exist among older people than among young children. Studies by Weinberger et al.[35 36] gauged the association in different comorbidity and pneumococcal serotype groups among Denmark populations. The results showed that influenza had a stronger impact on the incidence of low-invasiveness serotypes than medium- or high- invasiveness ones in the low comorbidity group, while the pattern reversed in the high comorbidity group. Another study that analysed clinical records of 919 patients with PP found that infrequently colonising pneumococcal serotypes were more likely to cause PP after preceding VARI, particularly in patients with immunodeficiency or chronic lung diseases.[42] These findings suggest the need for future studies to analyse the association by age group, pneumococcal serotype and comorbidity status. Moreover, the recent introduction of pneumococcal

vaccines has brought changes in the incidence of serotype-specific PD,[43] making the association of VARI and PD more complicated to understand. As a result, future studies should consider the possible serotype-specific influence that pneumococcal vaccines have on both individual immunity and herd immunity when analysing the association.

In addition to the factors discussed above, additional factors may influence the estimates of the association. The first is the change over time in the methodology of data collection, including changes in test method or diagnosis, clinical practice and health-seeking behaviour. The second is the possible delay in measurement, which happened most often in passive hospital-based studies. Thirdly, for ecological studies using aggregated data, "holiday spikes" could occur due to more social gatherings;[44] besides, weekends and holidays might influence timely tests or diagnosis as well as the health-seeking behaviour of patients.

We found many studies tended to conduct multiple statistical tests using different subgroups and time periods (e.g. age group, virus, time lag between VARI and PD) without specifying the primary study question a priori or making proper statistical adjustments to account for multiple testing. This could give rise to an increased risk of reporting false positive results. In this review, we applied Bonferroni corrections to adjust for the multiple tests where deemed necessary. Since the Bonferroni method is conservative and we are unable to adjust for studies where *P* values were not given, the adjustment in our review is intended for readers' reference and as caveats for future studies.

Given the substantial burden of VARI across the world,[1] even a modest association between VARI and subsequent PD could lead to a substantial burden of disease in terms of VARI-related PD cases. If proper anti-bacterial interventions could be applied to those with higher risk of PD due to a preceding VARI, subsequent pneumococcal infections could be prevented. The interventions would be more effective / better targeted if we could estimate the risk (i.e. the strength of association) according to timing of infection by week/month of a year, age, comorbidity status, virus type and

status of immunity. In turn, understanding the association between VARI and subsequent pneumococcal infection can help evaluate the full impact of viral vaccine programs.

In conclusion, the role of seasonal VARI on subsequent PD incidence remains controversial in population-based studies. Nevertheless, these studies provide valuable information and can help with the conception of future well-designed studies. Future work could explore the association by timing of infection, age, comorbidity status, virus type, pneumococcal serotype and presentation, and thus would identify potentially susceptible populations with VARI for preventive interventions.

Supplementary Materials

Table S1. Summary of findings from animal and in vitro studies.

Table S2. Summary of methodologies utilised in the included studies (n=28).

Text S1. Search strategy

File S1. Quality assessment of included studies

File S2. PRISMA checklist

File S3. Protocol registered in PROSPERO

Contributors: HN and HC conceived the study. YL did the literature search and reviewed the articles. YL and MP extracted and analysed the data independently with oversight from HN and HC. YL drafted the manuscript. MP, HN and HC critically reviewed the manuscript. All authors read and approved the final draft of the manuscript.

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REFERENCES

1. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2013;2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet 2016;388(10053):1459-544.
2. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet 2009;374(9693):893-902.
3. Drijkoningen JJC, Rohde GGU. Pneumococcal infection in adults: burden of disease. Clinical Microbiology and Infection 2014;20:45-51.
4. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev 2006;19(3):571-82.
5. Chien Y-W, Klugman KP, Morens DM. Bacterial Pathogens and Death during the 1918 Influenza Pandemic. N Engl J Med 2009;361(26):2582-83.
6. Fleming-Dutra KE, Taylor T, Link-Gelles R, et al. Effect of the 2009 influenza A(H1N1) pandemic on invasive pneumococcal pneumonia. J Infect Dis 2013;207(7):1135-43.
7. Launes C, Garcia-Garcia JJ, Trivino M, et al. Respiratory viruses, such as 2009 H1N1 influenza virus, could trigger temporal trends in serotypes causing pneumococcal disease. Clin Microbiol Infect 2014;20(12):O1088-90.
8. Nelson GE, Gershman KA, Swerdlow DL, et al. Invasive pneumococcal disease and pandemic (H1N1) 2009, Denver, Colorado, USA. Emerg Infect Dis 2012;18(2):208-16.
9. Pedro-Botet ML, Burgos J, Lujan M, et al. Impact of the 2009 influenza A H1N1 pandemic on invasive pneumococcal disease in adults. Scand J Infect Dis 2014;46(3):185-92.
10. Weinberger DM, Simonsen L, Jordan R, et al. Impact of the 2009 influenza pandemic on pneumococcal pneumonia hospitalizations in the United States. J Infect Dis 2012;205(3):458-65.
11. Allard R, Couillard M, Pilon P, et al. Invasive bacterial infections following influenza: a time-series analysis in Montreal, Canada, 1996-2008. Influenza other respi 2012;6(4):268-75.
12. Ampofo K, Bender J, Sheng X, et al. Seasonal invasive pneumococcal disease in children: role of preceding respiratory viral infection. Pediatrics 2008;122(2):229-37.
13. Burgos J, Larrosa MN, Martinez A, et al. Impact of influenza season and environmental factors on the clinical presentation and outcome of invasive pneumococcal disease. Eur J Clin Microbiol Infect Dis 2015;34(1):177-86.
14. Ciruela P, Broner S, Izquierdo C, et al. Invasive pneumococcal disease rates linked to meteorological factors and respiratory virus circulation (Catalonia, 2006-2012). BMC Public Health 2016;16(400).

15. Dangor Z, Izu A, Moore DP, et al. Temporal association in hospitalizations for tuberculosis, invasive pneumococcal disease and influenza virus illness in South African children. PLoS ONE 2014;9(3):e91464.

16. Domenech de Cellès M, Arduin H, Varon E, et al. Characterizing and Comparing the Seasonality of Influenza-Like Illnesses and Invasive Pneumococcal Diseases Using Seasonal Waveforms. Am J Epidemiol 2017:kwx336-kwx36.

17. Edwards LJ, Markey PG, Cook HM, et al. The relationship between influenza and invasive pneumococcal disease in the Northern Territory, 2005-2009. Med J Aust 2011;194(4):207.

18. Grabowska K, Hogberg L, Penttinen P, et al. Occurrence of invasive pneumococcal disease and number of excess cases due to influenza. BMC Infect Dis 2006;6:58.

19. Hendriks W, Boshuizen H, Dekkers A, et al. Temporal cross-correlation between influenza-like illnesses and invasive pneumococcal disease in The Netherlands. Influenza and other Respiratory Viruses 2017;11(2):130-37.

20. Jansen AG, Sanders EA, A VDE, et al. Invasive pneumococcal and meningococcal disease: association with influenza virus and respiratory syncytial virus activity? Epidemiol Infect 2008;136(11):1448-54.

21. Kim PE, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses. Clin Infect Dis 1996;22(1):100-6.

22. Kuster SP, Tuite AR, Kwong JC, et al. Evaluation of coseasonality of influenza and invasive pneumococcal disease: results from prospective surveillance. PLoS Med 2011;8(6):e1001042.

23. Murdoch DR, Jennings LC. Association of respiratory virus activity and environmental factors with the incidence of invasive pneumococcal disease. J Infect 2009;58(1):37-46.

24. Nicoli EJ, Trotter CL, Turner KM, et al. Influenza and RSV make a modest contribution to invasive pneumococcal disease incidence in the UK. J Infect 2013;66(6):512-20.

25. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. Clin Infect Dis 2000;30(5):784-9.

26. Opatowski L, Varon E, Dupont C, et al. Assessing pneumococcal meningitis association with viral respiratory infections and antibiotics: insights from statistical and mathematical models. Proc Biol Sci 2013;280(1764):20130519.

27. Peltola V, Heikkinen T, Ruuskanen O, et al. Temporal association between rhinovirus circulation in the community and invasive pneumococcal disease in children. Pediatr Infect Dis J 2011;30(6):456-61.

28. Shrestha S, Foxman B, Weinberger DM, et al. Identifying the interaction between influenza and pneumococcal pneumonia using incidence data. Sci Transl Med 2013;5(191):191ra84.
29. Stensballe LG, Hjuler T, Andersen A, et al. Hospitalization for respiratory syncytial virus infection and invasive pneumococcal disease in Danish children aged <2 years: a population-based cohort study. Clin Infect Dis 2008;46(8):1165-71.
30. Talbot TR, Poehling KA, Hartert TV, et al. Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation. Am J Med 2005;118(3):285-91.
31. Toschke AM, Arenz S, von Kries R, et al. No temporal association between influenza outbreaks and invasive pneumococcal infections. Arch Dis Child 2008;93(3):218-20.
32. Walter ND, Taylor TH, Shay DK, et al. Influenza circulation and the burden of invasive pneumococcal pneumonia during a non-pandemic period in the United States. Clin Infect Dis 2010;50(2):175-83.
33. Watson M, Gilmour R, Menzies R, et al. The association of respiratory viruses, temperature, and other climatic parameters with the incidence of invasive pneumococcal disease in Sydney, Australia. Clin Infect Dis 2006;42(2):211-5.
34. Weinberger DM, Grant LR, Steiner CA, et al. Seasonal drivers of pneumococcal disease incidence: impact of bacterial carriage and viral activity.[Erratum appears in Clin Infect Dis. 2014 Mar;58(6):908]. Clin Infect Dis 2014;58(2):188-94.
35. Weinberger DM, Harboe ZB, Viboud C, et al. Serotype-specific effect of influenza on adult invasive pneumococcal pneumonia. J Infect Dis 2013;208(8):1274-80.
36. Weinberger DM, Harboe ZB, Viboud C, et al. Pneumococcal disease seasonality: incidence, severity and the role of influenza activity. Eur Respir J 2014;43(3):833-41.
37. Weinberger DM, Klugman KP, Steiner CA, et al. Association between respiratory syncytial virus activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. PLoS Med 2015;12(1):e1001776.
38. Zhou H, Haber M, Ray S, et al. Invasive pneumococcal pneumonia and respiratory virus co-infections. Emerg Infect Dis 2012;18(2):294-7.
39. McCullers JA, Rehg JE. Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor. J Infect Dis 2002;186(3):341-50.
40. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection. Nat Med 2008;14(5):558-64.

41. Simell B, Auranen K, Käyhty H, et al. The fundamental link between pneumococcal carriage and disease. Expert Rev Vaccines 2012;11(7):841-55.

42. Song JY, Nahm MH, Cheong HJ, et al. Impact of preceding flu-like illness on the serotype distribution of pneumococcal pneumonia. PLoS ONE 2014;9(4):e93477.

43. Shiri T, Datta S, Madan J, et al. Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis. The Lancet Global Health 2017;5(1):e51-e59.

44. Walter ND, Taylor THJ, Dowell SF, et al. Holiday Spikes in Pneumococcal Disease among Older Adults. N Engl J Med 2009;361(26):2584-85.

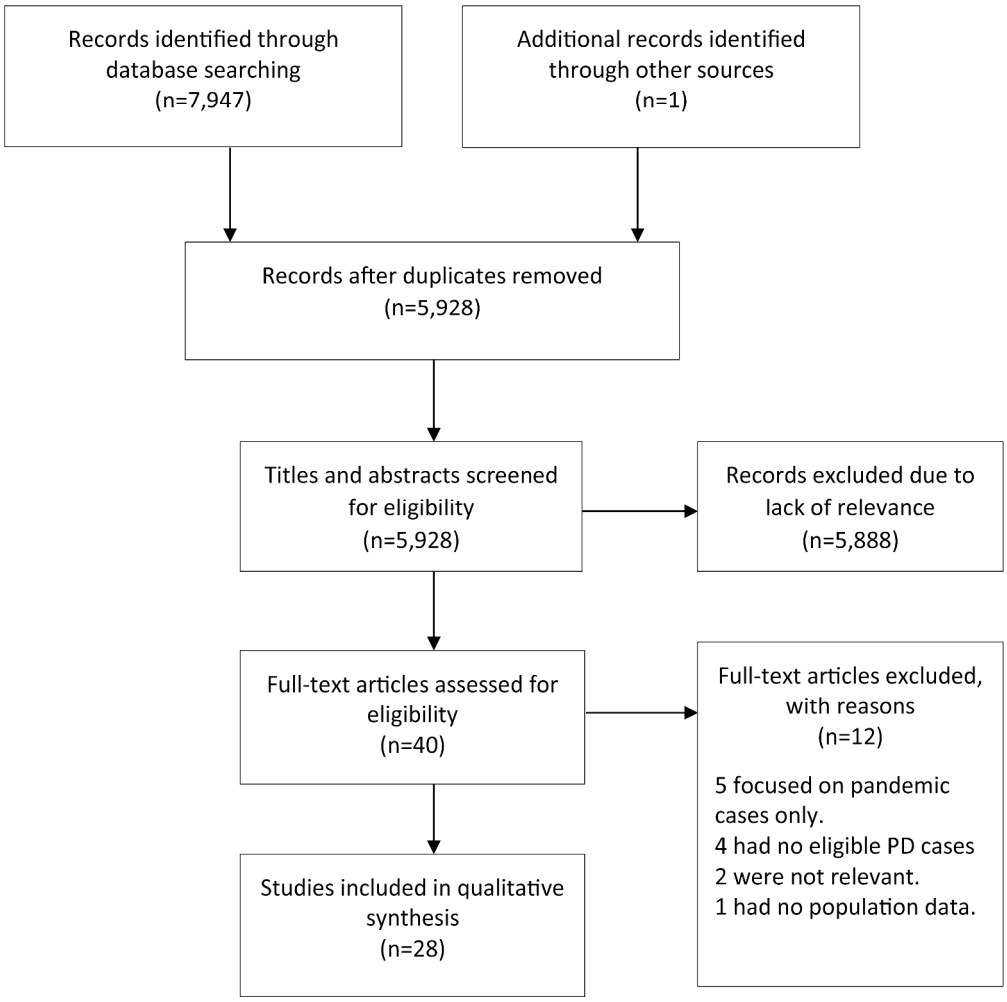

Figure 1. PRISMA flow diagram of the literature search. PD: pneumococcal disease.

314x310mm (300 x 300 DPI)

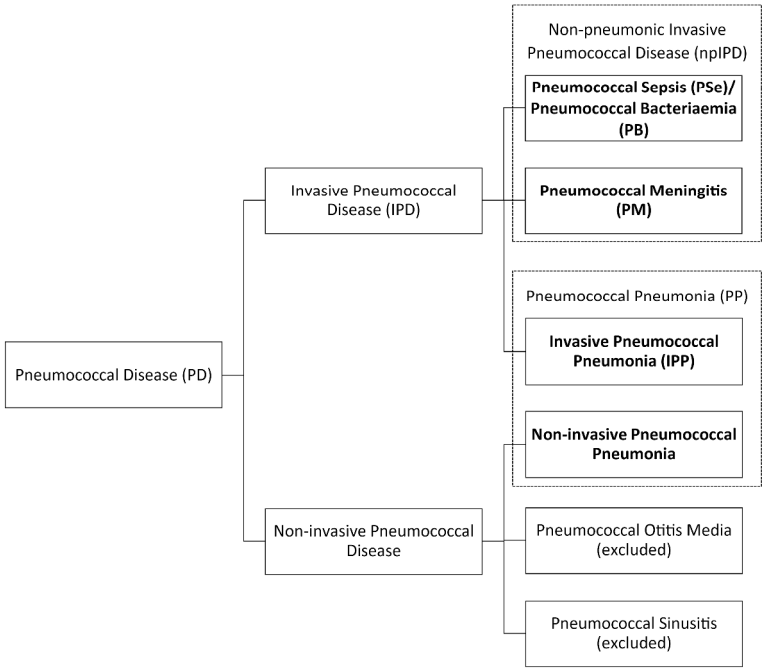

Figure 2. Category of pneumococcal disease in the present review.

391x289mm (300 x 300 DPI)

Table S1. Summary of findings from animal and in vitro studies.

Study	Material	Exposure	Main findings
Diavatopoulos et al. 2010[1]	Mice (n=~10 per group)	influenza A + pneumococcus (3d later)	On day 3 of pneumococcus challenge, pneumococcus numbers increased in the nasopharynx (50-fold, P=0.0002) and the lungs (300-fold, P=0.0005) in influenza A group, compared with mock-treated group; transmission of pneumococcus between littermates was dependent on infection with influenza A.
Hament et al. 2004[2]	Monolayers of human nasopharyngeal cells and pneumocyte type II cells	RSV + pneumococcus	After RSV infection of the monolayers, an increased adherence (2–10 fold) was observed among all serotypes compared with uninfected monolayers.
Hament et al. 2005[3]	Mice (n=7 per group)	RSV + pneumococcus (0 or 4d later)	At 24h of pneumococcus challenge, mice infected with RSV 0 or 4d before pneumococcus challenge had higher levels of bacteremia than control group.
Kukavica-Ibrulj et al. 2009[4]	Mice (n=18 per group)	hMPV/ influenza A + pneumococcus (5d later)	Pneumococcus numbers on day 7 of pneumococcus challenge: 5×10^2 CFU/lung in mock infection, 10^7 CFU/lung in hMPV group and 10^8 CFU/lung in influenza A group.

Study	Material	Exposure	Main findings
LeVine et al. 2001[5]	Mice (n=3 per group)	influenza A + pneumococcus (7d later)	Lungs of influenza-exposed mice demonstrated greater colony counts 24h and 48h following pneumococcus challenge.
Ludewick et al. 2011[6]	Mice (n=18 per group)	hMPV/ influenza A + pneumococcus (14d later)	Only mice infected with influenza A demonstrated an 8% weight loss 72h following pneumococcus challenge while hMPV group and mock group did not.
McCullers et al. 2002[7]	Mice (n=20 per group)	influenza A + pneumococcus (0 or 7d later)	60% of mice died 2–11d after pneumococcus challenge in influenza A group compared with 15% in mock group; reversal of the order of challenge led to protection from influenza; challenge of influenza and pneumococcus on the same day led to 100% mortality.
McCullers et al. 2010[8]	Ferrets (n=5 per group) and Mice (n=~5 per group)	influenza A + pneumococcus (7d later)	Prior influenza infection enhanced pneumococcal transmission and disease; the influenza-mediated effects were pneumococcal strain dependent.
Sharma-Chawla et al. 2016[9]	Mice (n=3–5 per group)	influenza A + pneumococcus T4, 19F or 7F (7d later)	Pneumococcal coinfection during the acute phase of influenza A infection increased degree of pneumonia and mortality for all tested pneumococcal strains. However, the incidence and kinetics of systemic dissemination remained strain dependent.

Study	Material	Exposure	Main findings
Smith et al. 2014[10]	Human ciliated respiratory epithelial cells and mice (n=10 per group)	RSV + pneumococcus	Following incubation with RSV, pneumococcus demonstrated a significant increase in the inflammatory response and bacterial adherence to human ciliated epithelial cultures and increased virulence in mice model.
Stark et al. 2006[11]	Mice (n>12 per group)	RSV + pneumococcus (7d later)	Pneumococcus numbers at 24h of pneumococcus challenge: 7.45×10^5 CFU/lung in RSV group, 5.9×10^3 CFU/lung in mock group.

The number in brackets in the column Material refers to the number of animals observed under each experiment condition; number of animals used in transmission models (used by some studies) were not displayed.

Abbreviations: CFU, colony-forming units; d, day(s); h, hour(s); hMPV, human metapneumovirus; RSV, respiratory syncytial virus.

Reference

1. Diavatopoulos DA, Short KR, Price JT, et al. Influenza A virus facilitates Streptococcus pneumoniae transmission and disease. Faseb J 2010;24(6):1789-98.

2. Hament J-M, Aerts PC, Fleer A, et al. Enhanced Adherence of Streptococcus pneumoniae to Human Epithelial Cells Infected with Respiratory Syncytial Virus. Pediatr Res 2004;55(6):972-78.

3. Hament JM, Aerts PC, Fleer A, et al. Direct binding of respiratory syncytial virus to pneumococci: a phenomenon that enhances both pneumococcal adherence to human epithelial cells and pneumococcal invasiveness in a murine model. Pediatr Res 2005;58(6):1198-203.

4. Kukavica-Ibrulj I, Hamelin ME, Prince GA, et al. Infection with human metapneumovirus predisposes mice to severe pneumococcal pneumonia. J Virol 2009;83(3):1341-9.

5. LeVine AM, Koeningsknecht V, Stark JM. Decreased pulmonary clearance of S. pneumoniae following influenza A infection in mice. J Virol Methods 2001;94(1-2):173-86.

6. Ludewick HP, Aerts L, Hamelin ME, et al. Long-term impairment of Streptococcus pneumoniae lung clearance is observed after initial infection with influenza A virus but not human metapneumovirus in mice. J Gen Virol 2011;92(Pt 7):1662-5.

7. McCullers JA, Rehg JE. Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor. J Infect Dis 2002;186(3):341-50.

8. McCullers JA, McAuley JL, Browall S, et al. Influenza enhances susceptibility to natural acquisition of and disease due to Streptococcus pneumoniae in ferrets. J Infect Dis 2010;202(8):1287-95.

9. Sharma-Chawla N, Sender V, Kershaw O, et al. Influenza A virus infection predisposes hosts to secondary infection with different Streptococcus pneumoniae serotypes with similar outcome but serotype-specific manifestation. Infection and Immunity 2016;84(12):3445-57.

10. Smith CM, Sandrini S, Datta S, et al. Respiratory syncytial virus increases the virulence of Streptococcus pneumoniae by binding to penicillin binding protein 1a. A new paradigm in respiratory infection. Am J Respir Crit Care Med 2014;190(2):196-207.

11. Stark JM, Stark MA, Colasurdo GN, et al. Decreased bacterial clearance from the lungs of mice following primary respiratory syncytial virus infection. J Med Virol 2006;78(6):829-38.

Table S2 Summary of methodologies utilised in the included studies (n=28)

Study	All VARI lab-confirmed	Exposure			Outcome				Data		Analysis at POP level			Seasonality Adjustment
		IFV	RSV	Others	PD	IPD	PP	Others	IDNV	POP	CORR	REGR	Others	
Allard et al. 2012[1]	Yes, multiple methods	✓				✓				✓		✓		✓
Ampofo et al. 2008[2]	Yes, IF and culture	✓	✓	✓		✓				✓	✓			
Burgos et al. 2015[3]	Yes, IF and PCR	✓				✓				✓	✓	✓		✓
Ciruela et al. 2016[4]	Yes, multiple methods	✓	✓	✓		✓				✓	✓	✓		✓
Dangor et al. 2014[5]	Yes, IF and culture	✓				✓				✓			✓	
Domenech de Cellès et al. 2017[6]	No	✓				✓				✓		✓	✓	✓
Edwards et al. 2011[7]	Yes, method not known	✓				✓			✓					
Grabowska et al. 2006[8]	Yes, multiple methods	✓				✓				✓		✓		✓
Hendriks et al. 2017[9]	No	✓				✓				✓			✓	✓
Jansen et al. 2008[10]	Yes, multiple methods	✓	✓			✓		✓		✓	✓			
Kim et al. 1996[11]	Yes, culture	✓	✓	✓		✓				✓	✓			
Kuster et al. 2011[12]	Yes, culture and DAT	✓				✓				✓		✓	✓	✓
Murdoch et al. 2009[13]	Yes, IF and culture	✓	✓	✓		✓				✓	✓	✓		✓
Nicoli et al. 2013[14]	Yes, multiple methods	✓	✓			✓				✓	✓	✓		✓
O'Brien et al. 2000[15]	Yes, serology	✓					✓		✓					✓
Opatowski et al. 2013[16]	No			✓				✓		✓		✓	✓	✓
Peltola et al. 2011[17]	Yes, multiple methods	✓	✓	✓		✓				✓	✓			
Shrestha et al. 2013[18]	No	✓					✓			✓			✓	
Stensballe et al. 2008[19]	No		✓	✓		✓			✓	✓	✓			
Talbot et al. 2005[20]	Yes, culture and RAT	✓	✓			✓				✓	✓			
Toschke et al. 2008[21]	Yes, PCR	✓				✓				✓			✓	
Walter et al. 2010[22]	Yes, method not known	✓				✓		✓		✓		✓		✓
Watson et al. 2006[23]	Yes, DAT	✓	✓	✓		✓				✓	✓			
Weinberger et al. 2014[24]	No	✓	✓			✓		✓		✓		✓		✓
Weinberger et al. 2013[25]	No	✓						✓		✓		✓		✓
Weinberger et al. 2014[26]	No	✓				✓	✓			✓		✓		✓
Weinberger et al. 2015[27]	No	✓	✓		✓		✓	✓		✓		✓		✓
Zhou et al. 2012[28]	Yes, method not known	✓	✓							✓		✓		✓

CORR, correlation; DAT, direct antigen test; IF, immunofluorescence; IFV, influenza virus; INDV, individual; IPD, invasive pneumococcal disease; PCR, polymerase chain reaction; PD, pneumococcal disease; POP, population; PP, pneumococcal pneumonia; REGR, regression; RAT, rapid antigen test; RSV, respiratory syncytial virus; VARI, viral acute respiratory infection.

Reference

1. Allard R, Couillard M, Pilon P, et al. Invasive bacterial infections following influenza: a time-series analysis in Montreal, Canada, 1996-2008. Influenza other respi 2012;6(4):268-75.
2. Ampofo K, Bender J, Sheng X, et al. Seasonal invasive pneumococcal disease in children: role of preceding respiratory viral infection. Pediatrics 2008;122(2):229-37.
3. Burgos J, Larrosa MN, Martinez A, et al. Impact of influenza season and environmental factors on the clinical presentation and outcome of invasive pneumococcal disease. Eur J Clin Microbiol Infect Dis 2015;34(1):177-86.
4. Ciruela P, Broner S, Izquierdo C, et al. Invasive pneumococcal disease rates linked to meteorological factors and respiratory virus circulation (Catalonia, 2006-2012). BMC Public Health 2016;16(400).
5. Dangor Z, Izu A, Moore DP, et al. Temporal association in hospitalizations for tuberculosis, invasive pneumococcal disease and influenza virus illness in South African children. PLoS ONE 2014;9(3):e91464.
6. Domenech de Cellès M, Arduin H, Varon E, et al. Characterizing and Comparing the Seasonality of Influenza-Like Illnesses and Invasive Pneumococcal Diseases Using Seasonal Waveforms. Am J Epidemiol 2017:kwx336-kwx36.
7. Edwards LJ, Markey PG, Cook HM, et al. The relationship between influenza and invasive pneumococcal disease in the Northern Territory, 2005-2009. Med J Aust 2011;194(4):207.
8. Grabowska K, Hogberg L, Penttinen P, et al. Occurrence of invasive pneumococcal disease and number of excess cases due to influenza. BMC Infect Dis 2006;6:58.
9. Hendriks W, Boshuizen H, Dekkers A, et al. Temporal cross-correlation between influenza-like illnesses and invasive pneumococcal disease in The Netherlands. Influenza and other Respiratory Viruses 2017;11(2):130-37.
10. Jansen AG, Sanders EA, A VDE, et al. Invasive pneumococcal and meningococcal disease: association with influenza virus and respiratory syncytial virus activity? Epidemiol Infect 2008;136(11):1448-54.
11. Kim PE, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses. Clin Infect Dis 1996;22(1):100-6.
12. Kuster SP, Tuite AR, Kwong JC, et al. Evaluation of coseasonality of influenza and invasive pneumococcal disease: results from prospective surveillance. PLoS Med 2011;8(6):e1001042.
13. Murdoch DR, Jennings LC. Association of respiratory virus activity and environmental factors with the incidence of invasive pneumococcal disease. J Infect 2009;58(1):37-46.
14. Nicoli EJ, Trotter CL, Turner KM, et al. Influenza and RSV make a modest contribution to invasive pneumococcal disease incidence in the UK. J Infect 2013;66(6):512-20.
15. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. Clin Infect Dis 2000;30(5):784-9.
16. Opatowski L, Varon E, Dupont C, et al. Assessing pneumococcal meningitis association with viral respiratory infections and antibiotics: insights from statistical and mathematical models. Proc Biol Sci 2013;280(1764):20130519.
17. Peltola V, Heikkinen T, Ruuskanen O, et al. Temporal association between rhinovirus circulation in the community and invasive pneumococcal disease in children. Pediatr Infect Dis J 2011;30(6):456-61.
18. Shrestha S, Foxman B, Weinberger DM, et al. Identifying the interaction between influenza and pneumococcal pneumonia using incidence data. Sci Transl Med 2013;5(191):191ra84.
19. Stensballe LG, Hjuler T, Andersen A, et al. Hospitalization for respiratory syncytial virus infection and invasive pneumococcal disease in Danish children aged <2 years: a population-based cohort study. Clin Infect Dis 2008;46(8):1165-71.
20. Talbot TR, Poehling KA, Hartert TV, et al. Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation. Am J Med 2005;118(3):285-91.

21. Toschke AM, Arenz S, von Kries R, et al. No temporal association between influenza outbreaks and invasive pneumococcal infections. Arch Dis Child 2008;93(3):218-20.
22. Walter ND, Taylor TH, Shay DK, et al. Influenza circulation and the burden of invasive pneumococcal pneumonia during a non-pandemic period in the United States. Clin Infect Dis 2010;50(2):175-83.
23. Watson M, Gilmour R, Menzies R, et al. The association of respiratory viruses, temperature, and other climatic parameters with the incidence of invasive pneumococcal disease in Sydney, Australia. Clin Infect Dis 2006;42(2):211-5.
24. Weinberger DM, Grant LR, Steiner CA, et al. Seasonal drivers of pneumococcal disease incidence: impact of bacterial carriage and viral activity.[Erratum appears in Clin Infect Dis. 2014 Mar;58(6):908]. Clin Infect Dis 2014;58(2):188-94.
25. Weinberger DM, Harboe ZB, Viboud C, et al. Serotype-specific effect of influenza on adult invasive pneumococcal pneumonia. J Infect Dis 2013;208(8):1274-80.
26. Weinberger DM, Harboe ZB, Viboud C, et al. Pneumococcal disease seasonality: incidence, severity and the role of influenza activity. Eur Respir J 2014;43(3):833-41.
27. Weinberger DM, Klugman KP, Steiner CA, et al. Association between respiratory syncytial virus activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. PLoS Med 2015;12(1):e1001776.
28. Zhou H, Haber M, Ray S, et al. Invasive pneumococcal pneumonia and respiratory virus co-infections. Emerg Infect Dis 2012;18(2):294-7.

Text S1. Search strategy

Medline

1. Meningitis, Pneumococcal/ or Pneumonia, Pneumococcal/ or exp Pneumococcal Infections/ or pneumococc*.mp.

2. exp Streptococcus pneumoniae/ or Streptococcus pneumoniae.mp.

3. virus.mp. or exp Viruses/

4. exp Virus Diseases/ or virus disease*.mp.

5. correlat*.mp.

6. associat*.mp.

7. interact*.mp.

8. relat*.mp.

9. 1 or 2

10. 3 or 4

11. 5 or 6 or 7 or 8

12. 9 and 10 and 11

13. limit 12 to yr="1990 -Current"

1,664 results by 27 Apr 2017

1,888 results by 31 Dec 2017

EMbase

1. exp pneumococcal infection/ or pneumococc*.mp.

2. Streptococcus pneumoniae.mp. or exp Streptococcus pneumoniae/

3. exp virus/ or virus*.mp.

4. exp virus infection/ or virus infection*.mp. or virus disease*.mp.

5. exp correlational study/ or exp correlation analysis/ or correlat*.mp.

6. associat*.mp.

7. interact*.mp.

8. relat*.mp.

9. 1 or 2

10. 3 or 4

11. 5 or 6 or 7 or 8

12. 9 and 10 and 11

13. limit 12 to yr="1990 -Current"

4,778 results by 27 Apr 2017.

5,098 results by 31 Dec 2017.

Global Health

1. Streptococcus pneumoniae.mp. or exp Streptococcus pneumoniae/

2. pneumococc*.mp.

3. virus*.mp. or viruses/

4. virus disease*.mp. or viral diseases.sh. or virus infection*.mp.

5. exp correlation/ or correlation analysis/ or correlat*.mp.

6. associat*.mp.

7. interact*.mp.

8. relat*.mp.

9. 1 or 2

10. 3 or 4

11. 5 or 6 or 7 or 8

12. 9 and 10 and 11

13. limit 12 to yr="1990 -Current"

1,164 results by 27 Apr 2017

961 results by 31 Dec 2017

Study information				Inclusion		Quality Assessment								
ID	First Author	Year	Title	Inclusion	Reason for Exclusion	Did the study address a clearly focused issue?	Were the subjects recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors (e.g. seasonal factors)	Have the authors taken account of the confounding factors in the design and/or analysis (e.g. seasonal factors)	Were the results reliable?	Can the results be applied to the local population	Do the results of this study fit with other available evidence?
H37	Allard, R	2012	Invasive bacterial infections follo	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H1	Ampofo, K	2008	Seasonal invasive pneumococca	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H2	Burgos, J	2015	Impact of influenza season and	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H38	Ciruela, P	2016	Invasive pneumococcal disease	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H3	Dangor, Z	2014	Temporal association in hospita	yes		Yes	Yes	Yes	Yes	No	No	No	No	Yes
H40	Domenech de Cellès, M	2017	Characterizing and Comparing t	yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
H4	Dominguez, A	2013	Benefit of conjugate pneumoco	no	no PD case	NA	NA	NA	NA	NA	NA	NA	NA	NA
H5	Edwards, LJ	2011	The relationship between influe	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H6	Eshaghi, A	2009	Infection with H274Y-positive in	no	no PD case	NA	NA	NA	NA	NA	NA	NA	NA	NA
H7	Fleming-Dutra, KE	2013	Effect of the 2009 influenza A(H	no	pandemic	NA	NA	NA	NA	NA	NA	NA	NA	NA
H8	Grabowska, K	2006	Occurrence of invasive pneumo	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H9	Grijalva, CG	2014	The role of influenza and parain	no	no PD case	NA	NA	NA	NA	NA	NA	NA	NA	NA
H39	Hendriks, W.	2017	Temporal cross-correlation betv	yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
H10	Jansen, AG	2008	Invasive pneumococcal and me	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H11	Kim, PE	1996	Association of invasive pneumo	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H12	Kuster, SP	2011	Evaluation of coseasonality of in	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H13	Launes, C	2014	Respiratory viruses, such as 200	no	pandemic	NA	NA	NA	NA	NA	NA	NA	NA	NA
H14	Madhi, SA	2004	A role for Streptococcus pneum	no	topic not r	NA	NA	NA	NA	NA	NA	NA	NA	NA
H15	Muhlemann, K	2006	The prevalence of penicillin-non	no	no PD case	NA	NA	NA	NA	NA	NA	NA	NA	NA
H16	Murdoch, DR	2009	Association of respiratory virus	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H17	Nelson, GE	2012	Invasive pneumococcal disease	no	pandemic	NA	NA	NA	NA	NA	NA	NA	NA	NA
H36	Nicoli, EJ	2013	Influenza and RSV make a mode	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H18	O'Brien, KL	2000	Severe pneumococcal pneumon	yes		Yes	Yes	No	No	Yes	Yes	Not sure	Not sure	Yes
H19	Opatowski, L	2013	Assessing pneumococcal mening	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H20	Pedro-Botet, ML	2014	Impact of the 2009 influenza A H	no	pandemic	NA	NA	NA	NA	NA	NA	NA	NA	NA
H21	Peltola, V	2011	Temporal association between r	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H22	Shrestha, S	2013	Time and dose-dependent risk c	no	no populat	NA	NA	NA	NA	NA	NA	NA	NA	NA
H23	Shrestha, S	2013	Identifying the interaction betw	yes		Yes	Yes	Not sure	Yes	No	No	Yes	Yes	Yes
H24	Stensballe, LG	2008	Hospitalization for respiratory s	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H25	Talbot, TR	2005	Seasonality of invasive pneumo	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H26	Toschke, AM	2008	No temporal association betwe	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H27	Walter, ND	2010	Influenza circulation and the bu	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H28	Watson, M	2006	The association of respiratory vi	yes		Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
H29	Weinberger, DM	2014	Seasonal drivers of pneumococ	yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
H30	Weinberger, DM	2013	Serotype-specific effect of influe	yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
H31	Weinberger, DM	2014	Pneumococcal disease seasonal	yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
H32	Weinberger, DM	2015	Association between respirator	yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
H33	Weinberger, DM	2012	Impact of the 2009 influenza pa	no	pandemic	NA	NA	NA	NA	NA	NA	NA	NA	NA
H34	Yoon, YK	2014	Impact of preceding respiratory	no	topic not r	NA	NA	NA	NA	NA	NA	NA	NA	NA
H35	Zhou, H	2012	Invasive pneumococcal pneumo	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Text S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-23
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6-23, File S3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-23
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	23-24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	23-28
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	28

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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NHS National Institute for Health Research

Systematic review

1. * Review title.

Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Association of seasonal viral acute respiratory infection (VARI) with pneumococcal disease (PD): a systematic review of population-based studies

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

3. * Anticipated or actual start date.

Give the date when the systematic review commenced, or is expected to commence.

07/12/2016

4. * Anticipated completion date.

Give the date by which the review is expected to be completed.

15/01/2018

5. * Stage of review at time of this submission.

Indicate the stage of progress of the review by ticking the relevant Started and Completed boxes. Additional information may be added in the free text box provided.
Please note: Reviews that have progressed beyond the point of completing data extraction at the time of initial registration are not eligible for inclusion in PROSPERO. Should evidence of incorrect status and/or completion date being supplied at the time of submission come to light, the content of the PROSPERO record will be removed leaving only the title and named contact details and a statement that inaccuracies in the stage of the review date had been identified.
This field should be updated when any amendments are made to a published record and on completion and publication of the review.

The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

You Li

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

7. * Named contact email.

Give the electronic mail address of the named contact.

You.Li2@ed.ac.uk

8. Named contact address

Give the full postal address for the named contact.

3.730 Doorway 1, Old Medical School
Teviot Place
Edinburgh
UK

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+44 (0)7871 566188

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

The University of Edinburgh

Organisation web address:

www.ed.ac.uk

11. Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Mr You Li. The University of Edinburgh
Ms Meagan Peterson. The University of Edinburgh
Professor Harish Nair. The University of Edinburgh
Professor Harry Campbell. The University of Edinburgh

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

None

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

What methods have been used in population-based studies analysing the association between VARI and subsequent PD?
What results have been reported in population-based studies analysing the association between VARI and subsequent PD?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

We searched three bibliographic databases (MEDLINE, Embase and Global Health) for primary research studies published between 1 January 1990 and 27 April 2017.
An update of the search was done for primary research studies published between 1 January 1990 and 31 December 2017.
No restrictions were placed on the language of publication.

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Viral acute respiratory infection; pneumococcal disease.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Population-based studies involving people with viral acute respiratory infection and pneumococcal disease.
Specifically, the following participants were considered:
(1) Those with laboratory confirmed viral infections;
(2) Those with ICD code for influenza and RSV infection;
(3) Those with a case definition of an influenza-like illness (ILI) and bronchiolitis.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Population-based studies involving people with viral acute respiratory infection and pneumococcal disease.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Not applicable.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

There were no restrictions imposed on the types of study design eligible for inclusion.We included population-based studies involving clinically diagnosed PD cases, and specifically, we accepted the following studies: (1) Those involving laboratory confirmed viral infections; (2) Those involving an ICD code for influenza and RSV infection; (3) Those involving case definitions of an influenza-like illness (ILI) and bronchiolitis. We excluded animal studies and theoretical studies in which no population data was applied. We focused our review on the association of seasonal VARI with PD, and thus excluded studies that reported influenza pandemic cases only.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24. * Primary outcome(s).

Give the pre-specified primary (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The association between VARI and subsequent PD.

Timing and effect measures

25. * Secondary outcome(s).

List the pre-specified secondary (additional) outcomes of the review, with a similar level of detail to that required for primary outcomes. Where there are no secondary outcomes please state 'None' or 'Not applicable' as appropriate to the review

Factors that could affect the association between VARI and subsequent PD.

Timing and effect measures

26. Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how

discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Risk of bias will be assessed by evaluating the power of the studies, the measures taken to control for confounders, and any multiple tests made without reasonable correction or justification.
Bias is expected to have little impact on the review because it is intended to provide a summary of all relevant studies, and no quantitative analysis will be conducted.

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

A descriptive synthesis is planned. A summary of both the methods and the results of eligible studies will be provided.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

None planned.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
No

Methodology
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Qualitative synthesis
No

Review of reviews
No

Service delivery
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions

No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Scotland

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33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published.

Please provide anticipated publication date

Review_Completed_not_published

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

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Give the link to the published review.

BMJ Open

Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019743.R2
Article Type:	Research
Date Submitted by the Author:	08-Mar-2018
Complete List of Authors:	Li, You; University of Edinburgh School of Molecular Genetic and Population Health Sciences, Centre for Global Health Research Peterson, Meagan; University of Edinburgh School of Molecular Genetic and Population Health Sciences, Centre for Global Health Research Campbell, Harry; University of Edinburgh School of Molecular Genetic and Population Health Sciences, Centre for Global Health Research Nair, Harish; University of Edinburgh School of Molecular Genetic and Population Health Sciences, Centre for Global Health Research
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Infectious diseases
Keywords:	respiratory tract infection, pneumococcal infection, viral acute respiratory infection, pneumococcal disease

Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies

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Abstract

Objective: Animal and *in vitro* studies suggest viral acute respiratory infection (VARI) can predispose to pneumococcal infection. These findings suggest that prevention of VARI can yield additional benefits for the control of pneumococcal disease (PD). In population-based studies, however, the evidence is not in accordance, possibly due to a variety of methodological challenges and problems in these studies. We aimed to summarise and critically review the methods and results from these studies in order to inform future studies.

Methods: We conducted a systematic review of population-based studies that analysed the association between preceding seasonal VARI and subsequent PD. We searched MEDLINE, Embase and Global Health databases using tailored search strategies.

Results: A total of 28 studies were included. After critically reviewing the methodologies and findings, 11 studies did not control for seasonal factors shared by VARI and PD. This, in turn, could lead to an overestimation of the association between the two illnesses. One case-control study was limited by its small sample size (n case=13). The remaining 16 studies that controlled for seasonal factors suggested that influenza and/or RSV infections were likely to be associated with the subsequent occurrence of PD (influenza: 12/14 studies; RSV: 4/5 studies). However, these 16 studies were unable to conduct individual patient data based analyses. Nevertheless, these studies suggested the association between VARI and subsequent PD was related to additional factors such as virus type and subtype, age group, comorbidity status, presentation of PD and pneumococcal serotype.

Conclusions: Population-based studies do not give consistent support for an association between preceding seasonal VARI and subsequent PD incidence. The main methodological challenges of existing studies include the failure to utilise individual patient data, control for seasonal factors of VARI and PD, or include other factors related to the association (e.g. virus, age, comorbidity and pneumococcal serotype).

Strengths and limitations of this study

- This is the first review that critically reviewed the methods and findings of population-based studies that reported an association between VARI and PD.
- Results of studies summarised according to study design and methods.
- No meta-analysis was conducted due to a variety of study designs, data sources and analytical methods in the studies so a narrative summary of the methods and results is provided.

Introduction

Both viral acute respiratory infection (VARI) and pneumococcal disease (PD) account for a substantial disease burden worldwide, especially in young children and the elderly.[1-3] The association of viral acute respiratory infection (VARI) and subsequent pneumococcal disease (PD) was not well recognised until the catastrophic 1918 influenza pandemic, which resulted in an estimated 40–50 million deaths;[4] it has been suggested that pneumococcus may have been a major cause of death.[5] Most recently, it was observed that the incidence of PD was higher during 2009 influenza H1N1 pandemic period than the same period in pre-pandemic[6-10] and post-pandemic years.[7 9 10]

During inter-pandemic periods, the associations of seasonal influenza and other seasonal respiratory viruses such as respiratory syncytial virus (RSV), human metapneumovirus (hMPV) and parainfluenza virus (PIV) with PD incidence are poorly understood and remain unclear. In animal and in-vitro studies, it has been suggested that viral respiratory infection could predispose to pneumococcal infection and might facilitate pneumococcal transmission; in turn, this co-infection could induce a lethal synergism that is much more severe than infection with either pathogen alone (a brief summary of findings displayed in **Supplementary Table S1**). However, these studies are all relatively small-scale studies and may be subject to publication bias favouring reporting of positive findings. In population-based studies, the findings were inconsistent. These studies differed substantially in study design, data sources and methods, making it difficult to compare and interpret the results across the studies. We conducted a systematic review of population-based studies on the association of preceding VARI on the occurrence of PD to summarise the methodology and results, critically review the findings and present recommendations for future studies.

Methods

Search Strategy and Selection Criteria

We searched MEDLINE, Embase and Global Health databases using tailored search strategies (search strategies in **Supplementary Text S1**, PRISMA flowchart in **Figure 1**). We restricted the search to studies published between 1 January 1990 and 31 Dec 2017. We included population-based studies

with clinically diagnosed PD cases (see below for detailed definition). In terms of VARI exposure, we accepted the following studies: (1) those with laboratory confirmed viral infections; (2) those with an ICD code for influenza and/or RSV infection; (3) those with case definition of influenza-like illness (ILI) and bronchiolitis as proxies for influenza and RSV, respectively. We excluded animal studies and theoretical studies where no population data were applied. We focused our review on the association of seasonal VARI and PD and thus excluded studies that reported pandemic influenza cases only. No language restrictions were applied. The reference lists of eligible studies were also checked to identify additional studies for inclusion. For all included studies, quality assessment was conducted using tailored Critical Appraisal Skills Programme (CASP) checklists for case-control studies and cohort studies (**Supplementary File S1**). The review was conducted and reported according to the PRISMA guidelines (**Supplementary File S2**). The protocol for this systematic review was registered on PROSPERO (registration number: CRD42017064760; **Supplementary File S3**).

Figure 1. PRISMA flow diagram of the literature search. PD: pneumococcal disease.

Definition of PD

We defined PD as any disease caused by *Streptococcus pneumoniae* (pneumococcus). Since this definition contains a broad range of diseases and symptoms, including some that are trivial to our review, we adopted a narrower definition. This narrowed definition includes invasive pneumococcal disease (IPD) and pneumococcal pneumonia (PP). We defined IPD as detection of pneumococcus in typical sterile sites (e.g. blood, pleural and cerebrospinal fluid). A detailed category of PD for our review is displayed in **Figure 2**. Additionally, we used the term “non-pneumonic invasive pneumococcal disease (npIPD)”, which referred to all IPD without diagnosis of pneumonia, in order to differentiate from non-invasive and invasive pneumococcal pneumonia.

Figure 2. Category of pneumococcal disease in the present review.

Definition of VARI

We defined VARI as a respiratory tract infection with viral aetiology. ILI was viewed as a proxy for influenza infection in the present review. We defined ILI as a symptomatic cough and fever ≥38°C with onset within 7 days.

Data Extraction

We used a standardised data extraction template to extract relevant data from the eligible full-text studies, including study design, data source, methods, results and conclusion. The principle summary measures of the association between VARI and PD include correlation coefficients, risk ratios, rate ratios, odds ratios and attributable percentage of PD to VARI. YL and MP independently extracted the data. HN or HC arbitrated any disagreement with the extraction.

Data Analysis

Since it was expected that methodology would differ substantially between studies and a quantitative meta-analysis would not be appropriate, a narrative synthesis was conducted. Studies were summarised according to methodology to allow for more appropriate comparisons of the results.

In addition, because of the concern of multiple testing, we determined the number of tests conducted in each study, so a Bonferroni correction could be applied where applicable; only the tests relevant to the association between VARI and pneumococcal infection were included as part of the correction. The Bonferroni-adjusted significance level was calculated as 0.05 divided by the number of relevant statistical tests within a study.

Patient and Public Involvement

No patients or public were involved in the present study.

Results

A total of 28 studies[11-38] were eligible and included in the review. We noticed a variety of study designs, exposures and outcomes of interest and analytical methods in these studies (summarised in **Table S2**). Due to the variety, we summarised the studies and displayed the results according to study design and methods.

Individual Patient Data Based Studies

Individual patient data based studies during the inter-pandemic period are sparse. Only three studies[17 25 29] were identified (**Table 1**), including two cohort studies[17 29] and one small case-control study by O'Brien et al[25]. The reported results consistently supported the role of preceding VARI on

occurrence of PD. However, the two cohort studies did not attempt to control the seasonal risk factors of VARI and PD that could potentially bias the estimated effect size.

Table 1. Summary of individual patient data based studies.

Study	Study Period	Population	VARI	PD (n of cases)	Methods	Main findings
Edwards et al. 2011[17]	2005–2009	all ages Northern Territory, Australia	IFV	IPD (n=346)	Using data from Notifiable Diseases System, relative risk of IPD calculated in ≤4w after IFV compared with background risk	RR=112.5 [48.9–224.8]
O'Brien et al. 2000[25]	1995–1996	<18y Iowa, US	ILI IFV A	Severe PP (n=13)	Case-control design: case from children with severe PP, 3 controls per case selected, from friends of cases or from the same primary care practice, matched by age (within 1y of the case). ILI history (7–28d within admission) investigated by telephone interview and IFV A convalescent serology collected.	OR (ILI history)=12.4 [1.7-306], OR (IFV A convalescent serology)=3.7 [1.0–18.1]
Stensballe et al. 2008[29]	1996–2003	all ages Denmark	RSV non-RSV	IPD (n=7,787)	Prospective cohort study: two exposure groups, RSV and non-RSV respiratory infection hospitalisations within 30d	RR for RSV=7.1 [3.6–14.3], RR for non-RSV=4.5 [2.0–10.0]

Abbreviations: d, day(s); IFV, influenza virus; ILI, influenza-like illness; IPD, invasive pneumococcal disease; OR, odds ratio; PD, pneumococcal disease; PP, pneumococcal pneumonia; RR, relative risk; RSV, respiratory syncytial virus; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Ecological Studies

In our review, 25[11-16 18-24 26-28 30-38] of the 28 studies were ecological studies. 16[11 13 14 16 18 19 22-24 26 32 34-38] out of the 25 ecological studies controlled for seasonal patterns of VARI and PD (**Table S2**). Additionally, the study by Stensballe et al.[29] analysed data at both population and individual level but did not control for the seasonal patterns.

Correlation analyses with no control for seasonal patterns

Table 2 shows a summary of 11 studies[12-14 20 21 23 24 27 29 30 33] using correlation analyses without controlling for seasonal patterns of VARI and PD. Since all studies conducted multiple tests in analysing the correlation (e.g. across age groups, viruses and lag time between VARI and PD), Bonferroni method was applied to adjust the significance level. The correlation between PD and influenza or RSV was statistically significant in all five studies [14 23 24 29 30] that analysed population data of all ages (correlation coefficient r: 0.40–0.71 for influenza at no time lag, 0.47–0.77 for RSV at no time lag).

139 **Table 2. Summary of ecological studies utilising correlation analysis.**

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Correlation Method	Correlation Coefficients (time lag)
Ampofo et al. 2008[12]	2001–2007	<18y Utah, US	IFV RSV PIV ADV hMPV	IPD (n=435)	Hospitalisation and lab data, fortnightly	Pearson	<18y, IPD coded by ICD-9 IFV: **0.23c** (0), **0.24c** (2w), **0.18c** (4w); RSV: **0.31a** (0), **0.35a** (2w), **0.34a** (4w); PIV: 0.03 (0), −0.01 (2w), −0.03 (4w); ADV: 0.01 (0), −0.05 (2w), −0.08 (4w); hMPV: **0.31a** (0), **0.39a** (2w), **0.37a** (4w) (similar results for culture-confirmed IPD)
Burgos et al. 2015[13]	1996–2012	≥18y Barcelona, Spain	IFV	IPD (n=1,150)	Hospitalisation and surveillance lab data, monthly	Spearman	≥18y IFV: **0.65a** (0), **0.45a** (1m)
Ciruela et al. 2016[14]	2006–2012	all ages Catalonia, Spain	IFV RSV ADV	IPD (n=8,044)	Microbiological reporting system, monthly	Spearman	All ages IFV: **0.71a** (0), **0.64a** (1m); RSV: **0.77a** (0), **0.80a** (1m); ADV: **0.61a** (0), **0.39a** (1m) (similar results for age-stratified analysis of IFV and RSV; results of ADV were only significant among <5y with no lag)
Jansen et al. 2008[20]	1997–2003	all ages Netherlands	IFV RSV	IPD (n=7,266; PM+PB)	Weekly Sentinel System, weekly	Spearman	0–4y, 5–17y, ≥18y IFV-PB: **0.24b**, **0.21b**, **0.62b** IFV-PM: **0.23b**, **0.14b**, **0.39b** RSV-PB: **0.29b**, **0.12b**, **0.59b** RSV-PM: **0.36b**, —, **0.44b**

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Correlation Method	Correlation Coefficients (time lag)
Kim et al. 1996[21]	1990–1993	all ages Houston, TX, US	IFV RSV ADV PIV non-IFV	IPD (n=480)	Hospitalisation and surveillance lab data, fortnightly	Pearson	≥18y IFV: **0.46a** (0), **0.35c** (4w) RSV: **0.56a** (0), **0.54a** (4w) ADV: **0.25c** (0), **0.29c** (4w) non-IFV: **0.38a** (0), **0.35c** (4w) <18y IFV: 0.08 (0), **0.23c** (4w), **0.47a** (8w) RSV: 0.13 (0), **0.28c** (4w), **0.32c** (8w) ADV: **0.31c** (0), **0.55a** (4w), **0.24c** (8w) non-IFV: **0.24c** (0), **0.39a** (4w), **0.21c** (8w)
Murdoch et al. 2009[23]	1995–2006	all ages Christchurch, New Zealand	IFV RSV ADV PIV	IPD (n=737)	Surveillance data, monthly	Spearman	All ages IFV A: **0.44a** (0), **0.37a** (1m) IFV B: **0.23c** (0), 0.13 (1m) RSV: **0.52a** (0), **0.47a** (1m) ADV: **0.27a** (0), **0.33a** (1m) PIV 1/2: **0.24c** (0), **0.31a** (1m) PIV 3: **0.34a** (0), **0.17c** (1m) (correlations were stronger in 5–65y and >65y)
Nicoli et al. 2013[24]	1996–2009	all ages England and Wales, UK	IFV RSV	IPD (n=71,333)	Surveillance data, weekly	Pearson and Spearman	All ages, Pearson IFV: **0.54a** RSV: **0.47a** All ages, Spearman IFV: **0.67a** RSV: **0.63a** (correlations were stronger in 15–64y and ≥65y than 0–4y and 5–14y)

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Correlation Method	Correlation Coefficients (time lag)
Peltola et al. 2011[27]	1995–2007	<5y Finland	RV EV RSV IFV PIV ADV	IPD (about 90 cases per year)	National Infectious Disease Register + 3 studies + virus database, fortnightly	Pearson	<u>≤5y</u> RV: **0.28c**, **0.25c**, 0.31, **0.23a** (from 4 studies) EV: **0.17c** RSV: 0.05 IFV: −0.03 IFV A: −0.08 PIV: 0.02 ADV: -0.05
Stensballe et al. 2008[29]	1996–2003	all ages Denmark	RSV non-RSV	IPD (n=7,787)	Population Based Registries Cohort, monthly	Pearson	<u>All ages</u> RSV: **0.55a** non-RSV: **0.65a** <u>≤2y</u> RSV: 0.08
Talbot et al. 2005[30]	1995–2002	all ages Tennessee, US	IFV RSV	IPD (n=4,147)	Surveillance data, weekly	Pearson	<u>All ages</u> RSV: **0.56a** (0), **0.60a** (1w), **0.59a** (2w), **0.57a** (3w), **0.55a** (4w) IFV: **0.40a** (0), **0.41a** (1w), **0.34a** (2w), **0.33a** (3w), **0.26a** (4w) (correlations were stronger in ≥18y than <18y)

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Correlation Method	Correlation Coefficients (time lag)
Watson et al. 2006[33]	2000 (May–Oct)	all ages New South Wales, Australia	IFV RSV PIV	IPD (n=681)	Surveillance data, weekly	Pearson	<u>≤18y</u> IFV: not significant RSV: **0.58a** PIV: **–0.40c** <u>≥18y</u> IFV: not significant RSV: not significant PIV: not significant RSV or IFV: **0.48c**

Time lag indicates the time difference between preceding VARI and subsequent PD incidence.

Abbreviations: ADV, adenovirus; EV, enterovirus; IFV, influenza virus; IPD, invasive pneumococcal disease; m, month(s); MPV, metapneumovirus; PB, pneumococcal bacteraemia; PD, pneumococcal disease; PIV, parainfluenza virus; PM, pneumococcal meningitis; RSV, respiratory syncytial virus; RV, rhinovirus; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Correlation coefficients **in bold** were statistically significant as originally reported in the study (P<0.05); correlation coefficients ending with “a” were statistically significant after Bonferroni adjustment (P< 0.05/number of relevant tests) or when the Bonferroni correction was deemed unnecessary; correlation coefficients ending with “b” did not have enough information to apply the Bonferroni correction; correlation coefficients ending with “c” were not statistically significant after Bonferroni adjustment.

Regression analyses controlling for seasonal patterns

Table 3 shows the summary of the 15 studies[11 13 14 16 18 22-24 26 32 34-38] that controlled for seasonal patterns by regression analysis. Results were inconsistent among the studies. In all-age population studies, preceding influenza infection was likely to be associated with IPD (12 studies[13 14 16 18 22-24 32 35-38] reported an association and two studies[11 34] reported no association). According to two studies[23 24] that reported age-stratified results, the association between influenza and IPD was more likely to exist among older people than among young children. In terms of preceding RSV infection, four[14 24 34 37] out of five studies[14 23 24 34 37] observed an association of RSV with PD incidence. Specifically, one study[14] found the association between RSV and IPD only existed among children <5 years. Studies reporting other viruses such as ADV and PIV were sparse (two[14 23] and one[23] studies, respectively). Five studies[14 23 24 34 37] that reported two or more viruses demonstrated that the association differed by the type of virus. Moreover, the association could differ among virus subtypes (e.g. influenza A *vs* influenza B[22] and PIV 1/2 *vs* PIV 3[23]). Notably, there are other factors that could influence the strength of the associations reported in these studies. For instance, the association could vary by presentation of PD (invasive pneumococcal pneumonia, IPP vs npIPD[32 34 36] and PP vs pneumococcal sepsis, PSe[37]); preceding VARI was more likely to be associated with the occurrence of pneumonia than other clinical presentations. Additionally, the results from studies in Denmark, where comorbidity status and pneumococcal serotype were available, demonstrated that influenza had a greater influence on the incidence of low-invasiveness serotypes than medium- or high- invasiveness among the low comorbidity group; among the high comorbidity group, the pattern was reversed.[35 36]

168 **Table 3. Summary of ecological studies controlling for seasonal patterns.**

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Allard et al. 2012[11]	1997–2008	all ages Montreal, Canada	IFV (case)	IPD (n=2,920)	Notification data and sentinel surveillance data, weekly	Negative binomial regression	long-term trends and seasonal trends of IPD	All ages IFV A: 1.01 (0), 1.00 (1w), 1.00 (2w), 0.99 (3w), 1.00 (4w), 1.00 (5w) IFV B: 1.01 (0), 1.01 (1w), 1.00 (2w), 1.01 (3w), 0.99 (4w), 1.01 (5w)	
Burgos et al. 2015[13]	1996–2012	≥18y Barcelona, Spain	IFV (IR per 1,000)	IPD (n=1,150)	Hospitalisation and surveillance lab data, monthly	Negative binomial regression	temperature	≥18y IFV: **1.23a** [1.03–1.47]	
Ciruela et al. 2016[14]	2006–2012	all ages Catalonia, Spain	IFV RSV ADV (IR per 100,000)	IPD (n=8,044)	Microbiological reporting system, monthly	Negative binomial regression	temperature >17°C	All ages IFV: **1.26b** [1.03–1.54] (0), 1.09 [0.87–1.36] (1m) RSV: 1.15 [0.89–1.48] (0), **1.81b** [1.36–2.41] (1m) ADV: 1.58 [0.88–2.74] (0), 1.32 [0.68–2.42] (1m) ≤5y IFV: 1.16 [0.90–1.50] (0), 1.06 [0.80–1.42] (1m) RSV: 1.41 [1.00–1.97] (0), **2.57b** [1.78–3.71] (1m) ADV: **2.47b** [1.38–4.53] (0), 1.00 [0.59–1.68] (1m) (not significant in 5–64y or ≥65y)	

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Domenech de Cellès et al. 2017[16]	2000–2014	all ages France	ILI (as a proxy for IFV)	IPD (n=64,542)	National surveillance system, weekly	Mixed-effect linear regression	seasonal trends of IPD		All ages ILI: median 4.9% across all study years (1w)
Grabowska et al. 2006[18]	1994–2004	all ages Sweden	IFV (binary)	IPD (n=11,637)	Surveillance data, weekly	Negative binomial regression	yearly trends and seasonal trends of IPD	All ages IFV: 1.03 [0.93–1.15] (0), 1.11 [1.00–1.23] (1w), 1.11 [0.99–1.22] (2w), **1.14c** [1.02–1.26] (3w), **1.12c** [1.01–1.23] (4w)	All ages **6%c** [1–12%] (3w)
Kuster et al. 2011[22]	1995–2009	all ages Toronto/ Peel area, Canada	IFV (100 cases)	IPD (n=6,191)	Population-based surveillance, weekly	Negative binomial regression	multi-year trends and seasonal trends of IPD, relative humidity, temperature, UV index	All ages IFV A&B: **1.09a** [1.05–1.14] (1w), **0.93c** [0.89–0.98] (3w) IFV A: identical to IFV A&B IFV B: not significant	
Murdoch et al. 2009[23]	1995–2006	all ages Christchurch, New Zealand	IFV RSV ADV PIV (binary)	IPD (n=737)	Surveillance data, monthly	Negative binomial regression	average daily temperature <10°C, PM10 >50µg/m^3, days with rainfall >10, mean daily 9 am humidity >75%, mean daily sunshine >6h	All ages IFV: **1.38c** [1.02–1.85] (0), 1.20 [0.91–1.58] (1m) RSV: 1.15 [0.87–1.52] (0), 0.90 [0.68–1.18] (1m) PIV 1/2: 1.04 [0.82–1.30] (0), 1.04 [0.84–1.29] (1m) PIV 3 outside IFV season: **1.64a** [1.18–2.30] (0), **1.49c** [1.07–2.08] (1m) ADV: 0.97 [0.78–1.20] (0), **1.26c** [1.02–1.54] (1m) (similar in 5–65y, >65y; not significant in <5y)	

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Nicoli et al. 2013[24]	1996–2009	all ages England and Wales, UK	IFV RSV (case)	IPD (n=71,333)	Surveillance data, weekly	Negative binomial regression	weekly temperature or monthly hours of sunshine (separately in models; results were similar)		All ages, 0–4y, 5–14y, 15–64y, ≥65y controlling for temperature, multiplicative model IFV: **5.6%b** [0.2–23.8%] , −0.4% [−1.8–0.0%], **2.9%c** [0.0–13.6%], **1.8%c** [0.1–7.4%], **3.2%b** [0.0–14.7%] RSV: **2.9%b** [0.1–14.2%], **1.4%c** [0.0–6.9%], **5.9%b** [0.0–27.6%], **14.5%b** [0.0–52.7%], **7.9%b** [0.0–27.4%] (no significant results in time lag analyses)
Opatowski et al. 2013[26]	2001–2004	all ages France	VARI (IR)	PM (n=1,383)	Surveillance data, weekly	Poisson regression using generalised estimating equations approach	seasonal trends of PM	All ages regression parameter: **19.4c** **23.1a** (1w) **23.9a** (2w)	
Walter et al. 2010[32]	1995–2006	all ages US	IFV (positive percentage)	IPD (IPP, npIPD; n=21,239)	Surveillance data, weekly	Negative binomial regression	seasonal trends and linear trends of IPP		Northeast, all ages IFV-IPP: **4.9%c** [4.5–5.3%] (1w) South, all ages IFV-IPP: **5.4%b** [5.0–5.9%] (1w) West, all ages IFV-IPP: **5.2%c** [4.8–6.0%] (1w) (not significant for IFV-npIPD)

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Weinberger et al. 2014[34]	1996–2012	<7y Navajo/White Mountain Apache population, US	Bronchiolitis (IR, as a proxy for RSV) IFV (IR)	IPD (IPP, npIPD; n=496)	4 community-based studies, monthly	Poisson regression	pneumococcal carriage prevalence, seasonal trends of IPD, PCV periods		<7y Bronchiolitis-PP: **15.5%b** [1.8–26.1%] Bronchiolitis-npIPD: 8.0% [−4.8–19.3%] (not significant for IFV)
Weinberger et al. 2013[35]	1977–2007	≥40y Denmark	ILI (case, as a proxy for IFV)	IPP (n=8,308)	Surveillance data + nationwide general practice reports, weekly	Poisson regression	seasonal trends of IPP, dummy variable for week 1,2,3,51,52 and its interaction with ILI		≥40y, low comorbidity and low serotype invasiveness ILI: **17.9%a** [13.6–21.9%] (1w) ≥40y, low comorbidity and high serotype invasiveness ILI: **6.7%a** [3.8–11.7%] (1w) ≥40y, medium/high comorbidity and low serotype invasiveness ILI: 1.3% [−1.6–5.4%] (1w) ≥40y, medium/high comorbidity and high serotype invasiveness ILI: **8.9%a** [6.6–11.8%] (1w)

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Weinberger et al. 2014[36]	1977–2007	all ages Denmark	ILI (case, as a proxy for IFV)	IPD (IPP, npIPD; n=13,882)	Surveillance data + nationwide general practice reports, weekly	Poisson regression	seasonal trends of IPD, dummy variable for week 1,2,3,51,52 and its interaction with ILI		15–39y, low comorbidity ILI-IPD: **9.9%a** [6.0–13.0%] (1w) ILI-IPP: **11.2%a** [6.5–14.8%] (1w) ILI-npIPD: 6.6% [−1.2–14.3%] (1w) 15–39y, medium/high comorbidity ILI-IPD: 0.3% [−8.4–9.7%] (1w) ILI-IPP: 5.4% [−5.0–18.7%] (1w) ILI-npIPD: −6.6% [−25.7–7.6%] (1w) ≥40y, low comorbidity ILI-IPD: **7.6%a** [5.1–11.6%] (1w) ILI-IPP: **7.8%a** [5.8–11.7%] (1w) ILI-npIPD: **6.9%a** [1.8–12.8%] (1w) ≥40y, medium/high comorbidity ILI-IPD: **6.2%a** [4.3–9.3%] (1w) ILI-IPP: **6.5%a** [4.4–10.1%] (1w) ILI-npIPD: **5.3%a** [2.5–8.9%] (1w)

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
Weinberger et al. 2015[37]	1992–2009	<2y 36 states in US	IFV RSV (IR)	PD (PP, PSe; n=17,404)	State inpatient databases, weekly	Poisson regression	seasonal trends of PD, PCV periods, IFV or RSV, state	0–2m, 3–11m, 0–11m, 12–23m RSV-PP: **1.42b** [1.30–1.55], **1.24b** [1.17–1.33], **1.23b** [1.19–1.30], **1.12b** [1.09–1.18]	0–2m, 3–11m, 0–11m, 12–23m IFV-PP: 2.1% [−4.5–1.4%], **2.2%a** [0.1–3.4%], 0.6% [−0.9–1.4%], **3.2%a** [1.7–4.7%] RSV-PP:**35.7%a** [27.9–42.7%], **20.0%a** [14.7–24.8%], **20.3%a** [17.4–25.1%], **10.1%a** [7.6–13.9%] IFV-PSe: 0.7% [−1.1–2.2%], **−2.7%a** [−3.7—1.7%], −0.6% [−1.4–0.3%], **1.9%a** [1.1–2.6%] RSV-PSe: **15.0%a** [13.1–17.1%], 0.1% [−4.9–5.0%], **7.2%a** [5.3–9.0%], **3.8%a** [2.5–5.2%]
Zhou et al. 2012[38]	1994–2005	all ages Atlanta, US	IFV RSV (positive percentage)	IPP (n=5,683)	Surveillance data, weekly	Negative binomial regression (comparison between models with and without IFV and RSV)	temperature, sunshine, precipitation	p values for the likelihood ratio test were <0.05 for 5 of 11 influenza seasons: 1994–95, 1996–97, 1998–99, 2003–04, 2004–05; after Bonferroni adjustment association was significant for 3 of 11 influenza seasons: 1996–97, 2003–04, 2004–05.	

169 Time lag indicates the time difference between VARI and subsequent PD incidence.

170 Abbreviations: ADV, adenovirus; AP, attributable percentage; CI, confidence interval; IFV, influenza virus; h, hour(s); ILI, influenza-like illness; IPD, invasive

171 pneumococcal disease; IPP, invasive pneumococcal pneumonia; IR, incidence rate; npIPD, non-pneumonic invasive pneumococcal disease; PCV,

pneumococcal conjugate vaccine; PD, pneumococcal disease; PIV, parainfluenza virus; PP, pneumococcal pneumonia; PSe, pneumococcal sepsis; RR, relative risk; RSV, respiratory syncytial virus; UV index, clear-sky ultraviolet index; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Relative risk or attributable percentage **in bold** were statistically significant as originally reported in the study (P<0.05); relative risk or attributable percentage ending with “a” were statistically significant after Bonferroni adjustment (P<0.05/number of relevant tests) or when the Bonferroni correction was deemed unnecessary, those ending with “b” did not have enough information to apply the Bonferroni correction; relative risk or attributable percentage ending with “c” were not statistically significant after Bonferroni adjustment.

Studies utilising other analyses

Seven ecological studies[15 16 19 22 26 28 31] utilised other analytical methods (**Table 4**). Except for studies by Hendriks et al.[19] and Toschke et al.[31], all studies reported an association between VARI and PD.

Table 4. Summary of ecological studies utilising other methods.

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Methods	Main findings
Dangor et al. 2014[15]	2005–2008	<15y Soweto, South Africa	IFV	IPD (n=636)	Hospitalisation and surveillance laboratory data, monthly	X-11 seasonal adjustment method to retain seasonal components. Peak timing compared by time series graph.	IFV peak in May–Jul, followed by IPD (Aug–Oct); no correlation analysis results reported
Domenech de Cellès et al. 2017[16]	2000–2014	all ages France	ILI (as a proxy for IFV)	IPD (n=64,542)	National surveillance system, weekly	Correlation analysis of waveforms of ILI and IPD	Correlation of peak timing of ILI and IPD peak 2: 0.42 [0.04-0.66]; correlation of total cases of ILI and IPD: 0.31 [0.03-0.56]
Hendriks et al. 2017[19]	2004–2014	all ages Netherlands	ILI (as a proxy for IFV)	IPD (n=6,572)	Surveillance data, weekly	Cross-correlations of the time series model (SARIMA) residuals	No significant cross-correlations observed

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Methods	Main findings
Kuster et al. 2011[22]	1995–2009	all ages Toronto/ Peel area, Canada	IFV	IPD (n=6,191)	Population-based surveillance, weekly	Spearman correlation for phase and amplitude between IFV and IPD; Granger methods to test whether influenza predicted IPD; Case-crossover analysis to evaluate short-term associations	Phase and amplitude between IFV and IPD not correlated; Granger test of IFV causing IPD: *P*<0.001; case-crossover OR: 1.10[1.02–1.18] at 1w lag
Opatowski et al. 2013[26]	2001–2004	all ages France	VARI	PM (n=1,383)	Surveillance data, weekly	Mathematic model of pneumococcus transmission, to estimate the interaction parameters between VARI and PM	Factor of VARI on pneumococcus acquisition or transmissibility: 8.7[4.6–14.4]; factor of VARI on pathogenicity: 92[28–361]
Shrestha et al. 2013[28]	1989–2009	all ages Illinois, US	IFV	PP (n not known)	Hospital data, weekly (Dataset I from 1989 to 1997, dataset II from 2000 to 2013)	Mathematic model of pneumococcal pneumonia transmission, to estimate the interaction parameters between VARI and PP	Factor of IFV on PP susceptibility: dataset I 115[70–200], dataset II 85[30–160]

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Methods	Main findings
Toschke et al. 2008[31]	1997–2003	<16y Germany	IFV A	IPD (n=1,474)	Surveillance data, monthly	Multivariate time series analysis using "3h algorithm", which fit an autoregressive Poisson or negative binomial model to time series	IFV A season did not affect IPD season (*P*=0.49); IFV A peak did not precede IPD peak

Abbreviations: IFV, influenza virus; IPD, invasive pneumococcal disease; PD, pneumococcal disease; PM, pneumococcal meningitis; PP, pneumococcal pneumonia; VARI, viral acute respiratory infection; w, week(s); y, year(s).

Discussion

In our review, we summarised population-based studies that evaluated the association of seasonal VARI and subsequent PD. To our knowledge, this is the first review that summarises the methodology and findings of existing epidemiological studies on this topic.

We found that reported associations between VARI and subsequent PD were inconsistent among the 28 included studies. Only three studies[17 25 29] analysed the association using individual patient data. The two cohort studies[17 29] did not account for the shared risk factors between VARI and PD that influenced their seasonality, substantially limiting the inferences that can be made from these data while the case-control study[25] was limited by its small sample size (n case=13). In ecological studies, only 16[11 13 14 16 18 19 22-24 26 32 34-38] of the 25[11-16 18-24 26-28 30-38] ecological studies accounted for seasonal patterns. In these studies, we found that influenza and/or RSV infections were likely to be associated with the subsequent occurrence of PD. For influenza, the association was stronger among younger populations compared to older adults[23 24] while the pattern was reversed for RSV.[14] Data from multiple studies suggested that virus type (five studies[14 23 24 34 37]) and subtype (two studies[22 23]),

comorbidity status (two studies[35 36]) and pneumococcal serotype invasiveness (one study[35]) could influence the association. However, these 16 ecological studies had various population characteristics (e.g. age, comorbidity, immunity status), PD datasets, VARI datasets and analytical methods. As such, heterogeneity among the studies, along with their ecological nature, limits the amount of valid inferences that can be made from the data (as summarised above).

Nevertheless, these studies provide important clues for the potential factors related to the association between VARI and subsequent PD, and thus could help with the conception and design of future studies. Ideally, in order to understand whether a particular preceding VARI can predispose an individual to PD, a prospective cohort study that monitors each individual for VARI and pneumococcal infection would be utilised, allowing analyses at both individual and population levels. However, such a design would not be feasible or affordable as inter alia pneumococcal infections are rare. Alternatively, utilisation of large-scale routine health data and reliable data linkage (through unique individual identifiers) from sources such as surveillance data and hospitalisation datasets may be feasible in many industrialised countries. An example of such data linkage in our review is the study by Stensballe and colleagues[29] that linked information from four Danish population-based registries. While the authors conducted individual-level analysis, the results were based on cases tested for both the presence of respiratory viruses and pneumococcal infection. The true number of VARI-associated PD cases is likely to be significantly higher due to incomplete testing of cases; the untested viral-pneumococcal cases could represent a crucial source of selection bias. Community-based active surveillance can likely address the issue of missing cases but such surveillance would be labour intensive and less cost-effective to conduct. Another option is a case-control study, which is affordable and practical, but not without its limitations. In addition to challenges in designing such studies, defining the history of VARI is likely to be inaccurate since the timing of viral serology may be less accurate (information bias).[27] In the case-control study by O'Brien and colleagues,[25] the authors used influenza-strain specific convalescent serology as evidence for preceding influenza infection. The authors also conducted telephone interviews to investigate ILI history but they did not

mention whether interviewers and interviewees were blind to case or control status. Moreover, the value of this case-control study is limited by its very small sample size (n case = 13).

Compared with individual patient data based studies, ecological studies are more feasible, and thus the most common study design included in our review (25/28). However, there are some caveats when interpreting results from ecological studies. First, causality can never be inferred from such studies. Second, the results should be interpreted at a population level and cannot be generalised to the individual level. Since ecological studies used data aggregated into broad categories, the potential biases introduced by the aggregation should be taken into account. For instance, while 16 out of 25 ecological studies used weekly data, others used fortnightly or monthly data. This may lead to misclassification as the time window of the association of VARI on PD susceptibility can be as short as one week.[39 40] Moreover, data from different sources in ecological studies should represent the same population.

Apart from the study design, one further challenge of analysing the association is accounting for the influence of seasonal factors of VARI and PD (confounding). Both VARI and PD have similar seasonal patterns, and thus are likely to correlate as indicated by the correlation results from ecological studies. The increased risk of PD during an epidemic season could be caused by VARI or by seasonal risk factors or by both. In the present review, 11 studies[12 15 17 20 21 27-31 33] did not attempt to control for seasonal confounders, likely leading to biased estimations of the association. For example, the study by Edwards and colleagues[17] reported a relative risk as high as 112.5 when not adjusting any seasonal factors. One way to address this problem in such studies would be to match the individuals with the onset timing of pneumococcal infection, keeping the risk of PD comparable between VARI cases and non-VARI cases; for ecological studies, regression analysis adding seasonal terms or climatic factors (such as temperature and humidity), or cross-correlation analysis of time series controlling for seasonal patterns could be considered.

Our review suggests that the association of VARI and subsequent PD could vary by virus type[14 23 24 34 35] and even by subtype[22 23]. Studies using combinations of viral infections such as all virus, influenza

+ RSV, non-influenza, or non-RSV could give biased estimations of the association. However, it is not always practical to analyse the association by virus type. In ecological studies, different types of viruses might co-circulate and thus be highly correlated in incidence, making it difficult to determine the role for each virus. In terms of PD, most studies used IPD as the outcome of interest. However, studies that categorised IPD into IPP and npIPD found that the association was more pronounced in IPP than in npIPD.[32 34 36] A similar finding, that the association was stronger in PP than PSe, was reported in another study.[37] These results suggest VARI is more likely to be associated with pneumonic pneumococcal infections than non-pneumonic infections. In our review, we excluded studies using information other than clinical diagnosis as a proxy for PD (e.g. prescription data and carriage data). Pneumococcal carriage could have a fundamental role in the transmission and incidence of PD.[41] In a study analysing the impact of pneumococcal carriage and viral activity, Weinberger and colleagues[34] found npIPD was associated with carriage prevalence, whereas IPP was associated with bronchiolitis (as a proxy for RSV). The authors also proposed that preceding VARI increased susceptibility but did not enhance transmission (indicated by carriage prevalence) in children. However, more studies are needed to confirm these findings.

The association could also vary by population characteristics. According to two studies that displayed age-stratified results,[23 24] the association of influenza and subsequent IPD was more likely to exist among older people than among young children. Studies by Weinberger et al.[35 36] gauged the association in different comorbidity and pneumococcal serotype groups among Denmark populations. The results showed that influenza had a stronger impact on the incidence of low-invasiveness serotypes than medium- or high- invasiveness ones in the low comorbidity group, while the pattern reversed in the high comorbidity group. Another study that analysed clinical records of 919 patients with PP found that infrequently colonising pneumococcal serotypes were more likely to cause PP after preceding VARI, particularly in patients with immunodeficiency or chronic lung diseases.[42] These findings suggest the need for future studies to analyse the association by age group, pneumococcal serotype and comorbidity status. Moreover, the recent introduction of pneumococcal

vaccines has brought changes in the incidence of serotype-specific PD,[43] making the association of VARI and PD more complicated to understand. As a result, future studies should consider the possible serotype-specific influence that pneumococcal vaccines have on both individual immunity and herd immunity when analysing the association.

In addition to the factors discussed above, additional factors may influence the estimates of the association. The first is the change over time in the methodology of data collection, including changes in test method or diagnosis, clinical practice and health-seeking behaviour. The second is the possible delay in measurement, which happened most often in passive hospital-based studies. Thirdly, for ecological studies using aggregated data, "holiday spikes" could occur due to more social gatherings;[44] besides, weekends and holidays might influence timely tests or diagnosis as well as the health-seeking behaviour of patients.

To our knowledge, this is the first review to summarise and critically appraise the methods and results of population-based studies about the association between seasonal VARI and subsequent PD. However, this review is not without its limitations. First, due to a variety of study designs, data sources and analytical methods in the studies included, no meta-analysis was conducted in the review. As such, we were unable to provide a quantitative measure of the association of seasonal VARI and PD. Second, no unpublished data sources were included in the review, which could mean the data reported favours positive associations due to publication bias. Thus, caution should be taken when interpreting the results. Thirdly, we found many studies tended to conduct multiple statistical tests using different subgroups and time periods (e.g. age group, virus, time lag between VARI and PD) without specifying the primary study question a priori or making proper statistical adjustments to account for multiple testing. This could give rise to an increased risk of reporting false positive results. In this review, we applied Bonferroni corrections to adjust for the multiple tests where deemed necessary. Since the Bonferroni method is conservative and we are unable to adjust for studies where *P* values were not given, the adjustment in our review is intended for readers' reference and as caveats for future studies.

Given the substantial burden of VARI across the world,[1] even a modest association between VARI and subsequent PD could lead to a substantial burden of disease in terms of VARI-related PD cases. If proper anti-bacterial interventions could be applied to those with higher risk of PD due to a preceding VARI, subsequent pneumococcal infections could be prevented. The interventions would be more effective / better targeted if we could estimate the risk (i.e. the strength of association) according to timing of infection by week/month of a year, age, comorbidity status, virus type and status of immunity. In turn, understanding the association between VARI and subsequent pneumococcal infection can help evaluate the full impact of viral vaccine programs.

In conclusion, the role of seasonal VARI on subsequent PD incidence remains controversial in population-based studies. Nevertheless, these studies provide valuable information and can help with the conception of future well-designed studies. Future work could explore the association by timing of infection, age, comorbidity status, virus type, pneumococcal serotype and presentation, and thus would identify potentially susceptible populations with VARI for preventive interventions.

Supplementary Materials

Table S1. Summary of findings from animal and in vitro studies.

Table S2. Summary of methodologies utilised in the included studies (n=28).

Text S1. Search strategy

File S1. Quality assessment of included studies

File S2. PRISMA checklist

File S3. Protocol registered in PROSPERO

Contributors: HN and HC conceived the study. YL did the literature search and reviewed the articles. YL and MP extracted and analysed the data independently with oversight from HN and HC. YL drafted the manuscript. MP, HN and HC critically reviewed the manuscript. All authors read and approved the final draft of the manuscript.

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REFERENCES

1. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2013;2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet 2016;388(10053):1459-544.

2. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates. Lancet 2009;374(9693):893-902.

3. Drijkoningen JJC, Rohde GGU. Pneumococcal infection in adults: burden of disease. Clinical Microbiology and Infection 2014;20:45-51.

4. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev 2006;19(3):571-82.

5. Chien Y-W, Klugman KP, Morens DM. Bacterial Pathogens and Death during the 1918 Influenza Pandemic. N Engl J Med 2009;361(26):2582-83.

6. Fleming-Dutra KE, Taylor T, Link-Gelles R, et al. Effect of the 2009 influenza A(H1N1) pandemic on invasive pneumococcal pneumonia. J Infect Dis 2013;207(7):1135-43.

7. Launes C, Garcia-Garcia JJ, Trivino M, et al. Respiratory viruses, such as 2009 H1N1 influenza virus, could trigger temporal trends in serotypes causing pneumococcal disease. Clin Microbiol Infect 2014;20(12):O1088-90.

8. Nelson GE, Gershman KA, Swerdlow DL, et al. Invasive pneumococcal disease and pandemic (H1N1) 2009, Denver, Colorado, USA. Emerg Infect Dis 2012;18(2):208-16.

9. Pedro-Botet ML, Burgos J, Lujan M, et al. Impact of the 2009 influenza A H1N1 pandemic on invasive pneumococcal disease in adults. Scand J Infect Dis 2014;46(3):185-92.

10. Weinberger DM, Simonsen L, Jordan R, et al. Impact of the 2009 influenza pandemic on pneumococcal pneumonia hospitalizations in the United States. J Infect Dis 2012;205(3):458-65.

11. Allard R, Couillard M, Pilon P, et al. Invasive bacterial infections following influenza: a time-series analysis in Montreal, Canada, 1996-2008. Influenza other respi 2012;6(4):268-75.

12. Ampofo K, Bender J, Sheng X, et al. Seasonal invasive pneumococcal disease in children: role of preceding respiratory viral infection. Pediatrics 2008;122(2):229-37.

13. Burgos J, Larrosa MN, Martinez A, et al. Impact of influenza season and environmental factors on the clinical presentation and outcome of invasive pneumococcal disease. Eur J Clin Microbiol Infect Dis 2015;34(1):177-86.

14. Ciruela P, Broner S, Izquierdo C, et al. Invasive pneumococcal disease rates linked to meteorological factors and respiratory virus circulation (Catalonia, 2006-2012). BMC Public Health 2016;16(400).

15. Dangor Z, Izu A, Moore DP, et al. Temporal association in hospitalizations for tuberculosis, invasive pneumococcal disease and influenza virus illness in South African children. PLoS ONE 2014;9(3):e91464.
16. Domenech de Cellès M, Arduin H, Varon E, et al. Characterizing and Comparing the Seasonality of Influenza-Like Illnesses and Invasive Pneumococcal Diseases Using Seasonal Waveforms. Am J Epidemiol 2017:kwx336-kwx36.
17. Edwards LJ, Markey PG, Cook HM, et al. The relationship between influenza and invasive pneumococcal disease in the Northern Territory, 2005-2009. Med J Aust 2011;194(4):207.
18. Grabowska K, Hogberg L, Penttinen P, et al. Occurrence of invasive pneumococcal disease and number of excess cases due to influenza. BMC Infect Dis 2006;6:58.
19. Hendriks W, Boshuizen H, Dekkers A, et al. Temporal cross-correlation between influenza-like illnesses and invasive pneumococcal disease in The Netherlands. Influenza and other Respiratory Viruses 2017;11(2):130-37.
20. Jansen AG, Sanders EA, A VDE, et al. Invasive pneumococcal and meningococcal disease: association with influenza virus and respiratory syncytial virus activity? Epidemiol Infect 2008;136(11):1448-54.
21. Kim PE, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses. Clin Infect Dis 1996;22(1):100-6.
22. Kuster SP, Tuite AR, Kwong JC, et al. Evaluation of coseasonality of influenza and invasive pneumococcal disease: results from prospective surveillance. PLoS Med 2011;8(6):e1001042.
23. Murdoch DR, Jennings LC. Association of respiratory virus activity and environmental factors with the incidence of invasive pneumococcal disease. J Infect 2009;58(1):37-46.
24. Nicoli EJ, Trotter CL, Turner KM, et al. Influenza and RSV make a modest contribution to invasive pneumococcal disease incidence in the UK. J Infect 2013;66(6):512-20.
25. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. Clin Infect Dis 2000;30(5):784-9.
26. Opatowski L, Varon E, Dupont C, et al. Assessing pneumococcal meningitis association with viral respiratory infections and antibiotics: insights from statistical and mathematical models. Proc Biol Sci 2013;280(1764):20130519.
27. Peltola V, Heikkinen T, Ruuskanen O, et al. Temporal association between rhinovirus circulation in the community and invasive pneumococcal disease in children. Pediatr Infect Dis J 2011;30(6):456-61.

28. Shrestha S, Foxman B, Weinberger DM, et al. Identifying the interaction between influenza and pneumococcal pneumonia using incidence data. Sci Transl Med 2013;5(191):191ra84.

29. Stensballe LG, Hjuler T, Andersen A, et al. Hospitalization for respiratory syncytial virus infection and invasive pneumococcal disease in Danish children aged <2 years: a population-based cohort study. Clin Infect Dis 2008;46(8):1165-71.

30. Talbot TR, Poehling KA, Hartert TV, et al. Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation. Am J Med 2005;118(3):285-91.

31. Toschke AM, Arenz S, von Kries R, et al. No temporal association between influenza outbreaks and invasive pneumococcal infections. Arch Dis Child 2008;93(3):218-20.

32. Walter ND, Taylor TH, Shay DK, et al. Influenza circulation and the burden of invasive pneumococcal pneumonia during a non-pandemic period in the United States. Clin Infect Dis 2010;50(2):175-83.

33. Watson M, Gilmour R, Menzies R, et al. The association of respiratory viruses, temperature, and other climatic parameters with the incidence of invasive pneumococcal disease in Sydney, Australia. Clin Infect Dis 2006;42(2):211-5.

34. Weinberger DM, Grant LR, Steiner CA, et al. Seasonal drivers of pneumococcal disease incidence: impact of bacterial carriage and viral activity.[Erratum appears in Clin Infect Dis. 2014 Mar;58(6):908]. Clin Infect Dis 2014;58(2):188-94.

35. Weinberger DM, Harboe ZB, Viboud C, et al. Serotype-specific effect of influenza on adult invasive pneumococcal pneumonia. J Infect Dis 2013;208(8):1274-80.

36. Weinberger DM, Harboe ZB, Viboud C, et al. Pneumococcal disease seasonality: incidence, severity and the role of influenza activity. Eur Respir J 2014;43(3):833-41.

37. Weinberger DM, Klugman KP, Steiner CA, et al. Association between respiratory syncytial virus activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. PLoS Med 2015;12(1):e1001776.

38. Zhou H, Haber M, Ray S, et al. Invasive pneumococcal pneumonia and respiratory virus co-infections. Emerg Infect Dis 2012;18(2):294-7.

39. McCullers JA, Rehg JE. Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor. J Infect Dis 2002;186(3):341-50.

40. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection. Nat Med 2008;14(5):558-64.

41. Simell B, Auranen K, Käyhty H, et al. The fundamental link between pneumococcal carriage and disease. Expert Rev Vaccines 2012;11(7):841-55.

42. Song JY, Nahm MH, Cheong HJ, et al. Impact of preceding flu-like illness on the serotype distribution of pneumococcal pneumonia. PLoS ONE 2014;9(4):e93477.

43. Shiri T, Datta S, Madan J, et al. Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a systematic review and meta-analysis. The Lancet Global Health 2017;5(1):e51-e59.

44. Walter ND, Taylor THJ, Dowell SF, et al. Holiday Spikes in Pneumococcal Disease among Older Adults. N Engl J Med 2009;361(26):2584-85.

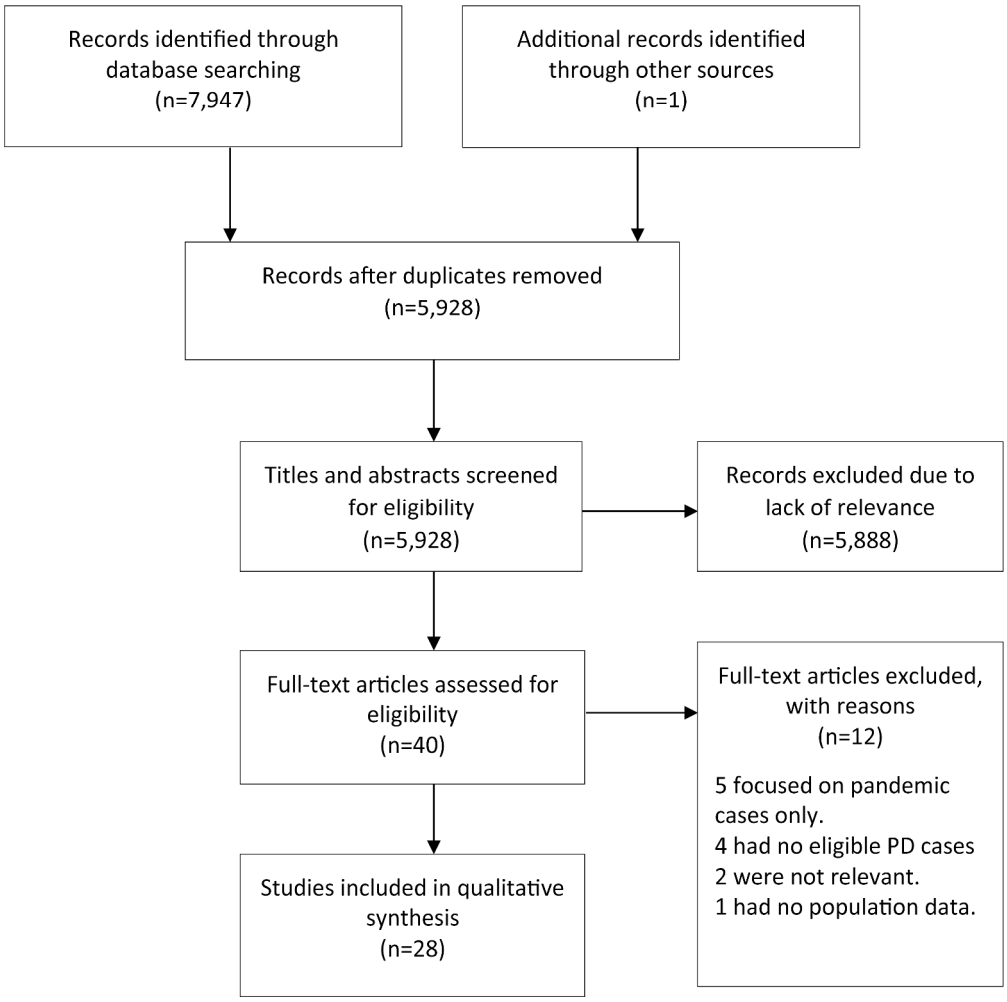

Figure 1. PRISMA flow diagram of the literature search. PD: pneumococcal disease.

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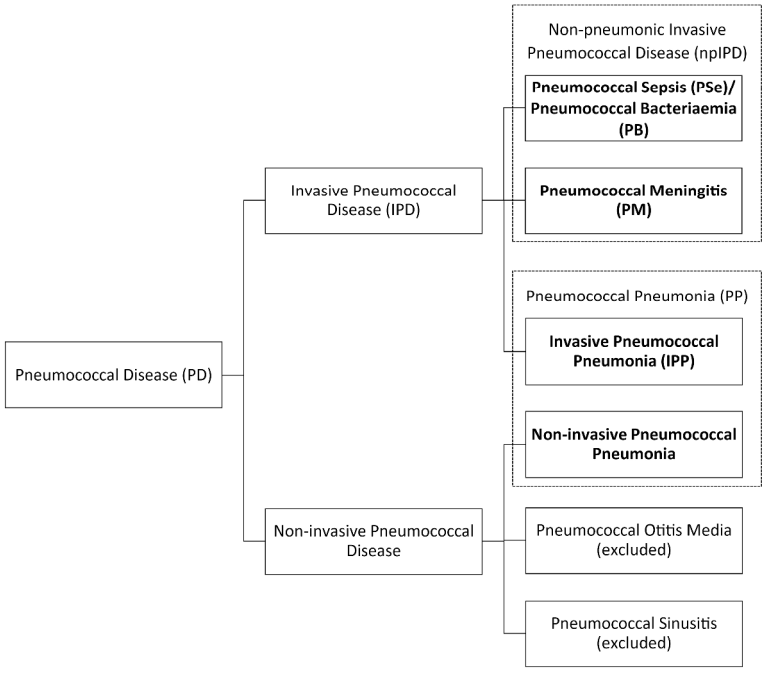

Figure 2. Category of pneumococcal disease in the present review.

391x289mm (300 x 300 DPI)

Table S1. Summary of findings from animal and in vitro studies.

Study	Material	Exposure	Main findings
Diavatopoulos et al. 2010[1]	Mice (n=~10 per group)	influenza A + pneumococcus (3d later)	On day 3 of pneumococcus challenge, pneumococcus numbers increased in the nasopharynx (50-fold, P=0.0002) and the lungs (300-fold, P=0.0005) in influenza A group, compared with mock-treated group; transmission of pneumococcus between littermates was dependent on infection with influenza A.
Hament et al. 2004[2]	Monolayers of human nasopharyngeal cells and pneumocyte type II cells	RSV + pneumococcus	After RSV infection of the monolayers, an increased adherence (2–10 fold) was observed among all serotypes compared with uninfected monolayers.
Hament et al. 2005[3]	Mice (n=7 per group)	RSV + pneumococcus (0 or 4d later)	At 24h of pneumococcus challenge, mice infected with RSV 0 or 4d before pneumococcus challenge had higher levels of bacteremia than control group.
Kukavica-Ibrulj et al. 2009[4]	Mice (n=18 per group)	hMPV/ influenza A + pneumococcus (5d later)	Pneumococcus numbers on day 7 of pneumococcus challenge: 5×10^2 CFU/lung in mock infection, 10^7 CFU/lung in hMPV group and 10^8 CFU/lung in influenza A group.

Study	Material	Exposure	Main findings
LeVine et al. 2001[5]	Mice (n=3 per group)	influenza A + pneumococcus (7d later)	Lungs of influenza-exposed mice demonstrated greater colony counts 24h and 48h following pneumococcus challenge.
Ludewick et al. 2011[6]	Mice (n=18 per group)	hMPV/ influenza A + pneumococcus (14d later)	Only mice infected with influenza A demonstrated an 8% weight loss 72h following pneumococcus challenge while hMPV group and mock group did not.
McCullers et al. 2002[7]	Mice (n=20 per group)	influenza A + pneumococcus (0 or 7d later)	60% of mice died 2–11d after pneumococcus challenge in influenza A group compared with 15% in mock group; reversal of the order of challenge led to protection from influenza; challenge of influenza and pneumococcus on the same day led to 100% mortality.
McCullers et al. 2010[8]	Ferrets (n=5 per group) and Mice (n=~5 per group)	influenza A + pneumococcus (7d later)	Prior influenza infection enhanced pneumococcal transmission and disease; the influenza-mediated effects were pneumococcal strain dependent.
Sharma-Chawla et al. 2016[9]	Mice (n=3–5 per group)	influenza A + pneumococcus T4, 19F or 7F (7d later)	Pneumococcal coinfection during the acute phase of influenza A infection increased degree of pneumonia and mortality for all tested pneumococcal strains. However, the incidence and kinetics of systemic dissemination remained strain dependent.

Study	Material	Exposure	Main findings
Smith et al. 2014[10]	Human ciliated respiratory epithelial cells and mice (n=10 per group)	RSV + pneumococcus	Following incubation with RSV, pneumococcus demonstrated a significant increase in the inflammatory response and bacterial adherence to human ciliated epithelial cultures and increased virulence in mice model.
Stark et al. 2006[11]	Mice (n>12 per group)	RSV + pneumococcus (7d later)	Pneumococcus numbers at 24h of pneumococcus challenge: 7.45×10^5 CFU/lung in RSV group, 5.9×10^3 CFU/lung in mock group.

The number in brackets in the column Material refers to the number of animals observed under each experiment condition; number of animals used in transmission models (used by some studies) were not displayed.

Abbreviations: CFU, colony-forming units; d, day(s); h, hour(s); hMPV, human metapneumovirus; RSV, respiratory syncytial virus.

Reference

1. Diavatopoulos DA, Short KR, Price JT, et al. Influenza A virus facilitates Streptococcus pneumoniae transmission and disease. Faseb J 2010;24(6):1789-98.

2. Hament J-M, Aerts PC, Fleer A, et al. Enhanced Adherence of Streptococcus pneumoniae to Human Epithelial Cells Infected with Respiratory Syncytial Virus. Pediatr Res 2004;55(6):972-78.

3. Hament JM, Aerts PC, Fleer A, et al. Direct binding of respiratory syncytial virus to pneumococci: a phenomenon that enhances both pneumococcal adherence to human epithelial cells and pneumococcal invasiveness in a murine model. Pediatr Res 2005;58(6):1198-203.

4. Kukavica-Ibrulj I, Hamelin ME, Prince GA, et al. Infection with human metapneumovirus predisposes mice to severe pneumococcal pneumonia. J Virol 2009;83(3):1341-9.

5. LeVine AM, Koeningsknecht V, Stark JM. Decreased pulmonary clearance of S. pneumoniae following influenza A infection in mice. J Virol Methods 2001;94(1-2):173-86.

6. Ludewick HP, Aerts L, Hamelin ME, et al. Long-term impairment of Streptococcus pneumoniae lung clearance is observed after initial infection with influenza A virus but not human metapneumovirus in mice. J Gen Virol 2011;92(Pt 7):1662-5.

7. McCullers JA, Rehg JE. Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor. J Infect Dis 2002;186(3):341-50.

8. McCullers JA, McAuley JL, Browall S, et al. Influenza enhances susceptibility to natural acquisition of and disease due to Streptococcus pneumoniae in ferrets. J Infect Dis 2010;202(8):1287-95.

9. Sharma-Chawla N, Sender V, Kershaw O, et al. Influenza A virus infection predisposes hosts to secondary infection with different Streptococcus pneumoniae serotypes with similar outcome but serotype-specific manifestation. Infection and Immunity 2016;84(12):3445-57.

10. Smith CM, Sandrini S, Datta S, et al. Respiratory syncytial virus increases the virulence of Streptococcus pneumoniae by binding to penicillin binding protein 1a. A new paradigm in respiratory infection. Am J Respir Crit Care Med 2014;190(2):196-207.

11. Stark JM, Stark MA, Colasurdo GN, et al. Decreased bacterial clearance from the lungs of mice following primary respiratory syncytial virus infection. J Med Virol 2006;78(6):829-38.

Table S2 Summary of methodologies utilised in the included studies (n=28)

Study	All VARI lab-confirmed	Exposure			Outcome				Data		Analysis at POP level			Seasonality Adjustment
		IFV	RSV	Others	PD	IPD	PP	Others	IDNV	POP	CORR	REGR	Others	
Allard et al. 2012[1]	Yes, multiple methods	✓				✓				✓		✓		✓
Ampofo et al. 2008[2]	Yes, IF and culture	✓	✓	✓		✓				✓	✓			
Burgos et al. 2015[3]	Yes, IF and PCR	✓				✓				✓	✓	✓		✓
Ciruela et al. 2016[4]	Yes, multiple methods	✓	✓	✓		✓				✓	✓	✓		✓
Dangor et al. 2014[5]	Yes, IF and culture	✓				✓				✓			✓	
Domenech de Cellès et al. 2017[6]	No	✓				✓				✓		✓	✓	✓
Edwards et al. 2011[7]	Yes, method not known	✓				✓			✓					
Grabowska et al. 2006[8]	Yes, multiple methods	✓				✓				✓		✓		✓
Hendriks et al. 2017[9]	No	✓				✓				✓			✓	✓
Jansen et al. 2008[10]	Yes, multiple methods	✓	✓			✓		✓		✓	✓			
Kim et al. 1996[11]	Yes, culture	✓	✓	✓		✓				✓	✓			
Kuster et al. 2011[12]	Yes, culture and DAT	✓				✓				✓		✓	✓	✓
Murdoch et al. 2009[13]	Yes, IF and culture	✓	✓	✓		✓				✓	✓	✓		✓
Nicoli et al. 2013[14]	Yes, multiple methods	✓	✓			✓				✓	✓	✓		✓
O'Brien et al. 2000[15]	Yes, serology	✓					✓		✓					✓
Opatowski et al. 2013[16]	No			✓				✓		✓		✓	✓	✓
Peltola et al. 2011[17]	Yes, multiple methods	✓	✓	✓		✓				✓	✓			
Shrestha et al. 2013[18]	No	✓					✓			✓			✓	
Stensballe et al. 2008[19]	No		✓	✓		✓			✓	✓	✓			
Talbot et al. 2005[20]	Yes, culture and RAT	✓	✓			✓				✓	✓			
Toschke et al. 2008[21]	Yes, PCR	✓				✓				✓			✓	
Walter et al. 2010[22]	Yes, method not known	✓				✓		✓		✓		✓		✓
Watson et al. 2006[23]	Yes, DAT	✓	✓	✓		✓				✓	✓			
Weinberger et al. 2014[24]	No	✓	✓			✓		✓		✓		✓		✓
Weinberger et al. 2013[25]	No	✓						✓		✓		✓		✓
Weinberger et al. 2014[26]	No	✓				✓	✓			✓		✓		✓
Weinberger et al. 2015[27]	No	✓	✓		✓		✓	✓		✓		✓		✓
Zhou et al. 2012[28]	Yes, method not known	✓	✓							✓		✓		✓

CORR, correlation; DAT, direct antigen test; IF, immunofluorescence; IFV, influenza virus; INDV, individual; IPD, invasive pneumococcal disease; PCR, polymerase chain reaction; PD, pneumococcal disease; POP, population; PP, pneumococcal pneumonia; REGR, regression; RAT, rapid antigen test; RSV, respiratory syncytial virus; VARI, viral acute respiratory infection.

Reference

1. Allard R, Couillard M, Pilon P, et al. Invasive bacterial infections following influenza: a time-series analysis in Montreal, Canada, 1996-2008. Influenza other respi 2012;6(4):268-75.
2. Ampofo K, Bender J, Sheng X, et al. Seasonal invasive pneumococcal disease in children: role of preceding respiratory viral infection. Pediatrics 2008;122(2):229-37.
3. Burgos J, Larrosa MN, Martinez A, et al. Impact of influenza season and environmental factors on the clinical presentation and outcome of invasive pneumococcal disease. Eur J Clin Microbiol Infect Dis 2015;34(1):177-86.
4. Ciruela P, Broner S, Izquierdo C, et al. Invasive pneumococcal disease rates linked to meteorological factors and respiratory virus circulation (Catalonia, 2006-2012). BMC Public Health 2016;16(400).
5. Dangor Z, Izu A, Moore DP, et al. Temporal association in hospitalizations for tuberculosis, invasive pneumococcal disease and influenza virus illness in South African children. PLoS ONE 2014;9(3):e91464.
6. Domenech de Cellès M, Arduin H, Varon E, et al. Characterizing and Comparing the Seasonality of Influenza-Like Illnesses and Invasive Pneumococcal Diseases Using Seasonal Waveforms. Am J Epidemiol 2017:kwx336-kwx36.
7. Edwards LJ, Markey PG, Cook HM, et al. The relationship between influenza and invasive pneumococcal disease in the Northern Territory, 2005-2009. Med J Aust 2011;194(4):207.
8. Grabowska K, Hogberg L, Penttinen P, et al. Occurrence of invasive pneumococcal disease and number of excess cases due to influenza. BMC Infect Dis 2006;6:58.
9. Hendriks W, Boshuizen H, Dekkers A, et al. Temporal cross-correlation between influenza-like illnesses and invasive pneumococcal disease in The Netherlands. Influenza and other Respiratory Viruses 2017;11(2):130-37.
10. Jansen AG, Sanders EA, A VDE, et al. Invasive pneumococcal and meningococcal disease: association with influenza virus and respiratory syncytial virus activity? Epidemiol Infect 2008;136(11):1448-54.
11. Kim PE, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses. Clin Infect Dis 1996;22(1):100-6.
12. Kuster SP, Tuite AR, Kwong JC, et al. Evaluation of coseasonality of influenza and invasive pneumococcal disease: results from prospective surveillance. PLoS Med 2011;8(6):e1001042.
13. Murdoch DR, Jennings LC. Association of respiratory virus activity and environmental factors with the incidence of invasive pneumococcal disease. J Infect 2009;58(1):37-46.
14. Nicoli EJ, Trotter CL, Turner KM, et al. Influenza and RSV make a modest contribution to invasive pneumococcal disease incidence in the UK. J Infect 2013;66(6):512-20.
15. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection. Clin Infect Dis 2000;30(5):784-9.
16. Opatowski L, Varon E, Dupont C, et al. Assessing pneumococcal meningitis association with viral respiratory infections and antibiotics: insights from statistical and mathematical models. Proc Biol Sci 2013;280(1764):20130519.
17. Peltola V, Heikkinen T, Ruuskanen O, et al. Temporal association between rhinovirus circulation in the community and invasive pneumococcal disease in children. Pediatr Infect Dis J 2011;30(6):456-61.
18. Shrestha S, Foxman B, Weinberger DM, et al. Identifying the interaction between influenza and pneumococcal pneumonia using incidence data. Sci Transl Med 2013;5(191):191ra84.
19. Stensballe LG, Hjuler T, Andersen A, et al. Hospitalization for respiratory syncytial virus infection and invasive pneumococcal disease in Danish children aged <2 years: a population-based cohort study. Clin Infect Dis 2008;46(8):1165-71.
20. Talbot TR, Poehling KA, Hartert TV, et al. Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation. Am J Med 2005;118(3):285-91.

21. Toschke AM, Arenz S, von Kries R, et al. No temporal association between influenza outbreaks and invasive pneumococcal infections. Arch Dis Child 2008;93(3):218-20.
22. Walter ND, Taylor TH, Shay DK, et al. Influenza circulation and the burden of invasive pneumococcal pneumonia during a non-pandemic period in the United States. Clin Infect Dis 2010;50(2):175-83.
23. Watson M, Gilmour R, Menzies R, et al. The association of respiratory viruses, temperature, and other climatic parameters with the incidence of invasive pneumococcal disease in Sydney, Australia. Clin Infect Dis 2006;42(2):211-5.
24. Weinberger DM, Grant LR, Steiner CA, et al. Seasonal drivers of pneumococcal disease incidence: impact of bacterial carriage and viral activity.[Erratum appears in Clin Infect Dis. 2014 Mar;58(6):908]. Clin Infect Dis 2014;58(2):188-94.
25. Weinberger DM, Harboe ZB, Viboud C, et al. Serotype-specific effect of influenza on adult invasive pneumococcal pneumonia. J Infect Dis 2013;208(8):1274-80.
26. Weinberger DM, Harboe ZB, Viboud C, et al. Pneumococcal disease seasonality: incidence, severity and the role of influenza activity. Eur Respir J 2014;43(3):833-41.
27. Weinberger DM, Klugman KP, Steiner CA, et al. Association between respiratory syncytial virus activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. PLoS Med 2015;12(1):e1001776.
28. Zhou H, Haber M, Ray S, et al. Invasive pneumococcal pneumonia and respiratory virus co-infections. Emerg Infect Dis 2012;18(2):294-7.

Text S1. Search strategy

Medline

1. Meningitis, Pneumococcal/ or Pneumonia, Pneumococcal/ or exp Pneumococcal Infections/ or pneumococc*.mp.

2. exp Streptococcus pneumoniae/ or Streptococcus pneumoniae.mp.

3. virus.mp. or exp Viruses/

4. exp Virus Diseases/ or virus disease*.mp.

5. correlat*.mp.

6. associat*.mp.

7. interact*.mp.

8. relat*.mp.

9. 1 or 2

10. 3 or 4

11. 5 or 6 or 7 or 8

12. 9 and 10 and 11

13. limit 12 to yr="1990 -Current"

1,664 results by 27 Apr 2017

1,888 results by 31 Dec 2017

EMbase

1. exp pneumococcal infection/ or pneumococc*.mp.

2. Streptococcus pneumoniae.mp. or exp Streptococcus pneumoniae/

3. exp virus/ or virus*.mp.

4. exp virus infection/ or virus infection*.mp. or virus disease*.mp.

5. exp correlational study/ or exp correlation analysis/ or correlat*.mp.

6. associat*.mp.

7. interact*.mp.

8. relat*.mp.

9. 1 or 2

10. 3 or 4

11. 5 or 6 or 7 or 8

12. 9 and 10 and 11

13. limit 12 to yr="1990 -Current"

4,778 results by 27 Apr 2017.

5,098 results by 31 Dec 2017.

Global Health

1. Streptococcus pneumoniae.mp. or exp Streptococcus pneumoniae/

2. pneumococc*.mp.

3. virus*.mp. or viruses/

4. virus disease*.mp. or viral diseases.sh. or virus infection*.mp.

5. exp correlation/ or correlation analysis/ or correlat*.mp.

6. associat*.mp.

7. interact*.mp.

8. relat*.mp.

9. 1 or 2

10. 3 or 4

11. 5 or 6 or 7 or 8

12. 9 and 10 and 11

13. limit 12 to yr="1990 -Current"

1,164 results by 27 Apr 2017

961 results by 31 Dec 2017

Study information				Inclusion		Quality Assessment								
ID	First Author	Year	Title	Inclusion	Reason for Exclusion	Did the study address a clearly focused issue?	Were the subjects recruited in an acceptable way?	Was the exposure accurately measured to minimise bias?	Was the outcome accurately measured to minimise bias?	Have the authors identified all important confounding factors (e.g. seasonal factors)	Have the authors taken account of the confounding factors in the design and/or analysis (e.g. seasonal factors)	Were the results reliable?	Can the results be applied to the local population	Do the results of this study fit with other available evidence?
H37	Allard, R	2012	Invasive bacterial infections follo	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H1	Ampofo, K	2008	Seasonal invasive pneumococca	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H2	Burgos, J	2015	Impact of influenza season and	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H38	Ciruela, P	2016	Invasive pneumococcal disease	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H3	Dangor, Z	2014	Temporal association in hospita	yes		Yes	Yes	Yes	Yes	No	No	No	No	Yes
H40	Domenech de Cellès, M	2017	Characterizing and Comparing t	yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
H4	Dominguez, A	2013	Benefit of conjugate pneumoco	no	no PD case	NA	NA	NA	NA	NA	NA	NA	NA	NA
H5	Edwards, LJ	2011	The relationship between influe	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H6	Eshaghi, A	2009	Infection with H274Y-positive in	no	no PD case	NA	NA	NA	NA	NA	NA	NA	NA	NA
H7	Fleming-Dutra, KE	2013	Effect of the 2009 influenza A(H	no	pandemic	NA	NA	NA	NA	NA	NA	NA	NA	NA
H8	Grabowska, K	2006	Occurrence of invasive pneumo	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H9	Grijalva, CG	2014	The role of influenza and parain	no	no PD case	NA	NA	NA	NA	NA	NA	NA	NA	NA
H39	Hendriks, W.	2017	Temporal cross-correlation betv	yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
H10	Jansen, AG	2008	Invasive pneumococcal and me	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H11	Kim, PE	1996	Association of invasive pneumo	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H12	Kuster, SP	2011	Evaluation of coseasonality of in	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H13	Launes, C	2014	Respiratory viruses, such as 200	no	pandemic	NA	NA	NA	NA	NA	NA	NA	NA	NA
H14	Madhi, SA	2004	A role for Streptococcus pneum	no	topic not r	NA	NA	NA	NA	NA	NA	NA	NA	NA
H15	Muhlemann, K	2006	The prevalence of penicillin-non	no	no PD case	NA	NA	NA	NA	NA	NA	NA	NA	NA
H16	Murdoch, DR	2009	Association of respiratory virus	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H17	Nelson, GE	2012	Invasive pneumococcal disease	no	pandemic	NA	NA	NA	NA	NA	NA	NA	NA	NA
H36	Nicoli, EJ	2013	Influenza and RSV make a mode	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H18	O'Brien, KL	2000	Severe pneumococcal pneumon	yes		Yes	Yes	No	No	Yes	Yes	Not sure	Not sure	Yes
H19	Opatowski, L	2013	Assessing pneumococcal mening	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H20	Pedro-Botet, ML	2014	Impact of the 2009 influenza A H	no	pandemic	NA	NA	NA	NA	NA	NA	NA	NA	NA
H21	Peltola, V	2011	Temporal association between r	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H22	Shrestha, S	2013	Time and dose-dependent risk c	no	no populat	NA	NA	NA	NA	NA	NA	NA	NA	NA
H23	Shrestha, S	2013	Identifying the interaction betw	yes		Yes	Yes	Not sure	Yes	No	No	Yes	Yes	Yes
H24	Stensballe, LG	2008	Hospitalization for respiratory s	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H25	Talbot, TR	2005	Seasonality of invasive pneumo	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H26	Toschke, AM	2008	No temporal association betwe	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H27	Walter, ND	2010	Influenza circulation and the bu	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H28	Watson, M	2006	The association of respiratory vi	yes		Yes	Yes	No	Yes	No	No	Yes	Yes	Yes
H29	Weinberger, DM	2014	Seasonal drivers of pneumococ	yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
H30	Weinberger, DM	2013	Serotype-specific effect of influe	yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
H31	Weinberger, DM	2014	Pneumococcal disease seasonal	yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
H32	Weinberger, DM	2015	Association between respirator	yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
H33	Weinberger, DM	2012	Impact of the 2009 influenza pa	no	pandemic	NA	NA	NA	NA	NA	NA	NA	NA	NA
H34	Yoon, YK	2014	Impact of preceding respiratory	no	topic not r	NA	NA	NA	NA	NA	NA	NA	NA	NA
H35	Zhou, H	2012	Invasive pneumococcal pneumo	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4-5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4-5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Text S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6-23
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	6-23, File S3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	6-23
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	23-24
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	23-28
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	28
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	29

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Give the working title of the review, for example the one used for obtaining funding. Ideally the title should state succinctly the interventions or exposures being reviewed and the associated health or social problems. Where appropriate, the title should use the PI(E)COS structure to contain information on the Participants, Intervention (or Exposure) and Comparison groups, the Outcomes to be measured and Study designs to be included.

Association of seasonal viral acute respiratory infection (VARI) with pneumococcal disease (PD): a systematic review of population-based studies

2. Original language title.

For reviews in languages other than English, this field should be used to enter the title in the language of the review. This will be displayed together with the English language title.

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The review has not yet started: No

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Provide any other relevant information about the stage of the review here (e.g. Funded proposal, protocol not yet finalised).

6. * Named contact.

The named contact acts as the guarantor for the accuracy of the information presented in the register record.

You Li

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

7. * Named contact email.

Give the electronic mail address of the named contact.

You.Li2@ed.ac.uk

8. Named contact address

Give the full postal address for the named contact.

3.730 Doorway 1, Old Medical School
Teviot Place
Edinburgh
UK

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.

+44 (0)7871 566188

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

The University of Edinburgh

Organisation web address:

www.ed.ac.uk

11. Review team members and their organisational affiliations.

Give the title, first name, last name and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong.

Mr You Li. The University of Edinburgh
Ms Meagan Peterson. The University of Edinburgh
Professor Harish Nair. The University of Edinburgh
Professor Harry Campbell. The University of Edinburgh

12. * Funding sources/sponsors.

Give details of the individuals, organizations, groups or other legal entities who take responsibility for initiating, managing, sponsoring and/or financing the review. Include any unique identification numbers assigned to the review by the individuals or bodies listed.

None

13. * Conflicts of interest.

List any conditions that could lead to actual or perceived undue influence on judgements concerning the main topic investigated in the review.

None

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members.

15. * Review question.

State the question(s) to be addressed by the review, clearly and precisely. Review questions may be specific or broad. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS where relevant.

What methods have been used in population-based studies analysing the association between VARI and subsequent PD?
What results have been reported in population-based studies analysing the association between VARI and subsequent PD?

16. * Searches.

Give details of the sources to be searched, search dates (from and to), and any restrictions (e.g. language or publication period). The full search strategy is not required, but may be supplied as a link or attachment.

We searched three bibliographic databases (MEDLINE, Embase and Global Health) for primary research studies published between 1 January 1990 and 27 April 2017.
An update of the search was done for primary research studies published between 1 January 1990 and 31 December 2017.
No restrictions were placed on the language of publication.

17. URL to search strategy.

Give a link to the search strategy or an example of a search strategy for a specific database if available (including the keywords that will be used in the search strategies).

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied. This could include health and wellbeing outcomes.

Viral acute respiratory infection; pneumococcal disease.

19. * Participants/population.

Give summary criteria for the participants or populations being studied by the review. The preferred format includes details of both inclusion and exclusion criteria.

Population-based studies involving people with viral acute respiratory infection and pneumococcal disease.
Specifically, the following participants were considered:
(1) Those with laboratory confirmed viral infections;
(2) Those with ICD code for influenza and RSV infection;
(3) Those with a case definition of an influenza-like illness (ILI) and bronchiolitis.

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the nature of the interventions or the exposures to be reviewed.

Population-based studies involving people with viral acute respiratory infection and pneumococcal disease.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Not applicable.

22. * Types of study to be included.

Give details of the types of study (study designs) eligible for inclusion in the review. If there are no restrictions on the types of study design eligible for inclusion, or certain study types are excluded, this should be stated. The preferred format includes details of both inclusion and exclusion criteria.

There were no restrictions imposed on the types of study design eligible for inclusion.We included population-based studies involving clinically diagnosed PD cases, and specifically, we accepted the following studies: (1) Those involving laboratory confirmed viral infections; (2) Those involving an ICD code for influenza and RSV infection; (3) Those involving case definitions of an influenza-like illness (ILI) and bronchiolitis. We excluded animal studies and theoretical studies in which no population data was applied. We focused our review on the association of seasonal VARI with PD, and thus excluded studies that reported influenza pandemic cases only.

23. Context.

Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion criteria.

24. * Primary outcome(s).

Give the pre-specified primary (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

The association between VARI and subsequent PD.

Timing and effect measures

25. * Secondary outcome(s).

List the pre-specified secondary (additional) outcomes of the review, with a similar level of detail to that required for primary outcomes. Where there are no secondary outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

Factors that could affect the association between VARI and subsequent PD.

Timing and effect measures

26. Data extraction (selection and coding).

Give the procedure for selecting studies for the review and extracting data, including the number of researchers involved and how discrepancies will be resolved. List the data to be extracted.

27. * Risk of bias (quality) assessment.

State whether and how risk of bias will be assessed (including the number of researchers involved and how

discrepancies will be resolved), how the quality of individual studies will be assessed, and whether and how this will influence the planned synthesis.

Risk of bias will be assessed by evaluating the power of the studies, the measures taken to control for confounders, and any multiple tests made without reasonable correction or justification.
Bias is expected to have little impact on the review because it is intended to provide a summary of all relevant studies, and no quantitative analysis will be conducted.

28. * Strategy for data synthesis.

Give the planned general approach to synthesis, e.g. whether aggregate or individual participant data will be used and whether a quantitative or narrative (descriptive) synthesis is planned. It is acceptable to state that a quantitative synthesis will be used if the included studies are sufficiently homogenous.

A descriptive synthesis is planned. A summary of both the methods and the results of eligible studies will be provided.

29. * Analysis of subgroups or subsets.

Give details of any plans for the separate presentation, exploration or analysis of different types of participants (e.g. by age, disease status, ethnicity, socioeconomic status, presence or absence or co-morbidities); different types of intervention (e.g. drug dose, presence or absence of particular components of intervention); different settings (e.g. country, acute or primary care sector, professional or family care); or different types of study (e.g. randomised or non-randomised).

None planned.

30. * Type and method of review.

Select the type of review and the review method from the lists below. Select the health area(s) of interest for your review.

Type of review

Cost effectiveness
No

Diagnostic
No

Epidemiologic
No

Individual patient data (IPD) meta-analysis
No

Intervention
No

Meta-analysis
No

Methodology
No

Network meta-analysis
No

Pre-clinical
No

Prevention
No

Prognostic
No

Prospective meta-analysis (PMA)
No

Qualitative synthesis
No

Review of reviews
No

Service delivery
No

Systematic review
Yes

Other
No

Health area of the review

Alcohol/substance misuse/abuse
No

Blood and immune system
No

Cancer
No

Cardiovascular
No

Care of the elderly
No

Child health
No

Complementary therapies
No

Crime and justice
No

Dental
No

Digestive system
No

Ear, nose and throat
No

Education
No

Endocrine and metabolic disorders
No

Eye disorders
No

General interest
No

Genetics
No

Health inequalities/health equity
No

Infections and infestations
No

International development
No

Mental health and behavioural conditions

No

Musculoskeletal
No

Neurological
No

Nursing
No

Obstetrics and gynaecology
No

Oral health
No

Palliative care
No

Perioperative care
No

Physiotherapy
No

Pregnancy and childbirth
No

Public health (including social determinants of health)
No

Rehabilitation
No

Respiratory disorders
No

Service delivery
No

Skin disorders
No

Social care
No

Tropical Medicine
No

Urological
No

Wounds, injuries and accidents
No

Violence and abuse
No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error.
English

There is an English language summary.

32. Country.

Select the country in which the review is being carried out from the drop down list. For multi-national collaborations select all the countries involved.

Scotland

PROSPERO
International prospective register of systematic reviews

National Institute for Health Research

33. Other registration details.

Give the name of any organisation where the systematic review title or protocol is registered (such as with The Campbell Collaboration, or The Joanna Briggs Institute) together with any unique identification number assigned. (N.B. Registration details for Cochrane protocols will be automatically entered). If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

Give the citation and link for the published protocol, if there is one

Give the link to the published protocol.

Alternatively, upload your published protocol to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Give brief details of plans for communicating essential messages from the review to the appropriate audiences.

Do you intend to publish the review on completion?

Yes

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords will help users find the review in the Register (the words do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

37. Details of any existing review of the same topic by the same authors.

Give details of earlier versions of the systematic review if an update of an existing review is being registered, including full bibliographic reference if possible.

38. * Current review status.

Review status should be updated when the review is completed and when it is published.

Please provide anticipated publication date

Review_Completed_not_published

39. Any additional information.

Provide any other information the review team feel is relevant to the registration of the review.

40. Details of final report/publication(s).

This field should be left empty until details of the completed review are available.

PROSPERO
International prospective register of systematic reviews

National Institute for Health Research

Give the link to the published review.