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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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3 **1 Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic**
4 **2 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

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3 33 • This is the first review that critically reviewed the methods and the findings of population-
4 based studies that reported an association between VARI and PD.
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7 35 • Results of studies summarised according to study design and methods
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9 36 • No meta-analysis was conducted due to a variety of study designs, data sources and analytical
10 methods in the studies so a narrative summary of the methods and results is provided.
11 37
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13 38 • The review is presented in a manner that would be accessible to a general audience so no
14 detailed statistical techniques are discussed.
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41 Introduction

42 Both viral acute respiratory infection (VARI) and pneumococcal disease (PD) account for a substantial
43 disease burden worldwide, especially in young children.^{1 2 2} The association of viral acute respiratory
44 infection (VARI) and subsequent pneumococcal disease (PD) was not well recognised until the
45 catastrophic 1918 influenza pandemic, which resulted in an estimated 40-50 million deaths;³ it has
46 been suggested that pneumococcus may have been a major cause the deaths.⁴ Most recently, it was
47 observed that the incidence of PD was higher during 2009 influenza H1N1 pandemic period than the
48 same period in pre-pandemic⁵⁻⁹ and post-pandemic years.^{6 8 9}

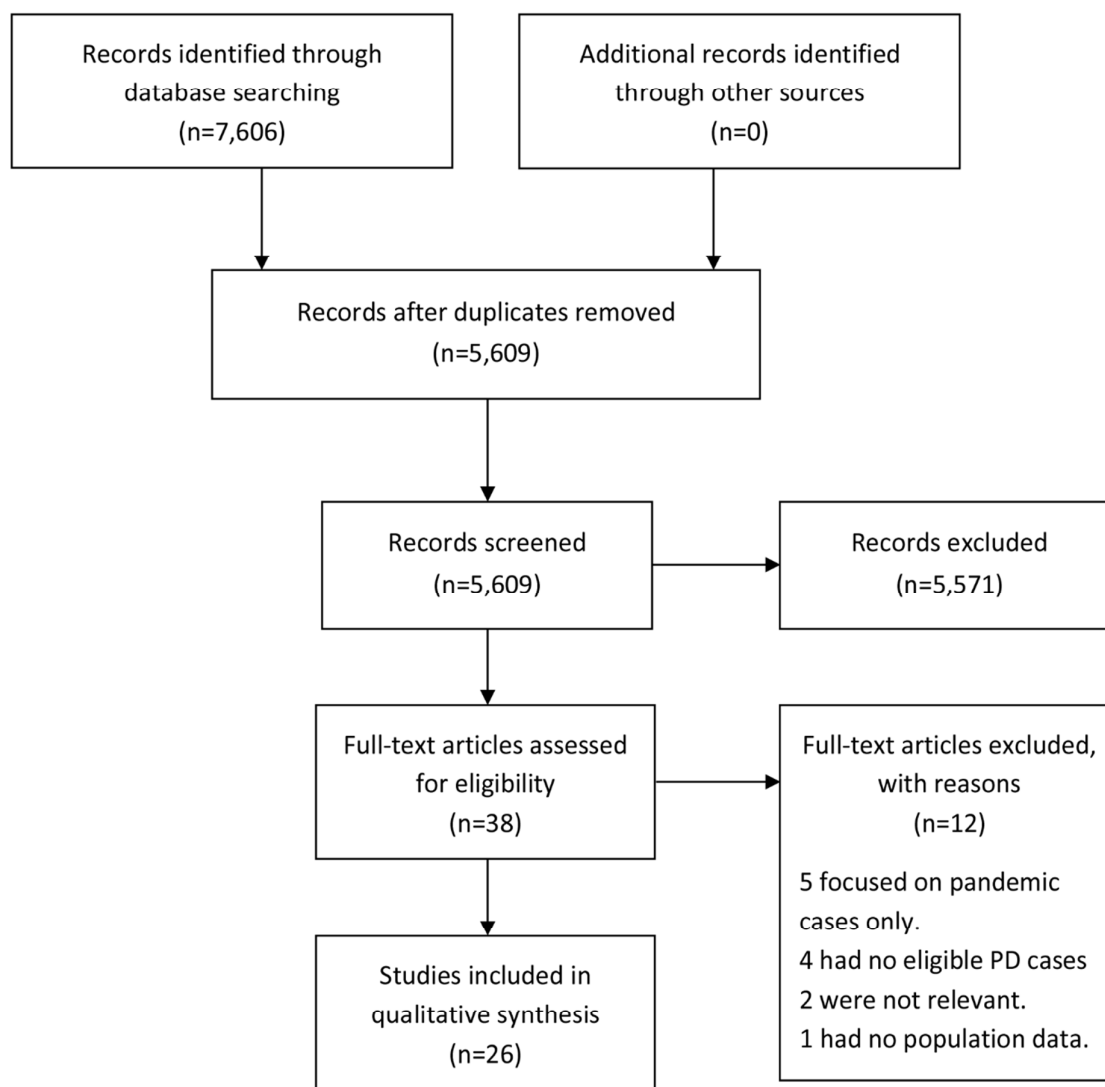
49 During inter-pandemic periods, the associations of seasonal influenza and other seasonal
50 respiratory viruses such as respiratory syncytial virus (RSV), human metapneumovirus (hMPV) and
51 parainfluenza (PIV) with PD incidence are poorly understood and remain unclear. In animal and in-
52 vitro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

62 Methods

63 Search Strategy and Selection Criteria

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

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3 67 clinically diagnosed PD cases (see below for detailed definition). In terms of VARI exposure, we
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5 68 accepted the following studies: (1) those with laboratory confirmed viral infections; (2) those with an
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7 69 ICD code for influenza and/or RSV infection; (3) those with case definition of influenza-like illness (ILI)
8
9 70 and bronchiolitis. We excluded animal studies and theoretical studies where no population data
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11 71 were applied. We focused our review on the association of seasonal VARI and PD and thus excluded
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13 72 studies that reported pandemic influenza cases only. No language restrictions were applied. The
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15 73 reference lists of eligible studies were also checked to identify additional studies for inclusion. The
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17 74 protocol for this systematic review was registered on PROSPERO (registration number:
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19 75 CRD42017064760).
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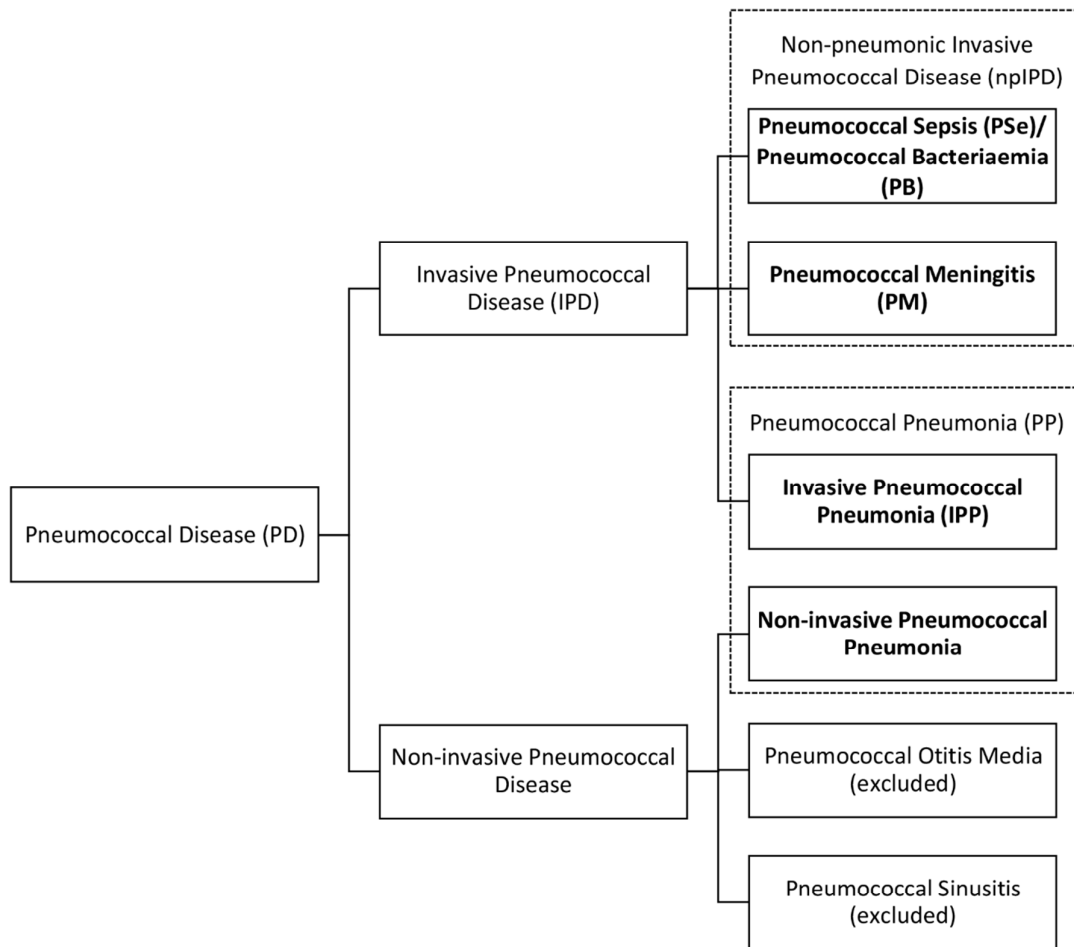


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78 **Figure 1. PRISMA flow diagram of the literature search.** PD: pneumococcal disease.79 **Definitions**

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

88 infection with laboratory-confirmed viral aetiology. We defined ILI as a symptomatic cough and fever
 89 $\geq 38^{\circ}\text{C}$ with onset within 7 days.



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

92 Data Extraction

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

100 Results

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

103 Individual Patient Data Based Studies

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

108 **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]

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

112 **Ecological Studies**

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

117 ***Correlation analyses with no control for seasonal patterns***

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

128 **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	<18y, 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	≥18y 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	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 ¹⁶	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

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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	<u>≥18y</u> 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)
							<u><18y</u> 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	<u>All ages</u> 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	<u>All ages</u> , Pearson IFV: 0.54a RSV: 0.47a <u>All ages</u> , 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	<u><5y</u> 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	<u>All ages</u> RSV: 0.55a non-RSV: 0.65a <u><2y</u> RSV: 0.08
Talbot et al. 2005 ²¹	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)

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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	<18y IFV: not significant RSV: 0.58a PIV: -0.40 ≥18y IFV: not significant RSV: not significant PIV: not significant RSV or IFV: 0.48

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

130 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).

133 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.

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3 136 *Analyses controlling for seasonal patterns*

4 137 **Table 3** shows the summary of 13 studies that controlled for seasonal patterns. Where required, we
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6 138 applied the Bonferroni correction to account for multiple tests. Results were inconsistent among the
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8 139 studies. In all-age population studies, preceding influenza infection was likely to be associated with
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10 140 IPD (11 of 13 studies reported an association). According to two studies that displayed age-stratified
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12 141 results,^{18,19} the association between influenza and IPD was more likely to exist among older people
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14 142 than among young children. In terms of preceding RSV infection, four out of five studies observed an
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16 143 association of RSV with PD incidence. Specifically, one study¹⁵ found the association between RSV
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18 144 and IPD only existed among children <5 years. Studies reporting other viruses such as ADV and PIV
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20 145 were sparse (two and one studies, respectively). Five studies that analysed two or more viruses
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22 146 demonstrated that the association differed by the type of the virus. Moreover, the association could
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24 147 differ among virus subtypes (e.g. influenza A vs influenza B²³ and PIV 1/2 vs PIV 3¹⁸). Notably, there
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26 148 are other factors that could influence the strength of the associations reported in these studies. For
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28 149 instance, the association could vary by presentation of PD (invasive pneumococcal pneumonia, IPP
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30 150 vs nIPD²⁴⁻²⁶ and PP vs pneumococcal sepsis, PSe²⁷). Preceding VARI was more likely to be associated
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32 151 with the occurrence of pneumonia than other clinical presentations. Additionally, the results from
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34 152 studies in Denmark, where comorbidity status and pneumococcal serotype were available,
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36 153 demonstrated that influenza had a greater influence on the incidence of low-invasiveness serotypes
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38 154 than medium- or high- invasiveness among the low comorbidity group; among the high comorbidity
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40 155 group, the pattern was reversed.^{26,28}
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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 >1 7°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	<u>All ages</u> 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)	<u>All ages</u> 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	<u>All ages</u> 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	<u>All ages</u> 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)	

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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, <u>all ages</u> IFV-IPP: 4.9% [4.5–5.3%] (1w) South, <u>all ages</u> IFV-IPP: 5.4%^b [5.0–5.9%] (1w) West, <u>all ages</u> 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)

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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	<p>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)</p> <p>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)</p> <p>≥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)</p> <p>≥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)</p>	

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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.	

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

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

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160 pneumococcal conjugate vaccine; PD, pneumococcal disease; PIV, parainfluenza virus; PP, pneumococcal pneumonia; PSe, pneumococcal sepsis; RR,
161 relative risk; RSV, respiratory syncytial virus; UV index, clear-sky ultraviolet index; VARI, viral acute respiratory infection; w, week(s); y, year(s).
162 Relative risk or attributable percentage **in bold** were statistically significant ($P < 0.05$); relative risk or attributable percentage ending with “a” were
163 statistically significant after Bonferroni adjustment ($P < 0.05/\text{number of relevant tests}$) or when the Bonferroni correction was deemed unnecessary, those
164 ending with “b” did not have enough information to apply the Bonferroni correction.

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166 **Studies utilising other analyses**

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

170 **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.

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

174 Discussion

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

178 We found that reported associations between VARI and subsequent PD were inconsistent among
 179 the 26 included studies. Only three studies¹⁰⁻¹² analysed the association using individual patient data.
 180 These studies did not account for the shared risk factors between VARI and PD that influenced their
 181 seasonality, such as temperature, length of sunshine and amount of rainfall, substantially limiting
 182 the inferences that can be made from these data. In ecological studies, only 13 of the 23 ecological
 183 studies accounted for seasonal patterns. In these studies, we found that influenza and/or RSV
 184 infections were likely to be associated with the subsequent occurrence of PD. For influenza, the
 185 association was stronger among younger populations compared to older adults^{18 19} while the pattern
 186 was reversed for RSV.¹⁵ Data from multiple studies suggested that virus type (five studies) and
 187 subtype (two studies), comorbidity status (two studies) and pneumococcal serotype invasiveness
 188 (one study) could influence the association. However, the 13 ecological studies had various
 189 population characteristics (e.g. age, comorbidity, immunity status), PD datasets, VARI datasets and

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3 190 analytical methods. As such, heterogeneity among the studies, along with their ecological nature,
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5 191 limits the amount of valid inferences that can be made from the data (as summarised above).
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7 192 Nevertheless, these studies provide important clues for the potential factors related to the
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9 193 association between VARI and subsequent PD, and thus could help with the conception and design
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11 194 of future studies. Ideally, in order to understand whether a particular preceding VARI can predispose
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13 195 an individual to PD, a prospective cohort study that monitors each individual for VARI and
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15 196 pneumococcal infection would be utilised, allowing analyses at both individual and population levels.
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17 197 However, such a design would not be feasible or affordable as inter alia pneumococcal infections are
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19 198 rare. Alternatively, utilisation of large-scale routine health data and reliable data linkage (through
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21 199 unique individual identifiers) from sources such as surveillance data and hospitalisation datasets may
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23 200 be feasible in many industrialised countries. An example of such data linkage in our review is the
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25 201 study by Stensballe and colleagues¹² that linked information from four Danish population-based
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27 202 registries. While the authors conducted individual-level analysis, the results were based on cases
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29 203 tested for both the presence of respiratory viruses and pneumococcal infection. The true number of
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31 204 VARI-associated PD cases is likely to be significantly higher due to incomplete testing of cases; the
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33 205 untested viral-pneumococcal cases could represent a crucial source of selection bias. Community-
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35 206 based active surveillance can likely address the issue of missing cases but such surveillance would be
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37 207 labour intensive to conduct. Another option is a case-control study, which is affordable and practical,
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39 208 but not without its limitations. In addition to challenges in designing such studies, defining the
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41 209 history of VARI is likely to be inaccurate since the timing of viral serology may be less accurate.²⁰ In
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43 210 the case-control study by O'Brien and colleagues,¹¹ the authors used influenza-strain specific
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45 211 convalescent serology as evidence for preceding influenza infection. The authors also conducted
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47 212 telephone interviews to investigate ILI history but they did not mention whether interviewers and
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49 213 interviewees were blind to case or control status. Moreover, the value of this case-control study is
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51 214 limited by its very small sample size (n case = 13).
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3 215 Compared with individual patient data based studies, ecological studies are more feasible, and
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5 216 thus the most common study design included in our review (23/26). However, the results should be
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7 217 interpreted at a population level and cannot be generalised to the individual level. Since ecological
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9 218 studies used data aggregated into broad categories, the potential biases introduced by the
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11 219 aggregation should be taken into account. For instance, while 14 out of 23 ecological studies used
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13 220 weekly data, others used fortnightly or monthly data. This may lead to misclassification as the time
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15 221 window of the association of VARI on PD susceptibility can be as short as one week.^{36 37} Moreover,
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17 222 data from different sources in ecological studies should represent the same population.

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19 223 Apart from the study design, one further challenge of analysing the association is accounting for
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21 224 the influence of seasonal factors of VARI and PD. Both VARI and PD have similar seasonal patterns,
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23 225 and thus are likely to correlate as indicated by the correlation results from ecological studies. The
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25 226 increased risk of PD during an epidemic season could be caused by VARI or by seasonal risk factors
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27 227 or by both. In the present review, ten ecological studies and all three individual patient data based
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29 228 studies did not attempt to control for seasonal confounders, likely leading to biased estimations of
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31 229 the association. For example, the study by Edwards and colleagues¹⁰ reported a relative risk as high
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33 230 as 112.5 when not adjusting any seasonal factors. One way to address this problem in such studies
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35 231 would be to match the individuals with the onset timing of pneumococcal infection, keeping the risk
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37 232 of PD comparable between VARI cases and non-VARI cases.

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39 233 Our review suggests that the association of VARI and subsequent PD could vary by virus type^{15 18 19}
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41 234^{25 28} and even by subtype^{18 23}. Studies using combinations of viral infections such as all virus, influenza
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43 235 + RSV, non-influenza, or non-RSV could give biased estimations of the association. However, it is not
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45 236 always practical to analyse the association by virus type. In ecological studies, different types of
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47 237 viruses might co-circulate and thus be highly correlated in incidence, making it difficult to determine
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49 238 the role for each virus. In terms of PD, most studies used IPD as the outcome of interest. However,
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51 239 studies that categorised IPD into IPP and npIPD found that the association was more pronounced in
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53 240 IPP than in npIPD.²⁴⁻²⁶ A similar finding, that the association was stronger in PP than PSe, was

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3 241 reported in another study.²⁷ These results suggest VARI is more likely to be associated with
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5 242 pneumonic pneumococcal infections than non-pneumonic infections. In our review, we excluded
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7 243 studies using information other than clinical diagnosis as a proxy for PD (e.g. prescription data and
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9 244 carriage data). Pneumococcal carriage could have a fundamental role in the transmission and
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11 245 incidence of PD.³⁸ In a study analysing the impact of pneumococcal carriage and viral activity,
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13 246 Weinberger and colleagues²⁵ found npIPD was associated with carriage prevalence, whereas IPP was
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15 247 associated with bronchiolitis (as a proxy for RSV). The authors also proposed that preceding VARI
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17 248 increased susceptibility but did not enhance transmission (indicated by carriage prevalence) in
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19 249 children. However, more studies are needed to confirm these findings.

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22 250 The association could also vary by population characteristics. According to two studies that
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24 251 displayed age-stratified results,^{18 19} the association of influenza and subsequent IPD was more likely
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26 252 to exist among older people than among young children. Studies by Weinberger et al.^{26 28} gauged the
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28 253 association in different comorbidity and pneumococcal serotype groups among Denmark
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30 254 populations. The results showed that influenza had a stronger impact on the incidence of low-
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32 255 invasiveness serotypes than medium- or high- invasiveness ones in the low comorbidity group, while
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34 256 the pattern reversed in the high comorbidity group. Another study that analysed clinical records of
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36 257 919 patients with PP found that infrequently colonising pneumococcal serotypes were more likely to
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38 258 cause PP after preceding VARI, particularly in patients with immunodeficiency or chronic lung
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40 259 diseases.³⁹ These findings suggest the need for future studies to analyse the association by age group,
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42 260 pneumococcal serotype and comorbidity status. Moreover, the recent introduction of pneumococcal
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44 261 vaccines has brought changes in the incidence of serotype-specific PD,⁴⁰ making the association of
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46 262 VARI and PD more complicated to understand. As a result, future studies should consider the
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48 263 possible serotype-specific influence that pneumococcal vaccines have on both individual immunity
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50 264 and herd immunity when analysing the association.

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53 265 In addition to the factors discussed above, additional factors may influence the estimates of the
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55 266 association. The first is the change over time in the methodology of data collection, including

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3 267 changes in test method or diagnosis, clinical practice and health-seeking behaviour. The second is
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5 268 the possible delay in measurement, which happened most often in passive hospital-based studies.
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7 269 Thirdly, for ecological studies using aggregated data, “holiday spikes” could occur due to more social
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9 270 gatherings;⁴¹ besides, weekends and holidays might influence timely tests or diagnosis as well as the
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11 271 health-seeking behaviour of patients.

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13 272 We found many studies tended to conduct multiple statistical tests using different subgroups and
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15 273 time periods (e.g. age group, virus, time lag between VARI and PD) without specifying the primary
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17 274 study question a priori or making proper statistical adjustments to account for multiple testing. This
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19 275 could give rise to an increased risk of reporting false positive results. In this review, we applied
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21 276 Bonferroni corrections to adjust for the multiple tests where deemed necessary. Since the
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23 277 Bonferroni method is conservative and we are unable to adjust for studies where *P* values were not
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25 278 given, the adjustment in our review is intended for readers’ reference and as caveats for future
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27 279 studies.

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30 280 Given the substantial burden of VARI across the world,¹ even a modest association between VARI
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32 281 and subsequent PD could lead to a substantial burden of disease in terms of VARI-related PD cases. If
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34 282 proper anti-bacterial interventions could be applied to those with higher risk of PD due to a
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36 283 preceding VARI, subsequent pneumococcal infections could be prevented. The interventions would
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38 284 be more effective / better targeted if we could estimate the risk (i.e. the strength of association)
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40 285 according to timing of infection by week/month of a year, age, comorbidity status, virus type and
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42 286 status of immunity. In turn, understanding the association between VARI and subsequent
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44 287 pneumococcal infection can help evaluate the full impact of viral vaccine programs.

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47 288 In conclusion, the role of seasonal VARI on subsequent PD incidence remains controversial in
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49 289 population-based studies. Nevertheless, these studies provide valuable information and can help
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51 290 with the conception of future well-designed studies. Future work could explore the association by
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53 291 timing of infection, age, comorbidity status, virus type, pneumococcal serotype and presentation,
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55 292 and thus would identify potentially susceptible populations with VARI for preventive interventions.

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3 293 **Supplementary Materials**

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5 294 **Table S1. Summary of findings from animal and in vitro studies.**

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7 295 **Text S1. Search strategy**

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9 296 **File S1. PRISMA checklist**

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11 297 **File S2. Protocol registered in PROSPERO**

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14 298 **Contributors:** HN and HC conceived the study. YL did the literature search and reviewed the articles.

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16 299 YL and MP extracted and analysed the data independently with oversight from HN and HC. YL

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18 300 drafted the manuscript. MP, HN and HC critically reviewed the manuscript. All authors read and

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20 301 approved the final draft of the manuscript.

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25
26 304 <http://dx.doi.org/10.7488/ds/2047>.

27
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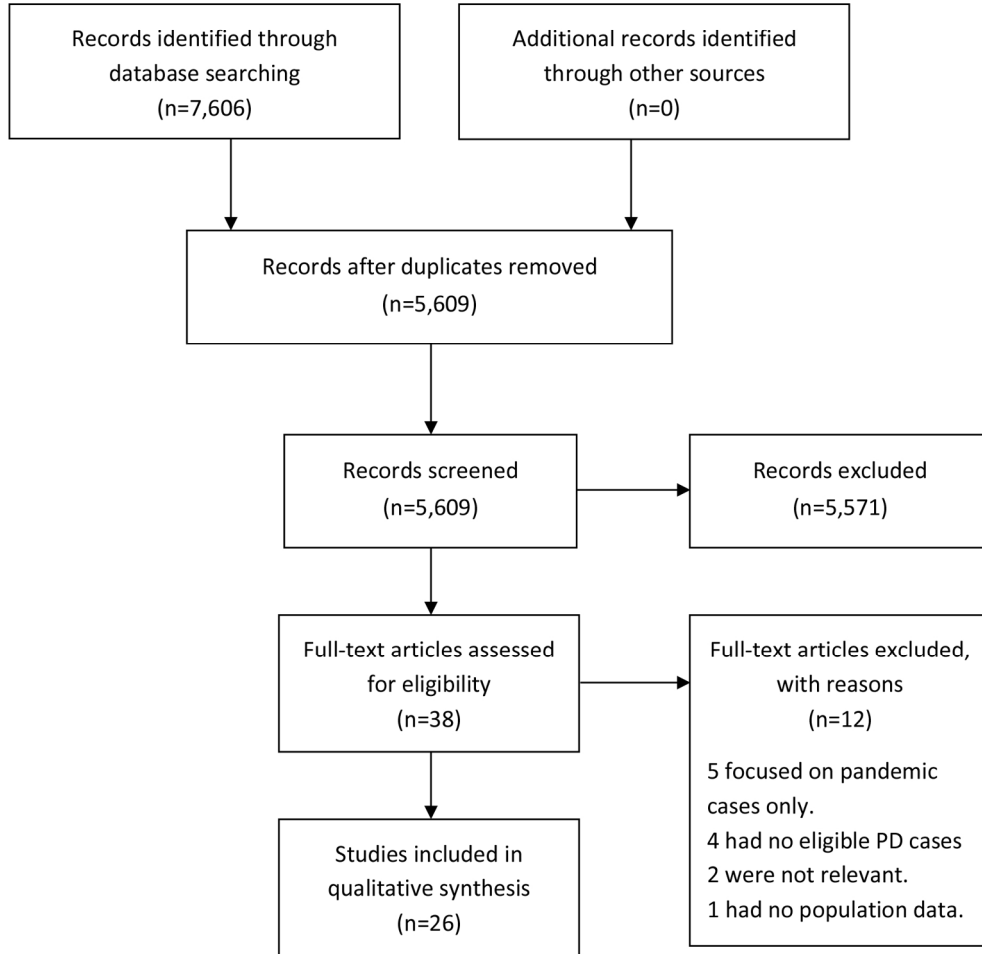
29
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31 **REFERENCES**

- 32
33
34 306 1. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause
35 307 mortality, and cause-specific mortality for 249 causes of death, 1980-2013;2015: a systematic
36 308 analysis for the Global Burden of Disease Study 2015. *The Lancet* 2016;388(10053):1459-544.
- 37
38 309 2. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by *Streptococcus pneumoniae* in
39 310 children younger than 5 years: global estimates. *Lancet* 2009;374(9693):893-902.
- 40
41 311 3. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. *Clin*
42 312 *Microbiol Rev* 2006;19(3):571-82.
- 43
44 313 4. Chien Y-W, Klugman KP, Morens DM. Bacterial Pathogens and Death during the 1918 Influenza
45 314 Pandemic. *N Engl J Med* 2009;361(26):2582-83.
- 46
47 315 5. Fleming-Dutra KE, Taylor T, Link-Gelles R, et al. Effect of the 2009 influenza A(H1N1) pandemic on
48 316 invasive pneumococcal pneumonia. *J Infect Dis* 2013;207(7):1135-43.
- 49
50 317 6. Launes C, Garcia-Garcia JJ, Trivino M, et al. Respiratory viruses, such as 2009 H1N1 influenza virus,
51 318 could trigger temporal trends in serotypes causing pneumococcal disease. *Clin Microbiol Infect*
52 319 2014;20(12):O1088-90.

- 1
2
3 320 7. Nelson GE, Gershman KA, Swerdlow DL, et al. Invasive pneumococcal disease and pandemic
4 321 (H1N1) 2009, Denver, Colorado, USA. *Emerg Infect Dis* 2012;18(2):208-16.
5
6 322 8. Pedro-Botet ML, Burgos J, Lujan M, et al. Impact of the 2009 influenza A H1N1 pandemic on
7 323 invasive pneumococcal disease in adults. *Scand J Infect Dis* 2014;46(3):185-92.
8
9 324 9. Weinberger DM, Simonsen L, Jordan R, et al. Impact of the 2009 influenza pandemic on
10 325 pneumococcal pneumonia hospitalizations in the United States. *J Infect Dis* 2012;205(3):458-65.
11
12 326 10. Edwards LJ, Markey PG, Cook HM, et al. The relationship between influenza and invasive
13 327 pneumococcal disease in the Northern Territory, 2005-2009. *Med J Aust* 2011;194(4):207.
14
15 328 11. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy
16 329 children: the role of preceding influenza infection. *Clin Infect Dis* 2000;30(5):784-9.
17
18 330 12. Stensballe LG, Hjuler T, Andersen A, et al. Hospitalization for respiratory syncytial virus infection
19 331 and invasive pneumococcal disease in Danish children aged <2 years: a population-based cohort
20 332 study. *Clin Infect Dis* 2008;46(8):1165-71.
21
22 333 13. Ampofo K, Bender J, Sheng X, et al. Seasonal invasive pneumococcal disease in children: role of
23 334 preceding respiratory viral infection. *Pediatrics* 2008;122(2):229-37.
24
25 335 14. Burgos J, Larrosa MN, Martinez A, et al. Impact of influenza season and environmental factors on
26 336 the clinical presentation and outcome of invasive pneumococcal disease. *Eur J Clin Microbiol Infect*
27 337 *Dis* 2015;34(1):177-86.
28
29 338 15. Ciruela P, Broner S, Izquierdo C, et al. Invasive pneumococcal disease rates linked to
30 339 meteorological factors and respiratory virus circulation (Catalonia, 2006-2012). *BMC Public Health*
31 340 2016;16(400).
32
33 341 16. Jansen AG, Sanders EA, A VDE, et al. Invasive pneumococcal and meningococcal disease:
34 342 association with influenza virus and respiratory syncytial virus activity? *Epidemiol Infect*
35 343 2008;136(11):1448-54.
36
37 344 17. Kim PE, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season,
38 345 atmospheric conditions, air pollution, and the isolation of respiratory viruses. *Clin Infect Dis*
39 346 1996;22(1):100-6.
40
41 347 18. Murdoch DR, Jennings LC. Association of respiratory virus activity and environmental factors with
42 348 the incidence of invasive pneumococcal disease. *J Infect* 2009;58(1):37-46.
43
44 349 19. Nicoli EJ, Trotter CL, Turner KM, et al. Influenza and RSV make a modest contribution to invasive
45 350 pneumococcal disease incidence in the UK. *J Infect* 2013;66(6):512-20.
46
47 351 20. Peltola V, Heikkinen T, Ruuskanen O, et al. Temporal association between rhinovirus circulation
48 352 in the community and invasive pneumococcal disease in children. *Pediatr Infect Dis J* 2011;30(6):456-
49 353 61.
50
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52
53
54
55
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2
3 354 21. Talbot TR, Poehling KA, Hartert TV, et al. Seasonality of invasive pneumococcal disease: temporal
4 355 relation to documented influenza and respiratory syncytial viral circulation. *Am J Med*
5 356 2005;118(3):285-91.
- 7 357 22. Watson M, Gilmour R, Menzies R, et al. The association of respiratory viruses, temperature, and
8 358 other climatic parameters with the incidence of invasive pneumococcal disease in Sydney, Australia.
9 359 *Clin Infect Dis* 2006;42(2):211-5.
- 11 360 23. Kuster SP, Tuite AR, Kwong JC, et al. Evaluation of coseasonality of influenza and invasive
12 361 pneumococcal disease: results from prospective surveillance. *PLoS Med* 2011;8(6):e1001042.
- 14 362 24. Walter ND, Taylor TH, Shay DK, et al. Influenza circulation and the burden of invasive
15 363 pneumococcal pneumonia during a non-pandemic period in the United States. *Clin Infect Dis*
16 364 2010;50(2):175-83.
- 18 365 25. Weinberger DM, Grant LR, Steiner CA, et al. Seasonal drivers of pneumococcal disease incidence:
19 366 impact of bacterial carriage and viral activity.[Erratum appears in *Clin Infect Dis*. 2014 Mar;58(6):908].
20 367 *Clin Infect Dis* 2014;58(2):188-94.
- 22 368 26. Weinberger DM, Harboe ZB, Viboud C, et al. Pneumococcal disease seasonality: incidence,
23 369 severity and the role of influenza activity. *Eur Respir J* 2014;43(3):833-41.
- 25 370 27. Weinberger DM, Klugman KP, Steiner CA, et al. Association between respiratory syncytial virus
26 371 activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. *PLoS*
27 372 *Med* 2015;12(1):e1001776.
- 29 373 28. Weinberger DM, Harboe ZB, Viboud C, et al. Serotype-specific effect of influenza on adult
30 374 invasive pneumococcal pneumonia. *J Infect Dis* 2013;208(8):1274-80.
- 32 375 29. Allard R, Couillard M, Pilon P, et al. Invasive bacterial infections following influenza: a time-series
33 376 analysis in Montreal, Canada, 1996-2008. *Influenza other respi* 2012;6(4):268-75.
- 35 377 30. Grabowska K, Hogberg L, Penttinen P, et al. Occurrence of invasive pneumococcal disease and
36 378 number of excess cases due to influenza. *BMC Infect Dis* 2006;6:58.
- 38 379 31. Zhou H, Haber M, Ray S, et al. Invasive pneumococcal pneumonia and respiratory virus co-
39 380 infections. *Emerg Infect Dis* 2012;18(2):294-7.
- 41 381 32. Dangor Z, Izu A, Moore DP, et al. Temporal association in hospitalizations for tuberculosis,
42 382 invasive pneumococcal disease and influenza virus illness in South African children. *PLoS ONE*
43 383 2014;9(3):e91464.
- 45 384 33. Opatowski L, Varon E, Dupont C, et al. Assessing pneumococcal meningitis association with viral
46 385 respiratory infections and antibiotics: insights from statistical and mathematical models. *Proc Biol Sci*
47 386 2013;280(1764):20130519.

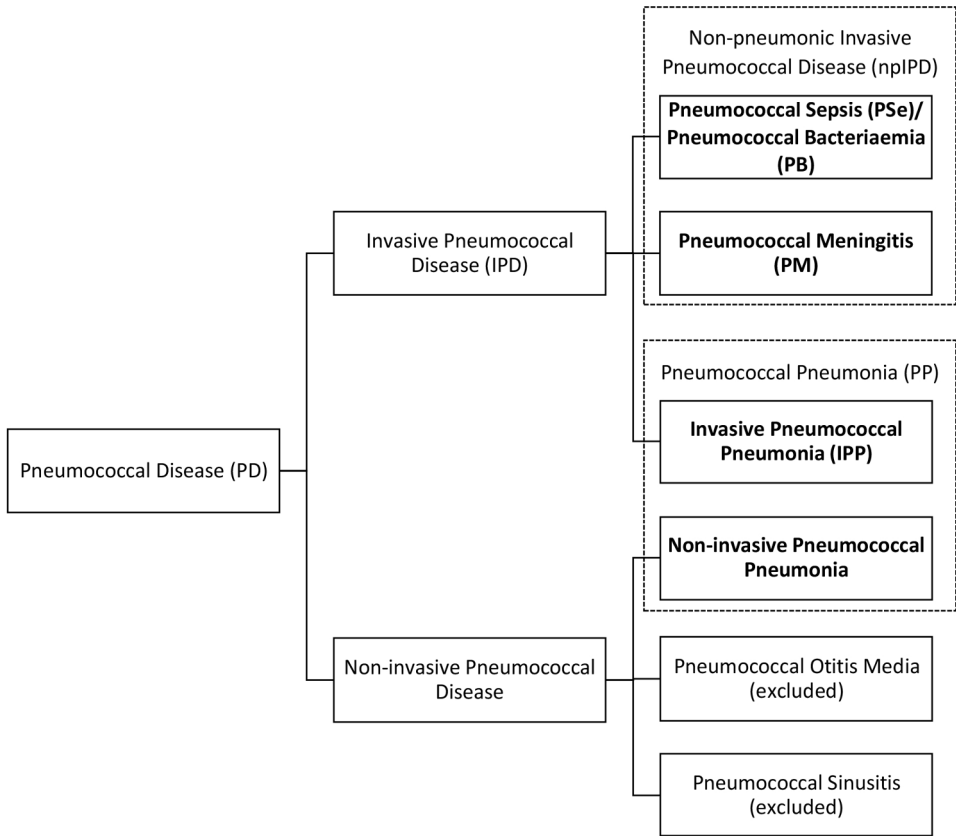
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3 387 34. Shrestha S, Foxman B, Weinberger DM, et al. Identifying the interaction between influenza and
4 388 pneumococcal pneumonia using incidence data. *Sci Transl Med* 2013;5(191):191ra84.
5
6 389 35. Toschke AM, Arenz S, von Kries R, et al. No temporal association between influenza outbreaks
7 390 and invasive pneumococcal infections. *Arch Dis Child* 2008;93(3):218-20.
8
9 391 36. McCullers JA, Rehg JE. Lethal synergism between influenza virus and *Streptococcus pneumoniae*:
10 392 characterization of a mouse model and the role of platelet-activating factor receptor. *J Infect Dis*
11 393 2002;186(3):341-50.
12
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14 394 37. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-gamma during
15 395 recovery from influenza infection. *Nat Med* 2008;14(5):558-64.
16
17 396 38. Simell B, Auranen K, Käyhty H, et al. The fundamental link between pneumococcal carriage and
18 397 disease. *Expert Rev Vaccines* 2012;11(7):841-55.
19
20 398 39. Song JY, Nahm MH, Cheong HJ, et al. Impact of preceding flu-like illness on the serotype
21 399 distribution of pneumococcal pneumonia. *PLoS ONE* 2014;9(4):e93477.
22
23 400 40. Shiri T, Datta S, Madan J, et al. Indirect effects of childhood pneumococcal conjugate vaccination
24 401 on invasive pneumococcal disease: a systematic review and meta-analysis. *The Lancet Global Health*
25 402 2017;5(1):e51-e59.
26
27 403 41. Walter ND, Taylor THJ, Dowell SF, et al. Holiday Spikes in Pneumococcal Disease among Older
28 404 Adults. *N Engl J Med* 2009;361(26):2584-85.
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PRISMA flow diagram of the literature search. PD: pneumococcal disease.

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Category of pneumococcal disease in the present review.

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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. 60% of mice died 2–11d after pneumococcus challenge in influenza A group compared with 15% in mock group;
McCullers et al. 2002 ⁷	Mice (n=20 per group)	influenza A + pneumococcus (0 or 7d later)	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.

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

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8. relat*.mp.

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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/

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1164 results by 27 Apr 2017

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
- 7 Named contact email
Enter the electronic mail address of the named contact.
You.Li2@ed.ac.uk
- 8 Named contact address
Enter the full postal address for the named contact.
3.730 Doorway 1, Old Medical School Teviot Place Edinburgh UK
- 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
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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.

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3 19 Participants/population
4 Give summary criteria for the participants or populations being studied by the review. The preferred format includes
5 details of both inclusion and exclusion criteria.
6 Population-based studies involving people with viral acute respiratory infection and pneumococcal disease.
7 Specifically, the following participants were considered: (1) Those with laboratory confirmed viral infections; (2) Those
8 with ICD code for influenza and RSV infection; (3) Those with a case definition of an influenza-like illness (ILI) and
9 bronchiolitis.
- 10 20 Intervention(s), exposure(s)
11 Give full and clear descriptions of the nature of the interventions or the exposures to be reviewed
12 Population-based studies involving people with viral acute respiratory infection and pneumococcal disease.
- 13 21 Comparator(s)/control
14 Where relevant, give details of the alternatives against which the main subject/topic of the review will be compared
15 (e.g. another intervention or a non-exposed control group).
16 Not applicable.
- 17 22 Types of study to be included
18 Give details of the study designs to be included in the review. If there are no restrictions on the types of study design
19 eligible for inclusion, this should be stated.
20 There were no restrictions imposed on the types of study design eligible for inclusion. We included population-based
21 studies involving clinically diagnosed PD cases, and specifically, we accepted the following studies: (1) Those
22 involving laboratory confirmed viral infections; (2) Those involving an ICD code for influenza and RSV infection; (3)
23 Those involving case definitions of an influenza-like illness (ILI) and bronchiolitis. We excluded animal studies and
24 theoretical studies in which no population data was applied. We focused our review on the association of seasonal
25 VARI with PD, and thus excluded studies that reported influenza pandemic cases only.
- 26 23 Context
27 Give summary details of the setting and other relevant characteristics which help define the inclusion or exclusion
28 criteria.
- 29 24 Primary outcome(s)
30 Give the most important outcomes.
31 The association between VARI and subsequent PD.
32 Give information on timing and effect measures, as appropriate.
- 33 25 Secondary outcomes
34 List any additional outcomes that will be addressed. If there are no secondary outcomes enter None.
35 Factors that could affect the association between VARI and subsequent PD.
36 Give information on timing and effect measures, as appropriate.
- 37 26 Data extraction (selection and coding)
38 Give the procedure for selecting studies for the review and extracting data, including the number of researchers
39 involved and how discrepancies will be resolved. List the data to be extracted.
- 40 27 Risk of bias (quality) assessment
41 State whether and how risk of bias will be assessed, how the quality of individual studies will be assessed, and
42 whether and how this will influence the planned synthesis.
43 Risk of bias will be assessed by evaluating the power of the studies, the measures taken to control for confounders,
44 and any multiple tests made without reasonable correction or justification. Bias is expected to have little impact on the
45 review because it is intended to provide a summary of all relevant studies, and no quantitative analysis will be
46 conducted.
- 47 28 Strategy for data synthesis
48 Give the planned general approach to be used, for example whether the data to be used will be aggregate or at the
49 level of individual participants, and whether a quantitative or narrative (descriptive) synthesis is planned. Where
50 appropriate a brief outline of analytic approach should be given.
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3 A descriptive synthesis is planned. A summary of both the methods and the results of eligible studies will be provided.
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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.

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- 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.
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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

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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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3 **1 Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic**
4 **2 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).

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33 **Strengths and limitations of this study**

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

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40 Introduction

41 Both viral acute respiratory infection (VARI) and pneumococcal disease (PD) account for a substantial
42 disease burden worldwide, especially in young children and the elderly.¹⁻³ The association of viral
43 acute respiratory infection (VARI) and subsequent pneumococcal disease (PD) was not well
44 recognised until the catastrophic 1918 influenza pandemic, which resulted in an estimated 40–50
45 million deaths;⁴ it has been suggested that pneumococcus may have been a major cause of death.⁵
46 Most recently, it was observed that the incidence of PD was higher during 2009 influenza H1N1
47 pandemic period than the same period in pre-pandemic⁶⁻¹⁰ and post-pandemic years.^{7 9 10}

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

61 Methods

62 Search Strategy and Selection Criteria

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

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3 66 with clinically diagnosed PD cases (see below for detailed definition). In terms of VARI exposure, we
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5 67 accepted the following studies: (1) those with laboratory confirmed viral infections; (2) those with an
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7 68 ICD code for influenza and/or RSV infection; (3) those with case definition of influenza-like illness (ILI)
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9 69 and bronchiolitis as proxies for influenza and RSV, respectively. We excluded animal studies and
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11 70 theoretical studies where no population data were applied. We focused our review on the
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13 71 association of seasonal VARI and PD and thus excluded studies that reported pandemic influenza
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15 72 cases only. No language restrictions were applied. The reference lists of eligible studies were also
16
17 73 checked to identify additional studies for inclusion. For all included studies, quality assessment was
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19 74 conducted using tailored Critical Appraisal Skills Programme (CASP) checklists for case-control
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21 75 studies and cohort studies (**Supplementary File S1**). The review was conducted and reported
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23 76 according to the PRISMA guidelines (**Supplementary File S2**). The protocol for this systematic review
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25 77 was registered on PROSPERO (registration number: CRD42017064760; **Supplementary File S3**).

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

29 30 31 **Definition of PD**

32 80 We defined PD as any disease caused by *Streptococcus pneumoniae* (pneumococcus). Since this
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34 81 definition contains a broad range of diseases and symptoms, including some that are trivial to our
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36 82 review, we adopted a narrower definition. This narrowed definition includes invasive pneumococcal
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38 83 disease (IPD) and pneumococcal pneumonia (PP). We defined IPD as detection of pneumococcus in
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40 84 typical sterile sites (e.g. blood, pleural and cerebrospinal fluid). A detailed category of PD for our
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42 85 review is displayed in **Figure 2**. Additionally, we used the term “non-pneumonic invasive
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44 86 pneumococcal disease (npIPD)”, which referred to all IPD without diagnosis of pneumonia, in order
45
46 87 to differentiate from non-invasive and invasive pneumococcal pneumonia.

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

50 51 **Definition of VARI**

52 90 We defined VARI as a respiratory tract infection with viral aetiology. ILI was viewed as a proxy for
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54 91 influenza infection in the present review. We defined ILI as a symptomatic cough and fever $\geq 38^{\circ}\text{C}$
55
56 92 with onset within 7 days.

93 Data Extraction

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

99 Data Analysis

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

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

109 Results

110 A total of 28 studies¹¹⁻³⁸ were eligible and included in the review. We noticed a variety of study
111 designs, exposures and outcomes of interest and analytical methods in these studies (summarised in
112 **Table S2**). Due to the variety, we summarised the studies and displayed the results according to
113 study design and methods.

114 Individual Patient Data Based Studies

115 Individual patient data based studies during the inter-pandemic period are sparse. Only three
116 studies^{17 25 29} were identified (**Table 1**), including two cohort studies^{17 29} and one small case-control
117 study by O'Brien et al²⁵. The reported results consistently supported the role of preceding VARI on
118 occurrence of PD. However, the two cohort studies did not attempt to control the seasonal risk
119 factors of VARI and PD that could potentially bias the estimated effect size.

120 **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]

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

124 **Ecological Studies**

125 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}
 126 out of the 25 ecological studies controlled for seasonal patterns of VARI and PD (**Table S2**).
 127 Additionally, the study by Stensballe et al.²⁹ analysed data at both population and individual level but
 128 did not control for the seasonal patterns.

129 **Correlation analyses with no control for seasonal patterns**

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

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3 133 Bonferroni method was applied to adjust the significance level. The correlation between PD and
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5 134 influenza or RSV was statistically significant in all five studies^{14 23 24 29 30} that analysed population data
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7 135 of all ages (correlation coefficient r: 0.40–0.71 for influenza at no time lag, 0.47–0.77 for RSV at no
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9 136 time lag).

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137 **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	<p><u>≥18y</u> 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)</p> <p><u><18y</u> 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)</p>
Murdoch et al. 2009 ²³	1995–2006	all ages Christchurch, New Zealand	IFV RSV ADV PIV	IPD (n=737)	Surveillance data, monthly	Spearman	<p><u>All ages</u> 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)</p>
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	<p><u>All ages</u>, Pearson IFV: 0.54a RSV: 0.47a</p> <p><u>All ages</u>, Spearman IFV: 0.67a RSV: 0.63a (correlations were stronger in 15–64y and ≥65y than 0–4y and 5–14y)</p>

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

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

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

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

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3 146 *Regression analyses controlling for seasonal patterns*

4 147 **Table 3** shows the summary of the 15 studies^{11 13 14 16 18 22-24 26 32 34-38} that controlled for seasonal
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6 148 patterns by regression analysis. Results were inconsistent among the studies. In all-age population
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8 149 studies, preceding influenza infection was likely to be associated with IPD (12 studies^{13 14 16 18 22-24 32 35-}
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10 150 ³⁸ reported an association and two studies^{11 34} reported no association). According to two studies^{23 24}
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12 151 that reported age-stratified results, the association between influenza and IPD was more likely to
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14 152 exist among older people than among young children. In terms of preceding RSV infection, four^{14 24 34}
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16 153 ³⁷ out of five studies^{14 23 24 34 37} observed an association of RSV with PD incidence. Specifically, one
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18 154 study¹⁴ found the association between RSV and IPD only existed among children <5 years. Studies
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20 155 reporting other viruses such as ADV and PIV were sparse (two^{14 23} and one²³ studies, respectively).
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22 156 Five studies^{14 23 24 34 37} that reported two or more viruses demonstrated that the association differed
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24 157 by the type of virus. Moreover, the association could differ among virus subtypes (e.g. influenza A vs
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26 158 influenza B²² and PIV 1/2 vs PIV 3²³). Notably, there are other factors that could influence the
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28 159 strength of the associations reported in these studies. For instance, the association could vary by
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30 160 presentation of PD (invasive pneumococcal pneumonia, IPP vs npIPD^{32 34 36} and PP vs pneumococcal
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32 161 sepsis, PSe³⁷); preceding VARI was more likely to be associated with the occurrence of pneumonia
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34 162 than other clinical presentations. Additionally, the results from studies in Denmark, where
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36 163 comorbidity status and pneumococcal serotype were available, demonstrated that influenza had a
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38 164 greater influence on the incidence of low-invasiveness serotypes than medium- or high- invasiveness
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40 165 among the low comorbidity group; among the high comorbidity group, the pattern was reversed.^{35 36}
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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		<u>All ages</u> 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	<u>All ages</u> 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)	<u>All ages</u> ILI: median 4.9% across all study years (1w) 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	<u>All ages</u> 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	<u>All ages</u> 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)

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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) ≥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)
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		

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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	<p>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)</p> <p>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)</p> <p>≥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)</p> <p>≥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)</p>	

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.	

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

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

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5 170 pneumococcal conjugate vaccine; PD, pneumococcal disease; PIV, parainfluenza virus; PP, pneumococcal pneumonia; PSe, pneumococcal sepsis; RR,
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7 171 relative risk; RSV, respiratory syncytial virus; UV index, clear-sky ultraviolet index; VARI, viral acute respiratory infection; w, week(s); y, year(s).
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9 172 Relative risk or attributable percentage **in bold** were statistically significant as originally reported in the study ($P < 0.05$); relative risk or attributable
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11 173 percentage ending with “a” were statistically significant after Bonferroni adjustment ($P < 0.05/\text{number of relevant tests}$) or when the Bonferroni correction
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13 174 was deemed unnecessary, those ending with “b” did not have enough information to apply the Bonferroni correction; relative risk or attributable
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15 175 percentage ending with “c” were not statistically significant after Bonferroni adjustment.
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177 **Studies utilising other analyses**178 Seven ecological studies^{15 16 19 22 26 28 31} utilised other analytical methods (**Table 4**). Except for studies179 by Hendriks et al.¹⁹ and Toschke et al.³¹, all studies reported an association between VARI and PD.180 **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

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

184 Discussion

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

188 We found that reported associations between VARI and subsequent PD were inconsistent among
 189 the 28 included studies. Only three studies^{17 25 29} analysed the association using individual patient
 190 data. The two cohort studies^{17 29} did not account for the shared risk factors between VARI and PD
 191 that influenced their seasonality, substantially limiting the inferences that can be made from these
 192 data while the case-control study²⁵ was limited by its small sample size (n case=13). In ecological
 193 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
 194 seasonal patterns. In these studies, we found that influenza and/or RSV infections were likely to be
 195 associated with the subsequent occurrence of PD. For influenza, the association was stronger among
 196 younger populations compared to older adults^{23 24} while the pattern was reversed for RSV.¹⁴ Data
 197 from multiple studies suggested that virus type (five studies^{14 23 24 34 37}) and subtype (two studies^{22 23}),

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3 198 comorbidity status (two studies^{35 36}) and pneumococcal serotype invasiveness (one study³⁵) could
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5 199 influence the association. However, these 16 ecological studies had various population
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7 200 characteristics (e.g. age, comorbidity, immunity status), PD datasets, VARI datasets and analytical
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9 201 methods. As such, heterogeneity among the studies, along with their ecological nature, limits the
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11 202 amount of valid inferences that can be made from the data (as summarised above).

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13 203 Nevertheless, these studies provide important clues for the potential factors related to the
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15 204 association between VARI and subsequent PD, and thus could help with the conception and design
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17 205 of future studies. Ideally, in order to understand whether a particular preceding VARI can predispose
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19 206 an individual to PD, a prospective cohort study that monitors each individual for VARI and
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21 207 pneumococcal infection would be utilised, allowing analyses at both individual and population levels.
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23 208 However, such a design would not be feasible or affordable as inter alia pneumococcal infections are
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25 209 rare. Alternatively, utilisation of large-scale routine health data and reliable data linkage (through
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27 210 unique individual identifiers) from sources such as surveillance data and hospitalisation datasets may
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29 211 be feasible in many industrialised countries. An example of such data linkage in our review is the
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31 212 study by Stensballe and colleagues²⁹ that linked information from four Danish population-based
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33 213 registries. While the authors conducted individual-level analysis, the results were based on cases
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35 214 tested for both the presence of respiratory viruses and pneumococcal infection. The true number of
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37 215 VARI-associated PD cases is likely to be significantly higher due to incomplete testing of cases; the
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39 216 untested viral-pneumococcal cases could represent a crucial source of selection bias. Community-
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41 217 based active surveillance can likely address the issue of missing cases but such surveillance would be
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43 218 labour intensive and less cost-effective to conduct. Another option is a case-control study, which is
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45 219 affordable and practical, but not without its limitations. In addition to challenges in designing such
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47 220 studies, defining the history of VARI is likely to be inaccurate since the timing of viral serology may
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49 221 be less accurate (information bias).²⁷ In the case-control study by O'Brien and colleagues,²⁵ the
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51 222 authors used influenza-strain specific convalescent serology as evidence for preceding influenza
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53 223 infection. The authors also conducted telephone interviews to investigate ILI history but they did not
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224 mention whether interviewers and interviewees were blind to case or control status. Moreover, the
225 value of this case-control study is limited by its very small sample size (n case = 13).

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

236 Apart from the study design, one further challenge of analysing the association is accounting for
237 the influence of seasonal factors of VARI and PD (confounding). Both VARI and PD have similar
238 seasonal patterns, and thus are likely to correlate as indicated by the correlation results from
239 ecological studies. The increased risk of PD during an epidemic season could be caused by VARI or by
240 seasonal risk factors or by both. In the present review, 11 studies^{12 15 17 20 21 27-31 33} did not attempt to
241 control for seasonal confounders, likely leading to biased estimations of the association. For example,
242 the study by Edwards and colleagues¹⁷ reported a relative risk as high as 112.5 when not adjusting
243 any seasonal factors. One way to address this problem in such studies would be to match the
244 individuals with the onset timing of pneumococcal infection, keeping the risk of PD comparable
245 between VARI cases and non-VARI cases; for ecological studies, regression analysis adding seasonal
246 terms or climatic factors (such as temperature and humidity), or cross-correlation analysis of time
247 series controlling for seasonal patterns could be considered.

248 Our review suggests that the association of VARI and subsequent PD could vary by virus type^{14 23 24}
249^{34 35} and even by subtype^{22 23}. Studies using combinations of viral infections such as all virus, influenza

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3 250 + RSV, non-influenza, or non-RSV could give biased estimations of the association. However, it is not
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5 251 always practical to analyse the association by virus type. In ecological studies, different types of
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7 252 viruses might co-circulate and thus be highly correlated in incidence, making it difficult to determine
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9 253 the role for each virus. In terms of PD, most studies used IPD as the outcome of interest. However,
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11 254 studies that categorised IPD into IPP and npIPD found that the association was more pronounced in
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13 255 IPP than in npIPD.^{32 34 36} A similar finding, that the association was stronger in PP than PSe, was
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15 256 reported in another study.³⁷ These results suggest VARI is more likely to be associated with
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17 257 pneumonic pneumococcal infections than non-pneumonic infections. In our review, we excluded
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19 258 studies using information other than clinical diagnosis as a proxy for PD (e.g. prescription data and
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21 259 carriage data). Pneumococcal carriage could have a fundamental role in the transmission and
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23 260 incidence of PD.⁴¹ In a study analysing the impact of pneumococcal carriage and viral activity,
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25 261 Weinberger and colleagues³⁴ found npIPD was associated with carriage prevalence, whereas IPP was
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27 262 associated with bronchiolitis (as a proxy for RSV). The authors also proposed that preceding VARI
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31 264 children. However, more studies are needed to confirm these findings.

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34 265 The association could also vary by population characteristics. According to two studies that
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36 266 displayed age-stratified results,^{23 24} the association of influenza and subsequent IPD was more likely
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38 267 to exist among older people than among young children. Studies by Weinberger et al.^{35 36} gauged the
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40 268 association in different comorbidity and pneumococcal serotype groups among Denmark
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42 269 populations. The results showed that influenza had a stronger impact on the incidence of low-
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44 270 invasiveness serotypes than medium- or high- invasiveness ones in the low comorbidity group, while
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46 271 the pattern reversed in the high comorbidity group. Another study that analysed clinical records of
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48 272 919 patients with PP found that infrequently colonising pneumococcal serotypes were more likely to
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50 273 cause PP after preceding VARI, particularly in patients with immunodeficiency or chronic lung
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52 274 diseases.⁴² These findings suggest the need for future studies to analyse the association by age group,
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54 275 pneumococcal serotype and comorbidity status. Moreover, the recent introduction of pneumococcal
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3 276 vaccines has brought changes in the incidence of serotype-specific PD,⁴³ making the association of
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5 277 VARI and PD more complicated to understand. As a result, future studies should consider the
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7 278 possible serotype-specific influence that pneumococcal vaccines have on both individual immunity
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9 279 and herd immunity when analysing the association.

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11 280 In addition to the factors discussed above, additional factors may influence the estimates of the
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13 281 association. The first is the change over time in the methodology of data collection, including
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15 282 changes in test method or diagnosis, clinical practice and health-seeking behaviour. The second is
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17 283 the possible delay in measurement, which happened most often in passive hospital-based studies.
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19 284 Thirdly, for ecological studies using aggregated data, “holiday spikes” could occur due to more social
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21 285 gatherings;⁴⁴ besides, weekends and holidays might influence timely tests or diagnosis as well as the
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23 286 health-seeking behaviour of patients.

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25 287 We found many studies tended to conduct multiple statistical tests using different subgroups and
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27 288 time periods (e.g. age group, virus, time lag between VARI and PD) without specifying the primary
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29 289 study question a priori or making proper statistical adjustments to account for multiple testing. This
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31 290 could give rise to an increased risk of reporting false positive results. In this review, we applied
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33 291 Bonferroni corrections to adjust for the multiple tests where deemed necessary. Since the
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35 292 Bonferroni method is conservative and we are unable to adjust for studies where *P* values were not
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37 293 given, the adjustment in our review is intended for readers’ reference and as caveats for future
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39 294 studies.

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41 295 Given the substantial burden of VARI across the world,¹ even a modest association between VARI
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43 296 and subsequent PD could lead to a substantial burden of disease in terms of VARI-related PD cases. If
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45 297 proper anti-bacterial interventions could be applied to those with higher risk of PD due to a
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47 298 preceding VARI, subsequent pneumococcal infections could be prevented. The interventions would
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49 299 be more effective / better targeted if we could estimate the risk (i.e. the strength of association)
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51 300 according to timing of infection by week/month of a year, age, comorbidity status, virus type and
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3 301 status of immunity. In turn, understanding the association between VARI and subsequent
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5 302 pneumococcal infection can help evaluate the full impact of viral vaccine programs.

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7 303 In conclusion, the role of seasonal VARI on subsequent PD incidence remains controversial in
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9 304 population-based studies. Nevertheless, these studies provide valuable information and can help
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11 305 with the conception of future well-designed studies. Future work could explore the association by
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13 306 timing of infection, age, comorbidity status, virus type, pneumococcal serotype and presentation,
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15 307 and thus would identify potentially susceptible populations with VARI for preventive interventions.

18 308 **Supplementary Materials**

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20 309 **Table S1. Summary of findings from animal and in vitro studies.**

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22 310 **Table S2. Summary of methodologies utilised in the included studies (n=28).**

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24 311 **Text S1. Search strategy**

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26 312 **File S1. Quality assessment of included studies**

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28 313 **File S2. PRISMA checklist**

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30 314 **File S3. Protocol registered in PROSPERO**

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34 315 **Contributors:** HN and HC conceived the study. YL did the literature search and reviewed the articles.

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36 316 YL and MP extracted and analysed the data independently with oversight from HN and HC. YL

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38 317 drafted the manuscript. MP, HN and HC critically reviewed the manuscript. All authors read and

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40 318 approved the final draft of the manuscript.

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42 319 **Competing interests:** none declared.

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44 320 **Data sharing statement:** Data extraction sheets are available in the Edinburgh DataShare repository,

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46 321 <http://dx.doi.org/10.7488/ds/2047>.

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REFERENCES

- 325 1. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause
326 mortality, and cause-specific mortality for 249 causes of death, 1980-2013;2015: a systematic
327 analysis for the Global Burden of Disease Study 2015. *The Lancet* 2016;388(10053):1459-544.
- 328 2. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by *Streptococcus pneumoniae* in
329 children younger than 5 years: global estimates. *Lancet* 2009;374(9693):893-902.
- 330 3. Drijkoningen JJC, Rohde GGU. Pneumococcal infection in adults: burden of disease. *Clinical*
331 *Microbiology and Infection* 2014;20:45-51.
- 332 4. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. *Clin*
333 *Microbiol Rev* 2006;19(3):571-82.
- 334 5. Chien Y-W, Klugman KP, Morens DM. Bacterial Pathogens and Death during the 1918 Influenza
335 Pandemic. *N Engl J Med* 2009;361(26):2582-83.
- 336 6. Fleming-Dutra KE, Taylor T, Link-Gelles R, et al. Effect of the 2009 influenza A(H1N1) pandemic on
337 invasive pneumococcal pneumonia. *J Infect Dis* 2013;207(7):1135-43.
- 338 7. Launes C, Garcia-Garcia JJ, Trivino M, et al. Respiratory viruses, such as 2009 H1N1 influenza virus,
339 could trigger temporal trends in serotypes causing pneumococcal disease. *Clin Microbiol Infect*
340 2014;20(12):O1088-90.
- 341 8. Nelson GE, Gershman KA, Swerdlow DL, et al. Invasive pneumococcal disease and pandemic
342 (H1N1) 2009, Denver, Colorado, USA. *Emerg Infect Dis* 2012;18(2):208-16.
- 343 9. Pedro-Botet ML, Burgos J, Lujan M, et al. Impact of the 2009 influenza A H1N1 pandemic on
344 invasive pneumococcal disease in adults. *Scand J Infect Dis* 2014;46(3):185-92.
- 345 10. Weinberger DM, Simonsen L, Jordan R, et al. Impact of the 2009 influenza pandemic on
346 pneumococcal pneumonia hospitalizations in the United States. *J Infect Dis* 2012;205(3):458-65.
- 347 11. Allard R, Couillard M, Pilon P, et al. Invasive bacterial infections following influenza: a time-series
348 analysis in Montreal, Canada, 1996-2008. *Influenza other respi* 2012;6(4):268-75.
- 349 12. Ampofo K, Bender J, Sheng X, et al. Seasonal invasive pneumococcal disease in children: role of
350 preceding respiratory viral infection. *Pediatrics* 2008;122(2):229-37.
- 351 13. Burgos J, Larrosa MN, Martinez A, et al. Impact of influenza season and environmental factors on
352 the clinical presentation and outcome of invasive pneumococcal disease. *Eur J Clin Microbiol Infect*
353 *Dis* 2015;34(1):177-86.
- 354 14. Ciruela P, Broner S, Izquierdo C, et al. Invasive pneumococcal disease rates linked to
355 meteorological factors and respiratory virus circulation (Catalonia, 2006-2012). *BMC Public Health*
356 2016;16(400).

- 1
2
3 357 15. Dangor Z, Izu A, Moore DP, et al. Temporal association in hospitalizations for tuberculosis,
4 358 invasive pneumococcal disease and influenza virus illness in South African children. PLoS ONE
5 359 2014;9(3):e91464.
6
7 360 16. Domenech de Cellès M, Arduin H, Varon E, et al. Characterizing and Comparing the Seasonality of
8 361 Influenza-Like Illnesses and Invasive Pneumococcal Diseases Using Seasonal Waveforms. Am J
9 362 Epidemiol 2017;kwx336-kwx36.
10
11 363 17. Edwards LJ, Markey PG, Cook HM, et al. The relationship between influenza and invasive
12 364 pneumococcal disease in the Northern Territory, 2005-2009. Med J Aust 2011;194(4):207.
13
14 365 18. Grabowska K, Hogberg L, Penttinen P, et al. Occurrence of invasive pneumococcal disease and
15 366 number of excess cases due to influenza. BMC Infect Dis 2006;6:58.
16
17 367 19. Hendriks W, Boshuizen H, Dekkers A, et al. Temporal cross-correlation between influenza-like
18 368 illnesses and invasive pneumococcal disease in The Netherlands. Influenza and other Respiratory
19 369 Viruses 2017;11(2):130-37.
20
21 370 20. Jansen AG, Sanders EA, A VDE, et al. Invasive pneumococcal and meningococcal disease:
22 371 association with influenza virus and respiratory syncytial virus activity? Epidemiol Infect
23 372 2008;136(11):1448-54.
24
25 373 21. Kim PE, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season,
26 374 atmospheric conditions, air pollution, and the isolation of respiratory viruses. Clin Infect Dis
27 375 1996;22(1):100-6.
28
29 376 22. Kuster SP, Tuite AR, Kwong JC, et al. Evaluation of coseasonality of influenza and invasive
30 377 pneumococcal disease: results from prospective surveillance. PLoS Med 2011;8(6):e1001042.
31 378 23. Murdoch DR, Jennings LC. Association of respiratory virus activity and environmental factors with
32 379 the incidence of invasive pneumococcal disease. J Infect 2009;58(1):37-46.
33
34 380 24. Nicoli EJ, Trotter CL, Turner KM, et al. Influenza and RSV make a modest contribution to invasive
35 381 pneumococcal disease incidence in the UK. J Infect 2013;66(6):512-20.
36
37 382 25. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy
38 383 children: the role of preceding influenza infection. Clin Infect Dis 2000;30(5):784-9.
39
40 384 26. Opatowski L, Varon E, Dupont C, et al. Assessing pneumococcal meningitis association with viral
41 385 respiratory infections and antibiotics: insights from statistical and mathematical models. Proc Biol Sci
42 386 2013;280(1764):20130519.
43
44 387 27. Peltola V, Heikkinen T, Ruuskanen O, et al. Temporal association between rhinovirus circulation
45 388 in the community and invasive pneumococcal disease in children. Pediatr Infect Dis J 2011;30(6):456-
46 389 61.

- 1
2
3 390 28. Shrestha S, Foxman B, Weinberger DM, et al. Identifying the interaction between influenza and
4 391 pneumococcal pneumonia using incidence data. *Sci Transl Med* 2013;5(191):191ra84.
5
6 392 29. Stensballe LG, Hjuler T, Andersen A, et al. Hospitalization for respiratory syncytial virus infection
7 393 and invasive pneumococcal disease in Danish children aged <2 years: a population-based cohort
8 394 study. *Clin Infect Dis* 2008;46(8):1165-71.
9
10 395 30. Talbot TR, Poehling KA, Hartert TV, et al. Seasonality of invasive pneumococcal disease: temporal
11 396 relation to documented influenza and respiratory syncytial viral circulation. *Am J Med*
12 397 2005;118(3):285-91.
13
14 398 31. Toschke AM, Arenz S, von Kries R, et al. No temporal association between influenza outbreaks
15 399 and invasive pneumococcal infections. *Arch Dis Child* 2008;93(3):218-20.
16
17 400 32. Walter ND, Taylor TH, Shay DK, et al. Influenza circulation and the burden of invasive
18 401 pneumococcal pneumonia during a non-pandemic period in the United States. *Clin Infect Dis*
19 402 2010;50(2):175-83.
20
21 403 33. Watson M, Gilmour R, Menzies R, et al. The association of respiratory viruses, temperature, and
22 404 other climatic parameters with the incidence of invasive pneumococcal disease in Sydney, Australia.
23 405 *Clin Infect Dis* 2006;42(2):211-5.
24
25 406 34. Weinberger DM, Grant LR, Steiner CA, et al. Seasonal drivers of pneumococcal disease incidence:
26 407 impact of bacterial carriage and viral activity.[Erratum appears in *Clin Infect Dis*. 2014 Mar;58(6):908].
27 408 *Clin Infect Dis* 2014;58(2):188-94.
28
29 409 35. Weinberger DM, Harboe ZB, Viboud C, et al. Serotype-specific effect of influenza on adult
30 410 invasive pneumococcal pneumonia. *J Infect Dis* 2013;208(8):1274-80.
31 411 36. Weinberger DM, Harboe ZB, Viboud C, et al. Pneumococcal disease seasonality: incidence,
32 412 severity and the role of influenza activity. *Eur Respir J* 2014;43(3):833-41.
33 413 37. Weinberger DM, Klugman KP, Steiner CA, et al. Association between respiratory syncytial virus
34 414 activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. *PLoS*
35 415 *Med* 2015;12(1):e1001776.
36 416 38. Zhou H, Haber M, Ray S, et al. Invasive pneumococcal pneumonia and respiratory virus co-
37 417 infections. *Emerg Infect Dis* 2012;18(2):294-7.
38 418 39. McCullers JA, Rehg JE. Lethal synergism between influenza virus and *Streptococcus pneumoniae*:
39 419 characterization of a mouse model and the role of platelet-activating factor receptor. *J Infect Dis*
40 420 2002;186(3):341-50.
41 421 40. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-gamma during
42 422 recovery from influenza infection. *Nat Med* 2008;14(5):558-64.
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3 423 41. Simell B, Auranen K, Käyhty H, et al. The fundamental link between pneumococcal carriage and
4 424 disease. *Expert Rev Vaccines* 2012;11(7):841-55.
5
6 425 42. Song JY, Nahm MH, Cheong HJ, et al. Impact of preceding flu-like illness on the serotype
7 426 distribution of pneumococcal pneumonia. *PLoS ONE* 2014;9(4):e93477.
8
9 427 43. Shiri T, Datta S, Madan J, et al. Indirect effects of childhood pneumococcal conjugate vaccination
10 428 on invasive pneumococcal disease: a systematic review and meta-analysis. *The Lancet Global Health*
11 429 2017;5(1):e51-e59.
12
13 430 44. Walter ND, Taylor THJ, Dowell SF, et al. Holiday Spikes in Pneumococcal Disease among Older
14 431 Adults. *N Engl J Med* 2009;361(26):2584-85.
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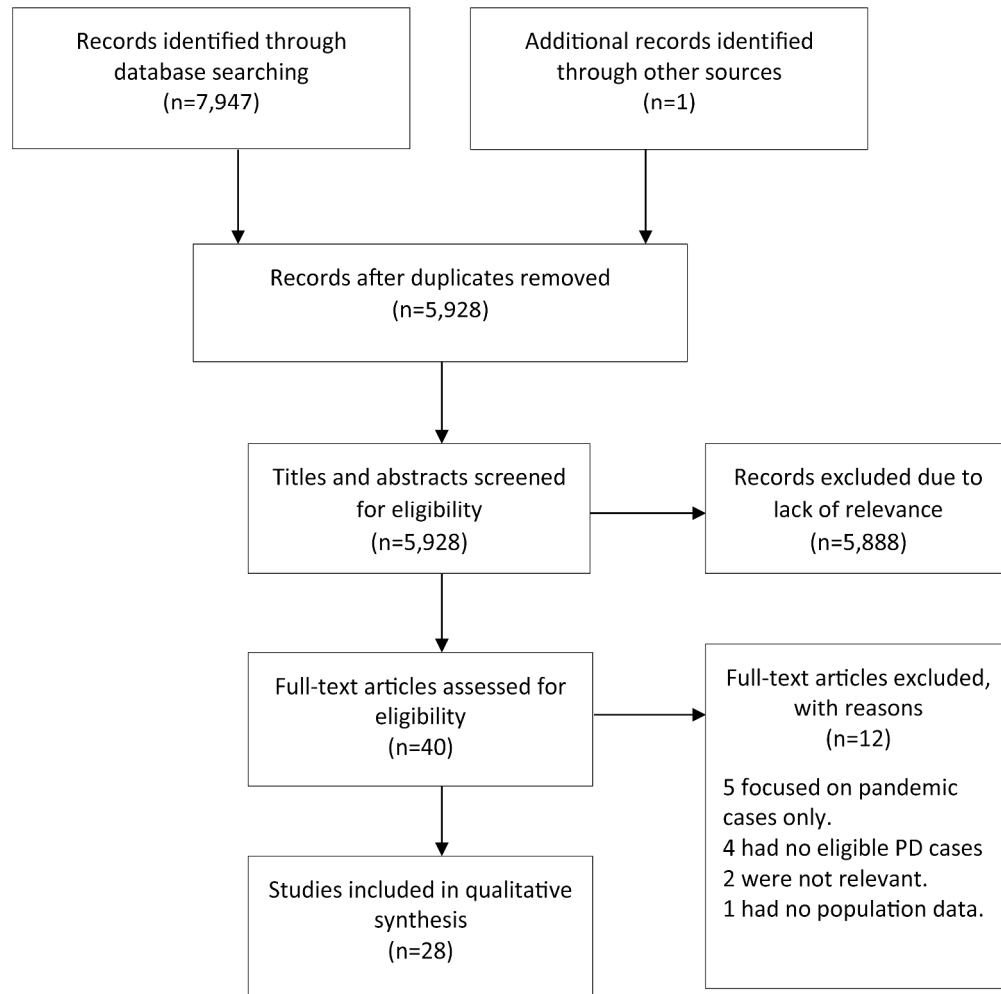


Figure 1. PRISMA flow diagram of the literature search. PD: pneumococcal disease.

314x310mm (300 x 300 DPI)



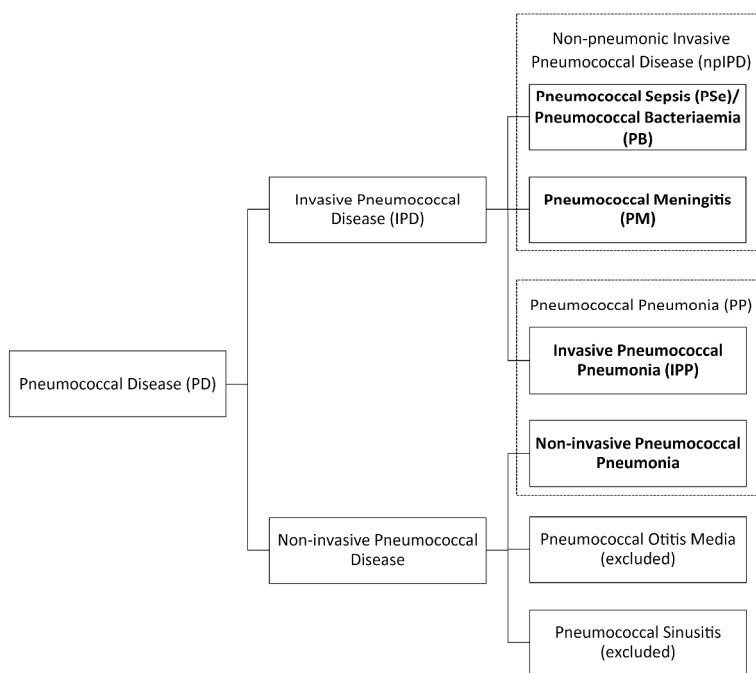


Figure 2. Category of pneumococcal disease in the present review.

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. 60% of mice died 2–11d after pneumococcus challenge in influenza A group compared with 15% in mock group;
McCullers et al. 2002 ⁷	Mice (n=20 per group)	influenza A + pneumococcus (0 or 7d later)	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, Fler 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, Fler 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.

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2
3 11. Stark JM, Stark MA, Colasurdo GN, et al. Decreased bacterial clearance from the lungs of mice
4 following primary respiratory syncytial virus infection. J Med Virol 2006;78(6):829-38.
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For peer review only

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* 2011;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.

- 1
- 2
- 3 2. Streptococcus pneumoniae.mp. or exp Streptococcus pneumoniae/
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- 6 3. exp virus/ or virus*.mp.
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- 9 4. exp virus infection/ or virus infection*.mp. or virus disease*.mp.
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38 4,778 results by 27 Apr 2017.

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41 **5,098 results by 31 Dec 2017.**

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44 **Global Health**

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- 47 1. Streptococcus pneumoniae.mp. or exp Streptococcus pneumoniae/
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15 10. 3 or 4
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18 11. 5 or 6 or 7 or 8
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21 12. 9 and 10 and 11
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24 13. limit 12 to yr="1990 -Current"
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27 1,164 results by 27 Apr 2017
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29 **961 results by 31 Dec 2017**
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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 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 follow	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H1	Ampofo, K	2008	Seasonal invasive pneumococcal	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 hospital	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 betw	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 pneumoni	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 in	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H22	Shrestha, S	2013	Time and dose-dependent risk d	no	no popula	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 bul	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

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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, PICCOs, 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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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

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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.

PROSPERO

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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).

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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

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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

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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

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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****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.

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BMJ Open

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

Journal:	<i>BMJ Open</i>
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

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3 **1 Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic**
4 **2 review of population-based studies**

5
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7
8 Authors: You Li* ¹, Meagan Peterson¹, Harry Campbell¹, Harish Nair¹
9

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11 ¹ Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics,
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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).

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33 **Strengths and limitations of this study**

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

39

For peer review only

40 Introduction

41 Both viral acute respiratory infection (VARI) and pneumococcal disease (PD) account for a substantial
42 disease burden worldwide, especially in young children and the elderly.¹⁻³ The association of viral
43 acute respiratory infection (VARI) and subsequent pneumococcal disease (PD) was not well
44 recognised until the catastrophic 1918 influenza pandemic, which resulted in an estimated 40–50
45 million deaths;⁴ it has been suggested that pneumococcus may have been a major cause of death.⁵
46 Most recently, it was observed that the incidence of PD was higher during 2009 influenza H1N1
47 pandemic period than the same period in pre-pandemic⁶⁻¹⁰ and post-pandemic years.^{7 9 10}

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

61 Methods

62 Search Strategy and Selection Criteria

63 We searched MEDLINE, Embase and Global Health databases using tailored search strategies (search
64 strategies in **Supplementary Text S1**, PRISMA flowchart in **Figure 1**). We restricted the search to
65 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 $\geq 38^{\circ}\text{C}$ with onset within 7 days.

93 Data Extraction

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

99 Data Analysis

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

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

109 Patient and Public Involvement

110 No patients or public were involved in the present study.

111 Results

112 A total of 28 studies¹¹⁻³⁸ were eligible and included in the review. We noticed a variety of study
113 designs, exposures and outcomes of interest and analytical methods in these studies (summarised in
114 **Table S2**). Due to the variety, we summarised the studies and displayed the results according to
115 study design and methods.

116 Individual Patient Data Based Studies

117 Individual patient data based studies during the inter-pandemic period are sparse. Only three
118 studies^{17 25 29} were identified (**Table 1**), including two cohort studies^{17 29} and one small case-control
119 study by O'Brien et al²⁵. The reported results consistently supported the role of preceding VARI on

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

122 **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]

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

126 Ecological Studies

127 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}
 128 out of the 25 ecological studies controlled for seasonal patterns of VARI and PD (**Table S2**).
 129 Additionally, the study by Stensballe et al.²⁹ analysed data at both population and individual level but
 130 did not control for the seasonal patterns.

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3 131 ***Correlation analyses with no control for seasonal patterns***

4 132 **Table 2** shows a summary of 11 studies^{12-14 20 21 23 24 27 29 30 33} using correlation analyses without
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6 133 controlling for seasonal patterns of VARI and PD. Since all studies conducted multiple tests in
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8 134 analysing the correlation (e.g. across age groups, viruses and lag time between VARI and PD),
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10 135 Bonferroni method was applied to adjust the significance level. The correlation between PD and
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12 136 influenza or RSV was statistically significant in all five studies^{14 23 24 29 30} that analysed population data
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14 137 of all ages (correlation coefficient r: 0.40–0.71 for influenza at no time lag, 0.47–0.77 for RSV at no
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16 138 time lag).
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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	<p><u>≥18y</u> 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)</p> <p><u><18y</u> 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)</p>
Murdoch et al. 2009 ²³	1995–2006	all ages Christchurch, New Zealand	IFV RSV ADV PIV	IPD (n=737)	Surveillance data, monthly	Spearman	<p><u>All ages</u> 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)</p>
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	<p><u>All ages</u>, Pearson IFV: 0.54a RSV: 0.47a</p> <p><u>All ages</u>, Spearman IFV: 0.67a RSV: 0.63a (correlations were stronger in 15–64y and ≥65y than 0–4y and 5–14y)</p>

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

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

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

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

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3 148 *Regression analyses controlling for seasonal patterns*

4 149 **Table 3** shows the summary of the 15 studies^{11 13 14 16 18 22-24 26 32 34-38} that controlled for seasonal
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6 150 patterns by regression analysis. Results were inconsistent among the studies. In all-age population
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8 151 studies, preceding influenza infection was likely to be associated with IPD (12 studies^{13 14 16 18 22-24 32 35-}
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10 152 ³⁸ reported an association and two studies^{11 34} reported no association). According to two studies^{23 24}
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12 153 that reported age-stratified results, the association between influenza and IPD was more likely to
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14 154 exist among older people than among young children. In terms of preceding RSV infection, four^{14 24 34}
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16 155 ³⁷ out of five studies^{14 23 24 34 37} observed an association of RSV with PD incidence. Specifically, one
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18 156 study¹⁴ found the association between RSV and IPD only existed among children <5 years. Studies
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20 157 reporting other viruses such as ADV and PIV were sparse (two^{14 23} and one²³ studies, respectively).
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22 158 Five studies^{14 23 24 34 37} that reported two or more viruses demonstrated that the association differed
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24 159 by the type of virus. Moreover, the association could differ among virus subtypes (e.g. influenza A vs
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26 160 influenza B²² and PIV 1/2 vs PIV 3²³). Notably, there are other factors that could influence the
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28 161 strength of the associations reported in these studies. For instance, the association could vary by
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30 162 presentation of PD (invasive pneumococcal pneumonia, IPP vs npIPD^{32 34 36} and PP vs pneumococcal
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32 163 sepsis, PSe³⁷); preceding VARI was more likely to be associated with the occurrence of pneumonia
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34 164 than other clinical presentations. Additionally, the results from studies in Denmark, where
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36 165 comorbidity status and pneumococcal serotype were available, demonstrated that influenza had a
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38 166 greater influence on the incidence of low-invasiveness serotypes than medium- or high- invasiveness
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40 167 among the low comorbidity group; among the high comorbidity group, the pattern was reversed.^{35 36}
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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	<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)	

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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		<u>All ages</u> 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	<u>All ages</u> 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)	<u>All ages</u> ILI: median 4.9% across all study years (1w) 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	<u>All ages</u> 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	<u>All ages</u> 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)

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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) <u>≥40y</u> , low comorbidity and low serotype invasiveness ILI: 17.9%^a [13.6–21.9%] (1w) <u>≥40y</u> , low comorbidity and high serotype invasiveness ILI: 6.7%^a [3.8–11.7%] (1w) <u>≥40y</u> , medium/high comorbidity and low serotype invasiveness ILI: 1.3% [-1.6–5.4%] (1w) <u>≥40y</u> , medium/high comorbidity and high serotype invasiveness ILI: 8.9%^a [6.6–11.8%] (1w)
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		

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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	<p>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)</p> <p>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)</p> <p>≥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)</p> <p>≥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)</p>	

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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,

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5 172 pneumococcal conjugate vaccine; PD, pneumococcal disease; PIV, parainfluenza virus; PP, pneumococcal pneumonia; PSe, pneumococcal sepsis; RR,
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7 173 relative risk; RSV, respiratory syncytial virus; UV index, clear-sky ultraviolet index; VARI, viral acute respiratory infection; w, week(s); y, year(s).
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9 174 Relative risk or attributable percentage **in bold** were statistically significant as originally reported in the study ($P < 0.05$); relative risk or attributable
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11 175 percentage ending with “a” were statistically significant after Bonferroni adjustment ($P < 0.05$ /number of relevant tests) or when the Bonferroni correction
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13 176 was deemed unnecessary, those ending with “b” did not have enough information to apply the Bonferroni correction; relative risk or attributable
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15 177 percentage ending with “c” were not statistically significant after Bonferroni adjustment.
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179 **Studies utilising other analyses**

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

182 **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

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

186 Discussion

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

190 We found that reported associations between VARI and subsequent PD were inconsistent among
 191 the 28 included studies. Only three studies^{17 25 29} analysed the association using individual patient
 192 data. The two cohort studies^{17 29} did not account for the shared risk factors between VARI and PD
 193 that influenced their seasonality, substantially limiting the inferences that can be made from these
 194 data while the case-control study²⁵ was limited by its small sample size (n case=13). In ecological
 195 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
 196 seasonal patterns. In these studies, we found that influenza and/or RSV infections were likely to be
 197 associated with the subsequent occurrence of PD. For influenza, the association was stronger among
 198 younger populations compared to older adults^{23 24} while the pattern was reversed for RSV.¹⁴ Data
 199 from multiple studies suggested that virus type (five studies^{14 23 24 34 37}) and subtype (two studies^{22 23}),

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3 200 comorbidity status (two studies^{35 36}) and pneumococcal serotype invasiveness (one study³⁵) could
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5 201 influence the association. However, these 16 ecological studies had various population
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7 202 characteristics (e.g. age, comorbidity, immunity status), PD datasets, VARI datasets and analytical
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9 203 methods. As such, heterogeneity among the studies, along with their ecological nature, limits the
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11 204 amount of valid inferences that can be made from the data (as summarised above).

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13 205 Nevertheless, these studies provide important clues for the potential factors related to the
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15 206 association between VARI and subsequent PD, and thus could help with the conception and design
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17 207 of future studies. Ideally, in order to understand whether a particular preceding VARI can predispose
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19 208 an individual to PD, a prospective cohort study that monitors each individual for VARI and
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21 209 pneumococcal infection would be utilised, allowing analyses at both individual and population levels.
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23 210 However, such a design would not be feasible or affordable as inter alia pneumococcal infections are
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25 211 rare. Alternatively, utilisation of large-scale routine health data and reliable data linkage (through
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27 212 unique individual identifiers) from sources such as surveillance data and hospitalisation datasets may
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29 213 be feasible in many industrialised countries. An example of such data linkage in our review is the
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31 214 study by Stensballe and colleagues²⁹ that linked information from four Danish population-based
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33 215 registries. While the authors conducted individual-level analysis, the results were based on cases
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35 216 tested for both the presence of respiratory viruses and pneumococcal infection. The true number of
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37 217 VARI-associated PD cases is likely to be significantly higher due to incomplete testing of cases; the
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39 218 untested viral-pneumococcal cases could represent a crucial source of selection bias. Community-
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41 219 based active surveillance can likely address the issue of missing cases but such surveillance would be
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43 220 labour intensive and less cost-effective to conduct. Another option is a case-control study, which is
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45 221 affordable and practical, but not without its limitations. In addition to challenges in designing such
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47 222 studies, defining the history of VARI is likely to be inaccurate since the timing of viral serology may
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49 223 be less accurate (information bias).²⁷ In the case-control study by O'Brien and colleagues,²⁵ the
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51 224 authors used influenza-strain specific convalescent serology as evidence for preceding influenza
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53 225 infection. The authors also conducted telephone interviews to investigate ILI history but they did not
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226 mention whether interviewers and interviewees were blind to case or control status. Moreover, the
227 value of this case-control study is limited by its very small sample size (n case = 13).

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

238 Apart from the study design, one further challenge of analysing the association is accounting for
239 the influence of seasonal factors of VARI and PD (confounding). Both VARI and PD have similar
240 seasonal patterns, and thus are likely to correlate as indicated by the correlation results from
241 ecological studies. The increased risk of PD during an epidemic season could be caused by VARI or by
242 seasonal risk factors or by both. In the present review, 11 studies^{12 15 17 20 21 27-31 33} did not attempt to
243 control for seasonal confounders, likely leading to biased estimations of the association. For example,
244 the study by Edwards and colleagues¹⁷ reported a relative risk as high as 112.5 when not adjusting
245 any seasonal factors. One way to address this problem in such studies would be to match the
246 individuals with the onset timing of pneumococcal infection, keeping the risk of PD comparable
247 between VARI cases and non-VARI cases; for ecological studies, regression analysis adding seasonal
248 terms or climatic factors (such as temperature and humidity), or cross-correlation analysis of time
249 series controlling for seasonal patterns could be considered.

250 Our review suggests that the association of VARI and subsequent PD could vary by virus type^{14 23 24}
251^{34 35} and even by subtype^{22 23}. Studies using combinations of viral infections such as all virus, influenza

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3 252 + RSV, non-influenza, or non-RSV could give biased estimations of the association. However, it is not
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5 253 always practical to analyse the association by virus type. In ecological studies, different types of
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7 254 viruses might co-circulate and thus be highly correlated in incidence, making it difficult to determine
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9 255 the role for each virus. In terms of PD, most studies used IPD as the outcome of interest. However,
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11 256 studies that categorised IPD into IPP and npIPD found that the association was more pronounced in
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13 257 IPP than in npIPD.^{32 34 36} A similar finding, that the association was stronger in PP than PSe, was
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15 258 reported in another study.³⁷ These results suggest VARI is more likely to be associated with
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17 259 pneumonic pneumococcal infections than non-pneumonic infections. In our review, we excluded
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19 260 studies using information other than clinical diagnosis as a proxy for PD (e.g. prescription data and
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21 261 carriage data). Pneumococcal carriage could have a fundamental role in the transmission and
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23 262 incidence of PD.⁴¹ In a study analysing the impact of pneumococcal carriage and viral activity,
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25 263 Weinberger and colleagues³⁴ found npIPD was associated with carriage prevalence, whereas IPP was
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27 264 associated with bronchiolitis (as a proxy for RSV). The authors also proposed that preceding VARI
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29 265 increased susceptibility but did not enhance transmission (indicated by carriage prevalence) in
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31 266 children. However, more studies are needed to confirm these findings.

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34 267 The association could also vary by population characteristics. According to two studies that
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36 268 displayed age-stratified results,^{23 24} the association of influenza and subsequent IPD was more likely
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38 269 to exist among older people than among young children. Studies by Weinberger et al.^{35 36} gauged the
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40 270 association in different comorbidity and pneumococcal serotype groups among Denmark
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42 271 populations. The results showed that influenza had a stronger impact on the incidence of low-
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44 272 invasiveness serotypes than medium- or high- invasiveness ones in the low comorbidity group, while
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46 273 the pattern reversed in the high comorbidity group. Another study that analysed clinical records of
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48 274 919 patients with PP found that infrequently colonising pneumococcal serotypes were more likely to
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50 275 cause PP after preceding VARI, particularly in patients with immunodeficiency or chronic lung
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52 276 diseases.⁴² These findings suggest the need for future studies to analyse the association by age group,
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54 277 pneumococcal serotype and comorbidity status. Moreover, the recent introduction of pneumococcal
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3 278 vaccines has brought changes in the incidence of serotype-specific PD,⁴³ making the association of
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5 279 VARI and PD more complicated to understand. As a result, future studies should consider the
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7 280 possible serotype-specific influence that pneumococcal vaccines have on both individual immunity
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9 281 and herd immunity when analysing the association.

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11 282 In addition to the factors discussed above, additional factors may influence the estimates of the
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13 283 association. The first is the change over time in the methodology of data collection, including
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15 284 changes in test method or diagnosis, clinical practice and health-seeking behaviour. The second is
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17 285 the possible delay in measurement, which happened most often in passive hospital-based studies.
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19 286 Thirdly, for ecological studies using aggregated data, “holiday spikes” could occur due to more social
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21 287 gatherings;⁴⁴ besides, weekends and holidays might influence timely tests or diagnosis as well as the
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23 288 health-seeking behaviour of patients.

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25 289 To our knowledge, this is the first review to summarise and critically appraise the methods and
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27 290 results of population-based studies about the association between seasonal VARI and subsequent
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29 291 PD. However, this review is not without its limitations. First, due to a variety of study designs, data
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31 292 sources and analytical methods in the studies included, no meta-analysis was conducted in the
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33 293 review. As such, we were unable to provide a quantitative measure of the association of seasonal
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35 294 VARI and PD. Second, no unpublished data sources were included in the review, which could mean
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37 295 the data reported favours positive associations due to publication bias. Thus, caution should be
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39 296 taken when interpreting the results. Thirdly, we found many studies tended to conduct multiple
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41 297 statistical tests using different subgroups and time periods (e.g. age group, virus, time lag between
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43 298 VARI and PD) without specifying the primary study question a priori or making proper statistical
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45 299 adjustments to account for multiple testing. This could give rise to an increased risk of reporting
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47 300 false positive results. In this review, we applied Bonferroni corrections to adjust for the multiple
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49 301 tests where deemed necessary. Since the Bonferroni method is conservative and we are unable to
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51 302 adjust for studies where *P* values were not given, the adjustment in our review is intended for
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53 303 readers’ reference and as caveats for future studies.
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304 Given the substantial burden of VARI across the world,¹ even a modest association between VARI
305 and subsequent PD could lead to a substantial burden of disease in terms of VARI-related PD cases. If
306 proper anti-bacterial interventions could be applied to those with higher risk of PD due to a
307 preceding VARI, subsequent pneumococcal infections could be prevented. The interventions would
308 be more effective / better targeted if we could estimate the risk (i.e. the strength of association)
309 according to timing of infection by week/month of a year, age, comorbidity status, virus type and
310 status of immunity. In turn, understanding the association between VARI and subsequent
311 pneumococcal infection can help evaluate the full impact of viral vaccine programs.

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

317 **Supplementary Materials**

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

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

320 **Text S1. Search strategy**

321 **File S1. Quality assessment of included studies**

322 **File S2. PRISMA checklist**

323 **File S3. Protocol registered in PROSPERO**

324 **Contributors:** HN and HC conceived the study. YL did the literature search and reviewed the articles.

325 YL and MP extracted and analysed the data independently with oversight from HN and HC. YL

326 drafted the manuscript. MP, HN and HC critically reviewed the manuscript. All authors read and

327 approved the final draft of the manuscript.

328 **Competing interests:** none declared.

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5 330 <http://dx.doi.org/10.7488/ds/2047>.

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REFERENCES

- 334 1. Wang H, Naghavi M, Allen C, et al. Global, regional, and national life expectancy, all-cause
335 mortality, and cause-specific mortality for 249 causes of death, 1980-2013;2015: a systematic
336 analysis for the Global Burden of Disease Study 2015. *The Lancet* 2016;388(10053):1459-544.
- 337 2. O'Brien KL, Wolfson LJ, Watt JP, et al. Burden of disease caused by *Streptococcus pneumoniae* in
338 children younger than 5 years: global estimates. *Lancet* 2009;374(9693):893-902.
- 339 3. Drijkoningen JJC, Rohde GGU. Pneumococcal infection in adults: burden of disease. *Clinical*
340 *Microbiology and Infection* 2014;20:45-51.
- 341 4. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. *Clin*
342 *Microbiol Rev* 2006;19(3):571-82.
- 343 5. Chien Y-W, Klugman KP, Morens DM. Bacterial Pathogens and Death during the 1918 Influenza
344 Pandemic. *N Engl J Med* 2009;361(26):2582-83.
- 345 6. Fleming-Dutra KE, Taylor T, Link-Gelles R, et al. Effect of the 2009 influenza A(H1N1) pandemic on
346 invasive pneumococcal pneumonia. *J Infect Dis* 2013;207(7):1135-43.
- 347 7. Launes C, Garcia-Garcia JJ, Trivino M, et al. Respiratory viruses, such as 2009 H1N1 influenza virus,
348 could trigger temporal trends in serotypes causing pneumococcal disease. *Clin Microbiol Infect*
349 2014;20(12):O1088-90.
- 350 8. Nelson GE, Gershman KA, Swerdlow DL, et al. Invasive pneumococcal disease and pandemic
351 (H1N1) 2009, Denver, Colorado, USA. *Emerg Infect Dis* 2012;18(2):208-16.
- 352 9. Pedro-Botet ML, Burgos J, Lujan M, et al. Impact of the 2009 influenza A H1N1 pandemic on
353 invasive pneumococcal disease in adults. *Scand J Infect Dis* 2014;46(3):185-92.
- 354 10. Weinberger DM, Simonsen L, Jordan R, et al. Impact of the 2009 influenza pandemic on
355 pneumococcal pneumonia hospitalizations in the United States. *J Infect Dis* 2012;205(3):458-65.
- 356 11. Allard R, Couillard M, Pilon P, et al. Invasive bacterial infections following influenza: a time-series
357 analysis in Montreal, Canada, 1996-2008. *Influenza other respi* 2012;6(4):268-75.
- 358 12. Ampofo K, Bender J, Sheng X, et al. Seasonal invasive pneumococcal disease in children: role of
359 preceding respiratory viral infection. *Pediatrics* 2008;122(2):229-37.
- 360 13. Burgos J, Larrosa MN, Martinez A, et al. Impact of influenza season and environmental factors on
361 the clinical presentation and outcome of invasive pneumococcal disease. *Eur J Clin Microbiol Infect*
362 *Dis* 2015;34(1):177-86.
- 363 14. Ciruela P, Broner S, Izquierdo C, et al. Invasive pneumococcal disease rates linked to
364 meteorological factors and respiratory virus circulation (Catalonia, 2006-2012). *BMC Public Health*
365 2016;16(400).

- 1
2
3 366 15. Dangor Z, Izu A, Moore DP, et al. Temporal association in hospitalizations for tuberculosis,
4 367 invasive pneumococcal disease and influenza virus illness in South African children. PLoS ONE
5 368 2014;9(3):e91464.
6
7 369 16. Domenech de Cellès M, Arduin H, Varon E, et al. Characterizing and Comparing the Seasonality of
8 370 Influenza-Like Illnesses and Invasive Pneumococcal Diseases Using Seasonal Waveforms. Am J
9 371 Epidemiol 2017:kwx336-kwx36.
10
11 372 17. Edwards LJ, Markey PG, Cook HM, et al. The relationship between influenza and invasive
12 373 pneumococcal disease in the Northern Territory, 2005-2009. Med J Aust 2011;194(4):207.
13
14 374 18. Grabowska K, Hogberg L, Penttinen P, et al. Occurrence of invasive pneumococcal disease and
15 375 number of excess cases due to influenza. BMC Infect Dis 2006;6:58.
16
17 376 19. Hendriks W, Boshuizen H, Dekkers A, et al. Temporal cross-correlation between influenza-like
18 377 illnesses and invasive pneumococcal disease in The Netherlands. Influenza and other Respiratory
19 378 Viruses 2017;11(2):130-37.
20
21 379 20. Jansen AG, Sanders EA, A VDE, et al. Invasive pneumococcal and meningococcal disease:
22 380 association with influenza virus and respiratory syncytial virus activity? Epidemiol Infect
23 381 2008;136(11):1448-54.
24
25 382 21. Kim PE, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season,
26 383 atmospheric conditions, air pollution, and the isolation of respiratory viruses. Clin Infect Dis
27 384 1996;22(1):100-6.
28
29 385 22. Kuster SP, Tuite AR, Kwong JC, et al. Evaluation of coseasonality of influenza and invasive
30 386 pneumococcal disease: results from prospective surveillance. PLoS Med 2011;8(6):e1001042.
31 387 23. Murdoch DR, Jennings LC. Association of respiratory virus activity and environmental factors with
32 388 the incidence of invasive pneumococcal disease. J Infect 2009;58(1):37-46.
33 389 24. Nicoli EJ, Trotter CL, Turner KM, et al. Influenza and RSV make a modest contribution to invasive
34 390 pneumococcal disease incidence in the UK. J Infect 2013;66(6):512-20.
35 391 25. O'Brien KL, Walters MI, Sellman J, et al. Severe pneumococcal pneumonia in previously healthy
36 392 children: the role of preceding influenza infection. Clin Infect Dis 2000;30(5):784-9.
37 393 26. Opatowski L, Varon E, Dupont C, et al. Assessing pneumococcal meningitis association with viral
38 394 respiratory infections and antibiotics: insights from statistical and mathematical models. Proc Biol Sci
39 395 2013;280(1764):20130519.
40 396 27. Peltola V, Heikkinen T, Ruuskanen O, et al. Temporal association between rhinovirus circulation
41 397 in the community and invasive pneumococcal disease in children. Pediatr Infect Dis J 2011;30(6):456-
42 398 61.
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45
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49
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2
3 399 28. Shrestha S, Foxman B, Weinberger DM, et al. Identifying the interaction between influenza and
4 400 pneumococcal pneumonia using incidence data. *Sci Transl Med* 2013;5(191):191ra84.
5
6 401 29. Stensballe LG, Hjuler T, Andersen A, et al. Hospitalization for respiratory syncytial virus infection
7 402 and invasive pneumococcal disease in Danish children aged <2 years: a population-based cohort
8 403 study. *Clin Infect Dis* 2008;46(8):1165-71.
9
10 404 30. Talbot TR, Poehling KA, Hartert TV, et al. Seasonality of invasive pneumococcal disease: temporal
11 405 relation to documented influenza and respiratory syncytial viral circulation. *Am J Med*
12 406 2005;118(3):285-91.
13
14 407 31. Toschke AM, Arenz S, von Kries R, et al. No temporal association between influenza outbreaks
15 408 and invasive pneumococcal infections. *Arch Dis Child* 2008;93(3):218-20.
16
17 409 32. Walter ND, Taylor TH, Shay DK, et al. Influenza circulation and the burden of invasive
18 410 pneumococcal pneumonia during a non-pandemic period in the United States. *Clin Infect Dis*
19 411 2010;50(2):175-83.
20
21 412 33. Watson M, Gilmour R, Menzies R, et al. The association of respiratory viruses, temperature, and
22 413 other climatic parameters with the incidence of invasive pneumococcal disease in Sydney, Australia.
23 414 *Clin Infect Dis* 2006;42(2):211-5.
24
25 415 34. Weinberger DM, Grant LR, Steiner CA, et al. Seasonal drivers of pneumococcal disease incidence:
26 416 impact of bacterial carriage and viral activity.[Erratum appears in *Clin Infect Dis*. 2014 Mar;58(6):908].
27 417 *Clin Infect Dis* 2014;58(2):188-94.
28
29 418 35. Weinberger DM, Harboe ZB, Viboud C, et al. Serotype-specific effect of influenza on adult
30 419 invasive pneumococcal pneumonia. *J Infect Dis* 2013;208(8):1274-80.
31
32 420 36. Weinberger DM, Harboe ZB, Viboud C, et al. Pneumococcal disease seasonality: incidence,
33 421 severity and the role of influenza activity. *Eur Respir J* 2014;43(3):833-41.
34
35 422 37. Weinberger DM, Klugman KP, Steiner CA, et al. Association between respiratory syncytial virus
36 423 activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. *PLoS*
37 424 *Med* 2015;12(1):e1001776.
38
39 425 38. Zhou H, Haber M, Ray S, et al. Invasive pneumococcal pneumonia and respiratory virus co-
40 426 infections. *Emerg Infect Dis* 2012;18(2):294-7.
41
42 427 39. McCullers JA, Rehg JE. Lethal synergism between influenza virus and *Streptococcus pneumoniae*:
43 428 characterization of a mouse model and the role of platelet-activating factor receptor. *J Infect Dis*
44 429 2002;186(3):341-50.
45
46 430 40. Sun K, Metzger DW. Inhibition of pulmonary antibacterial defense by interferon-gamma during
47 431 recovery from influenza infection. *Nat Med* 2008;14(5):558-64.
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3 432 41. Simell B, Auranen K, Käyhty H, et al. The fundamental link between pneumococcal carriage and
4 433 disease. *Expert Rev Vaccines* 2012;11(7):841-55.
5
6 434 42. Song JY, Nahm MH, Cheong HJ, et al. Impact of preceding flu-like illness on the serotype
7 435 distribution of pneumococcal pneumonia. *PLoS ONE* 2014;9(4):e93477.
8
9 436 43. Shiri T, Datta S, Madan J, et al. Indirect effects of childhood pneumococcal conjugate vaccination
10 437 on invasive pneumococcal disease: a systematic review and meta-analysis. *The Lancet Global Health*
11 438 2017;5(1):e51-e59.
12
13 439 44. Walter ND, Taylor THJ, Dowell SF, et al. Holiday Spikes in Pneumococcal Disease among Older
14 440 Adults. *N Engl J Med* 2009;361(26):2584-85.
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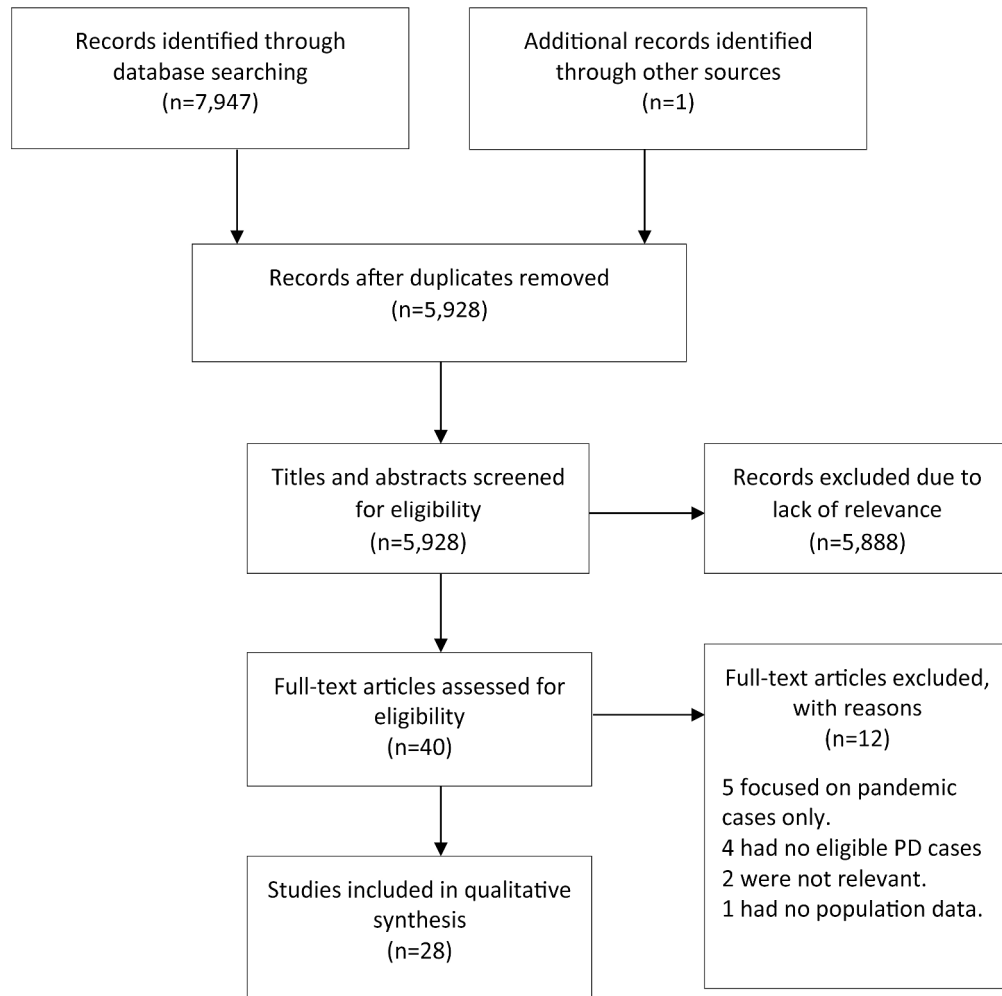


Figure 1. PRISMA flow diagram of the literature search. PD: pneumococcal disease.

314x310mm (300 x 300 DPI)



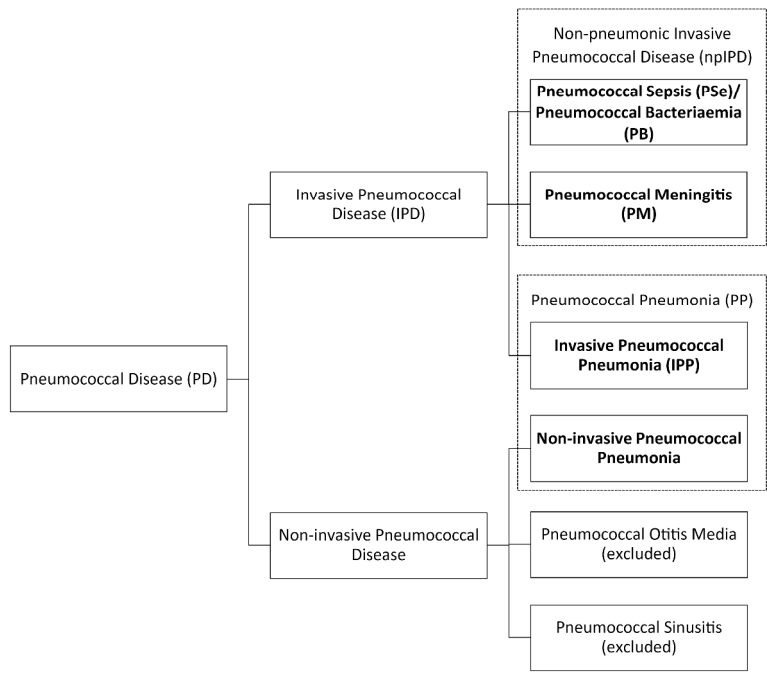


Figure 2. Category of pneumococcal disease in the present review.
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Table S1. Summary of findings from animal and in vitro studies.

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. 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. 2002 ⁷	Mice (n=20 per group)	influenza A + pneumococcus (0 or 7d later)	
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, Flier 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, Flier 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.

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

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	INDV	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* 2011;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.

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- 3 2. Streptococcus pneumoniae.mp. or exp Streptococcus pneumoniae/
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- 9 4. exp virus infection/ or virus infection*.mp. or virus disease*.mp.
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- 35 13. limit 12 to yr="1990 -Current"
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38 4,778 results by 27 Apr 2017.

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41 **5,098 results by 31 Dec 2017.**

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44 **Global Health**

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- 47 1. Streptococcus pneumoniae.mp. or exp Streptococcus pneumoniae/
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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 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 follow	yes		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
H1	Ampofo, K	2008	Seasonal invasive pneumococcal	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 hospital	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 betw	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 pneumoni	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	no	pandemic	NA	NA	NA	NA	NA	NA	NA	NA	NA
H21	Peltola, V	2011	Temporal association between in	yes		Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes
H22	Shrestha, S	2013	Time and dose-dependent risk	no	no popula	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	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

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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, PICCOs, 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

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

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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

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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.

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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).

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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

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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

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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

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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.

For peer review only

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