THE UNIVERSITY
of EDINBURGH

Global seasonality of respiratory viruses and the association between viral acute respiratory infection and subsequent pneumococcal disease

You Li, MSc

THE UNIVERSITY
of EDINBURGH

Doctor of Philosophy - The University of Edinburgh – 2019

Declaration

I, You Li, hereby declare that this thesis has been composed by me and that it has not been submitted, in whole or in part, for any other degree or professional qualification. I confirm that the work submitted is my own, except where work which has formed part of jointly-authored publications has been included. My contribution and those of the other authors to this work have been explicitly indicated below. I confirm that appropriate credit has been given within this thesis where reference has been made to the work of others.

The work presented in Chapter 2 has been published as "Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis" in Lancet Global Health, by You Li (myself), Rachel Reeves, Xin Wang, Quique Bassat, W. Abdullah Brooks, Cheryl Cohen, David P. Moore, Marta Nunes, Barbara Rath, Harry Campbell (co-supervisor), and Harish Nair (supervisor). In this publication, HN and HC conceptualised the study. I led the systematic literature review with contributions from RR and XW. I cleaned, analysed, and visualised the data. HN, HC, and I led the data interpretation. I wrote the first draft with inputs from RR, XW, HN and HC. All other named authors contributed to collection of unpublished research data and interpretation, and critically reviewed the initial manuscript.

The work presented in Chapter 4 has been published as "Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies" in BMJ Open, by You Li (myself), Meagan Peterson, Harry Campbell (co-supervisor), and Harish Nair (supervisor). This study was conceived by HN and HC. I did the literature search, reviewed the articles and drafted the manuscript. MP and I extracted and analysed the data independently. All authors critically reviewed the manuscript.

Signature: 李有 Date: 23-AUG-2019

Lay summary of thesis

Influenza virus (IFV), respiratory syncytial virus (RSV), parainfluenza virus (PIV), and metapneumovirus (MPV) are the most common viruses associated with acute lower respiratory infections. Global seasonality of these viruses is needed to inform public health strategies and programmes for their control. The viral-pneumococcal association has been recorded over the past one century but existing studies report inconsistent findings. This thesis aims to understand global seasonality of IFV, RSV, PIV, and MPV; aims to assess the effectiveness and efficiency of different approaches of RSV immunisation programmes in lower and middle income countries (LMICs); and aims to understand the viral-pneumococcal association.

For the global seasonality of respiratory viruses, this thesis uses viral activity data from systematic literature search, online datasets, and research datasets shared by collaborators in the RSV Global Estimates Network (RSV GEN). The thesis describes the global seasonal patterns of each virus and highlights the important differences between seasonality of IFV and RSV. An online practical tool was developed to predict IFV and RSV seasonal epidemics using temperature and humidity. Furthermore, this thesis shows that a seasonal approach for both RSV long-acting monoclonal antibody and maternal vaccine is favourable for most LMICs with clear RSV seasonality.

For viral-pneumococcal association, the thesis first presents a systematic review of existing studies on this topic and then presents an ecological study using laboratory confirmed data in Scotland, the results of which support an association between IFV and RSV, and invasive pneumococcal disease in all age groups.

The global seasonality work in the thesis has important implications for health-care planning and immunisation strategies, especially for RSV prevention strategies. Unveiling the viral-pneumococcal association can help improve guidelines for the clinical management for patients with viral infection.

Contents

Acknowledgements ..... **i**

Abstract ..... **iii**

Introduction iii

Methods iii

Results iv

Conclusion iv

Chapter 1 Introduction **1**

1.1 Common respiratory viruses 1

1.1.1 Influenza virus 2

1.1.2 Respiratory syncytial virus 5

1.1.3 Parainfluenza virus 8

1.1.4 Metapneumovirus 8

1.2 Seasonality of respiratory viruses 9

1.2.1 Global seasonality 9

1.2.2 Drivers of seasonality 15

1.2.3 Modelling of global seasonality 17

1.3 Interaction between viral respiratory infection and pneumococcal disease 20

1.3.1 Pneumococcal disease 20

1.3.2 Vaccine as a probe to understand the interaction between viral respiratory infection and pneumococcal disease 21

1.3.3 Viral-pneumococcal interaction during IFV pandemics 21

1.3.4 Current understanding of the interaction between viral respiratory infection and pneumococcal diseases 23

1.4 Aims of the thesis 24

1.4.1 To understand global seasonality of respiratory viruses (Chapter 2) 24

1.4.2 To understand the role of RSV seasonality on RSV prevention strategy planning in lower and middle income countries (Chapter 3) 24

1.4.3 To understand existing evidence in the association between viral respiratory infection and subsequent pneumococcal disease (Chapter 4) 24
1.4.4 To investigate the association between viral respiratory infection and subsequent invasive pneumococcal disease (Chapter 5) 25
Chapter 2 Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus and metapneumovirus: a systematic analysis 26
2.1 Introduction 26
2.2 "Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis" [version accepted for publication by Lancet Global Health] 28
2.2.1 Introduction 31
2.2.2 Method 32
2.2.3 Results 40
2.2.4 Discussion 55
2.3 Conclusion 61
Chapter 3 The role of RSV seasonality on national planning of introduction of RSV prevention strategies 62
3.1 Introduction 62
3.2 Method 63
3.2.1 RSV seasonality in LMICs 63
3.2.2 Assessment of the impact of RSV prevention programmes in LMICs 63
3.3 Results 69
3.3.1 RSV seasonality in LMICs 69
3.3.2 Effectiveness and efficiency of different approaches 75
3.4 Discussion 83
Chapter 4 Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review 87
4.1 Introduction 87

4.2 Full-text of the publication “Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies” 88
4.2.1 Introduction 89
4.2.2 Methods 90
4.2.3 Results 95
4.2.4 Discussion 116
4.3 Supplementary files to the publication “Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies” 123
4.4 Conclusion 130
Chapter 5 Association between respiratory virus activity and subsequent invasive pneumococcal disease 131
5.1 Introduction 131
5.2 Method 131
5.2.1 Data sources 131
5.2.2 Data analysis 132
5.3 Results 135
5.3.1 Study characteristics 135
5.3.2 Seasonality of IPD and viral-infections 135
5.3.3 Association between IPD and viral infection 139
5.4 Discussion 141
Chapter 6 Discussion 146
6.1 Strengths 147
6.1.1 Inclusion of unpublished data 147
6.1.2 Novel approach of modelling seasonality 147
6.1.3 Prediction of local IFV/RSV seasonal epidemics 148
6.1.4 Inclusion of laboratory-confirmed IPD and viral infection data 149
6.2 Limitations 149
6.2.1 Heterogeneity in viral activity data globally 149
6.2.2 Year-to-year variability in viral activity 149

6.2.3 Limited seasonality data of PIV and MPV 150
6.2.4 Lack of comorbidity and IPD serotype information 150
6.3 Comparisons among definitions of viral seasonal epidemics 151
6.4 Issues regarding controlling for shared seasonal risk factors between viral infection and PD 159
6.5 Implications for RSV immunisation strategies 161
6.5.1 Maternal vaccine — ResVax 161
6.5.2 Long-acting mAb — MEDI8897 162
6.6 Proposals for future studies 163
6.6.1 Proposals related to global seasonality of respiratory viruses studies 163
6.6.2 Proposals for future viral-pneumococcal association studies 165
Chapter 7 Conclusions 166
Appendices 180
A1. Glossary 180
A2. Search strategy for the global seasonality systematic literature review 183
A3. Details of seasonality data from online public sources 185
A4. Details of seasonality data from RSV GEN 186
A5. Questionnaire of quality assessment in seasonality papers 190
A6. Technical details of the seasonality model 191
A7. The user manual of the seasonality prediction tool 196
A8. Details of the included studies from systematic literature review of viral seasonality 198
A9. Study sites included in the seasonality analysis by IFV type and subtype 228
A10. Heat map of global monthly activity of IFV A and B, and IFV A subtypes 229
A11. Epidemic months of IFV, RSV, PIV and MPV grouped by country 230
A12. Subgroup analysis of duration of epidemics and site latitudes 259

A13. Proportion of the annual overlap between IFV A and B, between IFV and RSV, and between MPV and RSV 261
A14. Monthly activity of influenza virus and respiratory syncytial virus against mean-centred temperature and relative humidity: observed data 262
A15. Incidence rate ratios applied to the estimate of RSV incidence within under 1 year old 263
A16. Data availability of RSV seasonality in LMICs 264
A17. Comparisons of duration of RSV epidemics between temperate and tropical regions in LMICs 272
A18. Estimated of the coverage of mAb and mV 273
A19. Country-specific comparisons among different mAb immunisation approaches in preventing RSV-ALRI, considering year-to-year variations 274
A20. Country-specific comparisons among different mAb immunisation approaches in preventing RSV-severe-ALRI, considering year-to-year variations 275
A21. Country-specific comparisons among different mV immunisation approaches in preventing RSV-ALRI, considering year-to-year variations 276
A22. Country-specific comparisons among different mV immunisation approaches in preventing RSV-severe-ALRI, considering year-to-year variations 277
A23. List of ICD-10 codes used 278
A24. Number of IPD and viral infection cases included by year 279
A25. Percentage of IPD attributable to ICD-coded IFV and RSV hospitalisations by age group 279
A26. Percentage of PP attributable to each virus by age group 280
A27. Percentage of PP attributable to ICD-coded IFV and RSV hospitalisations by age group 280
A28. Publications related to this thesis 281

List of Tables

Table 1-1 The odds ratio (OR) and attributable fraction in the exposed (AFE, %) of each respiratory virus in ALRI cases compared with asymptomatic controls, from meta-analysis results 1
Table 1-2 Summary of the four IFV pandemics in the past one hundred years 3
Table 1-3 Summary of studies reporting global seasonality of respiratory viruses 11
Table 1-4 Summary of modelling studies on global seasonality of IFV 19
Table 1-5 Summary of studies reporting pneumococcal diseases during the 2009 swine flu 22
Table 2-1 Overview of sites included in the analysis 41
Table 2-2 Agreement on epidemic months between observed data and model prediction by leave-one-out cross validation 52
Table 3-1 The distribution of duration of RSV epidemics measured by site-years 72
Table 3-2 The distribution of year-to-year variation in the onset of RSV epidemics among sites with clear seasonality, measured by site-years 74
Table 3-3 The distribution of RSV coverage by the average RSV season ... 75
Table 4-1 Summary of individual patient data based studies 96
Table 4-2 Summary of ecological studies utilising correlation analysis 98
Table 4-3 Summary of ecological studies controlling for seasonal patterns 104
Table 4-4 Summary of findings from animal and in vitro studies 123
Table 4-5 Summary of methodologies utilised in the included studies (n=28) 128
Table 5-1 Number of IPD and viral infection cases included in the main analysis by age group 135
Table 5-2 Percentage of IPD attributable to each virus by age group in the main analysis 139
Table 5-3 Percentage of IPD attributable to each virus by age group in post-PCV-13 period as a sensitivity analysis 140

Table 5-4 Comparison of findings between previous studies and my study in the AP of IPD attributable to IFV and RSV among all ages 142
Table 6-1 Summary of global/regional reports that defined viral seasonal epidemics..... 153
Table 6-2 Comparisons between annual positive proportion and test-positive proportion..... 156
Table 6-3 Comparisons among annual positive proportion-based definitions of viral seasonal epidemics..... 157

List of Figures

Figure 1-1 RSV vaccine and mAb snapshot (Updated on 10th December 2018)..... 7
Figure 2-1 Study sites included in the analysis 42
Figure 2-2 Heat map of global monthly activity of influenza virus and respiratory syncytial virus, sorted by latitude. 45
Figure 2-3 Heat map of global monthly activity of parainfluenza virus and metapneumovirus, sorted by latitude 46
Figure 2-4 Latitudes of sites and duration of epidemics..... 47
Figure 2-5 Latitudes of sites and difference in timing of epidemics between A. influenza virus A and B, B. influenza virus and respiratory syncytial virus, and C. metapneumovirus and respiratory syncytial virus by subgroup analyses 49
Figure 2-6 Monthly activity of influenza virus and respiratory syncytial virus against mean-centred temperature and relative humidity: model-predicted output..... 51
Figure 2-7 Global maps of the estimated average epidemic months of influenza virus during 2013–2017 on a 5° by 5° scale 53
Figure 2-8 Global maps of the estimated average epidemic months of respiratory syncytial virus during 2013–2017 on a 5° by 5° scale 54
Figure 3-1 Schematic figure presenting the workflow of assessing the impact of RSV prevention strategies 64
Figure 3-2 Schematic figure presenting the five candidate approaches for mAb using Bolivia as an example 66
Figure 3-3 Schematic figure presenting the three candidate approaches for mV using Bolivia as an example 67
Figure 3-4 Data availability of RSV seasonality in LMICs 69
Figure 3-5 The distribution of duration of RSV epidemics (in months) in the temperate and tropical regions..... 70
Figure 3-6 Annual average monthly activity of RSV in LMICs..... 71
Figure 3-7 Monthly activity of RSV in sites with multi-year data..... 73

Figure 3-8 Proportion of RSV incidence averted by different approaches of RSV immunisation 76
Figure 3-9 Proportion of RSV incidence averted per dose by different approaches of RSV immunisation 77
Figure 3-10 Country-specific comparisons of different mAb administration approaches, sorted by duration of RSV epidemics 79
Figure 3-11 Country-specific comparisons of different mV administration approaches, sorted by duration of RSV epidemics 80
Figure 3-12 Country-specific comparisons of different mAb administration approaches, sorted by duration of RSV epidemics, considering multi-year variations 81
Figure 3-13 Country-specific comparisons of different mV administration approaches, sorted by duration of RSV epidemics, considering multi-year variations 82
Figure 4-1 PRISMA flow diagram of the literature search 92
Figure 4-2 Category of pneumococcal disease in the present review 93
Figure 5-1 Time series of number of cases in IPD and each viral infection, presented as 3-week moving average 137
Figure 5-2 Time series of number of cases in IPD and each viral infection by age group, presented as 3-week moving average 138
Figure 6-1 Comparisons among APP-based definitions for viral seasonal epidemics 158
Figure 6-2 Causal diagrams for the association between viral infection and subsequent pneumococcal disease (A. simple version; B. time-lag version) 160

List of Panels

Panel 1-1 Routes of IFV infection transmission 4
Panel 4-1 Search strategy 126
Panel 5-1 Negative binomial regression for main analysis..... 133
Panel 5-2 Sensitivity Analyses (negative binomial regression) 134

Acknowledgements

The work presented in this thesis was done in the University of Edinburgh from 2016 to 2019. This work would never be possible without the support from many people.

I would like to express my most sincere gratitude to my supervisors, Prof. Harish Nair and Prof. Harry Campbell for their invaluable guidance, advice and support. Their enthusiasm and dedication inspired me to become an independent researcher.

I would never have been able to complete this Ph.D. without the company of my beloved wife, Xin Wang. The completion of my Ph.D. is a milestone for us as this is the tenth year that we have been with each other. I feel grateful to have such a soulmate in my life. As the role of a researcher, Xin was also the second reviewer for one of the systematic reviews in my Ph.D. project and provided many useful thoughts on my Ph.D. project.

I would like to thank Rachel Reeves and Meagan Peterson for being the second reviewers for my systematic reviews. I would like to thank Anne Douglas and Rachel Reeves for their help with the application and management of the Scottish dataset for my Ph.D. project. I would like to thank Daniel Feikin for his advice and support on the comparison of RSV immunisation approaches work. I would like to thank Claire Parker, Diane White and Stephanie Scott for their assistance with the administrative matters.

I would like to thank all the members in the Respiratory Syncytial Virus Global Epidemiology Network (RSV GEN) for sharing their research data for my Ph.D. research on the global seasonality of respiratory viruses. I would also like to acknowledge the support of the eDRIS Team (National Services Scotland) for their involvement in obtaining approvals, provisioning and linking data and the use of the secure analytical platform within the National Safe Haven.

I would also like to take this opportunity to thank my MSc supervisor, Prof. Jian-meng Liu for his guidance and encouragement to my pursuit of Ph.D. I would also like to thank China Scholarship Council for the financial support throughout my study.

Finally, yet importantly, I feel grateful to my parents and Xin's parents for being so supportive and encouraging of our decisions to study abroad in Edinburgh, more than 5000 miles away from our homes. 爸爸妈妈，谢谢你们！

Abstract

Introduction

Influenza virus (IFV), respiratory syncytial virus (RSV), parainfluenza virus (PIV), and metapneumovirus (MPV) are the most common viruses associated with acute lower respiratory infections in young children and the elderly. A global report of seasonality of these viruses is needed to inform public health strategies and programmes for their control. The association between viral infection and subsequent pneumococcal disease has been long recognised but the existing studies report inconsistent findings, possibly due to a variety of methodological challenges in these studies. This thesis aims to understand global seasonality of IFV, RSV, PIV, and MPV, and to understand the role of RSV seasonality on lower and middle income countries (LMICs) planning of introduction of RSV prevention strategies. This thesis also aims to understand the existing evidence regarding the association between viral infection and pneumococcal disease as the first step, and as the second step, to assess the association using Scottish health data.

Methods

Laboratory-confirmed viral activity data were collected from systematic literature searches, public datasets, and research datasets shared by collaborators in RSV Global Epidemiology Network (RSV GEN). Monthly annual average percentage (AAP) was calculated for each site as the relative strength of virus activity. Duration of seasonal epidemics were defined as the minimum number of months to account for 75% of annual positive samples. Based on monthly AAP, IFV and RSV activity was modelled using site-specific temperature and relative humidity data. A prediction tool was used to help estimate local seasonal epidemics of IFV and RSV. Using RSV seasonality data in LMICs, the effectiveness and efficiency of different candidate approaches of RSV immunisation was compared. A separate systematic review was conducted to critically appraise the methodologies and findings of existing population studies on the association between viral

infection and subsequent pneumococcal disease. Based on the findings of this review, an ecological study was conducted using laboratory-confirmed viral and pneumococcal data to assess the association. The attributable percentage of invasive pneumococcal disease to IFV, RSV, PIV, and MPV was estimated in all ages, <6y, 6–64y, and >64y.

Results

IFV had clear seasonal epidemics in winter months in most temperate sites but the timing of epidemics was more variable and less seasonal with decreasing distance from the equator. Unlike IFV, RSV had clear seasonal epidemics in both temperate and tropical regions, starting in late summer months in the tropics of each hemisphere, reaching most temperate sites in winter months. PIV epidemics were found mostly in spring and early summer months in each hemisphere. MPV epidemics occurred in late winter and spring in most temperate sites but the timing of epidemics was more diverse in the tropics. The prediction model had good predictability of the local average epidemic months of IFV and RSV. RSV seasonality was distinct and was relatively stable over several years in most LMICs. Compared with a year-round approach, seasonal approaches were more supported in LMICs with clear seasonality. The systematic review of viral-pneumococcal association studies found that failure to account for shared seasonal factors between viral and pneumococcal infection was common and that the association was likely to differ by virus type, highlighting the needs for viral-specific analysis. Using laboratory-confirmed viral and pneumococcal data in Scotland, IFV and RSV were found to be associated with subsequent invasive pneumococcal pneumonia across all age groups.

Conclusion

This is the first study to provide global representations of month-by-month activity of IFV, RSV, PIV and MPV. The prediction model is helpful in predicting the local onset of IFV and RSV epidemics. The seasonality information presented in the thesis has important implications for health services planning, the timing of RSV passive prophylaxis and the strategy of

IFV and future RSV vaccination. A seasonal approach of RSV immunisation can be considered for most LMICs with clear RSV seasonality. The viral-pneumococcal association study finds a consistent support for the association between IFV and RSV in all age groups. Future individual-patient-level studies are warranted to confirm the findings.

Chapter 1 Introduction

1.1 Common respiratory viruses

Acute lower respiratory infection (ALRI), which mainly includes pneumonia and bronchiolitis, is one of the leading causes of mortality and morbidity in young children and older adults worldwide. It is estimated that ALRI caused over 2.3 million deaths globally in 2016 (Troeger et al. 2018). Influenza virus (IFV), respiratory syncytial virus (RSV), parainfluenza virus (PIV) and metapneumovirus (MPV) are the four most common respiratory viruses that are related to ALRI (Shi et al. 2015a; Shi et al. 2019) (**Table 1-1**). Globally, it is estimated that in 2016, there were 39.1 million IFV episodes and 24.8 million RSV episodes, resulting 58.2 thousand deaths and 76.6 thousand deaths in all ages, respectively. Currently, there are no global burden estimates for ALRI associated with PIV or MPV.

Table 1-1 The odds ratio (OR) and attributable fraction in the exposed (AFE, %) of each respiratory virus in ALRI cases compared with asymptomatic controls, from meta-analysis results

VIRUS	CHILDREN UNDER 5		ELDERLY OVER 65	
	OR (95%CI)	AFE (95%CI)	OR (95%CI)	AFE (95%CI)
IFV	5.1 (3.2–8.1)	80 (69–88)	8.3 (4.4–15.9)	88 (77–94)
IFV A	6.0 (3.3–10.8)	83 (70–91)	8.4 (3.9–17.8)	88 (75–94)
IFV B	2.7 (0.97–7.5)	63 (–3–87)	NA	~100
RSV	9.8 (5.0–19.3)	90 (80–95)	8.5 (3.9–18.5)	88 (74–95)
PIV	3.4 (1.6–7.2)	70 (37–86)	NA	~100
MPV	3.8 (2.5–5.8)	73 (59–83)	9.8 (2.3–41.0)	90 (57–98)
ADV	1.1 (0.7–1.8)	12 (–41–44)	NA	~100
RV	1.4 (1.0–2.0)	30 (3–49)	7.1 (3.7–13.6)	86 (73–93)
BOV	1.2 (0.4–4.0)	17 (–178–75)	5.6 (1.3–23.7)	82 (25–96)
COV	1.0 (0.8–1.3)	3 (–25–25)	2.8 (2.0–4.1)	65 (49–76)

IFV=influenza virus; RSV=respiratory syncytial virus; PIV=parainfluenza virus; MPV=metapneumovirus; ADV=adenovirus; RV=rhinovirus; BOV=bocavirus; COV=coronavirus; NA=not available

1.1.1 Influenza virus

IFV is a negative-sense, single-stranded RNA virus of the *Orthomyxoviruses* family and has four types—IFV A, IFV B, IFV C and IFV D. Only IFV A, IFV B, and IFV C infect human beings. Compared with IFV A and IFV B, IFV C is less common in human infections. A recent study tested 3300 human respiratory samples from Scotland using polymerase chain reaction (PCR) and found 3.2% positive for IFV A, 0.9% for IFV B, 0.2% for IFV C, and none for IFV D (D. B. Smith et al. 2016).

Influenza virus A

IFV A can be further categorised into subtypes, e.g. IFV A(H1N1) and IFV A(H3N2), based on surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA). There are 18 different HA subtypes and 11 different NA subtypes. Currently, IFV A(H1N1)pdm and IFV A(H3N2) are the two main circulating strains. The predominant IFV A subtypes differ each year and differ by region. Within IFV A subtypes, there are different strains due to IFV's antigenic change, including antigenic drift and antigenic shift. Antigenic drift is more common and is a result of point mutations in the genes encoding HA and NA. This may produce seasonal outbreaks of IFV. Antigenic shift is rare and is a result of viral assortment of two viruses, creating new virus strains. This may trigger an IFV pandemic, as humans are unlikely to have immunity to the novel strains. An IFV pandemic may also be triggered when an IFV strain that generally infects animals starts to be able to infect humans. In the past one hundred years, there were four pandemics that resulted from novel IFV strains: the 1918 H1N1 Spanish flu, the 1957 H2N2 Asian flu, the 1968 Hong Kong flu, and the 2009 swine flu (**Table 1-2**) (Saunders-Hastings and Krewski 2016).

Table 1-2 Summary of the four IFV pandemics in the past one hundred years

NAME	YEAR	STRAIN	SUSPECTED ORIGIN	NUMBER OF DEATH
SPANISH FLU	1918–1920	H1N1	China	40–50 million
ASIAN FLU	1957–1958	H2N2	China	1–2 million
HONG KONG FLU	1968–1970	H3N2	China	0.5–2 million
SWINE FLU	2009–2010	H1N1pdm	Mexico	up to 0.6 million

Influenza virus B

Unlike IFV A, IFV B does not have subtypes but can be further broken down into lineages and strains. Currently B/Yamagata and B/Victoria are the two circulating lineages. According to a recently published systematic review, there were very few differences in the clinical presentation of patients infected with different influenza subtypes/lineages (Saverio Caini et al. 2018).

Transmission

IFV infects and replicates in the epithelial cells of the human respiratory tract. The median incubation period, defined as the time between infection and symptom onset, is 1.4 days for IFV A and 0.6 days for IFV B (Lessler et al. 2009). Currently, there are three widely accepted routes of IFV transmission, defined as the process where an infectious organism moves from one host to another and induces disease: droplets, aerosols and contact (**Panel 1-1**), but it remains unclear regarding the relative significance of these routes (Killingley and Nguyen‐Van‐Tam 2013).

Panel 1-1 Routes of IFV infection transmission

Droplets: Droplets refer to particles generally >10 μm. These particles can adhere on mucous surfaces in the upper respiratory tract (e.g. mouth and nose). They can be inhaled but are too large to reach the lower respiratory tract.

Aerosols: Aerosols are smaller particles (<5 μm). These particles can be inhaled and reach the lower respiratory tract, in addition to the upper respiratory tract.

Contact: Contact includes direct contact and indirect contact. The former refers to the virus being physically transferred between two persons and the latter refers to an indirect transfer via contaminated surface or objects.

Influenza Vaccine

Vaccination is the most effective way for the prevention and control of IFV. Due to the antigenic drift and shift of IFV, circulating strains vary from year to year. Therefore, the vaccine needs to be administrated annually to be matched with the circulating strains of the year (World Health Organization 2018b). Interestingly, cross-lineage protection and residual effects from prior vaccination were observed (McLean et al. 2015) and the underlying mechanism warranted further investigation.

Currently, WHO recommends annual vaccination for:

- pregnant women at any stage of pregnancy
- children aged between 6 months to 5 years
- elderly individuals (aged more than 65 years)
- individuals with chronic medical conditions (e.g. diabetes)
- health-care workers

In order to better monitor global IFV activity, The Global Influenza Surveillance and Response System (GISRS) has been set up since 1950s. WHO recommends seasonal influenza vaccine compositions twice a year for

the northern hemisphere and southern hemisphere, in order to match with the prevalent IFV strains in each season.

1.1.2 Respiratory syncytial virus

Human RSV is a negative-sense, single-stranded RNA virus of the species *Human orthopneumovirus* of the family *Pneumovirinae* (formerly a subfamily within *Paramyxoviridae* family until 2016 (Afonso et al. 2016)). The RSV genome is approximately 15000 nucleotides in length, which encode 11 viral proteins including non-structural protein 1 (NS1) and NS2, nucleocapsid protein (N), phosphoprotein (P), matrix protein (M), small hydrophobic protein (SH), attachment glycoprotein (G), fusion glycoprotein (F), transcription regulatory proteins (M2-1 and M2-2), and a large polymerase (L) (Lee et al. 2012; Schobel et al. 2016). It has two antigenic groups, group A and B, based on antigenic and genomic differences found in several viral proteins, but especially the G protein.

RSV was first discovered more than sixty years ago in chimpanzees and then the next year in two children with respiratory illness (Chanock et al. 1957).

Transmission

RSV replicates in the nasopharyngeal epithelium. The median incubation period of RSV is 4.4 days (Lessler et al. 2009). RSV transmission is by direct inoculation of contagious secretions or by droplets (>10 μm) into the eyes and nose (Hall and Douglas 1981).

RSV Vaccine

Currently, there is no licensed RSV vaccine although there are more than 20 candidate vaccines undergoing clinical trials. The only licensed RSV prevention product is Palivizumab, a monoclonal antibody (mAb) providing passive immunisation. Palivizumab is short-acting and needs to be given on a monthly basis for 5 months starting from the onset of RSV season. Palivizumab is expensive. For a baby at 6 months weighing 7.5 kg, the cost of one dose of palivizumab is over £1000 (D. Wang et al. 2011). Therefore, Palivizumab is almost exclusively used in high-income countries. It is

expected that long-lasting mAb will be less expensive and might only need one dose at the onset of RSV season (Domachowske et al. 2018). In addition to mAb, maternal vaccination could be another option for a future prevention strategy. **Figure 1-1** below shows a snap shot of RSV vaccines and mAbs, which is regularly updated by PATH. More detailed information about RSV vaccine progress can be found in a recently published review (Mazur et al. 2018). Most recently, the topline results from the phase 3 clinical trial of maternal RSV vaccine (ResVax) were announced. Although the vaccine did not meet its primary efficacy endpoint (39.4%, 97.5%CI, -1.0% to 63.7%), the vaccine demonstrated efficacy in preventing RSV-hospitalization (44.4%, 95%CI, 19.6% to 61.5%) (Anonymous 2019b).

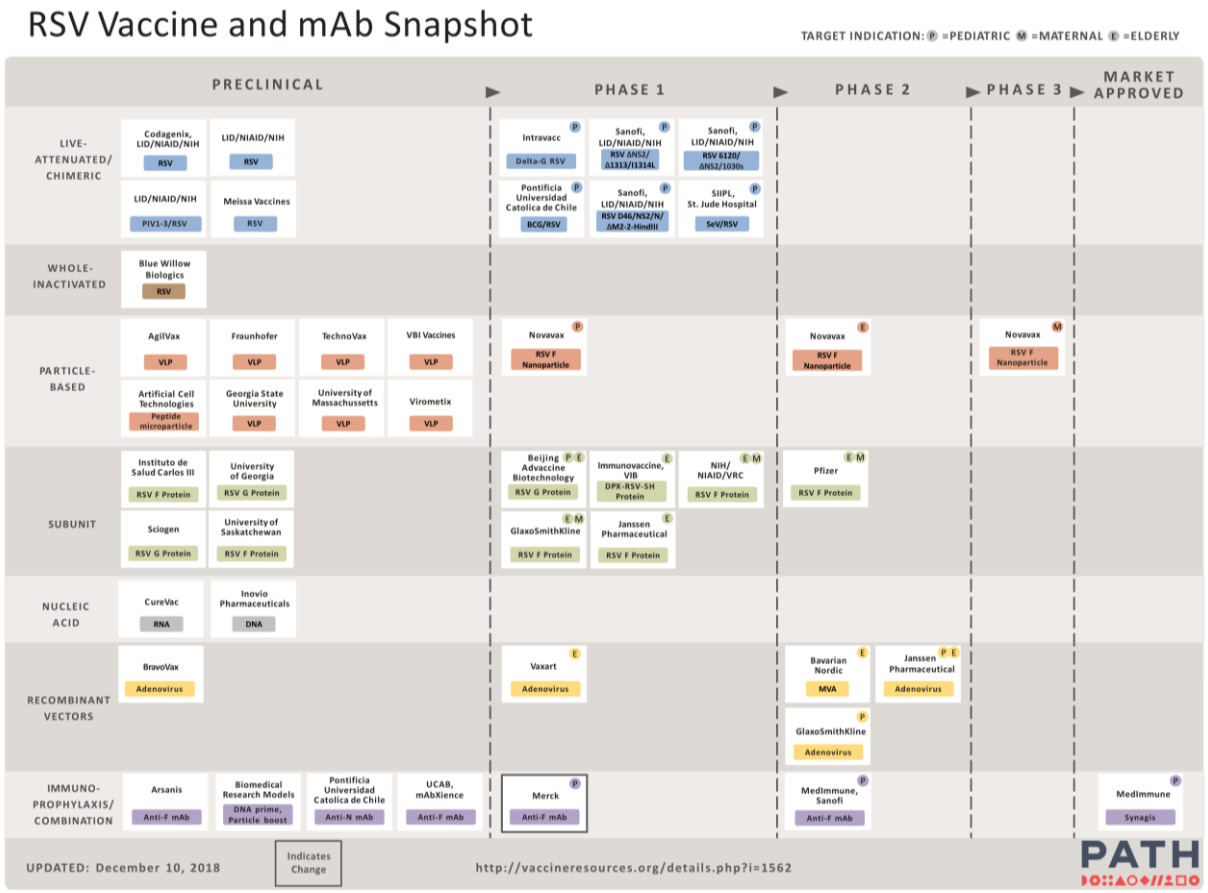


Figure 1-1 RSV vaccine and mAb snapshot (Updated on 10th December 2018)

1.1.3 Parainfluenza virus

PIV is a negative-sense, single-stranded RNA virus of the subfamily *Paramyxovirinae* in *Paramyxoviridae* family and has four subtypes, PIV 1–4. PIV 1–3 were more frequently reported whereas PIV 4, which could be further categorised into PIV 4A and PIV 4B, was less frequently reported, partly due to the difficulties in identifying the virus from cell culture (Lau et al. 2005).

Transmission

PIV infects epithelial cells. The median incubation period of PIV is 2.6 days (Lessler et al. 2009). Like RSV, PIV transmission is by direct or indirect (i.e. through contamination) contact (Henrickson 2003).

Vaccine

Currently, there is no licensed PIV vaccine. Several PIV vaccine candidates are currently under clinical trials (Schmidt et al. 2011).

1.1.4 Metapneumovirus

Human metapneumovirus (hMPV/MPV) is a negative-sense, single-stranded RNA virus of the family *Pneumovirinae*, same family as RSV and has two lineages, MPV A and B. MPV was first detected in respiratory specimens from children with respiratory tract infections in 2001 (B. G. van den Hoogen et al. 2001).

Transmission

MPV infects epithelial cells. The incubation period of MPV is around 5 days (Lessler et al. 2009). The mode of transmission of MPV is likely to be by direct or indirect contact.

Vaccine

Similar to PIV, there is no licensed MPV vaccine. Overall, a variety of vaccination strategies have been raised and tested in animals but none has yet been tested in humans (Ren et al. 2015).

1.2 Seasonality of respiratory viruses

1.2.1 Global seasonality

IFV and RSV

There are several reports describing the global seasonality of IFV and RSV. A summary of these studies attached below in **Table 1-3**. Both IFV and RSV have seasonal epidemics in winter months in the temperate region. In the tropics, IFV tends to have biannual activity or year-round activity; little is known about RSV seasonality but was presumed to be similar to IFV based on limited data (Bloom-Feshbach et al. 2013). Within IFV, IFV A and IFV B have similar seasonality but the peak of IFV A is around 4 weeks earlier than that of IFV B in the temperate region. IFV season coincides with lower temperature in the temperate region and with rainy seasons in the sub-tropical or tropical settings (J. D. Tamerius et al. 2013).

While different studies on IFV tended to have similar findings, the two main studies on global RSV seasonality had contradictory conclusions. The first study by Bloom-Feshbach et al (Bloom-Feshbach et al. 2013) concluded that RSV had weak latitudinal gradients in the timing of epidemics by hemisphere, with peaks occurring later with increasing latitude whereas the second study by Obando-Pacheco et al (Obando-Pacheco et al. 2018) concluded that RSV usually travelled from the south to the north. The inconsistency could be due to the lack of global representativeness of RSV data and also the limited number of data points in both studies.

Additionally, the WHO published a “influenza transmission zones” document during the 2009 swine flu pandemic, which showed the geographical groups of countries, areas or territories with similar influenza transmission patterns (World Health Organization 2011). However, this document did not give further details regarding the methodology.

PIV and MPV

No report was found describing the global seasonality of PIV or MPV. In the US, PIV 1 and PIV 2 were most frequently detected in the fall and winter

while PIV 3 was mostly detected in the spring. PIV 1 and PIV 2 had biennial patterns with increased activity in odd-numbered years (PIV 1)/even-numbered years (PIV 2) (Steffens et al. 2016). Similar patterns were reported in the UK (Zhao et al. 2017). Recently, PIV 4 was more frequently tested than the past and its seasonality was found similar to PIV 3 (Maykowski et al. 2018; Zhao et al. 2017).

Compared with PIV, seasonality of MPV was less frequently reported as this virus was not identified until 2001. In the US, MPV had distinct seasons with onsets ranging from November to February and offsets from April to July; RSV, IFV and MPV occurred sequentially and the seasonal patterns of MPV were similar to RSV (Haynes et al. 2016).

Table 1-3 Summary of studies reporting global seasonality of respiratory viruses

Study	Setting	Data Source	Major Selection Criteria	Seasonality Description Methods	Main Findings
IFV and RSV: one study					
Bloom-Feshbach, et al. 2013 (Bloom-Feshbach et al. 2013)	By study site; IFV: 77 sites from 40 countries RSV: 96 sites from 52 countries	Literature + surveillance website	Lab-confirmed, ≥1 consecutive year, ≥24 IFV or RSV/year.	Peak month, epidemic duration	IFV and RSV peaked during winter in temperate regions, while there was greater diversity in the tropics. Several temperate locations experienced semi-annual IFV activity with peaks occurring in winter and summer. Two annual peaks common in tropical areas of Southeast Asia for both viruses. Biennial RSV cycles in Northern Europe. Both viruses exhibited weak latitudinal gradients in the timing of epidemics by hemisphere, with peak occurring later with increasing latitude.
IFV: eight studies					
Muscatello. 2018 (Muscatello 2018)	By country; 84 countries	FluNet*	Lab-confirmed, ≥90% non-missing	Weekly annual average proportion, degree of seasonality measured by the difference between highest and lowest proportion	Degree of seasonality positively correlated with absolute latitudes Latitude negatively correlated with the proportion of IFV occurring during May through October In the tropics, concordance in seasonality within regions and between adjacent countries was limited In temperate countries, IFV B peaked 4 weeks after IFV A

Study	Setting	Data Source	Major Selection Criteria	Seasonality Description Methods	Main Findings
Newman, et al. 2018 (Newman et al. 2018)	By country; 118 countries	FluNet	Lab-confirmed, ≥50 IFV/year	Influenza activity (epidemics) by month, number of peaks/year-round activity	Average IFV duration: 4.7 months Of 118 countries, 85% with one peak season, 13% with two, 4% with year-round activity
Deyle et al. 2016 (Deyle et al. 2016)	By country; 67 countries	FluNet	Lab-confirmed	Degree of seasonality measured by the correlation between IFV and absolute humidity	IFV seasonality could be explained by absolute humidity and to a lesser extent, by temperate in both temperate and tropic regions.
Caini et al. 2016 (Saverio Caini et al. 2016)	By country; 30 countries (Except for China and Brazil where regional data included)	Global Influenza B Study	Lab-confirmed, ≥50 IFV/year	Peak week, duration, monthly activity by annual percentage	In tropical countries, IFV lasted longer and the peaks of IFV A and B coincided less frequently than in temperate countries. Temporal characteristics of IFV heterogeneous in the tropics. Seasons with co-circulation of IFV A and B longer than IFV A seasons, especially in the tropics.
Alonso, et al. 2015 (Alonso et al. 2015)	By country; 125 countries	FluNet	Lab-confirmed, ≥20 IFV, Brazil, India and China excluded.	Peak month, heat map of monthly virus activity	IFV peaks in temperate countries well aligned with the winter season. IFV peaks in tropical countries had little regard for hemispheric position.

Study	Setting	Data Source	Major Selection Criteria	Seasonality Description Methods	Main Findings
He et al. 2013 (He et al. 2015)	By country; 108 countries	FluNet	Lab-confirmed	Weekly activity	IFV A(H1N1)pdm outbreak did not occur in many countries in 2011/12, although occurred the following year ("skip-and-resurgence" pattern).
Tamerius et al. 2013 (J. D. Tamerius et al. 2013)	By study site; 78 sites	Literature + surveillance website	Lab-confirmed, ≥1 consecutive year, ≥24 IFV or RSV/year.	Peak month	Two types of environmental conditions related to IFV peak: "cold-dry" and "humid-rainy".
Azziz Baumgartner et al. 2012 (Azziz Baumgartner et al. 2012)	By country; 85 countries	FluNet + literature + website	Lab-confirmed, data ≤6 months excluded.	Peak month, duration, n of epidemics, start and end	>1 IFV epidemic period per year more common in tropical countries than in temperate countries. Year-round activity occurred mostly in subtropical and tropical countries. High IFV activity was associated with low temperature.
RSV: two studies					

Global seasonality of respiratory viruses and the association between viral acute respiratory infection and subsequent pneumococcal disease

Study	Setting	Data Source	Major Selection Criteria	Seasonality Description Methods	Main Findings
Obando-Pacheco, et al. 2018 (Obando-Pacheco et al. 2018)	By country; 27 countries	Surveillance report + medical database	Lab-confirmed or syndromic-based.	Start, peak, end and duration	RSV started in most countries in the southern hemisphere from March to June and in countries in the northern hemisphere from September to December. Decrease in RSV observed from August to October in the southern hemisphere and from February to May in the northern hemisphere. 5–6 months of duration in most countries. Seasonality fairly consistent within most regions from year to year.
Stensballe et al. 2003 (Stensballe et al. 2003)	By study site; n of sites not known	Literature	None	Month of the onset	RSV seasons depended on geographic location and altitude and tended to occur in clusters. Although RSV seasons varied by continent, they usually began in coastal areas.

* FluNet is a global web-based tool for influenza virological surveillance first launched in 1997.
IFV=influenza virus; RSV=respiratory syncytial virus; WHO=World Health Organization; PAHO=Pan American Health Organization; NIC=national influenza center; n=number; ECDC=European Centre for Disease Prevention and Control.

1.2.2 Drivers of seasonality

It has long been recognised that seasonality of respiratory viruses (e.g. IFV) is associated with seasonal meteorological stimuli such as temperature and humidity but the underlying mechanism is not well known. It is widely believed that there are three mechanisms that help explain the seasonality of respiratory viruses: human contact rates, virus survival rates, and human immunity levels.

Human contact rates

Human contact is an important stimulus of the spread of infectious diseases. Transmission is greater among school age children and among adults aged 20–40, and greater between children and their parents (Del Valle et al. 2013). It is noted in Chapter 1.1 that all of the four viruses, IFV, RSV, PIV, and MPV can be transmitted by direct/indirect contact. Therefore, seasonal fluctuation in human contact rates could drive viral seasonality. School closure/holiday is one of the seasonal stimuli that modifies human contact rates (Eames et al. 2011). Several studies from various regions showed that school closure reduced the transmission of IFV (Cauchemez et al. 2008; Cowling et al. 2008; Jackson et al. 2013). The incidence rate increased when the school was reopened, supporting a potential casual role for school closure in the reduction in incidence of IFV (Jackson et al. 2013). It was reported in the US that winter holidays delayed IFV seasonal epidemic peaks and shifted disease risk toward adults because of changes in contact patterns (Ewing et al. 2017). A recent study in Belgium had a similar finding for winter holidays and even weekends; the authors also reported that changes in travel behaviour did not alter the IFV epidemics (Luca et al. 2018). Human mobility, e.g. travelling or commuting, is another seasonal stimulus. Several studies in the US showed that IFV transmission was dominated by local work commutes rather than air traffic (Bozick and Real 2015; Charu et al. 2017). However, neither school closure/holiday nor human mobility is specific enough to explain the timing of viral seasonality. For example, this does not

explain why IFV does not peak in the early autumn when the students are back to school from holidays.

Apart from holidays/work, human contact patterns are also affected by meteorological factors (Horanont et al. 2013). For example, people tend to stay indoors in cold days (Graham and McCurdy 2004), potentially increasing transmission. However, a research study conducted in Belgium found general dominance of day-type (weekend, holiday, working day) over weather conditions in terms of contact duration, but nonetheless observed an increased duration on regular workdays with low temperatures, no precipitation and low humidity (Willem et al. 2012).

Virus survival rates

In order to survive the transport between humans, virus needs to endure certain environmental conditions. In general, virus survives longer on hard and nonporous surfaces (e.g. stainless steel) (Bean et al. 1982). Since some of the environmental conditions change in seasonal patterns (e.g. temperature and humidity), it is possible that viral seasonality is driven by its ability to survive. Unlike human contact rates, which uniformly affect all viruses, virus survival rates are specific to virus type and have the potential to explain the differences of seasonality among viruses.

In general, IFV, RSV, PIV, and MPV have similar changes in stability in response to changing environmental conditions. The survival of IFV was most studies among the four viruses. Unlike the other three viruses, IFV can also be transmitted through aerosol. Studies have shown that IFV survival increases both on surfaces or in aerosols when absolute humidity decreases; relative humidity decreases; or temperature increases (McDevitt et al. 2010; Myatt et al. 2010; Noti et al. 2013; Shaman and Kohn 2009). Absolute humidity was reported to be a better predictor of IFV survival compared to relative humidity and temperature (McDevitt et al. 2010; Shaman and Kohn 2009). In contrast, when in droplets, high humidity can increase the survival of IFV, which complicates the interaction between humidity and IFV survival

(Paynter 2014). Similar findings were reported for RSV. At room temperature, RSV survival rate in droplets was higher at the higher humidity levels over the first 5 hours; but over the next 67 hours, survival was higher at the lower humidity levels (Paynter 2014). Higher temperature was found to be associated with lower survival rate on surfaces for PIV and MPV (Henrickson 2003; Tollefson et al. 2010). In addition to temperature and humidity, higher ultraviolet levels were also found to decrease viral survival rates on surfaces (Vasickova et al. 2010). However, the relative contribution of these seasonal stimuli on viral seasonality is still unknown.

Human immunity levels

Human immunity levels can vary throughout a year and could be a non-specific contributor to viral seasonality. A recently published study measured the expression of immune-system-related genes and proteins found that seasonal rhythm existed in human immune system in both hemispheres (Dopico et al. 2015). Various predictors have been proposed to be associated with human immunity, including temperature, humidity, photoperiod (solar radiation), malnutrition, and so on (J. Tamerius et al. 2011). Seasonal malnutrition is one of the most important contributors to the seasonal fluctuation of human immunity levels. The change in food availability is reported to be the most important factor influencing the seasonality of malnutrition. In rural Ethiopia, acute child under-nutrition was relatively higher in the dry season than the wet season (Egata et al. 2013). In rural Bangladesh, the periods of greatest nutritional deficit began with the monsoon rains (Brown et al. 1982).

1.2.3 Modelling of global seasonality

IFV

The three modelling studies on global seasonality of IFV are summarised in **Table 1-4**. Although using different methods, these three studies all supported the role of temperature in shaping IFV seasonality in the temperate regions. The studies by Deyle et al and Tamerius et al reinforced the role of absolute humidity in influencing seasonality. At higher

temperatures, higher humidity was associated with higher IFV activity while at lower temperatures; lower humidity was associated with higher IFV activity. This corresponds to the so-called “cold-dry” IFV season in most temperate regions and “humid-rainy” IFV season in the subtropics and tropics.

RSV

To my knowledge, there are no modelling studies on global seasonality of RSV. Nevertheless, there is one systematic review published in 2014 summarising country-level or city-level modelling studies on seasonality of RSV (Tang and Loh 2014). This reported that RSV activity was consistently positively correlated with lower temperature and higher relative humidity in the subtropical and temperate regions. In the tropics, the correlation between RSV activity and meteorological factors was not consistent.

PIV and MPV

Little is known about the seasonal predictors of PIV or MPV.

Table 1-4 Summary of modelling studies on global seasonality of IFV

Study	Setting	Viral Data Source	Seasonal Predictors	Modelling Methods	Main Findings
Deyle et al. 2016 (Deyle et al. 2016)	By country; 67 countries	FluNet	AH, RH, T, rainfall	Empirical dynamic modelling: univariate and multivariate	IFV seasonality could be explained by AH and to a lesser extent, by T in both temperate and tropic regions. A U-shaped relationship between AH and IFV was found, which was mediated by T (of 75˚F): when T<75˚F, AH had negative effects on IFV; when T>75˚F, AH had positive effects on IFV.
Tamerius et al. 2013 (J. D. Tamerius et al. 2013)	By study site; 78 sites	Literature + surveillance website	T, RH, rainfall	Logistic regression: univariate and multivariate	Two types of environmental conditions related to IFV peak: “cold-dry” and “humid-rainy”.
Azziz Baumgartner et al. 2012 (Azziz Baumgartner et al. 2012)	By country; 85 countries	FluNet + literature + website	T, AH, rainfall, duration of sunlight	Multivariate linear regression	High IFV activity was only associated with low T, adjusted for AH, rainfall and duration of sunlight.

AH=absolute humidity; RH=relative humidity; T=temperature

1.3 Interaction between viral respiratory infection and pneumococcal disease

1.3.1 Pneumococcal disease

Pneumococcal disease refers to disease caused by the bacterium *Streptococcus pneumoniae* (*S. pneumoniae*), also known as pneumococcus. Pneumococcus was first discovered in 1881 from human saliva (D. A. Watson et al. 1993). Pneumococcus can infect multiple parts of human body and cause many types of diseases, some of which are life-threatening. Pneumococcal disease can be invasive, i.e. the infected site is normally sterile (e.g. blood, cerebrospinal fluid, and pleural), and non-invasive. Common invasive pneumococcal disease includes septicaemia (sepsis), meningitis and bacteraemic pneumonia. Common non-invasive pneumococcal disease includes non-bacteraemic pneumonia, otitis media, sinusitis and bronchitis.

Pneumococcal disease occurs more frequently in younger children and older adults (Ludwig et al. 2012). In young children, pneumococcal pneumonia and pneumococcal meningitis are the two major causes of deaths from pneumococcal diseases. It is estimated that there were 257000 pneumococcal pneumonia deaths and 37900 pneumococcal meningitis deaths among young children under the age of five globally in 2015 (Wahl et al. 2018).

Pneumococcal disease is vaccine-preventable. There are two types of pneumococcal vaccines: pneumococcal conjugate vaccines (PCV) and pneumococcal polysaccharide vaccines (PPV). There are three PCVs available, PCV-7, PCV-10, and PCV-13 and one PPV, PPV-23. The number after PCV/PPV indicates the number of different pneumococcal serotypes that the vaccines can cover. PCV can be given to children under the age of 2 years whereas PPV cannot due to low effectiveness. WHO recommends the inclusion of PCVs in childhood immunization programmes worldwide. US CDC also recommends PPV for all adults 65 years or older, people 2 through

64 years of age with certain medical conditions, and adults 19 through 64 years old who smoke cigarettes.

1.3.2 Vaccine as a probe to understand the interaction between viral respiratory infection and pneumococcal disease

The impact of PCV on influenza-associated hospitalisation was first described in a randomised trial of PCV-9, which achieved 45% (95% CI: 14–64) reduction in IFV-associated hospitalisation and 31% (95% CI: 15–43) reduction in any-virus-associated hospitalisation in South Africa (Madhi et al. 2004). Similar results were reported in the US in the PCV-7 trial, with a reduction of 39–50% in IFV hospitalisation in <2y (Simonsen et al. 2011).

1.3.3 Viral-pneumococcal interaction during IFV pandemics

As shown earlier in **Table 1-2**, the Spanish flu pandemic in 1918 caused 40–50 million deaths. It was believed that it was not flu alone that caused the majority of deaths during the pandemic. According to a historical review (Brundage 2006), in the US, there was a large flu outbreak at Camp Funston. Five days after the flu outbreak, a wave of pneumonia cases occurred. Among 1100 soldiers hospitalised for flu, 22% of them developed pneumonia, 20% of whom died. Similar findings were reported in other camps and the overall case fatality ratio was estimated to be 4.9%. Bacterial culture results in autopsy series from victims of the pandemic showed that at least 70% of the samples had positive bacterial culture results and that more than 20% of the samples had pneumococcus positive results (Fauci et al. 2008).

The 1957 Asian flu and 1968 Hong Kong flu pandemics were reported to be less severe, causing up to 2 million deaths each (**Table 1-2**). Most deaths were attributed to bacterial infection, with *Staphylococcus aureus* being predominant — different from in the Spanish flu pandemic (Fauci et al. 2008).

In the recent 2009 swine flu pandemic, results from large-scale population-based studies consistently demonstrated that higher incidence of invasive

pneumococcal disease was associated with the flu pandemic and that the cases with secondary pneumococcal infection were younger than similar cases in the inter-pandemic period (**Table 1-5**). At least 17% of the cases were associated with laboratory-confirmed IFV (Nelson et al. 2012).

Table 1-5 Summary of studies reporting pneumococcal diseases during the 2009 swine flu

Study	Setting	Main findings
Pedro-Botet et al (Pedro-Botet et al. 2014)	Barcelona, Spain	The incidence of IPD during the 7-week study period in 2009 (28.9/million) was statistically higher than that observed in 2008 (19.6/million) and 2010 (14.6/million). IPD cases were younger and healthier during the 7-week study period in 2009 than 2008 and 2010.
Launes et al (Launes et al. 2014)	Barcelona, Spain	The incidence of IPD during 2009–2010 season was approximately same as the total incidence of two flu seasons before 2009 or after 2010. IPD cases were younger in 2009–2010 than the other four non-pandemic flu seasons
Fleming-Dutra et al (Fleming-Dutra et al. 2013)	9 surveillance sites in US	The pandemic likely resulted in an out-of-season IPP peak among persons ≥5 years. (IPP rate per 10 million: 48 vs 9 in 5–124y, 74 vs 53 in 25–49y, 188 vs 114 in 50–64y, and 229 vs 187 in 65y–)
Weinberger et al (Weinberger et al. 2012)	US	There was a significant increase in pneumococcal hospitalizations during the pandemic. Individuals aged 5–19y had the largest relative increase in pneumococcal hospitalizations (ratio=1.6, 95% CI: 1.4–1.7). In contrast, there was no excess disease in the elderly.

Study	Setting	Main findings
Nelson et al (Nelson et al. 2012)	Denver, Colorado, US	During October 2009, there were 58 IPD cases, three times than the usual number in October (2004–2008). IPD cases in October 2009 were younger and more likely to have chronic lung disease than IPD cases in February 2009. >17% of IPD cases during the pandemic were associated with IFV A(H1N1)pdm.

IPD=invasive pneumococcal disease; IPP=invasive pneumococcal pneumonia

1.3.4 Current understanding of the interaction between viral respiratory infection and pneumococcal diseases

During interpandemic period, the association between seasonal IFV and pneumococcal disease as well as the association between other seasonal viral infections and pneumococcal disease remain to be studied in detail. Murdoch et al. found that IFV and PIV were associated with invasive pneumococcal disease; RSV was associated with invasive pneumococcal disease only in children under five years old (Murdoch and Jennings 2009). In the UK, it is estimated that 6–7.5% and 3–4% of invasive pneumococcal disease cases were attributable to IFV and RSV, respectively (Nicoli et al. 2013). However, a study in Germany found no association between IFV A peak and invasive pneumococcal disease peak (Toschke et al. 2008). A systematic literature review is warranted in order to better understand the existing evidence regarding the association between seasonal respiratory viral infection and pneumococcal disease.

1.4 Aims of the thesis

The aims of the thesis are listed below in each sub-section. Specific objectives are provided within each aim/sub-section. Briefly, the thesis has two parts. The first part focuses on the global seasonality of respiratory viruses and the second part focuses on the viral-pneumococcal associations.

1.4.1 To understand global seasonality of respiratory viruses (Chapter 2)

- To describe the global seasonal patterns of IFV (including all subtypes), RSV, PIV, and MPV.
- To understand the association between meteorological factors (e.g. temperature and humidity) and viral seasonality.
- To predict viral seasonality based on a selected set of meteorological factors and to valid the model.

1.4.2 To understand the role of RSV seasonality on RSV prevention strategy planning in lower and middle income countries (Chapter 3)

- To describe the RSV seasonality in lower and middle income countries (LMICs) based on the findings of **Chapter 2**, including the year-to-year variations where data are available.
- To compare the impact of a seasonal administration strategy and a year-round administration strategy for both maternal immunisation and long-acting mAbs in LMICs.

1.4.3 To understand existing evidence in the association between viral respiratory infection and subsequent pneumococcal disease (Chapter 4)

- To summarise findings from existing population-based studies.
- To critically review the methods used in existing studies.
- To summarise gaps in knowledge and inform future studies.

1.4.4 To investigate the association between viral respiratory infection and subsequent invasive pneumococcal disease (Chapter 5)

- To assess the association using laboratory-confirmed viral data and IPD data, both in all ages and by age group.
- To estimate the percentage of IPD that can be attributable to each virus, both in all ages and by age group.

Chapter 2 Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus and metapneumovirus: a systematic analysis

2.1 Introduction

Influenza virus (IFV), respiratory syncytial virus (RSV), parainfluenza virus (PIV), and metapneumovirus (MPV) are the four major viral pathogens associated with acute respiratory infection (ARI) and these represent a significant burden of disease particularly in young children (Shi et al. 2015b) and the elderly (Falsey et al. 2005; Shi et al. 2019). Understanding the seasonal patterns of these viruses is important for health-care services planning. This is particularly relevant to the immunisation strategies of IFV and RSV in the near future that rely on local seasonality information. However, seasonal patterns of IFV and RSV are still poorly understood in tropical and sub-tropical regions; no global reports described seasonal patterns of PIV and MPV.

Therefore, a systematic analysis of global seasonality of IFV, RSV, PIV, and MPV was conducted using data from systematic literature search, online public data, and unpublished data shared by a group of researchers. This work has been published in Lancet Global Health. (Li Y, Reeves RM, Wang X, et al. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. Lancet Glob Health. 2019;7(8):e1031-e1045)

In this publication, I led the systematic literature review with contributions from Rachel Reeves (RR) and Xin Wang (XW). I cleaned, analysed, and visualised the data. Harish Nair (HN), Harry Campbell (HC) and I led the data interpretation. I wrote the first draft with inputs from RR, XW, HN and HC. HN and HC conceptualised the study. All other named authors of this publication, Quique Bassat, W. Abdullah Brooks, Cheryl Cohen, David P. Moore, Marta

Nunes, and Barbara Rath, contributed to collection of unpublished research data and interpretation, and critically reviewed the initial manuscript. All group authors from RSV Global Epidemiology Network (RSV GEN) contributed to data collection, and reviewed the manuscript for intellectual content. All authors above read and approved the final draft.

The full-text of the publication (journal-accepted version) has been attached below. Some contents have been reordered to comply with the format of this thesis.

2.2 "Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis" [version accepted for publication by Lancet Global Health]

Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis

You Li MSc[1], Rachel M Reeves PhD[1], Xin Wang MSc[1], Prof. Quique Bassat MD*[2,3,4], W. Abdullah Brooks MD*[5,6], Cheryl Cohen PhD*[7,8], David P. Moore PhD*[9,10,11], Marta Nunes PhD*[10,11], Prof. Barbara Rath PhD*[12,13], Prof. Harry Campbell MD[1], Prof. Harish Nair PhD†[1], for RSV Global Epidemiology Network and RESCEU investigators

* Authors listed alphabetically

† Corresponding author

1. Centre for Global Health Research, University of Edinburgh, UK
2. Centro de Investigação em Saúde de Manhiça (CISM), Maputo, Mozambique
3. ISGlobal, Hospital Clínic - Universitat de Barcelona, Barcelona, Spain
4. ICREA, Pg Lluís Companys 23, 08010 Barcelona, Spain
5. Department of International Health, International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, MS, USA
6. International Centre for Diarrhoeal Disease Research, Bangladesh
7. Centre for Respiratory Disease and Meningitis, National Institute for Communicable Disease, Johannesburg, South Africa
8. School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

9. Department of Paediatrics and Child Health, Chris Hani Baragwanath Academic Hospital and Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
10. Medical Research Council: Respiratory and Meningeal Pathogens Research Unit, School of Pathology, University of the Witwatersrand, Johannesburg, South Africa
11. Department of Science and Technology/National Research Foundation: Vaccine Preventable Diseases, University of the Witwatersrand, Johannesburg, South Africa
12. Vienna Vaccine Safety Initiative, Berlin, Germany
13. School of Medicine, University of Nottingham, Nottingham, UK

Correspondence to:
Prof. Harish Nair, Centre for Global Health Research, University of Edinburgh, UK
Harish.Nair@ed.ac.uk; +44 (0) 131 650 6963

Abstract

Background: Influenza virus (IFV), respiratory syncytial virus (RSV), parainfluenza virus (PIV), and metapneumovirus (MPV) are the most common viruses associated with acute lower respiratory infections in young children and the elderly. A global report of the monthly activity of these viruses is needed to inform public health strategies and programmes for their control.

Methods: We compiled data from systematic literature review, online datasets and unpublished research data reporting seasonality of IFV, RSV, PIV, and MPV. We calculated monthly annual average percentage (AAP) as the relative strength of virus activity. We defined duration of epidemics as the minimum number of months to account for 75% of annual positive samples, with each component month defined as an epidemic month. Furthermore, we modelled monthly AAP of IFV and RSV using site-specific temperature and

relative humidity for the prediction of local average epidemic months. We also predicted global epidemic months of IFV and RSV on a 5° by 5° grid.

Results: We included 246 sites for IFV, 183 sites for RSV, 83 sites for PIV and 65 sites for MPV. IFV had clear seasonal epidemics in winter months in most temperate sites but timing of epidemics was more variable and less seasonal with decreasing distance from the equator. Unlike IFV, RSV had clear seasonal epidemics in both temperate and tropical regions, starting in late summer months in the tropics of each hemisphere, reaching most temperate sites in winter months. In most temperate sites, IFV epidemics occurred later than RSV (by 0.3 months, 95% CI: –0.3–0.9) while no clear temporal order was observed in the tropics. PIV epidemics were found mostly in spring and early summer months in each hemisphere. MPV epidemics occurred in late winter and spring in most temperate sites but the timing of epidemics was more diverse in the tropics. IFV epidemics had shorter duration (3.8 months, 95% CI: 3.6–4.0) in temperate sites and longer duration (5.2 months, 4.9–5.5) in the tropics. Duration of epidemics was relatively comparable across all sites for RSV (4.6 months, 4.3–4.8) and MPV (4.8 months, 4.4–5.1). By comparison, PIV had longer duration of epidemics (6.3 months, 6.0–6.7). Our model had good predictability in the average epidemic months of IFV in temperate regions, and RSV in both temperate and tropical regions. Through leave-one-out cross validation, the overall prediction error in the onset of epidemics was within one month (IFV: −0.2 months, 95% CI −0.6–0.1; RSV: 0.1 months, −0.2–0.4).

Interpretation: This is the first study that provides global representations of month-by-month activity of IFV, RSV, PIV and MPV. Our model is helpful in predicting the local onset month of IFV and RSV epidemics. The seasonality information presented in our study has important implications for health services planning, the timing of RSV passive prophylaxis and the strategy of IFV and future RSV vaccination.

2.2.1 Introduction

Influenza virus (IFV), respiratory syncytial virus (RSV), parainfluenza virus (PIV), and metapneumovirus (MPV) are the four major viral pathogens associated with acute lower respiratory infection (ALRI) and these represent a significant burden of disease particularly in young children (Shi et al. 2015b) and the elderly (Falsey et al. 2005; Shi et al. 2019). Globally, IFV is estimated to be associated with 39.1 million ALRI episodes (30.5–48.4) and 58 200 ALRI deaths (44 000–74 200) annually; RSV is estimated to be associated with 24.8 million ALRI episodes (19.7–31.4) and 76 600 ALRI deaths (55 100–103 500) annually (Troeger et al. 2018). To date, no global burden estimate has been reported for PIV and MPV.

Seasonality information of IFV, RSV, PIV, and MPV is important in health-care services planning and the development of appropriate disease prevention and control strategies, including immunisation strategies. The demand for a global overview of the seasonal patterns of IFV, RSV, PIV, and MPV has been growing steadily as this helps understand the seasonality in those under-reported countries or regions where the burden of viral respiratory infections is substantial while health-care resources are insufficient. For example, the seasonality of one country could be possibly estimated given the information of countries in geographic proximity or any other global patterns. As a result, several reports (Alonso et al. 2015; Azziz Baumgartner et al. 2012; Bloom-Feshbach et al. 2013; Saverio Caini et al. 2016; Deyle et al. 2016; He et al. 2015; Muscatello 2018; Newman et al. 2018; Obando-Pacheco et al. 2018; Stensballe et al. 2003; J. D. Tamerius et al. 2013) have described the global seasonality of IFV and/or RSV (**Table 1-3**). It is noted in these studies that both IFV and RSV circulation peaks were well aligned with winter months in temperate regions, while greater diversity in timing was observed in the tropics; and both viruses exhibited weak latitudinal gradients in the annual timing of epidemics by hemisphere, with peaks occurring later with increasing latitude. However, seasonal patterns of IFV and RSV are still poorly understood in tropical and sub-

tropical regions where seasonal patterns could not be well described simply by indicators such as peak timing and/or beginning and end of epidemics as done in temperate regions. Only three recent studies (Alonso et al. 2015; Saverio Caini et al. 2016; Newman et al. 2018) reported monthly country-level activity of IFV; nevertheless, these reports were unable to characterise any within-country variations that could help understand the latitudinal gradient of viral activity. In addition to the seasonal patterns reported, some studies (Azziz Baumgartner et al. 2012; Deyle et al. 2016; J. D. Tamerius et al. 2013) reported pronounced correlations between meteorological factors such as temperature and humidity, and IFV epidemics, suggesting the possibility in prediction of viral epidemics on a global scale. However, issues related to data availability impeded these studies from further looking into the prediction of viral epidemics.

In order to address the data gaps in global seasonality of IFV, RSV, PIV, and MPV, we compiled data from systematic literature review, online datasets and unpublished research data at both country level and sub-country level, and conducted a systematic analysis of global monthly activity of IFV, RSV, PIV, and MPV. Furthermore, with the compiled dataset, we aimed to model viral epidemics on a monthly basis using site-specific meteorological predictors.

2.2.2 Method

Data sources

We collected viral activity data for IFV, RSV, PIV, and MPV from a range of sources including systematic literature search, online public datasets, and the research datasets shared by the collaborators from RSV Global Epidemiology Network (RSV GEN)(Shi et al. 2017).

Systematic literature search

We searched three bibliographic databases, Medline, Embase, and Global Health, for articles reporting activity of IFV, RSV, PIV, or MPV using a tailored search strategy. The literature search used the following terms (with

synonyms and closely related words): "Influenza virus", "respiratory syncytial virus", "parainfluenza virus", "human metapneumovirus", "acute lower respiratory infection" combined with "seasonality" , "surveillance", "periodicity", and "temporal variation" (**Appendix A2**). In the present study, records related to all-cause ALRI without including any of the four viruses above were not included. We limited the literature search to the period of 1st Jan 2001 to 31st Dec 2017. We did not include studies published before 2000 because seasonality could change in the long term and our objective was to report on current global seasonality. References cited in retrieved articles were also examined for eligibility. No language restrictions were applied. The protocol for this systematic literature search was registered on PROSPERO (registration number: CRD42018091628).

Inclusion criteria

- Studies reporting laboratory-confirmed incidence data of human infection of IFV, RSV, PIV and/or MPV for at least 12 consecutive months (or 52 weeks equivalent).
- Studies with stable testing practice throughout all years reported (e.g. studies should be able to conduct IFV tests both in and out of IFV season with no interruption).
- Studies reporting virus results among residents in well-defined geographic locations.
- Studies reporting aggregated virus results at least on a monthly basis or, if possible, more frequently.

Exclusion criteria

- Studies reporting respiratory infections only among those under special medical conditions (e.g. patients with chronic obstructive pulmonary disease or patients infected with human immunodeficiency virus).
- Studies only reporting influenza during the 2009-2010 influenza pandemic period.
- Studies only reporting nosocomial infections.

- Studies reporting publicly available datasets (e.g. FluNet by World Health Organization, WHO), secondary data, commentary, or reviews. (corresponding original source of data was assessed for eligibility)
- Studies only reporting all-cause ALRI. These studies were excluded in the phase of full-text screening (i.e. they were still retained during title and abstract screening).

Data from online public sources and RSV GEN

We included open-access online data from the following sources: WHO FluNet (World Health Organization 2018a), Pan America Health Organization FluID (Pan American Health Organization 2018), Japan National Institute of Infectious Diseases (National Institute of Infectiou Disease Japan 2015), Hong Kong Department of Health (Department of Health Hong Kong 2018), Canada FluWatch (Government of Canada 2018), and New Zealand Ministry of Health (Ministry of Health New Zealand 2018). The detailed information about these data can be found in **Appendix A3**

We also included viral activity data shared by RSV GEN which is a collaboration of more than 70 investigator groups primarily in low-income and middle-income countries that was initially established to estimate RSV-ALRI disease burden (Shi et al. 2017). The detailed information of RSV GEN data can be found in **Appendix A4**.

Data extraction

Data extraction was conducted independently by YL and jointly by RR and XW through a three-stage process as detailed below. Any discrepancies were resolved through discussion among YL, RR, and XW.

During the first stage, general information of each study was collected including site, country, coordinates (extracted from Google Map), data source, diagnosis, virus type and subtype, specimen, test method, subject age, dates of data availability, number of total specimens tested, number of total positive tests, time interval of aggregated data (e.g. weekly and monthly), format of seasonality data presented (e.g. graph, table and

dataset), and measurement of seasonality data presented (e.g. case number, proportion positive, and incidence rate).

During the second stage, an assessment of accessibility of seasonality data was conducted in each included article. This assessment evaluated whether the seasonality data reported in the articles were extractable as aggregated number of cases per time interval (i.e. not proportion positive, incidence rate or any other proportional measures). Where seasonality data were not extractable, we attempted to contact the authors for gaining access to these data. We excluded studies when seasonality data were neither extractable nor accessible.

During the third stage, seasonality data were extracted. The extraction was done by site and virus with each record extracted referring to one virus in one site. The viruses extracted include IFV, IFV A, IFV B, IFV A(H1N1), IFV A(H3N2), IFV A(H1N1)pdm, RSV, PIV, and MPV. We did not extract subtypes of RSV, PIV or MPV due to the very limited number of studies with those data available. For IFV, IFV A, IFV A(H1N1), and IFV A(H1N1)pdm, data between April 2009 and August 2010 inclusive were excluded due to the irregular seasonality of these viruses during the influenza pandemic period. In each study, we only extracted full-year (i.e. 12 months, 24 months, etc.) data for appropriate comparisons among months. When two or more studies were available for the same virus at the same site, we only extracted and included the one with the highest number of positive cases. Additionally, we excluded any data with <25 positive tests for each virus in total. For articles where seasonality data were reported in graphs, we utilised the software WebPlotDigitizer to facilitate data extraction (Rohatgi 2018).

Quality assessment

For each article included in the systematic literature review, a quality assessment was independently conducted by YL and jointly by RR and XW. The quality assessment comprised three brief questions regarding data representativeness, test practice, and timely reporting (questionnaire in the

Appendix A5). Data representativeness indicated if the seasonality reported in the study could be representative of the seasonality in that given site. Test practice indicated if there were any changes in terms of viral testing during the study period that could affect the reported seasonality. Timely reporting indicated if issues related to the timing of reporting test positives affected the seasonality results. Any disagreement was addressed through discussion. Any study with any "D" (bad) rated in the quality assessment was excluded.

Data transformation

In order to acquire seasonality results comparable across all sites, we added the number of cases by month across all years reported for each data record. We converted any weekly data to monthly data by using the R package "wktmo" before we added these data by month (Li 2017).

Data analysis

Definitions of geographical region and meteorological season

We defined geographical regions as follows: temperate region (latitude < –23.5 or > 23.5), and tropical region (latitude between –23.5 and 23.5). We defined meteorological seasons as follows: spring (March–May in the northern hemisphere; September–November in the southern hemisphere), summer (June–August in the northern hemisphere; December–February in the southern hemisphere), autumn (September–November in the northern hemisphere; March–May in the southern hemisphere), and winter (December–February in the northern hemisphere; June–August in the southern hemisphere).

Description of monthly activity

For each month, we calculated annual average percentage (AAP) as a measurement of the strength of virus activity by the formula, $AAP_i = \frac{n_i}{\sum_1^{12} n_i} \times 100\%$, where *i* denotes the month *i* and *n* denotes the number of cases. We plotted heat maps displaying the activity of IFV, RSV, PIV, and MPV in each site sorted by latitude.

Duration of epidemics

In the main analysis, we estimated the duration of epidemics by the minimum number of months to account for a total AAP of 75%, a modified method based on Caini et al (Saverio Caini et al. 2016). The modified method could account for sites with more than one season per year. This was done by first sorting monthly AAP into descending order and then identifying the first n months to account for AAP of 75%, with each month being an "epidemic month" and n being the duration of epidemics. The onset month of epidemics at each site was defined by the first month of the longest consecutive epidemic months. Pearson's correlation was applied to assess the correlation between the onset month and latitude/longitude of the sites. In order to present the relationship between latitude and duration of epidemics, we plotted duration of epidemics against the latitude of the sites using local regression (LOESS) smoothing by virus, with the parameter span in LOESS set as 0.60.

Subgroup analysis

We conducted subgroup analyses determined *a priori* to compare the duration of epidemics of viruses of interest, using the same method as stated above. We pre-specified the following three comparison groups, IFV subtypes (IFV A vs IFV B), IFV vs RSV, and RSV vs MPV. For each comparison group, we conducted the analyses only among those sites with complete data of the viruses in the comparison group.

In order to study the relationship between seasonal timing of the viruses, we conducted cross-correlation analyses for each site between IFV A and B, between IFV and RSV, and between RSV and MPV, using −5 to 5 months of lag (a total of 11 correlation analyses). In consideration of the multiple correlation analyses within each site, we adjusted the significance level to 0.004 using the Bonferroni method (0.05/11≈0.004). If statistically significant correlation results were observed at a site, we reported the lag that maximised the correlation coefficient as the difference in timing between the

viruses. We also calculated the monthly overlapping AAP between each pair of viruses stated above and the overall annual overlapping AAP.

Prediction model of viral epidemics

For each site included, we extracted meteorological data from the site's nearest weather station provided by the US National Centers for Environmental Information using R package "GSODR" (Sparks et al. 2017). We modelled monthly AAP of virus using mean-centred monthly temperature and relative humidity as predictors in a LOESS model. This model is based on the assumption that for each month, the relative strength of viral activity (i.e. AAP) is associated with the relative measurements of the selected meteorological factors (i.e. mean-centred temperature and relative humidity). Details of model assumption, data preparation, model comparison, and model assessment are attached in the **Appendix A6**. The model-predicted AAP values for each site were then used to determine the epidemic months (i.e. a dichotomous result for each month, epidemic or non-epidemic). We required a minimum of 120 sites with ≥100 positives per virus for more robust models. With the available data, we were able to model IFV (including IFV subtypes) and RSV only.

To assess the model performance, we predicted the monthly AAP at each site using the model trained by data from the remainder sites (i.e. "leave-one-out" method) as the first step; based on the predicted AAP, we then determined the epidemic months and assessed the agreement between the predicted epidemic months and the observed epidemic months by calculating Cohen's kappa, sensitivity, specificity, positive predictive value, and negative predictive value. We also calculated the mean difference in months between the predicted and the observed onset of epidemics (i.e. prediction error) and its 95% confidence interval.

Based on the model, we estimated the global epidemic months of IFV and RSV on a 5° by 5° scale using gridded temperature and relative humidity data in 2013–2017 from the HadISDH dataset (4.0.0.2017f) (A. Smith et al.

2011; Willett et al. 2014). Moreover, using the R package "Shiny",(Chang et al. 2017) we developed an online interactive tool for the prediction of local epidemic months of IFV and RSV. This tool is available freely in http://resceu.ecdf.ed.ac.uk/shiny/ShinyPred/. The user manual of this tool is in the **Appendix A7**.

All data analyses were conducted using R software (version: 3.4.3) (R Core Team 2017). The seasonality data and key R functions developed for the analysis are available through the Edinburgh DataShare (https://doi.org/10.7488/ds/2531).

Role of the funding source

This study was supported by Respiratory Syncytial virus Consortium in EUrope (RESCEU). RESCEU has received funding from the Innovative Medicines Initiative 2 Joint Undertaking under grant agreement Nº 116019. This Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation programme and The European Federation of Pharmaceutical Industries and Associations (EFPIA). The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

2.2.3 Results

After excluding duplicates, the systematic literature search identified 21065 records and 1081 records were assessed in full-texts. Of these records, 542 studies were further checked for availability of monthly data and for any duplicates. A total of 185 studies were included at the final stage of the literature review (flow chart, details of these studies, and their quality assessment results are attached in **Appendix A8**. **Table 2-1** demonstrates the number of sites, number of positives and length in years of data from the published literature and other sources that were collected in our analysis. Compared with data from the published literature, data from other sources had greater number of positive samples and were collected over a longer time span. **Figure 2-1** demonstrates the geographical distribution of the sites included by virus (IFV subtypes in **Appendix A9**). IFV A(H1N1) was not included in the analysis due to the limited number of sites included (n sites = 39).

Table 2-1 Overview of sites included in the analysis

	Data Source	IFV						RSV	PIV	MPV
		All	A	B	A(H1N1)	A(H3N2)	A(H1N1)pdm			
Number of sites	All	246	209	200	39	183	165	183	83	65
	Literature	104	77	76	8	61	42	111	44	39
	Dataset†	142	132	124	31	122	123	72	39	26
Positive tests per site*	All	574[158–2996]	613[165–2868]	265[72–1396]	148[42–324]	307[104–1428]	429[148–1469]	306[116–1064]	176[48–461]	130[53–301]
	Literature	332[119–706]	279[120–613]	74[57–222]	42[36–59]	114[60–201]	225[122–416]	289[114–840]	106[46–310]	68[44–201]
	Dataset†	1510[316–6545]	1404[288–4775]	608[178–2279]	178[82–418]	634[179–2585]	664[180–2086]	366[128–2450]	304[74–874]	180[74–672]
Years of data per site*	All	4[3–6]	4[3–6]	5[3–7]	4[2–6]	5[3–7]	4[3–6]	3[2–7]	4[2–8]	4[2–7]
	Literature	3[2–4]	4[2–4]	5[2–5]	4[1–4]	5[2–5]	4[4–4]	3[2–6]	3[1–5]	2[1–4]
	Dataset†	6[3–7]	6[3–7]	6[4–9]	4[2–7]	7[4–9]	6[3–7]	4[3–8]	8[4–8]	8[4–8]

IFV=influenza virus; MPV=metapneumovirus; PIV=parainfluenza virus; RSV=respiratory syncytial virus.

*Median[1QR–3QR].

†From online public source and from research data shared by RSV GEN collaborators.

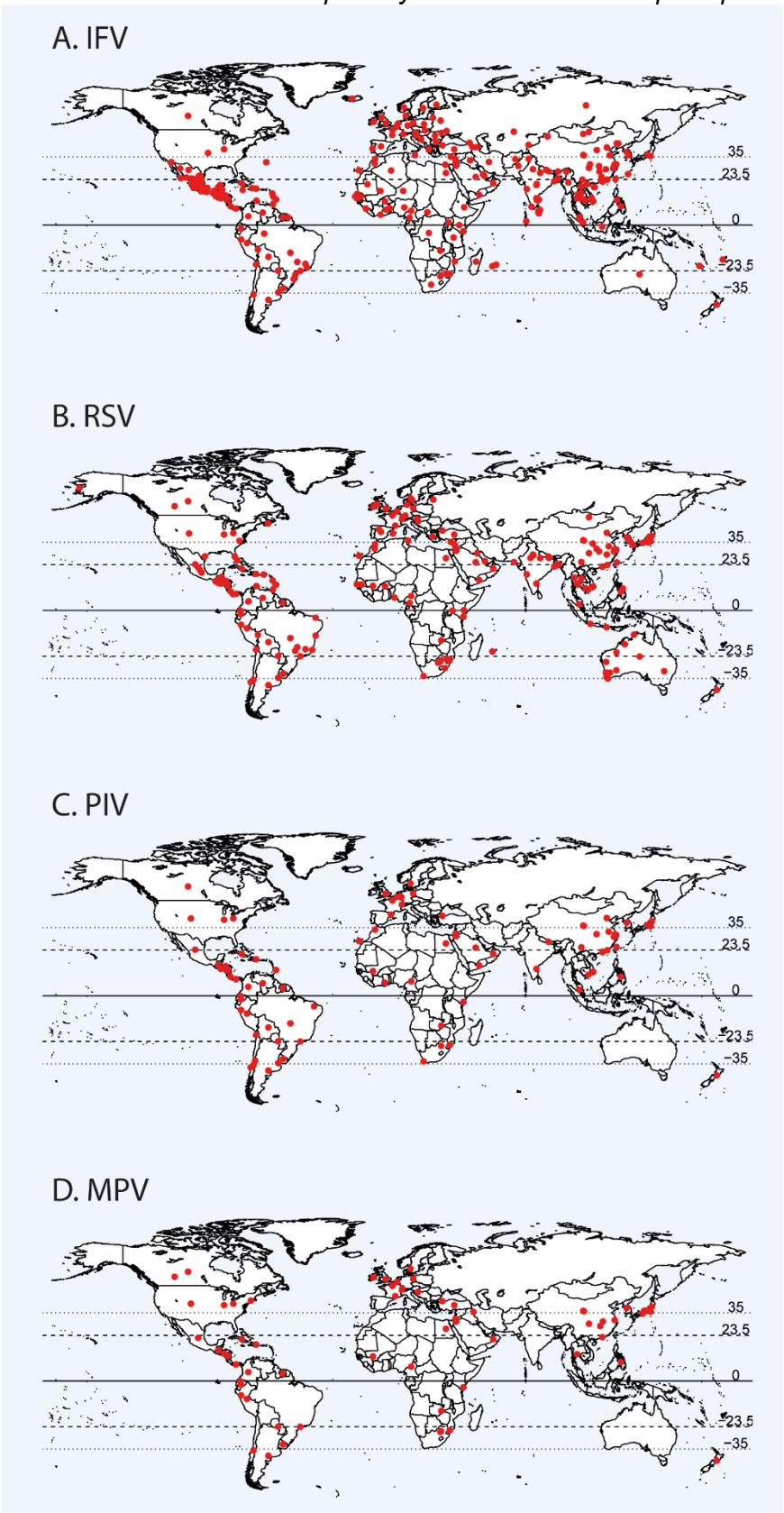


Figure 2-1 Study sites included in the analysis

Global monthly activity of IFV, RSV, PIV and MPV

Figure 2-2 and **Figure 2-3** demonstrate the global monthly activity of IFV, RSV, PIV and MPV by latitude (results of IFV subtypes in **Appendix A10**). Animated figures of global monthly activity of these four viruses can be found in the ShinyApp at http://resceu.ecdf.ed.ac.uk/shiny/ShinyGIF/. Distinct seasonality of virus activity was observed in most sites for the four viruses. Latitudinal variations of the onset month of epidemics were also observed, although patterns varied by virus. Detailed results of epidemic months grouped by country are attached in **Appendix A11**.

IFV epidemics occurred consistently during January–March in most temperate sites in the northern hemisphere and during June–August in most temperate sites in the southern hemisphere. These patterns became less pronounced closer to equator, with the emergence of summer epidemics in some sites. Variable timing of epidemics was observed in tropical sites. In both hemispheres, the onset of the major IFV epidemics was later with increasing latitudes (northern hemisphere: r=0.36, $P<0.001$; southern hemisphere: r=0.47, $P=0.003$)

RSV activity showed a latitudinal gradient in the timing of epidemics in each hemisphere. In the northern hemisphere, RSV activity was initiated in July in tropical sites. The activity was initiated later with increasing latitude until it reached high-latitude sites in around January. Subsequently, the RSV activity started to wane before another round of activity was initiated in around July in tropical sites. Similar patterns were observed in the southern hemisphere, where RSV activity was initiated around January in tropical sites first and in June in high-latitude sites. Interestingly, in the tropics, the timing of RSV epidemics was similar within each hemisphere but differed greatly between hemispheres, with only a few exceptions in equatorial sites; this pattern was not observed with any IFVs. In both hemispheres, the onset of major RSV epidemics was later with increasing latitudes (northern hemisphere: r=0.50, $P<0.001$; southern hemisphere: r=0.54, $P<0.001$).

In addition to latitudinal gradients in IFV and RSV onset month, we observed longitudinal patterns in Europe where most sites had comparable latitudes but different longitudes. The onset month of both IFV and RSV epidemics was observed to be later in the east (i.e. higher longitudes) than the west (IFV: r=0.46, *P*=0.006; RSV: r=0.45, *P*=0.025) while no significant latitudinal patterns were observed in this region (IFV: r=0.07, *P*=0.694; RSV: r=0.11, *P*=0.610). The average difference in the timing of onset between west and east of Europe (defined geographically by 20˚E) was 0.6 months for IFV and 0.8 months for RSV.

Seasonality of PIV was not as distinct as IFV or RSV. PIV epidemics were found mostly in spring and early summer months in both the northern and southern hemispheres. MPV epidemics occurred in late winter and spring in most temperate sites but the timing of epidemics was more diverse in the tropics.

Figure 2-2 Heat map of global monthly activity of influenza virus and respiratory syncytial virus, sorted by latitude.

"+" denotes the onset month of virus epidemics.

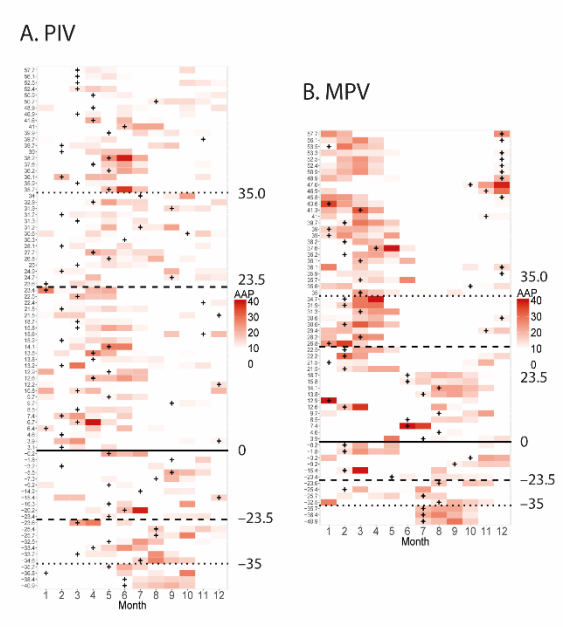


Figure 2-3 Heat map of global monthly activity of parainfluenza virus and metapneumovirus, sorted by latitude
"+" denotes the onset month of virus epidemics

Duration of epidemics

Overall, virus-specific latitudinal patterns were observed in duration of epidemics (**Figure 2-4**). PIV had longer duration of epidemics (6.3 months, 95% CI: 6.0–6.7) compared with the other three viruses. The duration of IFV epidemics varied greatly by latitude, with shorter duration (3.8 months, 95% CI: 3.6–4.0) in temperate sites and longer duration (5.2 months, 95% CI: 4.9–5.5) in the tropics. Within IFV subtypes, IFV A(H1N1)pdm had the shortest duration of epidemics (3.3 months, 95% CI: 3.1–3.5), followed by IFV A(H3N2) (4.2 months, 95% CI: 3.9–4.4) and IFV B (4.5 months, 95% CI: 4.3–4.8), regardless of the latitudes; the durations of IFV A(H1N1)pdm, A(H3N2) and B demonstrated similar latitudinal patterns. Compared with IFV, the duration of epidemics of RSV and MPV was relatively stable (RSV: 4.6 months, 95% CI: 4.3–4.8; MPV: 4.8 months, 95% CI: 4.4–5.1). Subgroup analyses using site-matched data replicated the results of the comparisons above (**Appendix A12**).

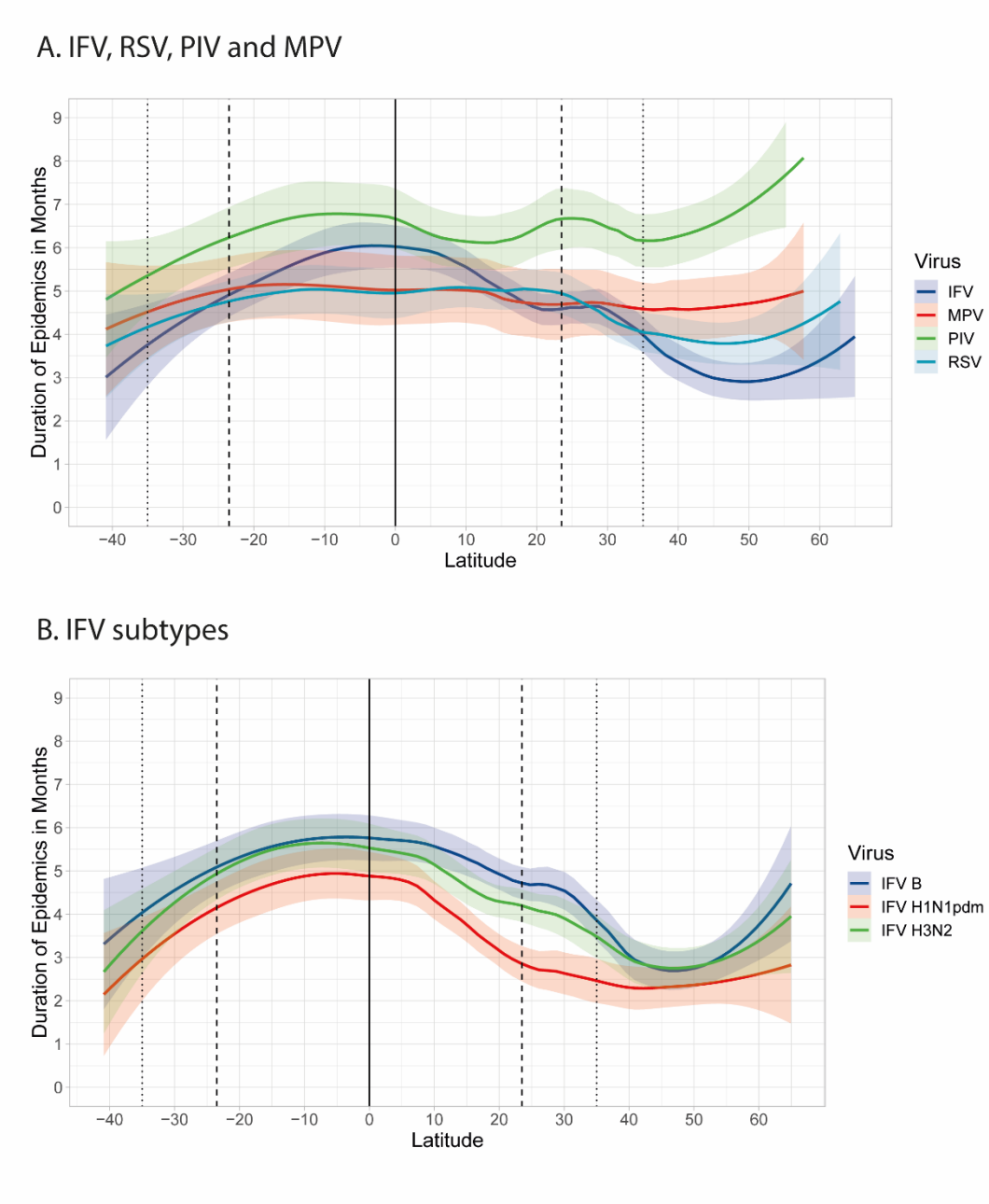


Figure 2-4 Latitudes of sites and duration of epidemics

Co-circulation of viruses

Results from subgroup analysis using sites with complete data of IFV A and B demonstrated that IFV A and B activity were statistically correlated in 78% of temperate sites (67/86) and 55% of tropical sites (55/100). In the temperate region, IFV A epidemics occurred 0.6 months (95% CI: 0.3–0.9) earlier than IFV B. In the tropics, no clear temporal order was observed (lag=0, 95% CI: −0.5, 0.5) and this was largely due to the greater variability in the timing of epidemics in the northern tropics. (Panel A in **Figure 2-5**)

IFV and RSV activity were statistically correlated in 67% of temperate sites (28/42) and 59% of tropical sites (28/47). IFV epidemics occurred later than RSV in most temperate sites with the average lag of 0.3 months (95% CI: −0.3, 0.9) while no clear temporal order was observed in the tropics (lag=0.1, 95% CI: −0.9, 1.2). (Panel B in **Figure 2-5**)

RSV and MPV activity were statistically correlated in 83% of temperate sites (29/35) and in 62% of tropical sites (14/22). In the temperate region, MPV epidemics occurred 1.7 months (1.1–2.3) later than RSV while no clear temporal order was observed in the tropics (lag=0.2, 95% CI: −0.9, 1.3). (Panel C in **Figure 2-5**)

We found that 61.2% (95% CI: 58.6–63.9) of IFV A and B activity overlapped annually, that 59.5% (95% CI: 55.4–63.6) of IFV and RSV overlapped, and that 60.3% (95% CI: 55.6–65.0) of MPV and RSV overlapped. The percentages did not differ significantly between the temperate and tropical region. (**Appendix A13**)

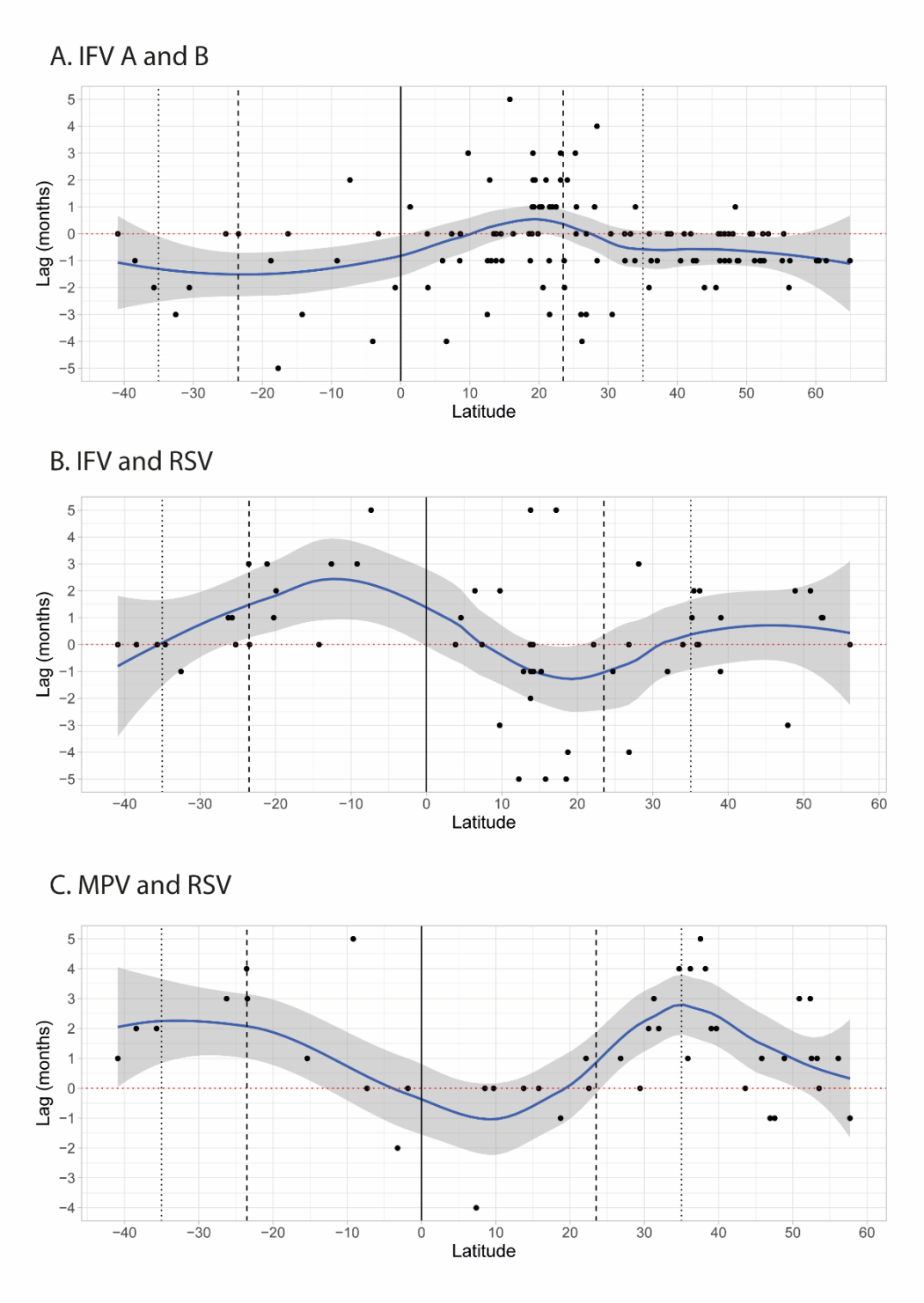


Figure 2-5 Latitudes of sites and difference in timing of epidemics between A. influenza virus A and B, B. influenza virus and respiratory syncytial virus, and C. metapneumovirus and respiratory syncytial virus by subgroup analyses

Positive lag indicates the former virus occurred after the latter; negative lag indicates the former virus occurred before the latter.

Prediction model of IFV and RSV

The model with mean-centred temperature and mean-centred relative humidity was selected for our main analysis (results of model comparison and selection in **Appendix A6)**.

Figure 2-6 demonstrates the model predicted monthly virus activity against mean-centred temperature and relative humidity (observed activity against temperature and relative humidity in **Appendix A14**). Lower temperature was associated with higher IFV and RSV activity. When temperature was lower than the annual average, higher relative humidity was also associated with higher RSV activity but not with higher IFV activity. When temperature was higher than the annual average, higher relative humidity was associated with higher IFV activity, especially for IFV A(H3N2), whereas this pattern was not observed for RSV.

Regarding the predictability of the model, the results of "leave-one-out" cross validation are demonstrated in **Table 2-2**. Overall, the model had good precision across all viruses in predicting local epidemic months. Better predictability was observed in the temperate regions than the tropics, especially for IFV. Regarding the prediction of the onset month of epidemics, the model prediction error was –0.2 months (95% CI: –0.6–0.1) for IFV, and 0.1 months (95% CI: –0.2–0.4) for RSV.

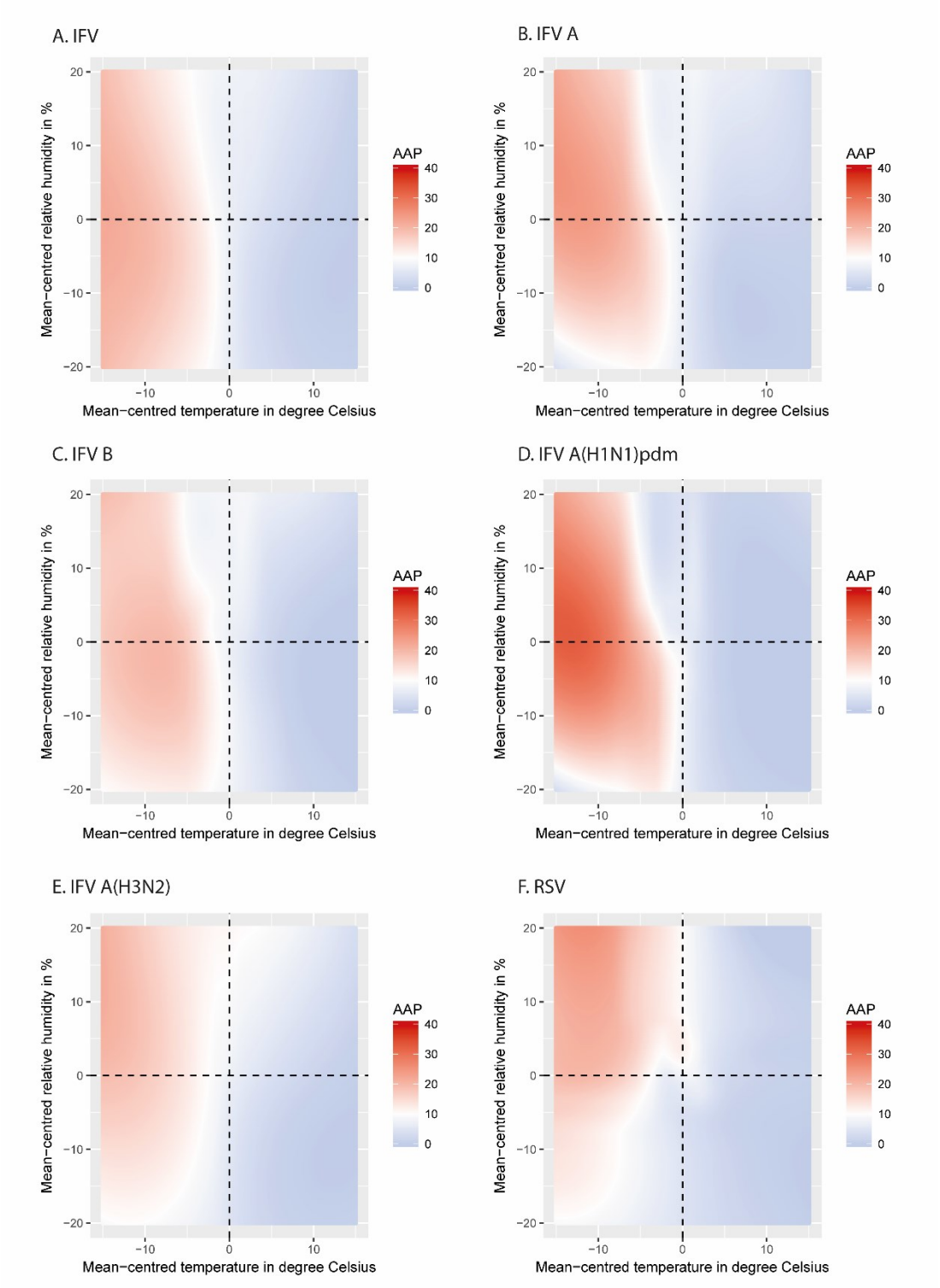


Figure 2-6 Monthly activity of influenza virus and respiratory syncytial virus against mean-centred temperature and relative humidity: model-predicted output

Table 2-2 Agreement on epidemic months between observed data and model prediction by leave-one-out cross validation

	Number of sites	Cohen's kappa with 95% CI	Agreement*	SEN*	SPE*	PPV*	NPV*	Prediction error in the month of onset with 95% CI†
Global								
IFV	200	0.36 [0.32, 0.40]	70	63	74	60	76	–0.2 [–0.6, 0.1]
IFV A	172	0.35 [0.31, 0.39]	70	62	73	55	79	–0.3 [–0.7, 0.1]
IFV B	127	0.37 [0.32, 0.42]	70	66	72	60	77	–0.7 [–1.0, –0.3]
IFV A(H1N1)pdm	129	0.39 [0.34, 0.44]	73	69	74	51	86	–0.6 [–1.0, –0.2]
IFV A(H3N2)	135	0.33 [0.29, 0.38]	68	67	68	55	78	–0.4 [–0.8, 0.1]
RSV	146	0.47 [0.42, 0.51]	75	65	81	69	78	0.1 [–0.2, 0.4]
Temperate Region								
IFV	97	0.59 [0.54, 0.64]	82	74	86	71	87	–0.4 [–0.8, –0.1]
IFV A	81	0.57 [0.51, 0.63]	82	72	86	68	88	–0.5 [–0.8, –0.1]
IFV B	73	0.49 [0.43, 0.55]	78	70	81	62	86	–1.0 [–1.3, –0.6]
IFV A(H1N1)pdm	61	0.61 [0.55, 0.68]	85	82	86	63	94	–0.7 [–1.0, –0.4]
IFV A(H3N2)	68	0.48 [0.42, 0.54]	77	73	78	59	87	–0.3 [–0.8, 0.3]
RSV	85	0.55 [0.49, 0.60]	79	66	87	75	82	0.5 [0.1, 0.8]
Tropical Region								
IFV	103	0.15 [0.09, 0.20]	58	55	60	52	63	–0.1 [–0.7, 0.5]
IFV A	91	0.16 [0.13, 0.23]	59	57	60	48	68	–0.1 [–0.8, 0.5]
IFV B	54	0.17 [0.10, 0.25]	59	62	55	58	59	–0.2 [–1.0, 0.5]
IFV A(H1N1)pdm	68	0.21 [0.14, 0.27]	62	61	62	44	76	–0.5 [–1.2, 0.2]
IFV A(H3N2)	67	0.17 [0.11, 0.24]	58	63	55	51	66	–0.5 [–1.2, 0.2]
RSV	61	0.35 [0.28, 0.42]	68	64	71	63	72	–0.4 [–0.9, 0.1]

CI=confidence interval; IFV=influenza virus; NPV=negative predictive value; PPV=positive predictive value; RSV=respiratory syncytial virus; SEN=sensitivity; SPE=specificity.

*in %.

†in month; a negative value indicates the onset predicted is earlier than the observed.

Moreover, based on the model, we present the estimated global epidemic months of IFV and RSV on a 5° by 5° scale. We also highlight the onset of the epidemic months for readers' reference. (**Figure 2-7** and **Figure 2-8**)

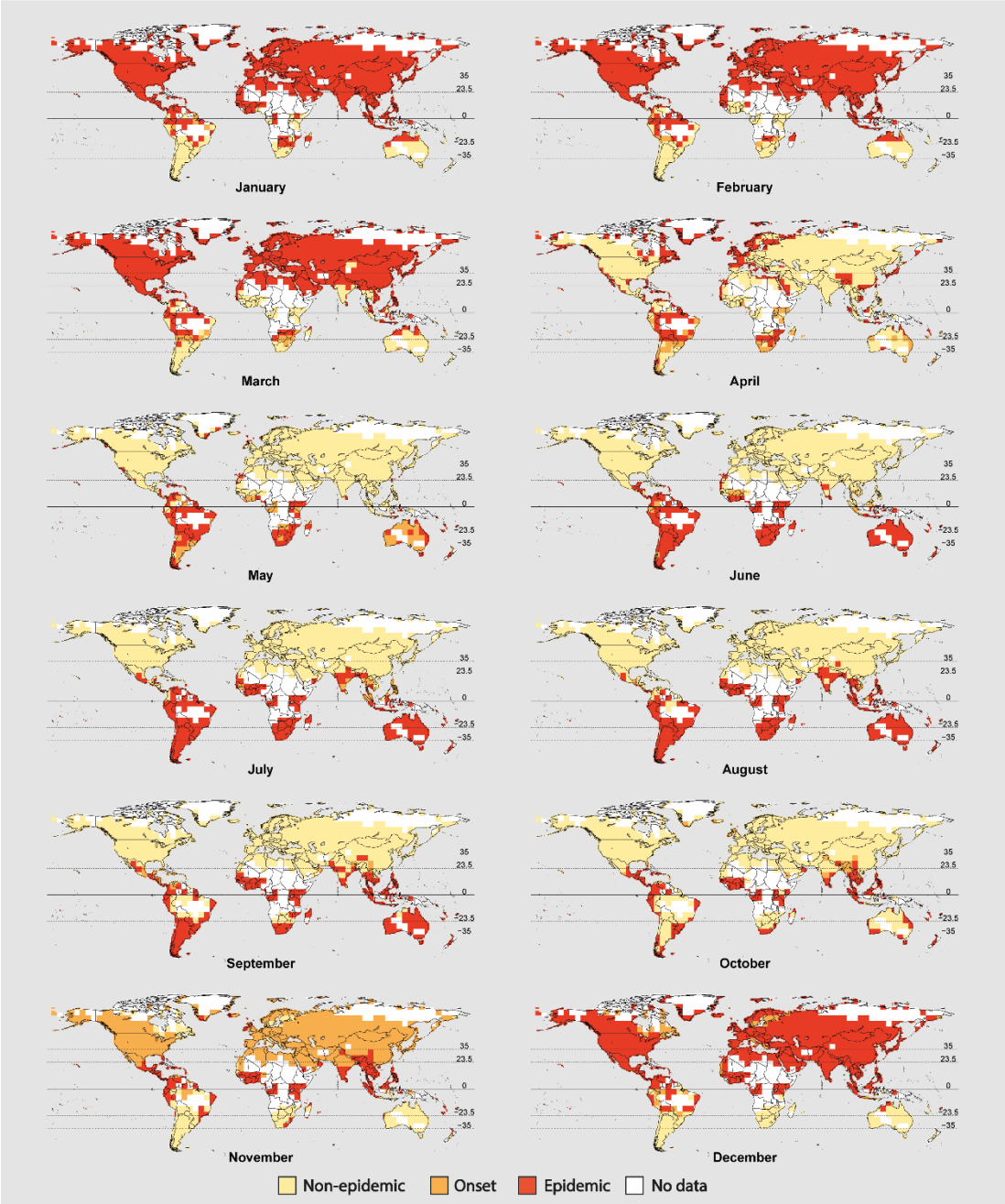


Figure 2-7 Global maps of the estimated average epidemic months of influenza virus during 2013–2017 on a 5° by 5° scale

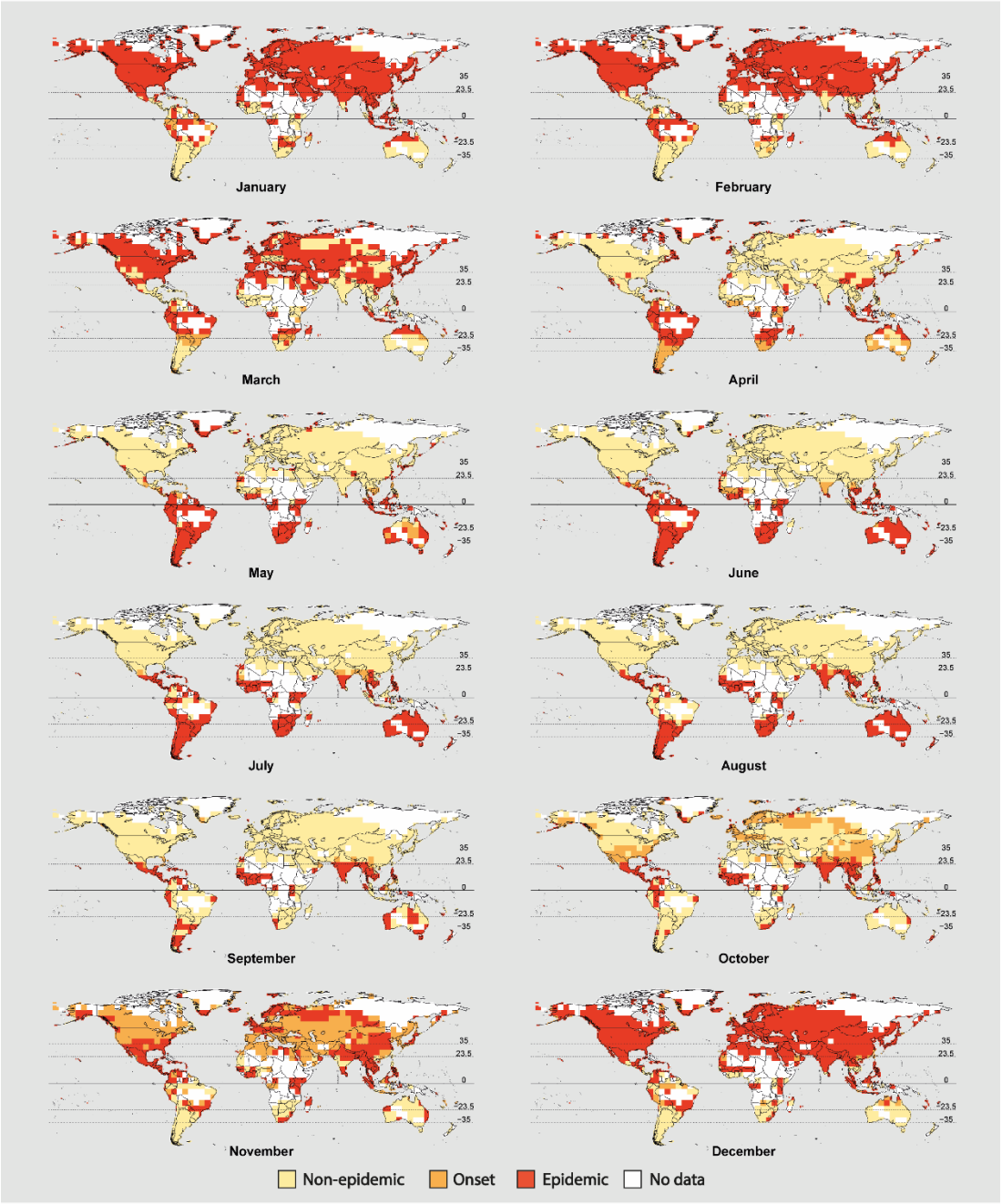


Figure 2-8 Global maps of the estimated average epidemic months of respiratory syncytial virus during 2013–2017 on a 5° by 5° scale

2.2.4 Discussion

To our knowledge, this is the first systematic analysis of global monthly activity of IFV, RSV, PIV and MPV at national and sub-national levels. With strict criteria, we compiled laboratory-confirmed viral activity from literature review, online surveillance datasets, and shared datasets by collaborators. We present global maps of monthly virus activity for IFV (including types and subtypes), RSV, PIV and MPV, demonstrating the distinct seasonal patterns for each virus. We found that latitudinal patterns in duration of epidemics were diverse among the four viruses. Furthermore, we modelled monthly virus activity using site-specific temperature and relative humidity for the prediction of epidemic months; developed an interactive tool for predicting the local epidemic months of IFV and RSV; and estimated the gridded global epidemic months of IFV and RSV on a 5° by 5° scale for the years 2013 through 2017.

Our results suggest that the global seasonal patterns of IFV and RSV are different in terms of both timing and duration of epidemics. At most temperate sites, IFV epidemics occurred later than RSV (by 0.3 months, 95% CI: −0.3, 0.9); in the tropics, RSV epidemics occurred in late summer and autumn months while timing of IFV epidemics varied greatly, and as a result, no clear temporal order was observed (lag=0.1 months, 95% CI: −0.9, 1.2). However, in a previous global review by Bloom-Feshbach et al (Bloom-Feshbach et al. 2013), the authors concluded that seasonal patterns of IFV and RSV were broadly similar in timing. The difference between the results of our study and those of Bloom-Feshbach et al (Bloom-Feshbach et al. 2013) is likely due to the smaller number of sites included in their review compared with the present study (IFV: 246 sites *vs* 77 sites; RSV: 183 sites *vs* 96 sites). With regard to duration of epidemics, IFV was more seasonal in the temperate region (duration of epidemics: 3.8 months, 3.6–4.0) than in the tropical region (5.2 months, 4.9–5.5) while RSV seasonality was weaker than IFV in the temperate region but stronger than IFV in the tropical region. This finding was

consistent with the review by Bloom-Feshbach et al (Bloom-Feshbach et al. 2013), despite different definitions for the duration of epidemics.

Our study found statistically significant positive correlations between the onset of epidemic months and absolute latitudes in each hemisphere, for both IFV and RSV. This is similar to the findings by Bloom-Feshbach et al (Bloom-Feshbach et al. 2013) using peak month instead of onset month. In addition to the latitudinal gradient stated above, we found a significant west-to-east gradient in the onset month for IFV and RSV in Europe, similar to country-level studies (S. Caini et al. 2017; Obando-Pacheco et al. 2018). The average difference in the timings of onset between west and east of Europe (defined geographically by 20˚E) was 0.6 months for IFV and 0.8 months for RSV.

Our study also found that seasonality was slightly different among IFV types and subtypes, similar to the findings from previous country-level regional reports (S. Caini et al. 2017; Finkelman et al. 2007). In our study, IFV A epidemics occurred 0.6 months (95% CI: 0.3–0.9) before IFV B in the temperate sites but no clear temporal order was seen in the tropical sites (lag=0, 95% CI: −0.5, 0.5). Moreover, we identified some interesting patterns not having been reported in previous reports; the latitudinal patterns of epidemic duration were similar among IFV subtypes, with IFV A(H1N1)pdm being the most seasonal virus (duration of epidemics=3.3 months, 95% CI: 3.1–3.5), followed by IFV A(H3N2) (4.2 months, 95% CI: 3.9–4.4) and IFV B (4.5 months, 95% CI: 4.3–4.8), regardless of the latitudes.

Compared with IFV and RSV, year-round laboratory-confirmed data of MPV and PIV are scarce and there is no global report on the seasonality of these two viruses. In the present study, we found that PIV epidemics occurred most often in the spring and early summer months in each hemisphere; MPV epidemics occurred in late winter and spring in most temperate sites but the peaks were more diverse in the tropics. PIV had longer duration of epidemics, which could be explained by the different circulation timings in

each PIV subtype (Fry et al. 2006; Mizuta et al. 2012). MPV had similar patterns to RSV in duration of epidemics, which may reflect known genetic similarities between the two viruses (Bernadette G. van den Hoogen et al. 2002). However, these two viruses did not co-circulate at most sites. In the temperate regions, MPV occurred 1.7 months (95% CI: 1.1–2.3) after RSV; in the tropics, no clear temporal order was observed. This indicates possible interference between these two viruses warranting further study.

The mechanisms that shape the global seasonal patterns of IFV, RSV, PIV and MPV remain unclear. Possible mechanisms include contact rates between susceptible and infected hosts, virus survival, and host immunity. Possible seasonal stimuli include temperature, humidity, precipitation, solar radiation, travel/work flows amongst other factors (J. Tamerius et al. 2011). In our study, all four viruses had different global patterns of timing and duration of epidemics; these patterns are unlikely to be well explained by non-virus-specific factors alone and one should be aware of potential spurious correlations between any non-virus-specific factors and virus activity. For example, travelling pattern is a potential factor that affects transmission but is not likely to explain the observed seasonal patterns well due to its non-virus-specific nature. Therefore, we did not select non-virus-specific factors in our candidate models. The two predictors that we included, temperature and relative humidity, were found to be associated with the seasonality of IFV and RSV in different ways. Although lower temperature was associated with higher activity of both IFV and RSV, higher relative humidity was associated with higher IFV activity when temperature was above annual average, and was associated with higher RSV activity when temperature was below annual average. Experimental studies on the transmission and survival of these viruses are needed in order to confirm our findings. Our findings regarding the predictors of IFV were similar to the two types of IFV peaks, “cold-dry” and “humid-rainy”, proposed by Tamerius et al (J. D. Tamerius et al. 2013) However, the model by Tamerius et al (J. D. Tamerius et al. 2013) was based on the activity of IFV of a dichotomous nature, i.e. peak and non-peak.

In our study, we modelled the activity of IFV and RSV of a continuous nature, thus allowing for more flexibility in our prediction.

Based on the gridded dataset of monthly temperature and relative humidity on a 5° by 5° scale (A. Smith et al. 2011; Willett et al. 2014), we mapped the global average epidemic months in 2013–2017. The results indicated that for those countries with a wide range of climate patterns, the viral epidemics varied within the country. For example, IFV and RSV epidemics occurred earlier in northern Australia than southern Australia. Moreover, given the global climate changes in the last few decades, we compared our prediction for 2013–2017 with our prediction for 1973–1977 but did not observe significant change in the predicted seasonal patterns for IFV and RSV.

Our study provides global maps of monthly virus activity, which have important implications for public health strategy. For IFV, vaccination is the most effective way to prevent disease.(World Health Organization 2018c) Seasonality data from existing country-level surveillance help inform the timing and composition of IFV vaccines but such surveillance is unable to account for any within country variations and under-sampled areas. By incorporating data from published and unpublished studies, our study potentially fills the data gap at sub-national level and for countries with no surveillance programme. This is particularly important for geographically large countries and tropical regions where great variations of virus activity may exist, as found in our study. For RSV, the seasonality information is important for immunisation strategy. In high-income countries, the administration of palivizumab prophylaxis, an RSV-neutralizing monoclonal antibody mainly used among high-risk infants, needs to be timed according to the local RSV season given the limited duration of its protection. For middle- and lower-income countries, RSV seasonality information is important for the development of affordable biologic equivalents of palivizumab and any vaccines with limited duration of protection (Q. Zhu et al. 2017). Moreover, the length of an RSV season defined by the duration of epidemics in our study is relatively stable at 4–5 months across all sites, in contrast to IFV,

which has irregular seasonality or year-round activity in the tropics. This could help optimise immunisation programmes by focusing on the pre-defined RSV seasons in both temperate and tropical regions. Unlike IFV for which surveillance data are widely available, RSV surveillance data are still lacking and WHO is in the process of implementing a global RSV surveillance programme (World Health Organization 2017). To this end, our prediction model estimates the local epidemic months for RSV epidemics, including the onset of epidemics, on a global scale. This information would be beneficial for lower and middle income countries. For all the viruses, the seasonality information is helpful in health-care services planning, especially when viruses co-circulate and impose pressure on hospital beds. It is also important for the patients' clinical management and for the appropriate use of antibiotics in the context of increased antimicrobial resistance and limited health resources in some settings (Sabuncu et al. 2009).

This study, however, is not without its limitations. First, like most studies of this type, the accuracy of the global activity data reported could be limited by the variety of methodologies applied in the studies and surveillance systems included. We were also unable to account for the variability regarding the age groups and severity of viral infections included at each site. While we aspired to have good geographical representativeness, we applied strict inclusion criteria and conducted additional quality assessment to exclude studies where the reported seasonality was likely to be biased by study subjects, testing practice, or reporting practice. Second, for better comparison across different sites, we calculated monthly AAP by aggregating multi-year data to determine virus activity. Although multi-year surveillance data suggest that the year-to-year change of IFV and RSV onset is within one month for most sites (Alonso et al. 2015; Obando-Pacheco et al. 2018), aggregating multi-year data could obscure the seasonal patterns of those sites with more notable year-to-year changes in seasonality. In particular, we were unable to identify multi-year periodicity of RSV activity which has been reported in some of countries in northern Europe (Broberg et al. 2018). Third, we were unable to report global seasonal patterns of any subtypes of RSV, PIV or

MPV due to a lack of relevant data reported; this could obscure the seasonality results of RSV, PIV and MPV, particularly PIV since the seasonal patterns were reported to differ greatly by type (Fry et al. 2006; Mizuta et al. 2012). Fourth, compared to IFV and RSV, there were fewer sites which reported data on MPV and PIV, thus limiting the representativeness of the results. Fifth, we were only able to summarise the global seasonality on a monthly basis instead of on a weekly basis. This was due to the scarcity of weekly data (e.g. only 20% of RSV data in our study were originally weekly aggregated), and methodologic challenges in order to accommodate the different definitions for "week" (e.g. a week can start with Saturday, Sunday or Monday by different definitions). Sixth, due to the lack of granularity of our training data, our prediction model might not be able to reflect the possible changes of viral epidemics induced by subtle short-term climate changes. However, such prediction is possible with data that are more granular in future (e.g. multi-year weekly data). Finally, our model is limited in its ability to predict the IFV epidemic months in the tropical region, partly due to the lack of clear seasonality and the failure to establish association between viral activity and meteorological factors. In the tropics, multi-year viral activity data from more countries are warranted and factors related to host immunity (e.g. seasonal fluctuation of nutritional status (Hillbruner and Egan 2008)) can be considered in future modelling studies.

Given the substantial health-care burden caused by IFV, RSV, PIV and MPV, their seasonal patterns described in our study are important for related health services planning. The model developed in our study is helpful in predicting the onset months of local IFV and RSV epidemics. This, together with the seasonality results presented, helps with the optimisation of any RSV immunisation strategies that rely on the information of local RSV season, especially in most middle- and lower- income countries where there may be no routine RSV surveillance. However, the model is limited regarding its performance on predicting IFV epidemics in the tropics, partly due to the lack of clear seasonality and the failure to establish association between IFV and meteorological factors. Besides, data gaps remain in PIV (including all

subtypes) and MPV and we are unable to model the epidemics of these two viruses. Future studies should consider describing and modelling the activity of IFV, RSV, PIV and MPV on a multi-year scale and should take into consideration the effects of climate change on respiratory viral epidemic seasonality.

2.3 Conclusion

The seasonality information of IFV, RSV, PIV and MPV is key for health services planning. The prediction tool developed in this study is helpful in predicting the onset months of local IFV and RSV epidemics, and serves as a supplement to existing surveillance. This, together with the summarised seasonality information, will help with the optimisation of RSV immunisation strategies that rely on the information of local RSV season, especially in most middle- and lower- income countries where routine RSV surveillance is not available. These implications will be further discussed in the next chapter.

Chapter 3 The role of RSV seasonality on national planning of introduction of RSV prevention strategies

3.1 Introduction

As noted in **Chapter 1**, several RSV prevention products are currently under clinical development and will hopefully be introduced in a few years. Currently, the only licensed RSV prevention product is Palivizumab, which is a short-acting mAb, exclusively administered in high income countries. Palivizumab is given every month for 5 months from the onset of the RSV season for infants in their first year of life and therefore, needs local RSV seasonality information. It is expected that future long-acting mAbs, will rely on RSV seasonality information (similar to Palivizumab). This is also the case for maternal RSV vaccine, which is designed to protect young infants during the first three to four months of their life.

Before this thesis, there have been no reports on RSV seasonality in LMICs. The data from existing RSV surveillance in high-income countries are not appropriate to use as a guide as they are all in temperate settings whereas the majority of LMICs are in the tropics. It remains unclear whether the seasonal approach, as adopted by the high income countries for Palivizumab, is suitable for LMICs; or alternatively, it might be suitable to adopt year-round administration if RSV is less seasonal in LMICs. The impact of various RSV prevention strategies for both long-acting mAb and maternal RSV vaccine needs to be estimated and compared in LMICs.

Therefore, based on the RSV data in **Chapter 2**, this chapter is aimed to understand the RSV seasonality in LMICs, including the year-to-year variations; and to assess and compare the impact of different RSV prevention strategies in LMICs.

3.2 Method

3.2.1 RSV seasonality in LMICs

The data on RSV seasonality in LMICs are a subset of the data described in **Chapter 2**. In order to understand the multi-year variation of RSV seasonality, I restricted the analysis to sites where multi-year data were available. To be eligible for multi-year data, the site should have at least three consecutive calendar years of monthly or weekly RSV positive cases and each year should have at least 25 positive cases.

For multi-year data, I calculated annual percentage (AP) similar to AAP. The duration of epidemics, epidemic month, and onset month for multi-year data are defined as was done for the annual average data in **Chapter 2**. If the duration of RSV epidemic was longer than five months, it was defined as "year-round" activity; otherwise, it was defined as "clearly seasonal". The cut-off of 5 months was based on the typical protection length of current mAb, Palivizumab (i.e. 5 doses * 1 month/dose of protection) and a mAb candidate, MEDI8897 (expected to have 5 months of protection per dose) (Domachowske et al. 2018).

3.2.2 Assessment of the impact of RSV prevention programmes in LMICs

The schematic figure of the analysis in this section is attached in **Figure 3-1**. The following subsections introduce the detailed methods of each main step.

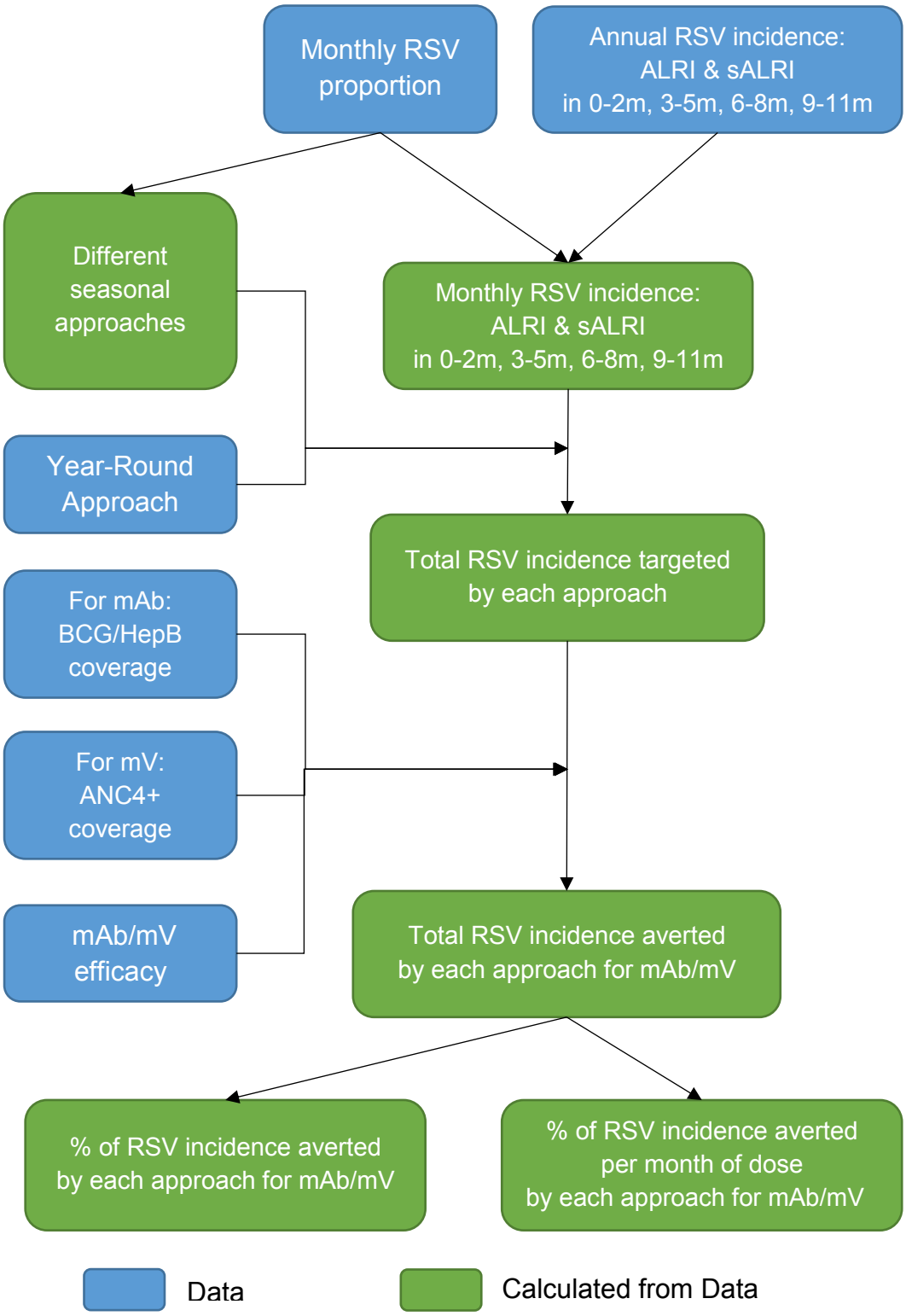


Figure 3-1 Schematic figure presenting the workflow of assessing the impact of RSV prevention strategies

RSV=respiratory syncytial virus; ALRI=acute lower respiratory infection; m=month; mAb=monoclonal antibody; mV=maternal vaccine.

sALRI refers to ALRI with chest wall indrawing; BCG refers to the birth dose of Bacillus Calmette–Guérin vaccine; HepB refers to the birth dose of Hepatitis B vaccine; ANC4+ refers to pregnant women attending antenatal clinics at least 4 times during pregnancy.

Candidate approaches

I considered both long-acting mAb (hereinafter referred to as “mAb”) and maternal RSV vaccine (hereinafter referred to as “mV”) programmes. mAb programme is aimed at newborns and mV programme is aimed at pregnant women at their third trimester. For mAb programme, five candidate approaches were considered, namely Seasonal Approach 1–4, and Year-Round Approach. All the four seasonal approaches were based on the epidemic months as defined previously in this thesis. In Seasonal Approach 1, mAb is administered before each epidemic month. In Seasonal Approach 2, 3, and 4, mAb is administered before a month if at least two epidemic months are anticipated in the upcoming 3, 4, and 5 months, respectively. Compared to Seasonal Approach 1, Seasonal Approach 2–4 was conceived to address the issues in Seasonal Approach 1 that an infant born several months before the season could not be immunised but would be exposed to high load of RSV during RSV season in very early months of life. In Year-Round Approach, mAb is administered all year round, regardless of RSV epidemic months. Similarly, two seasonal approaches and one year-round approach were considered for mV. There was no Seasonal Approach 3 or 4 for mV, due to the shorter protection duration of mV compared to mAb. **Figure 3-2** and **Figure 3-3** below present all the approaches for mAb and mV in Bolivia as an example.

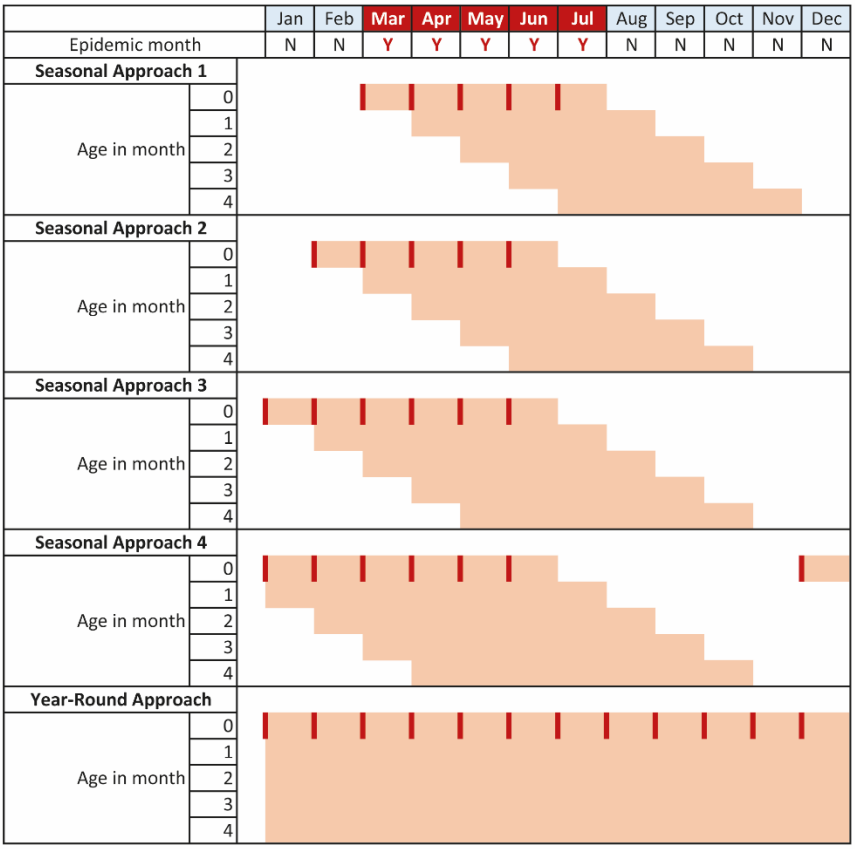


Figure 3-2 Schematic figure presenting the five candidate approaches for mAb using Bolivia as an example

mAb=monoclonal antibody. The red bar denotes the administration of mAb; the shaded area denotes protection by mAb.

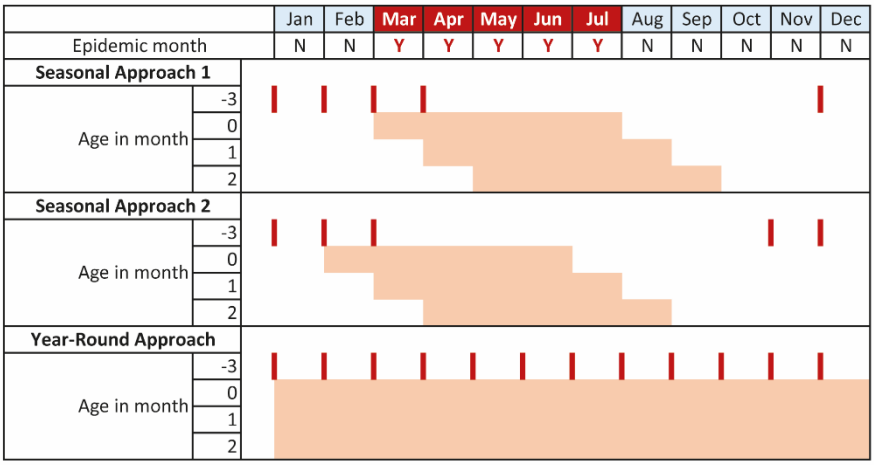


Figure 3-3 Schematic figure presenting the three candidate approaches for mV using Bolivia as an example

mV=maternal vaccine. Red bar denotes the administration of mV; shaded area denotes protection by mV.

Calculation of monthly RSV incidence by age group

The country-specific estimates of overall RSV-ALRI incidence in children under five years old were taken from a modelling study using six risk factors of RSV-ALRI as predictors, including prematurity, low birth weight, siblings in the household, maternal smoking, paediatric human immunodeficiency virus infection, and crowding (Shi et al. 2017). Both estimates for RSV-ALRI and RSV-severe ALRI in <5y were extracted. It was noted that severe ALRI was defined as ALRI with chest wall indrawing in the modelling study. To estimate RSV incidence in finer age bands for children aged <1y, the incidence rate ratios were calculated using the data in that study between <5y and each of the following age groups: 0-2m, 3-5m, 6-8m, and 9-11m (details of IRR in **Appendix A15**). For each country, the RSV monthly proportion was used to calculate the monthly RSV incidence. If more than one site was available for a country, the nearest site to the country's geographical centre was used.

Coverage and efficacy of mAb and mV

As birth dose was considered for mAb, I used the coverage data of existing vaccination programmes that had a birth dose, Bacillus Calmette–Guérin (BCG) vaccine and Hepatitis B (Hep B) vaccine. The coverage data of BCG and Hep B in LMICs in the year of 2017 were obtained from WHO website (Organization 2019). Where available, the coverage of BCG was applied as the coverage of mAb. For countries where BCG coverage was not available, Hep B coverage was applied.

For mV, there were little data on the maternal vaccine for IFV which is believed to provide the most suitable estimate of the potential coverage for RSV mV. As an alternative, antenatal care (ANC) visit data were used (WHO/RHR ANC4+ Global Database March 2019, personal communication). The ANC dataset contained the percentage of women aged 15–49 years who attended ANC at least four times during pregnancy. As the fourth ANC visit occurs in the third trimester, the percentage of women with at least four times of ANC visits is proposed as an acceptable proxy estimate of the coverage of RSV mV.

The efficacy of the long-acting mAb was obtained from the phase 2b trial results of MEDI8897: 70.1% (95% CI: 52.3–81.2) for medically attended ALRI and 78.4% (95% CI: 51.9–90.3) for ALRI hospitalisation on day 150 of administration. The efficacy of mV was obtained from the recent results of the phase-3 clinical trial of the Novavax RSV vaccine, ResVax; the efficacy was estimated to be 39.4% (95% CI: 5.3–61.2) for ALRI and 44.4% (95% CI: 19.6–61.5) for severe ALRI, at the age of 3 months (Anonymous 2019b).

Measures of effectiveness and efficiency

For each outcome, i.e. RSV-ALRI or RSV-severe ALRI, the proportion of incidence averted in <1y as the measure of effectiveness and the proportion averted per dose was calculated as the measure of efficiency. The results were then compared among different approaches. As it was anticipated that the duration of RSV epidemics would be associated with the efficiency of

seasonal approaches, all country-specific results were sorted by the duration of RSV epidemics as defined in the previous chapter.

All data analyses were conducted using R software (version: 3.4.3) (R Core Team 2017).

3.3 Results

3.3.1 RSV seasonality in LMICs

Data availability

RSV seasonality data were available in 110 sites from 46 LMICs (34% of LMICs). Multi-year RSV seasonality data were available in 36 sites from 23 LMICs (17% of LMICs). **Figure 3-4** below shows the distribution of data availability across LMICs. Only two sites from Turkey were available for the European region. The Americas had the best coverage among the six WHO regions, with 75% (18/24) of the countries having RSV seasonality data and 72% (13/18) of them having multi-year RSV data. Detailed information about data source and availability is attached **in Appendix A16**.

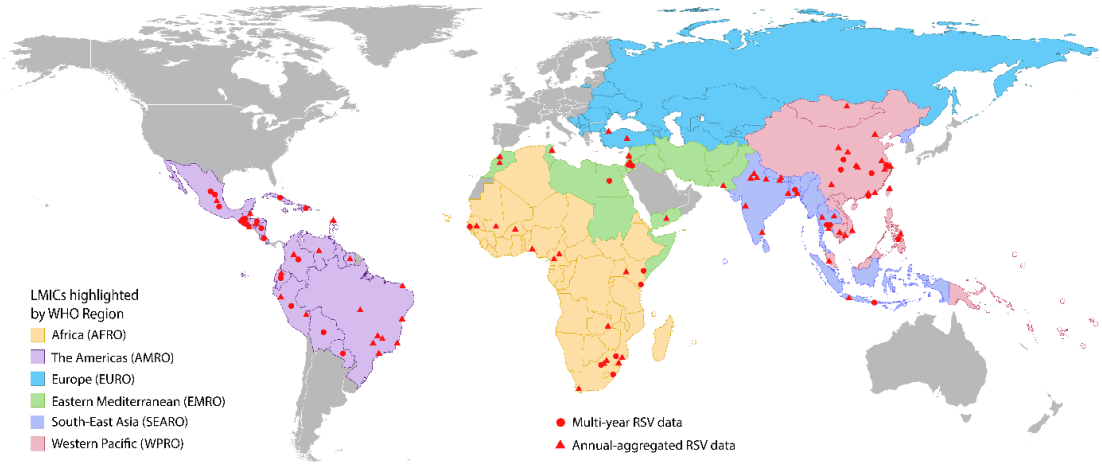


Figure 3-4 Data availability of RSV seasonality in LMICs

Annual average seasonality

More than two thirds (76/110, 69%) of the sites had clear RSV seasonality. **Figure 3-5** below shows the distribution of duration of RSV epidemics in the temperate and tropical regions. There was no statistical difference in terms of the distribution of RSV duration of epidemics between temperate and tropical

regions (P>0.05; **Appendix A17**). The mean duration was 4.51 months [95% CI: 4.03–4.99] in the temperate region and 4.82 months [95% CI: 4.45–5.20] in the tropical region. **Figure 3-6** shows the detailed monthly activity of RSV in LMICs. Sites with similar latitudes were more likely to have similar RSV seasonality.

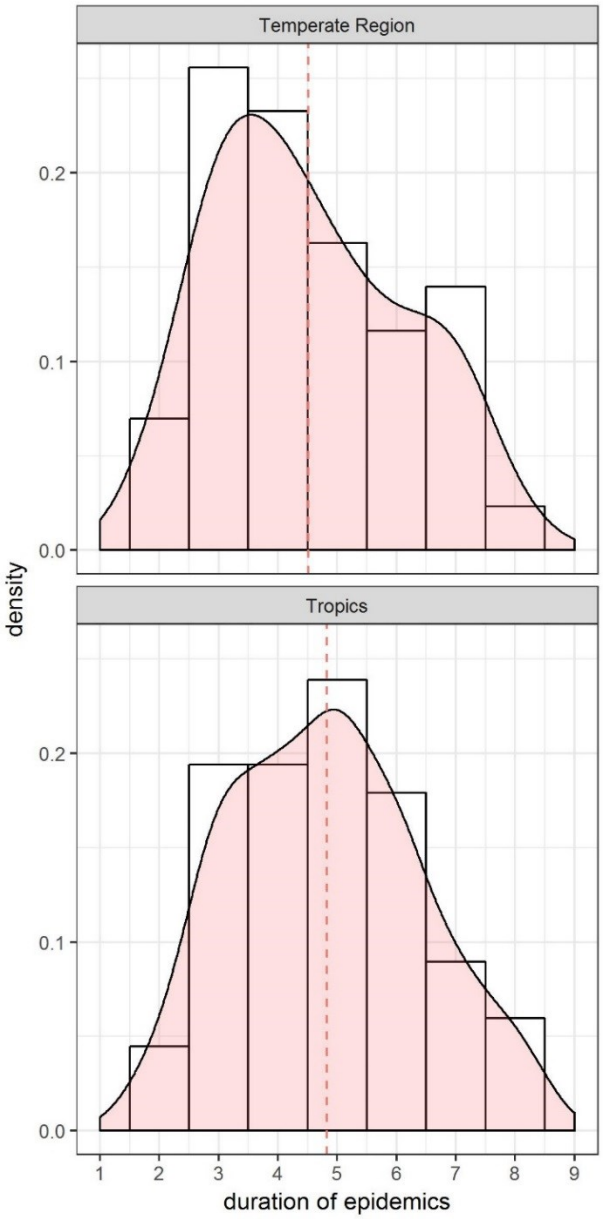


Figure 3-5 The distribution of duration of RSV epidemics (in months) in the temperate and tropical regions

The dashed line denotes mean duration.

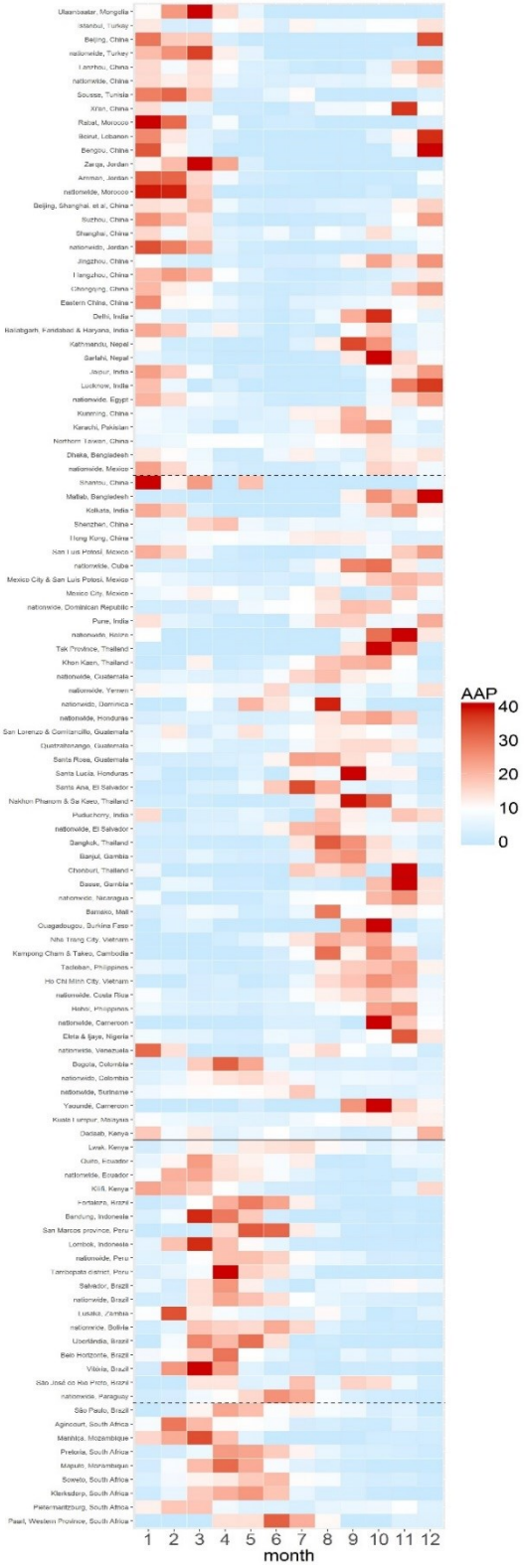


Figure 3-6 Annual average monthly activity of RSV in LMICs

Solid line=equator, dashed lines=tropics of Cancer and Capricorn

Year-to-year variation of RSV seasonality

Figure 3-7 on the next page shows the RSV monthly activity for the 36 sites with multi-year data available. Twenty-two of these 36 sites (61%) had clear seasonality when averaging the activity across the years. Within the 22 sites, when taking a closer look at the individual years per site, there was clear RSV seasonality during most years (106/115 site-years, 92.2%). Detailed results of duration of RSV epidemics are displayed in **Table 3-1**.

Table 3-1 The distribution of duration of RSV epidemics measured by site-years

		Duration of epidemics per site-year						
		Clear seasonality				Year-round activity		Total
		<4m	4m	5m	**⩽5m**	6m	>6m	
Annually average duration of epidemics	<4m	13 (81.3%)	3 (18.8%)	0	**16 (100%)**	0	0	16 (100%)
	4m	18 (47.4%)	17 (44.7%)	0	**35 (92.1%)**	3 (7.9%)	0	38 (100%)
	5m	31 (50.8%)	15 (24.6%)	9 (14.8%)	**55 (90.1%)**	5 (8.2%)	1 (1.6%)	61 (100%)
	⩽5m	**62 (53.9%)**	**35 (30.4%)**	**9 (7.8%)**	**106 (92.2%)**	**8 (7.0%)**	**1 (0.9%)**	**115 (100%)**
	6m	10 (21.3%)	14 (29.8%)	9 (19.1%)	**33 (70.2%)**	9 (19.1%)	5 (10.6%)	47 (100%)
	>6m	5 (18.5%)	1 (3.7%)	5 (18.5%)	**11 (40.7%)**	6 (22.2%)	10 (37.0%)	27 (100%)

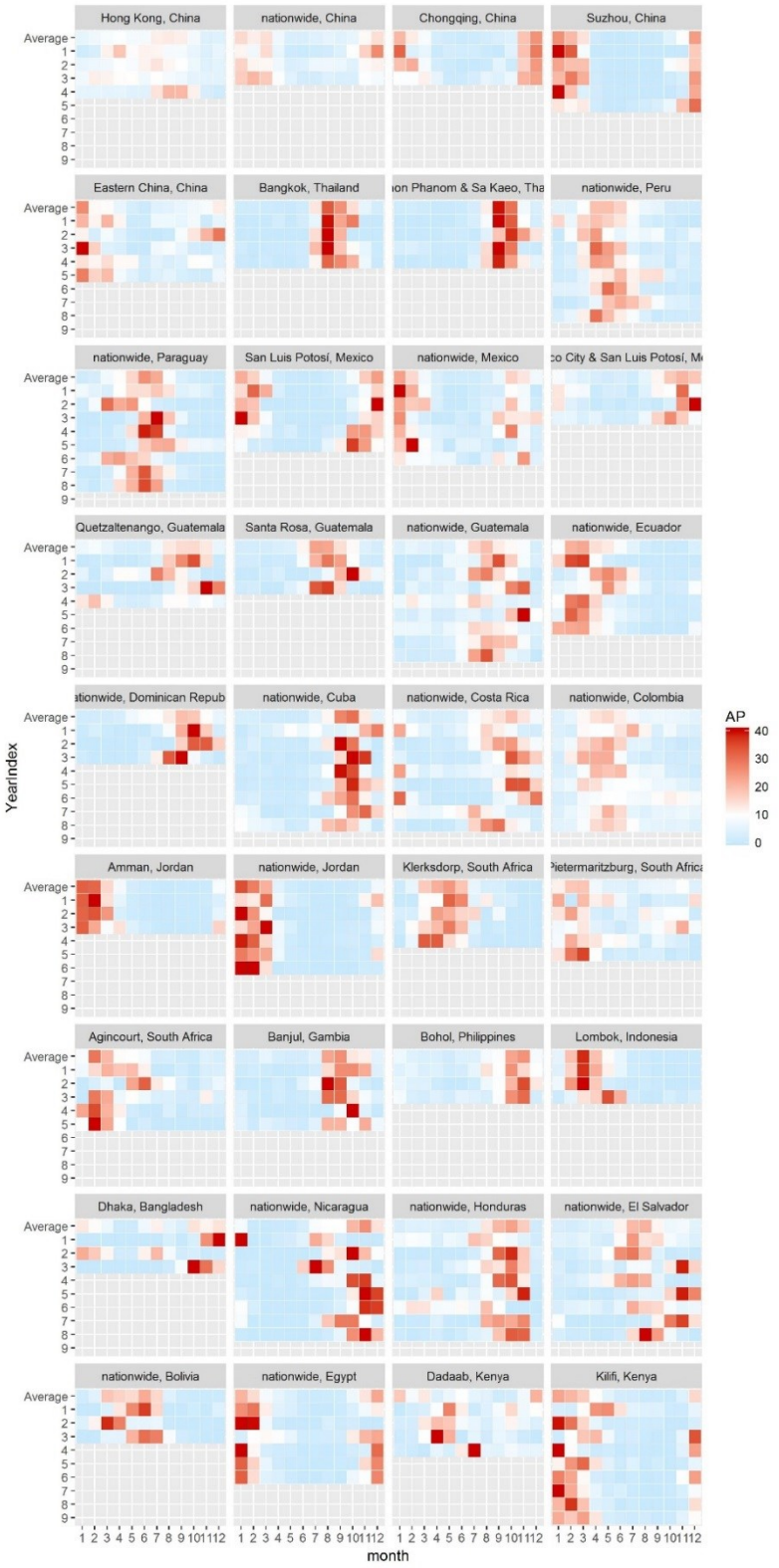


Figure 3-7 Monthly activity of RSV in sites with multi-year data

Among the 22 sites with clear seasonality, I then assessed the year-to-year variation in terms of the onset of RSV epidemics. 36.5% (42/115) of the site-years had the same onset as the average onset. The variation of the RSV onset was within 1 month for most of the site-years (86/115, 74.8%) and was within 2 months for more than 90% of the site-years (104/115, 90.4%). Detailed results are displayed in **Table 3-2**. I also assessed the year-to-year variation in terms of the proportion of RSV cases that could be covered by the average RSV season defined for each site. The results in **Table 3-3** show that most site-years (71/115, 61.7%) covered more than 80% of annual RSV positive cases during the average RSV season and that more than three quarters of the site-years covered more than 70% of annual RSV positive cases during the average RSV season.

Table 3-2 The distribution of year-to-year variation in the onset of RSV epidemics among sites with clear seasonality, measured by site-years

		0 months	1 month	2 months	3 months	>3 months	Total
Annually average duration of epidemics	<4m	11 (68.8%)	5 (31.3%)	0	0	0	16 (100%)
	4m	14 (36.8%)	18 (47.4%)	4 (10.5%)	2 (5.3%)	0	38 (100%)
	5m	17 (27.9%)	21 (34.4%)	14 (23.0%)	5 (8.2%)	4 (6.6%)	61 (100%)
	≤5m	**42 (36.5%)**	**44 (38.3%)**	**18 (15.7%)**	**7 (6.1%)**	**4 (3.5%)**	**115 (100%)**
	6m	13 (27.7%)	13 (27.7%)	5 (10.6%)	7 (14.9%)	9 (19.1%)	47 (100%)
	>6m	10 (37.0%)	11 (40.7%)	2 (7.4%)	2 (7.4%)	2 (7.4%)	27 (100%)

Table 3-3 The distribution of RSV coverage by the average RSV season

		>90%	80–90%	70–80%	60–70%	<60%	Total
Annually average duration of epidemics	<4m	2 (12.5%)	6 (37.5%)	4 (25.0%)	2 (12.5%)	2 (12.5%)	16 (100%)
	4m	12 (31.6%)	11 (28.9%)	6 (15.8%)	6 (15.8%)	3 (7.9%)	38 (100%)
	5m	24 (39.3%)	16 (26.2%)	7 (11.5%)	8 (13.1%)	6 (9.8%)	61 (100%)
	≤5m	**38 (33.0%)**	**33 (28.7%)**	**17 (14.8%)**	**16 (13.9%)**	**11 (9.6%)**	**115 (100%)**
	6m	7 (14.9%)	12 (25.5%)	17 (36.2%)	5 (10.6%)	6 (12.8%)	47 (100%)
	>6m	5 (18.5%)	8 (29.6%)	12 (44.4%)	2 (7.4%)	0	27 (100%)

3.3.2 Effectiveness and efficiency of different approaches

A total of 44 countries were included in the analysis. Overall, mAb had greater proportion averted and proportion averted per dose than mV, largely owing to the longer duration of protection and better coverage (the distribution of coverage in **Appendix A18**). For either mAb or mV, the proportion averted and proportion averted per dose was greater in RSV-severe ALRI cases than RSV-ALRI cases. Seasonal Approach 4 of mAb and Seasonal Approach 2 of mV performed well in terms of both effectiveness and efficiency. Detailed results are displayed in **Figure 3-8** and **Figure 3-9** below.

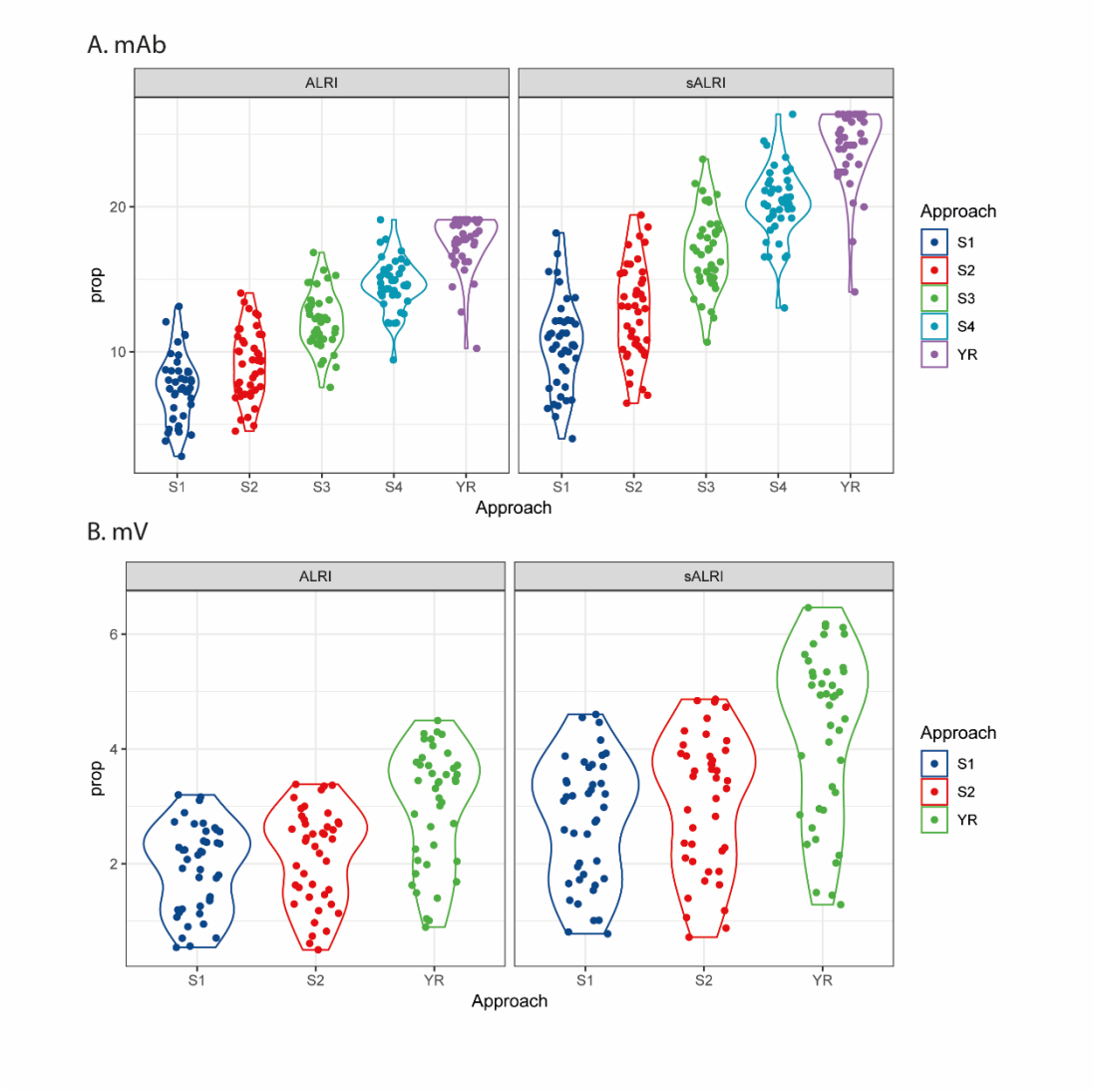


Figure 3-8 Proportion of RSV incidence averted by different approaches of RSV immunisation

S1–S4 denotes each seasonal approach; YR=year-round approach; mAb=monoclonal antibody; mV=maternal vaccine.

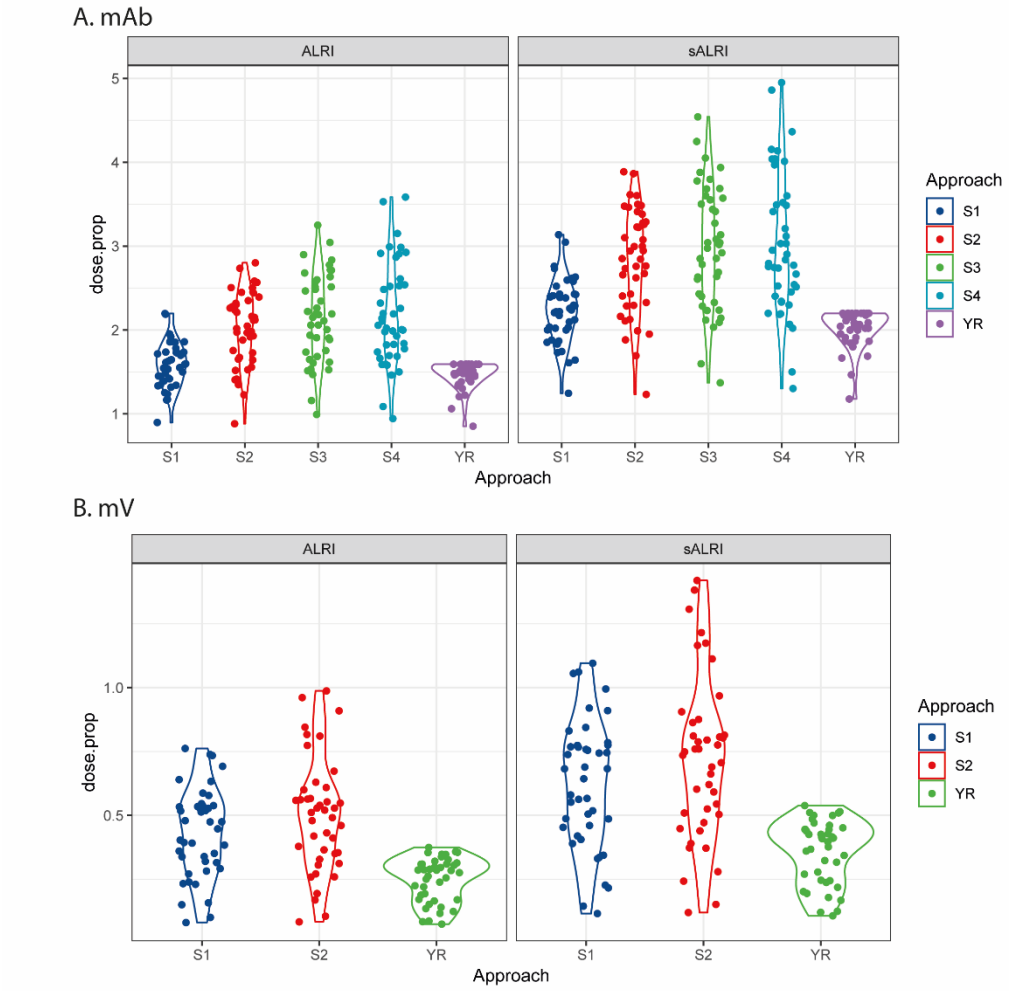


Figure 3-9 Proportion of RSV incidence averted per dose by different approaches of RSV immunisation

S1–S4 denotes each seasonal approach; YR=year-round approach; mAb=monoclonal antibody; mV=maternal vaccine.

Country-specific results

Compared with the year-round approach, the proportion averted per dose increased with decreasing duration of RSV epidemics. In terms of dose-efficiency, seasonal approaches were favoured in countries with ≤5 months of RSV epidemic duration (i.e. countries with clear seasonality) for both mAb and mV (**Figure 3-10** and **Figure 3-11**).

Country-specific results considering year-to-year variations

A total of 22/44 countries had multi-year level data that enabled evaluation of the performance of seasonal approaches given the year-to-year change of RSV seasonality. As shown in **Figure 3-12** and **Figure 3-13**, although year-to-year variations were observed in seasonal approaches, the advantage of seasonal approaches over the year-round approach remained in most countries with clear seasonality. Additionally, for each country, I plotted the proportion averted and proportion averted per dose in one plot as I anticipated that a "trade-off" between effectiveness and efficiency would likely to be of more interest to the policy makers from each country (**Appendix A19**, **A20**, **A21**, and **A22**).

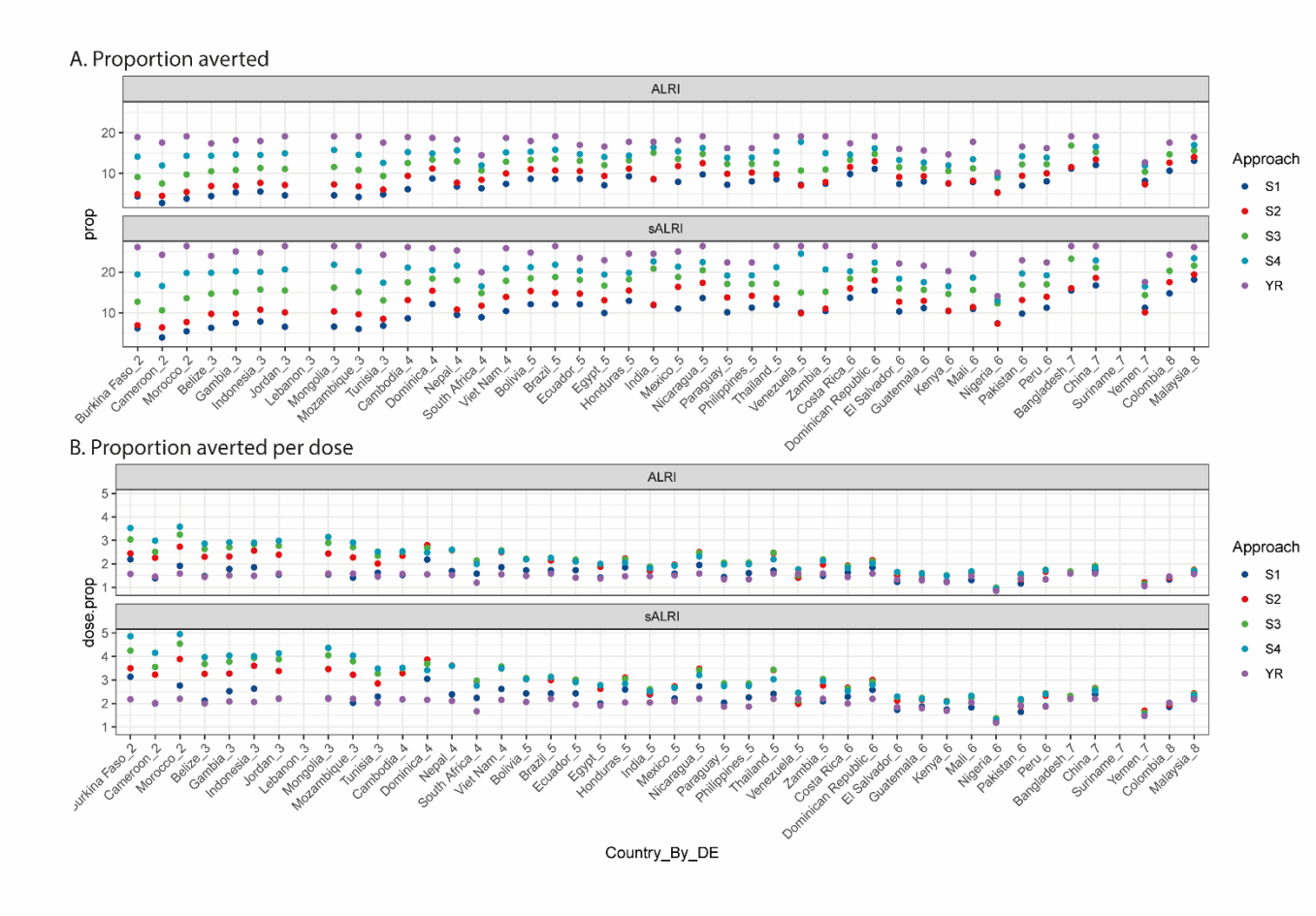


Figure 3-10 Country-specific comparisons of different mAb administration approaches, sorted by duration of RSV epidemics

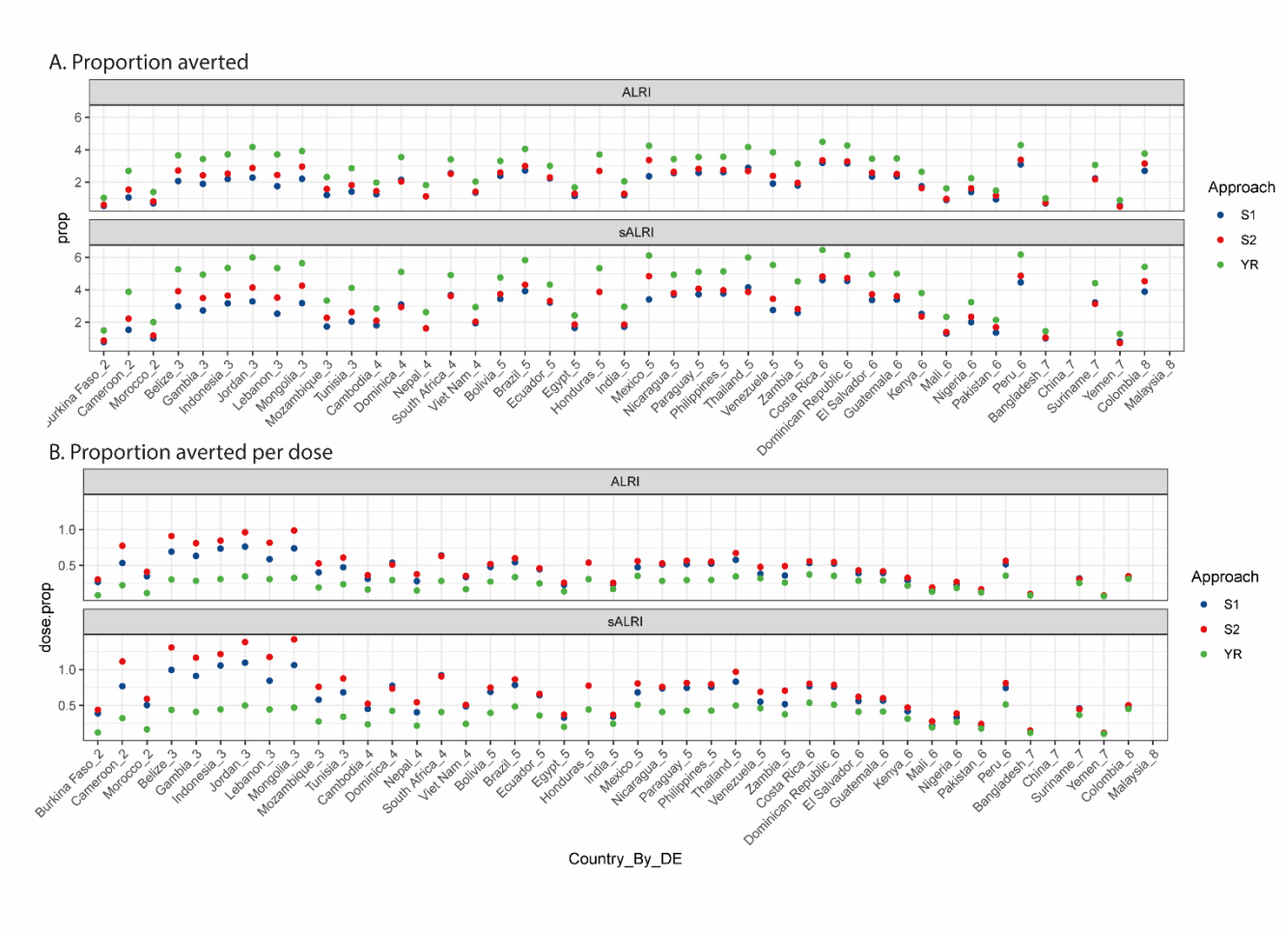


Figure 3-11 Country-specific comparisons of different mV administration approaches, sorted by duration of RSV epidemics

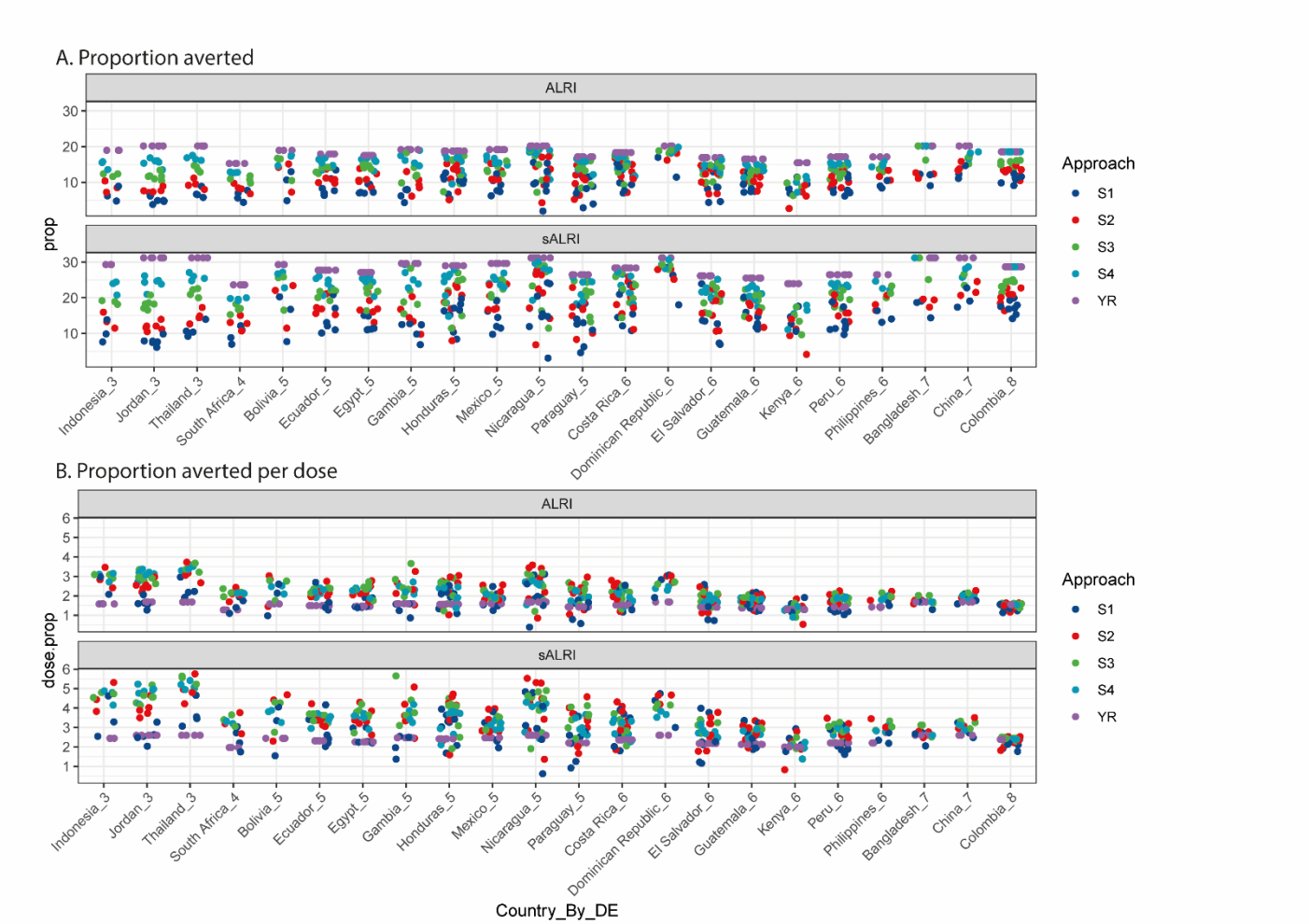


Figure 3-12 Country-specific comparisons of different mAb administration approaches, sorted by duration of RSV epidemics, considering multi-year variations

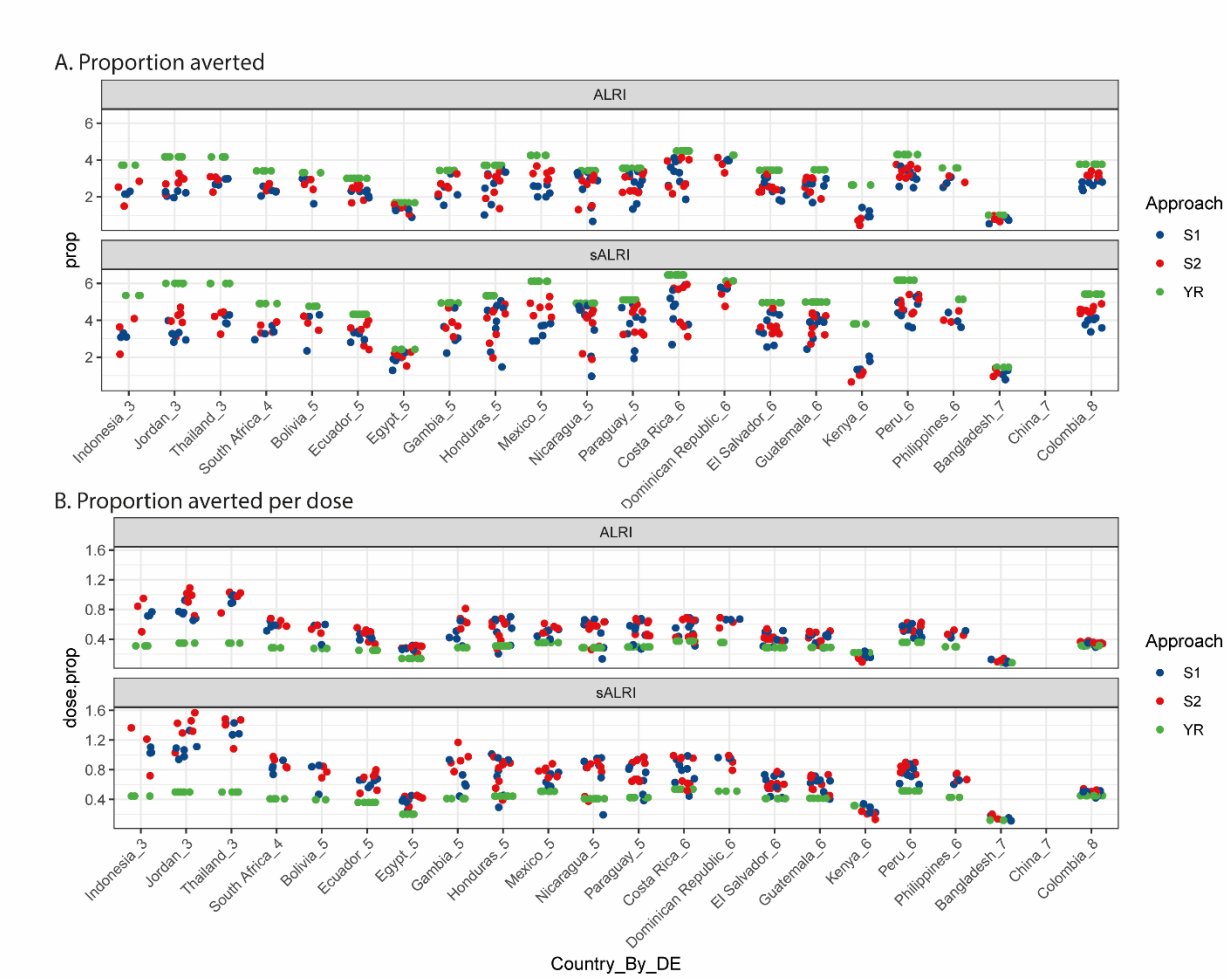


Figure 3-13 Country-specific comparisons of different mV administration approaches, sorted by duration of RSV epidemics, considering multi-year variations

3.4 Discussion

This study described the RSV seasonality in LMICs and found that RSV seasonality was distinct and was relatively stable over years in most LMICs. Compared with the year-round approach, seasonal approaches were more suitable in LMICs with clear seasonality (~two thirds of LMICs included) for both long-acting monoclonal antibody immunisation (mAb) and maternal RSV vaccine (mV). The findings were consistent in the subgroup analysis including only countries with multi-year RSV data.

As discussed in **Chapter 2**, unlike IFV in most LMICs, especially in the tropical region (Saverio Caini et al. 2016), RSV seasonality was distinct in most LMICs and sites with similar latitude tended to have similar RSV seasonality. Further to the analysis in **Chapter 2**, this study focused more on the multi-year variations of RSV in LMICs. For sites with clear seasonality, I found that these sites were very likely to have clear RSV seasonality for each year, and that the variation of the onset was within 1 month for most sites. Using the same average RSV season, more than 70% of the annual RSV cases could be covered in each year for most sites. These results suggest that a static seasonal approach can be considered for countries with clear seasonality and with no active RSV surveillance.

To further assess and compare different approaches (i.e. seasonal approaches *vs* year-round approach), several seasonal approaches were considered for mAb and for mV, separately. The different seasonal approaches differed mainly by the starting month. For example, while Seasonal Approach 1 only protected infants born right before an RSV epidemic month, Seasonal Approach 4 aimed to protect those infants born up to 3 months before an RSV epidemic month. This was limited to 3 months prior to onset of RSV epidemic so as to confer at least 2 months of protection during early infancy. For mV, only Seasonal 1 and 2 were considered as the duration of protection by mV was not suitable for the other two seasonal approaches.

For mAb, all the approaches were based on the strategy of birth dose only, for several reasons. First, birth-dose is logistically more feasible for LMICs; RSV mAb can be given to the newborns as soon as they are born (along with BCG and HepB), avoiding a separate visit. By contrast, immunising infants later can be challenging as immunisation coverage decreases with subsequent doses for vaccines in Expanded Programme on Immunisation (EPI) and organising catch-up campaigns can be challenging for the already weak and over-burdened health systems in LMICs (Hoest et al. 2017). Second, the incidence of RSV-severe ALRI is highest in infants aged 3–5m (**Appendix A15**) and the birth dose of mAb can protect infants for the first five months of life. Third, the phase 3 trial of the long-acting mAb will be initiated later in 2019. Although the protocol has not been registered publicly at the time of writing, the phase 3 trial is likely to be conducted among healthy newborns and the mAb will be given at birth (personal communication).

The results of the comparisons suggest that Seasonal Approach 4 for mAb had the highest effectiveness and efficiency among all the four seasonal approaches in countries with clear seasonality. When comparing this seasonal approach with the year-round approach in these countries, the Seasonal Approach 4 was favoured as it had comparable effectiveness to the year-round approach but much higher dose efficiency. Similarly, Seasonal Approach 2 for mV had the highest effectiveness and efficiency in countries with clear seasonality and had advantages in dose-efficiency over the year-round approach. These results supported the use of a seasonal approach in most LMICs with clear RSV seasonality when considering the introduction of long-acting mAb and/or maternal vaccine. The results from further subgroup analyses from sites with multi-year data consistently supported the seasonal approach, indicating that a fixed seasonal approach could be applied to LMICs with clear seasonality and with limited resources to conduct active RSV surveillance.

However, there are some limitations in this study. First, the estimate of proportion averted in each country could be biased due to various reasons. For mAb, the use of BCG or Hep B coverage could overestimate the coverage of mAb as the introduction of a new prophylaxis may not receive the same level of acceptance as the current vaccines . Even though being given at the same time as BCG, parents may still have concerns about having another injection to their fragile babies. Nevertheless, the potentially biased estimate of mAb coverage is not expected to affect the comparisons between different seasonal approaches and the year-round approach. For mV, there are several uncertainties around the estimate. According to the phase 3 trial results of the maternal vaccine, the efficacy of the late vaccination group (i.e. after 33 weeks of gestation) was lower than the 28–32 weeks group (Anonymous 2019b). In my study, the ANC data did not indicate the exact gestational week of the fourth visit so it was not possible to account for this factor. Therefore, the overall efficacy was applied to this study. Apart from the timing of the vaccination, prematurity is an important factor that could bias the estimate. On the one hand, prematurity reduces the placental transfer of RSV antibody and affects the vaccine effectiveness (Okoko et al. 2001). On the other hand, as the maternal vaccine is timed assuming a term delivery for the seasonal approaches, an earlier birth could leave the infants unprotected when the RSV season comes later. This could lead to an overestimate of the effectiveness and efficiency of the seasonal approaches. Given the high prevalence of preterm births in LMICs (Blencowe et al. 2012), one should interpret the results for mV with caution.

Second, this study only included 46 countries with available RSV seasonality data (only 23 having multi-year RSV data) and the seasonality results might not be representative of all LMICs. Same issues apply to the comparisons between seasonal approaches and year-round approach in mAb and mV programmes. Third, this study was conceived as a first-phase comparison of different immunisation approaches and no formal cost-effectiveness analysis was conducted. Such analysis is warranted in future studies.

In conclusion, there are still data gaps in RSV seasonality in LMICs. Most LMICs included in this study have clear and stable seasonality over time. The results of evaluating the effectiveness and efficiency of different RSV immunisation programmes are supportive of a seasonal approach for both long-acting monoclonal antibody and maternal vaccine in LMICs with clear seasonality. Further work is needed on the evaluation of different maternal vaccine strategies.

Chapter 4 Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review

4.1 Introduction

Pneumococcal disease is a major cause of communicable disease burden globally. It has been suggested by animal and in vitro studies that preceding viral acute respiratory infection can predispose to pneumococcal infection. In population-based studies, it is estimated that 6–7.5% of cases of invasive pneumococcal disease are attributable to influenza and 3–4% attributable to RSV in the UK (Nicoli et al. 2013) and that 20% of pneumococcal pneumonia cases are attributable to RSV among infants <1y in the US (Weinberger et al. 2015). These findings suggest prevention of VARI can yield additional benefit for the control of PD. However, evidence from population-based studies is not accordant. These studies differed substantially in study design, data sources and methods, making it difficult to compare and interpret the results across the studies.

Therefore, a systematic review of population-based studies about the association of viral acute respiratory infection with pneumococcal disease was conducted and this work in this chapter has been published in BMJ Open journal. (Li Y, Peterson ME, Campbell H*, et al* Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies *BMJ Open* 2018;**8:**e019743)

In this published work, I conducted the systematic literature review; extracted the data, drafted the manuscript and revised the manuscript according to the comments from the journal's peer review. Meagan Peterson conducted the second extraction independently and revised the manuscript for intellectual content. Prof. Harish Nair and Prof. Harry Campbell conceived and oversaw the work, and revised the manuscript for intellectual content.

4.2 Full-text of the publication "Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies"

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

Authors: You Li[1], Meagan E Peterson[1], Harry Campbell[1], Harish Nair[1]

Affiliation: Centre for Global Health Research, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, Edinburgh, UK

Correspondence author: You Li (you.li2@ed.ac.uk)

Abstract

Objective: Animal and in vitro studies suggest that viral acute respiratory infection (VARI) can predispose to pneumococcal infection. These findings suggest that the 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 respiratory syncytial virus (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 use individual patient data, control for seasonal factors of VARI and PD, or include other factors related to the association (eg, virus, age, comorbidity and pneumococcal serotype).

4.2.1 Introduction

Both viral acute respiratory infection (VARI) and pneumococcal disease (PD) account for a substantial disease burden worldwide, especially in young children and the elderly (Drijkoningen and Rohde 2014; O'Brien et al. 2009; H. Wang et al. 2016). The association of VARI and subsequent PD was not well recognised until the catastrophic 1918 influenza pandemic, which resulted in an estimated 40–50 million deaths;(McCullers 2006) it has been suggested that pneumococcus may have been a major cause of death (Chien et al. 2009). Most recently, it was observed that the incidence of PD was higher during 2009 influenza H1N1 pandemic period than the same period in prepandemic (Fleming-Dutra et al. 2013; Launes et al. 2014; Nelson et al. 2012; Pedro-Botet et al. 2014; Weinberger et al. 2012) and postpandemic years (Launes et al. 2014; Pedro-Botet et al. 2014; Weinberger et al. 2012).

During interpandemic periods, the associations of seasonal influenza and other seasonal respiratory viruses such as respiratory syncytial virus (RSV), human metapneumovirus and parainfluenza virus (PIV) with PD incidence are poorly understood and remain unclear. In animal and in vitro studies, it has been suggested that viral respiratory infection could predispose to pneumococcal infection and might facilitate pneumococcal transmission; in turn, this coinfection could induce a lethal synergism that is much more severe than infection with either pathogen alone (a brief summary of findings is displayed in supplementary **Table 4-4**). However, these studies are all relatively small-scale studies and may be subject to publication bias favouring reporting of positive findings. In population-based studies, the findings were inconsistent. These studies differed substantially in study design, data sources and methods, making it difficult to compare and interpret the results across the studies. We conducted a systematic review of population-based studies on the association of preceding VARI on the occurrence of PD to summarise the methodology and results, critically review the findings and present recommendations for future studies.

4.2.2 Methods

Search strategy and selection criteria

We searched MEDLINE, Embase and Global Health databases using tailored search strategies (search strategies in supplementary **Panel 4-1**, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart in **Figure 4-1**). We restricted the search to studies published between 1 January 1990 and 31 December 2017. We included population-based studies with clinically diagnosed PD cases (see next for detailed definition). In terms of VARI exposure, we accepted the following studies: (1) those with laboratory-confirmed viral infections; (2) those with the International Classification of Diseases (ICD) code for influenza and/or RSV infection and (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 checklists for case–control studies and cohort studies (online supplementary file S1 available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5914779/bin/bmjopen-2017-019743supp003.pdf). The review was conducted and reported according to the PRISMA guidelines. The protocol for this systematic review was registered on PROSPERO (registration number: CRD42017064760.

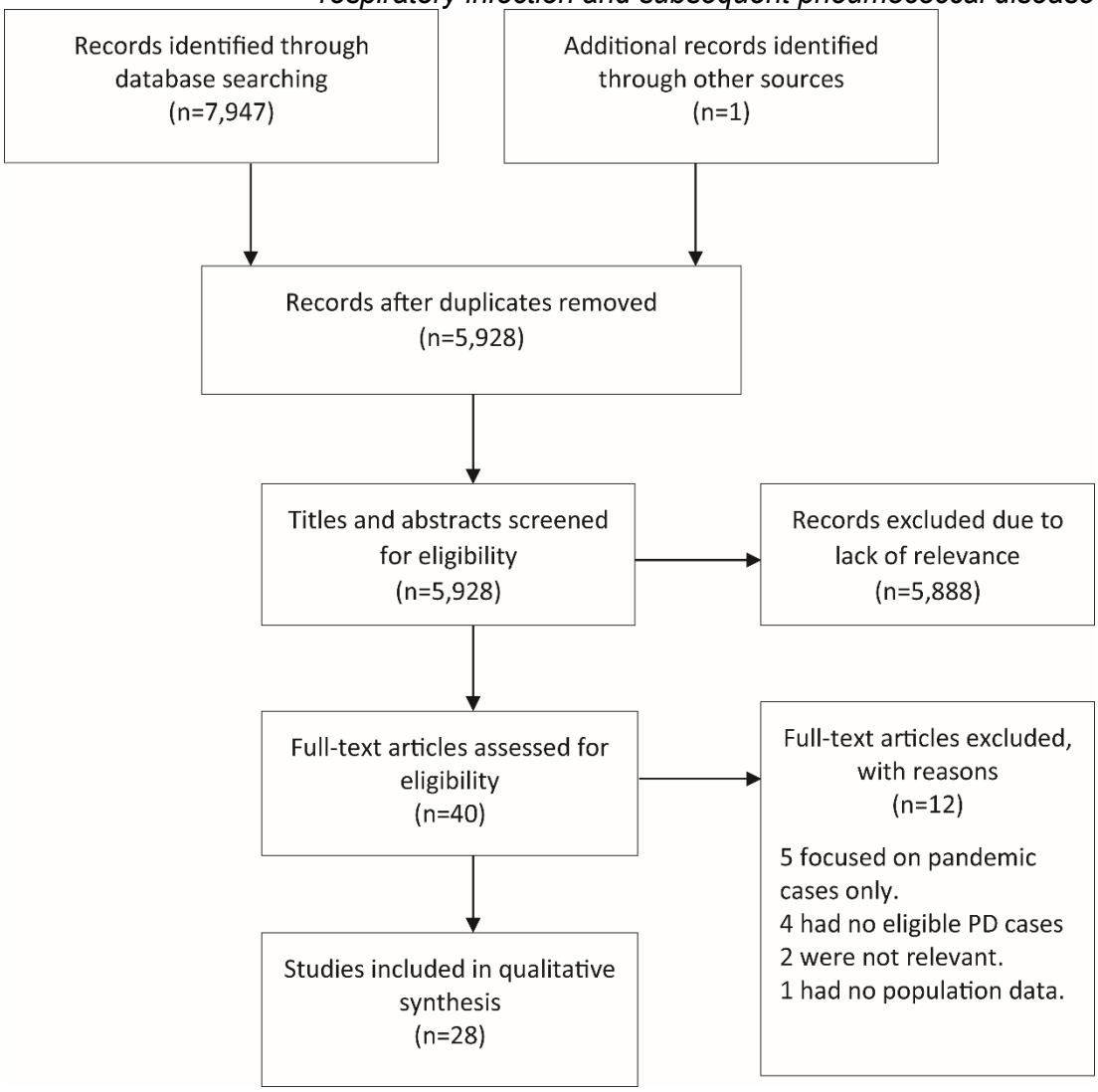


Figure 4-1 PRISMA flow diagram of the literature search

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 4-2**. 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 both invasive and non-invasive PP.

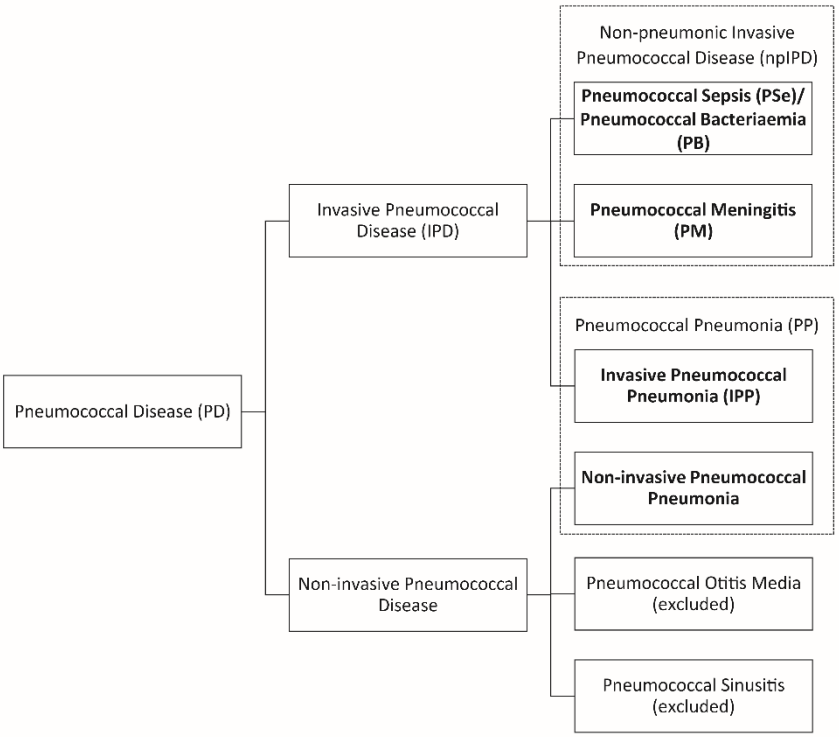


Figure 4-2 Category of pneumococcal disease in the present review

Definition of VARI

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

Data extraction

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

Data analysis

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

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

Patient and public involvement

No patients or public were involved in the present study.

4.2.3 Results

A total of 28 studies (Allard et al. 2012; Ampofo et al. 2008; Burgos et al. 2015; Ciruela et al. 2016; Dangor et al. 2014; Domenech de Cellès et al. 2017; Edwards et al. 2011; Grabowska et al. 2006; Hendriks et al. 2017; Jansen et al. 2008; Kim et al. 1996; Kuster et al. 2011; Murdoch and Jennings 2009; Nicoli et al. 2013; O'Brien et al. 2000; Opatowski et al. 2013; Peltola et al. 2011; Shrestha et al. 2013; Stensballe et al. 2008; Talbot et al. 2005; Toschke et al. 2008; Walter et al. 2010; M. Watson et al. 2006; Weinberger et al. 2013, 2014b; Weinberger et al. 2014a; Weinberger et al. 2015; Zhou et al. 2012) were eligible and included in the review. We noticed a variety of study designs, exposures and outcomes of interest and analytical methods in these studies (summarised in supplementary **Table 4-5**). Due to the variety, we summarised the studies and displayed the results according to study design and methods.

Individual patient data-based studies

Individual patient data-based studies during the interpandemic period are sparse. Only three studies(Edwards et al. 2011; O'Brien et al. 2000; Stensballe et al. 2008) were identified (**Table 4-1**), including two cohort studies(Edwards et al. 2011; Stensballe et al. 2008) and one small case-control study by O'Brien *et al*.(O'Brien et al. 2000) The reported results consistently supported the role of preceding VARI on the occurrence of PD. However, the two cohort studies did not attempt to control the seasonal risk factors of VARI and PD that could potentially bias the estimated effect size.

Table 4-1 Summary of individual patient data based studies

Study	Study Period	Population	VARI	PD (n of cases)	Methods	Main findings
Edwards et al. 2011(Edwards et al. 2011)	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(O'Brien et al. 2000)	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(Stensballe et al. 2008)	1996–2003	all ages Denmark	RSV non-RSV	IPD (n=7,787)	Prospective cohort study: two exposure groups, RSV and non-RSV respiratory infection hospitalisations within 30d	RR for RSV=7.1 [3.6–14.3], RR for non-RSV=4.5 [2.0–10.0]

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

Ecological studies

In our review, 25(Allard et al. 2012; Ampofo et al. 2008; Burgos et al. 2015; Ciruela et al. 2016; Dangor et al. 2014; Domenech de Cellès et al. 2017; Grabowska et al. 2006; Hendriks et al. 2017; Jansen et al. 2008; Kim et al. 1996; Kuster et al. 2011; Murdoch and Jennings 2009; Nicoli et al. 2013; Opatowski et al. 2013; Peltola et al. 2011; Shrestha et al. 2013; Talbot et al. 2005; Toschke et al. 2008; Walter et al. 2010; M. Watson et al. 2006; Weinberger et al. 2013, 2014b; Weinberger et al. 2014a; Weinberger et al. 2015; Zhou et al. 2012) of the 28 studies were ecological studies. 16(Allard et al. 2012; Burgos et al. 2015; Ciruela et al. 2016; Domenech de Cellès et al. 2017; Grabowska et al. 2006; Hendriks et al. 2017; Kuster et al. 2011; Murdoch and Jennings 2009; Nicoli et al. 2013; O'Brien et al. 2000; Opatowski et al. 2013; Walter et al. 2010; M. Watson et al. 2006; Weinberger et al. 2013, 2014b; Weinberger et al. 2014a; Weinberger et al. 2015) out of the 25 ecological studies controlled for seasonal patterns of VARI and PD (supplementary **Table 4-5**). Additionally, the study by Stensballe *et al (Stensballe et al. 2008)* analysed data at both population and individual levels but did not control for the seasonal patterns.

Correlation analyses with no control for seasonal patterns

Table 4-2 shows a summary of 11 studies (Ampofo et al. 2008; Burgos et al. 2015; Ciruela et al. 2016; Jansen et al. 2008; Kim et al. 1996; Murdoch and Jennings 2009; Nicoli et al. 2013; Peltola et al. 2011; Stensballe et al. 2008; Talbot et al. 2005; M. Watson et al. 2006) using correlation analyses without controlling for seasonal patterns of VARI and PD. Since all studies conducted multiple tests in analysing the correlation (e.g., across age groups, viruses and lag time between VARI and PD), the Bonferroni method was applied to adjust the significance level. The correlation between PD and influenza or RSV was statistically significant in all five studies (Ciruela et al. 2016; Murdoch and Jennings 2009; Nicoli et al. 2013; Stensballe et al. 2008; Talbot et al. 2005) that analysed population data of all ages (correlation coefficient r: 0.40–0.71 for influenza at no time lag, 0.47–0.77 for RSV at no time lag).

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

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

Global seasonality of respiratory viruses and the association between viral acute respiratory infection and subsequent pneumococcal disease

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)	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)	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)	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)
(M. Watson et al. 2006)	2000 (May–Oct)	all ages New South Wales, Australia	IFV RSV PIV	IPD (n=681)	Surveillance data, weekly	Pearson	<u>≤18y</u> IFV: not significant RSV: **0.58a** PIV: **−0.40c** <u>≥18y</u> IFV: not significant RSV: not significant PIV: not significant RSV or IFV: **0.48c**

Time lag indicates the time difference between preceding VARI and subsequent PD incidence.
Abbreviations: ADV, adenovirus; EV, enterovirus; IFV, influenza virus; IPD, invasive pneumococcal disease; m, month(s); MPV, metapneumovirus; PB, pneumococcal bacteraemia; PD, pneumococcal disease; PIV, parainfluenza virus; PM, pneumococcal meningitis; RSV, respiratory syncytial virus; RV, rhinovirus; VARI, viral acute respiratory infection; w, week(s); y, year(s).
Correlation coefficients **in bold** were statistically significant as originally reported in the study (P<0.05); correlation coefficients ending with “a” were statistically significant after Bonferroni adjustment (P< 0.05/number of relevant tests) or when the Bonferroni correction was deemed unnecessary; correlation coefficients ending with “b” did not have enough information to apply the Bonferroni correction; correlation coefficients ending with “c” were not statistically significant after Bonferroni adjustment.

Regression analyses controlling for seasonal patterns

Table 4-3 shows the summary of the 15 studies (Allard et al. 2012; Burgos et al. 2015; Ciruela et al. 2016; Domenech de Cellès et al. 2017; Grabowska et al. 2006; Kuster et al. 2011; Murdoch and Jennings 2009; Nicoli et al. 2013; Opatowski et al. 2013; Walter et al. 2010; Weinberger et al. 2013; Weinberger et al. 2014a; Weinberger et al. 2015; Zhou et al. 2012) that controlled for seasonal patterns by regression analysis. Results were inconsistent among the studies. In all-age population studies, preceding influenza infection was likely to be associated with IPD (12 studies(Burgos et al. 2015; Ciruela et al. 2016; Domenech de Cellès et al. 2017; Grabowska et al. 2006; Kuster et al. 2011; Murdoch and Jennings 2009; Nicoli et al. 2013; Walter et al. 2010; Weinberger et al. 2013; Weinberger et al. 2014a; Weinberger et al. 2015; Zhou et al. 2012) reported an association and two studies(Allard et al. 2012; Weinberger et al. 2014a) reported no association). According to two studies (Murdoch and Jennings 2009; Nicoli et al. 2013) that reported age-stratified results, the association between influenza and IPD was more likely to exist among older people than among young children. In terms of preceding RSV infection, four (Ciruela et al. 2016; Nicoli et al. 2013; Weinberger et al. 2014a; Weinberger et al. 2015) out of five studies (Ciruela et al. 2016; Murdoch and Jennings 2009; Nicoli et al. 2013; Weinberger et al. 2014a; Weinberger et al. 2015) observed an association of RSV with PD incidence. Specifically, one study (Ciruela et al. 2016) found the association between RSV and IPD only existed among children <5 years. Studies reporting other viruses such as ADV and PIV were sparse (two (Ciruela et al. 2016; Murdoch and Jennings 2009) and one (Murdoch and Jennings 2009) studies, respectively). Five studies (Ciruela et al. 2016; Murdoch and Jennings 2009; Nicoli et al. 2013; Weinberger et al. 2014a; Weinberger et al. 2015) that reported two or more viruses demonstrated that the association differed by the type of virus. Moreover, the association could differ among virus subtypes (e.g. influenza A *vs* influenza B (Kuster et al. 2011) and PIV 1/2 *vs* PIV 3 (Murdoch and Jennings 2009)). Notably, there are other factors that could influence the strength of the associations

reported in these studies. For instance, the association could vary by presentation of PD (invasive pneumococcal pneumonia, IPP vs npIPD (Walter et al. 2010; Weinberger et al. 2014a) and PP vs pneumococcal sepsis, PSe (Weinberger et al. 2015)); preceding VARI was more likely to be associated with the occurrence of pneumonia than other clinical presentations. Additionally, the results from studies in Denmark, where comorbidity status and pneumococcal serotype were available, demonstrated that influenza had a greater influence on the incidence of low-invasiveness serotypes than medium- or high- invasiveness among the low comorbidity group; among the high comorbidity group, the pattern was reversed (Weinberger et al. 2013; Weinberger et al. 2014a).

Table 4-3 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)	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)	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]	

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)
(Ciruela et al. 2016)	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)	
(Domenech de Cellès et al. 2017)	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)

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)	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> **6%c** [1–12%] (3w)
(Kuster et al. 2011)	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	

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)
(Murdoch and Jennings 2009)	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)	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)	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)	

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)
(Walter et al. 2010)	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%c** [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%c** [4.8–6.0%] (1w) (not significant for IFV-npIPD)
(Weinberger et al. 2014a)	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		<u><7y</u> 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)	1977 – 2007	≥40y Denmark	ILI (case, as a proxy for IFV)	IPP (n=8,308)	Surveillance data + nationwide general practice reports, weekly	Poisson regression	seasonal trends of IPP, dummy variable for week 1,2,3,51,52 and its interaction with ILI		≥40y, low comorbidity and low serotype invasiveness ILI: **17.9%a** [13.6–21.9%] (1w) ≥40y, low comorbidity and high serotype invasiveness ILI: **6.7%a** [3.8–11.7%] (1w) ≥40y, medium/high comorbidity and low serotype invasiveness ILI: 1.3% [−1.6–5.4%] (1w) ≥40y, medium/high comorbidity and high serotype invasiveness ILI: **8.9%a** [6.6–11.8%] (1w)

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

Study	Study Period	Population	VARI (unit used in model)	PD (number of cases)	Data Sources and Scale for Analysis	Statistical Methods	Covariates	RR [95% CI] (time lag)	AP [95% CI] (time lag)
(Weinberger et al. 2015)	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%]

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)
(Zhou et al. 2012)	1994 – 2005	all ages Atlanta, US	IFV RSV (positive percentage)	IPP (n=5,683)	Surveillance data, weekly	Negative binomial regression (comparison between models with and without IFV and RSV)	temperature, sunshine, precipitation	p values for the likelihood ratio test were <0.05 for 5 of 11 influenza seasons: 1994–95, 1996–97, 1998–99, 2003–04, 2004–05; after Bonferroni adjustment association was significant for 3 of 11 influenza seasons: 1996–97, 2003–04, 2004–05.	

Time lag indicates the time difference between VARI and subsequent PD incidence.
Abbreviations: ADV, adenovirus; AP, attributable percentage; CI, confidence interval; IFV, influenza virus; h, hour(s); ILI, influenza-like illness; IPD, invasive pneumococcal disease; IPP, invasive pneumococcal pneumonia; IR, incidence rate; npIPD, non-pneumonic invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine; PD, pneumococcal disease; PIV, parainfluenza virus; PP, pneumococcal pneumonia; PSe, pneumococcal sepsis; RR, relative risk; RSV, respiratory syncytial virus; UV index, clear-sky ultraviolet index; VARI, viral acute respiratory infection; w, week(s); y, year(s).
Relative risk or attributable percentage in bold were statistically significant as originally reported in the study (P<0.05); relative risk or attributable percentage ending with “a” were statistically significant after Bonferroni adjustment (P<0.05/number of relevant tests) or when the Bonferroni correction was deemed unnecessary, those ending with “b” did not have enough information to apply the Bonferroni correction; relative risk or attributable percentage ending with “c” were not statistically significant after Bonferroni adjustment.

Studies utilising other analyses

Seven ecological studies (Dangor et al. 2014; Domenech de Cellès et al. 2017; Hendriks et al. 2017; Kuster et al. 2011; Opatowski et al. 2013; Shrestha et al. 2013; Toschke et al. 2008) utilised other analytical methods (). Except for studies by Hendriks et al. (Hendriks et al. 2017) and Toschke et al. (Toschke et al. 2008), all studies reported an association between VARI and PD.

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Methods	Main findings
(Dangor et al. 2014)	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)	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)	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
(Kuster et al. 2011)	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

Study	Study Period	Population	VARI	PD (n of cases)	Data Sources and Scale for Analysis	Methods	Main findings
(Opatowski et al. 2013)	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)	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]
(Toschke et al. 2008)	1997–2003	<16y Germany	IFV A	IPD (n=1,474)	Surveillance data, monthly	Multivariate time series analysis using "3h algorithm", which fit an autoregressive Poisson or negative binomial model to time series	IFV A season did not affect IPD season (*P*=0.49); IFV A peak did not precede IPD peak

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

4.2.4 Discussion

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

We found that reported associations between VARI and subsequent PD were inconsistent among the 28 included studies. Only three studies (Edwards et al. 2011; O'Brien et al. 2000; Stensballe et al. 2008) analysed the association using individual patient data. The two cohort studies (Edwards et al. 2011; Stensballe et al. 2008) did not account for the shared risk factors between VARI and PD that influenced their seasonality, substantially limiting the inferences that can be made from these data while the case-control study (O'Brien et al. 2000) was limited by its small sample size (n case=13). In ecological studies, only 16 (Allard et al. 2012; Burgos et al. 2015; Ciruela et al. 2016; Domenech de Cellès et al. 2017; Grabowska et al. 2006; Hendriks et al. 2017; Kuster et al. 2011; Murdoch and Jennings 2009; Nicoli et al. 2013; Opatowski et al. 2013; Walter et al. 2010; Weinberger et al. 2013; Weinberger et al. 2014a; Weinberger et al. 2015; Zhou et al. 2012) of the 25 (Allard et al. 2012; Ampofo et al. 2008; Burgos et al. 2015; Ciruela et al. 2016; Dangor et al. 2014; Domenech de Cellès et al. 2017; Grabowska et al. 2006; Hendriks et al. 2017; Jansen et al. 2008; Kim et al. 1996; Kuster et al. 2011; Murdoch and Jennings 2009; Nicoli et al. 2013; Opatowski et al. 2013; Peltola et al. 2011; Shrestha et al. 2013; Talbot et al. 2005; Toschke et al. 2008; Walter et al. 2010; M. Watson et al. 2006; Weinberger et al. 2013; Weinberger et al. 2014a; Weinberger et al. 2015; Zhou et al. 2012) ecological studies accounted for seasonal patterns. In these studies, we found that influenza and/or RSV infections were likely to be associated with the subsequent occurrence of PD. For influenza, the association was stronger among younger populations compared to older adults (Murdoch and Jennings 2009; Nicoli et al. 2013) while the pattern was reversed for RSV (Ciruela et al. 2016). Data from multiple studies suggested that virus type (five studies (Ciruela et al. 2016; Murdoch and Jennings 2009;

Nicoli et al. 2013; Weinberger et al. 2014a; Weinberger et al. 2015)) and subtype (two studies (Kuster et al. 2011; Murdoch and Jennings 2009)), comorbidity status (two studies (Weinberger et al. 2013; Weinberger et al. 2014a)) and pneumococcal serotype invasiveness (one study (Weinberger et al. 2013)) could influence the association. However, these 16 ecological studies had various population characteristics (e.g. age, comorbidity, immunity status), PD datasets, VARI datasets and analytical methods. As such, heterogeneity among the studies, along with their ecological nature, limits the amount of valid inferences that can be made from the data (as summarised above).

Nevertheless, these studies provide important clues for the potential factors related to the association between VARI and subsequent PD, and thus could help with the conception and design of future studies. Ideally, in order to understand whether a particular preceding VARI can predispose an individual to PD, a prospective cohort study that monitors each individual for VARI and pneumococcal infection would be utilised, allowing analyses at both individual and population levels. However, such a design would not be feasible or affordable as inter alia pneumococcal infections are rare. Alternatively, utilisation of large-scale routine health data and reliable data linkage (through unique individual identifiers) from sources such as surveillance data and hospitalisation datasets may be feasible in many industrialised countries. An example of such data linkage in our review is the study by Stensballe and colleagues (Stensballe et al. 2008) that linked information from four Danish population-based registries. While the authors conducted individual-level analysis, the results were based on cases tested for both the presence of respiratory viruses and pneumococcal infection. The true number of VARI-associated PD cases is likely to be significantly higher due to incomplete testing of cases; the untested viral-pneumococcal cases could represent a crucial source of selection bias. Community-based active surveillance can likely address the issue of missing cases but such surveillance would be labour intensive and less cost-effective to conduct. Another option is a case-control study, which is affordable and practical, but

not without its limitations. In addition to challenges in designing such studies, defining the history of VARI is likely to be inaccurate since the timing of viral serology may be less accurate (information bias) (Peltola et al. 2011). In the case-control study by O'Brien and colleagues, (O'Brien et al. 2000) the authors used influenza-strain specific convalescent serology as evidence for preceding influenza infection. The authors also conducted telephone interviews to investigate ILI history but they did not mention whether interviewers and interviewees were blind to case or control status. Moreover, the value of this case-control study is limited by its very small sample size (n case = 13).

Compared with individual patient data based studies, ecological studies are more feasible, and thus the most common study design included in our review (25/28). However, there are some caveats when interpreting results from ecological studies. First, causality can never be inferred from such studies. Second, the results should be interpreted at a population level and cannot be generalised to the individual level. Since ecological studies used data aggregated into broad categories, the potential biases introduced by the aggregation should be taken into account. For instance, while 16 out of 25 ecological studies used weekly data, others used fortnightly or monthly data. This may lead to misclassification as the time window of the association of VARI on PD susceptibility can be as short as one week (McCullers and Rehg 2002; Sun and Metzger 2008). Moreover, data from different sources in ecological studies should represent the same population.

Apart from the study design, one further challenge of analysing the association is accounting for the influence of seasonal factors of VARI and PD (confounding). Both VARI and PD have similar seasonal patterns, and thus are likely to correlate as indicated by the correlation results from ecological studies. The increased risk of PD during an epidemic season could be caused by VARI or by seasonal risk factors or by both. In the present review, 11 studies (Ampofo et al. 2008; Dangor et al. 2014; Edwards et al. 2011; Jansen et al. 2008; Kim et al. 1996; Peltola et al. 2011; Shrestha et al. 2013; Stensballe et al. 2008; Talbot et al. 2005; Toschke et al. 2008; M.

Watson et al. 2006) did not attempt to control for seasonal confounders, likely leading to biased estimations of the association. For example, the study by Edwards and colleagues (Edwards et al. 2011) reported a relative risk as high as 112.5 when not adjusting any seasonal factors. One way to address this problem in such studies would be to match the individuals with the onset timing of pneumococcal infection, keeping the risk of PD comparable between VARI cases and non-VARI cases; for ecological studies, regression analysis adding seasonal terms or climatic factors (such as temperature and humidity), or cross-correlation analysis of time series controlling for seasonal patterns could be considered.

Our review suggests that the association of VARI and subsequent PD could vary by virus type (Ciruela et al. 2016; Murdoch and Jennings 2009; Nicoli et al. 2013; Weinberger et al. 2013; Weinberger et al. 2014a) and even by subtype (Kuster et al. 2011; Murdoch and Jennings 2009). Studies using combinations of viral infections such as all virus, influenza + RSV, non-influenza, or non-RSV could give biased estimations of the association. However, it is not always practical to analyse the association by virus type. In ecological studies, different types of viruses might co-circulate and thus be highly correlated in incidence, making it difficult to determine the role for each virus. In terms of PD, most studies used IPD as the outcome of interest. However, studies that categorised IPD into IPP and npIPD found that the association was more pronounced in IPP than in npIPD (Walter et al. 2010; Weinberger et al. 2014a). A similar finding, that the association was stronger in PP than PSe, was reported in another study (Weinberger et al. 2015). These results suggest VARI is more likely to be associated with pneumonic pneumococcal infections than non-pneumonic infections. In our review, we excluded studies using information other than clinical diagnosis as a proxy for PD (e.g. prescription data and carriage data). Pneumococcal carriage could have a fundamental role in the transmission and incidence of PD (Simell et al. 2012). In a study analysing the impact of pneumococcal carriage and viral activity, Weinberger and colleagues (Weinberger et al. 2014a) found npIPD was associated with carriage prevalence, whereas IPP was associated with

bronchiolitis (as a proxy for RSV). The authors also proposed that preceding VARI increased susceptibility but did not enhance transmission (indicated by carriage prevalence) in children. However, more studies are needed to confirm these findings.

The association could also vary by population characteristics. According to two studies that displayed age-stratified results (Murdoch and Jennings 2009; Nicoli et al. 2013), the association of influenza and subsequent IPD was more likely to exist among older people than among young children. Studies by Weinberger et al.(Weinberger et al. 2013; Weinberger et al. 2014a) gauged the association in different comorbidity and pneumococcal serotype groups among Denmark populations. The results showed that influenza had a stronger impact on the incidence of low-invasiveness serotypes than medium- or high- invasiveness ones in the low comorbidity group, while the pattern reversed in the high comorbidity group. Another study that analysed clinical records of 919 patients with PP found that infrequently colonising pneumococcal serotypes were more likely to cause PP after preceding VARI, particularly in patients with immunodeficiency or chronic lung diseases (Song et al. 2014). These findings suggest the need for future studies to analyse the association by age group, pneumococcal serotype and comorbidity status. Moreover, the recent introduction of pneumococcal vaccines has brought changes in the incidence of serotype-specific PD (Shiri et al. 2017), making the association of VARI and PD more complicated to understand. As a result, future studies should consider the possible serotype-specific influence that pneumococcal vaccines have on both individual immunity and herd immunity when analysing the association.

In addition to the factors discussed above, additional factors may influence the estimates of the association. The first is the change over time in the methodology of data collection, including changes in test method or diagnosis, clinical practice and health-seeking behaviour. The second is the possible delay in measurement, which happened most often in passive hospital-based studies. Thirdly, for ecological studies using aggregated data, “holiday spikes” could occur due to more social gatherings (Walter et al.

2009); besides, weekends and holidays might influence timely tests or diagnosis as well as the health-seeking behaviour of patients.

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

Given the substantial burden of VARI across the world,(H. Wang et al. 2016) even a modest association between VARI and subsequent PD could lead to a substantial burden of disease in terms of VARI-related PD cases. If proper anti-bacterial interventions could be applied to those with higher risk of PD due to a preceding VARI, subsequent pneumococcal infections could be prevented. The interventions would be more effective / better targeted if we could estimate the risk (i.e. the strength of association) according to timing of infection by week/month of a year, age, comorbidity status, virus type and status of immunity. In turn, understanding the association between VARI and subsequent pneumococcal infection can help evaluate the full impact of viral vaccine programs.

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

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

Competing interests: none declared.

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

Acknowledgement: YL is supported by a scholarship from the China Scholarship Council.

Funding: This research received no specific grant from any funding agency.

4.3 Supplementary files to the publication "Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies"

Table 4-4 Summary of findings from animal and in vitro studies

Study	Material	Exposure	Main findings
(Diavatopoulos et al. 2010)	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.
(J.-M. Hament et al. 2004)	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.
(J. M. Hament et al. 2005)	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)	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)	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)	Mice (n=18 per group)	hMPV/ influenza A + pneumococcus (14d later)	Only mice infected with influenza A demonstrated an 8% weight loss 72h following pneumococcus challenge while hMPV group and mock group did not.
(McCullers and Rehg 2002)	Mice (n=20 per group)	influenza A + pneumococcus (0 or 7d later)	60% of mice died 2–11d after pneumococcus challenge in influenza A group compared with 15% in mock group; reversal of the order of challenge led to protection from influenza; challenge of influenza and pneumococcus on the same day led to 100% mortality.
(McCullers et al. 2010)	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)	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
(C. M. Smith et al. 2014)	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)	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.

Panel 4-1 Search strategy

Medline

1. Meningitis, Pneumococcal/ or Pneumonia, Pneumococcal/ or exp Pneumococcal Infections/ or pneumococc*.mp.
2. exp Streptococcus pneumoniae/ or Streptococcus pneumoniae.mp.
3. virus.mp. or exp Viruses/
4. exp Virus Diseases/ or virus disease*.mp.
5. correlat*.mp.
6. associat*.mp.
7. interact*.mp.
8. relat*.mp.
9. 1 or 2
10. 3 or 4
11. 5 or 6 or 7 or 8
12. 9 and 10 and 11
13. limit 12 to yr="1990 -Current"

1,664 results by 27 Apr 2017

1,888 results by 31 Dec 2017

EMbase

1. exp pneumococcal infection/ or pneumococc*.mp.
2. Streptococcus pneumoniae.mp. or exp Streptococcus pneumoniae/
3. exp virus/ or virus*.mp.
4. exp virus infection/ or virus infection*.mp. or virus disease*.mp.
5. exp correlational study/ or exp correlation analysis/ or correlat*.mp.
6. associat*.mp.
7. interact*.mp.
8. relat*.mp.
9. 1 or 2
10. 3 or 4
11. 5 or 6 or 7 or 8
12. 9 and 10 and 11
13. limit 12 to yr="1990 -Current"

4,778 results by 27 Apr 2017.

5,098 results by 31 Dec 2017.

Global Health

1. Streptococcus pneumoniae.mp. or exp Streptococcus pneumoniae/
2. pneumococc*.mp.
3. virus*.mp. or viruses/
4. virus disease*.mp. or viral diseases.sh. or virus infection*.mp.
5. exp correlation/ or correlation analysis/ or correlat*.mp.
6. associat*.mp.

7. interact*.mp.
8. relat*.mp.
9. 1 or 2
10. 3 or 4
11. 5 or 6 or 7 or 8
12. 9 and 10 and 11
13. limit 12 to yr="1990 -Current"
1,164 results by 27 Apr 2017
961 results by 31 Dec 2017

Table 4-5 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)	Yes, multiple methods	✓				✓				✓		✓		✓
(Ampofo et al. 2008)	Yes, IF and culture	✓	✓	✓		✓				✓	✓			
(Burgos et al. 2015)	Yes, IF and PCR	✓				✓				✓	✓	✓		✓
(Ciruela et al. 2016)	Yes, multiple methods	✓	✓	✓		✓				✓	✓	✓		✓
(Dangor et al. 2014)	Yes, IF and culture	✓				✓				✓			✓	
(Domenech de Cellès et al. 2017)	No	✓				✓				✓		✓	✓	✓
(Edwards et al. 2011)	Yes, method not known	✓				✓			✓					
(Grabowska et al. 2006)	Yes, multiple methods	✓				✓				✓		✓		✓
(Hendriks et al. 2017)	No	✓				✓				✓			✓	✓
(Jansen et al. 2008)	Yes, multiple methods	✓	✓			✓		✓		✓	✓			
(Kim et al. 1996)	Yes, culture	✓	✓	✓		✓				✓	✓			
(Kuster et al. 2011)	Yes, culture and DAT	✓				✓				✓		✓	✓	✓
(Murdoch and Jennings 2009)	Yes, IF and culture	✓	✓	✓		✓				✓	✓	✓		✓
(Nicoli et al. 2013)	Yes, multiple methods	✓	✓			✓				✓	✓	✓		✓
(O'Brien et al. 2000)	Yes, serology	✓					✓		✓					✓

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	
(Opatowski et al. 2013)	No			✓				✓		✓		✓	✓	✓
(Peltola et al. 2011)	Yes, multiple methods	✓	✓	✓		✓				✓	✓			
(Shrestha et al. 2013)	No	✓					✓			✓			✓	
(Stensballe et al. 2008)	No		✓	✓		✓			✓	✓	✓			
(Talbot et al. 2005)	Yes, culture and RAT	✓	✓			✓				✓	✓			
(Toschke et al. 2008)	Yes, PCR	✓				✓				✓			✓	
(Walter et al. 2010)	Yes, method not known	✓				✓		✓		✓		✓		✓
(M. Watson et al. 2006)	Yes, DAT	✓	✓	✓		✓				✓	✓			
(Weinberger et al. 2014a)	No	✓	✓			✓		✓		✓		✓		✓
(Weinberger et al. 2013)	No	✓						✓		✓		✓		✓
(Weinberger et al. 2014a)	No	✓				✓	✓			✓		✓		✓
(Weinberger et al. 2015)	No	✓	✓		✓		✓	✓		✓		✓		✓
(Zhou et al. 2012)	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.

4.4 Conclusion

This is the first review that critically reviewed the methods and the findings of population-based studies that reported an association between VARI and PD. This review would serve as a comprehensive summary of existing studies on this topic, and thus assist in designing future studies that aim to understand the role of VARI on the occurrence of PD. Additionally, understanding the association between VARI and subsequent pneumococcal infection can help evaluate the full impact of viral vaccine programs. This is particularly relevant as novel vaccines for respiratory viruses (e.g. RSV) are being developed and likely to be introduced into national programmes in the next 5-7 years.

Chapter 5 Association between respiratory virus activity and subsequent invasive pneumococcal disease

5.1 Introduction

Association between respiratory virus activity and subsequent invasive pneumococcal disease (IPD) is long recognised. As introduced in **Chapter 3**, the systematic review (Li et al. 2018) reported that IFV and RSV infections were likely to be associated with the subsequent occurrence of pneumococcal diseases (IFV: 12/14 studies; RSV 4/5 studies). However, only a few of the studies were able to assess the association using laboratory-confirmed evidence of viral infection. For example, influenza-like illness was used in studies as a proxy of IFV infection and clinical bronchiolitis was used as a proxy of RSV infection. This would obscure the underlying viral-pneumococcal association. The present study aims to assess the association using laboratory-confirmed evidence of respiratory viral infection and invasive pneumococcal disease.

5.2 Method

5.2.1 Data sources

Laboratory-confirmed infection data of IFV, RSV, PIV, and MPV were obtained from the Electronic Communication of Surveillance in Scotland (ECOSS) dataset. In ECOSS, the samples tested for virus could originate from patients seeking medical attention in either primary or secondary care settings. Only respiratory samples were included for the current study. The date of the sample was recorded as the date when respiratory samples were taken. Data were available from 2009 to 2017 and aggregated on a weekly basis, stratified by age group: <6y, 6–64y, and >64y.

IPD data were obtained from the Scottish Pneumococcal Invasive Disease Enhanced Reporting (SPIDER) scheme from 2009 to 2017. This surveillance scheme is based on the local and reference laboratory test reports of

pneumococcus from invasive body sites. Similarly to the laboratory-confirmed viral data, the SPIDER data were aggregated by week and by age group.

Apart from ECOSS data and SPIDER data, I also included the Scottish Morbidity Record (SMR) data in the sensitivity analysis. I extracted ICD-10-coded IFV, RSV and pneumococcal pneumonia data from 2001 to 2016 and aggregated them by week and by pre-specified age groups (as stated for ECOSS and SPIDER data). Details regarding the ICD-10 codes used are in **Appendix A23**. No individually identifiable data were used throughout this study.

When presenting the age distribution (i.e. in <6y, 6–64y, and >64y) of IPD and viral cases, I also extracted age-specific Scottish population data from National Records of Scotland for comparison (Anonymous 2018). The population at the midpoint of the study period was used, i.e. the mid-2013. The proportion of population in <6y, 6–64y, and >64y was 6.6%, 75.6%, and 17.8%, respectively.

5.2.2 Data analysis

In the main analysis, I used weekly time series data of IPD and laboratory-confirmed viruses, including IFV, RSV, PIV, and MPV. Negative binomial regression analysis rather than Poisson regression was conducted to account for overdispersion (formula in **Panel 5-1**). For the convenience of description, week 0 is defined as the week of viral infection; week 1 is defined as one week after the week of viral infection, etc. For the dependant variable IPD, a range of lags (from 1 week to 6 weeks) between viral infection and subsequent IPD were explored, which were based on the choices in pre-existing population studies. To account for shared risk factors between viral infection and IPD, I included simultaneously all the four viruses and IPD at week 0. This can also account for the auto-correlation in IPD. Akaike information criterion (AIC) was applied to select the optimal lag in the model.

Panel 5-1 Negative binomial regression for main analysis

$$IPD_i \sim IFV + RSV + PIV + MPV + IPD_0$$

Where i indicates the week index; week 0 is the week of viral infection. i = 1, 2, 3, 4, 5, 6. Akaike information criterion (AIC) was applied for the selection of i.

The attributable percentage (AP) of IPD to each virus was calculated based on the corresponding model coefficient, using the same approach as Weinberger et al (Weinberger et al. 2015). This is a four-step approach: I first obtained the estimate of the predicted weekly IPD incidence using the model above, with independent variables set as the observed weekly values. Secondly, I obtained the estimate of the predicted weekly IPD incidence, using the same model (i.e. without refitting the model), with one of the viruses of interest (e.g. IFV) set as zero and the rest (i.e. RSV, PIV, and MPV) set as the observed weekly values. Thirdly, I summed all the weekly IPD incidence with all viruses set as observed values and all the weekly IPD incidence with one of the viruses (e.g. IFV) set as zero, to obtain the overall incidence of IPD and the overall incidence of IPD without one of the viruses (e.g. IFV), respectively. Then, as the final step, the overall incidence of IPD attributable to each virus could be obtained by subtracting the overall incidence of IPD without that virus from the overall incidence of IPD and the AP of IPD to each virus was calculated by the viral attributable incidence divided by the total incidence. 95% confidence intervals of AP were estimated using a yearly block bootstrap with 1000 replicates. The AP of a virus was arbitrarily set as zero if the coefficient of that virus in the model was not statistically significant.

The above analysis was conducted in all ages, <6y, 6–64y, and >64y.

Sensitivity analysis

A series of sensitivity analyses were conducted using different data for comparison with the main analysis as detailed above. Four sets of sensitivity analysis were conducted (**Panel 5-2**). The first set only included post-PCV-13

period (i.e. after 2011 in Scotland) to preclude the potential effect of the former PCV-7. The second set replaced laboratory-confirmed data with ICD-10-coded data. The third set replaced laboratory-confirmed IPD with ICD-10-coded pneumococcal pneumonia and the fourth set replaced all data with ICD-10-coded data.

Similar to the main analysis, all sets of sensitivity analysis were conducted in all ages, <6y, 6–64y, and >64y.

Panel 5-2 Sensitivity Analyses (negative binomial regression)

Sensitivity analysis 1: $IPD_i \sim IFV + RSV + PIV + MPV\ (After\ 2011)$

Sensitivity analysis 2: $IPD_i \sim IFV(ICD) + RSV(ICD)$

Sensitivity analysis 3: $PP_i(ICD) \sim IFV + RSV + PIV + MPV$

Sensitivity analysis 4: $PP_i(ICD) \sim IFV(ICD) + RSV(ICD)$

Where i indicates the week index; week 0 is the week of viral infection. i = 1, 2, 3, 4, 5, 6. Akaike information criterion (AIC) was applied for the selection of i.

5.3 Results

5.3.1 Study characteristics

From 2009 to 2017, I included 5130 cases of IPD, 31788 cases of IFV, 25138 cases of RSV, 10939 cases of PIV, and 6732 cases of MPV. With regard to the distribution across age groups, IPD and all viral infections were less frequently observed among 6–64y. Over 80% of the RSV cases and over 50% of the PIV and MPV cases were seen in young children. IFV was more frequently found in <6y and 6–64y. On the other hand, IPD was most prevalent among older adults. More detailed results are attached below in **Table 5-1**. Yearly number of IPD and viral infection cases are attached in **Appendix A24**.

Table 5-1 Number of IPD and viral infection cases included in the main analysis by age group

Age Group (% population)	IPD	IFV	RSV	PIV	MPV
<6y (6.6)	356 (6.9)	5461 (17.2)	20655 (82.2)	5926 (54.2)	3650 (54.2)
6–64y (75.6)	2297 (44.8)	17723 (55.8)	2513 (10.0)	3124 (28.6)	1896 (28.2)
>64y (17.8)	2477 (48.3)	8604 (27.1)	1970 (7.8)	1889 (17.3)	1186 (17.6)
All Ages (100.0)	5130 (100.0)	31788 (100.0)	25138 (100.0)	10939 (100.0)	6732 (100.0)

IPD=invasive pneumococcal disease; IFV=influenza virus; RSV= respiratory syncytial virus; PIV=parainfluenza virus; MPV=metapneumovirus; y=year(s)

5.3.2 Seasonality of IPD and viral-infections

As shown in **Figure 5-1**, IFV and RSV had one annual seasonal peak, without any secondary peaks before or after the primary peak. The only exception was for IFV during the swine flu pandemic in 2009. The peak timing of the three viruses were slightly different. RSV peak was before the end of each calendar year whereas seasonal IFV peak was at the beginning

of each calendar year. PIV had two annual seasonal peaks, one primary peak in early summer and one secondary peak in later autumn. PIV was also prevalent out of season, which was different from IFV or RSV. MPV had one annual peak in spring in generally but sometimes had secondary peaks before or after the primary peak. IPD had one primary peak at the beginning of each calendar year but it also had multiple peaks throughout other time of a year and was prevalent all year round. Seasonality of IPD and all the four viruses was similar among different age groups **Figure 5-2**.

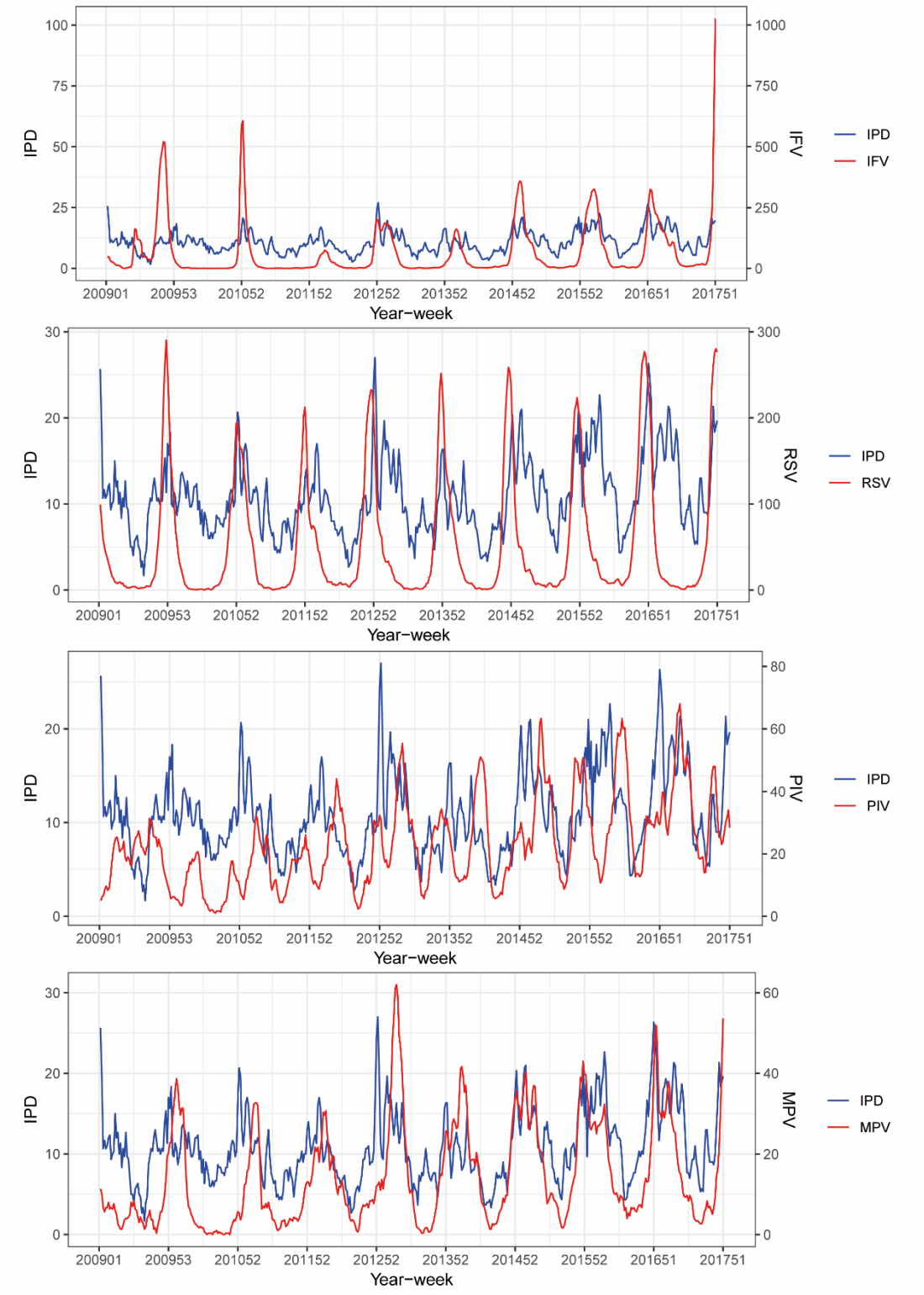


Figure 5-1 Time series of number of cases in IPD and each viral infection, presented as 3-week moving average

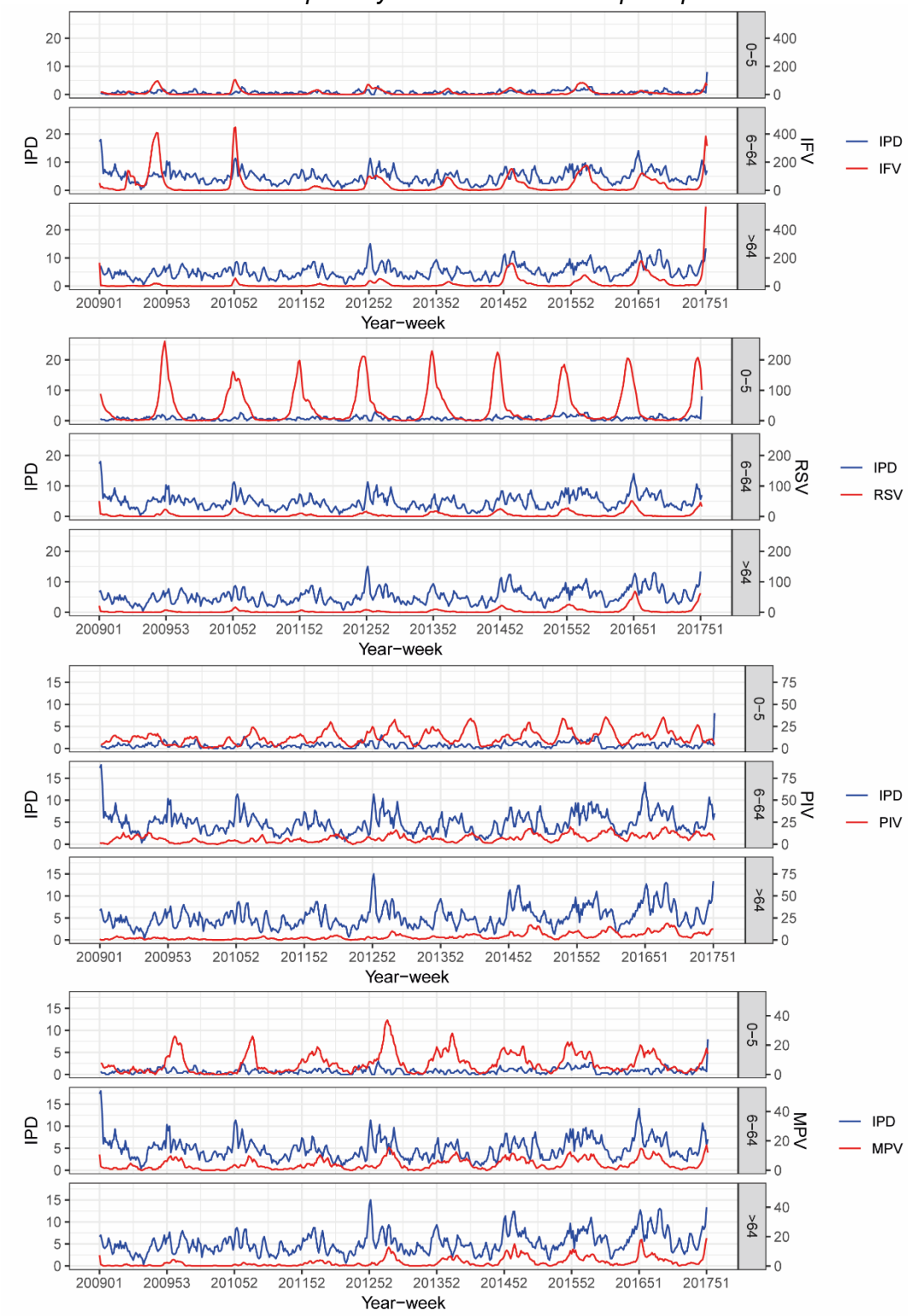


Figure 5-2 Time series of number of cases in IPD and each viral infection by age group, presented as 3-week moving average

5.3.3 Association between IPD and viral infection

In all ages, there was significant association between viral infection and subsequent IPD and the time lag was 1 week. The AP of IPD attributable to IFV, RSV, PIV, and MPV was 7.5%, 10.8%, 11.6%, and 11.1%, respectively. In age-group-stratified analysis, IFV and RSV were consistently associated with subsequent IPD with the time lag of 1–2 weeks. The AP of IPD to IFV and RSV was higher in young children than other age groups. PIV was associated with IPD in both young children and older adults whereas MPV was associated with IPD in the middle age group (i.e. 6–64y).

Table 5-2 Percentage of IPD attributable to each virus by age group in the main analysis

Age Group	Lag* (wk)	Attributable Percentage of IPD			
		IFV	RSV	PIV	MPV
<6y	1	12.7 (8.9–16.5)	9.3 (7.8–10.4)	18.7 (15.7–20.9)	0
6–64y	2	5.0 (3.2–6.8)	9.6 (6.6–13.4)	0	12.3 (9.6–15.1)
>64y	1	7.1 (3.1–11.8)	3.5 (1.6–6.3)	6.3 (3.8–8.9)	0
All ages**	1	7.5 (5.3–9.4)	10.8 (9.2–12.1)	11.6 (9.2–13.7)	11.1 (8.5–13.3)

*Time lag between viral infection and subsequent IPD.

**Separate models were used for each age group so the estimates of AP in all ages might not vary. IPD=invasive pneumococcal disease; wk=week; IFV=influenza virus; RSV=respiratory syncytial virus; PIV=parainfluenza virus; MPV=metapneumovirus; y=year(s)

Sensitivity analysis

In all sensitivity analyses, the optimal time lag between viral infection and subsequent IPD was generally consistent (1–2 weeks across all age groups). In the sensitivity analysis with viral data replaced by ICD-coded IFV and RSV hospitalisations data, the results were generally consistent with the main analysis (**Appendix A25**). In the sensitivity analysis only including data in

post-PCV-13 period, while most estimates were similar to the main analysis, I observed a significant increase in the AP to PIV in the group of all ages (20.3% vs 11.6%) (**Table 5-3**).

However, in the two sensitivity analyses that replaced IPD with clinically diagnosed PP, the results were different from all the other analyses (i.e. one main analysis and two sensitivity analyses) that used IPD data (**Appendix A26** and **Appendix A27**).

Table 5-3 Percentage of IPD attributable to each virus by age group in post-PCV-13 period as a sensitivity analysis

Age Group	Lag* (wk)	Attributable Percentage of IPD			
		IFV	RSV	PIV	MPV
<6y	1	14.9 (10.4–19.7)	10.6 (9.4–12.0)	0↓	0
6–64y	1	9.9 (6.7–12.9)	9.4 (6.5–12.8)	12.1↑ (9.6–14.6)	13.1 (10.5–15.2)
>64y	1	8.4 (3.3–13.6)	3.9 (1.7–6.9)	7.6 (4.7–10.4)	0
All ages	1	12.6 (8.5–16.2)	11.4 (10.2–12.8)	20.3↑ (17.0–23.2)	9.3 (7.4–10.6)

An arrow (↑ up or ↓ down) indicates a significant difference in the attributable percentage, compared with corresponding estimate in the main analysis.
*Time lag between viral infection and subsequent IPD; IPD=invasive pneumococcal disease; wk=week; IFV=influenza virus; RSV=respiratory syncytial virus; PIV=parainfluenza virus; MPV=metapneumovirus; y=year(s)

5.4 Discussion

Using laboratory-confirmed IPD and viral data in Scotland from 2009 to 2017, I found statistically significant associations between viral infection, including IFV, RSV, PIV, and MPV, and subsequent IPD incidence among all-age group. The time lag between viral infection and IPD incidence was estimated to be 1–2 weeks. It was estimated that 7.5%, 10.8%, 11.6%, and 11.1% of IPD cases could be attributable to IFV, RSV, PIV, and MPV, respectively. Results of age-group-stratified analysis showed that IFV and RSV were consistently associated with subsequent IPD across all age groups whereas the results of PIV and MPV were more variable and further study on PIV and MPV is warranted.

Although for the association between IFV and RSV, and IPD, the findings of this study were generally consistent with previous studies (Li et al. 2018). the estimate of AP of IPD attributable to IFV and RSV in all ages was statistically higher than some estimates in previous studies. More detailed comparisons are presented in **Table 5-4**. Only the study by Nicoli et al conducted further age-stratified analysis (Nicoli et al. 2013). However, the confidence intervals of the age-stratified estimates in that study were too wide and not very informative. In the age-stratified analysis of my study, the AP of IPD to IFV and RSV was higher in young children than other age groups. This is consistent with the findings by Weinberger et al (Weinberger et al. 2013, 2014b) that the AP due to influenza-like illness was higher in people with low comorbidity status than middle or high comorbidity status. This is also consistent with the experience from most historic pandemics of IFV that young people are more likely to be affected by the subsequent pneumococcal infection during pandemic IFV (summarised in **Section 1.3.3**). For young children, the findings of this study are also relevant to the evaluation of the immunisation programmes of IFV and RSV as prevention of IFV and RSV has potential effects on the prevention of subsequent pneumococcal infection.

Table 5-4 Comparison of findings between previous studies and my study in the AP of IPD attributable to IFV and RSV among all ages

Study	Setting	Virus	IPD	AP (95% CI)
(Domenech de Cellès et al. 2017)	France	ILI (as IFV)	IPD	4.9%*↓
(Grabowska et al. 2006)	Sweden	IFV	IPD	6% (1–12) –
(Nicoli et al. 2013)	England & Wales	IFV	IPD	5.6% (0.2–23.8) –
(Nicoli et al. 2013)	England & Wales	RSV	IPD	2.9% (0.1–14.2) ↓
(Walter et al. 2010)	North-eastern US	IFV	IPP	4.9% (4.5–5.3) ↓
(Walter et al. 2010)	Southern US	IFV	IPP	5.4% (5.0–5.9) –
(Walter et al. 2010)	Western US	IFV	IPP	5.2% (4.8–6.0) ↓

AP=attributable percentage; CI=confidence interval; IPD=invasive pneumococcal disease; IFV=influenza virus; RSV=respiratory syncytial virus; ILI=influenza-like illness; IPP=invasive pneumococcal pneumonia

* No confidence interval was reported.

↓ Estimate lower than the lower confidence interval of the estimate of my study.

– Estimate within the confidence interval of the estimate of my study.

In terms of the association between PIV and MPV, and IPD, few studies explored this in details, partly due to the lack of comprehensive laboratory testing of these two viruses and the lack of acceptable proxies for these two viruses. One study conducted in New Zealand found that PIV 3 outside of the IFV season was associated with IPD among all ages (Murdoch and Jennings 2009). No age-stratified analysis was done in that study. Therefore, I was not able to further compare the results by age group between the two studies. The sensitivity analyses conducted in my study suggest that the results for PIV and MPV might not be robust enough and the insufficient power could be a major reason for this (the number of PIV cases was less than half of IFV or RSV; the number of MPV cases was less than a quarter of IFV or RSV). Future studies with more sufficient samples of PIV and MPV are needed.

The sensitivity analysis of this study replacing IPD with clinically diagnosed PP showed different association results from the main analysis using IPD.

The difference could be due to the lack of microbiological evidence in these clinical diagnoses. Therefore, one should interpret the results of similar studies using ICD-coded pneumococcal diseases with caution. By contrast, the sensitivity analysis replacing laboratory-confirmed viral infection with ICD-coded viral infection had generally similar results as the main analysis.

In Scotland, IPD plus all of the four viruses, IFV, RSV, PIV, and MPV have their distinct seasonal patterns. For each virus, overlaps can be found between viral peaks and IPD peaks, which corresponds to the association between viral infection and IPD. However, there were other features of viral and IPD seasonality that did not support the association. For example, not every IFV peak was followed by an IPD peak (i.e. IFV is not sufficient for IPD); and an IPD peak could happen without a prior IFV peak (i.e. IFV is not necessary for IPD). This is also observed for during the past IFV pandemics. Unlike the 1918 Spanish flu, the 1957 Asian flu and 1968 Hong Kong flu had fewer secondary pneumococcal infections than 1918 Spanish flu. This raises the question whether viral strains modifies the viral-pneumococcal association.

In addition, other important questions about viral-pneumococcal association have not been well studied. First, it is not well understood whether co-seasonality exists in tropical and sub-tropical regions as the existing studies have focused almost exclusively on the temperate regions (Li et al. 2018). This question is relevant as the common seasonal risk factors (e.g. low temperature) between viral infection and pneumococcal infection could confound their association. These factors could be “naturally” controlled for in the tropics and perhaps in the subtropics. If no co-seasonality is observed there, then the association would not exist, at least at the population level. Nevertheless, if co-seasonality is observed, this does not indicate the association as one cannot rule out the possibility that other common seasonal risk factors than temperature in the tropics/subtropics confound the association. Second, it is not well understood whether the association exists at the individual-patient level. Although there were three existing individual-

patient based studies (Edwards et al. 2011), they all had methodological issues that biased the association (details discussed in the review in **Chapter 3**). Third, it is not well understood what the time lag between viral infection and pneumococcal infection is. In the current study, I found that 1–2 weeks of lag had the best model fit. From the experience of past IFV pandemics, the time lag was likely to be 1 week after the IFV symptoms. Active surveillance is warranted in order to confirm the findings from this study.

This study has several advantages. First of all, I used laboratory confirmed data for both IPD and all the four respiratory viruses, IFV, RSV, PIV, and MPV. Second, owing to the large number of laboratory-confirmed infections, this study was able to compare the viral-pneumococcal association among different age groups (i.e. <6y, 6–64y, and >64y). Thirdly, by modelling comparison among of lag periods, the study was able to identify the lag period that resulted in the best model fit of the viral-pneumococcal association. Fourthly, by conducting several sets of sensitivity analyses, the study was able to understand the robustness of the results under different scenarios.

This study is not without its limitations. First, all the results should be interpreted on a population-level basis, due to the ecological nature of the study. Second, it is nearly impossible to assess the uncertainty induced by the various choices in the time series approach (e.g. the choice of distribution of the residuals, the choice of covariates, the choice of seasonal smoothers, etc.) Thirdly, as indicated by the sensitivity analysis, the results regarding PIV and MPV in this study were not robust enough, partly due to the insufficient number of tests and therefore, should be interpreted with caution. Fourth, the study only included data in the post-PCV period and therefore was not able to assess the effect of the introduction of PCV on the viral-pneumococcal association.

In conclusion, the study suggests that there is association between infection of IFV and RSV and subsequent IPD among all broader age groups. The

time lag between the two infections is likely to be 1 to 2 weeks. Future individual-patient based studies are needed in order to confirm the findings of this study.

Chapter 6 Discussion

This thesis can be divided into two parts. The first part describes and models the global seasonality of the four respiratory viruses, IFV, RSV, PIV, and MPV (**Chapter 2**), and furthermore assesses the role of RSV seasonality in LMICs planning for the introduction of RSV immunisation products (**Chapter 3**). Global seasonality is different among the four viruses, IFV, RSV, PIV, and MPV: IFV has clear seasonal epidemics in winter months in most temperate sites but the timing of epidemics is more variable and less seasonal with decreasing distance from the equator. Unlike IFV, RSV has clear seasonal epidemics in both temperate and tropical regions, starting in late summer months in the tropics of each hemisphere, reaching most temperate sites in winter months. PIV epidemics are mostly in spring and early summer months and MPV epidemics are in late winter and spring in most temperate sites but the timing of epidemics is more diverse in the tropics. Based on the association between the monthly activity of IFV and RSV, and temperature and relative humidity, an online prediction tool was developed to predict local seasonal epidemics of IFV and RSV. Most LMICs have clear and stable RSV seasonality over time. A seasonal approach for RSV prophylaxis is found to achieve higher dose-efficiency and relative high effectiveness in LMICs with clear seasonality, compared with a year-round approach.

The second part includes a systematic review that critically reviews the existing literature reporting on the association between seasonal viral acute respiratory infection and subsequent pneumococcal disease (**Chapter 4**), and includes a population-based study using Scottish laboratory-confirmed data (**Chapter 5**). Both IFV and RSV are likely to be associated with subsequent IPD incidence among all broad age groups (i.e. <6y, 6–64y, and >64y). It is estimated that 7.5%, 10.8%, 11.6%, and 11.1% of IPD cases are attributable to IFV, RSV, PIV, and MPV, respectively. The time lag between the viral and pneumococcal infections is estimated to be 1 to 2 weeks.

6.1 Strengths

6.1.1 Inclusion of unpublished data

For the global seasonality of respiratory viruses work, I included unpublished viral data from RSV GEN research group, which was originally formed to estimate the global burden of RSV (Shi et al. 2017). On the basis of the original RSV GEN group, during my PhD, I added 26 more new members, identified from published literature and from academic conferences who were willing to share the viral seasonality data using the tailored template designed for this project. These shared data filled in the gaps in seasonality in lower-resource settings and added substantially to the geographical representativeness of the seasonality dataset.

6.1.2 Novel approach of modelling seasonality

Novelty 1: inclusion of monthly full-year data for modelling

Some seasonality modelling approaches had strict restrictions on the viral data. For example, a time-series modelling approach generally requires multi-year weekly viral data (Deyle et al. 2016). However, such data were only accessible in higher-income countries, which were almost exclusively in the temperate regions. Moreover, in order to have enough positive tests, researchers had to work on national-level datasets (e.g. FluNet), which compromised the geographical granularity. Other modelling studies, by contrast, went for the other extreme by including only the peak timing of a virus in the model while assuming a uniform distribution in all non-peak months (J. D. Tamerius et al. 2013). This did not provide enough information for understanding viral seasonality, e.g. no information on the onset was available. In this thesis, I used a novel approach as a trade-off between the two existing approaches. Instead of utilising data on viral peaks, I used monthly viral data to ensure that a general overview of viral seasonality was possible. Instead of excluding sites that did not provide multi-year data, I also included shorter-period data as long as they had at least one full-year of seasonality profile (i.e. 12 data points of viral activity, each for a month). In this way, I was able to include more sites, and more importantly, sub-

national-level datasets in the model, while ensuring that important seasonality information was still retained.

Novelty 2: conversion of meteorological data to mean-centred values
Unlike other modelling studies of this kind, I converted the monthly absolute values of each meteorological factor into mean-centred values (i.e. for a month, $\text{mean-centred value} = \text{absolute value} - \text{annual mean}$). The transformation was based on the assumption that change in viral activity depends on the relative change of meteorological factors in an annual circle. The relative measures of meteorological factors (i.e. mean-centred values) were expected to fit the relative measures of viral activity (i.e. monthly average percentage) better. For example, RSV peak was in December in England, which had the lowest temperature of the year, 3.4˚C (6.4˚C below the annual mean temperature, also noted as –6.4˚C) whereas in Alaska US, the temperature of RSV peak month was –14.5˚C (11.9˚C below the annual mean temperature, noted as –11.9˚C). Compared with absolute temperature, mean-centred temperature was less variable and thus was more suitable for modelling the fluctuation of viral activity.

6.1.3 Prediction of local IFV/RSV seasonal epidemics
Based on the viral seasonality model, the prediction tool developed as part of this thesis allows for predicting local IFV/RSV monthly epidemics if the local monthly temperature and relative humidity are provided. This is the first study that provides such a prediction tool for IFV/RSV activity. This tool provides important seasonality information for those countries where routine tests of IFV or RSV are not possible. As presented in **Chapter 3**, only about one third of the LMICs had RSV monthly activity data. The prediction tool could be useful for the rest LMICs if they plan to introduce RSV immunisation products in future do not have data from local RSV surveillance.

6.1.4 Inclusion of laboratory-confirmed IPD and viral infection data

In assessing the association between viral acute respiratory infection and IPD, both laboratory-confirmed pneumococcal infection and viral infection were included. This helps minimise the measurement error in terms of both exposure (i.e. viral infection) and outcome (i.e. IPD). In the sensitivity analysis that replaced IPD with clinically diagnosed PP, the association results changed significantly. The results highlighted the importance of including laboratory-confirmed data when assessing the association.

6.2 Limitations

6.2.1 Heterogeneity in viral activity data globally

In the study of global seasonality of respiratory viruses, heterogeneity in viral activity data was an important limitation. The viral activity data came from various sources including literature review, online datasets, and RSV GEN. These data were originally collected and reported for different research purposes. The study population (e.g. age group and respiratory symptoms/diagnoses) and methodology (e.g. respiratory samples and test approach) varied greatly among these data. The difficulty or challenge in extracting data also differed, depending on the data sources. About one third (440/1373, 32%) of the viral data points (i.e. data point = per virus per site) were extracted from the graphs in the original publications, which is more prone to errors.

Although, as an inclusion criterion, the viral data should be representative of the corresponding site, comparisons between sites using heterogeneous data should be interpreted with caution. The same caution should also be applied to the seasonality model and prediction model that pooled all viral activity data and treated them as if they were homogeneous.

6.2.2 Year-to-year variability in viral activity

Limited by the lack of multi-year data in most sites, all viral activity data were summed across the years in this study in order to have larger amount of

positive tests, averaging the possible year-to-year variability in viral activity. This could obscure the multi-annual patterns in some of the sites, e.g. the biannual RSV patterns in both timing and intensity in northern Europe (Broberg et al. 2018). This also limits the implications of the prediction model to predicting the "average" viral seasonality of a site rather than predicting viral seasonality for a specific year for a site.

6.2.3 Limited seasonality data of PIV and MPV

In the global seasonality work, although a total of 83 sites were included, PIV subtypes data were only available in a few studies in the US and in some European countries. According to the results from overall PIV data, PIV epidemics were found mostly in spring and early summer months in each hemisphere. These results, however, should be interpreted with caution as they were weighted by the prevalence of each PIV subtype. Regarding MPV, this work included a total of 65 sites globally, far fewer than the number of sites for IFV (246 sites) and RSV (183 sites). As a result, modelling was not possible for PIV or MPV.

6.2.4 Lack of comorbidity and IPD serotype information

In the viral-pneumococcal association study, the weekly time series of IPD and the four viruses, IFV, RSV, PIV, and MPV, were stratified by three broad age groups, <6y, 6–64y, and >64y. This allows for a stratified analysis by age group. However, no data were available on comorbidity, which was reported to be a key factor that modified the association (Weinberger et al. 2013, 2014b). Moreover, the study by Weinberger et al suggest that influenza-like illness was associated with the greatest increases in the incidence of disease caused by serotypes with lower invasive potential. Unfortunately, serotype data were not available for analysis as part of the thesis to confirm this finding using laboratory-confirmed viral infection.

6.3 Comparisons among definitions of viral seasonal epidemics

In order to describe viral seasonality on a global scale, a method is much needed that can be applicable to a variety of seasonal patterns globally. **Table 6-1** below is a summary of definitions used in existing global and regional reports of viral seasonality. In general, these definitions were based on one of the two types of viral activity measure, annual positive proportion (APP) or test positive proportion (TPP). APP is derived from positive tests only whereas TPP is derived from both positive and negative tests. Detailed comparisons between APP and TPP are attached below in **Table 6-2**.

In this work, APP was used to measure viral activity with several considerations. First, compared with TPP, APP requires only positive tests for each month. This is important in order to be able to include more sites worldwide, as a number of medical or laboratory records only had positive tests—negative tests would be left blank as if no tests had been done. Second, APP only focuses on specific viral positive tests and thus is not affected by the competing effects by other co-circulating viruses as TPP. Third, TPP is sensitive to the viral detection methods. For example, a study in the US compared the weekly TPP of RSV between the antigen-detection method and the PCR method, and found that weekly TPP of PCR was much lower than weekly TPP of antigen-detection method (Curns et al. 2017). Using APP can minimise the bias induced by the high heterogeneity of viral detection methods among different data sources.

In **Table 6-1**, two APP-based methods in defining viral seasonal epidemics have been presented: one, which was more commonly used, is based on a weekly/monthly threshold and the other is based on a cumulative (consecutive) threshold (Saverio Caini et al. 2016). In the current work, a new definition was proposed based on the cumulative non-consecutive threshold. These three methods are compared in **Table 6-3**. All of the three methods can define viral seasonal epidemics well in strong seasonality settings. However, the cumulative consecutive threshold cannot account for multiple

seasons in one year and the weekly/monthly threshold cannot define seasons well in weak seasonality settings. The proposed method in this work, i.e. cumulative non-consecutive threshold, is able to address all the scenarios above. Examples using real-world data are attached below to help demonstrate the performance of the three methods in defining seasons under different scenarios (**Figure 6-1**).

Table 6-1 Summary of global/regional reports that defined viral seasonal epidemics

Study	Virus	Data Frequency	Region	Definition of Season/Epidemics	Definition of Onset	Definition of Offset
(Azziz Baumgartner et al. 2012)	IFV	Monthly	Global	Periods when TPP* exceeded annual mean	The first month when TPP* exceeded annual mean	The first month after an epidemic when TPP* remained below annual mean
	IFV	Weekly	Global	Periods when TPP exceeded annual mean for ≥3 weeks*	The first week when TPP exceeded and remained annual mean for ≥3 weeks*	The first week after an epidemic when TPP remained below annual mean for ≥3 weeks*
(Bloom-Feshbach et al. 2013)	IFV, RSV	Monthly	Global	Months with ≥ 5%/10% of APP	Not defined	Not defined
	IFV, RSV	Weekly	Global	Weeks with ≥ 1.2% of APP	Not defined	Not defined
(Broberg et al. 2018)	RSV	Weekly	Europe	Weeks with ≥ 1.2% of APP	The first week with ≥ 1.2% of APP	The first week after an epidemic when APP fell below 1.2%

Study	Virus	Data Frequency	Region	Definition of Season/Epidemics	Definition of Onset	Definition of Offset
(Saverio Caini et al. 2016)	IFV	Weekly	Global	Minimum number of consecutive months to have ≥80% of APP	Not defined	Not defined
(Durand et al. 2016)	IFV	Monthly	American tropics	Model: log(TPP(1-TPP)) ~ year + month Periods when predicted TPP exceeded annual median for ≥2 months	Not defined	Not defined
(Hirve et al. 2016)	IFV	Monthly	Tropics and subtropics	Months with ≥10% of APP in at least 2 of 6 years (2010–2015)	Not defined	Not defined
	IFV	Monthly	Tropics and subtropics	Model: log(TPP(1-TPP)) ~ year + month Periods when predicted TPP exceeded annual median for ≥2 months	The first month when predicted TPP exceeded and remained annual median for ≥2 months	The first month after an epidemic when predicted TPP fell below annual median
(Newman et al. 2018)	IFV	Monthly	Global	Months with ≥10% of APP in at least 2 of 6 years (2011–2016)	Not defined	Not defined

Study	Virus	Data Frequency	Region	Definition of Season/Epidemics	Definition of Onset	Definition of Offset
(Obando-Pacheco et al. 2018)	RSV	Weekly	Global	Periods when TPP was ≥10% for ≥2 weeks	The first week when TPP was ≥10% for ≥2 weeks	The first week after an epidemic when TPP was <10% for ≥2 weeks

APP = annual positive proportion; IFV = influenza virus; RSV = respiratory syncytial virus; TPP = test-positive proportion

*When TPP is not available, APP is applied instead.

Table 6-2 Comparisons between annual positive proportion and test-positive proportion

Data type	APP	TPP
Definition	The proportion of positive tests during an interval* to annual positive tests	The proportion of positive tests during an interval
Formula	$APP = \frac{pos_i}{\sum pos}$ i: interval i	$TPP = \frac{pos_i}{pos_i + neg_i}$ i: interval i
Prerequisite(s)	Number of positive tests for the full year	Number of positive and negative tests for the interval
Advantage	Does not require the number of negative tests	Does not require the number of tests for other intervals of the year
Disadvantage	Results of an interval can be affected by other intervals of the year, thus requiring stable test practice all year round	Results can be affected by the co-circulation of other viruses Results are more sensitive to test methods

APP=annual positive proportion; TPP=test-positive proportion

*An interval is the smallest unit of aggregation of number of tests, usually a week or a month.

Table 6-3 Comparisons among annual positive proportion-based definitions of viral seasonal epidemics

	Weekly/monthly threshold	Cumulative threshold (consecutive)	Cumulative threshold (non-consecutive)
Example	(Bloom-Feshbach et al. 2013) etc.	(Saverio Caini et al. 2016)	This study
Definition of seasonal epidemics	Months with APP ≥ 5%/10% Weeks with APP ≥ 1.2%/2.5%	Minimum number of consecutive months to have ≥80% of APP	Minimum number of months to have ≥75% of APP
Allowing for multiple seasonal epidemics per year	Yes	No, due to the consecutiveness required by this method	Yes
Detection of strong seasonality	Yes	Yes	Yes
Detection of weak seasonality	No. Choice of threshold makes great difference. High threshold results in few or even no seasonal epidemics while low threshold results in all months/weeks being epidemic.	Yes	Yes

APP=annual positive proportion

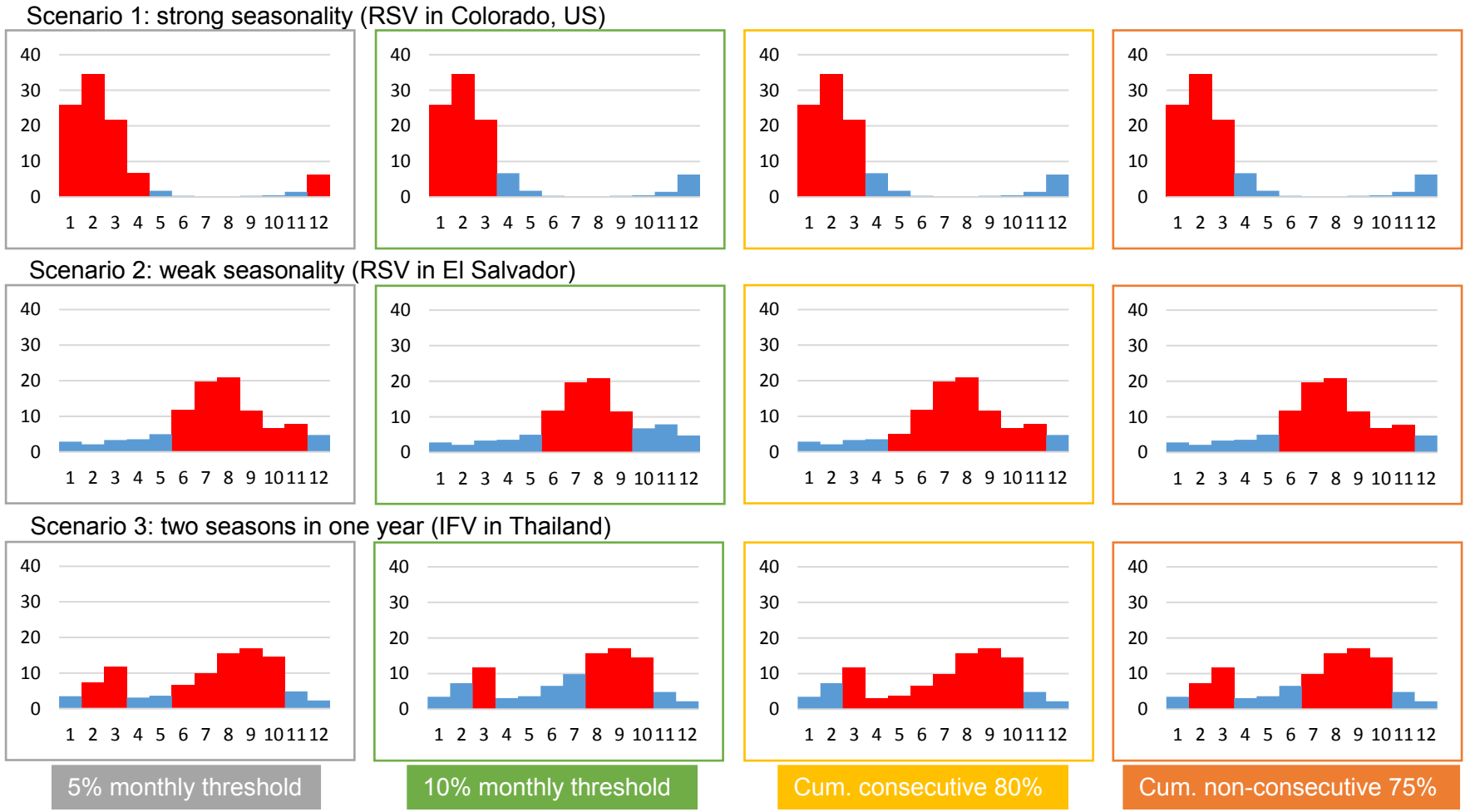


Figure 6-1 Comparisons among APP-based definitions for viral seasonal epidemics

6.4 Issues regarding controlling for shared seasonal risk factors between viral infection and PD

As proposed in previous studies, the shared seasonal risk factors can confound the association between viral infection and PD (**Figure 6-2A**). For example, lower temperature could be one of the shared risk factors of both viral infection and pneumococcal infection. To account for the shared seasonal factors, two different approaches had been used. The first approach is to control for common risk factors per se, e.g. temperature, rainfall, and/or humidity. The second approach is to add additional terms, e.g. annual and/or semi-annual harmonic terms, to the model as a proxy of all the shared seasonal risk factors. However, these shared seasonal factors are not all easy to control for. Both approaches might have the issue of residual confounding, i.e. factors that are not accounted for (e.g. human contact), or factors that are not well captured by the harmonic terms.

In this work, I proposed a new approach in order to control for the seasonal factors. In the new approach, PD is further divided into PD at the time of viral infection (i.e. week 0) and subsequent PD (i.e. week *i*), the outcome of interest (**Figure 6-2B**). The method is designed to control for PD at week 0, which can indirectly control for the shared seasonal factors that are normally difficult to control for. Then the results can be interpreted as how much of IPD at week *i* can be explained given the viral infection and pneumococcal infection at week 0. However, this method is not without its limitations. The method ignores the potential association between the shared seasonal factors at week 0 and PD at week *i*, which can confound the observed association presented in this work.

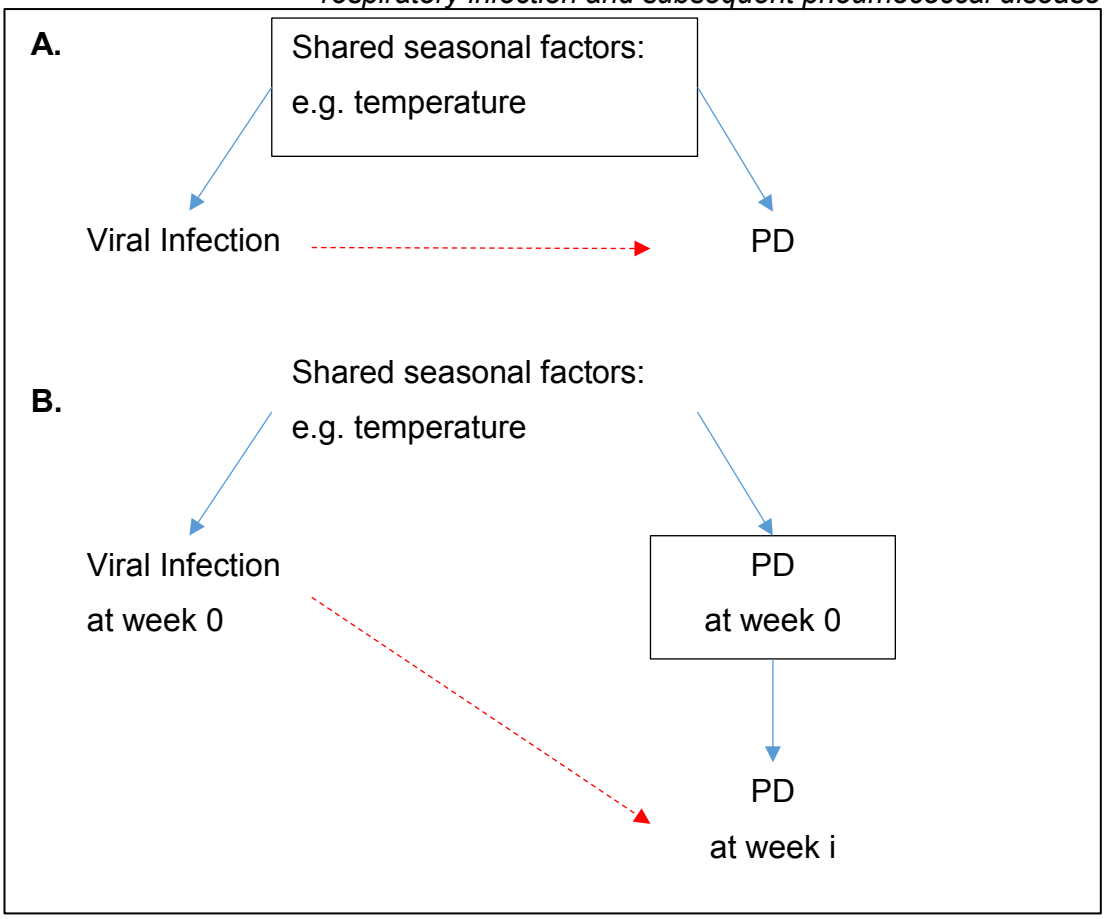


Figure 6-2 Causal diagrams for the association between viral infection and subsequent pneumococcal disease (A. simple version; B. time-lag version)
Squared outline indicates controlling for the corresponding factor in the statistical model.

6.5 Implications for RSV immunisation strategies

As introduced in **Chapter 1**, RSV represents a substantial burden of disease and health-care globally in young children, especially in the LMICs. In high income countries, Palivizumab, a short-acting mAb, is currently being administered during RSV season to young children at high risk, e.g. preterm children, children with congenital heart disease, and children with chronic lung diseases. There are two promising candidates that are expected to be available at vaccine-like pricing and could be considered for use in LMICs—the maternal vaccine ResVax and the long-acting mAb MEDI8897. Both candidates provide limited duration of protection and RSV seasonality is important to help decide on the immunisation strategy.

6.5.1 Maternal vaccine — ResVax

At the end of February 2019, Novavax announced the topline phase-3 trial results of ResVax (Anonymous 2019b). Although the final reports of the results have not yet been published at the time of writing, there are some important results in the initial slides released by Novavax: 1). The vaccine did not meet its primary endpoint, medically significant RSV lower respiratory tract infection (efficacy: 39.4%, 97.5% CI, –1.0% to 63.7%). 2). The vaccine did show efficacy in preventing RSV hospitalisation and RSV with hypoxemia. 3). The efficacy results showed that gestational age at the time of vaccination affected efficacy; earlier vaccination group (<33 weeks of gestation) had higher efficacy. 4). Compared to rest of the world, efficacy in US was low and it was speculated by the presenters that this seemed to be "related to timing of immunisation, including the negative effects of late gestational age immunization and short intervals to birth".

From my point of view, the vaccine seems to be effective even though the primary endpoint has not been met. Apart from the selection of the primary endpoint, which is academically contestable, I think the overall results were highly influenced by the results from US (US contributed one fourth of total data). It becomes important to identify the reasons for the low efficacy in US. While I agree that late timing of immunisation in US could explain the

observed low efficacy to some degree, this could not explain the results among <33 weeks of gestation vaccination group where the efficacy in US children was still lower (US: –9.7 [–259.2, 66.5]; South Africa: 55.4 [19.5, 75.3]; All: 41.4 [4.1, 64.2]) (Anonymous 2019b). One of the other reasons that could explain the low efficacy in the US is the failure to match the timing of vaccination with the local RSV seasonality. As a result, fewer RSV cases were captured and the power of the trial was reduced. Due to the nature of maternal immunisation, there were some inherent challenges in matching with the local RSV season. On the one hand, the actual date of delivery is never known at the time of vaccination; certain assumptions for both the date of delivery and the onset of the upcoming RSV season have to be made in order to determine eligibility. On the other hand, the susceptibility to RSV infection differs by gestational age at birth and could modify the protection conferred by the vaccine. Further investigations into the lower efficacy of this trial in the US are warranted.

6.5.2 Long-acting mAb — MEDI8897

MEDI8897 is a long-acting mAb that targets prefusion-F protein. The results of phase-2b trial showed a favourable safety profile in healthy preterm infants and an extended half-life of the mAb (Domachowske et al. 2018). In early 2019, MEDI8897 received fast track designation from both U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). Some topline results of the efficacy of MEDI8897 from the phase-2b trial were presented recently in the 37th European Society for the Paediatric Infectious Diseases conference: on day 150 post immunisation, MEDI8897 was reported to reduce medically attended ALRI by 70.1% [52.3, 81.2] and reduce ALRI hospitalisation by 78.4% [51.9, 90.3]. Phase-3 trial is planned to be initiated among healthy term newborns in 2019. Compared with the maternal vaccine, the timing of mAb only relies on the RSV seasonality. However, mAb is not without its limitations. All mAbs, by definition, only recognise one epitope each. For example, Palivizumab only recognises the site II antigenic site on the F protein and MEDI8897 is

a variant of antibody D25 which recognises the site Ø (Domachowske et al. 2018). Recently, it was reported that Palivizumab-resistant RSV was isolated from an infant treated with palivizumab (Adams et al. 2010). Escape mutant viruses with amino acid changes in site II were isolated from children treated with palivizumab (Qing Zhu et al. 2011). As MEDI8897 is planned to be used in a wider group of children than Palivizumab, epitope-specific resistance could be worse and would likely impact on the efficacy. A global baseline dataset is needed to monitor future variations of RSV sequence for the future in case there is selective pressure favouring escape mutants following widespread use of MEDI8897 or other mAbs. It is possible that the composition of mAbs would be reviewed and decided annually before each RSV season, similar to the IFV vaccine (WHO 2019). Although maternal vaccine would likely not have this limitation owing to polyclonal response, a recent study reported a narrower range of antibody specificities produced by B-lymphocytes from infants after RSV infection than from adults (Goodwin et al. 2018).

6.6 Proposals for future studies

6.6.1 Proposals related to global seasonality of respiratory viruses studies

An update of the description and modelling using multi-year viral data

An update of the description and modelling work in **Chapter 2** can be conducted using multi-year data. This can address the limitation of not being able to identify multi-year seasonal patterns for RSV that were reported in some northern European countries. There is increasing need for the forecast of IFV and RSV seasons so that their seasonal prophylaxis can be planned. In theory, such forecast is possible using the methodology presented in this work. However, due to the lack of multi-year viral data for IFV and RSV, the current prediction tool could not be applied to such forecast. For this update, at least three years of monthly/weekly viral data are necessary. There are two potential data sources that can be considered. The first one is based on

the ongoing WHO RSV surveillance which was initiated in 14 countries in 2016 (World Health Organization 2019); seven more countries have been added for the second phase in 2019 (personal communication). In a few years of time, at least five years of RSV data for some countries would be available for multi-year modelling. The second strategy is to apply the model to the data from European Centre for Disease Prevention and Control (ECDC). However, all ECDC member states are in the temperate regions and this limits the extrapolation of the model. Nonetheless, this could serve as a plausibility check of the model for prospectively predicting RSV seasons. It is also expected that labs from LMICs will have more capacities in future, e.g. multi-plex PCR will be available in more sites from LMICs. As a result, more PIV, including PIV subtypes 1–4, and MPV monthly activity data for at least three years will be available for modelling.

Understanding the impact of IFV pandemics on the seasonality of other respiratory viruses

In the seasonality study of this thesis, only IFV data during the 2009 swine flu pandemic were excluded while data of RSV, PIV, and MPV were included, assuming that their seasonality is not impacted by the pandemic IFV. However, there is one published study in Israel reporting that when IFV A(H1N1)pdm09 appeared, RSV seasons were delayed until IFV A(H1N1)pdm09 declined (Hirsh et al. 2014). This is potentially important for the preparedness for the next IFV pandemic. Should an IFV pandemic occur, RSV prophylaxis can be postponed accordingly. Future studies can compare the RSV seasons in pre-pandemic period (before 2009), pandemic period (2009–2010), and post-pandemic period (2011 onwards). Viral activity data of IFV A(H1N1)pdm can also be collected for each site to reflect the local IFV pandemic activity if available.

Understanding the global transmission dynamics of RSV, PIV, and MPV

Future studies can consider together the global transmission of RSV, PIV, and MPV. This requires multi-year viral activity data and sequence data of each virus, using similar methodology to the studies for IFV (Bedford et al.

2015; Lemey et al. 2014; Rambaut et al. 2008; Russell et al. 2008). However, genomic data of RSV, PIV, and MPV are still limited at the moment. For RSV, an international collaboration named “DIVERGE (DIVErsity in Rsv GEnomes)” has been established to carry out whole genome sequencing of over eight hundred RSV samples taken from children under five years of age in six LMICs (Anonymous 2019a). This could help better understand the transmission dynamics of RSV.

6.6.2 Proposals for future viral-pneumococcal association studies

The association between viral infection and pneumococcal infection is still not well understood on individual-patient level. Future individual-patient-level studies are warranted to confirm the findings from population-level studies. Moreover, it is important for future individual-patient-level studies to assess the risk of secondary pneumococcal infections given the age, comorbidity status, and even PCV immunisation status, which will be of great importance for the clinical management of patients with viral infections.

In terms of methodology, like population-level studies, it is essential for individual-patient-level studies to control for potential confounders, including seasonal and non-seasonal confounders. Self-controlled case series design could be one option as this design eliminates all time-invariant confounders. This study design was recently applied to assess the association between IFV infection and subsequent myocardial infarction (Kwong et al. 2018).

Chapter 7 Conclusions

This thesis provides an overall picture of global seasonality of IFV, RSV, PIV, and MPV by incorporating data from various sources, including systematic literature searches, online public datasets, and unpublished datasets shared by RSV GEN. It is the first study that highlights the difference in the seasonality of IFV and RSV, especially in the tropical regions. This is also the first study to describe global seasonality of PIV and MPV, two important viruses in the aetiology of ALRI. By modelling the association between meteorological factors and viral seasonality, this study presents a practical tool for the prediction of local IFV and RSV seasonality given the local monthly temperature and relative humidity. The global seasonality patterns presented in this study are important for health-care services planning and immunisation strategies. This thesis also evaluates the role of RSV seasonality in LMICs planning the introduction of RSV prophylaxis and supports the seasonal approach for LMICs with clear RSV seasonality. Future studies should consider describing and modelling the activity of IFV, RSV, PIV and MPV on a multi-year scale to enable the forecast of their seasonality.

This thesis critically reviews the methodologies and findings of published studies on the association between viral acute respiratory infection and subsequent pneumococcal disease. The main methodological challenges of existing studies include the failure to use individual patient data, control for seasonal factors of viral infection and pneumococcal disease, or include other factors related to the association (e.g., virus type, age, comorbidity and pneumococcal serotype). These challenges could explain the inconsistent results from the existing studies. Based on the findings of the systematic review, an ecological study was conducted using laboratory-confirmed viral infection and pneumococcal infection, stratified by age group. This study provides consistent support of the association between respiratory infection associated with IFV or RSV and subsequent invasive pneumococcal disease across all age groups. While addressing some of the methodological

challenges listed above, the study is unable to conduct an individual-patient-level analysis so is unable to incorporate factors including comorbidity status and pneumococcal serotypes. These limitations can be addressed in future studies to optimise the clinical management of patients with viral infection and to better evaluate the additional IFV and RSV vaccine effect on the prevention of potential secondary pneumococcal infection.

References

Adams, Ortwin, et al. (2010), 'Palivizumab-Resistant Human Respiratory Syncytial Virus Infection in Infancy', *Clinical Infectious Diseases,* 51 (2), 185-88.

Afonso, Claudio L., et al. (2016), 'Taxonomy of the order Mononegavirales: update 2016', *Archives of virology,* 161 (8), 2351-60.

Allard, R., et al. (2012), 'Invasive bacterial infections following influenza: a time-series analysis in Montreal, Canada, 1996-2008', *Influenza & Other Respiratory Viruses,* 6 (4), 268-75.

Alonso, W. J., et al. (2015), 'A global map of hemispheric influenza vaccine recommendations based on local patterns of viral circulation', *Sci Rep,* 5, 17214.

Ampofo, K., et al. (2008), 'Seasonal invasive pneumococcal disease in children: role of preceding respiratory viral infection', *Pediatrics,* 122 (2), 229-37.

Anonymous (2018), 'Population Estimates Time Series Data', (National Records of Scotland).

Anonymous (2019), 'DIVERGE (DIVErsity in Rsv GEnomes)', <https://www.ed.ac.uk/mrc-human-genetics-unit/diversity-in-rsv-genomes>, accessed 7 May.

Anonymous (2019), 'Prepare™ Trial Topline Results', <https://novavax.com/presentation.show>, accessed 19th Apr.

Azziz Baumgartner, E., et al. (2012), 'Seasonality, timing, and climate drivers of influenza activity worldwide', *J Infect Dis,* 206 (6), 838-46.

Bean, B., et al. (1982), 'Survival of Influenza Viruses on Environmental Surfaces', *The Journal of Infectious Diseases,* 146 (1), 47-51.

Bedford, Trevor, et al. (2015), 'Global circulation patterns of seasonal influenza viruses vary with antigenic drift', *Nature,* 523 (7559), 217-20.

Blencowe, H., et al. (2012), 'National, regional, and worldwide estimates of preterm birth rates in the year 2010 with time trends since 1990 for selected countries: a systematic analysis and implications', *Lancet,* 379 (9832), 2162-72.

Bloom-Feshbach, Kimberly, et al. (2013), 'Latitudinal Variations in Seasonal Activity of Influenza and Respiratory Syncytial Virus (RSV): A Global Comparative Review', *PLOS ONE,* 8 (2), e54445.

Bozick, Brooke A. and Real, Leslie A. (2015), 'The Role of Human Transportation Networks in Mediating the Genetic Structure of Seasonal Influenza in the United States', *PLOS Pathogens,* 11 (6), e1004898.

Broberg, Eeva K, et al. (2018), 'Seasonality and geographical spread of respiratory syncytial virus epidemics in 15 European countries, 2010 to 2016', *Eurosurveillance,* 23 (5), 17-00284.

Brown, Kenneth H, Black, Robert E, and Becker, Stan (1982), 'Seasonal changes in nutritional status and the prevalence of malnutrition in a longitudinal study of young children in rural Bangladesh', *Am J Clin Nutr,* 36 (2), 303-13.

Brundage, J. F. (2006), 'Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness', *Lancet Infect Dis,* 6 (5), 303-12.

Burgos, J., et al. (2015), 'Impact of influenza season and environmental factors on the clinical presentation and outcome of invasive pneumococcal disease', *European Journal of Clinical Microbiology & Infectious Diseases,* 34 (1), 177-86.

Caini, S., et al. (2017), 'The spatiotemporal characteristics of influenza A and B in the WHO European Region: can one define influenza transmission zones in Europe?', *Euro Surveill,* 22 (35).

Caini, Saverio, et al. (2018), 'Clinical characteristics and severity of influenza infections by virus type, subtype, and lineage: A systematic literature review', *Influenza and other respiratory viruses,* 12 (6), 780-92.

Caini, Saverio, et al. (2016), 'Temporal Patterns of Influenza A and B in Tropical and Temperate Countries: What Are the Lessons for Influenza Vaccination?', *PLOS ONE,* 11 (3), e0152310.

Cauchemez, Simon, et al. (2008), 'Estimating the impact of school closure on influenza transmission from Sentinel data', *Nature,* 452 (7188), 750.

Chang, Winston, et al. (2017), 'shiny: Web Application Framework for R.', (R package version 1.0.5).

Chanock, R., Roizman, B., and Myers, R. (1957), 'Recovery from infants with respiratory illness of a virus related to chimpanzee coryza agent (CCA). I. Isolation, properties and characterization', *Am J Hyg,* 66 (3), 281-90.

Charu, Vivek, et al. (2017), 'Human mobility and the spatial transmission of influenza in the United States', *PLOS Computational Biology,* 13 (2), e1005382.

Chien , Yu-Wen, Klugman , Keith P., and Morens , David M. (2009), 'Bacterial Pathogens and Death during the 1918 Influenza Pandemic', *New England Journal of Medicine,* 361 (26), 2582-83.

Ciruela, P., et al. (2016), 'Invasive pneumococcal disease rates linked to meteorological factors and respiratory virus circulation (Catalonia, 2006-2012)', *BMC Public Health,* 16 (400).

Cowling, Benjamin J, et al. (2008), 'Effects of school closures, 2008 winter influenza season, Hong Kong', *Emerging infectious diseases,* 14 (10), 1660.

Curns, Aaron T, et al. (2017), 'Determining the Seasonality of Respiratory Syncytial Virus in the United States: The Impact of Increased Molecular Testing', *The Journal of Infectious Diseases,* 216 (3), 345-55.

Dangor, Z., et al. (2014), 'Temporal association in hospitalizations for tuberculosis, invasive pneumococcal disease and influenza virus illness in South African children', *PLoS ONE [Electronic Resource],* 9 (3), e91464.

Del Valle, Sara Y., Hyman, J. M., and Chitnis, Nakul (2013), 'Mathematical models of contact patterns between age groups for predicting the spread of infectious diseases', *Mathematical biosciences and engineering : MBE,* 10 (5-6), 1475-97.

Department of Health Hong Kong (2018), 'Detection of pathogens from respiratory specimens', <https://www.chp.gov.hk/en/statistics/data/10/641/642/2274.html>, accessed 14 Feb.

Deyle, E. R., et al. (2016), 'Global environmental drivers of influenza', *Proc Natl Acad Sci U S A.,* 113 (46), 13081-86. doi: 10.1073/pnas.1607747113. Epub 2016 Oct 31.

Diavatopoulos, D. A., et al. (2010), 'Influenza A virus facilitates Streptococcus pneumoniae transmission and disease', *FASEB Journal,* 24 (6), 1789-98.

Domachowske, J. B., et al. (2018), 'Safety, Tolerability and Pharmacokinetics of MEDI8897, an Extended Half-life Single-dose Respiratory Syncytial Virus Prefusion F-targeting Monoclonal Antibody Administered as a Single Dose to Healthy Preterm Infants', *Pediatr Infect Dis J,* 37 (9), 886-92.

Domenech de Cellès, Matthieu, et al. (2017), 'Characterizing and Comparing the Seasonality of Influenza-Like Illnesses and Invasive Pneumococcal Diseases Using Seasonal Waveforms', *American Journal of Epidemiology*, kwx336-kwx36.

Dopico, Xaquin Castro, et al. (2015), 'Widespread seasonal gene expression reveals annual differences in human immunity and physiology', *Nature Communications,* 6, 7000.

Drijkoningen, J. J. C. and Rohde, G. G. U. (2014), 'Pneumococcal infection in adults: burden of disease', *Clinical Microbiology and Infection,* 20, 45-51.

Durand, L. O., et al. (2016), 'Timing of influenza epidemics and vaccines in the American tropics, 2002-2008, 2011-2014', *Influenza Other Respir Viruses,* 10 (3), 170-5.

Eames, Ken TD, Tilston, Natasha L, and Edmunds, W John (2011), 'The impact of school holidays on the social mixing patterns of school children', *Epidemics,* 3 (2), 103-08.

Edwards, L. J., et al. (2011), 'The relationship between influenza and invasive pneumococcal disease in the Northern Territory, 2005-2009', *Medical Journal of Australia,* 194 (4), 207.

Egata, Gudina, Berhane, Yemane, and Worku, Alemayehu (2013), 'Seasonal variation in the prevalence of acute undernutrition among children under five years of age in east rural Ethiopia: a longitudinal study', *BMC public health,* 13, 864-64.

Ewing, Anne, et al. (2017), 'Contact, Travel, and Transmission: The Impact of Winter Holidays on Influenza Dynamics in the United States', *The Journal of infectious diseases,* 215 (5), 732-39.

Falsey, Ann R., et al. (2005), 'Respiratory Syncytial Virus Infection in Elderly and High-Risk Adults', *New England Journal of Medicine,* 352 (17), 1749-59.

Fauci, Anthony S., Taubenberger, Jeffery K., and Morens, David M.. (2008), 'Predominant Role of Bacterial Pneumonia as a Cause of Death in Pandemic Influenza: Implications for Pandemic Influenza Preparedness', *The Journal of Infectious Diseases,* 198 (7), 962-70.

Finkelman, Brian S., et al. (2007), 'Global Patterns in Seasonal Activity of Influenza A/H3N2, A/H1N1, and B from 1997 to 2005: Viral Coexistence and Latitudinal Gradients', *PLOS ONE,* 2 (12), e1296.
Fleming-Dutra, K. E., et al. (2013), 'Effect of the 2009 influenza A(H1N1) pandemic on invasive pneumococcal pneumonia', *Journal of Infectious Diseases,* 207 (7), 1135-43.
Fry, A. M., et al. (2006), 'Seasonal trends of human parainfluenza viral infections: United States, 1990-2004', *Clinical Infectious Diseases,* 43 (8), 1016-22.
Goodwin, Eileen, et al. (2018), 'Infants Infected with Respiratory Syncytial Virus Generate Potent Neutralizing Antibodies that Lack Somatic Hypermutation', *Immunity,* 48 (2), 339-49.e5.
Government of Canada (2018), 'Open Government Portal', <https://open.canada.ca/data/en/dataset?portal_type=dataset&q=fluwatch>, accessed 20 Mar.
Grabowska, K., et al. (2006), 'Occurrence of invasive pneumococcal disease and number of excess cases due to influenza', *BMC Infectious Diseases,* 6, 58.
Graham, S. E. and McCurdy, T. (2004), 'Developing meaningful cohorts for human exposure models', *J Expo Anal Environ Epidemiol,* 14 (1), 23-43.
Hall, Caroline Breese and Douglas, R. Gordon (1981), 'Modes of transmission of respiratory syncytial virus', *The Journal of Pediatrics,* 99 (1), 100-03.
Hament, J. M., et al. (2005), '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', *Pediatric Research,* 58 (6), 1198-203.
Hament, Jeanne-Marie, et al. (2004), 'Enhanced Adherence of Streptococcus pneumoniae to Human Epithelial Cells Infected with Respiratory Syncytial Virus', *Pediatr Res,* 55 (6), 972-78.
Haynes, A. K., et al. (2016), 'Human Metapneumovirus Circulation in the United States, 2008 to 2014', *Pediatrics,* 137 (5).
He, Daihai, et al. (2015), 'Global Spatio-temporal Patterns of Influenza in the Post-pandemic Era', *Scientific Reports,* 5, 11013.
Hendriks, W., et al. (2017), 'Temporal cross-correlation between influenza-like illnesses and invasive pneumococcal disease in The Netherlands', *Influenza and other Respiratory Viruses,* 11 (2), 130-37.
Henrickson, Kelly J. (2003), 'Parainfluenza viruses', *Clinical microbiology reviews,* 16 (2), 242-64.
Hillbruner, C. and Egan, R. (2008), 'Seasonality, household food security, and nutritional status in Dinajpur, Bangladesh', *Food Nutr Bull,* 29 (3), 221-31.
Hirsh, Shira, et al. (2014), 'Epidemiological Changes of Respiratory Syncytial Virus (RSV) Infections in Israel', *PLOS ONE,* 9 (3), e90515.
Hirve, Siddhivinayak, et al. (2016), 'Influenza Seasonality in the Tropics and Subtropics – When to Vaccinate?', *PLOS ONE,* 11 (4), e0153003.

Hoest, Christel, et al. (2017), 'Vaccine coverage and adherence to EPI schedules in eight resource poor settings in the MAL-ED cohort study', *Vaccine,* 35 (3), 443-51.
Horanont, Teerayut, et al. (2013), 'Weather effects on the patterns of people's everyday activities: a study using GPS traces of mobile phone users', *PloS one,* 8 (12), e81153-e53.
Jackson, Charlotte, et al. (2013), 'School closures and influenza: systematic review of epidemiological studies', *BMJ open,* 3 (2), e002149.
Jansen, A. G., et al. (2008), 'Invasive pneumococcal and meningococcal disease: association with influenza virus and respiratory syncytial virus activity?', *Epidemiology & Infection,* 136 (11), 1448-54.
Killingley, Ben and Nguyen‐Van‐Tam, Jonathan (2013), 'Routes of influenza transmission', *Influenza and Other Respiratory Viruses,* 7 (s2), 42-51.
Kim, P. E., et al. (1996), 'Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses', *Clinical Infectious Diseases,* 22 (1), 100-6.
Kukavica-Ibrulj, I., et al. (2009), 'Infection with human metapneumovirus predisposes mice to severe pneumococcal pneumonia', *Journal of Virology,* 83 (3), 1341-9.
Kuster, S. P., et al. (2011), 'Evaluation of coseasonality of influenza and invasive pneumococcal disease: results from prospective surveillance', *PLoS Medicine / Public Library of Science,* 8 (6), e1001042.
Kwong, Jeffrey C., et al. (2018), 'Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection', *New England Journal of Medicine,* 378 (4), 345-53.
Lau, Susanna K. P., et al. (2005), 'Human Parainfluenza Virus 4 Outbreak and the Role of Diagnostic Tests', *Journal of Clinical Microbiology,* 43 (9), 4515.
Launes, C., et al. (2014), 'Respiratory viruses, such as 2009 H1N1 influenza virus, could trigger temporal trends in serotypes causing pneumococcal disease', *Clinical Microbiology & Infection,* 20 (12), O1088-90.
Lee, Wan-Ji, et al. (2012), 'Complete Genome Sequence of Human Respiratory Syncytial Virus Genotype A with a 72-Nucleotide Duplication in the Attachment Protein G Gene', *Journal of Virology,* 86 (24), 13810-11.
Lemey, P., et al. (2014), 'Unifying viral genetics and human transportation data to predict the global transmission dynamics of human influenza H3N2', *PLoS Pathog,* 10 (2), e1003932.
Lessler, Justin, et al. (2009), 'Incubation periods of acute respiratory viral infections: a systematic review', *The Lancet. Infectious diseases,* 9 (5), 291-300.
LeVine, A. M., Koeningsknecht, V., and Stark, J. M. (2001), 'Decreased pulmonary clearance of S. pneumoniae following influenza A infection in mice', *Journal of Virological Methods,* 94 (1-2), 173-86.

Li, You (2017), 'wktmo: converting weekly data to monthly data', (R package version 1.0.5).
Li, You, et al. (2018), 'Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies', *BMJ Open,* 8 (4), e019743.
Luca, Giancarlo De, et al. (2018), 'The impact of regular school closure on seasonal influenza epidemics: a data-driven spatial transmission model for Belgium', *BMC Infectious Diseases,* 18 (1), 29.
Ludewick, H. P., et al. (2011), 'Long-term impairment of Streptococcus pneumoniae lung clearance is observed after initial infection with influenza A virus but not human metapneumovirus in mice', *Journal of General Virology,* 92 (Pt 7), 1662-5.
Ludwig, E., et al. (2012), 'The remaining challenges of pneumococcal disease in adults', *European Respiratory Review,* 21 (123), 57-65.
Madhi, Shabir A., Klugman, Keith P., and The Vaccine Trialist, Group (2004), 'A role for Streptococcus pneumoniae in virus-associated pneumonia', *Nature Medicine,* 10, 811.
Maykowski, P., et al. (2018), 'Seasonality and clinical impact of human parainfluenza viruses', *Influenza Other Respir Viruses,* 12 (6), 706-16.
Mazur, N. I., et al. (2018), 'The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates', *Lancet Infect Dis,* 18 (10), e295-e311.
McCullers, J. A. (2006), 'Insights into the interaction between influenza virus and pneumococcus', *Clinical Microbiology Reviews,* 19 (3), 571-82.
McCullers, J. A. and Rehg, J. E. (2002), 'Lethal synergism between influenza virus and Streptococcus pneumoniae: characterization of a mouse model and the role of platelet-activating factor receptor', *Journal of Infectious Diseases,* 186 (3), 341-50.
McCullers, J. A., et al. (2010), 'Influenza enhances susceptibility to natural acquisition of and disease due to Streptococcus pneumoniae in ferrets', *Journal of Infectious Diseases,* 202 (8), 1287-95.
McDevitt, James, et al. (2010), 'Role of absolute humidity in the inactivation of influenza viruses on stainless steel surfaces at elevated temperatures', *Applied and environmental microbiology,* 76 (12), 3943-47.
McLean, H. Q., et al. (2015), 'Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type', *J Infect Dis,* 211 (10), 1529-40.
Ministry of Health New Zealand (2018), 'Virology Annual Report', <https://surv.esr.cri.nz/virology/virology_annual_report.php>, accessed 20 Mar.
Mizuta, K., et al. (2012), 'Epidemiology of parainfluenza virus types 1, 2 and 3 infections based on virus isolation between 2002 and 2011 in Yamagata, Japan', *Microbiology & Immunology,* 56 (12), 855-8.
Murdoch, D. R. and Jennings, L. C. (2009), 'Association of respiratory virus activity and environmental factors with the incidence of invasive pneumococcal disease', *Journal of Infection,* 58 (1), 37-46.

Muscatello, D. J. (2018), 'Redefining influenza seasonality at a global scale and aligning it to the influenza vaccine manufacturing cycle: a descriptive time series analysis', *J Infect,* 23 (18), 30309-8.
Myatt, Theodore A., et al. (2010), 'Modeling the airborne survival of influenza virus in a residential setting: the impacts of home humidification', *Environmental health : a global access science source,* 9, 55-55.
National Institute of Infectiou Disease Japan (2018), 'Isolation & Detection of Viruses in the past years', <https://www.niid.go.jp/niid/en/iasr-sp/230-iasr-data/5495-iasr-table-ve-p.html>, accessed 14 Feb.
Nelson, G. E., et al. (2012), 'Invasive pneumococcal disease and pandemic (H1N1) 2009, Denver, Colorado, USA', *Emerging Infectious Diseases,* 18 (2), 208-16.
Newman, Laura P., et al. (2018), 'Global influenza seasonality to inform country-level vaccine programs: An analysis of WHO FluNet influenza surveillance data between 2011 and 2016', *PLOS ONE,* 13 (2), e0193263.
Nicoli, E. J., et al. (2013), 'Influenza and RSV make a modest contribution to invasive pneumococcal disease incidence in the UK', *Journal of Infection,* 66 (6), 512-20.
Noti, John D., et al. (2013), 'High humidity leads to loss of infectious influenza virus from simulated coughs', *PloS one,* 8 (2), e57485-e85.
O'Brien, K. L., et al. (2000), 'Severe pneumococcal pneumonia in previously healthy children: the role of preceding influenza infection', *Clinical Infectious Diseases,* 30 (5), 784-9.
O'Brien, K. L., et al. (2009), 'Burden of disease caused by Streptococcus pneumoniae in children younger than 5 years: global estimates', *Lancet,* 374 (9693), 893-902.
Obando-Pacheco, Pablo, et al. (2018), 'Respiratory Syncytial Virus Seasonality: A Global Overview', *The Journal of Infectious Diseases*, jiy056-jiy56.
Okoko, J. B., Wesumperuma, H. L., and Hart, C. A. (2001), 'The influence of prematurity and low birthweight on transplacental antibody transfer in a rural West African population', *Tropical Medicine & International Health,* 6 (7), 529-34.
Opatowski, L., et al. (2013), 'Assessing pneumococcal meningitis association with viral respiratory infections and antibiotics: insights from statistical and mathematical models', *Proceedings of the Royal Society of London - Series B: Biological Sciences,* 280 (1764), 20130519.
Organization, World Health (2019), 'Immunization coverage', <https://www.who.int/immunization/monitoring_surveillance/routine/coverage/en/>, accessed 30th Apr.
Pan American Health Organization (2018), 'FluID', <http://ais.paho.org/phip/viz/flumart2015.asp>, accessed 14 Feb.
Paynter, S. (2014), 'Humidity and respiratory virus transmission in tropical and temperate settings', *Epidemiology and Infection,* 143 (6), 1110-18.
Pedro-Botet, M. L., et al. (2014), 'Impact of the 2009 influenza A H1N1 pandemic on invasive pneumococcal disease in adults', *Scandinavian Journal of Infectious Diseases,* 46 (3), 185-92.

Peltola, V., et al. (2011), 'Temporal association between rhinovirus circulation in the community and invasive pneumococcal disease in children', *Pediatric Infectious Disease Journal,* 30 (6), 456-61.
R Core Team (2017), 'R: A Language and Environment for Statistical Computing', (Vienna, Austria: R Foundation for Statistical Computing).
Rambaut, Andrew, et al. (2008), 'The genomic and epidemiological dynamics of human influenza A virus', *Nature,* 453 (7195), 615-19.
Ren, J., Phan, T., and Bao, X. (2015), 'Recent vaccine development for human metapneumovirus', *The Journal of general virology,* 96 (Pt 7), 1515-20.
Rohatgi, Ankit (2018), 'WebPlotDigitizer', (Austin, Texas, USA).
Russell, C. A., et al. (2008), 'The global circulation of seasonal influenza A (H3N2) viruses', *Science,* 320 (5874), 340-6.
Sabuncu, Elifsu, et al. (2009), 'Significant Reduction of Antibiotic Use in the Community after a Nationwide Campaign in France, 2002–2007', *PLOS Medicine,* 6 (6), e1000084.
Saunders-Hastings, Patrick R. and Krewski, Daniel (2016), 'Reviewing the History of Pandemic Influenza: Understanding Patterns of Emergence and Transmission', *Pathogens (Basel, Switzerland),* 5 (4), 66.
Schmidt, Alexander C., et al. (2011), 'Progress in the development of human parainfluenza virus vaccines', *Expert review of respiratory medicine,* 5 (4), 515-26.
Schobel, Seth A., et al. (2016), 'Respiratory Syncytial Virus whole-genome sequencing identifies convergent evolution of sequence duplication in the C-terminus of the G gene', *Scientific Reports,* 6, 26311.
Shaman, Jeffrey and Kohn, Melvin (2009), 'Absolute humidity modulates influenza survival, transmission, and seasonality', *Proceedings of the National Academy of Sciences,* 106 (9), 3243-48.
Sharma-Chawla, N., et al. (2016), 'Influenza A virus infection predisposes hosts to secondary infection with different Streptococcus pneumoniae serotypes with similar outcome but serotype-specific manifestation', *Infection and Immunity,* 84 (12), 3445-57.
Shi, T., et al. (2019), 'The Etiological Role of Common Respiratory Viruses in Acute Respiratory Infections in Older Adults: A Systematic Review and Meta-analysis', *J Infect Dis*.
Shi, T., et al. (2017), 'Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study', *Lancet,* 390 (10098), 946-58.
Shi, Ting, et al. (2015a), 'Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: A systematic review and meta-analysis', *Journal of global health,* 5 (1), 010408-08.
--- (2015b), 'Aetiological role of common respiratory viruses in acute lower respiratory infections in children under five years: A systematic review and meta–analysis', *Journal of Global Health,* 5 (1), 010408.
Shiri, Tinevimbo, et al. (2017), 'Indirect effects of childhood pneumococcal conjugate vaccination on invasive pneumococcal disease: a

systematic review and meta-analysis', *The Lancet Global Health,* 5 (1), e51-e59.
Shrestha, S., et al. (2013), 'Identifying the interaction between influenza and pneumococcal pneumonia using incidence data', *Science Translational Medicine,* 5 (191), 191ra84.
Simell, Birgit, et al. (2012), 'The fundamental link between pneumococcal carriage and disease', *Expert Review of Vaccines,* 11 (7), 841-55.
Simonsen, L., et al. (2011), 'Impact of pneumococcal conjugate vaccination of infants on pneumonia and influenza hospitalization and mortality in all age groups in the United States', *MBio,* 2 (1), e00309-10.
Smith, Adam, Lott, Neal, and Vose, Russ (2011), 'The Integrated Surface Database: Recent Developments and Partnerships', *Bulletin of the American Meteorological Society,* 92 (6), 704-08.
Smith, C. M., et al. (2014), '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,* 190 (2), 196-207.
Smith, Donald B., et al. (2016), 'Detection of influenza C virus but not influenza D virus in Scottish respiratory samples', *Journal of clinical virology : the official publication of the Pan American Society for Clinical Virology,* 74, 50-53.
Song, J. Y., et al. (2014), 'Impact of preceding flu-like illness on the serotype distribution of pneumococcal pneumonia', *PLoS ONE [Electronic Resource],* 9 (4), e93477.
Sparks, Adam H., Hengl, Tomislav, and Nelson, Andrew (2017), 'GSODR: Global Summary Daily Weather Data in R', *The Journal of Open Source Software,* 2 (10).
Stark, J. M., et al. (2006), 'Decreased bacterial clearance from the lungs of mice following primary respiratory syncytial virus infection', *Journal of Medical Virology,* 78 (6), 829-38.
Steffens, Andrea, et al. (2016), 'Population-based Surveillance for Medically Attended Human Parainfluenza Viruses From the Influenza Incidence Surveillance Project, 2010-2014', *The Pediatric infectious disease journal,* 35 (7), 717-22.
Stensballe, L. G., Devasundaram, J. K., and Simoes, E. A. (2003), 'Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus', *Pediatr Infect Dis J,* 22 (2 Suppl), S21-32.
Stensballe, L. G., et al. (2008), 'Hospitalization for respiratory syncytial virus infection and invasive pneumococcal disease in Danish children aged <2 years: a population-based cohort study', *Clinical Infectious Diseases,* 46 (8), 1165-71.
Sun, K. and Metzger, D. W. (2008), 'Inhibition of pulmonary antibacterial defense by interferon-gamma during recovery from influenza infection', *Nature Medicine,* 14 (5), 558-64.
Talbot, T. R., et al. (2005), 'Seasonality of invasive pneumococcal disease: temporal relation to documented influenza and respiratory syncytial viral circulation', *American Journal of Medicine,* 118 (3), 285-91.

Tamerius, J., et al. (2011), 'Global influenza seasonality: reconciling patterns across temperate and tropical regions', *Environ Health Perspect,* 119 (4), 439-45.

Tamerius, J. D., et al. (2013), 'Environmental predictors of seasonal influenza epidemics across temperate and tropical climates', *PLoS Pathogens,* 9 (3), e1003194.

Tang, J. W. and Loh, TzePing (2014), 'Correlations between climate factors and incidence - a contributor to RSV seasonality', *Reviews in Medical Virology,* 24 (1), 15-34.

Tollefson, Sharon J., Cox, Reagan G., and Williams, John V. (2010), 'Studies of culture conditions and environmental stability of human metapneumovirus', *Virus research,* 151 (1), 54-59.

Toschke, A. M., et al. (2008), 'No temporal association between influenza outbreaks and invasive pneumococcal infections', *Archives of Disease in Childhood,* 93 (3), 218-20.

Troeger, Christopher, et al. (2018), 'Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016', *The Lancet Infectious Diseases,* 18 (11), 1191-210.

van den Hoogen, B. G., et al. (2001), 'A newly discovered human pneumovirus isolated from young children with respiratory tract disease', *Nat Med,* 7 (6), 719-24.

van den Hoogen, Bernadette G., et al. (2002), 'Analysis of the Genomic Sequence of a Human Metapneumovirus', *Virology,* 295 (1), 119-32.

Vasickova, P., et al. (2010), 'Issues Concerning Survival of Viruses on Surfaces', *Food and Environmental Virology,* 2 (1), 24-34.

Wahl, B., et al. (2018), 'Burden of Streptococcus pneumoniae and Haemophilus influenzae type b disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15', *Lancet Glob Health,* 6 (7), e744-e57.

Walter, N. D., et al. (2010), 'Influenza circulation and the burden of invasive pneumococcal pneumonia during a non-pandemic period in the United States', *Clinical Infectious Diseases,* 50 (2), 175-83.

Walter , Nicholas D., et al. (2009), 'Holiday Spikes in Pneumococcal Disease among Older Adults', *New England Journal of Medicine,* 361 (26), 2584-85.

Wang, D., Bayliss, S., and Meads, C. (2011), 'Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses', *Health Technol Assess,* 15 (5), iii-iv, 1-124.

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

Watson, D. A., et al. (1993), 'A brief history of the pneumococcus in biomedical research: a panoply of scientific discovery', *Clin Infect Dis,* 17 (5), 913-24.
Watson, M., et al. (2006), 'The association of respiratory viruses, temperature, and other climatic parameters with the incidence of invasive pneumococcal disease in Sydney, Australia', *Clinical Infectious Diseases,* 42 (2), 211-5.
Weinberger, D. M., et al. (2015), 'Association between respiratory syncytial virus activity and pneumococcal disease in infants: a time series analysis of US hospitalization data', *PLoS Medicine / Public Library of Science,* 12 (1), e1001776.
Weinberger, D. M., et al. (2012), 'Impact of the 2009 influenza pandemic on pneumococcal pneumonia hospitalizations in the United States', *Journal of Infectious Diseases,* 205 (3), 458-65.
Weinberger, D. M., et al. (2013), 'Serotype-specific effect of influenza on adult invasive pneumococcal pneumonia', *Journal of Infectious Diseases,* 208 (8), 1274-80.
Weinberger, D. M., et al. (2014a), 'Seasonal drivers of pneumococcal disease incidence: impact of bacterial carriage and viral activity.[Erratum appears in Clin Infect Dis. 2014 Mar;58(6):908]', *Clinical Infectious Diseases,* 58 (2), 188-94.
Weinberger, D. M., et al. (2014b), 'Pneumococcal disease seasonality: incidence, severity and the role of influenza activity', *European Respiratory Journal,* 43 (3), 833-41.
WHO (2019), 'Recommended composition of influenza virus vaccines for use in the 2019-2020 northern hemisphere influenza season', <https://www.who.int/influenza/vaccines/virus/recommendations/2019_20_north/en/>, accessed 24 May.
Willem, Lander, et al. (2012), 'A Nice Day for an Infection? Weather Conditions and Social Contact Patterns Relevant to Influenza Transmission', *PLOS ONE,* 7 (11), e48695.
Willett, KM, et al. (2014), 'HadISDH land surface multi-variable humidity and temperature record for climate monitoring', *Climate of the Past,* 10 (6), 1983.
World Health Organization (2011), 'Influenza transmission zones', *Geneva, Switzerland: World Health Organization*.
--- (2018), 'WHO Global Respiratory Syncytial Virus Surveillance', <http://www.who.int/influenza/rsv/en/>, accessed 24 September.
--- (2018), 'FluNet', <http://www.who.int/influenza/gisrs_laboratory/flunet/en/>, accessed 14 Feb.
--- (2018b), 'Influenza (seasonal)', *Fact sheet*.
--- (2018), 'Fact sheet: Influenza (seasonal)', (updated Jan 2018) <http://www.who.int/mediacentre/factsheets/fs211/en/>, accessed 23 Apr.
--- (2019), 'WHO Global Respiratory Syncytial Virus Surveillance', <https://www.who.int/influenza/rsv/en/>, accessed 29 Apr.

Zhao, H., et al. (2017), 'Epidemiology of parainfluenza infection in England and Wales, 1998-2013: any evidence of change?', *Epidemiol Infect,* 145 (6), 1210-20.
Zhou, H., et al. (2012), 'Invasive pneumococcal pneumonia and respiratory virus co-infections', *Emerging Infectious Diseases,* 18 (2), 294-7.
Zhu, Q., et al. (2017), 'A highly potent extended half-life antibody as a potential RSV vaccine surrogate for all infants', *Sci Transl Med,* 9 (388).
Zhu, Qing, et al. (2011), 'Analysis of Respiratory Syncytial Virus Preclinical and Clinical Variants Resistant to Neutralization by Monoclonal Antibodies Palivizumab and/or Motavizumab', *The Journal of Infectious Diseases,* 203 (5), 674-82.

Appendices

A1. Glossary

Abbreviation	Fullname
ADV	adenovirus
AH	absolute humidity
AIC	Akaike information criterion
ALRI	acute lower respiratory infection
ANC	antenatal care
AP	attributable percentage
APP	annual positive proportion
ARI	acute respiratory infection
AUROC	area under the Receiver Operating Characteristic curve
BCG	Bacillus Calmette–Guérin
BOV	bocavirus
CFU	colony-forming units
CI	confidence interval
CORR	correlation
COV	coronavirus
d	day(s)
DAT	direct antigen test
ECDC	European Centre for Disease Prevention and Control
ECOSS	Electronic Communication of Surveillance in Scotland
EV	enterovirus
GISRS	Global Influenza Surveillance and Response System
Hep	Hepatitis
IF	immunofluorescence
IFV	influenza virus

Abbreviation	Fullname
ILI	influenza-like illness
INDV	individual
IPD	invasive pneumococcal disease
IR	incidence rate
LMIC	lower and middle income country
m	month(s)
mAb	monoclonal antibody
MPV	metapneumovirus
mV	maternal vaccine
NIC	national influenza center
npIPD	non-pneumonic pneumococcal disease
PAHO	Pan American Health Organization
PB	pneumococcal bacteraemia
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PD	pneumococcal disease
PIV	parainfluenza virus
POP	population
PP	pneumococcal pneumonia
PPV	pneumococcal polysaccharide vaccine
Pse	pneumococcal sepsis
RAT	rapid antigen test
REGR	regression
RH	relative humidity
RNA	Ribonucleic acid
RR	relative risk

Abbreviation	Fullname
RSV	respiratory syncytial virus
RV	rhinovirus
SPIDER	Scottish Pneumococcal Invasive Disease Enhanced Reporting
T	temperature
TPP	test-positive proportion
UV index	clear-sky ultraviolet index
VARI	viral acute respiratory infection
WHO	World Health Organization
y	year(s)

A2. Search strategy for the global seasonality systematic literature review

Medline

1. pneumonia.mp. or exp Pneumonia/
2. bronchiolitis.mp. or exp Bronchiolitis/
3. *Respiratory Syncytial Viruses/ or *Respiratory Syncytial Virus Infections/ or respiratory syncytial.mp. or *Respiratory Syncytial Virus, Human/
4. influenza.mp. or Influenza, Human/
5. parainfluenza.mp.
6. metapneumovirus.mp. or *Metapneumovirus/
7. lower respiratory infection*.mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Seasons/ or season*.mp.
10. temporal.mp. or exp Spatio-Temporal Analysis/
11. periodic*.mp. or exp Periodicity/
12. surveillance.ti,ab. or exp Population Surveillance/
13. 9 or 10 or 11 or 12
14. ep.fs.
15. 8 and 13 and 14
18. limit 15 to (humans and yr="2000 -2017")

12907 results returned

EMbase

1. pneumonia.mp. or exp pneumonia/
2. bronchiolitis.mp. or exp Bronchiolitis/
3. exp lower respiratory tract infection/ or (lower respiratory adj1 infection*).mp.
4. influenza.mp. or exp influenza/
5. exp Human respiratory syncytial virus/ or exp respiratory syncytial virus infection/ or exp Respiratory syncytial pneumovirus/ or respiratory syncytial.mp.
6. parainfluenza.mp. or exp Parainfluenza virus infection/

7. exp Human metapneumovirus/ or exp Human metapneumovirus infection/ or metapneumovirus.mp.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. exp season/ or season*.mp. or exp seasonal variation/

10. exp disease surveillance/ or exp sentinel surveillance/ or surveillance.ti,ab.

11. periodic*.mp. or exp periodicity/

12. exp spatiotemporal analysis/ or temporal.mp.

13. 9 or 10 or 11 or 12

14. ep.fs.

15. 8 and 13 and 14

16. limit 15 to (human and yr="2000 -2017")

10378 results returned

Global Health

1. pneumonia.mp. or exp pneumonia/

2. bronchiolitis.mp. or exp bronchiolitis/

3. (lower respiratory adj1 infection*).mp.

4. exp influenza/ or influenza.mp.

5. respiratory syncytial.mp. or Human respiratory syncytial virus.od.

6. exp parainfluenza/ or parainfluenza.mp.

7. exp Human metapneumovirus/ or metapneumovirus.mp.

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. exp seasonal variation/ or exp seasonality/ or season*.mp.

10. exp surveillance/ or surveillance.mp. or exp sentinel surveillance/

11. temporal.mp. or temporal variation/

12. periodic*.mp. or exp periodicity/

13. 9 or 10 or 11 or 12

14. 8 and 13

15. limit 14 to yr="2000 -2017"

14039 results returned

A3. Details of seasonality data from online public sources

Sources	Virus	Year	Site	Other Information
WHO FluNet	IFV all types and subtypes	2000–2017	123 countries with data available for ≥1 year	2009–2010 excluded
PAHO FluID	IFV all types and subtypes, RSV, PIV, MPV	2010–2017	26 countries PAHO countries with data available for ≥1 year	2010 excluded for IFV
Japan National Institute of Infectious Diseases	RSV, PIV, MPV	2000–2014	Japan	MPV started from 2002
Hong Kong Department of Health	IFV all types and subtypes, RSV, PIV	2014–2017	Hong Kong, China	
Canada FluWatch	IFV all types and subtypes, RSV, PIV, MPV	2008–2014	Canada	2009–2010 excluded for IFV; MPV started from 2009
New Zealand Ministry of Health	IFV all types and subtypes, RSV, PIV, MPV	2000–2015	New Zealand	2009–2010 excluded for IFV; MPV started from 2009

A4. Details of seasonality data from RSV GEN

Data Provider	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Rosalyn Singleton	YK Delta, Alaska	USA	-164.2, 62.9	ALRI	RADT		✓		
Barbara Rath	Berlin	Germany	13.4, 52.5	ALRI	PCR	✓	✓	✓	✓
Darmaa Badarch	Ulaanbaatar	Mongolia	106.9, 47.9	ALRI	PCR	✓	✓		
Jianwei Wang	Beijing	China	116.4, 39.9	ALRI	PCR		✓		
Eric A. F. Simões	Aurora, Colorado	USA	-104.8, 39.7	ALRI	PCR			✓	✓
Eric A. F. Simões	State of Colorado	USA	-105.8, 39.6	ALRI	PCR		✓		
Hongjie Yu	nationwide	China	104.2, 35.9	ALRI	PCR		✓		
Quique Bassat	Rabat	Morocco	-6.8, 34	ALRI	PCR	✓	✓	✓	
Najwa Khuri-Bulos	Amman	Jordan	35.9, 31.9	ALRI	PCR	✓	✓	✓	✓
Shobha Broor	Ballabgarh, Faridabad and Haryana	India	77.3, 28.3	ALRI	PCR		✓		
Nusrat Homaira	Kishoregonj, Bogra, Comilla and Barisal	Bangladesh	90.5, 23.8	ALRI	PCR	✓			
W. Abdullah Brooks	Kamalapur	Bangladesh	90.4, 23.7	ALRI	serology and PCR		✓		
Doli Goswami	Dhaka and Matlab	Bangladesh	90.7, 23.3	severe pneumonia	PCR		✓		

Data Provider	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Daniel E. Noyola	San Luis Potosí	Mexico	-101, 22.2	ALRI	IF or PCR		✓		
Claudia Turner	Tak Province	Thailand	99.1, 16.9	ALRI	PCR		✓		
Yong Poovorawan	Khon Kaen	Thailand	102.8, 16.4	ILI	PCR	✓	✓		
Nigel Bruce	San Lorenzo and Comitancillo	Guatemala	-91.7, 15.1	ALRI	RADT		✓		
John P. McCracken	Quetzaltenango	Guatemala	-91.5, 14.9	ALRI	PCR	✓	✓		
John P. McCracken	Santa Rosa	Guatemala	-90.4, 14.2	ALRI	PCR	✓	✓		
Wilfrido Clara	Santa Ana	El Salvador	-89.6, 14	ALRI	IFA		✓		
Somsak Thamtithiwat	Nakhon Phanom and Sa Kaeo	Thailand	101.1, 13.8	ALRI	PCR	✓	✓		
Yong Poovorawan	Bangkok	Thailand	100.5, 13.8	ILI	PCR	✓	✓		✓
Sujatha Sistla	Puducherry	India	78.9, 13.8	ILI	PCR	✓	✓	✓	
Yong Poovorawan	Chonburi	Thailand	101, 13.4	ILI	PCR		✓		
Martin Antonio	Basse	Gambia	-14.2, 13.3	severe pneumonia	PCR		✓		

Data Provider	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Karen L. Kotloff	Bamako	Mali	-8, 12.6	severe pneumonia	PCR		✓	✓	✓
Lay-Myint Yoshida	Nha Trang City	Vietnam	109.2, 12.2	ALRI	PCR	✓	✓	✓	
Philippe Buchy	Kampong Cham city and Takeo city	Cambodia	105.1, 11.5	ALRI	PCR		✓		
Socorro P. Lupisan	Tacloban	Philippines	125, 11.3	ALRI	serology, PCR or culture		✓		
Marilla G. Lucero	Bohol	Philippines	123.9, 9.7	ALRI	PCR or culture	✓	✓	✓	✓
Jorge Jara	David City, Chiriquí Province	Panama	-82.4, 8.4	ALRI	IF or PCR		✓		
Joel M. Montgomery	Lwak	Kenya	34.4, -0.1	ALRI	PCR		✓		
D. James Nokes	Kilifi	Kenya	40.1, -3.2	ALRI	DFA	✓	✓	✓	✓
Bradford D. Gessner	Lombok Island	Indonesia	116.3, -8.7	ALRI	RADT		✓		
Candice Romero	Tambopata district	Peru	-69.2, -12.6	ALRI	PCR	✓	✓		
Phil Seidenberg	Lusaka	Zambia	28.3, -15.4	severe pneumonia	PCR		✓	✓	✓
Maria Tereza da Costa Oliveira	Belo Horizonte	Brazil	-43.9, -19.9	ALRI	IFA or PCR	✓	✓		

Data Provider	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Rodrigo Fasce	Iquique	Chile	-70.1, -20.2	ALRI	IF	✓	✓	✓	
Peter Byass	Agincourt	South Africa	31.2, -24.8	ALRI	PCR	✓			
Cheryl Cohen	Agincourt	South Africa	31.2, -24.8	ALRI	PCR		✓		
Quique Bassat	Manhiça	Mozambique	32.8, -25.4	ALRI	PCR			✓	✓
Vicky L. Baillie	Soweto	South Africa	27.9, -26.2	severe pneumonia	PCR		✓		
Shabir A. Madhi	Soweto	South Africa	27.9, -26.2	ALRI	PCR	✓			✓
Cheryl Cohen	Klerksdorp	South Africa	26.6, -26.9	ALRI	PCR		✓		
Cheryl Cohen	Pietermaritzburg	South Africa	30.4, -29.6	ALRI	PCR		✓		
Nusrat Homaira	New South Wales	Australia	146.9, -31.3	respiratory symptoms	multiple tests		✓		
Heather J. Zar	Paarl, Western Province	South Africa	19, -33.7	ALRI	PCR		✓	✓	
Angela Gentile	Buenos Aires	Argentina	-58.4, -34.6	ALRI	PCR	✓			
Rodrigo Fasce	Concepcion	Chile	-73, -36.8	ALRI	IF		✓	✓	

LON=longitude; LAT=latitude; NK=not known; ALRI=acute lower respiratory infection; ARI=acute respiratory infection; ILI=influenza-like illness; PCR=polymerase chain reaction; IF=immunofluorescence; DFA=direct fluorescent antibody test; IFA=indirect fluorescent antibody test; RADT=rapid antigen-detection test.

*Any IFV includes IFV, IFV A, IFV B, IFV A(H1N1), IFV A(H1N1)pdm and IFV A(H3N2).

A5. Questionnaire of quality assessment in seasonality papers

Q1. Were subjects included representative of the population in the study site?	
A. Yes. Very good representativeness.	Subjects were all ages, without underlying medical conditions.
B. Yes. Good representativeness.	Subjects were not all ages, without underlying medical conditions.
C. Yes. Likely to be representative with regard to seasonality of viruses	Subjects were from very narrow age bands (e.g. neonatal), without underlying medical conditions.
D. No. Unlikely to be representative. (Should be excluded)	Subjects with underlying medical conditions.
Q2. Did the test method(s) and practice remain stable throughout study period?	
A. Yes. Very stable.	One or two test methods with stable test practice throughout study period.
B. Yes. Stable.	>2 test methods with stable test practice throughout study period.
C. No, but changes were unlikely to affect seasonality results.	>2 test methods with changes of test practice but should not affect seasonality results.
D. No. Changes were unlikely to affect seasonality results. (Should be excluded)	Changes of test methods or practice related to known seasonality.
Q3. What was the quality of the timings of positive test results reported?	
A. Very good.	Timings of positive tests were reported as the date when specimens were taken (often found in prospective studies).
B. Good.	Timings of positive tests were taken from related diagnosis (often found in hospital databases).
C. Fair.	Timings of positive tests were reported as the date when specimens were received in labs (can be found in laboratory databases).
D. Bad. (Should be excluded)	Timings of positive tests could be significantly inaccurate and could affect seasonality results.

A6. Technical details of the seasonality model

Model assumption

The model assumption is that, for each month of each site, the relative strength of viral activity (i.e. annual average percentage, AAP) is associated with the relative measurements of meteorological factors. For example, if the temperature of a month in a site is 10˚C lower than the site's annual average temperature, in other words, the mean-centred temperature of this month is –10˚C, then the viral activity of this month is likely to be higher compared to other months of the year. Of note, I allow the relationship between relative viral activity and relative measurements of meteorological factors to be non-linear by using local regression (LOESS).

Data preparation

For each site included in our study, I extracted meteorological data from the nearest weather station provided by the US National Centers for Environmental Information using R package "GSODR". The meteorological data I extracted included daily temperature, relative humidity, absolute humidity (calculated from temperature and relative humidity) and wind speed. In each site, I calculated the monthly average temperature, relative humidity, absolute humidity and wind speed during the period matched with the range of dates of the virus data. If no meteorological data were available to match with date of the virus data, other nearest years were included alternatively. I then calculated the mean-centred temperature, relative humidity, absolute humidity and wind speed by subtracting the annual average value from the monthly average value for inclusion in the model. Additionally, I included the duration of daytime in hours of each site, calculated using R package "suncalc".

Model comparison and selection

I modelled the monthly AAP by LOESS using candidate variables including mean-centred temperature, mean-centred relative humidity, mean-centred absolute humidity, mean-centred wind speed and duration of daytime. I required a minimum of 120 sites with ≥100 positives per virus for more robust

models. As such, I was able to model monthly activity of IFV and RSV only. The candidate models include all combinations of up to two candidate variables. I focused the model on the prediction of epidemic months (i.e. a dichotomous result, epidemic or non-epidemic). In the prediction model, I allow the threshold of determining an epidemic month to change (different from a fixed threshold of 75% in our observed data). Therefore, I was able to compare the models by their area under the Receiver Operating Characteristic curve (AUROC) in predicting the epidemic months, via leave-one-out cross validation.

The model comparison was done via a two-step process. At the first step, I explored a range of the parameter spans in LOESS from 0.05 to 0.95 within each candidate model and identified the optimum span that maximised the AUROC for that model. Then, as the second step, I compared the AUROCs across the candidate models with their optimum span parameters. The results showed that the model “Temperature + Relative Humidity” had higher AUROCs than the other candidate models (detailed results in the table on next page). Therefore, I chose the model “Temperature + Relative Humidity” in the main analysis.

Table Results of model comparison through leave-one-out cross validation

Candidate model (predictors)	IFV		IFV A		IFV B		IFV A(H1N1)pdm		IFV A(H3N2)		RSV	
	Span	AUROC	Span	AUROC	Span	AUROC	Span	AUROC	Span	AUROC	Span	AUROC
Temperature	0.25	**0.7363**	0.30	0.7419	0.45	0.7406	0.50	0.7531	0.30	0.7262	0.30	0.7501
Relative Humidity	0.90	0.5851	0.75	0.6022	0.25	0.5722	0.45	0.5624	0.60	0.6345	0.55	0.6751
Absolute Humidity	0.55	0.6640	0.90	0.6584	0.55	0.6867	0.65	0.7151	0.75	0.6065	0.50	0.6449
Hours of daytime	0.15	0.6880	0.20	0.6805	0.30	0.6944	0.35	0.7008	0.25	0.6980	0.10	0.7704
Wind Speed	0.10	0.5338	0.25	0.5151	0.60	0.5181	0.20	0.5365	0.10	0.5589	0.50	0.6205
Temperature + Relative Humidity	0.70	**0.7442**	0.60	**0.7468**	0.50	**0.7604**	0.40	**0.7769**	0.75	**0.7319**	0.30	**0.8023**
Temperature + Absolute Humidity	0.30	**0.7503**	0.55	**0.7493**	0.25	**0.7530**	0.30	0.7617	0.55	**0.7485**	0.20	**0.8038**
Temperature + Hours of daytime	0.95	0.7332	0.70	**0.7439**	0.20	**0.7780**	0.30	**0.7719**	0.10	**0.7371**	0.05	0.7677
Temperature + Wind Speed	0.60	0.7315	0.95	0.7305	0.75	0.7352	0.95	0.7556	0.85	0.7221	0.30	0.7871
Relative Humidity + Wind Speed	0.95	0.5757	0.95	0.6011	0.05	0.5456	0.90	0.5740	0.25	0.6274	0.25	0.6743
Relative Humidity + Hours of daytime	0.50	0.6931	0.35	0.7004	0.10	0.6837	0.45	0.7280	0.75	0.7131	0.55	**0.7992**
Absolute Humidity + Wind Speed	0.30	0.6661	0.95	0.6614	0.50	0.6814	0.10	0.6905	0.95	0.6259	0.15	0.7019
Absolute Humidity + Hours of daytime	0.05	0.6990	0.05	0.7017	0.05	0.7057	0.05	0.7392	0.10	0.7081	0.05	0.7846
Absolute Humidity + Relative Humidity	0.30	0.7136	0.30	0.7203	0.30	0.7343	0.30	**0.7632**	0.20	0.7039	0.60	0.7715
Wind Speed + Hours of daytime	0.15	0.6746	0.30	0.6770	0.90	0.6775	0.90	0.7087	0.15	0.6853	0.40	0.7834

AUROC = area under the receiver operating characteristic curve. For each virus, the three highest AUROCs are highlighted **in bold**.

After I determined the model, I identified the optimal threshold for determining the epidemic months for each virus. This was done by finding the threshold that maximised the Cohen's kappa. The Receiver Operating Characteristic (ROC) curves for all the viruses are attached in the figure below. The optimal threshold was 55% for IFV, IFV A, and RSV, and was 60% for IFV B, IFV A(H1N1)pdm, and IFV A(H3N2).

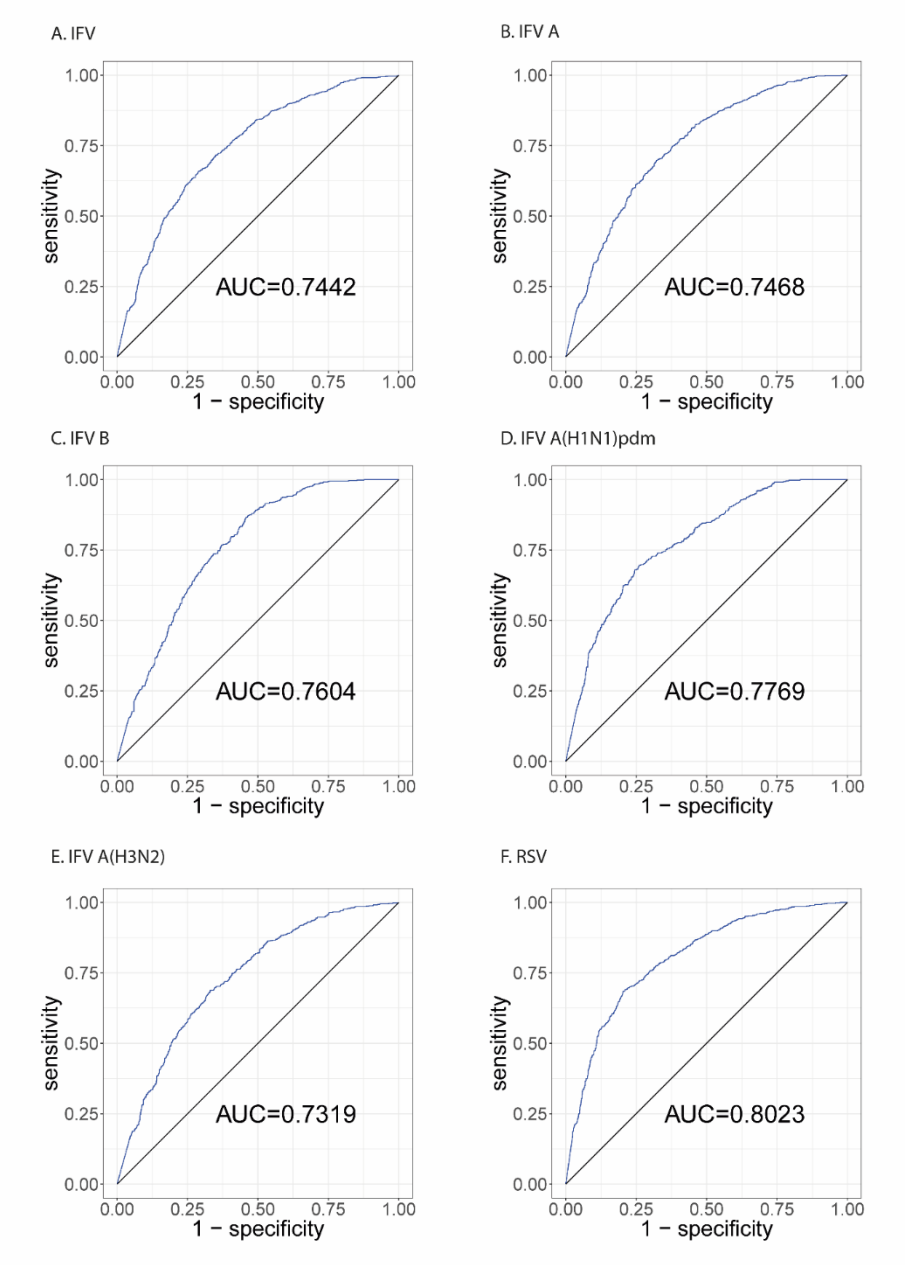


Figure ROC curves of the prediction models

Model assessment

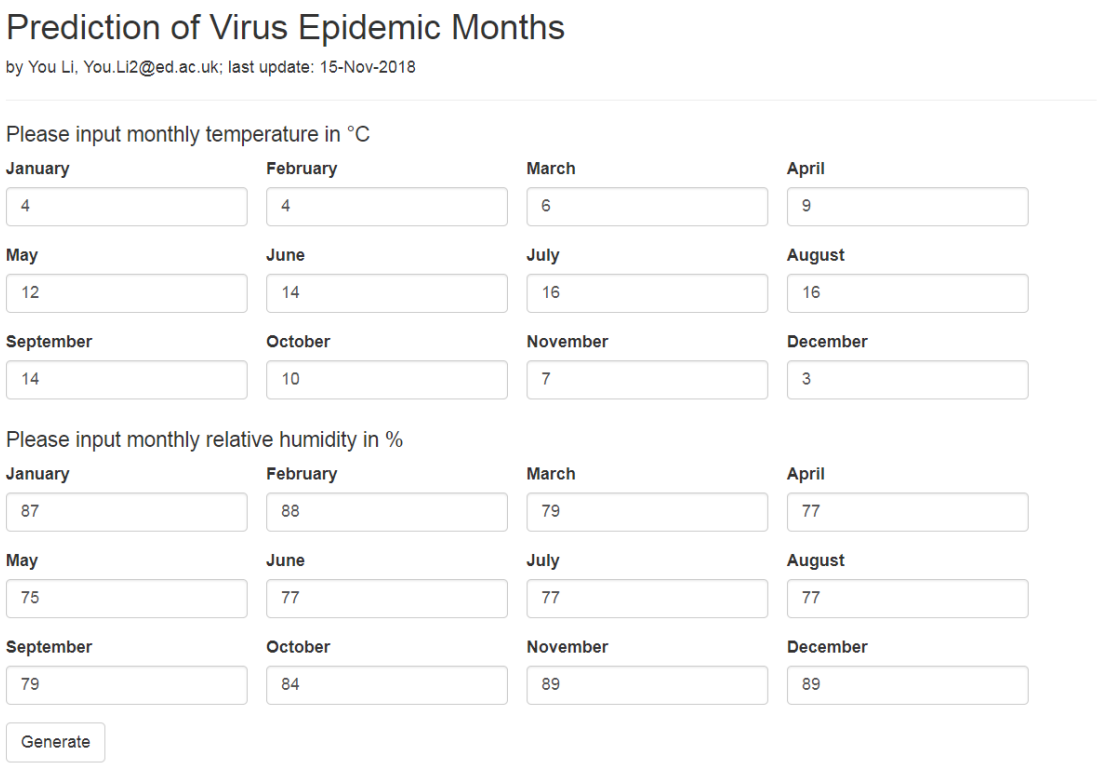
I assessed the model performance by quantifying the degree of agreement in determining the epidemic months between observation and prediction of each site, by the leave-one-out method. I calculated Cohen's kappa, sensitivity, specificity, positive predictive value and negative predictive value. Moreover, according to the observed and predicted epidemic months, I calculated the prediction error in the onset month of epidemics and its 95% confidence interval.

A7. The user manual of the seasonality prediction tool

Based on the prediction model, I developed an interactive tool for the local prediction of IFV and RSV epidemics. The tool is freely available in http://resceu.ecdf.ed.ac.uk/shiny/ShinyPred/. To use this tool, simply follow the step-by-step instructions below:

Prerequisite: make sure that you have monthly temperature and relative humidity data available for the site you would like to estimate for.

- Step 1: Go to http://resceu.ecdf.ed.ac.uk/shiny/ShinyPred/.
- Step 2: Input your temperature and relative humidity data in the corresponding cells. Make sure no cells are left blank.
- Step 3: Click “Generate” (may take a few seconds)



Interface of the data input

- Step 4: View results. Select the virus from the left panel. For each virus, the result is available in both figure and table.

- Step 5 (optional): Save results. To save a figure, right click the figure and select “Save image as”. To save a table, select the preferred format by clicking the corresponding button.

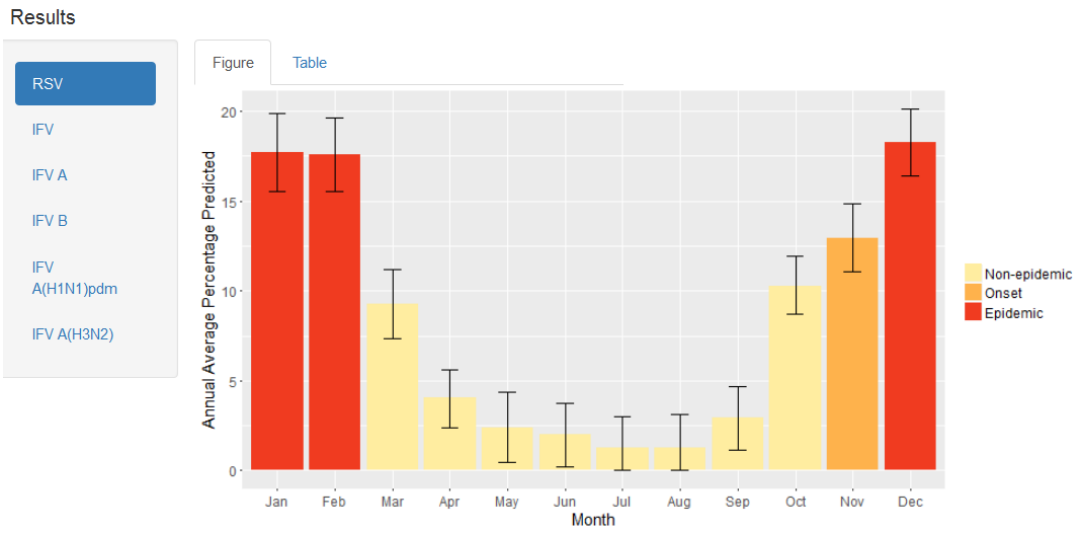
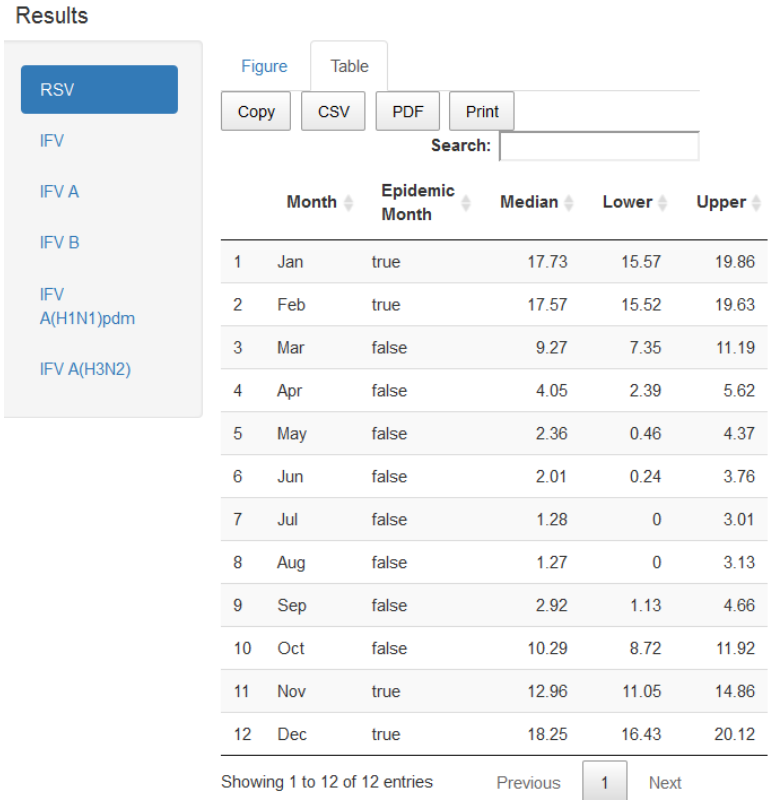


Figure output

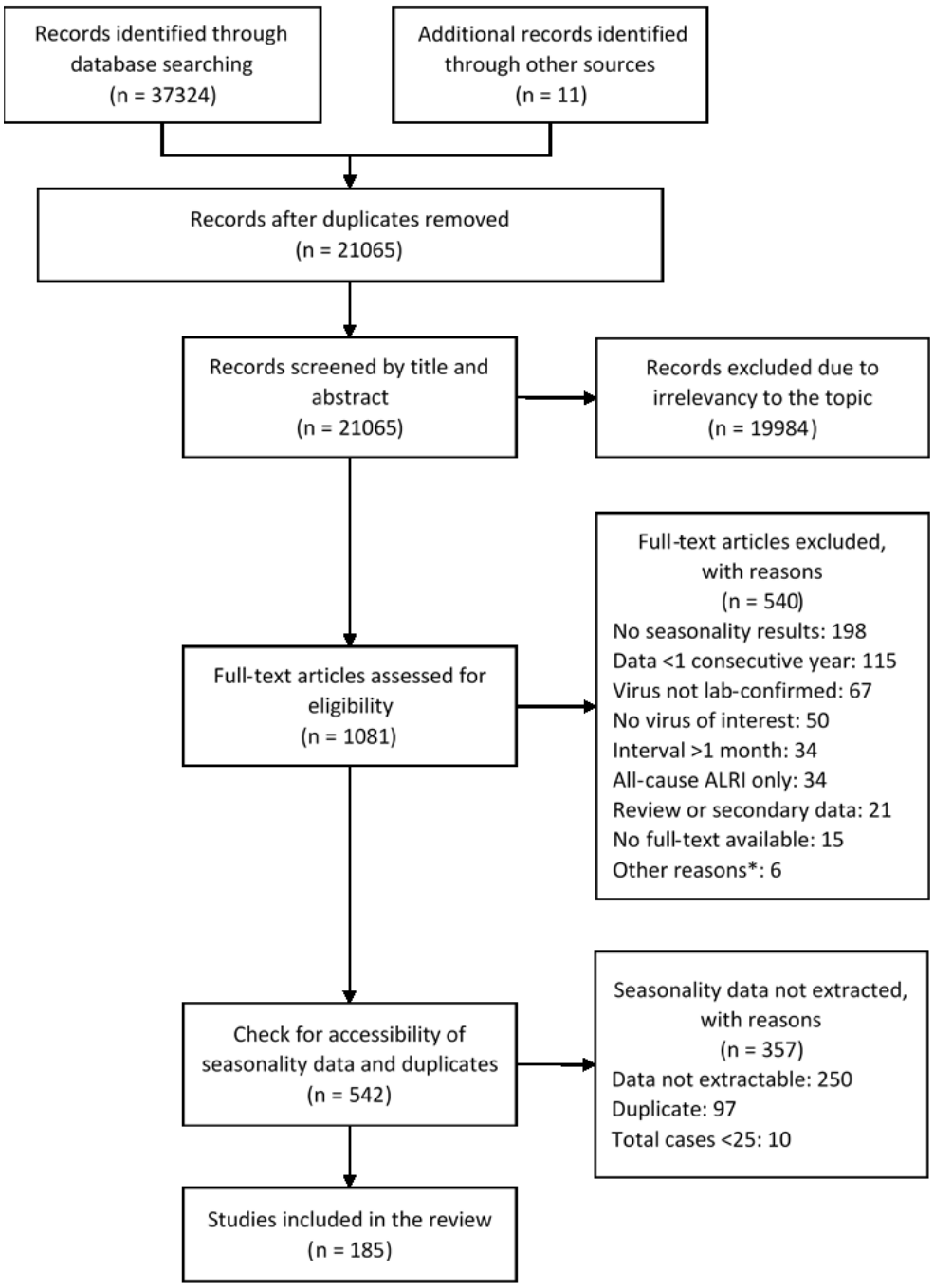


	Month	Epidemic Month	Median	Lower	Upper
1	Jan	true	17.73	15.57	19.86
2	Feb	true	17.57	15.52	19.63
3	Mar	false	9.27	7.35	11.19
4	Apr	false	4.05	2.39	5.62
5	May	false	2.36	0.46	4.37
6	Jun	false	2.01	0.24	3.76
7	Jul	false	1.28	0	3.01
8	Aug	false	1.27	0	3.13
9	Sep	false	2.92	1.13	4.66
10	Oct	false	10.29	8.72	11.92
11	Nov	true	12.96	11.05	14.86
12	Dec	true	18.25	16.43	20.12

Table output

A8. Details of the included studies from systematic literature review of viral seasonality

PRISMA flow chart



*Other reasons include military setting, special medical condition and no stable sampling practice; these studies were excluded by quality assessment.

Description of studies included from literature, by site latitude

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Brittain-Long, 2012 [1]	Gothenburg	Sweden	12, 57.7	respiratory symptoms	PCR	✓	✓	✓	✓
Balmaks, 2014 [2]	Riga	Latvia	24.1, 56.9	ALRI	PCR		✓		
Koetz, 2006 [3]	Halmstad and Halland County	Sweden	12.8, 56.8	ARI	PCR		✓		
McCormick, 2002 [4]	Belfast	UK	-5.9, 54.6	NK	NK		✓		
Weigl, 2002 [5]	Kiel	Germany	10.1, 54.3	ARI	EIA or PCR		✓		
Robinson, 2005 [6]	Edmonton	Canada	-113.5, 53.5	NK	PCR		✓		✓
Aberle, 2010 [7]	Vienna	Austria	-7.8, 53.3	ARI	PCR				✓
Aberle, 2008 [8]	Vienna	Austria	-7.8, 53.3	ARI	PCR		✓		
Reeves, 2017 [9]	England	UK	-1.2, 52.4	respiratory symptoms	multiple tests	✓	✓	✓	✓
Ramaekers, 2017 [10]	Leuven	Belgium	4.7, 50.9	ARI	PCR	✓	✓	✓	✓
Annan, 2016 [11]	Bonn	Germany	7.1, 50.7	ARI	PCR			✓	
Armengaud, 2007 [12]	Paris	France	2.4, 48.9	ARI	IFA		✓		
Visseaux, 2017 [13]	Paris	France	2.4, 48.9	ILI + pneumonia	PCR	✓		✓	✓
Terletskaia-Ladwig, 2005 [14]	Stuttgart	Germany	9.2, 48.8	suspected RSV	ELISA or PCR		✓		
Berner, 2001 [15]	Freiburg	Germany	7.8, 48	ARI	antigen test		✓		
Heininger, 2009 [16]	Basel	Switzerland	7.6, 47.6	ARI	PCR		✓		✓
Resch, 2000 [17]	Graz	Austria	15.4, 47.1	ARI	IF		✓		

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Sadeghi, 2011 [18]	Bern	Switzerland	7.4, 46.9	respiratory diseases	DFA			✓	✓
Muhlemann, 2006 [19]	Bern	Switzerland	7.4, 46.9	ARI	DFA		✓		
Ljubin-Sternak, 2014 [20]	Zagreb	Croatia	16, 45.8	ARI	DFA				✓
Mlinaric-Galinovic, 2008 [21]	Zagreb	Croatia	16, 45.8	ARI	culture		✓		
Guo, 2014 [22]	Karamay	China	84.9, 45.6	ILI	PCR	✓			
Al-Assam, 2009 [23]	Nova Scotia	Canada	-63.7, 44.7	NK	NK		✓		
Foulongne, 2006 [24]	Montpellier	France	3.9, 43.6	respiratory diseases	DFA and viral culture		✓		✓
Shi, 2014 [25]	Fuxin	China	121.7, 42	ILI	HAI	✓			
Sun, 2013 [26]	Liaoning	China	122.5, 41.9	ILI	HAI	✓			
Alonso, 2007 [27]	Sacyl	Spain	-4.7, 41.7	bronchiolitis	IF		✓		
Godoy, 2016 [28]	Catalonia	Spain	1.5, 41.6	NK	DFA			✓	
Esper, 2004 [29]	New Haven, Connecticut	USA	-72.9, 41.3	NK	DFA				✓
Goktas, 2016 [30]	Istanbul	Turkey	29, 41	ARI	PCR	✓	✓	✓	✓
Calvo, 2010 [31]	Leganés	Spain	-3.8, 40.3	bronchiolitis	PCR		✓		
Wu, 2016 [32]	Beijing	China	116.4, 39.9	ARI	PCR			✓	
Liu, 2013 [33]	Beijing	China	116.4, 39.9	ALRI	PCR	✓			
Williams, 2010 [34]	Davidson and Monroe County	USA	-82.3, 39.7	ARI or fever	PCR				✓

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Iwane, 2004 [35]	Davidson and Monroe County	USA	-82.3, 39.7	ARI	PCR or culture		✓	✓	
Hervas, 2012 [36]	Mallorca	Spain	2.7, 39.6	bronchiolitis	ELISA		✓		
Bayrakdar, 2016 [37]	nationwide	Turkey	35.2, 39	respiratory diseases	PCR				✓
Jain, 2015 [38]	Chicago and Nashville	USA	-87.2, 39	pneumonia	PCR	✓	✓		✓
Jain, 2015 [39]	Chicago and Nashville	USA	-87.2, 39	pneumonia	PCR			✓	
Kanra, 2005 [40]	nationwide	Turkey	35.2, 39	respiratory symptoms	EIA		✓		
Saha, 2016 [41]	Northern China	China	111.1, 38.6	ILI or SARI	PCR or culture	✓			
Mizuta, 2013 [42]	Yamagata	Japan	140.4, 38.2	ARI	HAI		✓	✓	✓
Sirimi, 2016 [43]	Athens	Greece	23.7, 38	NK	IF		✓		
Sato, 2005 [44]	Niigata City	Japan	139, 37.9	respiratory symptoms	PCR		✓		
Kang, 2013 [45]	Seoul	Republic of Korea	127, 37.6	NK	PCR		✓		✓
Kim, 2006 [46]	Seoul	Republic of Korea	127, 37.6	NK	IFA	✓		✓	
Huang, 2013 [47]	Lanzhou	China	103.8, 36.1	ARI	PCR			✓	
Jin, 2012 [48]	Lanzhou	China	103.8, 36.1	ALRI	PCR	✓	✓		✓
Nakamura, 2013 [49]	Fukui	Japan	136.2, 36.1	ARI	PCR				✓
Feng, 2014 [50]	nationwide	China	104.2, 35.9	ALRI	NA			✓	✓
Liu, 2016 [51]	Shandong	China	117.9, 35.9	ILI	PCR	✓			
Wilfret, 2008 [52]	North Carolina	USA	-79, 35.8	NK	DFA, EIA or culture		✓		

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Fodha, 2004 [53]	Sousse	Tunisia	10.6, 35.8	ALRI	DFA and PCR		✓		
Hamada, 2014 [54]	Tokyo	Japan	139.7, 35.7	ALRI	PCR		✓	✓	✓
Aziz, 2015 [55]	Sulaimani	Iraq	45.4, 35.6	ARI	DFA or PCR				✓
Saikusa, 2005 [56]	Yokohama	Japan	139.6, 35.4	ARI	PCR or culture	✓	✓		
Jeong, 2010 [57]	Busan	Republic of Korea	129.1, 35.2	ARI	PCR		✓		
Richter, 2016 [58]	Nicosia	Cyprus	33.4, 35.2	ARI	PCR	✓	✓		
Yoshioka, 2012 [59]	Kyoto	Japan	135.8, 35	ARI	PCR				✓
Kaneko, 2002 [60]	Shizuoka	Japan	138.4, 35	ALRI	ELFA or EIA		✓		
Kaida, 2006 [61]	Osaka	Japan	135.5, 34.7	ARI	PCR		✓		✓
Zhang, 2016 [62]	Xi'an	China	108.9, 34.3	ARI	PCR		✓		
Yang, 2012 [63]	Xuzhou	China	117.3, 34.2	ILI	NK	✓			
Chadha, 2015 [64]	Srinagar	India	74.8, 34.1	ILI or SARI	PCR	✓			
Finianos, 2016 [65]	Beirut	Lebanon	35.5, 33.9	ARI	PCR		✓		
Onozuka, 2015 [66]	Fukuoka	Japan	130.4, 33.6	respiratory illness	antigen test or PCR		✓		
Yin, 2017 [67]	Bengbu	China	117.4, 32.9	ARI	DFA		✓	✓	
Ayora-Talavera, 2017 [68]	Baja California Norte	Mexico	-115.3, 32.4	ILI + SARI	PCR	✓			
Bdour, 2001 [69]	Zarqa	Jordan	36.1, 32.1	ALRI	DFA		✓		
Bimouhen, 2016 [70]	nationwide	Morocco	-7.1, 31.8	ILI or SARI	PCR		✓		

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Feng, 2014 [71]	Beijing, Shanghai, Chongqing, Guangdong, Gansu and Sichuan	China	110.9, 31.7	pneumonia	PCR		✓	✓	
Zhao, 2012 [72]	Ma'anshan	China	118.5, 31.7	ILI	PCR	✓			
Ji, 2009 [73]	Suzhou	China	120.6, 31.3	ARI	PCR	✓			
Lu, 2015 [74]	Suzhou	China	120.6, 31.3	ALRI	PCR		✓		
Wan, 2009 [75]	Suzhou	China	120.6, 31.3	ARI	DFA			✓	✓
Fu, 2015 [76]	Shanghai	China	121.5, 31.2	ILI	PCR			✓	
Wang, 2016 [77]	Dazhou	China	107.5, 31.2	ILI	PCR	✓			
Zhao, 2013 [78]	Shanghai	China	121.5, 31.2	respiratory symptoms	PCR		✓		
Zhou, 2014 [79]	Shanghai	China	121.5, 31.2	ILI	PCR	✓			
Chen, 2016 [80]	Shanghai	China	121.5, 31	ILI	PCR	✓			
Refaey, 2016 [81]	Damanhour district	Egypt	30.5, 31	SARI	PCR	✓			
Kong, 2016 [82]	Wuhan	China	114.3, 30.6	ILI	PCR				✓
Horton, 2017 [83]	nationwide	Jordan	36.2, 30.6	SARI	PCR		✓	✓	✓
Huo, 2013 [84]	Jingzhou	China	112.2, 30.3	SARI	PCR		✓		
Tang, 2008 [85]	Hangzhou	China	120.2, 30.3	ALRI	DFA	✓	✓	✓	
Yang, 2011 [86]	Sichuan	China	102.8, 30.3	ILI	HAI	✓			
Zheng, 2016 [87]	Jingzhou	China	112.2, 30.3	SARI	PCR	✓			
Chen, 2010 [88]	Chongqing	China	106.9, 29.4	ALRI	PCR				✓
Qi, 2016 [89]	Chongqing	China	106.9, 29.4	ILI	PCR	✓			

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Zhang, 2010 [90]	Chongqing	China	106.9, 29.4	ARI	PCR		✓		
Khadadah, 2010 [91]	nationwide	Kwait	47.5, 29.3	ALRI	PCR		✓		
Yu, 2012 [92]	Zhejiang	China	119.8, 29.1	ILI	PCR	✓			
Ayora-Talavera, 2017 [68]	Sonora	Mexico	-110.6, 29.1	ILI + SARI	PCR	✓			
Binod, 2012 [93]	Delhi	India	77.1, 28.7	ILI	PCR	✓			
Chadha, 2012 [94]	Delhi	India	77.1, 28.7	ILI or SARI	HAI	✓			
Chadha, 2015 [64]	Delhi	India	77.1, 28.7	ILI or SARI	PCR	✓			
Cui, 2016 [95]	Eastern China	China	116.4, 28.7	ALRI	PCR		✓		
Liu, 2015 [96]	Nanchang	China	115.9, 28.7	ILI	PCR	✓			
Bharaj, 2009 [97]	Delhi	India	77.1, 28.7	ALRI	PCR		✓		
Ayora-Talavera, 2017 [68]	Chihuahua	Mexico	-106, 28.4	ILI + SARI	PCR	✓			
Chen, 2014 [98]	Changsha	China	112.9, 28.2	ILI	HAI	✓			
Xiao, 2013 [99]	Changsha	China	112.9, 28.2	ALRI	PCR				✓
Artiles-Campelo, 2006 [100]	Gran Canaria	Spain	-15.4, 28.1	ARI	RADT	✓	✓	✓	
Fergie, 2007 [101]	Corpus Christi, Texas	USA	-97.4, 27.8	NK	RADT		✓		
Light, 2008 [102]	Florida	USA	-81.5, 27.7	NK	RADT, PCR or culture		✓		
Mathisen, 2011 [103]	Kathmandu	Nepal	85.3, 27.7	severe pneumonia	PCR	✓	✓	✓	
Saha, 2016 [41]	Southern China	China	112.5, 27.6	ILI or SARI	PCR or culture	✓			
Chadha, 2015 [64]	Dibrugarh	India	94.9, 27.5	ILI or SARI	PCR	✓			

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Chu, 2016 [104]	Sarlahi	Nepal	85.6, 27	ARI	PCR		✓		
Swamy, 2017 [105]	Jaipur	India	75.8, 26.9	ARI	PCR		✓		
Chadha, 2015 [64]	Lucknow	India	80.9, 26.8	ILI or SARI	PCR	✓			
Dangi, 2014 [106]	Lucknow	India	80.9, 26.8	ILI or SARI	PCR	✓			
Jain, 2014 [107]	Lucknow	India	80.9, 26.8	SARI	PCR		✓		
Horton, 2017 [83]	nationwide	Egypt	30.8, 26.8	SARI	PCR		✓	✓	✓
Wu, 2010 [108]	Nanping	China	118.2, 26.6	ILI	HAI	✓			
Iha, 2016 [109]	Okinawa	Japan	127.7, 26.2	ILI	RADT	✓			
Light, 2007 [110]	Miami	USA	-80.2, 25.8	bronchiolitis	RADT		✓		
Ayora-Talavera, 2017 [68]	Nuevo Leon	Mexico	-100.2, 25.4	ILI + SARI	PCR	✓			
Wahab, 2001 [111]	Doha	Qatar	51.5, 25.3	NK	RADT		✓		
Ayora-Talavera, 2017 [68]	Coahuila De Zaragoza	Mexico	-100.6, 25.3	ILI + SARI	PCR	✓			
Hsieh, 2010 [112]	Taipei	China	121.6, 25	respiratory diseases	RADT or culture			✓	
Li, 2011 [113]	Quanzhou	China	118.7, 24.9	ILI	PCR	✓			
Wu, 2012 [114]	Kunming	China	102.8, 24.9	ALRI	DFA		✓	✓	
Asad, 2017 [115]	Karachi	Pakistan	67, 24.9	ARI	PCR		✓		
Qiu, 2014 [116]	Shaoguan	China	113.6, 24.8	ILI	PCR	✓			
Akhter, 2009 [117]	Riyadh	Saudi Arabia	46.7, 24.7	ILI or SARI	IF	✓	✓	✓	
Lee, 2007 [118]	Northern Taiwan	China	121.8, 24.7	NK	RADT		✓		
Luo, 2012 [119]	Yunnan	China	101.3, 24.5	ILI	NK	✓			

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Ayora-Talavera, 2017 [68]	Sinaloa	Mexico	-107.2, 24.5	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Baja California Sur	Mexico	-110.2, 24.1	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Durango	Mexico	-104.4, 24	ILI + SARI	PCR	✓			
Chen, 2014 [120]	Qingyuan	China	113.1, 23.7	ILI	PCR	✓			
Hsieh, 2016 [121]	Taiwan	China	121, 23.7	ILI	NK	✓			
Cui, 2015 [122]	Shantou	China	116.7, 23.4	respiratory symptoms	PCR	✓	✓	✓	
Huang, 2001 [123]	Guangdong	China	113.8, 23.4	ILI	culture	✓			
Ni, 2009 [124]	Honghe	China	103.4, 23.4	ILI	HAI	✓			
Ayora-Talavera, 2017 [68]	Tamaulipas	Mexico	-99.1, 23.4	ILI + SARI	PCR	✓			
Fang, 2013 [125]	Huizhou	China	114.4, 23.1	ARI	PCR	✓			
Guan, 2015 [126]	Guangzhou	China	113.3, 23.1	ALRI	PCR	✓			
Li, 2008 [127]	Guangzhou	China	113.3, 23.1	ILI	HAI	✓			
Liu, 2011 [128]	Dongguang	China	113.8, 23	ILI	culture	✓			
Agrawal, 2009 [129]	Kolkata	India	88.4, 22.6	ARI	PCR	✓	✓		
Chadha, 2012 [94]	Kolkata	India	88.4, 22.6	ILI or SARI	HAI	✓			
Chadha, 2015 [64]	Kolkata	India	88.4, 22.6	ILI or SARI	PCR	✓			
Chen, 2006 [130]	Shenzhen	China	114.1, 22.5	ILI	HAI	✓			
He, 2014 [131]	Shenzhen	China	114.1, 22.5	ARI	PCR		✓	✓	✓
Qin, 2015 [132]	Shenzhen	China	114.1, 22.5	ILI	HAI	✓			

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Wu, 2011 [133]	Shenzhen	China	114.1, 22.5	ILI	HAI	✓			
Ye, 2013 [134]	Shenzhen	China	114.1, 22.5	ILI	HAI	✓			
Ayora-Talavera, 2017 [68]	Zacatecas	Mexico	-102.3, 22.5	ILI + SARI	PCR	✓			
Noyola, 2005 [135]	San Luis Potosí	Mexico	-101, 22.2	ARI	DFA or PCR				✓
Ayora-Talavera, 2017 [68]	San Luis Potosí	Mexico	-101, 22.2	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Aguascalientes	Mexico	-102.2, 21.5	ILI + SARI	PCR	✓			
Horton, 2017 [83]	nationwide	Oman	56, 21.5	SARI	PCR		✓	✓	✓
Ayora-Talavera, 2017 [68]	Nayarit	Mexico	-104.5, 21.3	ILI + SARI	PCR	✓			
Chadha, 2015 [64]	Nagpur	India	79.1, 21.1	ILI or SARI	PCR	✓			
Nguyen, 2007 [136]	Hanoi	Vietnam	105.8, 21	ILI	HAI	✓			
Ayora-Talavera, 2017 [68]	Guanajuato	Mexico	-101.2, 21	ILI + SARI	PCR	✓			
Gamino-Arroyo, 2017 [137]	Mexico City and San Luis Potosí	Mexico	-100.1, 20.8	ILI	PCR		✓		
Ayora-Talavera, 2017 [68]	Yucatan	Mexico	-89.4, 20.6	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Jalisco	Mexico	-103.2, 20.4	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Queretaro de Arteaga	Mexico	-100.2, 20.4	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Hidalgo	Mexico	-98.4, 20.1	ILI + SARI	PCR	✓			

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Saha, 2016 [41]	nationwide	Lao PDR	102.5, 19.9	ILI or SARI	PCR or culture	✓			
Li, 2005 [138]	Hainan	China	109.9, 19.6	ILI	HAI	✓			
Hu, 2014 [139]	Danzhou	China	109.6, 19.5	ILI	PCR	✓			
Ayora-Talavera, 2017 [68]	Campeche	Mexico	-90.3, 19.5	ILI + SARI	PCR	✓			
Yusuf, 2007 [140]	Mexico City	Mexico	-99.1, 19.4	NK	RADT		✓		
Ayora-Talavera, 2017 [68]	Michoacan de Ocampo	Mexico	-101.1, 19.4	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Distrito Federal	Mexico	-99.1, 19.3	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Mexico	Mexico	-99.4, 19.2	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Tlaxcala	Mexico	-98.1, 19.2	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Colima	Mexico	-103.4, 19.1	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Veracruz-Llave	Mexico	-96.1, 19.1	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Puebla	Mexico	-98.1, 19	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Morelos	Mexico	-99.1, 18.6	ILI + SARI	PCR	✓			
Chadha, 2012 [94]	Pune	India	73.9, 18.5	ILI or SARI	HAI	✓			
Chadha, 2015 [64]	Pune	India	73.9, 18.5	ILI or SARI	PCR	✓			
Choudhary, 2013 [141]	Pune	India	73.9, 18.5	ILI or SARI	PCR		✓		

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Matias, 2015 [142]	San Juan	Puerto Rico	-66.1, 18.5	bronchiolitis	RADT		✓		
Ayora-Talavera, 2017 [68]	Quintana Roo	Mexico	-88.2, 18.3	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Tabasco	Mexico	-92.6, 17.6	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Guerrero	Mexico	-99.3, 17.3	ILI + SARI	PCR	✓			
Ayora-Talavera, 2017 [68]	Oaxaca	Mexico	-96.4, 17	ILI + SARI	PCR	✓			
Hasegawa, 2006 [143]	Yangon	Myanmar	96.2, 16.9	ILI	RADT or culture	✓			
Ayora-Talavera, 2017 [68]	Chiapas	Mexico	-93.1, 16.4	ILI + SARI	PCR	✓			
Diene Sarr, 2015 [144,145]	Ndiop	Senegal	-16.3, 15.9	Fever	PCR	✓			
Horton, 2017 [83]	nationwide	Yemen	48.5, 15.6	SARI	PCR	✓	✓	✓	
Dosseh, 2000 [146]	Dakar	Senegal	-17.5, 14.7	ILI	HAI or culture	✓			
Schlaudecker, 2012 [147]	Santa Lucía	Honduras	-87.1, 14.1	ILI	PCR	✓	✓	✓	✓
Diene Sarr, 2015 [144,145]	Dielmo	Senegal	-16.4, 13.7	Fever	PCR	✓			
van der Sande, 2004 [148]	Banjul	Gambia	-16.6, 13.5	ARI	IF		✓		
Timmermans, 2016 [149]	Battambang, Oddar Meanchey, Pailin and Banteay Meanchey	Cambodia	103, 13.4	ILI	PCR	✓			

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Chadha, 2012 [94]	Chennai	India	80.3, 13.1	ILI or SARI	HAI	✓			
Chadha, 2015 [64]	Chennai	India	80.3, 13.1	ILI or SARI	PCR	✓			
Chadha, 2015 [64]	Vellore	India	79.1, 12.9	ILI or SARI	PCR	✓			
Ouedraogo, 2014 [150]	Ouagadougou	Burkina Faso	-1.5, 12.4	ARI	DFA		✓		
Do, 2016 [151]	Ho Chi Minh City	Vietnam	106.6, 10.8	ALRI	PCR		✓	✓	
Chadha, 2015 [64]	Alapphuzha	India	76.3, 9.5	ILI or SARI	PCR	✓			
Njouom, 2012 [152]	nationwide	Cameroon	12.4, 7.4	ILI	PCR		✓	✓	✓
Perera, 2010 [153]	Ragama	Sri Lanka	79.9, 7	AURI	PCR	✓			
Annan, 2016 [11]	Kumasi	Ghana	-1.6, 6.7	ARI	PCR			✓	
Robertson, 2004 [154]	Eleta and Ijaye	Nigeria	3.4, 6.6	ALRI	ELISA		✓		
Shapiro, 2017 [155]	Galle	Sri Lanka	80.2, 6.1	ILI	PCR	✓			
Akoua-Koffi, 2007 [156]	Abidjan	Côte d'Ivoire	-4, 5.4	respiratory symptoms	ELISA	✓			
Rodriguez-Martinez, 2015 [157]	Bogota	Colombia	-74.1, 4.7	ALRI	RADT		✓		
Kenmoe, 2016 [158]	Yaoundé	Cameroon	11.5, 3.8	respiratory symptoms	PCR		✓		
Monamele, 2017 [159]	Yaoundé	Cameroon	11.5, 3.8	ILI + SARI	PCR	✓			
Khor, 2012 [160]	Kuala Lumpur	Malaysia	101.7, 3.1	ARI	IF or culture	✓	✓	✓	
Nyoka, 2017 [161]	Dadaab	Kenya	40.3, 0.1	ILI + SARI	NK		✓		
Jonnalagadda, 2017 [162]	Quito	Ecuador	-78.5, -0.2	severe pneumonia	PCR		✓	✓	✓
Alonso, 2012 [163]	Fortaleza	Brazil	-38.5, -3.7	ARI	IFA		✓		

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Alonso, 2007 [164]	North Brazil	Brazil	-65.9, -4.4	ILI	NK	✓			
Fe, 2008 [165]	Ceará	Brazil	-39.3, -5.5	ARI	IF			✓	
Robertson, 2004 [154]	Cikutra and Ujung Berung, Bandung	Indonesia	107.7, -6.9	ALRI	ELISA		✓		
Yamaoka, 2011 [166]	Surabaya	Indonesia	112.8, -7.3	ILI	PCR	✓			
Budge, 2014 [167]	San Marcos province	Peru	-78.2, -7.3	ARI	PCR	✓	✓	✓	✓
Fagan, 2017 [168]	the Top End	Australia	130.8, -12.5	NK	PCR		✓		
Bouzas, 2016 [169]	Salvador	Brazil	-38.5, -13	ARI	PCR		✓		
Hogan, 2016 [170]	Kimberley, Western Australia	Australia	125.9, -17.3	ALRI	multiple tests		✓		
Costa, 2006 [171]	Uberlândia	Brazil	-48.3, -18.9	ARI	IF or PCR	✓	✓		
Checon, 2002 [172]	Vitória	Brazil	-40.3, -20.3	ARI	IFA		✓		
Salomao Junior, 2011 [173]	São José do Rio Preto	Brazil	-49.4, -20.8	ALRI	PCR		✓		
Brottet, 2016 [174]	Réunion Island	France	55.5, -21.1	ILI	PCR	✓			
Sapin, 2001 [175]	Réunion Island	France	55.5, -21.1	ARI	DFA		✓		
Hogan, 2016 [170]	Pilbara, Western Australia	Australia	121.5, -21.6	ALRI	multiple tests		✓		
Alonso, 2007 [164]	Southeast Brazil	Brazil	-43.2, -21.7	ILI	NK	✓			
Bellei, 2008 [176]	São Paulo	Brazil	-46.6, -23.6	ILI or ARI	DFA, culture or PCR	✓			
Pecchini, 2015 [177]	São Paulo	Brazil	-46.6, -23.6	ARI	IF		✓	✓	
Thomazelli, 2007 [178]	São Paulo	Brazil	-46.6, -23.6	ALRI	PCR				✓

Study	Site Name	Country	LON, LAT	Case Definition	Methods of Tests	Virus Included			
						Any IFV*	RSV	PIV	MPV
Dede, 2010 [179]	Alice Springs	Australia	133.9, -23.7	bronchiolitis	DFA		✓		
Loscertales, 2002 [180]	Manhiça	Mozambique	32.8, -25.3	ALRI	ELISA or PCR		✓		
O'Callaghan-Gordo, 2011 [181]	Manhiça	Mozambique	32.8, -25.3	ARI	PCR	✓			
Vidal, 2008 [182]	Curitiba	Brazil	-49.3, -25.4	ILI or ARI	IFA	✓			
Venter, 2011 [183]	Pretoria	South Africa	28.2, -25.7	ARI	DFA or PCR	✓	✓	✓	✓
Pale, 2017 [184]	Maputo	Mozambique	32.6, -25.9	SARI	PCR		✓		
Hogan, 2016 [170]	Midwest-Murchison, Western Australia	Australia	116, -26.5	ALRI	multiple tests		✓		
Alonso, 2007 [164]	South Brazil	Brazil	-50.2, -27.7	ILI	NK	✓			
Hogan, 2016 [170]	Goldfields, Western Australia	Australia	121.5, -30.8	ALRI	multiple tests		✓		
Hogan, 2016 [170]	Wheatbelt, Western Australia	Australia	118, -32	ALRI	multiple tests		✓		
Hogan, 2016 [170]	Perth, Western Australia	Australia	115.9, -32	ALRI	multiple tests		✓		
Vega-Briceno, 2007 [185]	Santiago	Chile	-70.7, -33.4	respiratory diseases	PCR			✓	
Hogan, 2016 [170]	South West, Western Australia	Australia	116.2, -34.2	ALRI	multiple tests		✓		
Viegas, 2004 [186]	Buenos Aires	Argentina	-58.4, -34.6	ALRI	IFA	✓	✓	✓	
Hogan, 2016 [170]	Great Southern, Western Australia	Australia	117, -35	ALRI	multiple tests		✓		

Results of quality assessment of included studies from literature review

Study	Representativeness	Test Practice	Timely Reporting	Inclusion?
Bryce, 2012 [207]	D	A	A	No
Deng, 2009 [208]	A	D	A	No
Li, 2008 [209]	A	D	C	No
Mahamat, 2013 [210]	A	D	A	No
Matthew, 2009 [211]	D	A	A	No
Tantawy, 2015 [212]	D	A	A	No
Aberle, 2010 [27]	B	A	B	Yes
Aberle, 2008 [28]	B	A	B	Yes
Agrawal, 2009 [149]	B	A	A	Yes
Akhter, 2009 [137]	B	B	B	Yes
Akoua-Koffi, 2007 [176]	A	A	B	Yes
Al-Assam, 2009 [43]	B	C	C	Yes
Alonso, 2007 [47]	A	A	B	Yes
Alonso, 2012 [183]	B	A	A	Yes
Alonso, 2007 [184]	A	C	C	Yes
Annan, 2016 [31]	B	A	A	Yes
Armengaud, 2007 [32]	A	A	A	Yes
Artiles-Campelo, 2006 [120]	B	A	B	Yes
Asad, 2017 [135]	B	A	A	Yes
Ayora-Talavera, 2017 [88]	A	A	A	Yes
Aziz, 2015 [75]	B	A	B	Yes
Balmaks, 2014 [22]	B	A	A	Yes
Bayrakdar, 2016 [57]	A	A	B	Yes
Bdour, 2001 [89]	B	A	B	Yes
Bellei, 2008 [196]	B	A	A	Yes
Berner, 2001 [35]	B	C	C	Yes
Bharaj, 2009 [117]	B	A	A	Yes
Bimouhen, 2016 [90]	A	A	A	Yes
Binod, 2012 [113]	A	A	C	Yes
Bouzas, 2016 [189]	B	A	A	Yes
Brittain-Long, 2012 [21]	A	A	A	Yes
Brottet, 2016 [194]	A	A	B	Yes
Calvo, 2010 [51]	B	A	A	Yes
Chadha, 2012 [114]	A	A	A	Yes
Chadha, 2015 [84]	A	A	A	Yes
Checon, 2002 [192]	B	A	B	Yes
Chen, 2006 [150]	A	A	A	Yes
Chen, 2014 [118]	A	A	B	Yes
Chen, 2014 [140]	A	A	A	Yes
Chen, 2010 [108]	A	A	B	Yes
Chen, 2016 [100]	A	A	A	Yes
Choudhary, 2013 [161]	B	A	B	Yes

Study	Representativeness	Test Practice	Timely Reporting	Inclusion?
Chu, 2016 [124]	B	A	A	Yes
Costa, 2006 [191]	B	A	A	Yes
Cui, 2015 [142]	B	A	A	Yes
Cui, 2016 [115]	B	A	A	Yes
Dangi, 2014 [126]	A	A	A	Yes
Dede, 2010 [199]	B	A	C	Yes
Do, 2016 [171]	B	A	A	Yes
Dosseh, 2000 [166]	A	A	B	Yes
Esper, 2004 [49]	B	A	A	Yes
Fagan, 2017 [188]	A	C	C	Yes
Fang, 2013 [145]	A	A	A	Yes
Fe, 2008 [185]	B	A	A	Yes
Feng, 2014 [91]	B	A	A	Yes
Feng, 2014 [70]	A	A	A	Yes
Fergie, 2007 [121]	A	A	C	Yes
Finianos, 2016 [85]	B	A	A	Yes
Fodha, 2004 [73]	C	A	B	Yes
Foulongne, 2006 [44]	B	A	A	Yes
Fu, 2015 [96]	A	A	A	Yes
Gamino-Arroyo, 2017 [157]	A	A	A	Yes
Godoy, 2016 [48]	A	A	A	Yes
Goktas, 2016 [50]	A	A	C	Yes
Guan, 2015 [146]	B	A	B	Yes
Guo, 2014 [42]	A	A	A	Yes
Hamada, 2014 [74]	B	A	B	Yes
Hasegawa, 2006 [163]	A	A	A	Yes
He, 2014 [151]	B	A	A	Yes
Heininger, 2009 [36]	B	A	B	Yes
Hervas, 2012 [56]	B	A	B	Yes
Hogan, 2016 [190]	B	A	B	Yes
Horton, 2017 [103]	A	A	A	Yes
Hsieh, 2016 [141]	A	C	C	Yes
Hsieh, 2010 [132]	B	A	B	Yes
Hu, 2014 [159]	A	A	A	Yes
Huang, 2013 [67]	A	A	A	Yes
Huang, 2001 [143]	A	A	B	Yes
Huo, 2013 [104]	B	A	A	Yes
Iha, 2016 [129]	C	A	C	Yes
Iwane, 2004 [55]	B	A	B	Yes
Jain, 2014 [127]	A	A	A	Yes
Jain, 2015 [58]	A	A	A	Yes
Jain, 2015 [59]	B	A	A	Yes

Study	Representativeness	Test Practice	Timely Reporting	Inclusion?
Jeong, 2010 [77]	A	A	B	Yes
Ji, 2009 [93]	B	A	A	Yes
Jin, 2012 [68]	B	A	B	Yes
Jonnalagadda, 2017 [182]	B	A	A	Yes
Kaida, 2006 [81]	B	A	C	Yes
Kaneko, 2002 [80]	B	A	B	Yes
Kang, 2013 [65]	A	A	C	Yes
Kanra, 2005 [60]	B	A	A	Yes
Kenmoe, 2016 [178]	B	A	A	Yes
Khadadah, 2010 [111]	A	A	B	Yes
Khor, 2012 [180]	B	A	B	Yes
Kim, 2006 [66]	A	A	B	Yes
Koetz, 2006 [23]	B	A	B	Yes
Kong, 2016 [102]	B	A	B	Yes
Lee, 2007 [138]	B	A	B	Yes
Li, 2011 [133]	A	A	B	Yes
Li, 2008 [147]	A	A	A	Yes
Li, 2005 [158]	A	A	A	Yes
Light, 2007 [130]	B	A	B	Yes
Light, 2008 [122]	B	A	B	Yes
Liu, 2016 [71]	A	C	B	Yes
Liu, 2015 [116]	A	A	A	Yes
Liu, 2011 [148]	A	A	A	Yes
Liu, 2013 [53]	B	A	A	Yes
Ljubin-Sternak, 2014 [40]	B	A	A	Yes
Loscertales, 2002 [200]	B	A	A	Yes
Lu, 2015 [94]	B	A	A	Yes
Luo, 2012 [139]	A	A	C	Yes
Mathisen, 2011 [123]	B	A	A	Yes
Matias, 2015 [162]	B	A	B	Yes
McCormick, 2002 [24]	C	A	B	Yes
Mizuta, 2013 [62]	A	A	B	Yes
Mlinaric-Galinovic, 2008 [41]	B	A	B	Yes
Monamele, 2017 [179]	A	A	A	Yes
Muhlemann, 2006 [39]	B	C	C	Yes
Nakamura, 2013 [69]	A	A	A	Yes
Nguyen, 2007 [156]	A	A	A	Yes
Ni, 2009 [144]	A	A	C	Yes
Njouom, 2012 [172]	A	A	A	Yes
Noyola, 2005 [155]	B	A	B	Yes
Nyoka, 2017 [181]	C	C	C	Yes
O'Callaghan-Gordo, 2011 [201]	B	A	B	Yes

Study	Representativeness	Test Practice	Timely Reporting	Inclusion?
Onozuka, 2015 [86]	A	A	B	Yes
Ouedraogo, 2014 [170]	B	A	A	Yes
Pale, 2017 [204]	B	A	A	Yes
Pecchini, 2015 [197]	B	A	A	Yes
Perera, 2010 [173]	A	A	A	Yes
Qi, 2016 [109]	A	A	A	Yes
Qin, 2015 [152]	A	A	A	Yes
Qiu, 2014 [136]	A	A	A	Yes
Ramaekers, 2017 [30]	A	A	A	Yes
Reeves, 2017 [213]	B	B	A	Yes
Refaey, 2016 [101]	A	A	A	Yes
Resch, 2000 [37]	B	A	B	Yes
Richter, 2016 [78]	B	A	A	Yes
Robertson, 2004 [174]	B	A	A	Yes
Robinson, 2005 [26]	B	A	B	Yes
Rodriguez-Martinez, 2015 [177]	B	A	A	Yes
Sadeghi, 2011 [38]	B	A	B	Yes
Saha, 2016 [61]	A	C	C	Yes
Saikusa, 2005 [76]	B	A	B	Yes
Salomao Junior, 2011 [193]	B	A	B	Yes
Sapin, 2001 [195]	B	A	B	Yes
Sato, 2005 [64]	B	A	A	Yes
Schlaudecker, 2012 [167]	B	A	A	Yes
Shapiro, 2017 [175]	A	A	A	Yes
Shi, 2014 [45]	A	A	A	Yes
Sirimi, 2016[63]	B	A	B	Yes
Sun, 2013 [46]	A	A	A	Yes
Swamy, 2017 [125]	A	A	A	Yes
Tang, 2008 [105]	B	A	A	Yes
Terletskaia-Ladwig, 2005 [34]	B	B	A	Yes
Thomazelli, 2007 [198]	B	A	A	Yes
Timmermans, 2016 [169]	A	A	A	Yes
van der Sande, 2004 [168]	B	A	A	Yes
Vega-Briceno, 2007 [205]	B	A	B	Yes
Venter, 2011 [203]	B	A	A	Yes
Vidal, 2008 [202]	A	A	A	Yes
Viegas, 2004 [206]	B	A	B	Yes
Visseaux, 2017 [33]	B	A	B	Yes
Wahab, 2001 [131]	B	A	B	Yes
Wan, 2009 [95]	B	A	A	Yes
Wang, 2016 [97]	A	A	A	Yes
Weigl, 2002 [25]	B	A	A	Yes

Study	Representativeness	Test Practice	Timely Reporting	Inclusion?
Wilfret, 2008 [72]	A	A	A	Yes
Williams, 2010 [54]	B	A	A	Yes
Wu, 2010 [128]	A	A	A	Yes
Wu, 2011 [153]	A	A	C	Yes
Wu, 2012 [134]	B	A	A	Yes
Wu, 2016 [52]	A	A	A	Yes
Xiao, 2013 [119]	A	A	B	Yes
Yamaoka, 2011 [186]	A	A	A	Yes
Yang, 2011 [106]	A	A	A	Yes
Yang, 2012 [83]	A	A	A	Yes
Ye, 2013 [154]	A	A	A	Yes
Yin, 2017 [87]	B	A	A	Yes
Yoshioka, 2012 [79]	B	A	A	Yes
Yu, 2012 [112]	A	A	C	Yes
Yusuf, 2007 [160]	A	A	B	Yes
Zhang, 2016 [82]	A	A	A	Yes
Zhang, 2010 [110]	B	A	A	Yes
Zhao, 2013 [98]	B	A	A	Yes
Zhao, 2012[92]	A	A	C	Yes
Zheng, 2016 [107]	B	A	A	Yes
Zhou, 2014 [99]	A	A	C	Yes

List of reference in this section

1. Brittain-Long R, Andersson LM, Olofsson S, Lindh M, Westin J. Seasonal variations of 15 respiratory agents illustrated by the application of a multiplex polymerase chain reaction assay. *Scand J Infect Dis* 2012; **44**(1): 9-17.
2. Balmaks R, Ribakova I, Gardovska D, Kazaks A. Molecular epidemiology of human respiratory syncytial virus over three consecutive seasons in Latvia. *J Med Virol* 2014; **86**(11): 1971-82.
3. Koetz A, Nilsson P, Linden M, van der Hoek L, Ripa T. Detection of human coronavirus NL63, human metapneumovirus and respiratory syncytial virus in children with respiratory tract infections in south-west Sweden. *Clin Microbiol Infect* 2006; **12**(11): 1089-96.
4. McCormick J, Tubman R. Readmission with respiratory syncytial virus (RSV) infection among graduates from a neonatal intensive care unit. *Pediatr Pulmonol* 2002; **34**(4): 262-6.
5. Weigl JA, Puppe W, Schmitt HJ. Seasonality of respiratory syncytial virus-positive hospitalizations in children in Kiel, Germany, over a 7-year period. *Infection* 2002; **30**(4): 186-92.
6. Robinson JL, Lee BE, Bastien N, Li Y. Seasonality and clinical features of human metapneumovirus infection in children in Northern Alberta. *J Med Virol* 2005; **76**(1): 98-105.
7. Aberle JH, Aberle SW, Redlberger-Fritz M, Sandhofer MJ, Popow-Kraupp T. Human metapneumovirus subgroup changes and seasonality during epidemics. *Pediatr Infect Dis J* 2010; **29**(11): 1016-8.

8. Aberle SW, Aberle JH, Sandhofer MJ, Pracher E, Popow-Kraupp T. Biennial spring activity of human metapneumovirus in Austria. *Pediatr Infect Dis J* 2008; **27**(12): 1065-8.
9. Annual report on findings of infectious agents in Japan, 2002: Japanese Journal of Infectious Diseases; 2003. 56(Supplement):8-143.; 2003.
10. Ramaekers K, Keyaerts E, Rector A, et al. Prevalence and seasonality of six respiratory viruses during five consecutive epidemic seasons in Belgium. *J Clin Virol* 2017; **94**: 72-8.
11. Annan A, Ebach F, Corman VM, et al. Similar virus spectra and seasonality in paediatric patients with acute respiratory disease, Ghana and Germany. *Clinical Microbiology and Infection* 2016; **22**(4): 340-6.
12. Armengaud JB, El Hajje MJ, Moulin F, et al. [Simultaneous outbreaks of rotavirus and respiratory syncytial virus in Paris: a 12-year survey]. *Med Mal Infect* 2007; **37**(5): 262-5.
13. Visseaux B, Burdet C, Voiriot G, et al. Prevalence of respiratory viruses among adults, by season, age, respiratory tract region and type of medical unit in Paris, France, from 2011 to 2016. *PLoS ONE* 2017; **12**(7): e0180888.
14. Terletskaia-Ladwig E, Enders G, Schalasta G, Enders M. Defining the timing of respiratory syncytial virus (RSV) outbreaks: an epidemiological study. *BMC Infect Dis* 2005; **5**: 20.
15. Berner R, Schwoerer F, Schumacher RF, Meder M, Forster J. Community and nosocomially acquired respiratory syncytial virus infection in a German paediatric hospital from 1988 to 1999. *Eur J Pediatr* 2001; **160**(9): 541-7.
16. Heininger U, Kruker AT, Bonhoeffer J, Schaad UB. Human metapneumovirus infections--biannual epidemics and clinical findings in children in the region of Basel, Switzerland. *Eur J Pediatr* 2009; **168**(12): 1455-60.
17. Resch B, Gusenleitner W, Mandl C, Muller W. Epidemiology of respiratory syncytial virus infection in Southern Austria. *Pediatr Infect Dis J* 2000; **19**(6): 587-8.
18. Sadeghi CD, Aebi C, Gorgievski-Hrisoho M, Muhlemann K, Barbani MT. Twelve years' detection of respiratory viruses by immunofluorescence in hospitalised children: impact of the introduction of a new respiratory picornavirus assay. *BMC Infect Dis* 2011; **11**: 41.
19. Muhlemann K, Uehlinger DE, Buchi W, Gorgievski M, Aebi C. The prevalence of penicillin-non-susceptible Streptococcus pneumoniae among children aged < 5 years correlates with the biannual epidemic activity of respiratory syncytial virus. *Clin Microbiol Infect* 2006; **12**(9): 873-9.
20. Ljubin-Sternak S, Mlinaric-Galinovic G, Buntic AM, et al. Seasonal occurrence of human metapneumovirus infections in Croatia. *Pediatr Infect Dis J* 2014; **33**(2): 165-7.
21. Mlinaric-Galinovic G, Welliver RC, Vilibic-Cavlek T, et al. The biennial cycle of respiratory syncytial virus outbreaks in Croatia. *Virol J* 2008; **5**: 18.
22. Guo X, Wu M, Huang J. Analysis and detection of influenza-like cases in Karamay. [Chinese]. *Bulletin of Disease Control and Prevention* 2014; **29**(5): 39-40.
23. Al-Assam A, Langley JM, Sarwal S. Respiratory Watch: Development of a provincial system for respiratory syncytial virus surveillance in Nova Scotia, 2005-2008. *Canadian Journal of Infectious Diseases and Medical Microbiology* 2009; **20**(4): e153-e6.
24. Foulongne V, Guyon G, Rodiere M, Segondy M. Human metapneumovirus infection in young children hospitalized with respiratory tract disease. *Pediatr Infect Dis J* 2006; **25**(4): 354-9.
25. Shi H. Surveillance for influenza in Fuxin, Liaoning, 2010-2014. [Chinese]. *Disease Surveillance* 2014; **29**(12): 948-52.

26. Sun B, Yu W, Wang L, Tian J. Surveillance of influenza in Liaoning province, 2011-2012. [Chinese]. *Disease Surveillance* 2013; **28**(4): 297-9.
27. Alonso A, Andres JM, Garmendia JR, Diez I, Gil JM, Ardura J. Bronchiolitis due to respiratory syncytial virus in hospitalized children: a study of seasonal rhythm. *Acta Paediatr* 2007; **96**(5): 731-5.
28. Godoy C, Peremiquel-Trillas P, Andres C, et al. A molecular epidemiological study of human parainfluenza virus type 3 at a tertiary university hospital during 2013-2015 in Catalonia, Spain. *Diagnostic Microbiology and Infectious Disease* 2016; **86**(2): 153-9.
29. Esper F, Martinello RA, Boucher D, et al. A 1-year experience with human metapneumovirus in children aged <5 years. *J Infect Dis* 2004; **189**(8): 1388-96.
30. Goktas S, Sirin MC. Prevalence and seasonal distribution of respiratory viruses during the 2014 - 2015 season in Istanbul. *Jundishapur Journal of Microbiology* 2016; **9 (9) (no pagination)**(e39132).
31. Calvo C, Pozo F, Garcia-Garcia ML, et al. Detection of new respiratory viruses in hospitalized infants with bronchiolitis: a three-year prospective study. *Acta Paediatr* 2010; **99**(6): 883-7.
32. Wu Z, Yu X, Cui S, et al. Prevalence of human parainfluenza virus in patients with acute respiratory tract infections in Beijing. [Chinese]. *Disease Surveillance* 2016; **31**(5): 394-7.
33. Liu YF, Chen MF, Gao Y, et al. Etiologic characteristics of adult patients with community-acquired pneumonia in Beijing. [Chinese]. *National Medical Journal of China* 2013; **93**(26): 2043-7.
34. Williams JV, Edwards KM, Weinberg GA, et al. Population-based incidence of human metapneumovirus infection among hospitalized children. *J Infect Dis* 2010; **201**(12): 1890-8.
35. Iwane MK, Edwards KM, Szilagyi PG, et al. Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. *Pediatrics* 2004; **113**(6): 1758-64.
36. Hervas D, Reina J, Hervas JA. Meteorologic conditions and respiratory syncytial virus activity. *Pediatr Infect Dis J* 2012; **31**(10): e176-81.
37. Bayrakdar F, Altas AB, Korukluoglu G. [Phylogenetic variability of human metapneumovirus strains circulating in Turkey during two consecutive epidemic seasons]. *Mikrobiyol Bul* 2016; **50**(1): 63-72.
38. Jain S, Self WH, Wunderink RG, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med* 2015; **373**(5): 415-27.
39. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med* 2015; **372**(9): 835-45.
40. Kanra G, Tezcan S, Ylmaz G. Respiratory syncytial virus epidemiology in Turkey. *Turk J Pediatr* 2005; **47**(4): 303-8.
41. Saha S, Chadha M, Shu Y, Group of Asian Researchers on I. Divergent seasonal patterns of influenza types A and B across latitude gradient in Tropical Asia. *Influenza other respi* 2016; **10**(3): 176-84.
42. Mizuta K, Abiko C, Aoki Y, et al. Seasonal patterns of respiratory syncytial virus, influenza A virus, human metapneumovirus, and parainfluenza virus type 3 infections on the basis of virus isolation data between 2004 and 2011 in Yamagata, Japan. *Jpn J Infect Dis* 2013; **66**(2): 140-5.
43. Sirimi N, Miligkos M, Koutouzi F, Petridou E, Siahanidou T, Michos A. Respiratory syncytial virus activity and climate parameters during a 12-year period. *J Med Virol* 2016; **88**(6): 931-7.

44. Sato M, Saito R, Sakai T, et al. Molecular epidemiology of respiratory syncytial virus infections among children with acute respiratory symptoms in a community over three seasons. *J Clin Microbiol* 2005; **43**(1): 36-40.
45. Kang SY, Hong CR, Kang HM, Cho EY, Choi EH, Lee HJ. Clinical and epidemiological characteristics of human metapneumovirus infections, in comparison with respiratory syncytial virus A and B. [Korean]. *Korean Journal of Pediatric Infectious Diseases* 2013; **20**(3): 168-77.
46. Kim S, Huh J, Bae S, et al. Epidemiology of respiratory viral infection in 2004-2006. *Korean Journal of Laboratory Medicine* 2006; **26**(5): 351-7.
47. Huang G, Yu D, Mao N, et al. Viral Etiology of Acute Respiratory Infection in Gansu Province, China, 2011. *PLoS ONE* 2013; **8 (5) (no pagination)**(e64254).
48. Jin Y, Zhang RF, Xie ZP, et al. Newly identified respiratory viruses associated with acute lower respiratory tract infections in children in Lanzou, China, from 2006 to 2009. *Clin Microbiol Infect* 2012; **18**(1): 74-80.
49. Nakamura M, Hirano E, Ishiguro F, et al. Molecular epidemiology of human metapneumovirus from 2005 to 2011 in Fukui, Japan. *Jpn J Infect Dis* 2013; **66**(1): 56-9.
50. Feng L, Li Z, Zhao S, et al. Viral etiologies of hospitalized acute lower respiratory infection patients in China, 2009-2013. *PLoS ONE* 2014; **9**(6).
51. Liu T, Li Z, Lin Y, et al. Dynamic patterns of circulating influenza virus from 2005 to 2012 in Shandong Province, China. *Arch Virol* 2016; **161**(11): 3047-59.
52. Wilfret DA, Baker BT, Palavecino E, Moran C, Benjamin DK, Jr. Epidemiology of respiratory syncytial virus in various regions within North Carolina during multiple seasons. *N C Med J* 2008; **69**(6): 447-52.
53. Fodha I, Landolsi N, Vabret A, Sboui H, Trabelsi A, Freymuth F. Epidemiology and clinical presentation of respiratory syncytial virus infection in a Tunisian neonatal unit from 2000 to 2002. *Ann Trop Paediatr* 2004; **24**(3): 219-25.
54. Hamada H, Ogura A, Hotta C, Wakui T, Ogawa T, Terai M. [Epidemiological study of respiratory viruses detected in patients under two years old who required admission because of lower respiratory disease]. *Kansenshogaku Zasshi* 2014; **88**(4): 423-9.
55. Aziz TAG. Detection of human Metapneumovirus in hospitalized children with acute respiratory tract infections in Sulaimani province, Iraq. *Journal of Medical Microbiology and Diagnosis* 2015; **4**(2).
56. Saikusa M, Kawakami C, Noguchi Y, Toba M. [An epidemiological study of respiratory syncytial virus infection in Yokohama, Japan for five years]. *Kansenshogaku Zasshi* 2005; **79**(6): 381-7.
57. Jeong JW, Hwang YH, Cho KS, et al. Viral etiology and epidemiology of outpatients with acute respiratory illnesses in Busan: 2007-2008. [Korean]. *Korean Journal of Pediatric Infectious Diseases* 2010; **17**(2): 130-6.
58. Richter J, Panayiotou C, Tryfonos C, et al. Aetiology of Acute Respiratory Tract Infections in Hospitalised Children in Cyprus. *PLoS ONE* 2016; **11**(1): e0147041.
59. Yoshioka M, Ishikawa Y, Ikeda T, Shimizu T, Noda M, Kimura H. [Epidemiological analysis and clinical study of pediatric human metapneumovirus detected in patients with acute respiratory infection]. *Kansenshogaku Zasshi* 2012; **86**(6): 755-62.
60. Kaneko M, Watanabe J, Kuwahara M, et al. Impact of respiratory synctial virus infection as a cause of lower respiratory tract infection in children younger than 3 years of age in Japan. *J Infect* 2002; **44**(4): 240-3.
61. Kaida A, Iritani N, Kubo H, Shiomi M, Kohdera U, Murakami T. Seasonal distribution and phylogenetic analysis of human metapneumovirus among children in Osaka City, Japan. *J Clin Virol* 2006; **35**(4): 394-9.

62. Zhang L, Xu J, Shi W, et al. Epidemiological features of respiratory syncytial virus in Xi'an in 2009-2014. [Chinese]. *Chinese Preventive Medicine* 2016; **17**(2): 81-5.
63. Yang JC, Tong J, Zhang CL, et al. [Etiological analysis of influenza surveillance data in Xuzhou from 2005 to 2011]. *Chung Hua Shih Yen Ho Lin Chuang Ping Tu Hsueh* 2012; **26**(6): 412-4.
64. Chadha MS, Potdar VA, Saha S, et al. Dynamics of influenza seasonality at sub-regional levels in India and implications for vaccination timing. *PLoS ONE* 2015; **10**(5): e0124122.
65. Finianos M, Issa R, Curran MD, et al. Etiology, seasonality, and clinical characterization of viral respiratory infections among hospitalized children in Beirut, Lebanon. *J Med Virol* 2016; **88**(11): 1874-81.
66. Onozuka D. The influence of diurnal temperature range on the incidence of respiratory syncytial virus in Japan. *Epidemiol Infect* 2015; **143**(4): 813-20.
67. Yin R, Xu J, Liu X, Liu M, Gu R, Li Yn. Pathogenic analysis of 7 common respiratory viruses in 569 hospitalized children with respiratory tract infections. [Chinese]. *Zhongguo Weishengtaxixue Zazhi / Chinese Journal of Microecology* 2017; **29**(6): 684-8.
68. Ayora-Talavera G, Flores GMZ, Gomez-Carballo J, et al. Influenza seasonality goes south in the Yucatan Peninsula: The case for a different influenza vaccine calendar in this Mexican region. *Vaccine* 2017; **35**(36): 4738-44.
69. Bdour S. Respiratory syncytial virus subgroup A in hospitalized children in Zarqa, Jordan. *Ann Trop Paediatr* 2001; **21**(3): 253-61.
70. Bimouhen A, El-Falaki F, Ihazmad H, Regragui Z, Benkerroum S, Barakat A. Circulation of respiratory syncytial virus in Morocco during 2014-2016: findings from a sentinel-based virological surveillance system for influenza. (Special Issue: Influenza.). *East Mediterr Health J* 2016; **22**(7): 483-90.
71. Feng L, Lai S, Li F, et al. Viral etiologies of hospitalized pneumonia patients aged less than five years in six provinces, 2009-2012. [Chinese]. *Zhonghua liu xing bing xue za zhi = Zhonghua liuxingbingxue zazhi* 2014; **35**(6): 646-9.
72. Zhao Z, Yao W, Jiang L, Huo K, Shen Z. Analysis of influenza monitoring in Maanshan from 2010-2011. [Chinese]. *Zhongguo Bingyuan Shengwuxue Zazhi / Journal of Pathogen Biology* 2012; **7**(7): 527-30.
73. Ji W, Wu JH, Huang L, Luo YL, Zhang XL. [An etiological study on acute respiratory infection among inpatient children in Suzhou]. *Chung Hua Yu Fang I Hsueh Tsa Chih* 2009; **43**(10): 867-71.
74. Lu L, Yan Y, Yang B, et al. Epidemiological and clinical profiles of respiratory syncytial virus infection in hospitalized neonates in Suzhou, China. *BMC Infect Dis* 2015; **15**: 431.
75. Wan F, Tao Y, Zhang X, et al. Etiology investigation of acute respiratory tract infections in children. [Chinese]. *Clinical Focus* 2009; **24**(2): 106-9.
76. Fu Y, Pan L, Sun Q, et al. The clinical and etiological characteristics of influenza-like illness (ILI) in outpatients in Shanghai, China, 2011 to 2013. *PLoS ONE* 2015; **10**(3): e0119513.
77. Wang S, Luo X, Wang K, Miao N, Luo D, Zhou L. Analysis of influenza surveillance results in Dazhou city from 2010 to 2014. [Chinese]. *Modern Preventive Medicine* 2016; **43**(4): 733-5.
78. Zhao B, Yu X, Wang C, et al. High human bocavirus viral load is associated with disease severity in children under five years of age. *PLoS ONE* 2013; **8**(4): e62318.

79. Zhou Y, Zhao B, Guo J, Huang Z, Zhang X. Epidemiologic characteristics of H3N2 isolates in Shanghai, 2010-2013. [Chinese]. *Journal of Environmental & Occupational Medicine* 2014; **31**(6): 426-9.
80. Chen Z, Liu Q, Zou W, Wang Y, Zhu W. Analysis of etiology of influenza in Pudong New Area from 2012 to 2014. [Chinese]. *China Tropical Medicine* 2016; **16**(3): 233-6.
81. Refaey S, Hassan M, Mansour A, Kandeel A. Incidence of influenza virus-associated severe acute respiratory infection in Damanhour district, Egypt, 2013. *East Mediterr Health J* 2016; **22**(7): 503-12.
82. Kong W, Wang Y, Zhu H, et al. Circulation of human metapneumovirus among children with influenza-like illness in Wuhan, China. *J Med Virol* 2016; **88**(5): 774-81.
83. Horton KC, Dueger EL, Kandeel A, et al. Viral etiology, seasonality and severity of hospitalized patients with severe acute respiratory infections in the Eastern Mediterranean Region, 2007-2014. *PLoS ONE* 2017; **12**(7): e0180954.
84. Huo X, Fang B, Liu L, et al. Clinical and epidemiologic characteristics of respiratory syncytial virus infection among children aged <5 years, Jingzhou City, China, 2011. (Special Issue: Surveillance for respiratory syncytial virus in CDC's Global Disease Detection network: Epidemiology, disease burden and clinical characteristics.). *J Infect Dis* 2013; **208**(Suppl. 3): S184-S8.
85. Tang LF, Wang TL, Tang HF, Chen ZM. Viral pathogens of acute lower respiratory tract infection in China. *Indian Pediatr* 2008; **45**(12): 971-5.
86. Yang H, Pan M, Huang T. Analysis of influenza surveillance in Sichuan from 2010-2011. [Chinese]. *Modern Preventive Medicine* 2011; **38**(24): 5128-30.
87. Zheng J, Huo X, Huai Y, et al. Epidemiology, Seasonality and Treatment of Hospitalized Adults and Adolescents with Influenza in Jingzhou, China, 2010-2012. *PLoS ONE* 2016; **11**(3): e0150713.
88. Chen X, Zhang ZY, Zhao Y, Liu EM, Zhao XD. Acute lower respiratory tract infections by human metapneumovirus in children in Southwest China: a 2-year study. *Pediatr Pulmonol* 2010; **45**(8): 824-31.
89. Qi L, Xiong Y, Xiao B, et al. Epidemiological and virological characteristics of influenza in chongqing, China, 2011-2015. *PLoS ONE* 2016; **11 (12) (no pagination)**(e0167866).
90. Zhang ZY, Du LN, Chen X, et al. Genetic variability of respiratory syncytial viruses (RSV) prevalent in Southwestern China from 2006 to 2009: emergence of subgroup B and A RSV as dominant strains. *J Clin Microbiol* 2010; **48**(4): 1201-7.
91. Khadadah M, Essa S, Higazi Z, Behbehani N, Al-Nakib W. Respiratory syncytial virus and human rhinoviruses are the major causes of severe lower respiratory tract infections in Kuwait. *J Med Virol* 2010; **82**(8): 1462-7.
92. Yu Z, Fang Q, Zhou M, Li L, Wang W, Chai C. Surveillance of influenza in Zhejiang, 2008-2012. [Chinese]. *Disease Surveillance* 2012; **27**(9): 689-93.
93. Binod K, Pati DR, Madhu K, et al. Age-sex distribution and seasonality pattern among influenza virus infected patients in Delhi, 2009-2010. *Indian Journal of Community Medicine* 2012; **37**(1): 57-8.
94. Chadha MS, Broor S, Gunasekaran P, et al. Multisite virological influenza surveillance in India: 2004-2008. *Influenza other respi* 2012; **6**(3): 196-203.
95. Cui D, Feng L, Chen Y, et al. Clinical and epidemiologic characteristics of hospitalized patients with laboratory-confirmed respiratory syncytial virus infection in eastern China between 2009 and 2013: A retrospective study. *PLoS ONE* 2016; **11 (11) (no pagination)**(e0165437).

96. Liu Y, Li H, Wu J. Analysis of influenza surveillance in Nanchang City, Jiangxi Province, 2010-2012. [Chinese]. *Modern Preventive Medicine* 2015; **42**(7): 1306-9.
97. Bharaj P, Sullender WM, Kabra SK, et al. Respiratory viral infections detected by multiplex PCR among pediatric patients with lower respiratory tract infections seen at an urban hospital in Delhi from 2005 to 2007. *Virol J* 2009; **6**: 89-.
98. Chen JF, Sun BC, Yuan J, Zhang RS, Ou XH. Surveillance of influenza virus during 2010-2012 in Changsha, China. *Southeast Asian J Trop Med Public Health* 2014; **45**(2): 319-25.
99. Xiao NG, Zhang B, Xie ZP, et al. Prevalence of human metapneumovirus in children with acute lower respiratory infection in Changsha, China. *J Med Virol* 2013; **85**(3): 546-53.
100. Artiles-Campelo F, Perez-Gonzalez Mdel C, Caballero-Hidalgo A, Pena-Lopez MJ. [Etiology of acute viral respiratory tract infections in children from Gran Canaria, the Canary Islands (Spain)]. *Enferm Infecc Microbiol Clin* 2006; **24**(9): 556-61.
101. Fergie J, Purcell K. Respiratory syncytial virus laboratory surveillance and hospitalization trends in South Texas. *Pediatr Infect Dis J* 2007; **26**(11 Suppl): S51-4.
102. Light M, Bauman J, Mavunda K, Malinoski F, Eggleston M. Correlation between respiratory syncytial virus (RSV) test data and hospitalization of children for RSV lower respiratory tract illness in Florida. *Pediatr Infect Dis J* 2008; **27**(6): 512-8.
103. Mathisen M, Basnet S, Sharma A, et al. RNA viruses in young Nepalese children hospitalized with severe pneumonia. *Pediatr Infect Dis J* 2011; **30**(12): 1032-6.
104. Chu HY, Katz J, Tielsch J, et al. Respiratory syncytial virus infection in infants in rural Nepal. *J Infect* 2016; **73**(2): 145-54.
105. Swamy MA, Malhotra B, Reddy PV, Tiwari JK, Kumar N, Gupta ML. Trends of respiratory syncytial virus sub-types in children hospitalised at a tertiary care centre in Jaipur during 2012-2014. *Indian J* 2017; **35**(1): 134-6.
106. Dangi T, Jain B, Singh AK, et al. Influenza virus genotypes circulating in and around Lucknow, Uttar Pradesh, India, during post pandemic period, August 2010--September 2012. *Indian J Med Res* 2014; **139**(3): 418-26.
107. Jain B, Singh AK, Dangi T, et al. High prevalence of human metapneumovirus subtype B in cases presenting as severe acute respiratory illness: an experience at tertiary care hospital. *Clin Respir J* 2014; **8**(2): 225-33.
108. Wu C. Detection and strain typing of influenza viruses in Nanping, Fujian, 2009. [Chinese]. *Chinese Preventive Medicine* 2010; **11**(9): 923-5.
109. Iha Y, Kinjo T, Parrott G, Higa F, Mori H, Fujita J. Comparative epidemiology of influenza A and B viral infection in a subtropical region: A 7-year surveillance in Okinawa, Japan. *BMC Infect Dis* 2016; **16 (1) (no pagination)**(650).
110. Light M. Respiratory syncytial virus seasonality in southeast Florida: results from three area hospitals caring for children. *Pediatr Infect Dis J* 2007; **26**(11 Suppl): S55-9.
111. Wahab AA, Dawod ST, Raman HM. Clinical characteristics of respiratory syncytial virus infection in hospitalized healthy infants and young children in Qatar. *J Trop Pediatr* 2001; **47**(6): 363-6.
112. Hsieh YJ, Chin H, Chiu NC, Huang FY. Hospitalized pediatric parainfluenza virus infections in a medical center. *J Microbiol Immunol Infect* 2010; **43**(5): 360-5.
113. Li F, Liu J, Wang W. Influenza surveillance in Quanzhou in 2009. [Chinese]. *Journal of Tropical Medicine* 2011; **11**(2): 220-1.
114. Wu Q, Wen B, Li Y, et al. Clinical and etiological analysis of 1402 children with acute lower respiratory tract infections. [Chinese]. *Chinese Journal of Obstetrics and Gynecology and Pediatrics* 2012; **8**(3): 265-9.

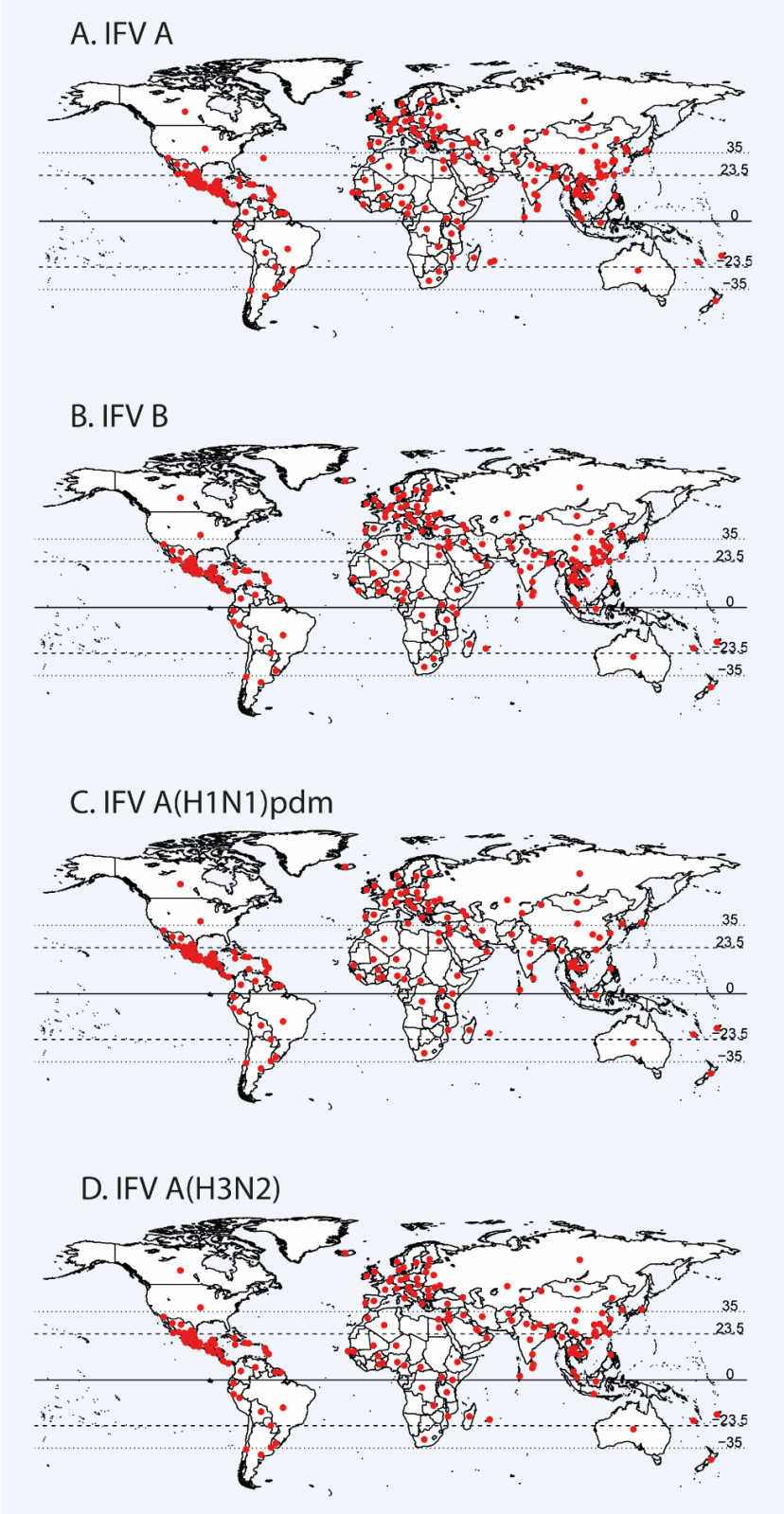
115. Asad A, Yousafzai MT, Rabbia W, et al. RSV associated hospitalizations in children in Karachi, Pakistan: implications for vaccine prevention strategies. *J Med Virol* 2017; **89**(7): 1151-7.
116. Qiu C, Gong P, Tang J, Xu L. Etiology surveillance of influenza in Shaoguan city from 2012 to 2013. [Chinese]. *Journal of Tropical Medicine* 2014; **14**(12): 1630-2.
117. Akhter J, Al Johani S, Dugaishm F, Al Hefdi R, Al Hassan I. Etiology of respiratory viral infections using rapid virus isolation methods at a tertiary care center in Riyadh, Saudi Arabia. *Saudi Pharmaceutical Journal* 2009; **17**(2): 177-81.
118. Lee JT, Chang LY, Wang LC, et al. Epidemiology of respiratory syncytial virus infection in northern Taiwan, 2001-2005 - Seasonality, clinical characteristics, and disease burden. *Journal of Microbiology, Immunology and Infection* 2007; **40**(4): 293-301.
119. Luo C, Zhao Q, Xiang Y, et al. Analysis of the epidemic characters of influenza in Yunnan Province from 2006-2010. [Chinese]. *Modern Preventive Medicine* 2012; **39**(16): 4275-8.
120. Chen W, Chen L, Deng Y, Li G, Luo W, Zhu J. Analysis of influenza surveillance in Qingyuan. [Chinese]. *Journal of Tropical Medicine* 2014; **14**(2): 263-4.
121. Hsieh YH, Huang HM, Lan YC. On temporal patterns and circulation of influenza virus strains in Taiwan, 2008-2014: Implications of 2009 pH1N1 pandemic. *PLoS ONE* 2016; **11 (5) (no pagination)**(e0154695).
122. Cui B, Zhang D, Pan H, et al. Viral aetiology of acute respiratory infections among children and associated meteorological factors in southern China. *BMC Infect Dis* 2015; **15**: 124.
123. Huang P, Ni H, Shen G, Zhou H, Peng G, Liu S. Analysis of the 1991-2000 influenza epidemic in Guangdong Province, China. *Southeast Asian J Trop Med Public Health* 2001; **32**(4): 787-90.
124. Ni G, Ni W, Li Q, Ding L, Zhang R. Surveillance of influenza in Honghe prefecture, Yunnan, 2006-2007. [Chinese]. *Disease Surveillance* 2009; **24**(7): 492-4.
125. Fang Q, Ju X, Zeng J. Study on the viral etiology of acute respiratory tract infections by real-time PCR. [Chinese]. *Chinese Preventive Medicine* 2013; **14**(5): 321-4.
126. Guan WD, Gong XY, Mok CK, et al. Surveillance for seasonal influenza virus prevalence in hospitalized children with lower respiratory tract infection in Guangzhou, China during the post-pandemic era. *PLoS ONE* 2015; **10**(4): e0120983.
127. Li T, Liu W, Yang Z, et al. Surveillance analysis of influenza in Guangzhou, 2006. [Chinese]. *Disease Surveillance* 2008; **23**(8): 478-80.
128. Liu Y, Zhong X, Zhang Q. Analysis on influenza surveillance in Dongguan city in 2009. [Chinese]. *Modern Preventive Medicine* 2011; **38**(7): 1316-8.
129. Agrawal AS, Sarkar M, Chakrabarti S, et al. Comparative evaluation of real-time PCR and conventional RT-PCR during a 2 year surveillance for influenza and respiratory syncytial virus among children with acute respiratory infections in Kolkata, India, reveals a distinct seasonality of infection. *J Med Microbiol* 2009; **58**(Pt 12): 1616-22.
130. Chen H, Guan C, Huang R. Preliminary analysis of results in monitoring of influenza in Nanshan District of Shenzhen City in 2005. [Chinese]. *China Tropical Medicine* 2006; **6**(11): 1981-2.
131. He Y, Lin GY, Wang Q, et al. A 3-year prospective study of the epidemiology of acute respiratory viral infections in hospitalized children in Shenzhen, China. *Influenza other respi* 2014; **8**(4): 443-51.
132. Qin Y, Fang S, Mei S, et al. Analysis of aetiological surveillance of influenza and outbreak in Shenzhen city during 2009-2013. [Chinese]. *Journal of Tropical Medicine* 2015; **15**(7): 985-8.

133. Wu C, Cheng X, Wang X, et al. Phyletic evolution and molecular variation of influenza B viruses in Shenzhen, 2009. [Chinese]. *Disease Surveillance* 2011; **26**(6): 442-5.
134. Ye W, Cao G, Liu Q, et al. Surveillance and analysis on influenza in Longgang District of Shenzhen City from 2010-2011. [Chinese]. *Occupation and Health* 2013; **29**(16): 2072-4.
135. Noyola DE, Alpuche-Solis AG, Herrera-Diaz A, Soria-Guerra RE, Sanchez-Alvarado J, Lopez-Revilla R. Human metapneumovirus infections in Mexico: epidemiological and clinical characteristics. *J Med Microbiol* 2005; **54**(Pt 10): 969-74.
136. Nguyen HL, Saito R, Ngiem HK, et al. Epidemiology of influenza in Hanoi, Vietnam, from 2001 to 2003. *J Infect* 2007; **55**(1): 58-63.
137. Gamino-Arroyo AE, Moreno-Espinosa S, Llamosas-Gallardo B, et al. Epidemiology and clinical characteristics of respiratory syncytial virus infections among children and adults in Mexico. *Influenza Other Respir Viruses* 2017; **11**(1): 48-56.
138. Li Z, Ma Y, Li Z. Establishment of Hainan Provincial Influenza Monitoring System and analysis of effect of operation. [Chinese]. *China Tropical Medicine* 2005; **5**(5): 960-1.
139. Hu B, Feng Y. Analysis of influenza in 2013 of Danzhou. [Chinese]. *Journal of Hainan Medical University* 2014; **20**(10): 1443-5.
140. Yusuf S, Piedimonte G, Auais A, et al. The relationship of meteorological conditions to the epidemic activity of respiratory syncytial virus. *Epidemiology and Infection* 2007; **135**(7): 1077-90.
141. Choudhary ML, Anand SP, Wadhwa BS, Chadha MS. Genetic variability of human respiratory syncytial virus in Pune, Western India. *Infection, Genetics and Evolution* 2013; **20**: 369-77.
142. Matias I, Garcia I, Garcia-Fragoso L, et al. Trends of Respiratory Syncytial Virus Infections in Children under 2 Years of Age in Puerto Rico. *P R Health Sci J* 2015; **34**(2): 98-101.
143. Hasegawa G, Kyaw Y, New HM, et al. Epidemiological study of influenza virus infections in Yangon, Myanmar. *Tropical Medicine and Health* 2006; **34**(1): 3-6.
144. Diene Sarr F, Niang M, Thiam D, et al. Acute Febrile Illness and Influenza Disease Burden in a Rural Cohort Dedicated to Malaria in Senegal, 2012–2013. *PLoS ONE* 2015; **10**(12): e0143999.
145. Diene Sarr F, Niang M, Thiam D, et al. Data from: Acute Febrile Illness and Influenza Disease Burden in a Rural Cohort Dedicated to Malaria in Senegal, 2012–2013. Dryad Digital Repository; 2015.
146. Dosseh A, Ndiaye K, Spiegel A, Sagna M, Mathiot C. Epidemiological and virological influenza survey in Dakar, Senegal: 1996-1998. *Am J Trop Med Hyg* 2000; **62**(5): 639-43.
147. Schlaudecker EP, Heck JP, Macintyre ET, et al. Etiology and seasonality of viral respiratory infections in rural Honduran children. *Pediatr Infect Dis J* 2012; **31**(11): 1113-8.
148. van der Sande MA, Goetghebuer T, Sanneh M, Whittle HC, Weber MW. Seasonal variation in respiratory syncytial virus epidemics in the Gambia, West Africa. *Pediatr Infect Dis J* 2004; **23**(1): 73-4.
149. Timmermans A, Melendrez MC, Se Y, et al. Human Sentinel Surveillance of Influenza and Other Respiratory Viral Pathogens in Border Areas of Western Cambodia. *PLoS ONE* 2016; **11**(3): e0152529.
150. Ouedraogo S, Traore B, Nene Bi ZA, et al. Viral etiology of respiratory tract infections in children at the pediatric hospital in Ouagadougou (Burkina Faso). *PLoS ONE* 2014; **9**(10): e110435.
151. Do LAH, Bryant JE, Anh Tuan T, et al. Respiratory syncytial virus and other viral infections among children under two years old in Southern Vietnam 2009-2010: clinical characteristics and disease severity. *PLoS ONE* 2016; **11**(8).

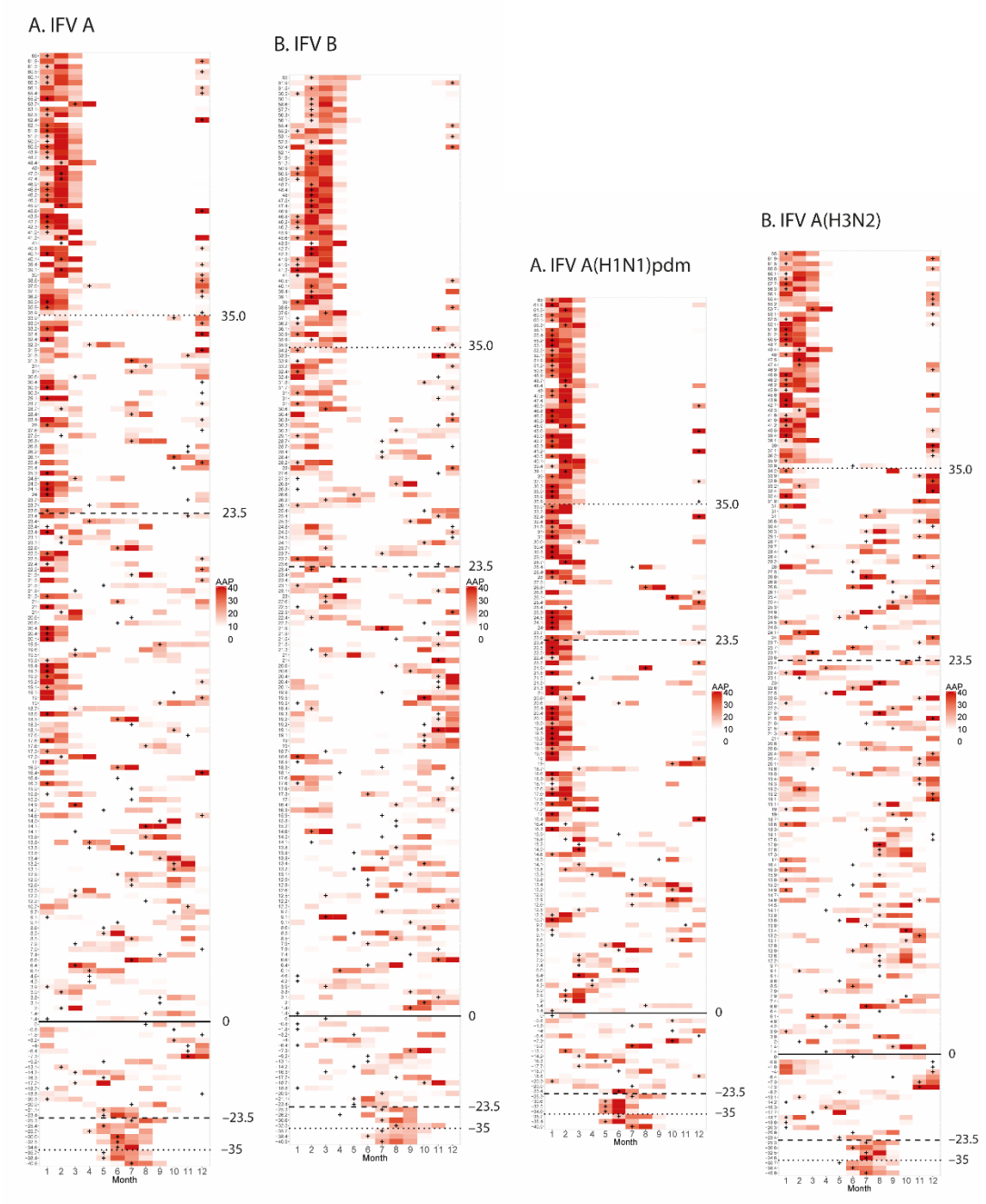
152. Njouom R, Yekwa EL, Cappy P, Vabret A, Boisier P, Rousset D. Viral etiology of influenza-like illnesses in Cameroon, January-December 2009. *J Infect Dis* 2012; **206 Suppl 1**: S29-35.
153. Perera KV, Chan KH, Ma E, Peiris JS. Influenza virus infections among a sample of hospital attendees in Ragama, Sri Lanka. *Ceylon Med J* 2010; **55**(2): 40-4.
154. Robertson SE, Roca A, Alonso P, et al. Respiratory syncytial virus infection: denominator-based studies in Indonesia, Mozambique, Nigeria and South Africa. *Bull World Health Organ* 2004; **82**(12): 914-22.
155. Shapiro D, Bodinayake CK, Nagahawatte A, et al. Burden and seasonality of viral acute respiratory tract infections among outpatients in southern Sri Lanka. *American Journal of Tropical Medicine and Hygiene* 2017; **97**(1): 88-96.
156. Akoua-Koffi C, Kouakou B, Kadjo H, et al. [Results of two-year surveillance of flu in Abidjan, Cote d'Ivoire]. *Med Trop (Mars)* 2007; **67**(3): 259-62.
157. Rodriguez-Martinez CE, Rodriguez DA, Nino G. Respiratory syncytial virus, adenoviruses, and mixed acute lower respiratory infections in children in a developing country. *J Med Virol* 2015; **87**(5): 774-81.
158. Kenmoe S, Tchendjou P, Vernet MA, et al. Viral etiology of severe acute respiratory infections in hospitalized children in Cameroon, 2011-2013. *Influenza and other Respiratory Viruses* 2016; **10**(5): 386-93.
159. Monamele GC, Vernet MA, Nsaibirni RFJ, et al. Associations between meteorological parameters and influenza activity in a subtropical country: Case of five sentinel sites in Yaounde-Cameroon. *PLoS ONE* 2017; **12**(10): e0186914.
160. Khor CS, Sam IC, Hooi PS, Quek KF, Chan YF. Epidemiology and seasonality of respiratory viral infections in hospitalized children in Kuala Lumpur, Malaysia: a retrospective study of 27 years. *BMC Pediatr* 2012; **12**: 32.
161. Nyoka R, Omony J, Mwalili SM, Achia TNO, Gichangi A, Mwambi H. Effect of climate on incidence of respiratory syncytial virus infections in a refugee camp in Kenya: A non-Gaussian time-series analysis. *PLoS ONE* 2017; **12**(6): e0178323.
162. Jonnalagadda S, Rodriguez O, Estrella B, Sabin LL, Sempertegui F, Hamer DH. Etiology of severe pneumonia in Ecuadorian children. *PLoS ONE* 2017; **12**(2): e0171687.
163. Alonso WJ, Laranjeira BJ, Pereira SA, et al. Comparative dynamics, morbidity and mortality burden of pediatric viral respiratory infections in an equatorial city. *Pediatr Infect Dis J* 2012; **31**(1): e9-14.
164. Alonso WJ, Viboud C, Simonsen L, Hirano EW, Daufenbach LZ, Miller MA. Seasonality of influenza in Brazil: a traveling wave from the Amazon to the subtropics. *Am J Epidemiol* 2007; **165**(12): 1434-42.
165. Fe MM, Monteiro AJ, Moura FE. Parainfluenza virus infections in a tropical city: clinical and epidemiological aspects. *Braz J Infect Dis* 2008; **12**(3): 192-7.
166. Yamaoka M, Palilingan JF, Wibisono J, et al. Virological surveillance of human influenza in Indonesia, October 2008-March 2010. *Microbiol Immunol* 2011; **55**(7): 514-7.
167. Budge PJ, Griffin MR, Edwards KM, et al. A household-based study of acute viral respiratory illnesses in Andean children. *Pediatr Infect Dis J* 2014; **33**(5): 443-7.
168. Fagan P, McLeod C, Baird RW. Seasonal variability of respiratory syncytial virus infection in the Top End of the Northern Territory (2012-2014). *Journal of Paediatrics and Child Health* 2017; **53**(1): 43-6.
169. Bouzas ML, Oliveira JR, Fukutani KF, et al. Respiratory syncytial virus A and B display different temporal patterns in a 4-year prospective cross-sectional study among children with acute respiratory infection in a tropical city. *Medicine (Baltimore)* 2016; **95**(41).

170. Hogan AB, Anderssen RS, Davis S, et al. Time series analysis of RSV and bronchiolitis seasonality in temperate and tropical Western Australia. *Epidemics* 2016; **16**: 49-55.
171. Costa LF, Yokosawa J, Mantese OC, et al. Respiratory viruses in children younger than five years old with acute respiratory disease from 2001 to 2004 in Uberlandia, MG, Brazil. *Mem Inst Oswaldo Cruz* 2006; **101**(3): 301-6.
172. Checon RE, Siqueira MM, Lugon AK, Portes S, Dietze R. Short report: seasonal pattern of respiratory syncytial virus in a region with a tropical climate in southeastern Brazil. *Am J Trop Med Hyg* 2002; **67**(5): 490-1.
173. Salomao Junior JB, Gardinassi LG, Simas PV, et al. Human respiratory syncytial virus in children hospitalized for acute lower respiratory infection. *J Pediatr (Rio J)* 2011; **87**(3): 219-24.
174. Brottet E, Jaffar-Bandjee MC, Li-Pat-Yuen G, Filleul L. Etiology of influenza-like illnesses from sentinel network practitioners in Reunion Island, 2011-2012. *PLoS ONE* 2016; **11**(9).
175. Sapin G, Michault A, Simac C. [Seasonal trends of respiratory syncytial virus infections on Reunion Island gathering data among hospitalized children]. *Bull Soc Pathol Exot* 2001; **94**(1): 3-4.
176. Bellei N, Carraro E, Perosa A, Watanabe A, Arruda E, Granato C. Acute respiratory infection and influenza-like illness viral etiologies in Brazilian adults. *J Med Virol* 2008; **80**(10): 1824-7.
177. Pecchini R, Berezin EN, Souza MC, et al. Parainfluenza virus as a cause of acute respiratory infection in hospitalized children. *Braz J Infect Dis* 2015; **19**(4): 358-62.
178. Thomazelli LM, Vieira S, Leal AL, et al. Surveillance of eight respiratory viruses in clinical samples of pediatric patients in Southeast Brazil. [Portuguese, English]. *J Pediatr (Rio J)* 2007; **83**(5): 422-8.
179. Dede A, Isaacs D, Torzillo PJ, et al. Respiratory syncytial virus infections in Central Australia. *J Paediatr Child Health* 2010; **46**(1-2): 35-9.
180. Loscertales MP, Roca A, Ventura PJ, et al. Epidemiology and clinical presentation of respiratory syncytial virus infection in a rural area of southern Mozambique. *Pediatr Infect Dis J* 2002; **21**(2): 148-55.
181. O'Callaghan-Gordo C, Diez-Padrisa N, Abacassamo F, et al. Viral acute respiratory infections among infants visited in a rural hospital of southern Mozambique. *Trop Med Int Health* 2011; **16**(9): 1054-60.
182. Vidal LR, Siqueira MM, Nogueira MB, et al. The epidemiology and antigenic characterization of influenza viruses isolated in Curitiba, South Brazil. *Mem Inst Oswaldo Cruz* 2008; **103**(2): 180-5.
183. Venter M, Lassauniere R, Kresfelder TL, Westerberg Y, Visser A. Contribution of common and recently described respiratory viruses to annual hospitalizations in children in South Africa. *J Med Virol* 2011; **83**(8): 1458-68.
184. Pale M, Nacoto A, Tivane A, et al. Respiratory syncytial and influenza viruses in children under 2 years old with severe acute respiratory infection (SARI) in Maputo, 2015. *PLoS ONE* 2017; **12**(11): e0186735.
185. Vega-Briceno LE, Pulgar BD, Potin SM, Ferres GM, Sanchez DI. [Clinical and epidemiological manifestations of parainfluenza infection in hospitalized children]. *Rev* 2007; **24**(5): 377-83.
186. Viegas M, Barrero PR, Maffey AF, Mistchenko AS. Respiratory viruses seasonality in children under five years of age in Buenos Aires, Argentina: a five-year analysis. *J Infect* 2004; **49**(3): 222-8.

A9. Study sites included in the seasonality analysis by IFV type and subtype



A10. Heat map of global monthly activity of IFV A and B, and IFV A subtypes



A11. Epidemic months of IFV, RSV, PIV and MPV grouped by country

IFV

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Africa Region	Algeria	nationwide	✓	✓										✓
Africa Region	Burkina Faso	nationwide		✓						✓	✓	✓	✓	✓
Africa Region	Cameroon	nationwide			✓	✓	✓				✓	✓	✓	✓
Africa Region	Cameroon	Yaoundé			✓		✓				✓	✓	✓	✓
Africa Region	Central African Republic	nationwide							✓	✓	✓			
Africa Region	Côte d'Ivoire	Abidjan			✓			✓				✓		
Africa Region	Democratic Republic of the Congo	nationwide	✓	✓		✓	✓	✓						✓
Africa Region	Ethiopia	nationwide	✓	✓	✓	✓						✓	✓	
Africa Region	Ghana	nationwide				✓	✓	✓	✓			✓	✓	✓
Africa Region	Kenya	Kilifi			✓				✓	✓		✓	✓	✓
Africa Region	Kenya	nationwide		✓	✓	✓			✓	✓	✓	✓	✓	
Africa Region	Madagascar	nationwide	✓	✓	✓		✓	✓	✓			✓	✓	✓
Africa Region	Mali	nationwide		✓	✓					✓	✓	✓		
Africa Region	Mauritania	nationwide		✓	✓	✓					✓			
Africa Region	Mauritius	nationwide	✓	✓	✓	✓	✓		✓		✓			
Africa Region	Mozambique	nationwide		✓				✓		✓		✓	✓	✓
Africa Region	Mozambique	Manhiça		✓	✓	✓	✓							
Africa Region	Niger	nationwide	✓	✓	✓								✓	✓
Africa Region	Nigeria	nationwide	✓	✓	✓	✓				✓	✓	✓	✓	

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Africa Region	Senegal	nationwide								✓	✓	✓	✓	
Africa Region	Senegal	Dielmo								✓		✓	✓	
Africa Region	Senegal	Ndiop		✓						✓		✓	✓	
Africa Region	Senegal	Dakar			✓			✓	✓	✓	✓	✓		
Africa Region	Sierra Leone	nationwide				✓			✓	✓		✓	✓	
Africa Region	South Africa	Soweto					✓	✓	✓	✓	✓			
Africa Region	South Africa	Agincourt						✓	✓	✓	✓			
Africa Region	South Africa	nationwide						✓	✓	✓	✓			
Africa Region	South Africa	Pretoria				✓	✓	✓		✓				
Africa Region	Tanzania	nationwide	✓	✓	✓		✓	✓					✓	✓
Africa Region	Togo	nationwide					✓	✓	✓			✓	✓	✓
Africa Region	Uganda	nationwide								✓	✓	✓	✓	
Africa Region	Zambia	nationwide		✓	✓	✓			✓	✓	✓	✓		
Eastern Mediterranean Region	Afghanistan	nationwide		✓								✓	✓	✓
Eastern Mediterranean Region	Bahrain	nationwide	✓	✓								✓	✓	✓
Eastern Mediterranean Region	Egypt	nationwide	✓	✓	✓								✓	✓
Eastern Mediterranean Region	Egypt	Damanhour district	✓	✓						✓	✓	✓	✓	✓
Eastern Mediterranean Region	Iran (Islamic Republic of)	nationwide	✓	✓										✓

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Eastern Mediterranean Region	Iraq	nationwide	✓	✓										
Eastern Mediterranean Region	Jordan	Amman	✓	✓			✓							✓
Eastern Mediterranean Region	Jordan	nationwide	✓		✓	✓								✓
Eastern Mediterranean Region	Lebanon	nationwide	✓	✓	✓									✓
Eastern Mediterranean Region	Morocco	Rabat	✓	✓										✓
Eastern Mediterranean Region	Morocco	nationwide	✓	✓									✓	✓
Eastern Mediterranean Region	Oman	nationwide	✓		✓	✓	✓					✓	✓	✓
Eastern Mediterranean Region	Pakistan	nationwide	✓	✓	✓								✓	✓
Eastern Mediterranean Region	Qatar	nationwide	✓	✓	✓							✓	✓	✓
Eastern Mediterranean Region	Saudi Arabia	Riyadh											✓	✓
Eastern Mediterranean Region	Yemen	nationwide	✓				✓	✓	✓				✓	✓
European Region	Armenia	nationwide		✓	✓	✓								
European Region	Aruba	nationwide	✓		✓	✓	✓		✓					✓
European Region	Austria	nationwide		✓	✓									
European Region	Azerbaijan	nationwide	✓	✓										

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
European Region	Belarus	nationwide			✓	✓								
European Region	Belgium	nationwide	✓	✓	✓									
European Region	Belgium	Leuven	✓	✓	✓									
European Region	Bermuda	nationwide		✓			✓	✓						
European Region	Bosnia and Herzegovina	nationwide	✓	✓										
European Region	Bulgaria	nationwide	✓	✓	✓									
European Region	Cyprus	Nicosia	✓	✓		✓								
European Region	Denmark	nationwide	✓	✓	✓									
European Region	Finland	nationwide	✓	✓	✓									✓
European Region	France	nationwide	✓	✓	✓									
European Region	France	Réunion Island					✓	✓	✓		✓	✓		
European Region	France	Paris	✓	✓	✓									
European Region	French Guiana	nationwide	✓	✓	✓	✓	✓	✓						
European Region	Georgia	nationwide	✓	✓	✓									
European Region	Germany	Berlin	✓	✓	✓									
European Region	Germany	nationwide	✓	✓	✓									
European Region	Greece	nationwide		✓	✓									
European Region	Guadeloupe	nationwide	✓	✓	✓								✓	
European Region	Iceland	nationwide	✓	✓	✓									
European Region	Ireland	nationwide	✓	✓	✓									
European Region	Kazakhstan	nationwide	✓	✓										
European Region	Kyrgyzstan	nationwide	✓	✓										

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
European Region	Lithuania	nationwide	✓	✓	✓									
European Region	Malta	nationwide	✓	✓										
European Region	Martinique	nationwide	✓	✓	✓									✓
European Region	Netherlands	nationwide	✓	✓	✓									
European Region	New Caledonia	nationwide			✓	✓			✓	✓	✓	✓		✓
European Region	Norway	nationwide	✓	✓	✓									✓
European Region	Poland	nationwide	✓	✓	✓									
European Region	Portugal	nationwide	✓	✓										✓
European Region	Republic of Moldova	nationwide		✓	✓									
European Region	Romania	nationwide		✓	✓									
European Region	Russian Federation	nationwide	✓	✓	✓									
European Region	Slovakia	nationwide	✓	✓	✓									
European Region	Slovenia	nationwide	✓	✓	✓									
European Region	Spain	nationwide	✓	✓										✓
European Region	Spain	Gran Canaria	✓	✓	✓	✓							✓	✓
European Region	Sweden	nationwide	✓	✓	✓									✓
European Region	Switzerland	nationwide	✓	✓	✓									
European Region	Turkey	nationwide	✓	✓										✓
European Region	Turkey	Istanbul	✓	✓	✓	✓								
European Region	UK	nationwide	✓	✓	✓									✓
European Region	UK	England	✓	✓										✓
European Region	Ukraine	nationwide		✓	✓	✓								

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Region of the Americas	Argentina	Buenos Aires					✓	✓	✓	✓				
Region of the Americas	Argentina	nationwide					✓	✓	✓	✓				
Region of the Americas	Barbados	nationwide		✓	✓			✓	✓			✓	✓	
Region of the Americas	Belize	nationwide		✓	✓	✓								
Region of the Americas	Bolivia	nationwide				✓	✓	✓	✓		✓	✓		
Region of the Americas	Brazil	Belo Horizonte				✓	✓	✓	✓	✓	✓			✓
Region of the Americas	Brazil	nationwide			✓	✓	✓	✓	✓	✓				
Region of the Americas	Brazil	North Brazil		✓	✓								✓	
Region of the Americas	Brazil	Southeast Brazil					✓	✓	✓	✓		✓		
Region of the Americas	Brazil	South Brazil						✓	✓			✓		
Region of the Americas	Brazil	São Paulo						✓	✓	✓	✓			
Region of the Americas	Brazil	Curitiba					✓	✓	✓	✓				
Region of the Americas	Brazil	Uberlândia			✓		✓		✓	✓				
Region of the Americas	Canada	nationwide	✓	✓	✓									✓
Region of the Americas	Chile	Iquique			✓			✓	✓					
Region of the Americas	Chile	nationwide					✓	✓	✓	✓	✓			
Region of the Americas	Colombia	nationwide	✓		✓	✓	✓	✓	✓	✓		✓	✓	
Region of the Americas	Costa Rica	nationwide	✓						✓		✓	✓	✓	✓
Region of the Americas	Cuba	nationwide					✓	✓	✓	✓	✓	✓	✓	
Region of the Americas	Dominican Republic	nationwide			✓	✓	✓	✓	✓	✓				
Region of the Americas	Ecuador	nationwide	✓	✓	✓	✓	✓		✓	✓				
Region of the Americas	El Salvador	nationwide					✓	✓	✓		✓	✓	✓	

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Region of the Americas	Guatemala	Santa Rosa			✓	✓		✓	✓	✓	✓			
Region of the Americas	Guatemala	Quetzaltenango	✓	✓	✓	✓						✓	✓	
Region of the Americas	Guatemala	nationwide	✓	✓	✓	✓		✓	✓			✓		
Region of the Americas	Haiti	nationwide									✓	✓	✓	✓
Region of the Americas	Honduras	nationwide	✓						✓	✓	✓	✓	✓	
Region of the Americas	Honduras	Santa Lucía								✓	✓	✓		
Region of the Americas	Jamaica	nationwide	✓	✓			✓	✓				✓	✓	✓
Region of the Americas	Mexico	nationwide	✓	✓	✓									✓
Region of the Americas	Mexico	Aguascalientes	✓	✓										✓
Region of the Americas	Mexico	Baja California Norte	✓	✓										
Region of the Americas	Mexico	Baja California Sur	✓	✓	✓									
Region of the Americas	Mexico	Campeche	✓	✓	✓				✓		✓	✓		
Region of the Americas	Mexico	Coahuila De Zaragoza	✓	✓							✓	✓		
Region of the Americas	Mexico	Colima	✓	✓	✓									✓
Region of the Americas	Mexico	Chiapas	✓											✓
Region of the Americas	Mexico	Chihuahua	✓	✓									✓	✓
Region of the Americas	Mexico	Distrito Federal	✓	✓										✓
Region of the Americas	Mexico	Durango	✓	✓										
Region of the Americas	Mexico	Guanajuato	✓	✓										✓
Region of the Americas	Mexico	Guerrero	✓	✓	✓			✓			✓	✓		
Region of the Americas	Mexico	Hidalgo	✓	✓										
Region of the Americas	Mexico	Jalisco	✓	✓										

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Region of the Americas	Mexico	Mexico	✓	✓										✓
Region of the Americas	Mexico	Michoacan de Ocampo	✓	✓										
Region of the Americas	Mexico	Morelos	✓	✓										
Region of the Americas	Mexico	Nayarit	✓	✓	✓								✓	
Region of the Americas	Mexico	Nuevo Leon	✓	✓										✓
Region of the Americas	Mexico	Oaxaca	✓	✓										
Region of the Americas	Mexico	Puebla	✓	✓										✓
Region of the Americas	Mexico	Queretaro de Arteaga	✓	✓										✓
Region of the Americas	Mexico	Quintana Roo	✓	✓					✓	✓	✓	✓		
Region of the Americas	Mexico	San Luis Potosí	✓	✓										✓
Region of the Americas	Mexico	Sinaloa	✓	✓	✓								✓	
Region of the Americas	Mexico	Sonora	✓	✓										
Region of the Americas	Mexico	Tabasco	✓	✓							✓			
Region of the Americas	Mexico	Tamaulipas	✓	✓									✓	✓
Region of the Americas	Mexico	Tlaxcala	✓	✓	✓									
Region of the Americas	Mexico	Veracruz-Llave	✓	✓	✓							✓	✓	✓
Region of the Americas	Mexico	Yucatan	✓						✓	✓	✓	✓	✓	
Region of the Americas	Mexico	Zacatecas	✓	✓										✓
Region of the Americas	Nicaragua	nationwide							✓	✓	✓	✓	✓	
Region of the Americas	Panama	nationwide					✓	✓	✓	✓				
Region of the Americas	Paraguay	nationwide					✓	✓	✓	✓				
Region of the Americas	Peru	Tambopata district	✓					✓	✓					

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Region of the Americas	Peru	nationwide	✓				✓	✓	✓	✓	✓			
Region of the Americas	Peru	San Marcos province										✓	✓	✓
Region of the Americas	Suriname	nationwide		✓	✓	✓			✓	✓	✓			
Region of the Americas	Trinidad and Tobago	nationwide	✓	✓							✓	✓	✓	
Region of the Americas	Uruguay	nationwide					✓	✓	✓	✓				
Region of the Americas	USA	nationwide	✓	✓	✓									✓
Region of the Americas	USA	Chicago and Nashville	✓	✓	✓									✓
Region of the Americas	Venezuela (Bolivarian Republic of)	nationwide			✓	✓	✓						✓	
Southeast Asia Region	Bangladesh	Kishoregonj, Bogra, Comilla and Barisal						✓	✓	✓				
Southeast Asia Region	Bangladesh	nationwide				✓	✓	✓	✓	✓	✓			
Southeast Asia Region	Bhutan	nationwide	✓	✓	✓	✓	✓		✓	✓				
Southeast Asia Region	India	Puducherry	✓	✓		✓	✓							
Southeast Asia Region	India	nationwide		✓	✓	✓			✓	✓	✓			
Southeast Asia Region	India	Chennai	✓	✓	✓	✓						✓	✓	✓
Southeast Asia Region	India	Srinagar	✓	✓	✓	✓								✓
Southeast Asia Region	India	Dibrugarh					✓	✓	✓	✓				✓
Southeast Asia Region	India	Lucknow							✓	✓	✓	✓		
Southeast Asia Region	India	Nagpur	✓		✓				✓	✓	✓	✓	✓	
Southeast Asia Region	India	Vellore	✓		✓					✓	✓	✓	✓	✓
Southeast Asia Region	India	Alapphuzha					✓	✓	✓	✓				
Southeast Asia Region	India	Delhi		✓	✓				✓	✓	✓			

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Southeast Asia Region	India	Kolkata		✓			✓	✓	✓	✓	✓			✓
Southeast Asia Region	India	Pune			✓	✓			✓	✓	✓	✓		
Southeast Asia Region	Indonesia	nationwide	✓	✓	✓	✓	✓						✓	✓
Southeast Asia Region	Maldives	nationwide		✓	✓	✓						✓		✓
Southeast Asia Region	Myanmar	nationwide							✓	✓				
Southeast Asia Region	Nepal	nationwide		✓	✓				✓	✓	✓			
Southeast Asia Region	Nepal	Kathmandu	✓	✓	✓					✓				
Southeast Asia Region	Sri Lanka	nationwide	✓	✓	✓	✓	✓	✓						✓
Southeast Asia Region	Sri Lanka	Ragama					✓		✓		✓		✓	✓
Southeast Asia Region	Sri Lanka	Galle				✓	✓	✓						
Southeast Asia Region	Thailand	Nakhon Phanom and Sa Kaeo		✓	✓				✓	✓	✓	✓		
Southeast Asia Region	Thailand	Bangkok		✓					✓	✓	✓	✓	✓	
Southeast Asia Region	Thailand	Khon Kaen		✓	✓			✓	✓	✓	✓	✓	✓	
Southeast Asia Region	Thailand	nationwide	✓	✓	✓				✓	✓	✓	✓	✓	
Western Pacific Region	Australia	nationwide							✓	✓	✓			
Western Pacific Region	Cambodia	nationwide							✓	✓	✓	✓	✓	
Western Pacific Region	Cambodia	Battambang, Oddar Meanchey, Pailin and Banteay Meanchey								✓	✓	✓	✓	
Western Pacific Region	China	nationwide	✓	✓	✓	✓			✓	✓				✓
Western Pacific Region	China	Hong Kong	✓	✓	✓	✓		✓	✓					
Western Pacific Region	China	Shantou	✓		✓	✓	✓							

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Western Pacific Region	China	Huizhou	✓	✓	✓	✓							✓	✓
Western Pacific Region	China	Guangzhou	✓	✓	✓	✓	✓							✓
Western Pacific Region	China	Karamay	✓	✓										✓
Western Pacific Region	China	Taiwan	✓	✓	✓				✓	✓	✓			✓
Western Pacific Region	China	Danzhou			✓	✓						✓	✓	✓
Western Pacific Region	China	Guangdong				✓	✓	✓	✓					
Western Pacific Region	China	Suzhou	✓		✓				✓	✓				
Western Pacific Region	China	Lanzhou	✓		✓	✓							✓	✓
Western Pacific Region	China	Hainan					✓		✓	✓	✓			
Western Pacific Region	China	Shandong	✓	✓	✓									✓
Western Pacific Region	China	Nanchang	✓	✓	✓		✓	✓	✓					
Western Pacific Region	China	Honghe	✓	✓	✓	✓				✓				
Western Pacific Region	China	Chongqing	✓	✓	✓			✓	✓					✓
Western Pacific Region	China	Shenzhen			✓		✓	✓	✓	✓		✓		✓
Western Pacific Region	China	Shaoguan		✓	✓	✓	✓	✓			✓			✓
Western Pacific Region	China	Northern China	✓	✓	✓									✓
Western Pacific Region	China	Southern China	✓	✓	✓				✓	✓	✓			✓
Western Pacific Region	China	Fuxin	✓		✓									✓
Western Pacific Region	China	Liaoning	✓	✓	✓									
Western Pacific Region	China	Hangzhou	✓	✓	✓	✓				✓	✓			✓
Western Pacific Region	China	Dazhou	✓	✓	✓				✓				✓	✓
Western Pacific Region	China	Zhejiang	✓	✓	✓									✓

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Western Pacific Region	China	Jingzhou	✓	✓						✓				✓
Western Pacific Region	China	Shanghai	✓	✓	✓				✓	✓				✓
Western Pacific Region	China	Beijing	✓	✓	✓								✓	
Western Pacific Region	Fiji	nationwide			✓	✓	✓				✓	✓		
Western Pacific Region	Japan	nationwide	✓	✓	✓									
Western Pacific Region	Japan	Okinawa	✓	✓	✓	✓	✓			✓				✓
Western Pacific Region	Japan	Yokohama	✓	✓	✓									
Western Pacific Region	Lao PDR	nationwide								✓	✓	✓	✓	✓
Western Pacific Region	Malaysia	nationwide	✓	✓	✓	✓	✓	✓	✓		✓			
Western Pacific Region	Malaysia	Kuala Lumpur	✓		✓		✓		✓		✓	✓	✓	✓
Western Pacific Region	Mongolia	Ulaanbaatar	✓		✓								✓	✓
Western Pacific Region	Mongolia	nationwide	✓	✓	✓									
Western Pacific Region	New Zealand	nationwide							✓	✓	✓			
Western Pacific Region	Philippines	Bohol	✓		✓		✓	✓	✓	✓				
Western Pacific Region	Philippines	nationwide						✓	✓	✓	✓	✓	✓	
Western Pacific Region	Republic of Korea	nationwide	✓	✓	✓	✓								
Western Pacific Region	Republic of Korea	Seoul	✓			✓	✓							✓
Western Pacific Region	Singapore	nationwide	✓	✓	✓	✓	✓	✓	✓	✓				
Western Pacific Region	Vietnam	Nha Trang City	✓	✓	✓	✓	✓	✓	✓					
Western Pacific Region	Vietnam	nationwide			✓	✓	✓	✓	✓	✓		✓	✓	
Western Pacific Region	Vietnam	Hanoi			✓		✓	✓	✓			✓		✓

RSV

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Africa Region	Burkina Faso	Ouagadougou									✓	✓		
Africa Region	Cameroon	Yaoundé									✓	✓	✓	
Africa Region	Cameroon	nationwide										✓	✓	
Africa Region	Gambia	Basse										✓	✓	✓
Africa Region	Gambia	Banjul			✓					✓	✓	✓	✓	
Africa Region	Kenya	Kilifi	✓	✓	✓									✓
Africa Region	Kenya	Lwak			✓		✓	✓	✓	✓	✓		✓	
Africa Region	Kenya	Dadaab	✓	✓	✓			✓					✓	✓
Africa Region	Mali	Bamako			✓					✓	✓	✓	✓	✓
Africa Region	Mozambique	Manhiça		✓	✓	✓								
Africa Region	Mozambique	Maputo		✓	✓	✓	✓							
Africa Region	Nigeria	Eleta and Ijaye	✓					✓	✓			✓	✓	✓
Africa Region	South Africa	Soweto			✓	✓	✓	✓	✓	✓				
Africa Region	South Africa	Agincourt	✓	✓	✓	✓	✓							
Africa Region	South Africa	Pietermaritzburg	✓	✓	✓	✓					✓	✓	✓	
Africa Region	South Africa	Klerksdorp			✓	✓	✓	✓						
Africa Region	South Africa	Paarl, Western Province				✓	✓	✓	✓					
Africa Region	South Africa	Pretoria				✓	✓	✓	✓					
Africa Region	Zambia	Lusaka	✓	✓	✓	✓				✓				
Eastern Mediterranean Region	Egypt	nationwide	✓	✓	✓								✓	✓

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Eastern Mediterranean Region	Jordan	Amman	✓	✓	✓									
Eastern Mediterranean Region	Jordan	Zarqa		✓	✓	✓								
Eastern Mediterranean Region	Jordan	nationwide	✓	✓	✓									
Eastern Mediterranean Region	Kwait	nationwide	✓	✓										✓
Eastern Mediterranean Region	Lebanon	Beirut	✓	✓										✓
Eastern Mediterranean Region	Morocco	Rabat	✓	✓										
Eastern Mediterranean Region	Morocco	nationwide	✓	✓										
Eastern Mediterranean Region	Oman	nationwide	✓	✓	✓						✓	✓	✓	✓
Eastern Mediterranean Region	Pakistan	Karachi	✓	✓						✓	✓	✓	✓	
Eastern Mediterranean Region	Qatar	Doha	✓	✓									✓	✓
Eastern Mediterranean Region	Saudi Arabia	Riyadh	✓											✓
Eastern Mediterranean Region	Tunisia	Sousse	✓	✓	✓									
Eastern Mediterranean Region	Yemen	nationwide	✓	✓	✓			✓			✓		✓	✓
European Region	Aruba	nationwide							✓	✓	✓	✓	✓	

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
European Region	Austria	Vienna	✓	✓	✓	✓								✓
European Region	Austria	Graz	✓	✓	✓	✓								✓
European Region	Belgium	Leuven	✓										✓	✓
European Region	Croatia	Zagreb	✓	✓	✓	✓								✓
European Region	Cyprus	Nicosia	✓	✓										
European Region	France	Paris	✓										✓	✓
European Region	France	Montpellier	✓	✓										✓
European Region	France	Réunion Island	✓	✓	✓	✓								✓
European Region	Germany	Berlin	✓	✓										✓
European Region	Germany	Stuttgart	✓	✓	✓									✓
European Region	Germany	Kiel	✓	✓	✓									✓
European Region	Germany	Freiburg	✓	✓	✓	✓	✓							✓
European Region	Greece	Athens	✓	✓	✓									
European Region	Latvia	Riga		✓	✓	✓								
European Region	Spain	Sacyl	✓	✓	✓							✓	✓	✓
European Region	Spain	Gran Canaria	✓										✓	✓
European Region	Spain	Leganés	✓										✓	✓
European Region	Spain	Mallorca	✓	✓										✓
European Region	Sweden	Gothenburg	✓	✓	✓									✓
European Region	Sweden	Halmstad and Halland County		✓	✓									
European Region	Switzerland	Basel	✓	✓										✓
European Region	Switzerland	Bern	✓	✓	✓									✓

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
European Region	Turkey	Istanbul	✓			✓	✓		✓			✓	✓	✓
European Region	Turkey	nationwide	✓	✓	✓									
European Region	UK	Belfast	✓	✓										✓
European Region	UK	England	✓										✓	✓
Region of the Americas	Argentina	nationwide					✓	✓	✓					
Region of the Americas	Argentina	Buenos Aires					✓	✓	✓					
Region of the Americas	Barbados	nationwide		✓	✓				✓	✓	✓	✓		
Region of the Americas	Belize	nationwide										✓	✓	✓
Region of the Americas	Bolivia	nationwide			✓	✓	✓	✓	✓					
Region of the Americas	Brazil	Belo Horizonte	✓	✓	✓	✓	✓				✓			
Region of the Americas	Brazil	nationwide			✓	✓	✓	✓	✓					
Region of the Americas	Brazil	Fortaleza				✓	✓	✓	✓					
Region of the Americas	Brazil	Salvador			✓	✓	✓					✓	✓	✓
Region of the Americas	Brazil	Vitória		✓	✓	✓								
Region of the Americas	Brazil	São Paulo			✓	✓	✓	✓	✓	✓				
Region of the Americas	Brazil	São José do Rio Preto			✓	✓			✓		✓	✓		
Region of the Americas	Brazil	Uberlândia			✓	✓	✓							
Region of the Americas	Canada	nationwide	✓	✓	✓									✓
Region of the Americas	Canada	Nova Scotia	✓	✓	✓	✓								
Region of the Americas	Canada	Edmonton	✓	✓	✓									
Region of the Americas	Chile	Concepcion						✓	✓	✓				
Region of the Americas	Chile	Iquique				✓	✓	✓						

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Region of the Americas	Chile	nationwide					✓	✓	✓	✓				
Region of the Americas	Colombia	nationwide			✓	✓	✓	✓	✓		✓	✓	✓	
Region of the Americas	Colombia	Bogota			✓	✓	✓	✓						
Region of the Americas	Costa Rica	nationwide	✓						✓	✓	✓	✓	✓	
Region of the Americas	Cuba	nationwide								✓	✓	✓	✓	
Region of the Americas	Dominica	nationwide			✓		✓	✓		✓				
Region of the Americas	Dominican Republic	nationwide						✓	✓	✓	✓	✓	✓	
Region of the Americas	Ecuador	nationwide	✓	✓	✓	✓	✓							
Region of the Americas	Ecuador	Quito		✓	✓	✓	✓	✓	✓					
Region of the Americas	El Salvador	Santa Ana					✓	✓	✓	✓				
Region of the Americas	El Salvador	nationwide						✓	✓	✓	✓	✓	✓	
Region of the Americas	Guatemala	Santa Rosa						✓	✓	✓	✓	✓		
Region of the Americas	Guatemala	Quetzaltenango	✓	✓					✓	✓	✓	✓	✓	
Region of the Americas	Guatemala	San Lorenzo and Comitancillo		✓			✓		✓	✓	✓	✓	✓	
Region of the Americas	Guatemala	nationwide						✓	✓	✓	✓	✓	✓	
Region of the Americas	Honduras	nationwide							✓	✓	✓	✓	✓	
Region of the Americas	Honduras	Santa Lucía							✓		✓	✓	✓	
Region of the Americas	Mexico	San Luis Potosí	✓	✓									✓	✓
Region of the Americas	Mexico	nationwide	✓	✓	✓							✓	✓	
Region of the Americas	Mexico	Mexico City		✓	✓	✓			✓	✓			✓	✓
Region of the Americas	Mexico	Mexico City and San Luis Potosí	✓								✓	✓	✓	✓

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Region of the Americas	Nicaragua	nationwide								✓	✓	✓	✓	✓
Region of the Americas	Panama	David City, Chiriquí Province							✓	✓	✓	✓	✓	
Region of the Americas	Panama	nationwide								✓	✓	✓	✓	✓
Region of the Americas	Paraguay	nationwide				✓	✓	✓	✓	✓				
Region of the Americas	Peru	Tambopata district				✓	✓	✓						
Region of the Americas	Peru	nationwide			✓	✓	✓	✓	✓	✓				
Region of the Americas	Peru	San Marcos province				✓	✓	✓						
Region of the Americas	Puerto Rico	San Juan	✓			✓					✓	✓	✓	✓
Region of the Americas	Suriname	nationwide	✓	✓	✓	✓	✓	✓	✓					
Region of the Americas	Trinidad and Tobago	nationwide	✓	✓	✓	✓	✓				✓	✓		
Region of the Americas	Uruguay	nationwide						✓	✓	✓				
Region of the Americas	USA	YK Delta, Alaska	✓	✓	✓	✓	✓					✓	✓	✓
Region of the Americas	USA	State of Colorado	✓	✓	✓									
Region of the Americas	USA	Corpus Christi, Texas	✓	✓										✓
Region of the Americas	USA	Miami	✓	✓						✓	✓	✓	✓	✓
Region of the Americas	USA	Florida	✓	✓	✓							✓	✓	✓
Region of the Americas	USA	North Carolina	✓	✓									✓	✓
Region of the Americas	USA	Chicago and Nashville	✓	✓	✓								✓	✓
Region of the Americas	USA	Davidson and Monroe County	✓	✓	✓									
Region of the Americas	Venezuela	nationwide	✓	✓					✓	✓	✓			
Southeast Asia Region	Bangladesh	Dhaka	✓	✓				✓	✓			✓	✓	✓

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Southeast Asia Region	Bangladesh	Matlab										✓	✓	✓
Southeast Asia Region	India	Ballabgarh, Faridabad and Haryana	✓	✓		✓					✓	✓		
Southeast Asia Region	India	Puducherry	✓							✓	✓		✓	✓
Southeast Asia Region	India	Kolkata	✓	✓								✓	✓	
Southeast Asia Region	India	Pune	✓						✓	✓	✓			✓
Southeast Asia Region	India	Lucknow	✓										✓	✓
Southeast Asia Region	India	Delhi	✓								✓	✓	✓	
Southeast Asia Region	India	Jaipur	✓	✓									✓	✓
Southeast Asia Region	Indonesia	Lombok Island		✓	✓	✓								
Southeast Asia Region	Indonesia	Cikutra and Ujung Berung, Bandung			✓	✓	✓							
Southeast Asia Region	Nepal	Sarlahi									✓	✓	✓	
Southeast Asia Region	Nepal	Kathmandu	✓							✓	✓	✓		
Southeast Asia Region	Thailand	Tak Province										✓	✓	
Southeast Asia Region	Thailand	Nakhon Phanom and Sa Kaeo								✓	✓	✓		
Southeast Asia Region	Thailand	Bangkok							✓	✓	✓	✓		
Southeast Asia Region	Thailand	Khon Kaen			✓				✓	✓	✓	✓		
Southeast Asia Region	Thailand	Chonburi							✓		✓		✓	
Western Pacific Region	Australia	New South Wales				✓	✓	✓	✓	✓				
Western Pacific Region	Australia	Alice Springs			✓	✓	✓	✓	✓	✓	✓			
Western Pacific Region	Australia	the Top End	✓	✓	✓	✓	✓							

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Western Pacific Region	Australia	Kimberley, Western Australia		✓	✓	✓	✓	✓		✓			✓	✓
Western Pacific Region	Australia	Pilbara, Western Australia			✓	✓	✓	✓	✓	✓	✓	✓		
Western Pacific Region	Australia	Midwest-Murchison, Western Australia						✓	✓	✓	✓	✓		
Western Pacific Region	Australia	Goldfields, Western Australia						✓	✓	✓	✓	✓		
Western Pacific Region	Australia	Wheatbelt, Western Australia						✓	✓	✓	✓			
Western Pacific Region	Australia	Perth, Western Australia						✓	✓	✓	✓			
Western Pacific Region	Australia	Great Southern, Western Australia						✓	✓	✓	✓	✓		
Western Pacific Region	Australia	South West, Western Australia						✓	✓	✓	✓	✓		
Western Pacific Region	Cambodia	Kampong Cham city and Takeo city								✓	✓	✓	✓	
Western Pacific Region	China	nationwide	✓	✓	✓	✓						✓	✓	✓
Western Pacific Region	China	Beijing	✓	✓										✓
Western Pacific Region	China	Hong Kong			✓	✓	✓	✓	✓	✓	✓	✓		
Western Pacific Region	China	Shantou	✓		✓		✓							
Western Pacific Region	China	Eastern China	✓	✓	✓							✓	✓	✓
Western Pacific Region	China	Beijing, Shanghai, Chongqing, Guangdong, Gansu and Sichuan	✓	✓	✓	✓							✓	✓
Western Pacific Region	China	Shenzhen	✓	✓	✓	✓	✓		✓	✓				✓

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Western Pacific Region	China	Jingzhou	✓								✓	✓	✓	✓
Western Pacific Region	China	Lanzhou	✓		✓	✓							✓	✓
Western Pacific Region	China	Northern Taiwan		✓	✓	✓	✓		✓	✓	✓	✓		
Western Pacific Region	China	Suzhou	✓	✓	✓									✓
Western Pacific Region	China	Hangzhou	✓	✓	✓									✓
Western Pacific Region	China	Xi'an	✓							✓		✓	✓	✓
Western Pacific Region	China	Chongqing	✓	✓									✓	✓
Western Pacific Region	China	Shanghai	✓	✓	✓			✓		✓		✓		✓
Western Pacific Region	China	Kunming	✓	✓					✓	✓	✓	✓		✓
Western Pacific Region	China	Bengbu	✓											✓
Western Pacific Region	Japan	nationwide	✓	✓							✓	✓	✓	✓
Western Pacific Region	Japan	Tokyo	✓	✓						✓		✓	✓	✓
Western Pacific Region	Japan	Osaka	✓						✓				✓	✓
Western Pacific Region	Japan	Yamagata	✓									✓	✓	✓
Western Pacific Region	Japan	Fukuoka	✓							✓	✓	✓	✓	✓
Western Pacific Region	Japan	Yokohama	✓									✓	✓	✓
Western Pacific Region	Japan	Shizuoka	✓	✓	✓	✓						✓		✓
Western Pacific Region	Japan	Niigata City									✓		✓	✓
Western Pacific Region	Malaysia	Kuala Lumpur	✓	✓					✓	✓	✓	✓	✓	✓
Western Pacific Region	Mongolia	Ulaanbaatar		✓	✓	✓								
Western Pacific Region	New Zealand	nationwide						✓	✓	✓	✓			
Western Pacific Region	Philippines	Bohol	✓							✓	✓	✓	✓	✓

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Western Pacific Region	Philippines	Tacloban								✓	✓	✓	✓	✓
Western Pacific Region	Republic of Korea	Busan										✓	✓	✓
Western Pacific Region	Republic of Korea	Seoul	✓	✓								✓	✓	✓
Western Pacific Region	Vietnam	Nha Trang City							✓	✓	✓	✓		
Western Pacific Region	Vietnam	Ho Chi Minh City								✓	✓	✓	✓	

PIV

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Africa Region	Cameroon	nationwide		✓	✓	✓		✓		✓				
Africa Region	Ghana	Kumasi			✓	✓	✓	✓						
Africa Region	Kenya	Kilifi		✓	✓	✓			✓	✓	✓		✓	✓
Africa Region	Mali	Bamako				✓	✓	✓	✓					
Africa Region	Mozambique	Manhiça					✓			✓	✓	✓	✓	✓
Africa Region	South Africa	Paarl, Western Province			✓	✓	✓		✓	✓	✓			
Africa Region	South Africa	Pretoria				✓				✓	✓	✓	✓	✓
Africa Region	Zambia	Lusaka	✓	✓	✓	✓	✓				✓			✓
Eastern Mediterranean Region	Egypt	nationwide					✓	✓	✓	✓	✓	✓		
Eastern Mediterranean Region	Jordan	Amman	✓			✓	✓		✓		✓	✓	✓	
Eastern Mediterranean Region	Jordan	nationwide	✓			✓	✓					✓	✓	✓

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Eastern Mediterranean Region	Morocco	Rabat			✓		✓		✓	✓	✓	✓	✓	
Eastern Mediterranean Region	Oman	nationwide	✓	✓	✓		✓			✓		✓		✓
Eastern Mediterranean Region	Saudi Arabia	Riyadh				✓			✓		✓	✓	✓	✓
Eastern Mediterranean Region	Yemen	nationwide	✓			✓	✓				✓		✓	✓
European Region	Belgium	Leuven	✓			✓	✓	✓	✓			✓	✓	✓
European Region	France	Paris	✓			✓	✓	✓	✓			✓		✓
European Region	Germany	Berlin	✓		✓	✓	✓	✓				✓	✓	✓
European Region	Germany	Bonn	✓		✓			✓		✓	✓	✓	✓	
European Region	Spain	Gran Canaria		✓	✓	✓	✓	✓				✓	✓	✓
European Region	Spain	Catalonia				✓	✓	✓	✓	✓			✓	
European Region	Sweden	Gothenburg			✓	✓	✓	✓				✓	✓	✓
European Region	Switzerland	Bern	✓		✓	✓	✓	✓				✓	✓	✓
European Region	Turkey	Istanbul	✓			✓		✓	✓	✓				
European Region	UK	England			✓	✓	✓	✓				✓	✓	✓
Region of the Americas	Argentina	nationwide						✓	✓	✓	✓	✓	✓	
Region of the Americas	Argentina	Buenos Aires							✓	✓	✓	✓		
Region of the Americas	Barbados	nationwide		✓	✓	✓				✓		✓	✓	
Region of the Americas	Bolivia	nationwide					✓	✓	✓	✓	✓	✓	✓	
Region of the Americas	Brazil	nationwide	✓			✓	✓		✓	✓	✓	✓	✓	
Region of the Americas	Brazil	Ceará	✓		✓			✓			✓	✓	✓	

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Region of the Americas	Brazil	São Paulo			✓	✓		✓			✓			
Region of the Americas	Canada	nationwide	✓		✓	✓	✓	✓	✓				✓	✓
Region of the Americas	Chile	Concepcion	✓			✓		✓		✓		✓		
Region of the Americas	Chile	Iquique				✓		✓	✓			✓		
Region of the Americas	Chile	nationwide					✓	✓	✓	✓	✓	✓		
Region of the Americas	Chile	Santiago				✓	✓	✓	✓			✓		
Region of the Americas	Colombia	nationwide		✓	✓	✓	✓	✓	✓		✓	✓	✓	
Region of the Americas	Costa Rica	nationwide	✓		✓		✓	✓	✓	✓		✓		
Region of the Americas	Cuba	nationwide		✓	✓	✓	✓	✓	✓	✓				
Region of the Americas	Dominican Republic	nationwide			✓	✓	✓	✓	✓	✓	✓		✓	
Region of the Americas	Ecuador	nationwide	✓	✓			✓	✓			✓	✓	✓	✓
Region of the Americas	Ecuador	Quito		✓			✓	✓	✓				✓	
Region of the Americas	El Salvador	nationwide		✓		✓	✓	✓	✓	✓	✓	✓		
Region of the Americas	Guatemala	nationwide			✓	✓	✓	✓	✓					
Region of the Americas	Honduras	nationwide		✓	✓	✓	✓	✓		✓	✓			
Region of the Americas	Honduras	Santa Lucía			✓		✓	✓	✓					
Region of the Americas	Mexico	nationwide	✓	✓	✓	✓	✓	✓		✓		✓		
Region of the Americas	Nicaragua	nationwide	✓				✓	✓	✓	✓				
Region of the Americas	Panama	nationwide	✓		✓	✓	✓	✓	✓	✓				
Region of the Americas	Paraguay	nationwide					✓	✓	✓	✓	✓	✓	✓	
Region of the Americas	Peru	nationwide	✓				✓	✓	✓	✓	✓	✓	✓	
Region of the Americas	Peru	San Marcos province	✓				✓			✓	✓	✓	✓	✓

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Region of the Americas	Suriname	nationwide	✓	✓	✓							✓		✓
Region of the Americas	Uruguay	nationwide					✓	✓	✓	✓	✓		✓	
Region of the Americas	USA	Aurora, Colorado	✓	✓	✓	✓	✓	✓					✓	✓
Region of the Americas	USA	Chicago and Nashville		✓	✓	✓	✓	✓	✓					
Region of the Americas	USA	Davidson and Monroe County		✓	✓	✓	✓			✓	✓			
Region of the Americas	Venezuela	nationwide	✓	✓	✓	✓		✓		✓				
Southeast Asia Region	India	Puducherry		✓		✓	✓		✓			✓		
Southeast Asia Region	Nepal	Kathmandu				✓	✓	✓	✓	✓				
Western Pacific Region	China	Hong Kong	✓	✓	✓	✓	✓	✓					✓	✓
Western Pacific Region	China	Shantou	✓	✓		✓	✓							
Western Pacific Region	China	Beijing, Shanghai, Chongqing, Guangdong, Gansu and Sichuan		✓	✓	✓	✓	✓	✓	✓				
Western Pacific Region	China	nationwide			✓	✓	✓	✓	✓	✓	✓	✓	✓	
Western Pacific Region	China	Shanghai				✓	✓		✓	✓	✓			
Western Pacific Region	China	Shenzhen			✓	✓	✓				✓	✓	✓	
Western Pacific Region	China	Taipei			✓	✓	✓	✓	✓	✓	✓			✓
Western Pacific Region	China	Lanzhou		✓	✓	✓	✓						✓	
Western Pacific Region	China	Hangzhou	✓		✓	✓		✓	✓	✓		✓	✓	
Western Pacific Region	China	Beijing					✓	✓	✓	✓	✓	✓	✓	
Western Pacific Region	China	Suzhou	✓		✓	✓	✓	✓	✓	✓		✓		
Western Pacific Region	China	Kunming		✓	✓	✓					✓		✓	✓

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Western Pacific Region	China	Bengbu				✓	✓	✓	✓					✓
Western Pacific Region	Japan	nationwide					✓	✓	✓	✓	✓	✓		
Western Pacific Region	Japan	Tokyo					✓	✓	✓	✓				
Western Pacific Region	Japan	Yamagata					✓	✓	✓					
Western Pacific Region	Malaysia	Kuala Lumpur		✓	✓	✓	✓	✓	✓	✓		✓		
Western Pacific Region	New Zealand	nationwide						✓	✓	✓	✓	✓		
Western Pacific Region	Philippines	Bohol	✓	✓	✓	✓	✓				✓	✓	✓	✓
Western Pacific Region	Republic of Korea	Seoul				✓	✓	✓	✓			✓	✓	
Western Pacific Region	Vietnam	Nha Trang City	✓	✓	✓	✓	✓	✓	✓					✓
Western Pacific Region	Vietnam	Ho Chi Minh City	✓		✓	✓								✓

MPV

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Africa Region	Cameroon	nationwide						✓	✓					
Africa Region	Kenya	Kilifi	✓	✓								✓	✓	✓
Africa Region	Mali	Bamako		✓	✓					✓				
Africa Region	Mozambique	Manhiça		✓	✓	✓		✓	✓					
Africa Region	South Africa	Soweto			✓			✓	✓	✓	✓			
Africa Region	South Africa	Pretoria		✓		✓	✓		✓	✓	✓			
Africa Region	Zambia	Lusaka		✓	✓					✓				✓
Eastern Mediterranean Region	Egypt	nationwide	✓	✓	✓									
Eastern Mediterranean Region	Iraq	Sulaimani	✓	✓	✓							✓	✓	✓

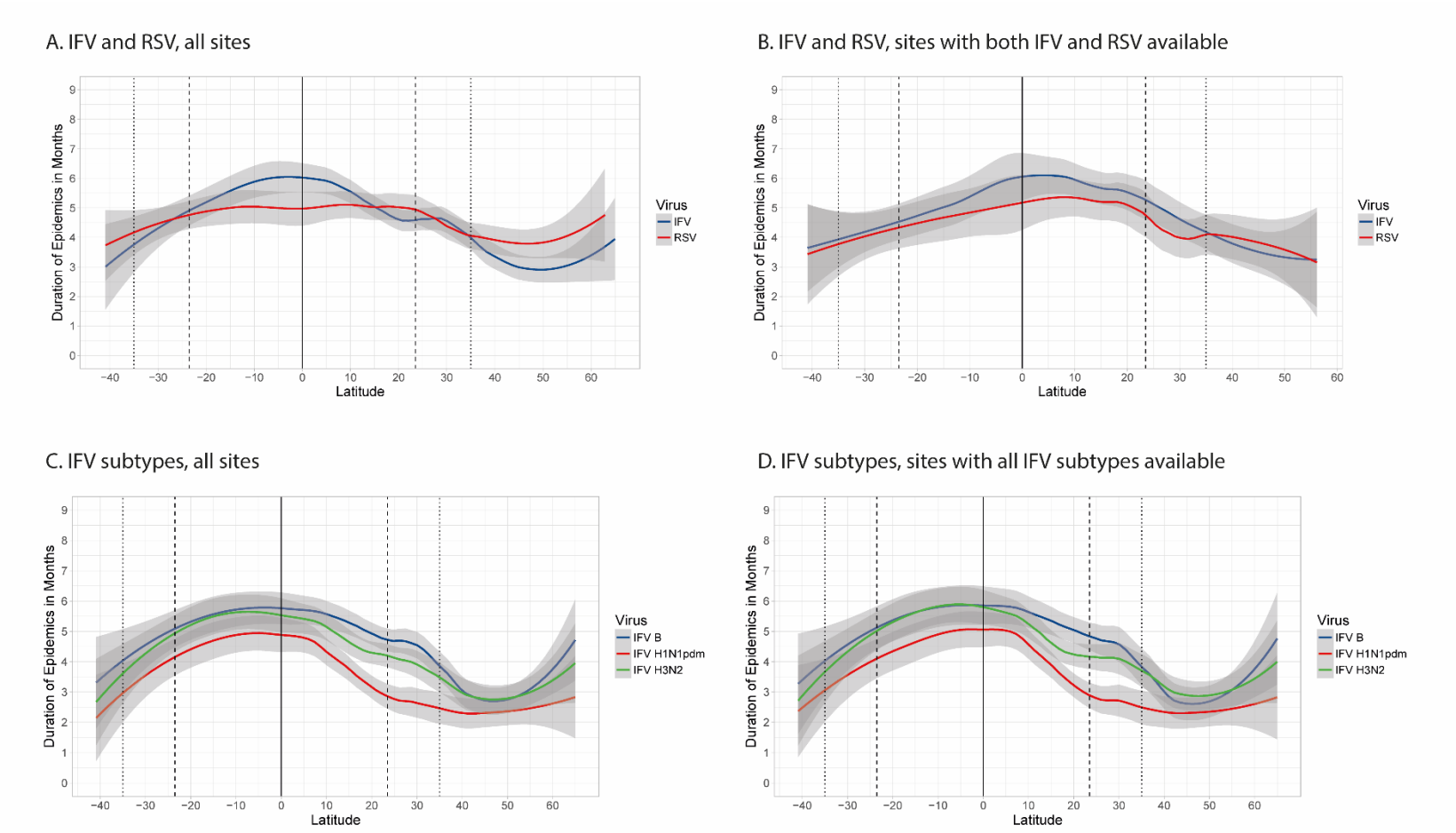
WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Eastern Mediterranean Region	Jordan	Amman		✓	✓	✓								
Eastern Mediterranean Region	Jordan	nationwide		✓	✓	✓								
Eastern Mediterranean Region	Oman	nationwide		✓	✓	✓	✓					✓		
European Region	Austria	Vienna	✓	✓	✓	✓	✓							✓
European Region	Belgium	Leuven	✓	✓	✓	✓								✓
European Region	Croatia	Zagreb	✓	✓	✓									✓
European Region	France	Montpellier	✓	✓	✓									
European Region	France	Paris	✓	✓		✓	✓							✓
European Region	Germany	Berlin	✓	✓	✓	✓								✓
European Region	Sweden	Gothenburg	✓	✓	✓									✓
European Region	Switzerland	Basel	✓									✓	✓	✓
European Region	Switzerland	Bern	✓	✓				✓					✓	✓
European Region	Turkey	nationwide	✓	✓	✓		✓							
European Region	Turkey	Istanbul	✓		✓	✓		✓					✓	✓
European Region	UK	England	✓	✓	✓	✓								✓
Region of the Americas	Argentina	nationwide							✓	✓	✓	✓		
Region of the Americas	Brazil	São Paulo					✓	✓		✓	✓	✓	✓	
Region of the Americas	Canada	nationwide	✓	✓	✓	✓								✓
Region of the Americas	Canada	Edmonton	✓	✓	✓	✓	✓							
Region of the Americas	Chile	nationwide							✓	✓	✓	✓		
Region of the Americas	Colombia	nationwide			✓	✓	✓	✓		✓	✓	✓	✓	✓
Region of the Americas	Cuba	nationwide	✓	✓	✓			✓		✓		✓	✓	

WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Region of the Americas	Dominican Republic	nationwide						✓	✓	✓	✓	✓		
Region of the Americas	Ecuador	nationwide		✓	✓	✓	✓							
Region of the Americas	Ecuador	Quito		✓	✓	✓	✓						✓	
Region of the Americas	Guatemala	nationwide						✓	✓	✓	✓	✓	✓	
Region of the Americas	Honduras	Santa Lucía								✓	✓	✓	✓	
Region of the Americas	Mexico	San Luis Potosí		✓	✓								✓	✓
Region of the Americas	Nicaragua	nationwide	✓									✓		
Region of the Americas	Panama	nationwide	✓					✓	✓	✓	✓	✓	✓	
Region of the Americas	Paraguay	nationwide					✓	✓	✓	✓	✓	✓	✓	
Region of the Americas	Peru	nationwide	✓	✓							✓	✓	✓	✓
Region of the Americas	Peru	San Marcos province				✓	✓	✓						
Region of the Americas	Suriname	nationwide			✓		✓		✓	✓			✓	✓
Region of the Americas	Uruguay	nationwide	✓							✓	✓	✓		
Region of the Americas	USA	Aurora, Colorado	✓	✓	✓	✓								
Region of the Americas	USA	New Haven, Connecticut	✓		✓	✓								
Region of the Americas	USA	Davidson and Monroe County		✓	✓	✓	✓							
Region of the Americas	USA	Chicago and Nashville	✓	✓	✓	✓	✓							
Southeast Asia Region	Thailand	Bangkok							✓	✓	✓	✓	✓	
Western Pacific Region	China	Chongqing	✓	✓	✓								✓	✓
Western Pacific Region	China	nationwide	✓	✓	✓	✓	✓	✓						✓

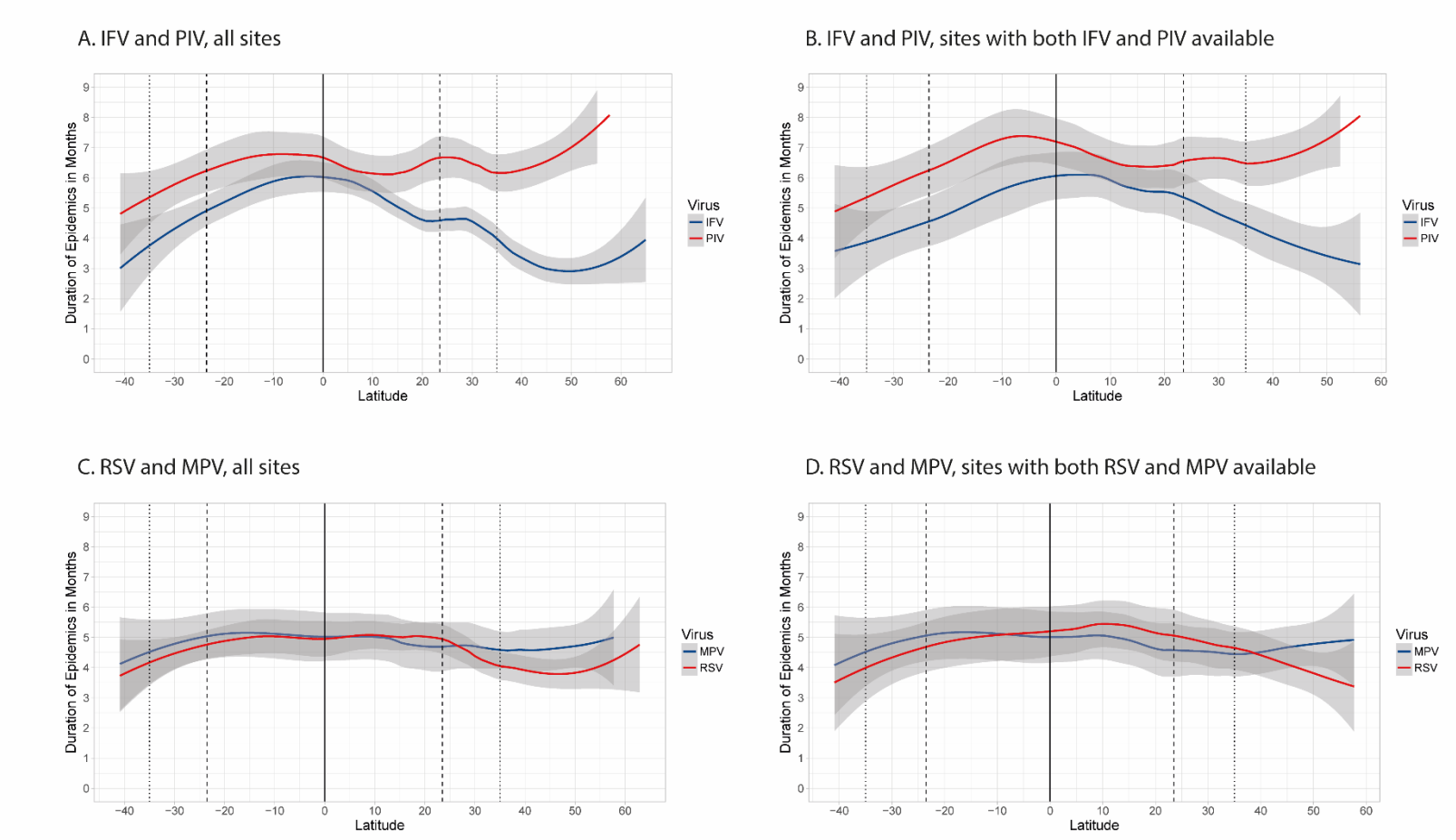
WHO Region	Country	Region	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Western Pacific Region	China	Shenzhen		✓	✓	✓	✓	✓				✓		
Western Pacific Region	China	Lanzhou	✓	✓	✓							✓		✓
Western Pacific Region	China	Wuhan	✓	✓	✓	✓	✓							✓
Western Pacific Region	China	Changsha	✓		✓	✓	✓							
Western Pacific Region	China	Suzhou			✓	✓	✓	✓						✓
Western Pacific Region	Japan	nationwide		✓	✓	✓	✓	✓						
Western Pacific Region	Japan	Tokyo			✓	✓	✓	✓			✓			
Western Pacific Region	Japan	Osaka		✓	✓	✓								
Western Pacific Region	Japan	Yamagata		✓	✓	✓	✓	✓						✓
Western Pacific Region	Japan	Fukui	✓		✓	✓	✓	✓						
Western Pacific Region	Japan	Kyoto			✓	✓	✓		✓		✓			
Western Pacific Region	New Zealand	nationwide							✓	✓	✓	✓		
Western Pacific Region	Philippines	Bohol	✓	✓						✓	✓	✓	✓	
Western Pacific Region	Republic of Korea	Seoul				✓	✓	✓						

A12. Subgroup analysis of duration of epidemics and site latitudes

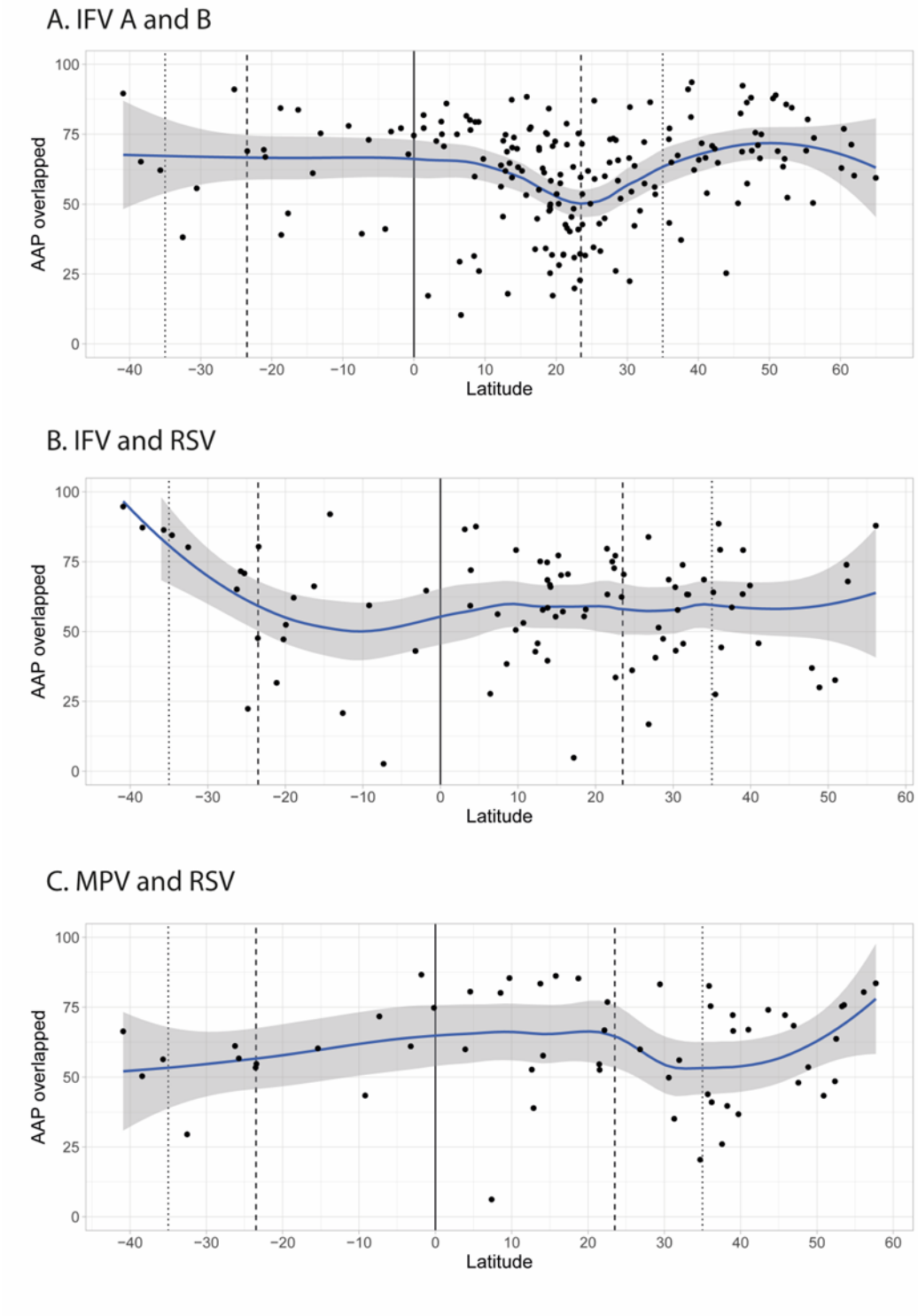
IFV vs RSV and within IFV subtypes



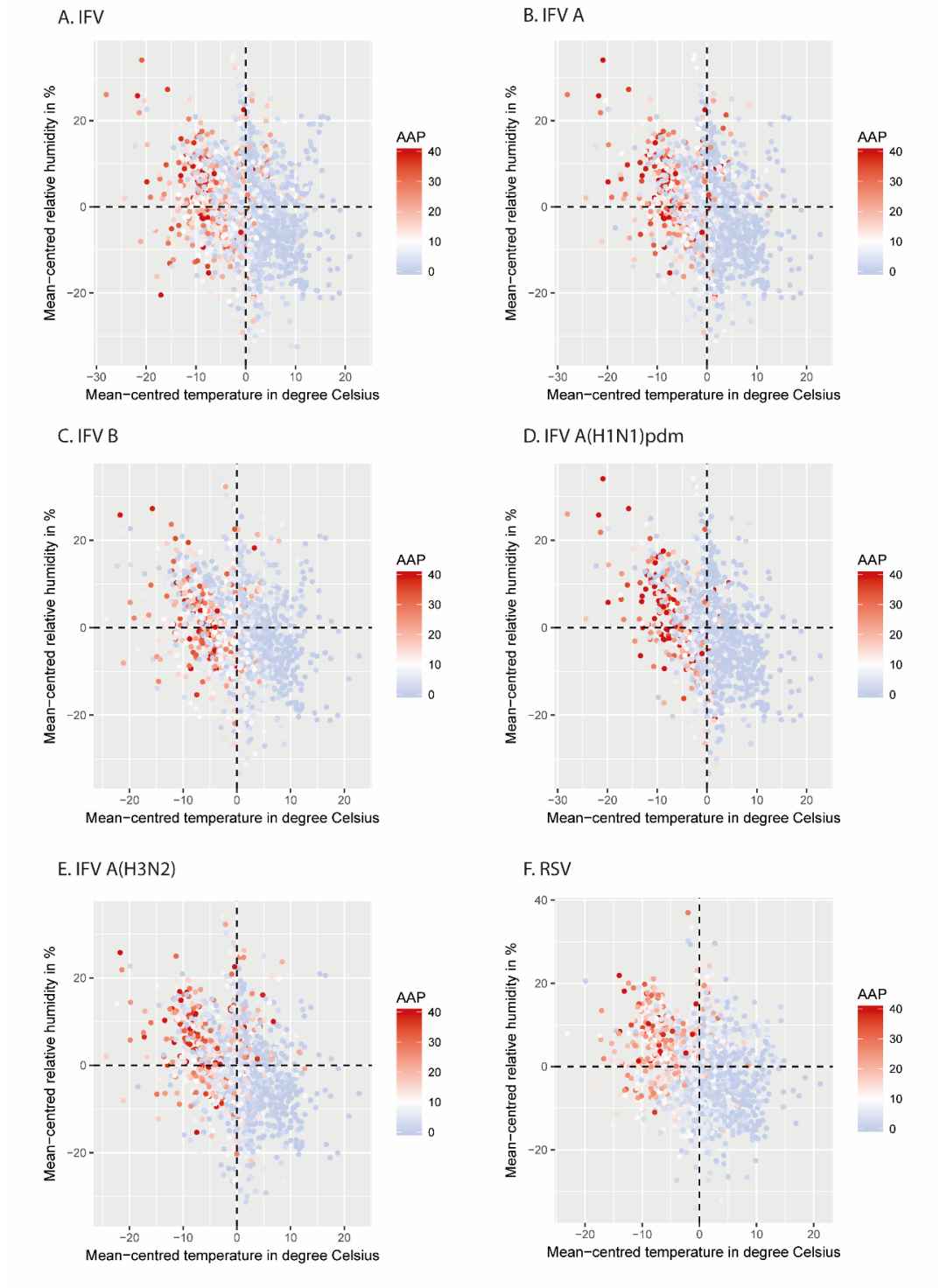
IFV vs PIV and RSV vs MPV



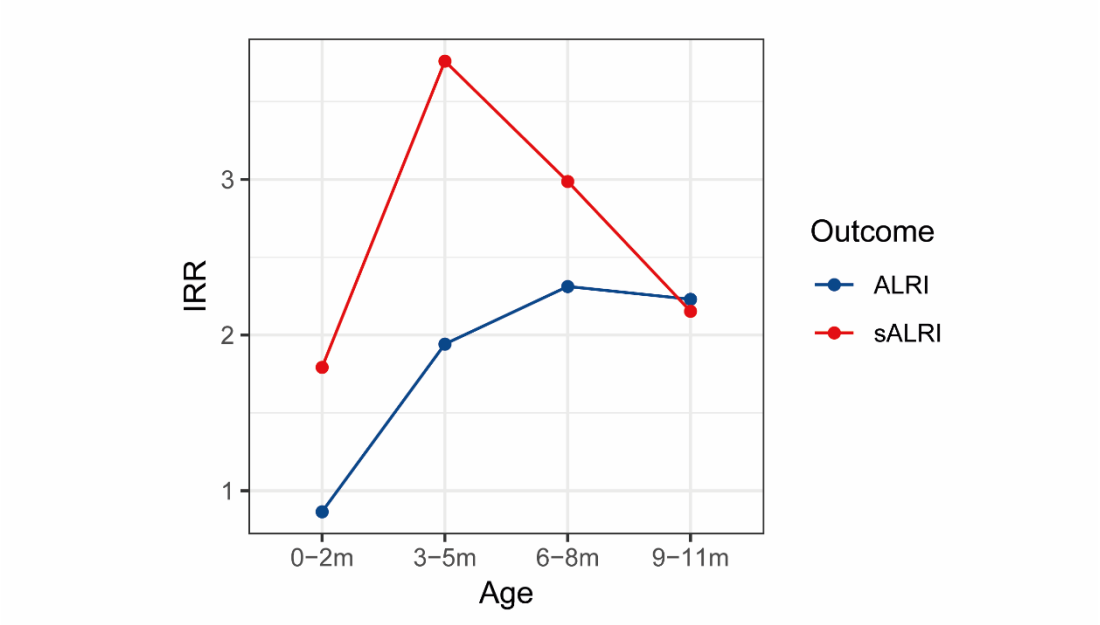
A13. Proportion of the annual overlap between IFV A and B, between IFV and RSV, and between MPV and RSV



A14. Monthly activity of influenza virus and respiratory syncytial virus against mean-centred temperature and relative humidity: observed data



A15. Incidence rate ratios applied to the estimate of RSV incidence within under 1 year old



IRR=incidence rate ratio; results were compared with <5y group.

A16. Data availability of RSV seasonality in LMICs

Country (n of sites)	Data source	Site name	Age of subjects	Unit of data	Available from	Available to	Multi-year
AFRICA REGION (available in 9/46 countries)							
Algeria (0)	—	—	—	—	—	—	—
Angola (0)	—	—	—	—	—	—	—
Benin (0)	—	—	—	—	—	—	—
Botswana (0)	—	—	—	—	—	—	—
Burkina Faso (1)	Ouedraogo, 2014	Ouagadougou	children	monthly	2010.7	2011.6	No
Burundi (0)	—	—	—	—	—	—	—
Cabo Verde (0)	—	—	—	—	—	—	—
Cameroon (2)	Kenmoe, 2016	Yaoundé	<16y	monthly	2011.9	2013.9	No
	Njouom, 2012	nationwide	all	monthly	2009.1	2009.12	No
Central African Republic (0)	—	—	—	—	—	—	—
Chad (0)	—	—	—	—	—	—	—
Comoros (0)	—	—	—	—	—	—	—
Congo, Dem. Rep. (0)	—	—	—	—	—	—	—
Congo, Rep. (0)	—	—	—	—	—	—	—
Côte d'Ivoire (0)	—	—	—	—	—	—	—
Equatorial Guinea (0)	—	—	—	—	—	—	—
Eritrea (0)	—	—	—	—	—	—	—
Ethiopia (0)	—	—	—	—	—	—	—
Gabon (0)	—	—	—	—	—	—	—
Gambia (2)	van der Sande, 2004	Banjul	<3y	monthly	1993.10	2002.9	Yes
	RSV GEN	Basse	28d-<5y	monthly	2011.11	2013.10	No
Ghana (0)	—	—	—	—	—	—	—
Guinea (0)	—	—	—	—	—	—	—
Guinea-Bissau (0)	—	—	—	—	—	—	—

Country (n of sites)	Data source	Site name	Age of subjects	Unit of data	Available from	Available to	Multi-year
Kenya (3)	RSV GEN	Kilifi	<5y	monthly	2002.1	2010.12	Yes
	RSV GEN	Lwak	<5y	monthly	2007.1	2010.12	No
	Nyoka, 2017	Dadaab	all	monthly	2007.9	2011.8	Yes
Lesotho (0)	—	—	—	—	—	—	—
Liberia (0)	—	—	—	—	—	—	—
Madagascar (0)	—	—	—	—	—	—	—
Malawi (0)	—	—	—	—	—	—	—
Mali (1)	RSV GEN	Bamako	28d-<5y	monthly	2012.1	2013.12	No
Mauritania (0)	—	—	—	—	—	—	—
Mauritius (0)	—	—	—	—	—	—	—
Mozambique (2)	Loscertales, 2002	Manhiça	children	monthly	1999.2	2000.1	No
	Pale, 2017	Maputo	<3y	monthly	2015.1	2015.12	No
Namibia (0)	—	—	—	—	—	—	—
Niger (0)	—	—	—	—	—	—	—
Nigeria (1)	Robertson, 2004	Eleta & Ijaye	<5y	monthly	1999.6	2001.5	No
Rwanda (0)	—	—	—	—	—	—	—
São Tomé and Principe (0)	—	—	—	—	—	—	—
Senegal (0)	—	—	—	—	—	—	—
Sierra Leone (0)	—	—	—	—	—	—	—
South Africa (6)	Venter, 2011	Pretoria	<5y	monthly	2006.1	2007.12	No
	RSV GEN	Soweto	28d-<5y	monthly	2011.9	2013.8	No
	RSV GEN	Agincourt	<5y	monthly	2010.1	2014.12	Yes
	RSV GEN	Pietermaritzburg	<5y	monthly	2010.1	2014.12	Yes
	RSV GEN	Klerksdorp	<5y	monthly	2011.1	2014.12	Yes
	RSV GEN	Paarl	2y-<5y	monthly	2012.1	2014.7	No
South Sudan (0)	—	—	—	—	—	—	—
Swaziland (0)	—	—	—	—	—	—	—

Country (n of sites)	Data source	Site name	Age of subjects	Unit of data	Available from	Available to	Multi-year
Tanzania (0)	—	—	—	—	—	—	—
Togo (0)	—	—	—	—	—	—	—
Uganda (0)	—	—	—	—	—	—	—
Zambia (1)	RSV GEN	Lusaka	28d-<5y	monthly	2011.11	2013.10	No
Zimbabwe (0)	—	—	—	—	—	—	—
REGION OF THE AMERICAS (available in 18/24 countries)							
Belize (1)	PAHO	nationwide	all	weekly	2016.1	2017.12	No
Bolivia (1)	PAHO	nationwide	all	weekly	2010.1	2017.12	Yes
Brazil (8)	Alonso, 2012	Fortaleza	1m-16y	weekly	2001.1	2008.12	No
	Bouzas, 2016	Salvador	6-23m	monthly	2009.9	2013.8	No
	Checon, 2002	Vitória	<5y	monthly	1997.7	1998.6	No
	Pecchini, 2015	São Paulo	<5y	monthly	2005.3	2007.2	No
	Salomao Junior, 2011	São José do Rio Preto	<7y	monthly	2004.5	2005.4	No
	Costa [22], 2006	Uberlândia	<5y	monthly	2001.1	2004.12	No
	PAHO	nationwide	all	weekly	2016.1	2016.12	No
	RSV GEN	Belo Horizonte	<5y	monthly	2011.1	2013.12	No
Colombia (2)	Rodriguez-Martinez, 2015	Bogota	<3y	monthly	2009.6	2011.5	No
	PAHO	nationwide	all	weekly	2010.1	2017.12	Yes
Costa Rica (1)	PAHO	nationwide	all	weekly	2010.1	2017.12	Yes
Cuba (1)	PAHO	nationwide	all	weekly	2010.1	2017.12	Yes
Dominica (1)	PAHO	nationwide	all	weekly	2015.1	2017.12	No
Dominican Republic (1)	PAHO	nationwide	all	weekly	2010.1	2017.12	Yes
Ecuador (2)	Jonnalagadda, 2017	Quito	2-59m	monthly	2008.2	2010.1	No
	PAHO	nationwide	all	weekly	2012.1	2017.12	Yes
El Salvador (2)	PAHO	nationwide	all	weekly	2010.1	2017.12	Yes

Country (n of sites)	Data source	Site name	Age of subjects	Unit of data	Available from	Available to	Multi-year
	RSV GEN	Santa Ana	<5y	monthly	2008.1	2012.12	No
Grenada (0)	—	—	—	—	—	—	—
Guatemala (4)	PAHO	nationwide	all	weekly	2010.1	2017.12	Yes
	RSV GEN	Santa Rosa	<5y	monthly	2008.1	2013.12	Yes
	RSV GEN	Quetzaltenango	<5y	monthly	2010.1	2013.12	Yes
	RSV GEN	San Lorenzo and Comitancillo	<2y	monthly	2013.1	2014.12	No
Guyana (0)	—	—	—	—	—	—	—
Haiti (0)	—	—	—	—	—	—	—
Honduras (2)	PAHO	nationwide	all	weekly	2010.1	2017.12	Yes
	Schlaudecker, 2012	Santa Lucía	<5y	monthly	2010.2	2011.1	No
Jamaica (0)	—	—	—	—	—	—	—
Mexico (4)	Yusuf, 2007	Mexico City	all	monthly	2001.1	2002.12	No
	Gamino-Arroyo, 2017	Mexico City and San Luis Potosí	all	monthly	2010.5	2014.4	Yes
	PAHO	nationwide	all	weekly	2010.1	2017.12	Yes
	RSV GEN	San Luis Potosí	<5y	monthly	2004.1	2014.12	Yes
Nicaragua (1)	PAHO	nationwide	all	weekly	2010.1	2017.12	Yes
Paraguay (1)	PAHO	nationwide	all	weekly	2010.1	2017.12	Yes
Peru (3)	Budge, 2014	San Marcos	<3y	weekly	2009.10	2011.9	No
	PAHO	nationwide	all	weekly	2010.1	2017.12	Yes
	RSV GEN	Tambopata	>5y	monthly	2013.1	2013.12	No
St. Lucia (0)	—	—	—	—	—	—	—
St. Vincent and the Grenadines (0)	—	—	—	—	—	—	—
Suriname (1)	PAHO	nationwide	all	weekly	2013.1	2017.12	No
Venezuela, RB (1)	PAHO	nationwide	all	weekly	2010.1	2017.12	No
EASTERN MEDITERRANEAN REGION (available in 7/16 countries)							

Country (n of sites)	Data source	Site name	Age of subjects	Unit of data	Available from	Available to	Multi-year
Afghanistan (0)	—	—	—	—	—	—	—
Djibouti (0)	—	—	—	—	—	—	—
Egypt, Arab Rep. (1)	Horton, 2017	nationwide	all	daily	2008.1	2013.12	Yes
Iran, Islamic Rep. (0)	—	—	—	—	—	—	—
Iraq (0)	—	—	—	—	—	—	—
Jordan (3)	Bdour	Zarqa	<2y	monthly	1997.6	1999.5	No
	Horton, 2017	nationwide	all	daily	2008.1	2013.12	Yes
	RSV GEN	Amman	<2y	monthly	2010.4	2013.3	Yes
Lebanon (1)	Finianos, 2016	Beirut	<17y	monthly	2013.10	2014.9	No
Libya (0)	—	—	—	—	—	—	—
Morocco (2)	RSV GEN	Rabat	<5y	monthly	2011.1	2011.12	No
	Bimouhen, 2016	nationwide	all	monthly	2015.5	2016.4	No
Pakistan (1)	Asad, 2017	Karachi	<5y	monthly	2009.8	2012.7	No
Sudan (0)	—	—	—	—	—	—	—
Syrian Arab Republic (0)	—	—	—	—	—	—	—
Tunisia (1)	Fodha, 2004	Sousse	<35d	monthly	2000.6	2002.5	No
West Bank and Gaza (0)	—	—	—	—	—	—	—
Yemen, Rep. (1)	Horton, 2017	nationwide	all	daily	2008.1	2013.12	No
EUROPEAN REGION (available in 1/20 countries)							
Albania (0)	—	—	—	—	—	—	—
Armenia (0)	—	—	—	—	—	—	—
Azerbaijan (0)	—	—	—	—	—	—	—
Belarus (0)	—	—	—	—	—	—	—
Bosnia and Herzegovina (0)	—	—	—	—	—	—	—
Bulgaria (0)	—	—	—	—	—	—	—

Country (n of sites)	Data source	Site name	Age of subjects	Unit of data	Available from	Available to	Multi-year
Georgia (0)	—	—	—	—	—	—	—
Kazakhstan (0)	—	—	—	—	—	—	—
Kyrgyz Republic (0)	—	—	—	—	—	—	—
Macedonia, FYR (0)	—	—	—	—	—	—	—
Moldova (0)	—	—	—	—	—	—	—
Montenegro (0)	—	—	—	—	—	—	—
Romania (0)	—	—	—	—	—	—	—
Russian Federation (0)	—	—	—	—	—	—	—
Serbia (0)	—	—	—	—	—	—	—
Tajikistan (0)	—	—	—	—	—	—	—
Turkey (2)	Goktas, 2016	Istanbul	all	monthly	2014.9	2015.8	No
	Kanra, 2005	nationwide	<2y	monthly	2000	2002	No
Turkmenistan (0)	—	—	—	—	—	—	—
Ukraine (0)	—	—	—	—	—	—	—
Uzbekistan (0)	—	—	—	—	—	—	—
SOUTHEAST ASIA REGION (available in 5/11 countries)							
Bangladesh (2)	RSV GEN	Dhaka	<5y	monthly	2005.1	2007.12	Yes
	RSV GEN	Matlab	28d-<5y	monthly	2012.1	2013.12	No
Bhutan (0)	—	—	—	—	—	—	—
India (7)	RSV GEN	Ballabgarh, Faridabad & Haryana	<5y	monthly	2010.1	2012.12	No
	RSV GEN	Puducherry	all	monthly	2011.11	2014.10	No
	Agrawal, 2009	Kolkata	<6y	monthly	2007.1	2008.12	No
	Choudhary, 2013	Pune	all	monthly	2009.9	2011.8	No
	Jain, 2014	Lucknow	all	monthly	2011.5	2013.4	No
	Bharaj, 2009	Delhi	<6y	monthly	2005.4	2007.3	No

Country (n of sites)	Data source	Site name	Age of subjects	Unit of data	Available from	Available to	Multi-year
	Swamy, 2017	Jaipur	<5y	monthly	2013.1	2014.12	No
Indonesia (2)	RSV GEN	Lombok	<2y	monthly	2000.1	2002.12	Yes
	Robertson, 2014	Bandung	<5y	monthly	1999.2	2001.1	No
Korea, Dem. People's Rep. (0)	—	—	—	—	—	—	—
Maldives (0)	—	—	—	—	—	—	—
Myanmar (0)	—	—	—	—	—	—	—
Nepal (2)	Chu, 2016	Sarlahi	<6y	monthly	2011.9	2013.8	No
	Mathisen, 2011	Kathmandu	<3y	monthly	2006.1	2007.12	No
Sri Lanka (0)	—	—	—	—	—	—	—
Thailand (5)	RSV GEN	Tak Province	<2y	monthly	2007.11	2010.10	No
	RSV GEN	Nakhon Phanom and Sa Kaeo	<5y	monthly	2008.1	2011.12	Yes
	RSV GEN	Bangkok	all	monthly	2011.1	2017.12	Yes
	RSV GEN	Khon Kaen	all	monthly	2011.1	2015.12	No
	RSV GEN	Chonburi	all	monthly	2013.2	2014.1	No
Timor-Leste (0)	—	—	—	—	—	—	—
WESTERN PACIFIC REGION (available in 6/19 countries)							
American Samoa (0)	—	—	—	—	—	—	—
Cambodia (1)	RSV GEN	Kampong Cham & Takeo	<5y	monthly	2007.4	2009.3	No
China (17)	Cui, 2015	Shantou	<17y	monthly	2010.12	2011.11	No
	Cui, 2016	Eastern China	all	monthly	2009.1	2013.12	Yes
	Feng, 2014	Beijing, Shanghai, Chongqing, Guangdong,	<5y	monthly	2009.1	2012.12	No

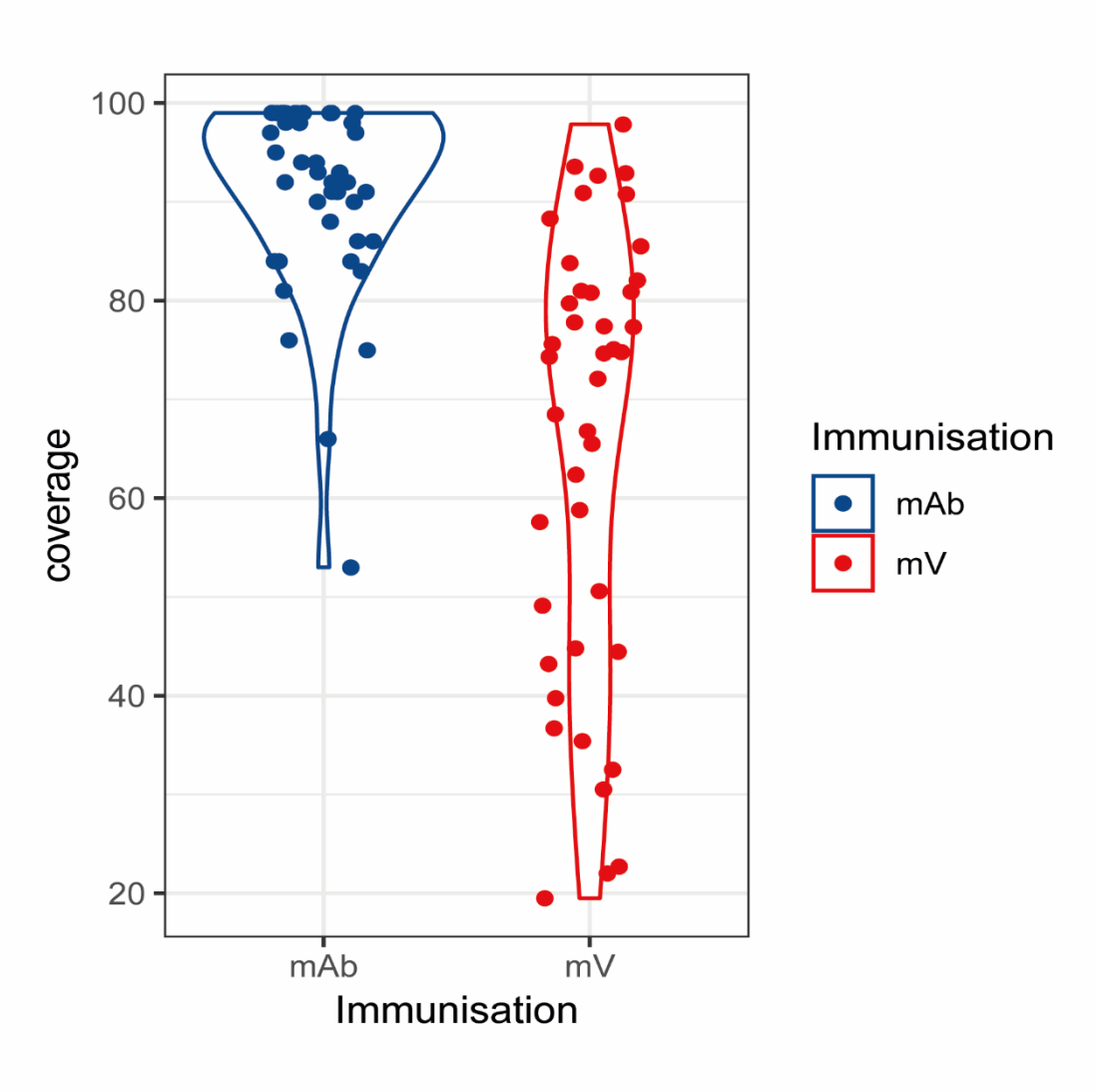
Country (n of sites)	Data source	Site name	Age of subjects	Unit of data	Available from	Available to	Multi-year
		Gansu and Sichuan					
	He, 2014	Shenzhen	>18y	monthly	2007.7	2010.6	No
	Huo, 2013	Jingzhou	<5y	monthly	2011.1	2011.12	No
	Jin, 2012	Lanzhou	<15y	monthly	2006.12	2009.11	No
	Lee, 2007	Northern Taiwan	<196m	weekly	2001.1	2005.12	No
	Lu, 2015	Suzhou	<=28d	monthly	2010.1	2014.12	Yes
	Tang, 2008	Hangzhou	<14y	monthly	2001.1	2006.12	No
	Zhang, 2016	Xi'an	all	monthly	2009.1	2014.12	No
	Zhang, 2010	Chongqing	<18y	monthly	2006.4	2009.3	Yes
	Zhao, 2013	Shanghai	<5y	monthly	2009.10	2012.9	No
	Wu, 2012	Kunming	<15y	monthly	2015.11	2017.10	No
	Yin, 2017	Bengbu	<15y	monthly	2015.7	2016.6	No
	Dept. Health, Hong Kong	Hong Kong	all	weekly	2014.1	2017.12	
	RSV GEN	nationwide	<5y	monthly	2009.9	2013.8	Yes
	RSV GEN	Beijing	2m-<5y	monthly	2011.1	2012.12	No
Fiji (0)	—	—	—	—	—	—	—
Kiribati (0)	—	—	—	—	—	—	—
Lao PDR (0)	—	—	—	—	—	—	—
Malaysia (1)	Khor, 2012	Kuala Lumpur	<6y	monthly	1982.1	2008.12	No
Marshall Islands (0)	—	—	—	—	—	—	—
Micronesia, Fed. Sts. (0)	—	—	—	—	—	—	—
Mongolia (1)	RSV GEN	Ulaanbaatar	1m-<2y	monthly	2015.6	2016.5	No
Nauru (0)	—	—	—	—	—	—	—
Papua New Guinea (0)	—	—	—	—	—	—	

Country (n of sites)	Data source	Site name	Age of subjects	Unit of data	Available from	Available to	Multi-year
Philippines (2)	RSV GEN	Bohol	28d-<2y	monthly	2000.7	2004.6	Yes
	RSV GEN	Tacloban	<5y	monthly	2008.5	2012.7	No
Samoa (0)	—	—	—	—	—	—	—
Solomon Islands (0)	—	—	—	—	—	—	—
Tonga (0)	—	—	—	—	—	—	—
Tuvalu (0)	—	—	—	—	—	—	—
Vanuatu (0)	—	—	—	—	—	—	—
Vietnam (2)	RSV GEN	Nha Trang City	<5y	monthly	2008.1	2012.12	No
	Do, 2016	Ho Chi Minh City	1m-<2y	monthly	2009.5	2010.4	No

A17. Comparisons of duration of RSV epidemics between temperate and tropical regions in LMICs

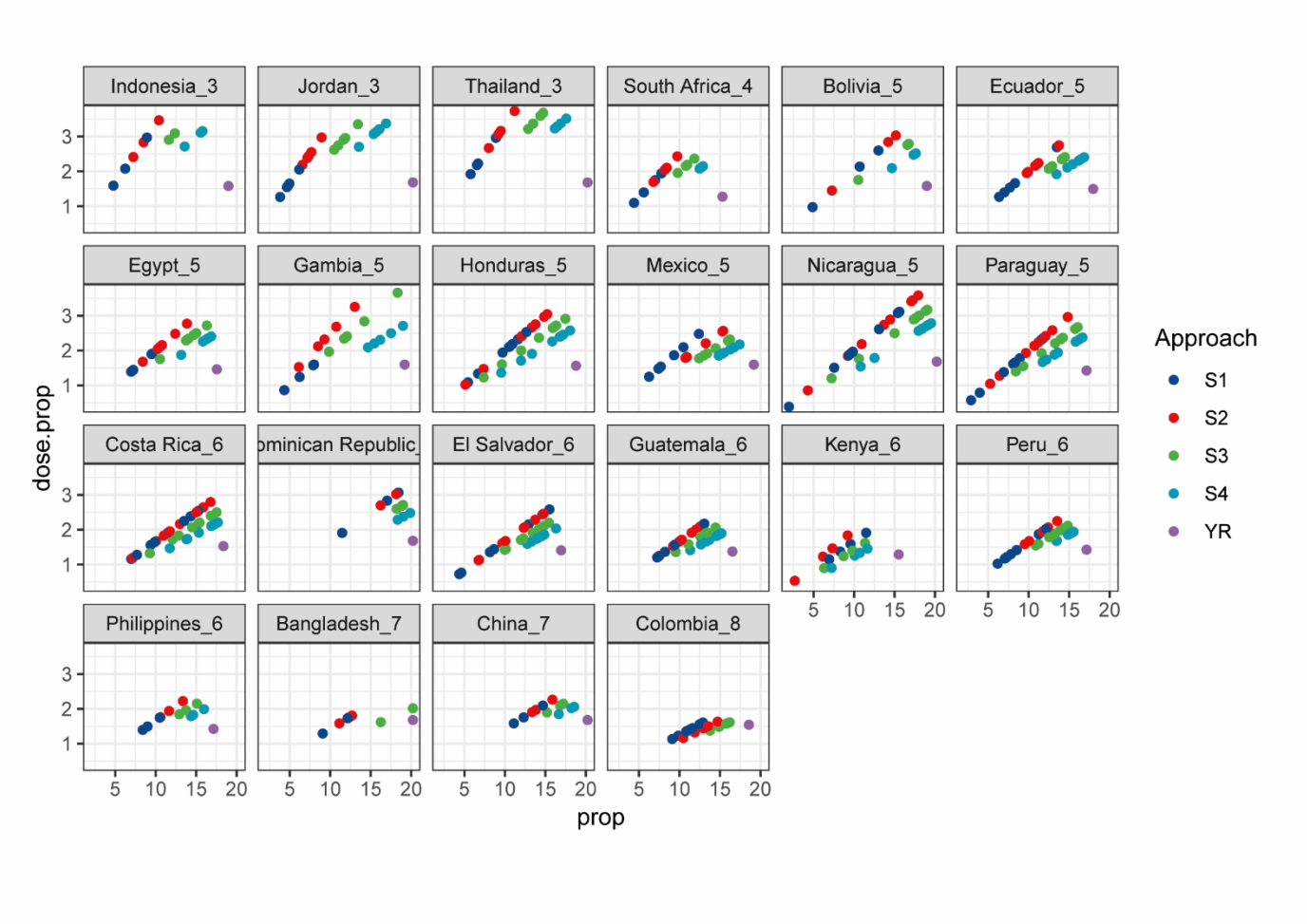
Region	Clear seasonality			Year-round activity	
	<4m	4m	5m	6m	>6m
Temperate region in the northern hemisphere	13 (38.2%)	6 (17.6%)	6 (17.6%)	3 (8.8%)	6 (17.6%)
Tropical region	16 (23.9%)	13 (19.4%)	16 (23.9%)	12 (17.9%)	10 (14.9%)
Temperate region in the southern hemisphere	1 (11.1%)	4 (44.4%)	1 (11.1%)	2 (22.2%)	1 (11.1%)
Total	30 (27.3%)	23 (20.9%)	23 (20.9%)	17 (15.5%)	17 (15.5%)

A18. Estimated of the coverage of mAb and mV

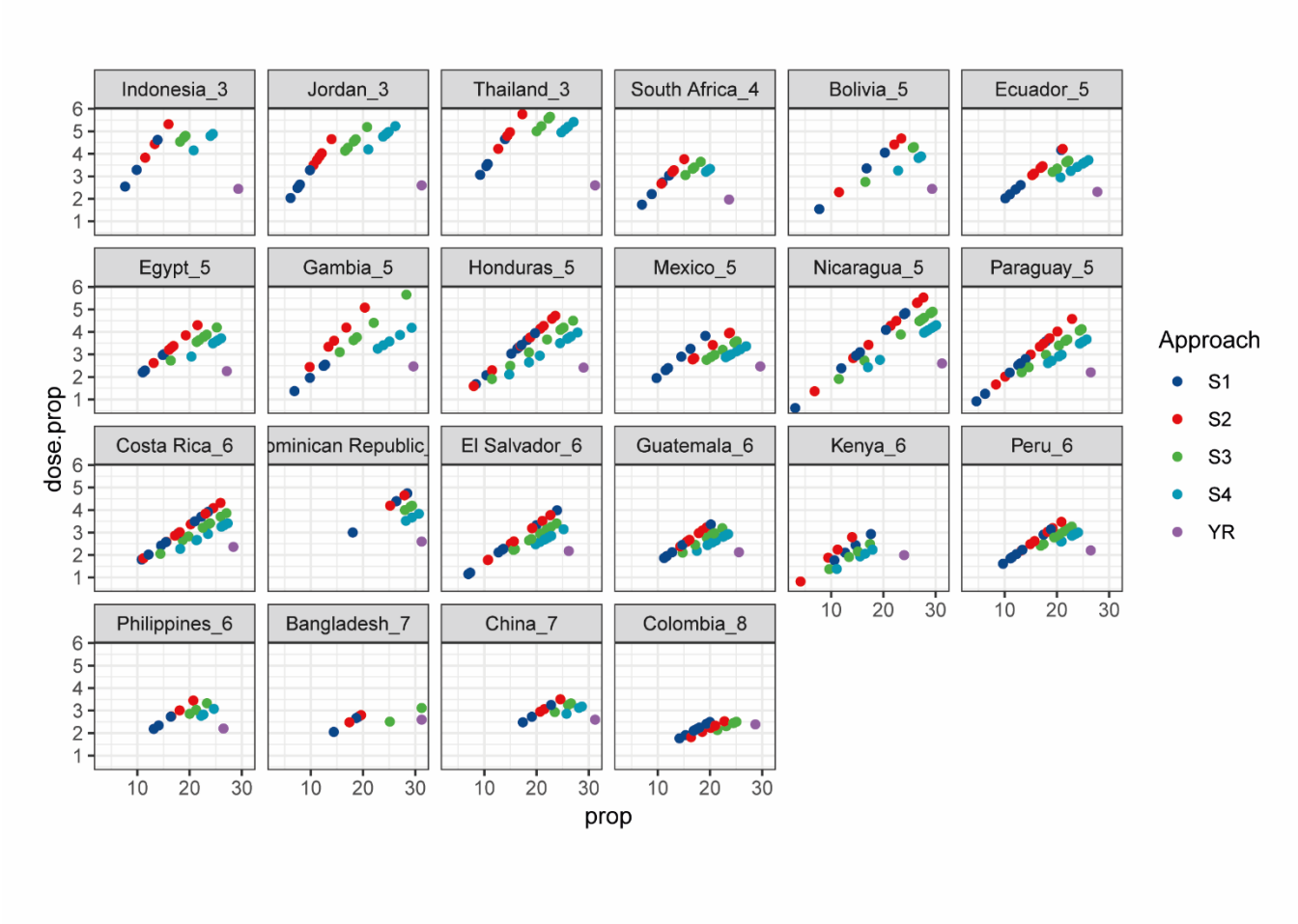


mAb=(long-acting) monoclonal antibody; mV=maternal vaccine

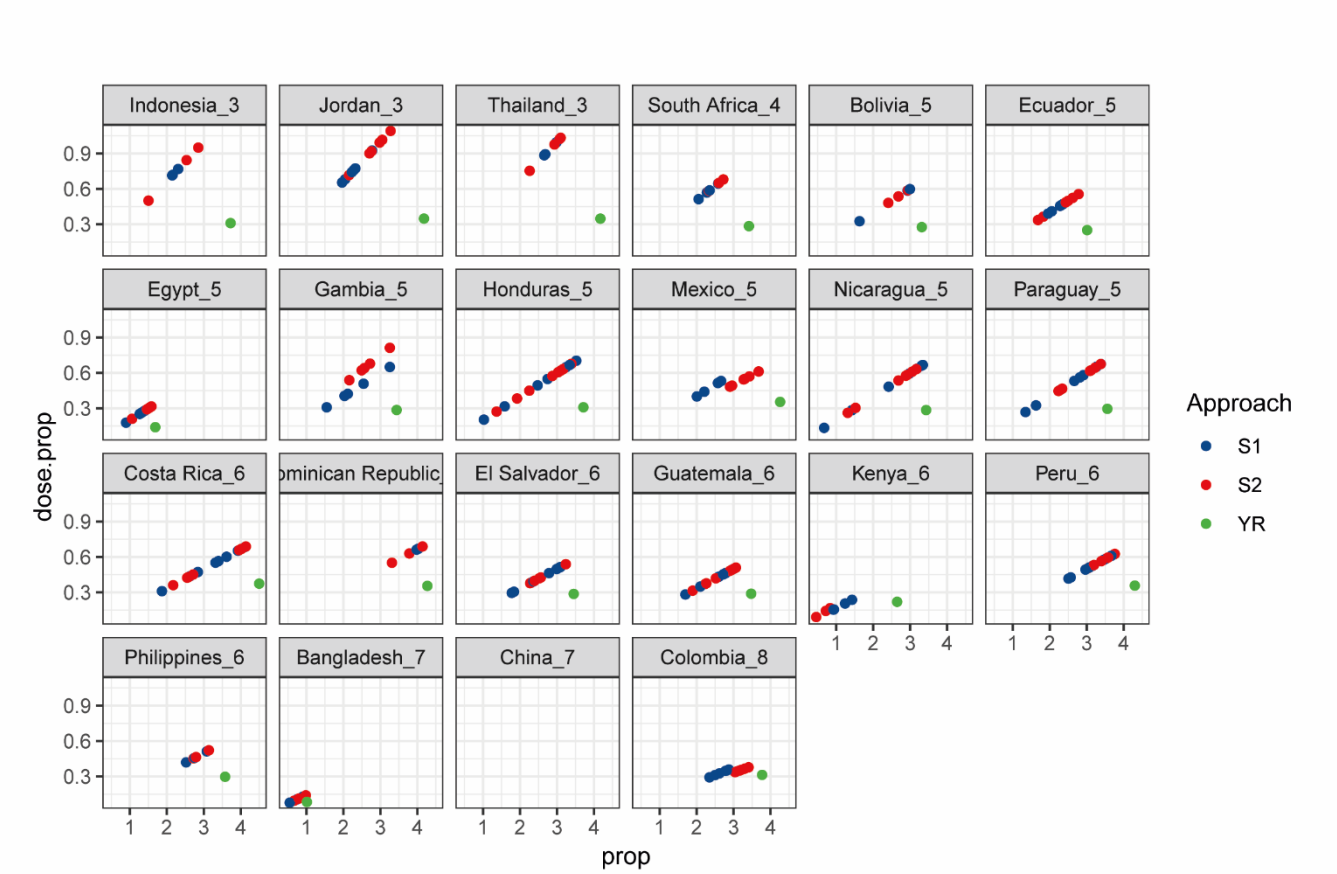
A19. Country-specific comparisons among different mAb immunisation approaches in preventing RSV-ALRI, considering year-to-year variations



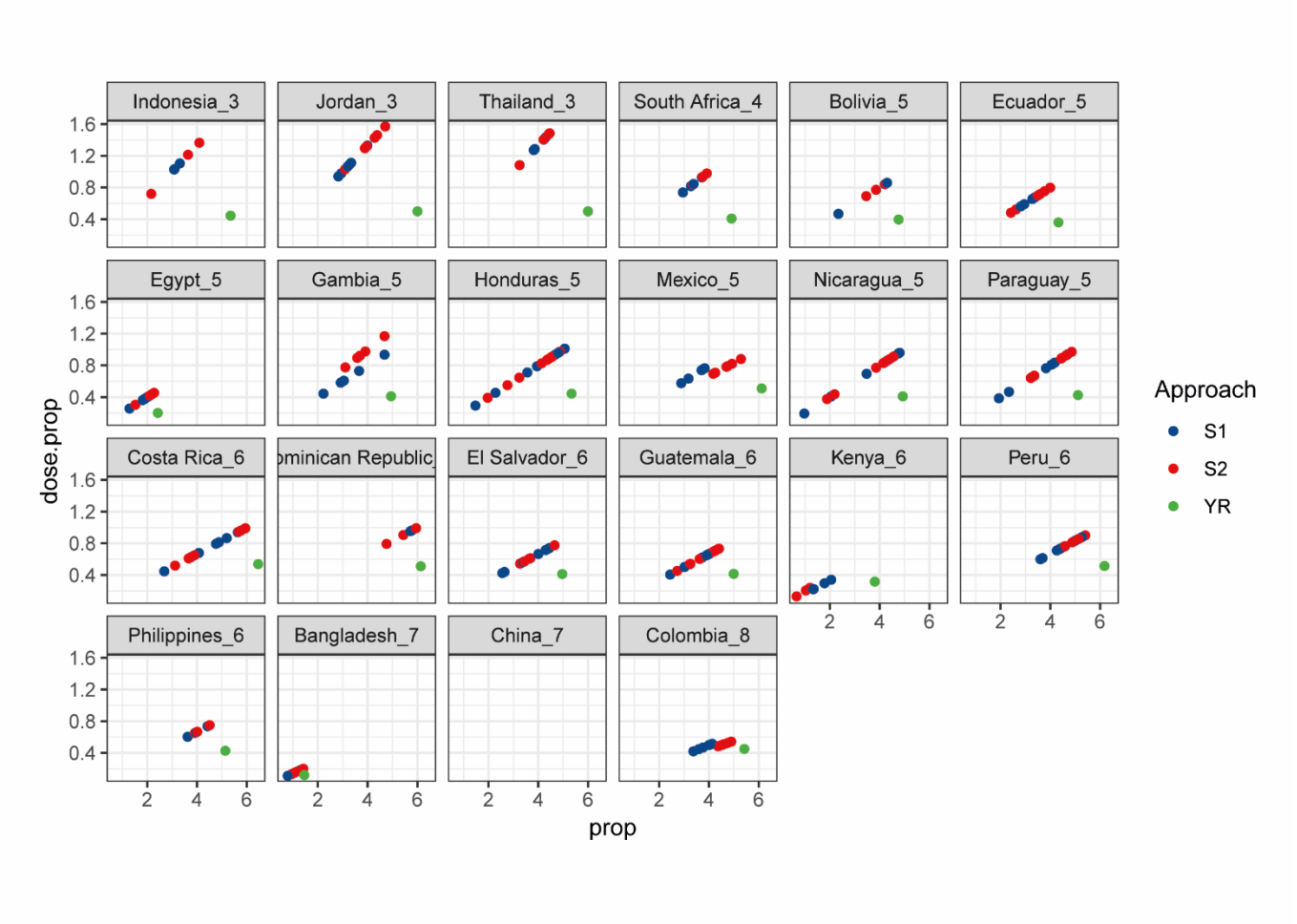
A20. Country-specific comparisons among different mAb immunisation approaches in preventing RSV-severe-ALRI, considering year-to-year variations



A21. Country-specific comparisons among different mV immunisation approaches in preventing RSV-ALRI, considering year-to-year variations



A22. Country-specific comparisons among different mV immunisation approaches in preventing RSV-severe-ALRI, considering year-to-year variations



A23. List of ICD-10 codes used

	ICD-10 codes	*Content*
Influenza virus infection	J09	Influenza due to certain identified influenza virus
	J10	Influenza due to other identified influenza virus
	J11	Influenza, virus not identified
Respiratory syncytial virus infection	J12.1	Respiratory syncytial virus pneumonia
	J20.5	Acute bronchitis due to respiratory syncytial virus
	J21.0	Acute bronchiolitis due to respiratory syncytial virus
Pneumococcal pneumonia	J13.0	Pneumonia due to *Streptococcus pneumoniae*

A24. Number of IPD and viral infection cases included by year

Year	IPD	IFV	RSV	PIV	MPV
2009	538	6022	2327	1006	310
2010	525	1430	1987	446	456
2011	499	1941	2785	839	493
2012	482	1422	3077	985	646
2013	576	2442	2270	1375	928
2014	439	1837	3102	1111	924
2015	653	4127	2892	1750	1101
2016	712	5028	3798	1566	899
2017	706	7539	2900	1861	975

IPD=invasive pneumococcal disease; IFV=influenza virus; RSV=respiratory syncytial virus; PIV=parainfluenza virus; MPV=metapneumovirus

A25. Percentage of IPD attributable to ICD-coded IFV and RSV hospitalisations by age group

Age Group	Lag* (wk)	Attributable Percentage of IPD	
		IFV	RSV
<6y	2	12.6 (8.4–16.5)	10.4 (9.5–11.4)
6–64y	2	7.2 (4.4–9.8)	3.8↓ (2.7–5.2)
>64y	1	8.1 (3.8–13.0)	2.5 (1.0–4.5)
All ages	2	8.1 (5.2–10.7)	12.6 (11.6–13.5)

An arrow (↑ up or ↓ down) indicates a significant difference in the attributable percentage, compared with corresponding estimate in the main analysis.
*Time lag between viral infection and subsequent IPD; IPD=invasive pneumococcal disease; wk=week; IFV=influenza virus; RSV=respiratory syncytial virus; y=year(s)

A26. Percentage of PP attributable to each virus by age group

Age Group	Lag* (wk)	Attributable Percentage of PP			
		IFV	RSV	PIV	MPV
<6y	1	0↓	0↓	0↓	50.5↑ (41.5–57.1)
6–64y	2	7.2 (4.5–11.1)	0↓	0	12.1 (9.4–14.6)
>64y	1	5.8 (2.2–10.5)	5.7 (3.2–8.4)	11.9 (7.2–17.0)	0
All ages	1	8.0 (5.1–10.5)	6.3↓ (5.7–6.8)	8.6 (6.8–10.2)	8.9 (6.5–10.8)

An arrow (↑ up or ↓ down) indicates a significant difference in the attributable percentage, compared with corresponding estimate in the main analysis.

*Time lag between viral infection and subsequent PP; PP=pneumococcal pneumonia; wk=week; IFV=influenza virus; RSV=respiratory syncytial virus; PIV=parainfluenza virus; MPV=metapneumovirus; y=year(s)

A27. Percentage of PP attributable to ICD-coded IFV and RSV hospitalisations by age group

Age Group	Lag* (wk)	Attributable Percentage of IPD	
		IFV	RSV
<6y	2	0↓	0↓
6–64y	1	2.3↓ (1.3–3.7)	2.9↓ (2.4–3.6)
>64y	1	2.2↓ (0.9–4.0)	0↓
All ages	1	0↓	0↓

An arrow (↑ up or ↓ down) indicates a significant difference in the attributable percentage, compared with corresponding estimate in the main analysis.

*Time lag between viral infection and subsequent PP; PP=pneumococcal pneumonia; wk=week; IFV=influenza virus; RSV=respiratory syncytial virus; y=year(s)

A28. Publications related to this thesis

1. Li Y, Reeves RM, Wang X, Bassat Q, Brooks WA, Cohen C, Moore DP, Nunes M, Rath B, Campbell H, Nair H. Global patterns in monthly activity of influenza virus, respiratory syncytial virus, parainfluenza virus, and metapneumovirus: a systematic analysis. **Lancet Global Health** 2019;7(8):e1031-e1045

2. Li Y, Peterson ME, Campbell H, Nair H. Association of seasonal viral acute respiratory infection with pneumococcal disease: a systematic review of population-based studies **BMJ Open** 2018;8:e019743.

3. Li Y. wktmo: Converting Weekly Data to Monthly Data. **R package version 1.0.5.** 2017. https://CRAN.R-project.org/package=wktmo (R software package)