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The role of influenza, RSV and other common respiratory viruses in severe acute respiratory infections and influenza-like illness in a population with a high HIV sero-prevalence, South Africa 2012–2015

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Abstract

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Conflicts of interest

None of the authors has a financial or personal conflict of interest related to this study. All the authors fulfill the uniform requirements criteria, and no assistance other than copy editing was provided in the preparation of the manuscript. The corresponding author has full access to all data in the study and final responsibility for the decision to submit this publication.

Ethical considerations

The SARI and ILI/control protocols was reviewed and approved by the University of the Witwatersrand Human Research Ethics Committee (HREC) and the University of KwaZulu-Natal Human Biomedical Research Ethics Committee (BREC) protocol numbers M081042, BF157/08 and BF 080/12 respectively. This surveillance was deemed non-research by the U.S. Centers for Disease Control and Prevention.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US Centers for Disease Control and Prevention.

Background—Viruses detected in patients with acute respiratory infections may be the cause of illness or asymptomatic shedding.

Objective—To estimate the attributable fraction (AF) and the detection rate attributable to illness for each of the different respiratory viruses

Study design—We compared the prevalence of 10 common respiratory viruses (influenza A and B viruses, parainfluenza virus 1–3; respiratory syncytial virus (RSV); adenovirus, rhinovirus, human metapneumovirus (hMPV) and enterovirus) in both HIV positive and negative patients hospitalized with severe acute respiratory illness (SARI), outpatients with influenza-like illness (ILI), and control subjects who did not report any febrile, respiratory or gastrointestinal illness during 2012–2015 in South Africa.

Results—We enrolled 1959 SARI, 3784 ILI and 1793 controls with a HIV sero-prevalence of 26%, 30% and 43%, respectively. Influenza virus (AF: 86.3%; 95%CI: 77.7–91.6%), hMPV (AF: 85.6%; 95%CI: 72.0–92.6%), and RSV (AF: 83.7%; 95%CI: 77.5–88.2%) infections were associated with severe disease., while rhinovirus (AF: 46.9%; 95%CI: 37.6–56.5%) and adenovirus (AF: 36.4%; 95%CI: 20.6–49.0%) were only moderately associated.

Conclusions—Influenza, RSV and hMPV can be considered pathogens if detected in ILI and SARI while rhinovirus and adenovirus were commonly identified in controls suggesting that they may cause only a proportion of clinical disease observed in positive patients. Nonetheless, they may be important contributors to disease.

Keywords

Disease association; Respiratory virus infection; Severe acute respiratory illness; Influenza like illness; Controls; Pneumonia; HIV; South Africa

1. Background

Pneumonia is a leading cause of childhood mortality globally, with about 1.6 million new cases per year, of which 1.2 million occur in the developing world [1] and approximately 10% are severe enough to require hospitalization [1]. Before the worldwide availability of vaccines, *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenzae* type b were identified as the main bacterial causes of pneumonia [1,2]. Now, viruses are more commonly detected in patients with acute respiratory infections including pneumonia [1,3,4].

Respiratory viruses infections have been detected by polymerase chain reaction (PCR) among patients hospitalized with lower respiratory tract infection (LTRI) in several studies [5–13]. While the use of sensitive PCR methods has significantly expanded the ability of laboratories to detect and identify pathogens, the clinical association between pathogen detection and disease remains difficult to interpret when considering viral shedding, replication and persistence of nucleic acids present during the pre- or post-syndromic phase of infection in the absence of comparison groups [3,4,6,11,12,14]. Without comparing to control groups, the clinical relevance of identifying some respiratory pathogens by PCR testing remains difficult to determine [3,4,11,12,14–18].

Understanding the contribution of respiratory viruses to illness would allow the prioritization of respiratory pathogens for inclusion in diagnostic tests, disease surveillance, vaccine development and treatment.

2. Objectives

To the attributable fraction of 10 common respiratory viruses among patients hospitalized with severe acute respiratory illness (SARI) and outpatients with influenza-like illness (ILI) compared to control subjects.

3. Study design

3.1. Study design and population

SARI surveillance—Study samples were obtained from participants enrolled in a prospective hospital-based surveillance program for SARI initiated in February 2009. The methodology and case definition of this study has been previously described [8,19]. For this study participants were enrolled at 3 public hospitals in 2 provinces of South Africa (Edendale Hospital, KwaZulu-Natal Province; and Klerksdorp and Tshepong Hospitals, North West Province) from May 2012 through April 2015.

ILI and control surveillance—Study samples were obtained from participants enrolled in an active surveillance program for ILI and controls initiated in May 2012 and running through April 2015. The methodology and case definitions of this study have been as previously described [14]. Patients presenting with ILI and controls were enrolled at two outpatient clinics in the same catchment area to the above mentioned hospitals: Edendale Gateway Clinic, KwaZulu-Natal Province, and Jouberton Clinic, North West Province. An ILI case was defined as an outpatient of any age presenting with either temperature >38 °C or history of fever, and cough of duration of ≤7 days.

A control was defined as an individual presenting at the same outpatient clinic with no history of fever, respiratory or gastrointestinal symptoms during the 14 days preceding the visit. We aimed to enroll one HIV-infected and one HIV-uninfected control every week in each clinic within each of the following age categories: 0–1, 2–4, 5–14, 15–54 and ≥55 years.

3.2. Respiratory virus detection

Nasopharyngeal aspirates for children <5 years of age and nasopharyngeal and oropharyngeal swabs from individuals ≥5 years of age were collected from all enrolled patients (SARI, ILI and Controls), placed in viral transport medium, stored at 4–8 °C. All specimens were tested for the presence of 10 respiratory viruses (influenza A and B viruses, parainfluenza virus (PIV) types 1–3, respiratory syncytial virus (RSV), adenovirus; rhinovirus; human metapneumovirus (hMPV), and enterovirus) using a real-time reverse transcriptase polymerase chain reaction (rRT-PCR) assay [8]. Among consenting study patients, HIV status was established by enzyme-linked immunosorbent assay (ELISA) or PCR assay depending on the patients' age [19].

3.3. Statistical analysis

We implemented a multivariable multinomial regression model to determine the association between specific respiratory viruses among patients with SARI or ILI compared to controls enrolled from May 2012 through April 2015. Multinomial regression allows modeling of outcome variables with more than 2 categories and relates the probability of being in category *j* to the probability of being in a baseline or reference category. A complete set of coefficients are estimated for each of the *j* levels (patients with ILI or SARI in this analysis) that are compared with the baseline category (controls for this analysis) and the effect of each predictor in the model is measured as relative risk ratio (RRR). The association of the 10 viruses with mild (ILI) or severe (SARI) illness was assessed simultaneously using a multivariable model to adjust for the potential effect of co-infections. In addition, all estimates were adjusted for age (<1, 1–4, 5–24, 25–44, 45–64 and ≥65 years of age), HIV serostatus and underlying medical conditions other than HIV.

In addition, we implemented an age-stratified analysis among individuals aged <5 and ≥5 years of age to evaluate potential differences in disease association in young children and older individuals. For both analyses we also adjusted the effect of the viral covariates by age within each age strata (<1 and 1–4 years of age for children aged <5 years and 5–24, 25–44, 45–64 and ≥65 years of age for persons aged ≥5 years), HIV serostatus and underlying medical conditions other than HIV.

Subsequently we estimated the attributable fraction (AF) from the relative risk (RR) obtained from the multinomial model for each virus using the following formula: AF = (RR − 1)/RR×100. Lastly, we adjusted the observed detection rate ($Prev_{Obs} = n/N$) for each virus among ILI or SARI cases by the corresponding AF to obtain the prevalence of each virus attributable to mild (ILI) or severe (SARI) illness (adjusted prevalence, $Prev_{Illness}$) using the following formula: $Prev_{Illness} = Prev_{Obs} \times AF/100$. The analysis was performed using STATA 13.1 (StataCorp®, Texas, USA).

4. Results

4.1. Characteristics of the study population and detection of respiratory viruses

Over the study period, we enrolled 1959 SARI cases, 3784 ILI cases and 1793 controls. Children <5 years of age accounted for 73% (1431/1953); 28% (1075/3783) and 37% (658/1135) of SARI cases, ILI cases and controls, respectively. The HIV serostatus was known for 79% (1550/1959) of SARI cases, 87% (3280/3784) of ILI cases, and 92% (1643/1793) of controls. Among individuals with known HIV serostatus, the HIV prevalence was 26% (410/1550) among SARI cases, 30% (974/3280) among ILI cases, and 43% (702/1643; reflecting the enrolment criteria) among controls. Among SARI and ILI cases the HIV prevalence was lowest among infants <1 year of age [SARI: 10% (75/740), ILI: 2% (3/304)] and highest among individuals 25–44 years of age [SARI: 89% (174/196), ILI: 59% (608/1035)].

A virus was identified in 70% (1381/1959) of SARI cases, 59% (2230/3784) of ILI cases and 36% (645/1793) of controls. Among SARI cases the most commonly detected viruses were rhinovirus (34%; 667/1959), RSV (20%; 391/1959) and adenovirus (29%; 379/1959).

Rhinovirus (28%; 1064/3784), influenza virus (15%; 577/3784) and adenovirus (12%; 434/3784) predominated among the ILI cases. Rhinovirus (21%; 374/1793) and adenovirus (12%; 207/1793) were the most prevalent among controls (Table 1).

4.2. Attributable fraction of respiratory virus infection to mild or severe illness

In the main unstratified analysis using multivariable multinomial regression, all viruses except adenovirus where significantly associated with mild illness (ILI) and all viruses except PIV2 were associated with severe illness (SARI) (Tables 1 and 4). Nonetheless, the level of association (i.e., magnitude of the AF) varied across pathogens. Among ILI cases the AF was highest for influenza (adjusted AF [aAF]: 93.3%; 95% confidence intervals [95%CI]: 89.6–95.7%), PIV2 (aAF: 90.8%; 95%CI: 60.5–97.9%) and hMPV (aAF: 86.6%; 95%CI: 74.9–92.9%) (Table 4). Among SARI cases the AF was highest for influenza (aAF: 86.3%; 95%CI: 77.7–91.6%), hMPV (aAF: 85.6%; 95%CI: 72.0–92.6%), and RSV (aAF: 83.7%; 95%CI: 77.5–88.2%) (Table 4).

In the age stratified analysis among children <5 years of age all viruses except adenovirus and enterovirus where significantly associated with mild illness (ILI) and all viruses except PIV2 were associated with severe illness (SARI) (Tables 2 and 4). Among SARI cases <5 years of age, the highest significant AF (≥90%) were observed for influenza, hMPV and RSV, while the lowest significant AF was observed for enterovirus (38.2%) (Table 4). In this group among viruses with significant AF the estimated detection rate attributable to illness (adjusted prevalence) was 22.4% for RSV, 18.1% for rhinovirus, 10.1% for adenovirus, 5.2% for hMPV, 4.7% for influenza, 2.9% for PIV3, 2.8% for enterovirus and 2.4% for PIV1 (Table 4).

Among individuals ≥5 years of age adenovirus, RSV and PIV1 were not significantly associated with mild illness (ILI) and adenovirus, PIV1-3 and hMPV were not significantly associated with severe illness (SARI) (Tables 3 and 4). Among SARI cases ≥5 years of age the highest significant AF (>80%) were observed for enterovirus and influenza, while the lowest significant AF was observed for rhinovirus (42.7%). In this group among viruses with significant AF the estimated detection rate attributable to illness was 8.1% for rhinovirus, 5.9% for influenza, 3.4% for RSV, and 2.2% for enterovirus (Table 4).

Among ILI cases influenza had the highest AF and estimated prevalence associated with illness among children <5 years (AF: 95.8%; $Prev_{Illness}$: 13.9%) as well as individuals ≥5 years (AF: 91.9%; $Prev_{Illness}$: 14.5%) (Table 4).

5. Discussion

We assessed the association between virus detection and mild or severe illness relative to controls. The estimated detection rate attributable to illness reported in this study reflects a more accurate description of the prevalence of viruses causing respiratory disease in both children and adults in South Africa than reporting viral detection rates alone. Most of the viral pathogens evaluated in this study were found to be associated with mild or severe disease irrespective of HIV status. Nonetheless, the magnitude of this association varied between pathogens. Our study suggest that influenza, RSV and hMPV infections are highly

associated with severe respiratory illness in South Africa relative to controls, especially in children <5 years of age, which mirror the findings of Self et al. [12]. While rhinovirus and adenovirus had the lowest estimated AF the estimated detection rate attributable to illness remained high indicating that, while these viruses could act both as pathogen and bystander, they could also be responsible for a substantial proportion of severe disease. RSV, rhinovirus, adenovirus, hMPV and influenza were the most common pathogens causing disease among SARI cases, especially in children <5 years of age.

Our findings differ from similar studies which used multiplex PCR to detect a viral aetiology in non-invasive respiratory specimens relative to a control group, where fewer viruses were associated with disease. A study conducted among children ≤12 years of age hospitalized with pneumonia in the Kilifi District hospital in Kenya [6] reported that only RSV (identified in 34% of cases) was associated with disease as well as a case-control study conducted among children ≤59 months in rural Kenya [11]. Conversely, another study conducted in children reported that RSV and influenza were more commonly found among cases than controls [20]. In adults RSV, influenza, and hMPV have been shown to be associated with disease [21]. It should be noted that these studies had a limited number of controls potentially resulting in a lack of power to detect significant disease association for pathogens with low detection rates.

In our study RSV was found to be significantly associated with severe respiratory disease relative to controls. RSV has been well documented as the leading cause of viral pneumonia in children <5 years of age [1,22], but is also increasingly recognized as a cause of severe disease in adults [23–27]. Several studies have shown that RSV infection is an important cause of illness in the elderly (≥65 years) and high-risk adults, with a disease burden similar to that of non-pandemic seasonal influenza [26,28]. Although we found that RSV was associated with disease among both children and adults, modeling studies conducted in South Africa have not found excess mortality or hospitalizations associated with RSV among adults [29,30]. This apparent contradiction may relate to the fact that the burden of RSV among older adults in South Africa may be too low to be detected in modeling studies.

While rhinovirus has been shown to be less associated with illness (low attributable fraction) in both children and adults, the estimated detection rate attributable to illness remained elevated when compared to other pathogens, suggesting that rhinovirus may still causes a substantial proportion of clinical disease that manifests either as ILI or SARI. The high prevalence of rhinovirus among controls indicates that rhinovirus may potentially have an extended shedding period and can be detected in patients without symptoms. Several studies have reported the high positivity rate of rhinovirus in asymptomatic individuals and none so far have been able to give a clear indication of rhinovirus' role in severe respiratory infection, although several have suggested that rhinovirus can act as both a bystander and a pathogen [12,31–34]. Similar results were obtained for adenovirus in this study [18].

In our study, influenza and hMPV were found to be significantly associated with severe disease among children less than 5 years of age. Influenza has been described as one of the leading causes of pneumonia in children, the elderly, and adults with HIV infection [1,19,35,36]. Since 2001, hMPV has been reported worldwide. However, so far studies of

hMPV have been limited; although it has been suggested that hMPV mirrors the epidemiology of RSV and influenza with more severe infections occurring in the very young, elderly and immune-compromised individuals [37,38].

Our study has limitations that warrant discussion. First, several viruses were detected at low prevalence in the control group which would account not only for the high adjusted relative risk ratios but also for the wide confidence intervals. Second, comparing detection rate of pathogens among symptomatic patients with controls does not prove or disprove disease association in individual patients. Other approaches such as viral load and host interactions are needed to determine what role some of these viruses play in severe respiratory disease, while taking into account factors such as replication or persistence of nucleic acids present during the pre-or post syndromic phase of infection. Third, we did not adjust for the potential role of bacterial infections as this information was not available. The role of bacterial super-infection on severe illness following a viral infection cannot be excluded. Last, whereas on multivariable analysis we adjusted for the HIV serostatus of the individuals enrolled in this study, we were not powered to provide estimates of the AF stratified by HIV due to the low detection rate of certain pathogens within each stratum.

In conclusion, influenza, RSV and hMPV can be considered likely pathogens if detected in South African patients with ILI or SARI; whereas rhinovirus and adenovirus were commonly identified also among controls suggesting that they may cause only a proportion of clinical disease observed in positive patients. Nonetheless, given their high estimated detection rate attributable to illness, they may be important contributors to disease. This data together with other matched case-control studies like PERCH (Pneumonia Etiology Research for Child Health) [16] will provide useful information on how each pathogen impacts disease severity and may assist to better interpret surveillance data, to prioritize pathogens to be included in surveillance programs and to guide prevention interventions.

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Table 1

Association of respiratory viruses among patients (all ages) with SARI and ILI compared to controls in South Africa, 2012–2015 (Controls cases were used as the reference groups for the multinomial regression model, aRRR highlighted in bold indicate factors significant at $p < 0.05$).

Factor	Control[a] *n* (%) *N* = 1793	ILI *n* (%) *N* = 3784	SARI *n* (%) *N* = 1959	Multivariable analysis	
				ILI aRRR[b] (95% CI)	SARI aRRR[b] (95% CI)
Influenza	25 (1.4)	577 (15.2)	111 (5.7)	**14.9 (9.6–23.2)**	**7.3 (4.5–11.9)**
Rhinovirus	374 (20.9)	1064 (28.1)	667 (34.1)	**2.1 (1.8–2.4)**	**1.9 (1.6–2.3)**
Adenovirus	207 (11.5)	434 (11.5)	379 (19.3)	1.1 (0.9–1.3)	**1.6 (1.3–1.9)**
Enterovirus	53 (3.0)	120 (3.2)	118 (6.0)	**1.7 (1.2–2.5)**	**1.9 (1.3–2.9)**
RSV	55 (3.1)	225 (5.9)	391 (19.9)	**2.7 (1.9–3.8)**	**6.1 (4.4–8.5)**
PIV 1	11 (0.6)	56 (1.5)	45 (2.3)	**4.0 (1.9–8.4)**	**4.3 (2.0–9.3)**
PIV 2	2 (0.1)	28 (0.7)	11 (0.6)	**10.9 (2.5–46.9)**	4.1 (0.8–21.6)
PIV 3	23 (1.3)	81 (2.1)	72 (3.7)	**2.9 (1.7–5.0)**	**2.6 (1.5–4.6)**
hMPV	13 (0.7)	141 (3.7)	86 (4.4)	**7.5 (4.0–14.1)**	**6.9 (3.6–13.4)**

[a] Reference group for the multinomial regression model.

[b] Relative risk ratio (aRRR) adjusted by age, HIV serostatus and underlying medical conditions at multivariable analysis. Parainfluenza virus (PIV) 1–3; respiratory syncytial virus (RSV); human metapneumovirus (hMPV).

Table 2

Association of respiratory viruses among children <5 years of age with SARI and ILI compared to controls in South Africa, 2012–2015 (Controls cases were used as the reference groups for the multinomial regression model, aRRR highlighted in bold indicate factors significant at $p < 0.05$).

Variable	Control[a] *n* (%) *N* = 658	ILI *n* (%) *N* = 1075	SARI *n* (%) *N* = 1431	Multivariable analysis[c]	
				ILI aRRR[b] (95% CI)	SARI aRRR[b] (95% CI)
Influenza	7 (1.1)	149 (13.9)	73 (5.1)	**24.0 (9.5–60.7)**	**12.7 (4.9–32.5)**
Rhinovirus	214 (32.5)	401 (37.3)	567 (39.6)	**1.6 (1.3–2.1)**	**1.8 (1.4–2.3)**
Adenovirus	122 (18.5)	212 (19.7)	323 (22.6)	1.1 (0.8–1.5)	**1.8 (1.4–2.4)**
Enterovirus	46 (6.7)	82 (7.6)	105 (7.3)	1.4 (0.9–2.2)	**1.6 (1.1–2.5)**
RSV	25 (3.8)	129 (12.0)	357 (24.9)	**4.1 (2.5–6.7)**	**9.9 (6.2–15.8)**
PIV 1	7 (1.1)	33 (3.1)	43 (3.0)	**4.1 (1.7–10.0)**	**4.8 (2.0–11.8)**
PIV 2	1 (0.1)	13 (1.2)	10 (0.7)	**12.1 (1.4–101.5)**	5.6 (0.6–49.4)
PIV 3	15 (2.3)	40 (3.7)	65 (4.5)	**3.2 (1.6–6.5)**	**2.8 (1.5–5.5)**
hMPV	4 (0.6)	53 (4.9)	79 (5.5)	**13.5 (4.1–44.9)**	**16.2 (4.9–53.4)**

[a] Reference group for the multinomial regression model.

[b] Age and HIV adjusted relative risk ratio (aRRR) at multivariable analysis.

[c] Only covariates significant at the multivariable analysis are reported. Parainfluenza virus (PIV) 1–3; respiratory syncytial virus (RSV); human metapneumovirus (hMPV).

Table 3

Association of respiratory viruses among patients ≥5 years of age with SARI and ILI compared to controls in South Africa, 2012–2015 (Controls cases were used as the reference groups for the multinomial regression model, aRRR highlighted in bold indicate factors significant at $p < 0.05$).

Variable	Control[a] *n* (%) *N* = 1135	ILI *n* (%) *N* = 2708	SARI *n* (%) *N* = 522	Multivariable analysis[c]	
				ILI aRRR[b] (95% CI)	SARI aRRR[b] (95% CI)
Influenza	18 (1.6)	428 (15.8)	38 (7.2)	**12.3 (7.5–20.3)**	**5.3 (2.9–9.9)**
Rhinovirus	160 (14.1)	663 (24.5)	100 (19.0)	**2.5 (2.0–3.0)**	**1.7 (1.3–2.4)**
Adenovirus	85 (7.5)	222 (8.2)	56 (10.6)	1.1 (0.8–1.4)	1.2 (0.8–1.8)
Enterovirus	7 (0.6)	38 (1.4)	13 (2.5)	**3.7 (1.4–9.7)**	**7.9 (2.7–23.5)**
RSV	30 (2.6)	96 (3.5)	34 (6.4)	1.4 (0.9–2.2)	**2.2 (1.2–3.9)**
PIV 1	4 (0.3)	23 (0.8)	2 (0.4)	2.4 (0.7–8.7)	1.7 (0.3–10.3)
PIV 2	1 (0.1)	15 (0.6)	1 (0.1)	**10.6 (1.3–82.9)**	Not estimated
PIV 3	8 (0.7)	41 (1.5)	7 (1.3)	**2.7 (1.1–6.3)**	2.5 (0.8–7.5)
hMPV	9 (0.8)	88 (3.25)	7 (1.3)	**4.8 (2.3–10.1)**	1.7 (0.6–5.3)

[a] Reference group for the multinomial regression model.

[b] Age and HIV adjusted relative risk ratio (aRRR) at multivariable analysis.

[c] Only covariates significant at the multivariable analysis are reported. Parainfluenza virus (PIV) 1–3; respiratory syncytial virus (RSV); human metapneumovirus (hMPV).

Table 4

Attributable fraction, observed prevalence and adjusted prevalence of respiratory viruses among patients with SARI and ILI in South Africa, 2012–2015 (a percentage highlighted in bold indicate a significance $p < 0.05$).

Viruses	Influenza-like-illness			Severe acute respiratory illness		
	Attributable fraction (%) (95% CI)	Observed prevalence (%)	Adjusted prevalence (%)[a]	Attributable fraction (%) (95% CI)	Observed prevalence (%)	Adjusted prevalence (%)[a]
Individuals of any age						
Influenza	**93.3 (89.6–95.7)**	15.2	14.2	**86.3 (77.7–91.6)**	5.7	4.9
Rhinovirus	**52.0 (44.0–58.9)**	28.1	14.6	**46.9 (37.6–56.5)**	34.1	20.2
Adenovirus	5.9 (−15.1 to 23.1)	11.5	0.7	**36.4 (20.6–49.0)**	19.3	7.0
Enterovirus	**41.8 (15.5–59.9)**	3.2	1.3	**49.0 (24.9–65.4)**	6.0	2.9
RSV	**63.1 (48.6–73.5)**	5.9	3.7	**83.7 (77.5–88.2)**	19.9	16.7
PIV 1	**75.3 (48.8–88.1)**	1.5	1.1	**76.9 (50.6–89.2)**	2.3	1.8
PIV 2	**90.8 (60.5–97.9)**	0.7	0.6	75.9 (−25.9 to 95.4)	0.6	0.5
PIV 3	**66.1 (42.5–80.0)**	2.1	1.4	**62.0 (34.1–78.1)**	3.7	2.3
hMPV	**86.6 (74.9–92.9)**	3.7	3.2	**85.6 (72.0–92.6)**	4.4	3.8
Children < 5 years of age						
Influenza	**95.8 (89.5–98.3)**	13.9	13.3	**92.1 (79.7–96.9)**	5.1	4.7
Rhinovirus	**38.2 (21.1–51.6)**	37.3	12.7	**45.7 (31.0–57.2)**	39.6	18.1
Adenovirus	9.3 (−21.6 to 32.3)	19.7	1.8	**44.9 (27.0–58.4)**	22.6	10.1
Enterovirus	29.4 (−9.7 to 54.6)	7.6	2.2	**38.3 (5.0–59.9)**	7.3	2.8
RSV	**75.7 (60.3–85.1)**	12.0	9.1	**90.0 (84.0–93.7)**	24.9	22.4
PIV 1	**75.5 (39.8–90.0)**	3.1	2.3	**79.3 (49.3–91.5)**	3.0	2.4
PIV 2	**91.7 (30.6–99.0)**	1.2	1.1	82.1 (−57.7 to 97.9)	0.7	0.6
PIV 3	**69.2 (38.6–84.6)**	3.7	2.6	**64.8 (31.8–81.8)**	4.5	2.9
hMPV	**92.6 (75.4–97.8)**	4.9	4.6	**93.8 (79.6–98.1)**	5.5	5.2
Individuals ≥ 5 years of age						
Influenza	**91.9 (86.6–95.1)**	15.8	14.5	**81.3 (65.3–89.9)**	7.2	5.9
Rhinovirus	**59.6 (50.2–67.3)**	24.5	14.3	**42.7 (21.6–58.1)**	19.0	8.1
Adenovirus	8.1 (−23.2 to 31.4)	8.2	0.7	16.8 (−27.1 to 45.5)	10.6	1.8
Enterovirus	**72.8 (28.3–89.7)**	1.4	1.0	**87.4 (62.9–95.7)**	2.5	2.2
RSV	28.2 (−13.2 to 54.5)	3.5	1.0	**54.8 (19.9–74.5)**	6.4	3.4

Viruses	Influenza-like-illness			Severe acute respiratory illness		
	Attributable fraction (%) (95% CI)	Observed prevalence (%)	Adjusted prevalence (%)[a]	Attributable fraction (%) (95% CI)	Observed prevalence (%)	Adjusted prevalence (%)[a]
PIV 1	58.7 (−48.4 to 88.5)	0.8	0.5	40.0 (−270.1 to 90.3)	0.4	0.1
PIV 2	**90.6 (26.2 to 98.1)**	0.6	0.5	Not estimated	0.1	Not estimated
PIV 3	**62.9 (13.5–84.1)**	1.5	0.9	59.4 (−24.3 to 86.7)	1.3	0.8
hMPV	**79.2 (56.1–90.1)**	3.25	2.6	41.7 (−81.5 to 81.3)	1.3	0.6

[a]Observed prevalence adjusted by the AF to obtain the prevalence attributable to illness. Parainfluenza virus (PIV) 1, 2, 3; Respiratory Syncytial Virus (RSV); human metapneumovirus (hMPV).