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RESEARCH ARTICLE

Mortality Time Trend for Major Viral Pathogens Causing Acute Respiratory Failure in Brazilian Children and Adolescents Before and During the SARS-Cov-2 Pandemic

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ABSTRACT

Background – Little is known about the time trend in mortality rates due to respiratory viruses other than SARS-CoV-2 and seasonal influenza among Brazilian children and adolescents.

Methods – Study outcomes were mortality rates due to influenza A, influenza B, respiratory syncytial virus, metapneumovirus, rhinovirus, parainfluenza, adenovirus, and bocavirus, for age groups <5, 5-9, and 10-19 years of age, in Brazil, over the 2009-2022 period. Secondary data from the Brazilian Ministry of Health were analyzed by interval regression, bounded between reported deaths and estimated upper limit of this number, which took into account the underestimation of deaths, the error in attributing its causes in official records, and the variation due to Poisson distribution.

Results - For all viruses, mortality varied little among the children under five years of age, and increased gradually among the 5-10 and 11-19-years old. The highest average mortality rates per million inhabitants over the 2009-2022 period were estimated for respiratory syncytial virus (1.04), with the lowest values for parainfluenza (0.54) and influenza B (0.55), and intermediate values in the range of 0.90 to 0.95 for influenza A, bocavirus, metapneumovirus, rhinovirus, adenovirus, and other respiratory viruses except SARS-Cov-2. Age groups of 5-9 and 10-19 years of age had similar mortality rates and were by far the largest contributors to the overall mortality rates for all viruses analyzed.

Conclusion - Schoolchildren mortality due to respiratory viruses in Brazil has been rising for at least five years before the COVID-19 pandemic, and remained elevated during the pandemic. In addition to SARS-CoV-2 and seasonal influenza, respiratory syncytial virus, metapneumovirus, rhinovirus, parainfluenza, adenovirus, and bocavirus, all showed a non-ignorable impact on mortality in this age group.

Keywords: Mortality, Children, Adolescents, Respiratory Viruses, Brazil.

Introduction

Since the start of the SARS-Cov-2 pandemic, this virus has concentrated most of the research interest concerning severe acute respiratory infections (SARI) due to its catastrophic consequences. Mortality estimates that took into account under-reporting of Coronavirus disease 2019 (COVID-19) deaths pointed to a staggering number of 18,2 million deaths attributed to this cause, almost three times the number in official country-based registers[1,2]. In 2022, COVID-19 caused over 57,000 deaths in Brazil, resulting in a mortality rate (MR) of 230 per million inhabitants[3]. Since mid-November, a significant increase in hospitalizations and deaths due to this disease was observed country-wise. This increase was registered in all age groups, including children and adolescents, where SARI incidence due to the COVID-19 peaked markedly in January and February, and less markedly in July. Virtually all COVID-19 deaths in this age group occurred among those not vaccinated.

However, other viral agents causing SARI have continued to exert their toll, despite being overshadowed by the SARS-Cov-2, especially in the pediatric population. At the beginning of the pandemic, it was widely believed that this population was not particularly at risk of severe COVID-19 but was more relevant as a means of viral transmission between schools and households. As the pandemic evolved, it became clear that children and adolescents could develop severe disease and die of it at a significant rate, thus being progressively included in anti-COVID-19 vaccination programs. The latter adversely affected other vaccines' coverage, such as against seasonal influenza, Hemophilus influenza B, measles-mumps-rubella, pneumococcal pathogens, and polio, especially in low-income countries[4,5].

With the advent of multiplex RT-PCR testing for respiratory viruses, their application at the point-of-care settings treating SARI has been amplified, resulting in a wide range of incidence and case-fatality rate (CFR) estimates, but rarely the MRs with population denominator[6,7]. Influenza strains have been routinely screened for decades because of related vaccine production, but their effectiveness has been evaluated mostly in terms of hospitalization-related outcomes and their economic burden, whereas associated MRs have been studied relatively rarely[8]. The latter is due to numerous challenges in calculating the attributable fraction for a single respiratory viral pathogen, not only because of co-infections but also because of their contribution to subsequent secondary infections, principally those leading to pneumonia – the most frequent cause of death in children <5 years of age worldwide[9].

In Brazil, some studies allow the calculation of the MRs associated with respiratory viruses from the published CFR data. A single-hospital study in the equatorial city of Fortaleza, the capital of the northeastern state of Ceará, pointed to the respiratory syncytial virus (RSV) MR of 20 per million children under 5 years of age, about a third of the MR for all-cause pneumonia[10]. Based on the nationwide analysis of the number of respiratory deaths during the period between December 2019 and October 2021[11] and the population estimates of the 0-12-years old, the MRs for influenza and all other respiratory viruses were 2.30 (95% CI 1.34-3.85) and 1.22 (0.72-2.03) on the same scale, respectively. Corresponding MRs per million among children <1 year of age were 0.24 (0.13-0.43) for influenza and 0.13 (0.07-0.23) for the other viruses. These findings are in line with the 0-5 per million range of the present study's MRs.

Other Brazilian studies found a significant association between the presence of RSV in SARI patients and a more severe disease course. A single-hospital study in the state capital São Paulo reported 27.3% of patients with RSV and 15.8% with adenovirus among the 0-14-years old hospitalized with lower respiratory tract infections[12]. Another single-hospital study in the city of Uberlândia in central Brazil also found an association between RSV and more severe diseases, such as pneumonia and bronchiolitis, among children and adolescents treated for SARI[13]. In the equatorial city of Belém, the capital of the Pará state, RSV-associated CFR was 3.6% among children under 5 years of age with community-acquired pneumonia[14].

Apart from influenza and more recently SARS-Cov-2, RSV has been the most extensively studied among respiratory viruses in Brazil, with a focus on its incidence, seasonality, and CFR[12,10,15,13,16]. In 2022, an upturn of this virus was registered in São Paulo and the southern states of Rio Grande do Sul, Santa Catarina, and Paraná[3]. The high burden of RSV on hospital admissions and stay was pointed out in other studies restricted to a particular Brazilian city[12,10,15,13], except for the equatorial city São Luis, the capital of the

Maranhão state, where 68% of SARI hospitalizations in children <5 years of age were caused by rhinovirus and 14% by RSV[16]. The latter result could have been influenced by the reported total coverage of the pneumococcal and influenza vaccine in this age group.

Brazil was among the countries hardest hit by COVID-19, due to the delayed start of the vaccination of both adult and pediatric population. Some studies pointed to the pitfalls of the Brazilian COVID-19 vaccination early on[17] and a sharp drop in the coverage of other routinely applied vaccines[18,19]. Nevertheless, to the best of the authors' knowledge, there has been no publication on the time trend in mortality caused by other viral pathogens that may cause SARI over a longer period in Brazilian children and adolescents. Therefore, this study aims to describe this time trend over the decade before the COVID-19 pandemic and three pandemic years.

Methods

The data on the number of deaths by selected viruses were downloaded from the InfoGripe site https://gitlab.fiocruz.br/marcelo.gomes/infogripe/, linked to the Brazilian Ministry of Health database SIVEP-Gripe, and maintained by the Fiocruz foundation. The outcomes were mortality rates (MRs) for SARI deaths by the following human viruses: influenza A, influenza B, parainfluenza viruses types 1-4, rhinoviruses, adenoviruses, respiratory syncytial virus (RSV), metapneumovirus, bocavirus, and other unspecified viruses capable of causing SARI[3]. The total number of deaths caused by the aforementioned viruses included the breakdown by federal state/district, calendar year, epidemiological week, age group, and sex. Mortality rates were calculated by dividing the number of cases by the corresponding population size, retrieved from the state-level projections of age-by-sex groups[20].

The case definition of SARI was adopted from the World Health Organization[21] and included fever ≥ 38 C°, cough or throat pain, dyspnea, or blood oxygen saturation <95%, breathing difficulty, need for hospitalization, or death.

A variety of laboratory kits were used to test nasopharyngeal swabs for the presence of respiratory viruses available in the SIVEP-Gripe database. In the first half of the period analyzed, direct immunofluorescence assay (D3 Ultra DFA Respiratory Virus Screening and Identification kit, Quidel, San Diego, CA, USA) predominated, whereas real-time polymerase chain reaction (SimplexaTM Flu A/B and RSV Direct kit, Focus Diagnostics, Cypress, CA, USA) were more frequently used in the second half.

Data quality was assessed by the percentage of deaths without laboratory testing, with delayed test result, and by the percentage of laboratory confirmed causes. Mortality rates were corrected for under-reporting of deaths in the target population and so-called "garbage codes" in the 10th Revision of the International Classification of Diseases (ICD-10) applied to the SARI, according to the algorithm proposed by Paes et al.[22].

Mortality rate correction included four steps. First, the number of reported deaths (N_r) for each pathogen was multiplied by the correction factor 1.3739[22]. Although this factor was estimated for the COVID-19 deaths in Brazil, the present study applied it to all pathogens analyzed here for simplicity. Second, the laboratory testing confirmation rate (c_r) was calculated by dividing the number of positive laboratory tests (T_p) by the sum of both positive and negative tests (T_n) and subsequently multiplied by the number of SARI deaths without laboratory results (N_x). The latter consisted of those not tested, waiting for or with inconclusive test results, or without information on laboratory testing. The expected number of deaths (E_2) was the sum of reported and estimated additional deaths for each virus analyzed:

$$E_1 = 1.3739\ N_r \quad (1)$$

$$c_r = T_p / (T_p + T_n) \quad (2)$$

$$E_2 = E_1 + (c_r\ N_x) \quad (3)$$

Finally, the upper limit of the number of deaths (L_{max}) was estimated assuming a Poisson distribution, at the mean plus three times square route of the mean for each virus, and divided by the population to obtain MR. Reported MR was considered the lower limit (L_{min}) of true MR (E_3) for each virus. Formally

$$\log(E_3) = E[\log(L_{min}, L_{max} \mid X)] \sim N \quad (4)$$

where the letter "E" stands for statistical expectation within the defined interval, conditional upon observed covariates ("| X"), and assuming a

normal distribution of true MR on the natural logarithmic scale ("~ N") to reduce kurtosis.

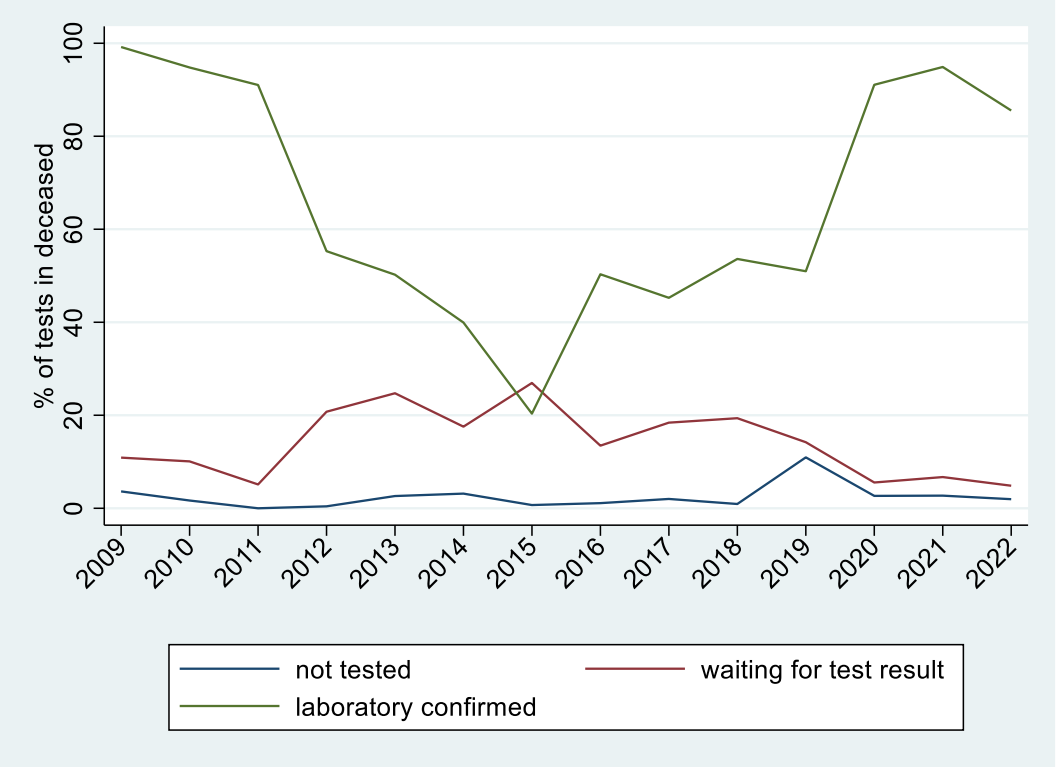
The plausible interval for true MR was defined by the aforementioned limits. The interval regression fitted a log-linear model with age group (0-4, 5-9, 10-19 years) and calendar year as categorical independent variables. These variables were enhanced with the federal state/district indicator for the analysis of the two most frequent causes of death (Influenza A and RSV) among the viruses analyzed. The variation of the MR estimates was expressed with a 95% confidence interval (CI).

Interval regression is a generalization of the Tobit model with an interval-measured dependent variable placed between lower and upper limits[23,24]. The calendar year was also used to model the variance. Maximum likelihood estimation and robust standard errors were used with Stata software[25].

Results

Judged by the percentage of laboratory-confirmed cases among the patients who died of acute respiratory failure falling to 50% or lower, the period between 2012 and 2019 had the least satisfactory data quality (Figure 1). The percentage of the patients not tested for respiratory viruses in a laboratory was about 5%, except in 2019 when it doubled. Over most of the years during the period analyzed, the percentage of the patients with delayed test results varied between 5% and 20%. Overall, the first and the last three years of the period showed better quality of laboratory testing data, and consequently a higher precision of the MRs based on these data.

Figure 1. Percentage (%) of patients not tested, waiting for test result, and laboratory confirmed cases among deceased from severe acute respiratory infection.



Before the COVID-19 pandemic, influenza A peaked every 2-3 years since the onset of the 2009 A(H1N1) pandemic (Figure 2).

Figure 2. Estimated mortality rate (MR) per million inhabitants for major viral pathogens causing severe acute respiratory sindrome in Brazilian paediatric population: 0-4 (solid line), 5-9 (dashed line), and 10-19 years of age (dotted line).

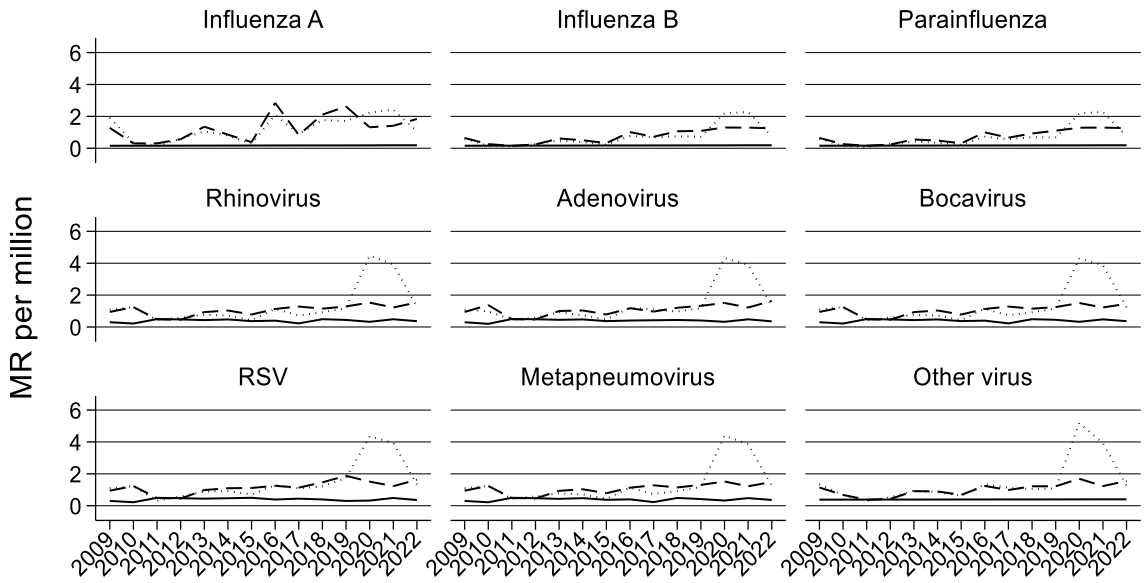
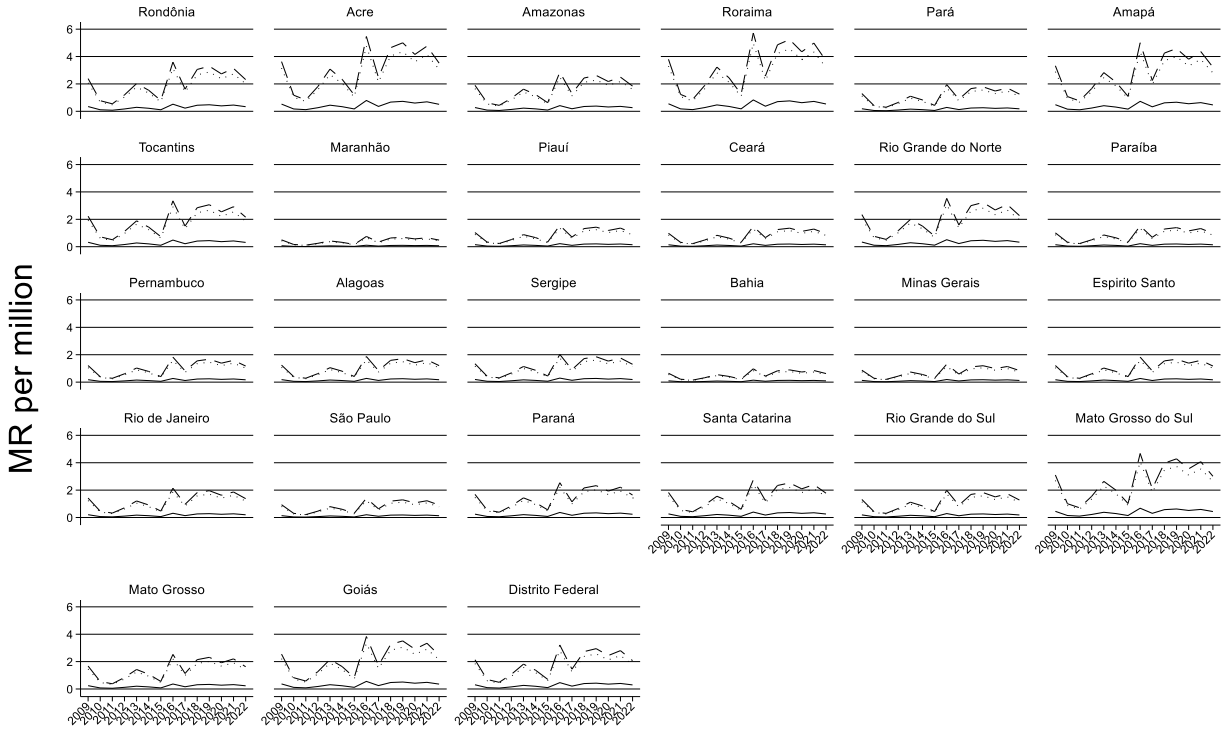


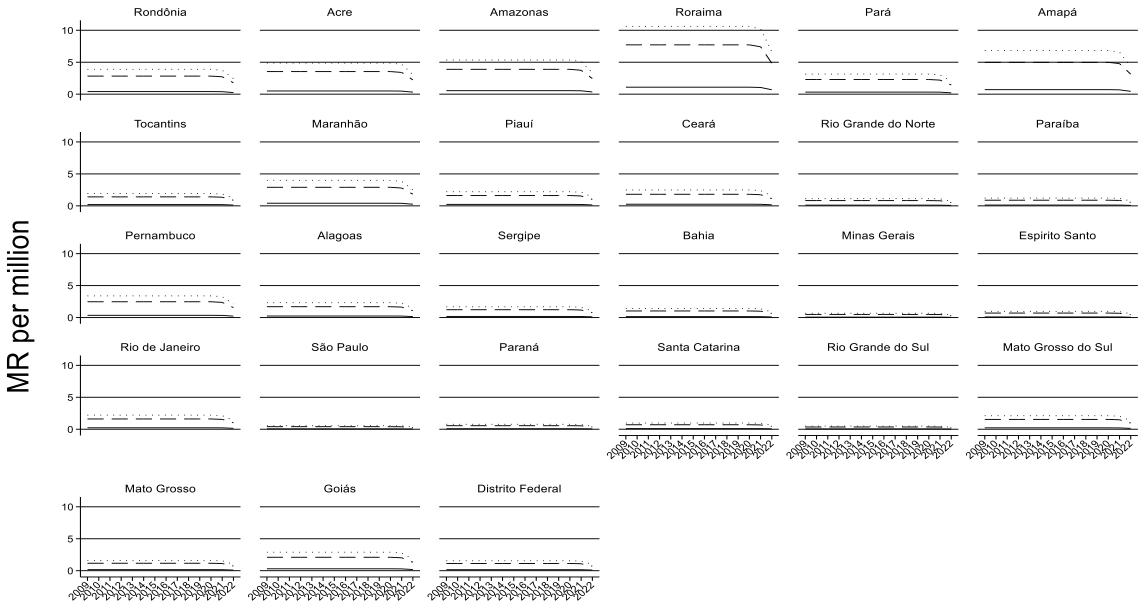
Figure 3. Estimated mortality rate (MR) per million for influenza A causing severe acute respiratory infection in Brazilian paediatric population by federal states/district: 0-4 (solid line), 5-9 (dashed line), and 10-19 years of age (dotted line).



The mortality due to the 2009 pandemic of A(H1N1) was registered in all Brazilian states but was particularly high in Roraima, Amapá, and Acre, all of which have tropical climates, and in Mato Grosso do Sul (Figure 3). Mortality rates for these states were estimated in the range of 4-6 per million inhabitants. On the other hand, the southern states of Rio Grande do Sul, Santa Catarina, and Paraná, with colder winters than the rest of this mostly tropical country, showed 2-3 times lower magnitude. Since the 2016 peak, the MRs of Rondônia, Amazonas, Tocantins, Goiás, and Distrito Federal, varied between 2 and 4 per million.

The children under 5 years of age had RSV mortality close to zero (Figure 4).

Figure 4. Estimated mortality rate (MR) per million for RSV causing severe acute respiratory infection in Brazilian paediatric population by federal states/district: 0-4 (solid line), 5-9 (dashed line), and 10-19 years of age (dotted line).



The oldest group (15-19 years) had slightly higher mortality compared to the 5-9-years old. Equatorial states of Roraima and Amapá showed the highest MRs (5-10 per million), followed by other tropical states of Amazonas, Acre, Rondônia, Maranhão, and Pará, with the MRs in the range of 2-5 per million. Northeastern states of Pernambuco, Ceará, and Alagoas, had slightly lower MRs (2-4 per million).

For all viruses, mortality varied little among the children under five years of age, and increased gradually among the 5-10 and 11-19-years old, except for a sharp blip in 2020 when the SARS-CoV-2 pandemic occurred, and subsequent reduction to the pre-pandemic level in this group (Figure 2). Joint MRs for all viruses averaged 5.12 per million in the first half of the 2009-2022 period and doubled in the second half of the period.

The highest average MR per million inhabitants over the 2009-2022 period was estimated for RSV (1.04), with the lowest values for parainfluenza (0.54) and influenza B (0.55), and intermediate values in the range of 0.90 to 0.95 for Influenza A, bocavirus, metapneumovirus, rhinovirus, adenovirus, and other respiratory viruses except SARS-Cov-2 (Supplementary Table 1). Age groups of 5-9 and 10-19 years of age had similar MRs and were by far the largest contributors to the overall MRs for all viruses analyzed. Among children <5 years of age, the MRs per million ranged between 0.17 for influenza A/B and parainfluenza, and about 0.40 for all other viruses.

Discussion

To the best of the authors' knowledge, this is the first comprehensive report on the state-wise MRs associated with respiratory viruses, except for

the SARS-CoV-2, in Brazilian children and adolescents since nationwide sentinel surveillance was established in 2009. The joint impact of respiratory viruses other than SARS-CoV-2 doubled over the period analyzed and exceeded 10 per million inhabitants under 20 years of age. RSV and influenza A were the most frequent causes of death among the viruses analyzed.

Outside Brazil, SARI-related CFR with laboratory identification of associated respiratory viruses provide some clue as to their impact on mortality. Among the children <5 years old and hospitalized with SARI presentation, the CFR was 3.4% in the cold climate of Manitoba in Canada[26], compared to 1.1-5.3% (depending on the viral strain) in Argentina's temperate climate[27]. In rural Kenia, a case-control cohort study found a MR of 385 (0-1100) per million person-years in children under 5 years of age[28]. Another study from the same country showed that RSV and influenza were the most frequent causes of SARI in urban slums with high population densities[29]. A meta-analysis of African studies found higher mortality from SARI due to respiratory viral infections among children <5 years of age whose immune system was compromised with HIV compared to those without HIV[30].

Non-pharmacological measures to prevent SARS-CoV-2 transmission, such as wearing a facial mask and reducing social contacts, were also effective in preventing other viral respiratory infections in various countries, such as the US [31,32,33], Finland[7], Japan[34], France[35], Australia[36], and Brazil[37]. The present study registered a sharp decrease in the MRs of these infections among Brazilian adolescents 10-19 years old in 2021 compared to 2020 when the COVID-19 pandemic hit the country in March. A steep increase in the MRs for all respiratory viruses in 2020 (Figure 2) may be due to the increased throughput of SARS-CoV-2 testing, which also brought about further testing for other viruses in the case of negative test results for the former. Also, the specificity of commercial kits for the SARS-CoV-2 in 2021 was significantly better compared to 2020, thus reducing false negative test results that could have triggered the search for other respiratory pathogens and therefore lowering the chance of their detection in 2021. Furthermore, non-pharmacological measures were better adhered to in Brazil in 2021 compared to the previous year, so that the chance of all respiratory infections was reduced.

Among Brazilian states, the MRs for influenza A in children <5 years old remained below one per million, whereas those for schoolchildren (5-19 years old) were several times higher and rose over the period analyzed (Figure 3). The rise accelerated since 2016, particularly in the tropical states of Rondônia, Acre, Roraima, Amazonas, and Mato Grosso do Sul. The influenza season in Brazil starts by the end of the first quarter of the year and spreads from northern tropical to southern states with temperate climates, where it peaks in the winter months of July and August[38]. However, low influenza vaccine coverage and the lack of its timeliness in tropical parts of the country are likely reasons for approximately doubling influenza A mortality in the aforementioned states over the second part of the period analyzed.

Although the MRs for respiratory viruses other than SARS-CoV-2 may appear low compared to the bacterial pneumonia MR, some authors warn that the joint mortality of the former may be as high as the latter[8]. Of note, respiratory viral infections are particularly deadly at the extremes of age distribution, that is, among children and the elderly. The infections are known to exacerbate pre-existing chronic diseases, such as asthma and chronic obstructive pulmonary disease[13,39], and are more common in immunocompromised patients[30]. Rhinovirus was most frequently associated with asthma exacerbation worldwide, except on the African continent[39].

By the end of the 2010 decade, RSV was considered responsible for 200,000 deaths among children aged less than five years worldwide[40]. In the US, viral pathogens were twice as frequent in causing community-acquired pneumonia compared to bacterial pneumonia[41,42]. RSV was deemed responsible for about a fifth of hospital-acquired pneumonia, rhinovirus for 70% of asthma exacerbations in <2 years-old children, metapneumovirus for over 10% of lower respiratory tract infections and 26% of the deaths among immunocompromised patients hospitalized with SARI[42].

The US surveillance of patients with an acute respiratory infection found rhinovirus/ enterovirus and RSV associated with 30.6% and 23.7% hospitalizations, respectively[43]. In South Africa, RSV and rhinovirus were the most frequent causes of severe pneumonia in <5 years old children[44]. In Hong Kong, the MRs per million were 28.5 for RSV, 77.1 for parainfluenza, 15.1 for

adenovirus, over the 1998-2012 period, excluding the year 2009 when pandemic influenza A(H1N1) broke out[6]. When adolescents (<15 years) were included, the MRs decreased to 8.2 for RSV, 3.5 for adenovirus, and 2.0 for parainfluenza, closer to the present study range of 0-5 per million.

Although influenza A has been the main target of universal immunization of young children and elderly in Brazil concerning respiratory diseases, precise MRs caused by this infection is hard to obtain as most epidemiological studies used pneumonia and influenza (P&I) outcome. For example, P&I MR over the 2002-2011 period in São Paulo state was in the range of 0-8 per million among <5 years old and not exceeding one per million among 5-19-years old[45], overlapping with influenza A only MR of 0-2 over the 2009-2011 period in the present study (Figure 2). However, a five-year follow-up of Brazilian birth cohorts over the 2012-2018 period found the P&I MR of 132 (126-137) per million for the subsequent five-year period[46].

Over half of all respiratory tract infections are caused by rhinoviruses through inflammation and obstruction of airways, and by promoting their hyper-responsiveness, thus exacerbating asthma and coronary obstructive pulmonary disease[47]. The infection can be fatal in people with compromised immune systems, such as transplant patients and the elderly. The same goes for other respiratory viruses analyzed here[48,49,50,51]. Metapneumovirus and RSV MRs are similarly high among children less than six months old in poor countries[51]. Global MR for metapneumovirus among children <5 years of age in 2019 can be calculated by dividing the estimated number of deaths[9] by the corresponding population at risk[52] providing an estimate of 11.24 per million with 95% confidence interval of 0.58-26.72.

Although parainfluenza, adenovirus, and bocavirus studies lack mortality rates to compare with those from the present study in the range of 0-2 per million, some publications allow us to gauge their impact. For example, in a high-risk environment due to overcrowding and lack of sanitation, parainfluenza, adenovirus, and metapneumovirus caused over one-fifth of all SARI cases[29]. Bocavirus circulation has been reported in Brazil in the studies restricted to a city[50,53] that reported no deaths caused by this virus.

Complex interactions between respiratory viruses concerning human hosts are beyond the scope of this study. For example, some studies found high parainfluenza incidence when influenza strains are at low levels in equatorial Brazil[54] and subtropical Asia[6]. Also, environmental factors such as temperature and humidity, behavioral factors (travel, masking, vaccination), and genetic diversity of respiratory viruses, essential for vaccine development, were all left out from the present study. These issues are warranted further research to prevent SARI.

Despite pneumonia being the deadliest secondary infection among influenza complications, universal immunization of Brazilian children with a 10-valent pneumococcal vaccine since 2010 effectively reduced this risk in children <5 years old, according to a review of nationwide studies on this topic[55]. These children are more vulnerable to respiratory infections compared to older children with more mature immune systems. However, schoolchildren have higher contact rates and lower coverage for seasonal influenza and pneumococcal vaccines, so the overall impact of all these factors on mortality is hard to gauge, let alone to disentangle their attributable fractions in the population. Although influenza A is an immunopreventable disease, the present study points to the significant mortality it caused in Brazilian schoolchildren. Other respiratory viruses, not vaccine-preventable over the period analyzed, also contributed significantly to this group's mortality.

The present study's limitations include those inherent to secondary data analysis, primarily concerning the lack of control over data quality, and not accounting for varying sensitivity and specificity of laboratory tests used over a long period. Moreover, the correction factor for under-reporting of deaths did not reflect considerable variation across states. Also, it may be difficult to differentiate between an asymptomatic virus carrier and active viral infection without the information on viral load[42], although the EPIC study suggested that laboratory-confirmed viral pathogen was causing respiratory infection in the vast majority of cases[41].

The present study is comprehensive both geographically (all states) and concerning the period (2009-2022). Furthermore, it takes into account various factors contributing to the under-reporting of deaths caused by respiratory viruses and sets a plausible interval for the magnitude of these effects. Population denominator used in the

present study is more stable and not prone to selection biases driven by varying implementations of SARI hospitalization criteria in the hospital-based studies, the differences in access to medical care, and care-seeking behavior.

Steady pressure to migrate from developing to developed countries underlines the need to invest more in global health and sustainable economic growth. By the end of the decade 2000, virtually all RSV deaths were concentrated in developing countries[40] – a result that has not changed much in the next decade[9]. The burden of respiratory viral infections has become increasingly evident and prompted the calls for developing effective vaccines, similar to those for seasonal influenza and SARS-CoV-2[45].

Conclusion

Schoolchildren mortality due to respiratory viruses in Brazil had been rising for at least five years before the COVID-19 pandemic and remained elevated during the pandemic. In addition to SARS-CoV-2 and seasonal influenza, RSV, metapneumovirus, rhinovirus, parainfluenza, adenovirus, and bocavirus, jointly contribute to significant mortality in this age group, especially among those with already compromised immune systems due to co-morbidity. Until vaccine development provides a better means of prevention, non-pharmacological measures remain an affordable method for particularly vulnerable individuals.

Conflict of Interest Statement

The authors declare no conflict of interest.

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References

1. Collaborators EM. Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020-21. *Lancet (London, England)*. 2022;399(10334):1513-1536. doi:10.1016/S0140-6736(21)02796-3
2. Msemburi W, Karlinsky A, Knutson V, Aleshin-Guendel S, Chatterji S, Wakefield J. The WHO estimates of excess mortality associated with the COVID-19 pandemic. *Nature*. 2023;613(7942):130-137. doi:10.1038/s41586-022-05522-2
3. Brasil. Ministério da Saúde. Nota Técnica nº 19/2022 - CGGRIPE/DEIDT/SVS/MS. Published 2022. https://www.gov.br/saude/pt-br/coronavirus/notas-tecnicas/2022/nota-tecnica-no-19-2022/view
4. Yunusa A, Cabral C, Anderson E. The impact of the Covid-19 pandemic on the uptake of routine maternal and infant vaccines globally: A systematic review. *PLOS Glob Public Heal*. 2022;2(10):e0000628. doi:10.1371/journal.pgph.0000628
5. SeyedAlinaghi SA, Karimi A, Mojdeganlou H, et al. Impact of COVID-19 pandemic on routine vaccination coverage of children and adolescents: A systematic review. *Heal Sci Reports*. 2022;5(2):1-12. doi:10.1002/hsr2.516
6. Chan PKS, Tam WWS, Lee TC, et al. Hospitalization incidence, mortality, and seasonality of common respiratory viruses over a period of 15 years in a developed subtropical city. *Med (United States)*. 2015;94(46):e2024. doi:10.1097/MD.0000000000002024
7. Kuitunen I, Artama M, Haapanen M, Renko M. Respiratory virus circulation in children after relaxation of COVID-19 restrictions in fall 2021—A nationwide register study in Finland. *J Med Virol*. 2022;94(9):4528-4532. doi:10.1002/jmv.27857
8. Gordon A, Reingold A. The Burden of Influenza: a Complex Problem. *Curr Epidemiol Reports*. 2018;5(1):1-9. doi:10.1007/s40471-018-0136-1
9. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet*. 2022;399(10340):2047-2064. doi:10.1016/S0140-6736(22)00478-0
10. Alonso WJ, Laranjeira BJ, Pereira SAR, et al. Comparative dynamics, morbidity and mortality burden of pediatric viral respiratory infections in an equatorial city. *Pediatr Infect Dis J*. 2012;31(1):1-13. doi:10.1097/INF.0b013e31823883be
11. Sansone NMS, Boschiero MN, Marson FAL. Epidemiologic Profile of Severe Acute Respiratory Infection in Brazil During the COVID-19 Pandemic: An Epidemiological Study. *Front Microbiol*. 2022;13(July). doi:10.3389/fmicb.2022.911036
12. Ferone EA, Berezin EN, Durigon GS, et al. Clinical and epidemiological aspects related to the detection of adenovirus or respiratory syncytial virus in infants hospitalized for acute lower respiratory tract infection. *J Pediatr (Rio J)*. 2014;90(1):42-49. doi:10.1016/j.jped.2013.05.005
13. Costa LF, da Silveira HL, Queiróz DAO, Mantese OC, Yokosawa J. Respiratory virus infections in hospitalized and non-hospitalized children: Determinants of severe course of the disease. *J Infect Dev Ctries*. 2022;16(1):196-205. doi:10.3855/jidc.15117
14. Lamarão LM, Ramos FL, Mello WA, et al. Prevalence and clinical features of respiratory syncytial virus in children hospitalized for community-acquired pneumonia in northern Brazil. *BMC Infect Dis*. 2012;12:1-7. doi:10.1186/1471-2334-12-119
15. Santos RO, Borges IC, Souza ML, Bouzas ML, Nascimento-carvalho CM. Seasonality of distinct respiratory viruses in a tropical city : implications for prophylaxis. 2021;26(6):672-679. doi:10.1111/tmi.13571
16. Hivylla L, Ferreira S, Oliveira GS, et al. High incidence of rhinovirus infection in children with community - acquired pneumonia from a city in the Brazilian pre - Amazon region. 2019;(December 2018):1751-1758. doi:10.1002/jmv.25524
17. Kupek E. Low COVID-19 vaccination coverage and high COVID-19 mortality rates in Brazilian elderly. *Rev Bras Epidemiol*. 2021;24:1-11. doi:10.1590/1980-549720210041
18. João Guilherme Alves, Figueiroa JN, Urquia ML. Impact of COVID-19 on immunization of

Brazilian infants. *Int J Infect Dis*. 2021;107(January):252-253. http://creativecommons.org/licenses/by-ncnd/4.0/

19. Mariangela F. Silveira, B CTT, C AGKM, et al. Missed childhood immunizations during the COVID-19 pandemic in Brazil: Analyses of routine statistics and of a national household survey. *Vaccine*. 2021;39(25, 8 June):3404-3409. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9756801/
20. Ministerio da Saúde D. Projeção da População das Unidades da Federação por sexo e grupos de idade: 2000-2030. Accessed January 11, 2023. https://datasus.saude.gov.br/populacao-residente
21. World Health Organization GESS for I. Global Influenza Programme. 2013. Accessed April 10, 2023. https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/case-definitions-for-ili-and-sari
22. Paes NA, Ferreira AMS, Moura L de A. Proposta metodológica para avaliação de registros de óbitos por COVID-19. *Cad Saude Publica*. 2023;39(1):e00096722. doi:10.1590/0102-311XPT096722
23. WH G. *Econometric Analysis*. 3rd ed. (International P-H, ed.).; 1997.
24. Cameron AC TP. *Microeconometrics Using Stata*. 2nd ed. (Station C, ed.). Stata Press; 2022.
25. Station C, ed. *StataCorp. Stata: Release 17. Statistical Software*. StataCorp LLC; 2021.
26. Alharbi S, Van Caeseele P, Consunji-Araneta R, et al. Epidemiology of severe pediatric adenovirus lower respiratory tract infections in Manitoba, Canada, 1991-2005. *BMC Infect Dis*. 2012;12(1):55. doi:10.1186/1471-2334-12-55
27. Barrero PR, Valinotto LE, Tittarelli E, Mistchenko AS. Molecular typing of adenoviruses in pediatric respiratory infections in Buenos Aires, Argentina (1999-2010). *J Clin Virol*. 2012;53(2):145-150. doi:10.1016/j.jcv.2011.11.001
28. Emukule GO, Spreeuwenberg P, Chaves SS, et al. Estimating influenza and respiratory syncytial virus-associated mortality in Western Kenya using health and demographic surveillance system data, 2007-2013. *PLoS One*. 2017;12(7):2007-2013. doi:10.1371/journal.pone.0180890
29. Breiman RF, Cosmas L, Njenga MK, et al. Severe acute respiratory infection in children in a densely populated urban slum in Kenya, 2007-2011. *BMC Infect Dis*. 2015;15(1):1-11. doi:10.1186/s12879-015-0827-x
30. Kenmoe S, Joel J, Fatawou A, et al. Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID- 19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information . 2020;(January).
31. Nasrullah A, Gangu K, Garg I, et al. Trends in Hospitalization and Mortality for Influenza and Other Respiratory Viruses during the COVID-19 Pandemic in the United States. *Vaccines*. 2023;11(2):1-14. doi:10.3390/vaccines11020412
32. Haddadin Z, Schuster JE, Spieker AJ, et al. Pandemic : Prospective Multicenter Study. *Pediatrics*. 2021;148(2). doi:10.1542/peds.2021-051462.Acute
33. Olsen SJ, Winn AK, Budd AP, et al. Changes in Influenza and Other Respiratory Virus Activity During the COVID-19 Pandemic — United States, 2020–2021. *MMWR Morb Mortal Wkly Rep*. 2021;70(29):1013-1019. doi:10.15585/mmwr.mm7029a1
34. Ujiie M, Tsuzuki S, Nakamoto T, Iwamoto N, Ujiie M. Resurgence of respiratory syncytial virus infections during covid-19 pandemic, tokyo, japan. *Emerg Infect Dis*. 2021;27(11):2969-2970. doi:10.3201/eid2711.211565
35. van Summeren J, Meijer A, Aspelund G, et al. Low levels of respiratory syncytial virus activity in Europe during the 2020/21 season: what can we expect in the coming summer and autumn/winter? *Eurosurveillance*. 2021;26(29):1-6. doi:10.2807/1560-7917.es.2021.26.29.2100639
36. Foley DA, Phuong LK, Peplinski J, et al. Examining the interseasonal resurgence of respiratory syncytial virus in Western Australia. *Arch Dis Child*. 2022;107(3):e7. doi:10.1136/archdischild-2021-322507
37. Varela FH, Scotta MC, Polese-Bonatto M, et al. Absence of detection of RSV and influenza during the COVID-19 pandemic in a Brazilian cohort: Likely role of lower transmission in the community. *J Glob Health*. 2021;11:1-5. doi:10.7189/jogh.11.05007
38. 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):1434-1442. doi:10.1093/aje/kwm012

39. Zheng X yan, Xu Y jun, Guan W jie, Lin L feng. Regional, age and respiratory-secretion-specific prevalence of respiratory viruses associated with asthma exacerbation: a literature review. *Arch Virol*. 2018;163(4):845-853. doi:10.1007/s00705-017-3700-y
40. Nair H, Nokes DJ, Gessner BD, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet*. 2010;375(9725):1545-1555. doi:10.1016/S0140-6736(10)60206-1
41. Jain S, Williams DJ, Arnold SR, et al. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Children and for the Centers for Disease Control and Prevention (CDC) Etiology of Pneumonia in the Community (EPIC) Study Team. *N Engl J Med*. 2015;372(9):835-845. doi:10.1056/NEJMoa1405870.Community-Acquired
42. Walter JM, Wunderink RG. Severe Respiratory Viral Infections: New Evidence and Changing Paradigms. *Infect Dis Clin North Am*. 2017;31(3):455-474. doi:10.1016/j.idc.2017.05.004
43. Perez A, Lively JY, Curns A, Weinberg GA, Halasa NB, Staat MA. Respiratory Virus Surveillance Among Children with Acute Respiratory Illnesses — New Vaccine Surveillance Network , United States , 2016 – 2021. 2022;71(40):2016-2021.
44. Tempia S, Moyes J, Cohen AL, et al. The national burden of influenza-like illness and severe respiratory illness overall and associated with nine respiratory viruses in South Africa , 2013 – 2015. 2022;(December 2021):438-451. doi:10.1111/irv.12949
45. Freitas ARR, Donalisio MR. Respiratory syncytial virus seasonality in Brazil: Implications for the immunisation policy for at-risk populations. *Mem Inst Oswaldo Cruz*. 2016;111(5):294-301. doi:10.1590/0074-02760150341
46. Rebouças P, Goes E, Pescarini J, et al. Ethnoracial inequalities and child mortality in Brazil: a nationwide longitudinal study of 19 million newborn babies. *Lancet Glob Heal*. 2022;10(10):e1453-e1462. doi:10.1016/S2214-109X(22)00333-3
47. Greenberg SB. Respiratory consequences of rhinovirus infection. *Arch Intern Med*. 2003;163(3):278-284. doi:10.1001/archinte.163.3.278
48. Gu J, Ting S. Adenovirus diseases : a systematic review and meta - analysis of 228 case reports. *Infection*. 2021;49(1):1-13. doi:10.1007/s15010-020-01484-7
49. Falahi S, Sayyadi H, Abdoli A, Kenarkoohi A, Mohammadi S. The prevalence of human bocavirus in < 2-year-old children with acute bronchiolitis. *New Microbes New Infect*. 2020;37:100736. doi:10.1016/j.nmni.2020.100736
50. Serra F, Rossana C, Cordeiro DA, Edna F, Moura A. The role of human bocavirus as an agent of community - acquired pneumonia in children under 5 years of age in Fortaleza , Ceará (Northeast Brazil). *Brazilian J Microbiol*. Published online 2022:1915-1924. doi:10.1007/s42770-022-00806-1
51. Wang X, Li Y, Deloria-Knoll M, et al. Global burden of acute lower respiratory infection associated with human metapneumovirus in children under 5 years in 2018: a systematic review and modelling study. *Lancet Glob Heal*. 2021;9(1):e33-e43. doi:10.1016/S2214-109X(20)30393-4
52. Our World in Data. Number of children under 5 years old: The total population under 5 years old, given as historic estimates and projections to 2100 based on the UN's median fertility scenario.
53. Pilger DA, Cantarelli VV, Amantea SL, Leistner-segal S. Detection of human bocavirus and human metapneumovirus by real-time PCR from patients with respiratory symptoms in Southern Brazil. 2011;106(June 2010):56-60.
54. Fé MM, Monteiro AJ MF. Parainfluenza Virus Infections in a Tropical City : Clinical and Epidemiological Aspects. *Braz J Infect Dis*. 2008;12(3):192-197. doi:10.1590/s1413-86702008000300006
55. Guzman-Holst A, de Barros E, Rubio P, DeAntonio R, Cintra O, Abreu A. Impact after 10-year use of pneumococcal conjugate vaccine in the Brazilian national immunization program: an updated systematic literature review from 2015 to 2020. *Hum Vaccines Immunother*. 2022;18(1):1-17. doi:10.1080/21645515.2021.1879578

SUPPLEMENTARY MATERIAL

Supplement-Table 1: Mortality rates per million for respiratory viruses in Brazil by age groups of 0-4, 5-9, and 10-19 years, 2009-2022.

	Age	Year														
Virus	**group**	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	**Total**
	0-4	0.16	0.16	0.16	0.16	0.17	0.17	0.17	0.17	0.18	0.18	0.18	0.18	0.19	0.19	0.17
	5-9	1.28	0.30	0.31	0.57	1.35	0.85	0.38	2.84	0.83	2.11	2.62	1.32	1.41	1.84	1.29
Influenza	10-19	1.92	0.35	0.12	0.60	1.06	0.80	0.29	2.08	0.89	1.77	1.71	2.24	2.42	1.07	1.24
A	Total	1.12	0.27	0.20	0.44	0.86	0.61	0.28	1.70	0.63	1.35	1.50	1.25	1.34	1.03	0.90
	0-4	0.16	0.16	0.16	0.17	0.17	0.17	0.17	0.17	0.18	0.18	0.18	0.18	0.19	0.19	0.17
	5-9	0.64	0.26	0.15	0.24	0.61	0.50	0.32	1.01	0.72	1.06	1.09	1.30	1.30	1.25	0.75
Influenza	10-19	0.6	0.15	0.11	0.27	0.48	0.38	0.23	0.77	0.70	0.75	0.72	2.19	2.27	0.75	0.74
B	Total	0.47	0.19	0.14	0.22	0.42	0.35	0.24	0.65	0.53	0.67	0.66	1.23	1.25	0.73	0.55
	0-4	0.16	0.16	0.16	0.17	0.17	0.17	0.17	0.17	0.18	0.18	0.18	0.18	0.19	0.19	0.17
	5-9	0.64	0.26	0.16	0.24	0.55	0.48	0.31	1.00	0.67	0.93	1.10	1.29	1.3	1.27	0.73
Para-	10-19	0.60	0.15	0.08	0.26	0.42	0.36	0.21	0.73	0.56	0.69	0.67	2.18	2.27	0.76	0.71
influenza	Total	0.47	0.19	0.13	0.22	0.38	0.34	0.23	0.63	0.47	0.60	0.65	1.22	1.25	0.74	0.54
	0-4	0.30	0.22	0.50	0.47	0.43	0.47	0.37	0.4	0.23	0.49	0.44	0.33	0.48	0.36	0.39
	5-9	0.94	1.24	0.48	0.46	0.94	1.04	0.78	1.13	1.28	1.15	1.29	1.53	1.23	1.54	1.07
Rhinovirus	10-19	1.10	1.24	0.44	0.58	0.77	0.71	0.43	1.14	0.72	0.93	1.17	4.48	3.92	1.28	1.35
	Total	0.78	0.90	0.47	0.50	0.71	0.74	0.53	0.89	0.74	0.85	0.97	2.11	1.88	1.06	0.94
	0-4	0.30	0.20	0.50	0.49	0.45	0.48	0.37	0.40	0.42	0.44	0.41	0.32	0.48	0.35	0.40
	5-9	0.94	1.38	0.49	0.48	1.00	1.04	0.78	1.18	0.97	1.21	1.33	1.51	1.22	1.64	1.08
Adenovirus	10-19	1.10	0.98	0.46	0.58	0.93	0.73	0.47	1.21	1.10	0.97	1.19	4.32	3.90	1.32	1.38
	Total	0.78	0.85	0.48	0.52	0.80	0.75	0.54	0.93	0.83	0.87	0.97	2.05	1.87	1.10	0.95
	0-4	0.30	0.22	0.50	0.48	0.43	0.47	0.37	0.40	0.23	0.49	0.45	0.32	0.48	0.36	0.39
	5-9	0.94	1.24	0.48	0.46	0.94	1.04	0.78	1.13	1.28	1.15	1.25	1.50	1.22	1.45	1.06
Bocavirus	10-19	1.10	1.24	0.44	0.58	0.77	0.71	0.43	1.14	0.74	0.93	1.16	4.30	3.87	1.23	1.33
	Total	0.78	0.90	0.47	0.51	0.71	0.74	0.53	0.89	0.75	0.85	0.95	2.04	1.86	1.02	0.93
Respiratory	0-4	0.30	0.22	0.50	0.47	0.44	0.47	0.50	0.39	0.44	0.39	0.30	0.32	0.48	0.36	0.40

Synsyntial Virus	5-9	0.94	1.24	0.48	0.45	0.98	1.10	1.12	1.25	1.14	1.47	1.87	1.51	1.23	1.63	1.17
	10-19	1.10	1.23	0.31	0.58	0.89	0.92	0.70	1.29	1.09	1.22	1.73	4.35	3.95	1.33	1.48
	Total	0.78	0.90	0.43	0.50	0.77	0.83	0.77	0.98	0.89	1.03	1.30	2.06	1.89	1.11	1.02
Metapneu-movirus	0-4	0.30	0.22	0.50	0.47	0.43	0.48	0.37	0.40	0.23	0.49	0.42	0.33	0.48	0.36	0.39
	5-9	0.94	1.24	0.48	0.45	0.94	1.04	0.78	1.13	1.28	1.15	1.31	1.52	1.22	1.48	1.07
	10-19	1.10	1.24	0.43	0.58	0.77	0.71	0.44	1.14	0.73	0.93	1.17	4.39	3.87	1.25	1.34
	Total	.78	0.90	0.47	0.50	0.71	0.74	0.53	0.89	0.75	0.85	0.97	2.08	1.86	1.03	0.93
Other virus	0-4	0.38	0.38	0.38	0.39	0.39	0.39	0.39	0.39	0.39	0.40	0.40	0.40	0.40	0.40	0.39
	5-9	1.14	0.68	0.38	0.43	0.92	0.90	0.68	1.24	0.99	1.22	1.22	1.69	1.23	1.55	1.02
	10-19	1.35	0.68	0.29	0.52	0.95	0.86	0.62	1.34	1.12	1.05	1.09	5.19	3.92	1.27	1.45
	Total	0.96	0.58	0.35	0.44	0.75	0.71	0.57	0.99	0.83	0.89	0.90	2.43	1.85	1.08	0.95
All viruses	0-4	0.26	0.21	0.37	0.36	0.34	0.36	0.32	0.32	0.27	0.36	0.33	0.29	0.37	0.31	0.32
	5-9	0.94	0.87	0.38	0.42	0.91	0.89	0.66	1.32	1.02	1.27	1.45	1.46	1.26	1.52	1.03
	10-19	1.10	0.81	0.3	0.51	0.78	0.69	0.43	1.20	0.85	1.02	1.18	3.74	3.38	1.14	1.22
	Total	0.77	0.63	0.35	0.43	0.68	0.65	0.47	0.95	0.71	0.88	0.99	1.83	1.67	0.99	0.86