Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Implications of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Pandemic on the Epidemiology of Pediatric Respiratory Syncytial Virus Infection

Oludare A. Odumade,[1,2,3] Simon D. van Haren,[1,2] and Asimenia Angelidou[1,2,4]

[1]Precision Vaccines Program, Division of Infectious Diseases, Boston Children's Hospital, Boston, Massachusetts, USA; [2]Department of Pediatrics, Harvard Medical School, Boston, Massachusetts, USA; [3]Department of Pediatrics, Division of Medicine Critical Care, Boston Children's Hospital, Boston, Massachusetts, USA; and [4]Department of Neonatology, Beth Israel Deaconess Medical Center, Boston, Massachusetts, USA

Respiratory viral infections account for a large percentage of global disease and death. Respiratory syncytial virus is a seasonal virus affecting immunologically vulnerable populations, such as preterm newborns and young infants; however, its epidemiology has changed drastically during the coronavirus disease 2019 pandemic. In this perspective, we discuss the implications of coronavirus disease 2019 on respiratory syncytial virus seasonality patterns and mitigation efforts, as well as the urgent need for vaccination as a preventive tool.

Keywords. COVID-19; epidemiology; respiratory syncytial virus (RSV); vaccine.

Lower respiratory tract infection (LRTI) was the fourth leading cause of disability-adjusted life years for all ages between 1990 and 2019 [1] and the third leading cause of death in child aged <5 years based on global data collected between 1980 and 2015 [2]. Acute LRTI is an important cause of hospitalization, and respiratory syncytial virus (RSV) is the most common viral pathogen identified in LRTI, accounting for 13%–22% of pediatric deaths [3]. Owing to limited pathogen detection and surveillance resources and limited access to hospital-based care in low- and middle-income countries, most available data on RSV epidemiology has historically been derived from high-income countries. However, studies in recent years show that the burden of RSV illness extends to low- and middle-income countries both in hospital and community settings [4–6] (Figure 1). Although all children <2 years old are at risk for severe RSV infection, preterm infants carry the highest risk for hospitalization, intensive care unit admission, and death [7] because of their distinct immune system and cardiorespiratory comorbid conditions related to prematurity [8].

THE IMPACT OF CORONAVIRUS DISEASE 2019 ON RSV EPIDEMIOLOGY AND SEASONALITY

The typical epidemiology of RSV infection is characterized by distinct winter peaks in temperate climates, such that outbreaks occur from November to March in the Northern hemisphere and from June to September in the Southern hemisphere [9], while the virus circulates year-round in the tropics [10]. Regional variations in the onset, offset, and duration of the RSV season exist and relate to demographic factors, population density, and climate [10–15]. Understanding the epidemiological dynamics of RSV infection is key for establishing targeted surveillance, developing forecasting models, evaluating disease control interventions, and tailoring prophylaxis to vulnerable populations.

The onset of the coronavirus disease 2019 (COVID-19) pandemic, which resulted in new hygiene and isolation protocols, disturbed preexisting seasonality patterns. The spread of RSV during the 2020 winter season was interrupted, while delayed surges of infection were noted in the summer of 2021 in several countries and regions [16–26]. For example, in Alaska, no children <3 years old were admitted to the hospital for acute respiratory infection for 4 consecutive weeks in 2019–2020, something not observed in the preceding 26 years of surveillance [19]. This was after implementation of COVID-19 mandates and before severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was detected in the community,

Correspondence: Oludare Odumade, Department of Pediatrics, Harvard Medical School, 300 Longwood Ave, CC BCH 3136, Boston, MA 02115 (oludare.odumade@childrens.harvard.edu)

Clinical Infectious Diseases® 2022;75(S1):S130–5

https://doi.org/10.1093/cid/ciac373

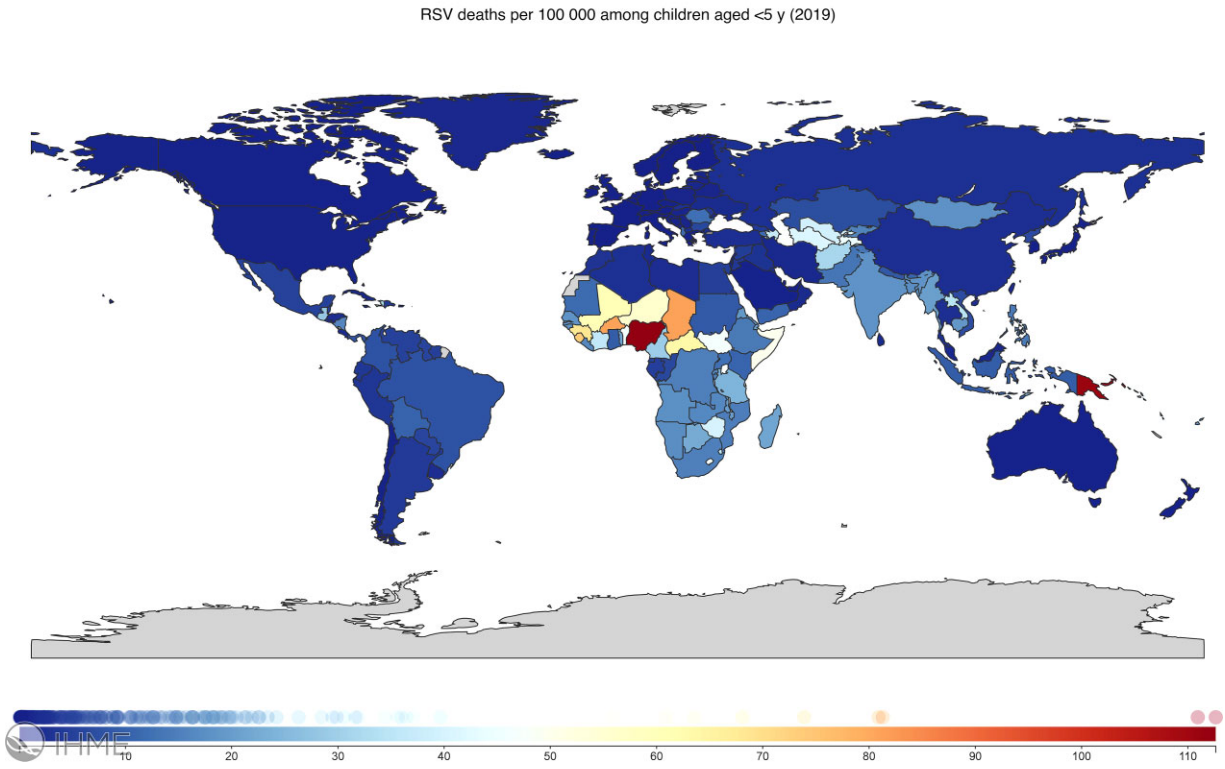

Figure 1. Deaths due to respiratory syncytial virus (RSV) in children aged <5 years per 100 000 population in 2019. (Figure generated from https://www.thelancet.com/lancet/visualisations/gbd-compare, with the following settings: display, "etiology"; etiology, "respiratory syncytial virus"; measure, "death"; year, "2019"; ages, "<5 years"; sex, "both"; units, "rate"; rate of change, "off"; scale, "unlocked:"; detail, "1"; available at http://ihmeuw.org/5orn).

suggesting that nonpharmaceutical interventions likely accounted for decreased viral circulation.

In Western Australia, an interseasonal surge in confirmed RSV cases was observed when local restrictions were lifted, schools returned to normal activity, and state border restrictions were relaxed, and the median patient age shifted from 10 to 18 months [18]. Similar findings were reported in Spain, where a reduction in the case rate of acute RSV bronchiolitis of −44.3 per thousand inhabitants <2 years of age was noted during the implementation of public health measures [20], as reported by the Pediatric Spanish Society [21]. Even in South Africa, the RSV incidence decreased initially (in weeks 14–22), not demonstrating the usual peak around week 8–20 (median week 12) but with a later surge around week 29 [24].

Strict infection mitigation measures, such as lockdowns, universal masking, social distancing, and isolation of symptomatic individuals are the most likely explanation for delayed RSV surges, as they likely resulted in an increasing number of RSV-naive children and waning population immunity against RSV [26, 27]. Decreased surveillance for non–SARS-CoV-2 respiratory viruses may also partially account for the observed case reduction at the peak of the pandemic in 2020. In addition, virus-virus interactions have the potential to influence dynamics of infection at the population level through transient immune-mediated interference within individual hosts [28]. For example, viral interference, whereby a concurrent or prior presence of one virus results in a measurable difference in the presence of another virus, has been demonstrated between RSV and both influenza [29] and human rhinovirus [30].

Accumulating data on viral coinfection shows rates varying between 3% in 20% in SARS-CoV-2–infected patients [31, 32], with RSV accounting for 1.5%–5.2% of coinfection cases. How potential SARS-CoV-2 viral interference might influence the severity of RSV illness remains unclear. In a single-center New York City cohort with a delayed RSV season, RSV cases were recorded in younger infants (median age, 6 vs 17 months in prepandemic seasons) and caused more severe disease (admission to ICU, 81% vs 45%, respectively) [33]. The observation of low RSV rates during times of high SARS-CoV-2 circulation raises the possibility of worse RSV epidemics in the future once SARS-CoV-2 is contained with vaccination, but more studies on RSV dynamics are needed during and after the pandemic phase to determine this.

IMPLICATIONS OF SHIFTING RSV EPIDEMIOLOGY FOR IMMUNOPROPHYLAXIS STRATEGIES

Preventive strategies for RSV infection are limited to general infection control measures, such as hand hygiene, avoidance of infectious settings, contact isolation of positive cases, and immunoprophylaxis of high-risk populations. Treatment of severe RSV infection is primarily supportive, and available therapeutics have limited use [34]. Aerosolized ribavirin is the only Food and Drug Administration (FDA)–approved antiviral for RSV infection, currently used in life-threatening infections of immunocompromised hosts [7, 35].

Palivizumab (brand name Synagis) is the only available FDA-approved formulation for RSV immunoprophylaxis in the United States. Palivizumab is a humanized monoclonal antibody requiring monthly dosing during the predicted RSV season via intramuscular injection to prevent severe RSV illness in high-risk infants [36]. Most recently, nirsevimab (MEDI8897), a monoclonal antibody with an extended half-life, was developed to protect infants for an entire RSV season with a single dose [37] and was found to be 70.1% efficacious against medically attended RSV and 78.4% against RSV hospitalization in a phase 3 clinical trial of healthy term and preterm infants (NCT03979313) [38]. As a result, it was granted breakthrough designation by the China Center for Drug Evaluation (NCT05110261), the US FDA, and the European Medicines Agency, paving the way for expedited development and anticipated regulatory review in 2022. Merck Sharp and Dohme have also developed clesrovimab (formerly MK 1654), a fully human, anti-RSV fusion (RSV F) glycoprotein monoclonal antibody, which is in late-stage clinical trials (NCT04767373, a phase 2b/3 study in term and preterm infants [≥29 weeks gestational age up to age 1 year], and NCT04938830, a phase 3 study comparing palivizumab and clesrovimab in children up to age 1 year).

Since 2014, the American Academy of Pediatrics (AAP) has recommended RSV immunoprophylaxis for infants born at <29 weeks gestational age, those born at <32 weeks gestational age with chronic lung disease, and those <12 months old with hemodynamically significant congenital heart disease [36]. Indeed, the risk of bronchiolitis hospitalization during "protected periods," meaning during the RSV season (November to March), when palivizumab is administered, and up to 30 days after the last dose of immunoprophylaxis, is lower than during "unprotected periods" (adjusted hazard ratio, .68 [95% confidence interval, .46–1]), and the benefit is greatest among infants with chronic lung disease [39]. Evidence from a recent Cochrane systematic review confirms that palivizumab significantly reduces RSV infections and hospitalizations [40], which, along with cost-effectiveness considerations, justifies the AAP's restrictive criteria for palivizumab eligibility.

In response to an evolving epidemic within a pandemic, special national and regional task forces were formed to reassess criteria for palivizumab administration and implement new policies for public health benefit. The shifting RSV epidemiology during COVID-19. Causing delayed and prolonged RSV seasons, led the AAP to revise its guidance in 2021. Specifically, the AAP supported consideration of palivizumab use in eligible patients outside the typical fall-winter season, especially in areas experiencing high interseasonal spread [41].

RSV immunoprophylaxis programs have also changed in other countries, such as the United Kingdom, where the number of doses has been extended from 5 to 7 and eligible children can start the schedule as early as July (rather than October) [42]. In Saudi Arabia, the Saudi Pediatric Pulmonology Association recommends increasing the number of RSV immunoprophylaxis program clinics and drive-through visits, establishing home vaccinations, and encouraging expedited referrals to specialists in the RSV immunoprophylaxis program [43]. Factors considered in these decisions include (1) increased severity of illness in vulnerable at-risk populations; (2) more prolonged RSV hospitalizations, further straining a COVID-stricken healthcare system; and (3) the negative socioeconomic sequelae of isolation/time missed from work or school. Overall, a flexible response to RSV activity will be required in the postpandemic era with frequent reassessment of prophylaxis guidelines by national scientific societies.

THE URGENT NEED FOR RSV VACCINATION AS A PREVENTIVE TOOL

While vaccines are often among the most cost-effective public health interventions, targeting childhood infectious diseases and saving millions of lives annually, there is no licensed vaccine to prevent pediatric RSV infection. In addition, palivizumab use may be cost prohibitive, especially for low- and middle-income countries [44], making the development of RSV vaccines a high public health priority.

The development of RSV vaccines has been slow for decades, after an unsuccessful clinical trial in which children immunized with a formalin-inactivated vaccine experienced an enhanced form of RSV-mediated disease characterized by high fever, bronchopneumonia, and wheezing when they became infected with wild-type virus in the community. Hospitalizations were frequent, and 2 immunized toddlers died after infection with wild-type RSV [45]. Lung and blood pathology of these immunized children, as well as mechanistic insight from murine studies, revealed that inappropriate antibody- and cell-mediated immune responses were correlated with severe disease. Induction of antibodies with poor neutralizing activity led to immune complex deposition and complement activation in small airways, and T-helper 2–biased T-cell responses coincided with excess infiltration of neutrophils and eosinophils into the lungs [46, 47].

Table 1. Pediatric Respiratory Syncytial Virus Vaccines in Clinical Development as of 21 April 2022, Based on ClinicalTrials.gov Database

Vaccine Type	Description	Target Population	Route of administration and Dosing	Trial No.	Clinical Trial Phase	Estimated Completion Date
Live attenuated	Codon deoptimized RSV (Codagenix/NIAID)	RSV-seronegative children aged 6–24 mo; RSV-seropositive children aged 2–5 y	Intranasal (drop); 2-dose series (28 d apart)	NCT04919109	Phase 1	February 2023
	MV-012-968; all viral proteins (Meissa Vaccines)	RSV-seronegative children aged 6–36 mo	Intranasal 1-dose vs 2-dose series (28 d apart)	NCT04909021	Phase 1	October 2023
	VAD00001; live attenuated RSV (Sanofi/NIAID)	RSV-seronegative children aged 6–18 mo	Intranasal 1-dose vs 2-dose series (56 d apart)	NCT04491877	Phase 2	April 2023
	RSV ΔNS2/Δ1313/I1314L, RSV 6120/ΔNS2/1030s, or RSV 276; live attenuated RSV (Sanofi/NIAID)	RSV-seronegative children aged 6–24 mo	Intranasal (drop); 1-dose series comparing the 3 formulations vs placebo	NCT03916185	Phase 1/2	April 2023
	RSV ΔNS2/Δ1313/I1314L; live attenuated RSV (MedImmune/NIAID)	Any infant aged 4–6 mo; RSV-seronegative children aged 6–24 mo; RSV-seropositive children aged 15–59 mo	Intranasal (drop); 1-dose series	NCT01893554	Phase 1	April 2023
	RSV 6120/ΔNS1 or RSV 6120/F1/G2/ΔNS1; live attenuated RSV (Sanofi/NIAID)	RSV-seronegative children aged 6–24 mo; RSV-seropositive children aged 15–59 mo	Intranasal (drop) 1-dose series Comparing the 2 formulations vs. placebo	NCT03596801	Phase 1	December 2023
	RSV LID/ΔM2-2/1030s; live attenuated RSV (Sanofi/NIAID)	RSV-seronegative children aged 6–24 mo	Intranasal (drop) 1-dose series	NCT04520659	Phase 1	December 2023
Protein based	Inactivated, particle, or subunit			no registered trials targeting children		
Nucleic acid	mRNA-1345; mRNA for RSV fusion protein (Moderna)	Participants aged 12 mo to 79 y (RSV-seropositive children aged 15–59 mo only)	Intramuscular injection for children; 3-dose series (56 d apart)	NCT04528719	Phase 1	September 2023
Recombinant vectors	Adenovirus Ad26.RSV-Pre-F (Janssen Pharmaceutical)	RSV-seronegative children aged 12– 24 mo	Intramuscular injection; 3-dose series (28 d apart)	NCT03606512	Phase 2	November 2021

Abbreviations: mRNA, messenger RNA; NIAID, National Institute of Allergy and Infectious Diseases; RSV, respiratory syncytial virus.

Given the prior experience of suboptimal immune responses of infants and children to RSV immunization, most RSV vaccines currently in clinical development are focused on maternal immunization and immunization of older adults, in order to confer passive immunity to young children and protection to their caregivers, parents, and grandparents via herd immunity [27, 48]. An important hurdle hindering development of safe and effective RSV vaccines, capable of generating neutralizing antibodies, has been the inability to target the appropriate, prefusion conformation of the RSV F glycoprotein (pre-F) [49–51]. However, structure-guided retainment of the pre-F state of the glycoprotein and recent advances in protein engineering techniques provide grounds for optimism over RSV vaccine candidates eliciting high-affinity neutralizing antibodies in the coming years [52–54].

Both GlaxoSmithKline (GSK) and Pfizer currently have subunit vaccines containing recombinant RSV F protein in the pipeline for maternal use and use in older adults. Janssen Pharmaceuticals has an adenovirus-based vector vaccine in phase II clinical trials for use in older adults [48]. A lower dose of this vaccine is also tested in phase II trials for pediatric use. Phase I studies using live attenuated RSV against RNA regulatory protein M2-2 (NCT03102034, NCT03099291, and NCT02601612) showed adequate immunogenicity after 1 dose (≥4-fold rise in serum-neutralizing antibodies) in up to 95% of vaccine recipients [55]; however, efficacy studies are still needed. Importantly, the most common vaccine adverse events were mild rhinorrhea, cough, and fever, and no serious adverse events were recorded. Other pediatric formulations currently in clinical development are listed in Table 1.

The ongoing and future development of RSV vaccines targeting a pediatric population, in particular children aged 6 months to 2 years, will require an increased emphasis on safety. The use of well-defined formulations, such as protein-based subunit or messenger RNA–based vaccines, which can be tailored to this age group by the addition of adjuvants seems an attractive approach to ensure vaccine safety as well as efficacy. The ongoing trials evaluating the safety and effectiveness of messenger RNA–based vaccines against SARS-CoV-2 in

children 6 months to 5 years old may be a good predictor of whether such an approach will be successful for RSV as well.

CONCLUSIONS

RSV is off its established seasonal schedule and poses a threat to newborns and young infants, especially those born preterm. Current and prior viral epidemiology data raise the possibility of future RSV epidemics of increased severity, intensity, and duration. Proactive surveillance and timely adjustment of immunoprophylaxis recommendations are necessary to mitigate future surges in RSV cases. Ultimately, the focus of the pediatric community should shift to precision vaccine development and implementation for more durable protection.

Notes

Author contributions. All authors edited, reviewed, and approved the manuscript before submission.

Disclaimer. All opinions expressed are individual and do not represent those of the authors' employers.

Supplement sponsorship. This supplement is sponsored by the *Precision Vaccines Program* of Boston Children's Hospital.

Potential conflict of interest. O. A. O. received 2 National Institute of Allergy and Infectious Diseases U19 grants and salary support from the Penta Foundation, Harvard Global Health Institute, the Mueller Health Foundation for tuberculosis-related research, Boston Children's Hospital Global Health Program, and the National Institute on Minority Health and Health Disparities Loan Repayment Program. O. A. O. and A. A. received a National Institute of Allergy and Infectious Diseases Development of Sample Sparing Assay Infrastructure and Opportunities Fund grant for comprehensive analysis of the neonatal immune system via high-throughput proteomics. A. A. received an honorarium for an invited review of an article on neonatal vaccination. S. D. v. h. received a research grant from the Bill & Melinda Gates Foundation and holds US patent US20170224811A1. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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