Commentary

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Respiratory syncytial virus with ongoing COVID-19: is it an emerging threat?

Ranjit Sah, MD[a,b,h,*], Kamran Zaman, MD[c], Aroop Mohanty, MD[d], Tareq Al-Ahdal, MD[f], Hamzeh Awad, MD[g], Bijay Kumar Padhi, PhD[e], Ashish Bhargava, MD[i]

Introduction

The COVID-19 pandemic is one of the most serious diseases of the modern era. Globally, 638 million COVID-19 cases and 6.6 million deaths have been reported as of 22 November 2022[1]. Public health initiatives or nonpharmaceutical interventions (NPI) such as routine mask usage, hand washing, social distancing, and the adoption of cough etiquette were helpful to curtail the spread of COVID-19 along with other endemic respiratory viruses[2,3]. Vaccination also played a key role in reducing the hospitalization for severe disease, and deaths from COVID-19[4]. However, with resurgence of new COVID variants, reduced willingness to masking and increased indoor gatherings, there has been a sporadic increase in COVID-19 cases in various geographic locations. Consequently, it has also increased the incidence of other respiratory viral illness with or without severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) coinfections. Recently, the Centers for Disease Control and Prevention (CDC) issued a health advisory related to increased respiratory infections from respiratory syncytial virus (RSV), influenza, and COVID-19[5].

HIGHLIGHTS

- Center for Disease Control and Prevention issued a health advisory related to increased respiratory infections from Respiratory Syncytial Virus (RSV), influenza and COVID-19.
- RSV is one of the leading causes of lower respiratory illnesses that affects new-borns, young children, and the elderly.
- RSV-associated acute lower respiratory infection in-hospital deaths were estimated to be about 26, 000 among children < 5 yrs. of age.

RSV is one of the leading causes of lower respiratory illnesses that affects newborns, young children, and the elderly. A recent systemic analysis estimated a global occurrence of 33 million episodes of RSV-associated acute lower respiratory infections, and three million hospitalizations[6]. Globally, RSV-associated acute lower respiratory infection in-hospital deaths were estimated to be about 26 000 among children less than 5 years of age of which 13 000 occurred among children 0–6 months of age[6]. In Africa and Asia, about 31% of total hospitalization for severe pneumonia were caused by RSV among children younger than 5 years[7]. In the USA, RSV causes an estimated 58 000 hospitalization and 100–500 deaths among children less than 5 years of age[8]. Among adults aged 65 and above, an estimated 160 000 RSV-associated hospitalization and 13 000 deaths occur each year[9]. The actual burden among all age groups is likely even higher due to underreporting of RSV infections. For every RSV-associated in-hospital death, there is an estimation of three times more deaths attributable to RSV in the community[6].

RSV is an enveloped negative-sense RNA virus that belongs to the family Pneumoviridae, order Mononegavirales, and genus *Orthopneumovirus*[10]. The virus first multiplies in the nasopharynx before spreading to the lower respiratory tract. Its incubation period is 3–5 days. RSV is typically known to affect 50% of children in their first year of life and nearly all children by 2 years of age[11]. The RSV disease burden is similar to that of nonpandemic influenza A among adults 65 years of age and above and those with chronic medical conditions[12]. The clinical manifestation of RSV infection ranges from mild

[a]Tribhuvan University Teaching Hospital, Institute of Medicine, Kathmandu, Nepal, [b]D.Y. Patil Medical College, Hospital and Research Centre, Pune, Maharashtra, [c]ICMR-National Institute of Traditional Medicine, Belagavi, Karnataka, [d]Department of Microbiology, All India Institute of Medical Sciences, Gorakhpur, Uttar Pradesh, [e]Department of Community Medicine and School of Public Health, Postgraduate Institute of Medical Education and Research, Chandigarh, Chandigarh, India, [f]Institute of Global Health (HIGH), Heidelberg University, Heidelberg, Germany, [g]Health Information Management and Health Informatics Research Chair, Higher College of Technology, Abu Dhabi, United Arab Emirates, [h]Harvard Medical School, Boston, Massachusetts and [i]Department of Internal Medicine, Wayne State University, Detroit, Michigan, USA

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*Corresponding author. Address: Infectious Diseases Fellowship, Clinical Research (Harvard Medical School), Global Clinical Scholars Research Training (Harvard Medical School), Systematic Review and Meta-analysis (London School of Hygiene and Tropical Medicine). Kathmandu, 44600 Nepal. E-mail address: ranjitsah@iom.edu.np; ranjitsah57@gmail.com.

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upper-respiratory-tract illness or otitis media to severe lower-respiratory-tract illnesses including bronchiolitis and pneumonia, especially among infants[11,13]. Natural infection does not offer long-lasting immunity and re-infections can happen throughout life[14]. Nasopharyngeal reverse-transcription PCR is the gold-standard method for detecting acute RSV infection with sensitivities ranging from 84 to 100%[15]. Treatment for RSV is primarily supportive and includes the use of supplemental oxygen, adequate hydration, and mechanical ventilation when necessary. Currently, there are no licensed vaccine against RSV[11,14]. Palivizumab, a humanized monoclonal immunoglobulin, is the only prophylactic agent currently approved and is recommended for high-risk pediatric population[16,17]. There are no treatment or prophylaxis options for most infants.

Before the COVID-19 pandemic, the WHO piloted an initiative to establish RSV surveillance among 14 countries through the Global Influenza Surveillance and Response System (GISRS)[18]. Among participating countries from the temperate regions (Argentina, Australia, Canada, Chile, Mongolia, Russian Federation, and the UK), seasonal RSV mainly occurred during the colder months. In subtropical countries like Brazil and Egypt, RSV peaked during the cooler months of the year while among tropical countries (Côte d'Ivoire, India, Mozambique, and Thailand) RSV peaks were observed primarily during rainy seasons while the residual viral activity was seen throughout the year[18]. Also, in the Northern hemisphere, the RSV season extends from October to May, peaking in January–February, while in Southern hemisphere, it extends from April to October, peaking in June–July.

During initial period of COVID-19 pandemic, many countries across the world implemented NPI targeted at controlling transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[19]. This implementation of NPI coincided with the near end of winters/RSV season in the Northern hemisphere and start of winters/RSV season in Southern hemisphere. Consequently, there was a substantial reduction in RSV illnesses from both the hemispheres during their typical season in 2020-21[19–25]. The CDC reported historically low RSV rates (< 1.0% per weekly positive rates compared with ~12–16% during peaks in previous years)[25]. Some countries (France, Iceland, and Australia) reported higher median age of symptomatic children who tested positive for RSV during 2020–2021 compared with previous seasons[26]. Minimal RSV activity since the start of the COVID-19 pandemic might explain this phenomenon as these at-risk children have not had the opportunity to develop immunity against severe infection earlier.

A temporal shift of the RSV epidemic was reported throughout 2021 after gradual relaxation of NPI. Countries across the world reported increased off-season RSV activity[26–30]. The delayed onset was most pronounced in the northern temperate region, followed by the southern temperate region, and was least pronounced in the tropics[26]. A similar pattern of RSV seasonality was noted following the 2009 influenza pandemic in a global-level systemic analysis[31]. Influenza pandemic delayed the onset of the first RSV season by 0.58 months and the start of the second RSV season by only 0.25 months; with no delayed onset observed for the third RSV season[31]. Immune debt with an accumulation of RSV-susceptible individuals after a 'missed' RSV season leading to an unusually high number of RSV infections in the subsequent season (2021/2022) was thought to be contributing[32].

Post COVID-19, simulation modeling study have predicted reemergent RSV epidemics in 2021 and 2022 to be more intense and to affect patients in a broader age range than in typical RSV seasons[33]. A recent upsurge of RSV cases has been reported in Egyptian schools where around 73% of the children with flu-like illness tested positive for RSV[34]. Similarly, Germany recorded an unprecedented surge with increasing number of children being hospitalized for RSV infections[35]. USA have been witnessing for the second year in row an early unprecedented spike in the number of RSV cases[36]. Although the current trend in RSV epidemics appears to be the opposite of what was noted post influenza pandemic, but it shows that the lack of immunity from previous seasons lead to increased susceptibility of the unexposed population with a more severe outbreak. Thus, the current RSV epidemics reflects a stronger dependence of infection susceptibility on immunity from previous exposure.

Currently, we are experiencing a strong upsurge in RSV infections in various regions of the world, the mystery surrounding the severity of these RSV infections remains to be uncovered. It has been anticipated that RSV outbreak this season might be more severe compared with previous RSV season due to combination of increased indoor activities with increased gatherings, reduction in face-masking, and lack of immunity from the previous RSV seasons. Another concern to gaze is age-related trends for RSV infections with the current RSV epidemic. A cross-sectional study in six US hospitals during a period of B.1.617.2 variant predominance noted an age-related trend among RSV and COVID-19-coinfected patients. Majority of coinfected cases were infants (23.9%), followed by children aged 1–4 years (21.3%), 5–11 years (2.8%) and 12–17 years (1.1%). They also reported that co-infection with RSV was associated with increased prevalence of severe illness (prevalence ratio of 3.6, 1.9, 2.2, and 2.4 among infants, children aged 1–4, 5–11, and 12–17 years, respectively)[37]. Similar observations with higher risk for lower respiratory tract infection and severe illness were reported among coinfected COVID patients with RSV[38]. Although incidences of viral coinfections during initial phase of COVID-19 pandemic were low, now with resurgences of other viral illnesses, these seems to be an urgency for monitoring these coinfections. Wide and easily availability of rapid diagnostic tools to detect and differentiate these viruses will be a key first step[39]. Robust data will be needed to determine the impact of coinfections on the severity, mortality, and long-term sequalae for these illnesses.

The impact of the interseasonal increase in RSV infections that are currently observed in some regions on future epidemiology remains unclear. Understanding the association of timing, intensity, and age distribution of reemergent RSV epidemics will be crucial for clinical and public health decision-making. Knowledge of the local seasonality patterns of RSV, serological surveys, and local modeling efforts will help determine the future dynamics and target intervention strategies for RSV, saving costs and allowing maximum benefit. Large-scale RSV genomic surveillance can help track transmission patterns and identify targets for vaccine developments.

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R.S., K.Z., and A.M. develop the original draft. T.A-.A., H.A., B. K.P., and A.B. review and edit the manuscript. All authors read and approved for the final manuscript.

Conflicts of interest disclosure

The authors declare that they have no financial conflict of interest with regard to the content of this report.

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