Received: 30 March 2021 | Revised: 7 June 2021 | Accepted: 7 July 2021

DOI: 10.1002/ppul.25582

COMMENTARY

WILEY

During the COVID-19 pandemic where has respiratory syncytial virus gone?

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Abstract

The diffusion of the SARS-CoV-2 virus and the implementation of restrictive measures led to a drastic reduction of respiratory syncytial virus (RSV) diffusion. Few RSV cases have been detected worldwide, even after the removal of the restrictions. We review the current literature and present possible explanations on why there has been a significant reduction of RSV detection during the COVID-19 pandemic. We also hypothesize what may happen when RSV begins to circulate again. The increase of an immunologically naïve population, with infants born from mothers who have not reinforced their immunity to RSV, could lead to greater RSV epidemics in the coming seasons. It is crucial to prepare the scientific community and to keep RSV surveillance active to avoid dramatic consequences.

KEYWORDS

epidemiology, infections, international health, pneumonia, TB, viral

The coronavirus disease 2019 (COVID-19) was declared a pandemic on March 11, 2020, and restrictive measures have been implemented worldwide, with the aim of reducing social contacts.[1] These measures had a positive effect not only on SARS-CoV-2 diffusion, but also significantly reduced the spread of respiratory infections caused by other respiratory viruses. The most evident impact is the significant reduction of respiratory syncytial virus (RSV) cases from March 2020, both in the Southern and in the Northern Hemisphere.[2–8]

RSV is the most common cause of acute lower respiratory tract infections in the pediatric population, with almost 33.8 million cases worldwide in children under 5 years of age, 3.4 million (10%) of hospitalizations, and 66,000–199,000 deaths. Forty-four percent of hospitalized infants have less than 2 months of age and 99% of deaths occur in developing countries.[9] RSV is not only a pediatric virus, but represents a significant cause of morbidity and mortality also in the elderly (>65 years old) and in immunocompromised patients.[10]

RSV is an enveloped, single-stranded, negative-sense RNA virus of the *Pneumoviridae* family, whose genome encodes for 11 proteins, with the external glycoproteins G and F being the major viral antigens.[11] A genetic drift pattern of mutations of the G gene causes the emergence of local variants, which could be associated to changes in disease severity.[12]

In the Northern Hemisphere, the RSV season starts in November and ends in March, with peaks in January and February, while in the Southern Hemisphere it lasts from June to September. In tropical countries, RSV circulates year-round, with peaks during the rainy season.[13,14] RSV epidemics are driven by a complex interaction between the climate, the virus, and the host.[11] Cold temperatures stabilize the RSV lipid envelope, humidity facilitates the deposition of heavy droplets on surfaces and, during cold and rainy periods, people stay indoors, where RSV transmission is easier.[15,16] Furthermore, it seems that new variants could drive yearly RSV outbreaks, finding a susceptible population. The simultaneous isolation of different RSV strains in distant geographic areas supports the hypothesis that epidemics are driven by locally evolved variants, and not by the diffusion of one species between contiguous areas.[17,18]

Considering that RSV seasonal outbreaks derive from the evolution of local strains, the question is: where is the virus in the off-season? Convincing evidence demonstrated that low RSV loads can be detected during the whole year in adults with chronic obstructive pulmonary disease (COPD), both in exacerbations and in stable periods.[19] RSV has been isolated year-round also in children with human immunodeficiency.[20] These RSV reservoirs allow a continuous, low-level, and asymptomatic replication of the virus that, when meteorological factors are favorable, drives local epidemics.[17]

It is estimated that nearly all children get the first and most severe RSV infection before the age of two and then subsequently experience milder infections later in life.[11] The most important reason explaining RSV reinfections is a poor and short-lived immune response: in infants, the immune system is still developing and the immaturity of the innate response may lead to an insufficient adaptive response and to an inappropriate immunological memory.[21] The presence of RSV IgG maternal antibodies in neonates and infants could be very important, but their role is still controversial. The presence of RSV IgG antibodies in infants could interfere with viral-induced immunogenicity,[22] but on the other hand, the transplacental transfer of protective maternal antibodies could be helpful in preventing severe disease in infants.[23] Maternal anti-RSV IgG are significantly higher in infants with siblings, supporting the hypothesis that RSV exposure during pregnancy correlates with the levels of protection.[24]

Knowing RSV clinical impact and epidemiology, it is critical to understand what may happen in the next epidemic seasons after the spread of SARS-CoV-2. Is RSV epidemiology changing? The SARS-CoV-2 pandemic in the Northern Hemisphere coincided with the epidemic peak of respiratory viruses like influenza and RSV. In the Northern Hemisphere, the implementation of restrictions, starting from March 2020, coincided with a drastic reduction of RSV infections. Reports from Italy, Finland, Belgium, UK, and the USA showed a sudden and earlier end of the RSV epidemic season starting from March 2020, compared to the previous years and almost no cases detected in the following months.[2–4,6–8] In the Southern Hemisphere, SARS-CoV2 restrictive measures were implemented just before winter and were maintained for different periods according to SARS-CoV-2 diffusion. A complete absence of RSV cases during winter 2020 (May–August) has been detected in Brazil, where restrictions are still ongoing due to the severity of the pandemic.[5] On the contrary, in Australia, restrictions were lifted in April 2020 due to the low number of SARS-CoV-2 cases and only social distancing and implemented hygiene measures were maintained. Even following the relaxation of restrictions, no RSV cases had been detected in Western Australia until the end of August 2020.[25] What are the reasons for this reduction? It is reasonable to hypothesize that the restrictive measures adopted to reduce SARS-CoV-2 diffusion had an impact on other respiratory viruses with similar routes of infection. The major interventions at a global level were stay-at-home orders, social distancing, and non-pharmaceutical interventions (NPI), such as hand hygiene and mandatory face masks. All of these interventions contribute to reduced RSV transmission through droplets and contact through dirty hands and fomites.[11] Specifically, hand washing reduces the virus' capability to infect the host, disrupting the viral envelope, face masks block RSV transmission through droplets, and social distancing reduces the chances to have contact with infected people.[7] Apart from total lockdowns, it seems that NPI are the most effective in reducing RSV transmission. In fact, both in Europe and in Australia, only a few RSV cases have been detected even after the removal of the most restrictive measures, when only hand washing, social distancing, and mandatory face masks were maintained.[6,8] The role of school closure in reducing respiratory infections is controversial. Data from the United States, where there is active RSV surveillance, showed that school reopening was not associated with an increase in RSV infections.[26,27] Similar data came from Finland, where RSV levels remained low even after school and daycare reopening during spring 2020.[28] An explanation for this phenomenon could be that even when children came back to school, hand hygiene and social distancing were maintained. Furthermore, children with even mild respiratory symptoms (i.e., rhinitis), were not admitted to school, reducing the possible circulation of viruses other than SARS-CoV-2.[28] Moreover, differently from the Rhinovirus, healthy children are not major reservoirs for RSV, detectable year-round only in adults with COPD or in children with immunodeficiency.[19,20] Another possible explanation to RSV reduction could be border closure and limited international travel, which could prevent the diffusion of the virus across different countries. However, this hypothesis is not supported by the epidemiological data on RSV, which shows that epidemics usually start locally and simultaneously in different countries.[17,18,25] Among other contributing factors to RSV reduction, one could be viral interference. Interference between influenza virus and other respiratory viruses has been described and a similar process may have happened between SARS-CoV-2 and RSV.[29] This hypothesis is supported by the low rate of coinfection between SARS-CoV-2 and other respiratory viruses.[30] In the absence of epidemics, it is crucial to evaluate whether RSV is still shedding between asymptomatic reservoirs. A similar reduction of infection was detected for the influenza virus as well, confirming that restrictive measures had an impact on respiratory viruses with similar routes of infections.[25,30,31] Rhinovirus, however, was less influenced by restrictions and a recent resurgence was reported in different countries: its nonenveloped structure, which is not altered by hand washing, and the presence of reservoirs in children, could play a role in its circulation.[7,32] Whatever the reasons of RSV disappearance during the year 2020, the future implications could be challenging. What will happen when these restrictions will be lifted? A recent paper by Foley et al.[33] showed a significant increase of RSV cases from September 2020 in Western Australia, which was greater than the average seasonal peak registered from 2012 to 2019. Restrictions were relaxed from June 2020, with school returning to normal activities, gatherings of more than 100 people allowed, and opening of international borders. However, the rise in RSV cases preceded borders reopening, confirming the insignificant role of limited international travel in its reduction. Surprisingly, the median age of the infected population (18.4 months) was significantly higher than in the previous epidemic seasons.[33] This publication highlights the risk of future changes in RSV epidemiology and the potential for alarming epidemics when restrictive measures will be abolished. The reduction in RSV transmission will result in the increase of a susceptible cohort of children. Infants born from mothers who have

not reinforced their immunity to RSV will not be protected. Thus, the risk is that when RSV will circulate again, like in Western Australia, it will find a larger cohort of immunologically naïve individuals and will cause major and more severe epidemics. A mathematical model predicted that the longer the control measures will reduce the RSV diffusion, the larger the future epidemics will be.[34] Considering the high mortality rate of RSV infection not only in infants but also in the elderly, efforts are needed to prevent a future RSV severe epidemic.[35] RSV surveillance must be implemented, reservoirs and circulating variants need to be isolated, and research for potential vaccines needs to be accelerated. Even in the presence of the SARS-CoV-2 pandemic, the other respiratory pathogens should not be forgotten, as the consequences could be dramatic.

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How to cite this article: Di Mattia G, Nenna R, Mancino E, et al. During the COVID-19 pandemic where has respiratory syncytial virus gone? *Pediatric Pulmonology*. 2021;56:3106-3109. https://doi.org/10.1002/ppul.25582