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SARS-CoV-2 pandemics and RSV off-season outbreaks

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To the Editor,

the emergence of SARS-CoV-2 pandemics triggered a worldwide-scale implementation of measures that seriously impacted the circulation of respiratory syncytial virus (RSV), as demonstrated inter-seasonal RSV epidemics in some southern hemisphere countries and late off-season outbreaks in several European countries and USA. In a multi-country longitudinal observation study, involving 18 countries that enforced non-pharmaceutical interventions (NPIs) to reduce the spread of SARS-CoV-2, You *et al.* found that all countries experienced delayed RSV onset and, based on data available by September 2021, in 61% there was a RSV rebound delayed by a range of 5 to 54 weeks (1).

The first example of shift in RSV seasonality was reported in Australia, in late 2020 and early 2021, with an off-season widespread of RSV infections after relaxing of COVID-19 restrictions, with unprecedented outbreaks and hospitalizations for RSV bronchiolitis, after being almost absent during 2020 winter (2, 3). Type A clades became dominant and responsible for the outbreaks in widely separated areas of Australia (4). The age distribution was also atypical with a higher-than-average number of RSV infections in older infants (3, 5).

Those findings were also reported in other southern hemisphere countries and raised the initial alert in the remaining globe, as mitigation measures for control of SARS-CoV-2 also impact dramatically the circulation of most respiratory viruses and may result in unusual seasonality and severe outbreaks of respiratory pathogens. The reality observed in the northern hemisphere also began with marked reductions in RSV activity in early 2020. However, the so-called “first wave” of SARS-CoV-2, in March 2020, overlapped

with the end of 2019-2020 bronchiolitis season. This resulted in a slight delay in the expected end of the epidemic bronchiolitis season, which explains why the reduced numbers of RSV activity were not as significant as those seen in southern countries.

When Stera *et al.* compared the 2019-2020 and 2020-2021 bronchiolitis seasons at a pediatric department in Italy, one of the world's first and largest clusters of SARS-CoV-2, discovered dramatic reductions in attendance and no hospitalizations for bronchiolitis during the epidemic season of 2020-2021 (6). Similar results were also found in Argentina, France, Belgium, and Japan at the beginning of the SARS-CoV-2 pandemic (7, 8). That drop was correlated and coincident with pandemic-driven prophylactic NPIs as social distance, hand hygiene and face masks, together with lockdown, resulting in lower circulation of RSV and other airborne infectious agents (9).

Like southern countries in the late 2020, some European countries and US southern states have reported out-of-season spikes in RSV activity in early-mid 2021, mainly after April.

What is behind that surge? It's probably due to the easing of COVID-19 restrictions, as more people got vaccinated: the masks and social distances became optional in many countries, the schools opened, and the gathering promoted the rise in RSV cases. Also, the lack of herd immunity to the disease due to lockdown that prevented contact with those viruses, thus reducing adaptive immune response, made children more susceptible to infection. Another explanation could be the higher susceptibility due to the immunocompromised lungs of previously infected COVID-19 patients (1, 9).

The reduction of viral interference, a mechanism by which the replication of respiratory viruses can be inhibited by SARS-CoV-2 infection, could also explain the rising numbers (5, 10, 11).

There is uncertainty about the RSV and other respiratory virus behavior and how long it will take to resume; extrapolation from other pandemics may be important - the impact on respiratory virus circulation of 2009 H1N1, for example, persisted for many years (11). Most works reporting the first off-season RSV epidemics raised the concern that in countries emerging from pandemic restrictions, the reintroduction of respiratory viruses within pediatric communities that have never contacted them, could result in uncontrolled transmission, probably at unusual times and with a higher magnitude and severity of cases (2-5).

Fortunately, several studies in different countries, while confirming earlier peaks and higher numbers of RSV than the usual pre-pandemic seasons, didn't confirm the higher severity of bronchiolitis episodes (5, 8).

More recent works, including the last cold season 2021-2022, confirm the epidemiological changes described in the previous season and the need to pay attention to the consequences of lack of immunity, in particular to those viruses that didn't resurge or did it weakly (5, 7).

Kume Y *et al.* examined changes in the detection rate of respiratory viruses in 1165 children hospitalized with bronchiolitis, from January 2018 to December 2021. This observational study confirmed that RSV infection was the most frequent in pre-pandemic years, but dramatically dropped between April 2020-April 2021, as confirmed by reverse transcription polymerase chain reaction (RT-PCR), coincident with the first state of emergency. Other viruses like flu and human metapneumovirus (HMPV) were almost undetectable during this period; non-enveloped viruses such as human bocavirus (HBoV) and human adenovirus (HAdV), although with reduced number of cases, were found more consistently.

After a non-epidemic period, RSV and HPIV (human parainfluenza virus) had a resurgence in the summer of 2021; however no reemergence was detected for HMPV and influenza virus, a fact deserving attention in near future (7).

Considering that most children in their second year of life missed the 2020 bronchiolitis season, due to restrictions, and might have experienced the first episode in following year, children under two years were enrolled in a multicenter prospective study conducted by Camporesi *et al.*, in Italy, from 1st July 2021 to 31st January 2022, in the second year of pandemic, outside the lockdowns. The epidemiology, disease severity and microbiology of bronchiolitis episodes were analyzed.

The authors found that the expected season started and peaked earlier than usual, with shorter duration, and that up to 1 in 5 children were older than 14 months, confirming a shift to higher average ages of children affected by RSV. Overall disease severity, however, was similar between the two groups, as well as those with bronchiolitis due to a single virus *versus* multiple viruses (5).

Despite the encouraging results of most published works, global and long-term studies are necessary to achieve more knowledge and provide us better preparation to manage future pandemics and outbreaks.

Fundings

None

Conflict of interests

The authors declare that they have no conflict of interests.

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