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Editorial

Respiratory syncytial virus infection in COVID-19 times: Trick or threat?

Infección por virus respiratorio sincitial en tiempos de COVID-19: ¿truco o amenaza?

Acute bronchiolitis (AB) is the most frequent lower respiratory tract infection in children and the most common cause of hospitalization in young infants.[1] Respiratory syncytial virus (RSV) is the leading agent of AB, accounting for the majority (50–80%) of cases. Other viruses such as rhinovirus, enterovirus, metapneumovirus and others, are responsible for the rest of the cases, and rates of coinfections vary greatly between different studies.[1]

RSV is a "very familiar" virus to pediatricians as it is responsible, each year, for millions of episodes of respiratory tract infections in children under 5 years. Although it usually causes a cold-like mild illness, in younger infants and vulnerable children it can cause serious diseases.[1] In a recent systematic analysis, the authors estimate that in 2019 globally, in infants aged 0–6 months, there were 6.6 million RSV-associated acute lower respiratory infection episodes, more than 1 million associated hospital admissions, and more than 10,000 associated in-hospital deaths, mainly in low and middle-income countries.[2] In developed countries RSV infection is also a frequent cause of hospitalization and Pediatric Intensive Care Unit (PICU) admission, mainly in infants aged < 2 months.[1,3]

RSV is easily spread by droplets of respiratory secretions and primary infection usually occurs during the first two years of life. Neonates, preterm infants (especially those born before 29 weeks of gestation), infants younger than 3 months and children with comorbidities represent the group with the highest risk of serious RSV infection.[1,3] Though most severe cases usually occur in young infants, RSV causes a wide range of infections during childhood, and it is not only a pediatric virus, it also represents a significant burden of disease in adults, especially in immunocompromised and elderly people with comorbidities.[4]

As there is no approved effective vaccine yet, children acquire RSV-immunity either by infection or by transmission of maternal neutralizing antibodies through the placenta, mainly during the third trimester of gestation. In premature infants, the lack of transplacental antibody passage at the end of pregnancy, could explain why they are prone to severe infections.[1,5] Reinfections are common through life but usually milder.[1] Since there is no effective antiviral therapy, the treatment of AB is supportive just to improve symptoms during the illness. The administration of the monoclonal antibody palivizumab is recommended monthly during the RSV season to children at highest risk.[1]

Annual RSV-outbreaks occur worldwide, but the number of episodes, the beginning, the peak incidence and the end of the outbreaks slightly differ each year and from one site to another, depending on latitude and climatic conditions.[1] Moreover, the surge of new variants of the virus may cause annual and more severe outbreaks especially in susceptible populations.[6]

In pre-pandemic years, RSV used to be a common "winter virus" and outbreaks, in the northern hemisphere, usually started in October–November with most episodes occurring in early winter and cases peaking from December to January.[1] In March 2020, the World Health Organization declared the COVID-19 pandemic and control measures were adopted all around the world (lockdowns, social restrictions, universal mask-wearing, etc.). During the first months of the pandemic, a disruption in the transmission of endemic respiratory viruses was observed, probably related but not only to an unexpected protective effect of the measures implemented to control the spread of SARS-CoV-2 virus.[7,8] In this issue of Enfermedades Infecciosas y Microbiología Clinica the authors, in two different studies conducted in two pediatric tertiary care hospitals in Spain, also report changes in the pattern of AB in children during the pandemic.[9,10]

In the first paper, Bermudez et al.[9] studied all cases of AB admitted to the Valladolid University hospital during the COVID-19 pandemic (March 15th 2020–August 31st 2021) and compared this period with eight pre-pandemic seasons (September 1st 2012–March 14th 2020) aiming to describe the differences between both periods. In the second one, Hernández-Rivas et al.,[10] retrospectively described the epidemiology and clinical data of RSV admissions during 2021 in a large hospital in Madrid comparing the results with the previous two seasons. Both studies registered very few cases of AB admitted in 2020–21, only 24 *vs.* an average of 61 admissions per season in the pre-pandemic period, in the first study, and 181 *vs.* 410 and 308 respectively in the two previous seasons in the second one, with more than a 50% decrease in hospital admissions.

Similar findings have been communicated in other Spanish studies, Montejo et al., described a huge decrease in both the incidence and hospitalization due to AB, in the Basque Country in children under two years of age, from October 2020 to March 2021, and Guitart et al., observed a clear decrease in admissions due to acute bronchiolitis in the PICU in Catalonia during the same period.[11,12]

Furthermore, surprisingly in all these studies, cases moved to spring-summer months, with no episodes in autumn and winter, and with an astonishing peak of incidence during June–July in con-

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trast to the usual presentation of AB during the coldest months of the year.[9,10,12] As in pre-pandemic outbreaks, RSV was, by far, the main etiological agent. Bermudez et al., also found an increased rate in PICU admissions (45.8%) during the pandemic period, probably due to a younger age, lower gestational age and body weight of patients during this period, however, Hernández-Rivas et al. did not find any clinical differences.

The emergence of SARS-CoV-2 virus was associated with a sharp reduction in other seasonal respiratory illnesses both in children and adults,[8,13,14] and, a significant decrease in invasive bacterial diseases (*S. pneumoniae*, *H. influenzae* and *N. meningitidis*) was observed worldwide during 2020–21.[15,16]

Several hypotheses have been considered to explain the changes in RSV epidemiology. Non-pharmacological measures implemented to mitigate the COVID-19 pandemic, could have limited not only the transmission of SARS-CoV-2, but also the spread of other seasonal viruses. SARS-CoV-2 could have competed with other viruses and displaced them during the pandemic. Nenna et al., in Italy, observed not only that RSV circulation was off-season during 2020–2021, but also that the number of RSV infections in children drastically dropped when Omicron, the novel variant of SARS-CoV-2, appeared.[17] By contrast, SARS-CoV-2 has been rarely reported as a causative agent of acute bronchiolitis.[12,13,18] In the Spanish cohort of children admitted to the hospital with COVID-19, less than 2% met diagnostic criteria of acute bronchiolitis, and affected children generally did not have severe disease.[18]

Reduced circulation of RSV and other pathogens during the pandemic probably led to very few children being exposed. Therefore, many children did not build immunity, especially young infants born during the pandemic.[15] This could explain the earlier and greater increase in cases observed with the easing of restrictive measures. In Australia, Foley et al., after registering almost no cases of AB during the winter of 2020, observed an unprecedented resurgence of RSV hospital admissions during the austral summer (November–December) when initial local restrictions were removed.[19] Moreover, the median age of affected children was higher than the upper range of patients of the previous seasons. The authors suggested that these findings might be related to an increased group of RSV-naïve children and probably waning population immunity.[20]

The COVID-19 pandemic has definitely changed the epidemiology of RSV infection, although we do not know if this will change forever. RSV is no longer an “exclusively” winter virus, and after “back to normality”, a huge wave of episodes of AB and other RSV lower respiratory tract infections have been observed in children, challenging all health services that care for pediatric patients.[21]

Etiological diagnosis of AB and notification of RSV cases is very important to plan future public health measures. Recent studies have shown promising results regarding the future prophylaxis of RSV infection.[5,22,23] Both a vaccine given to the elderly and the maternal vaccination during pregnancy would be effective measures to prevent infections in the most vulnerable populations.[1] Moreover, the European Medicines Agency has just approved the use of nirsevimab, a new monoclonal antibody with long half-life, in all newborns, not only for the highest-risk patients, to prevent infections in the first months of life.

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