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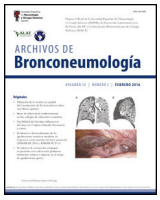

Editorial

[Translated article] Where does Respiratory Syncytial Virus Hide?

¿Dónde se esconde el virus respiratorio sincitial?

Every year, respiratory syncytial virus (RSV) makes its expected and dreaded seasonal appearance at a more or less predictable time, depending on multiple factors that still remain unclear but depend basically on a combination of latitude, relative humidity, and temperature.[1] There may be some incertitude, but we can be sure that the season will occur more or less within a certain timeframe, so we can prepare and plan the selective prophylaxis campaign with palivizumab and organize resources in hospitals, at least in pediatric units, where the impact is better characterized and anticipated. However, the advent of the COVID-19 pandemic has disrupted RSV seasonality, and the annual epidemic has all but disappeared, presumably due to the implementation of general anti-SARS-CoV-2 measures, although we cannot rule out other mechanisms such as viral competition. This lull in the storm leaves us in an uncertain and worrying position regarding what to expect and when to expect it, particularly in countries like Spain that do not have a specific epidemiological surveillance system for RSV – instead, we base our observations on the simple accumulation of cases or shared perceptions among clinicians, and events as they unfold in other countries.

It is intriguing to wonder where RSV, a virus whose only known reservoir is human, hides – a enigma that makes it even harder to understand and anticipate its seasonality. The strongest proposal is that RSV infects monocyte-derived dendritic cells, where it can remain dormant for long periods thanks to the endogenous production of nitric oxide.[2] More recently, RSV has been reported to replicate in Hofbauer cells, macrophages that play a central role in other viruses with marked vertical transmission, such as the Zika virus. This is worrying in a virus like RSV that is capable of producing viremia and extrapulmonary dissemination.[3] The recent demonstration of high concentrations of viable RSV in extracellular amoebal vesicles of a respirable size is another cause for concern, and one that forces us to rethink the currently accepted mechanisms for the spread and transmission of this virus, and even to reevaluate the usual non-pharmacological control measures.[4]

Significant pharmacological advances are being made in both the prevention and treatment of RSV. The latest generation of more potent, longer-lasting monoclonal antibodies, led by nirsevimab after the recent publication of its Phase 2b clinical trial results in healthy preterm infants,[5] is opening new horizons in prevention given their potential to cover the entire RSV season (at least the season as we understood it until the emergence of COVID-19) with a single dose. A clinical trial is currently underway evaluating nirsevimab in the prevention of RSV in healthy infants, a population that accounts for the vast majority of the known burden of disease. A beneficial outcome could revolutionize the current prevention strategy. The publication of data from the phase 3 clinical trial of a maternal RSV vaccine based on F protein nanoparticles has also marked a milestone in vaccine development. Although this vaccine failed to meet the primary efficacy objectives set out in the study by a very small margin, the safety data are consistent, and its clinical efficacy in secondary objectives justifies further investigation.[6] Several RSV-specific antivirals, both inhaled[7] and oral,[8] have shown promising early-stage results, although they are still a long way from the market. The only possible intervention, then, remains prophylaxis with the only drug currently approved and indicated for the prevention of RSV – palivizumab, an F protein monoclonal antibody that is administered monthly during the RSV season in certain high-risk groups, mainly preterm infants.

So, when do we administer it? Palivizumab has been administered in vain this season, but a more serious problem is that unless we can define when the season has started, we cannot know when it will really be necessary, or what room for maneuver we will have. We might need to protect our most vulnerable patients before the theoretical start of the next season. On the other hand, it might be absurd to continue to offer prophylaxis in the usual way if there is no RSV activity. Adaptive prophylaxis based on objective local or regional markers indicating the start and end of the season seems to be the most logical approach, but this relies on the re-definition and implementation of decision-making criteria and the introduction of specific surveillance programs that must include the adult population and molecular monitoring. RSV is important in adults, not only because of acute exacerbations in patients with chronic obstructive pulmonary disease, but also as a causative agent of acute infectious respiratory disease in adults.[9] Molecular surveillance of RSV is essential, as we should already be well aware after our experience with SARS-CoV-2 and its genetic variants. It is particularly important to implement a similar strategy in RSV before wide-scale prophylaxis programs begin. Various tactics and techniques, from simple sequencing[10] to targeted metagenomics,[11] can be used to correlate subtypes and variants with clinical phenotypes and detect possible escape variants.

Centering our attention on COVID-19 has dangerously relegated other pathogens to the background, and there is a risk of oversight if appropriate measures are not taken. RSV has not gone away,

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and the lack of exposure to this virus among new cohorts of children and their mothers paves the way to a future epidemic. It is impossible to predict when this might happen, but we can be sure that it will be different and probably more intense than previous waves, and also more acute the longer the current situation continues. While it is true that the older the infant, the lower the risk of hospitalization, the rate of admission among children is still considerable, and as weeks pass, increasing numbers of newborns who have not yet been in contact with RSV are added to the population. This situation may result in a significant increase in the absolute number of hospitalizations, leading eventually to the collapse of the pediatric care system. Another unknown is the impact this situation may have on nasopharyngeal and microbiota dynamics, and we must watch out for known synergies of RSV with other pathogens (pneumococcus and meningococcus) and how these can evolve or re-emerge. These circumstances call for additional epidemiological research and monitoring, and at the very least demand the immediate implementation of an active Spanish RSV surveillance program and the deployment of management and support plans that can respond to the possible scenarios that will occur when RSV returns. Which it will.

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Conflict of interests

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