



## EDITORIAL

## Changes in the epidemiology of infections in children. Is there an immune debt? Only for respiratory viruses?



## Cambios en la epidemiología de las infecciones en niños. ¿Existe la deuda inmunitaria? ¿solo para los virus respiratorios?

Cristina Calvo

*Servicio de Pediatría, Enfermedades Infecciosas y Tropicales, Hospital Universitario La Paz, Fundación IdiPaz, Red de Investigación Traslacional en Infectología Pediátrica (RITIP), CIBERINFEC, ISCIII, Madrid, Spain*

The implementation of strict public health measures and nonpharmacological interventions to prevent the transmission of SARS-CoV-2 is considered a success and practically eliminated all infections transmitted through the respiratory route in adults and children. This was particularly relevant in respiratory syncytial virus (RSV) and influenza, which completely disappeared in both hemispheres and resulted in a full year free of their characteristic winter epidemics.

However, this has elicited significant concern about the possibility of experiencing serious and larger epidemics in the near future on account of what is known as “immunity debt”. This term has been proposed to refer to the waning immunity or infrequent immunity developed in the population as a result of prolonged periods of low exposure to a given pathogen, leaving a higher proportion of the population susceptible to infection.

In the case of RSV, soon after the pandemic in 2021 it became evident that an epidemic was emerging outside the usual season, in summer, with an incidence that exceeded that of previous years by up to 5-fold in countries like New Zealand or Australia.<sup>1</sup> In Spain, and also in Europe, hospitals overflowed with bronchiolitis cases caused by RSV in July and August 2021, followed by an atypical winter with

a moderate incidence of infection, which persisted longer than usual.<sup>2</sup> Other infections, such as the annual epidemic by human metapneumovirus, shifted to the autumn–winter of 2021–2022, when it typically occurs in spring, and caused severe respiratory infection and pneumonia in children who were older than usual, around 2 years of age, which frequently required hospitalization.<sup>3</sup> The lack of circulation of the virus for more than 1 year and the lack of exposure of mothers and infants to respiratory infections has been considered a key contributor to this shift and to its emergent virulence.

The resurgence of RSV off season poses considerable challenges to health care systems, which are already strained by two and a half years of pandemic. Respiratory syncytial virus, and respiratory viruses in general, must be subject to epidemiological surveillance year-round, as out-of-season or unusually virulent epidemics are not only likely but actually happening, for instance in the autumn–winter of 2022, in which the epidemic season was early by more than 1 month, which interfered with the timely administration of recommended prophylaxis in at-risk individuals. Estimating the magnitude of these changes is essential for public health decision-making and to be prepared to face epidemics with a high incidence requiring an increased number of paediatric inpatient and intensive care beds.

E-mail address: [ccalvor@salud.madrid.org](mailto:ccalvor@salud.madrid.org)

But the question is of even greater import if we analyse other respiratory infections. What has happened to bacterial infections? The prolonged periods of low exposure, to both viruses and bacteria, carry a risk of epidemics that increases the longer social isolation and distancing measures were kept in place. The increase in the susceptible population, the decrease in herd immunity and delayed or missed vaccination, especially for vaccines that are not included in the routine immunization schedule funded by the public health system, such as those against rotavirus or meningococcal B disease, can result in the resurgence of those diseases. In fact, in 2021 the rotavirus epidemic of far greater magnitude compared to the pre-pandemic years.

There are data that clearly show a decrease in the incidence of bacterial infections transmitted through the respiratory route<sup>4</sup> in an epidemiological surveillance study conducted in 26 countries during the COVID-19 pandemic, with decreases in invasive infection by *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Neisseria meningitidis*, while the incidence of infections transmitted by other routes, for instance by *Streptococcus agalactiae*, did not change. In December 2022, the United Kingdom issued an alert on account of the unusual increase in infections by *Streptococcus pyogenes* observed in the preceding months, with an increase in the cases of tonsillitis and scarlet fever, which increased from an average 186 cases on week 46 of preceding years to 851 cases on week 46 of 2022. At the same time, there was an increase of invasive group A streptococcal disease (iGAS) in children aged less than 10 years, with an incidence of 2.3 cases per 100 000 children aged 1–4 years compared to an average of 0.5 cases in pre-pandemic seasons (2017–2019) and 1.1 cases per 100 000 children aged 5–9 years compared to an average of 0.3 in pre-pandemic seasons (2017–2019) at the same time of the year, while the associated mortality seemed to increase as well (<https://www.gov.uk/government/news/ukhsa-update-on-scarlet-fever-and-invasive-group-a-strep>). The most important detected severe were pneumonia, sepsis and fulminant septic shock, in addition to necrotising fasciitis, and a similar increase may become evident in other European countries, and was being investigated at the time of this writing. The obvious question is whether immunity debt could be behind this increase in incidence, especially given that the strains at play do not seem to be different from those documented before the pandemic.

Although this outbreak is particularly striking, it is not the only one worthy of attention. In France, for instance, there is evidence of an increase in infections by *Streptococcus pneumoniae* or *Neisseria meningitidis*.<sup>5</sup> Two letters published in the current issue ought to be mentioned in regard to Spain. One of them describes the evolution of invasive bacterial infections in the paediatric emergency department of the Hospital de Cruces and how the pandemic has brought changes in their incidence, demonstrating the need of maintaining the surveillance network in Spanish hospitals year-round.<sup>6</sup> The second draws attention to this issue in relation to the increasing tendency to treat group A streptococcal pharyngitis with short courses lasting 5–7 days.<sup>7</sup> Although the risk of rheumatic fever in Spain is

very low, in this shifting context in which we are experiencing unexpected and virulent outbreaks, maintaining a surveillance system that would allow us to implement early measures as needed seems crucial, and it may not be far-fetched to consider that immunity debt could be related to the outbreak of hepatitis of unknown origin that emerged in the Spring of 2022 in the United Kingdom and other European countries, including Spain, which was attributed in part to infections by adenovirus with a very severe clinical presentation that was unprecedented in recent years (<https://www.sanidad.gob.es/profesionales/saludPublica/ccayes/alertasActual/alertActu.htm>).

In conclusion, the lack of contact and exposure of the paediatric population to viruses and bacteria seems to have generated an immunity debt that, far from being beneficial, could be behind the unusual and virulent epidemics caused by viruses and bacteria we are currently experiencing. This poses a challenge for health care providers and administrations, and calls for the development of plans for their detection and management.

## References

- Hatter L, Eathorne A, Hills T, Bruce P, Beasley R. Respiratory syncytial virus: paying the immunity debt with interest. *Lancet Child Adolesc Health*. 2021;5:e44–5. [http://dx.doi.org/10.1016/S2352-4642\(21\)00333-3](http://dx.doi.org/10.1016/S2352-4642(21)00333-3). Epub 2021 Oct 23. PMID: 34695374; PMCID: PMC8598182.
- Billard MN, Bont LJ. Quantifying the RSV immunity debt following COVID-19: a public health matter. *Lancet Infect Dis*. 2022. [http://dx.doi.org/10.1016/S1473-3099\(22\)00544-8](http://dx.doi.org/10.1016/S1473-3099(22)00544-8). S1473-3099(22)00544-8. Epub ahead of print. PMID: 36063827; PMCID: PMC9439700.
- García-García ML, Pérez-Arenas E, Pérez-Hernández P, Falces I, Ruiz S, Pozo F, et al. Outbreak of severe human metapneumovirus infections during the COVID-19 pandemic. Comparison with previous epidemics. *Emerg Infect Dis*. In press.
- Brueggemann AB, Jansen van Rensburg MJ, Shaw D, McCarthy ND, Jolley KA, Maiden MCJ, et al. Changes in the incidence of invasive disease due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis* during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative: a prospective analysis of surveillance data. *Lancet Digit Health*. 2021;3:e360–70. [http://dx.doi.org/10.1016/S2589-7500\(21\)00077-7](http://dx.doi.org/10.1016/S2589-7500(21)00077-7).
- Cohen R, Ashman M, Taha MK, Varon E, Angoulvant F, Levy C, et al. Pediatric Infectious Disease Group (GPIP) position paper on the immune debt of the COVID-19 pandemic in childhood, how can we fill the immunity gap? *Infect Dis Now*. 2021;51:418–23. <http://dx.doi.org/10.1016/j.idnow.2021.05.004>. Epub 2021 May 12. PMID: 33991720; PMCID: PMC8114587.
- Martin-Irazaba G, Gangoiti I, Gomez B, Lizarraga L, Mintegi S. Impacto de la pandemia de COVID-19 en las infecciones bacterianas invasivas en urgencias de pediatría. *An Pediatr (Barc)*. 2023;98:228–9.
- Zafra Anta MA, García Nieto VM. Carta a la Editora de Anales de Pediatría (Barc) sobre el trabajo de Salinas-Salvador y colaboradores «Estudio retrospectivo sobre la efectividad y seguridad de la pauta antibiótica reducida a 5-7 días en la faringoamigdalitis aguda estreptocócica comparada con la pauta clásica de 10 días». *An Pediatr (Barc)*. 2023;98:244–5. <http://dx.doi.org/10.1016/j.anpedi.2022.12.002>.