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Opinion
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Acute Bronchiolitis in Post-COVID Era: Is the Immunity Debt Paid Off?

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Opinion

Acute bronchiolitis is a seasonal viral disease representing the most common acute inflammatory infection of the lower respiratory tract during the first year of life. It constitutes the leading cause of medical admission in developed countries (150 million new cases/year worldwide, 3% of which requires hospital admission), with a significant social and economic burden in this age group. More than half of cases are due to Respiratory Syncytial Virus (RSV), whose transmission is airborne through the contact of nasopharyngeal or conjunctival mucosa with respiratory secretions of infected individuals [1-3]. SARS-CoV-2 global diffusion and COVID-19 associated Public Health Measures (PHM) have profoundly modified the epidemiology of airborne communicable diseases. With the main purpose of curbing virus spread, from march 2020 governments imposed a broad range of non-pharmacological interventions (NPIs; e.g., social distancing, school closing, travel and gathering restrictions, mandatory face masks, promotion of hand washing...), determining radical changes in daily lifestyle and collaterally limiting the circulation of other airborne transmissible pathogens [4-8]. The major decline in infection rates concerned enveloped viruses (especially RSV and influenza), instable and easily neutralized by the widespread alcohol-based sanitizers. This did not affect envelope-free viruses (among all, rhinovirus), transmitted by either aerosol or fomites, which kept circulating and became the leading etiological agents of some clinical entities (e.g., bronchiolitis) [4-6,9-11]. The efficacy of PHM established to contain COVID-19 pandemic is consolidated evidence, nonetheless viral circulation in a certain area is the result of a complex interplay between local microbiology, climatical conditions, population susceptibility and social interactions [12]. Recent evidence points out that different pathogens can compete in the single host (viral interference), affecting each other's circulation at a population level: for instance, interferon response to rhinovirus is protective against influenza A virus, which may explain their asynchronous circulation in some areas and seasons [13,14]. Antiviral immunity activation may also explain the coincidence in time between the unexpected decrease of RSV infections and the parallel increase in SARS-CoV-2 Omicron cases recorded in late December 2021 (RSV usual epidemic peak) [2].

The seasonality of viral respiratory diseases is widely recognized. Cold temperatures and humidity foster viral transmission respectively stabilizing the envelope and facilitating the deposition of heavy droplets, other than encouraging indoor social gatherings [15,16]. RSV epidemiology, indeed, varies according to meteorologic conditions: in the Northern Hemisphere, transmissions rate increases from November to March, reaching its peak in January-February, while epidemic peak in the Southern Hemisphere takes place in May-July [17]. Data show that is not a contiguous spread rather locally evolved variants that underlie epidemics, because of susceptible reservoirs (e.g., adults with COPD or immunodeficient children) who guarantee a low-level continuous viral replication, periodically enhanced by favorable meteorological and social conditions [16,18]. Climate factors and pathogens mutual interactions do not fully explain the rebound effect we are experiencing after the relaxation of preventive measures, characterized by heavier disease burdens and infection rates peeking out of the conventional epidemic season or age range [7,19-21]. COVID-related Non-Pharmacological Interventions (NPIs) had indeed an impact on both, cross-border and local diffusion, generating off-season resurgences and incidence rate fluctuations correlated to the different intensity of containment measures throughout the entire pandemic period [22]. A matter of actual concern is the detrimental impact of NPIs on immune competence at host and population level. Abundant evidence demonstrates that recurrent antigenic stimulation increases immunity effectiveness. On the contrary, prolonged periods of reduced exposure to pathogens deprive immune system of antigenic stimulation, resulting in waning herd immunity and producing what is now referred to as "immune debt" [19,21]. In this perspective, social restrictions and hygiene measures facilitated the selection of a population susceptible to already known infections. With the gradual relaxation of community

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NPIs, previously disappeared viruses started to circulate again, facing an immunologically "naïve" population unable to build up an appropriate neutralizing response. Consequently, the association of relaxed anti-COVID restrictions and decreased protective immunity contributed to a paradoxical, intense and out-of-season resurgence of respiratory illnesses [7,20-25]. This is a particular concern for Respiratory Syncytial virus, for which susceptibility largely depends on age-dependent airway and immune development but mostly on protective immunity arising from repeated antigenic recognition. Transient immunity against reinfection (lasting from 7 to 15 months) is provided initially by vertical transmission and through periodic seasonal exposure thereafter [7,20,26]. The absence of seasonal viral circulation deprived the pediatric population of passive protection obtained with maternal antibodies and of the infection-related active immunization. The "immune debt" generated in such unexposed and therefore susceptible cohort of infants is held accountable for the growing trend in RSV infections observed with social restrictions easing [23].

It is legitimate to wonder what to expect in next seasons, in view of the likely necessity to employ effective containing measures for incoming SARS-CoV-2 periodic waves. Mathematical models predicted that the intensity and duration of NPIs reducing pathogens' spread are positively correlated with the size of their future epidemics [27]. This acquires significant implications in terms of prevention and health planning, since the unpredictability about Public Health burden of unexpected epidemics forces health systems to maintain a prolonged and source-consuming level of vigilance [21]. Preliminary data from both hemispheres report that 2022-2023 bronchiolitis seasons is going to be of high impact (personal data). Should we consider the immunity debt paid off? A better understanding of SARS-CoV-2 epidemiology – and more specifically of the impact that COVID-19 restrictions collaterally have on microbiological epidemiology and immune competence – is necessary to predict and consequently anticipate the resurgences of seasonal respiratory viruses. Concerning RSV, this would allow governments to timely and effectively allocate healthcare resources (e.g., prevention campaigns with monoclonal antibodies), primarily to preserve most fragile patients (e.g., under 3 months, premature, with comorbidities), at greater risk of hospitalization and severe complications [6,20]. With reasonable probability SARS-CoV-2 will become, like others, an endemic virus, and restrictive interventions necessary for its containment will no longer be necessary. Meanwhile, however, we advocate for an implementation of RSV epidemiological surveillance and hope that technological advancement will soon provide new tools (e.g., vaccines) to cope with unexpected outbreaks, thence balancing the immune debt of a population weakened by the need to face a greater threat.

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