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EDITORIAL

Rhinovirus and COVID-19 in children: a new order out of chaos?

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The SARS-CoV-2/COVID-19 pandemic has resulted in profound changes in nearly all aspects of life everywhere. Initially, this was most manifest in non-pharmacologic interventions (NPI) to mitigate the spread of the virus, forcing people around the world into various degrees of social isolation. Not surprisingly, this aspect of the world's response to the pandemic has had multiple impacts on population health, from mental health effects to delays in non-COVID care to worsening health disparities between groups. While outbreaks of SARS-CoV-2 ravaged country after country, there appeared to be a paradoxical benefit in that there were also dramatic reductions in respiratory viruses reported in several countries around the world.[1–6] But this apparent positive aspect of the pandemic may come at a cost, one we are already beginning to pay.

In this issue of *Jornal de Pediatria*, Varela and colleagues[7] report their analysis of epidemiologic trends in respiratory viruses using data from two hospitals in Porto Alegre. They enrolled 436 children with a median age of 5.4 years (IQR, 2.0-10.2; range 0.2-17.3). Quite strikingly, 49.5% of the children tested positive for human rhinovirus (hRV) while RSV was conspicuously absent at a time when it should have been the dominant viral pathogen. A little less than a quarter of the children (22.2%) were positive for SARS-CoV-2. Other common fall/winter/spring respiratory viruses were seen far less commonly (enterovirus 1.6%, adenovirus 1.4%, coronavirus NL63 0.5%, human metapneumovirus 0.5%). Combined infection with hRV and SARS-CoV-2 was found in 7.1% of the children and was not associated with increased hospitalization. No children were found to be infected with bocavirus, influenza A, influenza B, coronaviruses KHU1 or 229E, parainfluenza virus, or RSV. Also noted were historically low incidences of Bordatella pertussis and Mycoplasma pneumoniae.[7]

As noted by the authors, hRV was not subtyped in this study. hRV type C has been noted to produce higher viral loads (which could translate into greater transmission) and worse illness than other hRV types.[8] If that was the dominant subtype during the single-season period of data collection it might account for the increase in detection. However, a study from China describing the same predominance of hRV in children during times of aggressive mitigation efforts in 2020 noted both type A and type C hRV in circulation with the type A strains predominating.[9] Its existence as a non-enveloped RNA virus was posited by the researchers in Porto Alegre as enhancing the durability and detectability of hRV relevant to this study, but they also point out that there is no evidence for significant differences in length of viability/infectivity within the group of respiratory viruses evaluated in this study that would explain the hRV predominance seen.

The lower rate of detection and severity of SARS-CoV-2 infections in this study may be at least partially explained by

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viral interference. Cheemarla and colleagues[10] found that innate immune responses in the form of interferon production (primarily interferon lambda 1) associated with recent/current hRV infection accelerates interferon-stimulated viral defense genes in the upper respiratory tract and prevents SARS-CoV-2 replication. It remains to be seen whether any of the other common respiratory viruses can induce this heterologous viral interference as well. The high prevalence of these respiratory illnesses in children, especially young children may turn out to be a protective factor against severe SARS-CoV-2 infection that partially accounts for the decreased incidence and decreased severity of this disease seen in the pediatric age group.

The rapid development of multiple very effective vaccines against SARS-CoV-2 has been nothing short of spectacular. But one of the lessens SARS-CoV-2 and the vaccines are teaching us is that the immunity that results is relatively fleeting. A number of studies have documented a waning of immunity following immunization or infection[11—14] prompting the implementation of booster immunization. But a perhaps equally important lesson from the pandemic is that rapidly waning immunity is not unique to SARS-CoV-2.

With the development of effective vaccines and declining rates of SARS-CoV-2 (perhaps resulting from a combination of vaccination, development of post-infection immunity, and natural evolution of the disease), communities and governments are relaxing NPI's. As the world emerges from the NPIs it has become clear that the pre-pandemic patterns of viral "seasons" do not hold. This first became manifest with reports of increased interseasonal respiratory syncytial virus (RSV) infections in Australia in late 2020 followed by similar reports from South Africa in early 2021.[15,16] In mid-2021 the US began to experience the same, prompting the Centers for Disease Control and Prevention to issue an official health advisory[17] and the American Academy of Pediatrics to issue updated guidance on the use of palivizumab for prophylaxis against RSV infection.[18] Many other shifts in RSV patterns have been reported (reviewed in[19]). Anecdotally, my institution is seeing changes in seasonal respiratory viral patterns for several other viruses as well, among them Influenza A, hRV and parainfluenza virus. And immunity debt has resulted in children being more severely ill with viruses that previously would have been associated with mild symptoms.

These shifts in long-standing viral patterns, combined with the uncertainty (or perhaps the certainty) that new variants and subvariants of SARS-CoV-2 will emerge pose challenges for the pediatric community around the world. If healthcare workers are to continue to provide the best care for the children and communities that we serve, we must learn to think differently and proactively seek solutions for as many of these challenges as we can.

The most immediate need is to promote vaccination against SARS-CoV-2. Vaccination of children 5—11 years of age in Brazil started January 14, 2022 with priority being placed on immunizing indigenous people, quilombolas and children with disabilities and comorbidities. In the first month after vaccination in this age group was started only 21% of children were vaccinated; eight months after vaccine was authorized for adolescents 12—17 on June 11, 2021 an estimated 25% had completed the two-dose regimens. Pediatricians in both the United States and Brazil are facing high levels of vaccine mistrust promulgated by political leaders and, in Brazil, even government agencies. Since vaccinating children is key to protecting not only them but also high-risk family members, it is crucial to overcome this barrier and achieve as high an immunization rate as possible. Children have also fallen behind on other routine childhood immunizations during the pandemic. These must be brought up to date as well. A concerted effort must be made to see that all eligible infants receive passive immunoprophylaxis against RSV with palivizumab.

Despite the effectiveness of vaccines, the low rates of vaccination completion make it important to continue with NPIs to help further reduce the spread. The opportunity for new variants to evolve remains so long as active outbreaks continue. Hopefully, more extreme measures such as shutdowns of schools, businesses and industries will not be necessary, but this may depend upon early use of less burdensome NPIs such as frequent handwashing/sanitizing, wearing masks indoors when in large groups of people (including on buses, trains and airplanes) and improving ventilation in buildings. Exercising personal responsibility by staying home (or keeping children home from daycare or school) when ill will be important. Creative alternatives, such as cohorting sick children in daycare or school when parents cannot stay home with them, should be discussed and explored. The recommendation for implementation of NPIs can be linked to community levels of SARS-CoV-2 as has been done in the US.[20]

The unpredictability of interseasonal outbreaks of respiratory viruses creates challenges for clinic and hospital staffing over and above those presented by the pandemic itself. This may be especially acute in places where the healthcare workforce has been significantly reduced through illness, death, burnout, and resignations among nurses, respiratory therapists, laboratory technicians, radiological technicians, and others. Bringing staff out of recent retirement to fill in at times of high need could be considered. Accelerating training and using students under the guidance of seasoned practitioners where possible is another strategy. If there are sufficient resources in a community, alternatives to hospitalization for the lower acuity children, such as expanded use of home oxygen, home nursing visits, or telehealth into the home for close follow-up can help reduce the burden on healthcare facilities in times of high respiratory viral activity (SARS-CoV-2 or others). No one strategy will work for all communities and some strategies may already be in place. The response must be tailored to each community's resources and needs. But taking inventory of community resources in advance and having a plan to implement such short-term programs will enhance the nimbleness with which a community's healthcare system can respond to surges in respiratory viral activity.

Finally, there is a need for continued work like that presented by Dr. Varela and her colleagues. Vigilance and regular assessment of disease trends such as their work will help inform the pediatric community and health system responses to these uncertainties. It is also necessary to allow us to adapt to new patterns or anticipate a return to old patterns of respiratory virus activity. The work of Dr. Varela and colleagues gives us a start, bringing some order at least to the authors' understanding of new viral patterns. Without

it, we will be doomed to always act in a reactive rather than a proactive way.

The challenges are great and the stakes are high. But with foresight, planning, and above all a partnership between the pediatric community, community leaders, and health systems the challenge can be met with *Ordem e Progresso*.

Conflicts of interest

The author declares no conflicts to declare.

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