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Respiratory infections

Children's immunity at risk

Young children who have spent much of their lives under coronavirus restrictions now seem more vulnerable to a number of other conditions, finds **Donna Lu**

THE coronavirus pandemic has left children vulnerable to other infections, in part due to reduced interactions as a result of lockdowns and social distancing.

In Australia, which has largely been covid-free for the past six months, there has been a delayed surge in cases of respiratory syncytial virus (RSV), a common, flu-like illness that causes a lung infection called bronchiolitis and often has the most serious effects in children under the age of 2.

RSV infections typically peak in winter, but in 2020, the RSV season in Australia was curtailed by covid-19 stay-at-home orders and public health measures.

In Western Australia, a recent analysis of hospital presentations shows that RSV cases dropped by 98 per cent during the winter months of 2020 compared with the same period in previous years, but began to surge in spring, in late September, eventually exceeding the median seasonal peak from 2012 to 2019 (*Clinical Infectious Diseases*, doi.org/f8s5).

Daniel Yeoh, an infectious diseases clinician at Perth Children's Hospital who co-authored the analysis, estimates that the proportion of children in hospital who tested positive for RSV jumped from less than 1 per cent in April 2020 to 70 per cent in the summer months.

Other Australian states have seen similar trends, most recently Victoria, which only recently relaxed mask-wearing rules.

"You've got a larger group of children who've never seen RSV before in their life, 18 months and below, and then older children who may have seen RSV 18 months ago but their immunity from that particular encounter with RSV might have waned," says Yeoh.

As northern hemisphere countries ease their lockdowns,



Wearing face coverings in schools could help avoid a spike of other infections

98%
Year-on-year reduction of respiratory syncytial virus (RSV) cases during Australia's winter

3 months
Delay in French peak RSV season

0-6 years
Key age for the development of a child's immune system

there is a risk they could also see surges in RSV, he says.

There are already signs of similar trends in other countries. An analysis of French data on RSV diagnoses in winter, which hasn't yet been peer reviewed, has found a delayed peak in the 2020-21 season. The epidemic began in February this year, 12 weeks later than in the previous five RSV seasons, in the Île-de-France region, which includes Paris, before spreading to other regions.

In the US, a study published in December used RSV cases from 2020 to model the impact of social distancing measures on the spread of other circulating infections. It concluded that "substantial outbreaks of RSV may occur in future years, with peak outbreaks likely occurring in the winter of 2021-2022" (*PNAS*, doi.org/gh9zv8).

Paediatric services in the northern hemisphere should be adequately staffed in preparation

for a potential surge, says Yeoh. While there is no vaccine available for RSV, monoclonal antibodies are used as a prophylactic treatment for high-risk children, including those who have heart conditions or were born prematurely.

"Based on the reports from Australia, services in the UK will be watching their numbers very closely with a view to maybe starting that sort of antibody preventative treatment for those high-risk babies, even though it's not the RSV season for them, if they do see a rise in their summertime," says Yeoh.

A gradual reduction in public health measures, instead of an instant return to pre-pandemic levels of social interaction, may mitigate the surge in countries with a high burden of covid-19.

A delayed surge in influenza infections may also be on the cards in future years, says Byram Bridle at the University of Guelph in Canada.



Yeoh advises that parents should continue to implement measures such as keeping sick children home from school and maintaining good cough etiquette and handwashing habits. “Those things can go some way to limit the spread of other respiratory viruses like RSV and flu,” he says.

Mystery solved

As for susceptibility to other pathogens, it is too soon to tell, says Yeoh. “In terms of immunity in general, there are a whole range of pathogens that children encounter in their first couple of years of life,” says Yeoh. “I think we probably don’t know enough to say for certain how reduced social interactions because of covid will affect the development of immunity to all those pathogens.”

What we do know, however, is that children don’t tend to get severe covid-19. This has been a key mystery of the pandemic, but more than a year on from its start, several possible reasons for this have emerged.

Statistics compiled in April by the American Academy of Pediatrics found that children represented about 14 per cent of the total covid-19 cases in the US, but less than about 3 per cent of reported hospitalisations. And a March analysis of child mortality in seven countries, including the UK, France and Italy, found that covid-19 accounted for 0.48 per cent of all deaths in children and adolescents up to the age of 19.

Other respiratory infections such as influenza often have the most severe impacts on very young and very old people, in a U-shaped distribution, says Amy Chung at the University of Melbourne in Australia. “We see a very different kind of trend in kids [for covid-19],” says Chung.

Studies of household transmission in different countries point to children being less susceptible to getting the virus than adults.

The virus enters host cells by binding to ACE2 receptors and several studies have found that children have fewer of these in the cells lining their upper airway.

“If there’s less of that receptor available on the surface of a cell, then it means that it’s a little bit

harder for SARS-CoV-2 to come in and infect them,” says Chung.

For children who are infected with the virus, there seems to be no difference in the amount of it they carry compared with adults, but there are differences in their immune response.

In general, children tend to have a more active innate immune system than adults, says Melanie Neeland at the Murdoch Children’s Research Institute in Australia.

The innate immune system is the body’s first line of defence. It rapidly responds to infectious viruses, and also primes cells of the adaptive immune system to produce antibodies targeted to attack a pathogen.

Neeland and her colleagues have monitored children and adults with mild covid-19, finding that in the acute phase of infection, children had greater activation of immune cells called neutrophils. “Neutrophils mop up infection and they secrete a lot of proteins that kill virally infected cells,” she says.

Another difference was that children had lower levels of other innate immune cells in

Asthma and allergies

It is too early to know for certain, but extended coronavirus lockdowns could have a long-term effect on the development of children’s immune systems, affecting allergic responses.

The majority of the components of the immune system go through a process of maturation between birth and the age of 6.

“Immune systems learn to regulate themselves during these early years,” says Byram Bridle at the University of Guelph in Canada. Regular exposure to the natural environment and a variety of microbes enables immune systems to learn to differentiate between things that are foreign but not dangerous and foreign

things that are pathogenic.

A failure to properly differentiate between the two may result in hypersensitivities including allergies and asthma.

Bridle suspects that for “covid kids” – children who have spent a significant proportion of their life under lockdown – there may be a higher eventual incidence of such allergies, asthma and autoimmune diseases.

Until covid-19 restrictions ease and pre-pandemic interactions resume, what can concerned parents of young children do?

“People should be very much encouraged to stay in close physical contact within the confines of their homes, especially if they have young children,” says Bridle.

“Hug them very regularly,” he says. “Sharing your microbes with your very young child is going to help with this development of their immune system.”

Even though the most beneficial interactions are with other human microbiomes, the presence of household pets is also a boon.

“When people have an opportunity, try and get out in the natural environment,” adds Bridle.

Hugging pets, and family members, can help the immune system mature



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“Older people may be disadvantaged by their past exposure to other coronaviruses”

the blood. “This suggests to us that they were migrating away from the blood into the tissue, so that they could clear the virus more quickly,” says Neeland.

There are also key differences in adaptive immunity, which learns from past infections. Chung and her team have found that children mount less experienced but more effective antibody responses against the coronavirus. Older people may be disadvantaged by their past exposure to other common coronaviruses, those that cause the common cold.

“They preferentially induce antibody responses that are relevant for the common cold viruses, but aren’t actually very important for protection from covid-19,” says Chung.

Children, who have fewer past exposures to other coronaviruses, are better able to induce immune responses that specifically target the covid-19 virus, she says. ■