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What do we know about covid-19 and children?

Since the beginning of the pandemic, it's been clear that children are far less at risk of severe disease from SARS-CoV-2 than adults. Less clear are how it manifests in them and their susceptibility to the virus. **David Cox** asks what three years of research and experience has uncovered so far

David Cox *freelance journalist*

How does covid-19 affect children today?

Incidents of critical covid-19 in children remain rare, even though the delta and omicron variants have proved considerably more adept at infecting children than previous variants. In the early stages of the pandemic, estimates indicated that children were less likely to become infected with SARS-CoV-2 in the first place.¹ And one of the first major retrospective studies about children and covid-19, by Chinese scientists in the first year of the pandemic, found that up to 90% of paediatric cases were asymptomatic, mild, or moderate.²

"Children are more likely than adults to have asymptomatic or mild infections," says Anna Sick-Samuels, assistant professor of paediatrics at Johns Hopkins Medical School. "The majority of children hospitalised with severe covid-19 have been unvaccinated, and many have had additional comorbidities." Sick-Samuels describes children with type 2 diabetes or obesity as being most at risk of developing severe covid-19. UK studies have found children with neurodisabilities or multiple comorbidities to be especially vulnerable to hospital admission or death.^{3 4}

Children produce more interferons at the mucosal surface, which rapidly alert the immune system at the first sign of infection, making it harder for the virus to penetrate the body.⁵ They are also thought to have a faster innate immune response, because their T cells are mostly untrained, giving them a greater capacity to respond to novel viruses. In addition, they might have acquired specific antibodies or memory cells through previous exposure to the endemic coronaviruses that commonly circulate among infants.⁶ This layer of immunity has been found to be more active in the parents of infants and toddlers than in other adults. One study found that adults who live in households with young children are less likely to have severe covid-19, potentially owing to acquired immunity from regular coronavirus infections.⁶

Most children are also much less likely to have autoantibodies in their blood, which target the body's own cells and actively disable interferons, hindering the body's capability to fend off viruses.⁷ Autoantibodies tend to increase in the body with age, as mutations accumulate over the course of our lifetimes, with much high levels found in people aged 50 onwards. Adults are also more likely to have endothelial damage owing to a variety of health conditions and behaviours including smoking, type 2 diabetes, hypertension, and obesity. This damage

is associated with inflammation, which rapidly becomes excessive with immune system activation in response to SARS-CoV-2 infections. "As people get older, there is some evidence that the response of the immune system can cause more tissue damage," says Sick-Samuels. "So, older people may have a slower and more intense immune response that leads to more significant illness."

To what extent do children spread covid-19?

One of the major talking points through the pandemic has been the extent to which children transmit the virus—an issue directly linked to policies about closing schools. Determining the relative infectiousness of children has been far from straightforward, partly because asymptomatic cases tend to go undetected and it can be difficult to identify the index case when the virus spreads through a household. Many studies now indicate that children have had a substantial role in spreading the virus even when asymptomatic. Faecal analysis studies have found prolonged viral shedding in children who did not display any symptoms of infection.⁸

"In 2020, many people did not think children could commonly get covid-19, and if they did, they were not effective transmitters," says Lael Yonker, a paediatric pulmonologist at Massachusetts General Hospital in Boston. "Now people are generally in agreement that often kids are the ones bringing SARS-CoV-2 into the household. We've shown that children, even when asymptomatic or pre-symptomatic, can carry high levels of virus in their nose and upper airways."

Does vaccination help children?

Vaccination cannot completely prevent SARS-CoV-2 infection in children, but it does seem to halt the spread of the virus.⁹ Research attempting to trace how the virus passes from one child to another has helped identify the importance of vaccination in blunting community transmission. One epidemiological study, examining Australian schools affected by omicron outbreaks, found that child-to-child spread is more than eight times higher in primary school children than in high schoolers.¹⁰ The authors concluded that this was linked to the high uptake of vaccines among 12 to 18 year olds in the country; another possibility is the closer contact between younger children. As a result, some scientists think that the relatively low vaccine uptake among primary school children around the world is contributing to the rising numbers of cases. "Children currently account for nearly 20% of covid cases in

the US,” says Yonker. “Now with schools back in session, we expect cases will rise. Locally, we are starting to see wastewater levels of virus rise, and children likely are contributing to this increase in community levels.”

Other paediatricians, however, point out that the risk-benefit trade-off of vaccinating younger children to prevent covid-19 spreading in the wider population is not straightforward. Shamez Ladhani, a paediatric infectious diseases specialist at St George's Hospital London, says that, although vaccinating children with underlying health conditions is a 'no brainer,' repeatedly vaccinating healthy children will divert resources away from other important child immunisation campaigns. “You end up having to vaccinate a lot of children to have a little bit of improvement in terms of outcomes at a population level,” says Ladhani. “It becomes more challenging to assess the risk-benefits because we know that the risk [of covid-19] for healthy children is low.”

Are older or younger children more susceptible—and why?

Although severe covid-19 is unusual in children, paediatricians say that most cases now tend to be in very young children who are unvaccinated. “Even though vaccines are available for children aged between 6 months and 4 years in the US, uptake is quite low, so this increased risk of developing severe disease persists in the youngest children,” says Yonker. “Vaccinating mum helps protect infants, but this benefit wanes by 6 months or so.”

Scientists have been able to identify some of the reasons why certain children seem to be more susceptible than others. Underlying health conditions such as type 2 diabetes and obesity are key risk factors,¹¹ but in very rare cases children can have genetically related immunodeficiencies that affect the ability of the type 1 interferon system to operate correctly.

What do we know about multisystem inflammatory syndrome?

Multisystem inflammatory syndrome in children (MIS-C) is a very rare but serious complication of covid-19 that affects the heart and other major organs such as the stomach, liver, and intestines, and can prove fatal. Before vaccines became widely available, estimates indicated that it affected approximately 316 in every 1 000 000 children infected with SARS-CoV-2.¹² MIS-C was a concern for paediatricians in 2020, although researchers say that hospital admissions for this complication have become much rarer over the past two years,¹³ with vaccines seeming to reduce the risk, along with increasing population immunity from existing infections.¹⁴

We are just starting to understand what causes MIS-C. Because the symptoms typically begin four to six weeks after the initial infection, immunologists think that it might represent the most severe form of long covid. One study has shown that children with MIS-C tend to initially have mild illness, but the virus lingers in their gut, irritating the lining and causing viral antigens to leak into the blood where they can reach other organs. One of these antigens might even act as a superantigen, triggering a major inflammatory response—a hypothesis that is now being explored further.¹⁵

“The most well supported theory in my opinion is that a superantigen from SARS-CoV-2, and other microbes as a second hit following covid-19, could trigger unspecific activation of T-cells similar to what is seen in toxic shock syndrome,” says Petter Brodin, professor of paediatric immunology at Imperial College London. “There is indirect evidence of this from multiple groups and different cohorts.”

The incidence of MIS-C has been found to be higher among those of black, Hispanic, or Asian ethnicities than in white children,¹⁶ and some research groups have identified an HLA type that corresponds with MIS-C, along with other genetic factors.¹⁷ “Under the UNDINE Horizon Europe research project, we are actually studying the genetics of MIS-C, which most certainly exist,” says Isabelle Meyts, a paediatric immunologist at UZ Leuven. “As an example, MIS-C has been described in patients with STAT2 and SOCS1 and IFNAR1 deficiency, alluding to a dysregulated type 1 interferon immunity with excessive inflammation as an underlying cause.”

How can we distinguish between covid-19 and other childhood illnesses?

If anything, it has become harder to distinguish covid-19 from other respiratory viral infections without specific diagnostic testing. Sick-Samuels recommends that doctors look at which diseases are circulating in their local area to decide whether what they see is unusual and requires further testing, as well as prior knowledge of known exposures. “If the parents currently have covid-19, it is more likely their child does as well,” she says.

Like adults, the most common symptoms of covid-19 in children are fever, cough, headache, congestion, and fatigue.¹⁸ But children can also experience gastrointestinal symptoms like nausea, vomiting, and diarrhoea, sometimes as the sole presenting feature of the illness.¹⁹ “There is also increased recognition that SARS-CoV-2 can cause upper airway infections like croup in children,” says Sick-Samuels. In very young children, some of these symptoms can be initially difficult to detect, with fever and other more subtle signs the main indicators that something is amiss. “Similar to other viral respiratory infections, infection in infants can manifest as poor feeding, irritability, or apnea,” adds Sick-Samuels.

Of course, many of the symptoms of covid-19 overlap with those of other viruses that commonly infect children such as respiratory syncytial virus, rhinovirus, and enterovirus. Sick-Samuels says that further monitoring of children is vital as we grapple with future variants. Changes in how SARS-CoV-2 is affecting children might be multifactorial and related to changes in the virus itself, protection from vaccination, or the effect of having had a previous infection. “As we've seen this far, it is hard to predict how SARS-CoV-2 could evolve, so it continues to be important to study how the virus is impacting children,” she says.

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