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FDA authorizes COVID vaccines for the littlest kids: what the data say

The Moderna and Pfizer shots are hard to compare, so researchers and parents have lingering questions.

Cassandra Willyard

Kids under five years old are the largest group of people in the United States not yet eligible for COVID-19 vaccines. Credit: John Tlumacki/*The Boston Globe* via Getty

The US Food and Drug Administration (FDA) has given emergency authorization to COVID-19 vaccines for children aged five and younger. Assuming the Centers for

Disease Control and Prevention (CDC) also signs off the decision, an extra 18 million people in the United States will be eligible for inoculation — the last large group to be granted access.

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Vaccine makers Moderna and Pfizer each presented clinical-trial data to an FDA advisory panel on 15 June, showing that their mRNA-based vaccines are safe for children, and trigger antibody levels similar to those that have provided protection for adults. But researchers and parents still have questions about the real-world benefits of the vaccines, and which will perform best.

Young children have the lowest risk of becoming seriously ill with COVID-19. But that doesn't mean the disease is benign. Since the pandemic began, 442 children aged 4 and younger have died of the disease in the United States, and thousands have been hospitalized. The coronavirus variant Omicron hit kids especially hard this year. After its emergence, the hospitalization rate for children under five was five times what it was during the previous surge, caused by the Delta variant. The numbers might seem small, says Yvonne Maldonado, a paediatrician and infectious-disease specialist at Stanford University in California, but children "shouldn't be dying of anything". "If we have a way to prevent deaths, we should be preventing them."

Head to head

If the CDC green-lights the vaccines — which looks likely — parents will be eager for information about which to give their children. The most notable difference is in the number and timing of the doses. Moderna's vaccine will be administered as two doses one month apart, each one-quarter of the amount given to adults. Pfizer's will be given as three doses, with three weeks between the first two, and eight weeks between the second and third. Each shot is one-tenth the amount given to adults.

Safety was a top concern among FDA panel members, and both vaccines met the mark (the panel recommended authorizing them in a 21–0 vote). Most side effects

were mild, such as pain at the injection site and fatigue, and resolved quickly.

Moderna paediatric-trial results, at a glance

Age group	6 months to 23 months	2–5 years
Participants who received vaccine	1,762 (versus 593 placebo)	3,040 (versus 1,008 placebo)
Efficacy against symptomatic illness	50.6% (confidence interval 21.4% – 68.6%)	36.8% (confidence interval 12.5% – 54%)
Participants who had a fever after receiving second dose	14.6% (versus 8.4% placebo)	16.0% (versus 4.5% placebo)

Source: Moderna data

The firms disclosed that serious adverse reactions related to the vaccine had occurred, but were rare. Moderna, based in Cambridge, Massachusetts, reported that one child who received its vaccine had a seizure triggered by a high fever (see 'Moderna paediatric-trial results, at a glance'), and Pfizer, based in New York City, reported one case of fever and calf pain that might have been linked to vaccination (see 'Pfizer paediatric-trial results, at a glance').

"Beyond the one febrile seizure, there wasn't anything that was highly concerning," says Andrew Janowski, a paediatric infectious-disease specialist at Washington University School of Medicine in St. Louis, Missouri, who tuned in to the meeting virtually. "That's what was very reassuring to me."

Pfizer paediatric-trial results, at a glance

Age group	6 months to 23 months	2–4 years
Participants who received vaccine	386 (versus 184 placebo)	606 (versus 280 placebo)

Age group	6 months to 23 months	2–4 years
Efficacy against symptomatic illness	75.6% (confidence interval −369.1% – 99.6%)	82.4% (confidence interval −7.6% – 98.3%)
Participants who had a fever after receiving third dose	6.8% (versus 5.9% placebo)	5.1% (versus 4.2% placebo)

Source: Pfizer data

Efficacy against infection with the coronavirus SARS-CoV-2 was a bit harder to parse for each vaccine. Regulators allowed the vaccine makers to infer efficacy by demonstrating that the vaccines could elicit antibody levels similar to those that have been protective for teens and young adults, a concept known as immunobridging. That helped to speed up the trials.

But the companies did manage to collect some efficacy data. In the Moderna trial, 265 out of 5,476 kids contracted COVID-19, and the efficacy ranged from about 50% in infants and toddlers to less than 40% in children aged 2–5. The Pfizer vaccine seemed to do better, with an average efficacy of about 80% in children aged 6 months to 4 years. But these figures are based on a tiny number of cases — just seven infections in the placebo group and three in the vaccine group. Doran Fink, deputy director of vaccines and related products applications at the FDA in Silver Spring, Maryland, said at the panel meeting that he regards those estimates as “preliminary” and “imprecise”.

Concerns remain

Despite wide agreement among panellists that the benefits of both vaccines outweigh the risks, some concerns did bubble up. Paul Offit, a vaccine and infectious-disease specialist at Children’s Hospital of Philadelphia in Pennsylvania, worried about the apparent lack of efficacy against Omicron demonstrated by the first two doses of the Pfizer vaccine, which was developed in partnership with biotechnology firm BioNTech, based in Mainz, Germany. Offit told *Nature* after the meeting: “You

didn't see any evidence for protection." In other age groups, he added, the Moderna and Pfizer vaccines "track side by side in terms of efficacy". This age group is "the first time you see them separate".

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That leaves young children who get the Pfizer vaccine potentially vulnerable for longer. It also means that children must have three doses to get protection, which could present a logistical challenge. "I have a lot of concern that many of these kids will not get the third dose, as we know the struggle to get people in for two," said Jeannette Lee, a biostatistician at the University of Arkansas for Medical Sciences in Little Rock and a member of the advisory panel, during the meeting. "We've already seen with the boosters for adults, lots of people don't take them."

Wayne Marasco, a cancer immunologist at the Dana-Farber Cancer Institute in Boston, Massachusetts, brought up another concern that is relevant to both vaccines. He said that the first strain of a virus that a person is exposed to can bias their immune response to new variants of that virus for life — a phenomenon known as immune imprinting. That can be a problem for both children and adults. If young kids are given a vaccine against an early version of SARS-CoV-2, the question is whether their immune systems will protect them against a heavily evolved variant such as Omicron.

In a study published this month in *Science*[1], triple-vaccinated health-care workers who became infected with Omicron displayed a boost in their T-cell, B-cell and antibody responses, but only against variants of concern that evolved before Omicron.

Despite these worries, says Andy Pekosz, an immunologist at Johns Hopkins University in Baltimore, Maryland, "you're still much better off getting a vaccine and getting that immunity, than really taking a risk and acquiring that immunity via infection".

An agonizing wait

This decision comes more than seven months after the first vaccine was authorized for US children aged five and older, and after a series of delays. The wait has been agonizing for some parents, and their frustration was palpable during the public-comment segment of the panel meeting. "I cannot know the FDA internal workings, but I can say the lack of transparency as to why the Moderna under-five review has taken longer than any other age cohort has made me feel like vaccinating my kids was not a priority for the FDA," said Lauren Dunnington, who works in global public health and has two children under five.

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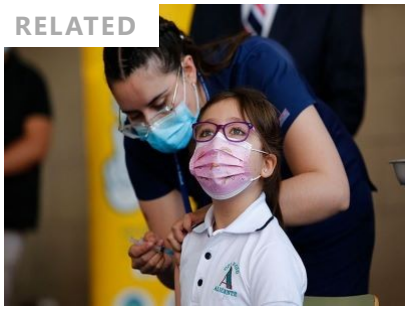

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According to a survey published in May by KFF, a health-policy organization based in San Francisco, California, these frustrated parents represent a minority. In the poll, just 18% of parents of under-fives planned to get their kids vaccinated "right away". Another 38% would "wait and see". And more than one-quarter — 27% — would not get their young children vaccinated at all. Eleven per cent would do so only if required. That could be due in part to a lack of information. A little more than half of the parents polled said they didn't have enough information about the safety and effectiveness of vaccines in this age group.

Given the expected low uptake, the vaccine isn't likely to have much of an impact on the pandemic. But it could make a substantial difference in the lives of families that choose to get their children vaccinated — especially those that have been completely isolating their children socially to protect them. Vaccinated kids might also miss fewer days of school and childcare owing to illness or quarantine restrictions.

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The two vaccines are likely to be authorized by the FDA in the coming days. But it is up to the CDC to decide how they should be used. That agency's Advisory Committee on Immunization Practices is expected to make its recommendation within days, and then the

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agency's director, Rochelle Walensky, must sign off on it. Offit predicts that the vaccines will receive a full recommendation from the committee, but he notes that there is some precedent for recommending one vaccine over another.

If all goes to plan, the first shots could go into arms as soon as 21 June, according to senior White House officials. When that happens, the United States will join just a handful of countries that are vaccinating children under five, including Argentina, Bahrain, China, Cuba and Venezuela. It is unclear whether other countries will follow the US decision to make vaccines available to the youngest kids.

doi: https://doi.org/10.1038/d41586-022-01689-w

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1. Reynolds, C. J. *et al. Science* https://doi.org/10.1126/science.abq1841 (2022).

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