ordered the country's manufacturers to stop exporting COVID-19 vaccines — including to the COVAX initiative, which was established by groups including the World Health Organization (WHO) to distribute vaccines to LMICs. This was a major setback, Taylor says.

COVAX has pledged to vaccinate one-fifth of the population of each LMIC by delivering two billion doses by the end of this year. It has purchased 2.4 billion doses — up from 1.1 billion in March, according to data from the Duke Global Health Innovation Center. But as of 2 July, COVAX had shipped just 95 million doses, up from 65 million in May.

Meanwhile, COVID-19 cases are now surging across Africa. The World Health Organization's Africa office, based in Brazzaville, Republic of Congo, says the number of COVID-19 infections rose by 39% from 13 to 20 June, and by 25% in the week ending 27 June. At least 20 countries, including Zambia, Uganda, South Africa and the Democratic Republic of the Congo, are experiencing a third wave of infections, according to the Africa Centres for Disease Control and Prevention (Africa CDC), based in Addis Ababa. Health facilities are becoming overwhelmed.

Behind schedule

Pharmaceutical company AstraZeneca, based in Cambridge, UK, is one of COVAX's main sources of vaccine doses. In June 2020, the company signed a deal with the Serum Institute of India (SII) in Pune, one of the world's largest vaccine makers, to manufacture one billion doses of the vaccine that the company developed with the University of Oxford, UK, and send them to LMICs. Of these, 400 million doses were to be provided before the end of 2020.

But infections began to resurge in India's second wave in March. The government's order that the SII divert all vaccine supplies to meet domestic demand has hit COVAX particularly hard.

By the end of March this year, COVAX had received just 28 million doses of the AstraZeneca–Oxford vaccine. It was due to receive another 90 million by the end of April; these are now on hold.

Overall, between February and May, African countries received only 18.2 million of the 66 million doses they had expected through COVAX. Out of nearly 1.3 billion people in Africa, just 2% have received one dose of a COVID-19 vaccine. And a little over 1% — 26 million people — are fully vaccinated, according to the WHO's Africa office.

An SII spokesperson told *Nature* that the company expects to resume global exports by the end of 2021. A COVAX spokesperson says that in spite of the delays, the organization is confident that it can meet its goal of supplying two billion doses by the end of the year.

The African Union is, meanwhile, exploring other options. With financial help from the World Bank, it has secured 400 million doses of the single-shot vaccine developed by pharmaceutical company Johnson & Johnson, based in New Brunswick, New Jersey.

"Let me put it bluntly, we are not winning in Africa this battle against the virus so it does not really matter to me whether the vaccines are from COVAX or anywhere. All we need is rapid access to vaccines," said Africa CDC director John Nkengasong at a briefing at the end of last month.

Individual African countries are also negotiating deals with vaccine companies to fill the hole left by the SII. But these countries are often at the back of the queue, Taylor says, because they lack the purchasing power of richer countries.

Vaccines needed now

With India's manufacturers out of the picture for now, the United States is emerging as the world's leading supplier of vaccine doses to LMICs, Taylor explains, and has begun to distribute some of its surplus supplies.

However, according to WHO chief scientist Soumya Swaminathan, this could be too late. "The inequitable distribution of vaccines has allowed the virus to continue spreading," she says. Unvaccinated populations are already at risk, especially from new coronavirus variants, such as Delta (also known as B.1.617.2). "We need countries with substantial supply to donate 250 million doses for September," Swaminathan says.

The WHO is calling on its member states to support a huge effort to vaccinate at least 10% of people in every country by September, along with a "drive to December" to vaccinate at least 30% by the end of the year. This will happen only if countries immediately share doses with COVAX and if manufacturers prioritize COVAX orders, Swaminathan says.

The timing is extremely important, adds Taylor. "Doses shared now will be so much more impactful than doses in six months. We need wealthy countries to send doses immediately."

WILL COVID BECOME A DISEASE OF THE YOUNG?

Rising infections among unvaccinated teenagers and children are highlighting their role in the pandemic.

By Smriti Mallapaty

On 21 June, Israel's Ministry of Health recommended that all individuals aged 12–15 be vaccinated against COVID-19 — making the nation one of the few to approve vaccinations for adolescents. The decision came in response to a trend that many countries with high vaccination rates are experiencing: an ever-increasing proportion of new infections are in younger people (see 'Trending younger').

Israel's swift vaccination campaign — which has reached more than 85% of the adult population — saw case numbers drop to around a dozen a day in early June. But later that month, cases rose to more than 100 a day, many in people under 16, leading the government to open up vaccinations to all those aged 12 and above.

The younger profile of infected people is not surprising, says Ran Balicer, an epidemiologist at Israel's largest health-care provider, Clalit Health Services in Tel Aviv. But it highlights the possibility that subsequent waves of community spread could be driven by younger age groups, especially in the presence of more-transmissible variants.

It's a trend that's not restricted to Israel. In the United States and the United Kingdom, COVID-19 has "become a disease of the unvaccinated, who are predominantly young", says Joshua Goldstein, a demographer at the University of California, Berkeley.

This shift is occurring in many countries that vaccinated older people first, and are now reaching high levels of vaccination in adults. It follows an earlier drop in the age profile of infected people as a result of public-health measures to prevent the spread of COVID-19 among older people who are most at risk of severe disease, such as those in nursing homes, say researchers.

And the shift has brought fresh impetus to studies of transmission and disease in younger age groups. To make better policy decisions, "it's becoming more and more important to understand the burden of disease among children and adolescents", says Karin Magnusson, an epidemiologist at the Norwegian Institute of Public Health in Oslo.

Magnusson has looked at the impact of COVID-19 in children on Norway's health-care system. In a 5 June preprint, she reported that although they didn't need specialist care,

children often needed to see their doctor repeatedly for up to six months after contracting the virus (K. Magnusson *et al*. Preprint at medRxiv https://doi.org/gmtq; 2021).

Balicer is studying viral spread in multigenerational households in Israel. Beyond decisions about vaccinating children, the changing patterns of COVID-19 infection have also fuelled discussions about extending health measures such as mask wearing to adolescents and kids in Israel, he says.

"As the burden of cases shifts towards younger people, arguments for vaccinating adolescents will become slightly more compelling," agrees Nick Bundle, an epidemiologist at the European Centre for Disease Prevention and Control in Stockholm.

However, the overall risk of severe disease in children remains low, and in many countries that have observed the proportion of cases rising in younger age groups, the total number of cases has fallen, he points out.

And countries also need to consider the global context, say researchers. "Are we really better off giving the vaccine to kids in rich countries than to older people [in less wealthy countries] where it might have a much bigger impact on people's lives?" says Jennie Lavine, who studies infectious-disease dynamics at Emory University in Atlanta, Georgia. "It seems hard for me to imagine a really good argument for that."

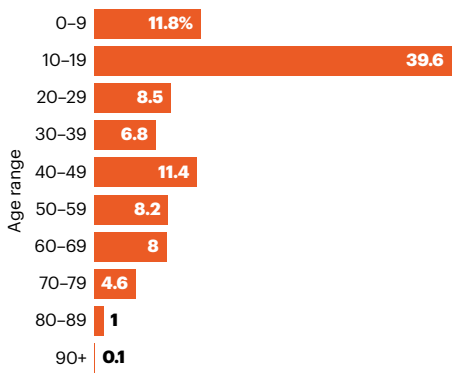
Although the downward shift in the average age of infected people in countries with high COVID-19 vaccination rates is an interesting phenomenon, it might be short-lived, say some researchers.

A few scenarios could shift the balance back, says Henrik Salje, an infectious-disease epidemiologist at the University of Cambridge, UK. Many countries could start to vaccinate younger people — as Israel and the United States are already doing — or new variants and waning immunity among older age groups could make them freshly susceptible, he says.

TRENDING YOUNGER

With the majority of adults in Israel now vaccinated, just over half of the country's new COVID-19 cases in the month up to 5 July were in people aged 19 and under.

Proportion of recent COVID-19 cases in Israel by age group



SOURCE: ISRAEL MINISTRY OF HEALTH

THE CASE IS GROWING FOR MIX-AND-MATCH COVID VACCINES

Many studies suggest mixing vaccines provokes potent immune responses, but questions remain.

By Dyani Lewis

Mixing COVID-19 vaccines is emerging as a good way to get people the protection they need when faced with safety concerns and unpredictable supplies. Most vaccines against SARS-CoV-2 must be given in two doses, but multiple studies now back up the idea that mixing the Oxford–AstraZeneca jab and the Pfizer–BioNTech vaccine triggers an immune response similar to — or even stronger than — two doses of either vaccine.

We can now feel "more comfortable" with mix-and-match, says immunologist Leif Erik Sander at Charité University Hospital in Berlin.

The results are also giving researchers confidence that combining other COVID-19 vaccines, that haven't yet been tested together, might also work. But at least 16 vaccines have been approved for use in one or more countries, and mix-and-match studies so far have been small, so more extensive trials and long-term monitoring for side effects are sorely needed.

Immune-system boost

Mix-and-match studies were prompted, in large part, by concerns over the safety of the vaccine developed by the University of Oxford and pharmaceutical company AstraZeneca in Cambridge, both in the United Kingdom. The jab has been associated with rare instances of a blood-clotting condition known as thrombosis with thrombocytopenia — and in March, some European countries decided to halt its use in some groups of people. This left many people partially vaccinated, unless they switched to a different brand for their second dose.

In May, researchers at the Carlos III Health Institute in Madrid announced results[1] from the CombiVacS trial. The study found a strong immune response in people who were dosed with the vaccine developed by pharmaceutical company Pfizer, based in New York City, and biotechnology firm BioNTech in Mainz, Germany, 8–12 weeks after receiving a dose of the Oxford–AstraZeneca vaccine.

There was no head-to-head comparison with people who received two doses of the same vaccine, but the authors found that in laboratory tests, those who received the combination produced 37 times more SARS-CoV-2 neutralizing antibodies and 4 times more SARS-CoV-2-specific immune cells, called T cells, than did people who had just one dose of the Oxford–AstraZeneca jab.

By the end of June, more results had emerged showing a similar effect.

Sander and his colleagues looked at 340 health-care workers who had received either two doses of the Pfizer–BioNTech vaccine or an initial shot of the Oxford–AstraZeneca vaccine followed by a dose of Pfizer–BioNTech. Both regimens triggered an immune response that included neutralizing antibodies and T cells[2].

A third study, by researchers at Saarland University in Homburg, Germany, found[3] that the mixed regimen was better at eliciting an immune response than were two Oxford–AstraZeneca shots. It was also as good as or better than two shots of Pfizer–BioNTech.

And on 25 June, the team behind a UK trial — known as the Com-COV study — posted a preprint online[4] showing that a good immune response resulted irrespective of the order in which the two vaccines were given.

However, the trials so far have been too small to test how effective combinations of vaccines are at preventing people from developing COVID-19. "As long as you don't have any long-term or any follow-up studies with efficacy calculations, it's hard to say" the level or duration of protection, says Martina Sester, an immunologist who led the Saarland study.

Another limitation is that there's no easy way to compare different combinations between studies. Large-scale efficacy studies are becoming more difficult, says Sester: as infection rates decrease, the number of people in a study must increase to detect any difference in rates of infection and disease. Trials pitting mix-and-match vaccine sequences against a placebo control would be unethical, she adds.

That's one reason why efforts are under way to determine a 'correlate of protection' — a defined level of immune response that confers protection against infection and disease. "This is extremely urgent," says Sander.

A nuanced picture

But a nuanced picture is emerging of the magnitude and type of immune response from mixing vaccines. And these differences could be exploited to provide protection.

DIBYANGSHU SARKAR/AFP/GETTY