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Britain is one of several countries looking to administer booster shots for COVID-19 in the coming months; some have already started.

COVID VACCINE BOOSTERS: THE MOST IMPORTANT QUESTIONS

Concerns over waning immunity and SARS-CoV-2 variants have convinced some countries to deploy extra vaccine doses – but it's not clear to scientists whether most people need them. **By Ewen Callaway**

To boost or not to boost? That is the question facing countries fortunate enough to have vaccinated much of their adult population. In the face of soaring infection numbers caused by the highly contagious Delta variant of SARS-CoV-2, and hints that immunity triggered by COVID-19 vaccines might fade over time, some countries are considering whether to give further doses to those who have been fully vaccinated. Germany and Israel have announced plans for booster-shot

programmes, and a growing list of countries including the United Arab Emirates, China and Russia have already started administering extra doses.

But scientists say that the case for COVID-19 vaccine boosters at this point is weak. They might not be necessary for most people, and could divert much-needed doses away from others. On 4 August, the World Health Organization called for a moratorium on boosters until at least the end of September. “Wasting resources on boosters for those who are

already protected against severe disease does not really make too much sense,” says Laith Jamal Abu-Raddad, an infectious-disease epidemiologist at Weill Cornell Medicine–Qatar in Doha. “Down the line, probably, we would need to think of it. But really, we don’t have strong arguments for it right now.”

The data on whether and when boosters might be needed are trickling in. But it's likely that key gaps will remain for some time. As a result, people might start getting boosters that have no real benefit. Meanwhile, not enough

is known about groups that might really need extra doses, such as older people and those with compromised immune systems. And, as the Delta variant surges in many countries, health authorities might not have the luxury of waiting around for definitive answers. “It’s a difficult call and it will almost certainly have to be made on incomplete evidence,” says Robert Aldridge, an infectious-disease epidemiologist at University College London.

Here, *Nature* looks at what scientists know – and what they wish they knew – about COVID-19 vaccine boosters.

Do boosters actually work?

Vaccination produces an initial surge in the number of immune cells churning out antibodies and other molecules, which then slowly drops. This leaves behind a small pool of long-lasting ‘memory’ B and T cells that patrol the body for future infections by that pathogen.

A booster does several things to these cells, says Ali Ellebedy, a B-cell immunologist at Washington University in St. Louis, Missouri. It causes antibody-making B cells to multiply, elevating the levels of antibodies against the pathogen once more. In time, their numbers will dwindle again, but the pool of memory B cells left behind will be larger than before, leading to a faster, stronger response to subsequent exposures. Boosters also promote a process called affinity maturation, in which ‘engaged’ B cells – those that have been triggered by the vaccine – travel to the lymph nodes. Here, they gain mutations, making the antibodies they produce bind to pathogens more strongly, potentially enhancing their potency.

Numbers of memory B cells and antibody levels will eventually plateau with repeated boosting (or reinfection), but it is unlikely that such levels have been reached in people who have had the recommended regimen of COVID-19 vaccine or a previous infection, says Ellebedy. A booster shot should elicit stronger immune responses, says Rafi Ahmed, an immunologist at Emory University in Atlanta, Georgia. “It will boost.”

The few trials to have tested extra doses support this. Third doses of vaccines developed by Moderna, Pfizer–BioNTech, Oxford–AstraZeneca and Sinovac prompted a spike in levels of infection-blocking ‘neutralizing’ antibodies, when administered several months after the second dose. An ongoing UK trial will test various combinations of boosters, including using a different vaccine from the original inoculations. Preliminary studies of these ‘mix and match’ strategies suggest that they could lead to more robust immune responses, characterized by high levels of both antibodies and T cells, which kill infected cells and support other antiviral responses^{1–3}.

These trials also suggest that common

vaccine-related side effects, such as headache and fever, aren’t very different from those seen with earlier immunizations. “I would take a third dose at some point,” Ahmed says. “I don’t see a downside.”

Is immunity from vaccines waning?

Scientists typically look at antibody levels, or titres, as a proxy for how well a vaccine has worked. These usually spike along with the surge in short-lived B cells and then fall as the cells dwindle. Memory B cells and bone-marrow plasma cells continue to churn out antibodies, but at reduced levels, for decades. That’s expected. “There isn’t a vaccine where you don’t see a drop over time in antibody titres and T-cell titres,” says Ahmed. “There is always a drop.”

Early indications suggest that antibody levels triggered by most COVID-19 vaccines are fall-



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ing, too⁴. What scientists don’t know is whether these drops reflect a decline in protection against the virus. Teams around the world are racing to determine what level of neutralizing antibodies or another immune marker is most closely associated with a vaccine’s effectiveness. They’re seeking what’s known as a correlate of protection.

“What that magic number is, is something that we have a hint of – but not a firm handle on,” says Kanta Subbarao, a virologist at the Peter Doherty Institute for Infection and Immunity in Melbourne, Australia. Knowing this threshold would allow researchers to determine more precisely whether and when a booster becomes necessary – such as in response to waning immunity or to the emergence of new variants that evade antibody recognition. “Without having that properly defined correlate, it’s hard to say if we really need a booster,” says Ellebedy.

Are vaccinations given months ago still preventing infections?

In the absence of a reliable correlate of protection, researchers are looking for signs of waning immunity in real-world data from countries that have advanced vaccination programmes. Are people who were vaccinated early on getting infected at higher rates than those who were vaccinated more recently? Drawing clear

conclusions from such data is fraught, says Dvir Aran, a biomedical data scientist at Technion – Israel Institute of Technology in Haifa.

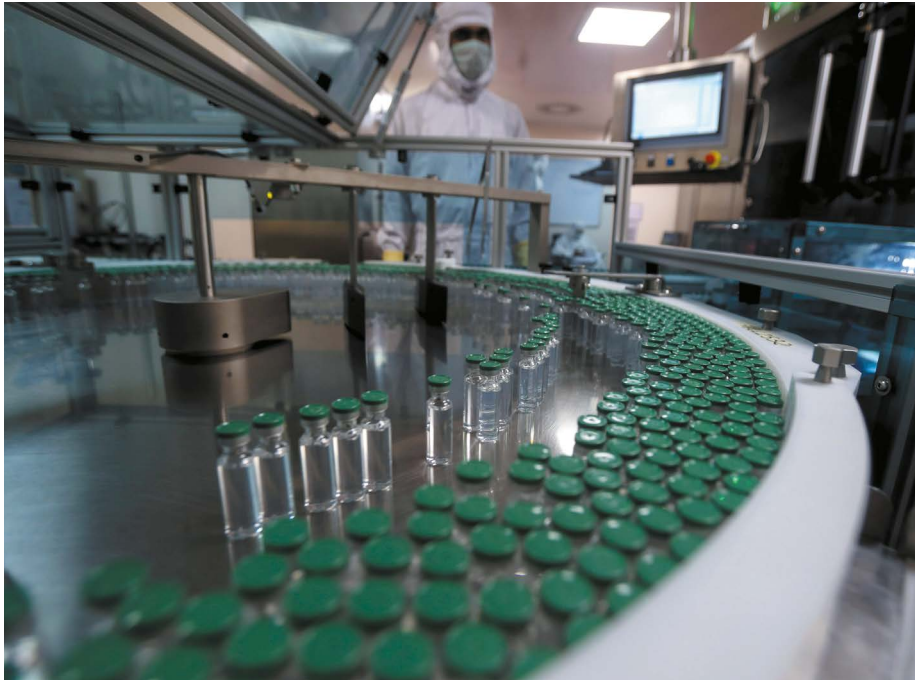
Last month, the Ministry of Health in Israel, a country that has one of the world’s highest vaccination rates, released raw data on vaccinations and infections from December 2020 to July 2021. The ministry estimated that vaccine protection against both infection and disease had dropped from above 90% in the early months of its programme to around 40% by late June – a decline that could be due to the effects of the Delta variant.

To look more closely for evidence of waning protection, scientists at Kahn Sagol MacCabi in Tel Aviv – the research arm of Israeli health-maintenance organization Maccabi Healthcare Services – analysed health records from more than 1.3 million people who were vaccinated between January and April 2021. Those vaccinated in January and February were 53% more likely to test positive for SARS-CoV-2 during those four months, compared with people vaccinated in March and April. The differences were even starker among the earliest and latest vaccinated⁵.

But reduced protection isn’t the only explanation for this observation, says Aran. Data were stratified by age groups, and younger individuals who were vaccinated early on tended to be health-care workers, who are at a higher risk of infection than the younger people vaccinated later. Early-vaccinated individuals also tended to be wealthier than people who got vaccinated later in Israel, and might have taken COVID-19 tests at a higher rate because of worries over the virus or an eagerness to travel internationally. That could introduce biases into the data, says Aran.

Another way to weigh the evidence in support of boosters is efficacy trials – the double-blinded, placebo-controlled, randomized studies used to earn vaccine authorization by health authorities. On 28 July, researchers at Pfizer–BioNTech, who have pushed strongly for third doses, published data on the preprint server medRxiv showing that the vaccine’s efficacy against symptomatic disease had slipped from 96% to 84% after 6 months⁶. Before that, an April press release from Moderna put its vaccine’s efficacy at “greater than 90%” after half a year, compared to its original efficacy figure of 94%.

These trials are meant to minimize confounding variables that dog real-world studies. But once vaccines became publicly available, Pfizer and other vaccine-makers unblinded the studies, allowing participants to learn whether they had received a vaccine or a placebo. “All the participants heard the news about the 95% protection and those that received the vaccine would clearly feel more safe and will take more risks,” says Aran, who thinks this behaviour change – and not waning protection – could explain the apparent drop in the efficacy of the



A machine fills vials with COVID-19 vaccine at the Serum Institute of India in Pune.

Pfizer–BioNTech vaccine. Representatives from Pfizer had no comment on this hypothesis.

What about protection from serious illness with COVID-19?

It is clear from the trial data that protection against severe disease remains high. Pfizer–BioNTech and Moderna reported percentage efficacy estimates in the high 90s against severe COVID-19, after 6 months. Real-world data from Israel, the United Kingdom and elsewhere suggest that vaccines are hugely effective at keeping people out of hospital – even when the Delta variant is the cause.

COVID-19 vaccines were largely developed with this goal in mind, researchers point out. “It should be enough,” says Ellebedy. But what’s unclear is whether relatively mild infections among vaccinated individuals being observed now are a harbinger of further loss of protection, says Aldridge. “Is that an early warning sign? That’s what we don’t know.”

Natalie Dean, a biostatistician at Emory University, says that discussions around boosters need to look at their incremental value to improving protection against various outcomes, from stopping transmission to preventing symptomatic infections and severe disease.

In this context, many scientists see offering extra doses in the coming months as a poor use of resources, on both global and national levels. “A small dent in the efficacy against infection does not justify, in my view, someone like me getting a booster when someone else has not even had one dose,” says Abu-Raddad. Dean agrees: “We just don’t have clear evidence of enough of a loss of efficacy to change our focus or distract from the main goal, which is trying to get as many people first doses” as possible.

The lack of evidence around boosters also means that scientists do not have a clear picture of who would benefit most. A large proportion of organ-transplant recipients on immunosuppressive drugs do not generate high levels of antibodies after two doses of a COVID-19 vaccine, for instance. One study⁷ found that only about half of them produced detectable levels. There is evidence that a third dose can elevate those titres, but for many people, they remain below levels seen in other vaccinated groups⁷. Unfortunately, without a correlate of protec-

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tion, it’s not clear what level is adequate for transplant recipients or older people, whose immune systems tend to be less robust than those of younger individuals, or how to achieve such a level, says Ellebedy. If these groups don’t mount protective immune responses after two doses, he says, “that’s when booster immunization is not going to be a luxury”.

Aldridge’s team is tracking the vaccine responses of thousands of people in the United Kingdom, while collecting information about

immunosuppressive drug regimens, blood cancers and other health factors that could compromise immunity. He hopes his team’s study can inform the deployment of boosters.

What else could change the calculation on boosters?

The surge in cases caused by the Delta variant have caused some countries to look more closely at boosters, says Subbarao. “I think everybody is really quite sobered by what’s happening with the Delta variant.”

Countries that have relied heavily on inactivated-virus vaccines, which seem to be less effective at preventing symptomatic infections than viral vector and messenger RNA vaccines, have been among the first to deploy boosters. The United Arab Emirates is giving people who received Sinopharm’s inactivated-virus vaccine a booster with the Pfizer–BioNTech vaccine, and China plans to use domestically produced mRNA and protein-based vaccines as boosters for its inactivated-virus vaccine.

There is anecdotal evidence of large outbreaks in some countries that deployed both inactivated-virus vaccines and other vaccine types, such as the Seychelles and Chile. But Subbarao says it’s not yet clear whether such breakthrough infections are more likely in people who received the inactivated-virus vaccines than in those given other vaccines, or whether they lead to more severe disease. For countries that have decided to offer third doses to people who received inactivated-virus vaccines, she adds, “I haven’t seen the data that’s prompting those decisions.”

Despite the lack of evidence in favour of offering boosters now, Aran expects policymakers to err on the side of caution and begin offering boosters to at-risk groups in the coming weeks. “The risk is low, the advantage is high,” he says. After initially spurning the idea of third doses for most people, the US government is now considering them, according to news reports. And on 29 July, Israel announced plans to give people aged over 60 a third dose of the Pfizer–BioNTech vaccine. The United Kingdom has drawn up tentative plans to offer vaccines to those over 50, as well as other high-risk groups, from September.

“It’s a gamble,” says Aran. “Is it based on enough evidence? I think not.”

Ewen Callaway reports for *Nature* from Somerset, UK.

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