



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Immunity

Are booster shots coming?

Vaccine top-ups might boost immune systems and block new coronavirus variants, but there are many unknowns, reports **Graham Lawton**

AS THE UK and some other wealthy countries edge towards a fully vaccinated adult population, a new question is being asked: will people need booster vaccines against covid-19?

The answer depends on three unknowns: how quickly immunity fades, whether current vaccines protect against existing and future coronavirus variants, and whether booster shots actually work. There are also issues of vaccine nationalism and equity to consider (see “Boost or bust?”, right).

60m

Doses of vaccine ordered by the UK for possible booster campaign

Booster vaccines are routinely used for some infectious diseases, either to top up immunity or to update it for new virus variants. Tetanus boosters, for example, are recommended every 10 years to renew waning immunity, and annual flu shots are designed to protect against that season’s variants.

Israel is ahead of the curve. The country has already vaccinated more than 80 per cent of over-16s and announced last month that it would run a booster campaign in October. Prime Minister Benjamin Netanyahu said in a televised address that Israel had secured 16 million extra doses of the Pfizer/BioNTech and Moderna vaccines to immunise its under-16s and boost everybody else.

Other countries whose immunisation programmes are progressing well are more circumspect. The UK is on course to have offered a first vaccine dose to its adult population by the end of July, and is now weighing up an autumn booster campaign. “We haven’t made any decisions on

this yet,” says Anthony Harnden at the University of Oxford, deputy chair of the Joint Committee on Vaccination and Immunisation (JCVI), which advises UK health departments.

The UK has ordered a further 60 million doses of the Pfizer/BioNTech vaccine in preparation for a possible booster campaign but “we can’t make the decision until we’ve seen all the evidence”, says Harnden. It is possible that the JCVI will recommend a booster for the vulnerable groups that were first in line for a vaccine in the UK, he says. The JCVI will announce its decision as soon as it is made.

The US has also yet to make a call. A statement from the Centers for Disease Control and Prevention, which oversees the US vaccination programme, says: “The need for and timing for COVID-19 booster doses have not been established. No additional doses are recommended at this time.”

The first piece of evidence needed is how quickly immunity fades after a vaccine. “I don’t think we know, because we’ve not really got the data on what happens nine months after a [covid-19] vaccine,” says virologist Deenan Pillay at University College London (UCL).

That information should be forthcoming soon, says Alex Richter, an immunologist at the University of Birmingham, UK. Various research projects on the duration of immunity in healthcare workers are due to report results over the next few weeks, she says. For example, the SIREN study, which is following more than 44,000 staff at 135 hospitals across the UK, is looking at the duration of immunity after having a Pfizer/BioNTech vaccine. The first vaccines were given in December and a six-month assessment is due



People receive a covid-19 vaccine in Cologne, Germany

It might be best to give people a booster of a different vaccine



out in June, says Richter. “If data at that point is showing significant waning [of antibodies], then that will influence policy,” she says. “Most healthcare workers are really fit and healthy, so if they are not hanging onto their antibodies then it’s highly likely we’re going to need to be vaccinating in the autumn with a booster.”

Another consideration is whether the current vaccines protect against viral variants. If they don’t, then a booster campaign may be needed using shots tailored to protect against specific variants.

According to Harnden, lab studies show that vaccine-induced antibodies remain effective against the B.1.1.7 variant first seen in the UK and the P.1 variant from Brazil, but there are concerns about B.1.351, first identified in South Africa. “We do know that the vaccines are not quite as effective against the South African variant



in a group of 417 fully vaccinated people, due to what seems to be a new variant (*NEJM*, doi.org/gjsbr9). “That is the level of data we’ve currently got, which is clearly inadequate to determine a major policy,” says Pillay.

Despite the uncertainties, Israel has acted already on this too. It has negotiated an option to buy doses of Moderna’s variant-specific booster vaccines, assuming they are approved. Moderna has two such booster vaccines in clinical trials. One is designed to protect against B.1.351, the other is a combination of this and the firm’s original vaccine. Moderna is also testing booster shots of its initial vaccine and recently announced positive results from two of its trials. Pfizer is also testing booster shots of its first coronavirus vaccine and a variant-specific one.

Another factor to weigh up in relation to variants is an immunological phenomenon called original antigenic sin. This is where an updated vaccine reactivates an earlier immune memory rather than creating a new one. It has been seen with other viral infections including flu, says Anthony Costello at UCL, but whether it will be a problem with the virus that causes covid-19, SARS-CoV-2, remains to be seen. Studies to establish this are urgently needed, says John Moore at Weill Cornell Medicine in New York, because original antigenic sin could render a variant-specific booster campaign pointless.

Booster shots could fail for other reasons. A third dose of viral-vector vaccines like the Oxford/AstraZeneca one could just boost the immune response to the harmless virus used as a vehicle to deliver the active ingredient. “One of the concerns is that we may not be able to augment the antibodies against the [SARS-CoV-2] spike

in terms of preventing disease, although they do seem to be pretty good at preventing severe disease, hospitalisations and deaths,” says Harnden.

If any variant proves capable of escaping the immunity conferred by current vaccines, then a variant-busting booster campaign is on the cards, he says.

Inadequate data

Right now, we don’t know if vaccine escape is a genuine danger. “This is a critical question,” says Pillay. “We really need a coherent assessment of the nature of breakthrough infections – in other words, infections that are happening in those who are fully immunised. Is that driven by variants, or is it to do with declining antibody and immunity from the first two doses [of vaccine]?”

A recent study documented two cases of breakthrough infections

Boost or bust?

Rich countries like Israel and the UK are already buying up tens of millions of extra vaccine doses for potential immunity booster campaigns (see main story), but the strategy could end up making the covid-19 pandemic worse.

As the World Health Organization has repeatedly said, the pandemic can’t end until the whole world is vaccinated.

Unvaccinated populations could act as a source of yet more new variants, and vaccine-resistant variants could push the vaccinated part of the world back to square one.

Rich countries have already bought up far more than their fair share of vaccines, and ordering booster doses

just exacerbates that problem.

“When we talk about boosting and revaccination, it’s also important to bear in mind globally what is needed in terms of vaccination access where the progress has been much, much slower,” says Tolullah Oni at the University of Cambridge’s MRC Epidemiology Unit.

“If there’s anything we can see from the tragedy that is playing out in India at the moment it is that, yes, we have to maximally suppress [the virus] locally but also do everything in our power to support vaccination access globally,” she says. “That is a really critical point when we’re talking about how to get out of this pandemic.”

protein,” says Teresa Lambe at the University of Oxford, who worked on the vaccine’s development. She is doing experiments to determine the immune response to a third dose.

“The idea that you can continually boost immunity is both logistically and immunologically difficult”

For this reason and others, it may be preferable to boost people’s immunity with a different vaccine from the one they got the first two times.

There is some evidence that using different vaccines for the first and second dose – a method called heterologous prime-boost vaccination – produces a stronger immune response than using the same vaccine for both.

Russia’s Sputnik V, for example, is a heterologous prime-boost vaccine and the latest real-world

figures from the country show that it is 97.6 per cent effective, which would make it the most effective covid-19 vaccine in the world.

Ongoing experiments in the UK are examining the effects of mixing and matching first and second vaccine doses, and the results could inform decisions on a booster campaign, says Harnden.

All of these uncertainties emphasise an important point that has been largely forgotten amid vaccine euphoria, says Costello. “The idea that you can continually boost [immunity] is both logistically difficult and may be immunologically difficult.” We may face breakthrough infections that can’t be vaccinated against and so we will still need interventions such as masks, ventilation and social distancing. “Vaccination has been great, but it’s not going to solve the problem in its entirety,” says Costello. ■