population — around 400 million people, says Gagandeep Kang, a vaccinologist at the Christian Medical College in Vellore, India. But that is a huge number of vaccine doses that need to be made and shared out, researchers say.

The government has assembled a task force to determine how best to distribute the vaccines. It is headed by Vinod Paul, a member of the National Institution for Transforming India, a government think tank, and has representatives from state and central government agencies. The government is also working with vaccine makers to speed up clinical trials and regulatory approvals.

World's supplier

The world's largest vaccine maker, the Serum Institute of India in Pune, has an agreement to manufacture one billion doses of a coronavirus vaccine being developed by scientists at the University of Oxford, UK, and UK pharmaceutical company AstraZeneca if it is approved for use. The vaccine is currently undergoing phase III clinical trials in Brazil, the United Kingdom and the United States to test its effectiveness.

If the vaccine works, the Serum Institute and the Indian government have committed to reserve half the company's stock of it for India, and to supply half to low-income nations through Gavi, the Vaccine Alliance, which funds immunizations for low-income nations, says Adar Poonawalla, Serum's chief executive.

So far, the company has invested 11 billion rupees (US$200 million) to manufacture the vaccine, Poonawalla says, and it has produced about 2 million doses for use in regulatory clearances and testing, even before the trials have ended. Two factories that were producing other vaccines have been redirected to this effect, and the company can make 60 million to 70 million doses a month at full capacity, says Poonawalla.

The decision to stockpile the Oxford vaccine "has been solely taken to have a jump-start on manufacturing, to have enough doses available if the clinical trials prove successful", says Poonawalla. If the vaccine doesn't work, Serum will shift its attention to other candidates, he adds. The company is also developing and testing four other COVID-19 vaccines — two developed through in-house initiatives and two being developed in collaboration with biotechnology companies Novovax in Gaithersburg, Maryland, and Codagenix in Farmingdale, New York.

Drug firm Biologicals E, headquartered in Hyderabad, India, has also entered into a partnership to manufacture a vaccine candidate. This one is being developed by pharmaceutical company Janssen, a subsidiary of Johnson & Johnson based in Beerse, Belgium, and is currently going through early-stage safety trials. Biologicals E might also manufacture a candidate being developed by Baylor College of Medicine in Houston, Texas, the company says. And Indian Immunologicals, also in Hyderabad, is working with Australia's Griffith University in Brisbane to test and manufacture the university's vaccine. Two other Indian companies — Hyderabad-based Bharat Biotech and Zydus Cadila in Ahmedabad — are working on vaccines that are in phase I and II safety trials.

Scientists have applauded the Indian government for allowing the country's pharmaceutical companies to export some of their vaccine stocks to other nations. The decision to share supplies contrasts with the stance of countries such as the United States and the United Kingdom, which have each pre-ordered hundreds of millions of doses of coronavirus vaccines under development, enough to supply their respective populations many times over.

"The vaccine has to be kept cold, people have to be trained."

But even with manufacturers' commitment to supply a portion of their vaccines locally, scientists say that making the required 400 million doses for people who are most at risk of contracting severe COVID-19 will still take time. And by that point, the brunt of the epidemic, which is currently in major cities, will probably have shifted to rural areas, where health services are weaker, says Deo.

This means that the biggest hurdle will be getting vaccines to people across India. "It is a huge challenge," says Randeep Guleria, director of the All India Institute of Medical Sciences in New Delhi and a member of the government's vaccine task force. "India is a huge country, we have a very large population and we have remote areas, like the Northeast and Ladakh" in the Himalayas.

The immunization programme will probably take years, says Kang. One of the country's largest vaccination campaigns so far — delivery of the measles–rubella vaccine to 405 million children, starting in 2017 — has taken 3 years.

Guleria says that innovative approaches will be needed to distribute vaccines in rural and remote regions. He says national election campaigns could offer lessons. In 2019, 11 million poll workers journeyed across India to set up polling stations, so that people didn't need to travel more than 2 kilometres to vote. The network reached 900 million voters, including those in the most remote areas, in just over 6 weeks. A similar network of health officials to give vaccines could cover much of the country, says Guleria.

But it's not as simple as getting the vaccine to people, says Kang. "The vaccine has to be kept cold, people have to be trained." It will also be expensive to buy syringes and needles, to train people to vaccinate, and to purchase the vaccine.

The Serum Institute has priced the Oxford vaccine at 225 rupees (US$3) a dose. That means the cost of vaccinating 400 million people will be at least $1.2 billion. Typically, the government buys vaccines for less than the price of bottled water — 60 rupees. It's unlikely that the Indian government will bear the entire cost of immunizing its people, Deo notes. It will probably pay for vaccinations for the poorest citizens, and ask everyone else to buy their own vaccines, he says.

COVID-19 REINFECTION: THREE QUESTIONS SCIENTISTS ARE ASKING

Repeat infections raise questions about long-term immunity and the prospects for a vaccine.

By Heidi Ledford

When news broke last month that a man living in Hong Kong had been infected with the coronavirus again, months after recovering from a previous bout of COVID-19, immunologist Akiko Iwasaki had an unusual reaction. "I was really kind of happy," she says. "It's a nice textbook example of how the immune response should work."

For Iwasaki, who has been studying immune responses to the SARS-CoV-2 virus at Yale University in New Haven, Connecticut, the case was encouraging because the second infection did not cause symptoms. This, she says, suggested that the man's immune system might have remembered its previous encounter with the virus and fought off the repeat infection before it could do much damage.

But less than a week later, her mood shifted. Public-health workers in Nevada reported another reinfection — this time with more severe symptoms. Was it possible that the

immune system had not only failed to protect against the virus, but had also made things worse? "The Nevada case did not make me happy," Iwasaki says.

Duelling anecdotes are common in the see-saw world of the COVID-19 pandemic, and Iwasaki knows that she cannot draw firm conclusions about long-term immune responses to SARS-CoV-2 from just a few cases. But in the coming weeks and months, Iwasaki and others expect to see more reports of reinfection, and, in time, a more detailed picture could emerge.

As data trickle in, *Nature* runs through the key questions that researchers are trying to answer about reinfection.

How common is reinfection?

Reports of possible reinfections have circulated for months, but the recent findings are the first to seemingly rule out the possibility that a second infection was merely a continuation of a first.

To establish that in each person, the two infections were separate events, both the Hong Kong and Nevada teams sequenced the viral genomes from the first and second infections. Both found enough differences to convince them that separate variants of the virus were at work.

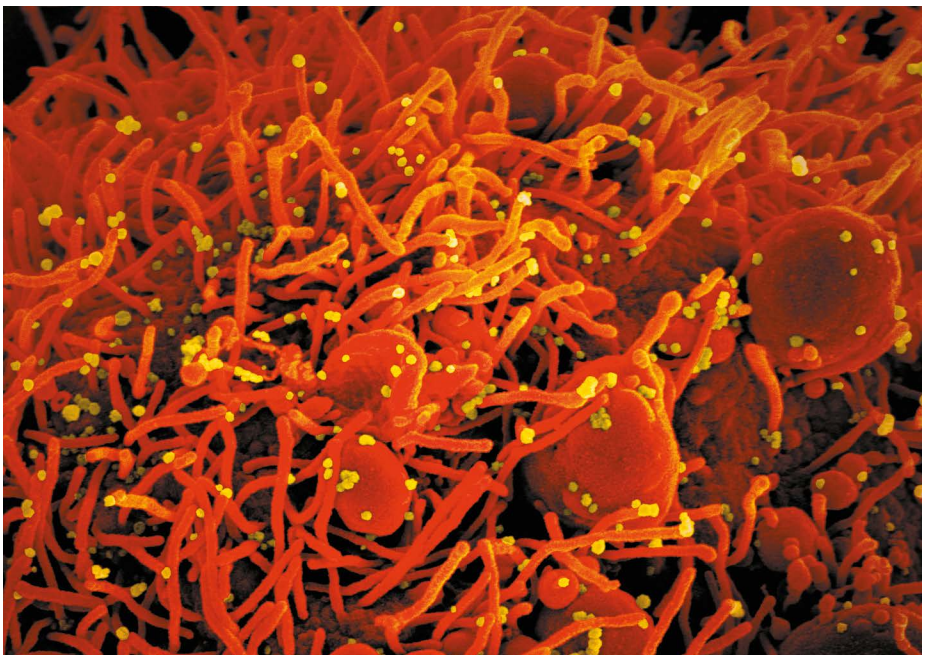
But, with only two examples, it is still unclear how frequently reinfections occur. And with 26 million known coronavirus infections worldwide so far, a few reinfections might not be cause to worry – yet, says virologist Thomas Geisbert at the University of Texas Medical Branch in Galveston. We need a lot more information on how prevalent this is, he says.

That information might be on the horizon: timing and resources are converging to make it possible to identify more instances of reinfection. Some regions are experiencing fresh outbreaks, providing an opportunity for people to be re-exposed to the virus. Testing has also become faster and more available.

And scientists in public-health laboratories are beginning to find their feet again, says Mark Pandori, director of the Nevada State Public Health Laboratory in Reno, and an investigator on the Nevada team. During the first wave of the pandemic, it was hard to imagine tracking reinfections when testing labs were overwhelmed. Since then, Pandori says that his lab has had time to breathe – and to set up sequencing facilities that can rapidly sequence large numbers of viral genomes from positive SARS-CoV-2 tests.

How severe are reinfections?

Unlike Iwasaki, virologist Jonathan Stoye at the Francis Crick Institute in London took no comfort from the lack of symptoms in the Hong Kong man's second infection. Drawing conclusions from a single case is hard, he says. "I'm not certain that really means anything at all." Stoye notes that the severity of COVID-19 varies enormously from person to person, and might also vary from infection to infection in the same person. Variables such as the initial dose of virus, possible differences between variants of SARS-CoV-2 and changes in a person's overall health could all affect the severity of a reinfection.



NIAID/NIH/SPL

Electron microscope image of SARS-CoV-2 coronavirus particles (yellow) on a cell (red).

Sorting out whether 'immunological memory' affects symptoms during a second infection is crucial, particularly for vaccine development. If symptoms are generally reduced the second time, that suggests the immune system is responding as it should.

"Reinfection shouldn't scare people. It shouldn't imply that a vaccine is not going to be developed."

But if symptoms are consistently worse during a second bout of COVID-19, the immune system might be making things worse, says immunologist Gabrielle Belz at the University of Queensland and the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia. For example, some cases of severe COVID-19 are worsened by rogue immune responses that damage healthy tissue. People who have experienced this during a first infection might have immune cells that are primed to respond in a disproportionate way again the second time, says Belz.

Another possibility is that antibodies produced in response to SARS-CoV-2 help, rather than fight, the virus during a second infection. This phenomenon, called antibody-dependent enhancement, is rare – but researchers found worrying signs of it while trying to develop vaccines against the coronaviruses responsible for severe acute respiratory syndrome and Middle East respiratory syndrome.

What does this mean for vaccines?

Historically, the vaccines that have been easiest to make are against diseases in which primary infection leads to lasting immunity, says Richard Malley, a paediatric infectious-disease specialist at Boston Children's Hospital in Massachusetts. Examples include measles and rubella.

But the capacity for reinfection does not mean that a vaccine against SARS-CoV-2 can't be effective, he adds. Some vaccines, for example, require 'booster' shots to maintain protection. "It shouldn't scare people," Malley says. "It shouldn't imply that a vaccine is not going to be developed or that natural immunity to this virus can't occur."

As public-health officials grapple with the dizzying logistics of vaccinating the world's population, a booster shot would hardly be welcome news, but it would not place long-term immunity against SARS-CoV-2 completely out of reach, says Malley. However, he is concerned about the possibility that vaccines will only reduce symptoms during a second infection, rather than prevent that infection altogether. This could effectively turn vaccinated people into asymptomatic carriers, putting vulnerable populations at risk.

For this reason, Malley is keen to see data on how much virus people 'shed' when reinfected with SARS-CoV-2. "They could still serve as an important reservoir of a future spread," he says. "We need to understand that better following natural infection and vaccination if we want to get out of this mess."