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.

Covid-19

How can we end the pandemic?

Two years since it emerged, the coronavirus isn't going anywhere. We can "live with covid", but how we choose to do that will have huge consequences, reports **Michael Marshall**

AFTER two years of mass deaths, long covid, social distancing, cancelled weddings and isolated funerals, increasing numbers of political leaders are saying it is time to "live with covid". In England, legal requirements for self-isolation and contact tracing could end in March, while measures such as working from home where possible and covid passports may be removed within weeks. But just how close to the end of the pandemic are we? And what will the end really look like?

In a sense, the pandemic won't end until the World Health Organization (WHO) declares it over, just as it first declared the coronavirus outbreak a pandemic on 11 March 2020. That won't mean that the SARS-CoV-2 virus has been eliminated, however. Instead, the end will come when new infections occur at a fairly constant rate, as opposed to the big, unpredictable waves we have experienced so far.

"The pandemic's end will come when new infections occur at a constant rate rather than in big waves"

This is the point at which covid-19 becomes "endemic". The virus will still spread from person to person, but on average each infected person will infect only one other. This will mean fewer people being hospitalised, dying or developing long covid.

It is important to understand that there are different kinds of endemicity (see "What covid-19 becoming 'endemic' really means", page 14). "Whether it becomes endemic at a low level or a high level really matters," says Christina Pagel at University College London.

A commonly cited benchmark is that covid-19 might become about as widespread and severe as influenza, which causes annual mini-epidemics in many countries. But this example illustrates the ambiguity of the phrase "living with covid". While it is true that countries around the world "live with flu", that doesn't mean their governments do nothing. The UK and many other countries have an annual flu surveillance programme, and new vaccines are developed and given every year.

"There are all kinds of things we do to get flu deaths down, and we've massively got them down in the last 20 years," says Pagel.

Nonetheless, were covid-19 to become similar to flu, that "would be a disaster for the UK", says Pagel, because flu already strains the country's national health services in winter. If covid-19 ends up equally serious, it would still represent a significant and permanent increase in case load every winter.

The vaccination race

Bringing the number of covid-19 deaths down depends on four factors: global vaccination rates, the evolution of the virus, medical advances in covid-19 treatments and preventative measures like improved ventilation and social distancing.

So far, the race between vaccinations and virus evolution is a dead heat. As of 17 January, 9.68 billion doses of covid-19 vaccines had been administered in a little over a year. This is a huge number, and has substantially brought down the fatality rate in high-income countries, but the United Nations estimates that there were 7.88 billion people on Earth in 2021. That means the vaccine doses so far represent slightly more than one per person.

Mask wearing at a theatre in Antwerp, Belgium, last month

JONAS ROOSENS/BELGA/AFP VIA GETTY IMAGES

In practice, there is enormous inequity. Many children worldwide haven't been vaccinated and in low-income countries only 9.5 per cent of people have had even one dose.

"If SARS-CoV-2 behaves like other coronaviruses, we need to forget about herd immunity"

For the original virus, and older variants like alpha and delta, two doses of vaccine gave sufficient protection. The implication was that almost 16 billion doses were needed to vaccinate everyone. Achieving that by the end of 2022 would be a challenge, but not an insurmountable one.

However, the omicron variant is a game changer: two doses of vaccine aren't enough to give decent protection against infection or severe disease. "As things currently stand, you definitely do need three doses," says Lance Turtle at the University of Liverpool, UK.

That means almost 24 billion doses of vaccine need to be delivered to give everyone on the planet three doses. To achieve this by the end of 2022, vaccines must be delivered this year at almost twice the average rate they were delivered in 2021.

That looks difficult, but the rate of vaccine delivery has accelerated over the past year. Currently, nearly 33 million doses are given every day. If that was sustained throughout 2022, an additional 12 billion doses would be delivered, for a total of 21.7 billion. In theory, it wouldn't take a huge increase in the daily rate to get to 24 billion by the end of the year.

But in practice, delivering vaccines to lots of people in low-income countries is hard.

"The technological solution is only part of it – you've got to have all the steps from invention to manufacture to financing to the health systems to deliver it," says Anne Johnson, president of the Academy of Medical Sciences in London. People in low-income countries often live in crowded, informal settlements where record-keeping is poor, or far from major cities in hard-to-access remote areas. "It's a huge organisational challenge," she says.

This has been compounded by high-income countries hoarding vaccine doses. Lower-income countries have struggled to obtain vaccines, and more doses have been given as boosters in high-income countries than have been given in total in all low-income countries.

A collaboration called COVAX has tried to send vaccines to low-income countries, but for much of 2021 it struggled to do this. So far, it has shipped 1 billion doses to 144 countries. It may get a boost from a vaccine called Corbevax, developed by Texas Children's Hospital and licensed to Indian pharmaceutical firm Biological E. Corbevax is designed to be more easily made and stored, and is given patent-free to manufacturers.

Even three doses per person may not be enough to bring the pandemic under control. With omicron, the protection against symptomatic infection wanes within weeks of a third dose. Israel is already giving people over the age of 60 a fourth dose and other countries may follow suit. Vaccinating everyone on the planet every six months would be a vast undertaking, however.

Some form of regular vaccination is likely to be needed to keep the covid-19 death rate down. "For respiratory infections, we don't get lifelong immunity that prevents us getting infected," says Rustom Antia of Emory University in Atlanta, Georgia. If SARS-CoV-2 behaves like other human coronaviruses, "we need to forget about herd immunity".

"I think it will be with us forever in the population, most likely, and I think we'll need annual vaccines," says Turtle.

That will include young children, says Pagel: "I imagine eventually it'll be part of your childhood immunisation programme."

IRFAN KHAN/LOS ANGELES TIMES VIA GETTY IMAGES

A 7-year-old after her vaccination in California

0.75
million people tested positive for covid-19 in the UK between 10 and 16 January

3 to 6
Number of years between reinfections of an endemic coronavirus, OC43

45,000
Approximate number of daily OC43 infections in the UK

Immunising children

Vaccinating children will be important, because we are unlikely to bring infection rates down if a substantial part of the population – especially one that mixes together in schools on a daily basis – is unprotected.

After initially focusing solely on vaccinating adults, the UK government announced in September 2021 that it would offer vaccines to 12-to-15-year-olds. But it hasn't widely offered vaccines to younger children.

This is in contrast to other countries including the US, which has been vaccinating ›

5-to-11-year-olds after the Food and Drug Administration authorised the use of the Pfizer/BioNTech vaccine for that age group in October 2021. Ireland also recently announced it would offer that vaccine to 5-to-11-year-olds.

But in the UK, while the Pfizer/BioNTech vaccine for 5-to-11-year-olds has been approved, the Joint Committee on Vaccination and Immunisation has only recommended that the vaccine be offered to children in this age group if they "are in a clinical risk group or who are a household contact of someone (of any age) who is immunosuppressed".

An evolving virus

The roll-out of vaccines to children in other countries follows extensive and ongoing clinical trials. In a November statement, the WHO said the authorised vaccines were "safe and effective" for children. The WHO also noted that children who can't attend school, either because it is closed or because they are ill with covid-19, are missing out on education, and in some cases may struggle to go back.

Meanwhile, the vaccines are being tested, in smaller doses, in even younger children. Pfizer and BioNTech have an ongoing trial in children aged 6 months to 5 years. However, in December, the firms announced that they were adding a third dose to the regimen, after a second dose didn't provide enough protection. As a consequence, no results are available yet.

Similarly, Moderna says it expects data on its vaccine in 2-to-5-year-olds by March. If the results are satisfactory, the companies will seek approvals to deliver the vaccines.

Even as governments run their vaccination programmes, the

Analysis

What covid-19 becoming 'endemic' really means

Clare Wilson

There have been many mentions of covid-19 becoming "endemic" in recent weeks. But the term has no single agreed definition and the virus becoming endemic wouldn't necessarily mean that it is safe to stop measures such as mask wearing.

On 11 January, Marco Cavaleri at the European Medicines Agency told a press briefing that "what we're seeing is that we are moving towards the virus being more endemic". The previous day, Spain's prime minister, Pedro Sánchez, said European officials should reclassify covid-19 as an endemic illness due to falling death rates. UK education minister Nadhim Zahawi recently said the country is "witnessing the transition of the virus from pandemic to endemic".

But at a press conference on 11 January, Catherine Smallwood at the World Health Organization Europe said "we're still a way off" endemicity. "Endemicity assumes that there's stable circulation of the virus, at predictable levels with predictable waves of transmission… that doesn't rely on external forces being placed in order to maintain that stability."

Among infectious disease specialists, endemic may be used in contrast to the term epidemic. An epidemic of a disease means there is a surge in cases, perhaps because a pathogen has crossed over to a new species, as in the case of covid-19. A pandemic is an epidemic that has spread over several continents.

"We're not actually anywhere near endemic. A lot of it is wishful thinking"

If a disease is endemic, on the other hand, the number of cases is broadly stable, although there can be seasonal fluctuations. Measles is said to be endemic in many countries. Malaria is endemic in some regions, although cases may rise in the rainy season.

Endemic diseases can still cause serious illness and require stringent measures. Malaria kills hundreds of thousands of people every year. Smallpox, too, was endemic before we eradicated it, and it killed nearly a third of those who caught it.

Given that many countries are experiencing a massive surge of cases caused by the omicron variant, it seems hard to argue that covid-19 is currently endemic. "I don't think we're actually anywhere near endemic," says Lawrence Young at the University of Warwick, UK. "I think a lot of it is wishful thinking."

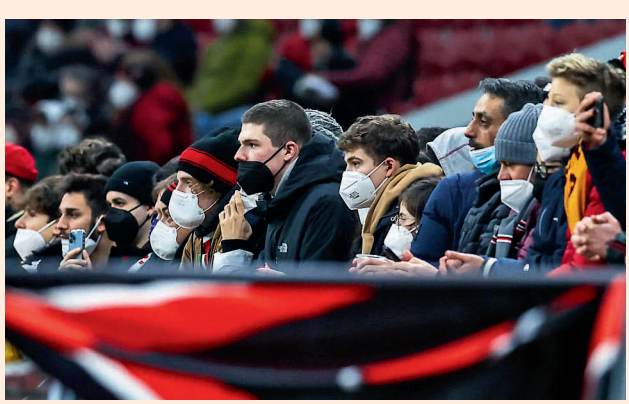
What might endemic covid-19 look like? The coronaviruses that cause common colds, such as OC43, seem to reinfect people every three to six years. As with covid-19, immunity to reinfections doesn't last long, but immunity to serious illness does.

If OC43 reinfections occur every four years, that would mean about 45,000 infections a day in the UK. "That is a reasonable estimate of how many covid-19 infections there will be each day, averaged over a few years, when we reach the endemic equilibrium," says Paul Hunter at the University of East Anglia, UK. At the moment, the UK is recording about 108,000 covid-19 cases a day and there will be many more going unconfirmed by testing.

The number of daily new omicron cases in the UK recently started falling, as they previously did in South Africa, where the variant was first seen.

But another covid-19 variant may well emerge this year or next to cause a further surge – although it is possible that the level of immunity in populations, caused by both vaccines and infections, will continue to offer increasing protection against severe illness.

So we may only be able to say when covid-19 has become endemic by looking backwards. "Often you don't know when that transition has occurred, except in retrospect," says Hunter.



Mask wearing at a football match in Milan, Italy, this month

FABRIZIO CARABELLI/LIVEMEDIA/NURPHOTO VIA GETTY IMAGES

virus continues to evolve. It is hard to say what will happen next, because the virus has repeatedly confounded expectations. "I don't think any of us imagined that 18 months down the line we'd be still here," says Johnson.

In one respect, the omicron variant isn't as bad as it might have been: it causes less severe illness than other variants such as delta. However, the next variant may be different. "You hear this said quite often that viruses adapt to their hosts and become less virulent," says Turtle. "The evidence for that is not that great. In Ebola, in 2014, the opposite happened."

"There's no real selection pressure on this virus to become milder," says Aris Katzourakis at the University of Oxford. That is because most of the spread happens in the early stages of an infection, before the person becomes ill enough to be bed-bound and thus unable to spread it. "If a virus hospitalises its host straight away, that might lead to selection pressure for a milder strain," he says. But that isn't the case here.

Instead, the lesson of omicron is that "there could be more surprises in store", says Turtle. "Who knows how many other variants that could escape or be radically different and still infect humans are possible," he says.

Better vaccines could make a real difference. Katzourakis says future ones could target more parts of the virus, rather than just the spike protein that enables it to enter cells. This would make it harder for the virus to evolve to escape them.

Some researchers are even aiming for a universal coronavirus vaccine, which would protect against all possible variants. But the work is in its early stages.

ANTHONY DEVLIN/GETTY IMAGES

Distancing signs at a school in Stalybridge, UK, last September

"For some, the phrase 'living with covid' has become shorthand for 'let's not do anything else'"

A putative universal vaccine developed at the Walter Reed Army Institute of Research in Silver Spring, Maryland, has been tested in primates and is undergoing phase I trials to find out whether it is safe to give to humans. But more testing is needed, so a widespread roll-out is months away at best.

A global plan

Even without such advances, simply giving people more vaccine doses makes it less likely that another game changer like omicron will emerge this year. As more people are immunised, fewer copies of the virus will circulate and its evolution will slow. "So far, none of the variants have arisen in countries with high vaccination rates," says Pagel, suggesting that vaccination tempers the virus's ability to transform itself.

Ultimately, ending the pandemic will take coordinated global action: something that has been sorely lacking so far.

On 3 January, Pagel, Katzourakis and their colleagues called for a global "vaccines-plus" plan. As well as vaccinating the world, they argue for a suite of measures, including high-quality face masks for indoor mixing, effective means of testing, tracing, isolating and supporting people who get infected, and better ventilation and filtration of indoor air.

"In the way Victorians went for clean water, sanitation, we have to go for clean air," says Pagel. She emphasises that this offers multiple benefits. "There's no individual liberty taken away that way, and it works against all kinds of airborne diseases."

So far, no such global initiative is on the cards. Hence the statement given by Tedros Adhanom Ghebreyesus, director-general of the WHO, on 30 December: "As we enter the third year of this pandemic, I'm confident that this will be the year we end it – but only if we do it together."

It is theoretically possible for the pandemic to end in 2022, but the logistical and sociopolitical challenges are immense. "I think it's mathematically but not politically possible," says Katzourakis.

The reality is that we have been "living with covid" for two years, and are likely to do so in some form for the rest of our lives. The crucial question is, how much of it will we live with? That will determine how many more people die or develop long covid, and how many more times countries will have to implement drastic restrictions after the emergence of new variants.

For some, the phrase "living with covid" has become a shorthand for "let's not do anything else". But without something like a global vaccines-plus plan, "we're going to be in a race of chasing after variants for years to come", says Katzourakis.