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# How will the COVID-19 pandemic end?

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## What has happened in the world since the pandemic began?

More than two years after the COVID-19 pandemic outbreak, the status of the disease is still unclear to us. Up to August 1, 2022, the disease has killed about 6.4 million people worldwide, although the actual death toll is estimated to be three times more than the official death toll [1]. During this time, safe vaccines with high efficacy against the virus have been developed, methods of viral transmission and pathogenicity are better understood, and more effective treatments have been proposed that have helped better control the disease over time. A significant percentage of the world's population has acquired the infection at least once, more than 65% of the world's population has received at least one dose of a COVID-19 vaccine, and about 25% have received at least one booster dose of the COVID-19 vaccine. More than 12 billion doses have been administered globally, with 5.5 million added daily. However, the vaccine distribution is inequitable, and in low-income countries, only about 20% of people have received at least one dose of the vaccine [2].

Along with vaccines, antiviral drugs are another important achievement available. Many antiviral drugs, such as molnupiravir, fluvoxamine, and paxlovid have shown good therapeutic effects for COVID-19 patients [3].

The different timing of the arrival of the virus in countries, the way governments and people respond to the pandemic, the rate of infection in different waves of the epidemics and with different variants, the nature and extent of coverage by the primary vaccines and booster shots have led to differences in the timing and intensity of countries' engagement with pandemic peaks. However, COVID-19 cases and deaths have reached their lowest level since the beginning of the pandemic in most countries and regions in June 2022 [4].

## Are we close to the end of the COVID-19 pandemic?

Due to the emergence of COVID-19 variants in a short time, the antibodies disappearance after a relatively short period, and the vaccine resistance of some variants that were able to resist earlier forms of the virus partially, we

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should speak with more caution about the future of this disease [5, 6].

Proper knowledge of two important questions is critical in determining whether we are nearing the end of a pandemic and epidemic phase. The first question is how long immunity through vaccination or hybrid immunity will protect society, especially from severe forms and deaths from COVID-19, and the second question is how quickly the COVID-19 virus can evolve and what capabilities the new variants will have. Some of the virus variants that have become prevalent over the past two years were more transmissible than the original Wuhan variant, some had more power to cause severe disease and death, and some have shown some degree of immune escape. Finally, the current variant (Omicron) has a high reinfection potential in milder forms of the disease [7]. Recently, some studies reported that the BA.4 and BA.5 Omicron subvariant are probably the most contagious virus among all known variants and subvariants. Laboratory studies also showed that antibodies triggered by vaccination are less effective against these two newly emerged subvariants, quickly becoming the dominant global variants [8], so the vaccine manufacturers must develop their vaccines based on the new variants as the booster dose to minimize the virus circulation.

However, the disease is expected to reach an endemic level from the current pandemic level, meaning that the high immunity acquired in the community will offset the spread and circulation of the virus and lead to a stable level of infection. The end of the epidemic phase and entering the endemic (indigenous) phase of the disease is achieved when two basic principles are met: first, the development of high levels of immunity (natural or acquired by vaccines) in the communities, and second, no evolving of new variants capable of partially breaching the safeguards and escaping the immunity. Ending the epidemic phase in this way is a possible optimistic prediction currently supported by some scientists. Although there is evidence of endemic disease in some parts of the world, more time is needed to study the epidemic to make a more accurate judgment [9].

The question here is whether the endemic levels of the disease may still be associated with the annual peak of severe forms of the disease. Under these circumstances, are new variants of the virus still capable of partially injuring the immune system, and can these new variants escape the protection that vaccines provide against hospitalization and death?

**Challenges of leaky/imperfect vaccines**

Some researchers believe that one of the problems in managing the current pandemic is the repeated injection of vaccines that have not been able to stop the virus replication and have further reduced the incidence of severe forms of the disease and death. Such vaccines are called leaky vaccines. If a virus can reproduce under the influence of vaccine or natural immunity, due to the pressure that immunity puts on the virus, mutations have the possibility of natural selection that releases the virus from this pressure. Since the widespread use of leaky vaccines and higher replication of the virus in people who have not received any vaccine, the emergence of elusive variants has accelerated. Therefore, updating vaccines to prevent virus replication should be an essential priority for vaccine companies [10].

**How will this disease end?**

COVID-19 will not end anytime soon, but there is a hypothesis that in countries with high vaccination rates, the disease may be in its final throes before it reaches endemic levels. It should be noted that at the endemic level of the disease, regular and recurrent fluctuations can be expected, like the seasonal fluctuations seen with influenza. Because the virus circulates in the population during the cold season, coinfection with other respiratory viruses may be a potential challenge, and the problem of the long COVID-19 that follows mild to asymptomatic cases should also be considered.

In countries with low vaccination coverage, primarily low-income countries, there are often no adequate systems of healthcare to diagnose and report cases properly. Therefore, reports from these countries are not valid, and it is impossible to correctly assess the course of the disease in these countries. However, it is likely that subsequent variants of the virus have a greater chance of early development and spread in these countries [12].

**How should governments and international health organizations plan for the future?**

We still do not know whether there will be a relapse into severe forms of the disease as the immune system wears down and the virus continues to evolve and change. Nevertheless, as immunity declines over time, we may need to inject boosters and develop new vaccines. It should be noted that if the disease reaches endemic levels, regular vaccination may still be needed, especially for at-risk groups. Therefore, an initiative to provide vaccines to many people (like the influenza vaccine) should be envisioned. In the meantime, some precautions need to be taken on public acceptance of vaccination, and making different vaccines available might increase people's motivation to vaccinate. Thus, the willingness of countries and the international community to develop and provide such vaccines must continue.

The countries and the international community should be more specific and accurate for people who have not received any vaccine despite its availability. Finding a solution to this problem can also be significant and helpful in controlling other epidemics or subsequent pandemics.

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Continuous surveillance of the effectiveness of the vaccines, conducting immunological studies to assess cellular and humoral immunity of individuals, reviewing circulating variants and their rate of vaccination avoidance, and pursuing a policy of increasing vaccination coverage among the population, especially in high-risk groups, should be earnestly pursued by health and executive policymakers and national research centers.

Indeed, as the epidemic magnitude and the population's involvement change over time, health managers and administrators will need to adapt the procedures developed at the outset of the pandemic and tailor them to new conditions. Authorities should not assure the population that everything has become usual with the current decline in illness and deaths. At the same time, some imposed restrictions must be modified appropriately.

State policymakers need to prepare for either an endemic disease scenario or the recurrence of epidemic peaks to respond appropriately to the coming conditions. COVID-19 demonstrated that countries and international organizations should increase their efforts to strengthen health infrastructure and improve public health. We must use the lessons learned from the COVID-19 pandemic to manage better the next (re-)emerging disease and prepare for similar pandemics in the future.

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