Unvaccinated People Are 11 Times More Likely To Die Of COVID-19, New Research Finds

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Unvaccinated people are **11 times more likely** to die from COVID-19 than those who are fully vaccinated, new research has found, bolstering evidence that the inoculations continue to provide powerful protection, even against the delta variant.

The latest studies from the Centers for Disease Control and Prevention released on Friday also found that **vaccinated people were nearly five times less likely to get infected and 10 times less likely to get so sick they ended up in the hospital.**

The CDC "looked at COVID-19 cases, hospitalizations and deaths in 13 states and offers further evidence of the power of vaccination," Dr. Rochelle Walensky, director of the CDC**,** said at a White House COVID-19 briefing on Friday.

"As we have shown, study after study, vaccination works," she added.

However, the studies — which analyzed data from 600,000 Americans between April 4 and July 17 — suggest that the effectiveness of the vaccines may have dropped as the delta variant became dominant. One explanation could be waning immunity. A second is that the variant is better at evading the immune system. It also could be some combination of the two factors.

Another study examining data from nine states from June through August indicated that the Moderna vaccine may be the most effective of the three available in the United States.

The research found that across all ages, vaccine effectiveness was "significantly higher" among Moderna vaccine recipients — at 95% — than among Pfizer or Johnson & Johnson vaccine recipients, with vaccine effectiveness of 80% and 60%, respectively.

As of Friday, White House officials said **nearly 75% of eligible Americans — those 12 and older** — have gotten at least their first shot, and the CDC reported about 54% of the total population is fully vaccinated.

Take home points: even with the expected tapering of the effectiveness of the vaccines, which is expected, they remain overwhelmingly successful in preventing people who are infected with COVID-19 from requiring hospitalization and dying from the infection.

The lightning-fast quest for COVID vaccines — and what it means for other diseases

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The speedy approach used to tackle SARS-CoV-2 could change the future of vaccine science.

When scientists began seeking a vaccine for the SARS-CoV-2 coronavirus in early 2020, they were careful not to promise quick success. The fastest any vaccine had previously been developed, from viral sampling to approval, was four years, for mumps in the 1960s. To hope for one even by the summer of 2021 seemed highly optimistic.

But by the start of December, the developers of several vaccines had announced excellent results in large trials, with more showing promise. And on 2 December, a vaccine made by drug giant Pfizer with German biotech firm BioNTech, became the first fully-tested immunization to be approved for emergency use.

That speed of advance "challenges our whole paradigm of what is possible in vaccine development", says Natalie Dean, a biostatistician at the University of Florida in Gainesville. It's tempting to hope that other vaccines might now be made on a comparable timescale. These are sorely needed: diseases such as malaria, tuberculosis and pneumonia together kill millions of people a year, and researchers anticipate further lethal pandemics, too.

The COVID-19 experience will almost certainly change the future of vaccine science, says Dan Barouch, director of the Center for Virology and Vaccine Research at Harvard Medical School in Boston, Massachusetts. "It shows how fast vaccine development can proceed when there is a true global emergency and sufficient resources," he says. New ways of making vaccines, such as by using messenger RNA (mRNA), have been validated by the COVID-19 response, he adds. "It has shown that the development process can be accelerated substantially without compromising on safety."

The world was able to develop COVID-19 vaccines so quickly because of years of **previous research on related viruses** and **faster ways to manufacture** vaccines, **enormous funding** that allowed firms to run multiple trials in parallel, and **regulators moving more quickly than normal**. Some of those factors might translate to other vaccine efforts, particularly speedier manufacturing platforms.

Years of advance research

The research that helped to develop vaccines against the new coronavirus didn't start in January. For years, researchers had been paying attention to related coronaviruses, which cause SARS

(severe acute respiratory syndrome) and MERS (Middle East respiratory syndrome), and some had been working on new kinds of vaccine — an effort that has now paid off spectacularly.

Conventional vaccines contain viral proteins or disabled forms of the virus itself, which stimulate the body's immune defences against infection by a live virus. But the first two COVID-19 vaccines for which efficacy was announced in large-scale (phase III) clinical trials used just a string of mRNA inside a lipid coat. The mRNA encodes a key protein of SARS-CoV-2; once the mRNA gets inside our cells, our bodies produce this protein. That acts as the antigen — the foreign molecule that triggers an immune response. The vaccines made by Pfizer and BioNTech and by the US pharmaceutical company Moderna both use mRNA that encodes the spike protein, which docks to human cell membranes and allows the coronavirus to invade the cell.

"A lot went into the mRNA platform that we have today," says immunologist Akiko Iwasaki at the Yale School of Medicine in New Haven, Connecticut, who has worked on nucleic-acid vaccines — those based on lengths of DNA or RNA — for more than two decades. The basic research on DNA vaccines began at least 25 years ago, and RNA vaccines have benefited from 10–15 years of strong research, she says, some aimed at developing cancer vaccines. The approach has matured just at the right time; five years ago, the RNA technology would not have been ready.

For instance, researchers at the US National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, knew from their research on MERS and SARS that it was best to tune the RNA sequence to stabilize the resulting spike protein in the form it adopts before it docks with a host cell. "If you can trap it in its original pre-fusion state, it becomes a much better vaccine antigen," says Barney Graham, deputy director of NIAID's vaccine research centre. That work gave the NIAID team, which worked with Moderna, a head start once SARS-CoV-2 was sequenced in January. "The fact that people had been paying close attention to coronaviruses really allowed this whole process to accelerate," says Dean.

Vaccine researchers were fortunate with SARS-CoV-2 in many respects, says Iwasaki. The virus doesn't mutate a lot or have effective strategies for foiling the human immune system, she says, unlike HIV, herpes or even influenza. The herpes virus, by contrast, has more evasion capability — it actively blocks antibodies from binding, which makes it harder to find an effective agent against it. And the fast mutation of flu viruses requires a different vaccine formulation for every flu season.

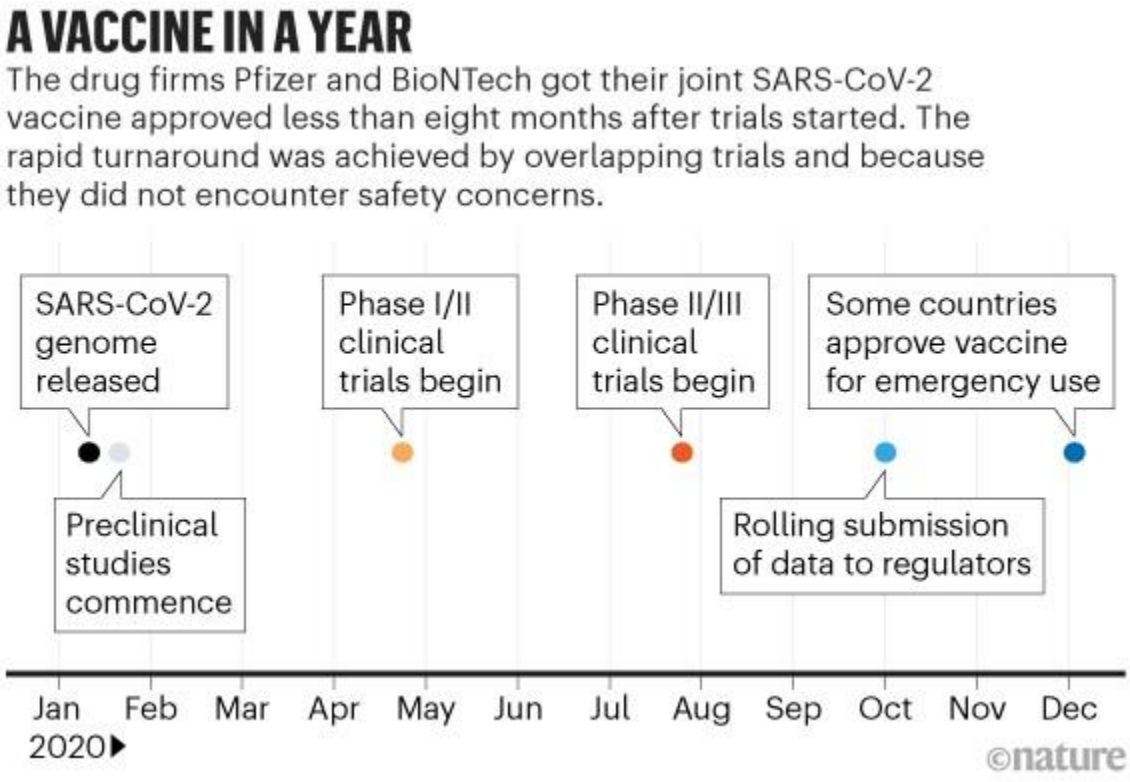
Supercharged with funding

The **slowest part of vaccine development isn't finding candidate treatments, but testing them**. This often takes years (see 'Vaccine innovation'), with companies running efficacy and safety tests on animals and then in humans. Human testing requires three phases that involve increasing numbers of people and proportionately escalating costs. The COVID-19 vaccines went through the same trials, but the billions poured into the process made it possible for companies to take financial risks by running some tests at the same time (see 'A vaccine in a year').

With large sums given to vaccine firms by public funders and private philanthropists, “they could do preclinical and phase I, II and III trials, as well as manufacturing, in parallel instead of sequentially”, says Rino Rappuoli, chief scientist at GlaxoSmithKline’s vaccines division in Siena, Italy. This meant that companies could gamble on starting large-scale testing and manufacturing of candidates that might not work out. “It was totally de-risking the entire development process,” says Kampmann.

The vaccine science would not have produced such fast results without this funding, she says. “It didn’t happen with Ebola, which was devastating communities in Africa [in 2014–16]” — and Ebola vaccines accordingly took longer to develop. The money only materialized this time because all countries, including wealthy ones, faced economic devastation: suggesting that the development of future vaccines, including for existing diseases such as malaria, will not be as speedy. “Unless you put in the money, there’s no way to accelerate,” says Rappuoli.

Virologist Peter Hotez at Baylor College of Medicine in Houston, Texas, suggests that large pharmaceutical companies might have been motivated not just by the desire to stop the pandemic, but also by the opportunity for governments to fund their research and development. With public investment of around US$10 billion, the US Operation Warp Speed vaccine programme “represents the largest government stimulus package the pharma companies have ever seen”, says Hotez.



Sources: BioNTech/Pfizer; *Nature* analysis

In the final stages of trials, it helped that COVID-19 was everywhere because firms need infections to show that vaccines work. It's hard to run efficacy trials when the diseases themselves aren't prevalent — especially, says Dean, in cases such as MERS, for which outbreaks of disease were patchy, with peaks in some areas and low infection rates in others.

The COVID-19 experience might also prompt a regulatory rethink. Although there has been no relaxing of the stringent criteria for vaccine approval, the first candidates are mostly being approved under emergency-use regulations. These are faster but require companies to conduct follow-up surveys to look for side effects and continuing efficacy. National regulators also swapped information on COVID-19 vaccine trials under the auspices of a global body called the International Coalition of Medicines Regulatory Authorities, set up in 2012. It has aimed to reach consensus on issues such as the best end-points for vaccine trials, and how to harmonize the monitoring of side effects as vaccines are rolled out (see also *Nature* 588, 195; 2020).

The large clinical trials for COVID-19 vaccines, and others in development, should provide data that are more widely useful for understanding immune responses, says Hotez. "Given all the different technologies, and detailed information collected on clinical volunteer demographics, antibody and cellular responses, we might learn as much or more from human vaccine responses this year than in previous decades. Human vaccinology could make a quantum leap."

Still, other vaccines can probably only be developed at a comparable speed when infection levels are high — making it possible to run massive trials relatively quickly — and with huge amounts of funding. And other viruses might be harder to target than SARS-CoV-2 turned out to be.

That's why we need to know more about all families of viruses, say researchers. There are at least 24 other virus families that can infect humans, says Graham. Rather than waiting to sink resources into fighting the next virus that pops up, money would be better spent now setting up systems to monitor all these viruses and to generate data on prototype infections in each of these families, he says.

In other words, no amount of money will help without a solid platform of basic science to build on. The extraordinary success of the COVID-19 vaccines "is a good example of what science can do very quickly", says Iwasaki, "but it didn't happen overnight."

Take home message:

1. *the development of the COVID-19 vaccine was not a quick and careless effort. It was the culmination of research on coronaviruses that started years earlier. The infrastructure was already in place from the years of ongoing research done on SARS and MERS.*
2. *The safety of the vaccine has now been demonstrated after dosing billions of people world-wide.*
3. *the speed of the development of the COVID-19 vaccines was only made possible by the tremendous influx of funding which allowed research facilities to work much more aggressively without fear of running out of money.*

4. *The 'fortunate' benefit of COVID-19 is that is spreads so rapidly and infected some many people quickly, that it allowed testing of the vaccine in large clinical trials which provided information of effectiveness and safety much faster than ever before.*