

6 CORE CONCEPTS

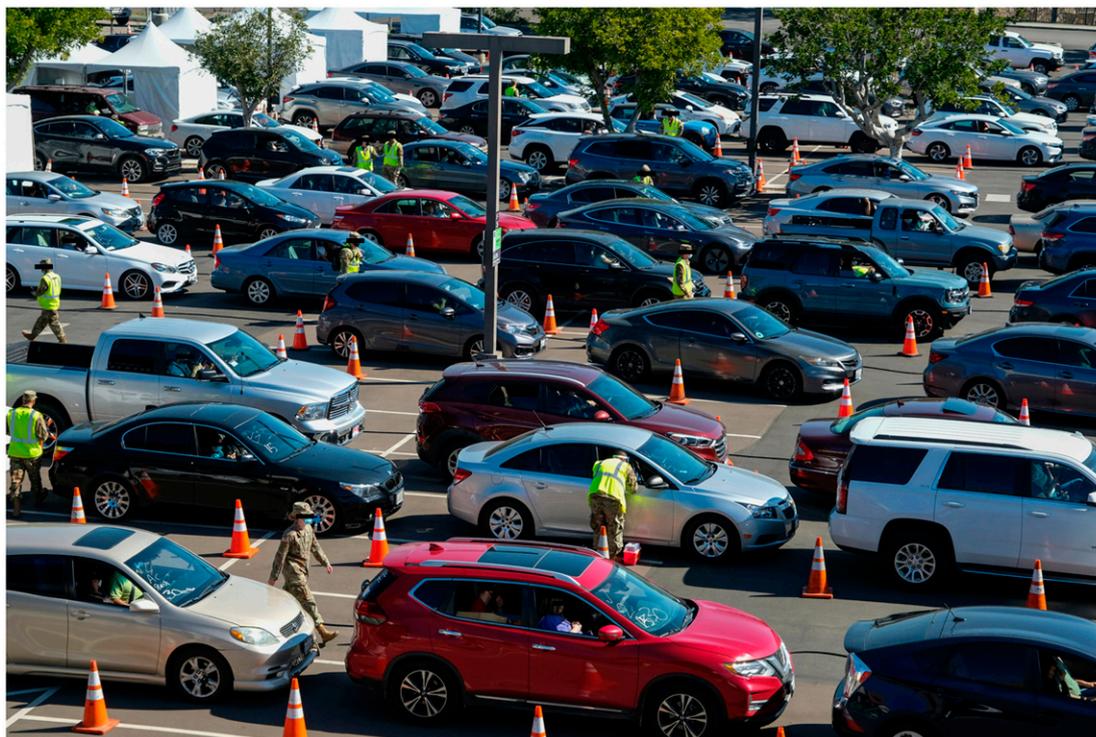
Herd immunity is an important—and often misunderstood—public health phenomenon

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In December, Anthony Fauci predicted that 70 to 85% of the United States population may need to be vaccinated to achieve “herd immunity” against SARS-CoV-2 (1). Yet he was very careful to qualify his comments. “We need to have some humility here,” he said in a *New York Times* interview, “We really don’t know what the real number is.” (2) Fauci, director of the National Institute of Allergy and Infectious Diseases, admitted that the number could be as high as 90%. But even a year into the pandemic, there were too many uncertainties to offer a definite threshold. And with vaccine hesitancy widespread, he worried that setting the bar at such a high number would cause the public to despair of ever reaching it.

Since the earliest months of the COVID-19 pandemic, “herd immunity” has become shorthand for the day when enough people are immune to the virus that social distancing can end and healthcare systems are no longer overwhelmed. People have been clamoring to know when we’ll get there. But even as Fauci and other officials continue to try to calculate—and communicate—when it might happen, they have to contend with both public misunderstanding of the term and scientific disagreement over what it means.

The public health concept of herd immunity has a more nuanced definition than its popular usage, which is one reason why predicting when we’ll achieve it remains difficult. In theory, estimating the threshold to reach herd immunity through vaccination or natural



As millions of Americans get vaccinated, the country seeks a return to normalcy. But the concept of “herd immunity” may not be the best way to articulate how we get there. Image credit: Shutterstock/Ringo Chiu.

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infections involves a simple mathematical calculation. But it's one that's more easily done with a well-understood pathogen and a well-characterized population. And although the basic equations are straightforward, choosing the right inputs and interpreting the results are not.

When asked for his definition of herd immunity, communicable disease epidemiologist Paul Fine laughs. He's heard many definitions of the term in his long career at the London School of Hygiene & Tropical Medicine in the United Kingdom (3). "I won't speak for everyone," he says, but the majority of epidemiologists now frame the concept as "what proportion of the people in, say, the United States need to be immune for the rate of new infections to decline?"

Technically, then, a population can reach herd immunity even with low levels of the pathogen still circulating, which means it hasn't necessarily been eradicated for good. The point, ultimately, is that herd immunity may not be the right shorthand to refer to the end of the pandemic. It's been bandied about incorrectly, certainly imprecisely, Fine says. "I think people often haven't a clue what they're saying."

Simple Origins, Complex Connotations

In the summer of 1918, the farmers and ranchers of Kansas fought two diseases at once. One threatened their lives; the other, their livelihoods. Six months earlier, in January, cases of what came to be called the Spanish Flu had bloomed across Haskell County, in the southwest of the state (4). That same summer, veterinarian George Potter wrote about a second disease, caused by the bacterium *Brucella abortus*, that triggered contagious and spontaneous abortions in cattle and threatened Kansas' cattle industry throughout the early 1900s (5). Potter recommended that farmers not kill sick cows, because individual females would clear the infection on their own. Therefore, letting an infection run its course would lead to "herd immunity," Potter surmised, meaning that once enough cows developed immunity, the disease would come under control and no longer trouble the

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—Jennie Lavine

rancher. Potter was among the first to coin the term, according to a history published in *The Lancet* in 2020 (6).

"The phrase initially comes from the veterinary field, no surprise," Fine explains, noting that usage in its more modern sense dates to the 1970s. That decade saw the campaign to eradicate smallpox, and with it, the need for simple calculations to estimate how many people had to be vaccinated to drive the virus out of human populations (7). Equally or more important than smallpox at the time, Fine says, was the start of the World Health Organization's Expanded

Program on Immunization, which aimed to provide vaccines for a number of diseases globally. Today, the herd immunity threshold is generally agreed to be the proportion of the population that needs to be immune to tip a disease into decline. It occurs when the "typical" person goes on to infect fewer than one other person as a result of naturally acquired or vaccine-induced immunity, explains evolutionary biologist Katrina Lythgoe at the University of Oxford in the United Kingdom.

The idea underlying herd immunity is that the proximity of immune individuals shields others who are still susceptible from infection, Fine explains. And, with enough immune people in the population, the herd becomes a defensive wall that denies the virus pathways to keep spreading.

Mathematically, the herd immunity threshold can be very simply calculated as $1 - 1/R_0$, where R_0 ("R-naught") is the basic reproduction number, meaning the average number of secondary cases caused by the typical infection (8). Early in the pandemic, SARS-CoV-2 was estimated to have an R_0 of about 3, meaning that every case infects three other people, on average, and that figure has remained fairly stable (9, 10).

That's higher than the R_0 of 1.3 for seasonal flu (11), for example, but much lower than, say, measles, with its R_0 somewhere between 12 and 18 (12). Based on that overall average of three new cases per infected person, the herd immunity threshold for COVID-19 would therefore be $1 - (1/3)$, or 0.67. Hence, according to the simplest calculation, 67% of the population would need to be 100% immune to push SARS-CoV-2 into decline. Of course, in the real world, the calculus for COVID-19 has not proven quite so straightforward. Key inputs keep changing; some are as yet unknown.

A Loaded Question

One problem with seeking the threshold for COVID-19 herd immunity is that although the mathematical answer is quite simple, the assumptions underlying it are not, says epidemiologist Marc Lipsitch at the Harvard T.H. Chan School of Public Health in Boston, MA. In fact, there can be considerable disagreement about what those basic assumptions are. The calculations yielding 67% assume that a population mixes at random and that anyone who catches SARS-CoV-2 will pass it to about three other people in a totally susceptible population, Fine says. Clearly, in modern society, humans don't interact at random and the virus spreads at different rates in different communities, so the calculation of real-world R_0 for specific populations can get very complicated when there is heterogeneity and nonrandom mixing.

The simplest calculation also relies on a major assumption: that being vaccinated confers perfect protection, meaning zero chance of getting infected and transmitting the virus, Lipsitch says. If this were true, then vaccinating 67% of the population would cut about two-thirds of transmission, meaning the typical infection would jump to one other person instead of three. But one of the biggest unknowns continues to be whether people can become immune to SARS-CoV-2,

with vaccines or otherwise, says physician scientist Larry Corey, at the Fred Hutchinson Cancer Research Center in Seattle, WA.

In the past year, it's become clear that immune responses to infections vary widely, they may wane with time, and people can certainly catch COVID-19 more than once. So past infections, asymptomatic or not, are not useful to gauge population protection (13, 14). Complicating matters, new, more infectious virus variants, in South Africa and Brazil for example, have been shown to dodge natural and vaccine-induced immunity to older versions of the virus (15). What would help, Lipsitch notes, is if public health experts knew the total number of cases worldwide, tested or otherwise, and how much protection those cases had from reinfection—two types of data that are still lacking.

That leaves vaccination as the only way to reliably establish predictable levels of immunity in the population. Data from the Centers for Disease Control and Prevention (CDC), released in late March and focused on healthcare workers and other essential personnel, suggest that the Moderna and Pfizer-BioNTech messenger-RNA vaccines provide a high degree of protection from infection (16), but there are too few data yet to know how much the current vaccines will reduce transmission. Trial results already show that some proportion of COVID-19 vaccine recipients will still get infected, although the real number also remains unclear. Corey, who helped design and oversee the Phase III vaccine trials at a network of sites, including Fred Hutchinson in Seattle, explains that participants in the Moderna and AstraZeneca trials received a COVID-19 diagnostic swab test on the day of their first shot, and about a month later, on the day of their second shot. The tests provide a snapshot of a patient's current infection status, but the swabs don't screen for antibodies to indicate whether patients caught and cleared the virus in the month between the first and second shots.

If the basic mechanism behind herd immunity is blocking the transmission routes that sustain a pathogen in the host population, then researchers need to know how well vaccines prevent even asymptomatic infections as well as transmission by those who do get infected. "That's a totally different kind of study," Corey says. "You vaccinate people and swab their nose every day, and if they become positive, do contact tracing to see if they're transmitting it."

Those kinds of data are just beginning to come in, and they will vary depending on which vaccine is involved. At least for the Pfizer-BioNTech and Moderna messenger-RNA vaccines, which reduced disease by a spectacular 91 to 94% in trials, the recent CDC study of US healthcare workers and first responders showed the vaccines also reduced infections by about 90% (17). The herd immunity threshold calculus can allow for an "imperfect" vaccine that is less than 100% effective at preventing infections—it simply raises the proportion of people who need to be vaccinated (18). But it still wouldn't address the question of what herd immunity really represents.

Victory or Stalemate?

Herd immunity is a slippery concept; there are multiple ways to force an epidemic into decline. Social distancing and mask-wearing alone can push R_0 below one. But is that herd immunity? Some might say it is, notes epidemiologist Jennie Lavine, a postdoc at Emory University in Atlanta, GA. But without actual immunity from vaccination or prior infection, as soon as people stop those behaviors R_0 would increase again.

Even within public health circles "some of our colleagues have disagreed with one another" on the definition of herd immunity, says biologist Joshua Weitz at Georgia Tech in Atlanta. Changes in behavior can lead to declines in cases, he says, "that do not imply that the population has reached herd immunity." Populations develop immunity through a combination of vaccination and natural infections, Weitz says, and the safe and ethical route to reach herd immunity is through vaccinations.

But if herd immunity is too slippery of a concept, then what's the best way to convey how the pandemic ends? One key point is that the "end" of the pandemic likely will not mean the end of the virus. Few scientists think eradication of SARS-CoV-2 is possible in the foreseeable future. Many, including epidemiologist Lavine, believe instead that the virus will eventually be tamed through some combination of naturally acquired and vaccine-induced resistance, which doesn't drive SARS-CoV-2 out of sight but rather turns it into a more benign disease and just another endemic, cold-causing coronavirus. In a February study, Lavine, along with her coauthors, modeled how the novel coronavirus might spread through the US population over the next 10 years (19).

In the models, daily COVID cases spike when the virus is first introduced. Eventually, infections reach a pinnacle, and case numbers begin to fall during a refractory period when a large proportion of the population is presumed to be immune. This would be the point when the population crosses the herd immunity threshold, Lavine says—there are no longer enough susceptible individuals to support long viral transmission chains. But if the virus keeps evolving or immunity fades over time, say in six months or a year after infection or vaccination, then as people become vulnerable to reinfection, transmission chains will start up again and the conditions of herd immunity would no longer be met. "Our group has taken to calling it 'transient herd immunity,'" Lavine says.

Manaus, Brazil's seventh largest city, offers an unsettling example of what transient herd immunity might look like. Based on cases and antibody testing, researchers estimated late last year that 76% of Manaus' population of more than 2 million had already been infected with the virus. As hospitalizations leveled off and then declined, it seemed the city had crossed the theoretical herd immunity threshold (20). However, infections took off and deaths spiked again in early 2021. Greater genomic surveillance and monitoring of SARS-CoV-2 infections will help researchers understand how much waning immunity, a highly contagious new variant labeled P1, or other

factors might have contributed to the resurgence (21, 22).

If reinfections are more contagious and lead to high death rates, “that would be much scarier,” Lavine says, than the situation in which COVID essentially becomes another common cold.

In December, when Fauci estimated that as much as 90% of the US population—but certainly more than 67%—would need to be vaccinated to reach the herd immunity threshold, he was very likely accounting for

imperfect vaccine protection, unreliable immunity from natural infections, and an ever-evolving virus that keeps moving the goal posts. With so little certainty about what’s required to even reach herd immunity—and what that would accomplish, and how long it would last—the only thing that seems clear is that the idea itself may have become something of a mirage. Researchers and public health officials might need a different way to describe an end to the pandemic—and a return to “normal.”

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