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## Vaccinating people who have had covid-19: why doesn't natural immunity count in the US?

The US CDC estimates that SARS-CoV-2 has infected more than 100 million Americans, and evidence is mounting that natural immunity is at least as protective as vaccination. Yet public health leadership says everyone needs the vaccine. **Jennifer Block** investigates

Jennifer Block *freelance journalist*

When the vaccine rollout began in mid-December 2020, more than one quarter of Americans—91 million—had been infected with SARS-CoV-2, according to a US Centers for Disease Control and

Prevention (CDC) estimate.<sup>1</sup> As of this May, that proportion had risen to more than a third of the population, including 44% of adults aged 18-59 (table 1).

Table 1 | Estimated total infections in the United States between February 2020 and May 2021\*

Age group (years)	No of infections (millions) (95% uncertainty interval)	Population in 2019 (millions)	% previously infected (95% uncertainty interval)
0-17	26.8 (22 to 33.1)	73	37 (30 to 45)
18-49	60.5 (50.4 to 73.2)	138	44% (36 to 53)
50-64	20.4 (17.0 to 24.6)	63	32% (27 to 39)
65+	12.3 (9.9 to 15.5)	54	23% (18 to 29)
All ages	120.3 (103.3 to 140.9)	328	37% (31 to 43)

\* Sources: CDC (estimated infections) and US Census (2019 estimated population).

The substantial number of infections, coupled with the increasing scientific evidence that natural immunity was durable, led some medical observers to ask why natural immunity didn't seem to be factored into decisions about prioritising vaccination.<sup>2-4</sup>

"The CDC could say [to people who had recovered], very well grounded in excellent data, that you should wait 8 months," Monica Gandhi, an infectious disease specialist at University of California San Francisco, told *Medpage Today* in January. She suggested authorities ask people to "please wait your turn."<sup>4</sup>

Others, such as Icahn School of Medicine virologist and researcher Florian Krammer, argued for one dose in those who had recovered. "This would also spare individuals from unnecessary pain when getting the second dose and it would free up additional vaccine doses," he told the *New York Times*.<sup>5</sup>

"Many of us were saying let's use [the vaccine] to save lives, not to vaccinate people already immune," says Marty Makary, a professor of health policy and management at Johns Hopkins University.

Still, the CDC instructed everyone, regardless of previous infection, to get fully vaccinated as soon as they were eligible: natural immunity "varies from person to person" and "experts do not yet know how long someone is protected," the agency stated on its website in January.<sup>6</sup> By June, a Kaiser Family Foundation survey found that 57% of those previously infected got vaccinated.<sup>7</sup>

As more US employers, local governments, and educational institutions issue vaccine mandates that

make no exception for those who have had covid-19,<sup>8</sup> questions remain about the science and ethics of treating this group of people as equally vulnerable to the virus—or as equally threatening to those vulnerable to covid-19—and to what extent politics has played a role.

### The evidence

"Starting from back in November, we've had a lot of really important studies that showed us that memory B cells and memory T cells were forming in response to natural infection," says Gandhi. Studies are also showing, she says, that these memory cells will respond by producing antibodies to the variants at hand.<sup>9-11</sup>

Gandhi included a list of some 20 references on natural immunity to covid in a long Twitter thread supporting the durability of both vaccine and infection induced immunity.<sup>12</sup> "I stopped adding papers to it in December because it was getting so long," she tells *The BMJ*.

But the studies kept coming. A National Institutes of Health (NIH) funded study from La Jolla Institute for Immunology found "durable immune responses" in 95% of the 200 participants up to eight months after infection.<sup>13</sup> One of the largest studies to date, published in *Science* in February 2021, found that although antibodies declined over 8 months, memory B cells increased over time, and the half life of memory CD8<sup>+</sup> and CD4<sup>+</sup> T cells suggests a steady presence.<sup>9</sup>

Real world data have also been supportive.<sup>14</sup> Several studies (in Qatar,<sup>15</sup> England,<sup>16</sup> Israel,<sup>17</sup> and the US<sup>18</sup>) have found infection rates at equally low levels among people who are fully vaccinated and those who have previously had covid-19. Cleveland Clinic surveyed its more than 50 000 employees to compare four groups based on history of SARS-CoV-2 infection and vaccination status.<sup>18</sup> Not one of over 1300 unvaccinated employees who had been previously infected tested positive during the five months of the study. Researchers concluded that that cohort “are unlikely to benefit from covid-19 vaccination.” In Israel, researchers accessed a database of the entire population to compare the efficacy of vaccination with previous infection and found nearly identical numbers. “Our results question the need to vaccinate previously infected individuals,” they concluded.<sup>17</sup>

As covid cases surged in Israel this summer, the Ministry of Health reported the numbers by immunity status. Between 5 July and 3 August, just 1% of weekly new cases were in people who had previously had covid-19. Given that 6% of the population are previously infected and unvaccinated, “these numbers look very low,” says Dvir Aran, a biomedical data scientist at the Technion–Israel Institute of Technology, who has been analysing Israeli data on vaccine effectiveness and provided weekly ministry reports to *The BMJ*. While Aran is cautious about drawing definitive conclusions, he acknowledged “the data suggest that the recovered have better protection than people who were vaccinated.”

But as the delta variant and rising case counts have the US on edge, renewed vaccination incentives and mandates apply regardless of infection history.<sup>8</sup> To attend Harvard University or a Foo Fighters concert or enter indoor venues in San Francisco and New York City, you need proof of vaccination. The ire being directed at people who are unvaccinated is also indiscriminate—and emanating from America’s highest office. In a recent speech to federal intelligence employees who, along with all federal workers, will be required to get vaccinated or submit to regular testing, President Biden left no room for those questioning the public health necessity or personal benefit of vaccinating people who have had covid-19: “We have a pandemic because of the unvaccinated ... So, get vaccinated. If you haven’t, you’re not nearly as smart as I said you were.”

## Staying firm

Other countries do give past infection some immunological currency. Israel recommends that people who have had covid-19 wait three months before getting one mRNA vaccine dose and offers a “green pass” (vaccine passport) to those with a positive serological result regardless of vaccination.<sup>19</sup> In the European Union, people are eligible for an EU digital covid certificate after a single dose of an mRNA vaccine if they have had a positive test result within the past six months, allowing travel between 27 EU member states.<sup>20</sup> In the UK, people with a positive polymerase chain reaction (PCR) test result can obtain the NHS covid pass up until 180 days after infection.<sup>21</sup>

Although it’s too soon to say whether these systems are working smoothly or mitigating spread, the US has no category for people who have been infected. The CDC still recommends a full vaccination dose for all, which is now being mirrored in mandates. A spokesperson told *The BMJ* that “the immune response from vaccination is more predictable” and that based on current evidence, antibody responses after infection “vary widely by individual,” though studies are ongoing to “learn how much protection antibodies from infection may provide and how long that protection lasts.”

In June, Peter Marks, director of the Food and Drug Administration’s Center for Biologics Evaluation and Research, which regulates vaccines, went a step further and stated: “We do know that the immunity after vaccination is better than the immunity after natural infection.” In an email, an FDA spokesperson said Marks’s comment was based on a laboratory study of the binding breadth of Moderna vaccine induced antibodies.<sup>22</sup> The research did not measure any clinical outcomes. Marks added, referring to antibodies, that “generally the immunity after natural infection tends to wane after about 90 days.”<sup>23</sup>

“It appears from the literature that natural infection provides immunity, but that immunity is seemingly not as strong and may not be as long lasting as that provided by the vaccine,” Alfred Sommer, dean emeritus of the Johns Hopkins Bloomberg School of Public Health tells *The BMJ*.

But not everyone agrees with this interpretation. “The data we have right now suggests that there probably isn’t a whole lot of difference” in terms of immunity to the spike protein, says Matthew Memoli, director of the Laboratory of Infectious Diseases Clinical Studies at the NIH, who spoke to *The BMJ* in a personal capacity.

Memoli highlights real world data such as the Cleveland Clinic study<sup>18</sup> and points out that while “vaccines are focused on only that tiny portion of immunity that can be induced” by the spike, someone who has had covid-19 was exposed to the whole virus, “which would likely offer a broader based immunity” that would be more protective against variants. The laboratory study offered by the FDA<sup>22</sup> “only has to do with very specific antibodies to a very specific region of the virus [the spike],” says Memoli. “Claiming this as data supporting that vaccines are better than natural immunity is shortsighted and demonstrates a lack of understanding of the complexity of immunity to respiratory viruses.”

## Antibodies

Much of the debate pivots on the importance of sustained antibody protection. In April, Anthony Fauci told US radio host Maria Hinajosa that people who have had covid-19 (including Hinajosa) still need to be “boosted” by vaccination because “your antibodies will go sky high.”

“That’s still what we’re hearing from Dr Fauci—he’s a strong believer that higher antibody titres are going to be more protective against the variants,” says Jeffrey Klausner, a clinical professor of preventive medicine at the University of Southern California and former CDC medical officer, who has spoken out in favour of treating prior infection as equivalent to vaccination, with “the same societal status.”<sup>23</sup> Klausner conducted a systematic review of 10 studies on reinfection and concluded that the “protective effect” of a previous infection “is high and similar to the protective effect of vaccination.”

In vaccine trials, antibodies are higher in participants who were seropositive at baseline than in those who were seronegative.<sup>24</sup> However, Memoli questions the importance: “We don’t know that that means it’s better protection.”

Former CDC director Tom Frieden, a proponent of universal vaccination, echoes that uncertainty: “We don’t know that antibody level is what determines protection.”

Gandhi and others have been urging reporters away from antibodies as the defining metric of immunity. “It is accurate that your antibodies will go down” after natural infection, she says—that’s how the immune system works. If antibodies didn’t clear from our bloodstream after we recover from a respiratory infection, “our blood would be thick as molasses.”

“The real memory in our immune system resides in the [T and B] cells, not in the antibodies themselves,” says Patrick Whelan, a paediatric rheumatologist at University of California, Los Angeles. He points out that his sickest covid-19 patients in intensive care, including children with multisystem inflammatory syndrome, have “had loads of antibodies ... So the question is, why didn’t they protect them?”

Antonio Bertoletti, a professor of infectious disease at Duke-NUS Medical School in Singapore, has conducted research that indicates T cells may be more important than antibodies. Comparing the T cell response in people with symptomatic versus asymptomatic covid-19, Bertoletti’s team found them to be identical, suggesting that the severity of infection does not predict strength of resulting immunity and that people with asymptomatic infections “mount a highly functional virus specific cellular immune response.”<sup>25</sup>

### Already complicated rollout

While some argue that the pandemic strategy should not be “one size fits all,” and that natural immunity should count, other public health experts say universal vaccination is a more quantifiable, predictable, reliable, and feasible way to protect the population.

Frieden told *The BMJ* that the question of leveraging natural immunity is a “reasonable discussion,” one he had raised informally with the CDC at start of rollout. “I thought from a rational standpoint, with limited vaccine available, why don’t you have the option” for people with previous infection to defer until there was more supply, he says. “I think that would have been a rational policy. It would have also made rollout, which was already too complicated, even more complicated.”

Most infections were never diagnosed, Frieden points out, and many people may have assumed they had been infected when they hadn’t. Add to that false positive results, he says. Had the CDC given different directives and vaccine schedules based on prior infection, it “wouldn’t have done much good and might have done some harm.”

Klausner, who is also a medical director of a US testing and vaccine distribution company, says he initiated conversations about offering a fingerprick antibody screen for people with suspected exposure before vaccination, so that doses could be used more judiciously. But “everyone concluded it was just too complicated.”

“It’s a lot easier to put a shot in their arm,” says Sommer. “To do a PCR test or to do an antibody test and then to process it and then to get the information to them and then to let them think about it—it’s a lot easier to just give them the damn vaccine.” In public health, “the primary objective is to protect as many people as you can,” he says. “It’s called collective insurance, and I think it’s irresponsible from a public health perspective to let people pick and choose what they want to do.”

But Klausner, Gandhi, and others raise the question of fairness for the millions of Americans who already have records of positive covid test results—the basis for “recovered” status in Europe—and equity for those at risk who are waiting to get their first dose (an argument being raised anew as US officials announce boosters while the virus spreads in countries lacking vaccine supply). For people who did not have a confirmed positive result but suspected previous infection, reliable antibody tests have been accessible “at least since April,” according to Klausner, though in May, the FDA announced that “antibody tests should not be used to evaluate a person’s level of immunity or protection from covid-19 at any time.”<sup>26</sup>

Unlike Europe, the US doesn’t have a national certificate or vaccination requirement, so defenders of natural immunity have simply advocated for more targeted recommendations and screening availability—and that mandates allow for exemptions. Logistics aside, a recognition of existing immunity would have fundamentally changed the target vaccination calculations and would also affect the calculations on boosters. “As we continued to put effort into vaccination and set targets, it became apparent to me that people were forgetting that herd immunity is formed by both natural immunity and vaccine immunity,” says Klausner.

Gandhi thinks logistics is only part of the story. “There’s a very clear message out there that ‘OK, well natural infection does cause immunity but it’s still better to get vaccinated,’ and that message is not based on data,” says Gandhi. “There’s something political going on around that.”

### Politics of natural immunity

Early in the pandemic, the question of natural immunity was on the mind of Ezekiel Emanuel, a bioethicist at the University of Pennsylvania and senior fellow at the liberal think tank Center for American Progress, who later became a covid adviser to President Biden. He emailed Fauci before dawn on 4 March 2020. Within a few hours, Fauci wrote back: “you would assume that their [sic] would be substantial immunity post infection.”<sup>27</sup>

That was before natural immunity started to be promoted by Republic politicians. In May 2020, Kentucky senator and physician Rand Paul asserted that since he already had the virus, he didn’t need to wear a mask. He has been the most vocal since, arguing that his immunity exempted him from vaccination. Wisconsin senator Ron Johnson and Kentucky representative Thomas Massie have also spoken out. And then there was President Trump, who tweeted last October that his recovery from covid-19 rendered him “immune” (which Twitter labelled “misleading and potentially harmful information”).

Another polarising factor may have been the Great Barrington declaration of October 2020, which argued for a less restrictive pandemic strategy that would help build herd immunity through natural infections in people at minimal risk.<sup>28</sup> The John Snow memorandum, written in response (with signatories including Rochelle Walensky, who went on to head the CDC), stated “there is no evidence for lasting protective immunity to SARS-CoV-2 following natural infection.”<sup>29</sup> That statement has a footnote to a study of people who had recovered from covid-19, showing that blood antibody levels wane over time.

More recently, the CDC made headlines with an observational study aiming to characterise the protection a vaccine might give to people with past infections. Comparing 246 Kentuckians who had subsequent reinfections with 492 controls who had not, the CDC concluded that those who were unvaccinated had more than twice the odds of reinfection.<sup>30</sup> The study notes the limitation that the vaccinated are “possibly less likely to get tested. Therefore, the association of reinfection and lack of vaccination might be overestimated.” In announcing the study, Walensky stated: “If you have had covid-19 before, please still get vaccinated.”<sup>31</sup>

“If you listen to the language of our public health officials, they talk about the vaccinated and the unvaccinated,” Makary tells *The BMJ*. “If we want to be scientific, we should talk about the immune and the non-immune.” There’s a significant portion of the population, Makary says, who are saying, “‘Hey, wait, I’ve had [covid].’ And they’ve been blown off and dismissed.”

## Different risk-benefit analysis?

For Frieden, vaccinating people who have already had covid-19 is, ultimately, the most responsible policy right now. “There’s no doubt that natural infection does provide significant immunity for many people, but we’re operating in an environment of imperfect information, and in that environment the precautionary principle applies—better safe than sorry.”

“In public health you are always dealing with some level of unknown,” says Sommer. “But the bottom line is you want to save lives, and you have to do what the present evidence, as weak as it is, suggests is the strongest defence with the least amount of harm.”

But others are less certain.

“If natural immunity is strongly protective, as the evidence to date suggests it is, then vaccinating people who have had covid-19 would seem to offer nothing or very little to benefit, logically leaving only harms—both the harms we already know about as well as those still unknown,” says Christine Stabell Benn, vaccinologist and professor in global health at the University of Southern Denmark. The CDC has acknowledged the small but serious risks of heart inflammation and blood clots after vaccination, especially in younger people. The real risk in vaccinating people who have had covid-19 “is of doing more harm than good,” she says.

A large study in the UK<sup>32</sup> and another that surveyed people internationally<sup>33</sup> found that people with a history of SARS-CoV-2 infection experienced greater rates of side effects after vaccination. Among 2000 people who completed an online survey after vaccination, those with a history of covid-19 were 56% more likely to experience a severe side effect that required hospital care.<sup>33</sup>

Patrick Whelan, of UCLA, says the “sky high” antibodies after vaccination in people who were previously infected may have contributed to these systemic side effects. “Most people who were previously ill with covid-19 have antibodies against the spike protein. If they are subsequently vaccinated, those antibodies and the products of the vaccine can form what are called immune complexes,” he explains, which may get deposited in places like the joints, meninges, and even kidneys, creating symptoms.

Other studies suggest that a two dose regimen may be counterproductive.<sup>34</sup> One found that in people with past infections, the first dose boosted T cells and antibodies but that the second dose seemed to indicate an “exhaustion,” and in some cases even a deletion, of T cells.<sup>34</sup> “I’m not here to say that it’s harmful,” says Bertoletti, who coauthored the study, “but at the moment all the data are telling us that it doesn’t make any sense to give a second vaccination dose in the very short term to someone who was already infected. Their immune response is already very high.”

Despite the extensive global spread of the virus, the previously infected population “hasn’t been studied well as a group,” says Whelan. Memoli says he is also unaware of any studies examining the specific risks of vaccination for that group. Still, the US public health messaging has been firm and consistent: everyone should get a full vaccine dose.

“When the vaccine was rolled out the goal should have been to focus on people at risk, and that should still be the focus,” says Memoli. Such risk stratification may have complicated logistics, but it would also require more nuanced messaging. “A lot of public health people have this notion that if the public is told that there’s even the slightest bit of uncertainty about a vaccine, then they won’t get it,” he says. For Memoli, this reflects a bygone paternalism. “I always think it’s much better to be very clear and honest about what

we do and don’t know, what the risks and benefits are, and allow people to make decisions for themselves.”

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