


Necessity of COVID-19 vaccination in previously infected individuals

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ABSTRACT

Background The purpose of this study was to evaluate the necessity of COVID-19 vaccination in persons previously infected with SARS-CoV-2.

Methods Employees of the Cleveland Clinic Health System working in Ohio on Dec 16, 2020, the day COVID-19 vaccination was started, were included. Any subject who tested positive for SARS-CoV-2 at least 42 days earlier was considered previously infected. One was considered vaccinated 14 days after receipt of the second dose of a SARS-CoV-2 mRNA vaccine. The cumulative incidence of SARS-CoV-2 infection over the next five months, among previously infected subjects who received the vaccine, was compared with those of previously infected subjects who remained unvaccinated, previously uninfected subjects who received the vaccine, and previously uninfected subjects who remained unvaccinated.

Results Among the 52238 included employees, 1359 (53%) of 2579 previously infected subjects remained unvaccinated, compared with 22777 (41%) of 49659 not previously infected. The cumulative incidence of SARS-CoV-2 infection remained almost zero among previously infected unvaccinated subjects, previously infected subjects who were vaccinated, and previously uninfected subjects who were vaccinated, compared with a steady increase in cumulative incidence among previously uninfected subjects who remained unvaccinated. Not one of the 1359 previously infected subjects who remained unvaccinated had a SARS-CoV-2 infection over the duration of the study. In a Cox proportional hazards regression model, after adjusting for the phase of the epidemic, vaccination was associated with a significantly lower risk of SARS-CoV-2 infection among those not previously infected (HR 0.031, 95% CI 0.015 to 0.061) but not among those previously infected (HR 0.313, 95% CI 0 to Infinity).

Conclusions Individuals who have had SARS-CoV-2 infection are unlikely to benefit from COVID-19 vaccination, and vaccines can be safely prioritized to those who have not been infected before.

Summary Cumulative incidence of COVID-19 was examined among 52238 employees in an American healthcare system. COVID-19 did not occur in anyone over the five months of the study among 2579 individuals previously infected with COVID-19, including 1359 who did not take the vaccine.

Competing Interest Statement

The authors have declared no competing interest.

Funding Statement

There was no funding for this study.

Author Declarations

I confirm all relevant ethical guidelines have been followed, and any necessary IRB and/or ethics committee approvals have been obtained.

Yes

The details of the IRB/oversight body that provided approval or exemption for the research described are given below:

The study was approved by the Cleveland Clinic Institutional Review Board. A waiver of informed consent and waiver of HIPAA authorization were approved to allow access to personal health

information by the research team, with the understanding that sharing or releasing identifiable data to anyone other than the study team was not permitted without additional IRB approval.

All necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.

Yes

I understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).

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Comparing SARS-CoV-2 natural immunity to vaccine-induced immunity: reinfections versus breakthrough infections

Siyan Gazit, Roei Shlezinger, Galit Perez, Roni Lotan, Asaf Peretz, Amir Ben-Tov, Dani Cohen, Khitam Muhsen, Gabriel Chodick, Tal Patalon

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Abstract

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Abstract

Background Reports of waning vaccine-induced immunity against COVID-19 have begun to surface. With that, the comparable long-term protection conferred by previous infection with SARS-CoV-2 remains unclear.

Methods We conducted a retrospective observational study comparing three groups: (1) SARS-CoV-2-naïve individuals who received a two-dose regimen of the BioNTech/Pfizer mRNA BNT162b2 vaccine, (2) previously infected individuals who have not been vaccinated, and (3) previously infected *and* single dose vaccinated individuals. Three multivariate logistic regression models were applied. In all models we evaluated four outcomes: SARS-CoV-2 infection, symptomatic disease, COVID-19-related hospitalization and death. The follow-up period of June 1 to August 14, 2021, when the Delta variant was dominant in Israel.

Results SARS-CoV-2-naïve vaccinees had a 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection with the Delta variant compared to those previously infected, when the first event (infection or vaccination) occurred during January and February of 2021. The increased risk was significant ($P < 0.001$) for symptomatic disease as well. When allowing the infection to occur at any time before vaccination (from March 2020 to February 2021), evidence of waning natural immunity was demonstrated, though SARS-CoV-2 naïve vaccinees had a 5.96-fold (95% CI, 4.85 to 7.33) increased risk for breakthrough infection and a 7.13-fold (95% CI, 5.51 to 9.21) increased risk for symptomatic disease. SARS-CoV-2-naïve vaccinees were also at a greater risk for COVID-19-related-hospitalizations compared to those that were previously infected.

Conclusions This study demonstrated that natural immunity confers longer lasting and stronger protection against infection, symptomatic disease and hospitalization caused by the Delta variant of SARS-CoV-2, compared to the BNT162b2 two-dose vaccine-induced immunity. Individuals who were both previously infected with SARS-CoV-2 and given a single dose of the vaccine gained additional protection against the Delta variant.

Competing Interest Statement

The authors have declared no competing interest.

Funding Statement

There was no external funding for the project.

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Yes

The details of the IRB/oversight body that provided approval or exemption for the research described are given below:

This study was approved by the MHS (Maccabi Healthcare Services) Institutional Review Board (IRB). Due to the retrospective design of the study, informed consent was waived by the IRB, and all identifying details of the participants were removed before computational analysis.

All necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived.

Yes

I understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance).

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Footnotes


- The authors declare they have no conflict of interest.
- **Funding:** There was no external funding for the project.

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Massive Israeli Study Comes to Bombshell Conclusion About Natural COVID Immunity



Israelis wait to get a rapid COVID-19 antigenic test at Israel's Magen David Adom medical service in Jerusalem on Aug. 8, 2021. (Menahem Kahana - AFP / Getty Images)



By Jack Davis • August 30, 2021 at 10:47am

BioNTech vaccine.

The study found those who were once infected with COVID-19 were less likely to get the delta variant, develop symptoms or become hospitalized with a serious case of COVID than vaccinated individuals who were never infected, according to a report in the peer-reviewed journal Science.

The study also found those who were previously infected with COVID and received one dose of the vaccine were even more protected against the delta variant.

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“This study demonstrated that natural immunity confers longer-lasting and stronger protection against infection, symptomatic disease and hospitalization caused by the Delta variant of SARS-CoV-2, compared to the BNT162b2 two-dose vaccine-induced immunity. Individuals who were both previously infected with SARS-CoV-2 and given a single dose of the vaccine gained additional protection against the Delta variant,” the study said.

The study pointed out its unique nature.

“This is the largest real-world observational study comparing natural immunity, gained through previous SARS-CoV-2 infection, to vaccine-induced immunity, afforded by the BNT162b2 mRNA vaccine,” the study said.

“Our large cohort, enabled by Israel’s rapid rollout of the mass-vaccination campaign, allowed us to investigate the risk for additional infection – either a breakthrough infection in vaccinated individuals or reinfection in previously infected ones – over a longer period than thus far described.”

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In the Science report, Meredith Wadman wrote it was a good news/ bad news situation.

“The study demonstrates the power of the human immune system, but infectious disease experts emphasized that this vaccine and others for COVID-19 nonetheless remain highly protective against severe disease and death,” she wrote, noting the risk of the disease is such that people should not seek to be intentionally infected.

Wadman noted the report could impact policy because “Vaccine mandates don’t necessarily

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exempt those who had a SARS-CoV-2 infection already and the current U.S. recommendation is that they be fully vaccinated,” adding that some experts believe those already infected should get one dose of the vaccine and no more.

“It’s a textbook example of how natural immunity is really better than vaccination,” said Charlotte Thålin, a physician and immunology researcher at Danderyd Hospital and the Karolinska Institute. “To my knowledge, it’s the first time [this] has really been shown in the context of COVID-19.”

There is a caution. While the study shows the benefits of natural immunity, it “doesn’t take into account what this virus does to the body to get to that point,” said Marion Pepper, an immunologist at the University of Washington, Seattle.

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when you bolster that with one dose of vaccine, you take it to levels you can't possibly match with any vaccine in the world right now.”

Writing in the Spectator, columnist Ross Clark offered his take on the study.

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The study “suggests that the efficacy of the Pfizer vaccine — so impressive in trials — is not strong enough to bring about the kind of herd immunity we might have gained by letting the virus pass through the population,” he wrote.

“It also suggests that we might be wasting our time trying to foist jabs on the young when they may have gained better, stronger immunity to COVID through natural infection.”

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“But one of the most interesting issues is the new light it sheds on the debate over vaccinating children; perhaps it is better to simply allow them to be infected on the grounds they're highly

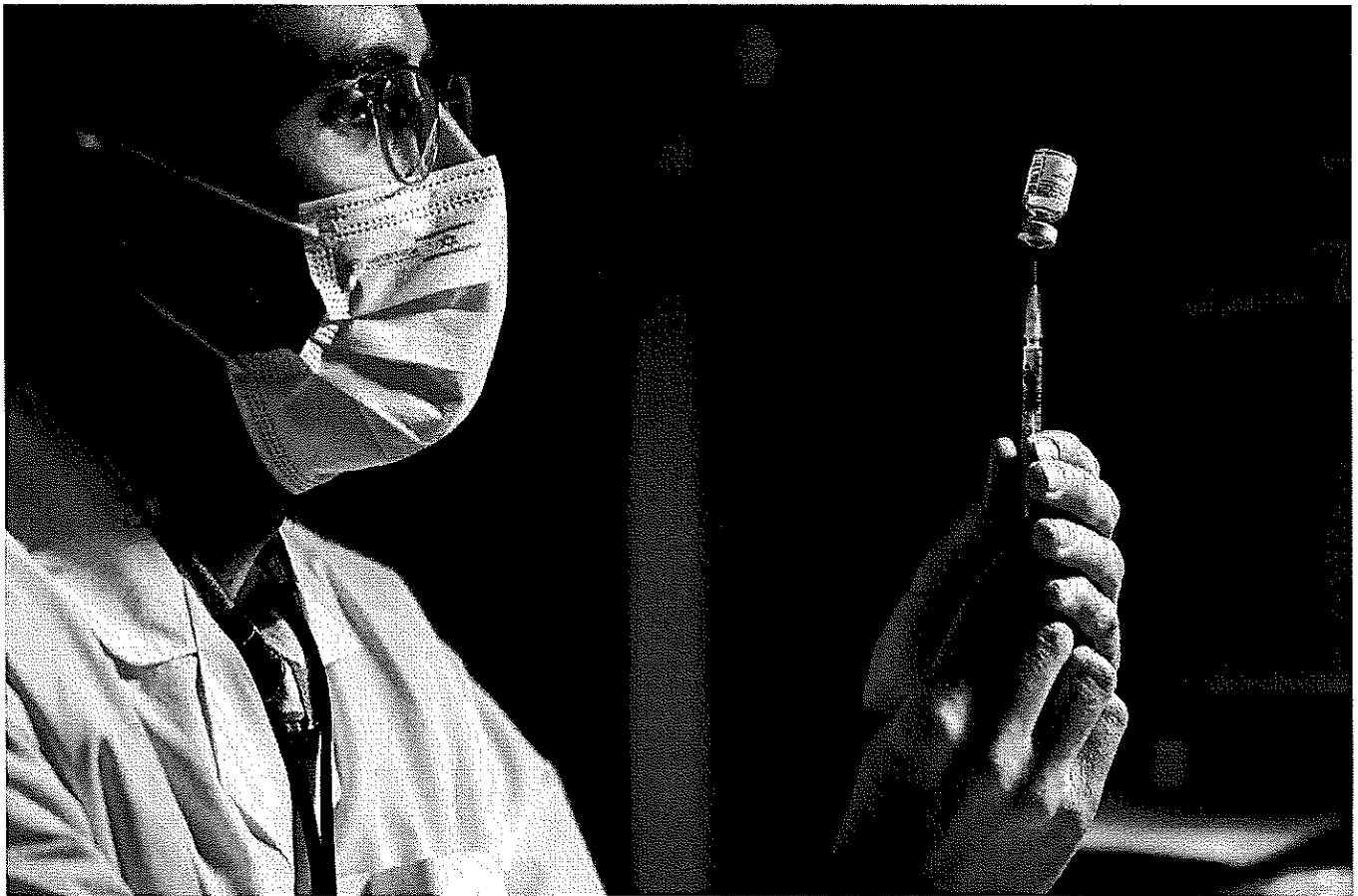
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SCIENCEINSIDER HEALTH

Having SARS-CoV-2 once confers much greater immunity than a vaccine—but vaccination remains vital

Israelis who had an infection were more protected against the Delta coronavirus variant than those who had an already highly effective COVID-19 vaccine

26 AUG. 2021 • 8:00 P.M. • BY MEREDITH WAGMAN



A Jerusalem health care worker in January prepares a dose of the Pfizer-BioNTech vaccine designed to prevent COVID-19. AHMAD GHARABLI/AFP VIA GETTY IMAGES

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A version of this story appeared in Science, Vol 373, Issue 6559.

The natural immune protection that develops after a SARS-CoV-2 infection offers considerably more of a shield against the Delta variant of the pandemic coronavirus than two doses of the Pfizer-BioNTech vaccine, according to a large Israeli study that some scientists wish came with a “Don’t try this at home” label. The newly released data show people who once had a SARS-CoV-2 infection were much less likely than never-infected, vaccinated people to get Delta, develop symptoms from it, or become hospitalized with serious COVID-19.

The study demonstrates the power of the human immune system, but infectious disease experts emphasized that this vaccine and others for COVID-19 nonetheless remain highly protective against severe disease and death. And they caution that intentional infection among unvaccinated people would be extremely risky. “What we don’t want people to say is: ‘All right, I should go out and get infected, I should have an infection party,’” says Michel Nussenzweig, an immunologist at Rockefeller University who researches the immune response to SARS-CoV-2 and was not involved in the study. “Because somebody could die.”

The researchers also found that people who had SARS-CoV-2 previously and received one dose of the Pfizer-BioNTech messenger RNA (mRNA) vaccine were more highly protected against reinfection than those who once had the virus and were still unvaccinated. The new work could inform discussion of whether previously infected people need to receive both doses of the Pfizer-BioNTech vaccine or the similar mRNA vaccine from Moderna. Vaccine mandates don’t necessarily exempt those who had a SARS-CoV-2 infection already and the current U.S. recommendation is that they be fully vaccinated, which means two mRNA doses or one of the Johnson & Johnson adenovirus-based vaccine. Yet one mRNA dose might be enough, some scientists argue. And other countries including Germany, France, Italy, and Israel administer just one vaccine dose to previously infected people.

The study, conducted in one of the most highly COVID-19–vaccinated countries in the world, examined medical records of tens of thousands of Israelis, charting their infections, symptoms, and hospitalizations between 1 June and 14 August, when the Delta variant predominated in Israel. It’s the largest real-world observational study so far to compare natural and vaccine-induced immunity to SARS-CoV-2, according to its leaders.

The research impresses Nussenzweig and other scientists who have reviewed a preprint of the results, posted yesterday on medRxiv. “It’s a textbook example of how natural immunity is really better than vaccination,” says Charlotte Thålin, a physician and immunology researcher at Danderyd Hospital and the Karolinska Institute who studies the immune responses to SARS-CoV-2. “To my knowledge, it’s the first time [this] has really been shown in the context of COVID-19.”

Still, Thålin and other researchers stress that deliberate infection among unvaccinated people would put them at significant risk of severe disease and death, or the lingering, significant symptoms of what has been dubbed Long Covid. The study shows the benefits of natural immunity, but “doesn’t take into account what this virus does to the body to get to that point,” says Marion Pepper, an immunologist at the University of Washington, Seattle. COVID-19 has already killed more than 4 million people worldwide and there are concerns that Delta and other SARS-CoV-2 variants are deadlier than the original virus.

The new analysis relies on the database of Maccabi Healthcare Services, which enrolls about 2.5 million Israelis. The study, led by Tal Patalan and Sivan Gazit at KSM, the system’s research and innovation arm, found in two analyses that never-infected people who were vaccinated in January and February were, in June, July, and the first half of August, six to 13 times more likely to get infected than unvaccinated people who were previously infected with the coronavirus. In one analysis, comparing more than 32,000 people in the health system, the risk of developing symptomatic COVID-19 was 27 times higher among the vaccinated, and the risk of hospitalization eight times higher.

“The differences are huge,” says Thålin, although she cautions that the numbers for infections and other events analyzed for the comparisons were “small.” For instance, the higher hospitalization rate in the 32,000-person analysis was based on just eight hospitalizations in a vaccinated group and one in a previously infected group. And the 13-fold increased risk of infection in the same analysis was based on just 238 infections in the vaccinated population, less than 1.5% of the more than 16,000 people, versus 19 reinfections among a similar number of people who once had SARS-CoV-2.

No one in the study who got a new SARS-CoV-2 infection died—which prevented a comparison of death rates but is a clear sign that vaccines still offer a formidable shield against serious disease, even if not as good as natural immunity. Moreover, natural immunity is far from perfect. Although reinfections with SARS-CoV-2 are rare, and often asymptomatic or mild, they can be severe.

In another analysis, the researchers compared more than 14,000 people who had a confirmed SARS-CoV-2 infection and were still unvaccinated with an equivalent number of previously infected people who received one dose of the Pfizer-BioNTech vaccine. The team found that the unvaccinated group was twice as likely to be reinfected as the singly vaccinated.

“We continue to underestimate the importance of natural infection immunity ... especially when [infection] is recent,” says Eric Topol, a physician-scientist at Scripps Research. “And when you bolster that with one dose of vaccine, you take it to levels you can’t possibly match with any vaccine in the world right now.”

Nussenzweig says the results in previously infected, vaccinated people confirm laboratory findings from a series of papers in *Nature* and *Immunity* by his group, his Rockefeller University colleague Paul Bieniasz and others—and from a [preprint](#) posted this month by Bieniasz and his team. They show, Nussenzweig says, that the immune systems of people who develop natural immunity to SARS-CoV-2 and then get vaccinated produce exceptionally broad and potent antibodies against the coronavirus. The preprint, for example, reported that people who were previously infected and then vaccinated with an mRNA vaccine had antibodies in their blood that neutralized the infectivity of another virus, harmless to humans, that was engineered to express a version of the coronavirus spike protein that contains 20 concerning mutations. Sera from vaccinated and naturally infected people could not do so.

As for the Israel medical records study, Topol and others point out several limitations, such as the inherent weakness of a retrospective analysis compared with a prospective study that regularly tests all participants as it tracks new infections, symptomatic infections, hospitalizations, and deaths going forward in time. “It will be important to see these findings replicated or refuted,” says Natalie Dean, a biostatistician at Emory University.

She adds: “The biggest limitation in the study is that testing [for SARS-CoV-2 infection] is still a voluntary thing—it’s not part of the study design.” That means, she says, that comparisons could be confounded if, for example, previously infected people who developed mild symptoms were less likely to get tested than vaccinated people, perhaps because they think they are immune.

Nussenzweig’s group [has published data](#) showing people who recover from a SARS-CoV-2 infection continue to develop increasing numbers and types of coronavirus-targeting antibodies for up to 1 year. By contrast, he says, twice-vaccinated people stop seeing increases “in the potency or breadth of the overall memory antibody compartment” a few months after their second dose.

For many infectious diseases, naturally acquired immunity is known to be more powerful than vaccine-induced immunity and it often lasts a lifetime. Other coronaviruses that cause the serious human diseases [severe acute respiratory syndrome](#) and [Middle East respiratory syndrome](#) trigger robust and persistent immune responses. At the same time, several other human coronaviruses, which usually cause little more than colds, are known to reinfect people regularly.

**Clarification, 28 August, 1:20 p.m.: This article has been updated to reflect that in an analysis involving previously infected people who received one vaccine dose, not all people received that dose after, rather than before, becoming infected. It has also been updated to clarify that the vaccinated people in the other two analyses had never been infected prior to being vaccinated.*

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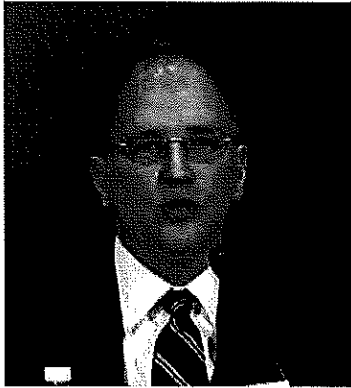


[Meredith Wadman](#) ✉ 🐦

Author

After filing a lawsuit arguing he obtained "natural immunity" from COVID-19 after being infected with the novel coronavirus, George Mason University granted a professor a medical exemption from its COVID-19 vaccine mandate.

Lawyers for Todd Zywicki, a law professor at the Fairfax, Virginia, university, announced the agreement Tuesday, the Washington Post reported.



George Mason University Professor Todd Zywicki testifies to the Senate Banking Committee on April 5, 2016. (Wikimedia Commons)

"I am gratified that George Mason has given me a medical exemption to allow me to fulfill my duties this fall semester in light of unprecedented circumstances," Zywicki said.

"I speak for tens of millions of Americans in the same circumstances I am in, and I call on leaders across the country to develop humane and science-based approaches as opposed to one-size-fits-all policies."

Zywicki filed affidavits from his doctor stating he has natural immunity from the virus after having fully recovered from COVID-19. And the lawsuit argued there is substantial scientific evidence indicating natural immunity from the virus is stronger than immunity through various vaccines.

A spokesman for George Mason University declined comment on any medical accommodation, citing "state policy regarding personnel information and confidentiality of health information."

But no accommodation will be given based on natural immunity to COVID, the spokesman said, arguing it conflicts with CDC guidance.

"His litigation had no impact on the consideration of his request for a medical exemption from the vaccination requirement," the spokesman said. "Mason encourages everyone, including those who previously had COVID-19, to get vaccinated, and will continue to take the steps necessary to protect the Mason community from COVID."

'Robust and durable protection'

Zywicki, who has been at George Mason for 24 years, explained his case in an op-ed published Aug. 6 by the Wall Street Journal.

He said he contracted and recovered from COVID-19 in the spring of 2020, which later was confirmed through a positive antibody test. And multiple positive antibody tests "have since confirmed that I continue to have a robust level of immune protection."

The university's "coercive mandate," he wrote, "violates my constitutional right to bodily integrity for no compelling reason."

The university requires students to be vaccinated by Aug. 1 and faculty and staff by Aug. 15. Those who do not comply must show a medical or religious exemption.

In his op-ed, Zywicki cited clinical studies from Israel, the Cleveland Clinic, England and elsewhere that have demonstrated that natural immunity to SARS-CoV-2 "provides robust

and durable protection against reinfection comparable to or better than that provided by the most effective vaccines.”

He argued further that it “isn’t merely unnecessary for me to get the shot.”

“It’s potentially dangerous. Covid-recovered individuals have been mostly excluded from the vaccine clinical trials, rendering any claims about the purported safety for this group largely speculative,” he wrote.

Last week, the Times noted, the CDC highlighted a new study indicating unvaccinated people were twice as likely to get reinfected with COVID-19.

But many a recent Israeli study cited by Zywicki showed natural immunity is 6.7 times greater than for vaccinated people.

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