Surveying large swaths of the public for antibodies to the new coronavirus promises to show how widespread undiagnosed infections are, how deadly the virus really is, and whether enough of the population has become immune for social distancing measures to be eased. But the first batch of results has generated more controversy than clarity.

The survey results, from Germany, the Netherlands, and several locations in the United States, find that anywhere from 2% to 30% of certain populations have already been infected with the virus. The numbers imply that confirmed COVID-19 cases are an even smaller fraction of the true number of people infected than many had estimated and that the vast majority of infections are mild. But many scientists question the accuracy of the antibody tests and complain that several of the research groups announced their findings in the press rather than in preprints or published papers, where their data could be scrutinized. Critics are also wary because some of the researchers are on record advocating for an early end to lockdowns and other control measures, and claim the new prevalence figures support that call.

Some observers warn the coronavirus' march through the population has only just begun, and that even if the antibody results can be believed, they don't justify easing controls. "You would have hoped for 45% or even 60% positive," says Mark Perkins, a diagnostics expert at the World Health Organization. "That would mean that there is lots of silent transmission, and a lot of immunity in the population. It now looks like, sadly, that's not true. Even the high numbers are relatively small."

The many different academic and commercial tests for coronavirus antibodies are still being refined and validated. They can show whether someone's immune system has encountered the virus. But because no one knows what level of antibodies, if any, confers protection against the new virus, the tests can't tell whether a person is immune to a future infection. And no one knows how long such immunity might last.

A German antibody survey was the first out of the gate several weeks ago. At a press conference on 9 April, virologist Hendrik Streeck from the University of Bonn announced preliminary results from a town of about 12,500 in Heinsberg, a region in Germany that had been hit hard by COVID-19. He told reporters his team had found antibodies to the virus in 14% of the 500 people tested. By comparing that number with the recorded deaths in the town, the study suggested the virus kills only 0.37% of the people infected. (The rate for seasonal influenza is about 0.1%.) The team concluded in a two-page summary that "15% of the population can no longer be infected with SARS-CoV-2, and the process of reaching herd immunity is already underway." They recommended that politicians start to lift some of the regions' restrictions.

Streeck had argued even before the study that the virus is less serious than feared and that the effects of long shutdowns may be just as bad if not worse than the damage the virus could do. However, Christian Drosten, a virologist at Charité University Hospital in Berlin, told reporters later that day that no meaningful conclusions could be drawn from the antibody study based on the limited information Streeck presented. Drosten cited uncertainty about what level of antibodies provides protection and noted that the study sampled entire households. That can lead to overestimating infections, because people living together often infect each other.

Streeck and his colleagues claimed the commercial antibody test they used has "more than 99% specificity," but a Danish group found the test produced three false positives in a sample of 82 controls, for a specificity of only 96%. That means that in the Heinsberg sample of 500, the test could have produced more than a dozen false positives out of roughly 70 the team found.
A California serology study of 3300 people released last week in a preprint also drew strong criticisms. The lead authors of the study, Jay Bhattacharya and Eran Bendavid, who study health policy at Stanford University, worked with colleagues to recruit the residents of Santa Clara county through ads on Facebook. Fifty antibody tests were positive—about 1.5%. But after adjusting the statistics to better reflect the county’s demographics, the researchers concluded that between 2.49% and 4.16% of the county’s residents had likely been infected. That suggests, they say, that the real number of infections was as many as 80,000. That’s more than 50 times as many as viral gene tests had confirmed and implies a low fatality rate—a reason to consider whether strict lockdowns are worthwhile, argue Bendavid and co-author John Ioannidis, who studies public health at Stanford.

On the day the preprint posted, co-author Andrew Bogan—a venture capitalist with a molecular biology Ph.D.—published an op-ed in The Wall Street Journal asking, “If policy makers were aware from the outset that the Covid-19 death toll would be closer to that of seasonal flu … would they have resourced tens of millions of jobs and livelihoods?” The op-ed did not initially disclose its role in the study.

Yet Twitter threads and blog posts outlined a litany of apparent problems with the Santa Clara study. Recruiting through Facebook likely attracted people with COVID-19–like symptoms who wanted to be tested, boosting the apparent positive rate. Because the absolute numbers of positive tests were so small, false positives may have been nearly as common as real infections. The study also had relatively few participants from low-income and minority populations, meaning the statistical adjustments the researchers made could be way off. “I think the authors of the paper owe us all an apology,” wrote Columbia University statistician and political scientist Andrew Gelman in an online commentary. The numbers “were essentially the product of a statistical error,” Bhattacharya says he is preparing an appendix that addresses the criticisms. But, he says, “The argument that the test is not specific enough to detect real positives is deeply flawed.”

Bhattacharya and Bendavid have also collaborated with Neeraj Sood, a health policy expert at the University of Southern California, to do a similar study in Los Angeles county. They used the same antibody test on 846 people selected by a marketing firm to represent the county’s demographics. In a press release issued this week, they estimated that roughly 4% of the county’s adult population has antibodies to the virus—as many as 300,000 people. (Sood told Science that 35 subjects tested positive.)

Another serology study, in the Netherlands, produced a similar figure for antibody prevalence that was revealed in the country’s House of Representatives on 16 April. Hans Zaaier, a virologist at Sanquin, the Dutch national blood bank, who helped lead the study, says the team used a commercial test, which “consistently shows superior results” in validation studies, but didn’t provide more details. The results made it clear that the country was not yet near the “herd immunity” that some had hoped for. Nevertheless, the government said on 21 April that it would start to lift some restrictions in the coming weeks, opening elementary schools and allowing children’s sports teams to practice.

A small study in the Boston suburb of Chelsea has found the highest prevalence of antibodies so far. Prompted by the striking number of COVID-19 patients from Chelsea colleagues had seen, Massachusetts General Hospital pathologists John Iafrate and Vivek Naranbhai quickly organized a local serology survey. Within 2 days, they collected blood samples from 200 passersby on a street corner. That evening, they processed the samples—and shared the results with a reporter from The Boston Globe. Sixty-three were positive—31.5%. The result carries several large caveats. The team used a test whose maker, BioMedicines, says it has a specificity of only about 90%, though Iafrate says MGH’s own validation tests found a specificity of higher than 99.5%. And pedestrians on a single corner “aren’t a representative sample” of the town, Naranbhai acknowledges.

The pair says a paper describing the team’s results has been submitted to a journal but they shared the data with The Boston Globe first because “we felt there was an urgent infection control issue in Chelsea that warranted getting the information out.” The Boston researchers do not think quarantines should be eased, however. Better containment is urgently needed in Chelsea, they say, to help prevent further spread both within the community and in the larger Boston area.

Even if the antibody surveys show a COVID-19 death rate well below 1%, says Michael Osterholm, an infectious disease expert at the University of Minnesota, Twin Cities, control measures will be needed for a long time to avoid overwhelmed hospitals. “The seroprevalence data only confirm the challenge we face. The data [these studies] are generating ... is just showing how hard this is,” he says.

COVID-19

Firms to help prioritize treatment and vaccine trials

By Jocelyn Kaiser

n a remarkable display of urgency, researchers are already developing more than 100 treatments and vaccines to stem the COVID-19 pandemic. But some onlookers worry the sprawling effort could waste time and resources on duplicated studies and weak candidates.

In one key activity, the Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV) initiative will inventory drug and vaccine candidates and decide which should get priority for U.S. funding and testing in humans. The top-rated compounds will get preferred access to NIH’s $1.8 billion pot of COVID-19 research money, as well as to a dozen or more NIH clinical trial networks originally set up for other diseases. ACTIV also aims to streamline trials by establishing “master protocols” for assessing a drug’s efficacy. The public-private partnership will “bring all the full resources and ideas together in a variety of ways that neither sector could do alone,” NIH Director Francis Collins said.

NIH says ACTIV is primarily focused on the United States, but it will work with the European Medicines Agency and other COVID-19 research coordination efforts around the world to avoid duplication.

One major player is noticeably absent from the list of ACTIV’s partners: the World Health Organization (WHO), which is coordinating a large global trial of several drugs called SOLIDARITY (Science, 27 March, p. 1412). WHO Chief Scientist Soumya Swaminathan says her agency welcomes ACTIV, especially to develop treatments. For vaccines, she says WHO is well-positioned to coordinate global trials. “The best and most efficient way would be to consider one large global study which would look at different vaccine candidates,” she says. NIH says ACTIV will take WHO’s programs into account as it seeks to accelerate studies.

With reporting by Jon Cohen and David Malakoff.
First antibody surveys draw fire for quality, bias
Gretchen Vogel

Science 368 (6489), 350-351.
DOI: 10.1126/science.368.6489.350