for COVID-19 deaths in the United Kingdom, because the lockdown started a week later than the results of any of the models assume, by which time higher amounts of the disease were already circulating.

"They didn't get it right," says Coveney. "They ran the simulation correctly: it's just that they didn't know how to extract the correct probabilistic description from it." Coveney said he couldn't comment on whether running an ensemble model would have altered policy, but Rowland Kao, an epidemiologist and data scientist at the University of Edinburgh, UK, points out that the government compares and synthesizes the results of several different COVID-19 models. "It would be overly simplified to consider that decision-making is based on a single model," he says.

Improved models

Ferguson accepts most of Coveney's points about the benefits of performing probabilistic forecasts, but says that "we just weren't in a position to do that in March". The Imperial group has significantly improved its models since then, he adds. For example, it now presents the uncertainty in CovidSim inputs using Bayesian statistical tools — already common in some models of illnesses such as the livestock disease foot-and-mouth. And a simpler model, he adds, was used to inform the UK government's decision to reintroduce lockdown measures in England this month. This model is more agile than CovidSim: "Because we can run it several times a week, it's much easier to fit the data in real time, allowing for uncertainty," Ferguson says.

"This sounds like a step in the right direction, and is aligned with the conclusions of our paper," says Coveney.

The choice of technique often comes down to a computational trade-off, Ferguson says. "If you want to routinely properly characterize all the uncertainty, then that is much easier with a less computationally intensive model."

Bayesian tools are an improvement, says Tim Palmer, a climate physicist at the University of Oxford, UK, who pioneered the use of ensemble modelling in weather forecasting. But only ensemble modelling techniques that are run on the most powerful computers will deliver the most reliable pandemic projections, he says. Such techniques transformed the reliability of climate models, he adds, helped by the coordination of the Intergovernmental Panel on Climate Change (IPCC).

"We need something like the IPCC for these pandemic models. We need some kind of international facilities where these models can be developed properly," Palmer says. "It has been rushed because of the urgency of the situation. But to take this forward, we need some kind of international organization that can work on synthesizing epidemiological models from around the world."

Roughly one in five people infected with SARS-CoV-2 don't experience symptoms.

WHAT THE DATA SAY ABOUT ASYMPTOMATIC COVID INFECTIONS

People without symptoms can transmit the virus, but estimating their contribution to outbreaks is tricky.

By Bianca Nogrady

Many people don't experience any symptoms after becoming infected with SARS-CoV-2. But how many, and what is their role in spreading COVID-19? These have been key questions since the beginning of the pandemic.

Now, evidence suggests that about one in five infected people will experience no symptoms, and they will transmit the virus to significantly fewer people than someone with symptoms. But researchers are divided about whether asymptomatic infections are acting as a silent driver of the pandemic.

Although there is a growing understanding of asymptomatic infections, researchers say that people should continue to use measures to reduce viral spread, including social distancing and wearing masks, regardless of whether they have symptoms.

The issue with estimating the rate of asymptomatic COVID-19 is distinguishing between people who are asymptomatic and pre-symptomatic, says Krutika Kuppalli, an infectious-disease researcher at the Medical University of South Carolina in Charleston. "Asymptomatic is someone who never developed symptoms ever throughout the course of their disease, and pre-symptomatic is somebody who has mild symptoms before they do go on to develop symptoms," Kuppalli says.

Research early in the pandemic suggested that the rate of asymptomatic infections could be as high as 81%. But a meta-analysis

"These people are not the secret drivers of this pandemic."

published last month[1], which included 13 studies involving 21,708 people, calculated the rate of asymptomatic presentation to be 17%. The analysis defined asymptomatic people as those who showed none of the key COVID-19 symptoms during the entire follow-up period, and the authors included only studies that followed participants for at least seven days. Evidence suggests that most people develop symptoms in 7–13 days, says lead author Oyungerel Byambasuren, a biomedical researcher at the Institute for Evidence-Based

EZRA ACAYAN/GETTY

Healthcare at Bond University in Gold Coast, Australia.

The review also found that asymptomatic individuals were 42% less likely to transmit the virus than symptomatic people.

One reason that scientists want to know how frequently people without symptoms transmit the virus is because these infections largely go undetected. Testing in most countries is targeted at those with symptoms.

As part of a large population study in Geneva, Switzerland, researchers modelled viral spread among people living together. In a manuscript posted on medRxiv this month[2], they report that the risk of an asymptomatic person passing the virus to others in their home is about one-quarter of the risk of transmission from a symptomatic person.

Although transmission risk from asymptomatic people is lower, they might still present a public-health risk because they are more likely to be out in the community than isolated at home, says Andrew Azman, an infectious-disease epidemiologist at the Johns Hopkins Bloomberg School of Public Health in Baltimore, Maryland, who is based in Switzerland and was a co-author on the study. "This massive pool of interacting 'asymptomatics' in the community probably suggests that a sizeable portion of transmission events are from asymptomatic transmissions," he says.

But other researchers disagree about the extent to which asymptomatic infections are contributing to community transmission. If the studies are correct in finding that asymptomatic people are a low transmission risk, "these people are not the secret drivers of this pandemic", says Byambasuren. They "are not coughing or sneezing as much".

Muge Cevik, an infectious-disease researcher at the University of St Andrews, UK, points out that because most people are symptomatic, concentrating on identifying them will probably eliminate most transmission events.

To understand what is happening in people with no symptoms, Cevik and colleagues conducted a systematic review and meta-analysis[3] of 79 studies on the viral dynamics and transmissibility of SARS-CoV-2. Some studies showed that those without symptoms had similar initial levels of viral particles in a throat swab when compared with people with symptoms. But asymptomatic people seem to clear the virus faster and are infectious for a shorter period.

The immune systems of asymptomatic individuals might be able to neutralize the virus more rapidly, says Cevik.

1. Byambasuren, O. *et al. J. Assoc. Med. Microbiol. Infect. Dis. Can.* https://doi.org/10.3138/jammi-2020-0030 (2020).
2. Bi, Q. *et al*. Preprint at medRxiv https://doi.org/10.1101/2020.11.04.20225573 (2020).
3. Cevik, M. *et al. Lancet Microbe* https://doi.org/10.1016/S2666-5247(20)30172-5 (2020).

FUNDING FOR DISPUTED STEM-CELL INSTITUTE SPARKS DEBATE

California agency will receive billions from the state — but some scientists oppose the plan.

By Nidhi Subbaraman

Voters in California have approved US$5.5 billion in funding for stem-cell and other medical research, granting a lifeline to a controversial state agency. But scientists are split over whether the California Institute for Regenerative Medicine (CIRM) in Oakland is a worthwhile investment for the US state — or for the field of stem-cell research.

A measure to authorize new funds for CIRM, called Proposition 14, appeared on California ballots in the recent US election. After more than a week of vote counting, on 12 November the Associated Press announced that California had passed the proposal.

Critics of CIRM are concerned about oversight at the state agency, which has faced complaints about potential conflicts of interest among its board members for years. They also point out that the field has grown and now receives federal support, making state funding hard to justify — especially amid a pandemic that has imperilled California's economy.

"Unfortunately, Proposition 14 sets a bad example for the use of public money for the advancement of science," says Zach Hall, a neurobiologist who led CIRM as its first president between 2005 and 2007.

Launched 16 years ago, CIRM drew top researchers to the state, and put California on the map as a hub for regenerative-medicine research. With CIRM's original $3 billion in state money running out last year, California property developer Robert Klein — an advocate of stem-cell research after his son was diagnosed with type 1 diabetes, and the agency's original backer — began canvassing support for new funding. His efforts landed Proposition 14 on this year's ballot.

"It is extraordinary that the patient-advocacy groups and the medical societies and the scientific societies have been able to act as a single coalition to reach millions of California voters," says Klein, who co-wrote the 2004 ballot measure creating the agency.

Some scientists are proponents of the agency. "It is very exciting that Prop. 14 passed and that CIRM will continue its funding," says Cato Laurencin, a biomedical engineer at the University of Connecticut in Farmington, who is not funded by the institute. "This field is at a bit of an inflection point in terms of our understanding of stem-cell science."

CIRM emerged in 2004, when stem-cell research was a nascent field. Stem cells' ability to renew themselves offered the promise of treatments for challenging conditions such as heart disease and stroke, in which cells are irreversibly damaged. Much work at the time relied on stem cells obtained from human embryos donated by fertility clinics. Citing ethical concerns about the destruction of fertilized embryos, in 2001, US president George W. Bush severely restricted research in this area, and the science hit a wall.

Three years later, CIRM's launch was a boon. "It gave a tremendous boost to the field at a time when things looked very bad," says Hall.

CIRM has since handed out (as of June 2020) $2.7 billion in grants to California scientists studying a variety of diseases, including diabetes, AIDS and leukaemia. It has built a dozen research facilities, funded more than 60 clinical trials and, according to an independent, agency-funded report, helped create more than 56,500 jobs in the state.

A worthwhile investment?

But the agency has also drawn criticism for poor management of its public funds. A 2012 Institute of Medicine report pointed out that CIRM's policy of allowing board members to vote on grants or issues benefiting their institutions posed a potential conflict of interest.

CIRM attempted to address some of the criticism in 2013, when it asked board members from agency-funded universities to abstain from voting on grants, among other changes.

Hall says that Proposition 14 doesn't describe a clear scientific vision. "You could argue that California would do better, economically and scientifically, to have a CRISPR institute," he says, arguing that the revolutionary precision gene-editing tool is better placed to benefit from such a huge infusion of cash.

Responding to the criticisms, Klein says he crafted the proposal with the guidance of multiple groups of experts, and kept the mandate deliberately broad to allow for flexibility as the field grows. "There's an intent here," he says, "to have the agency be responsive to the development of science."