at the end of April, software engineers disparaged its quality and said the simulation needed to be repeated by others. Media articles cast further doubt on the work by reporting online comments suggesting that other scientists had problems rerunning the code.

Ferguson — who didn't comment on the criticisms at the time — agrees that the simulation didn't use best-practice coding methods, because it was adapted from a model created more than a decade ago to simulate an influenza pandemic. There was no time to generate new simulations of the same complexity from scratch, he says, but criticisms of the code didn't affect the science of the simulation.

The politicized debate around the Imperial code demonstrates why scientists might still hesitate to openly release the code underlying their work, researchers say: academic programs often have shortcomings that software engineers can pick at. Although some journals now ask peer reviewers to rerun and verify code, sharing it publicly is still far from

"The test is the best possible verification given the state of the art in computational science."

an academic norm. The time researchers might have to spend either helping people use their software or refuting claims stemming from its misuse is a "big worry" among many academics, says Neil Chue Hong, founding director of the Software Sustainability Institute in Edinburgh.

Even so, scientists ought to release their code and document how it works, says Stephen Eglen, the neuroscientist at the University of Cambridge, UK, who reran the Imperial code and reported his results on 1 June (go.nature.com/3fqihs8).

Reproducible software

This year, Eglen co-founded an organization called Codecheck to help to evaluate the computer programs behind scientific studies. His work tests whether it is possible to reproduce the results of a computational analysis, given its data inputs and code. He didn't review the epidemiology that went into the Imperial simulation — such as estimates of the fatality rate associated with the coronavirus. British science advisers, however, asked multiple teams to model the emerging pandemic, and they produced results similar to Imperial's.

Researchers working with London's Royal Society as part of the Rapid Assistance in Modelling the Pandemic (RAMP) effort have told *Nature* that they also privately ran exercises to verify the code in March. After the original Imperial study was posted online, RAMP researchers worked with Ferguson's team and software firms Microsoft and GitHub to clean up the software for public release on the GitHub website, a repository where developers (including scientists) share code. As part of this, they checked that the public and original code reliably produced the same findings from the same input.

The RAMP group's work included a separate effort to test the robustness of the simulation by trying to break it under various operating conditions, says Graeme Ackland, a physicist at the University of Edinburgh, UK. The team involved posted comments on GitHub as it went. It was these comments that newspaper articles erroneously quoted as casting doubt on whether the code could be reproduced.

Asked what he'd learnt from the furore over the code, Ferguson emphasized how fast the work had to be done. On 27 February, he presented basic estimates of the impact of the pandemic at a private meeting of the main UK scientific advisory group for emergencies; his figures already gave estimates of 500,000 deaths. His team then worked long days to produce the more complex simulations estimating how some policy actions might change the result. Cleaning up and releasing the code was not a top priority at the time, he says.

JAIME REINA/AFP/GETTY

Children account for fewer than 2% of confirmed COVID-19 infections in the United States.

WHY HEALTHY ARTERIES MIGHT HELP KIDS AVOID COVID COMPLICATIONS

Evidence suggests that resistance to blood clotting protects children from serious effects such as strokes.

By David Cyranoski

Since the coronavirus outbreak began, scientists have been trying to work out why children are much less likely than adults to experience severe complications from the infection. Now, research suggests that the answer might lie in children's healthy blood vessels.

Children make up only a small proportion of those infected by SARS-CoV-2, the virus that causes COVID-19. A large survey by the US Centers for Disease Control and Prevention in Atlanta, Georgia, found that children aged 17 and under, who make up 22% of the US population, account for fewer than 2% of confirmed COVID-19 infections across the United States. And, of 2,572 children included in the survey, only 5.7% went to hospital and only 3 died (see go.nature.com/2yocpzf).

Several theories have been proposed to explain why children aren't getting so ill. These include the possibility that they have a stronger and more effective initial immune response to the virus than adults do, and that they might have some immunity as a result

of recent exposure to similar viruses. But a growing number of researchers think that the difference between adults and children might be the condition of their blood vessels.

Many adults with serious COVID-19 experience clotting in their blood vessels, which leads to heart attacks or strokes. The clotting seems to be linked to a malfunctioning endothelium, the smooth tissue that lines blood vessels and normally prevents clotting, says Frank Ruschitzka, a cardiologist at the University Hospital Zurich in Switzerland. Normally, blood clots form only to stop bleeding from an injury, but if the endothelium is damaged, clots can also form.

Ruschitzka and his colleagues have found that SARS-CoV-2 can infect endothelial cells, which are found throughout the body. In a study of three people with COVID-19, two of whom died, Ruschitzka's team found that SARS-CoV-2 had infected the endothelium and caused inflammation and signs of clotting (Z. Varga *et al*. *Lancet* **395**, 1417–1418; 2020). The study was small, so such complications will need to be investigated further, but problems with the endothelium seem to be involved in most cases of COVID-19 that progress to severe or fatal disease in adults, he says.

The endothelium is typically in much better condition in children than in adults. "A kid's endothelium is set up perfectly and then just deteriorates with age," says Paul Monagle, a paediatric haematologist at the Melbourne Children's Campus in Australia.

Monagle and others think that children's blood vessels are better able to withstand a viral attack than are adults'. Further support for this theory is the observation that few children with COVID-19 present with excessive clotting and damaged vessels, he says.

Monagle is trying to understand what happens when the virus enters endothelial cells. He thinks it probably disrupts communication between the cells, platelets and plasma components involved in clotting, and that this communication breakdown leads to excess clots.

He has launched experiments to try to understand this mechanism and to see whether there is something protective about kids' blood vessels that makes them less likely to produce excess clots in response to viral infection. In the first experiment, his team will try to recreate conditions inside the blood vessels of children and adults in the laboratory. The researchers will take cultured endothelial cells infected with SARS-CoV-2 and bathe them in plasma from three sources – children, healthy adults and adults with vascular disease. By comparing how the infected cells interact with the different types of plasma, they should be able to see what makes the signalling in the vessels go awry.

Monagle hopes that studying samples from children will offer clues about what's going wrong in some adults.

LAB-GROWN CELLS MIMIC CRUCIAL MOMENT IN EMBRYO DEVELOPMENT

Artificial structures have developed the rudimentary components of a heart and nervous system.

By David Cyranoski

Scientists have created embryo-like structures that mimic a crucial yet enigmatic stage of human development.

The structures, created from stem cells and called gastruloids, are the first to form a 3D assembly that lays out how the body will take shape. The gastruloids developed rudimentary components of a heart and nervous system, but lacked the components to form a brain and other cell types that would make them capable of becoming a viable fetus.

Researchers are creating ever more sophisticated artificial structures to study embryo development in the laboratory. The latest method for making these structures, published in *Nature* on 11 June, could shed light on the causes of pregnancy loss and early developmental disorders, such as congenital heart conditions and spina bifida (N. Moris *et al*. *Nature* http://doi.org/dzhm; 2020).

The model could help scientists to understand the role of genetics and environmental factors in such disorders, says Fu Jianping, a bioengineer at the University of Michigan in Ann Arbor. "That is now on the horizon."

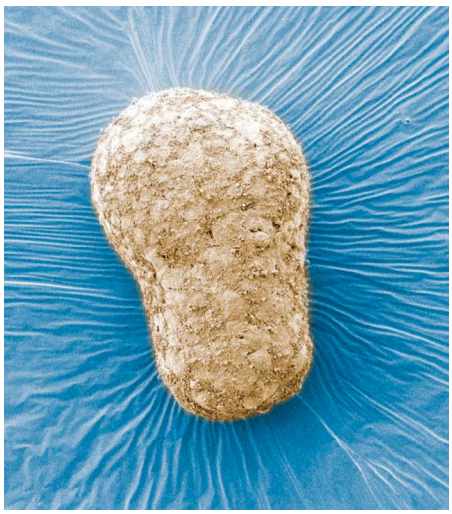
"This is a new system that opens up a whole host of questions."

The artificial structures make it possible to avoid some of the ethical concerns about doing research on human embryos. But as the structures become more advanced and life-like, they, too, might push ethical boundaries, scientists say.

Body blueprint

Human embryos take a momentous leap in their third week, when the largely homogeneous ball of cells starts to differentiate and develop specific characteristics of the body parts they will become, a process known as gastrulation. During this process, the embryo elongates and lays down a body plan with a head and 'tail', often called the head-to-tail axis.

But scientists have never seen this process in action. That is partly because many countries have regulations that stop embryos from being grown in the laboratory for research beyond 14 days after conception.



NAOMI MORIS

Gastruloid structures mimic processes in early embryos.

Over the past year, several research groups have cultured embryonic stem-cell structures that model when cells start to differentiate. The latest model, developed by Naomi Moris and Alfonso Martinez Arias, developmental biologists at the University of Cambridge, UK, and their colleagues in the Netherlands, is the first to show what happens when the blueprint for the body's development is laid out, around 18–21 days after conception.

"This important finding will help us to understand the critical mechanisms of human body planning," says Li Tianqing, a developmental biologist at the Institute of Primate Translational Medicine in Yunnan, China, who also works on embryo-like structures.

The most thrilling result, Moris says, was the formation of pockets of cells that symmetrically straddle the head-to-tail axis. Genetic analysis showed that the cells were those that would eventually go on to form muscles in the trunk, vertebrae, heart and other organs.

Moris says the embryo model will help scientists to study how the pattern of cells emerges, and where it can go wrong. Many diseases are caused by errors in this process, including scoliosis, which causes curvature of the spine. "This is a new system that opens up a whole host of questions," she says.