

# First past the post

From the moment the mysterious illness known as SARS was declared a global threat to health, virologists were racing to develop a diagnostic test. Alison Abbott visits the tiny German lab that got there first.

**C**hristian Drosten is exhausted, but last week he was putting on a brave face for the television crews trying to squeeze into his poky lab. Drosten's fatigue, and his sudden celebrity, both stem from the fact that his team developed the first diagnostic test for severe acute respiratory syndrome (SARS).

Remarkably, Drosten and his colleagues pulled off this feat just 11 days after the World Health Organization (WHO) issued its alert about the disease. And since the test was unveiled on 26 March it has been distributed to more than 150 labs around the world. All in all, it's a considerable achievement for such a small team, given the high-powered virology labs that were engaged in the same quest.

For Drosten, who develops diagnostic tests for viruses and bacteria at the Bernhard Nocht Institute for Tropical Medicine in Hamburg, Germany, the past few weeks have been a whirlwind. The story began in early March, when Drosten and his team — research scientist Stefan Günther and a handful of students — were reading daily Internet postings about a mysterious respiratory illness in Vietnam. “Then, on 15 March, the WHO issued its global SARS alert, and two infected people, a doctor and his wife, landed at Frankfurt airport,” Drosten recalls.

Drosten's speciality is polymerase chain reaction (PCR) diagnostics, in which a ‘primer’ corresponding to a distinctive sequence from a known virus or bacterium is used to amplify the pathogen's genetic material, if it is present in a sample. Initial tests in Frankfurt and elsewhere drew a blank in the search for a viral culprit in sputum taken from the doctor. So when a second sample, taken on 17 March, was sent to the Hamburg



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World-beater: Christian Drosten burned the midnight oil to be the first to produce a rapid test for SARS.

institute to see if a tropical virus might be involved, it fell into Drosten's hands.

Having ruled out the obvious tropical viruses, Drosten began to think about rare viruses that might cause symptoms similar to SARS. He first fixated on the family of paramyxoviruses, whose members include the rare Hendra and Nipah viruses, which can jump from animals to people. “Frankfurt colleagues had looked at the patient's sputum sample under the electron microscope, and the shape, like a squashed sphere, was reminiscent of a typical paramyxovirus,” says Drosten.

## Think again

Having worked through the night of 18 March on paramyxovirus tests, Drosten got nothing but negative results. He couldn't quite believe it — particularly when Canadian researchers working on samples from patients in Toronto suggested that the causal agent was a metapneumovirus, a type of paramyxovirus. So Drosten sent his sample to Europe's leading paramyxovirus expert, Albert Osterhaus at Erasmus University in Rotterdam, the Netherlands, who confirmed the negative diagnosis.

The remaining option was to try to fish out the elusive virus with a less-specific series of PCR reactions that can amplify the genetic material of a wide range of viruses. This required a pure culture of the virus — the patient's sample would be too full of human genetic material to yield a clean result. Here, Drosten's connections to Frankfurt were crucial. He went to medical school in the city, and many of his former colleagues still work there. And on 20 March, while he was in Frankfurt preparing a presentation with one such colleague, Drosten learned that a culture set up at the university had just begun to yield the virus.

Drosten sped back to Hamburg with a sample on 22 March. His new series of PCR tests took him through a sleepless weekend, during which the machine he was using to sequence the genetic material being amplified failed. But by 25 March, the recalcitrant device had delivered 20 or so sequences.

Two of these matched up with sequences from the coronavirus family. But just as the coronavirus sequence was coming off the machine in Hamburg, researchers at the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, announced that they had identified the SARS agent as a coronavirus. They also had an electron micrograph, which showed the typical crown-like appearance of a coronavirus that had been masked in the Frankfurt image.

Having been pipped by the CDC in implicating a coronavirus, Drosten wasted no time in creating primers that would allow other labs to test for its presence. The next day, he described them on the institute's website and offered to provide them for free. He also made available synthetic sequences that mimic the behaviour of the virus in the PCR test. These ‘positive controls’ are important, as negative PCR results can often mean simply that the procedure has failed. Although scientists in Hong Kong and at the CDC have since developed similar tests, they have not distributed them as widely, nor provided positive controls.

After such a hectic few weeks, Drosten is looking forward to life returning to normal. His colleagues, meanwhile, are basking in the reflected glory. “But we think he needs a long rest and a good feeding up,” says one. ■

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