vaccines and the appropriate doses, as well as side effects, and use those insights to guide efficacy trials to be carried out in affected countries next year. "Next month we'll have information on all of the candidates," Hill says.

One issue is how to interpret the effects of the vaccines. Conventional wisdom says that having high levels of antibodies is the best sign of immunity. But animal studies have hinted that $CD8^+$ T cells could be more important. A vaccine that raises both would be ideal, but if either remains low, developers are likely to add a booster in efficacy trials (some safety trials are already testing this approach). Data from the ongoing trials in Mali will be especially important to working out the best dose, because vaccines often generate weaker immune responses in sub-Saharan African populations than in others. This is partly because of the presence of malaria, which can suppress the immune system.

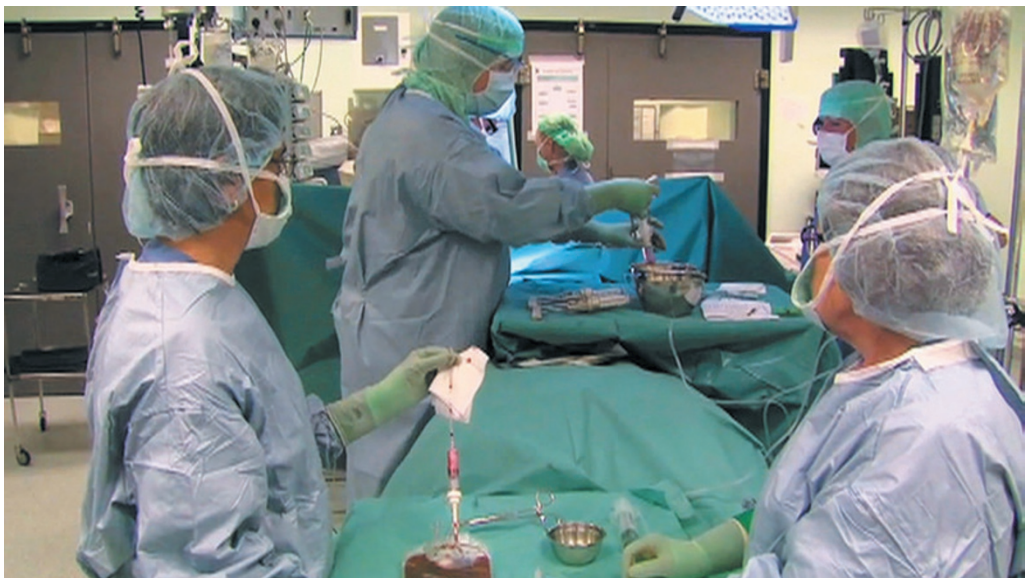
Testing vaccinated monkeys often involves exposing them to much higher levels of Ebola than humans typically encounter, so scientists may be overestimating the immune reaction needed to prevent infection, says Daniel Bausch, a physician at Tulane University School of Public Health and Tropical Medicine in New Orleans, Louisiana.

There are also side effects to consider. Two of the ten people who got the high dose developed a brief fever. Some researchers worry that vaccines that cause symptoms that overlap with those of Ebola, such as fever, could sow confusion. But based on past studies of other adenovirus vaccines, Hill does not expect such side effects to be common and says that they will be manageable, if people who get the vaccine are warned that they may develop.

"Next month we'll have information on all of the candidates."

The GSK/NIAID vaccines are not the only candidates set to deliver data. A vaccine made from a virus that infects livestock is being tested in the United States and Gabon, and soon in Kenya. The vaccine was developed by the Public Health Agency of Canada and licensed to NewLink Genetics in Ames, Iowa, and to Merck in Whitehouse Station, New Jersey. Phase 1 trials are to begin early next year for a regimen involving an adenovirus-based vaccine developed by the US pharmaceutical company Johnson & Johnson and the NIAID, and a booster made from vaccinia (a virus similar to the one that causes cowpox) by Bavarian Nordic in Denmark.

"What you have is something close to a race," says Hill, "and the best ones should go forward." ■



KAROLINSKA UNIV. HOSPITAL VIA SCANPIX/CORBIS/REUTERS

Surgeon Paolo Macchiarini carrying out the first transplant of a bioengineered synthetic trachea in 2011.

BIOENGINEERING

Artificial tracheas under scrutiny

The Karolinska Institute is carrying out two inquiries into an experimental transplant procedure.

BY DAVID CYRANOSKI

One of Europe's most prestigious medical universities, the Karolinska Institute in Stockholm, has launched two investigations into the clinical procedures of a doctor famed for performing potentially revolutionary, bioengineered trachea transplants.

Since 2008, Paolo Macchiarini, a thoracic surgeon at the Karolinska Institute, has replaced parts of airways damaged by injury, cancer or other disorders in 17 patients. In the earlier cases, he transplanted parts of tracheas taken from cadavers; in his later work, he transplanted synthetic tracheas. In both procedures, before transplantation, he would treat the tracheas with stem cells taken from the patient's bone marrow, which he says helps the transplants to act like biological tissue.

Bioengineering experts contacted by *Nature* say that Macchiarini's procedures were considered a great leap for their nascent field because tracheas demand a high level of biological function — including the ability to defend against the constant assault of inhaled bacteria and to form a seal with the adjoining airway tissue.

Macchiarini's reports were a "bright spot" for the field, says David Mooney, a bioengineering specialist at Harvard University in Cambridge, Massachusetts.

One of the investigations is being conducted by an external expert in the relevant fields, who is due to report the findings on 15 January. It focuses on the three procedures that Macchiarini carried out at the Karolinska Institute, all of which involve artificial tracheas.

The investigation comes in response to a report filed in August by four thoracic doctors at the affiliated Karolinska Hospital — Matthias Corbascio, Thomas Fux, Karl-Henrik Grinnemo and Oscar Simonson — who helped to treat the three patients.

The doctors compared results in a paper Macchiarini published in *The Lancet* (*Lancet* **378,** 1997–2004; 2011), describing the first use of a synthetic trachea seeded with stem cells, with the medical records of the patient. According to the doctors, there are discrepancies.

For example, the *Lancet* paper says that the synthetic trachea was "partly covered by nearly healthy epithelium", indicating the growth of a protective cell layer, whereas the doctors say they could find no evidence in biopsy reports for healthy growth. The paper also says that the implanted trachea showed

signs of tight connection with the adjacent tissue and that it was acting like "an almost normal airway", whereas bronchoscopy reports note gaps between the trachea and the bronchus, the tube that leads from the trachea to the lungs, and the need for stents to stabilize the airway.

"The problems alluded to are irreconcilable with the published reports," says one US-based thoracic surgeon who reviewed the report but asked not to be named.

Macchiarini says that he will not reply to specific questions about alleged discrepancies between his publications and the medical records yet, because the allegations against him "now have to be investigated by an external expert, which is the normal process following cases of accusations of scientific misconduct". He adds: "I certainly do welcome that investigation." He is confident that "there is nothing suspect, unethical, inflated or misleading about anything I have done or reported".

The Lancet says: "At this stage, we can't comment on the allegations regarding Dr Macchiarini's procedures."

The complaint filed by the four doctors also claims that there were no informed-consent forms in the medical records for two of the three procedures carried out at the Karolinska Hospital. The one form on record was signed 17 days after the procedure.

Macchiarini says:"Of course there was consent. We would never have proceeded with the transplants if there wasn't." He adds: "I do not know why the form is dated 17 days after the procedure and can only assume it is some kind of clerical issue." The patient "signed it in my presence, prior to the operation". He adds that "there was absolutely no ethical breach".

INVESTIGATION UNDER WAY

The Karolinska Institute's ethics council, meanwhile, is carrying out the second investigation, which was launched in response to a report it received in June from Pierre Delaere, a head and neck surgeon at the University Hospital, KU Leuven, Belgium. Delaere complains, for example, that published descriptions of the transplants minimize complications faced by patients, such as the need for stents.

In August, Macchiarini sent a 15-page response to the Karolinska, acknowledging that he had "shortened" discussion of complications because "of the editor's requirements during the review process". But overall, he maintains that "all aspects of the patients' outcomes are discussed in detail". In an accompanying letter, Macchiarini says that he has "thoroughly reviewed" Delaere's allegations and believes that they are "unfounded".

The ethics council plans to interview the concerned parties during January, and to give recommendations to the vice-chancellor of the Karolinska Institute, Anders Hamsten, by the end of February at the earliest. Hamsten will then decide how to proceed.

Hamsten says that the institute had initiated investigations into Macchiarini's publications twice in the past, following allegations of scientific misconduct from other complainants. Both investigations concluded — one in July 2013, the other in September 2014 — that there was no scientific misconduct.

Macchiarini, who is currently spending part of his time at the Kuban State Medical University in Krasnodar, Russia, leading a project into the regeneration of lung airways, recently put on hold his own trial there into the use of synthetic tracheas after the death of a patient on 20 September 2014. The patient had had a synthetic transplant in June 2012 and, when that one began to fail, another in August 2013.

Macchiarini told *Nature* that the patient's doctor has now reported the cause of death as "bilateral acute pneumonia with heart–lung insufficiency", which he says is unrelated to the trachea transplant. He says that she was "breathing normally and asymptomatic" two weeks before her death. "We will be considering the restarting of the clinical trial now that this cause has been ascertained," he told *Nature*.

The most recent of Macchiarini's total of eight synthetic trachea-transplant patients, who was operated on in June, "is doing very well, is asymptomatic", he says.

Six have died, with their post-transplant life-spans ranging from 3 to 31 months. Macchiarini says that one died because of complications following an accident, another from drinking too much alcohol, and another from "respiratory failure and subsequent multisystem organ failure". In none, he says, has the death been linked to the transplant.

The remaining patient has been in intensive care ever since her procedure, more than two years ago. Macchiarini says this is not a result of the procedure. "When this patient came to Karolinska, her situation was dire," he says. "Her doctors gave her a life expectancy of 3 to 6 months." He also says that the surgery revealed more extensive damage to her airways than had been apparent from the examination before the operation. The damage could not have been diagnosed before the surgery, he says.

Nine other patients have received tracheas from cadavers. According to a paper by Macchiarini this year, four of those patients have died, either from recurrence of tumours or from gastrointestinal bleeding. Of the five still living, the paper reports that four are dependent on stents, and one has no need for stents (P. Jungebluth and P. Macchiarini *Thorac. Surg. Clin.* **24,** 97–106; 2014).

Macchiarini emphasizes that the procedure is experimental. "Given the nature of this work, we are not in a position to guarantee them long-term survival and they are all abundantly aware of that going in," he says. "We at least give them a chance, a chance at a longer life, and the hope of being the patient who survives long-term." ■