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Is this our best shot?

A. WONG/GETTY IMAGES

We have the means to make a vaccine against pandemic flu. But quarrels over money, science and politics mean it could come too late, says Erika Check.

On a Tuesday afternoon in early April, a young woman with intense green eyes sits in a hospital examining room in Rochester, New York. Pressing a ball of cotton into the crook of her elbow, she explains why she has just allowed a nurse to draw two and a half teaspoons of blood from her slender arm, even though she hates needles. Oksana, 29, is testing a vaccine that could save humanity from bird flu. "Each of us has to do something to stop it — as much as we can," she says.

Oksana — who asked *Nature* not to use her real name — has volunteered for a trial to test a vaccine against the H5N1 avian influenza virus. The study, funded by the US National Institutes of Health (NIH), includes 450 volunteers like Oksana. But their efforts could go to waste unless health officials, world leaders, scientists and businesses find fast answers to a mass of difficult issues. Money troubles, politics and hiccups in production processes could stymie the development of a vaccine to protect us from a flu pandemic.

> "We had three pandemics in the last century — and there is no reason to believe there won't be one in this century." — Klaus Stöhr

Vaccination against the common varieties of influenza that have been infecting people for years is nothing new. In 2003, drug companies sold some 292 million doses of the seasonal flu shot[1]. But a pandemic strain that has crossed over from birds will be so different from common flu that that the immune response created by our run-of-the-mill vaccines will be useless.

A dangerous avian flu virus such as the H5N1 strain could morph into a pandemic virus in two ways. The virus could mutate so that it can be passed between people, or it could exchange genes with a common human flu strain (see 'Deadly combinations', overleaf). Once a pandemic strain is born, researchers will find themselves in a frantic race to create a vaccine that is effective against it.

But that could take months — and in the meantime, a pandemic virus could circle the globe. So scientists are now gearing up to test human vaccines against H5N1 and H9N2, the two most threatening strains of avian flu. If a pandemic strain evolves from either of these viruses, it may not be an exact match for the vaccines we are testing now. But hopefully it will look similar enough for the vaccine to provide some protection.

At least ten such trials are scheduled this year across Australia, Canada, France, Germany and Japan. Thailand and Vietnam are drawing up plans for trials, and the United States has already begun its studies with Oksana and her fellow volunteers.

This is welcome news. Just seven months ago, Klaus Stöhr, the chief influenza expert at the World Health Organization (WHO), warned that the world was asleep at the wheel. Back then, only two countries had plans to test a human vaccine against avian flu, and the WHO called a meeting of vaccine makers and government officials to sound the alarm. "There is currently too little momentum in the development of pandemic influenza vaccines," Stöhr said at the meeting, held in Geneva. "We had three pandemics in the last century, and there is no reason to believe there won't be one in this century."

A shot in the arm

Results from earlier, small trials of H9N2 vaccines suggest that the human immune system might respond well to an avian flu vaccine only if it gets an extra kick from an ingredient called an adjuvant[2–4]. Adjuvants are chemical additives that seem to 'irritate' the immune system, dramatically boosting the response to a vaccine. But most countries have not approved the use of adjuvants in flu vaccines, so they need to undergo additional testing — and that will take extra time. The US government has said that it will pay for tests of an H5N1 vaccine boosted by an adjuvant. But for now, the vaccine trial in which Oksana is enrolled — which doesn't include an adjuvant — is the only game in town.

To make a flu shot, scientists usually inject flu viruses into fertilized chicken eggs, let the viruses copy themselves, and then kill them with chemicals. But before this step, researchers have to modify the viruses so

that they grow well in eggs. Traditionally, researchers have done this by infecting eggs with two different flu strains: a 'wild' virus, which causes illness, and a lab virus, which grows well in eggs. If everything goes according to plan, the two viruses mix their genes and reassemble into a vaccine strain that works against the wild flu virus. But this takes time and luck — and if your luck is out, vaccine production can be delayed by months.

Today, it is possible to save time by using a technique called reverse genetics, perfected for flu viruses just five years ago[5]. This involves stitching flu-virus genes into loops of DNA called plasmids. The plasmids can assemble into whole flu viruses in the lab. By using reverse genetics, scientists can create exactly the types of virus they need, avoiding the lottery of natural reassortment.

Researchers have already used reverse genetics to create candidate vaccines against H5N1 flu[6,7]. Each flu virus is named after the types of two proteins that make up its outer coat (see Graphic, below) — haemagglutinin (H) and neuraminidase (N). The genes for these proteins are constantly mutating and come in many different varieties. To make their H5N1 vaccines, the researchers first altered the haemagglutinin gene from an H5N1 strain to make it less deadly, and then applied reverse genetics to create their mix-and-match vaccine strains.

Oksana's trial is testing one of these vaccines, developed by a team at the St Jude Children's Research Hospital in Memphis, Tennessee. At the NIH, meanwhile, researchers led by Kanta Subbarao and Brian Murphy are creating a library of vaccines against a range of different avian flu strains, including H5N1 and H9N2. Unlike conventional flu vaccines, these would contain live, weakened viruses in a nasal spray, instead of dead viruses in a shot. The researchers hope that this will generate a stronger immune response.

> "After the pandemic occurs, many scientists will be held accountable for what we did or didn't do to prevent it." — Michael Osterholm

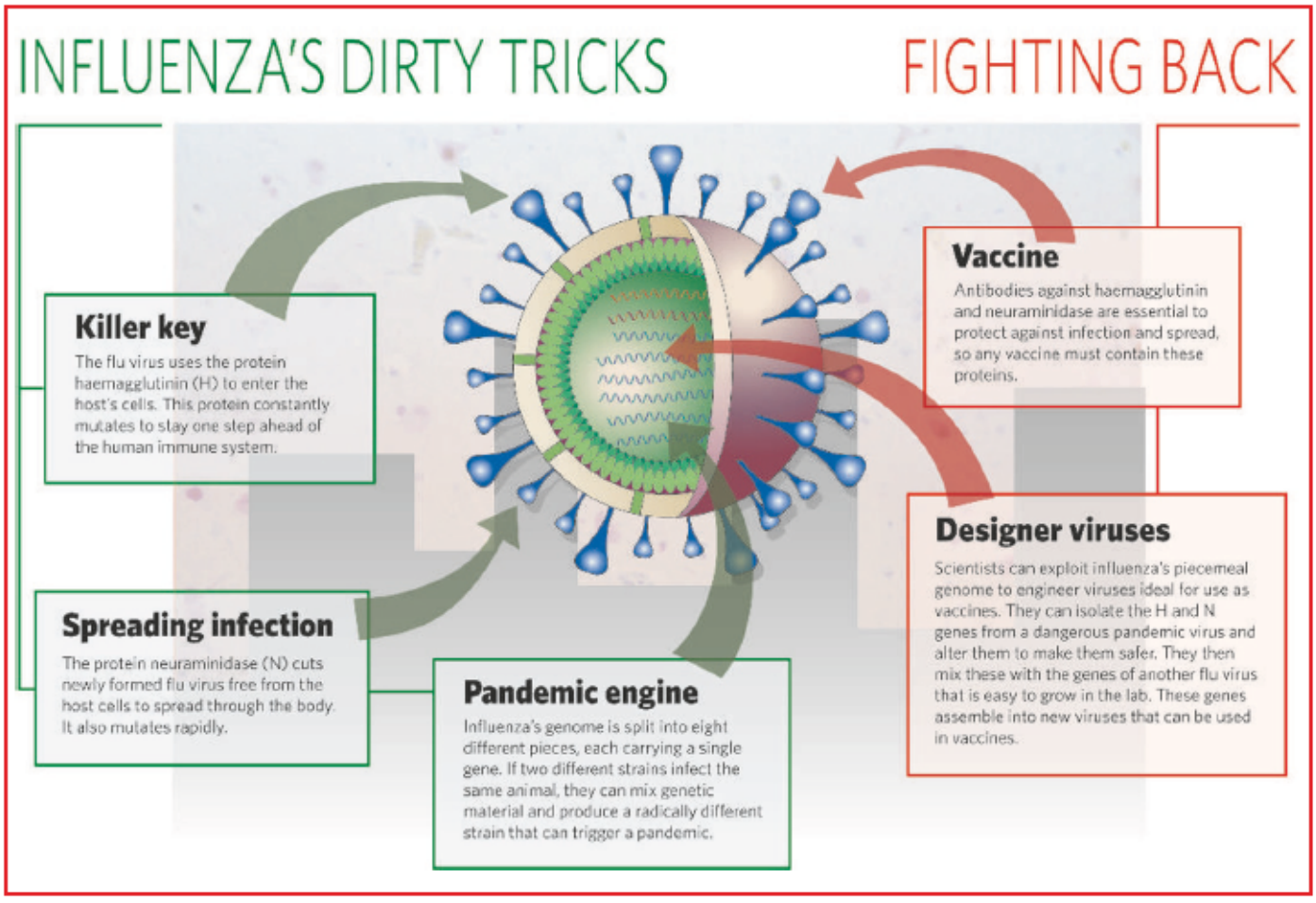
Back to square one

But if a pandemic strain is vastly different from the vaccine strains that have already been tested, scientists will have to make a new vaccine from scratch. The St Jude researchers say that they could make a vaccine strain just four weeks after they get their hands on a sample of the pandemic strain[8]. But there's a problem: reverse genetics has been patented, so companies that make the vaccine would have to pay royalties to the patent holders. Companies are reluctant to do this, but scientists working in the field say that industry is trying to hammer out this issue now.

Even if the intellectual-property issues are resolved, it will be very difficult to step up global vaccine production to make enough to halt a pandemic. Vaccine companies currently make 300 million flu shots a year. But in a pandemic, we could need billions of doses. So why haven't vaccine makers leapt to fill this gap?

The answer is money. Flu vaccines are simply not a lucrative prospect for drug companies, which can make much higher profits on blockbuster drugs. And vaccines are risky: anything injected into a healthy person can end up doing more harm than good, leading to costly lawsuits and bad press. What's more, a flu pandemic might never hit, so business leaders are reluctant to spend money on new factories that might never be used.

So at present, vaccine manufacturers have limited production capacity, which could be further constrained by the supply of lab-standard fertilized chicken eggs. Growing the virus in huge metal fermenters containing a soup of cultured cells could be faster than using eggs. But retooling entire factories is an expensive business. "We are talking about a totally unpredictable, very rare event, so it's difficult to commit a company to these



Deadly combinations

Dog kidney cells can help experts to assess whether a deadly avian flu virus will mix its genes with a common human strain to create a virus that could kill millions. In these cells, virologists at the US Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, are now running tests using various genetic combinations of the H5N1 avian flu virus and a common human flu strain.

In January, under tight security, CDC virologists began to mimic natural genetic 'reassortment' using reverse genetics (see main text). Using the H5N1 strain as a backbone, they have been substituting various combinations of eight genes from the H3N2 human flu virus.

There are 254 possible combinations, so early experiments are simply screening them to see whether they can survive in mammals — which is where the canine cells come in. "We're trying to approach this in a systematic way," explains Nancy Cox, who heads the CDC's influenza branch.

In the autumn, Cox's team plans to test the most viable and dangerous blends in live animals, to see which ones are readily transmissible. The idea is to get a preview of what a pandemic strain might look like, so workers in the field can be primed to look for novel viruses that may pose a particular threat.

Virologist Albert Osterhaus of Erasmus University in Rotterdam, the Netherlands, expects to get approval from national authorities in the next two months to begin similar research. The animal studies will prove the most challenging, he says: "Transmission experiments are notoriously difficult. You have to mimic the normal human situation."

Osterhaus also aims to conduct transmissibility studies of other strains of bird flu, including H7N7 — which jumped to people in the Netherlands in 2003, causing symptoms including conjunctivitis, and killing one person. "The attention the H5 virus has received is logical, but we should not forget that other avian viruses could do the same thing," he says.

Such research is intensely controversial, because of the potential for giving bioterrorists a recipe to create mayhem. Cox and Osterhaus point out that the genetic engineering involved is beyond the reach of most terrorist groups. "But if we found something that was truly horrific, we might not release that information," Cox adds.

The bigger danger, in fact, is that nature will do the job first. Cox and Osterhaus know they're in a race against time that they can't be sure of winning. "We just don't know when a pandemic strain will strike," says Osterhaus.

Roxanne Khamsi

CDC

Nancy Cox is seeking the likely form of a pandemic strain of flu.

preparational approaches," says Norbert Hehme, who manages GlaxoSmithKline's vaccine facility in Dresden, Germany.

Governments could help to coax drug companies back into the flu-vaccine business by increasing the use of shots against common, non-pandemic flu. The Canadian province of Ontario, for example, gives standard flu shots to its entire population each year. And last August, the US government added flu shots to the list of vaccines recommended for all infants. These sorts of steps are reassuring companies that someone will buy their products. Bruce Gellin, head of the National Vaccine Program Office at the US Department of Health and Human Services, says that more companies are discussing the possibility of making pandemic vaccines. "The fact that manufacturers are interested says that it's a much more attractive marketplace now," he says.

S. ANANDA/AFP/GETTY

Out of luck: creating a flu vaccine by growing viruses in eggs has a relatively high failure rate.

But as companies follow the money, some countries will be left behind. In 2003, nine rich nations, led by Japan and the United States, used 62% of the world's influenza vaccines[1]. But bird flu is most rampant in poorer countries that do not buy a lot of flu shots. Although Vietnam and Thailand are planning clinical trials of influenza vaccines, the plans are preliminary. So there is a high risk that the countries at ground zero will be defenceless in the early days of a pandemic.

That would be a tragedy for the countries concerned — and could threaten us all. If rich nations lock down their vaccine supplies and watch pandemic flu rage through southeast Asia, they will hasten its spread across the globe. Public-health experts say that governments should pledge now to share their vaccine supplies. But no formal talks have been scheduled. "Some ideas exist on how to organize sharing, but the reality is that no country with a vaccine producer has come forward with a proposal," says Stöhr.

Experts say that we must tackle these problems soon — before it's too late. In Washington DC last month, Michael Osterholm of the University of Minnesota spelled out the issues to a room full of experts gathered by the US Institute of Medicine. "After the pandemic occurs, there will be a post-9/11-like commission," Osterholm said, referring to the high-level US panel that investigated preparedness against the 2001 terrorist attacks. "And many scientists will be held accountable to that commission for what we did or didn't do to prevent a pandemic." The same will be true for government officials and business leaders who control our ability to deploy an effective pandemic vaccine. ■

Erika Check is *Nature*'s Washington biomedical correspondent.

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