long contended that traditional efficacy trials could not be done because past outbreaks have ended quickly with the help of standard infection control procedures such as isolating confirmed cases, testing their contacts, and making sure that all health care workers wear personal protective equipment.

Instead, researchers had planned to take advantage of what's known as the Animal Rule at the U.S. Food and Drug Administration (FDA). The rule says when efficacy studies "are not ethical or feasible," FDA will license vaccines for diseases if they work in two animal models and if large-scale phase II studies conducted in humans prove they are safe and trigger immune responses that mirror those in protected animals.

But with today's fast-moving epidemic, which has spread to five West African countries and killed more than half of the roughly 4000 cases, talk about large phase II studies in unaffected populations has gone out the window. Now, the push is to vaccinate people at high risk and try to gain interpretable data, says Adrian Hill, director of the Jenner Institute at the University of Oxford in the United Kingdom. Hill's group will soon launch a small safety study of the NIAID/GSK vaccine, and he is confident it will pass muster. "Then it's decision time," he says. "Not just whether we go forward but how to go forward."

Traditionally, efficacy trials randomly assign participants to receive the vaccine or a dummy shot. That's clearly not ethical here, so some researchers are calling for a "stepwedge" trial, which analyzes what happens to people at similar risk who receive the vaccine at different times. That way those who have been vaccinated can be compared with others who have yet to receive their shots. "You can't give everyone the vaccine the same day," Hill notes.

But a step-wedge design could face serious limitations. The rate of spread can differ between sites because one might have, say, better or worse personal protection measures, which could cloud analyses of a vaccine's shortcomings or strengths. Researchers might also have trouble detecting efficacy if a vaccine offers only partial protection, NIAID's Mascola says. "If there's a 50% mortality with Ebola and you use the vaccine and it's 40% protective, what does that mean?" he asks.

Impassioned debates also surround which experimental vaccine to deploy. As the *Nature Medicine* study shows, the chimp adenovirus vaccine worked best when boosted with the MVA-Ebola construct. But that's not being assessed in the initial human trials. Mascola says a company has made the MVA preparation in bulk but it's not ready for testing.

Thomas Geisbert, a researcher at the University of Texas Medical Branch in Galveston who helped develop several VSV Ebola vaccines, including the one made by NewLink Genetics, contends "it's a much stronger vaccine system." The VSV replicates, unlike the chimpanzee adenovirus vector, stimulating an immune response that Geisbert argues is as good as the one achieved by the prime-boost approach NIAID has championed. "In the context of an outbreak, where you are going to put first responders on an airplane, you don't have time for a prime-boost," he says. "You need a single injection."

But even though this VSV is weakened, safety concerns remain about the possibility that it could cause neurological disease, as it has in some animal studies, or infect livestock. And Anthony Fauci, who heads NIAID, says that the chimpanzee adenovirus vaccine may work well enough without the extra boost, noting that a single injection protected 100% of monkeys challenged with Ebola virus at 5 weeks. "The vaccine was developed to be able to induce immunity really fast," he says.

No experimental vaccine has ever been on a faster track toward widespread use. "It's absolutely unprecedented," says WHO's Marie-Paule Kieny.

Fauci and his NIAID colleagues say it makes sense to test different vaccine strategies in parallel. "We've been fooled by trying to translate monkey findings to humans before," says Fauci, who notes that an AIDS vaccine worked well in monkeys and actually increased HIV infection rates when tested in humans.

Gary Nabel, who headed NIAID's VRC before leaving in 2012 to join Sanofi in Cambridge, Massachusetts, says manufacturers should massively scale up production now, before trial results are in. "If it were me personally, I'd err on the side of caution, and I'd think carefully about stockpiling doses," Nabel says. "If it isn't safe, you throw away those lots. In the worst case you've wasted some money."

If the virus spreads even farther and one of these vaccines does prove safe and effective but is not available, "I think there'll be a lot of finger-pointing," Nabel says. "Extraordinary times call for extraordinary measures, and this is an extraordinary time." ■

INTERVIEW

Ebola: 'Wow, that is really tough'

WHO's Bruce Aylward says international action is needed right now

By **Leslie Roberts**

Bruce Aylward is used to mobilizing armies of health workers. An assistant director-general at the World Health Organization (WHO) in charge of polio and emergencies, he leads the massive global effort to eradicate the poliovirus. But Aylward says he has never encountered a challenge as great as the Ebola outbreak in West Africa, which has infected more than 4000 people and killed more than 2000. Margaret Chan, who heads WHO, asked Aylward to help with the response in August; since then, he has been running operations and helped draw up WHO's Ebola Response Roadmap, released on 28 August. He spoke with *Science* on 4 September. (This interview has been edited for clarity and brevity.)

Q: Margaret Chan has said that all organizations involved in the outbreak, including WHO, underestimated its complexity and magnitude. How did this happen?

A: I didn't live through it all, but as I've gone back and asked what was happening, clearly these guys [in the response effort] have been flat-out on this for 6 months. And they've put 450 people in the field. Those are unheard-of numbers in responding to Ebola. But the virus got ahead of them.

Could the response have been scaled up faster? Maybe they were off by 2 weeks at one point here or there. As Margaret says, you're always a couple of weeks behind this virus, and there are so many reasons why. It's a dangerous pathogen. Foreign medical teams and NGOs [nongovernmental organizations] are used to dealing with trauma and primary health care; they're not trained to deal with pathogens.

Q: I've heard there are tensions between WHO and Doctors Without Borders (MSF), the organization that has treated more patients than any other. They have criticized WHO for being too slow and doing too little.

A: Probably at local levels there's some tension in some places, but certainly not here, in Geneva at senior levels. There's a great respect for the organization. MSF is great at two things: They're fantastic at their field operations and at telling the rest of us how bad we are at them. Sure, people are going to go out and say, "Oh, that's unfair." You have to have a tough skin. You're in the World Health Organization; you're dealing with a major international threat, and our job is to be accountable. And if MSF feels that this is public accountability, it's their right.

Q: Why is stopping this outbreak so hard compared with controlling polio?

A: The polio program is really tough because of the level of programmatic perfection you need. You have to get to every single kid with vaccine over a huge geography and in very challenging environments. But even if you don't, you still have a level of control over the virus. Now, when I look at Ebola, you need a whole other level of perfection.

You have to do perfect contact tracing, because one contact can blow open a whole new chain of transmission. You have to get your burials perfectly safe. You have to get your laboratory testing right. There isn't a lot of capacity in the world on that. You have to get your social messages right. You have to be perfectly safe and protect health care workers. And you have to do all this in incredibly weak environments, in three countries that are near the bottom of the development index, and also deal with the embers that land in Nigeria or in Senegal. Wow, that is really tough.

Q: Do you think it's still possible to contain the outbreak with the standard procedures—isolating patients, tracing contacts, burying the dead safely?

A: Absolutely. But with an important difference. What's happened is you've got a caseload that far exceeds the capacity of the standard Ebola strategies to manage them, so you have to innovate on these strategies. Each infected person is having a heap of contacts because they're basically being left in their communities for long periods of time. What you've got to do is first of all cut down the outward spread from every patient, which means you've got to get many new Ebola treatment centers up. And you've got to adapt your strategies in a way that communities can play a much bigger role and help them scale up their own Ebola community care units. This is absolutely critical and must be done in September.

Will it be done? Well, that's going to depend on whether the international community will put the money on the table, help the people get in, and understand the conditions they need to operate.

A massive influx of money and people is needed immediately to stop Ebola, says Bruce Aylward.

Q: WHO's Ebola road map calls for the epidemic to be ended in 6 to 9 months. Isn't that overly optimistic?

A: I don't know, because no one's ever had to do something on this scale before. What I do know is if this road map is not implemented, you're not going to stop it in 6 to 9 months. In 1 month you need at least 10 new facilities operational with additional bed capacity and teams on the ground, and money so that people doing this stuff are getting paid, and a way to evacuate the responders that get into medical trouble there. You have to start implementing the road map today.

But the usual relief organizations aren't lining up to do it. These aren't bad people and these aren't cowards. These are people who go into the most dangerous operating environments—wars and natural disasters. But they don't normally deal with hazardous pathogens.

Q: So you need more people and you need more money, but it's simply not coming?

A: Not yet, but I'm optimistic. I think it's taking the world time to grapple with this. It is so new, and it plays to people's deepest fears and their greatest uncertainties. People will learn MSF is going to stay on the ground there. And then one or two NGOs are going to go in and run a facility, and they're going to do fine. And then it's going to escalate. The world doesn't want to be beaten by a pathogen. But the question is: Are they going to do it fast enough?

Q: So who are the players that you hope will come to build and run treatment centers?

A: A lot of foreign medical teams are linked to governments, and some affected countries have deep relationships: the U.S. with Liberia; the U.K. with Sierra Leone; France with Guinea. Now those countries are very keen to look at what they can do and how to do it, but they are having trouble mobilizing. They might be able to put up a field hospital, but can they staff it? Because a field hospital that's not staffed is just one more building, that's not an Ebola treatment center.

Q: Two vaccine candidates are soon going to be tested in phase I studies and may be deployed later this year (see p. 1228). How important do you think they and candidate drugs will be for ending the epidemic?

A: You want to have as many tools as possible to help drive down that reproductive number to where you can manage it with traditional strategies. You want to do both things in parallel and go flat-out. The vaccines and new therapies would be hugely helpful—they would help get responders in and keep the responders that are there healthy. That may give us an edge to shut this thing down more quickly. But if we say we need these drugs and vaccines, then you're setting yourself up for defeat because you might not get them. And then you also have the risk of people saying: "There's going to be a vaccine or med, let's wait," and then an awful lot of people are going to die. I'm not going to sit around twiddling my thumbs waiting to find out, and neither is my organization. ■

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