Ebola: a game changer for vaccines, or a scare that will soon be forgotten?

Scientists say that many more hitherto neglected infectious diseases could now cause another global public health emergency. So will the world now make these diseases a priority? **Sophie Arie** reports

In March 2014 the first case of a new outbreak of Ebola virus disease was confirmed in Guinea. After months of growing global panic that the virus was out of control and might rapidly spread worldwide, the World Health Organization agreed for the first time that, as part of the global response, it would support clinical trials of experimental Ebola drugs on the affected population.

Trials are rushed through at record speed

Treatments and vaccines developed in laboratories more than a decade earlier that had been mothballed for lack of commercial interest were put through human safety trials and small scale efficacy trials at record speed. Ethical issues were carefully tackled and trial protocols produced—again, at record speed—so that today, a year after that first case was reported, large scale phase II and III clinical trials for Ebola are under way in west Africa. A process that normally can take as long as 10 years was compressed into a year.

Yet, for more than 10 000 people who have died, this is still way too slow—and, because very few new Ebola cases are now occurring, it may also be too late to gather solid enough data to gain market approval for any of the experimental drugs in the pipeline.

So, how can the global community move even more quickly to develop drugs for potentially devastating infectious disease outbreaks in the future? Scientists are desperate to capitalise on progress made during the Ebola outbreak by focusing on developing drugs for more than 10 other neglected infectious diseases (see box 1) that, like Ebola, they say, have the potential to spread far further and more quickly today than in the past, in large part because of increased population density and cheap air travel.

The need to prepare and stockpile

"The way our society has changed, we have to be able to move within days and weeks now, not months or years," said Jeremy Farrar, director of the Wellcome Trust, which has invested £10m (€13.6m; $15.2m) in the current trials. "We need a paradigm shift in thinking about how we develop and license these drugs."

Farrar and many of the leading scientists involved in the Ebola response are calling for the global community not to wait until the next outbreak before reacting. Experimental treatments and vaccines for all of the long neglected outbreak pathogens must be fast tracked "in peace time," he says, so that safety is affirmed, candidate drugs are manufactured and stockpiled, ethical issues are resolved, and protocols are put in place for clinical trials to begin within days or weeks of a future outbreak.

"Make them, have them ready in a stockpile, have everything ready to go," said Adrian Hill, of the University of Oxford, who is the lead researcher in the trials of six different candidate vaccines and treatments in west Africa. "Then, when an outbreak comes, you move very quickly and nip it in the bud."

The world must also develop a global mechanism for unlicensed drugs to be authorised for distribution to large numbers of people in emergencies, scientists have urged. During the Ebola outbreak a handful of infected Western health workers did not hesitate to try experimental treatments, but those drugs were not available in sufficient quantities or affordably enough for people in west Africa to try them.

Farrar, Hill, and an international group of scientists calling themselves the "B Team" outlined this vision in a document mainly about the Ebola response but also drawing wider conclusions, published in February.[1]

Funding and motivation

Funding, of course, is the major obstacle. The outbreak pathogens that the scientists believe are worth investing in have, until now, been far off the radar of the global drug companies. Candidate treatments and vaccines for Ebola were developed only because the United States considered the virus a potential weapon for bioterrorism.

Major drug companies have participated in the fast tracked trial process for Ebola largely because they have not had to pay for it (the Wellcome Trust and the US and UK governments have funded most of the trials) or because they have been guaranteed a certain number of sales. GAVI, the global alliance set up in 2000 to improve access to vaccines in the developing world, has created a unique "push" funding model for the Ebola outbreak, setting aside £196m to cover production costs without knowing how many doses of vaccine this will buy.

"It's the first time we've guaranteed funding for a vaccine that hasn't yet completed development," Aurelia Nguyen, director of policy and market shaping at GAVI, told *The BMJ*. GAVI is not, however, thinking of this as the way to approach all infectious disease outbreaks in the future, she said. Because of the level of global panic over the Ebola outbreak, "the global community wanted to produce and deliver whatever product is viable," Nguyen explained. "So it's not a normal commercial dynamic."

Motivation is the other barrier. Hill noted that, rather than sidestepping any of the normal bureaucratic procedures for approving the Ebola trials, the relevant regulatory authorities—such as the Medicines and Healthcare Products Regulatory Agency and the research ethics committees in all of the countries involved, which review hundreds of trial protocols—put Ebola "on the top of the pile." In this sense, he said, it is a question of people changing their priorities about which diseases to focus on.

But accelerating the process does not in any way compromise safety, Hill insisted. The University of Oxford is the "sponsor" that bears legal responsibility for most of the six Ebola trials Hill is leading and, if they result in harmful side effects or deaths, these trials are covered by the same indemnity policy that covers all clinical trials run by the university.

Hill believes that, where the moral arguments for finding vaccines for these 15 outbreak pathogens have failed, economic arguments should now motivate governments, foundations, and organisations such as the World Bank to invest in preempting the next Ebola-like outbreak.

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JOHN MOORE/STAFF/GETTY

Vaccine trials at Redemption Hospital, Monrovia, Liberia

Box 1 | : Similar threats

Scientists warn that some other neglected infectious disease pathogens have the potential now to pose a similar threat to Ebola:
Marburg virus disease
African sleeping sickness
Rift Valley fever
Lassa fever
Crimean-Congo haemorrhagic fever
Leishmaniasis (also known as kala azar)
Hendra and Nipah virus diseases
West Nile fever
Pandemic influenza
Middle East respiratory syndrome (MERS)
Hantavirus pulmonary syndrome
Chapare haemorrhagic fever

industry would provide what only it can provide, which is large scale manufacturing capacity."

Farrar said, "There does seem to be the will to do this among the governments, drug companies, and scientists. I just hope that we don't find that, once the Ebola scare has passed, it's just back to business as usual and people forget or just have other priorities."

The problem with a reactive response

Peter Hotez, director of the Sabin Vaccine Institute in the US, is somewhat less optimistic. Rather than seeing the unprecedented global collaboration on Ebola as a game changer for vaccine development, he said that it would be a "one-off."

"The problem with the global response is that it is always going to be reactive. We're still too myopic to look beyond the end of our nose," Hotez told *The BMJ*. "We wait for catastrophe to emerge and then try to mobilise the pharmaceutical companies."

The Sabin Vaccine Institute developed a candidate vaccine for severe acute respiratory syndrome (SARS) and has more recently done the same for Middle East respiratory syndrome (MERS) coronavirus. But, said Hotez, "so far there is no financial backer to take this to the next stage. Even now, the US government is not interested." He said he believed that the key to moving more quickly in future was not to rely on the cooperation of the big drug companies at all.

Jennifer Cohn, medical director of the Médecins Sans Frontières access campaign, agrees. "We can no longer link research to the cost of a drug," she said. "Resources for developing drugs should be delinked from profitability. Governments are going to have to pay, one way or another."

Hotez, who was made a US science ambassador for the Obama administration in January, has opened discussions with Morocco and Saudi Arabia, which currently import most of the drugs that they need, to explore ways in which the US could support these countries developing their own drug industries. "Building vaccine development and production capacity [in these countries] could take 10 years," he said. "But it has to be done. It's like going to Mars."

China, Indonesia, and several other countries in Asia have already begun to do this, added Hotez. But the next potentially devastating epidemic will emerge in the Middle East or in north Africa, he believes, because of the disruption caused by the Syria-Iraq conflict: "This is going to be the next wave, and once again the world will be taken by surprise."

The animal rule

In the US the federal drug authority's so called "animal rule" was introduced in 2002 amid concern over bioterrorism, to allow approval, in a health emergency, of the use of experimental drugs that have shown potential only in animal trials.[2]

The European Union has similar mechanisms, but other parts of the world—crucially, the developing countries where these diseases are most likely to break out—do not. Many developing countries rely on the World Health Organization's recommendations on drugs; as a result of the Ebola crisis WHO is now developing its own "emergency use assessment and listing procedure"[3] to ensure quality, safety, and performance standards for diagnostics, vaccines, and medicines procured by United Nations agencies. It also aims to give guidance on the use of unlicensed products to member countries in future public health emergencies of international concern.

But it is not clear whether populations in developing countries would be as eager as Westerners to try unlicensed treatments or diagnostics, however serious a health threat they face. As the Ebola outbreak has shown, some countries have a great mistrust of authorities and of Western backed health interventions.

Part of the reason for the rapid spread of Ebola in west Africa was a reluctance among many to seek medical assistance. Similarly, drug trials are facing deep mistrust from the population, and some reports say that potential participants have been too suspicious to participate.

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Box 2 | : The race to find Ebola drugs

14 April 2015: Phase III trials of candidate vaccine VSV-ZEBOV (NewLink Genetics, Canada, and Merck) began in Sierra Leone, involving 6000 health and frontline workers.[4-6]

March 2015: Phase II trials in Liberia showed two candidate vaccines—Cad3-EBOV (GSK) and VSV-ZEBOV (NewLink Genetics, Canada; Merck, USA)—to be safe,[7] but planned phase III trials in Liberia were not viable because only one confirmed new case of Ebola has been reported since February 19.

Phase II trials began in Sierra Leone for TKM-100802 (siRNA), a candidate treatment made by a Canadian firm, Tekmira.

February 2015: Preliminary data presented from a phase II trial of the influenza drug favipiravir (Fujifilm/Toyama), which began in Guinea in December 2014, were insufficient, so the trial continues.

Phase II trials began in Liberia for ZMapp (MappBio, USA.

Phase I trials for a recombinant protein candidate Ebola vaccine developed by Novavax began in Australia.

January 2015: Phase II trials of brincidofovir (Chimerix, USA), an antiviral in Liberia, were halted after Chimerix pulled out.

Phase I trials of two other candidate vaccines, Ad26-EBOV and MVA-EBOV (Johnson and Johnson/Bavarian Nordic), began in several countries outside west Africa.

December 2014: Phase I trials of VSV-ZEBOV in Geneva, Switzerland, were delayed for a month after some people complained of joint pains.