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Ebola vaccines line up while industry calls for change

As the west African Ebola outbreak slows, the world has a suite of experimental vaccines in various stages of development. But manufacturers are warning of problems ahead. Anna Petherick reports.

WHO has been working on a definition for what it calls its target product profile for an Ebola vaccine, says Marie-Paule Kieny, the organisation’s Assistant Director-General for Health Systems and Innovation. This is a list of a vaccine’s ideal characteristics. Kieny has two profiles: a single-dose vaccine that can jump-start protective immunity in just a week or so—for which protection beyond 6 weeks is unimportant—plus a multishot version that might be slow to build immunity, but once established, would last for years. The former would be for emergency outbreak deployment in a vulnerable community; the latter would be for front-line responders.

Identifying products that fit the bill is not straightforward, given that the frequency of cases in west Africa has now fallen to a level that prohibits further efficacy studies. The world has five Ebola vaccines with at least some clinical data behind them, and several more that have been tested in non-human primates. All of the candidate vaccines do the same thing: they prevent infection by blocking the same viral glycoprotein that binds Ebola to host cells.

**Front runners**

Of the five in the clinic, two are ahead of the others, both of which, says Kieny, are of the outbreak-control variety. One has been developed by NewLink Genetics, of Ames, IA, USA, in collaboration with Merck, and is composed of a vesicular stomatitis virus (VSV) with a gene that encodes the Zaire Ebolavirus glycoprotein inserted into its RNA genome. This is the vaccine that made headlines in late July when interim results of a phase 3 trial in Guinea showed zero new infections among immediately vaccinated contacts, while there was a small crop of new infections among those who received the vaccine 3 weeks later. The second vaccine has been developed by GlaxoSmithKline (GSK); it inserts the Ebola glycoprotein code into a chimpanzee adenovirus vector. The details of how these vaccines work are still somewhat mysterious, but antibodies that attach to the crucial glycoprotein seem to be responsible for most of the effect. “As a bonus you also get very good T-cell response with the adenovirus,” says Adrian Hill, a pioneer of the adenovirus vector approach, and director of Oxford University’s Jenner Institute, UK.

A direct comparison of how well these front-runners protect those exposed to Ebola has not been possible. The two vaccines were about to go head-to-head in a randomised trial in Liberia, but it was halted after 8 weeks. “By the time we’d finished the introductory safety portion of the trial, the Monrovian health authorities—through contact tracing and all those things that are standard management practices—were able to bring the epidemic under control, and there were very few cases”, explains Ripley Ballou, head of GSK’s Ebola vaccine research. “But it wasn’t wasted energy by any means. The trial will still provide very interesting immunogenicity and safety data.” A separate trial of the VSV-vector vaccine in Sierra Leone came up against the same thankful problem.

**Next steps**

The key questions now centre on what kind of licensing decisions should be made given existing data, and the additional studies might yet help. Even for the successful trial in Guinea, where new infections are also petering out, regulators will have little insight into how long protection lasts. In that case, even though the comparison of immediate and delayed vaccination groups yielded impressive results, an intention-to-treat analysis produced a measure of vaccine effectiveness of 75.1%, which falls short of statistical significance. In sum, “we don’t know if the VSV vaccine is the best available, or if the others that did not get a chance to prove they were effective are as good or better”, says Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases.

From the perspective of Kieny’s pair of ideal profiles, the other clinical candidates—although slower to reach the point of being injected into a human arm—warrant attention. One would fall into the same epidemic-control category as Merck’s VSV and GSK’s adenovirus vaccines; it is poorly publicised, and under development in China. But the other two, “are the ones that need two doses, and you therefore need a month to produce protective immunity—but when you look at the level of antibodies, it’s higher”, says Kieny. “So you would...
imagine that these two vaccines are more of the type that you would use to immunise health-care workers.’

Of these, a candidate developed by Johnson & Johnson and Bavarian Nordic, a Danish biotechnology company, should be tested in a large safety and immunogenicity study in Sierra Leone before the year is out, which would replace a more traditional phase 3 design. And a different kind of vaccine made of the purified glycoprotein rather than its gene within a viral vector has been well tolerated by healthy Australians, and was also found to fully protect monkeys in three separate studies, says Greg Glenn, head of research and development at Novavax in Gaithsburg, MD—the firm that created it.

Indeed, the winding down of the west African outbreak does not present a barrier to licensing and stockpiling, even though only one efficacy trial has produced results. Various pathways to approval are under intense discussion between drug companies, the US Food and Drug Administration, and European regulators, says Kierny. For example, the VSV-vector vaccine trial in Guinea might count as supporting evidence for the other vaccines, if they can demonstrate equivalent antibody response outcomes in human beings and strong virus protection in animals. Fauci concurs that a series of non-inferiority studies is the way forward. Meanwhile, the VSV-vector vaccine itself might still have to allay concerns about side-effects; the lead scientist of NewLink Genetics’s BioProtection Systems subsidiary, Thomas Monath, thinks it is still at least a year from licensure.

Reassuringly, whatever the details of remaining studies, GSK has promised to get plenty of vaccine ready. A large portion of its Ebola effort went to improving methods of mass production. “In the next couple of days, we’ll begin a manufacturing campaign that will last until the end of this year that will produce hundreds of thousands if not millions of doses for stockpile”, says Ballou, “We made that commitment last November when there were the most dire predictions of depopulation of west Africa by April, 2015.”

That is good news given that an unrelated outbreak could occur, and in view of concerns that Ebola might linger as a sexually transmitted disease. Seminal fluid seems to retain live viruses in men who have recovered from Ebola and whose blood is virus-free. Does that mean there is a pressing need to deploy vaccines in Guinea, Liberia, and Sierra Leone right away, even though only very occasional new infections are currently reported? Hill thinks not, unless cases keep mushrooming where the disease was thought to have died out. Nonetheless, this is something the US National Institutes of Health (NIH) is watching closely, says Fauci. “We don’t know what percentage of men who recover have persistence of the virus in semen, and for what variable periods of time, [which are] often measured in months”, he says. An NIH study in Liberia of 1500 Ebola survivors and 6000 of their close contacts is trying to establish exactly this, and put numbers on the risk of sexual transmission.

Broken system
That’s a concern in the short-to-medium term. But the longer-term, broad view presents an even bigger worry. The consensus among experts is that the current model of vaccine development against known pathogens that present a potentially serious threat to public health is broken—and the world has yet to heed the lessons of Ebola.

The VSV and adenovirus-based Ebola vaccines are casualties of the so-called death valley of biotechnology, says Ian Lipkin, an epidemiologist at Colombia University, NY, USA. Both were created some time ago—the VSV vaccine by John Rose in the 1990s, the adenovirus-vector vaccine at the NIH facility in Bethesda, MD—but languished in laboratories because there were no financial incentives driving work on. “You don’t have a clear market because epidemics occur rarely, and planning large-scale efficacy trials for a disease that might never happen is almost impossible”, says Ballou. To develop the adenovirus vaccine candidate, GSK had to pull many researchers off core projects, lumping the company with opportunity costs, he says: “We did this with assurances from governments that we would not be left holding the bag at the end of the day, and the reality is we still are.”

Kierny agrees: “If this is the model, then maybe next time there’s an epidemic, GSK will turn around and say, ‘Well, we have something else to do!’”

The alternative way of doing things that Ballou proposes involves moving GSK’s vaccine technologies outside of the company’s for-profit business, thus allowing ongoing development of products that would hopefully protect against threats such as Middle East respiratory syndrome and Marburg virus disease. Ballou is cagey about the details because he does not want to jinx ongoing discussions. Kierny offers that this kind of programme would be paid for by public funds, and probably cost about US$15 million yearly, though she warns that plenty of questions remain, such as whether such a set-up should be replicated for each drug company, or whether they could work together.

As if to illustrate the problem, Novavax’s Glenn makes the case that his company’s candidate is stable in a normal fridge, at about 2–8°C, unlike the other options that need to be kept in liquid nitrogen—and it might be cheaper because tiny doses of the pure glycoprotein seem to generate immunity. “But we’re not going to move it forward beyond where we are today without a partner”, he says. “It needs to be clear that we have funding support.”

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