How to develop a Rift Valley fever vaccine

A FRIDAY AFTERNOON VACCINE

Virologist Jeroen Kortekaas and his team at Wageningen Bioveterinary Research in Lelystad have developed vaccines against the dangerous Rift Valley fever virus. One for animals and one for humans.

Text Roelof Kleis

The world is in the grip of Covid-19. But coronaviruses are not the only viral threats to humans and animals. The African Rift Valley fever virus is another pathogen that should be prioritized for vaccine development, according to the WHO. So far, Rift Valley fever has rarely struck outside Africa, where it mainly affects sheep. But it can affect humans too. Extraordinary professor of Virology Jeroen Kortekaas and his team have succeeded in developing both human and veterinary vaccines against the disease. That is to say: the vaccines exist, and ahead lies the long road towards getting them registered and onto the market. 'We've got the vaccines and it is almost certain that a fund will be set up,' says Kortekaas. 'There are no further obstacles as far as effectiveness and safety are concerned.' These are crucial factors. 'When you make a vaccine you always seek a balance between safety and effectiveness,' explains Kortekaas. 'In general, it is roughly the case that the safer the vaccine is, the less effective it is. Our vaccine is a live attenuated virus. It grows well but has no pathogenic capacity. Once injected, it infects cells and initiates an immune response that is very close to the natural immune response. It sets various alarm bells off in the cell.'

Jeroen Kortekaas
extraordinary professor

It sounds risky to use a live virus as a vaccine. 'The Rift Valley fever vaccine is potentially dangerous,' acknowledges Kortekaas. 'If you want to create a live attenuated virus to use as a vaccine, you must do so very precisely, and you need to know a lot about the virus's Achilles' heel. They would probably never do it for Ebola, because people find that disease much too scary. But we know exactly how to weaken the virus and it has been tested in a lot of different animal models. It is safe.'

Friday afternoon experiment

When CEPI (see inset) put out a call two years ago for proposals for the development of a human vaccine against Rift Valley fever, Kortekaas and his team opted for the approach using a live attenuated virus. Kortekaas: 'The obvious choice for a human vaccine is actually a "subunit vaccine", which is based on a specific protein from the virus that provokes an immune response. But those vaccines are expensive to make and don't work for very long. A live virus stimulates a much broader immune response. Also, we

The high-security research lab of Wageningen Bioveterinary Research (WBVR) in Lelystad. Photo Maarten Spoek

already had a lot of data about the veterinary vaccine at that time. So we knew that a safe live attenuated vaccine would be possible for humans too.' Kortekaas formed a consortium of companies and institutions, including the WUR spinoff BunyaVax, where he is research director. The group won the contract and was allocated 12.5 million dollars to develop the vaccine.

Funnily enough, the vaccine they ended up with came out of a 'Friday afternoon experiment' by Kortekaas's colleague Paul Wichgers Schreur. Researchers use this term for experiments they do pretty much for the fun of it in a spare couple of hours. 'Purely out of curiosity to see what happens,' says Kortekaas. Some years ago now, the researcher cut one of the three segments of the virus genome in two. The virus survived this procedure remarkably well, although its growth was slowed down somewhat. A test on mice followed to see whether the virus was still pathogenic. 'Nothing at all happened, except that they developed a good immune response.'

And that is how, technically, a vaccine was born. The edited virus proved no longer to be pathogenic because it now had a kind of packaging problem. The virus genome normally consists of three segments. Kortekaas: 'Once one of them

'THE YET-TO-BE UNIDENTIFIED DISEASE X INTRIGUES ME – WHICH VIRUS WILL BE NEXT?'

LARISSA project

The search for a human Rift Valley fever vaccine is financed by the Coalition for Epidemic Preparedness Innovations (CEPI), established in 2017. CEPI wants to develop vaccines that the pharmaceutical industry is not interested in because they do not have enough commercial potential. This initiative receives both public funding from governments and private funding from organizations including the Bill & Melinda Gates Foundation. Rift Valley fever is just one of CEPI's targets. The LARISSA project, which Kortekaas heads, is working on the human vaccine against Rift Valley fever.

Rift Valley

Rift Valley fever is named after the region of Kenya where the first outbreak struck sheep in 1931. The disease spread across Africa from the Rift Valley. Sheep are the most susceptible to the disease. Newborn lambs do not survive an infection, and 30 per cent of adult sheep are killed by one. The disease almost always leads to abortion in pregnant ewes. Humans can catch it via infected meat or mosquitoes. The death rate among infected humans is one to three per cent. Rift Valley fever has not reached Europe yet, but tests have shown that mosquitoes that are found here can transmit the disease.

is split, the virus has to package not three but four segments to form a complete virus particle. And that costs energy and takes more time than packaging three segments. That delay gives the host cell's immune system enough time to slow down replication and thus prevent disease from developing.'

In order to weaken the virus further, the code was cut out of another segment of the genome for a protein that inhibits the host's interferon. Interferon ensures that the host cell makes various proteins with antiviral effects. By deactivating interferon, intact viruses disarm the host. The adapted virus lacks that possibility and cannot therefore fight back against the host's immune response.

More exciting

The approach to creating a vaccine against Rift Valley fever is the same for humans and animals, says Kortekaas. 'The difference lies in the virus strain we use. And in the end, the formulation – the way the manufacture produces it – is different too. But the technology is identical. For two reasons, it's a nice example of One Health. We are using technology from veterinary science to develop a human vaccine. And by protecting animals, you protect people too in the end.'

Kortekaas and his group previously developed a vaccine against swine fever. But to him, human vaccines are more exciting. 'I'm more interested in viruses that infect humans because their impact is far bigger. However important swine fever may be, its impact is not like that of Rift Valley fever. If I want to grab everyone's attention in a lecture, I have to start talking about a disease that's dangerous for humans.' His passion is for viruses that can suddenly turn up somewhere. 'The yet-to-be identified Disease X intrigues me – which virus will be next?

'SLOWING DOWN THE VIRUS PREVENTS DISEASE DEVELOPING'

Why does it make people and animals sick? Zika virus and West Nile virus had hardly been studied at all until they caused the first major outbreaks. West Nile virus has now arrived in the Netherlands. I am very curious to see how that will play out.'

Meanwhile, he has enough work on his hands with the vaccines against Rift Valley fever. The veterinary vaccine is currently being produced by the pharmaceutical industry and prepared for registration. The first clinical trial of the human vaccine is expected to take place at the end of this year in Belgium. Kortekaas: 'Phase two will take place after that in Kenya, where the virus is circulating. To some extent, you have to start all over again there, because the African population may have a slightly different immunological response to Europeans. Then comes a large-scale phase three trial, to demonstrate the positive impact of vaccination in regions affected by the virus. It is not yet entirely clear how we are going to do that. It's not easy to set up that kind of trial, since outbreaks of Rift Valley fever cannot be predicted.' In view of all this, it will take at least three years before the vaccine is on the market. ■