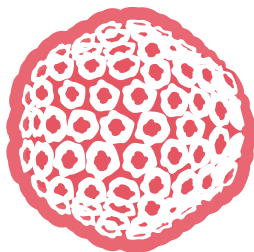


Preparing for Virus X

Tropical viral diseases are on the rise worldwide. Zika, swine flu, Rift Valley fever and SARS are just a few of the many diseases threatening humans or animals. Virologists are researching ways of preventing new outbreaks and epidemics. 'There is no doubt at all that a new virus will turn up somewhere some time.'

TEXT ARNO VAN 'T HOOG ILLUSTRATIONS KAY COENEN

An unusual species of mosquito was caught in a mosquito trap in Flevoland, the Netherlands, in June. *Aedes flavopictus*, a species from Japan and Korea, can potentially transmit Dengue virus. A local eradication campaign has been launched to prevent the species getting established in the area. Several other exotic mosquitoes have been found in Flevoland in recent years, among them the Asian tiger mosquito and the Asian bush mosquito, both of which are thought to have entered the country via used car tyres. Attempts to wipe them out are not always successful: since 2014 the Asian bush mosquito has



RIFT VALLEY FEVER

Transmitted by *Aedes* and *Culex* mosquitoes
Hosts Wild and domesticated ruminants, humans

been so widespread around the town of Lelystad that the eradication campaign has been abandoned. It turned out that these tropical mosquitoes were not carrying any pathogens, but they do raise the risk of a tropical virus spreading should it enter the country in future.

‘It is logical for the media to pay attention to these kinds of reports,’ says professor of Veterinary Arbovirology Jeroen Kortekaas, who works at Wageningen Bioveterinary Research. Something is definitely going on, he thinks. Population growth, globalization and climate change are creating a world in which diseases can spread faster and further.

PUBLIC HEALTH EMERGENCY OF INTERNATIONAL CONCERN

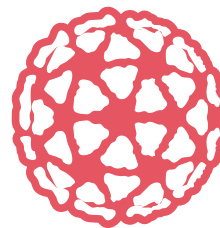
On 18 July 2019, the World Health Organization (WHO) declared the outbreak of Ebola in Africa a Public Health Emergency of International Concern.

Since the outbreak in the Democratic Republic of the Congo in August 2018, more than 2000 cases of Ebola have been registered and more than 1500 people have died. The earliest outbreaks of the disease – described in 1976 – were limited to small communities in Central Africa, but between 2014 and 2016, several countries in West Africa were afflicted by an epidemic which cost the lives of 12,000 people, according to official estimates, and in reality probably many more. The disease occasionally rears its head outside Africa too, but so far these outbreaks have been contained thanks to immediate isolation of patients and the use of protective clothing. The Congo has faced a new epidemic since August 2018. Ebola is high on the WHO list of diseases for which a vaccine is urgently needed. More than 160,000 people in the Congo have recently been inoculated with an experimental vaccine.

The WHO declares an international public health emergency if a disease threatens several countries and calls for coordinated international efforts. Previous occasions when an emergency was declared were the outbreak of Zika virus (2016), the outbreak of Ebola in West Africa (2014), the spreading of polio (2014) and the swine flu epidemic (2009).

One example is the mosquito-borne West Nile virus, which went all the way from Israel to America, while spreading in Europe at the same time. Greece reported 316 human cases last year, with 50 deaths, mostly from meningitis. The virus has not reached the Netherlands yet, but nine species of mosquito live here which could transmit it from migrating birds to humans. No vaccine for humans is available.

Kortekaas: ‘North-west Europe has got off relatively lightly up to now, mainly because of the mild climate. Exotic insects have always been introduced from time to time, but now that our climate is becoming warmer and wetter, the conditions for mosquitoes are becoming more favourable.’ Viral diseases are spreading to new tropical regions as well: in 2015, the originally African Zika virus caused serious brain damage in thousands of new-borns in Brazil. Animals are often the victims of emerging viruses too. At the end of last year, African



CHIKUNGUNYA

Transmitted by *Aedes* mosquitoes
Hosts Humans

swine fever virus turned up in a wild boar population in the Belgian Ardennes. This disease had been spreading in Russia and Eastern Europe since 2012. There has been a massive outbreak in Asia that started in 2018: by the end of June 2019, 2.8 million pigs had been culled in Vietnam. The virus is not a threat to humans, but infections in pigs are nearly always fatal. By culling wild



PHOTO ALAMY

An experimental Ebola vaccine is administered in the Democratic Republic of Congo.

‘Viruses are extremely flexible genetically’

occurs mainly in East and Southern Africa. It is at home amongst wild and domesticated ruminants and humans. The latter can also be infected through contact with the meat or blood of infected animals. The infection usually causes relatively mild symptoms in humans, but complications may result in death or serious brain abnormalities. Its widespread distribution and public health impact have put Rift Valley fever on the WHO's priority list.

EPIDEMIC PREPAREDNESS

In July, a consortium led by Kortekaas was allocated a budget of 12.5 million dollars by the Coalition for Epidemic Preparedness Innovations (CEPI) and the European Union to develop a human vaccine. ‘At Wageningen Bioveterinary Research we have so far only developed veterinary vaccines. We will carry out a phase 1 clinical study in Europe, using volunteers, to show that the vaccine is safe to use. We are also looking at how immune cells and antibodies counteract the virus. In a follow-up study, we will vaccinate people in Africa in an area where there is Rift Valley fever,’ says Kortekaas.

If you line up these developments, you get the feeling that we can hardly keep up with the whims of Mother Nature. What is the best strategy and what can science contribute? To start with, says Wim van der Poel, professor of Emerging and Zoonotic Viruses at Wageningen Bioveterinary Research, it is good to realize that a high standard of living in a country forms a key barrier to outbreaks of disease. ‘Ebola could never wreak such havoc in the Netherlands ➤

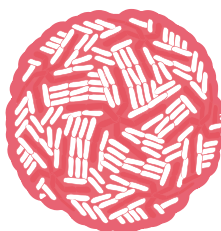
boar and putting up hundreds of kilometres of fencing in Denmark and France, it is hoped that the virus can be kept at bay in Western Europe. There is no prospect of a vaccine at present.

Actually, we are always one step behind in the battle against new viruses, notes Kortekaas. ‘Industry only starts developing vaccines after a significant outbreak has occurred. Whereas there are a lot of viral diseases, some of them affecting people, for which we need to have vaccines on the shelf.’

Since the outbreak of Ebola in West Africa in 2013, and of Zika in Brazil in 2015, there is greater awareness internationally that preparation is half the battle when combatting diseases. In 2018, the World Health Organization (WHO) reviewed its ‘R&D Blueprint’ list of priority viral diseases for which a vaccine is urgently needed, such as SARS, Zika, Ebola and Rift Valley fever. But developing a vaccine is costly, and the coun-

tries with the biggest problem are usually poor, which puts a damper on investment in research by pharmaceutical companies. The WHO and charities are among the organizations trying to plug the gaps.

Kortekaas is closely involved in vaccine development. He designed a vaccine that protects sheep and other ruminants against Rift Valley fever, a mosquito-borne virus that

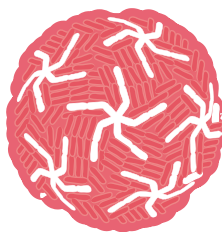


DENGUE

Transmitted by *Aedes* mosquitoes
Hosts Humans

because healthcare and hygiene are better here. Ebola goes on causing problems in Africa because disease control is so badly organized in countries like the Congo. You can reduce risks considerably by improving healthcare, sewage systems and drinking water quality.'

Secondly, Van der Poel sees a crucial role for experienced vets and doctors, who are always the first to encounter new infections. They are the first to notice unusual symptoms in humans or animals. This requires experience and an eye for detail, because the initial symptoms of most tropical viral infections are similar to flu symptoms. Van der Poel: 'That leading role was played by doctors in the SARS outbreak in 2002: the doctor who first reported the disease in Hong Kong, and who ended up dying of SARS himself, said: this is something new, I've never seen this in a patient before.' The same thing happened in veterinary medi-



ZIKA

Transmitted by Aedes mosquitoes
Hosts Apes, humans

cine, says Van der Poel, in the cases of the sheep disease Bluetongue, the Schmallenberg virus and the avian flu H7N7. 'There were a couple of vets who said, something strange is going on, we need further diagnosis. So medical experience and the case descriptions are very important for getting outbreaks in our sights quickly. That can be underestimated.' Finally, Van der Poel says that virologists are developing better and better molecular techniques for tracking down viruses fast. 'When SARS broke out in



PHOTO HOLLANDE HOOGTE

African swine fever is on the move, threatening pigs and wild swans. A signboard with information about preventing infection on the side of the road in Groesbeek, the Netherlands.

2002, they struggled for months to identify the virus. That would definitely go faster with the DNA techniques we use nowadays.'

FINANCIAL DAMAGE

The risk of infections could indeed increase in the near future, but we are better prepared technologically, says Van der Poel. 'In that sense, it is a bit of a gamble. If we stay alert, we can keep it under control, especially in a country like ours. But we shouldn't be complacent. Perhaps we've forgotten what it's like when a completely unknown virus like SARS rears its head. The financial damage caused by the panic and the grounding of air traffic during the SARS outbreaks was estimated at 40 billion dollars. There is no doubt at all that a new virus will turn up somewhere some time. We just don't know when.' To underline that danger, the WHO's priority list of dangerous viruses now includes Disease X: an unknown virus that might cause an epidemic in the future. But scientists are not just waiting in the wings like the fire brigade, ready for the next report of a virus outbreak. Virologists want to improve their understanding now of where the main risks of an outbreak could arise. One branch of research focuses on what is known as vector competence. Researchers look into whether the species of mosquito or other insects found in the Netherlands are capable of transmitting

tropical viruses. Kortekaas: 'For instance, we have established that Dutch mosquitoes can transmit Rift Valley virus from one sheep to another. That transmission was remarkably efficient.'

So what's going to happen when a person or a mosquito carrying the Rift Valley virus crosses national borders? Kortekaas: 'The crucial question is whether the virus feels at home in a new environment. And what determines that? Often, we have no idea why some tropical viral diseases have not reared their heads here yet. One important aspect is their interaction with local mosquito species, which may not be optimal for spreading the disease. On the other hand, viruses are extremely flexible and can evolve easily. If they get a chance, they eventually find a way to adapt to local hosts and conditions.'



EBOLA

Transmitted by direct contact
Hosts Apes, humans

Kortekaas's research data on the transmission of viruses by Dutch mosquitoes are very useful to quantitative veterinary epidemiologist Mart de Jong, another Wageningen professor. He has a lot of experience with building statistical and mathematical models that show the distribution of diseases such as avian flu and swine fever, or calculate the effect of a vaccination campaign. De Jong: 'You need models like that to interpret experiments and observations. To find answers to the question of when a vaccine is effective, for example.' De Jong was involved in an Irish study on the experimental vaccination of badgers against bovine tuberculosis (TB), a bacterium that can infect badgers, cattle and humans. An outbreak of the infec-



YELLOW FEVER

Transmitted by Aedes mosquitoes
Hosts Apes, humans

tion means culling cattle and badgers, while posing a danger to humans too. Calculations showed that if at least 30 per cent of the Irish badgers are vaccinated, bovine TB can be eradicated. Based on that result, the Irish government decided to start vaccinating badgers.

MOSQUITO-BORNE

Bovine TB is not spread by mosquitoes but through milk and droplets from coughing, and the bacterium infects far fewer animal species than tropical viruses. It is more of a challenge for a veterinary epidemiologist to make a model for mosquito-borne diseases. De Jong: 'For that you need a knowledge of the main insect species in our region for the

transmission of a virus such as Rift Valley fever. We don't really know that. The question is whether transmission is determined by a few dominant insects, or whether several different species play a role at the same time. A big project aiming to answer questions like that has just started with funding from the Dutch National Science Agenda. My group is involved in that. It focuses on infectious diseases that are likely to spread towards the Netherlands, and especially those spread by mosquitoes, such as West Nile fever, Rift Valley fever and Chikungunya.' The reproductive success of mosquitoes provides an important key to understanding the risks, says De Jong. As far back as 1900, the Scottish doctor and Nobel Prize winner Ronald Ross showed that the distribution of the malaria parasite depends on the density of the mosquito population in an area. 'Based on that insight, people started draining swamps. Malaria was once present in Zeeland and Amsterdam. The disease gradually disappeared, but not by eliminating every last mosquito. Mosquito numbers went down, so transmission was no longer effective.'

Managing the density of mosquito populations is therefore a good strategy for controlling outbreaks of infections. De Jong wants to combine knowledge of mosquito population density and transmission between humans and farm animals. 'So we will be able to say: if a virus arrives here, does the model show that the infection can spread effectively? Can we do something about that? Where could an outbreak happen? And

**'The crucial question is:
Will the virus feel at home
in a new environment?'**



SARS

Transmitted by direct contact
Hosts Civet cats, bats, humans

what is the best monitoring method to prevent that? This is all quite complicated, partly because it is not easy to predict mosquito population density. That depends on rainfall and local conditions. The challenge is to be creative with new research so you can say something sensible about it.' ■

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COURSE GLOBAL ONE HEALTH

In autumn, Wageningen Centre for Development Innovation will run the course Global One Health: towards Human, Animal and Plant Health.
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