Dies oration 2022 by Meta Roestenberg

Infectious diseases without borders

Thank you for your insights, Matthias. Madame Rector, distinguished audience: it is 2022 and I do not need to explain how infectious diseases can disrupt society. Chances are your life has changed considerably over the past two years. Testing, 2R or FFP2 face masks, quarantine and QR codes have become part of our low-contact COVID society. However, not so very far away from our own country, people's lives have been shaped by infectious diseases for generations. *Plasmodium falciparum* malaria is the permanent COVID crisis in Africa. With half a million deaths per year, malaria is an everyday reality for 3.4 billion people. The malaria society is equipped with mosquito nets, mosquito traps, insecticides, endless testing and repeated treatment. In contrast to COVID, malaria mainly affects children below the age of five. Diseases such as hookworms (450 million people infected worldwide) and Schistosoma worms (around 200 million people infected worldwide) have an enormous impact on children's health worldwide, for whom constant infestation with these worms leads to anaemia, protein deficiency and delayed growth. But chances are, you were not even aware of the existence of these, as we call them, 'neglected tropical diseases'. The name says it all. These infectious diseases cannot be found in the daily statistics on the news because they are beyond our national borders and out of range of social media.

Who is actually responsible for the health of these children? With the aid of vaccines, we are now emerging from the COVID crisis. In under two years, we have around 120 vaccines that are clinically used or tested: an incredible scientific achievement by people like Matthias. By comparison: after decades of research, there are around 15 vaccines in development against malaria. Against hookworms and schistosomiasis, a total of two and four vaccines respectively are in clinical trials worldwide. The target group for malaria, schistosomiasis or hookworm vaccines is not wealthy, so developing vaccines to fight these diseases is not an attractive prospect for big pharma. So who will do that then?

The sustainable development goals are clear: *ensure healthy lives and promote wellbeing for all at all ages*[1]. Within this goal, we as academics can take our own responsibility, in our scientific research, teaching and the debate on social inequality. Leiden University has a rich tradition of this, with Professor Cleveringa as a leading example. But today too, in the year 2022, in light of Leiden University's new strategic plan and the lessons that we have learned from the COVID crisis, there are opportunities to contribute to this.

For example, academic pharma is focusing on developing new products within the public sector. Vaccines against malaria, hookworm and schistosomiasis are currently all being developed and tested in the public domain. That's no mean feat. The public sector is not really equipped to globally prioritise the most promising candidates as a large pharmaceutical company would. Investment, that is to say in the form of research grants, is obtained piecemeal and depends on the right calls. Very few grant providers want to commit to the full development of a product. And so the public sector pipeline of products for poverty-related infectious diseases is as good as dry, and the development of the existing candidates is agonisingly slow. This must change. Thanks in part to the COVID crisis,

we are learning that infectious diseases require a global approach, and there is increasing awareness of the need for innovation in the development of vaccines and drugs for infectious diseases.

One such innovation is the use of controlled human infection models early in the clinical development pipeline. This is a study design that has caused quite a stir because it involves the deliberate infection of healthy young adults. These kinds of small, highly complex and therefore academic studies make it possible to see whether a new vaccine works early in the clinical development process. A small group of volunteers are fully informed before being included in the study. Volunteers are randomised between the candidate vaccine and the placebo. Then everyone is exposed to the pathogen, for instance malaria mosquito bites. Those who contract malaria are treated immediately, preferably even before symptoms arise. These experimental infections of healthy volunteers have become a central element of clinical tests of new malaria vaccines. Thanks to studies like these, the first malaria vaccine, Mosquirix, was recently approved [2]. This is an enormous achievement, thanks in part to co-funding from the Bill and Melinda Gates Foundation, but with a somewhat limited efficacy of 30-50%, that bears no comparison with the 90% efficacy of COVID vaccines.

And so, closer to home, at the LUMC's Leiden University Center for Infectious Diseases (LU-CID), molecular biologists such as Chris Janse, Shahid Khan and Blandine Franke-Fayard are working on a new malaria vaccine based on a genetically weakened malaria parasite. Last October and November we tested the first prototype vaccine on people and the expected genetic change did indeed translate into a product that can be safely administered to humans. This is an incredible achievement by a cross-border team of driven scientists.

Research into schistosomes has also been going on in Leiden for decades. The tropical water snails that are responsible for the transmission of the parasite were already being bred here in Leiden before I was born. Thanks to years of investment in knowledge about this parasite, transferred down generations of dedicated technicians, and the tireless efforts of researchers in ultrasensitive laboratory techniques to diagnose this parasitic disease, we have now succeeded in developing a controlled infection model for this parasite too in healthy volunteers[3]. And we will test a promising Schistosoma vaccine here on Leiden soil next year. But perhaps even more importantly: our parasites that are now born and bred in Leiden will travel back to Africa next year, where they will be used for experimental infection studies in humans in Uganda.

I understand that this idea of deliberate infection with worms may not immediately appeal to you. And you may understand in turn that the ethical and scientific considerations of whether and under what conditions we do these kinds of study is complex. Some of you may even find it a bit radical. But if we realise that the impact of infectious diseases on global health and the socioeconomic effects are gigantic, is it not justified to take a radical approach to such a profound problem?

Less radical but no less important is the investment in and use of new technologies for infectious diseases. For example, we could, as illustrated by Matthias, also apply the latest mRNA vaccine techniques to infectious diseases such as malaria, hookworms and

schistosomiasis and thus amplify the impact of our research. Another example is my collaboration with Professor Fijs van Leeuwen – who usually does radiology research at the department into making tumours visible. He applies the tools he is developing for this in our collaboration on parasites. Here you will see a film from his group that shows the Schistosoma parasite penetrating the human skin. This is not just a powerful image that helps make schistosomiasis less *neglected* – tonight at dinner many of you will share a description of these images with your loved ones – but making the parasite visible in the context of human tissue improves our understanding of how the human immune system responds to these invaders. This kind of cross-border research isn't without the odd hitch: just as I have to learn the language of another culture in our collaboration with our African partners, we also have to learn the language of other disciplines if we want to work outside our own one. And in an attempt to build a proverbial bridge, I am therefore happily studying Lipinsky's rules, fluorescence spectra and anime groups that are available for hydrogen bonding. Science is and remains – more than ever – teamwork.

Imagine we do manage to develop a new vaccine. How do we ensure that this vaccine also reaches the people who need it most? This is another way we are learning from the COVID crisis. The COVAX programme was initiated to speed up global access to vaccines. A globalist effort to minimise the impact of the pandemic for everyone. But COVAX continues to struggle to achieve the promised 20% vaccination rate and previous targets have been delayed. Just 5% of the population of low-income countries has been fully vaccinated[4]. Only 22% of the vaccines produced worldwide are delivered to the low-income countries in the COVAX programme, with the remaining nearly 80% going to people like you and me and our children. Did you know that our own country of the Netherlands has only delivered just over half of the promised vaccine donations to COVAX[5]? By the way, we can catch up today by donating en masse via gogiveone.org.

So despite the scientific breakthrough of COVID vaccines within two years of the start of the pandemic, the benefits are mainly being reaped by the populations of high-income countries. And that, while the COVID crisis has pushed some 97 million people into extreme poverty[6] – although not in the high-income countries. My PhD candidate in Uganda tells me that children in her country have not been to school for as long as two years. It's painfully clear that the socioeconomic impact of the COVID crisis is mainly being borne by the world's poorest. How can we ensure that people all around the world benefit from scientific progress? What if we were to invest in actively sharing our scientific knowledge with low-income countries?

Again we are learning from the COVID crisis. In countries like Cuba, forced to be independent as a result of years of economic embargo, there have been decades of investment in local research and vaccine production. As a result, this low-income country had a vaccination rate of 89% by November 2021, with fully proprietary vaccines such as Soberana and Abdala, the results of which have been published on medRxiv[7,8]. And so vaccine donations to Cuba aren't necessary.

The COVID pandemic has taught us that infectious diseases do not respect borders. The University's new Strategic Plan is all about connecting. If we want to arm the world against infectious diseases, we must not allow ourselves to be limited to national borders or the

boundaries of our discipline. It is our duty to master the new languages of other disciplines. It is our duty to train a new generation of researchers, in high- and low-income countries. In the post-COVID era, the new digital learning methods provide relatively easy opportunities to do just that.

The development process for the Strategic Plan was given the name Leiden Forward. In view of the up-and-coming new generation of researchers and the daily impact of pandemics and endemic infectious diseases, I think we should christen the plan's implementation Leiden Fast Forward. I sincerely hope that I will have the opportunity to meet you in the coming years, if necessary at a distance of 1.5 metres, to rapidly exchange jargon and thus together discover the boundaries of science.

I have spoken.

Prof. M. Roestenberg

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