INAUGURAL SPEECH

Janneke van de Wijgert was appointed by the Executive Board of the University of Utrecht as professor at the Faculty of Medicine on 1 November 2018 to undertake activities in the field of 'Epidemiology of infectious and immune-mediated diseases'. This speech was delivered on 23 May 2022 to celebrate that she assumed this position.

[Slide 1: Title] **The female microbiome: from exploration to application.**

Honourable Vice-Chancellor, esteemed colleagues, dear family and friends, esteemed audience,

My scientific career has been rather atypical, but from the very beginning, I was drawn towards infection and immunity. Even now – more than 30 years later – I am still fascinated by those subjects.

The human immunodeficiency virus – or HIV – was discovered just before I started studying Medical Biology at Utrecht University. An HIV test became available during my first year at university. While I was watching this news on Dutch television, I decided that I wanted to work on that epidemic. The main goal of the Master's course in Medical Biology – currently called Biomedical Sciences – was to teach us how to conduct laboratory research. This proved to be a strong foundation for my career, but was not exactly what I was looking for. I first encountered epidemiologists when I was doing a microbiology internship at Emory University in Atlanta in de United States. These epidemiologists worked for the Centers for Disease Control and Prevention in that same city, and I was immediately drawn towards the type of work that they did. [Slide 2: UCB, UCSF]. At that point in time, epidemiology degree courses were rare in the Netherlands and I therefore joined the University of California (UC): I studied Public Health on the Berkeley campus and worked as a research assistant on the San Francisco campus. Meanwhile, HIV was spreading in the general sub-Saharan African population, in contrast to the epidemics in Europe and North America that had remained concentrated. I wanted to work on HIV in African women, and was given that opportunity by my UC Berkeley PhD supervisors Professor Arthur Reingold and Professor Nancy Padian, the late Professor David Katzenstein of Stanford University, and my University of Zimbabwe mentors Professor Zvavahera Chirenje and Professor Mike Mbizvo. In 1994, I left for Zimbabwe and stayed for 5 years.

[Slide 3: HIV mortality over time]. The HIV epidemic in sub-Saharan Africa was at its worst in the second half of the 1990s, when I was living there. Many people became infected, and often passed away within a few years because vaccines and medicines were not yet available. Women sometimes passed the virus to their children during pregnancy, childbirth, or breastfeeding. Today we still do not have an HIV vaccine nor medicines that can cure HIV infection. However, there was a breakthrough in 1996: it had been discovered that cocktails of multiple medications that each inhibit the HIV-virus in a different manner – the so-called antiretroviral drugs – could save lives. I still remember the excitement about this discovery at the International AIDS Conference in Vancouver as if it were yesterday. Antiretroviral drugs also turned out to be capable of preventing the transmission of the HIV-virus from mother to child. Unfortunately, it took the international community an additional 7 years – until 2003 – to finance large-scale HIV treatment programmes in Africa and other low-income countries. My future Dutch mentors at the Amsterdam University Medical Center (UMC), the late Professor Joep Lange and Professor Peter Reiss, would end up playing important roles in that endeavour.

[Slide 4: Zimbabwe, UZ-UCSF]. The group of American and Zimbabwean researchers that I was a part of in the second half of the 1990s, as well as other research groups, had noticed that African women became infected with HIV more often and at younger ages than their male counterparts. Even today, one of the four new HIV infections in sub-Saharan Africa is in young women aged 15-24 years. Some of the reasons for this became immediately clear. Women were for the most part financially

dependent on men and therefore often had little say over when and with whom they had sex, and whether or not a condom was used. Women who wanted to become pregnant had no choice but to risk acquiring HIV in the process because HIV prevention products that allow for pregnancy were not available. Yet other women were suffering from domestic or sexual abuse. The impact of the HIV epidemic on African women was and is devastating, but one good thing about the epidemic is that gender inequality and hidden abuse have become much more visible.

[Slide 5: HIV acquisition in women] My own PhD research focussed on the potential biological reasons why women were more vulnerable for HIV than men. I will first explain to you how the HIV virus infects women. A virus has to enter a cell and take over that cell's mechanisms in order to survive and multiply. The HIV virus targets cells of the human immune system. These HIV target cells are present in blood, the lymphatic system, and in tissues throughout the human body. HIV cannot reach those cells easily from outside the body because human keratinised skin is difficult to penetrate. However, the urogenital, gastrointestinal, and respiratory tracts have open connections with the outside world and are covered with mucous membranes instead of keratinised skin. Those mucous membranes are more vulnerable. This slide shows the natural barriers that the HIV virus encounters when it tries to enter the body via the vagina. The virus will first encounter a sticky mucous layer. In addition, healthy bacteria that produce lactic acid and antimicrobial compounds are present on and in that mucous layer, creating an inhospitable environment for other micro-organisms in the lumen. Next, the virus encounters multiple layers of epithelial cells that are tightly anchored together. If the virus manages to break through the mucous and epithelial layers, it will encounter immune cells. Normally speaking, these cells will inactivate and remove micro-organisms, but HIV may hijack them for its own advantage. Immune cells infected by HIV can spread throughout the body via blood and lymphatic vessels. My PhD research focussed on factors that may weaken these natural barriers. At the time, studies by others had suggested that women with bacterial vaginosis, a condition in which too few healthy and too many unhealthy vaginal bacteria are present, may have an increased risk of acquiring HIV. This was a worrisome finding as approximately one of every three to four women in sub-Saharan Africa has bacterial vaginosis. My PhD research, and subsequent larger studies by myself and others, confirmed the links between various urogenital infections and HIV acquisition, and unravelled the underlying mechanisms. I will come back to this later in this lecture.

[Slide 6: Pop Council setting] In 1999, I moved from Zimbabwe to New York. I had joined Beverly Winikoff's group at the Population Council. The Population Council had been founded in 1952 by John D. Rockefeller III to improve understanding of population growth trends. Over the years, the Population Council's mission widened significantly to include sexual and reproductive health and women's empowerment. [Slide 7: Pop Council team]. I told you earlier that women did not have many options to protect themselves from HIV in the early years of the HIV epidemic, and the Population Council had initiated a program aimed at changing that. I was hired to coordinate that program. We conducted clinical trials of a promising new HIV prevention product for women in South Africa and Thailand, but unfortunately, this product was not successful. [Slide 8: Rwanda setting] I continued working on this line of research after I had returned to the Netherlands in 2003. I had joined the Amsterdam Institute for Global Health and Development or AIGDH, a not-for-profit organisation affiliated with the Amsterdam UMC, headed by the late Professor Joep Lange. AIGHD had received grants to provide on-the-job training to Rwandan and Ugandan PhD students within its HIV, malaria and tuberculosis projects in those countries. In parallel, I had received funding from the International Partnership for Microbicides or IPM and the European Developing Countries Clinical Trials Partnership to establish the research clinic 'Rinda Ubuzima' in Kigali together with Rwandan colleagues. The main aim of Rinda Ubuzima was to conduct sexual and reproductive health research in women in Rwanda. [Slide 9: Rinda Ubuzima team] I ended up conducting many clinical trials and other studies with the Rinda Ubuzima team for 14 years, which was a delightful experience. [Slide 10: CIDI-team] In the same time period, AIGHD colleagues and I also started collaborating with the CIDI

team of the Catholic University of Mozambique in Beira, and with American colleagues of FHI360. Both Rinda Ubuzima and CIDI were part of worldwide networks of research clinics conducting HIV prevention trials in women. [Slide 11: IPM, dapivirine ring, AVAC-pipeline] After many disappointments, the network led by IPM achieved registration of its vaginal dapivirine ring this year. This vaginal ring can be worn for one month and releases the antiretroviral drug dapivirine into the vaginal environment resulting in protection from HIV. Unfortunately, the degree of protection is not yet optimal. IPM, the Population Council and others therefore continue the development of next generation rings that are more user-friendly or effective, such as rings that can be worn for three months, rings containing other or multiple antiretroviral drugs, and rings containing antiretroviral drugs together with hormones to achieve protection from both HIV infection as well as unwanted pregnancy. All of these rings are examples of the use of antiretroviral drugs for protection against HIV infection, which is referred to as pre-exposure prophylaxis or PrEP. PrEP pills had been approved in 2012, and a PrEP injection providing protection for two months in 2021. The PrEP rings have been developed specifically for women, and PrEP pills and injections can be used by both men and women. The field is therefore finally able to offer women and girls multiple HIV prevention options, after approximately 30 years of lobbying and research. However, these new prevention options must be made accessible and used on a large scale to achieve a continuation of the downward trend in HIV incidence in women. Many challenges remain, but the first steps have been taken. [Slide 12: Global Campaign for Microbicides]. For about 25 years, I was fortunate to have had opportunities to make modest contributions towards this achievement, and to have been part of a large, diverse, international group of people who gave their hearts and souls to this cause. These experiences taught me that activism and science can mutually reinforce one another. They also taught me that capacity building via international cooperation based on equality requires mutual trust, time, and energy, but is well worth all those efforts in the end.

[Slide 13: Human microbiome] In addition to my international HIV research, my work at AIGHD, and later also the University of Liverpool and the University Medical Center Utrecht, increasingly focussed on the human microbiome. A microbiome is a community of micro-organisms, mostly bacteria, viruses including bacteriophages, and fungi, that live together in a specific habitat. Examples of habitats are water or soil, but also the human body. Our bodies contain multiple microbiome habitats, including the vagina and uterus, but also the urinary, gastrointestinal, and respiratory tracts, and the skin. In fact, the human body contains at least as many cells of micro-organisms as human cells. The immune system tries to contain the total number of micro-organisms, as well as balance healthy and potentially harmful organisms, in all human body habitats.

I had not been able to study all vaginal micro-organisms in my PhD research due to technical limitations. In subsequent years, new molecular techniques – particularly next generation sequencing – had revolutionised the microbiome field. These techniques are capable of identifying all genetic material in one sample, such as a swab, including the genetic material of all micro-organisms that are present in that sample. From about 2005 onwards, it became possible and affordable to analyse large numbers of samples with these molecular techniques, which caused a worldwide explosion of human microbiome studies.

The term dysbiosis refers to an imbalanced microbiome that has negative health effects. However, it is difficult to define dysbiosis more precisely because an unhealthy imbalance in one habitat looks different from an unhealthy imbalance in another habitat, and within one habitat, also depends on circumstances. In addition, imbalances usually follow a gradient instead of a cut-off threshold. I suspect that you have heard that ‘the microbiome’ should consist of as many different bacteria as possible. It is important to realise that this statement refers to the gut microbiome. Healthy guts should indeed be filled with lots of different micro-organisms fulfilling different functions, such as metabolising different types of foods. The microbiome of the vagina and cervix, the so-called cervicovaginal microbiome, also contains many bacteria, but fewer and less diverse than the gut.

Internal organs such as the uterus, bladder, and lungs do not contain many micro-organisms, and if they do, we speak of a uterine or bladder infection, or pneumonia. One could therefore say that these common conditions are dysbiotic conditions.

[Slide 14: VMB + UMB] I started collaborating with laboratories at TNO in Zeist, the Public Health Service (GGD) in Amsterdam, the Amsterdam UMC, the University of Liverpool, and the UMC Utrecht. The microbiome data that we collected and analysed together contributed much to the current state of knowledge related to the cervicovaginal and urinary tract microbiomes of women. Briefly, we now know that both habitats, which are connected with one another and with the rectum via the perineum, mostly contain lactobacilli, and especially two *Lactobacillus* species: *Lactobacillus crispatus* and *Lactobacillus iners*. All urogenital *Lactobacillus* species have in common that they do not cause inflammation and do not become invasive, but we now also know that *Lactobacillus crispatus* is the 'healthiest' and *Lactobacillus iners* the 'unhealthiest'. *Lactobacillus crispatus* bacteria produce a lot of lactic acid and antimicrobial compounds, making the vaginal environment inhospitable to many other micro-organisms. Furthermore, the *Lactobacillus crispatus* bacteria themselves grow in a well-controlled manner. *Lactobacillus iners* bacteria are much less able to keep other micro-organisms at bay, can grow to much higher densities, and when other bacterial species are present, produce the compound 'inerolysin', which can have harmful effects. The most common type of cervicovaginal dysbiosis is bacterial vaginosis, the condition that I mentioned earlier in the context of increased HIV risk. In the case of bacterial vaginosis, the microbiome is highly diverse and dense, consisting of bacteria that cannot tolerate oxygen, the so-called BV-anaerobes. Important BV-anaerobes include *Gardnerella* species, *Prevotella* species, and *Fannyhessea vaginae*, but there are tens of others. These BV-anaerobes are usually part of a diverse community and will hardly ever dominate the microbiome by themselves. *Gardnerella* is an exception to that rule. *Gardnerella* species seem to play an important role in the development of bacterial vaginosis and some of them make biofilms or lysins. Another type of dysbiosis is caused by the outgrowth of a third group of urogenital bacteria that I will refer to as 'pathobionts'. These are facultative anaerobic bacteria that can tolerate different levels of oxygen. Most physicians will recognise them as the bacteria that cause hospital infections or life threatening infections in newborns. The most important pathobionts in the cervicovaginal microbiome are Gram-positive *Streptococcus* species, but Gram-negative bacteria such as *E. coli* or *Klebsiella* can also be present. The most important pathobionts in the urinary tract are these Gram-negative pathobionts, but in postmenopausal women, we also often see Gram-positive pathobionts. Lactobacilli thrive when the oestrogen level is high. When it starts to decline in menopause, the lactobacilli in both habitats are replaced by BV-anaerobes and pathobionts. Some bacterial pathobionts, as well as *Candida* yeasts, can tolerate the acidic environment that lactobacilli create really well, in contrast to BV-anaerobes. They occur less frequently than BV-anaerobes, and in smaller quantities. However, they are potentially important anyway, because they may cause inflammation or become invasive even when present in small quantities.

[Slide 15: RUTI] You may wonder why this new microbiome knowledge is important. First, urogenital infections in women are very common and can become recurrent, especially in postmenopausal women. In the Netherlands, these infections are among the most common conditions seen by general practitioners. The new microbiome knowledge taught us that not all lactobacilli are equally healthy, that BV-anaerobes and pathobionts cause different types of vaginal dysbiosis, and that the causative urinary tract infection agents in postmenopausal women are more diverse than in premenopausal women. [Slide 16: Complications]. Second, dysbiosis in either habitat is associated with several severe complications. Potentially harmful cervicovaginal bacteria can travel through the cervix to the uterus, fallopian tubes, or even further into the abdominal cavity. Potentially harmful urinary tract bacteria can travel to the kidneys or end up in the bloodstream. This can cause the life-threatening conditions pelvic inflammatory disease and sepsis, respectively. I already told you about the links between cervicovaginal dysbiosis and HIV acquisition. Such links also exist between cervicovaginal dysbiosis and other sexually transmitted pathogens, including oncogenic human

papillomaviruses that can cause cervical cancer. In addition, cervicovaginal bacteria can cause infertility, and miscarriage or preterm birth in pregnant women. Urogenital, gut, and skin bacteria can be transmitted from a mother to a newborn baby, sometimes resulting in neonatal sepsis and even death of the newborn. The latter is, unfortunately, much too common in low-income countries, but also still happens occasionally in the Netherlands. Finally, urinary tract bacteria can cause kidney stones, incontinence, or bladder cancer. After we and others had mapped cervicovaginal and urinary tract microbiomes in women worldwide, it was time to start investigating the causal pathways leading to these complications, as well as new diagnostic tests and interventions.

[Slide 17: UoL] In the meantime, I had been appointed Professor at the University of Liverpool in England in 2012 and also in the UMC Utrecht in the Netherlands in 2018. During my time in Liverpool, my PhD students and I, together with colleagues in England, the Netherlands, and Belgium, would contribute to the unravelling of some of the mechanisms explaining the link between cervicovaginal dysbiosis and HIV acquisition. [Slide 18: dysbiosis-HIV link] It was already known that lactobacilli, and especially *Lactobacillus crispatus*, are good at producing large amounts of lactic acid. Women with anaerobic dysbiosis, who carry fewer or no lactobacilli, have less lactic acid in their cervicovaginal environment, allowing more micro-organism – including the HIV virus – to survive. Our genomics, proteomics, and immunological assessments suggested that women with dysbiosis, compared to those without, have a cervicovaginal environment that is also less antimicrobial and more inflammatory. In addition, they have a thinner and less sticky mucous layer and weakened epithelial layers. If these women are exposed to HIV, it would be easier for virus particles to travel through the lumen, mucous, and epithelial layers, and once through, they would encounter more target cells to infect.

We also investigated the potential role of cervicovaginal dysbiosis in the development of cervical cancer. As I mentioned before, cervical cancer is caused by a persistent infection with an oncogenic human papillomavirus, but cervicovaginal dysbiosis could be an additional trigger on the carcinogenesis pathway. Several cross-sectional studies had found an association between dysbiosis and precancerous lesions. However, causality turned out to be difficult to prove. In our longitudinal study, we saw that some women with dysbiosis were less likely to clear their human papillomavirus infection, which means that their cancer risk was indeed increased, but that other women only developed dysbiosis after they had already developed the precancerous lesions. This is a good example of the importance of longitudinal studies in which participants are followed over time. Only then it becomes clear in which order exposures and biomedical processes take place.

[Slide 19: Preterm birth] Children who are born prematurely can suffer livelong effects. Preterm birth has several well-known causes, and one suspected cause is the presence of infection or inflammation in the birth canal. However, it has been difficult to prove the latter definitively, even after next generation sequencing became available, because it is not possible to collect samples from the uterus or cervix during pregnancy. Preterm birth studies to date have had to resort to examining the vaginal microbiome only, even though it is likely that some vaginal bacteria can travel to, or establish themselves in, the uterus more easily than others. These vaginal microbiome studies showed that women with a *Lactobacillus crispatus*-dominated microbiome were the least likely to have a preterm birth, but the findings for *Lactobacillus iners*, BV-anaerobes and pathobionts were inconsistent. Obstetricians at the *Liverpool Women's Hospital* decided to study this in Liverpudlian women as well and asked me to assist them. Most microbiome studies up to then had only determined the microbiome composition proportionally, for example, the percentage of all bacteria consisting of *Lactobacillus* species. We decided to also determine quantitative bacterial loads, and found that the overall vaginal bacterial load was associated with preterm birth. This does not contradict earlier findings by others because *Lactobacillus crispatus* does seem to be best able to limit the total bacterial load. Our results still have to be replicated by others, but it seems likely that bacterial load is important even though it had hardly ever been assessed in previous studies. I am currently

investigating the uterus microbiome in women undergoing in vitro fertilisation together with UMC Utrecht gynaecologists. As we had expected, the bacterial load in the uterus is much lower than in the vagina and cervix, but we are detecting similar bacteria, with lactobacilli being the most common. Again, *Lactobacillus crispatus* seems to be associated with a good outcome, in this case a successful pregnancy and live birth after in vitro fertilisation.

[Slide 20: Diagnostics] Unfortunately, at this point in time, it is difficult to diagnose and treat women with a refractory unbalanced urogenital microbiome. In the Netherlands, diagnostic testing for vaginal infections is not widely available. Some specialised laboratory can do a *Gardnerella* culture or microscopy, but neither are optimal. Diagnostic testing for urinary tract infections is much more available. Urine culture and molecular tests that detect the genetic material of specific micro-organisms in urine are available in central laboratories, and simple urine dipstick and dipslide tests are available to general practitioners. However, as I mentioned before, urinary tract infections in postmenopausal women are often not caused by *E. coli*, unlike in premenopausal women, even though many of the diagnostic tests have been optimised for *E. coli*. Furthermore, urine cultures have to incubate for several days, many of the molecular tests require large platforms, and the simple dipstick and dipslide tests are less sensitive than molecular tests. In recent years, several molecular tests that can detect one or multiple micro-organisms in one sample using a small instrument have become available. However, the test cartridges are expensive and the multiplex tests often produce too many results, including results that are not clinically actionable and therefore confusing to clinicians. In my opinion, another problem is that diagnostic testing is not done often enough. For example, women with a high-risk pregnancy are not often comprehensively screened for urogenital infections or dysbiosis, even though this might prevent complications. Women reporting symptoms are also often not tested. Instead, the physician judges which antibiotic or antifungal drug is most likely to be effective; if the first drug is not effective, a second drug is subsequently tried. In many low-income countries, both physicians and diagnostic tests are in short supply. As a result, urogenital infections are often managed following the World Health Organisation syndromic management guidelines: patients receive multiple antimicrobial medications at the same time to cover all infections that might cause a specific symptom. We and others have shown that this type of infection management without diagnostic testing in women can lead to missed infections and to inappropriate use of antimicrobial drugs, which in turn can lead to antimicrobial resistance. In my opinion, we now know enough about the urogenital microbiome and urogenital pathogens to be able to improve our diagnostic strategies. The point-of-care molecular tests are a good start but should be better aligned with clinical practice. In addition, we need cheap, accurate point-of-care tests that can be conducted by physicians, nurses, or patients themselves without an instrument, including tests that can detect all micro-organisms that might cause a specific symptom in one sample.

[Slide 21: Treatments] Urogenital infection treatments typically consist of antibiotic and antifungal drugs. These are usually quite effective in the short-term, unless antimicrobial resistance is at play, but the infection often recurs in the longer term. We assessed the effect of metronidazole, the most commonly used antibiotic to treat bacterial vaginosis, with next generation sequencing. We discovered that the usual dose and treatment duration did reduce the total BV-anaerobes bacterial load in almost all women but eliminated BV-anaerobes in only a handful of women. We also noticed that metronidazole was less effective in women who had a relatively high abundance of *Gardnerella* in their microbiome, perhaps because the *Gardnerella* was drug-resistant or because they had a *Gardnerella*-containing biofilm that the metronidazole could not penetrate well. Furthermore, we noticed that not *Lactobacillus crispatus* but *Lactobacillus iners* filled the microbiome gap that was caused by metronidazole treatment. In a clinical trial in Rwanda, we evaluated the so-called “weed and seed” treatment principle. We first attempted to remove the BV-anaerobes using metronidazole, and then attempted to fill the microbiome gap with vaginally applied probiotic lactobacilli. The probiotics did have beneficial microbiome effects while being used, but these effects disappeared after cessation of use. Unfortunately, most commercially available lactobacilli are not of human

cervicovaginal origin, and do not seem to be able to colonise human cervicovaginal or urinary tract microbiomes. Recent American trials with an experimental *Lactobacillus crispatus* probiotic of human origin showed better colonisation, but even those results were not yet optimal. The *Bill and Melinda Gates Foundation* in the United States is currently investing in the development of more effective *Lactobacillus crispatus* probiotics, and other organisations and companies are also developing new probiotics and drugs. Examples include lysins originating from bacteriophages targeting *Gardnerella* or urogenital pathobionts, and compounds that disrupt biofilms. Improving the local cervicovaginal oestrogen level is an often overlooked intervention. In one of our Rwandan trials, we saw that the cervicovaginal microbiome of women who initiated the Nuvaring contraceptive ring, which contains an oestrogen, gradually improved over time. In the case of refractory urogenital dysbiosis, we could combine a few interventions: we should perhaps not only weed, but also remove the biofilm and optimise the oestrogen level, and then seed. I hope that we can evaluate some of the promising new interventions in Dutch patients in the future. I also hope that countries where HIV is endemic start taking the prevention and control of urogenital and sexually transmitted infections more seriously than many of them have done thus far.

[Slide 22: STORMS] Microbiome research is the type of research that requires multidisciplinarity. Unfortunately, not all microbiome research teams are sufficiently multidisciplinary. As a result, many microbiome studies are of dubious quality. I gave you some examples earlier of studies that produced misleading results because they were cross-sectional instead of longitudinal or because they were not sufficiently quantitative. In addition, 'compositional data', which is data expressed as proportions, are often interpreted as absolute quantities. Statistical testing is often too much focussed on exploration and p-values, and too little on hypothesis-testing, taking microbiological properties such as pathogenicity and behaviour within bacterial communities into account. For example, I think that it may have added value to analyse bacteria that always live together in a community – such as BV-anaerobes – as a group and not only as many different individuals. Finally, many microbiome studies do not sufficiently incorporate tried epidemiological methods to minimalise bias and confounding and to optimise statistical power. Microbiome data typically are highly variable, not only between persons but also within one person over time, and one must take that into account when designing studies. I therefore call on microbiome researchers to turn the tide. All the low-hanging fruit has been picked.

[Slide 23: COVID-19] Just like so many other infectious disease epidemiologists, I spend most of my time in the last two years working on the coronavirus pandemic, which was the second worldwide pandemic that I experienced from up close. I had the opportunity to contribute to vaccination trials, vaccine effectiveness studies, evaluations of rapid tests and self-tests, and evaluations of eHealth applications such as the Dutch CoronaMelder and CoronaCheck mobile telephone apps for contact-tracing and proof of vaccination/immunity respectively. I also had the opportunity to provide epidemiological input into the mathematical models of colleagues at the UMC Utrecht, Dutch National Institute of Public Health and the Environment (RIVM) and the Technical University at Delft that attempted to estimate the impact of interventions. My UMC Utrecht microbiome colleagues and I could of course not resist studying the nose-throat microbiomes of persons with and without a coronavirus infection; those studies are still ongoing. The past two corona-years were very difficult, especially due to the loss of loved ones. The one positive aspect for me personally was that I became much more integrated into the network of Dutch infectious disease professionals than I had ever been before, for which I am grateful.

[Slide 24: Utrecht] My career has taken me all over the world. However, the University of Utrecht has been a common thread. I not only became a professor here, I also completed my very first university degree here, and much later – from 2010 to 2016 – a second degree: the SUMMA programme in medicine. Many thought that I had lost my senses. However, I loved the opportunity to experience clinical practice after all those years in biomedical research. It was a unique experience, and it helped

me to make my research even more translational. I am very grateful to the Executive Boards of the University of Utrecht and the UMC Utrecht, and also to Professor Marc Bonten, who is the head of the UMC Utrecht Infectious Disease Epidemiology Programme. This year, I was seconded on a part-time basis to the Dutch National Institute of Public Health and the Environment (RIVM) to fulfil a new role as chief science officer in addition to my professorship. This means a further diversification of the public health topics that I will be working on, as well as stronger ties with public health practice. I would like to thank Hans Brug and Jaap van Dissel of the RIVM for the trust that they placed in me.

[Slide 25: Acknowledgments] Dear mentors, PhD students, and close teammates over the years: some of you are here today but most of you could not attend because you are abroad. I have tried to include you in this ceremony anyway by showing the audience pictures of you. I would like to thank all of you from the bottom of my heart because without you, I would not be standing here today.

The academic world can be a lonely and insecure world, a world of every-man-for-himself. I learned something from every colleague who crossed my path over the years. However, I appreciated colleagues who consistently pursued public health goals collectively, with less emphasis on personal glory, the most. This sounds like a no-brainer, but it is not, because there are many perverse incentives in academia. Despite this, many of you fell into that category, and I can therefore not mention all of you by name. I want you to know that I managed to endure academia for so many years because of you.

Dear friends in the Netherlands, the United States, the United Kingdom, Zimbabwe, and other places in the world: I have experienced and seen so many wonderful things with you. You made sure that I was never consumed too much by my work, that I felt at home everywhere I lived and worked, and that I managed to cope with difficult periods in my life. I want you to know that you are precious to me.

I could spread my wings because I knew that I would be welcomed with open arms by my relatives in the South of the Netherlands at any time. Dear uncles, aunts, and cousins: thank you that you were always there for us and for each other, in good and bad times. Dear sister José, brother Hein, brother-in-law Taco, sister-in-law Petra, niece Anne Merel, and nephews Jelle, Jules and Maaren: I do not say often enough that I am very lucky to have you. I cherish the close ties that we have with one-another and I hope to enjoy them for many more years. And last but not least: I dedicate this inaugural speech to my father, Jan van de Wijgert, who is with us here today, and to my mother, Mien van den Oetelaar, who is sadly no longer amongst us but is very much in my thoughts. The two of you were my towers of strength.

I have spoken.