One Health MAGAZINE

SPECIAL EDITION I 2019
COMPLEX SYSTEMS

Solutions to Global One Health Challenges

netherlands centre for one health

Challenges affecting daily life

Infectious diseases pose challenges for the world community concerning health and environment that potentially affect our daily life. NCOH aims at mitigating risks and improving our quality of life by initiating innovative research. A group of related NCOH PhD projects on targeted One Health research topics like metagenomics and complex systems are initiated and over 30 PhD positions will be filled in 2019. NCOH expects that the knowledge generated by these projects contributes to solutions to existing global One Health challenges!

In this magazine you will read more about “Complex Systems” and how this concept can help us understand the dynamics and resilience of various systems ranging from ecosystems to health.

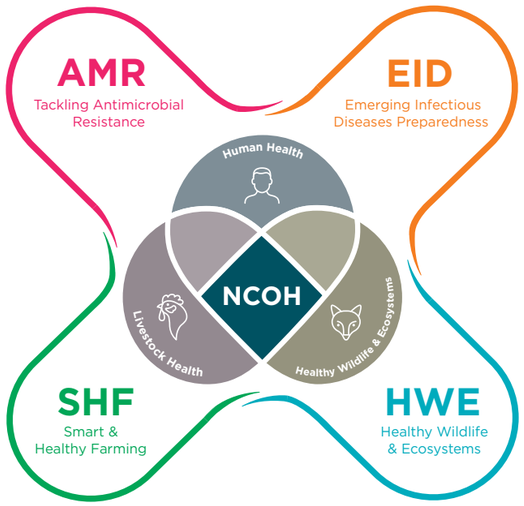
Dick Heederik
Chair NCOH Executive Board

To better understand the emergence, transmission and dynamics of AMR and improve tools for AMR prevention and intervention.

AMR
Tackling Antimicrobial Resistance

EID
Emerging Infectious Diseases Preparedness

To advance understanding of infection biology and dynamics and improve the prevention, detection, and control of (re)emerging infectious diseases in humans and animals.



To improve livestock farming, animal health, welfare, and sustainable productivity to ensure food-chain quality and reduce human health risks arising from livestock and food production.

SHF
Smart & Healthy Farming

HWE
Healthy Wildlife & Ecosystems

To limit the effects of wildlife-related diseases on human health, livestock production, and eco-systems through understanding, anticipation, and prevention of environmental factors driving spread of wildlife diseases.

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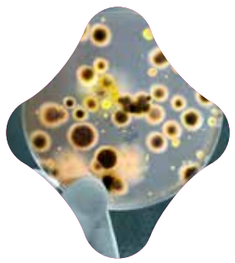


PhD PROJECTS & INTERVIEWS

AWARDS & PRIZES

What is NCOH all about

NCOH brings together academic research institutes in the Netherlands that are active in One Health research together with other leading parties to forge an open innovation network with the capacity to take joint responsibility for finding answers to global One Health challenges. Below a number of examples of joint projects.

Guillemot

Wildlife mortality

Wildlife mortality can sometimes assume striking proportions. One could think of the surge in dead starlings in The Hague in October 2018, or the dead guillemots that washed up on the beaches of the Wadden Islands in January 2019, to name but a few. A wide range of organisations in the Netherlands cooperate to determine the causes of unusual mortality among wild animals, each working on the basis of a specific expertise and allocated role. Close collaboration and sharing knowledge about wildlife health and disease as well as environmental factors are essential for determining the underlying cause.

For example, researchers from two NCOH partners worked closely together to determine the cause of the recent widespread mortality among guillemots, namely Wageningen Marine Research - dietary research and ecology, Wageningen Bioveterinary Research – diagnosis of notifiable diseases, legal infringements and unnatural toxifications, and the Dutch Wildlife Health Centre (DWHC), which is accommodated at Utrecht University, at the Faculty of Veterinary Medicine - pathology research and the allocated point of contact in the Netherlands for wildlife mortality.

Volunteering to become ill to help researchers

Radboudumc has combined its research into controlled human infection models to create a new program: the Radboudumc Controlled Human Infection Models (RCHIM). By studying the interaction between pathogens and humans under controlled conditions, researchers can improve their understanding of the underlying disease mechanisms. This understanding contributes to a more targeted development of medicines and vaccines and to improved control of infectious diseases. For the time being, the RCHIM is conducting research into malaria, sepsis and respiratory infections.

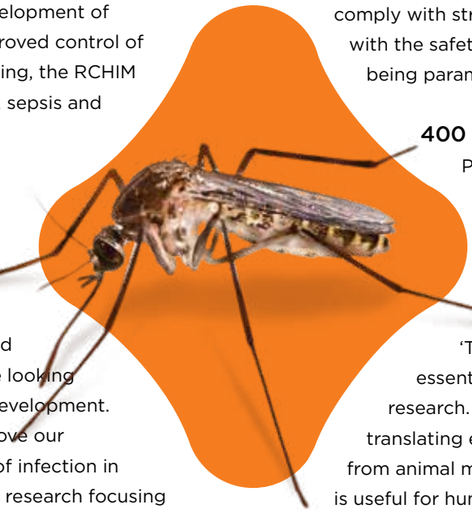
Infectious diseases are a constant threat to our health. Effective medicines and vaccines are therefore essential to control them. However, the development of new medicines and vaccines is costly and time-consuming, so researchers are looking for more efficient ways to do this development. One promising approach is to improve our understanding of the mechanisms of infection in humans. To accomplish this, clinical research focusing directly on infection mechanisms in humans is crucial, but this research must obviously be safe.

Malaria, sepsis and respiratory infections

With this underlying idea, several controlled human infection models have been developed at the Radboudumc in recent years, including models for malaria and sepsis. The Radboudumc Center for Infectious Diseases has now included these models in the new research program, which is called the Radboudumc Controlled Human Infection Models (RCHIM). The initial focus will be on models for malaria, sepsis and respiratory infections in humans. Models for other infectious diseases will be added over time.

Safety of participants is paramount

In controlled human infections, selected healthy volunteers receive – after approval by the medical ethics committee – a small dose of a well-characterized microorganism (or a component of the microorganism). Then the volunteers are carefully monitored and treated. Controlled human infection models must comply with strict laws and regulations, with the safety of the participants always being paramount.



400 volunteers

Peter Pickkers, professor of Experimental Intensive Care Medicine, theme Infectious diseases and global health, explains this approach: ‘These models are an essential part of pharmaceutical research. They are needed for translating experimental results from animal models to a model that is useful for human patients.’ Robert Sauerwein, professor of Medical Parasitology, theme Infectious diseases and global health, adds: ‘Approximately 400 volunteers have participated in our controlled human malaria studies so far. With this initiative, we are joining forces at Radboudumc to further improve quality and efficiency in this field.’

For more information, go to: www.radboudumc.nl/rchim.

New antibiotic named after Leiden

Increasing resistance and a lack of new antibiotics are a serious problem for public health. Against this background, Gilles van Wezel, Scientific director / professor of Molecular Biotechnology at the Institute of Biology Leiden, is looking for new medicines. Together with former PhD student Changsheng Wu and colleagues, he discovered the special antibiotic lugdunomycin, which they named after Leiden. The discovery was recently published in the journal Angewandte Chemie.

The antibiotic discovered by Wu, Van Wezel and co-promoter Young Hae Choi is also a sleeping antibiotic, produced by a still unknown Streptomyces bacterium from the Qinling Mountains in China. They called it lugdunomycin, after the Latin name for Leiden (Lugdunum batavorum). 'Wu has looked at a strain that did not produce anything at first sight. But after imitating different growing conditions, we nevertheless witnessed biological activity here. This led to the discovery of a chemical molecule with an unforeseen complex structure!' Lugdunomycin is derived from a well-known family of molecules with mainly anti-tumour activity but underwent such large modifications that it no longer looks like it. 'The addition of three extra rings make it look like a helicopter,' says Van Wezel. 'We have never seen this before, but it will certainly occur more often in nature. But in such small quantities that they must have been overlooked until now'. The discovery of such a radically different chemical structure is rare. Now that Wu, Choi and Van Wezel have published the structure of lugdunomycin, the next challenge is: to make Streptomyces produce more of it. They also have to investigate the exact activity of the molecule, and whether it is actually clinically applicable. Possibly, the Leiden antibiotic will be able to serve as real medicine in the future.

Read more: www.universiteitleiden.nl/en/news/2019/03/new-antibiotic-named-after-leiden

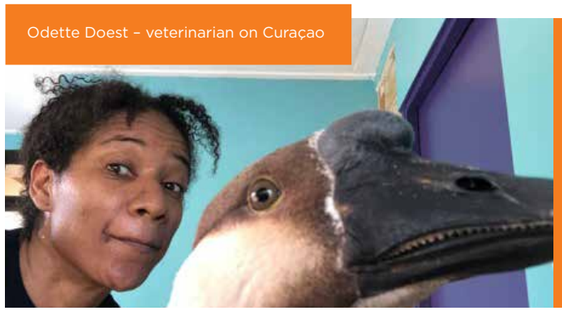
Taking a viral approach to fighting tuberculosis

The tuberculosis bacterium is becoming increasingly resistant to antibiotics, and new breakthroughs are therefore needed to combat the disease. Ad Koets, Wageningen Bioveterinary Research, thinks that a vaccine against tuberculosis will eventually be found. Tuberculosis is the deadliest infectious disease in the world. It kills about 1 million people each year, and on average, one in three people carry the bacteria. In the Netherlands, we have had the disease under control for decades and therefore we scarcely see it as a problem these days. Nevertheless, the resistance of tuberculosis to antibiotics is increasing, and almost no effective drugs are available in several countries already. A new approach to controlling the disease is therefore required.

Just like Q fever or chlamydia, tuberculosis has a specific characteristic: the bacteria enter human cells and converts these into a biotype where it can easily replicate. In that respect, the bacteria's modus operandi is similar to that of a virus. We are therefore no longer thinking in terms of antibiotics but a vaccine instead. We are using a previous study as a starting point, namely a recently developed a vaccine platform. As this virus targets the same groups as tuberculosis, humans and ruminants, we are working on a proof of concept: does the approach we have devised actually work in practice?

'We are seeking to limit both the spread and the impact. That can be achieved both if a vaccinated individual infects fewer other people after infection and if people become infected less quickly once vaccinated', Koets says.

Odette Doest – veterinarian on Curaçao



'Better one bird in the hand, than ten in the air.'

Dutch caribbean preparedness for mosquito-borne infectious diseases

DUCAMID brings together key players in Curaçao and Sint Eustatius with NCOH partners (represented by Erasmus MC and Wageningen University & Research). With their dependence of tourism, the climate conditions favoring mosquito establishment, and their central position in wildlife migratory routes, the Dutch Caribbean are potential hot spots for outbreaks of virus diseases spread by arthropod vectors (arboviruses), like Zika virus, yellow fever, and others. The Dutch Caribbean have staff with expert knowledge on arboviruses in the local context, but limited resources to detect and investigate such biological invasions and pathogen spread, both in terms of tools and infrastructure. DUCAMID is a project subsidized by the Dutch grant agency NWO and is aimed to investigate potential factors that facilitate introduction of new viruses in the Dutch Caribbean, where Curacao and St Eustatius are the representatives of the different islands. The approach of this project is to screen resident mosquitoes for presence of different arboviruses and factors such as a their virome as determinant of susceptibility.

Read more: www.cbhri.com/project/ducamid/

Antibiotic resistance in the Netherlands under control

Contamination with resistant bacteria in patients admitted at Dutch hospitals does not result in higher mortality than contamination by non-resistant bacteria. Although the problem of antibiotic resistance in the Netherlands currently seems manageable, it is important to remain vigilant in view of the ever-changing epidemiology of resistant bacteria, according to Wouter Rottier, who was awarded a PhD in Utrecht. Some studies have suggested that antibiotic resistance is also a problem in the Netherlands and leads to extra mortality. The problem with research on antibiotic resistance is that the context of policies on antibiotic use and diagnostic procedures must also be included in the analysis and interpretation of studies. The way in which this is discounted determines to a large extent the study outcome.

No increased mortality

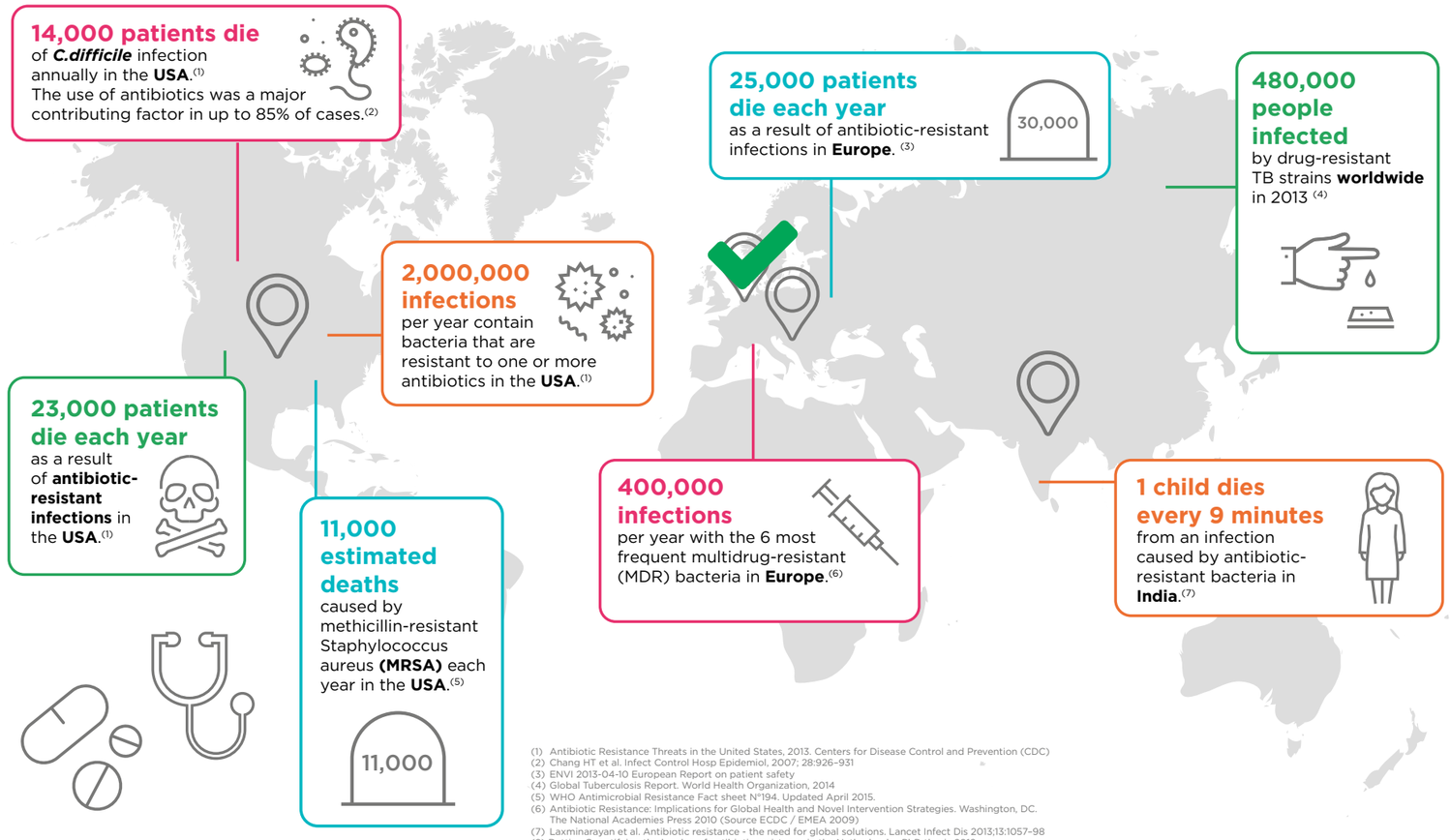
Investigator Wouter Rottier investigated during his doctoral research at UMC Utrecht what the consequences are if people incur infections with resistant bacteria. Therefore, infections in patients in eight Dutch hospitals were compared between infections caused by (1) resistant bacteria and (2) infections caused by the usual, non-resistant variants of those bacteria. Rottier found that in case of infection with resistant bacteria, it takes longer for doctors to prescribe the right type of antibiotics. However, this delay does not lead to an inferior outcome for the patient: the mortality due to infection with resistant bacteria does not appear to be higher than in infection with sensitive bacteria.

Use spare antibiotics to reduce

In addition, he addressed the question of how to anticipate resistant bacteria when a doctor prescribes antibiotics for a patient with a severe infection. At the early stage of an infection it is usually unknown which bacterium is the cause and the outcome of laboratory results can take hours to days. In such a case, Dutch guidelines state that with the help of certain criteria, an assessment must be made of which antibiotics will work best for an individual patient. However, Rottier's research shows that this strategy leads to significant unnecessary use of reserve antibiotics. By extending the number of factors to be weighed up, a better estimate of the likelihood of resistant bacteria can be made. With this information, undesirable use of reserve antibiotics can be reduced.

Antibiotic resistance awareness

ncoh tackling antimicrobial resistance



source: www.myrolematters.com

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(2) Chang HT et al. Infect Control Hosp Epidemiol, 2007; 28:926–931
(3) ENVI 2013-04-10 European Report on patient safety
(4) Global Tuberculosis Report. World Health Organization, 2014
(5) WHO Antimicrobial Resistance Fact sheet N°194. Updated April 2015.
(6) Antibiotic Resistance: Implications for Global Health and Novel Intervention Strategies. Washington, DC. The National Academies Press 2010 (Source ECDC / EMEA 2009)
(7) Laxminarayan et al. Antibiotic resistance - the need for global solutions. Lancet Infect Dis 2013;13:1057–98
(8) Rottier, Quantifying the burden of antibiotic resistance in the Netherlands, PhD thesis 2019

netherlands antibiotic development platform

Accelerating research and development of new antibiotics and alternatives

In the Netherlands, the lack of new antibiotics and alternatives led to the establishment of the Netherlands Antibiotic Development Platform (NADP). It brings together Dutch academic institutions, medical centers, and private organizations working on R&D of antibiotics and alternative therapies spanning the entire spectrum from basic research to clinical Phase IV studies. It is an initiative that was taken by the Ministry of Public Health, Welfare and Sports together with already existing collaborative networks of public and/or private organizations active in antimicrobial research and drug development in the Netherlands. The NADP aims to accelerate research and development of new antibiotics and alternative therapies for infectious diseases in humans and animals. NADP is strategically and organizationally embedded in NCOH-AMR. Read more: www.ndap.nl

Complex Systems

Whether we are talking about ecosystems, animals, people or societies: these are all complex dynamic systems that can be investigated and compared from an abstract mathematical point of view. Ingrid van de Leemput and Marten Scheffer investigate how resilient and dynamic a system can be. How it responds to a disruption says something about the system's "health".

I: 'Systems can suddenly change as a result of a disruption, something we call "tipping". In other words: they can respond to change or stress in a non-linear manner. As a system gets closer to that tipping point, its response to that delay becomes slower. The system needs more time to recover. That longer recovery time indicates that the system is approaching its tipping point.'

M: 'There are scarcely any warnings about such a tipping point – unless one looks at those micro recoveries, and then it can be seen coming. And ultimately, if a system is close to its tipping point, then such a small disruption can cause it to cross the tipping point. This insight can be applied in various scientific fields, and we are therefore collaborating with a wide range of departments from different universities. For example, with the Radboudumc: we are collaborating with the Geriatric Department of Marcel Olde-Rikkert and his colleagues. Tipping points can also be applied within psychiatry, and so we are working with the University of Amsterdam, with professor Han van der Maas from the Department of Psychology and with professor Denny Borsboom, who specialises in research into depression. Furthermore, we also collaborate with various researchers in Wageningen who focus on the animal welfare of cattle and pigs. However, tipping points can also be observed in human medicine. An epileptic seizure, a heart attack and a migraine are all examples of systems that can pass that point. And of course, we would like to know whether a person is close to such a tipping point. In the old days, a doctor would measure heart rate, temperature and blood pressure and establish that someone was "healthy". However, that was merely a snapshot. Nowadays, we search for signals that reveal the resilience; these signals are called DIORs, Dynamic Indicators of Resilience.'

M: 'Take depressions, for example. There are similar aspects. Ingrid has demonstrated that the rate at which one recovers from natural small disruptions, such as modest setbacks, or negative experiences, predicts the risk of developing a genuine depression a year later. She wrote a highly cited publication on the subject that has now led to many new studies. Another example is the research with the balance disc together with the Geriatrics Department at Radboudumc...'

Ingrid van de Leemput, Wageningen University & Research

Marten Scheffer, Wageningen University & Research

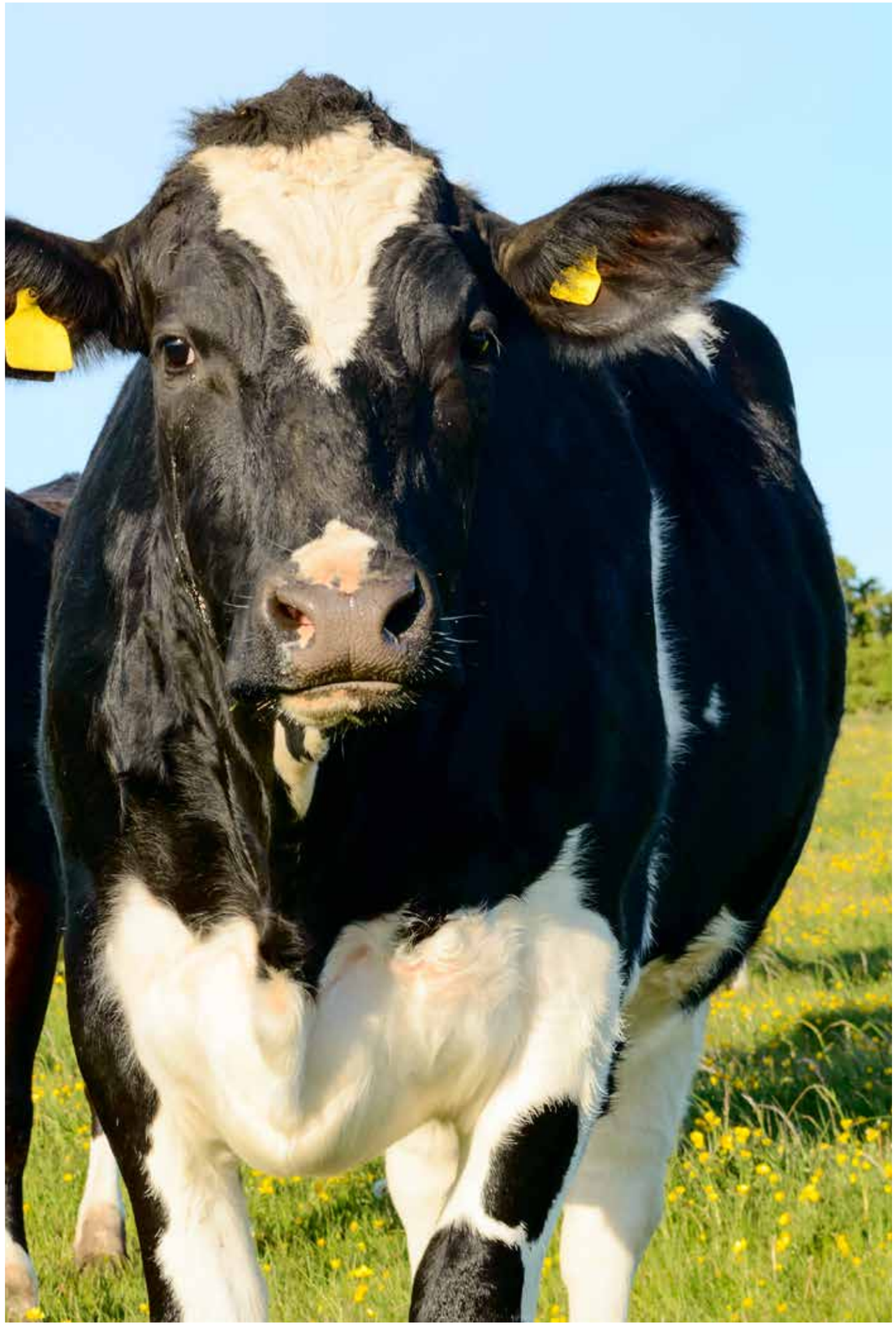
I: 'Prior to the International Four Days Marches Nijmegen, we asked a large number of elderly people (>80 years) who took part to stand on a balance disc. When people have to stand still, they are never truly immobile: they are constantly "dynamically" balancing to maintain their balance. Such a disc allows measuring that balancing. In addition, we measured a number of elderly people who did not take part in the event as the control group. We assumed (as additional measurements demonstrated) that the first group was on average healthier than the second group. With that balance disc, we observed that the elderly people in the marching group corrected their balance far faster. So with respect to balance, healthy elderly people have a more responsive and alert system.'

M: 'A person consists of an interaction of dynamic subsystems, such as balance – which consists of muscles and sensors –, the circulatory system, the metabolic system and the cognitive system. All these subsystems can gradually deteriorate or have a tipping point. The resilience of each of these systems should therefore be measured. Resilience can also be examined at the cellular level. Ageing is a slow, gradual process at the cellular level. This allows us to say something about ageing in general. However, if we really want to know whether that is associated with depression or with heart complaints, then we will need to observe at a higher level. Those systems are also correlated with each other. When somebody deteriorates cognitively, then they will have fewer social contacts and exercise less. The weakening of one system weakens the others too. That provides leads for geriatric medicine. If we know that "this system is relatively weak", then we can train it to prevent other systems from deteriorating too.'

I: 'It remains a fascinating question: what can we best measure, which subsystem, to say something about the resilience in general? What is the best part? Fortunately, there are now a growing number of sensors that continually measure and provide us with more information to monitor those systems.'

M: 'Those technological developments have given us many benefits. Vast quantities of data are being produced, and everybody wonders: what can we do with those? We might not be medics or bioscientists, but we like to interact with these fields. And it just so happens that we have developed the methods to do something with all these data! In that sense, we live in fantastic times.'

Ingrid van de Leemput *is assistant professor in the Chair Group Aquatic Ecology and Water Quality Management of Wageningen University & Research.*
Marten Scheffer *is a professor in the same chair group.*



Projects

PhD projects cycle 2019
COMPLEX SYSTEMS

In the beginning of 2019, 11 proposals were submitted as part of the NCOH PhD programme call “Complex systems”, which comprise a total of 17 PhD projects. That means that a considerable number of PhD projects will be allocated in the NCOH PhD programme, which is funded from the Partner contributions to the NCOH. Together with the first round of 8 PhD students in the “Metagenomics” call, and additional in-kind projects, over 30 PhD positions will soon be filled.

COMPLEX SYSTEMS
& infectious diseases

The spread of infectious diseases is characterized by dependency between potential hosts (human and animal), whereby non-linear patterns emerge. These patterns are influenced by the characteristics of human/animal, such as network structures and properties of the pathogen (e.g. host specificity). The rapidly growing availability of “big (omics) data” provides opportunities to better understand interactions between host and pathogen, but traditional analytical methods are not sufficient. A better understanding of complex systems can contribute to better prediction of the evolution of a particular problem, enabling earlier and more effective prevention measures.

All awarded projects - together with all previously-allocated NCOH projects - have thematically been clustered into three overarching Research Topics; i.e. Complex systems & gene flows & metagenomics, Prophylactic vaccines & new therapeutics, and Vector-borne diseases. The programmes for the Research Topics will be available soon.

Projects

Projects

Staphylococcus aureus infection dynamics in cattle (UU; 1 project)

Innovative antibody-based strategies to combat future emergence of zoonotic viral infections (UU, EMC; 4 projects)

Improving the functional activity of monoclonal antibodies against Gram-negative bacteria (UMCU, 1 project)

BRICK study- Bacteriophage Research on Immune response, Clinical use and Knowledge on virome changes (UMCU, EMC; 2 projects)

Development of Bayesian Inference Methods for Estimating Transmission Trees for Antibiotic-Resistant Pathogens in Hospitals and Farms (UMCU; 1 project)

Gene flow networks in animals, the food chain and the environment (UMCU, WUR; 2 projects)

Antimicrobial resistance in relation to the persistence of antimicrobial residues after treatment of farm animal: input for risk management (*RESRISK*) (UU; 1 project)

Towards circular livestock farming practices (WUR, UU; 2 projects)

How the virome of vector mosquitoes affects pathogen transmission (Radboudumc; 1 project)

Accelerating drug development against emerging vector-borne viruses (LUMC; 1 project)

Disease X is not science fiction

Will we be able to respond adequately when an unknown virus with pandemic potential emerges? The recent outbreak of MERS in the Middle East was an interesting testcase. Martine van Roode, Erasmus MC and Carolina dos Santos Ribeiro, RIVM analysed the factors that hampered, or enabled, the flow of information, in Qatar and the wider Arabian peninsula.

C: 'The MERS-virus first emerged in April 2012 in Jordan, but no alert was given then. Months later an Egyptian doctor in Saudi Arabia came across a patient who had symptoms that looked like a severe flu but a test turned out negative for the main suspicion of swine flu (H1N1). The doctor remained suspicious and sent samples to Erasmus Medical Center in Rotterdam. There they sequenced the virus and discovered it was a new type of coronavirus.'

M: 'Coronavirus infection in humans could have a zoonotic origin, and soon there was evidence that camels were a host reservoir species for this virus.'

C: 'When you have a human case infected with an unknown virus with pandemic potential, the rules are that you have to notify WHO, in the case of MERS the first Alert came from a Promed mail. The WHO alerts the national authorities from the countries involved and starts its own investigation in order to update and inform the international community of the risks.'

M: 'In the case of MERS there was a gap in time between the sequencing and the WHO alert. What happened in that time? Might barriers have existed that hampered the flow of data and information between relevant stakeholders?'

M: 'We focused our case study on events that related to Qatar, reflecting on the wider region of the Arabian Peninsula. We managed to interview a lot of people from several organizations in different countries but nobody from Saudi Arabia. Still, I think our research is a unique collaboration, between the RIVM, Erasmus MC, the Ministry of Public Health in Qatar, the Vrije Universiteit in Amsterdam and many scientific and governmental organizations. Especially the government of Qatar was really willing to collaborate. That really helped us to see the collaboration between stakeholders and corresponding flow of data shared between stakeholders during the MERS outbreak response, on the national level.'

C: 'An important barrier from the NCOH point of view was the collaboration between human and animal health organizations.'

M: 'MERS was an emergency for public health and camels were suspected to play an important part – but the animals don't get sick from the virus.'

C: 'And camels are very economically important in the region giving them a very high social status. Camel owners simply didn't want to believe their animals were in any way involved, since they were not even sick. And what would happen? Would they kill the animals? Because of these fears it took the authorities a lot of time to gain the trust of the sector and implement measures.'

M: 'Here in the Netherlands we had similar problems in One Health collaboration with the outbreak of Q-fever. It shows how difficult it is to take effective measures when it involves different sectors.'

C: 'I think what really is needed, is more coordination at the top level. When an emergency arises the top organizations (WHO, FAO, OIEOIE) are still working according to their own rules and mandates. What we must have is an integrated and coordinated response.'

M: 'And countries must have an integrated infrastructure in place before the outbreak occurs. Take Qatar, that was also faced with the outbreak of MERS. It formed a joint One Health investigation team that was effective and helpful towards a coordinated outbreak response. But that was activated only when the epidemic started. These systems should be established before an outbreak occurs and be continuously tested and improved.'

Carolina dos S. Ribeiro *is senior advisor at the RIVM (Netherlands Institute for Public Health and the Environment) Center for Infectious Disease Control, and an external PhD student connected to the Vrije Universiteit Amsterdam (Athena Institute).*
Martine van Roode *is project manager grants at the department of Viroscience, Erasmus MC.*

You can find the long read about disease X on the NCOH website.

Carolina dos S. Ribeiro, RIVM

Martine van Roode, Erasmus MC

NCOH PhD projects cycle 2017
METAGENOMICS

Metagenomics is the overarching theme for the first 8 PhD tracks of the NCOH projects cycle 2017 to create new interdisciplinary, inter-thematic, and inter-institutional research collaborations.
Recent technological developments now allow large-scale, in-depth (and affordable) investigation of microbial populations and communities at the molecular level. Microbial interactions, within hosts, between hosts and between populations, are a fundamental aspect in the societal problems addressed in the four research themes of the Netherlands Centre for One Health. Metagenomics was therefore chosen as the overarching theme for the first 8 PhD tracks of the NCOH, with the explicit task to create – where possible – new interdisciplinary, inter-thematic, and inter-institutional research collaborations. All projects - together with some of the NCOH projects currently allocated in the complex systems call 2019 - have thematically been clustered into the overarching Research Topic “Complex systems & gene flows & metagenomics”. The programme for the Research Topic will be available soon.

Host-microbe interactions as elicitors of cryptic antibiotics in actinomycetes and spread of antimicrobial resistance under low antibiotic stress
PhD student: Doris van Bergeijk, Leiden University

Molecular mechanisms of microbiota-mediated colonization resistance against intestinal outgrowth of multidrug-resistant Enterobacteriaceae (E. coli, K. pneumoniae) and enterococci
PhD student: Paul Stege, University Medical Center Utrecht

Mechanisms of microbiota-mediated defence against various infectious diseases
PhD student: Quinten Ducarmon, Leiden University Medical Center

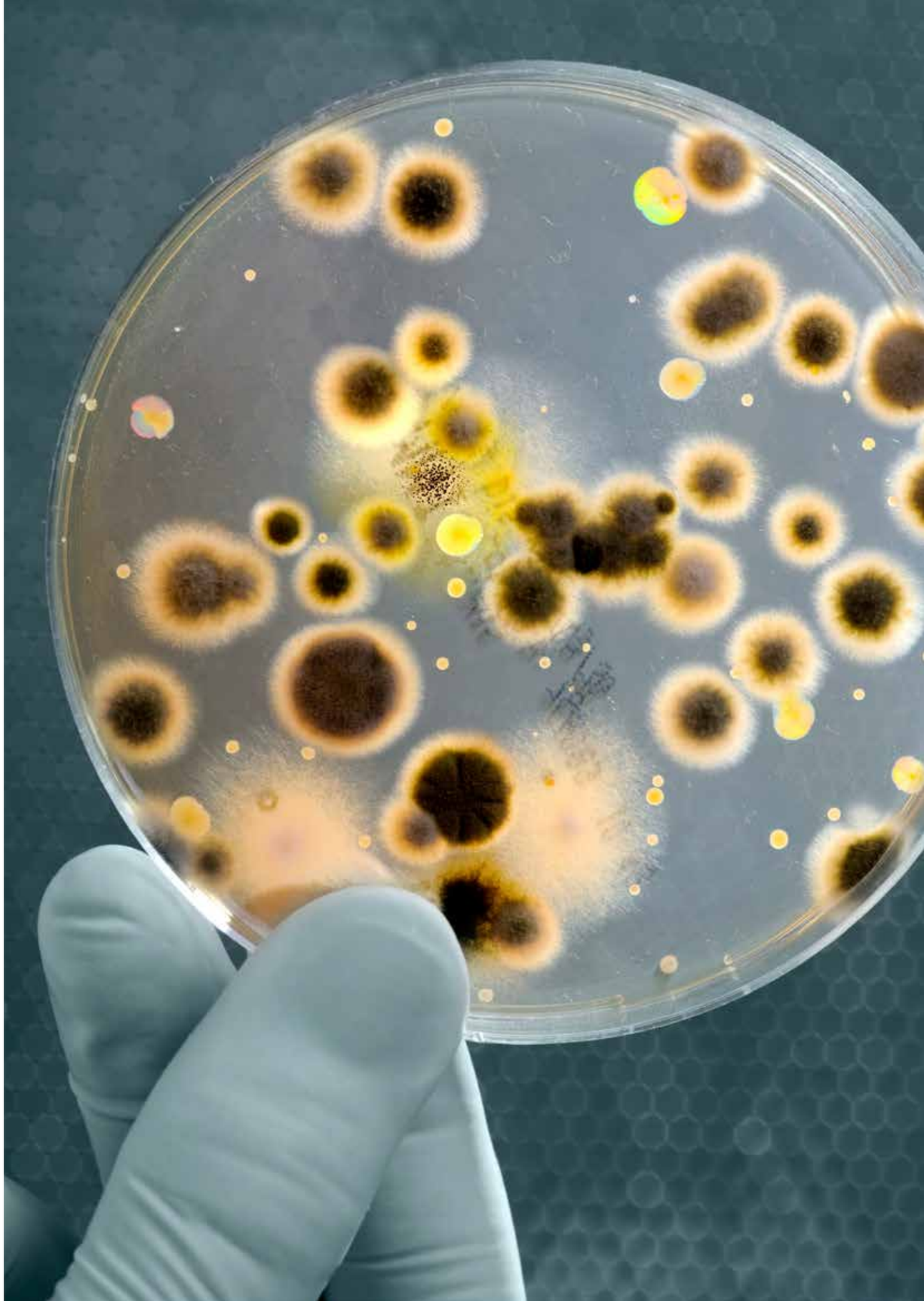
Metagenomic analysis of animal, environmental and human microbiomes in the context of excess pneumonia risk around livestock production farms in the Netherlands: effects in humans
PhD student: Warner van Kersen, Utrecht University/Institute for Risk Assessment Sciences

Microbiome fortification for healthier pigs through metagenomics-driven culturomics and microbial bioactive metabolite discovery
PhD student: Simen Fredrikesen, Wageningen University & Research

CoCoNod (Coma, Convulsions and Nodding Syndrome): aetiology, risk factors and outcome of paediatric neuroemergencies in resource poor settings.
PhD student: Arthur Edridge, Academic Medical Center

Metagenomic analysis of animal, environmental and human microbiomes in the context of excess pneumonia risk around livestock production farms in the Netherlands: flow of microorganisms
PhD student: Kirsty Kwok, Erasmus MC

Immunological, microbiological and pharmacological aspects of invasive fungal infections
PhD Student: Nico Janssen, Radboudumc



Zoonoses in the night – which viruses do Dutch bats carry?

Bats are not particularly popular among the general public. Many people think that bats spread rabies and other life-threatening diseases. The truth is more nuanced, of course. Bats can indeed transmit zoonoses (diseases that can be transferred from animals to people). But in the Netherlands, only one potentially dangerous zoonosis has been demonstrated so far in bats; a virus that can cause rabies. Transmission of this virus to people is very rare, and only five cases have ever been reported in Europe, none of which were in the Netherlands.

Whether bats in the Netherlands can transmit other zoonoses is not known. The research project "Zoonoses in the night" has been set up to improve our knowledge in this area. In this project, researchers are working on several questions: Which viruses do the 17 species of bat in the Netherlands carry? Is there any evidence of viruses being transmitted from bats to people? But also: how much actual contact is there between people and bats, and how well-informed is the average Dutch citizen about the factual risks?

Research methods

Answers are being obtained in various ways. Blood from people and cats who have been in contact with bats is investigated. Bats found dead are also examined, and bat droppings are analysed. Questionnaires have also been drawn up for bat professionals and the general public. Various organisations are collaborating in the project, including Erasmus MC, the National Institute for Public Health and the Environment (RIVM), the Dutch Mammal Society and Wageningen University & Research. Each party has its own motives to participate in the research.

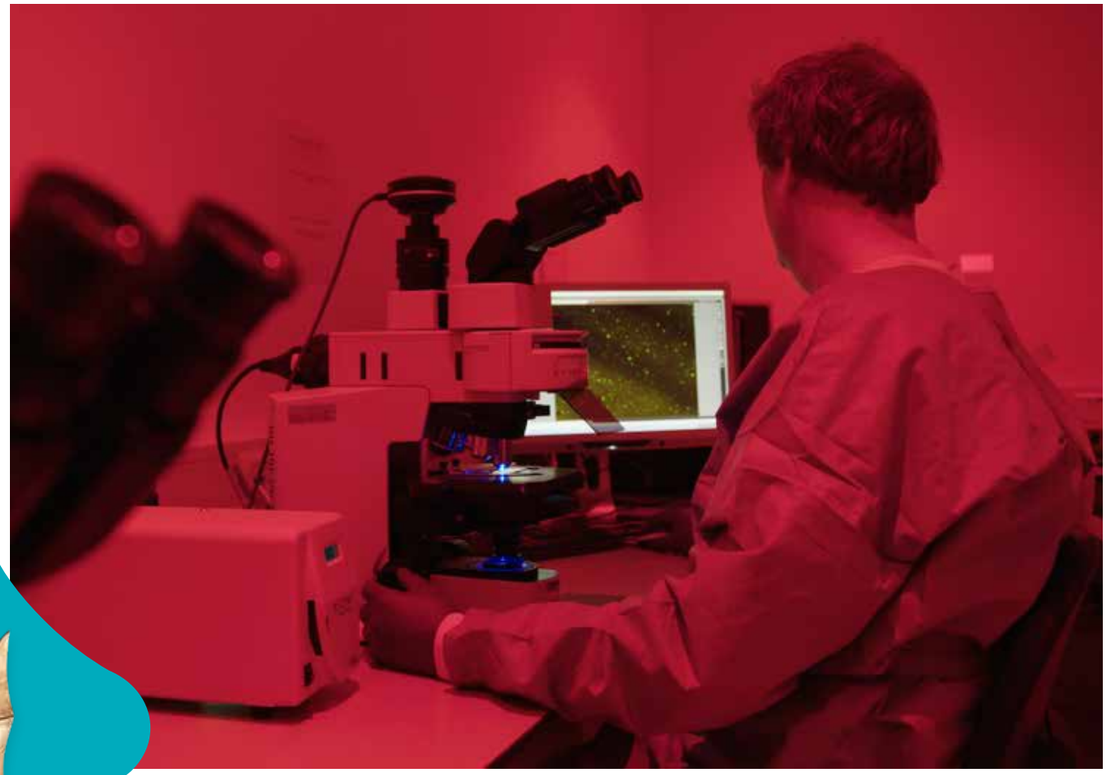
RIVM: improving public awareness

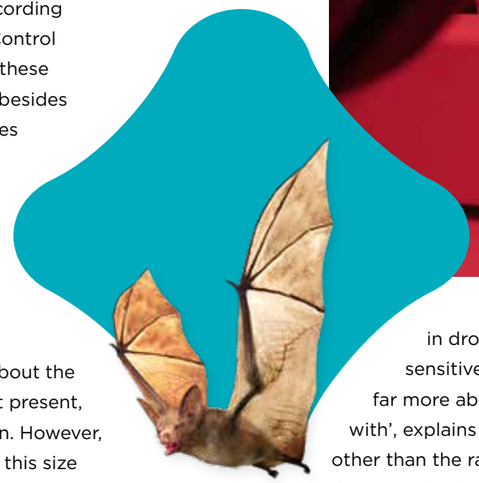
RIVM wants to use the outcomes of the research to improve public awareness. Their National Coordination Centre for Communicable Disease Control advises people who have been in direct contact with bats. According to Corien Swaan, head of the Prevention and Control Department, it is extremely important to keep these guidelines up-to-date. 'If research reveals that besides the rabies virus Dutch bats carry other zoonoses too, then we need to modify our information accordingly.'

Wageningen Bioveterinary Research: increased insight into the risk of transfer

For Bart Kooi, researcher at Wageningen Bioveterinary Research, the project is mainly about the transmission of viruses from bats to people. 'At present, we know far too little about the risk of infection. However, we suspect that the risk is very low. A study of this size will provide us with far better insight into the subject.'

Among other aspects, the researchers search for viruses





in droppings and tissues of bats by use of sensitive molecular technigues. 'That will tell us far more about the viruses that such a bat is infected with', explains Kooi. 'That will also include virus species other than the rabies virus. We might also be able to detect antibodies against those viruses in the blood of people and cats that have had contact with bats. That will increase our knowledge of the risk of transmission.'

Dutch Mammal Society: The bat's image

Marcel Schillemans, Team Leader Bats at the Dutch Mammal Society, hopes that the research will lead to a better protection of bats. Bats are at risk due to their poor image. 'Some people seal the gaps in their cavity walls because they are scared for the diseases that bats could transmit', Schillemans explains. 'This means that some bat species lose their home, which is a shame because they are useful animals. They eat many insects, for example.'

According to Schillemans we do not need to fear bats: 'They always avoid direct contact with people. So far, there is no reason why we could not live in close proximity with bats in the Netherlands. And I do not expect that to change as a result of this study. We can inform the public about these scientific outcomes. And if the study does reveal a different picture, then it is important that we know that too.'

Erasmus MC: Department of Viroscience – Research into viruses

The project Zoonoses in the Night is coordinated by the Department of Viroscience at Erasmus MC. For her PhD research at Erasmus MC in Rotterdam, Lineke Begeman is investigating the viral diversity of bats and their zoonotic potential in the Netherlands. She is doing this in collaboration with professor Thijs Kuiken, dr Chantal Reusken, dr Judith van den Brand, professor Marion Koopmans and all external partners. 'Droppings of bats and sera of bat workers are used to investigate the viral diversity and the zoonotic potential. Bat droppings of the common pipistrelle, Nathusius's pipistrelle and serotine bat are needed from across the Netherlands. This is only possible because of the excellent collaboration with all NCOH partners, the Dutch Mammal Society and RIVM!'

This project is funded by the Netherlands Organisation for Health Research and Development (ZonMw) and runs until March 2021.

The Young NCOH Board is glad to play an active role in building the Young NCOH network. From left to right: Romy Zwittink, Jochem Buil, Arthur Edridge, Dennis Doorduijn and Doris van Bergeijk. Blanca Fernandes Ciruelos is missing in the photo.

Young NCOH

Kick off Young NCOH network

Young NCOH is the network for PhD students and post-docs from the NCOH research groups. Aim of the network is sharing knowledge and expertise in One Health related disciplines, which can lead to new collaborations in research. The kick off of the network has taken place at the Annual Scientific Meeting, 17 May 2019 (ASM2019).

Young NCOH Board

The appointment of the Young NCOH Board is the next step in the development of the Young NCOH network. The NCOH Executive Board has appointed the Young NCOH Board with members from various NCOH partners:

Romy Zwittink – LUMC (Chair)
Arthur Edridge - AMC
Blanca Fernandez Ciruelos - WUR
Dennis Doorduijn - UMC Utrecht
Doris van Bergeijk - Leiden University
Jochem Buil - Radboudumc

Joining Young NCOH

Interested in great opportunities for expanding your network, knowledge sharing and interesting meetings? You can join the early career network via our website: www.ncoh.nl/young

young netherlands centre for one health

‘The Young NCOH Board plays an active role in building the Young NCOH network and brings young scientists together by organising activities including masterclasses, pitch competitions, network meetings and (inter)national site visits.’

Romy Zwittink, chair Young NCOH Board

Microbiome fortification for healthier pigs

Interview with Simen Fredriksen, PhD candidate of the Metagenomics project “Microbiome fortification for healthier pigs through metagenomics-driven culturomics and microbial bioactive metabolite discovery’ at Wageningen University & Research.

‘I chose to do a PhD in metagenomics due to having an interest in microbial ecology as well as a more general interest in science. The work I do is similar to what I did as a master student at the University of Oslo, so I knew what I was signing up for. I find microbiome research interesting in part due to it being a relatively new and fast developing field that still has many unanswered questions. Apart from the academic side, I am happy to be working on a project that has concrete goals towards improving animal and human health.’

‘The ultimate goal of my project is to reduce the prevalence of infectious disease in pig farms. As antimicrobials have been widely used to prevent and treat infections (some of which have zoonotic potential), antimicrobial resistance has emerged. Thus, my project also impacts on the health of humans and the global one health. Methodically, my project is centered around integrating sequencing technology and bioinformatics with culturing of bacteria and other microbiological methods. Most importantly, I utilize metagenomics to detect genetic markers associated with healthy and diseased animals. These markers can be used to identify members of the microbiota which can antagonize pathogens as well as previously unknown synergies between co-infecting organisms.’

‘The most challenging part of my position is acquiring metagenomics samples from diseased farm animals, as the window of time between the observation of relevant symptoms and antibiotic treatment can be small. Additionally, it is not always straightforward to identify what disease a pig is suffering from. The most enjoyable part of my position is working with bioinformatics on large datasets. It is also nice to be conducting multidisciplinary science in collaboration with researchers from a range of different universities and countries. Similarly, I find it important to interact with veterinarians and other members of the pig farming industry in order to properly understand my study system.’

From the past to the future...

Interview with Doris van Bergeijk, PhD student of the Metagenomics project "The effect of host-microbe interactions on the secondary metabolism of actinomycetes' at Leiden University (Institute of Biology Leiden).

'My interest in antibiotic research started during a microbiology course in the second year of my bachelor. We had to test bacteria from the sewage against different antibiotics and I was shocked by their multi-drug resistance. To me it was clear that we were in need of new antibiotics (or alternatives) and I am very excited that I am now working on a project that will hopefully contribute to the discovery of new antibiotics.'

'Actinomycetes are filamentous bacteria that are well known for their antibiotic production. Sequencing has shown that the genomes of actinomycetes contain a wealth of undiscovered biosynthetic gene clusters and this discovery has spiked research into this direction. Signals from the host/environment of these bacteria might influence the expression of these clusters.'

'I aim to find host-specific signals, for example stress hormones, that can influence the antibiotic production with the ultimate goal to use actinomycetes to control microbial infections.'

'So far, I have discovered that certain signaling molecules indeed influence the antibiotic production of actinomycetes. I now aim to identify the biosynthetic gene clusters that respond to these hormones and the corresponding metabolites. Additionally, I have had the unique opportunity to isolate and sequence actinomycetes from mammoth stool. This data, together with the metagenomics data of the gut microbiome of the mammoth, allows us to study bacteria from the past and analyse the biosynthetic gene clusters that are present. Hopefully this can give us insight in the way these genes have developed over time and what role actinomycetes can play in the protection of higher organisms.'

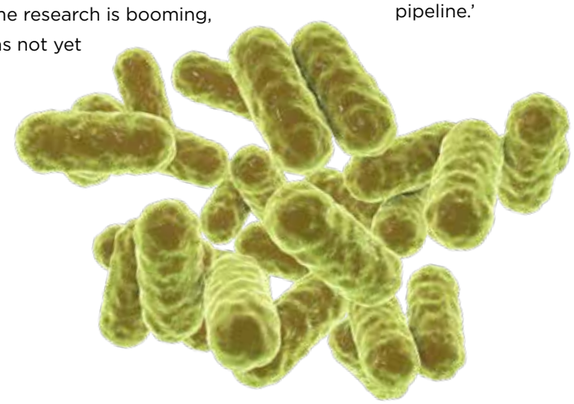
‘Microbiome and its relation with disease is the perfect topic for me’

Interview with Quinten Ducarmon, PhD student of the Metagenomics PhD project: “Mechanisms of microbiota-mediated defence against various infectious diseases” at the LUMC Center for Microbiome Analyses and Therapeutics (CMAT).

‘I have been curious about the human body since a young age. And especially in why some people fall ill, while others do not. During my education I learned a lot about human health and disease, but something was still missing. After my master MSc internship at the department of Microbiology & Systems Biology at TNO, I knew that I wanted to continue in the field of microbiome research. Its intriguing relationship with many different diseases and even with effectiveness in response to therapy is what makes this topic perfect for me.’

‘Microbiome research is booming, but this has not yet led to a lot of implementations for improved clinical outcome. With my research I hope to identify microbes that can subsequently be used for further in vitro and in vivo studies, with the ultimate aim of using these for improved clinical outcome of disease treatment, or even prevention of disease altogether.’

‘I very much enjoy the working environment at the LUMC Center for Microbiome Analyses and Therapeutics (CMAT), with equally enthusiastic people as myself. The fact that we have projects with many different departments, ranging from cancer to infectious diseases to psychiatric disease, perfectly fits my broad interest in human health. My PhD project started in January 2018 and we already have several promising results. First, several microbes have been identified which may be associated with C. difficile colonization and/or infection. In line with this, I am writing a review on how the gut microbiota can mediate colonization resistance against enteric pathogens. Lastly, for now, is that we are optimizing the microbiome workflow, from sampling to the choice of a bioinformatics pipeline.’



Emerging **virus infections**

ncoh
emerging
infectious diseases
preparedness

1	Junin virus	5	Dengue virus
2	Sabia virus	6	Hantavirus
3	Oropouche virus	7	Lassa fever virus
4	Machupo virus	8	Rift Valley fever virus

9	Marburg virus	13	West Nile virus
10	Ebola virus	14	SARS coronavirus
11	Hendra virus	15	Avian influenza virus
12	Nipah virus	16	Zika virus

NCOH interview

‘We’ve come a long way, thanks to a unique partnership!’

A malaria vaccine, based on genetically manipulated malaria parasites. That is the goal of Meta Roestenberg (LUMC) and Robert Sauerwein (Radboudumc). More than ten years of collaboration is nearing completion. But the vaccine could be even better...

M: ‘The partnership began over ten years ago, as part of the TI Pharma program, intended to stimulate collaboration between academic research and business to make a vaccine on the basis of genetic modification. So a contract was concluded between the RUMC, LUMC and an American bio-technology company, Sanaria. At that time in Leiden, Chris Jansen and Shahid Kahn of the parasitology department, were able to genetically manipulate the malaria parasite. In Nijmegen their experience served as the basis for developing a harmless mutant of the human malaria parasite Plasmodium falciparum, potentially for use as vaccine. A falciparum parasite, that enters the body by means of a mosquito bite, nestling first in the liver, to spread later through the blood and multiply further. That makes you ill.’

‘We wanted to develop a mutant that, after it has come into the body, never comes any further than the liver and is therefore never capable of growing in the blood. But one that does activate the immune system. In Leiden, first we searched for the genes that needed to be disabled. Then, in Nijmegen, we used that knowledge to de-activate the equivalent genes in falciparum. That could be a vaccine that needs to be tested on human guinea pigs. So that is really exciting because if you don’t manage to grab the essential genes and a couple of parasites manage to leave the liver anyway and start reproducing in the blood, things will go wrong. That absolutely must not happen.’

M: ‘Finally, we succeeded in identifying two genes and remove them from the genome, which completely inhibits parasite development in the liver at an early stage.’

R: ‘On the one hand you want the parasite to stay in the liver for a long time and to reproduce there, on the other hand you do not want a single parasite to succeed in leaving the liver. You have to find that very precarious balance.’

R: ‘We sent our genetically manipulated parasites to Sanaria, who made an approved product from them for administering to people, according to the strict requirements applicable to drug development. This three-way partnership is one of the successful projects of the TI Pharma program. What is really great is that, now we are entering the phase of testing this vaccine on humans, the LUMC and Radboudumc have decided to jointly fund the clinical study.’

M: ‘In a joint Leiden/Nijmegen study the vaccine has already been tested for safety on healthy human subjects. You start by giving a small group a low dose, and if no problems arise, you give a second group a higher dose, until you have a group that is given the dose you want to administer in daily practice. In the end, we did that with two groups of 24 human subjects, one in Nijmegen and one in Leiden. The whole experiment was double-blind and placebo controlled.’

R: ‘We saw no breakthrough of parasites from the liver to the blood and no significant side effects. That was a huge success of course. Also from a scientific point of view

Robert Sauerwein, Radboudumc & Meta Roestenberg, LUMC

because it was the first malaria vaccine of its type in the world. A completely new territory. It took a year before we had permission from the Dutch authorities to do this.'

M: 'However, the trial currently running is the jewel in the crown of our work – we've worked on it for ten years. In this case, we vaccinated a large group of people and then exposed them to the real parasite. Now we have to wait: will they develop malaria or not. We expect to have the results in a couple of months.'

R: 'But we're not there yet. The vaccine can certainly be improved. What we want to achieve is that the parasite stays in the liver longer, so that the immune reaction becomes more intense. That is a challenge. And we have to see what that does to the "memory" of the immune system. How long will it remain alert? That is one of the major issues in vaccinology in general. Some vaccines provide lifelong protection; others just six months. There are numerous theories as to why that happens, but it is to a large extent a question of trial and error. When it comes to micro-organisms, they can make "diversionary moves" to mislead the immune system. If you can put a lock for falciparum, you're much better off. Again, that's a huge challenge, but we've come a long way!'

M: 'That's why we still need that "leg" of fundamental research to refine the vaccine by means of genetic manipulation.'

R: 'With modern techniques like CRISPR-CAS it has become much easier to also manipulate human malaria parasites but without collaboration we would never have come this far. '

Meta Roestenberg *is internist-infectiologist at the Department of Parasitology and Infectious Diseases of the LUMC.*
Robert Sauerwein *is professor at the Department of Medical Microbiology at Radboud Centre for Infectious Diseases of the Radboudumc.*

Awards & Prizes...

Wim van der Poel

Special professor Emerging and zoonotic viruses

The Supervisory Board of Wageningen University & Research (WUR) has appointed Dr. Wim van der Poel as Special Professor Emerging and Zoonotic Viruses. The chair commenced on November 1 2018 and is facilitated by Wageningen Bio veterinary Research (WBVR). “Emerging and zoonotic viruses” are new, threatening viruses that can be transmitted from animal to human.

We are familiar with a number of recent introductions of these types of infectious diseases such as Aviaire Influenza and Q fever. Primarily for public health and animal health, and secondarily for food supply and the economy, it is increasingly important to react fast and effectively to outbreaks of infectious diseases in order to get them under control as quickly as possible. Wim van der Poel is Principal Investigator within NCOH and co-coordinator of the WUR investment theme Global One Health. Managing the risk of infectious diseases and reducing chronic illnesses are extremely important to food security, public health, climate and biodiversity.

Robert Sauerwein

Knight in the Order of the Dutch Lion

Robert Sauerwein, professor Microbiology Radboudumc, was appointed by His Majesty as Knight in the Order of the Dutch Lion, a highly prestigious decoration. Robert Sauerwein has been researching malaria for thirty years. His research is focused on the development of a vaccine against malaria and thanks to his dedication, such a vaccine is now closer than ever. Robert Sauerwein is an internationally recognized malaria expert and is regularly consulted by international organizations such as the Bill & Melinda Gates Foundation.

Dik Mevius

RIVM Jenner medal

Jaap van Dissel, Director of the RIVM Centre for Infectious Disease Control, presented the RIVM Jenner medal to Dik Mevius, Wageningen University & Research. ‘The RIVM Jenner medal was presented to Dik for the many years he has devoted to controlling antibiotic resistance in the veterinary sector, working closely with RIVM. As a founder of the One Health policy in antibiotic resistance he made a tangible contribution to the national policy that RIVM depends on in its daily work advising on and combating resistant micro-organisms,’ said van Dissel.

Rory de Vries

Beijerinck Virology Premium for young virologists

Rory de Vries (born 1982) has received the premium for his research on the human body’s defences against respiratory viral infections, and for his ability to communicate his knowledge of virology and infectious diseases to a wide audience. Rory de Vries is a post-doctoral researcher at Erasmus MC in Rotterdam.

Bart-Jan Kullberg

International SWAB award

Bart-Jan Kullberg, Radboudumc has received the international SWAB award from the Dutch Working Party on Antimicrobial Stewardship. The SWAB Award is a lifetime achievement award for important contributions to antimicrobial stewardship and infectious diseases. Bart-Jan Kullberg received the award based on his role in initiating the national antimicrobial stewardship program in hospitals in the Netherlands, and as one of the nestors of the national antimicrobial guidelines program for antimicrobial therapy in the Netherlands. Bart-Jan Kullberg is member of theme Infectious diseases and global health Radboudumc.

Marion Koopmans

Stevin Prize

In 2018 prof. dr. Marion Koopmans of Erasmus MC has been awarded a NWO-Stevin Prize for her research on the transfer of viruses from animals to humans. This award of 2,5 million euros is rewarded to scientists of international excellence and can be used for scientific research and activities related to knowledge utilization. The Stevin Prize is, together with the Spinoza Prize, the highest award in Dutch science.

Marion Koopmans

KNAW member

Erasmus MC professor Marion Koopmans, head of the Viroscience department at Erasmus MC and scientific director Emerging Infectious Diseases of the NCOH, has been chosen by the Royal Netherlands Academy of Arts and Sciences (KNAW) as a new member. In total, the KNAW has selected 19 new members. Members of the KNAW, leading scientists from all disciplines, are chosen on the basis of their scientific achievements. The KNAW has around five hundred and fifty members and membership is for life. The new Academy members will be installed on Monday 16 September. Marion Koopmans has strongly contributed to the fight against outbreaks of Ebola, Zika and Corona viruses. She is a world leader in virus spread research and ensures that the results are applied. To map out contamination pathways, Koopmans uses the genetic variation in viruses. She is the initiator of the worldwide NoroNet network for research on noroviruses. As an advisor to the Health Council and the WHO, she plays an important role in combating infectious diseases. In 2018 she received the NWO Stevin premium of 2.5 million euros, the highest distinction in Dutch science.

Read more about all 19 new members on the KNAW website: https://www.knaw.nl/nl/actueel/nieuws/knaw-kiest-negentien-nieuwe-leden (Dutch)

Mei Wang

Qihuang prize

Dr. Mei Wang, chair of “Leiden University - European Center for Chinese Medicine and natural compounds’ has been awarded the ‘Qihuang prize’. The prize is awarded by the Chinese Medicine Society in recognition of her significant contribution to Chinese medicine outside China and to further stimulate her initiative and creativeness.

Dr. Mei Wang is the founder of the Leiden University - European Center for Chinese Medicine and natural compounds (LUECCM). The LUECCM is a virtual research center for studies on Chinese herbal medicine and natural compounds located in the Sylvius Laboratory and bringing together expertise from within the Institute of Biology Leiden (IBL) and Fytagoras, a 20 year old TNO-spin-off company specialised in horticulture and seed technology. The LUECCM brings together a variety of research projects by investigators from different scientific and cultural backgrounds. They target a better understanding of synergistic and opposing principles underlying Chinese herbal medicine and applications of natural compounds by combining the best of two worlds: scientific methods from the west and holistic knowledge from the east.

‘It is an honor to receive the Qihuang prize and to be recognised for my work and activities’

Mei Wang has been working for more than ten years for the European pharmacopoeia: a single reference work for the quality control of medicines in Europe and beyond. She contributed to about twenty monographs on Chinese herbal medicine. ‘It is an honor to receive the Qihuang prize and to be recognised for my work and activities,’ says Mei Wang. Wang will continue to contribute with dedication to the study, recognition and application of Chinese medicine outside China. ‘Scientific proof and insight into the underlying mechanisms is key for acceptance of Chinese herbal medicine in western society. It is my ambition that people from all over the world will have access to the benefits of this rich and valuable knowledge base’ - says Wang.

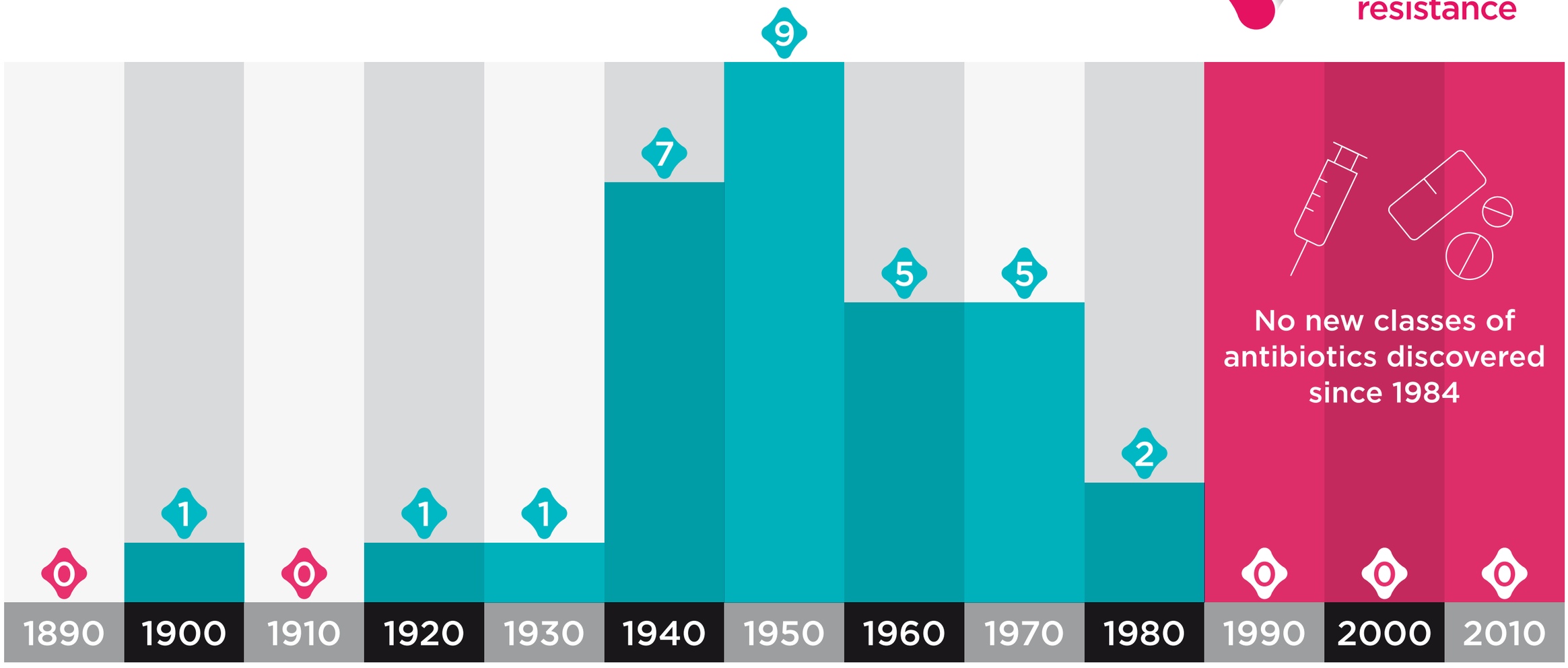
International grants for tuberculous meningitis research

Following a series of smaller trials that showed a benefit of high-dose rifampicin for tuberculous meningitis, Reinout van Crevel (Dept of Internal Medicine, Radboudumc) and Rob Aarnoutse, Lindsey te Brake and Elin Svensson (Dept of Pharmacy/Pharmacology, Radboudumc), theme Infectious diseases and global health, have received funding (4 million British Pounds) from the MRC Wellcome Trust global health trials scheme for a phase 3 randomized clinical trial evaluating high-dose rifampicin in 500 tuberculous meningitis patients in Indonesia, Uganda and South Africa.

Besides intensified antibiotic treatment, targeting damaging inflammation might also improve survival of tuberculous meningitis patients. Following the discovery of a critical role for cerebral tryptophan metabolism (Van Laarhoven et al, Lancet Inf Dis 2018), Van Crevel and colleagues Arjan van Laarhoven, Vinod Kumar and Mihai Netea from the department of Internal Medicine, theme Infectious diseases and global health, have also received 5-year funding (4 million Euro) from the National Institute of Health (NIH, Washington) to apply a ‘multi-omics’ approach in >2000 tuberculous meningitis patients from Vietnam and Indonesia, aiming to find more effective host-directed therapy with collaborators from Boston, Vietnam and Indonesia.

No new antibiotics **in 35 years**

ncoh
tackling
antimicrobial
resistance



Number of antibiotics classes discovered or patented

Source: Shore & Coukell, 2016, Nat. Micro, 1-16083

Impact NCOH

The challenges we face concerning health and environmental issues with regard to infectious diseases affect daily life.

- Our job: to explore and prioritize research gaps through a One Health perspective
- Our goal: to create durable solutions
- Our focal concerns: emerging infectious disease outbreaks, antibiotic resistance, including veterinary and environmental factors

Our research and results also affect daily life: solutions to global one health challenges!

We do so by

1. Research

Identify and prioritize research gaps in the One Health field of infectious diseases, including veterinary and environmental factors which impact these diseases, and advocate the resulting scientific research agenda - both at the scientific and the policy level.

A group of related NCOH PhD projects on One Health research topics are initiated yearly.

- NCOH PhD projects cycle 2017: Metagenomics
- NCOH PhD projects cycle 2019: Complex systems

2. Knowledge sharing

Provide a national coordinating platform for One Health research through exchange and discussion of scientific research, progress, and future actions in an international context. Create, synergies, and facilitate the sharing of data between researchers and research groups in order to train future scientists.

3. Visibility

Enhance communication and dissemination at national and international level via the NCOH website, newsletters, support of scientific meetings, and several social media channels with i.e. infographics.

NCOH Executive Board (from left to right)

prof. dr. Andrea Gröne (Utrecht University), Scientific Director NCOH-HWE
prof. dr. Marion Koopmans (Erasmus MC), Scientific Director NCOH-EID
prof. dr. ir. Dick Heederik (Utrecht University), Chair NCOH Executive Board
dr. Annemarie Rebel (Wageningen University & Research), Scientific Director NCOH-SHF
prof. dr. Marc Bonten (UMC Utrecht), Scientific Director NCOH-AMR

NCOH Partners

More information

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YOUNG NCOH

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Colophon

Concept: Annet Blanken (WUR), Marry van den Top (WUR), Marcel Wortel (Radboud UMC), Paul Geurts (UMC Utrecht), Myrna Tinbergen (Utrecht University), Sharon Verbeek Rijkaart (LUMC), Maaike van Zuilen (Erasmus MC).

Photography: Marion Koopmans, Jan de Groen, Jeroen Hofman, Maaike van Zuilen, Bart Kooi, Marcel Schillemans.

Concept & design: Edwin Marks

Thanks to all organizations, researchers and other professionals who contributed to the realization of this magazine.