HZI HELMHOLTZ Centre for Infection Research

InFact

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ARTIFICIAL INTELLIGENCE

An accelerator for research

EDITORIAL

Dear readers,

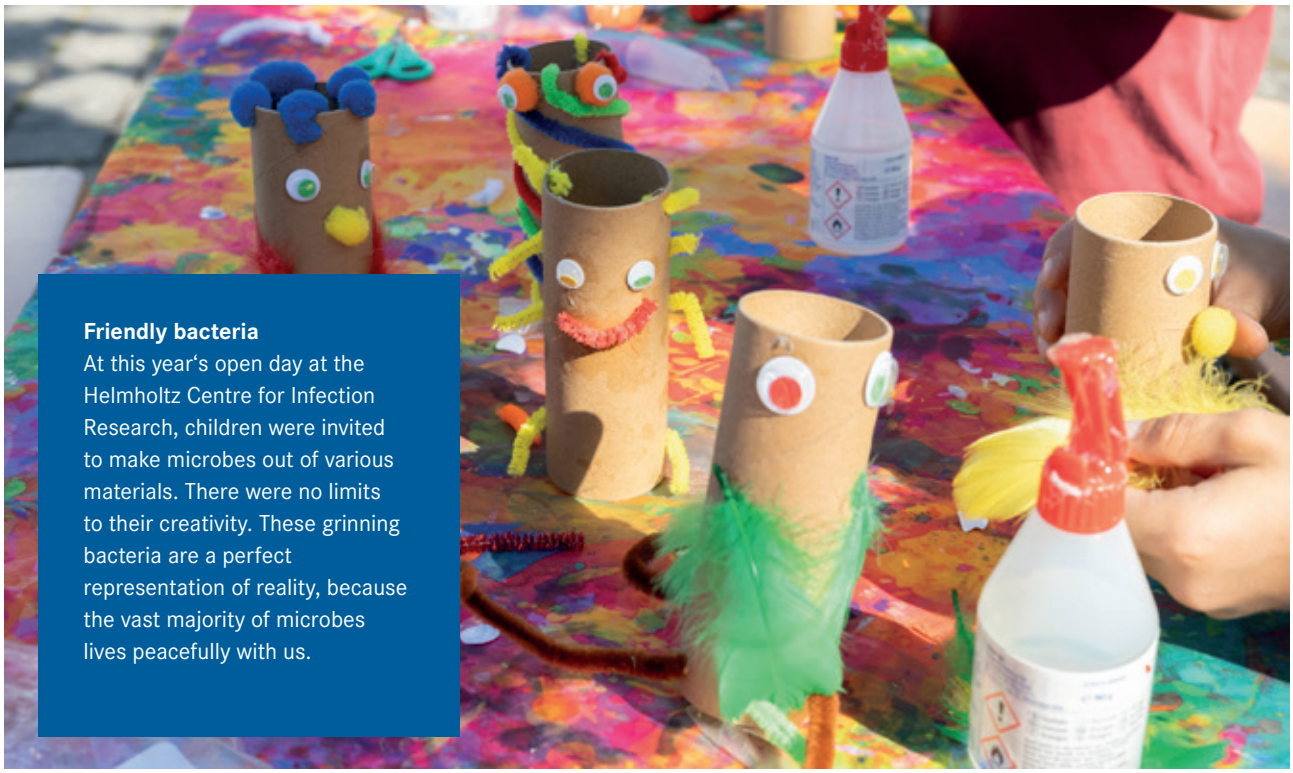
We encounter artificial intelligence – AI for short – everywhere in our everyday lives: whether searching the internet or in various applications on our cell phones, whether in our personal fitness tracker, navigation system or as a chat bot in customer services. In research, AI plays a particularly important role when it comes to dealing with large amounts of data. In a comparatively short time, well-trained systems can draw insights from research data that might otherwise remain hidden from us or take years to analyze. In an interview with Yang Li and Andreas Keller, we discuss how AI can advance infection research and enable ever more individualized treatments.

Multitudes of microbes live peacefully with us on and in our bodies. They not only help us with digestion and the utilization of nutrients, for example, but also protect us from pathogens. From page 7 onwards, you can read about the contribution our microbial community makes to our health and how it could be used therapeutically in the future. We also spoke to Fee Zimmermann about how research into biodiversity can warn us of future disease outbreaks.

I wish you a pleasant read!

Andreas Fischer, *Editor-in-chief*

EYE-CATCHER



Friendly bacteria
At this year's open day at the Helmholtz Centre for Infection Research, children were invited to make microbes out of various materials. There were no limits to their creativity. These grinning bacteria are a perfect representation of reality, because the vast majority of microbes lives peacefully with us.

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The HZI Podcast – Science that is contagious

SEVEN-LEAGUE BOOTS FOR PRECISION MEDICINE

by Nicole Silbermann

A conversation about artificial intelligence (AI) in individualized infection medicine

There is a lot of AI in our everyday lives today, for example in search engines, in voice assistants and in various apps on our smartphones. How much AI is there in your research now?

Andreas Keller: (*laughs*) A lot! AI plays a very central role in our research. Machine learning, which is a subarea of AI, has been used in infection research for several decades. So the use of AI is not really new here. Neural networks, which in principle function in a similar way to a human brain, are another frequently used form of AI. AI models are valuable tools that enable us to analyze huge amounts of data and extract knowledge and correlations from them. This is also known as data science and is a very important part of our research today. Choosing the right AI model is just as important as the quality of the data.

Yang Li: I completely agree with that! You can't get good analytical results from a poor data basis, even with the help of AI. High-quality, detailed and comprehensive data resources are essential if we are to use AI models efficiently for our research and achieve meaningful results. With modern high-throughput methods, valuable data sets can now be generated faster and more cost-effectively, which we use for our research projects. We also work closely with the Hannover Medical School and therefore have access to large patient cohorts. In my working group, we regularly use AI tools for our data analyses.

How can AI specifically help in individualized infection medicine?

Andreas Keller: What is already being done in some clinics today is to determine the gene sequence of the pathogen in patients with bacterial infections and a severe course of the disease and, with the help of AI tools, derive possible points of attack and receive suggestions for suitable antibiotics. Of course, such rapid diagnostics are not used for every common cold. The process is still too complex and too expensive for that.

▽ *Yang Li (left) in conversation with her CiiM colleague Jennifer Debarry*

△ *Andreas Keller heads the "Clinical Bioinformatics" department at the HIPS in Saarbrücken*

Yang Li: But we will certainly continue in this direction in the future. It is conceivable that there will be medical AI assistants in everyday clinical practice that can support doctors on a much broader level in making diagnoses and planning treatment. The emphasis here is on "support", as AI cannot completely replace doctors. One thing is certain: AI will make many things possible in individualized infection medicine in the future that will benefit patients.

Where else could it go in the future? What are you researching?

Andreas Keller: We are interested in the interaction between bacteria and humans. Which bacteria are found in a healthy human microbiome, for example on the skin, in saliva, in the gut? What is the composition of the microbiome when a person suffers from a certain infectious disease? What substances are produced by the bacteria that colonize healthy or sick people? And do these substances possibly have an antibacterial effect?

So you want to find new antibiotic substances!

Andreas Keller: Exactly, we want to use AI to track down new natural substances that could be used as medical active compounds. Against the background of increasing antibiotic resistance, there is an urgent need for research here. But we also want to gain a better understanding of the composition and balance of the human microbiome. Because if we know which bacteria are particularly important candidates for our health, sick patients could perhaps benefit from the targeted administration of customized probiotics, i.e. the "good" bacteria they lack. In future, treatment could thus become more individualized and at the same time gentler. This is because antibiotics, which are always associated with more or less severe side effects, could then be dispensed with in such cases.

Professor Li, what is the focus of your research?

Yang Li: Our focus is particularly on genetics. We want to find out which genetic variants are responsible for the fact that some people have a higher risk of becoming seriously ill with an infectious disease. Or to develop certain symptoms or a particularly high or low immune response. We are also working on models that should make it possible to predict whether a patient will respond to a certain medical treatment or not. Our investigations are based on extensive data sets generated using the latest molecular biology methods, which are summarized under the term "multi-omics". To analyze these multi-omics data sets, we use various selected AI tools depending on the issue at hand, which we adapt and further develop according to the underlying task. Our aim is to identify the key genetic variants that cause patients to be at risk. Based on this knowledge, tailored active substances or therapies can then be developed that can be used as treatment or prevention for risk groups.

What have you been able to find out in your latest studies?

Yang Li: We were able to identify genetic markers that can be used to predict whether a person will develop a protective immune response after an influenza vaccination or not. By taking these correlations into account, vaccination recommendations could be even more tailored and individualized in the future. The development of alternative vaccines would also be conceivable. The new knowledge that we generate comparatively quickly with AI can advance individualized infection medicine enormously at various levels. Another example is a single-cell multi-omics study with patients suffering from COVID-19. Here, we used multi-omics methods to investigate genetic and epigenetic regulation at the single-cell level. Genetics refers to the instructions encoded in our DNA, while epigenetics involves changes that affect the way these instructions are used. The DNA code itself remains unchanged. By examining the genetic and epigenetic processes at the single cell level, we can see how each individual cell in the body regulates its functions. This gives us a detailed understanding of how our immune system reacts to infections. From the resulting huge data sets, we were then able to use AI to identify molecular markers that could only be found in severely ill patients. We were then able to elucidate the regulatory mechanisms that led to the severe disease. This new knowledge generated with the help of AI now opens up new possibilities and starting points for therapies that could be researched in the coming years.

Professor Keller, you are also looking at the risk of patients developing severe and long-lasting symptoms after an infection.

Andreas Keller: Yes, our aim is to find out more about the so-called post-acute infection syndrome. Many bacterial infectious diseases can be associated with sometimes severe late effects, which often only occur years after infection or after the acute illness. They are then often no longer associated with the previous infection. In cooperation with Alice McHardy's department "Computational Biology for Infection Research" at the Braunschweig Integrated Centre of Systems Biology, we will use AI-supported data analysis to search through existing studies in order to track down the connections between all known bacterial pathogens and documented late effects of infected patients. We want to shed more light on this so that the risk of a post-acute infection syndrome in infectious diseases can be better assessed in future and patients can benefit from

better treatment and, in the best case, even prevention. We are focusing our research on the brain, particularly with regard to ageing processes and neurodegenerative diseases such as Alzheimer‘s and Parkinson‘s disease. We want to gain a better understanding of the role that infectious diseases can play as triggers or amplifiers. In one of our studies, we were able to show that an infection with SARS-CoV-2 can leave molecular traces in the brain that occur in a similar form in neurodegenerative and other diseases of the central nervous system.

Are there also risks when using AI tools in infection research?

Yang Li: If you simply run data blindly through an AI application and take the results at face value without checking them, that would be negligent and definitely dangerous for later use in infection medicine, yes. It is important to note that the data sets must first be carefully examined, cleaned and prepared for data analysis. Raw data is generally unsuitable here. These preparatory steps mean extra work, but they are absolutely crucial. In addition, the AI tools must be selected according to the research question to be investigated. And last but not least: The analysis results must be carefully checked for plausibility. This means that expertise is required at various levels.

What do you think, is AI the seven-league boot for individualized infection research?

Andreas Keller: Yes, absolutely! Perhaps even the seven[x]-league boot! The increase in knowledge that AI has made possible in recent years is truly fantastic. And I estimate that it will continue just as rapidly in the future.

Yang Li: It‘s a really great time to be doing research into individualized infection medicine. And yes, AI is taking us leagues forward in a very short space of time. The data resources and the AI models available are excellent - and they are getting better and better. So it‘s going to be incredibly exciting!

Our conversation was also exciting - thank you very much!

△

PROF. YANG LI

has headed the department “Computational Biology for Individualised Medicine” of the Centre for Individualised Infection Medicine (CiiM), a joint institution of the HZI and Hannover Medical School, since 2019 and has also been appointed Director of CiiM. Her research focuses on understanding the molecular mechanisms of immunological/ infectious diseases through the integration of multi-omics data.

△

PROF. ANDREAS KELLER

has headed the department ”Clinical Bioinformatics” at the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), a site of the HZI in collaboration with Saarland University, since 2022. Additionally, he has held the professorship for Clinical Bioinformatics at Saarland University since 2013. He researches the interaction between bacteria and humans with the aim of finding new natural substances that can serve as the basis for the development of medical active compounds. Another focus of his work is to better understand the influence of infectious diseases on the brain, ageing processes and neurodegenerative diseases of old age.

THE ONE AND A HALF KILOGRAM COMMUNITY IN OUR INTESTINES

by Christian Heinrich

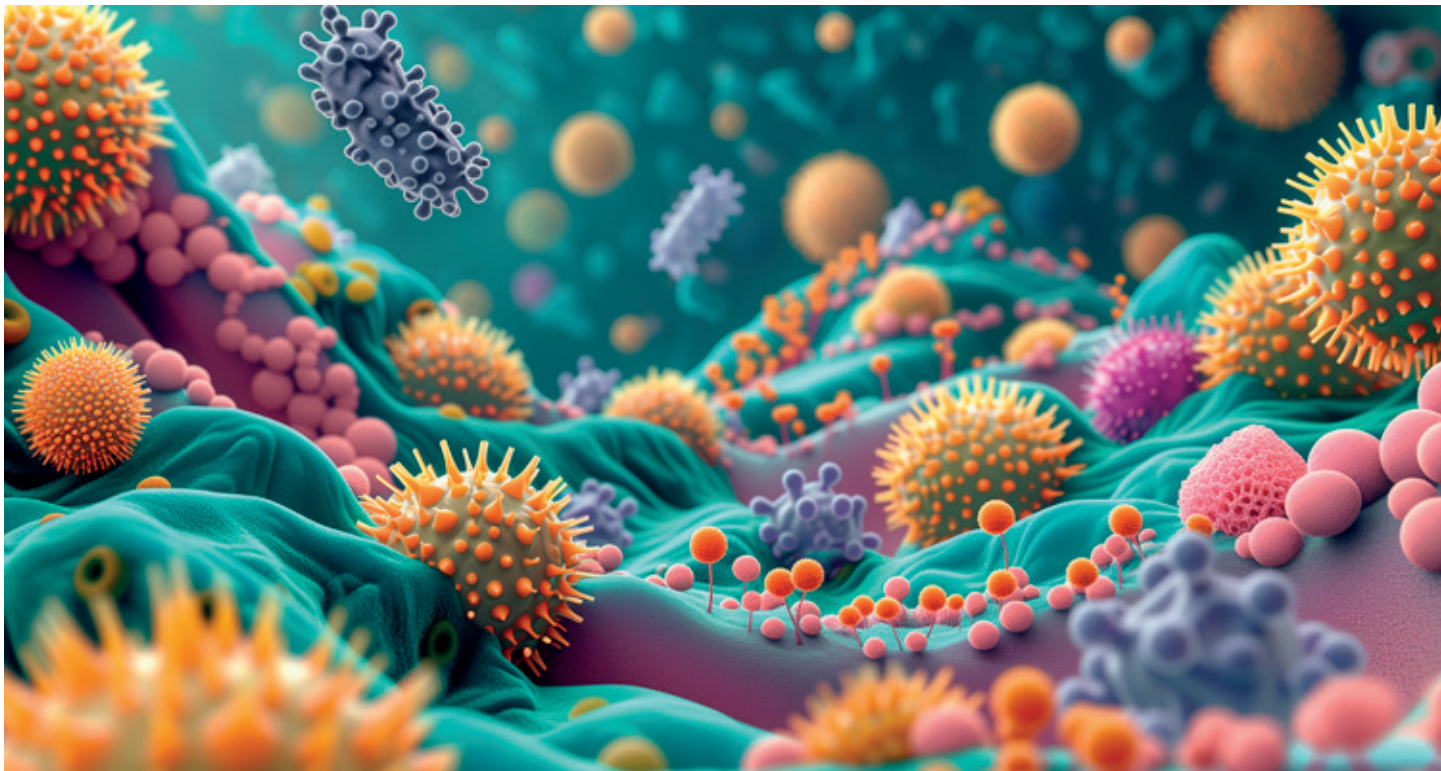
Strengthening our microbiome with a pill so that it can effectively fight diseases? HZI researchers are striving to make this vision of the future a reality

Let‘s start with a wedding celebration. The bride has just given a speech and is now opening the buffet. There is only one problem: There are too many guests. This is because some unwanted guests have sneaked in. Fortunately, the invited guests have more practice in “active queuing”. This way, many of the unwanted guests at the buffet go away empty-handed. They leave the wedding hungry. For the celebration, this is a blessing. Who wants uninvited guests?

“The situation is similar in our intestines: The fuller and more diverse the microbiome there is, the more difficult it is for some rather harmful microorganisms to settle, because there is less food left for the unwanted intruders,” says scientist Dr. Lisa Osbelt-Block, who is researching the microbiome and microbiome-based therapies in Prof. Till Strowig‘s team at the Helmholtz Centre for Infection Research (HZI).

The microbiome is like a huge community of subtenants in our intestines: around one and a half kilograms of microorganisms, mainly bacteria, but also viruses, fungi and yeasts. In recent years, research on the microbiome has exploded, and it is increasingly apparent that the influence of the microbiome on our health and our lives is huge. Not only do the bacteria break down food components, which is essential for our digestion, they also produce important vitamins and messenger substances. Changes in the microbiome have been observed in various types of intestinal diseases. Its contribution to the development of the diseases is currently being researched. The microbiome could also play a role in the development of various types of cancer. There is also evidence that it even influences aspects of our behavior, such as the development of depression. The cause and effect of all these impacts have not yet been conclusively clarified, but it is clear that the microbiome plays an important role.

▽ *The microbiome is a large microbial community in our body*



This offers great potential for new therapeutic approaches. To do this, we would "just" need to know which of the approximately 1000 bacterial species that colonize our intestines are more beneficial and which are problematic. "It's very complex and varies from person to person: Some strains of the same species – such as *Escherichia coli* – can have beneficial or adverse effects, which makes everything even more complicated. We are only just beginning to understand these complex interactions. But we do know whether a few types of bacteria tend to be more positive or more negative," says Osbelt-Block.

"Really beneficial bacteria are, for example, so-called lactobacilli, which are present in yogurt, for instance. Then there are bacteria that are part of the natural microbiome, but could be harmful under certain conditions and in larger numbers. And finally, there are a large number of bacteria that are considered to be rather neutral. They are called commensals and, depending on their interactions with other bacteria or in response to certain environmental factors, can have rather bad or good properties.

"The commensals can act like the invited wedding guests: They occupy many niches and thus prevent unfavorable bacteria from settling," says Osbelt-Block. However, occupying such niches is only a small part of the health-preserving effect that the microbiome has on us. Among other things, it can positively influence numerous metabolic processes in our body through messenger substances and strengthen the immune system. Conversely, however, an unfavorably composed microbiome can put a strain on the body and promote the development of diseases.

△

Lisa Osbelt-Block is researching the microbiome at the HZI

What has an unfavorable effect on the composition of the microbiome? First and foremost, a wide range of medications, especially antibiotics, says Osbelt-Block. This is because they attack many types of bacteria in a non-specific way – including the "good" ones. "I would like to emphasize that antibiotics are among the greatest achievements of modern medicine and it is right that we cannot imagine treatment without them today. But they also damage the microbiome, which is why they should not be used lightly," she says.

The problem is exacerbated by increasing antibiotic resistance. For example, after antibiotics are administered, pathogens that are resistant to antibiotics have even more space to spread due to the death of other sensitive bacteria.

Researchers like Lisa Osbelt-Block and Till Strowig are working towards a better understanding of the microbiome – and the ability to modify it in a targeted way. "If we can identify certain findings and imbalances and have effective levers to counteract them, for example by positively influencing the microbiome through a specific diet or the ingestion of certain substances, then this opens up a completely new approach to treatment," says Till Strowig.

And this approach is ideally personalized. The researchers' vision is something like this: A patient suffering from a particular disease not only gives a blood sample at the doctor's office, but also a stool sample. The microbiome is analyzed in the stool sample – which has implications for diagnostics and therapy. "If certain imbalances are found in the microbiome, it may be possible to deduce from this that a particular drug will work better or worse or have stronger side effects, and adjust the therapy accordingly," says Strowig.

△

Till Strowig heads the HZI department "Microbial Immune Regulation"

Taking this idea a step further, a problem can be treated not only at the disease level, but also at the microbiome level: "If, for example, we have found an imbalance, then in the future we may be able to combat this imbalance specifically with a capsule of certain bacterial strains," says Osbelt-Block.

Although such an approach still seems a long way off, it is not unrealistic. In the United States, for example, the first two microbiome-based therapies have recently been approved, in which mixtures of different bacterial species are introduced into the intestines of patients in a targeted manner. This means that serious and recurrent infections with the hospital germ *Clostridioides difficile* can now be treated effectively. A first customized treatment for the intestinal microbiome. Lisa Osbelt-Block is hopeful that many more will follow in the future.

“CARRION FLIES ARE VERY GOOD DNA COLLECTORS”

by Benjamin Blank

Veterinarian Dr. Fee Zimmermann collects long-term data on human, animal and environmental health in the African tropics and on her doorstep - in Mecklenburg-Western Pomerania. She heads a research group at the Helmholtz Institute for One Health (HIOH) in Greifswald. In this interview, she talks about the importance of the tropics for future disease outbreaks and about animal helpers in data collection

Dr. Zimmermann, you head the One Health Surveillance Core Unit at the HIOH. Sounds complicated, what exactly is it and what is your group working on?

One Health research is about always considering the health of humans, animals and the environment together and that they cannot be separated from each other. Especially when you are researching antimicrobial resistance or zoonoses, i.e. diseases that spread from animals to humans, you have to consider all sides. The Core Unit aims to set up long-term One Health studies in various indicator regions and collect comprehensive long-term data, which will then serve as a basis for the various research departments at the HIOH and for our partner institutions. What is also particularly important to us is the responsible use of resources. It often makes sense to carry out different analyses with the same sample or to use the same infrastructure for different analyses so that not everyone does everything twice.

You mentioned indicator regions. Where exactly are they located and what does your work there look like?

Our study areas are relatively small, very precisely defined regions. On the one hand in the African tropics, but also here in Germany. We look at which pathogens are circulating and what actually leads to disease in humans. We have also ensured wildlife monitoring at our two indicator regions in the tropics - the Taï National Park in the Republic of Côte d‘Ivoire and the Dzanga Sangha

▽ *Flies help to determine biodiversity*

Protected Areas in the Central African Republic - for a long time. We carry out autopsies on wild animals that are found dead in the forest, which gives us an idea of which diseases are relevant in wildlife.

What we are still setting up are cohort studies at our two field sites in Africa, where we will regularly collect health data from the population, but also look at the health of domestic and farm animals and which pathogens are present in people's homes. We also look at rodents, bats and mosquitoes and collect climate and biodiversity data. All together and at the same location, so that we can better understand complex interrelationships. The tropics in particular are a very relevant area for us because they have a high level of biodiversity. Deforestation and human encroachment into remote areas can lead to transmission of new pathogens to humans and - in combination with the unfortunately often poor health infrastructure - lead to outbreaks.

What exactly do these cohort studies look like?

In Africa, we are working with eight to nine villages in both countries that lie directly on the borders of the national park. We would like to recruit around 2,000 people for the cohorts and carry out various clinical examinations and distribute questionnaires every two to three years in order to gain information on the state of health in the population. We are currently developing the study design for this together with the Department of Epidemiology at the HZI. As these cohorts are to be true One Health cohorts, the extensive data already mentioned above will be collected at the same time.

How willing is the population to participate?

In both countries, people were very interested and very open. We tend to come from the field of wildlife research, and the locals think it's great that we are now also doing something in the villages and for the local population. In Germany, there tends to be cohort fatigue, which we absolutely cannot confirm for Africa.

▽ HIOH scientist Ariane Düx tested mosquito traps in Taï National Park in April 2024. Mosquitoes are also to be monitored as vectors, i.e. carriers of pathogens, as part of One Health Surveillance

If you derive behavioral measures from your findings that affect the population: How do people react to them?

Since the major Ebola outbreak in Africa in 2014/15, awareness and interest in such recommendations have been really high. In Central Africa, for example, we are also working with the local radio station to disseminate our findings. One focus at the HIOH is on research on the emergence of infectious diseases. As we take a long-term approach, the great thing is that we see the effects of natural and man-made interventions, such as climate change. We can see how biodiversity is changing and what effect this has on human health. And we can also see the effects of measures to combat climate change, such as reforestation.

Do you have an example of an effect of climate change?

My colleague Lorenzo Lagostina has been looking at the composition of rodent populations from villages to forests every year for some time now and can clearly see, for example, that biodiversity has decreased in recent years. Mainly generalists are spreading, i.e. species that can cope in all habitats.

△ *HIOH researchers also determine the composition of bat species*

For example, the composition of bat species can change, which in turn can lead to a change in the number of mosquitoes present and thus in exposure to disease.

How do you monitor biodiversity? That must be very difficult, especially in the rainforest.

We catch the bats in the traditional way with nets in the forest and identify the species. But we also work with environmental DNA, which my colleague Jan Gogarten collects from leaf swabs or carrion flies. He uses genome analyses to see which animals are present in the forest. Great apes and bats are key for us, as the great apes are so closely related to us. In Taï National Park, for example, we discovered a new anthrax pathogen years ago, *Bacillus cereus biovar anthracis*. It causes 40 percent of wild animal deaths there, especially among chimpanzees. A study has shown that there is a seroprevalence in the population around the park, meaning that people have antibodies against the pathogen and must therefore have come into contact with it. However, we still do not know whether this also leads to cases of disease in humans and hope to be able to clarify this aspect soon.

Let's go to another region. What are the investigations underway in Mecklenburg-Western Pomerania?

We are currently working on site with the University of Greifswald, the University Medicine Greifswald and the Friedrich Loeffler Institute. We have six seed grant projects together with the various founding partners to set up the study design for our One Health Surveillance. In one of these projects, for example, we want to improve and standardize wildlife monitoring in Western Pomerania. Wildlife samples are usually tested for parasites in cooperation with hunters, but we want to extend this to bacteria, viruses and antimicrobial resistance. In a joint project with the Department of Epidemiology at the HZI, we are looking at which cohort studies already exist in northeast Germany and how we can expand these to turn them into real One Health cohorts. For example, there is already the SHIP study (short for "Study of Health in Pomerania"). It has a One Health module in which the study participants are asked whether they have pets. If so, their dogs, cats and chickens are also examined.

The HIOH is also running a citizen science project called CiFly. What is its aim?

Our CiFly team works together with schools. The pupils develop their own study protocols and catch carrion flies, which they use to determine local biodiversity. Carrion flies are very good DNA collectors as they feed on feces and carcasses. By studying carrion flies, it is possible to gain an overview of mammal biodiversity and also of circulating antimicrobial resistance. For example, the children thought about comparing biodiversity in their gardens with the city center or investigating if they could find more antimicrobial resistance around the sewage treatment plant. They had some really great ideas. Introducing children to science and getting them excited about it is the most important effect for us - because the HIOH also needs young talent.

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Fee Zimmermann on a preparatory mission to the Dzanga-Sangha Protected Areas in February 2024

NEW RESEARCH GROUPS AT THE HZI

In 2024, the Helmholtz Centre for Infection Research (HZI) has seen a major expansion in research: Seven new research groups have been set up.

Personalised Immunotherapy
Prof. Kathrin de la Rosa,
Centre for Individualised Infection Medicine (CiiM, Hannover)

Kathrin de la Rosa and her team are researching new applications of antibodies and B cells for the treatment and prevention of infectious diseases in humans, because effective vaccines are still lacking for some viruses that can evade an antibody response. Prior to this, de la Rosa had headed the research group “Immune Mechanisms and Human Antibodies” at the Max Delbrück Center in Berlin since 2018.

Complexes in Phage-Infected Cells
Dr. Milan Gerovac,
Helmholtz Centre for Infection Research (HZI, Braunschweig)

Milan Gerovac‘s junior research group is studying the biology of jumbo phages and developing medically relevant tools from it. Since 2020, he has been working at the Helmholtz Institute for RNA-based Infection Research (HIRI), a site of the HZI in cooperation with the Julius-Maximilians-Universität Würzburg (JMU), where he developed methods for the discovery and characterization of RNA-binding proteins.

Immune Signaling
Dr. Lina Herhaus,
Helmholtz Centre for Infection Research (HZI, Braunschweig)

Lina Herhaus researches the interplay of signal transmission, autophagy and infection. She has previously been team leader at the Institute of Biochemistry II at Goethe University Frankfurt. There she investigated how signaling chains influence cellular equilibrium and react to invading pathogens.

Molecular Principles of RNA Phages
Jun.-Prof. Jens Hör,
Helmholtz Institute for RNA-based Infection Research (HIRI, Würzburg)

Jens Hör‘s research group is investigating the mechanisms of infection, host takeover and phage defense in the context of the interaction of RNA phages with their hosts. Their goal is to decipher the molecular principles underlying these processes in order to develop new and improved antibacterial treatment strategies in the field of phage therapy. Previously, Hör researched the mechanisms of bacterial anti-phage defense at the Weizmann Institute of Science (Rehovot, Israel).

Bacterial Infection Ecology
Dr. Martin T. Jahn,
Helmholtz Centre for Infection Research (HZI, Braunschweig)

Martin Jahn and his junior research group are developing new tools to better understand the structure and mechanisms of the intestinal microbiome in health and disease. Most recently, the microbiologist has been conducting research as a postdoc at the University of Oxford (UK) since 2020 to gain new insights into microbial communities to improve resistance to infection.

Laboratory of Transmission Immunology
Dr. Julia Rebecca Port,
Helmholtz Centre for Infection Research (HZI, Braunschweig)

In her junior research group, Julia Port is investigating the mechanistic basis of virus transmission to enable the development of better containment strategies. To do this, she combines immunology with aerobiology and environmental virology. Port previously worked as a postdoc at the Rocky Mountain Laboratories (NIAID, NIH) in the USA, where her research included the transmission of SARS-CoV-2 and Mpox.

Early Life Immunity
Dr. Natalia Torow,
Helmholtz Centre for Infection Research (HZI, Braunschweig)

Natalia Torow and her junior research group are investigating neonatal immunity in the gut and how this affects vaccinations and infections in newborns. Her particular aim is to optimize the development of oral vaccines for newborns. She previously worked as a postdoctoral fellow at the Institute of Medical Microbiology at the University Hospital Aachen. (afi)