THE RACE AGAINST GERMS

Understanding Infections – Fighting Pathogens

HZI HELMHOLTZ Centre for Infection Research

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Understanding Infections – Fighting Pathogens

GOOD GERMS, BAD GERMS?

INFECTIONS KNOW NO BORDERS

TAYLOR-MADE MEDICINES

PROFILE

“At the HZI, outstanding scientists are tackling the major challenges of our time related to infectious diseases: new pandemics, climate change, increasing antibiotic resistance and the search for effective medications as well as the modern possibilities of precision medicine.”

Prof. Josef Penninger, Scientific Director of the HZI

TINY PATHOGENS, HUGE DANGER

Research for Society

The coronavirus pandemic has made it abundantly clear: The fight against infections is a race against pathogens. Thanks to improved hygiene and effective medication, we can nowadays prevent or effectively treat many infectious diseases. However, bacteria, viruses and fungi often develop creative evasion strategies that we want to counter with even more creative and innovative approaches.

The Helmholtz Centre for Infection Research (HZI) is Germany‘s largest state research institution dedicated to the global challenges of infectious diseases. The results of basic research must be quickly and systematically translated into applications for patients. This brochure gives you an overview of our most important research topics.

→ *www.helmholtz-hzi.de/en*

The challenges

Many bacterial pathogens develop so-called “resistance” and, accordingly, become less sensitive to antibiotics. We travel more often with infectious agents in our luggage. New infectious and rapidly spreading pathogens, such as the Ebola virus, EHEC bacteria or the coronavirus SARS-CoV-2, pose new dangers. Chronic and poverty-related infectious diseases cause serious problems. Infection research, therefore, is instrumental in developing the basis for new approaches to the prevention and therapy of infectious diseases.

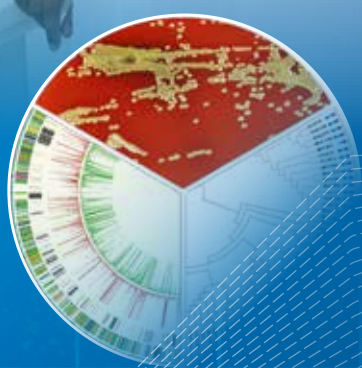
THE FIGHT AGAINST SUPERBUGS

In the race against resistant bacteria

More than 30,000 people in Europe and 1.3 million people worldwide die every year from multi-resistant pathogens, which most often spread in hospitals.

A small cut on the finger or dental surgery could suddenly become life-threatening – because more and more bacteria are becoming resistant to available antibiotics.

In contrast to traditional culture-based methods, the molecular analysis of a pathogen enables the rapid diagnosis of resistance properties and also reveals its relationship to other clinical isolates.



Focus hospital: Improved diagnostics

"It still takes two to three days to isolate and identify the pathogens from an infectious site and to determine its antimicrobial resistance profile as the basis for the initiation of a targeted antimicrobial therapy in the infected patients. At HZI, we are therefore developing more efficient molecular analytical methods for resistance profiling in the clinic."

Prof. Susanne Häußler,
Head of the Department "Molecular Bacteriology" at HZI

“The global threat posed by multi-resistant pathogens remains high and is already costing over one million lives a year. AMR is referred to as a ‘silent’ pandemic. At the same time, development of truly new antibiotics has slowed considerably. We therefore urgently need new, effective medicines.“

Prof. Mark Brönstrup,
Head of the Department “Chemical Biology” at HZI

LIFE-SAVING NEW ANTIBIOTICS

Bacteria develop resistance to antibiotics as a natural consequence of their capacity for rapid evolution. Because bacteria can exchange their resistance genes with each other, several “superbugs” have developed against which almost no available antibiotic is effective.

These antibiotic resistances are one of the greatest threats to global health.* They lead to prolonged hospital stays and, thus, to rising treatment costs and increased mortality. There are several reasons for their spread: For example, antibiotics are prescribed too readily to treat the common cold where they are usually ineffective, and are taken too briefly or used indiscriminately in mass livestock farming.

Scientists from the HZI and its site in Saarbrücken, the Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), together with scientists from the Saarland University are investigating the mechanisms underlying resistance formation, and developing methods both for the early detection of resistant pathogens and for new treatment concepts that specifically address resistance. They are also investigating natural substances as potential sources for new drugs.

**WHO - World Health Organization*

Myxobacteria (showing *Chondromyces crocatus*) produce an enormous variety of chemical substances, many of which exert biological effects.

“About 80 percent of antibiotics are based on natural products. The challenge for the coming years is to make them usable in medicine. Currently, the development of new antibiotics is unattractive for large pharmaceutical companies. Non-university research institutions such as the HZI are left to fill this gap.”

Prof. Rolf Müller,
Managing Director of the HIPS in Saarbrücken

HEALING TREASURES FROM NATURE

Almost all antibiotics originate from natural products. They are often derived from bacteria and fungi which have to compete for habitat and nutrients against other microorganisms. These active compounds work so precisely and effectively because evolution has developed them over millions of years.

Organisms on land and in water still possess a vast reservoir of potentially active substances yet to be discovered. HZI scientists are striving to exploit these treasures. They are searching for substances which have the potential to combat pathogens, notably in soil and in marine bacteria, tropical fungi and soil samples from all over the world. In order to cure infections and aid patients in hospitals in the future, however, these substances must first be optimized for clinical use: They should, for example, be able to reach their target destinations in the body by means of suitable “active substance taxis” and unfold their effect only there. Scientists at the HZI and HIPS in Saarbrücken are working on this challenge.

STOWAWAYS

When herpes, hepatitis & co. become chronic

We still need effective vaccines against the widespread hepatitis C virus and most herpes viruses.

The hepatitis C virus is transmitted mainly via blood contact. It is carried by approximately 70 million people worldwide in the liver as a stowaway sometimes with grave, often fatal long-term damage such as cirrhosis of the liver and hepatic cancer.

“The treatment of chronic hepatitis C infections with antiviral agents works very well. However, the treatment does not protect against repeated infections. In addition, many people do not know that they are infected and continue to transmit the virus. For these reasons, we are looking for a universal vaccine to prevent the transmission of the virus in the future.”

Prof. Thomas Pietschmann, Head of the HZI Department and the TWINCORE Institute “Experimental Virology”

HEPATITIS VIRUSES: HIDDEN KILLERS

Five hepatitis viruses – A, B, C, D and E – are known to cause infections. In 2020 alone, around 1.3 million deaths were caused by this liver-destroying disease. The insidious circumstance about hepatitis C is that those affected often don’t notice it for years, because the symptoms only become apparent after the liver has already been severely damaged.
A vaccine against hepatitis C infection, which affects 1.7 million people every year, is urgently needed.*

This cleverly adapted virus exclusively infects humans and chimpanzees. Therefore, it has been difficult to develop new vaccination strategies since the infection can only be investigated in cell cultures and therefore without an intact immune system present. Scientists from the HZI and TWINCORE, which was established jointly with the Hannover Medical School (MHH), laid the foundations for new humanized mouse models for the infection. This will make it possible to develop urgently needed vaccines against the pathogen. In the long term, an effective vaccine could eradicate hepatitis C worldwide.

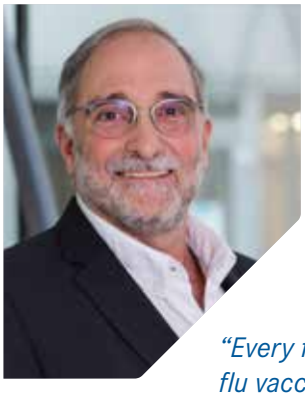
** WHO, RKI – Robert Koch Institute*

Global Strategy

There is still no effective treatment for some forms of hepatitis, while others lack any vaccine. Many people in poorer countries rarely have any access to the expensive therapies or vaccinations currently available. The WHO has set itself the goal of testing 90 percent of people for hepatitis by 2030 and reducing deaths by 65 percent.

Virus attack under the magnifying glass

Our researchers are currently investigating in detail how the host cell is attacked by the virus and how special "cell entry inhibitors" make infections less likely.



“Every fall, a new flu vaccine is needed. Viruses are constantly changing their components to which our immune protection responds. At HZI, we are trying to create artificial antigens from stable parts of the flu virus. Our vision is to develop a universal influenza vaccine 2.0 based on the designer antigens.”

Prof. Carlos A. Guzmán,
Head of the HZI Department
“Vaccinology and Applied Microbiology”

VACCINES OF THE FUTURE

Tailor-made, efficient and universal

Doctors have been using the basic principle of vaccination for centuries: They specifically expose the body to weakened or dead pathogens. Our awakened immune system then prevents a severe course of the disease in the event of any subsequent infection. The art of vaccine researchers is to find substances which prevent us from contracting diseases such as influenza, viral hepatitis or HIV/AIDS. But what should a vaccine have to do to protect us effectively? To this end and in order to develop new, better vaccination strategies, HZI scientists are investigating how the immune system reacts to new vaccine prototypes. Hitherto, there are no therapies or vaccinations available against many infectious diseases. People with a weakened immune system are particularly at risk. Researchers are currently learning from patients who defeat a disease naturally, i.e. whose immune system spontaneously produces a suitable reaction.

Safe and painless: Vaccinate with nasal spray

Researchers at the HZI and its HIPS site are looking for alternatives to vaccination by syringe, such as creams or sprays. Without the painful prick with the needle, vaccinations would be much better accepted.

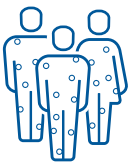
Optimal vaccine booster

Following a standard vaccination against influenza, only a small proportion of people over 60 years of age develop sufficient protection. If the vaccine is administered with an oil-water emulsion or other adjuvants, its effectiveness is significantly improved. Accordingly, researchers at the HZI are striving to develop the optimal vaccine booster.

GOOD GERMS, BAD GERMS?

Understanding microbial languages better

Billions of microorganisms inhabit our body – notably the intestine – and thus contribute to our wellbeing, but also to disease. How exactly this happens remains a puzzle, but has emerged as a major research topic.



In patients with chronic inflammatory bowel diseases, such as Crohn's disease or ulcerative colitis, the diversity of intestinal microbes is reduced. As a result, the immune system reacts excessively to germs. Inflammatory intestinal diseases, for which therapies are still lacking, are thus aggravated.

HZI researchers cultivate and decipher the intestinal bacteria of mice, for example.

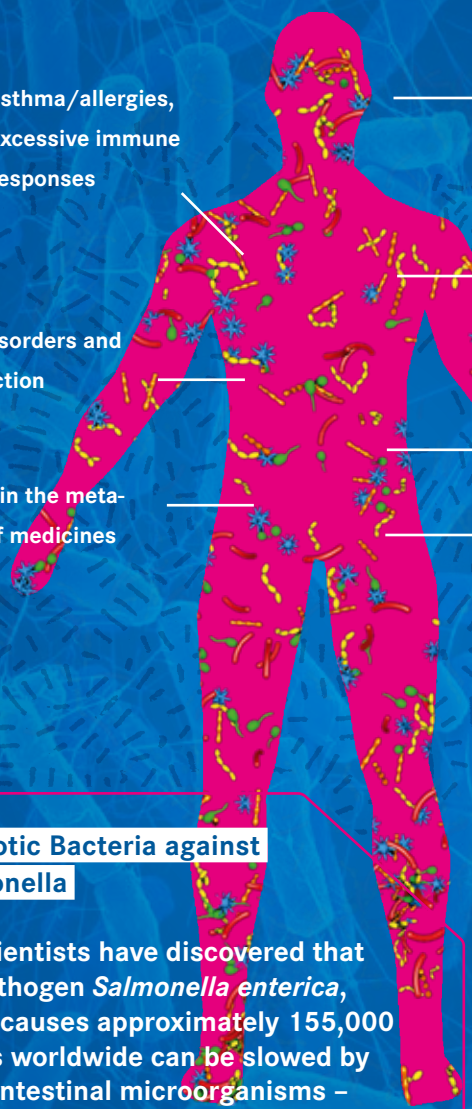
"In order to better understand how we humans interact with our microbial colonizers, we need model systems that allow for experimental changes – both in the host and in the microbes."

Prof. Till Strowig, Head of the HZI Department "Microbial Immune Regulation"

COLON MICROBES – LITTLE HELPERS AGAINST INFECTIONS

The microbial community – often referred to as the microbiome or microbiota – that lives in or on a host, such as humans or animals, is a very diverse community. It inhabits many parts of the body, for example the skin and the intestine. The composition of the human microbiome is very variable and influenced by the organism and nutrition, but also by drugs and diseases. Current research findings indicate that many diseases are associated with changes in the balance of the microbiota. If, for example, the bacterial flora in the intestine is decimated, this disturbs the protective effect of benign intestinal bacteria against invading pathogens. HZI scientists are investigating how these microbial communities impact infectious diseases and are investigating new ways to exploit their findings therapeutically.

Diseases associated with an imbalance in the microbiota are connected to:



asthma/allergies, excessive immune responses

autism, depression, anxiety disorders

cardiovascular diseases, hypertension

biliary disorders and liver function

obesity

changes in the metabolism of medicines

bowel cancer, inflammatory bowel diseases

Probiotic Bacteria against Salmonella

HZI scientists have discovered that the pathogen *Salmonella enterica*, which causes approximately 155,000 deaths worldwide can be slowed by other intestinal microorganisms – so-called probiotic bacteria – thus mitigating the infection. The studies provide valuable information on how people could better protect themselves against dangerous pathogens in future.

“Single cell analysis is interesting for many applications in biomedicine. For example, infected and healthy cells can be analyzed separately and with unprecedented accuracy. This will enable us in future to perform highly precise interventions regarding the interaction of pathogen and host.”

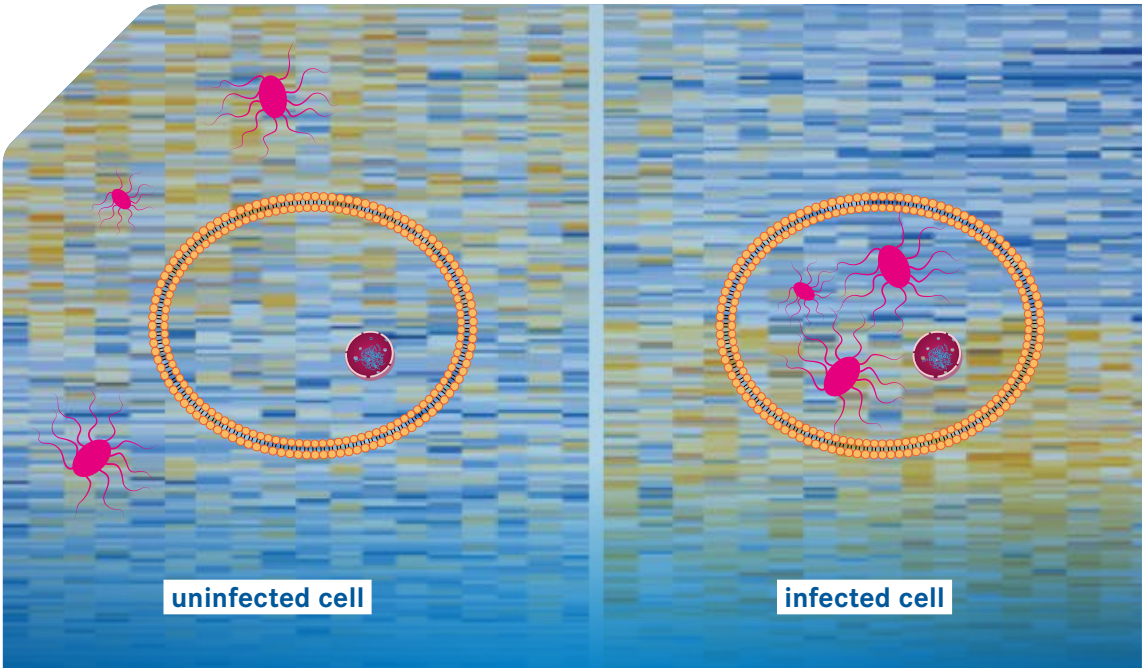
Prof. Jörg Vogel, Director of the HZI site Helmholtz Institute for RNA-based Infection Research (HIRI)

EACH INFECTED CELL BEHAVES DIFFERENTLY

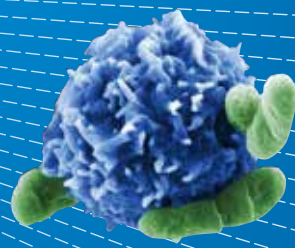
The microscope of the future – single cell analysis

So-called single cell analysis brings light into the darkness and was accounted the most important advance of the year 2018 by the journal *Science*. For the first time, it is now possible to make gene expression visible, the intracellular path from genes to gene products such as proteins. Researchers at the Helmholtz Institute for RNA-based Infection Research (HIRI) and the University of Würzburg have further developed the method in order to investigate the interaction between pathogens and humans in unprecedented detail. They are focusing in particular on RNA molecules. This provides unprecedented insights into the complex regulatory processes involved in an infection.

Many pathogens can remain hidden in their hosts throughout their lives and cause infections again and again. Salmonella, which are food-borne pathogens, have a particularly clever strategy: They infect the immune cells that are supposed to fight them. In these ecological niches, they are protected from the host’s defense and can hide from antibiotics. Single cell analysis enables researchers to better understand the different sites of infection. The aim is to identify disease characteristics in individual cells as early as possible in order to counteract them promptly with treatments tailored to individual patients.



What does a Salmonella infection do with an immune cell?
Single cell analysis shows a map of the active genes in a non-infected immune cell (left) in contrast to an infected immune cell (right). Different genes are active in both cells, as shown by the color change of the lines from orange to blue (not infected) and from blue to orange (infected). Each line represents a single gene.

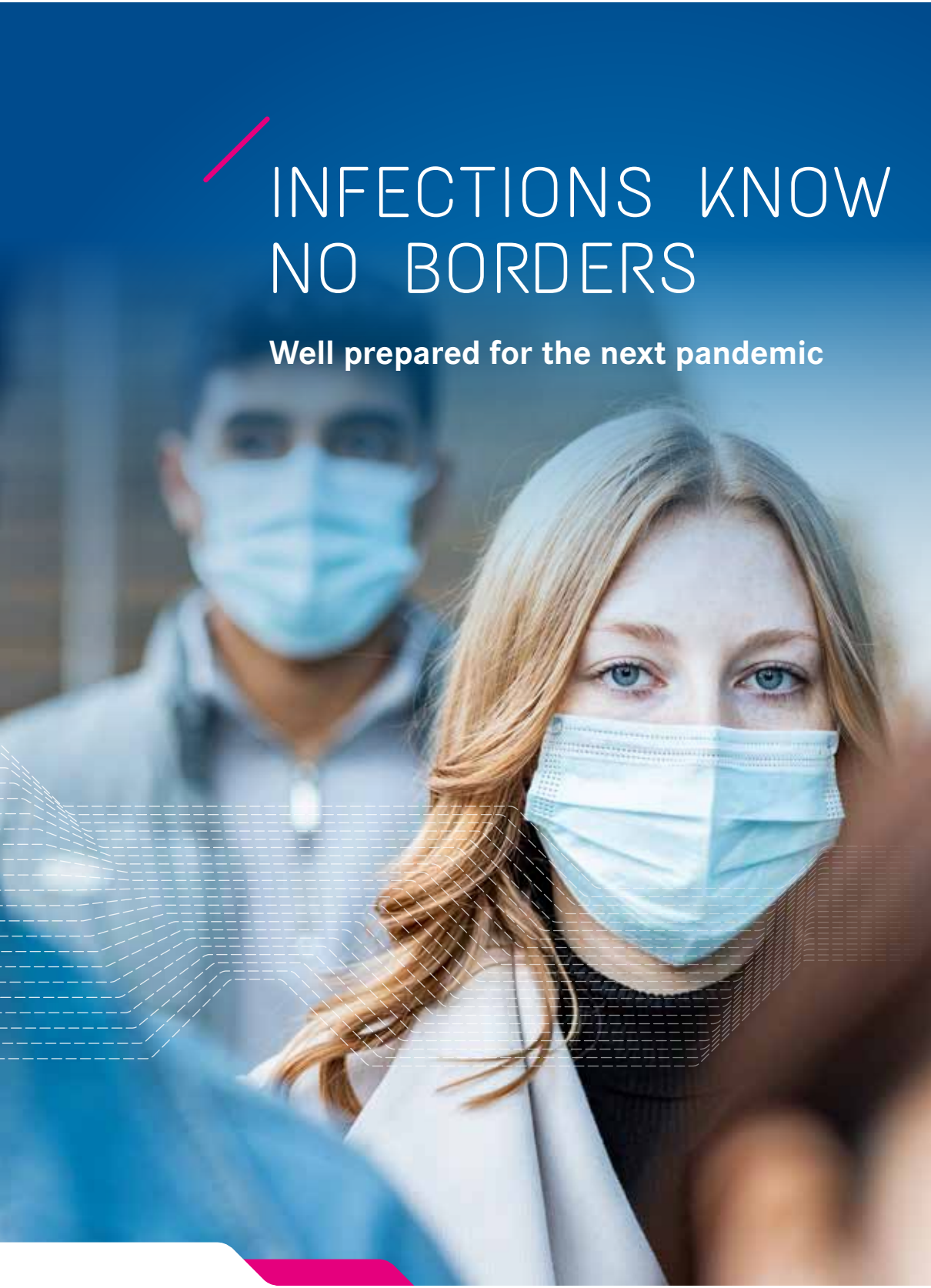


An immune cell in which bacteria have multiplied

How do bacteria manage to protect themselves from immune cells? How pathogens affect our immune system and spread despite its control remains poorly understood. HZI researchers are unveiling the secrets of individual cells – and entire tissues – using a groundbreaking new method.

INFECTIONS KNOW NO BORDERS

Well prepared for the next pandemic



We are becoming increasingly mobile and so are the pathogens that travel with us. In addition, we are living in ever closer quarters - not only with our fellow human beings, but also with wild and farm animals. The growing risk of infection requires innovative solutions for prevention and surveillance. Modern information technologies and artificial intelligence are opening up new ways of analyzing data in infection research.

The One Health approach to tackle the next pandemic

The health of humans, animals and the environment is closely linked. It is precisely these connections that the researchers at the HIOH are investigating using the One Health approach. The aim is to gain a better understanding of zoonotic diseases, i.e. diseases transmitted from animals to humans, antimicrobial resistance and the evolution of pathogens as a prerequisite for successful pandemic preparedness and prevention.

“The One Health concept is the key to pandemic preparedness and prevention.”

Prof. Fabian Leendertz, Founding Director of the HZI site Helmholtz Institute for One Health (HIOH)

LOOKING AT THE BIG PICTURE

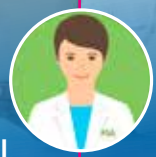
Climate change, globalization, loss of biodiversity - a whole range of risk factors are now promoting the emergence and spread of infectious diseases and threatening global health. In response, the One Health approach recognizes the interconnectedness of human, animal and environmental health and considers them as one big picture. For example, in order to decipher the conditions under which antimicrobial resistance develops or infectious diseases are transmitted, researchers at the Helmholtz Institute for One Health (HIOH) are conducting studies not only on their doorstep in Mecklenburg-Western Pomerania, but also in high-risk areas. These include biodiversity hotspots in the African tropics, where human-animal contact is frequent and the health infrastructure is inadequate. There is an increased risk of novel zoonotic diseases - infections that are transmitted from animals to humans. The HIOH is developing a long-term strategy to systematically record the health of humans, animals and ecosystems as well as climatic changes in order to detect the occurrence and spread of infectious diseases at an early stage and, ideally, prevent them.

→ *www.helmholtz-hioh.de/en*

Cultural landscape and diversity hotspot in perspective
Focal regions of One Health Surveillance are located in sub-Saharan Africa and Mecklenburg-Western Pomerania along population density gradients.

PIA: New app simplifies data collection

Scientists at the HZI use the eResearch system PIA to monitor the incidence of infection in the population. The app, specially developed for this purpose in the Department "Epidemiology", enables study participants to document their health status and symptoms over a longer period of time in real time and, for example, to take nasal swabs independently in the event of a cold. This means that relevant information, including biosamples, can be transmitted without the need to return to the study center. Participants also benefit from information and feedback functions such as laboratory results, which are displayed to them in-app. PIA is constantly being further developed in line with the highest data protection and IT security requirements.



„During the COVID-19 pandemic, it became clear that we lacked relevant research infrastructures in infection epidemiology. We have now made great progress in setting up and establishing them. This will allow for a quicker detection of the spread of pathogens and an even better epidemiological assessment of different infections in the future."

Dr. Berit Lange, Acting Head of the Department "Epidemiology" at HZI

PANDEMIC PREPAREDNESS WITH REAL-TIME DATA

The COVID-19 pandemic has shown that we are not yet optimally prepared for a pandemic. According to official figures, there have been almost 7 million deaths worldwide due to the SARS-CoV-2 coronavirus - the number of unreported cases is estimated to be significantly higher. These are alarming figures that need to be prevented for future pandemic outbreaks. To this end, the HZI is coordinating population-based cohorts that can quickly determine continuous estimates of infection frequency and burden during epidemics and identify risk groups. These studies are supplemented by modelling initiatives for early warning systems, medical and public health applications. Modern digital tools in particular, which are also being developed and evaluated at the HZI, help to identify and contain the spread of infections and the burden of disease. Examples include the SORMAS software and the PIA app. In close collaboration with drug and vaccine research and bioinformatics, the epidemiologists at the HZI are helping to better prepare our society and our healthcare system for the next pandemic or epidemic.

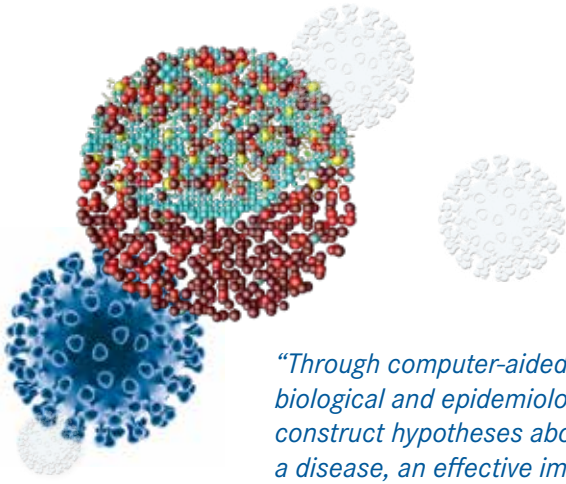
Establishment of an epidemic panel as a research infrastructure for pandemic preparedness

In order to support targeted measures in a pandemic, the Department "Epidemiology" has set up an epidemic panel. Real-time data from population studies can be collected quickly and linked to other population studies in a network. This can be used to create models for various infectious diseases, which are of great importance for advising decision-makers in the event of a pandemic in order to develop protective measures for the population as quickly as possible.

The course in which an infection will develop is difficult to determine on the basis of isolated measurements alone. Systems biologists therefore design mathematical models that can predict dynamic processes in the human body.

Resistance profiles of bacteria at the touch of a button

The bacterial pathogen *Pseudomonas aeruginosa* can cause severe acute infections and is characterized by a particularly high resistance to a variety of antibiotics. Detailed data collected by HZI researchers on this pathogen are fed into an automatic database.
The aim is to make accurate predictions for antibiotic resistance of *Pseudomonas* in the future and thus to be able to choose a suitable therapy for patients.



“Through computer-aided analysis of large biological and epidemiological data sets, we construct hypotheses about the development of a disease, an effective immune response or the development of antibiotic resistance.”

Prof. Alice McHardy, Head of the Department "Computational Biology for Infection Research" at the HZI and the HZI site Braunschweig Integrated Centre of Systems Biology (BRICS)

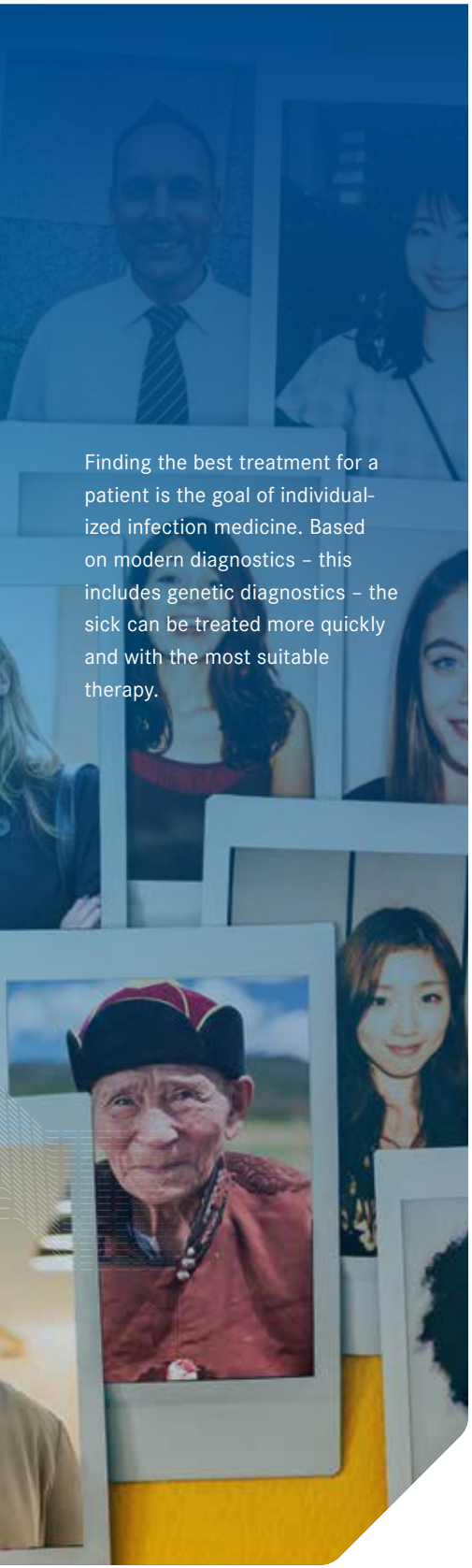
EARLY WARNING OF PATHOGENS

From prediction to therapy

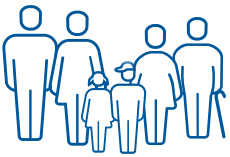
Is it possible to predict the next flu epidemic? Computer-assisted analyses no longer remain a mere vision for more reliable statements about the influenza pathogen of the coming season: Researchers at HZI can already stratify the potential risk of certain influenza viruses at an early stage by observing and evaluating genetic changes in the pathogens. Thanks to state-of-the-art mainframe computers and big data from laboratory experiments and clinical cohort studies, mathematical models and computer analyses are becoming increasingly important in infection research. At the Braunschweig Integrated Centre of Systems Biology (BRICS), scientists from HZI and the Technische Universität Braunschweig are exploring the approach of machine learning for the characterization of infection processes. For example, they use their computers to analyze processes of our body’s immune defense. In close cooperation with partners, hypotheses are tested in the laboratory and will in future support medical diagnostics and treatment of infections.

TAYLOR-MADE MEDICINES

Man, woman, child, risk patient?



Finding the best treatment for a patient is the goal of individualized infection medicine. Based on modern diagnostics – this includes genetic diagnostics – the sick can be treated more quickly and with the most suitable therapy.



People react differently to therapies. For example, gastrointestinal diseases or lung infections can be much more severe in immunocompromised people. If researchers could identify high-risk patients in time, more effective therapies would be possible at an earlier stage.

Flu vaccination is less effective in the elderly

The immune system of older people reacts slower to vaccination and is less versatile than that of younger people. As a result, seniors are less well protected against new variants of the constantly changing flu virus. This relationship is being researched at the HZI and CiiM to design more effective vaccination strategies.

INDIVIDUALIZED THERAPIES AGAINST BACTERIA AND VIRUSES

Each person is unique with distinguishing characteristics which can also influence the course of infections. In recent years, it has become increasingly clear that the success of a treatment depends to a large extent on the molecular profile of a patient, i.e. on the molecular or cellular makeup of the patient. Individualized infection medicine, also known as personalized or precision medicine, seeks to apply this knowledge for the benefit of patients and derive the most effective treatment and with as few side effects as possible by making use of specific biomarkers.

Treating infections individually

Optimally, by analyzing large amounts of data from patient groups, researchers will know even before treatment which therapy will prove unsuccessful or whether an antibiotic or vaccine is effective. At the Centre for Individualised Infection Medicine (CiiM) in Hannover, HZI scientists and MHH physicians advance strategies for personalized medicine.

Artificial intelligence simulates hepatitis B therapy

Bioinformaticians from the BRICS and clinicians at the CiiM combine their expertise. Recently, using special software based on machine learning, they were able to identify a set of signaling substances that can be used to predict with 90 percent certainty the consequence of terminating hepatitis B therapy.

"We are searching for biomarkers – characteristic properties or molecules – which we can use to stratify patients into different groups and thus make the most appropriate therapy decisions for each individual group in the future."

Prof. Yang Li, Head of the Department "Computational Biology for Individualised Medicine", and Prof. Markus Cornberg, Clinical Director of the HZI, are the dual leaders of the Centre for Individualised Infection Medicine (CiiM).

Good efficacy up to no efficacy

Efficacy of drugs in each patient
Differing efficacies of drugs and therapies depend on individual patient parameters and the pathogen causing the disease.

Individualized medicine

The susceptibility of the patient to infections and the severity of the disease course are determined by individual patient characteristics and the types of colonizing microorganisms (microbiomes).

Pathogens can, for example, develop resistances that must be taken into account when choosing a therapy.

BRAUNSCHWEIG

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www.helmholtz-hzi.de/en
Braunschweig Integrated Centre of Systems Biology
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GREIFSWALD

Helmholtz Institute for One Health
www.helmholtz-hioh.de/en

HANNOVER

TWINCORE – Centre for Experimental and Clinical Infection Research
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CiiM – Centre for Individualised Infection Medicine
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HAMBURG

Centre for Structural Systems Biology
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Helmholtz Institute for Pharmaceutical Research Saarland
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ONE CENTER - SIX SITES

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NUMBERS & FACTS

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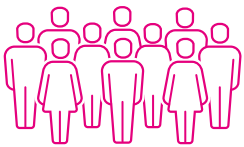

>1000	200	70
Employees	**Visiting scientists**	**Nationalities**

95 MIO	37 MIO
EUR core budget	**EUR third party funding**

>500	81
Publications	**Patent families**

HZI HELMHOLTZ Centre for Infection Research

THE HELMHOLTZ CENTRE FOR INFECTION RESEARCH

The more than 1000 employees at the Helmholtz Centre for Infection Research (HZI) use their expertise to bring closer a healthier society. Scientists at the HZI in Braunschweig and its other sites in Germany are investigating bacterial and viral infections as well as the body's defense mechanisms. Their profound knowledge of natural substance research comprises an invaluable resource for driving forward development of novel anti-infectives. As a member of both the Helmholtz Association, Germany's largest non-university research organisation, and the German Center for Infection Research (DZIF), the HZI conducts translational research to lay the foundation for new therapies and vaccines against infectious diseases. Together with clinical and industrial partners, the results of basic research are promptly and systematically transferred to application at the patient's bedside.

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