ROBERT KOCH INSTITUT

WHO WE ARE
WHAT WE LOOK BACK ON
WHAT WE DO AND WILL DO

Protecting Health
Assessing Risks

Contents

The Institute for the Health of the Nation

In its role as the Federal Government's leading scientific and medical institution, the Robert Koch Institute sets its sights on public health. Its two major areas of responsibility lie in combatting infectious diseases and analysing health trends in the population but it also focuses on developing methods and drawing up scientific standards, acting as the reference body for investigating suspected cases of intentional release of pathogens, for example, or developing growth curves for children and young people in Germany. Moreover, the RKI is very active in the field of qualifying scientists, including doctoral dissertations and trainee programmes.

In order to fulfil this extensive mission, the RKI depends on the excellence of its scientists. Without their fundamental and measure-related research activities the institute would be unable to file recommendations for improving public health. The degree of specialist expertise is illustrated, amongst others, by the large number of national reference centres and specialist bodies based at the Robert Koch Institute, such as the Commission of Hospital Hygiene and Infection Prevention (KRINKO) or the German Standing Committee on Vaccination (STIKO).

The objective of infection research is to be and remain a reliable and competent contact point in meeting health-related challenges. The relevant research fields include in-depth studies into the spread of pathogens and their ability to trigger disease or develop resistance to therapeutics. The research outcomes provide the basis for risk assessment and recommendations for public health measures on issues like the fight against antibiotic resistance and tuberculosis or the prevention of HIV and other sexually-transmitted infections. Acquiring significant information is the cornerstone of these efforts. The RKI therefore develops and operates a number of nationwide surveillance systems like the working group on Influenza (Arbeitsgemeinschaft Influenza, AGI), which go well beyond the data generated by notifications.

Since the early 1980s, the RKI has conducted major health studies not only surveying thousands of participants but also examining them in detail. In the last few years, this research has been extended: Health monitoring, which was launched in 2008, continuously collects data on the health of children, young people, adults and the elderly. The well-established system of monitoring studies covers a broad spectrum of questions on health status, health behaviour, risk factors, prevention and care. The data generated flow into health reporting, developing health objectives, and preparing and screening health-policy decisions.

Not only the research themes but also the RKI's focus and structure are regularly reviewed and, if necessary, realigned with the help of external experts. In 2007, for instance, a project group of national and international experts formulated priorities for developing the RKI into a public health institute. In consequence, the German parliament decided to expand the institute's human resources ("RKI 2010") which means that the RKI has been in a better position to meet the new challenges to health and infection protection posed by issues like globalisation and an ageing society. A big new project to build modern laboratories and office accommodation, including a high-security lab, complemented the expansion under "RKI 2010".
However, safeguarding health does not stop at national borders. The major Ebola outbreak in West Africa clearly demonstrated that the RKI needs to engage more with the international community in order to help support local public health services as well as scientific and medical expertise. In Germany, too, an efficient public health service is required, especially at municipal level. Only local health authorities can investigate suspected cases, introduce quarantine measures or collate data on the local health situation.

In accordance with statutory requirements, the Robert Koch Institute first and foremost advises external experts and policy-makers. Nevertheless, it considers it its inherent duty to inform patients and people in general about relevant infection risks and health trends, or to draw their attention to sources of information. As many people as possible should be empowered to make their own judgements in order to respond appropriately to potentially threatening situations and improve their own health situation.

This is the fourth, updated edition of this brochure. It introduces the Robert Koch Institute and its work and is intended for readers who do not have any special medical knowledge. The first chapter describes the institute's core tasks: to protect against infectious diseases and to analyse the health situation in Germany. An overview of the institute's history, which dates back to 1891, is the subject of the second chapter. The following eight chapters elucidate the research fields, showcasing examples of their work. Two of these chapters are quite new. One is dedicated to the RKI's health monitoring and is designed to present a more comprehensive picture of the institute's research into non-communicable diseases. A further new chapter on Big Data and bioinformatics was included because of their increasing significance for the institute's research.

I certainly hope you enjoy your visit behind the scenes at the Robert Koch Institute!

Lothar H. Wieler
President of the Robert Koch Institute

ROBERT KOCH'S HEIRS

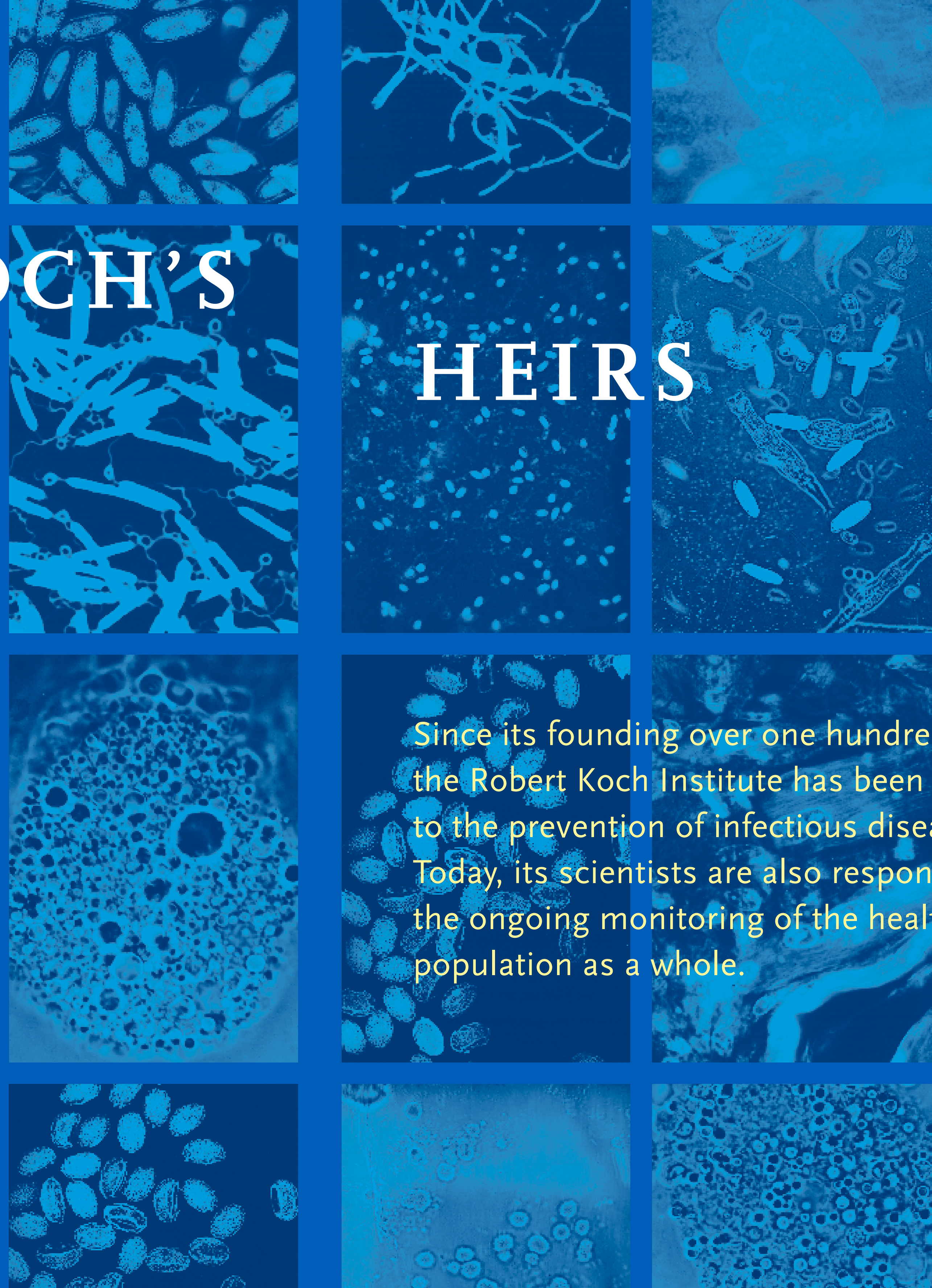
'The public benefit is what motivates me'

'The ability to be creative is appealing'

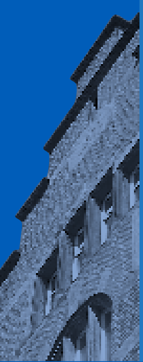
'We are pioneers in our field'

'To me the Robert Koch Institute is simply an employer'

'The name carries with it a responsibility'



Since its founding over one hundred years ago, the Robert Koch Institute has been dedicated to the prevention of infectious diseases. Today, its scientists are also responsible for the ongoing monitoring of the health of the population as a whole.



Lothar H. Wieler, President of the Robert Koch Institute. In this interview Wieler talks about the work, goals and philosophy of the institute.

Protecting Health – Assessing Risks

Mr Wieler, why do we need the Robert Koch Institute?

◂ It is important to have an institute in this country that focuses on health and can evaluate the factors that influence it at an early stage, both scientifically and independently – this is precisely what we do. The Robert Koch Institute sees itself as a public health institute for Germany. This means that we continually analyse the health situation in the population not only with regard to infections but also common diseases such as cardiovascular diseases, allergies and psychiatric disorders. Our studies serve as a reference for the medical community as well as for health policy decision-makers. All this is based on the work of our excellent scientists and that is why the Robert Koch Institute has to offer them a really great environment.

The name Robert Koch Institute itself evokes close associations with infections: what do they mean to us today?

◂ They are very topical. On the one hand, it is a simple fact that pathogens do not respect borders, perhaps less today than ever before. Globalisation, migration, changes in land use as well as burgeoning tourism and contact with previously intact ecosystems all harbour the risk that viruses will go global or suddenly start being passed from animals to humans. New pathogens are discovered every year. On the other hand, there are very positive developments here in Germany which, in their own right, advantage certain infections: nowadays, many older people and patients with underlying diseases are treated in hospitals at a very high level. Usually this involves intensive use of antibiotics which, in turn, fosters the spread of resistant pathogens. With regard to Germany, we are able to provide an overall picture of such infection risks because we record a large number of infections centrally and also analyse the dynamics of antibiotic resistance.

This nationwide perspective can be applied to chronic diseases as well.

◂ Definitely. To cardiovascular diseases and cancers, for example, but we also monitor the relevant risk factors very closely. Are Germans getting too fat? Do we get enough exercise? Which social factors have an impact on health? What do children suffer from? Which factors over the course of a lifetime determine the disease burden in later life? We paint a representative picture of the really important health trends for the whole of Germany.

Is collecting health data your main activity?

◂ Collecting quality-assured data is an important activity, but certainly not the only one. We do experimental research in our laboratories from which we derive concrete proposals and issue recommendations on hygiene and immunisation. We can only do this because of our innovative, competitive research work which helps us to establish diagnostic standards. Even in the case of an acute disease outbreak, thanks to modern, high-throughput sequencing we can identify the exact genetic type and danger potential of a pathogen within hours. We are also pioneers in the epidemiological field. Our nationwide monitoring studies, for example, have been the first to generate systematic insights into child and adolescent health. We have a unique wealth of research data which is also accessible to external researchers.

'We want to paint a representative picture of the really important health trends.'

'The institute has become an international hub for health protection networks.'

What do you see as the challenges for the future?

◂ The Robert Koch Institute's capabilities have constantly grown, but so have expectations – which is part of the reason why the institute has increased staff numbers and added modern labs and office buildings in the last few years. We have built major expertise in special pathogens, which could be released in a bioterrorist attack, for example, and the demand for such knowledge from abroad is growing all the time. Internationalisation of this kind is certainly one of the challenges. During the Ebola epidemic in West Africa we were on the spot, helping to elucidate and fight the disease. And within the EU, for example, we cooperate with certain countries in order to be able to test their samples for high-risk pathogens in our labs if the need arises. The Robert Koch Institute has long since become an international hub for health protection networks.

How much influence do you have on politics in this context?

◂ We conceive of our role as conducting independent, scientifically-based studies, from which we derive recommendations that we deliver in the form of policy advice. We create a scientifically sound basis for political decision-making – an exciting challenge.

You yourself are a veterinary scientist and infection researcher. What fascinates you about your current work?

◂ I spent many years successfully doing research at universities. What I'm now interested in is turning scientific results directly into recommendations and measures for health protection. This is an exciting, life-affirming task. The work we do here really can make a difference.

The Robert Koch Institute in profile

The Robert Koch Institute (RKI) is a central body for the safeguarding of public health in Germany. As the leading government institution in the field of biomedicine, the RKI plays an important role in the prevention and combating of infectious diseases as well as in the analysis of long-term public health trends in the German health system.

Research and prevention of infections is a classic field of work for the RKI. For example, its scientists conduct research into the molecular properties and transmission modes of all groups of pathogens, including not only bacteria and viruses but also fungi, parasites and prions such as the BSE pathogen. In addition, the RKI, according to the Protection against Infection Act, records and analyses data on the occurrence of numerous infectious diseases throughout Germany.

The RKI also analyses the distribution and trends in noncommunicable diseases and combines the data from the federal states on the frequency of cancer. RKI researchers conduct regular monitoring surveys on quality of life, life style and health risks of children and adults in Germany. These analyses are merged into a system of continuous health reporting that sets standards internationally – in addition to the research on infectious diseases, federal health reporting has become a trademark of the institute.

Characteristic for the RKI is its advisory role towards the federal government, state and local health authorities and medical specialists. For example, through its scientific work, the institute supports legally competent commissions located at the RKI with their recommendations for vaccination and for hygiene measures in hospitals. The RKI provides expert teams to help in investigations of regional epidemic outbreaks and collaborates with other authorities and experts to draw up epidemic emergency plans for extraordinary scenarios such as a worldwide influenza pandemic. A further example is the Framework Ebola Virus Disease that was developed in collaboration with state and federal authorities and received worldwide attention. National reference centres and consultant laboratories for various pathogens are also located at the RKI that, above all else, serve as central contact points for research and diagnosis. The RKI also functions as an important interface in numerous international cooperative projects.

Since 2002, prevention of bioterrorism has become a new and major task of the institute. The Centre for Biological Threats and Special Pathogens established at that time develops tests

The Robert Koch Institute, main site, entrance. The historic building completed in 1900 is located at Nordufer in Berlin-Wedding

THE TASKS OF THE ROBERT KOCH INSTITUTE

Improve protection from infection

Examples:

- *Which vaccinations are recommended?*
- *How can infections in hospitals be avoided?*

Provide policy advice

Examples:

- *What are the most important approaches for preventing chronic diseases?*
- *What risks to the general population are posed by a newly discovered pathogen?*

Analyse health trends

Examples:

- *Is the number of overweight people increasing?*
- *Which psychological stresses are children and youths exposed to?*

Develop standards

Examples:

- *With which molecular tests can high-risk pathogens be reliably identified?*
- *How can the elderly be integrated into health surveys?*

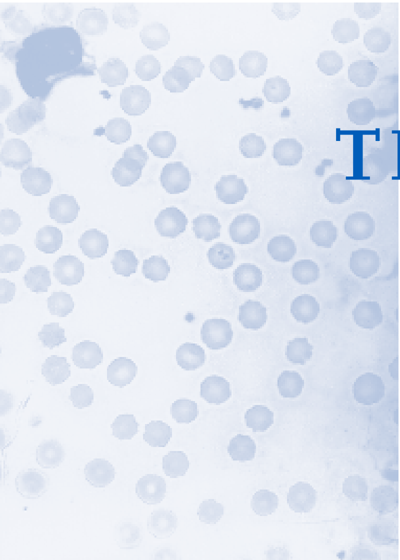
for bioterrorism-relevant pathogens and concepts for defence against attacks. At the same time it also serves as a national and international hub for information and contact and handles queries, particularly from medical specialists.

Since 2002, the RKI has also acted as approval authority for the import and use of human embryonic stem cells. Moreover, the RKI is also in charge of the office of the interdisciplinary and independent Commission on Genetic Testing, which is responsible for the drafting and issuing of directives as stipulated in §23 of the Genetic Diagnosis Act. The commission, established in 2010 by the Genetic Diagnosis Act, consists of 18 members who are appointed by the Federal Ministry of Health for a three year period.

The RKI has its headquarters and two additional locations in Berlin as well as a branch in Wernigerode in the Harz region. In the long term, only two sites will remain in Berlin, both situated in the district of Wedding in the direct vicinity of the Charité university hospital and other research facilities.

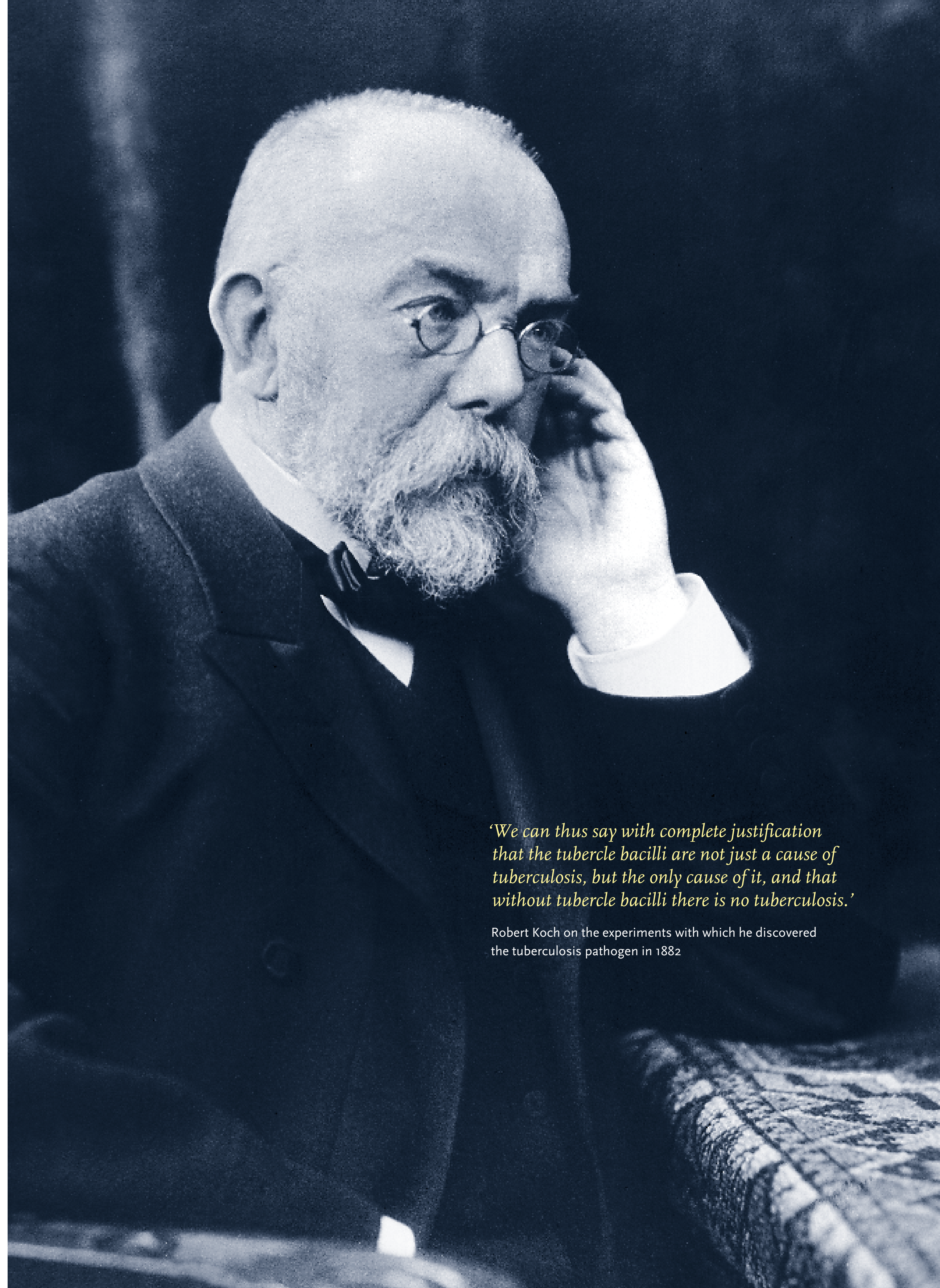
In the scope of the "RKI 2010" initiative – a programme designed to further define the profile of the institute – the RKI has also been reinforced with additional personnel, following a decision by the German parliament. Its staff of around 1100 includes approximately 450 scientists, including Ph.D. students and trainees. The Robert Koch Institute regularly seeks third-party funding for its research projects. Specific scientific issues are investigated in project groups. Young researchers have the opportunity to raise their profile in the scope of junior research groups. An internal institutional research board and an external scientific advisory council continuously monitor the quality of the scientific work.

Left side: Inside view of the main building at Nordufer (left) and in the laboratory building at Seestraße (right). *Top:* The Wernigerode site in the Harz region. *Bottom:* The daily tasks of staff at the institute include laboratory research as well as statistical analyses supported by state-of-the-art computer software



THE DISCOVERY OF MICROBES

In the late 19th century, microscopically small pathogens were identified as the cause of numerous infectious diseases – Robert Koch is considered one of the co-founders of this medical revolution. The history of the Robert Koch Institute is shaped by the visions of its Nobel Prize winning namesake.



'We can thus say with complete justification that the tubercle bacilli are not just a cause of tuberculosis, but the only cause of it, and that without tubercle bacilli there is no tuberculosis.'

Robert Koch on the experiments with which he discovered the tuberculosis pathogen in 1882

Sensation in Berlin

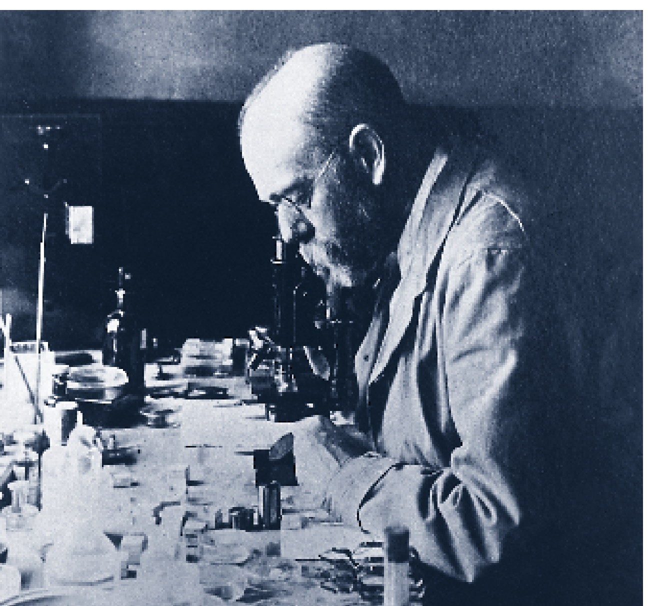
A cure for consumption?

Berlin, summer of 1890: hundreds of doctors and scientists are crowding in for the opening of an international congress. The speakers talk of state-of-the-art medical methods of the Kaiser's era. The visitors listen to Robert Koch's words with fascination. Koch has proved in animal tests that tuberculosis – one of the scourges of the century – could possibly be cured. The news becomes an immediate sensation.

'The illness process can be brought to a complete halt,' says Koch, describing his discovery. He had treated consumptive guinea pigs with a seemingly magic substance: "tuberculin".

The tests have still not been completed, the bacterial researcher cautions. But the enthusiasm cannot be curbed: the press is in tumult worldwide. The hospitals in Berlin conduct courses in which the tuberculin method is demonstrated. Doctors and patients flock to the capital, where lung clinics are springing up on every corner. Souvenirs are sold everywhere – cups, handkerchiefs, watches – with Robert Koch's picture. The spectacular results of the tuberculosis research induce the Prussian government to build an independent research institute for Robert Koch: in 1891 the "Royal Prussian Institute for Infectious Diseases" is opened, with Koch as its first director.

The enthusiasm regarding tuberculin marks the beginning of the story of the Robert Koch Institute. But the hopes initially placed in the substance soon begin to fall apart. Long-term healing fails to occur, on the contrary, there are even deaths. In front of a Berlin "Tuberculosis Cure Sanatorium", a contemporary witness describes 'hearse after hearse stopping a few months later'. The initial triumph begins to turn into the greatest disappointment in Robert Koch's life.



Robert Koch at his microscope, 1896

TUBERCULIN

Tuberculin is still used for the recognition of tuberculosis today along with newer methods. The substance that was first created by Robert Koch is a mixture of particles of disrupted tubercle bacilli. If the tuberculin is injected into the skin, it causes an immune reaction and leads to nodular swelling in the event of infection with the tuberculosis pathogen. Today, specially purified substances are used for this so-called tuberculin test. The idea for this test can be traced back to Clemens von Pirquet, a contemporary of Koch.

The discovery of microbes

The tuberculin flop is typical for the dilemma at that time: numerous pathogens are discovered in the late 19th century – however, efficient weapons against microbes are largely absent. It is only with the 20th century that treatment with antibiotics brings a breakthrough against infections. Nevertheless, the foundations of the fight against bacilli were laid in the era of Robert Koch. Alongside the Frenchman Louis Pasteur, Koch is regarded as the father of a new field of science – bacteriology.

What makes us sick? This question can be answered in a completely new way by bacteriology. Not emissions from the ground or air impurities – "malaria" literally means "bad air" – but tiny living germs, entering the body from outside, are now known to be the cause of contagious diseases.

In order to prove this hypothesis, Koch utilises the most innovative methods of the age, and develops them further: he breeds microbes on special culture media, utilises special dyeing techniques and works consistently with the microscope. He also introduces so-called microphotography to bacteriology in order to objectively secure and communicate the knowledge gained regarding microbes – against the objections of distrustful colleagues that the photographic images are retouched and faked.

In 1876, as a country doctor, he is successful in the experimental transfer of the anthrax disease in animal tests, isolating the pathogens concerned. He discovers anthrax spores, the dormant form of the pathogen, in the process explaining the infection chain that had until then remained a mystery. Robert Koch was therefore the first to prove the connection between a microorganism and the cause of an infectious disease. After his move to the Imperial Health Office of Berlin in 1880 he identifies the pathogen of tuberculosis in 1882 – a discovery that will make him famous. In

Insight into the world of microbes. Reproduction of a glass negative from Robert Koch's estate

With state-of-the-art microscopic methods it is possible to directly monitor and portray the interaction of bacteria with cells of the host organisms

The Robert Koch Institute in 1900

1905 Koch is awarded the Nobel Prize in Medicine for his discovery.

A further discovery is linked closely to the name Robert Koch. In 1884 he proves on an exploration expedition to Calcutta, India, that cholera is also caused by bacteria and that the germs spread via contaminated water. The Italian physician Filippo Pacini had first identified the cholera bacillus in 1854 in the bowels of cholera corpses, although his discovery was subsequently forgotten. When a cholera outbreak is registered for the last time in Germany, in Hamburg in 1892, Koch participates in identifying the cause of the epidemic: he discovers that improper treatment of drinking water in the Hanseatic city had led to the spread of the cholera germ. At this point, at the latest, bacteriological research and public health protection are considered to be two sides of the same coin.

VIRUSES

Viruses are distinct from all other pathogens. Viruses can only reproduce with the help of the cell machinery of a host organism. For that purpose they invade, for example, cells of the human body. In many virus infections, including diseases such as rubella, measles or mumps, the affected cells are destroyed. Certain viruses – amongst them so-called retroviruses such as HIV – incorporate their genetic information into the cell's own genetic material, allowing them to remain in the organism for many years.

The second breakthrough

In 1885, a short time after the cholera expedition to India, Koch becomes Professor of Hygiene at the Friedrich Wilhelms University in Berlin. Numerous renowned scientists subsequently work in his team, amongst them Emil von Behring and Paul Ehrlich, who will later go on to win the Nobel Prize. Nevertheless, many infectious diseases still remain inexplicable. Regarding diseases such as smallpox or measles, Koch is forced to admit in the early 1890s: 'there is not the slightest clue as to what kind of pathogens they may be.' The second breakthrough did not occur until shortly before the turn of the century. A previously totally unknown type of pathogen becomes a talking point – viruses.

Substantial proof of their existence is initially discovered in animals. Two former students of Robert Koch, Friedrich Loeffler and Paul Frosch, discover that the lymph fluid of animals with foot and mouth disease is still infectious even after being sanitised with a special bacteria filter. The conclusion is self-evident: the pathogen must be significantly smaller than a bacterium, which is why it passes through the pores of the microbe filters unhindered. Loeffler and Frosch already assumed that the triggers of formerly inexplicable infections such as smallpox, influenza or measles also belong to this group of tiny pathogens – an assumption which is later to be proved correct.

Nevertheless, the clues indicating the viral pathogen remain indirect for some time. They do not become visible until the 1930s, after the invention of the electron microscope. The newly-created branch of infection medicine – virology – becomes one of the most important research fields of the Robert Koch Institute in the 20th century.

Main entrance, detail

Pathogen of sleeping sickness: reproduction of an original photograph (detail)

Aberrations and times of crisis

In addition to bacteria and viruses, a third type of germ becomes the focus of attention in the Robert Koch era: parasites. These include, for example, the pathogens for malaria or sleeping sickness – an infection occurring in Africa and transferred by the Tsetse fly which infects the brain and is fatal if not treated appropriately. In fact, a devastating sleeping sickness epidemic wreaks havoc in the Congo basin and on Lake Victoria in the time around 1900. The German colonies also appear to be threatened – Robert Koch himself, now one of the most influential microbiologists in the world, sets off for German East Africa with a team of scientists by appointment to the imperial government in 1906, in order to examine possible courses of treatment. It is to be the last of his numerous research expeditions.

Koch initially achieves successful results in the treatment of the sleeping sickness. He is one of the first to systematically apply a chemical arsenic compound called atoxyl. However, it then becomes apparent that the substance only offers temporary resistance to the parasites, with no healing effect. Koch doubles the dose – even though he is aware of the risks of the drug. Many patients begin to suffer from pain and colic, some even go blind.

Nevertheless, Koch remains convinced of the benefits of atoxyl in principle. After his return to Berlin in late 1907 he proposes to the Imperial Health Council that he should set up special isolation and treatment camps for the sleeping sickness sufferers, utilising the substance consistently to stem the epidemic – a strategy which is also propagated by British tropical medical doctors besides Koch. Koch's last scientific research trip also proves to be his most ignominious one.

Just two and a half years later, in May 1910, Robert Koch dies. His ashes are taken to a purpose-built mausoleum in his institute in Berlin-Wedding. Today, the mausoleum is part of the publicly accessible museum on the main site of the Robert Koch Institute.

The post-Koch period remains a vibrant one. Several smallpox epidemics sweep over Germany between 1916 and 1920. At the same time, it emerges that dangerous meningitis infections can occur following administration of the smallpox vaccine – which induces the researchers in Berlin to examine the effectiveness and safety of

The institute's history at a glance

1891 "The Royal Prussian Institute for Infectious Diseases" is opened, with Robert Koch as its first director. He heads the institute until 1904

1900 A new site in Berlin-Wedding is completed, and remains the headquarters of the Robert Koch Institute to this day

1912 30 years after the discovery of the tuberculosis bacillus by Robert Koch the institution is renamed the "Royal Prussian Institute for Infectious Diseases 'Robert Koch'"

1919 The institute continues its work as "Prussian Institute for Infectious Diseases 'Robert Koch'"

1935 The institute is subordinated to the Reich Health Office

1942 As "Robert Koch Institute" the institute becomes an independent Reich institute

1952 The institute becomes part of the newly-established Federal Health Office

1991 The Robert Koch Institute incorporates several former GDR offices

1994 The Federal Health Office is dissolved and the Robert Koch Institute continues its work as an independent higher federal authority

1998 Following an evaluation by the German Council of Science and Humanities, the institute is thoroughly reorganised and hones its thematic profile

2001 The Protection against Infection Act enters into effect and supports the competences of the institute

2008 The German parliament resolves expansion into an institute for public health in Germany with the RKI 2010 programme

The institute's historic library

their vaccines in greater depth. Other epidemics, for example the diphtheria wave of the early 1930s, force the researchers into a rapid response. They are successful in improving the available vaccination methods and protecting many children in diphtheria areas from the frequently fatal bacterial disease.

However, the radical political upheaval under National Socialism has a profound impact on the work of the institute. The first Jewish employees begin to be dismissed and forced to emigrate shortly after the National Socialists come to power in 1933. Subsequently, due to its central role in the German health system, the institute is substantially involved in the violent policies of the National Socialists – some individual employees are even directly involved in human experiments in concentration camps. Towards the end of World War II the institute can only function in a limited capacity due to bomb damage and a shortage of personnel and materials.

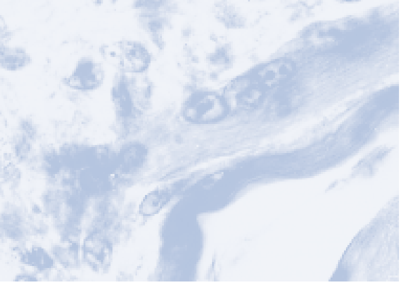
Development of the modern institute

'Keep out, risk of contamination!' is posted in Cyrillic letters on a sign in front of the institute, which the Red Army occupies and cordons off shortly before the end of World War II in April 1945. All cultures of disease-causing germs that had served for research and vaccine production are destroyed by order of the Soviet military doctors – not least because of fear of biological sabotage.

After the war, the remaining employees initially resume their work under makeshift conditions. In 1952 the institute becomes part of the newly-established Federal Health Office, but it is not until the 1960s that the scientists are able to work with improved equipment and modernised rooms again. 1974 sees work commence on the construction of a new laboratory building.

In the 1990s the Robert Koch Institute undergoes a change once again. Several former GDR departments are incorporated in the aftermath of German reunification. The research facility in Wernigerode in the Harz region, which had served the GDR as central facility for bacteria research, becomes an important branch of the Berlin institute. In 1994 the Federal Health Office is abolished – the Robert Koch Institute enters a new era as an independent authority to the government with extended tasks. After an evaluation by the the German Council of Science and Humanities in the late 1990s the institute is thoroughly reorganised and hones its thematic profile. In 2008 the German parliament resolves expansion into an institute for public health in Germany with the RKI 2010 programme.

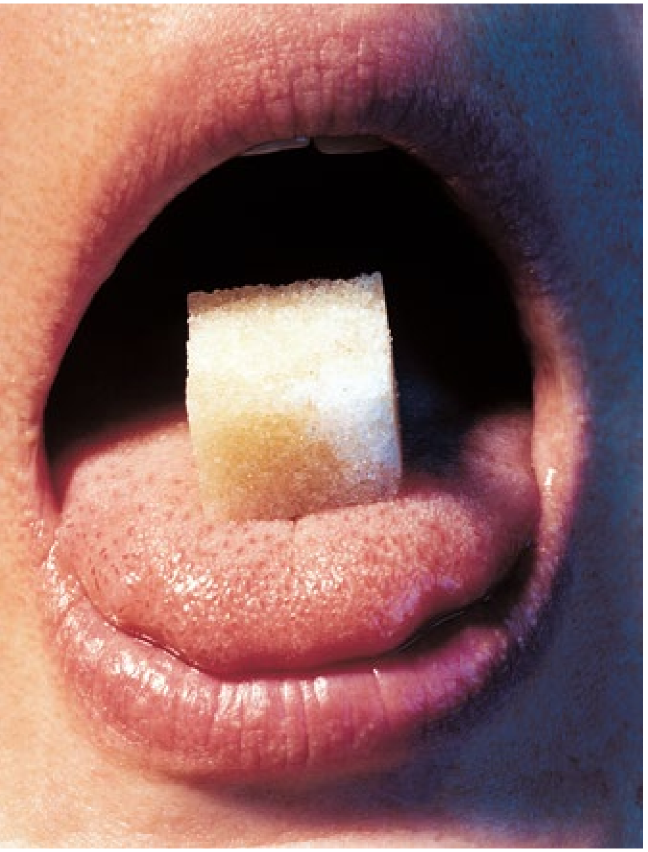
A new laboratory building at the Wernigerode site includes parts of an old brewery



AN EYE
ON VACCINATION

Immunisations can prevent infections and can help to completely eradicate some pathogens. However, not all pathogens are easy to come to grips with.

Effective protection



Sweet victory over polio: the oral vaccination

'Oral vaccination is sweet, polio is cruel,' used to be the motto of a nationwide TV spot. Now, this campaign against polio is no longer necessary in Germany. The elimination of the polio pathogen domestically as well as in vast parts of the world is one of the great victories in medical history.

Until the early 1960s, polio affected several thousand people each year in Germany, particularly small children. The virus disease often leads to persistent muscle paralysis – several hundred infected people died each year as a result. 'In severe cases the respiratory muscles can fail and death occurs,' says Sabine Diedrich, head of the National Reference Centre for Poliomyelitis and Enteroviruses at the RKI. Using virological and molecular biological analysis, Diedrich's team still examines all suspicious cases of sudden paralysis in children and viral meningitis to identify whether the polio pathogen could be involved. In November of 1998 the last polio case was reported in Europe, in 2002 the World Health Organisation (WHO) officially confirmed Europe to be polio-free – the third of six WHO regions after America (1994) and the Western Pacific Region (2000). In 2014 Southeast Asia became the fourth region to be proclaimed polio-free.

The disease was not successfully contained until the American doctor Albert Sabin developed a simple and ingenious method of vaccinating against polio in the middle of the 20th century. Sabin's method, where weakened polio viruses were applied with drops to a sugar cube and then swallowed, enabled nationwide immunisations to be carried out. As a consequence, the number of polio cases in Germany – as in other countries – was drastically reduced as of 1962, says Diedrich. In the 1980s there were only a few isolated polio cases registered in Germany. In 1998 the oral vaccination was replaced by an intramuscular vaccine injection in this country.

There is a reason why routine childhood vaccination against polio is still in place for children in Germany. Although the polio virus is only found in very few countries of South Asia today – it can still be imported again from those regions. In 2010 the disease occurred unexpectedly in Tajikistan, which belongs to the WHO region Europe. Originally imported from India, the virus strain was then transferred to Russia. It cannot be fully excluded that the pathogen would reach Germany in the course of such an epidemic.

An immunisation programme not only offers protection to individuals who received the vaccine: population-wide immunisation against polio also serves to eradicate the pathogen globally. This is possible because the polio virus only reproduces in humans. If a high percentage of the population is immune to polio, then the virus is unable to find sufficient unprotected hosts to infect – and thus becomes extinct. Under the leadership of the World Health Organisation great efforts are currently being taken to sustainably eliminate the virus in countries where polio is still active, by means of immunisation programmes.

This method has already proved successful in the context of another virus disease: smallpox. Smallpox was long considered to be one of the most infamous of plagues. In 1980 the WHO was able to declare the world smallpox-free, following a ten-year international vaccination campaign, and smallpox vaccination was discontinued. Global eradication might be also possible for measles which, like smallpox and polio, is likewise dependent on humans for spreading. The eradication of measles in the European region is also a major target of the health authorities in Germany and other European member states.

Of course, the eradication option is not possible for all types of pathogens. The tetanus bacterium, for example, has a natural habitat in the ground and is found in many places, including flower beds. Nonetheless, tetanus vaccination numbers are amongst the most effective immunisations ever and reliably protects the individual against tetanus if the vaccination is regularly renewed.

VACCINATION

Vaccination trains the body's own immune system: special immune cells develop an immunological memory for the structure of the vaccines – on contact with the pathogen, which resembles the vaccine, the body's immune system is activated faster and more efficiently and the disease is suppressed. Vaccines can be composed of purified pathogen particles, of whole-inactivated or attenuated pathogens or of pathogen particles that are produced using the methods of modern gene technology.

Tetanus bacteria can be found in flower beds – vaccination offers protection

Vaccinations against cancer

Vaccinations are applied not only against acute infectious diseases, but also against certain types of cancer. The hepatitis-B vaccination, for example, prevents a spread of the hepatitis-B virus to the liver, which could normally cause chronic inflammation and malignant liver tumours. In Taiwan, for example, a universal hepatitis-B vaccination programme for newborn babies launched in 1984 lead to a major decrease in cancer of the liver in the following decades.

An even better known example which has been applied in Germany since 2007 is the vaccination against the human papillomavirus HPV, the trigger for cervical cancer. The vaccination protects against an infection with the most common carcinogenic HPV types. There were initially intensive public discussions regarding HPV vaccination, mainly because of the comparatively high costs and the unknown long-term effects. 'We not only want to know the extent of a problem caused by a certain pathogen, but also what durable benefit the vaccination provides,' stresses Ole Wichmann, head of the immunisation unit of the RKI. Today scientists assume, based on clinical studies, that the majority of cancer cases caused by HPV can be prevented by sufficient immunisation. In order to review the effect of the HPV vaccination at the public level, Wichmann and colleagues are now conducting surveys throughout Germany to identify how many girls receive the vaccination, to what extent young women are affected by high-risk HPV infections and what influence the vaccination has.

Wichmann is convinced that such data are indispensable in order to be able to optimally evaluate and adapt the recommendations published by the RKI about which vaccination is appropriate at which age and for whom. Vaccination recommendations are developed in Germany by the Standing Committee on Vaccination, STIKO, an independent expert committee that Wichmann's team coordinates and supports, for example, via the systematic review of scientific literature and preparation of the evidence. This is supposed to ensure the highest possible transparency and acceptance for all recommendations. The STIKO recommendations are complemented by further detailed information for the medical public.

STIKO

The members of STIKO are honorary experts from different disciplines of science and research, from the ranks of the public health service and doctors with their own practice. The STIKO members are appointed by the Federal Ministry of Health in coordination with the state health ministries for a three-year period. The STIKO recommendations form the basis for the immunisation schedule recommendations of the federal states and the vaccination guidelines of the Federal Joint Committee.

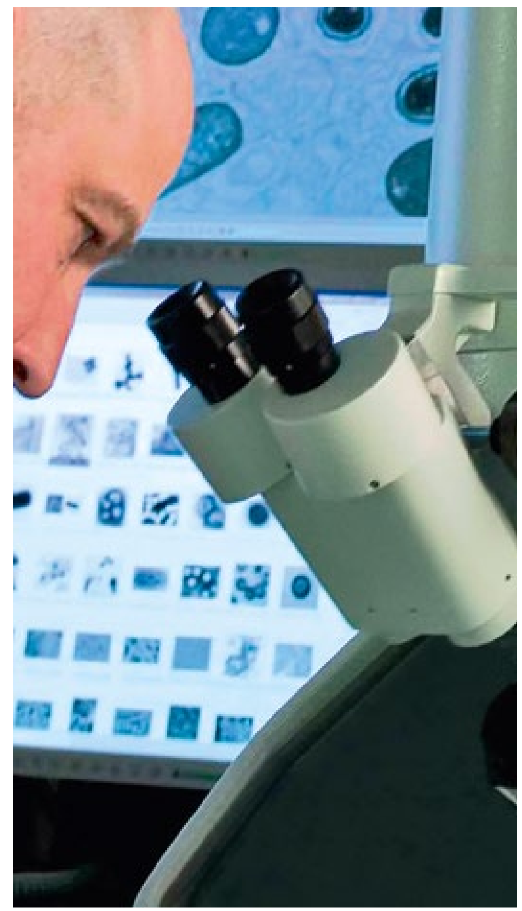
Beating measles

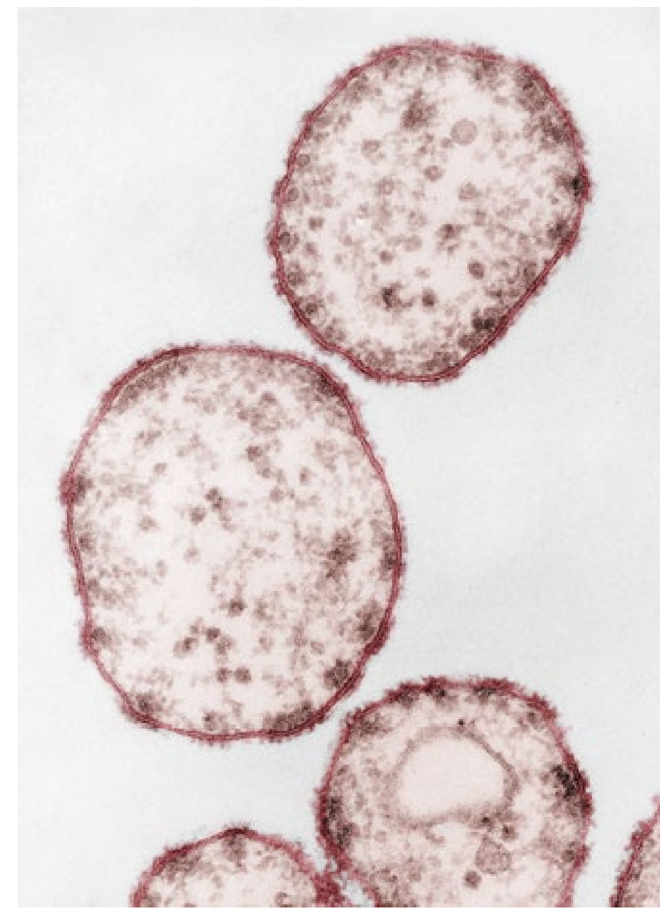
Improvement of measles immunisation coverage is a key objective of the RKI experts. The vaccination rates have significantly increased in recent years, especially among infants. However, although the WHO recommends a 95 percent vaccination rate for the second dose of the measles vaccine in order to eliminate the disease in Europe (a rate already attained in the Americas), in two year-olds the rate is still significantly lower. Even in children starting school the vaccination rate is below the desired level.

The measles virus also continues to be exported from Germany, as observed during a measles outbreak in Hamburg in 2009. 'From there the virus was exported all the way to Bulgaria,' reports Annette Mankertz of the National Reference Centre for Measles, Mumps and Rubella at the RKI. In Bulgaria, 24 deaths were subsequently recorded and the virus then spread to other European countries and even returned to Germany.

'Today we are able to precisely trace the chains of transmission using molecular-biological analysis of the virus strains,' states Mankertz. This permits the precise determination of the genetic virus type responsible for a measles case, using throat swabs or urine samples. The results obtained from different patients are compared and help to identify the transmission pathways of the virus.

A large outbreak of measles also occurred in Berlin from the autumn of 2014 until early 2015: over 1,300 people were infected and one child died. About 25 percent of those infected required hospitalisation. The affected were comprised predominantly of youths and young adults, populations that still have gaps in vaccination uptake. In 2010, the STIKO recommended that every adult born after 1970 should be vaccinated if they had so far received only one vaccination or if their vaccine status is unclear.





Measles viruses photographed with an electron microscope and coloured

Electron microscopes are indispensible in virus research. Instead of light beams they use electron beams, giving them a resolution up to 1,000 times higher than that of optical microscopes

Tracking influenza

In order to recognise and respond to disease outbreaks as quickly as possible, a comprehensive system of infection surveillance is essential. This has long been practiced for the influenza virus, with an estimated excess mortality of more than 10,000 people in Germany in some years. German sentinel doctors report cases of acute respiratory illness occurring throughout the year to the RKI. In addition, they also send in swab samples for pathogen identification and characterisation.

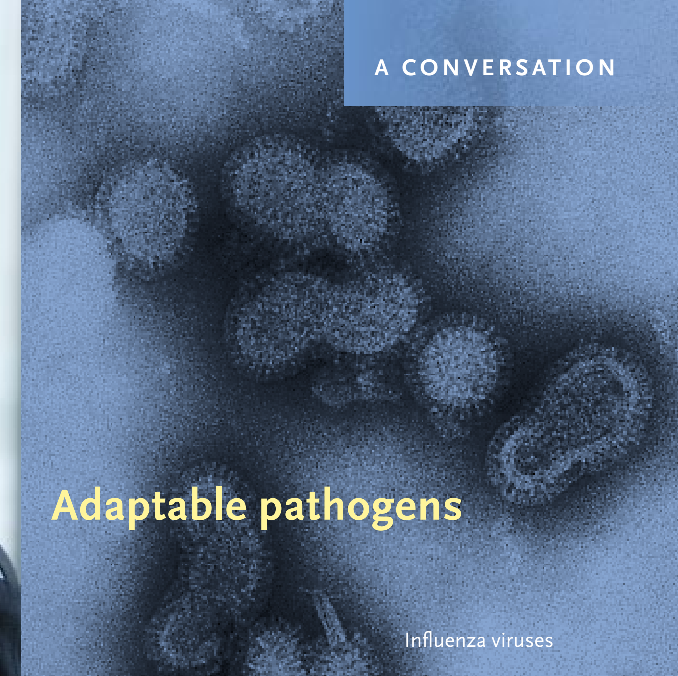
Brunhilde Schweiger, who leads the National Reference Centre for Influenza at the RKI, has established efficient molecular-genetic methods with her work group, by which a suspected case of influenza can be recorded within hours and the exact virus type identified. These methods also make it possible to determine whether the viruses are resistant to the drugs available and how the patterns of circulating virus variants are changing over time. Over one hundred reference laboratories worldwide are investigating the evolution of the highly variable influenza pathogen. These data can then be used to produce the best possible vaccines for the following influenza season.

This analysis also plays a prominent role in unexpected epidemics such as the so-called swine flu. In 2009 the swine flu virus migrated from pigs to humans, triggering a global wave of infection. 'In the shortest of times we adapted the molecular virus tests at the RKI in order to ensure reliable diagnosis,' states Thorsten Wolff, who heads the unit carrying out research into influenza and other respiratory illnesses. Amongst other issues, Wolff and his colleagues are researching which features distinguish the influenza viruses of animal origin from the human influenza pathogen and which genetic changes support the species migration from animals to humans.

At a glance

Vaccinations stimulate the immune system and can prevent numerous infectious diseases. They helped achieve global eradication of the smallpox virus and contain the pathogen of poliomyelitis. Researchers at the Robert Koch Institute (RKI) are monitoring the final eradication of poliomyelitis in Germany, which is targeted by the World Health Organisation. Moreover, they are also examining the long-term benefits of new vaccinations such as the one against the carcinogenic human papillomaviruses (HPV), and conduct systematic analyses of the available scientific data in order to optimally develop annually-issued vaccination recommendations. The RKI researches the spreading behaviour of measles, which can occur domestically, as vaccination cover is still fragmented. In addition, circulating influenza pathogens are analysed with regard to their molecular properties. The data are used for the development of optimally-adapted influenza vaccines.

Virus cultivation in an egg: influenza viruses are injected into an egg, where they reproduce. This is necessary for diagnostic purposes and for the production of vaccines



Adaptable pathogens

Influenza viruses

Brunhilde Schweiger
Influenza expert at the Robert Koch Institute

Dr. Schweiger, we need a new influenza vaccine every year, because new virus strains are constantly appearing. How is the pathogen able to repeatedly adapt itself?

◂ When the influenza virus reproduces there are errors in the way its genetic information is read. The results are minor mutations – experts speak of genetic drift – which lead to changes in the viral envelope (antigenic drift). As a consequence, the antibodies that the organism formed against related influenza viruses in previous years are no longer able to correctly recognise the pathogen. Antigenic drift is one of the most common reasons why new influenza viruses occur and take the immune system by surprise.

What is the other reason?

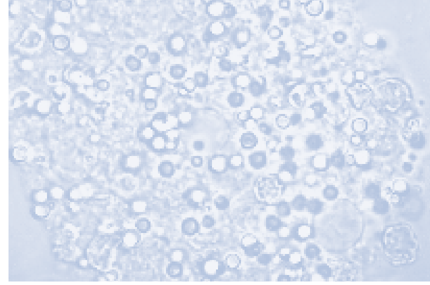
◂ Influenza viruses are also found in animals, for example in aquatic birds, chickens or pigs. Normally these viruses do not infect humans. However, the influenza viruses of animal origin are also subject to a constant evolution, just like the human influenza pathogen. If two viruses attack the same cell, they are also able to exchange their genes with each other. Once every few decades a completely genetically remixed pathogen is created, which spreads to human beings and results in a worldwide epidemic – a pandemic. The latest example is the so-called swine flu of 2009.

The swine flu was mild in comparison to former pandemics.

◂ Right, each pandemic has its own dynamic, which is also dependent on the molecular properties of the pathogens. The three pandemics of the 20th century also varied in their severity. The worst was the Spanish influenza of 1918/19, which cost the lives of over 25 million people worldwide.

Will we ever be able to get rid of influenza completely?

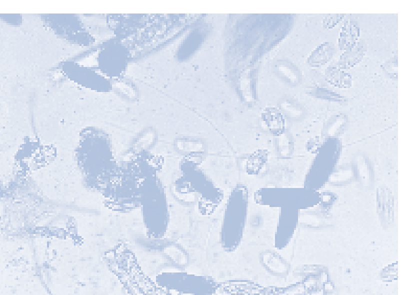
◂ No, because the pathogens occur in animals as well. What we need is a vaccine that is effective against many different variants of the influenza virus. Research is being conducted on such vaccines. Moreover, new drugs need to be developed. For years we have been observing that influenza viruses can become resistant to key drugs – new compounds will therefore be essential in future.



ON THE TRAIL

OF HOSPITAL PATHOGENS

Hospital-acquired infections are among the most common infections of all. One of the biggest threats comes from those bacteria that can no longer be effectively treated with antibiotics.



Traces of microorganisms on the skin: a hand print becomes visible on an incubated culture medium

Hands with living organisms

'If a poor servant comes to the hospital with a small wound which would have healed within 14 days under good hospital conditions, he will be on the threshold of death, lies maybe 100 to 150 days seriously ill suffering painfully and when he is finally released from the hospital, thin as a rake and still not able to work, he will be forced to pay from his savings.' This drastic illustration of the faults of hospital hygiene was given by a commentator in the medical journal "Ärztliches Intelligenzblatt" – back in 1875, a time when the most severe wound infections were commonplace in medicine.

The progress achieved since then is enormous: surgical instruments are rendered free of microorganisms by sterilisation procedures, contamination of wards is reduced by means of surface disinfection; and infections that do occur are treated with antibiotics.

Despite this, hospital-acquired infections are some of the most common problems in medicine. An estimated 400,000 to 600,000 people a year catch an infection during a stay in a German hospital. The most common hospital-acquired infections are surgical site infections, urinary tract infections or pneumonia. Hospital-acquired infections frequently increase the length of stay and thus increase the costs of treatment, sometimes they are even life-threatening. It has been estimated that 10,000 to 15,000 deaths are caused by hospital infections in Germany each year.

'At least some of these infections could be avoided by compliance to good hygiene,' notes Mardjan Arvand, head of the unit for Hospital Hygiene, Infection Prevention and Control at the Robert Koch Institute (RKI). The Robert Koch Institute regularly publishes updated guidelines, which are developed by a national advisory board of experts – the Commission for Hospital Hygiene and Infection Prevention at the Robert Koch Institute – and serve as authoritative basis and standard for the necessary prevention measures.

It is thus well proven that pathogens are often transferred from one patient to the next by the hands of health care workers – and the number of hospital infections could be significantly reduced simply by regular hand disinfection. However, surveys reveal that compliance with hand disinfection is still unsatisfactory in German hospitals.

Hygiene training for health care workers in particular needs to be further reinforced, assesses Mardjan Arvand. 'The responsible heads of departments and hospitals should not see hygiene as a necessary evil – but as one of the best and most inexpensive measures of preventing complications in treatment.'

This is precisely the direction followed by the "clean hands campaign", in which the RKI is also a partner. This German-wide programme supported by numerous clinics as well as nursing homes and home care services aims to improve hygiene behaviour, for example by training staff in the organisations concerned.

A further instrument for obtaining an improved grasp of the issue is a recording system especially tailored for hospital infections, known as KISS (Krankenhaus-Infektions-Surveillance-System). A large proportion of German clinics voluntarily record how many of their patients are infected with particular pathogens and provide the data for statistical analysis. In the particularly sensitive area of premature birth medicine all relevant intensive care units take part. KISS – which is operated by the German National Reference Centre for the Surveillance of Nosocomial Infections in co-operation with the RKI – is not only intended to document the extent of the infection situation. It also aims to help resolve specific hygiene issues and to spread awareness of the often hidden infection threat associated with medical procedures.

The number of bacteria colonies growing on test culture mediums is a measure for the effect of disinfectants

Resistant pathogens

In fact, there are several reasons as to why infections are commonplace in hospitals. Patients treated in hospitals are often seriously ill and therefore particularly likely to catch an infection. At the same time, invasive procedures such as respirator tubes and venous or bladder catheters, known to be classic entry portals to the human body for pathogens, and the use of medical equipment and materials is considerable, especially in intensive care units.

Particularly problematic is also the frequent use of antibiotics in hospitals. The intensive use of these drugs creates an environment in which antibiotic-resistant bacteria have a survival advantage over their fellow susceptible strains and are therefore able to spread effectively. Some of these microbes are resistant to multiple drugs – the chemical weapons of infection medicine are being blunted.

A notorious example is that of Staphylococcus aureus, a spherical bacterium that is well known to cause wound infections and blood poisoning. Multiple-resistant strains of this pathogen, MRSA for short, are resistant to important antibiotics and are therefore difficult to treat. The role of MRSA as a pathogen has particularly increased in Germany since the early 1990s. ‘Today, about one-sixth of all infections with Staphylococcus aureus are caused by MRSA strains. Happily though, the trend has been downwards in recent years,’ says Guido Werner who, together with his team at the RKI site in Wernigerode in the Harz region, is studying the genetic properties of resistant hospital pathogens, particularly MRSA.

‘We are now also increasingly concerned about other pathogens,’ says Martin Mielke, head of the Department of Infectious Diseases. Some bacteria produce highly potent enzymes – known as ESBL (Extended Spectrum Beta Lactamases) – using these to render the majority of common antibiotics inactive. Such bacteria include strains of Escherichia, Pseudomonas or Klebsiella, pathogens that, for example, can trigger pneumonia and have been increasingly found in hospitals in recent years. If that was not enough, bacteria have also developed defence mechanisms against compounds deployed as “reserve antibiotics“. ‘There are currently very few possible treatment options for an infection with such pathogens, which are usually so-called gram-negative bacteria residing in the intestines,’ states Mielke.

‘In order to launch effective countermeasures we need extensive data on where the resistant pathogens occur each time and how the spectrum is changing in the long run,’ says Tim Eckmanns of the RKI Department of Infectious Disease Epidemiology. Eckmanns and his colleagues have established a unique nation-wide surveillance system for that purpose – the so called Antimicrobial Resistance Surveillance (ARS). This is part of the German antimicrobial resistance strategy (DART), enacted by the government in 2008, which aims at the containment of the resistance problem.

‘As many German hospitals and medical practices as possible should be integrated into the ARS system in the long run,’ emphasises Eckmanns. The principle is that microbiological laboratories that conduct resistance testing for health care providers transmit the results online to the RKI. There the data are analysed with special statistical methods for dangerous trends in the resistance spectrum and reports of the results are immediately submitted back to the participating laboratories and health care professionals – in order to promptly contain the spread of the resistant microbes. Moreover, part of the resistance data is also available as an interactive database on the internet, as is a similar database with the results of antibiotic use surveys (AVS).

ANTIMICROBIAL RESISTANCE

Antimicrobial resistance is described as the ability of certain bacteria to resist treatment with antibiotics. Resistant pathogens can degrade the substances, for example with special enzymes. This ability is genetically determined. The resistance genes concerned are often found on mobile genotype elements (plasmids) that can be interchanged between different bacterial strains. If bacteria have multiple resistance genes at the same time, they can no longer be destroyed by conventional drugs. Such bacteria are then referred to as “multi-resistant”.

‘The spread of antimicrobial resistance is one of the biggest threats for success of modern medicine,’ says Martin Mielke, head of the Department of Infectious Diseases

A pathogen can be identified by its genetic pattern – and rendered visible in a special procedure

The tracking of microbes

Today, the ways resistant pathogens are spread can be reconstructed down to the tiniest detail. For example, it is known that the transfer of patients from one hospital to another can result in the distribution of problematic microbes. If e.g. staphylococci of the MRSA type appear in two different hospitals, genetic analysis can be done to identify whether they belong to the same bacterial strain – which then enables conclusions to be drawn regarding the route taken by the pathogen.

For such analyses the RKI experts in Wernigerode use so-called sequence-based typing. Certain parts of the genome of bacterial pathogens which exhibit sequence polymorphisms are analysed in detail – the result is a kind of genetic fingerprint of the respective pathogen strain. Microbiological samples are received from all over Germany where staphylococci bacteria are involved in infections. Moreover, the typing data are now exchanged in international research networks, enabling the spread of resistant strains to be traced even across borders.

Remarkably, bacteria are not only spread by patient transport or by the travel of infected people. The spread of pathogens within and between livestock farms is also a commonly observed phenomenon. For example, MRSA bacteria are often found in livestock, including pigs, fattening poultry and calves. These pathogens are spread within the framework of the international trade in piglets and can also be transmitted to humans.

‘Farmers and veterinarians (and, although relatively rare, members of their families) are the principal carriers of MRSA bacteria originating in animals,’ reports Guido Werner's colleague Christiane Cuny, who has demonstrated the connection through painstaking investigations of German pig farms. If the individuals carrying resistant pathogens are treated in a hospital, for example, they may introduce infections that are difficult to treat.

As is now known, resistant pathogens are often then transferred from the hospitals to the domestic environments of discharged patients or appear in nursing facilities when patients are moved there.

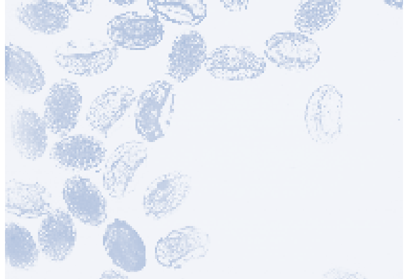
Molecular-epidemiological studies carried out in Wernigerode in collaboration with scientists in Denmark had already in the 90s demonstrated the transmission of antimicrobial resistance between livestock and humans. Either the resistant bacteria themselves or their genes were being transferred, showing that livestock represent an important reservoir of resistance genes.

It has long been apparent that these multiple transfer chains can only be broken with the cooperation of different stakeholders. For example, the analyses of MRSA bacteria from livestock farming have contributed to the recommendation that people who work in such facilities are systematically examined for pathogens prior to being treated in hospitals. ‘Moreover, hospitals, medical practices and nursing facilities have joined together to form regional prevention networks in many regions in Germany in order to exchange information on patients affected and to fight resistant pathogens by means of a coordinated strategy,’ explains Martin Mielke.

At a glance

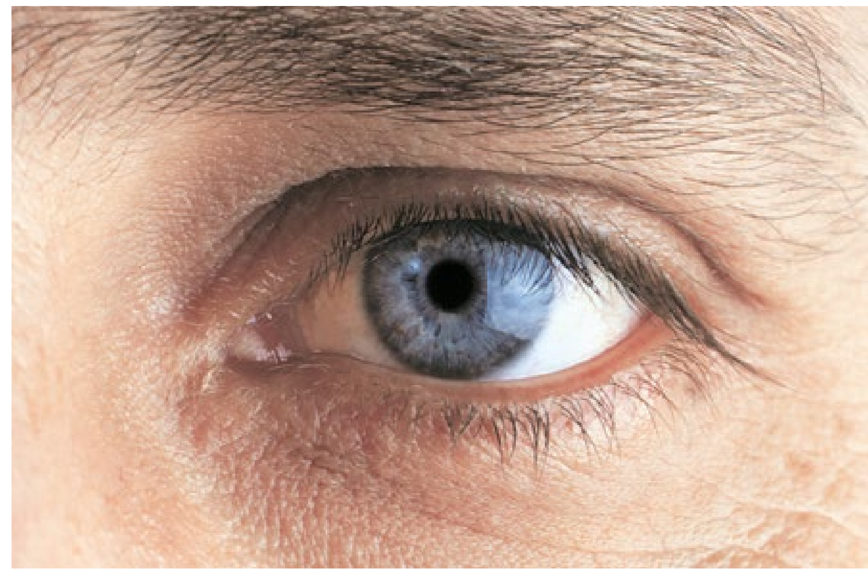
It has been estimated for Germany that each year 400,000 to 600,000 patients suffer a hospital-acquired infection and 10,000 to 15,000 of them die as a consequence. Typical problems for health care providers are surgical site infections, as well as urinary tract infections and pneumonia. Since the early 1990s an increasing role is being played by bacteria with a growing resistance to antibiotics which are therefore difficult to treat. Scientists at the Robert Koch Institute are researching the molecular-genetic properties of the resistant microorganisms. Moreover, they analyse the ways in which the resistant pathogens are spreading and provide data on antimicrobial resistance and antibiotic use online. Regularly updated guidelines are published on how the hospital infections can be avoided with hygiene measures.

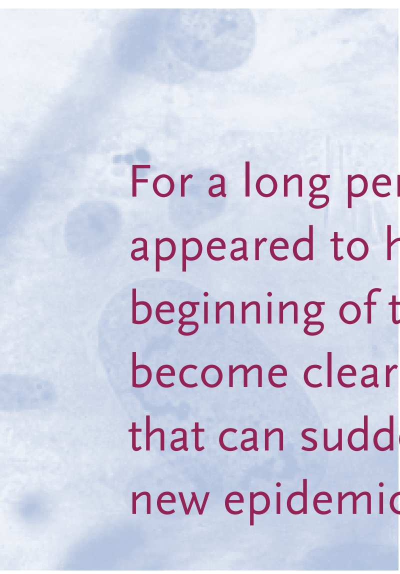
In the strain collection at the Wernigerode site, the bacterial strains handled are archived continuously and can be re-cultured at anytime



NEW PATHOGENS

IN FOCUS





For a long period of time infectious diseases appeared to have been defeated. Since the beginning of the AIDS epidemic, however, it has become clear: as long as there are pathogens that can suddenly spread from animals to humans, new epidemics will always appear.

Rise of a virus

There were times when infectious diseases seemed to have been defeated. When antibiotics such as penicillin enabled undreamed-of success in the treatment of infections in the decades after World War II and new vaccines helped contain familiar diseases, some doctors already believed that the end of epidemics was nigh.

That never happened and infectious diseases continue to play a major role. Pathogens are able to change their genetic properties and acquire resistance against antibiotics or antiviral drugs. Globalisation and climate change as well as the intrusion of man into increasingly remote areas can accelerate the appearance of new pathogens. A new, clinically relevant pathogen has appeared almost every year over the course of the past decades. The animal kingdom is an almost inexhaustible reservoir of unforeseen infectious diseases.

SARS coronaviruses, which cause serious respiratory infections, also have their origin in animals

One example is the so-called swine flu: in 2009 a new type of influenza virus appeared in Mexico – and subsequently spread worldwide. A comparison with gene banks soon revealed that similar H1N1 viruses had been circulating amongst pigs in the USA a few years previously. These precursor viruses contained genes of influenza viruses from pigs, birds and humans, but seldom affected humans. The pandemic H1N1 virus, first identified in 2009, also contained two genes of the influenza viruses familiar from pigs in Europe and Asia and originated from birds. Aquatic birds are considered to be the most common reservoir of influenza viruses.

The pathogen of the lung disease SARS, which was initially observed in China in late 2002 and occurred on several continents in the spring of 2003, also originated in the animal kingdom. The SARS virus most likely spread to humans via wild civet cats, which are traded as a delicacy in China. The virus causing MERS (which is related to the SARS pathogen) apparently comes from camels. MERS first appeared in 2012 and since then has remained a cause of disease and death, mainly on the Arabian Peninsula.

The great Ebola outbreak of 2014/2015 also had its origin in animals. An international research team, which included members of the RKI, was already in Guinea to search for the source a few days after the outbreak was first recognised. The RKI veterinarian Fabian Leendertz has for many years been investigating, in collaboration with the Max Planck Institute for Evolutionary Anthropology in Leipzig and with scientists from Ivory Coast and the Democratic Republic of Congo, whether primates in the African jungle regions carry pathogens that pose a threat to humans.

In contrast to earlier outbreaks of Ebola virus disease in Central Africa, the epidemic in West Africa was not associated with an increased mortality in great apes. In Guinea, Leendertz's team found that the first West African Ebola patient, a two-year-old boy, was apparently infected by a bat while playing in a hollow tree trunk. 'Although the tree had been burned shortly before our arrival, we were able to identify the DNA of a bat species that had previously been suggested to be a possible reservoir,' says Fabian Leendertz.

However, no other pathogen has such significant hazard potential via a species switch from animal to human as the human immunodeficiency virus HIV. It belongs to the family of retroviruses which integrate their genetic material into the genome of the host cell. The virus, which leads to the long-term development of the immune deficiency AIDS following an infection, most probably migrated from apes to humans for the first time in the early 20th century and began to spread around the globe in the late 1970s.

Today, over 36 million worldwide are infected with HIV. The highest disease burden is caused by the AIDS epidemic in sub-Saharan African countries. However, recently the largest increase in new HIV infections has been seen in Eastern Europe, particularly in Russia and Ukraine.

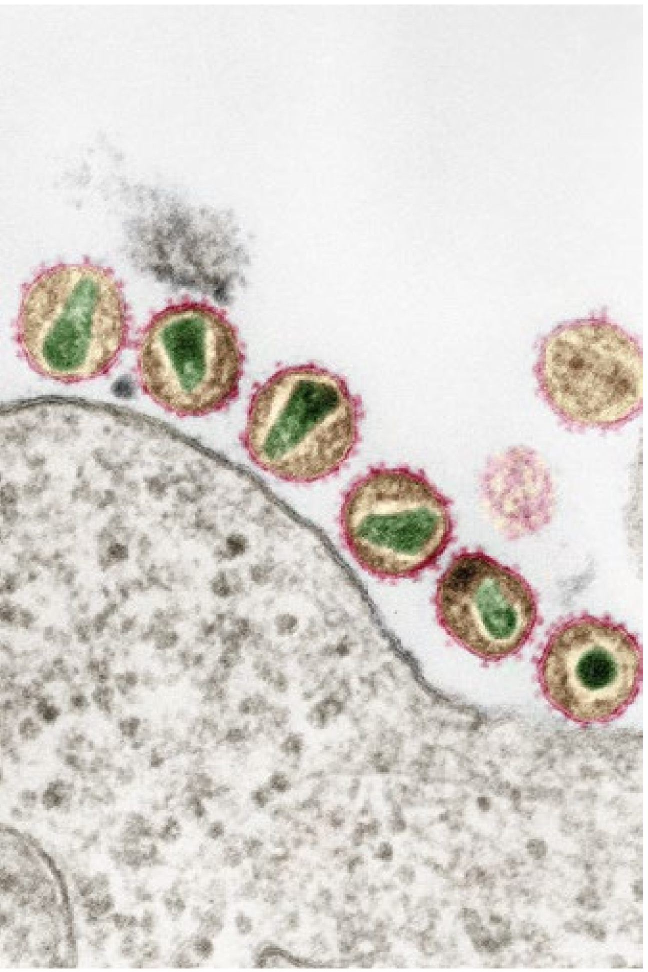
In Africa RKI scientists analyse whether new pathogens of animal origin could become dangerous to humans

HIV

The human immunodeficiency virus (HIV) is numbered amongst the most common causes of death by pathogens worldwide. Transmission typically occurs during sexual intercourse but also by virus transmission from an HIV-positive pregnant woman to her baby or if a drug user uses the needle from an infected person. Infection with HIV, which affects the T helper cells of the immune system in particular, often causes no symptoms at all during the initial years but without regular treatment it leads to the immune deficiency disease AIDS. So far there is no cure for an HIV infection.

In Germany there are more than 80,000 people living with an HIV infection, the majority of which are men who have sexual contact with other men. Each year about 3,500 people are newly infected and 500 to 600 die from AIDS. 'The still-high number of new HIV infections proves that prevention and research remain important,' emphasises Viviane Bremer of the Department of Infectious Disease Epidemiology at the RKI. Bremer's team systematically analyses information on the spread of HIV and AIDS in Germany and works on the continuous further development of surveillance tools. In this manner it has proved possible in recent years to define more precisely the proportion of fresh infections in newly-diagnosed cases. This information is important in order to better estimate the dynamics of the spread of HIV according to the new diagnoses submitted to the RKI.

In the so-called seroconverter study which started in 1997, data on the course of disease in HIV-infected people with known infection dates are collected and analysed. In the case of a fresh HIV infection the presence of antibodies can first be detected in the blood about two to three weeks after the infection (seroconversion). About 3 000 patients from around 60 clinics and specialist practices all over Germany are now participating in the study, which is designed as a longitudinal study over the course of many years. Amongst other aspects, the aim is to predict how long people infected with HIV can now live without major health limitations. In addition, molecular genetic analysis also investigates the influence of certain virus variants and drug resistances over the course of the disease and how the prevalence of resistant pathogens is changing.



HIV: mature virus particles (red-edged structures with green core) penetrate cells of the immune system

'The resistance situation for HIV is currently stable in Germany, but this has to be monitored constantly,' highlights Norbert Bannert, head of the unit HIV and Other Retroviruses at the RKI. One core task is to constantly develop and refine the molecular methods for analysing resistance. 'We also need to be able to determine resistance to newly-introduced HIV drugs quickly and reliably,' says Bannert. Generally speaking, the virologist confirms that resistant HIV variants need to be identified before commencing therapy to allow drugs to be selected in a more targeted manner.

In addition to this, the RKI researchers are also eager to achieve one of the most ambitious targets of all in AIDS research: eradication of the virus from patients undergoing therapy. 'We want to pursue basic approaches for this and investigate the cellular reservoir in which the virus can remain hidden for many years. The aim is to identify and eliminate the cells containing the dormant viruses so that upon stopping antiretroviral therapy a reactivation of the virus is no longer possible. A cure is still a long way off, however,' says Bannert.

Viral pathogens in the genome

One of the most remarkable properties of the retroviruses is that they integrate into the genome of the infected cells and in this manner can survive in the organism. In the past, a number of these pathogens have been monitored closely by health professionals. A retrovirus known to experts as HTLV-1 (Human T-lymphotropic virus 1) leads to a special type of blood cancer in one to three percent of infected people, so-called T-cell leukaemia. An estimated 15 to 20 million people worldwide are infected with this virus that may have migrated from apes to humans about 20,000 years ago.

Retroviral pathogens were also the focus of particular attention in another case: a few years ago US scientists reported that a new type of retrovirus called XMRV could play a role in the development of prostate cancer as well as in chronic fatigue syndrome. It was conspicuous that the XMRV was similar to a retrovirus that can cause leukaemia in mice.

'Within the shortest of times we developed a reliable molecular-genetic test for XMRV,' reports Norbert Bannert. With the new virus test the RKI experts and researchers at the Charité – Universitätsmedizin Berlin were able to check the American results in tissue samples of approximately 600 German prostate cancer patients. No single case of XMRV was found; the result was confirmed by studies conducted by other researchers. In addition, the RKI team was also able to rebut the causal connection between the retrovirus and chronic fatigue syndrome within the scope of national and international investigations.

However, retroviruses are by no means only of importance to scientific research as infectious pathogens. Instead, they are also found in the genomes of healthy people, as so-called endogenous retroviruses. Retroviruses were integrated into the genomes of our ancestors millions of years ago and are at least partially beneficial to humans. Today we know that retroviral gene sequences are important for the development of

Genetic analyses in the virus laboratory

RETROVIRUSES

Retroviruses incorporate their genetic information into the body's own genome in the nucleus of infected cells. The viruses to which HIV also belongs can infect humans as pathogens from external sources – they are known as exogenous retroviruses. On the other hand there are so-called endogenous retroviruses already present in the chromosomes of all people that have been integrated in the human genome during evolution and are passed on from generation to generation. Such endogenous retroviruses are also found in animals.

Viruses can only be propagated in cell cultures

the placenta in pregnancy. On the other hand, endogenous retroviruses could also favour the development of cancer. Under certain conditions some of the normally dormant retroviruses in the genome are reactivated and their regulatory regions then intervene in the regulation of adjacent host genes. An important role in the initiation of cancer can also be ascribed to individual viral proteins that are formed in human cells after the reactivation of the viruses. One of these virus proteins seems to contribute to the mutation of cells in two ways. It appears to increase the activity of the human protein which recognises a certain hormone, as well as another protein that regulates the cell division and is often involved in the initiation of tumours. The RKI researchers now want to find out how this occurs at the molecular level.

Endogenous retroviruses are also found naturally in the genomes of most vertebrates including pigs. 'This is important because, for example, insulin producing cells from the pancreas of pigs are already being used for the treatment of individual diabetics,' explains RKI expert Joachim Denner. Such a transplant of tissue from animal origin, known as xenotransplantation, could therefore risk giving rise to new infections.

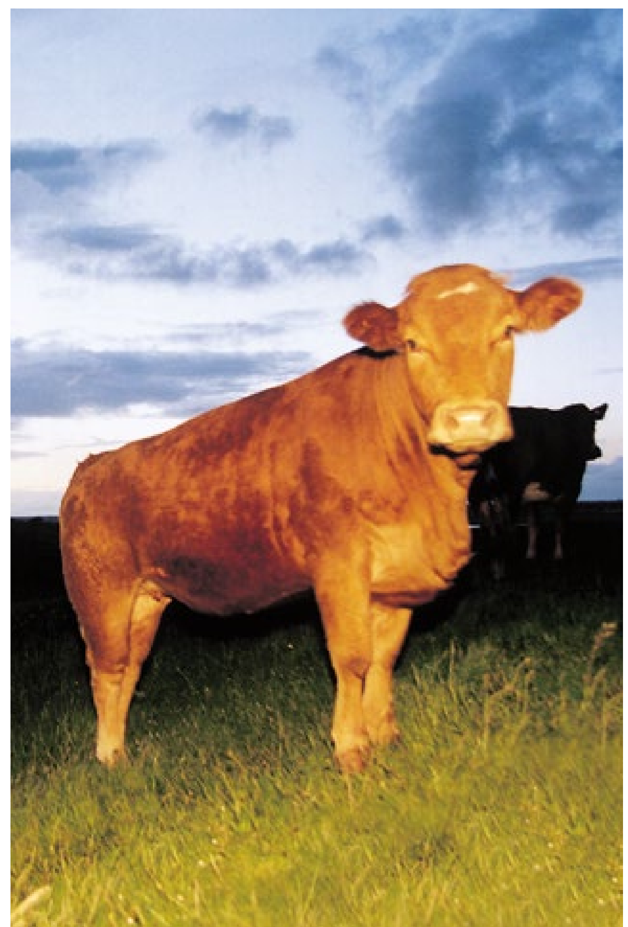
'So far there is no evidence that patients who have been treated with cells and tissue from pigs as part of these studies worldwide have become infected,' says Denner, whose working group was involved in the development of highly-sensitive detection assays for swine retroviruses and investigated a collection of patient samples. In order to further minimise the risk, the scientists are investigating, for example, whether a retrovirus infection could be avoided during xenotransplantation by using genetically modified pigs in which the endogenous viruses are blocked or even inactivated.

BSE and its consequences

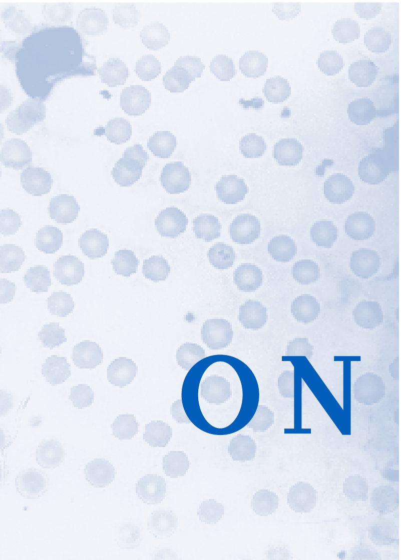
Besides retroviruses, the RKI experts are also tracking a completely different new type of pathogen that is no less astounding: prions. These are misfolded pathogenic proteins that trigger certain brain diseases. The most famous example is bovine spongiform encephalitis or BSE, also known as mad cow disease. The epidemic struck more than 180,000 cows in Great Britain, mostly in the 1980s and 1990s, and an even greater number without symptoms were slaughtered as a precaution. In Germany over 400 cases were identified, mainly in the first half of the last decade. Human infection via the food chain can lead to fatal brain degeneration, the so-called variant Creutzfeldt Jacob Disease (vCJD).

At a glance

Numerous pathogens originate in animals and have given rise to new epidemics after transfer to humans. The most famous example is HIV, the cause of the global AIDS epidemic. Scientists of the Robert Koch Institute systematically analyse data on HIV infections in Germany and conduct specific studies on various aspects of HIV. Moreover, different teams adapt basic methods for the research and diagnosis of other new types of pathogens. For example, they analyse whether the transplantation of animal tissue (xenotransplantation) during the course of medical treatment can possibly give rise to new forms of infection and which role is played by those viruses that have been integrated into the human genome during evolution. Furthermore, the scientists of the institute also analyse how potential long-term risks from the spreading of the BSE pathogen in the 1990s can be reliably detected and minimised.



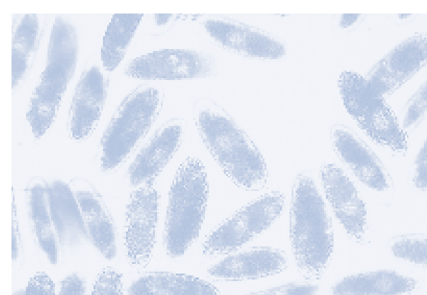
More than 200 people have died of vCJD since the beginning of the BSE affair; most of them in Great Britain. 'In Germany there have been no known cases of vCJD identified so far,' reports Michael Beekes, who researches the prions with his team at the RKI. They analyse the precise ways in which the prions spread through the organism – and how their deadly impact could be possibly better dealt with by means of early diagnosis and therapy. Moreover, the RKI experts are involved in the development of methods intended to exclude as far as possible the transfer of prions from human to human, for example, from contaminated blood products or surgical instruments. The procedures that damage the nervous system in the course of a prion infection are probably the same as those responsible for other neurodegenerative diseases. Knowledge of the disease mechanisms of BSE could therefore also lead to new insights regarding diseases such as Alzheimer's and Parkinson's.



ON THE ALERT

FOR EPIDEMICS

What needs to be done in the case of an outbreak? Infection alarm plans ensure better control of imported epidemics or those that arise locally. Moreover, a “rapid-reaction force” is on hand to help resolve outbreaks of disease on-site.



EHEC bacteria can cause serious intestinal infections

Managing epidemics

When so-called swine flu began to spread around the world in April 2009, originating from Mexico and the USA, this was the acid test for global epidemic prevention. On 24 April, a Friday, cases of disease caused by a new influenza virus first became known – it contained genes of pathogens that were familiar from pigs in Europe and Asia. The next day World Health Organisation declared a Public Health Emergency of International Concern (PHEIC).

A situation room was also immediately established at the Robert Koch Institute (RKI). In a promptly arranged telephone conference the RKI team coordinated their actions with the federal and state authorities with regard to possible risks, shortly thereafter the public was informed in an initial press release. The first confirmed cases of the disease were already received by April 29th: the swine flu had reached Germany.

'In such situations it is essential to evaluate how the public health can be safeguarded in the best possible way – and as quickly as possible,' stresses Osama Hamouda, who leads the Department of Infectious Disease Epidemiology at the RKI. In this it is of no consequence whether it is an influenza epidemic, the outbreak of the lung disease SARS in 2002/03 or the wave of sickness caused by the so-called EHEC bacteria in Germany in 2011. In each of these cases Hamouda's team analyses the actual risk of infection and whether international alarms need to be raised – as well as which preventive measures are necessary in Germany.

For the swine flu epidemic of 2009, for example, the RKI initially recommended that the individuals affected should be quickly diagnosed and contact persons identified in order to prevent further human to human transmission and to delay spreading to the general public. The aim of this was to gain time – which was largely successful – in order to prepare vaccinations against the new pathogen across Germany. However, based on the RKI assessment the decision was made not to undertake a proactive closure of schools as an attempt to delay the spread of the disease.

'It is our task to reliably advise the federal and state authorities,' emphasises Hamouda. The execution of the infection prevention measures subsequently lies in the scope of competence of the federal state authorities and the local health authorities.

With regard to the often drastic measures that can sometimes be necessary in acute infection hazard situations, there is obviously a requirement for a well-drilled and coordinated procedure which nevertheless provides sufficient flexibility for tailored measures to be taken.

In the event of an influenza pandemic – a worldwide wave of disease caused by a new type of influenza virus – the cascade of possible infection prevention measures is regulated in the German Influenza Pandemic Preparedness Plan. In 2005 the RKI published the first framework document, signed by government and state authorities, which marks a unified strategy of all stakeholders and authorities and serves as a basis for corresponding emergency plans of states and communities. In 2007 the RKI published an updated issue of the pandemic preparedness plan, which has now been further developed to incorporate the result of the evaluation and experience gained from the swine flu pandemic.

A well-planned approach with the prompt recognition of the first cases and speedy implementation of multiple measures adapted to the epidemiological situation are prerequisites to mitigate the effects of an influenza epidemic, says Walter Haas, who, together with his team at the Department of Infectious Disease Epidemiology and a group of external experts, is responsible for the scientific part of the pandemic preparedness plan. Besides the swine flu of 2009, three main influenza pandemics are known from the 20th century, with the most feared being the so-called Spanish influenza of 1918/19, during which it is estimated at least 20 million people worldwide lost their lives. Almost all experts share the view that further worldwide influenza epidemics will occur in the future – although it is obviously not possible to predict when.

Travelling pathogens

Nonetheless, the preparations for an influenza pandemic are merely a particularly prominent example for a general outbreak management strategy of the RKI. For example, the institute has developed an extensive infection alarm plan which – irrespective of the type of pathogen – specifies principal procedures to be followed in response to an outbreak.

International travel in particular means that rare pathogens can be imported from tropical regions from time to time, explains Klaus Stark, expert for tropical infections at the RKI. In the case of particularly dangerous pathogens such as Ebola or Lassa viruses the treatment is handled in special treatment centres in Berlin, Dusseldorf, Frankfurt, Hamburg, Leipzig, Munich or Stuttgart. The wards are equipped with features such as their own entrances and airlocks, with air-conditioning systems equipped with virus-proof filters. Since 2003 there exists a network

Travellers can spread pathogens around the world

The Asian tiger mosquito could also spread pathogens in this country in the future

comprising the centres of excellence and treatment centres of the different states for managing and caring for people with highly contagious and life-threatening diseases. Together with other facilities, a permanent task force (STAKOB) was established at the RKI in 2014.

The precise confirmation of a diagnosis of, for example, an Ebola virus infection should be conducted in laboratories of the highest safety level, that until recently were only available in Germany in Hamburg and Marburg. However, there is now also a high-security laboratory at the Robert Koch Institute, in the direct vicinity of the special infectiology department of the Charité – Universitätsmedizin Berlin.

The comprehensive management of imported infections also includes the investigation and screening of possible contact persons, such as the passenger seated next to you on an aircraft. If they also display signs of the disease they are treated – in isolation if necessary. The close cooperation of the RKI with the World Health Organisation (WHO) as well as the European Centre for Disease Prevention and Control (ECDC) in Stockholm also makes it possible to trace the paths of imported pathogens internationally.

In fact, cross-border information networks play a decisive role in epidemic defence. The WHO informs all national infection prevention centres of new disease outbreaks worldwide by means of an e-mail early warning system. Working around the clock, RKI experts evaluate such news and check whether infectious disease outbreaks in Germany call for an international warning to be given, as well as which measures need to be taken in Germany. For example, when an outbreak of SARS in East Asia resulted in the first suspected case in Germany the RKI took immediate action and advised the relevant health authorities in Frankfurt as well as the Hessian ministry of health on the necessary measures. Moreover, all of the approximately 400 German health authorities were supplied with prompt information in order to register further possible suspected cases according to standardised criteria.

The RKI scientists are also focusing on a further risk: the fact that tropical pathogens could settle in Germany under changing climate conditions. A possible example is the pathogen of Chikungunya fever, says Klaus Stark. The virus is transmitted by the Asian tiger mosquito, which is now also found in many southern European countries. In fact, there was a Chikungunya epidemic in Italy in 2007 after the virus had probably been imported by a traveller returning from India. A moderate climate warming is probably sufficient to allow the mosquito to settle in the warmer regions on the upper Rhine Valley, where its eggs were already detected some years ago and in 2014 and 2015 the first small breeding colonies of tiger mosquitos were found. If these colonies were to become established, imported viruses such as the Chikungunya or also the Dengue virus could spread in this country.

Rapid reaction force

Nevertheless, tropical infections should remain the exception in this country, at least in the near future. In contrast, disease outbreaks due to native pathogens will always require the efforts of the RKI experts. For example, if numerous people are suddenly struck down by a wave of infection in a certain region, a team of specially-trained scientists is ready to support the local health authorities at the request of the federal states with epidemiological investigations on the scene and to provide a quick resolution to a case of infection.

Equipment for a rapid response: laptops, mobile phones and office supplies stand ready to go in bags and suitcases

Epidemiological Situation Centre at the RKI. Left, Osamah Hamouda, head of the Department of Infectious Disease Epidemiology

The specialists at the RKI are called upon in cases like these eight to ten times per year. These could be waves of sickness in a specific region, but also outbreaks in individual facilities such as nursing homes or hospitals. Increasingly, foreign deployment is also requested, for example during the large Ebola outbreak in West Africa in 2014/2015, where RKI epidemiologists provided support to the WHO. Eventually, in order to dampen the spread of this virus, every new case must be traced and isolated, and every contact identified, placed under quarantine and observed. A large number of RKI virologists were also present to help, on the one side, with the analysis of blood samples from suspected Ebola cases and, on the other, with the establishment of a diagnostic laboratory in Ivory Coast.

A particularly serious case of infection in this country was the outbreak caused by the EHEC bacteria type O104:H4 in the spring of 2011. This intestinal germ, which may enter the organism via contaminated foods, produces a toxin that leads to kidney failure in many patients. The morning after the first call was received from the health authorities in Hamburg, epidemiologists of the RKI were already on the scene to examine and question the individuals affected. It soon was clear that this was an exceptionally large-scale outbreak caused by EHEC germs. The third day after the first reported suspected case a team of 15 RKI experts was therefore sent to Hamburg, where they interviewed over 120 patients and healthy controls the very same day, whilst statisticians at the institute immediately evaluated the data.

The analysis supported the suspicion that uncooked vegetables or salad could be the cause of the severe infection. However, it was not initially possible to identify an individual kind of salad or vegetable. The RKI experts therefore conducted further methodically elaborate epidemiological studies, with the responsible foodstuff agencies also searching for the pathogen in foods and tracing distribution channels of suspicious products. In this manner it was finally possible to identify the consumption of raw fenugreek sprouts as the definite cause of the disease.

As a rule, the RKI scientists employ epidemiological methods on their resolving missions – using, for example, standardised interviews to determine whether the patients had eaten the same food or had been to the same event. If a common pattern of behaviour is determined, it is also possible to conclude the means of spread, the source and the type of the pathogen. Comparing the behaviour patterns of sick and healthy people often reveals important clues to the cause of the disease. Moreover, scientists use diagnostic laboratory methods for their analyses and cooperate closely with local health authorities and doctors.

Trainees, who study epidemiologic methods in infectious diseases in the context of a two year Master's study programme at the RKI with the goal of applying these methods in public health service after their studies, are nearly always involved in the investigation of outbreaks. Local health authorities in particular play a key role in combating outbreaks, even though they have been struggling for years with significant cuts in funding. However, no laboratory network or surveillance system, as good as they may be, is sufficient for the investigation of suspect cases on-site or implementing quarantine measures. 'Qualified personnel and state-of-the-art equipment is needed for that – in every municipality in Germany,' states Osama Hamouda.

The RKI experts do not limit themselves to merely responding to cases of sudden infection outbreaks. 'Increasingly, we are also conducting long-term, systematically-planned studies into the patterns of infectious diseases in this country,' explains Osama Hamouda. One example is the so-called DRUCK study ("Drogen und chronische Infektionskrankheiten": "Drugs and chronic infectious diseases"). In this project the RKI scientists, in cooperation with addiction facilities, study the spread within intravenous drug users of chronic infections with hepatitis B, hepatitis C and HIV. In questionnaire-supported interviews, the scientists in eight cities gather information concerning risks of infection, behavioural patterns and the understanding of transmission risks and methods of protection against these infections. In parallel, they test blood samples for markers of these diseases, in order to obtain data about the spread of hepatitis B, C and HIV. This knowledge can then help with the further development of recommendations for reducing the dangers of infection in this group.

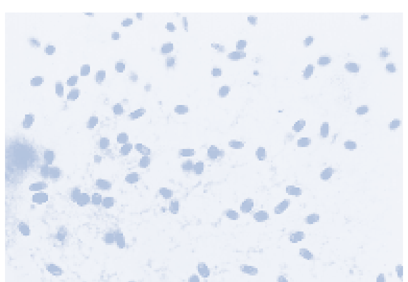
At a glance

For different epidemic events such as influenza pandemics or the import of dangerous tropical viruses, the Robert Koch Institute (RKI), in coordination with federal and state agencies, has developed extensive infection response plans to reduce risks. They provide graded and situationally-adapted preventive measures including, for example, mass vaccinations or quarantine. The RKI mediates the flow of information between the state and municipal health authorities on the one hand and international players such as the World Health Organisation and the European Centre for Disease Prevention and Control on the other. The scientists are researching the causes and risk factors of infectious diseases. Moreover, specially trained teams are ready to help resolve epidemic outbreaks in this country and abroad by means of specific investigation work on-site.

WATCHING

HEALTH TRENDS

Continuous analysis of the health situation in Germany reveals how the spectrum of diseases changes and where there is the greatest need for prevention and health promotion.



Reporting on the state of health

Are Germans getting too fat? Do children get enough movement? Are psychological disorders on the increase?

'We could continue adding to the list of questions that interest us for ever,' says Bärbel-Maria Kurth. She heads the Department of Epidemiology and Health Monitoring at the Robert Koch Institute (RKI) – the group of scientists who want to discover who gets which diseases and why the spectrum of diseases changes over time.

Federal Health Reporting, which is conducted by Kurth's department, has long been one of the RKI's signature activities. These expert reports are based on data collected from the Federal Statistical Office, health insurance providers, doctors and special registries as well as the results of the most recent research and surveys carried out by the scientists at the institute themselves.

'Not all that long ago, systematic assessment of the health situation here in Germany was in its infancy,' Kurth points out. 'In this field, we are now one of the best in Europe.'

The objective is quite straightforward: scientists want to deliver up-to-date, meaningful data on health risks in the population and thus help to predict the need for medical care as well as to set the health-policy course for appropriate prevention measures. In this way, the RKI creates one of the pre-requisites for improving public health. The analyses it produces serve as a reference not only for doctors and scientists but also for the media and the general public.

HEALTH REPORTING

Health reporting is designed to help piece together a picture of people's state of health in Germany, identify risks and analyse the costs and benefits of the health service. It comprises a continuous series of experts' reports on the most diverse problems – such as diabetes and depression in adults or the correlation between poverty and health in children. The Robert Koch Institute is responsible for health reporting at federal level and works together closely with the Federal Statistical Office. It is also involved in developing a European reporting system and collaborates with those federal states that conduct health reporting in their own areas themselves.

Bärbel-Maria Kurth
Head of the Department of Epidemiology and Health Monitoring

Healthy Germans?

Ms Kurth, How healthy are people in Germany?

◂ In comparison with other European countries, Germany is average. Happily, our life expectancy has been growing for decades. Certain risk factors do influence the outcomes, though, especially those related to behaviour. Germans drink too much alcohol, for example, and don't eat enough fruit and vegetables. Obesity rates are increasing and, unfortunately, diabetes is becoming ever more common – here there is huge potential for prevention. But there are positive behavioural trends, too. Both men and women do more sport and take more exercise. There is still a lot that could be improved, but on the whole our health is not bad.

Is this also true of psychological well-being?

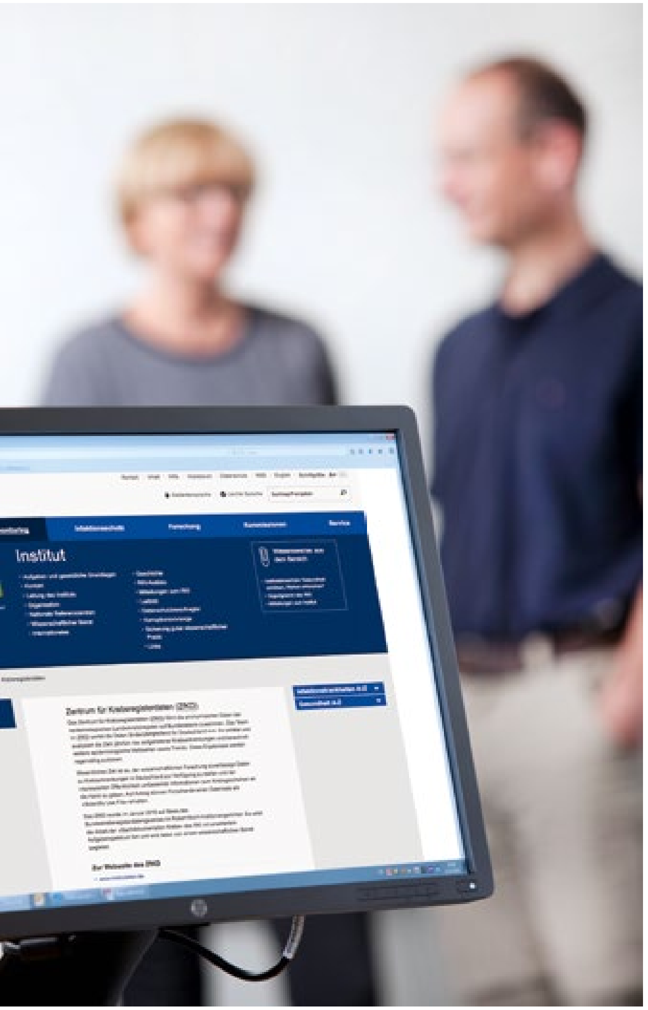
◂ Basically, yes. In modern societies, psychological problems are frequently the cause of work absences. This has to do with changing pressures in the workplace. Despite this, the percentage of people in Germany who generally feel well is growing – and there are ever fewer who feel really bad. Even at an advanced age there are many who are still active and experience satisfaction and joy in life.

Not all groups in the population are equally healthy – where do the differences stem from?

◂ That is precisely what we want to know more about. On the one hand, apart from genetic factors, each person's own lifestyle plays a major role. On the other, health is always dependent on social factors as well. Children from poorer families with an underprivileged educational background eat less healthily and are more prone to obesity. In many respects they are a vulnerable group within the population with high health risks. The same can be said of single parents and the unemployed who have to cope with greater pressure.

Is health a product of social conditions?

◂ To some extent, it is. The chance of getting a good education or job has an impact on the health situation – and this, in its turn, ricochets back on opportunities for participating equally in society. The experience of migration and flight can leave a permanent mark on a person's health as well. How can people from different backgrounds achieve a high level of health and continue to stay healthy as they get older? To deliver sound data and discover points of departure for prevention and health promotion – that is our mission.



Trends in cancer

A well-known example is analysing the frequency of cancer. 'It is our task to analyse the distribution of specific cancers throughout Germany,' says Klaus Kraywinkel, the head of the German Centre for Cancer Registry Data at the RKI. Eleven state cancer registries – one covering the east German federal states, including Berlin, and one in each of the ten west German states – record how often specific cancers occur across the country. The RKI bundles this data, checks its plausibility and completeness and employs statistical methods to produce an overall picture of the situation in Germany.

Nationwide, nearly 500,000 men and women are diagnosed with malignant tumours every year, according to Kraywinkel. With an ageing population, these figures are bound to keep growing, especially as most cancers tend to develop in later life. At the same time, the survival rates for many cancers are also increasing thanks to advances in medical care.

'The data are of major interest to doctors and health policy makers,' Kraywinkel emphasises. Only on the basis of reliable nationwide figures is it possible to make valid international comparisons or judge the general effectiveness of preventive health programmes. Longitudinal analyses, for example, show that bowel cancer has been occurring less frequently in Germany for a number of years, 'which is probably due at least in part to the introduction of screening colonoscopy in 2003,' Kraywinkel affirms. By contrast, vulva cancer, which is still rare, was diagnosed in an increasing number of women during the last ten years. Although the relevant epidemiological data cannot produce a definitive explanation of why this is the case, they may help to draw attention to the urgent need for research and provide working hypotheses, says Kraywinkel.

Health monitoring tools

Whilst the cancer registries generate fairly precise information about the frequency of cancer in Germany, a great deal less tends to be known about the trends in other diseases, let alone about the disease burden in individual groups within the population. Moreover, standard official statistics do not reveal how frequently certain risk factors occur or how the socio-economic situation relates to the quality and style of life. But this is precisely where one of the main causes for the development of many chronic diseases – and a key to prevention – might be found.

Scientists at the RKI are keen to close this gap in our knowledge using long-term health monitoring. Specially designed, representative repeat surveys covering the entire country are the core component of this internationally exemplary epidemiological research programme.

In the context of the German Health Interview and Examination Survey for Adults (DEGS), for example, more than 8,000 individuals above the age of 18 were surveyed between 2008 and 2011 on diseases and risk factors as well as behaviour and living conditions. At some 180 study centres, the survey teams measured the majority of the subjects' blood pressure, height and weight, took blood and urine samples, used ergometers to determine cardiovascular fitness and, in the case of older participants, tested their physical and cognitive functioning. Most of those surveyed were also interviewed on their psychological health.

As it was possible to compare many of the findings with the results of the similarly-designed 1998 Federal Health Survey 'we can already undertake trend analyses for a whole decade,' Bärbel-Maria Kurth emphasises. Regular repeat surveys are also part of future planning. DEGS is complemented by a shorter-cycle update (GEDA) surveying 20,000 adults, which provides for flexible adjustment to immediate urgent issues and, thanks to the large number of participants, also allows comparisons to be made between the individual federal states.

HEALTH MONITORING

Health monitoring refers to the continuous collection and analysis of data on public health. In addition to official health statistics, special surveys are required for this purpose, which deliver information on people's state of health in Germany that would not otherwise be available; they are repeated at specific intervals. They include the German Health Interview and Examination Survey for Children and Adolescents (KiGGS), the German Health Interview and Examination Survey for Adults (DEGS) and the German Health Update (GEDA). The RKI's health monitoring targets both physical and psychological health and also considers social and behavioural factors. It can thus identify starting points for tailored preventive measures. The outcomes of monitoring are continuously processed and published in the framework of Federal Health Reporting.

Even more pioneering, as it turned out, was the RKI's German Health Interview and Examination Survey for Children and Adolescents, known as KiGGS, which was conducted from 2003 to 2006. It was the first representative nationwide study on the health situation of the next generation. More than 17,000 girls and boys between 0 and 17 years of age as well as their parents took part in the survey which involved not only interviews but also laboratory analyses and physical examinations. Between 2009 and 2012, the first follow-up survey was conducted by telephone, and a second repeat survey with interviews and some examinations has been underway since 2014.

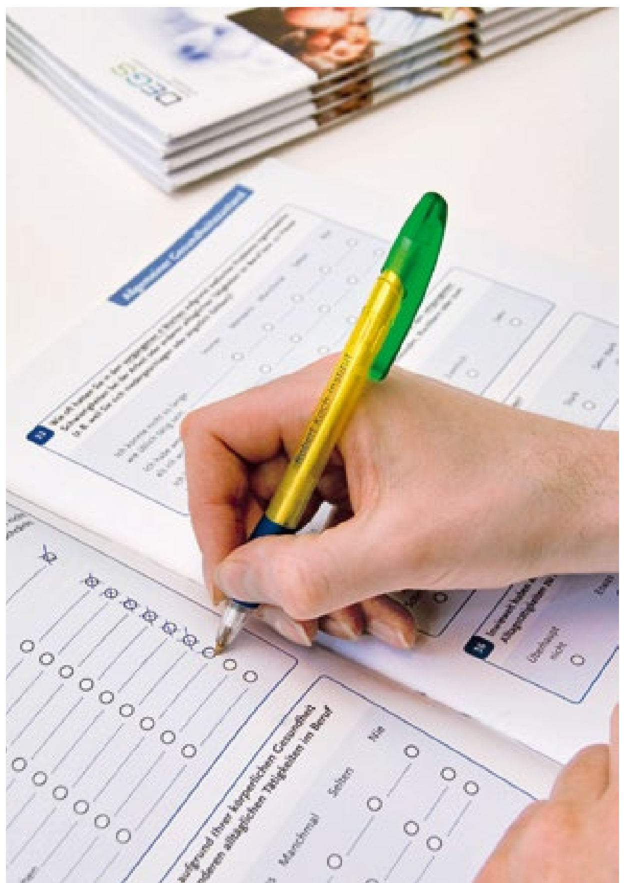
One of the most important outcomes of these surveys was that more than 90 per cent of children and young people as well as the majority of adults were in good to very good health – and that well-being had even increased in the previous ten years. The figure for the number of smokers had dropped across the board and the population did more sport than it used to. At the same time, the majority of adults is at least slightly overweight, a smaller but growing group is actually obese; being overweight is already a major issue amongst children as well. Just as in other European countries, there is a high, though stable, level of psychological disorders.

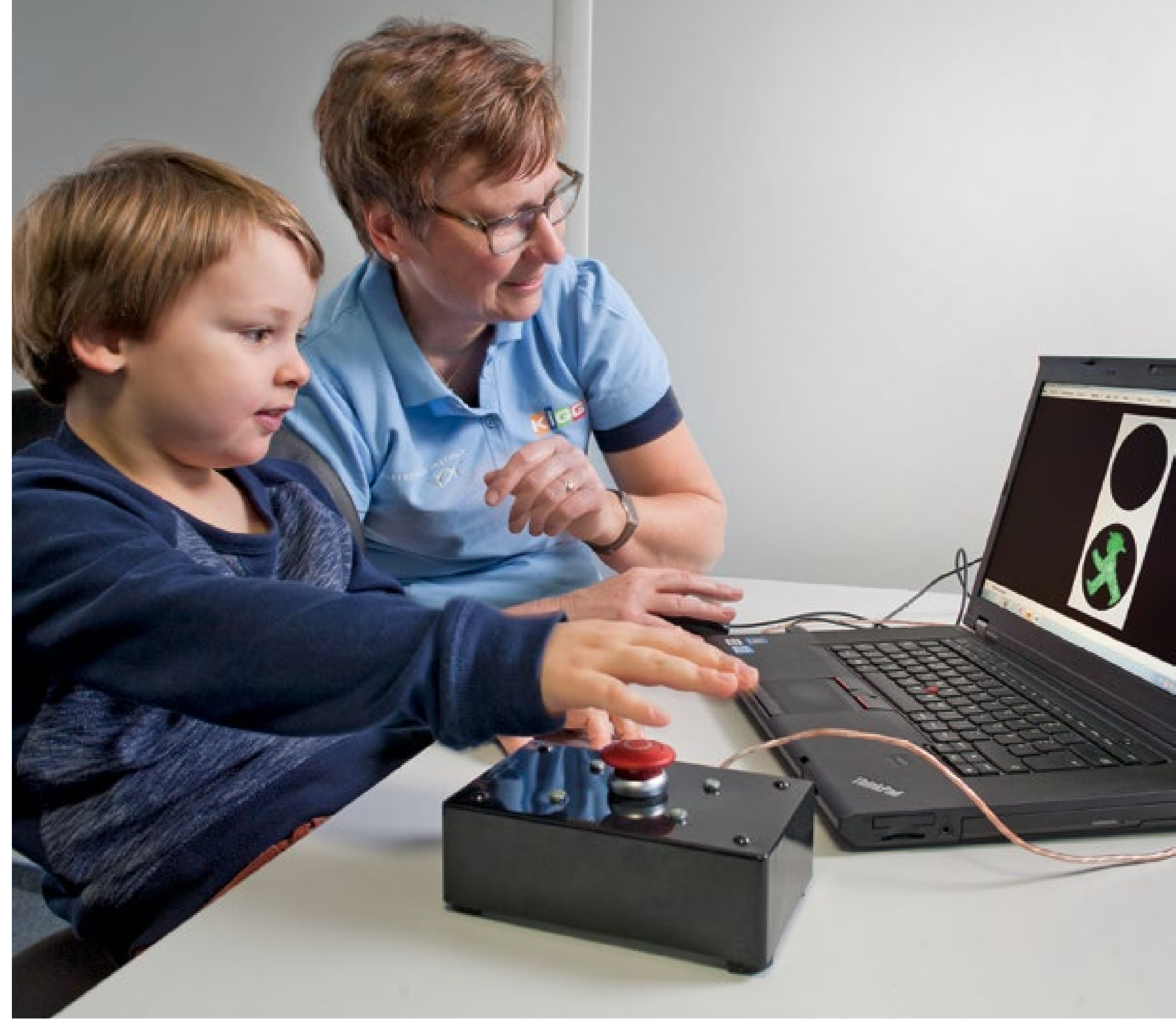
Experts at the RKI, however, do not only use their wealth of data for their own detailed analyses. They also open it up to external scientists after checking and preparing the data in accordance with modern standards. Thanks to its vast experience in epidemiological research, the RKI has also taken on external quality assurance for the German National Cohort. Initiated in 2014 and due to run for the coming decades, this longitudinal study involving 200,000 adult participants is being undertaken by a nationwide research alliance with the aim of investigating the most important common diseases in great depth.

Health in the course of life

And the RKI's experts have another ambitious goal as well: to capture health in terms of the individual lifespan. 'We know that health problems can accumulate and interrelate in the course of a lifetime,' says the health researcher Hannelore Neuhauser. There are also critical phases that can indeed shape health later on. Biological and social influences may interact, unfavourable constellations and behaviour may reinforce each other or change for the better.

According to the KiGGS data, one example is that the percentage of overweight girls and boys grows rapidly when they reach primary school age – which is why preventive measures are particularly important at this stage, Neuhauser notes. The transition into adolescence and working life or retirement are also significant periods of upheaval from a health point of view. With the aid of health monitoring, it is these course settings scientists at the RKI want to understand better.





Testing the reactions of a four-year-old boy for the KiGGS child health survey

When is youth obesity just a temporary constellation and when does it imply permanent consequences? What impact do lifestyle and cardiovascular risk factors have on cognitive fitness in old age? How sustainable are certain prevention programmes? The high percentage of those participating in the RKI's repeat surveys is one of the reasons why answers can be found to questions like these. Of the 17,000 plus families who took part in the first KiGGS study, some 12,000 agreed to participate in the repeat survey six years later and more than 10,000 of the original cohort will take part in the current second repeat survey. In addition, new individuals are also included in the studies.

In the long term, researchers at the RKI would particularly like to recruit significantly more participants from the oldest age groups. So far, health monitoring allows representative statements to be made on people between the ages of 0 and 79. 'But meaningful data on over 80s are still few and far between internationally,' Neuhauser's colleague Christa Scheidt-Nave comments. Particularly amongst the infirm, those living in homes and elderly migrants, participation in studies is almost non-existent 'although the need for sound analyses for these groups of the population

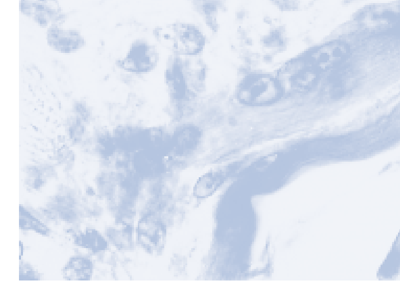
is enormous,' Scheidt-Nave emphasises. After all, it is becoming ever more important to plan care provisions for the elderly.

In the meantime, epidemiologists at the RKI are working on ways of solving the issue. It might be possible to cooperate with family doctors and migrant networks on future surveys or take additional random samples amongst nursing home residents, Scheidt-Nave suggests. If such innovative approaches are successful, this will open the perspective to get a precise picture of the health situation of adults in Germany including the oldest members of the population.

At a glance

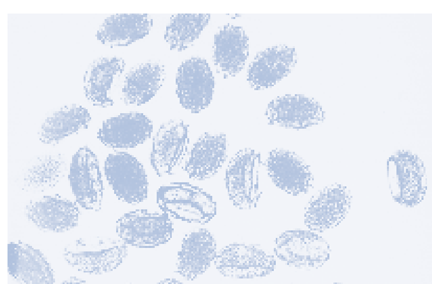
With its internationally exemplary health reporting the Robert Koch Institute (RKI) delivers continuous analyses of the changing spectrum of disease, health risks and impact factors as well as people's health behaviour in Germany. For this purpose, it makes use of data collected from the Federal Statistical Office, health insurance providers, doctors and registries as well as the results of representative repeat surveys that the RKI regularly conducts in the framework of comprehensive health monitoring. This helps to close the gaps in epidemiological data and acquire, for example, important insights into the health of children and young people. The long-term monitoring also facilitates research into health changes in the course of life and the pre-requisites for healthy ageing.

How is the carotid artery? Ultrasonic testing in the context of the RKI health monitoring



A FOCUS ON HEALTH DRIVERS

Some sections of the population are less healthy than others. Scientists at the institute are therefore trying to discover which circumstances make us ill in the long term – and what keeps us healthy.



Setting the course in childhood

Good health is more than just a happy coincidence. A person's state of health is closely related to the interplay between a host of internal and external influences: genes and gender are just as significant as behavioural habits, family structures and social living conditions. This all helps to explain why some sections of the population are less healthy than others and identify where prevention and health promotion can help to balance out the differences.

One thing is indisputable: the enormous influence exerted by the complex inter-impact of health risk factors, protective resources and social influences starts in childhood. 'In the early years, the course is set for our later health,' emphasises Heike Hölling, a child health expert at the Robert Koch Institute (RKI). As children and young people go through many developmental processes, both physical and psychological, any health issues may not just affect their well-being at the time, but lead to problems that can accompany them into adulthood. Hölling and her colleagues in the Department of Epidemiology and Health Monitoring want to understand the background of such developments better: which constellations in our lives make us ill sooner or later – and what keeps us healthy?

The researchers are not banking on easy answers. 'Health is always a multifactorial event,' says Hölling. None the less, for various health problems it is possible to identify significant risks.

Take allergies: genetic disposition seems to play a decisive role – everyone is basically born with a certain risk burden. The data collected by the RKI during the nationwide Health Interview and Examination Survey for Children and Adolescents (KiGGS), for example, shows that the risk of disease is twice as high in children with even just one parent who suffers from an allergic disease like hay fever, neurodermatitis or asthma.

However, genetic components are not able to explain the enormous rise in allergies (that has since levelled off) since the 1970s. Today, allergies are one of the most frequent illnesses suffered by children in Germany. Increased pollen concentrations, changes in eating habits and modified hygienic conditions are considered to be contributory factors.

According to the KiGGS data, growing up in a rural environment seems to protect children against allergies, which is probably because they get greater exposure to certain microbes on farms which promote the maturation of the immune system. Children who start kindergarten at an early age and have older brothers and sisters also seem to be more resistant to allergies.

Health and family ties

Just how important the constellation in the family is for children's well-being is illustrated by another widespread health problem. According to KiGGS, every fifth adolescent between the ages of 3 and 17 shows signs of behavioural problems or hyperactivity, emotional stress or difficulties with their peers. The figures are similar in the rest of Europe. Not that all psychological abnormalities of this kind necessarily lead to a full-blown disorder in the medical sense, but they do reveal that these boys and girls are more vulnerable emotionally.

Family conflicts, in particular, but also conflicts in the parents' families, dissatisfaction in a partnership or parental psychiatric illness all contribute to promoting adolescents' problems, says Hölling. Children of single parents – especially if these parents are unemployed – may also be at greater risk.

The Robert Koch Institute in Berlin-Tempelhof

Importance of the social situation

'Of course, a child is not per se in danger just because it lives in a one-parent family,' Hölling clarifies. 'A child can grow up happily in the most diverse constellations.' But some single parents see themselves confronted with far greater challenges in their everyday life. Particularly if they do not have a satisfying job experience they are often insecure and are less able to offer their children emotional stability, says Hölling. Moreover, some single parents tend to live less healthily, are more prone to smoke, consume more alcohol and sleeping tablets and eat less regularly.

Socially-determined correlations sometimes start having an impact even before a child is born. 'The course is even set to some extent during pregnancy,' Hölling's colleague Thomas Lampert corroborates. He and his team are investigating how aspects of social status like income, education and professional position shape health.

Data from the RKI's health monitoring does indeed reveal that amongst pregnant women with a high social status only about one in fifty smokes – amongst socially-disadvantaged mothers in the low status group, on the other hand, the figure is one in four. 'This social difference in smoking behaviour can have health implications for children years later,' Lampert emphasises. International longitudinal studies have shown that adults, whose mothers smoked during pregnancy, suffer more frequently from respiratory and cardiac diseases.

Overall, a whole raft of correlations can be discovered between health issues and social status. 'In low status groups, certain illnesses don't only occur more frequently, they also develop earlier and are often more serious,' says Lampert. In Germany, for instance, heart attacks, strokes and diabetes mellitus occur almost twice as often in adults with a low social status as they do in the

SOCIAL STATUS

Social status is a term coined by sociology and refers to a person's standing within a social order. In epidemiological studies it is often applied in the form of an index including the participants' household net income, occupational status and level of education. Usually, the index differentiates between high, middle and low status, effectively, between three social classes. The standardised status index only partly reflects the individual's concrete reality of life. But it does facilitate comparatively simple and statistically relevant studies on the social influences on health.

In the context of the nation-wide health monitoring the Robert Koch Institute conducts regular health surveys on the phone

An intact environment of family, friends and colleagues is good for your health

upper status group. Obesity is also more prevalent amongst those who are socially disadvantaged, a trend which can already be observed in childhood. Children from affluent families, by contrast, are more prone to suffer from allergies.

The impact of such socio-economic factors is obvious, but the real causes are diverse and not always easy to comprehend. In itself, money does not make you healthy – but it does allow a higher standard of living, opens up opportunities for social participation and ensures social security. On the one hand, self-worth, recognition and prestige are all linked with an individual's occupational status; on the other hand, a job can become a permanent emotional burden if a person feels unappreciated or not in control, or if the work involves physical risks, such as road building.

Finally, according to Lampert, a good education does not only mean that people usually know more about health and illness, rather, it opens up a different perspective on life in general, strengthens the feeling of being able to influence one's own future and facilitates the search for information within the health system as well as communication with doctors. The extent to which communication barriers can impede health care is graphically illustrated by many international studies involving migrants and refugees: apart from having experienced violence and discrimination, they often lack the linguistic means to formulate their needs and interests or to take sufficient advantage of therapy and prevention opportunities.

Protective influences

Health issues and crises do not, however, have to be inevitable – in many cases they are compensated by other, protective influences. Thus scientists at the RKI always have an eye to protective factors as well as risks. Resilience is the term used to describe the ability to withstand crises.

A study of representative data has shown, for example, that the impact of unemployment on health, which is often extremely serious, is much attenuated by a strong network of social connections, Lampert reports. An intact environment of family, friends, neighbours or colleagues – sociologists speak of social capital – seems to guarantee health across all classes.

'Even children who temporarily digress from the norm, but receive good outside support, can usually master their difficulties,' Heike Hölling agrees. A big circle of friends can help to compensate for family problems. No less important for children's resilience are stimulation and success at school. Statistics prove that primary school children who manage to go on to grammar school exhibit fewer behavioural abnormalities at a later stage. Moreover, they are less likely to smoke or suffer from obesity – which conversely means that a good education is also an investment in maintaining health.

In addition to this, there are the protective effects that stem from the individual's own psychological resources: people who are positive, curious and have a strong will can often deal better with difficulties than others. Those who have experienced happiness and a sense of security have something in their arsenal if crises occur. And those who see some point to the world and their own lives and are convinced that they can do something with it are more likely to re-think and change the kind of health behaviour which might have far-reaching consequences.

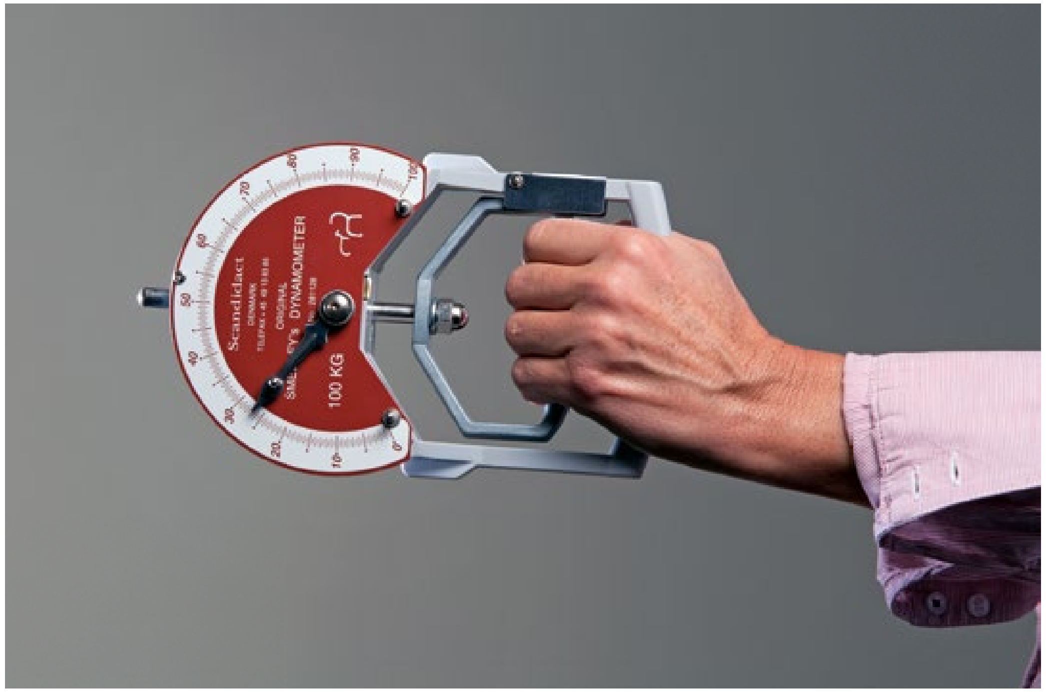
RESILIENCE

In health research, resilience denotes the ability to withstand health risks and crises. It is based on various factors such as genetic and psychological characteristics as well as support from the family and social community. Resilience is not a static attribute; it can change in the course of life and be learned. The opposite of resilience, increased susceptibility to health issues, is known as vulnerability.

Roughly half of all adults regularly do at least an hour of sport every week

The new ageing

Particularly when it comes to chronic diseases, which become more prevalent with increasing age, individuals' behavioural habits are amongst the most important avoidable risk factors. It has long been known, for example, that smoking, a lack of exercise, an unhealthy diet and excess weight help prepare the ground for heart attacks in later life. And it is remarkable that, to some extent, people's health behaviour has changed – for the better. As the RKI's study on adult health in Germany (DEGS) has shown, significantly fewer men and women smoke in Germany than did even at the end of the 1990s, and people also do more sport. On top of this, the blood cholesterol level, one of the most important risk parameters in the development of cardiovascular diseases, is now lower on average in both sexes. This could be due, above all, to better eating habits and more movement but also to improvements in medical therapies.



Using dynamometry to measure grip strength in older people. Testing this important everyday ability allows insights into the state of health in general

'Changing behavioural patterns and conditions of life continually shift the health risks and disease spectrum as well,' says Christa Scheidt-Nave, who analyses the health data together with colleagues. This can be seen, for example, in the situation of older people.

There has been a particularly large increase in sporting activity amongst older people. According to DEGS, the proportion of men and women between the ages of 70 and 79 who do at least one hour of sport per week has increased in the last two decades from under 20 per cent to over 40 per cent. As comparisons between the DEGS data and the 1998 Federal Health Survey reveal, day-to-day physical functioning has also improved: today, in general, people in the 50 to 79 age group are better able to carry out daily activities like climbing stairs than they were even just ten years ago.

But it is not only the physical operating range that is increasing. Evidence from other epidemiological studies suggests that older people today are also fitter mentally, says Scheidt-Nave. Ageing – and the way we look upon our own ageing – is changing. One facet of this is the increasing dominance of digital communication media in ever more areas of life. Whilst working adults sometimes feel they are being forced to be on call 24/7 and that work knows no boundaries, smartphones and internet can certainly provide mental stimulus for older people, Scheidt-Nave explains.

Social developments of this kind are significant not least, for example, because according to what we know today, the risk of dementia is reduced not only by the decline in cardiovascular disease, the increase in physical activity and a healthier diet, but also by better education and the mental impact of a stimulating everyday life. 'We are going to continue observing and analysing the development of important factors that influence the risk of dementia over time using the data we collect on Germany in nationwide health studies,' Scheidt-Nave confirms.

At a glance

Health is determined by the interplay of many different influences including genetic characteristics and gender as well as behavioural habits, environmental factors, family structure and social living conditions. All this can lead to an unequal distribution of health risks within the population. On the basis of representative data collected nationwide, scientists at the Robert Koch Institute investigate issues like the impact of the family and school environment on children's well-being, the health significance of income, occupation, educational level or migration status in combination with lifestyle factors like nutrition, physical activity, smoking and alcohol consumption, and what it is that influences the health situation in old age. These studies generate important starting points for targeted prevention and health promotion to reduce risks and strive to offset health differences.

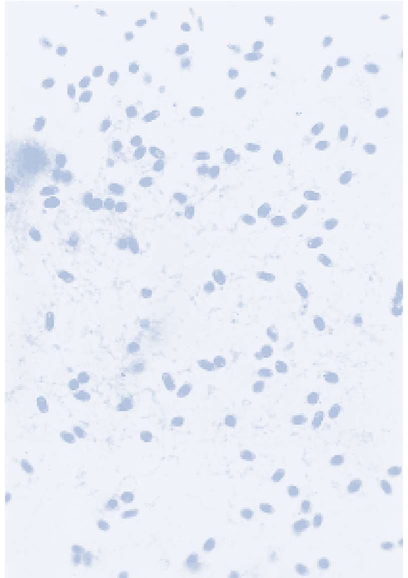
Nevertheless, maintaining health and coping with health crises in old-age is still a real challenge, she adds. In later life, a number of illnesses often occur simultaneously, and physical and psychological health are very closely linked. With regard to health care for older people it is especially relevant that patients who suffer from depression often get diabetes, heart conditions or dementia as well. This age group also typically uses a lot of different medicines with potential side-effects which, in their turn, involve new risks.

Sometimes, old people's health hangs on a fine thread and depends on finding a balance between risk factors and protective factors, says Scheidt-Nave. In this context, the social character of being healthy plays a particularly big role. It is well known that the loss of social contacts often means that chronic illnesses become even more acute and lead to frailty. 'Whereas people who are supported by others can often maintain their autonomy and quality of life for a longer period of time.'

Elderly people have better mental health nowadays

ANALYSING

DATA STREAMS



Algorithmic bioinformatics and mathematical models help uncover connections hidden in complex mass data, understand the risks of infection better, and even predict the dynamics of epidemics.

Protection in the age of Big Data

Streams of data not only shape our daily lives. The management and analysis of mass data has long become a core element in researching infectious diseases and public health protection. Smart data analysis could, for instance, help us to understand chains of infection or the spread of antibiotic resistance better – and even partially predict the dynamics of epidemics.

'Algorithmic bioinformatics is becoming increasingly important for our work,' says Lothar H. Wieler, President of the Robert Koch Institute (RKI). Several teams at the RKI are engaged in developing innovative strategies, not only to automatise data, but also to analyse it in real time with the help of adaptive algorithms and mathematical models.

'The sheer amount of data we are dealing with today is impressive,' Wieler notes. The analysis of pathogens, for instance, often generates data from high-resolution electron microscopes as well as from molecular genetic procedures, which can quickly become overwhelming. In 2015 alone, the RKI produced a data volume of about 100 terabytes – that is about 20,000 standard DVDs' worth of storage space. 'We expect this amount to triple with each successive year,' Wieler adds. Owing to the significance of the topic, the RKI is the first non-university research institute in Germany to institute its own data policy – a codex that sets out basic rules on how research data is to be collected, verified, processed, stored and made accessible. In addition, the RKI is continuously developing its data protection regulations in order to keep abreast of increasing demands in this field, as well.

Today's data explosion is generally summed up by the catch phrase "Big Data", which denotes data streams that are too large, too complex, too diverse or too volatile to be analysed satisfactorily using traditional data processing methods. Such mass data accrues in scientific fields such as molecular genetics, climate research, or nuclear physics as well as many other areas of life, for example in global stock market transactions or in social media communication.

In fact, many infectious disease experts speculate that connecting and analysing mass data will shed more light on dynamic phenomena such as disease outbreaks. In other words, the rapidly growing mountain of data might contain some undetected signals that could help to enhance infection protection.

Signals from the pathogen genome

One example is analysing the genetic data of pathogens. Today, thanks to rapid technological progress in genome sequencing – referred to as second- and third-generation sequencing methods – entire genomes can be deciphered quickly and at low cost. The complete DNA of a bacterium, for instance, typically consists of several million individual building blocks. 'But we have now reached a stage when a single experiment can sequence several billion DNA bases,' explains Bernhard Renard, head of a research group on bioinformatics. He and his team are developing special computer algorithms to filter out the interesting signals from genomic pathogen data – and they 'fill up entire hard drives in the blink of an eye. The challenge is no longer so much about collecting data – but analysing it,' Renard concludes.

Modern high-throughput methods are, of course, a valuable tool to protect us from infectious diseases. In contrast to earlier, less comprehensive methods, complete sequencing of the pathogen genome delivers more precise information on the exact sub-type of a pathogen that is behind an outbreak, or whether there are several, slightly different strains circulating – which might need to be combatted with different methods. In fact, Renard says, the difference between antibiotic-resistant bacteria and their non-resistant counterparts sometimes comes down to fewer than ten DNA building blocks.

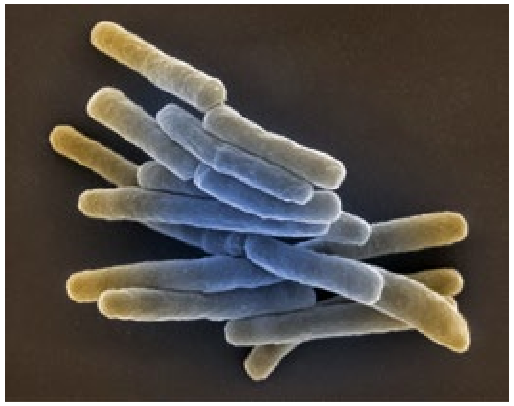
Hidden chains of infection can also be understood better using such small sequencing variations, adds Torsten Semmler, head of the junior research group "Microbial Genomics". This may be a decisive factor if, for example, cities such as Munich, Cologne and Hamburg experience a surge in infections caused by tuberculosis bacteria – yet it remains unclear whether there is a connection between the cases, or whether this sub-type might also be occurring frequently abroad. This could provide information on how to interrupt the chain of infection. Since molecular evolution changes pathogens over time, identical pathogen genomes from different patient samples may indicate that the individuals in question became infected directly – whilst diverging genetic codes may imply longer chains of infection, or entirely different types of pathogen.

It is these connections that Renard and his colleagues want to analyse in an automated fashion with the help of machine learning driven algorithms and mathematical network models. 'We not only want to elucidate the most probable chains of infection, but also the statistical reliability of the model,' Bernhard Renard emphasizes. Sequence analyses in the lab are never one hundred percent accurate – very large amounts of data, in particular, require refined corrective mechanisms in the algorithms used in data analysis in order to avoid deceptive misinterpretations.

One of the long-term goals of the experts at the RKI is to routinely capture the entire genome for a whole series of notifiable pathogens – from tuberculosis bacteria via salmonella to HIV. Renard is convinced that molecular surveillance

BIG DATA

The catch phrase "Big Data" refers to complex and often rapidly changing mass data that cannot be analysed satisfactorily using traditional data processing methods. Even though the term has not been defined precisely and is constantly changing, it generally denotes the phenomenon of an explosive growth in data streams in numerous areas of life. Examples include data traffic on the internet and the rapid increase in genetic data available in medicine. Big Data analyses often use special computer algorithms and artificial intelligence methods in order to detect unexpected statistical patterns and connections even in unstructured and heterogeneous data sources. This approach can also facilitate a better understanding of dynamic phenomena such as the spread of infectious diseases.



New insights into infection events: using bioinformatics to study bacteria causing tuberculosis

of this kind will provide completely new insights into the dynamics of infection in this country. Today, the RKI already has several high-speed sequencing machines and a high-performance IT infrastructure. In addition, a partnership with Freie Universität Berlin allows the RKI access to their super-computers.

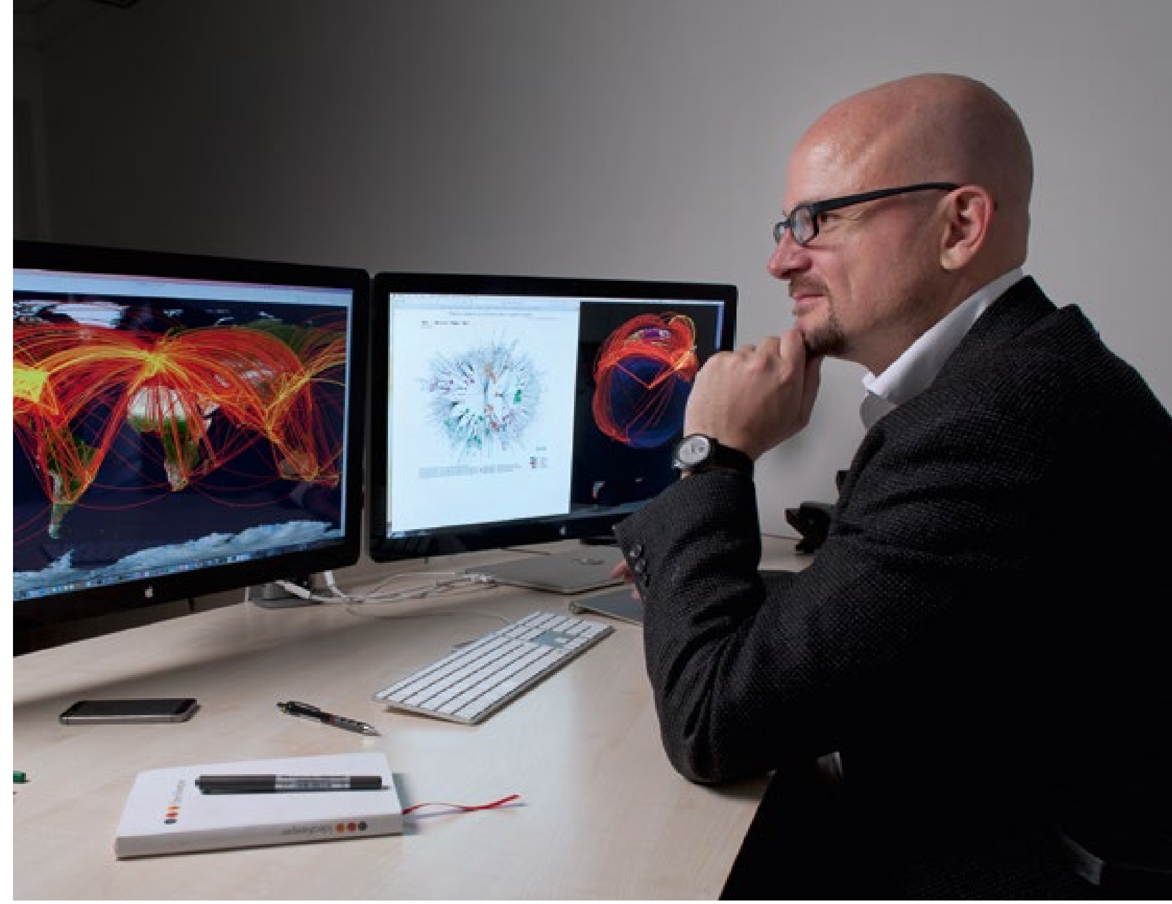
The hidden geography of epidemics

Innovative data models can even predict the dynamics of epidemics. This is not primarily about genomic data, however – but rather about information on traffic and transport routes. 'We asked ourselves how we could explain seemingly highly complex phenomena, such as the spread of a global flu epidemic,' Dirk Brockmann explains. At the RKI, he leads the project group "Epidemiological Modelling of Infectious Diseases", a collaborative project with Humboldt-Universität zu Berlin. Traditionally, scientists would try to understand the spread of the pathogen using conventional maps, Brockmann says. This, however, requires extremely complex models and is not always successful because the speed of an outbreak often has nothing to do with the actual distance between two locations; in many cases, the spread does not seem to follow a specific pattern.

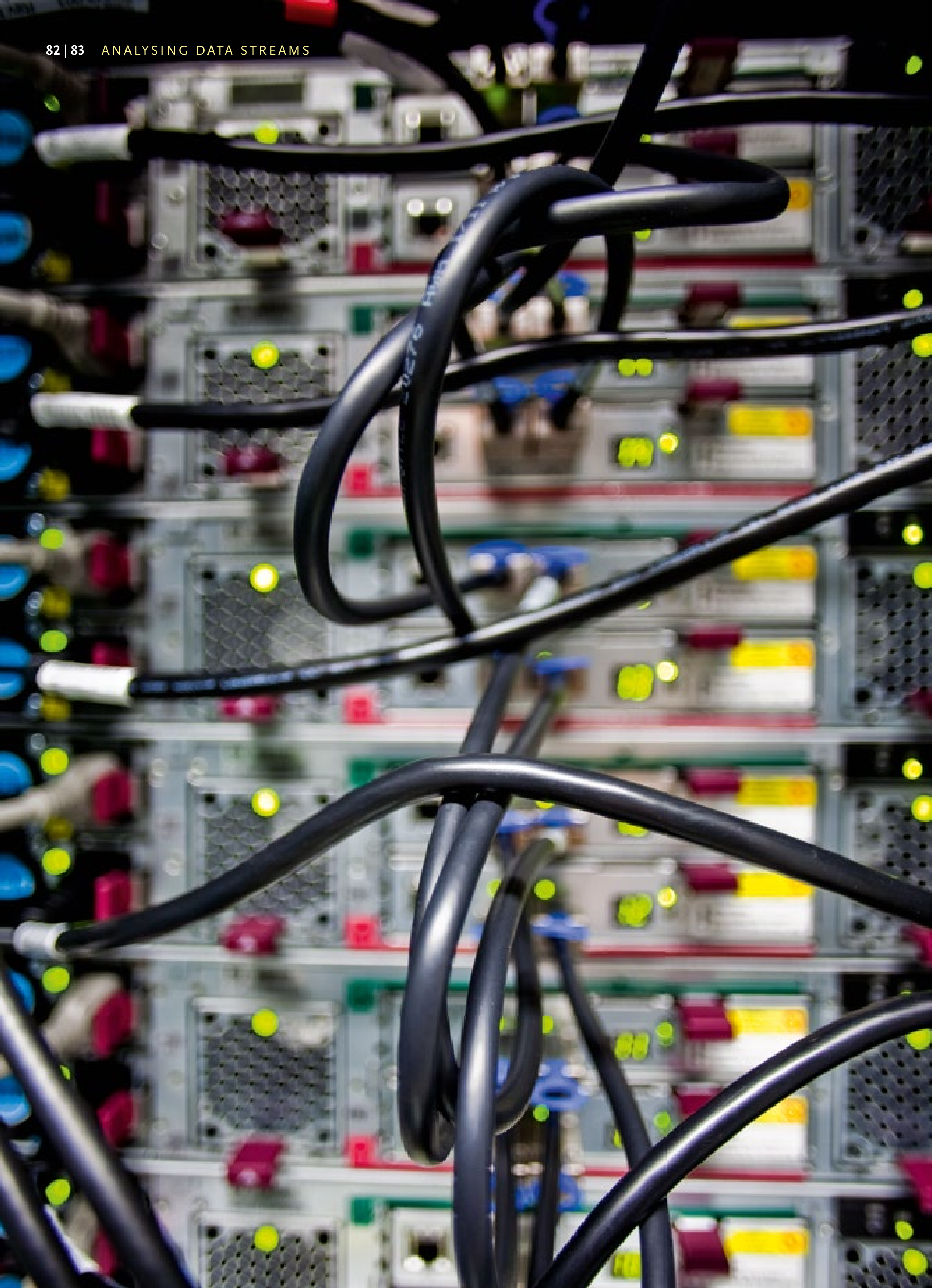
Brockmann's team therefore pursued a different approach. Cleverly analysing the web of global flight routes and adjusting the geographic distances based on passenger volume in a computer simulation, they created a sort of new world map in which London is closer to New York than many small towns in England. 'If you think about it, it's obvious: the more traffic there is between two locations, the closer together they effectively are, and the more likely it is that pathogens will travel that way,' Brockmann explains. In fact, the new, mathematically modelled maps showed that the so-called swine flu of 2009, for example, rippled across the world from Mexico in a very predictable circular wave (like a pebble dropped in water).

For significant viral infections such as flu or Ebola, which are passed directly from human to human, the global network of air routes with its approximately 4,000 airports and three billion passengers annually is key to understanding global epidemics, Brockmann says. In the event of a limited local outbreak in an urban agglomeration on the other hand, daily commuter patterns may be the decisive factor in spreading the pathogen. Whilst in the case of foodborne infections, the effective epidemiological distance between locations has more to do with commercial transport routes than passenger traffic. 'For different pathogens we have to analyse different mobility networks,' Brockmann says. Each epidemic thus exhibits its own geography.

In the meantime, RKI experts have been refining their models. In the case of a flu pandemic, for instance, it makes sense to include information about the molecular evolution of the virus genome in the simulation in addition to the flight data. Genetic variations provide additional clues for the trajectory of the pathogen. 'Integrating very diverse data in combined models is one of the most exciting research fields right now,' Brockmann says. 'Of course, each computer model is a mere approximation of reality,' he adds. Human behaviour, in particular, is nearly impossible to simulate in advance – for example, whether the population will keep their cool or panic, or how well quarantine measures will be implemented. Therefore, it is usually impossible to predict exactly how many people will fall ill. However, with current models good prognoses can be made, such as where a newly surfaced flu virus in China will end up next, and which routes it will take to spread most intensively – which is invaluable information for planning disease control measures. Moreover, Brockmann and his colleagues are endeavouring to dynamically adapt their models to any given outbreak data and also to better predict locally limited waves of infection, such as within a federal state.



'Every epidemic exhibits its own geography, so to speak.' The physicist Dirk Brockmann investigates the spread of infectious diseases



Big Data for doctors' prescriptions

At the same time, RKI scientists plan to use their data analyses to gain insights into yet another infection risk: the spread of antimicrobial resistance in hospitals and doctors' surgeries. Resistant microbes are considered one of the major global challenges facing infection medicine – and their spread is closely connected with the consumption of antibiotics.

'In the future, we want to aggregate data on both aspects for the whole country,' says Tim Eckmanns. He and his team have built a nationwide monitoring system called ARS (Antimicrobial Resistance Surveillance). Today, 600 clinics and 7,000 doctors' surgeries are part of the system, which transmits resistance test results from the labs to the RKI online – feeding about 1.5 million test results into its database every year.

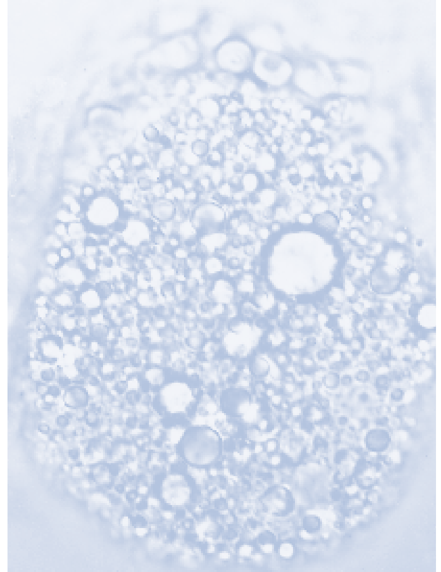
Analysing the ARS data stream alone requires special algorithms in order to detect dangerous trends and suspicious patterns in the resistance spectrum on the one hand without raising unnecessary false alarms on the other, Eckmanns explains. His team is also working with the Charité to build another system to capture the volume of antibiotics issued by hospital pharmacies and transmit it to the RKI. It is generally known that intensive use of antibiotics, in intensive care units, for instance, promotes the development of resistant microbes – these are exactly the correlations Eckmanns' team hopes to understand better through the integrated analyses of both data streams. About 100 clinics are currently participating in antibiotics consumption surveillance. In the long run, the experts at the RKI hope to achieve a level of coverage similar to that for ARS.

The results of combined surveillance could also be linked to a third data source – data on in-patient infections at hospitals in Germany, which is compiled by the National Reference Centre for the Surveillance of Nosocomial Infections at the Charité in Berlin in cooperation with the RKI. Such networking of various, sometimes heterogeneous data sets is trend-setting in modern bioinformatics and a typical feature of Big Data approaches, Eckmanns says. 'This holds great potential for public health protection in general.'

Today already, in order to quickly halt the spread of resistant germs, participating labs and clinics are immediately notified of any abnormal results that pop up in antibiotics resistance surveillance. In the future, Eckmanns and his team want to work with doctors' associations to reach out to doctors in private practices and inform them about the current resistance problem in their region or even in their own practice. Analysing data streams at the RKI would help out-patient physicians prescribe antibiotics in a more targeted manner.

At a glance

Today, analysing large data streams is a core element of infection research and public health protection. Innovative bioinformatics methods, computer algorithms and mathematical models are growing in importance. Scientists at the Robert Koch Institute use these approaches to detect hidden paths of infection employing tools such as high-throughput genome sequencing. They also investigate the potential of computer-based simulation and prediction of epidemics using, for example, international air traffic data. In addition, they develop algorithms to gain a better understanding of the spread of resistant pathogens and the correlation with the use of antibiotics based on data collected nationwide.



UNDER OBSERVATION

BIOTERRORISM

Pathogens can be released deliberately. The Robert Koch Institute plays a central role in the identification and combating of such incidents in Germany.

Evil greetings by mail

The samples arrived on November 2nd 2001, a Friday afternoon. The experts of the Robert Koch Institute (RKI) immediately began with their analysis, whilst press and public awaited the results with great anticipation: would the suspicion of a bioterror attack prove true?

Since the anthrax attacks of October 2001 in the USA it has become evident to all that attacks can also be committed by means of pathogens or biological toxins. At that time American newspaper offices and politicians received letters containing a white powder – spores of anthrax, a bacterial infection were found inside. Five people died, dozens had to be treated in hospitals; many thousands received antibiotics as a precaution.

In Germany, too, suspicious letters were found, even if there were no pathogens related to bioterror in any of the envelopes. In the case of the samples that reached the Robert Koch Institute on November 2nd 2001, the situation was more complex. A specialist microbiological laboratory had discovered possible indications for anthrax bacteria with an initial test; however, the test was only suitable for clinical use and not for environmental samples. So, was there a threat of hazardous material? After few hours, the answer was clear: no. Using a special molecular-genetic analysis method – the polymerase chain reaction (PCR) – the RKI experts were able to clarify that the sample in question indeed contained bacteria which resembled the anthrax pathogens in some properties, but were completely harmless.

Subsequent attempts to attack American governmental agencies with other agents emerged, for example the mailing of letters that contained the phytotoxin ricin. 'Fortunately there has been no single case of a confirmed bioterror attack in Germany to date,' emphasises Lars Schaade, head of the Centre for Biological Threats and Special Pathogens at the RKI, which was established as a consequence of the volatile autumn of 2001. Scientists as well as politicians had rapidly agreed that preparations had to be made for a real bioterror attack. By the end of 2001 a Federal Information Centre for Biological Threats and Special Pathogens (IBBS) had already been established at the RKI. The IBBS collects and evaluates scientific information on the pathogens and toxins, develops recommendations for safety measures and advises emergency services and authorities. Further teams of scientists followed, with these focused on researching particularly highly pathogenic viruses, bacteria and toxins and developing new microbiological diagnostic methods. With a staff of approximately 100, the Centre for Biological Threats and Special Pathogens has become the central body in Germany for the recognition, evaluation and handling of bioterror risk situations.

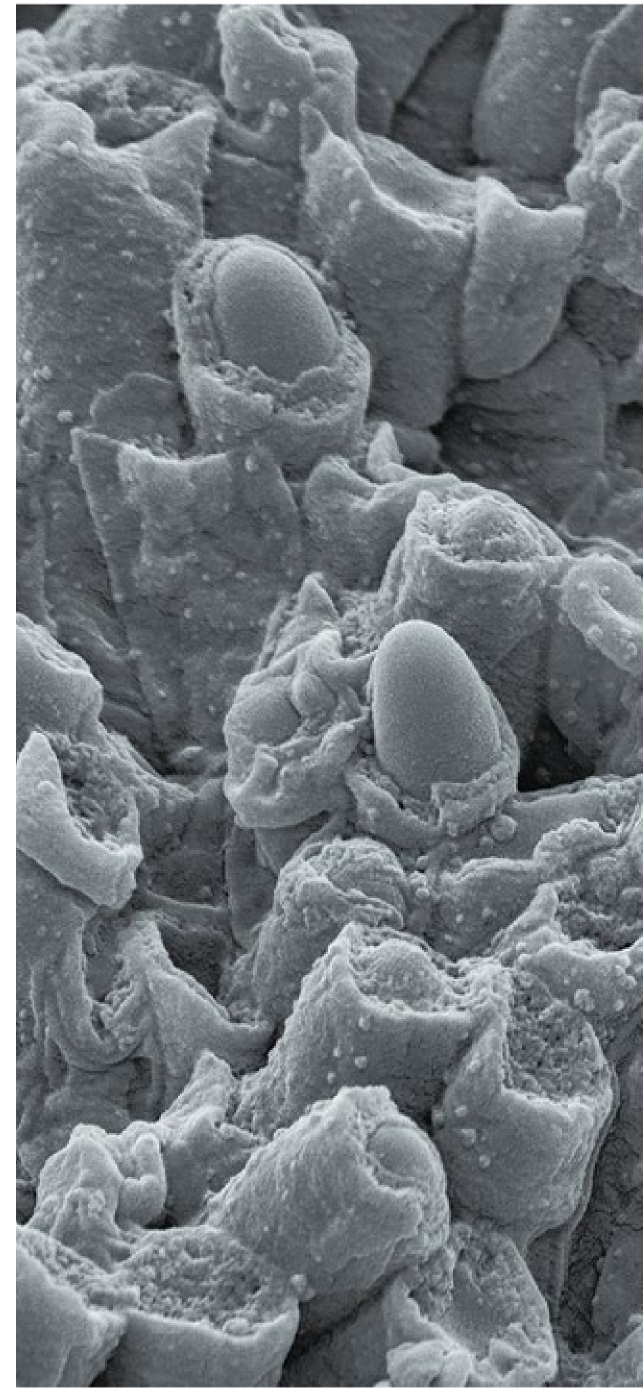
The dirty dozen

The "dirty dozen" – this is the name given by some experts to the ensemble of pathogens and toxins that are at least theoretically conceivable for terror attacks. In addition to anthrax bacteria, these include the pathogens of plague and tularemia, together with smallpox and Ebola viruses as well as the bacteria-based botulinum toxin and the phytotoxin ricin.

One of the best-known examples is smallpox: This viral disease, characterised by typical skin pustules, was long the cause of severe epidemics from which more than one quarter of the patients died. Only after World War II, international vaccination campaigns lead to a victory over smallpox, and with the last recorded case of smallpox worldwide occurring in 1978, the obligation to vaccinate was subsequently lifted. But what would happen if an individual infected with smallpox were to travel through the subway system of a major city? What would be the consequences of an intentional release of the virus in a football stadium? Is the level of immunisation amongst the population still sufficient to prevent a major epidemic?

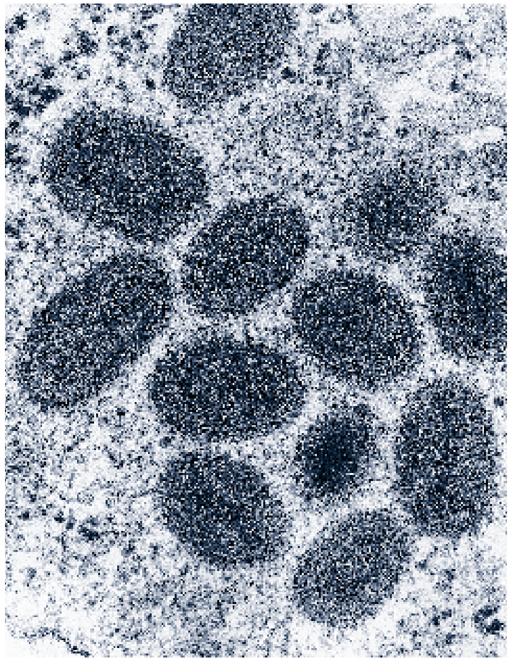
'Potential hazards need to be assessed in a sober and foresighted manner,' emphasises Christian Herzog, head of IBBS. For example, a Smallpox Preparedness Plan has been drawn up that defines how the government, authorities and disaster control units should react in the event of a sudden smallpox outbreak.

Moreover, the RKI conducts special trainings for doctors and rescue services in the handling of patients infected with highly contagious pathogens. For example, they train the correct donning of personal protective equipment and the special measures required for the transport and handling of highly infectious individuals. In addition, the Centre for Biological Threats and Special Pathogens also advises federal ministries on national and international decision making. The Federal Foreign Office regularly turns to this expertise with regard to the biological weapons convention, for example.



Anthrax bacteria forming egg-shaped spores, the resistant, dormant form of the bacilli. Electron microscope image

Risky pathogens in everyday life



Smallpox viruses from the last pox case in Germany in 1972. Electron microscope image

Almost all of the pathogens conceivable for terrorist attacks occur naturally and can also cause spontaneous disease outbreaks. From 2009 to 2012, for example, there have been cases of anthrax infection – some of them fatal – amongst heroin users, in Great Britain in particular but also in Germany. They were probably caused by anthrax spores in contaminated heroin batches. In 2010 several dogs died in North Rhine-Westphalia after they had eaten organic fertilisers in which excessive concentrations of the phytotoxin ricin were found. RKI research traced the causal connection, which lead to an increase in safety in fertilisers.

There have been several outbreaks of cowpox viruses in the past years. It emerged that owners of pet rats had been infected with the viruses, which occur in different animal species and are far less dangerous than human pox but can still lead to serious illness. 'The expertise that we develop for the recognition and prevention of bioterror attacks, is naturally of considerable benefit in such cases,' emphasises Schaade. For example, the RKI was able to contribute to the quick resolution of the cowpox cases with its highly-sensitive analysis methods.

However, the experts of the Centre for Biological Threats and Special Pathogens are by no means restricted to the planning of scenarios for emergencies. 'We also want to obtain a fundamentally better understanding of highly-pathogenic diseases like smallpox, anthrax or botulism,' explains Lars Schaade. For example, RKI scientists are trying to clarify why some pox viruses only infect humans while others affect various animal species. Other analyses might help developing a new smallpox vaccine with limited side-effects, as well as special therapeutic antibodies or medication to counteract the pathogen.

SMALLPOX PREPAREDNESS PLAN

The smallpox preparedness plan is an emergency plan coordinated between the federal government, state authorities and scientists and is developed under the scientific lead of the Robert Koch Institute. It provides precise recommendations as to which national and international authorities must be informed in a suspected case of smallpox, how to identify contacts in the environment of the sick person and when large-scale vaccination campaigns are necessary. The plan also gives recommendations for information management in the event of a smallpox attack and provides details of how to inform the public.

Lars Schaade
Head of the Centre for Biological Threats and Special Pathogens

How good is the protection against bioterrorism?

Dr. Schaade, which pathogens have especially significant potential for terrorism?

◂ There are a range of "usual suspects" and this is why we prepare for a series of different cases. An attack with variola smallpox viruses would certainly be the most severe. The pathogen can be transmitted from person to person, more than one fourth of those that fall ill with it die without vaccination. Only two high-security laboratories in the USA and Russia officially stock pathogens, for research purposes. The likelihood of an attack with the smallpox virus is therefore extremely low. However, no-one can say with certainty if smallpox pathogens were obtained by third parties in the past.

How can we prepare for attacks?

◂ Firstly, it is important to identify the pathogen. Our goal is therefore to make the diagnostic process as quickly and reliably as possible. With knowledge of the pathogen and other information, such as how many people have been infected, at what locations and who they have been in contact with, the situation can be assessed and recommendations made to the authorities involved with regard to the initiation of measures such as quarantine, vaccination and the issuing of medication on site. The possible measures involved are stipulated in emergency plans such as the smallpox preparedness plan and are adapted accordingly to suit the situation. It is important that doctors and emergency services are made aware that a bioterror attack could occur, the form that the disease could take and the correct action to be taken in such an event. We aim to achieve this via training courses and materials.

How well would the population be protected if the worst came to the worst?

◂ One key aspect is that information channels work in emergencies. For example, are the address lists of the key bodies involved up to date? Have the crisis teams in a region already dealt with an outbreak of an epidemic? Is sufficient protective equipment available? Is it clear where the casualties in a town are to be treated? Exercises are carried out to systematically test the plans; this enables loopholes to be identified and remedied. If we remain with the subject of smallpox, for example, in just a few days there would be sufficient vaccine available for the entire population, the plans have been rehearsed. Germany is well prepared here, also in comparison to other countries.

The fact that this can be difficult is down to a simple reason: the cowpox virus, like the monkeypox virus, is closely related to the human pox virus. Together, they are referred to as orthopox. 'An exact distinction between the different virus types is indispensable, however, in order to recognise potential bioterror hazards on the one hand and avoid the far-reaching consequences of raising a false alarm on the other,' says virologist Andreas Nitsche.

Bacteria are bred in special culture media – still an important step in the diagnosis of bacterial pathogens

Effective diagnostics

As a consequence, the RKI has developed a system of diagnosis that enables the prompt and reliable identification of the pathogens in question. In a suspected case of pox, for example, the diagnostic process follows two parallel paths: on the one hand, sample material from the infected patients is analysed with an electron microscope. 'This helps us clarify whether it is an orthopox virus at all – and not, for example, the pathogen for chicken pox, which belongs to the family of herpes viruses,' explains Michael Laue, specialist for electron microscopy. On the other hand, molecular-genetic analyses are conducted simultaneously by means of a polymerase chain reaction (PCR), which enables distinction between the different orthopox viruses. The combination of electron microscopy and genetic analysis practically excludes diagnostic errors.

'When there is a suspicion of orthopox, we need four to five hours for an exact diagnosis,' estimates Schaade, whose team is also on standby at weekends. Using state-of-the-art high-speed DNA sequencers the researchers are currently working on establishing methods with which it would be possible to decode complex cocktails of different pathogens, for example.

The RKI experts are also capable of determining dangerous toxins, such as the botulinum neurotoxins made by bacteria. In this, they employ a combination of immunological, spectrometric, functional and molecular biological methods. The botulinum neurotoxins, which can lead to fatal paralysis if left untreated, are a family of over 40 related proteins, a fact only identified in recent years. The main reason why the bacterial toxins are still hard to identify today actually lies in the molecular complexity of the toxin family. 'We still have some catching up to do in Germany as far as the standardisation of diagnostics is concerned,' confirms the toxin specialist Brigitte Dorner.

Many biological materials can only be stored at very low temperatures. Arranged neatly, everything can be found easily, even at –80 degrees Celsius

Apart from anthrax, tularemia (rabbit fever) also plays a crucial role in the diagnosis of bacteria. Although rare in Germany, the disease can take a fatal course; the pathogen Francisella tularensis is counted among the "dirty dozen". RKI researchers Klaus Heuner and Roland Grunow have detected a new Francisella species whose effects on humans and animals are now being investigated.

At an international level, too, the RKI is pursuing the goal of reliable and, where possible, standardised pathogen and toxin analysis. For some time now, several special laboratories have been participating in a European project coordinated by the RKI. The laboratories are sent bacteria samples for diagnosis – without the type of pathogen being disclosed. 'We not only want to find out jointly with the partners whether all laboratories reach the same analysis results, but also whether they are able to handle a large number of sensitive samples with the necessary speed,' declares Roland Grunow who coordinates the project. Similar projects have been coordinated by the RKI in the field of toxin analysis; they will be continued in future.

At a glance

The Centre for Biological Threats and Special Pathogens at the Robert Koch Institute (RKI) is the central body in Germany for the recognition, evaluation and handling of bioterror risks. Bioterror attacks could be committed with anthrax bacteria, pox viruses or biological toxins, for example. The RKI scientists are therefore developing special diagnostic methods for recognise the possible agents quickly and reliably. Moreover, the Federal Information Centre for Biological Threats and Special Pathogens also supports the work of responsible authorities and facilities for health and disaster control and develops emergency plans for the safeguarding of public health, for example, in the event of an attack with the smallpox virus. Furthermore, the RKI also provides its expertise and diagnostic methods to identify naturally-occurring disease outbreaks by highly pathogenic pathogens or toxins.

The Robert Koch Institute: Facts, Figures, Information

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The Robert Koch Institute has around 1,100 **employees**, 450 of them scientists, including Ph.D. students and trainees. Approximately 450 are on limited contracts and 320 are working part-time. The RKI also offers the possibility for further education through Bachelor and Master Theses, Ph.D's, training programmes and apprenticeships. The Robert Koch Institute is a federal institute within the portfolio of the Federal Ministry of Health and is financed by the federal budget. This is supplemented by project-related grants, mostly from the European Union, federal ministries, the German Research Foundation and other foundations.

The Robert Koch Institute has several **National Reference Centres** – influenza · measles, mumps, rubella · poliomyelitis and enteroviruses · salmonella and other enteric pathogens · staphylococci and enterococci – and **Consultant Laboratories** – Bacillus anthracis · Clostridium botulinum · electron microscopic diagnostics in infectious diseases · cryptococcosis, scedosporiosis, and imported systemic mycoses · Listeria · noroviruses · respiratory syncytial viruses, parainfluenza viruses and metapneumoviruses · poxviruses · rotaviruses · tularemia.

The Robert Koch Institute is also the site of the regional reference laboratories of the **WHO/Europe** for poliomyelitis as well as for measles and rubella.

The following **scientific committees** have their scientific offices at the Robert Koch Institute:
- Advisory Committee of the German Centre for Cancer Registry Data
- Central Ethics Committee for Stem Cell Research
- Commission on Anti-Infectives, Resistance and Therapy (ART)
- Commission on Genetic Testing
- Commission for Hospital Hygiene and Infection Prevention (KRINKO)
- Committee for Environmental Medicine
- Committee for Health Reporting and Health Monitoring
- Competence and Treatment Centres for Highly Contagious and Life-Threatening Diseases (STAKOB)
- Editorial Board of the Bundesgesundheitsblatt
- National Advisory Committee Blood
- National Certification Committee for Polio Eradication – Germany (NCC)
- National Verification Committee for Measles and Rubella Elimination in Germany
- RKI Expert Advisory Board on Influenza
- Scientific Advisory Board for Public Health Microbiology
- The German Standing Committee on Vaccination (STIKO)

Regular **publications** by the Robert Koch-Institute are:
- Bundesgesundheitsblatt (Journal for Public Health, Health Research and Health Protection), co-editor, monthly
- Epidemiologisches Bulletin (Epidemiological Bulletin), weekly
- RKI Publications (books, journals)
- Gesundheitsberichterstattung des Bundes (Federal Health Reporting)
- Infektionsepidemiologisches Jahrbuch (Epidemiological Yearbook of Notifiable Infectious Diseases), annually
- RKI-Ratgeber für Ärzte (fact sheets for physicians)
- Recommendations by the Commission for Hospital Hygiene and Infection Prevention (KRINKO)
- Umweltmedizinischer Informationsdienst (Information about environmental medicine), co-editor
- Publications in peer reviewed scientific journals

On the **internet** (www.rki.de/EN) the Robert Koch Institute provides insights into its work and research, in particular providing extensive information on different topics for medical specialists – for example on vaccination recommendations, pathogens and health reporting, as well as providing numerous further links. In addition, the RKI is active on Twitter (@rki_de) and publishes various newsletters.

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