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Antibiotic resistance
a global challenge

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e-mail: pharma-brief@bukopharma.de
Homepage: www.bukopharma.de

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Introduction: the problem of resistance

The World Health Organization (WHO) is not afraid to talk about how drastic the issue of antibiotic resistance has become: ‚Unless we take fast and coordinated action, the world is about to enter a post-antibiotic era where common infections and minor injuries – the kinds of things we have been able to treat for decades – will emerge as killers once more.'[1]

Antibiotics are a real blessing for the field of medicine. Following their discovery in the early part of the twentieth century, they have been in widespread use since the 1950s. As a result, infections which had previously caused tremendous suffering and killed large numbers of people have become amenable to treatment.[1] But the situation is changing dramatically: ever more bacteria are becoming resistant to an increasing number of antibiotic agents. In particular, the typical pathogens responsible for common conditions such as urinary tract infections or pneumonia are becoming difficult to treat once more.[1]

The development of resistance is a natural process. The fact this has now become such a pressing problem is undoubtedly the result of the massive misuse of this class of medicines. For example, antibiotics are often used to treat colds, despite these generally being associated with viral infections against which antibiotics are totally ineffective. This kind of folly is common practice around the world and is exacerbated by antibiotics being available without prescription in many countries. Another problem is the massive use of antibiotics in livestock farming – not only to treat infections, but sometimes even to accelerate growth in otherwise healthy animals. In Europe this method of fattening animals has been banned since 2006, although the practice continues in places like the USA. This kind of misuse leads to tremendous selection pressure: if bacteria are permanently having to contend with antibiotics, only the resistant will remain and will then find themselves free to multiply.

Photograph: WHO, P. Virot

The scenario: a post-antibiotic era

The resulting situation is perfectly illustrated by gonorrhoea, a sexually transmitted infection that actually used to be very amenable to treatment. But the pathogens have now developed resistance to all antibiotics in a number of countries, and WHO is warning that gonorrhoea will soon become untreatable.[1]

Every year tens of thousands of people worldwide die as a result of multi-resistant microbes which have found their way into hospitals. In Germany MRSA is probably the best-known hospital microbe. But it no longer presents the biggest problem. More critical now are what are known as ESBL-producing bacteria, which are able to render several antibiotics ineffective at the same time. They can also pass on this unpleasant trait to other species of bacteria, in addition to their own 'offspring'. It is becoming increasingly difficult to treat urinary tract infections (mostly caused by E. coli) and other simple infections. Treatment is taking longer, producing more side effects, and becoming more expensive. Hospital stays – ostensibly recommended for curative purposes – are starting to constitute a health risk, with the risk of infection particularly increasing after surgery.

In the USA resistance within hospitals is estimated to cost some USD 26 billion (EUR 23 billion) a year. If one were to count lost productivity and other costs to society as well, resistant pathogens are swallowing up nearly USD 70 billion (EUR 64 billion) in these areas.[2]

One Health: resistance as a global problem

Resistance does not stop at national borders: it develops anywhere and spreads everywhere. This is why the solution must be every bit as global as the causes. The slogan ‚One Health' should therefore be understood in its broadest sense: the Global North and Global South, human and veterinary medicine, social aspects, and technical solutions all need to be factored in.

The German government, the European Commission, and WHO have already adopted action plans. But more is urgently needed: many countries do not even have a surveillance system for recording resistance and the problems associated with it.

This brochure sets out the major problems, illustrates measures taken so far at a national and international level, and points out the gaps that need to be plugged.

Our relationship with bacteria

Bacteria are important – we cannot live without them. Each one of us carries 1-2 kilograms of bacteria inside us, most of which inhabit the gut, where they perform certain key digestive functions.

More often than not, bacteria do not cause any infection. They simply colonise us, and those on our skin and mucous membranes also form part of our immune system to some extent. The microbiome – the term for all the various microorganisms that can be found in the human body – varies from person to person. So much so, that a bacterial colony inside a home quickly adapts when a new family moves in.

People with a weakened immune system – as may occur following chemotherapy or surgery – are more likely to fall ill. Typical bacterial diseases include infections of the upper respiratory tract, pneumonia, inflammation of the bile ducts, urinary tract infections, and wound infections which can sometimes spread to the rest of the body (sepsis or 'blood poisoning').

Development of resistance

For as long as bacteria have been around, the organisms affected by them have also found ways of keeping them in check. This mainly involves the immune system, something which practically every living being possesses. Some organisms form antibacterial substances as well, a famous example being the penicillin formed by fungi. Bacteria in turn develop mechanisms that help them nullify the effects of antibiotics.

Gerry Wright, an American biochemist, has found evidence of this kind of natural ecosystem in soil samples, some 30,000 years old, taken from Alaska's permafrost. These soil samples contained genetic material from bacteria, which was found to be resistant to penicillin, tetracycline, and vancomycin among other things.[3]

But how does resistance develop? When bacteria multiply, there are always genetic mutations. This allows bacteria to develop that are different from their parents: they demonstrate various forms of resistance. When they subsequently come into contact with antibiotics, the bacteria with some form of resistance have better chances of survival and will multiply to a greater degree.

The spread of resistance

Bacteria are able to swap genetic material. This means they can also pass on forms of resistance to other types of bacteria. Pathogens spread through

- Contact between humans
- Contact between humans and animals (farmers working with animals and people cuddling pets)
- Contaminated drinking water (faecal-oral transmission): a significant factor in the spread of ESBL-resistant E. coli, particularly in South-East Asia
- Farming: resistant bacteria found on vegetables originate from slurry (excrement from stalls where animals are kept) used as fertiliser. Resistance genes can survive in soil for years. Antibiotics themselves can end up on fields along with slurry. Vegetable crops may take up antibiotics.

Which microbes present a problem?

Often bacteria are not just resistant to one specific agent, but may even be resistant to several antibiotics. These are known as **multi-resistant pathogens.** Generally speaking, they do not present a problem to healthy individuals, and many people are colonised by such bacteria without even noticing. The situation only becomes critical for those with a weakened immune system or when these pathogens are able to penetrate deeper into the body, such as during surgery.

MRSA = methicillin-resistant Staphylococcus aureus bacteria. S. aureus lives in some 20-30% of all healthy individuals, on either the skin or

mucous membranes. This particular bacterium is mainly transmitted via the hands. Infections are mostly local in nature, restricted to the skin or inside wounds. They become dangerous when surgical wounds or cases of pneumonia are involved. Depending on their source, a distinction is made between **healthcare-associated MRSA (HA-MRSA)** – involving infections occurring within a healthcare establishment – and **community-associated MRSA (CA-MRSA)** – involving those occurring within the general population. Cases of **livestock-associated MRSA (LA-MRSA)** affect humans and animals in equal measure in regions associated with intensive livestock farming.

VRE = vancomycin-resistant enterococci live in the gut. They can trigger infections of the urinary tract, peritonitis, and blood poisoning. They mainly occur in hospitals.

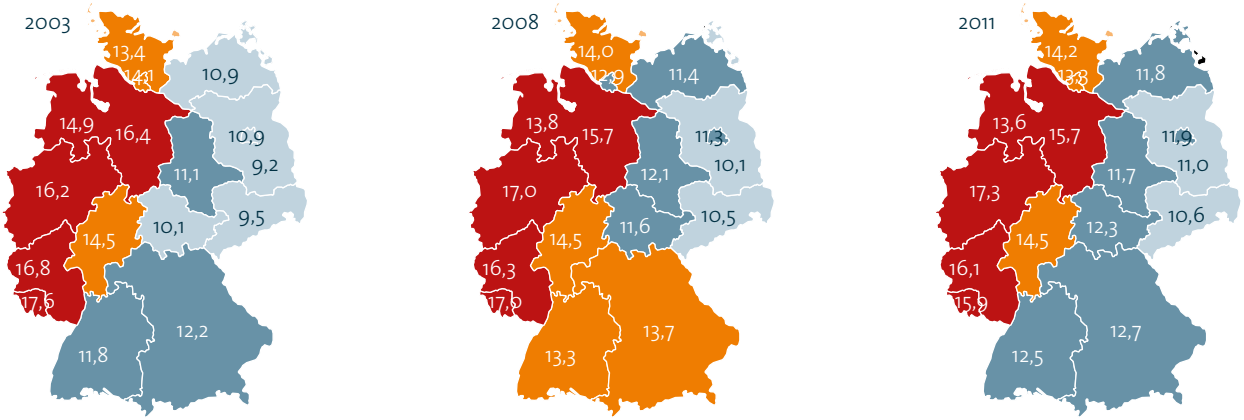
ESBL-producing bacteria: ESBL[4] are enzymes which render antibiotics ineffective. ESBL is not a specific type of bacteria (like MRSA), but refers to a mechanism for developing resistance which can occur in many types of bacteria and also be swapped between different types. The bacteria deactivate antibiotics such as penicillins or cephalosporins. ESBL-producing bacteria are mainly found among Escherichia coli (E. coli), one of the most common types of bacteria in the gut. E. coli can trigger a wide variety of infections inside the body, including urinary tract infections, pneumonia, blood poisoning, and wound infections after surgery. Klebsiella species, which also count the digestive system as a natural habitat, are increasingly showing the mechanism for ESBL resistance.

Carbapenemase-producing bacteria are resistant to carbapenems and other antibiotics. Bacteria such as these are even harder to treat. In Germany these have so far only been found inside hospitals.

There are no reliable figures regarding the prevalence of problematic microbes. While some estimates put deaths from multi-resistant microbes in Europe at 25,000 a year,[5] other authors have even come up with 30,000 deaths in Germany alone after assessing documents from hospitals.[6]

The situation in Germany

In Germany most antibiotics are prescribed to outpatients (85%), with hospitalised patients only accounting for 15%.[7] In 2014 some 39 million antibiotics prescriptions were issued, which equates to 374 million defined daily doses (DDD[8]) and sales worth EUR 699 million.[9] Use has remained relatively constant over recent years, although reserve antibiotics are being prescribed increasingly often (see box). The main users are the elderly and children under 15.



Regional density of antibiotics prescriptions for 2003, 2008, and 2011 (in DDD/1,000)[7]

The frequency with which antibiotics are prescribed tends to vary across Germany, with fewer being prescribed in the East in particular. This phenomenon cannot be explained by different morbidity rates.

Particularly concerning is the fact that at least 30% of prescriptions for antibiotics are inappropriate.[11] For example, prescriptions are frequently issued for colds, i.e. viral diseases, against which antibiotics are not effective at all. Similarly, certain bacterial diseases such as tonsillitis or otitis media should generally not be treated with antibiotics.

Reserve antibiotics

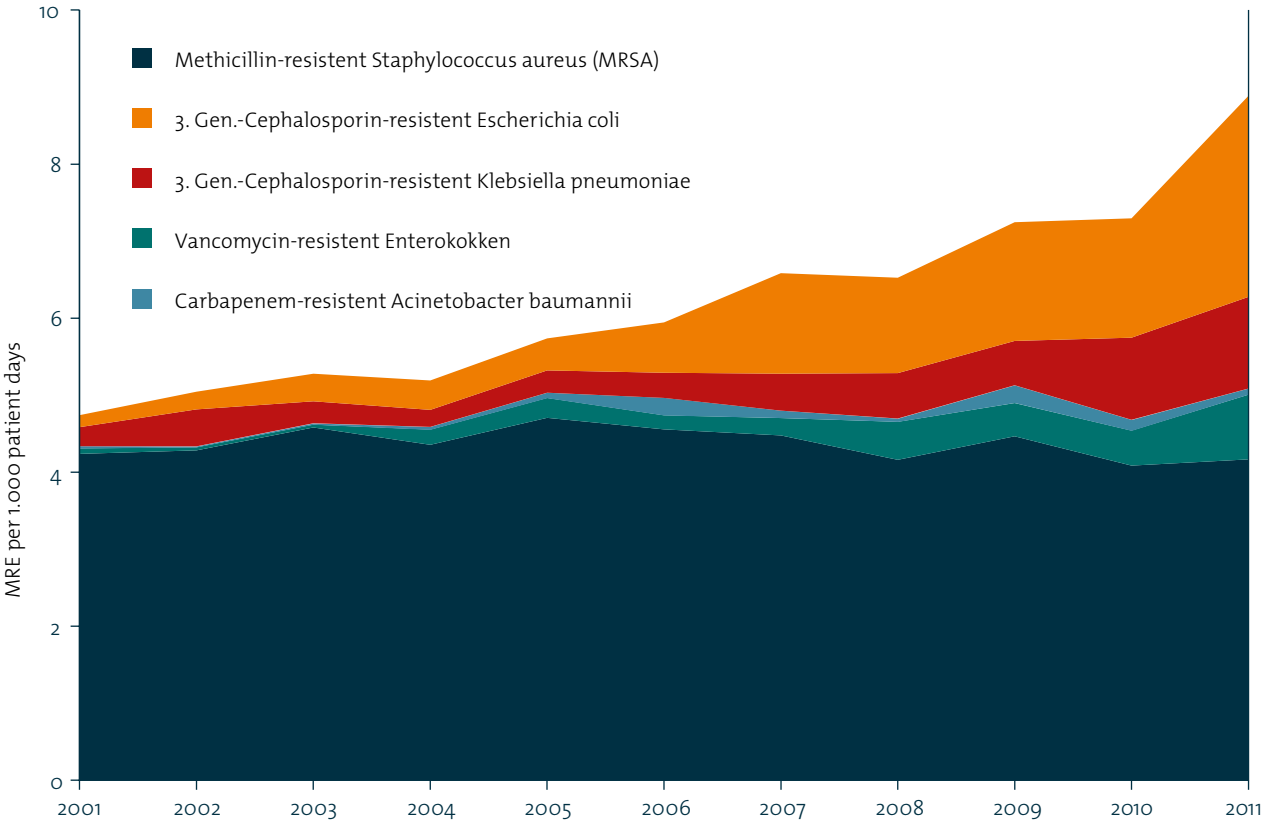
Reserve antibiotics should only be used on a targeted basis in cases involving resistant pathogens or where diseases take a more severe turn. Reserve antibiotics include third- and fourth-generation fluoroquinolones and cephalosporins. Almost a quarter of prescriptions for antibiotics involve reserve medicines.[10] In many cases, however, a standard antibiotic would be adequate.

Cases of resistance

In Germany the prevalence of MRSA is declining. In contrast, occurrences of ESBL-producing E. coli and other resistant types are on the increase.[7] The proportion of multi-resistant E. coli has risen from less than 1% in 1995 to 14% in 2010.

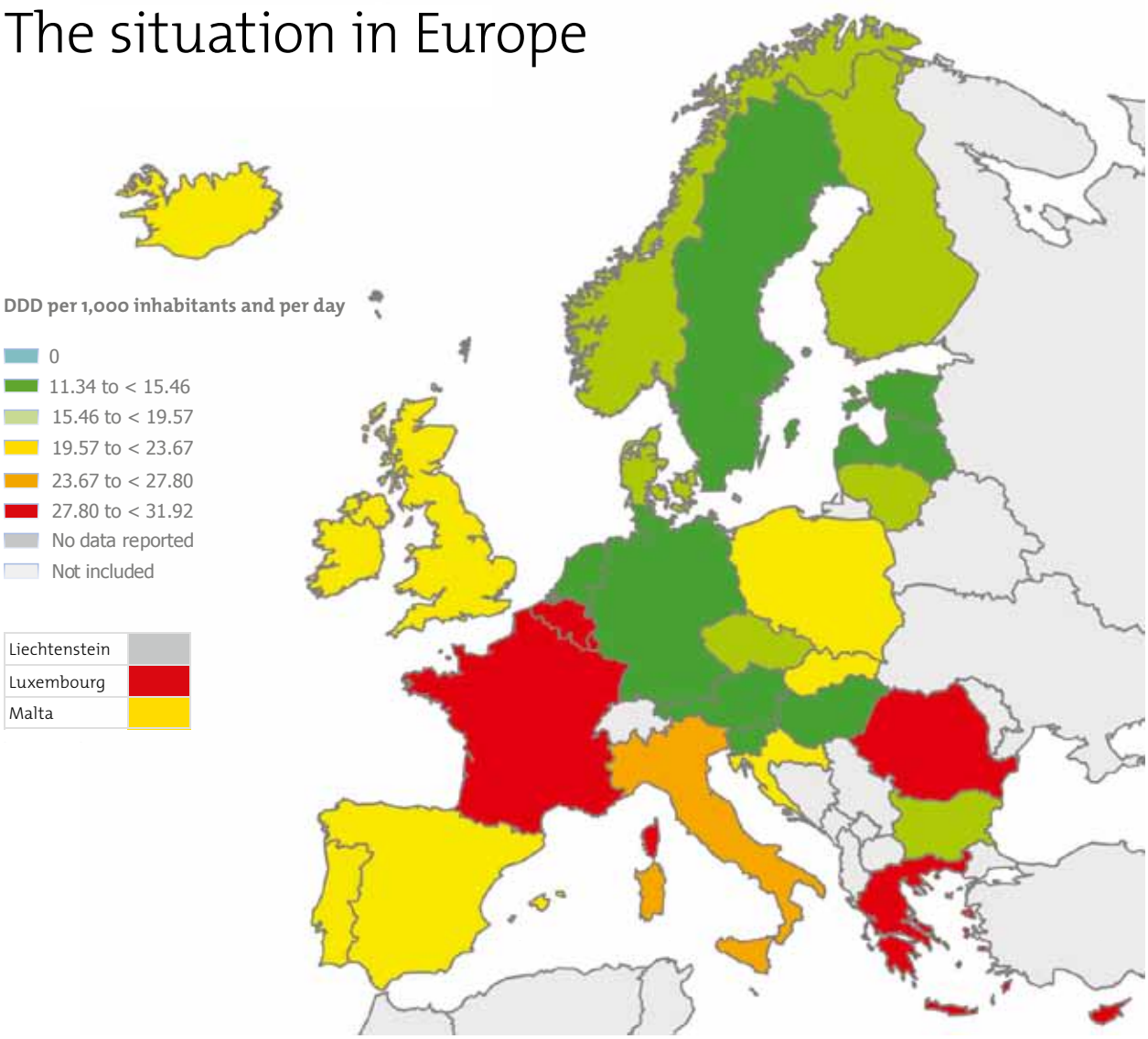
Based on projections, approximately every tenth person in Germany carries some form of multi-resistant pathogen.[11]

Selected MRPs	Colonisation rate (%)	MRP carriers in Germany
MRSA	1-2%	1.1 million
Vancomycin-resistant enterococci	1%	810,000
ESBL-producing E. coli	7%	5.7 million
Carbapenemase-producing bacteria	0.1-0.3%	162,000
Total	Approx. 10%	7.8 million



Increase in resistant microbes across German intensive care units (per 1,000 patient days) [7a]

The situation in Europe



There is a clear North-South divide in terms of antibiotic use in Europe. (DDD [8] per 1,000 inhabitants per day, 2012) Image: ECDC (2014) [13]

The situation in Europe is similar to Germany, with most antibiotics (90%) being used outside the hospital environment.[12] In terms of outpatient use in Europe, the average figure is 21.5 DDD per 1,000 inhabitants per day, which compares with 2.0 DDD in hospitals. The most commonly used are broad-spectrum antibiotics, which are effective against many different types of bacteria.

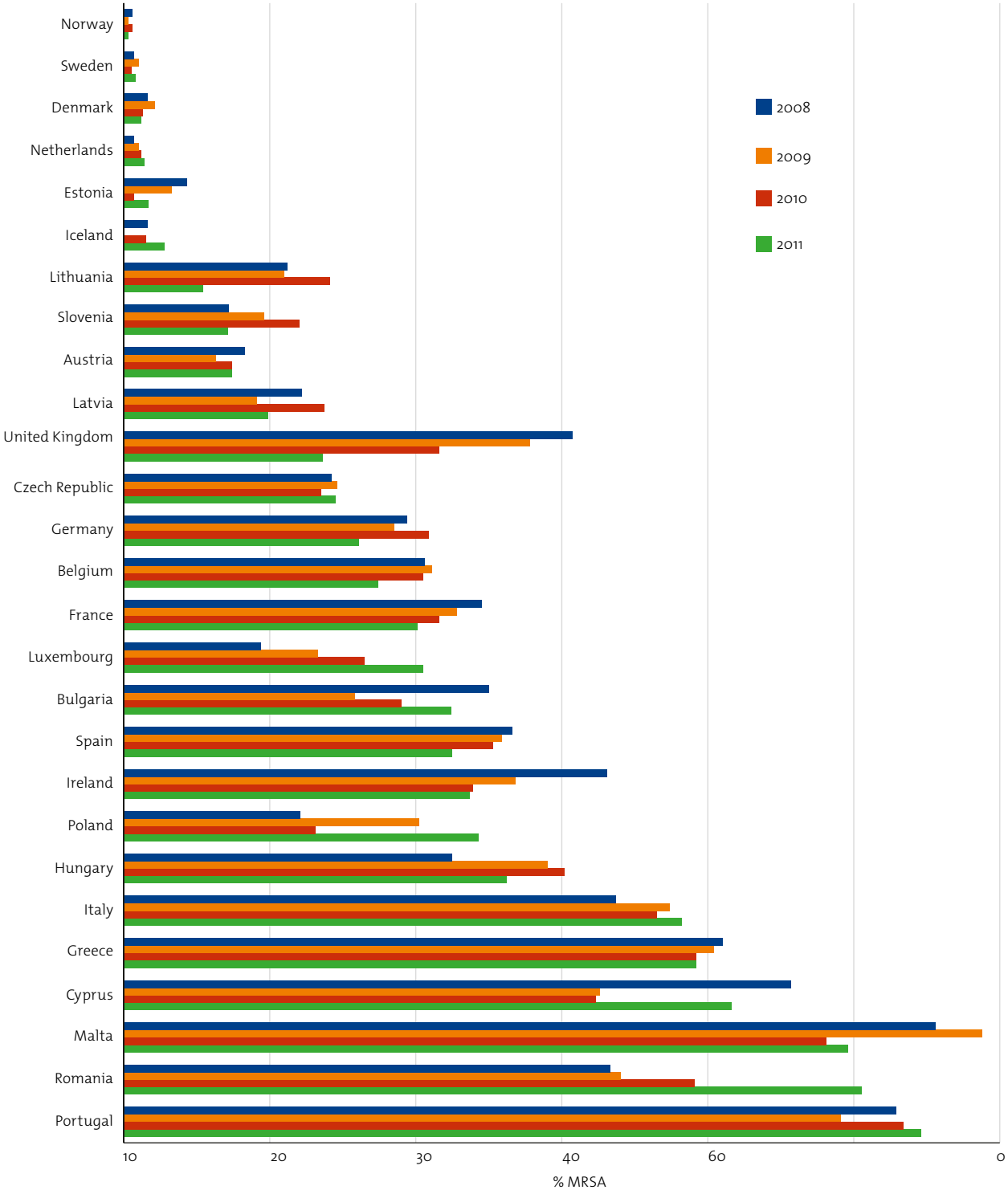
There is a noticeable North-South divide: Greece leads the field for antibiotic use (31.9 DDD per 1,000 inhabitants per day), while the Dutch consume the least (11.3 DDD). As regards use in hospitals, Finland is out in front (2.8 DDD), with the Dutch again bringing up the rear (1.0 DDD).

All things considered, there is no simple explanation for these differences. Given the fact that pointless prescriptions and incorrect use apply across the board, we are dealing here with a complex system involving medical, cultural, political, and economic factors. Investigations undertaken during 2008/2009 show that antibiotics are quite often sold without a prescription in the countries of southern and south-eastern Europe.[13] But countermeasures are possible here too, with Greece managing to reduce antibiotic use in recent years through publicity campaigns and regular training for doctors.[14]

Most countries are seeing an ongoing increase in the prescription of broad-spectrum antibiotics, but attempts to explain this have so far proved inconclusive.

Resistance rates

A clear North-South divide also emerges in terms of resistance rates. Particularly high resistance rates are found where antibiotic use is high too (see graphic).[14] The problem is most acute in southern and south-eastern Europe.

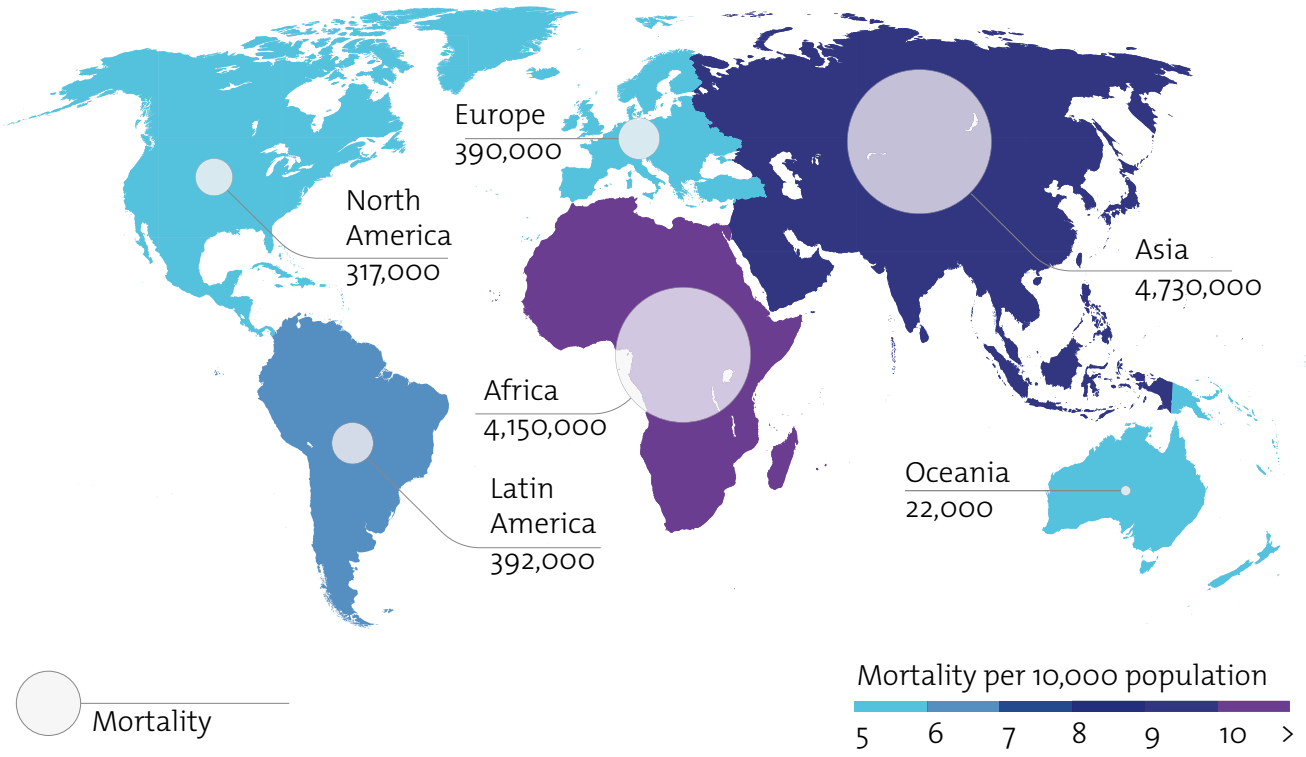


The prevalence of MRSA also shows a clear North-South divide. [7b]

The situation worldwide

The worldwide use of antibiotics increased by 36% between 2000 and 2010.[15] Three quarters of this increase can be attributed to South Africa and the BRIC countries, namely Brazil, Russia, India, and China, which are enjoying a significant economic upturn. The growth in population experienced by these countries is not the only reason for the increase,

The uncontrolled sale of medicines via street traders, drug stores, or even pharmacies and doctors' surgeries promotes this practice. In many cases the problem is not helped either by a lack of awareness of the risks involved and a lack of knowledge about how to use products properly.
WHO published a worrying inventory in 2015.[17]



A projection to the year 2050: there will be particularly high death rates as a result of multi-resistant pathogens in Africa and Asia. However, the risk will continue to increase in Europe too.

Image: O'Neill J (2014) [18]

as more antibiotics are also being used per capita. In contrast, the USA and countries in Central America and Europe in particular have been able to reduce their rate of use.

The causes of the increasing use of antibiotics are the same across the world: misuse and overuse. Self-medication – particularly for respiratory tract infections – is mainly widespread in countries with low and average income levels.[16]

The main point to emerge was that resistance is spreading worldwide. Comprehensive programmes are needed to combat this, but **national programmes** for controlling infection and managing antibiotic use are often either non-existent or inadequate. For example, there is often a lack of coordination across different sectors.

Surveillance: Intensive monitoring and documentation of all cases of resistance is

important with a view to taking targeted measures. This kind of thing calls for laboratories with qualified personnel and adequate financialresources, and both are lacking in many countries. But at least there is a reference laboratory in each of the six WHO regions.

Quality of medicines: Poor-quality medicines are also available in many countries. This results in incorrect doses being administered unintentionally, which in turn promotes the development of resistance. Counterfeit medicines are a problem here, particularly substandard products with too little active agent or even medicines which contain antibiotic substances not stated on the label. The primary cause is the inadequate regulation and control of the supply of medicines in poor countries.

Sales without prescription remain a fact of life in many countries. Medicines are often even available from street markets, although they can be obtained without prescription in pharmacies or drug stores too.

Lack of treatment guidelines: Many countries have no standards as regards the treatment of infectious diseases. This promotes the misuse of antibiotics by healthcare personnel.

Lack of awareness: Many people around the world are simply unaware of the problem of resistance, sometimes in spite of information campaigns. Many also continue to believe that antibiotics can help combat viruses.

Price plays an ambivalent role as far as antibiotics are concerned. Depending on the active agent and the country, an antibiotic can be very expensive and make some of the treatment available unaffordable for poor people. In other cases, however, antibiotics may be so cheap that there is a danger of somewhat cavalier (mis)use – particularly in uncontrolled markets.

Case study: antibiotics in Ghana[19]

Ghana is a comparatively stable country in West Africa, although its approach to antibiotics is rather problematic:

- Barely any surveillance of antibiotic use
- Inadequate controls allow a free exchange of merchandise within West Africa
- Uncontrolled use of antibiotics in farming
- First measure: formation of an Antimicrobial Resistance Working Group with the aim of bringing together doctors, vets, politicians, scientists, and media representatives
- Introduction in 2011 of a policy for controlling infection, although practical implementation has so far been patchy

Infectious diseases – not just a question of medicine

When discussing the significance of infectious diseases in global terms, it can be helpful to look to the past too. Historically speaking, victory over the major infectious diseases has been about more than medicines and vaccines – even if the importance of these cannot be doubted. It is clear from the figures, however, that there are other factors at play too.[20] When Robert Koch discovered the pathogen responsible for tuberculosis in the 1870s, mortality rates in England had already fallen dramatically. By this time, there were already only half as many deaths as in the 1830s, when epidemiology mapping first began. And even before synthetic antibiotics first offered truly effective treatment options in the 1940s, the number of infection-related deaths had already fallen to an eighth of the previous figure. The decline in TB can be explained by the onset of decisive social changes: improvements in living conditions, food, working conditions, income, and education, as well as the development of antiseptic working practices in the field of medicine.

Photograph: ind_sanitation_who211190

Tuberculosis – the social infectious disease

Tuberculosis (TB, Tbc) is caused by infection with Mycobacterium tuberculosis. It predominantly affects the lungs (although other organs may be affected too) and can destroy lung tissue over a period of years. Around a third of the world's population is infected with TB pathogens. In most cases, however, the disease only takes hold if the immune system has become too weak – as a result, for example, of malnutrition or other diseases. The close association with living conditions makes TB a social disease closely linked to poverty. This is because cramped living conditions favour contagion.

In 2013 some 9 million people worldwide were suffering with tuberculosis, with 1.5 million dying from the disease – the vast majority in poorer countries. A third of TB cases are not even recorded. It is also likely that many children die of TB without the disease being documented as the cause of death.

Many people lost their lives to tuberculosis in Germany too up to the middle of the last century.[21] Thomas Mann created a literary monument to 'consumption' and its treatment at the spa resort of Davos with his novel The Magic Mountain. TB has been amenable to treatment with medicines for 50 years now, so should really be nothing to fear. Globally speaking, however, the disease remains a major problem.

Tuberculosis case study

Interview with Dr Eva-Maria Schwienhorst from the German Leprosy and Tuberculosis Relief Association (DAHW), Würzburg

Photograph: missio

Dr Schwienhorst, which countries are currently the worst affected by TB?

Schwienhorst: The most cases per capita occur in the countries of southern Africa. But the highest numbers of new cases (in absolute terms) are found in India and China at two and one million per year. Then again, the countries of the former Soviet Union have the highest proportion of resistant TB pathogens.

Why is TB still a problem?

Schwienhorst: Part of the reason why TB is making a comeback is the ongoing spread of HIV. Every third person worldwide is infected with the TB pathogen, although only every tenth person infected falls ill during their lifetime. Compare this with the risk for those infected with HIV, which stands at 10% a year! Other factors which weaken the immune system, such as diabetes, can increase the risk too. TB is clearly also a disease associated with poverty and poor social conditions and mainly tends to affect vulnerable groups within the population.

What form does treatment take?

Schwienhorst: Four different medicines are taken daily at first, and then two over a period of six to nine months. The prospects of recovery are good with this approach. Problems occur because people start to feel better after a few weeks. If patients are not given the right kind of support, they tend to stop taking their treatment too soon – one of the main reasons behind the development of resistance.

Is multidrug-resistant TB (MDR-TB) amenable to treatment too?

Schwienhorst: Yes, but the process takes at least two years, far more medicines are required, and there are lots of side effects. One of the medicines must be injected for at least six months. In Germany some kind of permanent feed would be inserted in such cases – which makes things far easier – whereas patients in countries with only moderate or low income levels need to put up with painful daily injections in the gluteal muscle. Many patients also become deaf or suffer depression as a result of treatment.

Is treatment administered to similar standards across the board?

Schwienhorst: In rich countries cases of resistance can be identified and then treated in a targeted manner on an individual basis. The choice of medicines is also wider. Countries with moderate or low income levels tend to use standard therapies. There is less flexibility and, unfortunately, many more patients stop taking their treatment due to a lack of proper support.

What are the prospects for people with extensively drug-resistant TB (XDR-TB)?

Schwienhorst: Even though there is a form of resistance to very many antibiotics, the chances of success remain within the 20-40% range. Having said this, some 20-30% of people die, many stop their therapy, and side effects such as loss of hearing and psychological problems can be very severe. There are more and more cases of patients with TB pathogens showing resistance to all available medicines. These patients face the prospect of lifelong isolation with no hope of a cure.

What is the social impact of TB?

Schwienhorst: MDR-TB represents a special challenge to healthcare systems, particularly those in poorer countries. The medicines cost many times more than a normal course of TB treatment. There are also indirect costs, which place a tremendous burden on patients and wider society, particularly in poorer countries

without effective social security systems: those falling ill often lose their jobs or have no income for a period, which means they can no longer pay their children's school fees. Not to mention questions of stigma and social exclusion.

What about the situation in Germany?
Schwienhorst: The number of people falling ill is slightly up again at the moment, mainly as a result of immigration from regions with a lot of TB. This poses no real threat to the population, however; it is more of a challenge for our doctors, who are not really prepared for the task of diagnosing and treating TB.

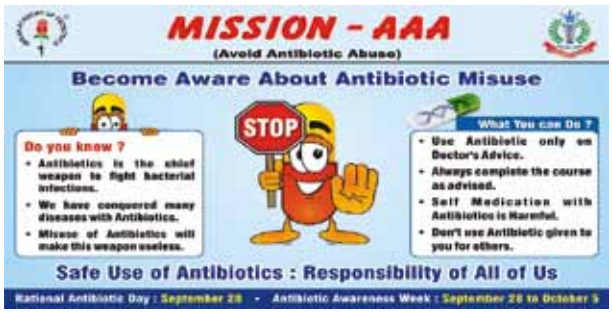
What can Germany do to help it cope with tuberculosis more effectively?
Schwienhorst: It is vitally important to make an appropriate financial contribution to the global fund! We are one of the richest countries in the world and have a responsibility in this area. We also need more incentives for research and development involving new TB medicines.

The global fund for fighting AIDS, tuberculosis, and malaria provides USD 4 billion a year to support healthcare projects in countries with moderate and low levels of income.

Preventing resistance

Patients – the ignorant users?

Ignorance is definitely a problem: according to one survey, four out of ten Germans believe that antibiotics can help treat viruses.[10] This misconception leads many people to try and treat colds with antibiotics, even though these agents are only effective against bacterial diseases. It may be the case – in Germany at least – that antibiotics are prescribed by doctors, and one might be entitled to think they would know better. But a cavalier attitude to prescription can often develop, driven by patients' expectations and the tremendous time constraints associated with day-to-day clinical practice. Doctors are clearly often not taking the time to convince their patients of the merits of other suitable therapies which do not involve antibiotics (see the interview on page 16). All the same, 82% of Germans have heard of antibiotic resistance and 64% of people are anxious about this issue.[22] However, most people attribute the reasons to livestock farming, with only a quarter believing that the source of the problem is human medicine. This suggests people need more information – not just about when antibiotics are appropriate, but also about how to use them properly. A survey conducted by DAK (a German health insurance provider) revealed that 11% of those asked failed to complete their course of treatment properly.[10] As soon as they feel better, they either reduce the dose or stop taking their medicine altogether. As a result, not all bacteria are killed off, and those which survive develop resistance accordingly.
The survey also revealed that a similar number of those asked stop taking antibiotics, only to start taking them again later in the event of similar symptoms. The risk of misuse is therefore high.



Campaign in India: 'Kill the bug, not the drug' "
Source: www.iapindia.org

Information campaigns do help

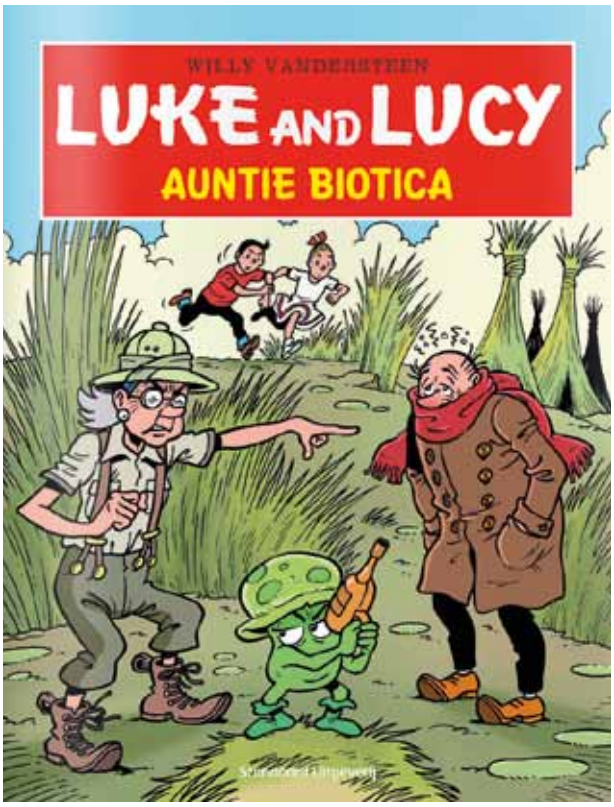
Education and information do help. Health insurance providers in France, for example, launched a media campaign in 2002 with the slogan 'Les antibiotiques c'est pas automatique' (Antibiotics should not be the automatic choice).[23] Particularly in winter, the typical time for people to catch colds, a series of brief films was

Canada: Do bugs need drugs? Hygiene education from nursery school through to primary school

shown on TV. This helped reduce prescriptions of antibiotics by 27% within five years, with prescriptions for children falling by as much as 36%. In 2014 WHO established which countries were already running information campaigns for users.[24] So far, the industrialised nations have done most to tackle the issue. The USA, Canada, and Australia hold an antibiotics week every November. Similarly, various European countries, as well as Thailand, Hong Kong, and Mexico, hold an antibiotics day on November 18 with the specific aim of providing information. The range of media used is really quite broad, with posters, brochures, comics, online games, and materials for schools all being produced to cater for different age groups. While the focus is on hygiene for those of nursery school age, the idea with adults is to raise awareness of rational antibiotic use.

In India too the national association of paediatricians runs an annual campaign, but there do not seem to have been any large-scale campaigns in other developing countries so far. The situation will hopefully change when the global action plan agreed in 2015 is rolled out (see page 31).

Poster from Germany's Federal Centre for Health Education *(Source: www.bzga.de)*



Comic from Belgium: 'Auntie Biotica'

Doctors: the professionals need to catch up

Since antibiotics are only available on prescription in Germany, any overuse or misuse is clearly the responsibility of the doctors who prescribe them. Every third German or so was prescribed a course of antibiotics during the past 12 months – often to combat viral infections such as bronchitis, colds, and coughs. The reasons for this become clear in an interview with a clinical practitioner, who talks about his own day-to-day experiences (see column on the right).

Even when it does make sense to prescribe an antibiotic in a given case, it is then a question of which active agent to choose, with several dozen antibiotic agents currently available. Broad-spectrum antibiotics are prescribed in many cases, although these do not always constitute first-line therapies (between them, amoxicillin, cefuroxime, and ciprofloxacin account for 34% of all prescriptions in Germany).[25] This approach to prescription promotes the development of resistance.

Price also appears to play a role in the choice of prescription. It is no bad thing in principle for doctors to be aware of cost implications, but this can sometimes lead to unintended consequences too. Statistics from Germany and Denmark show that any given antibiotic will be prescribed more frequently following a sharp fall in its price. After the patent protection expired for ciprofloxacin, its use doubled within seven years.[26]

More recent active agents, which have not been on the market as long, are generally much more expensive than long-established products. They are no more effective in normal cases, but they can certainly be justified in cases involving resistance. This is why a targeted approach makes sense when selecting a suitable active agent. To facilitate this, a laboratory needs to produce an antibiogram listing the pathogens contained in a sample of, say, urine along with any instances of resistance.

Day-to-day clinical practice

Photograph: private

Most antibiotics in Germany are prescribed by general practitioners. We talked to Dr Eckhard Schreiber-Weber, a GP from Bad Salzuflen, about why there are so many incorrect prescriptions.

Colds are mainly triggered by viruses, but doctors in Germany often prescribe antibiotics for such infections. Are they acting against their better judgement?

Schreiber-Weber: I think so. Doctors often prescribe antibiotics 'to be on the safe side'. But this is wrong, except before surgery, and actually constitutes a case of misprescribing from a clinical perspective.

Why do doctors do this?

Schreiber-Weber: Many do not take the time to make a distinction between viral and bacterial diseases. But this needs to happen, even in November and December when the waiting rooms are full. It will often then turn out to be some form of bronchitis, which can mostly be treated without antibiotics given that 90% of cases are of viral origin.

Do some patients demand antibiotics too?

Schreiber-Weber: There are two tribes. Some are pleased if I don't prescribe an antibiotic. Others want antibiotics if the infection is slow to clear up – they want to get back to work. This is where information becomes so important: studies show that almost every other person is unaware that antibiotics are no use against viruses.

What can be done about this?
Schreiber-Weber: Doctors must not issue prescriptions simply to keep people happy. When infections are doing the rounds, I find myself saying – several times a day – that the infection is a virus and that antibiotics are no use in this case. It's easy enough to explain.

Is there room for improvement in terms of bacterial infections too?
Schreiber-Weber: A classic example would be otitis media, which clears up on its own in 80% of cases. There is no evidence that antibiotics make any significant contribution towards reducing complications. A study by Witten-Herdecke University found that 17 children needed to be treated for just one of them to feel less pain after two days. And you also need to bear in mind that one of the 17 children will also suffer adverse effects associated with antibiotics, such as vomiting or skin rash. These figures are no secret, but almost all paediatricians and GPs still immediately prescribe antibiotics in such cases. That simple piece of advice – wait a couple of days and then see how things stand – is ignored more often than not.

What about urinary tract infections?
Schreiber-Weber: There are good guidelines for doctors to follow, but they don't stick to them. Germany's national S3 guidelines for uncomplicated urinary tract infections no longer refer to the broad-spectrum antibiotic ciprofloxacin, but recommend other antibiotics instead. In spite of this, urologists and GPs very often prescribe ciprofloxacin all the same. And while prescription rates have doubled over the past seven years, the resistance to ciprofloxacin by E. coli, the pathogen most commonly involved in urinary tract infections, has risen too.

Would better laboratory-based diagnostics help in terms of day-to-day clinical practice?
Schreiber-Weber: Laboratory-based diagnostics do have a role to play. Blood tests can help distinguish viruses from bacteria for things like respiratory tract infections. The most important thing for a GP, however, is to perform a thorough examination: perform auscultation, ask the patient questions, and be sure to assess the symptoms correctly. For example, it is no longer standard practice to take a throat swab when checking for streptococci, because not all streptococci in the throat will cause people to fall ill.

Photograph: vista_pixelio.de/Fotolia.com

Does advertising shape prescription behaviour?
Schreiber-Weber: Yes, that's certainly the case. Broad-spectrum antibiotics, particularly the quinolones (e.g. ciprofloxacin) are advertised as panaceas. Doctors are then happy to prescribe them too. They may well enjoy a false sense of security as a result, but in practice they will often have misprescribed something.

Do doctors in Germany receive feedback on their prescription behaviour from, say, health insurance providers?
Schreiber-Weber: Pretty rarely on the whole. But health insurance providers could easily make recommendations, given that they have the data from prescriptions and know which doctor is prescribing what.

What would be your appeal to your colleagues in the medical profession?
Schreiber-Weber: To give patients more information. And to have the courage not to be pressurised into prescribing antibiotics. They also need to stick to the guidelines more closely, rather than being lulled into a false sense of security.

Photograph: sudok1/Fotolia.com

The hospital as a crime scene: no handshakes allowed

German hospitals make people better, but things are not quite as simple as that. Many people will have heard these stories from those they know: up to 600,000 people fall ill every year through infections picked up while in hospital (nosocomial infections). As many as 15,000 die as a result, although a third or so of these deaths could actually be avoided.[27]

It is perfectly clear what is causing these infections, with 90% of them being transmitted via the hands of clinical staff.[10] The immune system of someone lying in hospital will often have been weakened by disease, surgery, or other circumstances. Open wounds, catheters, and infusion needles provide entry points for pathogens. The considerable amount of hand contact in the course of care and treatment actually facilitates transmission. So an important rule for avoiding infections is to avoid shaking hands if at all possible!

Staffing ratios for nurses are also an important factor: severely ill patients requiring ventilation are more likely to fall ill as a result of hospital microbes when staff-patient ratios are low.[28] Staff find themselves having to switch between individual patients more frequently, and there is less time for thorough disinfection of hands. This is why adequate nursing staff levels play such an important part in terms of preventing infections.

Of every 100 infections acquired in hospital, six or so can be attributed to multi-resistant pathogens. 30,000 out of a total of 400,000 to 600,000.[29] So resistant microbes account for very few of the microbes found in hospitals.

In Germany hospitals account for 15% of antibiotic use, with most being administered for prophylaxis purposes prior to surgery.[30] This seems fairly sensible on the face of it, because unwanted hospital infections are ultimately something to be avoided. But here too the statistics reveal widespread pointless use, with nearly one in two patients being given prophylactic treatment – not just over the

course of a day, but for longer periods – despite them never having had any bacterial infection previously. This is unnecessary and introduces additional risks.[31]

A systematic approach to improving hygiene

Germany's Protection Against Infection Act (Infektionsschutzgesetz – IfSG) was amended in 2011 with a view to improving the situation.[32] The Act states that hygiene standards are required in hospitals and that infections must be documented and assessed – as must the use of antibiotics. The intention is to use specialist hygiene personnel to ensure work is carried out by qualified staff. But if these sensible regulations are still not being implemented as well as they might, this may also have something to do with the fact that healthcare is dealt with at state level in Germany (as opposed to federal level) and the individual states within Germany have so far failed to adopt a uniform policy in this area.

There is still a shortage of specialist hygiene personnel and infectious disease specialists to advise doctors regarding treatment options.[33] This is where the 'Antibiotic Stewardship' initiative comes in:[34] doctors working in hospitals are trained in rational antibiotic use (with a view to becoming ‚ABS experts') – an important source of support, particularly for smaller hospitals with fewer than 500 beds.[35]

MRSA screening prior to hospital admission – a sensible measure?

The practice of MRSA testing for all patients allocated a hospital bed was introduced in the Netherlands as long ago as the 1980s. Those found to be affected were isolated immediately, with targeted treatment initiated in order to kill off the MRSA. But is this a sensible model and can it be transferred to Germany?

Systematic investigations in the United Kingdom found that focusing screening on specific risk groups meant only half as many patients needed to be tested, with 81% of all MRSA cases being detected all the same. Mass screening based on the Dutch model hardly provides any additional security, but does result in higher costs. With this in mind, several associations of experts in Germany have argued against general screening and recommend targeted screening based on specific risk factors instead.[36] GPs can arrange for screening as required. In the event of MRSA colonisation, which is mostly a localised phenomenon, antimicrobial treatment can be administered to the skin or mucous membranes concerned (mainly using special ointments).

Networks for providers of outpatient and inpatient care

While MRSA screening has played a part in the success enjoyed by the Netherlands, it is likely that many other factors are involved too. Antibiotic use is significantly lower than in other countries, there are more specialists in infectious diseases, compliance with guidelines is monitored at a national level, and all the various healthcare institutions work together as a matter of course to care for MRSA patients. By contrast, there are large areas of Germany without any networks to bring together the various strata of care providers (hospitals/GPs/nursing units). An MRSA patient will normally leave hospital before antimicrobial treatment – this mostly lasts several weeks – is complete. It is important to continue treatment on an outpatient basis, but this often fails to materialise, leaving microbes free to cause more problems further down the line. And special protective measures cease to be taken outside the hospital environment, so others become infected in places like retirement homes.

Several local and regional MRSA networks have been formed recently with a view to encouraging providers of outpatient and inpatient care to exchange information.[37]

Photograph: danielschoenen/Fotolia.com

Veterinary medicine: livestock farming

As well as producing milk and meat, industrialised livestock farming produces its fair share of problems too. And the kinds of things that animal welfare activists have been criticising for so long were given official recognition in an export report on turkey farming following an appraisal by the Ministry of the Environment for North Rhine-Westphalia in 2014.[38] Nine out of ten turkeys were being treated with antibiotics, while two of the four most widely used agents (colistin and enrofloxacin) were from classes of substances of great importance to humans as reserve antibiotics. A third of treatments administered even involved preparations which are not authorised for turkeys at all. According to Germany's Medicines Act, this kind of thing is only permitted in certain individual cases where something of an emergency applies in therapy terms. There clearly is an emergency of sorts, but the conditions in which animals are kept are making them sick, with almost one in five farming businesses inspected exceeding the maximum permissible density in terms of the number of animals for a given amount of stall space. The current limits are 52 kg of hens or 58 kg of cocks per square metre.

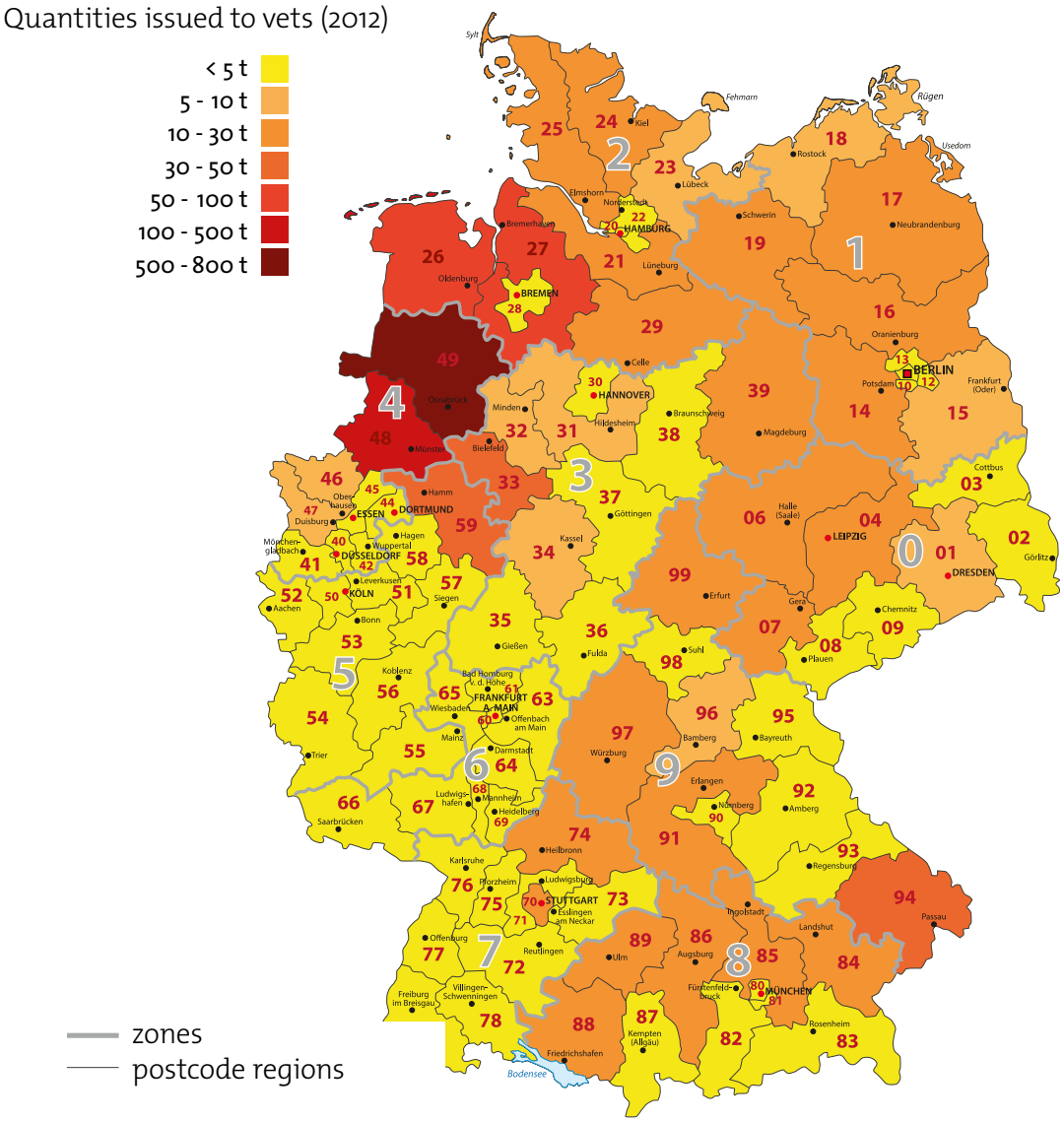
The conditions revealed by a 2012 study of broilers were no better, with nine out of ten being treated with antibiotics and up to eight agents often being administered at the same time.[39] The period of use was only one to two days in nearly half of cases, which is shorter than what is really permitted. Smaller farming businesses (involving fewer than 20,000 animals) emerged in a more positive light, with these taking longer to fatten poultry up and using antibiotics less often.[40]

Germany near the front of the pack

In European terms, Germany is among the

leading users of antibiotics for livestock farming. It is certainly true that the overall volume has reduced in recent years (from 1,706 tonnes in 2011 to 1,238 tonnes in 2014).[41] But this does not tell the whole story, since different agents are administered in different doses and the amount of medicine used also depends on the animal's body weight. When these factors are taken into consideration, antibiotic use has practically remained the same. The main change has been in the range of agents used, with classes of agents of special importance to human medicine being used with increasing frequency (e.g. fluoroquinolones: an increase from 8.2 tonnes in 2011 to 12.3 tonnes in 2014).

Comparisons within Europe are difficult, with sales figures for antibiotics varying significantly from country to country.[42] There is no clear reason why this is the case.[43] A detailed analysis of use is important, however, with a view to developing targeted improvements. A clearer picture is slowly emerging in Germany. Manufacturers and wholesalers are supposed to have been giving a regional breakdown of their sales figures on a voluntary basis since 2011, while the VETCAB pilot study has determined how often antibiotics are used (although participation by farmers and vets was again on a voluntary basis). [44]



Antibiotic use is highest in the North West of Germany, where cattle farming is most intensive.[7c]

Case study: the Netherlands

Until recently the Netherlands was Europe's biggest user of antibiotics for livestock farming. But in 2008 a national programme was launched with the aim of drastically reducing the use of medicines. The measures also had fundamental implications for the role played by vets.

Year	Measure
2008	Monitoring of antibiotic use; improvements in herd health; setting of targets for reducing antibiotic use
2011	Guidelines for the use of frequently used antibiotics; introduction of a traffic light system intended to alert the surveillance authority to high levels of use
2011	Introduction of three antibiotics categories based on importance to humans and animals; compulsory herd health agreements between vets and farmers; ban on mixing medicines and feedr
2012	Ban on the preventive use of antibiotics
2013	Introduction of treatment plans; stricter health criteria; rules for fitting out stalls; setting of targets for reducing the use of critical antibiotics

A study by Germany's Federal Ministry of Food and Agriculture summarises the experiences of the Netherlands, with which it shares a border:[52] 'Before efforts to reform were introduced in 2008, sales of veterinary medicines accounted for almost 60% of a vet's turnover. Some 5% of Dutch vets had specialised in intensive livestock farming and were prescribing 80% of antibiotics. Thanks to the reforms, sales of antibiotics fell by more than 50% between 2009 and 2012, with the plan being to achieve a 70% reduction from 2009 levels by 2015. Vets continue to have the right to dispense medicines, but extensive measures have been taken to reduce antibiotic use, which has influenced the way Dutch vets go about their business.'

- Pigs: 115 days' fattening, including 4.2 days' antibiotics
- Chickens: 39 days' fattening, including 10.1 days' antibiotics
- Dairy cows: 3.5 days' antibiotics per year

Since 2014 an amendment to the Medicines Act has stipulated that livestock farmers must provide records of the type and quantity of antibiotics used. Farming businesses which exceed a given value must draft an action plan for reducing the use of antibiotics, such as vaccinations and improvements in hygiene and other conditions associated with livestock farming. These benchmarks were first defined in 2015.[45] Implementation remains unsatisfactory, however, with research undertaken by journalists in early 2015 showing that thousands of farmers had still to fulfil their reporting obligations.[46] Politicians and journalists are even complaining that the Federal Ministry of Agriculture is allegedly keeping detailed data under wraps to prevent any regional assessment.[47]

Antibiotics as a fattening aid

Antibiotics in small quantities can influence the composition of intestinal flora to such a degree that an animal's metabolism changes and it puts on weight. The reason for this is that pathogens can be suppressed at low doses too, leaving more nutrients available for the animal. Also, the metabolites produced by 'good' bacteria can improve digestion and help break down nutrients.

Since 2006 the use of antibiotics as a fattening aid has been banned in the EU. Given, however, that sales figures have barely declined in the intervening years,[48] it seems likely that there has

Measures for recording and reducing antibiotic use within livestock farming An overview of selected countries	Denmark	Netherlands	Germany	European Parliament's position
Recording of sales figures for antibiotics	✔	✔	✔	✔
Monitoring of use at individual farming businesses/database	✔	by private sector	✘	✔
Penalties for non-compliant use	✔	✘	✘	✘
Distinction between prescription and sales	✔	✘	✘	✔
Restrictions for important antibiotics	✔	✔	✘	✔
Target for reductions	✘	✔	✘	✘
Priority given to administering treatment on an individual basis	planned	✘	✘	✘
Improvements to livestock farming	✘	✘	✘	✔

Measures for reducing antibiotic use in farming: comparison involving Germany/Netherlands/Denmark (as per Birkel[50])

merely been a change in prescription practices, with antibiotics simply being prescribed more often for ‚treatment' purposes or to prevent infections within herds (metaphylaxis) rather than to promote growth.

The global significance of this problem is enormous. In the USA the use of antibiotics for fattening purposes is still allowed, and the fact that industrialised fattening of animals is becoming more common in emerging and developing countries does not augur well for the future. But it would also be a mistake to underestimate use by small-scale farmers, because the antibiotics trade is not subject to any controls in many countries. Not to mention the fact that antibiotics are often seen as a kind of panacea – including for animals!

Types of resistance

Different forms of resistance are associated with different species of animals. S. aureus, for example, is resistant to antibiotics in 70% of poultry, while the multi-resistant variety (MRSA) has been found in 15% of birds. As for pigs, almost all strains of Bordetella bronchiseptica are resistant to ß-lactam antibiotics, with the highest levels of resistance among E. coli being found in calves.

The situation is particularly critical for ESBL-producing bacteria, which are resistant to many different antibiotics. This trait can easily be transferred between different types of bacteria – even those quite unlike each other. The Federal Institute for Risk Assessment (BfR) states that ‚ESBL-producing bacteria have been found in livestock populations (poultry, pigs, cattle) and numbers are increasing. [...] ESBL-producing Salmonella and E. coli strains have also been isolated in food samples (pork, poultry meat, and unpasteurised milk). As such, the BfR believes it is possible in principle for humans to become infected with ESBL-producing pathogens through their food. It is currently impossible, however, to estimate how high the risk of infection might be.' [49]

The Netherlands has shown just how far antibiotic use can be reduced within industrialised livestock farming (see box). In 2009 a clearly defined reduction target was announced with the intention of encouraging livestock farmers to halve the use of antibiotics for fattening purposes within the space of four years. Although there were problems, things largely went to plan and the target was actually achieved within three years. From the outset, the government had placed the emphasis on people taking the initiative themselves and on developing a 'public-private partnership'. But when it emerged that farmers and vets were guilty of widespread abuse and of deceiving the authorities, the regulatory aspect of the authorities' role was stepped up considerably.[50]

Transmission from animals to humans

The emergence of various forms of resistance in connection with livestock farming is of real significance, since resistance can migrate to humans: ‚The transfer of antibiotic-resistant bacteria or of resistance genes between humans and animals [is] possible in either direction.' [7] There are some German regions where microbes associated with animals (e.g. LA-MRSA) now account for over 10% of those found in hospitals.[51] At Münster University Hospital, the proportion of resistant bacteria originally from animals is as high as a third – the area around Münster being among the biggest for meat production.[10]

The right to dispense: when vets sell antibiotics to farmers

When German farmers need an antibiotic for their chickens, they do not need to visit a pharmacy. The vet will bring it along instead. The advantage of this approach is that sick animals can be treated as soon as the vet identifies an infection, which also reduces the risk of it spreading to the rest of the herd. But this system – referred to as the right to dispense – offers vets dangerous financial incentives to prescribe antibiotics, with sales of medicines reputed to account for 50-80% of their income.[53] Journalists have not been afraid to point out how drastic the situation has become: ‚People are also starting to call the larger practices "motorway" vets – they spend their time driving from farm to farm to sell their products, as opposed to examining animals and helping them get well.'[51] Vets receive discounts from pharmaceutical companies if they purchase large quantities of stock. A journalist at Germany's Die Zeit newspaper describes one example where vets in the state of Hesse were offered an 88% discount on a reserve antibiotic if they were prepared to purchase 500 bottles.[53] In Denmark the right to dispense was abolished in 1995, and the use of medicines fell by a half thereafter. In terms of whether this would be possible in Germany, it is worth remembering that the major operations involved in the fattening up of animals now only tend to be served by a handful of large veterinary practices. These would be able to appoint a pharmacist and simply carry on as before. This could not happen in Denmark, since vets are not allowed to establish a business relationship with pharmacies or pharmaceutical companies.[54] But even if the right to dispense were preserved, it would still be possible to introduce certain measures such as abolishing discounts on antibiotics and setting minimum prices. It is also essential that farmers find it worth their while to invest in vaccines, which are more expensive in comparison. It may be worth considering a general overhaul of the payment system for vets to bring it in line with the Dutch model.[54] In that country vets conclude herd health agreements with farmers with a view to providing preventive care. They inspect livestock at least once a month, regardless of whether they are sick.

A vet's perspectives

An interview with Dr Matthias Link, a vet and animal health consultant for organic farming based in Varrel (Germany)

Photograph: private

Dr Link, is there any difference between organic and conventional farming as regards the use of antibiotics?

Link: Yes, organic farming sets out to keep animals in such good health that no antibiotics are required. This is achieved through the way they are bred, kept, fed, and generally treated. Also, organic farmers tend to wait that bit longer after medicines have been administered. There are statutory rules regarding how many courses of treatment an animal may receive in its lifetime. Organic farmers do not use any reserve antibiotics from human medicine either.

Would it make sense to introduce different classes of antibiotics, with some to be used in human medicine and others in veterinary medicine?

Link: No, because the active agents are the same in many instances. You also get cases of cross-resistance, whereby resistance to one active agent might imply resistance to a totally different agent as well.

What can farmers do to reduce the likelihood of infection?

Link: The day-to-day farming routine offers plenty of opportunities: high-quality feed for animals, improvements in stall hygiene and the general stall environment, dry bedding, regular cleaning of stalls and changes of bedding, reductions in density levels, keeping different age groups separate, vaccination programmes against specific pathogens, additional feed to ward off problems when the likelihood of infection is high, immediate treatment and segregation of sick animals, and intensive diagnostic measures to identify prevalent pathogens.

Would it make sense to switch to older breeds? Are these less prone to disease?

Link: I would not recommend this approach across the board. Diversity would actually be very helpful from a breeding perspective. It is risky to focus solely on 'performance' and on reducing the number of paternal lines. More importance should be attached to other breeding criteria such as longevity, hoof and udder health, etc. Old breeds may offer favourable characteristics in this regard.

What role does the price of meat or milk play?

Link: A very important one! If farmers are getting 3 to 7 cents for every litre of milk they sell, there is nothing left for investment in animal health. It's quite a different story in actual fact, and farming businesses are having to look at all their costs to see if any savings can be made. Quick savings can be made by cutting back on preventive health measures. But to be honest, it's not as though money is always ploughed straight into animal health when milk prices are high either. Things being they as they are, there is an onus on the legislative authority to see that existing animal welfare requirements are enforced.

What role does the international livestock trade play?

Link: The spread of the classical livestock diseases we have been very successful in eradicating within Western Europe is becoming a problem. This means foot and mouth disease, classical swine fever, African swine fever, and bluetongue are posing a new threat to us once more. Other infections also spread as a result of livestock transport, and the stress of transport often leads to outbreaks of disease which then affect otherwise healthy holdings. This is why the practice of administering long-term antibiotics on a preventive basis to new groupings of transported animals is so popular within the conventional livestock farming community. The alternative is simple: we need to have regional structures and to restrict the international trade in animals to embryos, sperm, or breeding animals on a case-by-case basis. The export of

animals for slaughter should be avoidable if regional structures are used, with meat being exported thereafter.

What about large-scale slaughterhouses?
Link: Large-scale production structures increase the risk of consumers being given infected food. Not only Salmonella or Campylobacter species, but also harmless microbes are carried from animal to animal during the slaughter process, including any forms of resistance. In a nutshell, these microbes then end up in consumers' kitchens, from where they colonise people's healthy flora and are carried in turn into hospital by these same people. Once there, these resistant pathogens tend to affect chronically ill patients or those with weakened immune systems and result in the dreaded untreatable infections.

How do you rate the chances of things changing within farming?
Link: Politically speaking, it is certainly very difficult to reduce production volumes, and this will inevitably involve some negative effects and a degree of unfairness, with some seeking to secure an advantage under false pretences. Also, this is really just the effect rather than the cause of what we actually want to improve: namely the unsatisfactory situation as regards animal welfare and health. For decades it's all been about increasing volume and reducing costs, and the success of this approach has resulted in surpluses and price erosion at the expense of animals, whose welfare has been neglected. For me, the work we do to resolve this issue will only bear fruit if we define our objectives: improve animal welfare, leave tails, beaks, and testicles alone, minimise disease levels, minimise the use of antibiotics, avoid losses, prevent excess fertilisation with slurry, limit the emissions associated with livestock farming, no genetically modified feed, etc. This would make for tougher production conditions as it would no longer be possible to produce volume on the previous scale and cost efficiency considerations would have to reflect the objectives too. We really need to define a legal framework for these objectives and introduce monitoring mechanisms at the same time. The antibiotics database is a good start, although it will take time before the data is reliable.

Photograph: bluedesign/Fotolia.com

What do you think about having labels for meat and fish products which contain antibiotics?
Link: The concept of consumer decision-making has been overstated since the onset of the organic movement some decades ago. I think it has already become difficult to make sense of the wide range of certification you see on the shelves. Anyone without a particular understanding of the issues is now barely able to compare the contents of different brands. If I had to suggest anything, I believe a traffic light system might work, whereby red equals animals kept in stalls, amber equals free range, and green equals organic. This has proved very successful in terms of labelling for eggs, with everyone able to understand what is meant.
There are a couple of other problems, however. More and more food types are being sold in a highly processed state, which makes it difficult to provide information about individual ingredients. And consumers can only make decisions if they actually have a choice, which isn't always the case on our supermarket shelves. If you have to drive another five kilometres just to buy an organic product, it's no longer really a straight choice.
I'd reject the idea of a certificate for antibiotic-free products. Livestock are always going to suffer from disease and injury, even in the healthiest environment. Antibiotics are our most important medicine when it comes to dealing with infections. Anyone marketing products that do not contain antibiotics is either failing to treat these unavoidable diseases, disposing of this material via the market for conventional products, or simply lying.

Actively tackling resistance in human medicine

A success story from Thailand: the Antibiotic Smart Use programme (ASU)

The Thai term for antibiotics is ya-gae-ug-sep, which more or less translates as 'medicine for treating inflammation'. Not surprisingly, antibiotics are seen as a panacea for treating swelling, pain, and fever. They are prescribed by doctors, but are also available without prescription. Thailand's Antibiotic Smart Use programme provides an example of a successful national programme from the Global South.[55,56]

The objective was to change doctors' prescription behaviour and modify patients' expectations.

Photograph: private

An interview with Dr Nithima Sumpradit from the Bureau of Drug Control, Food and Drug Administration, Ministry of Public Health, Thailand

Dr Sumpradit, what was the trigger for the 'Antibiotic Smart Use' programme (ASU) in Thailand?

Sumpradit:

The widespread of irrational use of medicines, particularly antibiotics, is a serious health threat and needs concrete actions that address this issue. So, there is a challenge that if we can't even treat common conditions such as colds and diarrhoea properly, then what will the situation be like for more complicated conditions? For us, rational use of medicines simply means: 1) do not use medicine if not necessary and 2) if necessary to use, use it wisely. This is why we have chosen the motto 'No antibiotics for non-bacterial infections' – and made specific reference to three conditions: urinary tract infections, acute diarrhoea and minor injuries.

How are you training health professionals/workers for the purposes of your campaign?

Sumpradit: ASU incorporates a number of measures aimed at changing prescription behavior. Holding training courses at a local level is a way of reaching out to the doctors. Other personnel, such as nurses, pharmacists and healthcare workers, were also invited to attend the training courses. We subsequently initiated a 'training for trainer' course for key doctors and pharmacists based in hospitals who would reach out to other health professionals in local areas. Apart from clinical information, the training also incorporates persuasive tactics to lower patients' expectations on antibiotics and to enhance doctors' confidence when choosing not to prescribe antibiotics. Doctors were also given materials to facilitate ASU implementation in their settings.

How did you reach out to the general public?

Sumpradit: During the first phase of the project between 2007 and 2008 we provided support to ten hospitals and 87 healthcare units. We simply relied on the face-to-face communication that occurs between healthcare workers and the people within their communities in the hope that this would change their attitude towards antibiotics. In order to achieve sustainable success once the project has ended, it is absolutely vital to get people 'on the ground' involved in the project. Simultaneously, since 2009 the ASU campaign has gradually been made to avail in wider media such as national campaigns, newspaper, radio, television and social media. This dual approach (face-to-face vs. mass media communication) helps spreading ASU knowledge and practice to the general public.

Did your concept also cover Thai traditional medicine?

Sumpradit: Yes, Thai traditional medicine is used as an alternative for patients who are not given antibiotics but still need some treatment for their symptoms. For fever, sore throats or diarrhoea, we recommend traditional medicines from the Thailand's List of Essential Medicines.

It all began with few staff and a small budget.

How did you manage to extend the scope of the project?

Sumpradit: We had to prove that our approach can change antibiotic prescribing behavior effectively and practically without negative impact on patient health. With this in mind, we chose a quasi-experimental study design for Phase 1, which involved a control group. We phoned patients seven days after they saw a doctor and asked them whether they were feeling any better or worse. Based on this evidence, we were able to extend ASU during Phase II to test for feasibility and identify effective and practical approaches to scale up ASU practice.

Can you quantify the success in numerical terms?

Sumpradit: Data from more than 800 hospitals was recorded for the period from 2012 to 2015. The prescription rate for antibiotics fell from 53.6 to 40.2% for urinary tract infections and from 48.6 to 35.7% for acute diarrhoea. A survey of 1,200 patients not treated with antibiotics revealed that 97% had fully recovered and felt better and approximately 90% were satisfied with the outcome of their treatment.

Phase III saw ASU become an integral part of the national healthcare system. An important tool is 'pay for performance'. What does this actually mean?

Sumpradit: The pay for performance (P4P) is a tool used by the National Health Security Office (NHSO) to motivate hospitals to improve quality of service. Hospitals with prescribing rates of antibiotics for urinary tract infections or acute diarrhoea in no more than 20% are awarded a score of 5 (the top possible score) and are fully rewarded financially. Prescription rates of 21-30% and 31-40% result in lower scores, with less being rewarded accordingly. Above 40%, the score is zero without reward. Prescription rates are recorded electronically as routine work required by the Ministry of Public Health (MOPH) and submitted to MOPH, and such information can be assessed by the NHSO. This means there is no extra workload for hospitals. Hospitals can also use an 'e-tool program' provided by the NHSO, which allows them to assess themselves.

ASU has been running since 2008. What is the current situation like?

Sumpradit: ASU as action research has undergone further step-by-step development backing up by practical experiences and evidence. Although funding ceased in 2012, ASU is still running at many different locations. I think there are several reasons for this: 1) the core message of no antibiotics for non-bacterial infections is beyond dispute. 2) ASU is practical to implement, and there are alternative treatments for those not given antibiotics. 3) ASU has been integrated into policies, practice and campaigns by many agencies to promote rational use of medicines as well as to combat antimicrobial resistance.

How is the team currently organised?

Sumpradit: ASU is organized as a decentralised network (also known as a starfish model) to strengthen capacities and creativities as well as to promote senses of ownerships on ASU implementation and successes for all central and local partners. While there may still be central and local partners, the roles have changed somewhat. Central partners include the medicines authority, the NHSO, professors from various universities and an NGO called the Drug System Monitoring and Development Centre. These are no longer really the driving force, but are there to help the local partners who are providing patients with medical care on the 'front line'. Many local partners have made the transition themselves from passive recipients to active players driving things forward. At present, there are ASU networks and champions in many settings.

Mirror, mirror on the wall [57]

In many cases, Thailand's pharmacists are finding a make-up mirror is all they need to convince a customer that a cold can be treated without antibiotics. The CPAT association of pharmacists has put together a kit consisting of a mirror and clinical images showing sore throats of both bacterial and viral origin. This gives the customer a chance to see for themselves, there and then, whether their throat shows signs of a bacterial infection. As part of the SMART programme, other pharmacists offer to take a photograph of the customer's throat for self-diagnosis purposes.

Programmes to combat resistance

One thing is certainly clear: it is impossible to rule out resistance completely. Forms of resistance will develop time and again to every new antibiotic – it is simply a question of when. This is the survival strategy on which bacteria rely. As such, the goal must be to delay the development of resistance for as long as possible. The less often bacteria are confronted with antibiotic agents, the less chance they have to develop resistance against them.

One World – One Health

Bacteria do not recognise borders, and the same is true of resistance. This is why the slogan 'One Health' is often heard in discussions regarding health policy. Two main aspects are evoked by this phrase: on the one hand, 'One Health' means the same medicines are being used worldwide, that forms of resistance are developing worldwide and spreading, and that similar patterns of behaviour among patients and doctors worldwide must be overturned in order to deal with the problems at hand. This means programmes need to be global in their scope if at all possible, activities need to be coordinated, and mutual support must be provided – particularly for countries with scant resources.

'One Health' is also concerned with the relationship between humans and animals. Bacteria are passed on wherever there is close contact between the two. This happens on industrialised livestock farms where workers breathe in microbes via the air in the stalls and also in a village-based subsistence farming environment where humans and hens live in close proximity. Children cuddling their dog, cat, or guinea pig form part of the world's ecosystem too, a system where pathogens recognise no barriers. From a healthcare perspective, this means programmes to combat resistance to antibiotics must include measures which target the exchange of bacteria between animals and humans.

Preventing spread: surveillance

For an anti-resistance system to work, it must make surveillance a core component. Once the pathogens occurring and the forms of resistance they are transporting are known, it becomes possible to identify the transmission routes and introduce countermeasures on a targeted basis. These kinds of reporting and surveillance systems require laboratory tests and trained personnel. But most important of all, the system

adopted must be as uniform as possible to ensure any data which emerges is amenable to rational assessment. Reporting systems remain rather fragmentary and there is a lack of uniformity.[58] But even when systems are introduced, there are sometimes problems with implementation due to resistance from individual stakeholder groups, such as those associated with livestock farming in Germany (see page 22). More than 70 countries have no reliable data on the situation in respect of resistance.[59]

The next few pages will cover the most important activities currently devoted to this issue.

German Antimicrobial Resistance Strategy (DART) (2008 and 2015)

This German programme was launched in 2008.[60] It was driven by an interministerial working group led by the Federal Ministry of Health in conjunction with the Federal Ministry of Food, Agriculture, and Consumer Protection and the Federal Ministry of Education and Research. The One Health approach was adopted here too, with a host of different players being brought around the table, including ministries, health insurance providers, and professional associations for doctors and vets. The first programme (which ran from 2008 to 2013) was replaced by the DART 2020 programme which succeeded it (which is to run from 2015 to 2018).[61]

Key aspects are as follows:

- Expansion of the recording and surveillance system
- Development of guidelines
- Arranging diagnostics
- Promotion of training and development for specialist hygiene personnel and infectious disease specialists
- Improvements in terms of national and international collaboration
- Special focus on animal-to-human transmission
- Promotion of research projects
- Development of new antibiotics and new fast diagnostics

Ten-point plan from the Federal Ministry of Health (2015)

The Federal Ministry of Health (BGM) published a ten-point plan in 2015.[62] In principle, it pursues the same objectives set out by DART and was revealed a few months before DART 2020 was made public. The BGM is keen to stress that stricter measures are needed than anything undertaken so far: 'The issues of hygiene, quality assurance, and transparency are [...] still not being given the priority they deserve. It is also important that initial successes, such as declining rates of MRSA infections, do not give people the wrong impression. With this in mind, the ten-point plan is designed to boost further still the efforts being made at all levels, both national and international.'[63]

The ten individual measures are as follows:

- Preventing the spread of multi-resistant pathogens by improving the screening of patients at risk
- Continuing to extend hygiene standards across all institutions
- Providing patients with better information about hygiene quality in hospitals
- Tightening up reporting obligations to facilitate early detection of resistant pathogens
- Mandatory continuous professional development for medical personnel
- Improving healthcare research with a view to avoiding nosocomial infections
- Reinforcing the 'One Health' philosophy: updating the German Antimicrobial Resistance Strategy (known as DART)
- Facilitating research and development work for new antibiotics (promoting a dialogue about pharmaceuticals)
- Using broader German healthcare policy as a means of combatting antibiotic resistance – helping partner countries develop national strategies
- Fighting antibiotic resistance via cooperation through the G7

European Union: Action Plan against the Rising Threats from Antimicrobial Resistance (2011)

Having been reminded by the European Council and the European Parliament about the need to take action against antimicrobial resistance, the European Commission put forward an action plan in 2011.[64] This defines various objectives and deadlines, and a report was released in February 2015 about how things were progressing.[65]

The Commission is responsible for the measures concerned and is charged with implementing them in conjunction with the member states:

- Producing guidelines regarding appropriate use of antibiotics for humans and animals
- Preventing microbial infections and their spread. A European law on animal health is currently being drafted, with the aim being prevention rather than treatment
- Developing new antibiotics: coming up with research incentives for pharmaceutical companies (as part of the Innovative Medicines Initiative IMI) and other, smaller research projects
- Establishing links between programmes at an international level (e.g. with UN organisations such as WHO and FAO, as well as with individual states such as China)
- Improving monitoring and surveillance within the fields of human and veterinary medicine: harmonised data gathering
- Public relations, information and training

World Health Organization (WHO)

In 2011 WHO brought together the various strands of its antimicrobial resistance activities and published a first report taking stock of the global situation.[66] As well as bacteria, the focus was also on other pathogens such as malaria parasites, influenza viruses, and HIV. In 2014 a global action plan was mapped out at the World Health Assembly,[67] which was finally adopted in 2015.[68,69] The nature of the work being done in terms of resistance is closely linked with the issue of rational medicine use.[70,71] The idea is that WHO countries should help support the introduction of a medicines policy.

Here are the main points of the global action plan:

- One Health Approach: the problem concerns humans, animals, farming, food safety, and economic development
- Hence the need for WHO to collaborate with UN organisations involved in food (Food and Agriculture Organization FAO) and animal health (World Organisation for Animal Health OIE)
- All countries are to have devised national action plans by 2017, for which funding must be secured
- WHO, FAO, and OIE are to help countries devise plans
- Prioritising prevention over treatment: avoiding infections through the use of sanitary facilities and hygiene measures
- Access to healthcare provision = access to diagnostics and treatment
- Development of new medicines, diagnostic techniques, vaccines, and other methods

G7 summit (2015)

The G7 summit is an opportunity for the heads of government of seven powerful Western economies to come together.[72] Announcements made about possible deals are not legally binding, but the symbolism involved may send important signals regarding further concrete agreements. The 2015 summit, which was hosted by Germany, saw the German government put antibiotic resistance high on the agenda.

A few weeks before the WHO resolution was adopted, the G7 heads of government made the following announcements:

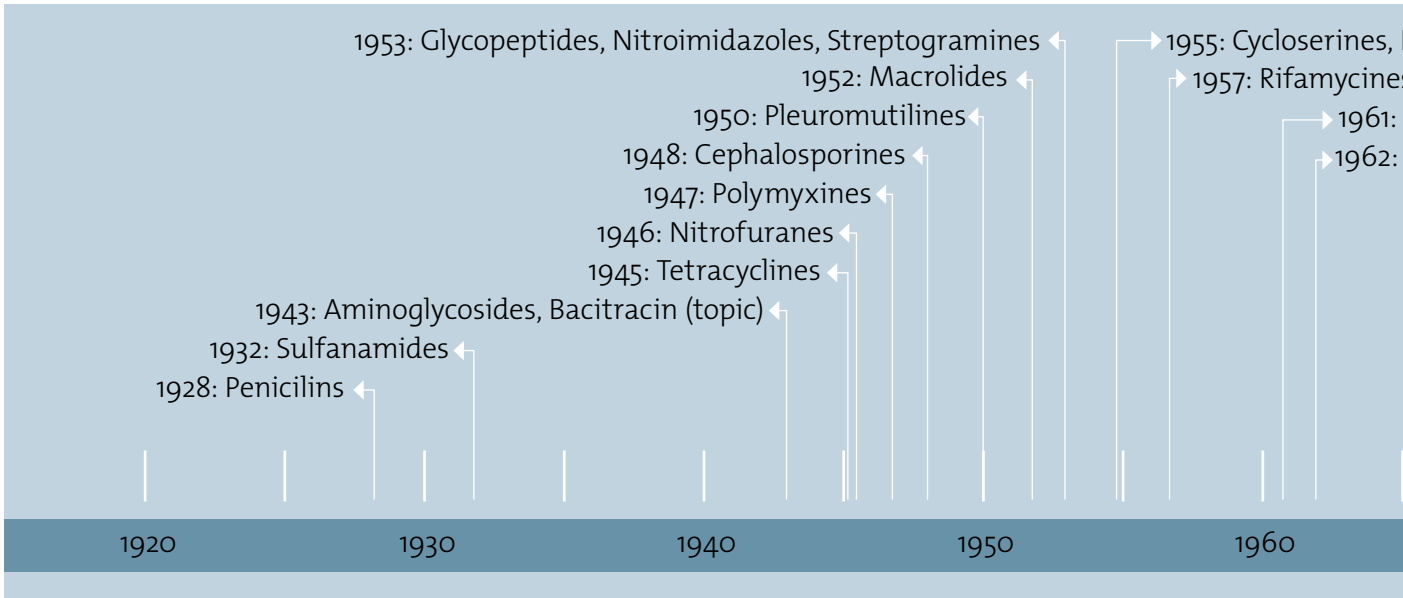
- The G7 states are to draft or revise their own national action plans
- Development of new antibiotics, vaccines, alternative treatments, and fast tests
- Commitment to the One Health approach
- A more cautious attitude to the use of antibiotics as a tool for fattening animals
- Dialogue with the pharmaceuticals and food industry

Photograph: Alexander Raths/Fotolia.com

The antibiotics research gap: the pipeline is empty

The need for research into new classes of active agents

Research too must make its own contribution towards tackling the problem which resistance will present in the future. New antibiotics need to be developed – and even new classes of active agents for which no resistance mechanisms currently exist. Although it may only be a question of time before bacteria come up with a survival strategy to cope with these too, new active agents provide more room for manoeuvre and should only therefore be used as reserve antibiotics. The challenges associated



with the development of new active agents are highlighted in the interview on page 34.
The last new class of active agents (the lipopeptides) was developed in 1987. Since then an increasing number of major pharmaceutical companies have pulled out of developing antibiotics, leaving the field to be dominated by SMEs.[73] The issue has limited commercial appeal: companies want to sell as many of their medicines as possible, but restrictions on use – the core element of the various action programmes – reduce the potential for profit.[74]

The need for research into diagnostics

There is a pressing need for new methods and products in terms of diagnostics too. The main task is to answer the following three questions:

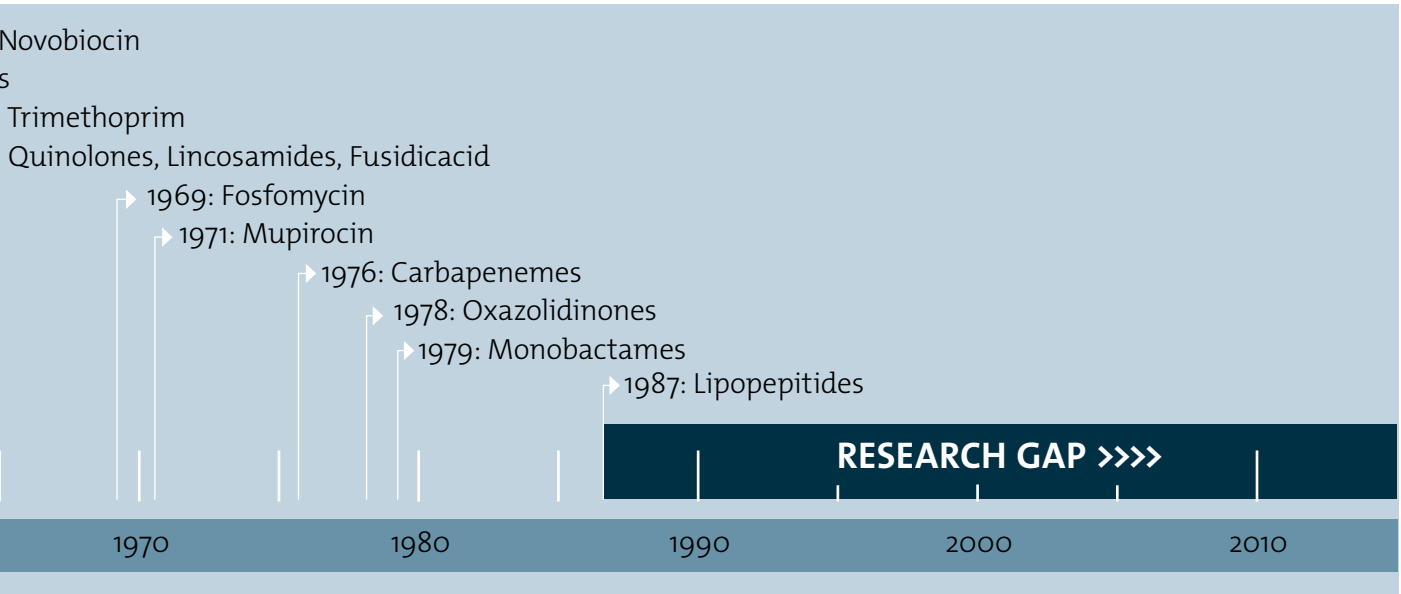
1. Is there a bacterial infection – yes or no? No bacteria means no antibiotics!
2. Are there any forms of resistance?
3. What would be a suitable antibiotic?

Ideally, these issues should be clarified in future during the actual consultation with the patient or on the ward where care is being provided (point-of-care diagnostics). As things stand, however, laboratory tests are still necessary for diagnostic purposes, although these take several days and are not always cheap. Poorer countries do not have enough laboratories. We are currently short of test methods for making the necessary investigations quick, cheap, and easy to perform on site. Associated research projects have already been advertised, with the Longitude Prize in the United Kingdom offering the prospect of GBP 10 million for the winning point-of-care diagnostic system, which must be easy to use, cheap, and available worldwide (see page 37).

The search for new antibiotics

The worldwide search is on for new methods and agents capable of tackling infections. A good deal of basic research is also taking place in Germany. For example, the German Center for Infection Research (DZIF) combines 32 university and non-university research institutions across seven sites, while the InfectControl 2020 consortium brings together 31 partners from the worlds of academia and business. Other institutions are also dedicated to this issue, such as the Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute in Jena.

The last new class of active agents was developed in 1987. Graphic: ReAct (2015) www.reactgroup.org



How do you find new antibiotics?

An interview with Prof. Axel A. Brakhage, Director of the Leibniz Institute for Natural Product Research and Infection Biology – Hans Knöll Institute

Photograph: hki

Prof. Brakhage, how do you go about searching for new active ingredients?

Brakhage: Almost all antibiotics that we know about come from nature. Until now the approach has been to isolate fungi and bacteria, before cultivating them in the laboratory and isolating new substances from these in turn. Thanks to genome analysis, a technique which is now fairly easy to use, we can start to look at new ways of doing things.

Why genome analysis?

Brakhage: These investigations have taught us that bacteria, such as streptomycetes, have genetic information for significantly more substances than they actually produce. It is a case, so to speak, of simply flicking the right switches to make these bacteria suddenly produce 30 antibiotic agents as opposed to just five. We estimate that only 5% of the substances which known microorganisms can produce have been discovered to date. And we still don't know about most microorganisms, because these have not been cultivated.

Why is it that natural substances in particular are so interesting?

Brakhage: Fungi and bacteria communicate via these substances. They send messages to each other, such as 'stop, you're getting too close', or seek to attract others. So all these substances are associated with some kind of biological activity.

Is this why research tends to concentrate on soil and the sea?

Brakhage: Soil is home to an incredible density of various microorganisms, which all have to coexist somehow. They communicate and fight with each other. This provides the backdrop for the search for active agents. The sea is home to interesting communities, with bacteria forming symbiotic relationships with sponges and creating a host of interesting combinations.

Is there a systematic approach to the screening of natural substances?

Brakhage: Yes, the genomes of microorganisms are systematically sequenced. It then becomes possible to come up with prognoses based on bioinformatical analyses and modelling: where might something of interest be found? Much of this information is available in public databases.

Are pharmaceutical companies picking up on the results?

Brakhage: Companies are finding it is hardly worth their while to develop new antibiotics. This is what prompted us to set up the InfectControl 2020 consortium.[75] The 15 research institutions and 16 businesses involved are keen to work together to develop new treatments and help close the gap between research and the development required to produce a medicine.

Are there other lines of research which do not involve antibiotics?

Brakhage: Antibiotics are wonder molecules, which is why we need new ones urgently. And the fact that new mechanisms of action are constantly being discovered means their potential is still far from exhausted. And yes, there are other strategies. People have been working for a long time now, mainly in eastern Europe, with specific viruses known as bacteriophages. This involves an empirical approach, but I'm not aware of any clinical trials. I imagine that applications on the surface of the body will be more likely, possibly for things like burns. Systemic therapy strikes me as more problematic, as bacteriophages are large foreign bodies to which the body will respond by producing antibodies. This in turn can trigger allergic reactions.

More promising, to my mind, is the approach based on strengthening the immune system. You have to remember that infection involves a degree of interplay between host and pathogen. The host, for example, can be strengthened via vaccination. Or we can activate immune cells so they are better able to recognise pathogens.

Photograph: tilialucida/Fotolia.com

Creating new incentives for research and development

Those involved in the research and development of new antibiotics are facing a particular challenge: new medicines must be made available on a global basis, which means they must also be affordable for the populations of poor regions. At the same time, they must be used as little as possible to help delay the development of resistance. These kinds of reserve antibiotics are of little interest from a commercial research perspective, since the combination of low prices and small production volumes would be difficult to justify in terms of business. So where are the incentives to help new products emerge?

The traditional approach to promoting research: push mechanisms

Direct funding (to deliver a 'push') is the traditional means of promoting basic research. The Federal Ministry of Education and Research finances various projects whose findings might be useful in terms of developing new active agents and diagnostic methods. The following are examples of key funding programmes:

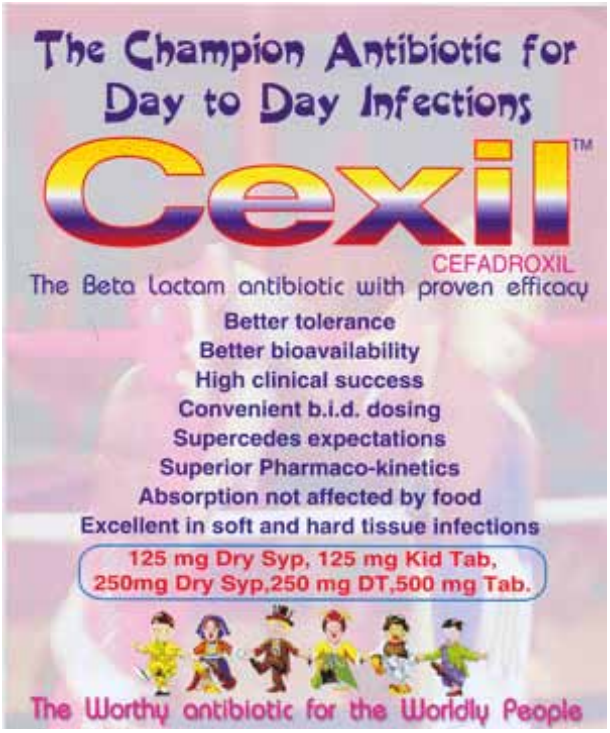
German Center for Infection Research (DZIF): DZIF is a virtual institute, a 'front' effectively for a group of 35 renowned publicly funded institutions. It brings together a host of research projects, but does not represent all German research activities concerned with the issue of infection.

Innovative Medicines Initiative: This European research concept is jointly financed by the European Commission and the European Federation of Pharmaceutical Industries and Associations (EFPIA). The funding programme known as 'New Drugs 4 Bad Bugs' is concerned with antibiotics.

Direct funding of product development takes things further than basic research. In the USA there is still only one national programme for 'pushing' the commercial development of antibiotics: the Biomedical Advanced Research and Development Authority (BARDA) is providing the manufacturer GlaxoSmithKline with USD 200 million of funding.

Traditional incentives for commercial research

The usual incentives for a company to invest in the development of a product are high product prices and market exclusivity. Certain property rights enshrined in law – such as patent protection and data exclusivity – can help in this respect. As regards neglected diseases of less commercial interest and rarer diseases (known as orphan diseases), there are discussions about how to broaden this kind of exclusivity by, say, speeding up or simplifying the approval process. The drawback with this traditional model is that decisions regarding which products to develop are still taken by the businesses themselves – which means the priorities set in terms of product development will continue to be determined by commercial criteria. A high price makes access problematic and exclusive rights prevent the kind of competition that lowers prices. There is also a danger that broad-based marketing (which would suit the company, of course) will promote new forms of resistance. So the problem of ‚access' versus ‚protection' cannot be resolved through the mechanisms traditionally used to fund research.



Broad-based marketing of antibiotics leads to misuse – as illustrated by this advertisement concerning 'day-to-day infections' from Kenya

Prizes can provide new incentives for research
www.ec.europa.eu/horizonprize/antibiotics

Basic research – in Germany, for example – is very active in the field of active agents for use in antibiotics. Less is being done, however, in the way of clinical trials for these active agents, and this ‚translational gap' is often and rightly proclaimed to be a challenge that needs to be addressed. That said, the equally common view that this can be achieved by offering further financial incentives to pharmaceutical companies is not particularly helpful.

An alternative approach: research and development as public policy

Alternative mechanisms are possible if the approach taken is based on ‚medicine as a public good'. Medicines benefit the global community, so the community needs to take care of the development of these goods and ensure they are used in a responsible and sustainable manner.
One way of doing this is to separate the price of the product from the costs involved in research and development (an approach known as de-linkage). These costs are not recouped through the final price – as per the traditional model applied in industry – but via other mechanisms. The benefits are twofold: high sales of the product are not necessary to recoup the outlay involved, and the selling price can be fixed at a level close to the cost of manufacture.

Pull mechanisms: prizes

If the inventor has to finance development up front and can only expect a return at some point in the future, this is referred to as a 'pull mechanism'. This mechanism has already proven successful in the form of prizes awarded

Screenshot https://longitudeprize.org/

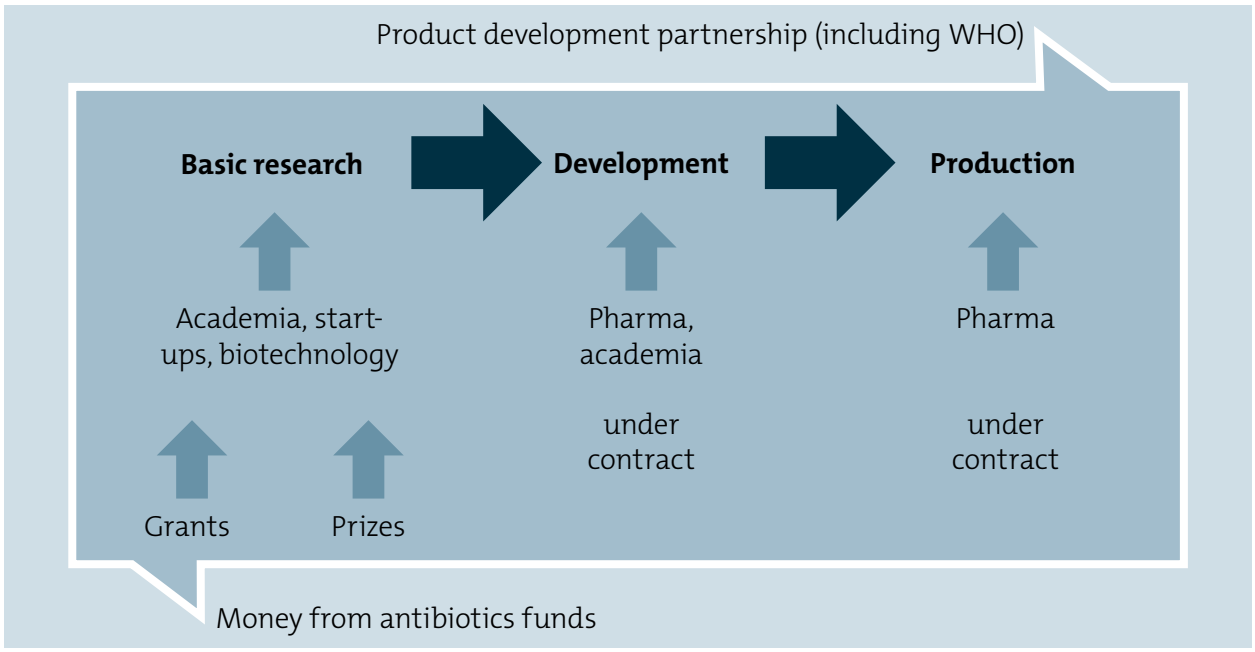
for various projects, which is why it is now being trialled in the field of antibiotics research too. For the first time, the European Commission has offered a prize worth EUR 1 million. This will be awarded to someone developing diagnostics for respiratory tract infections. The test in question is supposed to determine whether or not an antibiotic is required when a person is suffering from a cold.

The United Kingdom is taking things to another level. The Longitude Prize worth GBP 10 million has also been devised with point-of-care diagnostics in mind, but stipulates further conditions insofar as the test must be easy to use, inexpensive, and available worldwide. These kinds of prizes are also conceivable for medicines. Given, however, that medicines cost far more to develop before they are market-ready, the sensible approach is to split the prize money across various predefined milestones.

Antibiotics platform

Cooperation as opposed to competition – bringing together a large number of research activities on a single platform saves resources and can really stimulate research and development. An antibiotics research platform could also conceivably be used as a means of combining various push and pull mechanisms[76,77] – similar to what has been happening with the product development partnerships (PDPs) which have been around for some 15 years now within the field of neglected tropical infectious diseases. PDPs allow various players to work together, such as public research institutions, businesses, and NGOs. Within these kinds of networks the partners bring their respective specialist knowledge to bear during the various phases of the project concerned. It makes sense for a non-commercial player to provide the necessary guidance.

WHO, in collaboration with the non-profit organisation DNDi, has now come up with a framework for checking the feasibility of such a



Model for a global platform for the development of new antibiotics as a public good (modified from the Chatham House (2013) Roundtable on Antibiotic Resistance)[80]

structure and for devising a business plan.[78] An international agreement could create a legally binding framework with a view to lending these kinds of ambitious projects a degree of long-term sustainability.[79]

As far as antibiotics are concerned, a publicly accessible library of active agents might provide the basis required. In terms of identifying new lead structures, it would make sense to advertise some kind of prize (a milestone prize, in other words). The work required to optimise the lead structure and develop it through to the approval stage could be offered to publicly funded product development partnerships under a non-exclusive licence.

Important characteristics associated with a public good might include open-source data sharing with clear rules regarding property rights, whereby knowledge generated by the platform has to be fed back into the platform. Several companies would eventually be allowed to become involved in production and the results of the research would therefore be made available as reasonably priced generics. A global fund would have to be set up for funding purposes, with several countries making voluntary contributions. This approach has long been discussed in connection with other diseases.[81] Some form of affiliation with WHO would also be worth considering.

Summary: Technical solutions alone are not enough

This brochure gives some idea of the size of the challenge presented by antibiotic-resistant bacteria. A host of small and larger individual measures are required: educating patients to adopt a more considered and careful approach to antibiotics; changing the behaviour of doctors, who prescribe antibiotics too often and sometimes even against their better judgement; fostering as matter of urgency a more cautious attitude within hospitals to important active agents – more infectious disease and hygiene specialists are also needed.

A global comparison reveals how catastrophic the situation is in many countries and how unaware most people are that antibiotic medicines are something of a special case. When combined with uncontrolled trading of medicines and inadequate healthcare systems, a pretty devastating cocktail results. With consequences for the entire planet.

It is good that many countries have now devised action plans for tackling the issue at a worldwide level too and providing support for countries with limited resources. The WHO action plan endorsed in 2015 will be crucially important.

But is there something missing?

The brochure shows that there are numerous aspects not properly covered or even not covered at all by the plans. **Livestock farming** may well be afforded considerable importance within the One Health concept, but the economic context associated with the industrialised and globalised production of milk, meat, and eggs is something of a political minefield where no senior political figure has so far dared to venture.

As regards **the development of new antibiotics,** the action plans remain very vague and are more concerned with creating financial incentives for companies than promoting alternative research concepts. This leaves us facing a particular challenge inasmuch as new medicines need to be used as sparingly as possible. So it is a case of somehow reconciling considerations which appear to represent polar opposites: the need for innovation and the drive to generate money on the back of broad-based marketing. This will only be possible if new approaches are tried.

What must never be forgotten is the social dimension of the issue.[82] Many infectious diseases could be prevented by eradicating poverty and malnutrition, providing clean drinking water, treating waste water, and improving working conditions – all factors which could be described as social determinants of health levels. So the use of antibiotics to combat infections is nothing more than a sticking plaster in many places.

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Antibiotic resistance: a global challenge

Antibiotics have been a blessing for medicine. Their discovery meant that infections which had previously caused great suffering and many deaths could now be treated. But the situation is changing dramatically, with ever more bacteria becoming resistant to an increasing number of active agents used in antibiotics. Each year tens of thousands of people die worldwide as a result of multi-resistant microbes. And resistance does not stop at national borders: it develops anywhere and can spread anywhere. This is why any attempts to resolve the problem of resistance must be as global as its causes. The slogan 'One Health' must be understood in the broadest terms: the Global North and Global South, human and veterinary medicine, and both social components and technical solutions must be taken into consideration.

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For more than 30 years now BUKO Pharma-Kampagne has been committed to people's right to health through its international lobbying and the educational and publicity work it carries out across Germany. It is one of the few organisations in Germany to draw attention to and criticise the darker side of the medicines market in the North and South. Pharma-Kampagne advocates access to indispensable medicines across the countries of the South, as well as research into neglected diseases. It also promotes rational medicine use.

BUKO Pharma-Kampagne
August-Bebel-Straße 62, D-33602 Bielefeld
Tel.: +49 (0)521 60550, Fax: +49 (0)521 63789
email: info@bukopharma.de
Web: www.bukopharma.de

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