

ANTIMICROBIAL RESISTANCE

TIME TO ACT

A PARLIAMENT MAGAZINE SPECIAL SUPPLEMENT

**STOP
AMR**

AMR

ANTIMICROBIAL RESISTANCE: 300 MILLION DEATHS BY 2050
UNLESS WE ACT NOW



Time to act

The antibacterial resistance (ABR) crisis is a man-made and therefore we, the people, must put an end to this impending threat, say MEPs

Adina-Ioana Vălean, Pavel Poc and Fredrick Federley

When Susan Fallon fell silent during her opening address at our recent conference in June, she helped lift the scientific veil on antibacterial resistance (ABR). This man-made crisis unnecessarily kills hundreds of thousands of people each year – including Susan Fallon’s daughter.

ABR is caused by overproduction and the consequential overuse of low-priced antibiotics. Another pharma business model is needed. In fact, two-thirds of all antibiotics are used in animal husbandry and then mainly spent on growth promotion – a purpose that many researchers now doubt has any useful function.

In this Parliament Magazine Special Supplement, globally renowned experts from the UN, FAO, research institutions, health practitioners and industry sectors come together to address ABR causes, consequences and solutions. Unique new research from China – one of the largest users of antibiotics in animal husbandry – shows that specialised feed additives may assist farmers with health and growth promotion without having to resort to antibiotics. In four countries virtually unstoppable bacteria have already emerged.

Meanwhile the World Bank has identified six countries that say they are prepared to deal with a potential health crisis of this sort. Strikingly, only one, Finland, is in the European Union. In a recent Chinese report the devastating consequences of a potential ABR outbreak warned of im-

mediate damage of some \$67bn, a halt to tourism, a break in trade and a virtual end to foreign investment. We cannot let that happen at a global scale. Antimicrobial resistance is a challenge for our whole society and the one health approach is key. We politicians must address this challenge in both human medicine and animal husbandry. We believe that EU can take the role as a leading global actor, and as a first step, EU member states must agree on the new veterinary medicine legislation so that we can end the excess use of antibiotics in animal husbandry.

AMR is often seen as solely a health issue. But that is simply not true, as it truly is an issue of our own ecology. Rooted within much of our agriculture and healthcare systems, AMR is now impacting on our food production and as well as our personal human health. We need to understand, that the development of resistance is a natural process, which cannot be completely eradicated. We therefore have to change our behaviour if we want to be the winner of this ancient evolutionary battle. If we fail, there will be nobody to ask for mercy.

The European Commission recently published its new EU AMR Action Plan. This Special Supplement can help you judge whether this plan will prevent a catastrophe. What should be added? What should be changed? Please let us know what you think. Our call is simple. ABR is a man-made crisis and we, the people, can and must put an end to it. ★



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“Two-thirds of all antibiotics are used in animal husbandry and then mainly spent on growth promotion – a purpose that many researchers now doubt has any useful function”

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Personal tragedy, collective responsibility

The loss of **Susan Fallon's** daughter to an antibiotic resistant superbug was the waste of a beautiful young life that could so easily have been avoided

Behind the stark statistics surrounding the growing crisis of antimicrobial resistance (AMR), lie a host of personal tragedies. One such case is that of Susan Fallon and her teenage daughter Samantha who, nine years ago, died after contracting a hospital borne infection. Fallon, from Stoke-on-Trent in England, told an audience of EU policymakers, physicians and experts in the field, that the tragic loss of Samantha highlighted the need for EU policymakers to take a strong lead on efforts to combat the spread of AMR. Before a packed conference in the European Parliament, she gave a moving and emotional testimony on how 17-year-old Samantha never left hospital after being admitted for a relatively minor virus. The college student

contracted Methicillin-resistant *Staphylococcus aureus* (MRSA), a bacterial infection resistant to many leading antibiotics. Her health deteriorated rapidly, eventually leading to catastrophic organ failure. The youngster's death certificate stated that she died from major organ failure brought on by MRSA.

Soon after Samantha's loss her mother joined MRSA Action UK (she is now its deputy chairman) and says her personal tragedy sadly illustrates the growing threat of AMR. Fighting back tears, Fallon told the conference, co-organised by the PA International Foundation, that "My daughter was admitted to hospital with a virus. The ward that she was admitted to I later discovered had

two cases of MRSA. The infection was definitely caught in hospital." Poignantly, Fallon added, "I often think of where Samantha would be now. She would have been 26 years old, and would she have been married with children of her own? I want to call on the European Parliament to put in place rules and regulations to prevent people falling victim to AMR. We are the

Fallon also said that concerns regarding AMR had been repeatedly raised with the UK Government by her group but, "No-one seemed to be taking [the issue] very seriously, especially around putting information out to the public and explaining the threat posed by bacteria building up resistance to these magic bullets called antimicrobials." Government responsibility is at

"Since containing AMR is a matter of collective responsibility... it is the moral duty of political leaders to make sure that we, collectively fulfil this responsibility... governments worldwide are under a moral obligation to regulate the use of antibiotics and farming"

Dr Hannah Maslen

golden generation who have been born and live in an antibiotic era, who have enjoyed the greatest leap in medical science in mankind. But I am asking for you to take the action required so that no one else has to go through what my family and I have been through."

the heart of the ethical and moral debate around AMR. According to Dr Hannah Maslen of the Oxford Uehiro centre for practical ethics, "Since containing AMR is a matter of collective responsibility... it is the moral duty of political leaders to make sure that we, collectively fulfil this responsibility... governments worldwide are under a moral obligation to regulate the use of antibiotics and farming."

Fallon, who was given a standing ovation for her intervention, warned, "We are rapidly running out of time to change things around. Anyone can be affected by AMR, the bacteria know no boundaries. Nothing matters until it becomes personal. The loss of my daughter Samantha was the waste of a young beautiful life that could so easily have been avoided, let her legacy be that she is the last." ★



Regulatory Reform

Belgian Best Practice

The EU could honour Samantha Fallon's memory by significantly improving its AMR Action Plan, argues former Belgian Prime Minister and Chair of PA International Foundation, **Mark Eyskens**

According to the UN, antimicrobial resistance (AMR) is set to overtake cancer and become the world's largest cause of death by 2050. Uniquely, AMR is a man-made disaster, so it's up to mankind to fix the problem. We can prevent former WHO Director-General Dr Margaret Chan's apocalyptic prophecy, "The end of modern medicine as we know it", by taking four immediate measures.

First, and I quote the UK Review on AMR Chairman Lord Jim O'Neill,

that pharmaceutical industries must stop being "balance-sheet managers first". The 2016 UN General Assembly's Special Session on AMR urged antibiotics producers to stop considering these lifesaving drugs as profit centres - a profit-making activity that requires no further investment. To secure this, antibiotics production must be limited by law, just as the EU limits, for example, steel production to prevent unsustainably low steel prices. Many of the world's husbandry industries have already

indicated their willingness to stop pumping antibiotics into poultry, pigs and other production animals - if governments guarantee total industrial compliance through strict enforcement. EFPIA, the European association of pharmaceutical industries, should now follow suit. It should leave no stone untouched to ensure that it will never be accused of killing people instead of keeping them alive.

Second, globally, all antibiotics except those used in a lifesaving role should be subjected to taxes. The generated income can be used to assist farmers to transition from antibiotics use for health and growth promotion to non-antibiotic alternatives. This income can also be used to research and develop feed additives that can replace antibiotics. The development of adequate vaccines should also be funded.

Third, the Belgian government's proposal to adapt EU regulation 1831/2003 on additives for use in animal nutrition must be swiftly adopted. I recently had the privilege of meeting the high representatives of the Estonian EU Council presidency. They decided to prioritise AMR. Before the end of their presidency in December 2017 a new claim category can be added to the Annex of 1831/2003. Unless feed additives can correctly claim to promote health and growth - without being medicines - how would farmers find their way to such alter-

natives? The artificial curse on the regulatory use of the words 'health' and 'growth' should be lifted. If the European Commission promotes fruits and vegetables on a child's menu, this is hardly to promote its 'welfare'. So scientifically vetted feed additive claims should include the words 'health' and 'growth'.

"We all know about Ebola - which killed around 12,000 people in total. Why don't we know about AMR - which kills at least 25,000 people every year in Europe alone?"

Lastly, a truly massive information campaign must warn all citizens to stay away from unrequired intake of antibiotics. We all know about Ebola - which killed around 12,000 people in total. Why don't we know about AMR - which kills at least 25,000 people every year in Europe alone?

The Commission's DG SANTE recently published its new EU AMR Action Plan. It is a continuation of 10 years of actions and more than €1bn in investments - statistically leading to more antibiotics used both in human health and in animal husbandry. The European Parliament should call on Health and Food Safety Commissioner Vytenis Andriukaitis to improve the Action Plan, now. Dear Ms Fallon, your daughter Samantha will be remembered. ★



Tipping Point

High-level, coordinated and determined political commitment is central to tackling the scourge of antibiotic resistance

Antibacterial resistance is a threat to both the world's economy and health and to the next generation. This was a recurring theme of the recent antibacterial resistance conference in the European Parliament, and a point seized on by the WHO's Dr Marc Sprenger, who said that while resistance is not new, its remarkable rise in recent years has been massively sped up by the "overuse and misuse" of antibiotics, both in humans and in veterinary medicine.

Sprenger, director of the antimicrobial resistance secretariat at the WHO, said, "it's not only modern

medicine in developed countries which depends on effective antibiotics. Basic medical care relies on access to effective antibiotics. AMR is not just a global threat, it is a reality that can affect all of us. But often a nasty resistant germ is not recognised as the cause of death. We know the figures, but it's only the tip of the iceberg because often AMR is not recognised."

Political commitment will be extremely important in tackling AMR and, in this respect, Sprenger cited the 2016 high-level meeting of the UN General Assembly. That meeting, crucially, established the Ad Hoc Interagency Coordination

Group (IACG) on AMR. The IACG was mandated after member states asked the Secretary General to provide "practical guidance and global action" against AMR. Remarkably it is only now that commonly shared definitions and actions will be developed. What exactly, for example, do terms such as the 'prudent use' of antibiotics in husbandry mean?

Following the IACG, a group of academics, writing in the international science journal *Nature*, urged that "as one of the first steps, this group will coordinate a review of the terminology used by key actors". They expressed concern that the currently used terminology is often "misunderstood, interpreted differently or loaded" as well as "counterproductive". It is important

to note that antibacterial resistance (ABR) and antimicrobial resistance (AMR) refer to a different yet relatable phenomenon. ABR refers to resistance only among bacteria, while AMR refers to a broader category which includes not just bacteria but also fungi, viruses and other microorganisms. Food and Agriculture Organization of the United Nations (FAO) official Dr Sarah Cahill also sought to emphasise the "important" difference between ABR and AMR. She said, "I realise that the title of this event relates specifically to antibacterial resistance, yet we talk a lot about antimicrobial resistance. Certainly, antibacterial resistance is arguably the area that is most studied, the area which we know most about and has most



"The numbers are just simply missing from our public debate. If we have close to a million people dying of resistant pathogens, just from surgeries, we really should be giving it a lot more attention"

Prof. Ramanan Laxminarayan

Prof. Ramanan Laxminarayan (right) with fellow keynote speakers at the recent European Parliament conference on the socio-economic aspects of antibacterial resistance, (L-R) Fredrick Federley MEP, Dr Marc Sprenger, director of the AMR secretariat of the WHO and Dr Sarah Cahill, food safety officer at the Food and Agriculture Organization of the UN



impact and greatest concern for human health. And for this reason, we primarily focus on this."

Cahill accepted that "dealing with antimicrobial resistance in the food and agriculture sector is not easy." The FAO does not believe farmers are using antibiotics "because they want to" but because they want to produce food and raise healthy animals. Therefore "we need to provide them with support to minimise the therapeutic use of antibiotics and avoid the use of antibiotics as growth promoters. But coming from the food and agriculture sector, we would do well to also learn the lessons of our experience with antibacterial resistance because many of the infections we face when it comes to animal or crop production systems come from viruses, parasites or even fungi."

Cahill explained that irrespective of the ability or inability to control other zoonotic (a disease that can be

transmitted from animals to people) diseases, "at the end of the day, those who are food insecure are among the most vulnerable of our society and often more susceptible to illness and therefore more in need of safe and nutritious food."

Prof. Ramanan Laxminarayan, director of the US Center for Disease Dynamics, Economics and Policy, said he feared that, so far, lessons had not been learned, adding, "We always expected this, we anticipated it. But we did nothing to prepare for it and now we're faced with it." He said there were hundreds of thousands of AMR related deaths every year, each carrying a "lot of painful stories." Even so, "The numbers are just simply missing from our public debate. If we have close to a million people dying of resistant pathogens, just from surgeries, we really should be giving it a lot more attention."

Looking to the future, he told the

Types of AMR

Resistance in tuberculosis

The WHO estimates that, in 2014, there were about 480,000 new cases of multidrug-resistant tuberculosis. Only about a quarter of these (123,000 cases) were detected and reported.

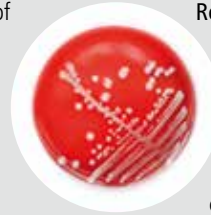
in humans were resistant to one category of antiviral drugs.

Resistance in HIV

In 2010, an estimated seven per cent of people starting antiretroviral therapy (ART) in developing countries had drug-resistant HIV. In developed countries, the same figure was 10–20 per cent. Some countries have recently reported levels at or above 15 per cent amongst those starting HIV treatment.

Resistance in influenza

Antiviral drugs are important for treatment of epidemic and pandemic influenza. So far, virtually all influenza A viruses circulating



packed event, "There is the need for additional coordinated support to be provided to member states as well as more and better monitoring of AMR and AMR-related

activities." This, he argued, should include more support for research and innovation, improved knowledge on detection and effective infection control and surveillance. ★

The Silent Tsunami

The relentless spread of antimicrobial resistance across the world has highlighted the need for a strong, global response to the crisis

The excessive and inappropriate use of antibiotics both in humans and animals has turned AMR into a massive threat and one of the biggest health challenges facing humankind. But European health and food safety Commissioner Dr Vytenis Andriukaitis says he is heartened by the ever-increasing focus on "this crucial

issue" including events such as the European Parliament conference on the socio-economic aspects of antibacterial resistance. Speaking at that event in June, he told experts, policymakers, and stakeholders that despite the many initiatives undertaken over recent decades, "we have collectively failed to keep pace with the rise of antibiotic-resistant infections. Certain superbugs

are now in the ascendency. We have now reached a critical point where AMR is jeopardising both human and animal health. We are witnessing the concentration of antimicrobials in the vicinity of big farms, hospitals, production facilities, waste water treatment plants and big cities in general."

The relentless spread of the colistin resistant MCR-1 gene was a perfect example of the risk posed by AMR, he said, adding that with climate change and the spread of new infections, this risk will only increase. Branding AMR as a "silent tsunami" Andriukaitis said "decisive corrective actions" are urgently needed to avoid "slipping backwards towards the pre-antibiotic age, when even minor infections and injuries often resulted in death." He added: "If left unchecked AMR may also threaten to overwhelm our healthcare systems, both in a medical and economic sense." In

the EU alone, Andriukaitis told the packed audience, it is estimated that AMR already costs €1.5bn each year in healthcare expenses and productivity losses. The World Bank, he pointed out, warns that by 2050, drug-resistant infections could cause global economic damage on a par with the 2008 financial crisis. His message? "No single country or region can hope to defeat AMR working individually. People, animals, foods and goods move around the world every day, every hour, every minute. Bacteria move together with them, freely crossing borders."

In 2011, the European Commission launched a five-year Action Plan in response to the growing need for stronger and more coordinated action against AMR. But he admitted: "This has not proved strong enough to curb the rise of resistant infections." It was for these reasons, he said, that the Commission was committed to

European Commissioner for Health and Food Safety Vytenis Andriukaitis (left) with the MEP co-hosts of the recent European Parliament conference on the socio-economic aspects of antibacterial resistance, Pavel Poc, Adina-Ioana Vălean and Fredrick Federley



stepping up current efforts to fight AMR and recently adopted a new European “One Health” Action Plan against AMR. Andriukaitis, a former surgeon, declared, “With the new Action Plan, the Commission aims to raise the level of all member states to that of the highest performing country.” Priorities include boosting innovation and research along with establishing the EU as a “best practice” region in the field of AMR. Another aim of the new Plan, he noted, will be to “strengthen the EU’s voice” in this area. At the end of a sometimes highly emotional and impassioned speech, he concluded: “Let me stress once again that more needs to be done to address AMR right across the board – by stakeholders, individual countries, groups of countries and through stronger global initiatives.”

The conference was also shown a video produced by scientists from Harvard Medical School who designed a simple way to observe how bacteria evolve to become impervious to drugs. The experiments are thought to provide the first large-scale glimpse of the movements of bacteria as they encounter increasingly higher doses of antibiotics and adapt to survive – and thrive – in them. To do so, the team constructed a giant petri dish and filled it with 14 litres of agar, a seaweed-derived jellylike substance commonly used in labs to nourish organisms as they grow.

To see how the bacterium *Escherichia coli* (*E. coli*) adapted to increasingly higher doses of antibiotics, researchers divided the dish into sections and saturated them with various doses of antibiotics.

“We have collectively failed to keep pace with the rise of antibiotic-resistant infections. Certain superbugs are now in the ascendency. We have now reached a critical point where AMR is jeopardising both human and animal health”

European health and food safety Commissioner Vytenis Andriukaitis

The outermost rims of the dish were free of any drug. The next section contained a small amount of antibiotic — just above the minimum needed to kill the bacteria — and each subsequent section represented a 10-fold increase in dose, with the centre of the dish containing 1000 times as much antibiotic as the area with the lowest dose. In the span of just 12 days, the

bacteria became resistant to 1000 times the concentration of antibiotic that would normally kill it.

The device, dubbed the Microbial Evolution, and Growth Arena (MEGA) plate, represents a simple, and more realistic platform to explore the interplay between space and evolutionary challenges, showing just how quickly the AMR threat can evolve. ★

The need for a precautionary approach

The increasing use of antibiotics is driving resistance and creating a global health threat



Has the overuse of antibiotics created a global health time bomb?

The increasing use of antibiotics could potentially “rewind decades of progress in modern medicine”, the recent European Parliament AMR conference was told. Professor Ramanan Laxminarayan, director and senior fellow of the US Center for Disease Dynamics, Economics & Policy, told the audience that while Europe has taken a lead on the issue, AMR action “is important in nearly every developing country.” Despite antibiotic resist-

ance having been around “for millions of years ... what has happened in the last 15 years is that resistance has gone up from being under one per cent to being as high as 80 per cent in many countries.” While the international community had “always expected and anticipated this, we have done nothing to prepare for it and now we’re faced with it.”

The hospital superbug MRSA is now a “huge problem” in developing countries in Latin America, South and South East

Asia and Russia. The young and elderly are particularly vulnerable. Laxminarayan provided figures suggesting that there had been 250,000 neonatal deaths associated with drug resistance across five countries. “India alone has about 60,000 deaths. This has received a lot of attention but we are not seeing the action that it really needs. I think we are seeing more words than action really,” he said.

Laxminarayan told the audience that resistance to carbapenem antibiotics was of particular concern “because carbapenem is really our last effective antibiotic against Gram-negative bacteria.” Resistance to this is again

“extremely” high in most parts of the world. NDM-1, a gene which encodes for carbapenem resistance, was discovered five years ago in a Swedish patient traveling from India and is now present in 110 countries. Laxminarayan highlighted a similar spread with 23-F for streptococcal pneumonia. And he highlighted that the MCR-1 gene, which provides colistin resistance, was discovered just two years ago in China, and is now “a global phenomenon”. He added, “We have to remember that

even as we talk about drug resistance, there are still lots of people who are dying because of lack of access to antibiotics. Our enthusiasm to deal with resistance should not in any way deny people antibiotics.” In terms of global antibiotic consumption India leads the way, followed by China and the United States. However, “On a per capita basis, European countries consume more and, if everyone got to the same per-capita consumption that Europe does, it is like climate change, the world just can’t afford it.”

Dr Thomas Van Boeckel, an AMR expert at Zurich’s Institute of Integrative Biology, also spoke at the conference. He explained that “antimicrobial use in humans is

“AMR is not just a global threat, ... it is a reality that can affect all of us...[and] has the potential to rewind decades of progress in modern medicine”

Dr Marc Sprenger

only the tip of the iceberg”, with far greater amounts being used in animal husbandry. “In animals, antimicrobials are given regularly in small doses to prevent infection and in some countries as growth promoters to increase productivity.”

When it comes to considering the global impact of antimicrobial

use in animals on the resistance in humans, Van Boeckel noted there are "hundreds of case studies from all around the world" ranging from Switzerland and Vietnam to Kenya and Thailand. "We have multiple years of data and the trend is indicating that the problem is indeed increasing." The vast majority of

"An AMR outbreak seems unavoidable"

Pavel Poc MEP

independently funded studies "all go in the same direction, which is to reduce antimicrobial use in animals." An overwhelming body of work has linked antimicrobial use in animals and resistance in humans, especially in "hotspots" of

antibiotic consumption in animals, which include the "poultry belt" in the south east of the United States and Sichuan Province in China. Van Boeckel told the audience that "In fact, the whole south east of China is virtually a hotspot of consumption of antimicrobials." "The central question is, what can we do to

reduce the consumption of antimicrobial in food production on a global scale?" He warned that without action, agricultural antibiotics consumption is expected to grow by 217 per cent globally by 2030.

In a 2015 publication, Dr Mark Sprenger, director of the AMR Secretariat at the WHO, warned about "untreatable infections" if bacteria which are already highly resistant acquire colistin resistance

A silent expansion

The dangers of transmitting AMR while travelling have been highlighted by the University of Bern. Studying 38 people living in Switzerland that had travelled to India for 8 to 35 days, the team uncovered that 76.3% returned with resistant bacteria. Of the returning travellers, 10.5% carried colistin resistant bacteria, with one individual carrying mcr-1. It concluded: "The spread of non-ESC-R could contribute to the silent expansion of this life-threatening resistance gene in both human and non-human settings.

via MCR-1. At the conference, he issued a stark warning: "AMR is not just a global threat, it is a reality that can affect all of us. AMR has the potential to rewind decades of progress in modern medicine. AMR happens naturally over time but this process has been accelerated by the overuse and the misuse of

antibiotics both in humans and in veterinary medicine." Echoing Sprenger, Czech MEP Pavel Poc, who co-hosted the conference in the European Parliament, warned that without international collaboration on the scale of the Paris climate change agreement, an "AMR outbreak seems unavoidable". ★



Time to shut down the world's disease factories

Changing the global food production business model would have a spectacular impact on the overuse and misuse of antibiotics

The driving source of antimicrobial resistance (AMR) is the overuse and misuse of antibiotics, especially in agriculture. As early as 1945, Alexander Fleming warned "the time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." In 1969 the so-called Swann report in the UK recommended limiting the use of antibiotics as growth promoters in husbandry. Despite these warnings, antibiotics use continues to grow. Science, health and nutrition journalist

pean Federation of Pharmaceutical Industries and Associations (EFPIA) director general Dr Nathalie Moll, explained "the development of antibiotics is a unique case in healthcare because these are products that are supposed to be used as a last resort, in very small quantities. Clearly antibiotics is not the best model for that [return on investment] because of the way they are used and they have to be used". Therefore, argued Moll, "we need to think about new models... [and] create the right environment [for investment in the fight against AMR]". Lord Jim O'Neill, Chairman of the UK Review on AMR, commented recently that, "Pharmaceutical companies have essentially become balance-

Oxford University suggested that "pharmaceutical company interests in profit are at the lower end of moral priority". Professor Ramanan Laxminarayan, director and senior fellow of the US Center for Disease Dynamics, Economics and Policy meanwhile argued that "We have to think of antibiotics as a societal resource." Despite industry promises, antibiotics continue to be sold to farmers and vets at discounted prices. In 2014 the Association of German Veterinarians (WDT) offered an 88 per cent discount on antibiotics to vets. When confronted about the issue, Joachim Lattman, a WDT board member stated, "noteworthy discounts are just common practice".

Summarising current industry practices, Laxminarayan said, "A year ago, the pharmaceutical industry made a commitment that in its manufacturing operations it will make sure that antibiotics are not released into the environment. We have seen very little progress on that commitment. In India for instance, there are pharmaceuticals that are still being released from the waste water and the concentrations of antibiotics in the water, in natural water bodies surrounding these pharmaceutical factories is higher than what one would expect to get in a patient's bloodstream after being treated with antibiotics. This is just not acceptable".

In June this year, the World Health Organization (WHO)

"Pharmaceutical companies have essentially become balance-sheet managers first, and drug makers second. Someone needs to flip that model on its head"

Lord Jim O'Neill, Chairman UK Review on AMR

Melinda Moyer famously described agricultural antibiotics use as "transforming innocent farm animals into disease factories".

An inherent contradiction exists within the antibiotics market. At its core, the purpose of an industry is to generate revenue, achieved by maximising the volume of products sold. However, during the recent antimicrobial resistance conference in the European Parliament, Euro-

sheet managers first, and drug makers second. Someone needs to flip that model on its head."

The January 2016 Davos Declaration on combatting AMR, signed by over 80 pharmaceutical, biotechnology and diagnostics companies, stipulates that a new commercial model must be established. Commenting on the current business model during the conference, Dr Hannah Maslen of





Abandoning antibiotics as growth promoters globally would result in little loss in the value of meat production

published their new Essential Medicines List which controversially divided antibiotics into three categories, Access, Watch, and Reserve. Antibiotics in the last category are only to be used when all other treatments have failed. Colistin, used in agriculture, is one of these 'reserves'. Commenting on the new division of antibiotics, WHO Director of Essential Medicines, Dr Suzanne Hill, said there may be "a very large economic impact"

for companies producing the most restricted category of antibiotics as the current incentive model in drug development revolves around sales.

Globally the husbandry sector consumes nearly two thirds of all antibiotics. Speaking during the European Parliament event, Dr Thomas Van Boeckel of the Institute of Integrative Biology in Zurich highlighted OECD and US statistics demonstrating that the financial loss of abandoning antibiotic growth promoters globally would

"Competition among pharmaceutical producers keeps prices of many common antibiotics and other antimicrobials low, which gives yet stronger incentives for overuse, both in livestock and other agricultural production, and in humans"

result in a loss in the value of meat production of between just one to three per cent. He concluded, "the [financial] loss is probably minimal and it's probably not worth it to use antimicrobials as growth promoters" which generates resistance.

Despite widespread recognition that the antibiotics business model is broken, the global trend suggests that the use of agricultural antibiotics will continue to grow dramatically unless action is taken. According to the World Bank, "Competition among pharmaceutical producers keeps prices of many common antibiotics and other antimicrobials low, which gives yet stronger incentives for overuse, both in livestock and other agricultural production, and in humans."

The EU has invested €1.3bn over

15 years to combat AMR. No new antibiotics and few if any alternatives have come forward, while the use of antibiotics in husbandry continued to grow. Laxminarayan argues that, "We need to find a way to incentivise new drug development that is novel but we also need to develop in a way that ensures the continued effectiveness of antibiotics." In November 2017 EFPIA will launch a new business model proposal for Europe's pharma and antibiotics producers. The global husbandry industry has requested regulations and even taxes to take competition out of the equation. These are moves in the right direction – particularly if the European Commission supports this development with the earliest possible effective regulations.★

Non-Antibiotic Alternatives: Real and Viable

The link between antibiotics use and AMR is no longer in question. So what's the alternative?

The UK Review on AMR reports "much of their [antibiotics] global use is not for treating sick animals, but rather to prevent infections or simply to promote growth".

However, abandoning the incorrect use of antibiotics, namely as growth promoters, does not prevent farms from being viable and productive. In Denmark, antibiotic

Vytienis Andriukaitis referenced Norway where the introduction of a vaccine "reduced the use of antibiotics in fish farming by 99 per cent," and helped the country develop aquaculture in a "very sustainable" manner. As the world's largest salmon producer, Norway produced 1.4 million tonnes of salmon using 972 kilograms of antibiotics in 2013. By contrast,

in 2014, Chile, the world's second largest salmon farmer produced 895,000 tonnes of salmon using 563,200 kilograms of antibiotics.

In December 2016, when studying antibiotics use in agriculture, Scientific American magazine reported that in 2014 "nearly 21 million pounds of medically important antibiotics [were sold] for use in food animals, more than three times the amount sold for use in people." As high-

lighted by Dr Thomas Van Boeckel of the institute of integrative biology in Zurich, the impact of these antibiotics for growth promotion is minimal, 1-3 per cent. As early as 1951 academics from the University of California recognised that the public health implications of developing "antibiotic-resistant flora in the poultry population are obvious" and called for the development of non-antibiotic alternatives in agriculture, arguing that, "it is strongly

"Alternatives have the potential to replace antibiotics in many situations. This can reduce antibiotics use in animal agriculture, and allow these lifesaving drugs to be preserved for use when absolutely needed to protect human or animal health"

The Pew Charitable Trusts


growth promoters (AGPs) were banned in pig production back in 1995. As a result, antibiotics use dropped by 51 per cent between 1992 and 2008. In the same period, pig production increased by 47 per cent. Speaking at the 28 June 2017 Scientific, Human Health, Husbandry, and Socio-Economic Aspects of Antibacterial Resistance: Time to Act conference in the European Parliament, European Commissioner for Health & Food Safety



felt that a few years of research are likely to elucidate the fundamental mechanisms underlying this growth promoting effect and that this information will permit agriculturalists to secure more rapid animal growth without inflicting potential hazards on public health".

However, little progress had been made in the succeeding six decades. According to science and health journalist Melinda Moyer, "the industry has fought hard against these plans [banning AGPs] by arguing there was no definitive proof of harm". However, the impact of antibiotics use and its link to AMR is no longer in question. The EU's

second Joint Interagency Antimicrobial Consumption and Resistance Analysis (JIACRA) report "confirms the positive association between AMC [antimicrobial consumption] and AMR in both humans and food-producing animals" and calls for a reduction in use. Equally, the 2017 EU AMR Action Plan unequivocally establishes that "The main cause of AMR is antimicrobial use". Van Boeckel highlighted the importance of focusing on animal use "because antimicrobial use in humans is only the tip of the iceberg... the vast majority of independently funded stud[ies] are going the same direction, which is to reduce anti-



Norway's success in producing healthy, farmed Salmon without the use of prophylactic antibiotics has helped the country develop a thriving and sustainable aquaculture

microbial use in animals." Professor Ramanan Laxminarayan, director and senior fellow of the US Center for Disease Dynamics, Economics & Policy, identified that the growing demand for animal protein is exemplified by China, where "the consumption of pork has gone up six-fold in the last 30 years and commensurate with that is a huge increase in the consumption of antibiotics. This is not stopping, this is going up even further which means that we cannot produce animal protein in the way that we have done for the last 50 or 60 years. It just has to change."

One option outlined by Diederik

"To win the war against AMR, we must stop doling out antibiotics like sweets"

Lord Jim O'Neill, Chairman of the UK Review on AMR

Standaert, Head of Management Office, DG Animal, Plant and Nutrition at the Belgian Health Ministry, is to offer farmers "officially regulated and registered substances as an alternative, this may further reduce their demands for antibiotics as a preventative tool." After an extensive literature review, a 2017 report by the Pew Charitable Trusts concluded that, "alternatives have

the potential to replace antibiotics in many situations. This can reduce antibiotics use in animal agriculture, and allow these

lifesaving drugs to be preserved for use when absolutely needed to protect human or animal health".

Over 200 representatives from the husbandry sector, including CEOs, were challenged on the issue of antibiotics use in farming during the 2017 AgriVision Conference in the Netherlands. When asked are antibiotics in husbandry too cheap in relation to human and financial

costs, 77.9 per cent responded yes. When asked if governments should stimulate the replacement of antibiotics in husbandry by feed additives for growth and health promotion, 92.1 per cent responded yes. The representatives of the agricultural sector recognised the need for change and have given their governments a clear mandate to act. Lord Jim O'Neill, Chairman of the UK Review on AMR, remarked "To win the war against AMR, we must stop doling out antibiotics like sweets. To that end, we will need new technologies and other measures to change how antibiotics are prescribed and administered." ★

Nutritional Prevention better than any cure

AMR may not be stopped, but it can be managed using alternatives to antibiotics



The growing awareness of the AMR threat should serve as a 'wake-up' call in finding alternatives to antibiotics.

That was the message from Knut Nesse, the CEO of Dutch animal feed producer, Nutreco.

Speaking in the European Parliament, Nesse said more and more companies are now pressing for food production to be either

antibiotic free or are "significantly reducing the usage" of antibiotics. Addressing EU policymakers and stakeholders during the 28 June 2017 European Parliament conference on tackling antibacterial resistance, Nesse largely focused on alternatives to antibiotics, stating that industry "wants to be part of the solution" to what he described as "one of the greatest threats to public health."

Government and industry, along with other stakeholders, managed to reduce antibiotics use in the Netherlands by 58 per cent, he said. If a world population of nine billion by 2050 is to be fed, similar initiatives are needed. "If we do not change practices we will use a lot more antibiotics. Not fewer. So a fundamental change is truly needed." Echoing the statements on ethics and morality by

"AMR is the biggest threat to public health so it's all about finding alternatives, and through alternatives, reducing the use of antibiotics"

Nutreco CEO, Knut Nesse

Michael Kuhn, assistant secretary general of the Commission of the Bishops' Conferences of the European Community (COMECE), and Dr Hannah Maslen, deputy director, Uehiro Chair in Practical Ethics at the University of Oxford, Nesse remarked that preventative health is key. "It's about feed management, it is about farm management, and it is also about health management" which "should be seen as the first line of defence - the most important thing to get right. And only when the first line of defence is not working properly, only then as a last resort, should you use antibiotics when animals are truly sick."

Nutreco is highly engaged in developing alternative strategies.

Nesse added, "As well as more generic trials, we are also working with a number of companies and have very many good examples."

One of those cited managed to raise 99 per cent of their animals without using antibiotics.

Another company had managed to raise 60 per cent of their pigs without using any antibiotics.

Nesse argued that companies and the food sector – together with governments – need to set and communicate "ambitious" reduction targets.

He also had another message for policymakers and regulators, arguing that they need to fund research programmes on alternatives to antibiotics.

Farmers will only abandon high volumes of antibiotics use if they are provided with cost-effective alternatives.

The conference questioned why these had not been prioritised in the past decades.

For husbandry, such alternatives are already underway, however the search for alternatives in fish and shrimp farming is just starting. "AMR is the biggest threat to public health, so it's all about finding alternatives, and through alternatives, reducing the use of antibiotics. Certainly there is hope." He added, "AMR may not be stopped, but it can be managed. And there are alternatives today."

Validation trials have demonstrated that feed ad-

ditives "can do equal or in some cases even better" than antibiotic growth promoters.

Two of China's top food experts, Prof Dr Zhang Junmin, Director of the Institute of Animal Sciences at the Chinese Academy

demonstrated that certain feed additives appeared to perform similar, or sometimes better, than antibiotics in terms of health and growth promotion.

According to Prof Dr Adam Cohen of Leiden University in

"Government and industry, along with other stakeholders, managed to reduce antibiotics use in the Netherlands by 58 per cent. If a world population of nine billion by 2050 is to be fed, similar initiatives are needed"

of Agricultural Sciences, and his Deputy Director, Prof Dr Chen Jilan presented findings based on their pioneering research into non-antibiotic alternatives for animal health and growth promotion.

The tests were carried out under the supervision of the Chinese Government Institute for Veterinary Drug Control.

Supervisor Prof Dr Jiang was in the audience. The tests included both 'normal' and 'challenge' circumstances and

The Netherlands, this may also prove that antibiotics no longer have the desired result.

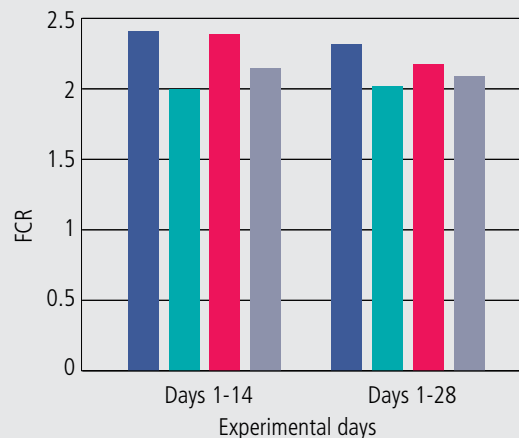
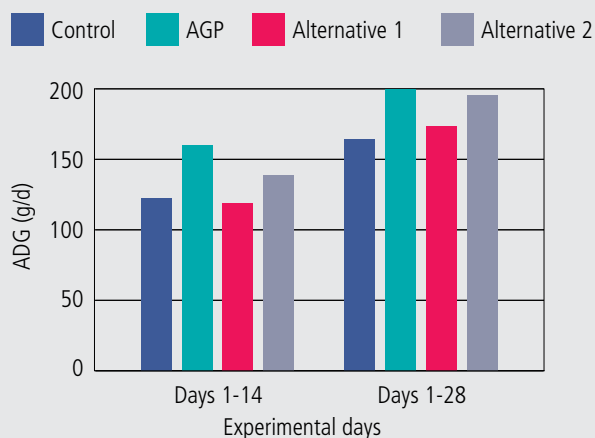
In the words of Prof Dr Chen, who compared antibiotics and feed additives performance under similar conditions in poultry farming, "the alternatives showed the potential to replace antibiotic growth promoters." Prof Dr Chen also told the Conference that the tests, "are very important in China's development."

According to Dr Thomas Van



Prof Dr Zhang's piglet trials

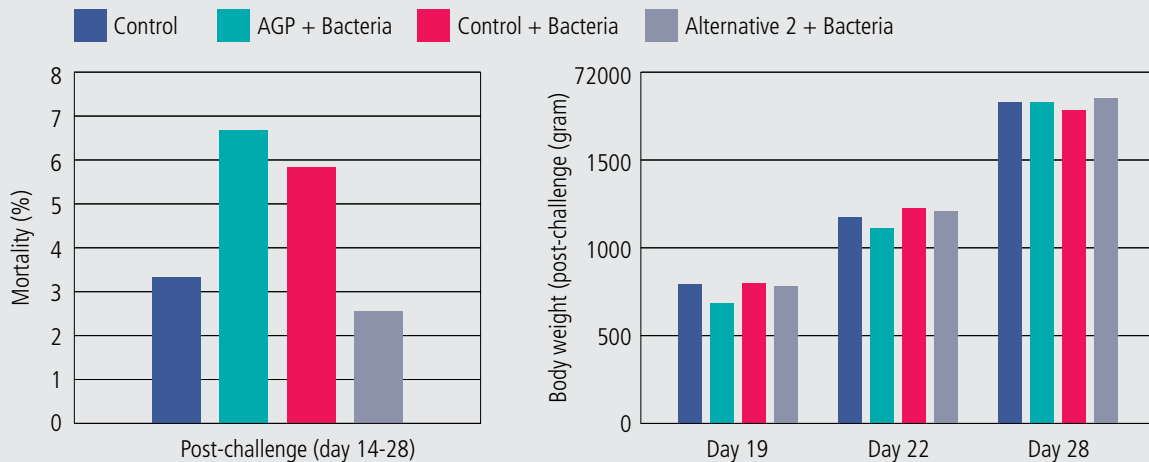
The left-hand graph outlines piglet growth, expressed as Average Daily Gain (ADG). The ADG of pigs on antibiotic growth promoters (AGP) and those on alternative feed additives can be compared. Both performed notably better than the control group. The right-hand graph illustrates the feed conversion ratio, i.e., the amount of food needed to grow. The lower the score, the better. Here again, AGPs and alternatives performed comparably.





Prof Dr Chen's poultry trials

The left-hand graph depicts the mortality rate of chickens. The mortality rate for chickens consuming alternative feed additive products was the lowest. The graph on the right depicts the increase in bodyweight after a bacteria challenge. The alternative with a bacterial challenge was the top performer by the end of the trial, doing even better than the control without a bacterial challenge.



[Note to this graph and previous page] The Institute of Animal Science of the China Academy of Agricultural Science performed tests on piglets and poultry in the period 2016-2017. The tests included comparisons of test results acquired with normal feed, normal feed with antibiotics in a preventive/growth promotion role, and normal feed with the feed additives Presan and SelkopH. The tests took place under the supervision of the Chinese Government's Institute for Veterinary Drug Control.

Boeckel of the Swiss Institute of Integrative Biology, China, India, Pakistan and Indonesia are among the largest users of antibiotics and therefore experience the highest AMR threat.

China produced its first AMR Action Plan last year, taking measures including the banning of certain antibiotics used in animal husbandry, including one of the 'last resort' antibiotics, Colistin. ★

"The [feed additive] alternatives showed the potential to replace antibiotic growth promoters"

Prof Dr Chen Jilan

A pharmacologist in a pig-pen

Is it right to knowingly threaten human health for the sake of a purpose that is probably not even being achieved, asks **Professor Adam Cohen**, CEO of the centre for human drug research in Leiden

As surgical interns, when we did hernia operations and were allowed to close the wound, in some cases we were instructed to sprinkle antibiotic powder in the wound, but not in all. Now we know that local antibiotic treatment is useless. Such irrational approaches to treatment have luckily largely gone. How different this is when you do a ward round in a pig-pen, chicken coop, or fish farm. Large amounts of antibiotics are added to the food of these animals, presumably to prevent disease and promote growth. The end result must be that we can eat more meat at a lower price.

Imagine if over the course of 20 years we had added antibiotics to human food in the Netherlands. During that period, the average Dutch person would have grown by about 2.1 cm and gained around 5.6 kg. A 'people farmer' would have been thrilled with the result. More meat for the same price! Yes, probably some infections would have been prevented as well, but at the cost of bacterial resistance on an enormous scale. In this scenario, a proposal to abolish antibiotics would have probably led to strong opposition from the people farmers and the antibiotic producers over fears of shrinking profits. Of course, none of this happened. If it

had, we would have immediately noted that the causal link between antibiotics use and growth was accidental and that growth was due to better nutrition (even too much nutrition) and disease prevention by vaccination. Such a coincidence is called bias, and to prevent it randomised and controlled, blind clinical trials were invented.

So, the question of a clinical pharmacologist in the pig-pen is: is there any evidence that prophylactic antibiotics - which cause life threatening AMR - even work for the purpose they are intended for, namely, more meat production? The shocking answer is that evidence from good trials is absent. Aside from questionable data collected in the 1950s and some other trials looking at the effect of stopping antibiotics (proving that stopping use had little negative effects), there seems to be nothing. If antibiotics work at all, they did so under husbandry circumstances from the 1950s and should now be abolished. It is almost unbelievable that we are knowingly threatening human health by creating AMR,

all for a purpose that is probably not even being achieved. The solution is simple. Let's check if it works. This can be done by a placebo (unsupplemented food) controlled, blind and randomised experiment. Then you check growth, wellbeing and infection rates. By randomising some badly run farms, you can check if modern farming techniques accomplish the same as antibiotics. All of this is standard stuff, costs some money but nowhere near what AMR will cost.

Antibiotics may be of use in overcrowded, dirty, and badly run farms, but the solution for that is also clear and not found in antibiotic treatment. My solution would be simple. Take one year to do large scale trials, designed to get a precise estimate of the potential advantages of prophylactic antibiotic supplementation in animals. There are many human clinical trialists ready to assist. ★



"If antibiotics work at all, they did so under husbandry circumstances from the 1950s and should now be abolished"

Should the Polluter Pay?

Imposing taxes on the use of antibiotics in food production may be the most successful approach to tackling AMR

A post-antibiotic age in which common infections and minor injuries can kill is, for most people, too frightening to contemplate. EU policymakers including MEPs are now aware that this is a very real possibility. To help slow the emergence of bacteria resistant to antibiotics we need to reduce our dependence on antimicrobial drugs and drastically cut their misuse and overuse in humans and animals. That was

feed and pharmaceutical industries to invest in the development of feed additives that may reduce the need for antibiotics. Standaert said, "We have been proposing the creation of a new and very specific functional group within regulation 1831/2003 on feed additives. The main idea here is to keep animals in good health by way of balanced feeding which will reduce the need for antibiotics later."

Standaert, a former Belgian representative to the Standing

Committee on plants, animals, food, and feed, pointed out that a text had been tabled which refers to animal growth and performance, as "a well-known secondary effect of antibiotics." He told the conference, "Offering farmers officially regulated and registered substances as an alternative may further reduce their demands for

the message from experts invited to address the issue at the recent antibacterial resistance conference in the European Parliament.

Diederik Standaert, who heads up the management office of the Belgian government's directorate for animal, plant and nutrition, addressed how antibiotics can be misused. He referred to an EU initiative on animal nutrition that aimed to create extra incentives for Europe's

antibiotics." The use of certain feed additives to drinking water may also "positively" influence the health of animals and consequently reduce the need for antibiotics, he said. He also highlighted the European Commission's 2014 proposal revising rules concerning medicated feed, saying, "Discussions are currently on hold at the Council level but this contains some important elements in the fight

against antibacterial resistance."

Another speaker, Dr Hannah Maslen of the University of Oxford, noted the importance of raising consumer awareness about AMR. She said, "Informing farmers and consumers about the need to address antimicrobial resistance will

be crucial, both to justify these policies to them and to further reduce the production, and consumption of meat farmed using antibiotics. Indeed, there are broader reasons to provide information, not only so that consumers and farmers can make better informed choices, but actually there is some evidence suggesting that consumers seem to be more sensitive to this sort of information than we might think and even be willing to pay a bit more for meat that is antibiotic-free."

Denmark and Belgium are leading the way when it comes to limiting antibiotics use through taxation. Will the rest of the world follow their lead?



"What can we do to reduce the consumption of antimicrobials in food production on a global scale? One potential approach that has been suggested is that we could start by imposing a global user fee on non-human antibiotic use"

Dr Thomas Van Boeckel

She added, "This might actually go some way towards already changing the incentive structure if consumers have such preferences."

Recent media reports have however highlighted several loopholes in differing "no antibiotics" labelling regimes currently in use in the United States. The debate also explored the thorny issue of antibiotics taxation, with Maslen telling participants that, in trying

to curb the growth of AMR, the "most ethical course of action" would be by imposing taxes, including a consumer tax on meat products farmed using antibiotics. The revenue generated would be invested in developing alternatives for farmers and subsidising alternative sources of protein.

Dr Thomas Van Boeckel, of the Institute of Integrative Biology in Zurich, argued that the "central" question in tackling AMR was: what can we do to reduce the consumption of antimicrobials in food production

on a global scale? "One potential approach that has been suggested is that we could start by imposing a global user fee on non-human antibiotic use", said Van Boeckel. "This approach seems logical and easy because it could be implemented at the level of imports or at the level of the manufacturer. The approach would also generate revenues that could be used to contribute to globally improve hygiene conditions as well as potentially investing in

the development of new drugs."

One country – Denmark – is leading the way in reversing current trends. Over the past two decades the country has instituted reforms to antibiotic use for livestock that are showing solid progress in reducing the prevalence of resistant bacteria.

"The basic idea is based on the 'polluter pays' principle and the money collected helps finance the set up and maintenance of official national data collection systems that monitor antibiotics use in the animal husbandry sector"

Diederik Standaert

The country has drastically limited how much veterinarians can profit from the sale of antibiotics and outlawed all nontherapeutic use of antibiotics in pigs – a huge change in a nation that is the world's leading exporter of pork.

Standaert noted that Belgium had also introduced a specific tax for all authorisation holders that market antimicrobial drugs for animals. "The basic idea is based on the 'polluter pays' principle and the money collected helps finance the set up and maintenance of official national data collection systems that monitor antibiotics use in the animal husbandry sector." He said that in the past four years Belgium had cut its total antibiotic use in farm animals by 15.9 per cent. "We hope that the additional measures we have been taking will help us to achieve our ambitious targets for 2020 (to reduce overall use of antibiotics in animals by 50 per cent). We have still some work to do but I am sure we will succeed." ★



The moral majority

Could taxation be the simplest and most ethical way to reduce antibiotic use in farming?

For many attending the 28 June 2017 European Parliament conference on the scientific, human health, husbandry, and socio-economic aspects of antibacterial resistance, the moments of heart-wrenching silence as Susan Fallon fought to maintain her composure said more about the growing threat of AMR than decades of 'expert' debate. Fallon's moving keynote testimony on the tragic loss of her daughter to hospital-acquired MRSA ensured that the high-level event maintained a focus on the human and socio-economic consequences of the looming AMR crisis.

The ethical and moral aspects of AMR were the primary focus for another keynote speaker at the

to ensure that antibiotics will continue to be usable in the future. "Given the scale of the threat, the actions to be taken need to be firm, determined and expedient," stressed Kuhn, who cautioned, "They will not be adequate as long as we do not understand or refuse to see that the mixtures of antibiotics and medicines, and medicines in livestock breeding are just a symptom of something of a much deeper concern."

Expanding on this, he explained, "It is the idea that we own the earth and see it mainly as a commodity we can exploit. What we have lost is a sense of stewardship. We tend to look for technical solutions to a problem that requires nothing less than a change of mentality and the ability to broaden our vision." Kuhn referred to the encyclical letter of Pope Francis, where the pontiff proclaimed, "Politics must regain its supremacy over economy." Kuhn, who advises on ecology, sustainability, education, culture

and youth policy to COMECE, recognised that there is a need to feed ourselves, and that farmers must be able to make a living, but advocated the respectable treatment of what he called, 'our co-creatures'. "The way animals are kept today in the livestock industry, a method that encourages the

pre-emptive use of antibiotics, necessary to avoid illnesses is, from the point of the Catholic Church-led teaching, simply unethical." Therefore, he argued the "Food industry, our wholesale and, retail trade, and finally our behaviour as consumers" must be re-thought. He told attendees at the packed event, "If politics remains caught up in inconsequential discussions we will continue to avoid facing the major problems of humanity".

His emphasis of the "natural laws" and moral imperatives relating to AMR was partly endorsed by Dr Hannah Maslen, deputy director, Uehiro Chair in Practical Ethics at the University of Oxford, who argued that "moral obligation and responsibility" ought to be incorporated into policymaking discussions. Maslen said, "It's clear that AMR must be a moral as well as a practical issue". She cited as evidence the findings of a 2016 review on antimicrobial resistance commissioned by the UK government which warns that by 2050, drug resistant infections will put 10 million lives a year and at least \$100 trillion worth of economic output at risk. "Such significant physical and economic harms," she added, "are clearly morally important." She went on, "The interests of those who will die or whose health will be otherwise substantially deteriorating as a result of AMR indisputably carries great moral weight. The question that we need to ask when considering action - or inaction - is which are morally relevant?" Health interests, Maslen noted, are "fundamental" and so "clearly constitute the weightiest consideration". She argued that, "Without our health, we cannot protect any other interest and this interest is also held by the largest number of people. On the other hand, largescale farming operations that have commercially



viable alternatives to meat production or to using methods involving antibiotics would not have their commercial viability threatened by such restrictions on antibiotics".

The most ethical course of action, Maslen believes, would be to start imposing taxes, including a consumer tax, on meat products farmed using antibiotics.

As well as regulatory measures, another proposal she suggested would be to inform farmers and consumers about the need to

"If politics remain caught up in inconsequential discussions we will continue to avoid facing the major problems of humanity"

Michael Kuhn

event, Michael Kuhn, assistant secretary general of the Commission of the Bishops' Conferences of the European Community (COMECE). Highlighting that the main objective of the meeting was to reflect on how an "imminent catastrophe" could be averted, he called for immediate action to be taken



address antimicrobial resistance. "This will be crucial, both to justify these policies to them and to further reduce the production, and consumption of meat farmed using antibiotics." She added that "Banning antibiotics completely in farming tomorrow would put the interests of farmers and those dependent on their meat in jeopardy". Farmers' interests are "not morally negligible".

However, her "initiatives do not have to do all or nothing

straight away." Maslen acknowledged the role of non-antibiotic alternatives in assisting the transition away from antibiotics. She concluded by saying governments worldwide are under a moral obligation to regulate the use of antibiotics and farming. "Containing AMR is a matter of collective responsibility requiring the effort of a large portion of the population. It is

"Individuals by themselves do not have the necessary incentives to be relied upon to make their own contribution to this international issue so it is incumbent upon states to fulfil this obligation"

Dr Hannah Maslen

the moral duty of political leaders to make sure that we collectively fulfil this responsibility."

"Individuals by themselves do not have the necessary

incentives to be relied upon to make their own contribution to this international issue so it is incumbent upon states to fulfil this obligation." ★

Undermined by overuse

The routine use of antibiotics for women experiencing a healthy pregnancy is transforming childbirth from a normal physiologic process into a potentially harmful medical procedure, with significant health and social consequences, argues ICM President, **Franka Cadée**

Antimicrobial resistance (AMR) is a serious and growing threat to public health and the health of childbearing women and their newborn infants. AMR increasingly poses a grave danger to women and infants as antibiotics become compromised through overuse.

The International Confederation of Midwives (ICM) recognises that technological advances in maternal and newborn care have significantly reduced maternal and infant mortality. However, we are concerned that some interventions have become so commonplace

that they now pose their own serious health risks to the public. The routine use of interventions for women experiencing a healthy pregnancy does not reflect reliable evidence and only serves to transform childbirth from a normal physiologic process into a potentially harmful medical or surgical procedure, with significant health and social consequences.

The use of antibiotics during pregnancy and childbirth is a telling example of a critical health tool which is becoming alarmingly undermined by overuse. When first introduced, antibiotics represented one of the most important techno-

logical advances to save the lives of mothers and babies alike. Today, an estimated 30,000 women and 40,000 newborn infants still die annually due to severe infections resulting from the period of birth. Many of these infections could be prevented by simple handwashing by all health professionals before every interaction with a mother and her infant. For those infections which do occur, antimicrobial medication can be life-saving but only if the afflicting microbes are susceptible to the antibiotics available. Unfortunately, globally,

carries a host of potentially negative consequences for a woman and her newborn, we call for midwives and other health professionals to promote practices which serve to decrease the health risks of antimicrobial resistance. Working so closely with women and their families, midwives are strategically placed to protect those in their care by these practices such as regular hand-washing, limiting interventions, promoting skin-to-skin contact between mother and her new-born and the judicious use of (prophylactic) antibiotics.

The key mechanisms

in reducing maternal and newborn morbidity and mortality are not found in the over-use of antimicrobials, but rather via primary prevention of infection, though appropriate Water, Sanitation and Hygiene (WASH) measures, accurate treatment of infec-

“Unfortunately, globally, we are quietly being confronted by more and more organisms which can no longer be killed by our current arsenal of antibiotics”

we are quietly being confronted by more and more organisms which can no longer be killed by our current arsenal of antibiotics.

Given that unnecessary or inappropriate use of antimicrobials

tion and AMR prevention.

Accordingly, we advise our member associations to advocate for, and work with relevant partners to establish WASH at birth, neonatal and postpartum settings, and antimicrobial resistance as a core component of education, training, and professional development. We also support training and education on infection prevention measures as a mandatory requirement in education and professional development and the development of a code of conduct for appropriate training in, education about, and marketing, purchasing and use of antimicrobial agents.

As midwives, we believe it is crucial to promote the importance of skin-to-skin contact between mother and baby to support the development of a healthy microbiome and to promote judicious use of (prophylactic) antibiotics. ★



Effective education, better outcome

Without coordinated planning at national, regional and European level, action to address antibiotic resistance will remain fragmented and ineffective, warns ESNO Executive Secretary, **Ber Oomen**

There's nothing quite so devastating for a nurse than being paralysed by a situation beyond their control. Over recent years, nurses have been increasingly confronted by antimicrobial resistance (AMR) a phenomena which conflicts with the very core of their work. The key question, of course is, if healthcare professionals and hospitals are 'running out of options' when should antibiotics be used? AMR is, for many professionals, relatively new to them and has been described by European health Commissioner, Vytis Andriukaitis as a "silent tsunami" but also one "without a warning system". This why the

European Specialist Nurses Organisations (ESNO) fully endorses the European One Health Action Plan against AMR. The guidelines on the prudent use of antimicrobials by the European Centre for Disease Prevention and Control (ECDC) are also welcome because they have a practical element and that is where nurses have a role to play.

However, we fear that there will have to be a significant rise in the number of victims in order for Europe's three million nurses to have a greater awareness of AMR. Nurses see patients at home, in the community and in a clinical setting. They see patients using medication according to prescribed guidelines but also see misuse, overuse and no use. Due to heavy caseloads though, there might be a tendency to overlook this. We therefore believe there should be a

greater emphasis around awareness-raising as well as improved education and training on AMR.

Without a clear structure or planning at national, regional and European level, action on dealing with AMR could end up fragmented

and ineffective. The challenge facing the health workforce and the threat posed to human health by AMR should not be underestimated. If AMR is not effectively addressed, the problem is likely to increase rather than decrease. We believe that better cooperation in tackling AMR

could be an opportunity to show the world how Europe can be the benchmark for best practice. Across the European network of nurses and in specialised areas, there seems to be an understanding on the AMR phenomenon but whether it is understood enough to include this in the wider context such as guidelines and programmes is still unfortunately unclear.

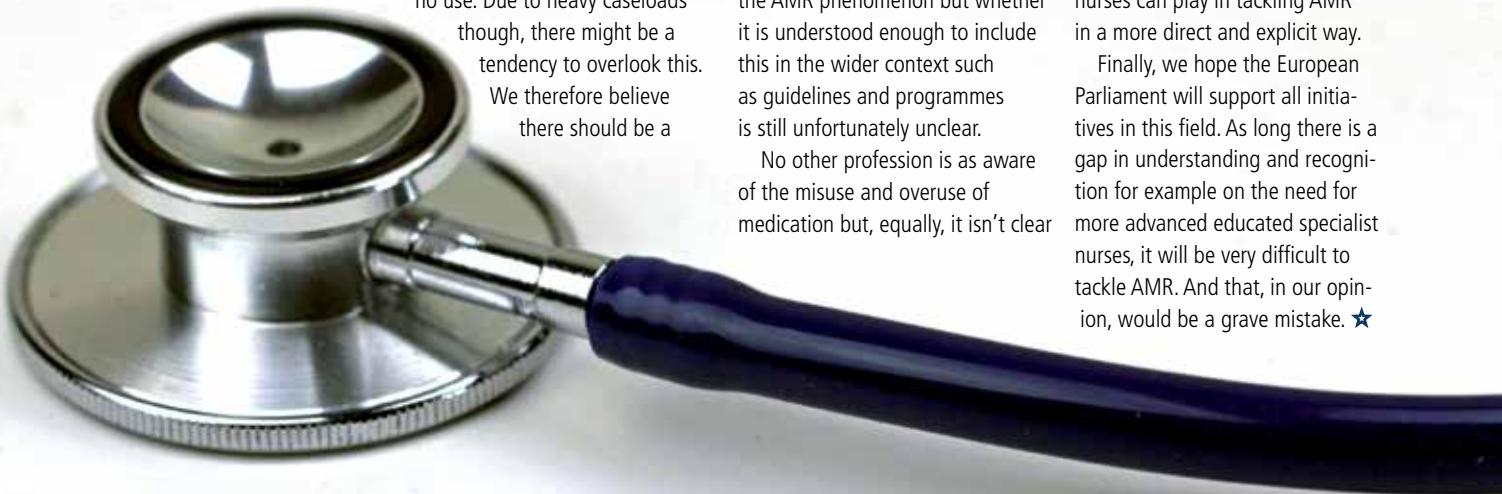
No other profession is as aware of the misuse and overuse of medication but, equally, it isn't clear

if there is enough understanding of AMR's impact, especially for the most vulnerable, such as children, people with rare diseases and the elderly. Nurses could, and should, be better involved in monitoring AMR cases and in contributing

"The challenge facing the health workforce and the threat posed to human health by AMR should not be underestimated. If AMR is not effectively addressed, the problem is likely to increase rather than decrease"

to research and clinical data programmes. We call on national health regulatory bodies to address AMR, to invest in specialist nurses and also to invite the Commission to address the key role that nurses can play in tackling AMR in a more direct and explicit way.

Finally, we hope the European Parliament will support all initiatives in this field. As long there is a gap in understanding and recognition for example on the need for more advanced educated specialist nurses, it will be very difficult to tackle AMR. And that, in our opinion, would be a grave mistake. ★



AMR IN NUMBERS

Should AMR continue its relentless march, it could result in one person dying of antimicrobial resistance (AMR) every three seconds by 2050. The global death toll could exceed 300 million in the same period with 10 million dying annually thereafter, exceeding yearly cancer deaths. Commenting on the looming health crisis, Dame Sally Davies, England's Chief Medical Officer, cautioned that should we return to a pre-antibiotics era, "40 per cent of people could die of infections."

The European Parliament has warned that AMR "Is expected to become the world's largest cause of death." Currently, the EU estimates that 25,000 people die of AMR in Europe annually. However, concrete figures show that at least 12,000 people die of AMR in the UK alone. This makes up almost half of the overall European estimate, so the fact that the UK accounts for only 13 per cent of Europe's population suggests that the death toll could be much higher than currently anticipated.

Former WHO Director-General Dr Margaret Chan has warned that a

post-antibiotics era would, in effect, mean "The end of modern medicine as we know it. If current trends continue, sophisticated interventions, like organ transplantation, joint replacements, cancer chemotherapy, and care of pre-term infants, will become more difficult or even too dangerous to undertake." During the recent Scientific, Human Health, Husbandry, and Socio-Economic Aspects of Antibacterial Resistance: Time to Act conference, Professor Ramanan Laxminarayan, director and senior fellow of the US Center for Disease Dynamics, Economics & Policy, remarked that 92 million surgeries take place per year in low-income countries, with 5.5 million surgical site infections. "Between 400,000 and a million deaths from these are caused by resistant pathogens." Children are notably susceptible.

75 per cent of all antimicrobials in Europe and the United States are used in agriculture. Dr Thomas Van

Antimicrobial usage in agriculture, at current estimates

\$44.1bn

Estimated financial loss to the meat industry from banning antibiotics as growth promoters



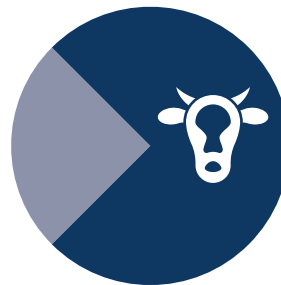
\$3.4 trillion

Estimated global GDP loss by 2030 as a result of AMR

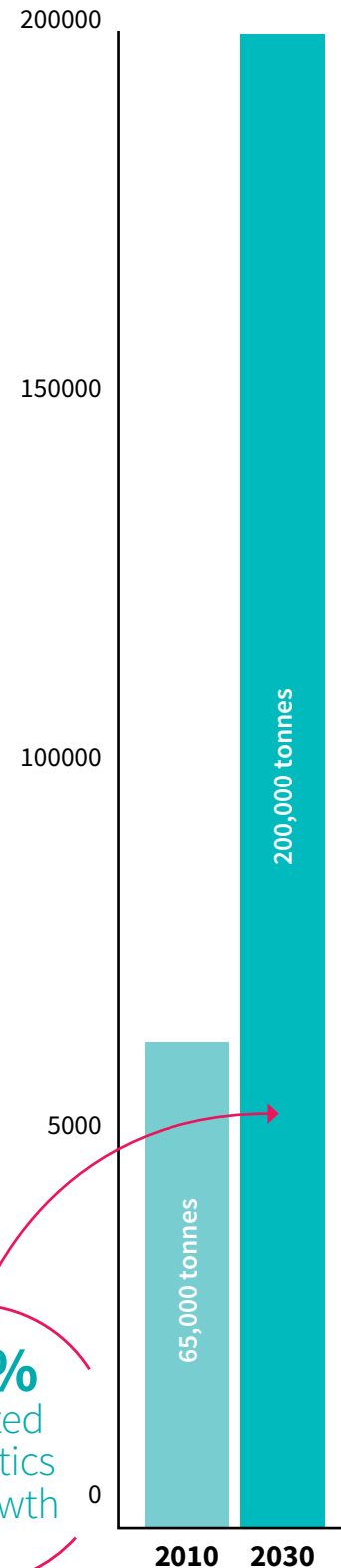


\$210 trillion

Estimated global GDP loss by 2050 as a result of AMR



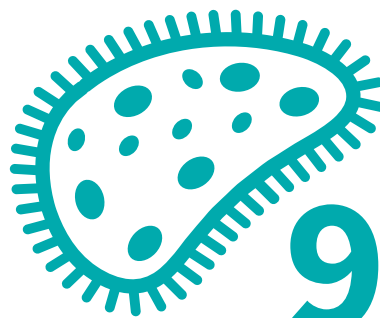
75 per cent of all antimicrobials in Europe and the US are used in animal husbandry



217%
Expected antibiotics use growth



A return to a pre-antibiotics era, could see **40 per cent** of people dying from infections



90%

Bacteria originating in seawater that are resistant to one or more antibiotics

20%



Percentage of bacteria in seawater that are resistant to at least five antibiotics



By 2050, **one person** could be dying of an AMR-related infection **every three seconds**



90 per cent of the world's aquaculture production takes place in developing countries

Boeckel, an AMR expert at Zurich's Institute of Integrative Biology reported that "at the very least 65,000 tonnes" of antimicrobials were used in agriculture in 2010. Based on more recent data Van Boeckel maintains "If we keep the business as usual, consumption will reach 200,000 tonnes by 2030." Between 2010 and 2030, the use of agricultural antibiotics could increase by 217 per cent.

The cumulative loss of global meat production following a global ban on antibiotics as growth promoters would range between one and three per cent to which Van Boeckel argues, "Is probably minimal and it's probably not worth it to use antimicrobials as growth promoters." The decrease in meat production would correspond to a financial loss somewhere between \$13.5bn and \$44.1bn. By contrast, the World Bank suggests that by 2030, GDP shortfalls resulting from AMR could range between at least \$1 trillion and \$3.4 trillion annually. By 2050, between \$40 trillion and \$120 trillion dollars would have been lost. An AMR crisis would be comparable to the global financial crisis, however, unlike the 2008 financial crisis, the

AMR phenomenon would not be limited to a few years. Independently, the UK Review on AMR has calculated that by 2050 - when including the secondary impacts of AMR - the total global GDP loss could amount to \$210 trillion. Lastly, the World Bank

also suggests that an AMR outbreak could decrease global livestock production by 7.6 per cent by 2050.

Aquaculture is a major source of protein in developing countries. 60 per cent or more of the protein in certain lower income countries (54 per cent in Indonesia) stems from fish which is believed to be infested with antibiotics. Aquaculture systems and farms have been described as "genetic reactors" and "hotspots for AMR genes". Van Boeckel believes that "Aquaculture is associated with extremely high rates of antimicrobial consumption per PCU (Population Correction Unit)". Dr Joy Watts and her colleagues at the University of Portsmouth's School of Biological Sciences have estimated that 90 per cent of the world's aquaculture production takes place in developing countries which lack regulation and enforcement on antibiotic use. In fact, "It has been estimated that 90 per cent of bacteria originating in seawater are resistant to one or more antibiotics and up to 20 per cent of the bacteria are resistant to at least five". Troublingly, data on antibiotics use in aquaculture is very scarce.

Despite being primed to become one of the major global killers, AMR and its causes are not widely understood by the general population and policymakers. An unrecognised threat, it lingers in the shadows, but could become what Vytenis Andriukaitis, European Commissioner for health and food safety, dubbed, a "silent Tsunami". ★

One health, one plan



Combatting the spread of AMR needs joint efforts and concerted political focus, argues Estonia's Deputy Secretary General for Health, **Maris Jesse**

Antimicrobial resistance (AMR) has become a serious concern, both at European Union level and globally. The European Commission has estimated that within the EU, antimicrobial resistance kills 25,000 people every year while additional healthcare costs and associated productivity losses amount to more than €1.5bn a year.

Besides human use, antibiotics are also used in veterinary medicine. In fact, more than half of all antibiotics produced in the world are used in agriculture, mainly to treat or prevent diseases in food-producing animals. Thus, antimicrobial resistance often spreads to the human population through food or through the environment, including water and wild fauna. The environ-

ment, being a cross-border open system, unfortunately creates ideal conditions for antimicrobial resistance to spread across the world.

We, as policymakers, have to take steps now to stem the spread of antimicrobial resistance and bring this potential threat under control. The 'One health' approach needs to be targeted jointly by the health, agriculture and environment sectors across all European Union countries, and joint actions are also needed at the global level. Antibiotics usage in healthcare and animal husbandry needs to be better targeted and all the main stakeholders should be aware of the correct use of antibiotics.

The Estonian EU Council-Presidency is dedicated to bringing forward the discussions on the veterinary medicines package in the

Council, as many of the proposed measures will help contribute to reducing antimicrobial resistance. Previous EU Council presidencies have made considerable progress with the proposal and we believe the Estonian Presidency has the advantage of building upon this work. We will focus our efforts on reaching an agreement on a mandate to start negotiations with the European Parliament.

The importance of discussing and implementing the new One Health Action Plan is clear. In June 2017, the European Commission adopted a new action plan on AMR - which had been requested by the member states in their Council conclusions of June 2016 on the next steps

under the One Health approach. The Estonian Presidency will focus on enhancing discussions between member states, the European Commission and with experts on how to best implement the One Health Action Plan at member state level.

"A high-level meeting on AMR will be organised in Brussels on 23 November 2017. It will bring together all the main sectors involved – health, agriculture and environment"

With this aim, a high-level meeting on AMR will be organised in Brussels on 23 November 2017. It will bring together all the main sectors involved – health, agriculture and environment. The discussions will focus on the new European Union One Health Action Plan, its implementation and evidence-informed policy decisions on antimicrobial resistance. The outcome of the high-level meeting will be presented to the Union's health ministers on 8 December. The Estonian Presidency will make efforts to shape the outcome of the high-level meeting, and to ensure that it will also serve as an input for the next EU Council Presidencies to initiate actions to combat antimicrobial resistance in the EU. ★



Time for genuine leadership

Europe needs to take action and tell it like it is, argues Lithuania's former minister of European affairs, MEP **Laima Andrikiienė**

Some five years ago, many of us hadn't even heard of antimicrobial resistance (AMR). Last year the UN General Assembly devoted a complete day to the subject. So now no politician can claim that they "didn't know" about the looming AMR crisis. In December 2016, an AMR amendment to the European Parliament's annual report on human rights and the EU's policy on the matter was voted down. We cannot allow this to happen again. Yes, this document acknowledged that AMR is expected to become the world's largest cause of death, "victimising in particular the

vulnerable and the weak in developing countries". But declaratory policies do not bring millions of AMR victims back to life. If Europe does not tell it like it is, who will?

I am inspired by the statements of Dr Michael Kuhn and Dr Hannah Maslen at the June 2017 European Parliament conference on the socio-economic aspects of antibacterial resistance.

Whether Christian or not, we cannot brush away the Pope's statement, "Politics must regain its supremacy over economy." Europe is confronted with many obstacles to greater union and - may I say it - common purpose. Just judge the combined Dieselgate/Cartel case; the slow motion on access to the market for Low Risk Bio-pesticides in an evident effort to unnecessarily protect chemical industrial interests; and a new EU AMR Action Plan that after 10 years of efforts offers plans but no action! What are we doing with our vow to protect the lives and livelihoods our people? Maslen convincingly proved that genuine

European leaders must now act ethically and morally in regard to antibiotics regulations. The terrifying prospect of 10 million lost lives per year by 2050 must be avoided by any means available – including developing alternatives for antibiotics in husbandry and

fish farming possibly through taxes and labelling. Our future is worth that. I applaud the AMR conference's initiative and that of my fellow MEPs, Adina-Ioana Vălean, Pavel Poc and Fredrick Federley, and I fully support the conference's call for EU leadership. ★



"The terrifying prospect of 10 million lost lives per year by 2050 must be avoided by any means available"

Taking action on AMR

- Establish an AMR crisis mechanism;
- Develop legislation or a horizontal reflection in existing legislation on both EU and its member states level to limit any possible misuse of antibiotics to possibly zero;
- Establish accountability, responsibility and strict enforcement particularly at member state level as only they can enforce and implement European legislation;
- Invest heavily in both new antibiotics molecules and in alternatives particularly for antibiotics currently used to promote animal health and growth;
- Shift to less intensive, less traumatising, less brutal husbandry to ensure fewer antibiotics and pesticides are used, which could have a role in the development of antibiotics resistance;
- Agree to enforce these new rules not only in Europe, but also in the context of the United Nations using a name and shame approach when UN member states do not perform properly;
- Develop a truly global and effective information plan to ensure that every mother really understands the risks to their unborn and newly born child of consuming food containing antibiotics;
- Create new forms of labelling to ensure that every customer knows what they eat and has information not only about the content of main nutrients and allergens like now, but also the way of production;
- Establish mechanisms to help farmers step away from antibiotics for any reason other than to cure disease.

Global Media Monitor

Over the past four years the PA International Foundation has circulated a global media monitor on Antimicrobial Resistance. Twice a week our colleagues in Beijing, Jakarta and Brussels inform a select group of experts on human, medical, scientific, technological, technical, regulatory and other relevant AMR matters. We have been told that this remarkable effort has assisted policy and decision makers in China in adopting their first AMR action plan. If you are interested in receiving the global AMR Media Monitor, including just signals, facts and figures, no comments, you can send a request to AMR@pa-international.org As an example, the abstracts below were included in the 1 September 2017 media overview.

Chicken is full of resistant bacteria

A quarter of chicken meat in supermarkets contains bacteria that are insensitive to "last resort" antibiotics. Recent research suggests that the percentage of supermarket chicken with bacteria that are insensitive to the crucial antibiotic colistin is much higher than previously thought. The research on resistant bacteria was led by clinical microbiologist Jan Kluytmans, who works at Breda's Amphia Hospital in the Netherlands. Kluytmans wants the Dutch Food and Welfare Authority (NVWA) to explore the issue further. The fact that Kluytman found many more

resistant genes in bacteria does not mean that Dutch poultry farmers treat their animals with antibiotics on a preventive basis. "The Netherlands is with the low users," says Kluytmans. "Germany uses a lot of colistin. Spain and Italy even use incredibly much." Where the supermarket chickens with resistant bacteria come from is unknown says Kluytmans. The NVWA may be able to find out if they start an official examination. Then the seller is required to find out where the animals have been.

<https://www.trouw.nl/home/kip-zit-vol-resistente-bacterien-a76b5750/>

Hypervirulent, highly resistant *Klebsiella* identified in China

Researchers say an outbreak of severe pneumonia at a Chinese hospital was caused by hypervirulent, highly drug-resistant, and highly transmissible strains of *Klebsiella pneumoniae*. The ST11 carbapenem-resistant hypervirulent *K pneumoniae* strains were identified in five patients in the intensive care unit of a hospital in Hangzhou, in eastern China. All five patients died of severe lung infection, multi-organ failure, or septic shock. The report warned that "Due to acquisition of a virulence plasmid by classic ST11 carbapenem-resistant *K pneumoniae* strains, these new strains are simultaneously hypervirulent, multidrug resistant, and transmissible, and should therefore be regarded as a real superbug that could pose a serious threat to public health."

In a commentary in the same journal, two experts from Rutgers University in the United

States, wrote that the study describes an alarming evolutionary event: plasmid-mediated convergence of multidrug-resistance and hypervirulence in an epidemic carbapenem-resistant *K pneumoniae* clone. Though a similar event had been reported before, the new report on five fatal cases characterises the virulence and resistance plasmids. The two wrote that the transfer of the virulence plasmids raises worries that the organisms might not only cause untreatable hospital infections, but also serious life-threatening ones in the community. The new findings underscore the need for new effective antibiotics, and new strategies such as vaccines, phage therapy, and gene therapy for battling drug-resistant organisms offer optimism.

<http://www.cidrap.umn.edu/news-perspective/2017/08/hypervirulent-highly-resistant-klebsiella-identified-china>