Uppsala HEALTH SUMMIT

Pre-conference report

# A world without antibiotics

2–3 June 2015
Uppsala, Sweden

#uhs_2015

We all know that healthcare today is faced with ever greater challenges. We are faced with both economic and ethical dilemmas, and while advances may open new possibilities for improved health and care, many do not reach the patient today.
Continuing research and innovation open new possibilities. But as possibilities expand, so do the issues.

Uppsala Health Summit is an international arena for frank and challenging dialogue, exploring possibilities and dilemmas associated with medical advancements that can improve health and health outcome. Uppsala Health Summit stimulates dialogue from various perspectives, such as medical, economic and ethical.

Uppsala Health Summit lays the foundation for long-term relationships and insights that can help you in your work to improve health outcome in your part of the world.

Uppsala Health Summit is arranged in Uppsala, Sweden, by partners with long experience of healthcare development, who see the potential for improving healthcare and health outcome in a global perspective.

The effort is run as a collaboration between Uppsala University, the Swedish University for Agricultural Sciences, Uppsala County Council, the City of Uppsala, the Swedish Medical Products Agency, the National Veterinary Institute, the network World Class Uppsala and VINNOVA, Sweden's Innovation Agency.

**CONTENTS**

# Preface

This year might prove to be the turning point in the work against antimicrobial resistance. The World Health Assembly is about to adopt a global action plan that addresses the worrying development of increasing resistance. This document should be welcomed as an important starting point, but we should also realize that the action plan is just a beginning.

At Uppsala Health Summit 2015 we will focus on concrete action to deal with bacteria that develop resistance against available treatments. Diseases travel fast in a globalized world and no country can handle the challenges of antibiotic resistance alone. Some medical conditions that we have previously considered minor are suddenly life-threatening. We know what is at stake – we have to change the way we use antibiotics, and we have to do it now.

Uppsala Health Summit was created by a number of actors in Uppsala: universities, hospitals, the city, the region, public authorities located in Uppsala and elsewhere, initiated by Worldclass Uppsala, a network of local stakeholders.

The aim of Uppsala Health Summit is to bring some of the best minds in the world to Uppsala, to address challenges and dilemmas in order to improve utilization of medical advancements so that health outcomes can be significantly improved in all parts of the world, despite limited resources. Uppsala Health Summit is a good arena to combine different perspectives and approaches, and to discuss how to take next step on the issues concerning antibiotic resistance.

Our hope lies with you – the experts who are summoned to Uppsala – to help humanity by coming up with the necessary answers, and finding the best ways to implement the policy documents in medical practice.

The challenge lies in the fact that you have to be pragmatic, innovative and constructive. It is not an easy challenge. We ask a lot of you, but there is a lot at stake. We have done our utmost to create the best conditions possible for you all. I welcome you to an interesting, productive and stimulating stay in Uppsala and hope that this Uppsala Health Summit will become the turning point it has the potential to be.

Anders Malmberg, Professor
Chairman of Uppsala Health Summit
Steering Committee
Deputy Vice-Chancellor Uppsala University

# A world without antibiotics

**Thomas Tängdén**, Assistant Professor, Uppsala University,
Dept of Medical Sciences, Medical Director at ReAct

The widespread use of antibiotics over the past 70 years has saved millions of lives and eased much human misery. However, the massive use, misuse and overuse of antibiotics have eroded their efficacy and the pipeline of new antibiotics is almost dry (see Figure 1). There is a global consensus that antimicrobial resistance poses a profound threat to human health. Estimates of the costs of antimicrobial resistance mentions up to 700 000 deaths annually. If no action is taken, this number could reach 10 million by 2050 (Hoffman *et al*, 2015).

Antibiotic resistance makes it difficult and sometimes impossible to treat even the most common bacterial infections. It prolongs recovery, and leads to increased morbidity and mortality for severely ill patients. Resistance is a huge economic burden for health care and society at large. The overall societal costs of antibiotic resistance is estimated to be 1,5 billion euros per year in the European Union and up to 55 billion US dollars per year in the United States.[1] Without effective antibiotics to prevent and treat bacterial infections, as a result from increasing resistance and lack of new drugs, the achievements of modern medicine will be jeopardized.

[1] Source: ECDC 2007, US CDC 2013

Chemotherapy for cancer, intensive care, care of preterm babies and routine surgical procedures might be considered too dangerous in the future, due to the high risk for difficult-to-treat infections.

Surveillance on antibiotic resistance is lacking in large parts of the world, which makes it difficult to get a full overview of the situation. Existing data show that resistance rates are increasing rapidly globally, and with considerable differences between countries and continents (see for example Figure 2 and 3). Multidrug resistance spreads easily around the world through transfer of patients between countries, asymptomatic acquisition of resistant bacteria in the normal gut flora of healthy international travellers, imported food and even wildlife migratory birds.

### The use of antibiotics in humans

Antibiotic consumption for human health is reported to have increased by 36 per cent globally between 2000 and 2010. Continued increasing rates of antibiotic use in hospitals and the community cause selection of resistant strains, resulting in a need to use antibiotics with a broader antibacterial spectrum and further resistance development to these drugs. The variation in

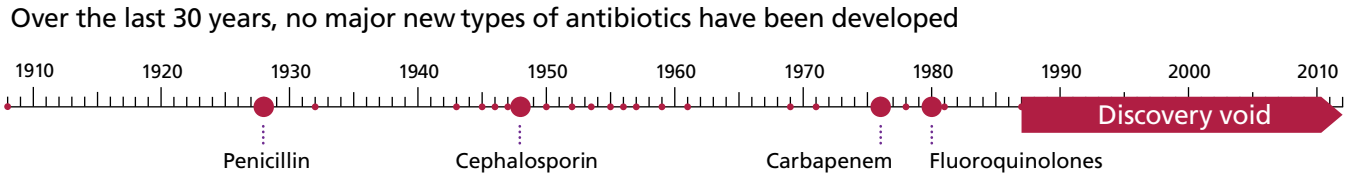



Figure 1. Over the last 30 years, no major new types of antibiotics have been developed.
Source: WHO, Antimicrobial resistance, Global report on Surveillance, 2014.

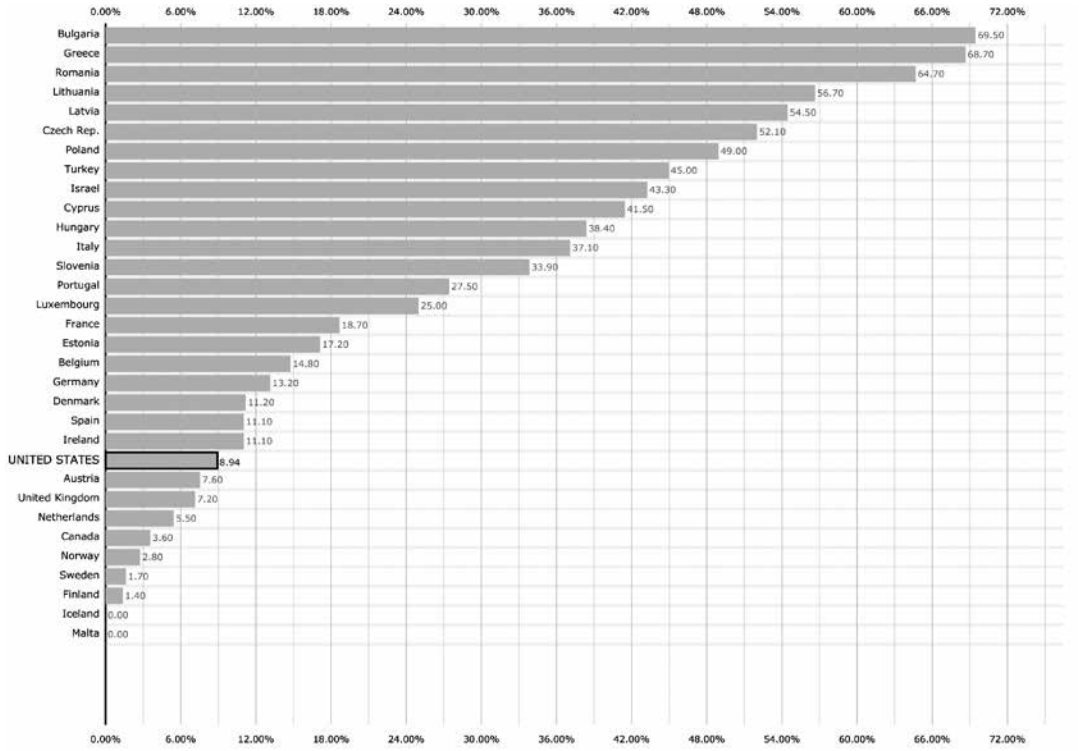



Figure 2. 3rd gen. cephalosporin-resistant K pneumoniae, % RESISTANT (2009).
Source: Center for Disease Dynamics, Economics & Policy, Resistance map.

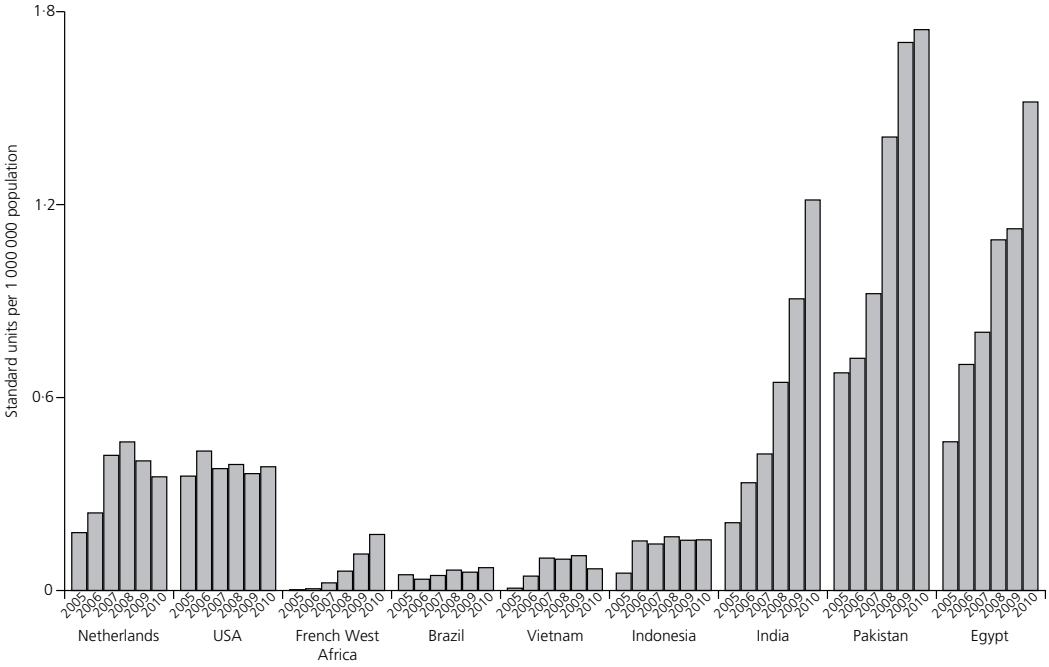



Figure 3. Trends in retail sales of carbapenem antibiotics for Gram-negative bacteria.
Source: Laxmanaryan, 2013. Based on data from IMS Health's MIDAS™ database.

resistance rates within and between countries reflects the variations in antibiotic use, which is the key driver for resistance development. The reasons for variations in antibiotic use include socioeconomic factors, cultural differences, and remuneration incentives. It has been estimated that as much as 50% of antibiotic prescriptions are inappropriate. In many countries outside Europe and North America non-prescription use is still common. Such usage has been reported to account for as much as 19% of all consumption, in some cases even up to 100% (Laxminarayan *et al*, 2013).

## The use of antibiotics in animals

The use of antibiotics in animals and its potential effect on human health has been controversial for at least half a century, states Greko. Antimicrobials are used in livestock production to treat sick animals, protect healthy animals in contact with sick animals and during periods of transport or similar stresses. They are also

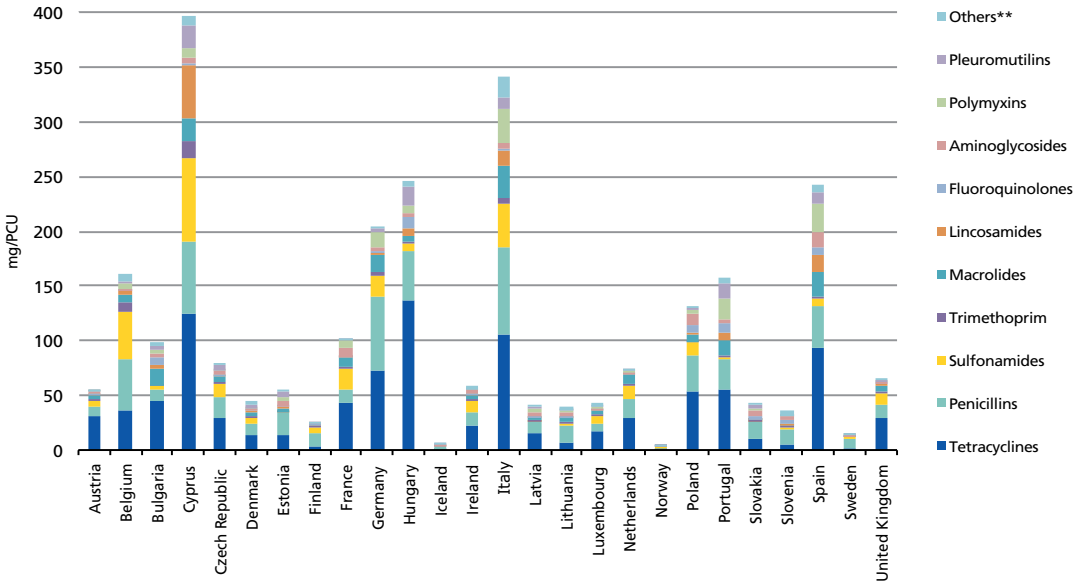



Figure 4. Sales for food-producing animals, including horses, in mg/PCU, of the various veterinary antimicrobial classes, for 26 countries in 2012.* Source: European Medicines Agency, EMA.

* Differences between countries can partly be explained by differences in animal demographics, in the selection of antimicrobial agents, in dosage regimes and in type of data sources, among other factors.

** Amphenicols, cephalosporins, other quinolones and other antibacterials (classified as such in the ATCvet system).

used as growth promoters in some countries and production systems in the absence of clinical disease. This is controversial and has led to a number of countries limiting or banning antimicrobials used in this way. However it is still widely used in for example the US, South America, East and Southeast Asia. In Europe, the use of antibiotics in animals varies greatly between countries (see figure 4).

## Access and excess

Securing access to effective antibiotic treatment is as important as reducing antibiotic overuse (excess). Access to assured quality antimicrobials is considered part of the human right to health, state Mendelson *et al*. Yet universal access is often undermined in low- and middle-income countries due to financial, infrastructural and human resources limitations.

The issue of *access* does not only include access to medical treatment but also to appropriate diagnostic tools, which is an essential component in the evaluation and improvement of global health, states RAND Health in their Research Highlights. Diagnostics are critical for identifying the cause of disease and for determining the appropriate treatment. The overarching challenge is: How can *access* and *excess* be simultaneously addressed, where health resources are one per cent (low-income countries) or 10 per cent (middle-income countries) of those in high-income countries?

## Innovation and conservation

There is a need to increase development and innovation within the field of antibiotics research. Recently, several public and private investments have been made in the area of antimicrobials, vaccines and diagnostics. However, the need for new collaborative economic models is emphasized by a range of stakeholders. The need is highlighted from several different aspects where the aim is to simultaneously address the access to and the excessive use of antibiotics. Innovations in related areas will also help. As an example Rex highlights that improved diagnostic tools will assist more effective antibiotic stewardship but further argues that they are inadequate without new business models that address the tension between the global need to implement the use of newly developed drugs and the equally clear need for their appropriate use.

While considerably reducing the efficacy of existing antibiotics, antimicrobial resistance also reduces their economic value and profitability. Prescribers strive to use new antibiotics judiciously as last resort agents, in order to prevent rapid emergence of resistance to the new drugs. This has contributed to the progressive disengagement of the pharmaceutical industry from developing this type of medicines (Kinch *et al*, 2014). Hence, the established business model for antibiotics based on maximizing sales and use is no longer viable in the face of antimicrobial resistance. Models that allow conservation and responsible use of these valuable and increasingly scarce resources are required.

## Antibiotic resistance in the environment

Without considering environmental influences, selection of antibiotic resistant bacteria will be fuelled even further, especially in those parts of

the world that still have inadequate sanitation and poor water quality (Graham *et al*, 2014).

The environment might play two important roles with regard to antibiotic resistance; The first is as a vector for transmission of several pathogens. The second role is as a reservoir for resistance development in harmless environmental bacteria that provide a source for novel resistance factors that can be transferred into pathogens causing infections in humans. Reducing the risk for both these processes should be addressed in the joint efforts to counter antimicrobial resistance, in line with the draft Global action plan (WHO, 2014).

## A Global action plan on antimicrobial resistance

The draft Global action plan, which is one of the plans and strategies that have been presented during the last couple of years, sets out five strategic objectives for the coming years.

The strategic objectives are to:

1. improve awareness and understanding of antimicrobial resistance;
2. strengthen knowledge through surveillance and research;
3. reduce the incidence of infection;
4. optimize the use of antimicrobial agents; and
5. ensure sustainable investment in countering antimicrobial resistance.

The goal of the Global action plan, which was put forward in a draft last year, is "to ensure, for as long as possible, continuity of successful treatment and prevention of infectious diseases with effective and safe medicines that are quality-assured, used in a responsible way, and accessible to all who need them. It is expected that countries will develop their own national action plans on antimicrobial resistance in line with the global plan" (WHO, 2014).

In May of this year the World Health Assembly (WHA) and the Member States are set to vote on a revised and final version of the Global action plan. Since the presentation of the draft in 2015, a far-reaching consultative process has been on-going. The process has included both informal and formal consultations.

## The way forward

The draft Global action plan emphasizes that operational action plans to combat antimicrobial resistance are needed at the national level to support strategic frameworks, and that stakeholders at all levels and of all kinds must be involved. So what could be the next steps to take, by who, and how?

Uppsala Health Summit will be one of the first arenas gathering stakeholders from different sectors and geographies where the operationalization will be focus for the dialogue, and where concrete proposals can be conceived.

**References**


*Antibiotic Resistance Coalition – Civil Society Declaration in Antibiotic Resistance*, (2014), Antibiotic Resistance Coalition

Center for Disease Dynamics, Economics & Policy, Resistance map. www.cddep.org/projects/resistance_map/3rd_generation_cephalosporin_resistant_klebsiella_pneumoniae#sthash.8Tfbbmix.dpuf

European Medicines Agency, EMA. Sales of veterinary antimicrobial agents in 26 EU/EEA countries 2012. 4th ESVAC report.

Graham, D.W., (2014) *Underappreciated Role of Regionally Poor Water Quality on Globally Increasing Antibiotic Resistance*, Environ. Sci. Technol. 2014, 48, 11746-11747

Greko, C., (2013) *Antibiotic resistance—the need for global solutions, Part 4: The interface between people and animals,* The Lancet Infectious Diseases Commission, Lancet Infect Dis 2013; 13: 1057–98

Hoffman, S.J., Outterson, K., Røttingen, J-A., Cars, O., Clift, C., Rizvi, Z., Rotberg, F., Tomson, G. and Zorzet, A. (2015) *An international legal framework to address antimicrobial resistance*, Bull World Health Organ 2015;93:66

Kinch, M.S., Patridge, E., Plummer, M. and Hoyer, D., *An analysis of FDA-approved drugs for infectious disease: antibacterial agents*, Drug Discovery Today, Volume 19, Number 9, September 2014

Laxminarayan, R., Duse, A., Wattal, C. and Zaidi, A.K.M., (2013) *Antibiotic resistance—the need for global solutions, Part 1: Global epidemiology of antibiotic resistance and use,* The Lancet Infectious Diseases Commission, Lancet Infect Dis 2013; 13: 1057–98

Mendelson, M., Balasegaram, M., Gopinathan, U., Hamer, D.H., Wertheim, H., Basnyat, B., Butler, C., Röttingen, J-A. And Tomson, G. (2015) *Maximising access whilst curbing excess: achieving appropriate human antimibrobial use in low and middle income countries*, Resubmitted Jan 2015, Lancet Global health

Rex, J.H., *Comment: ND4BB: addressing the antimicrobial resistance crisis,* Nature Reviews Microbiology, AOP, published online 10 March 2014

WHO, *Antimicrobial resistance, Draft global action plan on antimicrobial resistance, Report by the Secretariat*, EB136/20, 12 dec 2014

WHO, *Antimicrobial resistance, Global report on Surveillance,* 2014

**Workshop**

# Access not excess

## – rational use of antibiotics

**Stefan Swartling Peterson**, Professor of Global Health, Uppsala University, Karolinska Institutet and Makerere University.

A majority of the world's population live in low- or middle-income countries, where health expenditure per capita is substantially smaller than in high-income countries. In addition, the infrastructure to enforce regulation is generally much weaker. The private healthcare sector is strong and often the first care provider. In many of these settings, it is the access to effective antibiotics that is the problem, which explains why childhood pneumonia is the world's number one cause of death among children under the age of five. At the same time excess, and irrational use of antibiotics is widespread.

How can *access* and *excess* be simultaneously addressed, where health resources are one per cent (low-income countries) or 10 per cent (middle-income countries) of those in high-income countries? What should be the strategies for *controlled distribution and use* in order for them to have some effect?

**The main focus areas for the workshop are:**

- How can improved access to and reduced excess use of antibiotics be addressed simultaneously?
- What would be the effects on access and excess of different strategies for controlled distribution and use?
- Which are different stakeholders' views on different options for controlled distribution and use?

*Access* to assured quality antimicrobials is considered part of the human right to health, states Mendelson *et al*. Yet universal access is often undermined in low- and middle-income countries due to financial, infrastructural and human resources limitations.

At the same time *excess*, and irrational use of antibiotics is widespread. A study in a tertiary care hospital in Thailand showed that bacteria caused only 7.9 per cent of the upper respiratory tract infections in the facility. Despite this, Sumpradit *et al* comment that most upper respiratory tract infections in Thailand are treated with antibiotics by hospitals, health centres, drug stores and patients themselves. Furthermore, antibiotics are sometimes used when no other therapy is available, it is also in many cases cheaper to treat than to test. Studies have also shown that even if there, from a resistance standpoint, might be more favourable therapeutic treatment (other types of antibiotics) they might not be available. In other settings introduction of *e.g.* malaria diagnostic tests may paradoxically lead to increased antibiotic use when the malaria test is negative.

In such complex settings, how can we simultaneously address access *and* excess use, while remembering that lack of access to antibiotics presently causes more deaths than resistance?

## Global action is required

Antimicrobial resistance causes an estimated 700 000 deaths annually, a figure that Hoffman *et al* states is estimated to be 10 million deaths annually by 2050 if action is not taken. They conclude that *global*, *collective* and *simultaneous* action is required in three areas: access, conservation and innovation. Conservation refers to the reduction of need for antimicrobials and to ensure that they are responsibly used through for example prevention efforts, infection control, surveillance and appropriate prescriptions.

A prerequisite for success is changing behaviours among both healthcare personnel and patients. It is not obviously so that an available diagnostic tool changes the behaviour of personnel or patients, behaviours are often more deeply set than that. Furthermore, there is a social dimension to acceptance of test-results and it is important that treatment is not issued anyway, for the reason that the patient is evidently ill from something. It is vital to have a person-focus when discussing these issues, for example it is only possible to reach adherence if an appropriate alternative treatment is available.

An important aspect that Bloom *et al* highlight in *Addressing resistance to antibiotics in pluralistic health systems* is that, in many low- and middle-income countries, where the majority of the world's population live, there is much less information regarding antimicrobial resistance and often much less pressure on governments to act. This highlights the need for global action. Hoffman *et al* argues that solving the issues of access, conservation and innovation simultaneously will require new coordination and financing mechanisms, some of which must be organized globally. The authors also state that while a small number of high-income countries can make progress on innovation, long-term success on conservation and access presupposes near universal participation. However, state Bloom *et al*, there are considerable differences in the risks and challenges faced by governments and populations across the world. It is important that actions account for these diverse realities. How do we find distribution models that increase access to effective antibiotics while reducing excess use in low- and middle-income countries? And in the peripheral distribution chain, where a parent may seek treatment from a small private drug shop, with a turnover of some 10 dollars per day, how can rational use of antibiotics be upheld, rather than maximized sales?

## There is not one solution

As Mendelson *et al* emphasize there is *no single model* that increases access while limiting excess. Sumpradit *et al* highlight some important programmes that have been implemented in high income countries. They include Strama in Sweden; the *Get Smart: know when antibiotics work* programme of the US Centers for Disease Control and Prevention, and several national public campaigns in Europe. The challenge is to find what models or components of models that can be transferred between countries, including countries of varying level of income.

Heyman *et al* emphasize, as do other authors, that the interventions should be system-wide. Mendelson *et al* have in their review studied the evidence-based interventions that may increase access to appropriately prescribed antimicrobi-

als, and the key global enablers of sustainable financing, governance and leadership that will be necessary to achieve access, whilst preventing excess antimicrobial use. They conclude that in order to achieve appropriate antimicrobial prescribing, low- and middle-income countries must strengthen their health systems including health insurance, provision of laboratory support, and increased access to diagnostics and primary prevention measures. Heyman *et al* found in their analysis that all represented stakeholder categories viewed controlled distribution as a long-term goal for future antibiotics. The question is what the strategies should be for *controlled distribution and use* in order to be effective, while not curtailing access?

### Cross-cutting, long-term ownership for progress in Thailand

The *Antibiotics Smart Use* programme was introduced in Thailand in 2007 as a model to promote the rational use of medicines, starting with antibiotics. The programme consists of three distinct phases. The first phase consists of assessing interventions intended to change prescribing practices. The second phase examined the feasibility of broadening the extent of the programme. The programme in Thailand is now in its third phase, which focuses on sustainability.

To change antibiotic prescription practices, multi-layered interventions at both the individual and organizational levels were implemented. This included rectifying misunderstandings and attitudes to increase confidence in diagnosis and non-antibiotic treatment on the individual level and building a supportive climate for rational use of antibiotics on the organizational level. To maintain behaviour change and scale up the programme, interventions at the network and policy levels were used, comments Sumpradit *et al*. This entailed both developing collaborative, decentralized networks and the integration of the model into national policies.

The *Antibiotics Smart Use* is a workable model for promoting the rational use of medicines, conclude Sumpradit *et al*. It is a crosscutting exercise that seeks to promote the rational use of medicines by strengthening human resources, improving health facility infrastructure and empowering communities. It can also be applied to rationalize the use of medicines other than antibiotics. However, Sumpradit *et al* emphasize that the model's sustainability is dependent on programme ownership and commitment by local teams, an enabling environment and integration into routine systems with appropriate financial incentives and an effective audit system.

### Extending the reach of public health services in Uganda

In 2010 Uganda adopted the *integrated community case management* of childhood illnesses where community health workers provide malaria, pneumonia, and diarrhoea treatment for children less than five years of age. Integrated community case management is an equity-focused strategy that complements and extends the reach of public health services through community agents by providing diagnostics and timely and effective treatment in the form of prepackaged antibiotics, antimalarials and ORS/zinc to populations with limited access to facility-based health care providers. The implementation was based on the recommendation from the World Health Organization and UNICEF to provide integrated management of common childhood illnesses at the community level.

Kayalango *et al*. conclude that integrated community case management of malaria and pneumonia does increase prompt and appropriate treatment for pneumonia symptoms in children less than five years of age in eastern Uganda. The positive results found in Uganda are similar to those reported in a study in Zambia where prompt and appropriate treatment was more common among children treated by community health workers that could treat both malaria and pneumonia. These are important findings when trying to identify what components can be effective in simultaneously addressing access and excess in low- and middle-income countries.

### Access is more important than excess

*Access* refers to ensuring that the prevention tools, diagnostics and therapies needed to reduce the infectious disease burden are available and affordable to everyone, everywhere, state Hoffman *et al*. Irrational use of antibiotics – *excess*, is a great problem today, but it is in the present likely a larger challenge that people who have for instance pneumonia do not receive effective treatment. Access is more important than excess in the present, but the two are intertwined and need to be addressed simultaneously.

Access to antibiotic treatment is highly sought after by the rich and poor alike in most countries conclude Bloom *et al*. Where governments have been unable to provide this access, markets have emerged to meet this demand. In the absence of supportive institutional arrangements, undesirable practices have developed. Measures to slow the emergence of organisms resistant to antibiotics must include interventions to increase access to the benefits of effective and appropriate antibiotic treatment, if they are to secure wide support in low and middle-income countries. A proportion of the resources invested in the global response to antibiotic resistance should be allocated for this purpose to ensure they are managed justly, as well as sustainably, argue Bloom *et al*.

Hoffman *et al* conclude that one of the main barriers to rational access to antibiotics is balancing access and excess, but they also state that without conservation and innovation, universal access will simply drive resistance and deplete existing stocks of effective antimicrobials. They argue that equitable pricing or licensing models could facilitate access, but external resources will be required to subsidize access for the world's poorest people. Such subsidies create common benefit, by reducing disease transmission and preventing reservoirs of resistant pathogens created by inconsistent use.

Heyman *et al* conclude that there is currently no model of distribution ready for a new antibiotic that ensures access and protects against excessive or inappropriate use in rural settings in low- and middle-income countries where the burden of communicable diseases is high and access to quality health care is low. In their study they found that the tension between access to antibiotics and rational use stems from shortcomings found in the healthcare systems of low- and middle-income countries. They conclude that constructing a sustainable yet accessible model of antibiotic distribution for low- and middle-income countries is a task of healthcare system-wide proportions, which is why they strongly suggest using systems thinking in future research on this issue.

Heyman *et al* found that interviewees from all represented stakeholder categories view controlled distribution as a long-term goal for future antibiotics. However, the question that remains unanswered is: When a new, effective antibiotic enters the market some years from now, which distribution mechanism can be used to achieve controlled distribution and use while giving access to those in need? How do the approaches in low- versus middle-income settings differ?

## The way forward

It is important to focus on short term as well as long-term interventions in addressing both access and excess. Lessons from successful interventions, both in high-income countries, but also in low- and middle-income countries need to be studied to identify success factors and to see which of these might be transferable between contexts and settings. Which are the central stakeholders and how can initiatives regarding access, conservation and innovation be taken simultaneously, collectively and globally?

**References**


Bloom, G., Wilkinson, A., Tomson, G., Awor, P., Zhang, X., Masud Ahmed, S., Ali Khan, W. and Blessing, V., (2014) *Addressing resistance to antibiotics in pluralistic health systems*, STEPScentre, Economic & Social Research Council, ESRC

Heyman, G., Cars, O., Bejarano, M-T. And Peterson, S. (2014) *Access, excess, and ethics —towards a sustainable distribution model for antibiotics*, Upsala Journal of Medical Sciences. 2014; 119: 134–141

Hoffman, S.J., Outterson, K., Røttingen, J-A., Cars, O., Clift, C., Rizvi, Z., Rotberg, F., Tomson, G. and Zorzet, A. (2015) *An international legal framework to address antimicrobial resistance*, Bull World Health Organ 2015;93:66

Kalyango, J.N., Alfven, T., Peterson, S., Mugenyi, K., Karamagi, C. and Rutebemberwa, E., (2013) *Integrated community case management of malaria and pneumonia increases prompt and appropriate treatment for pneumonia symptoms in children under five years in Eastern Uganda*, Malaria Journal 2013, 12:340

Mendelson, M., Balasegaram, M., Gopinathan, U., Hamer, D.H., Wertheim, H., Basnyat, B., Butler, C., Röttingen, J-A. And Tomson, G. (2015) *Maximising access whilst curbing excess: achieving appropriate human antimibrobial use in low and middle income countries*, Resubmitted Jan 2015, Lancet Global health

Sumpradit, N., Chongtrakul, P., Anuwong, K., Pumtong, S., Kongsomboon, K., Butdeemee, P., Khonglormyati, J., Chomyong, S., Tongyoung, P., Losiriwat, S., Seesuk, P., Suwanwaree, P. and Tangcharoensathien, V. (2012) *Antibiotics Smart Use: a workable model for promoting the rational use of medicines in Thailand*, Bull World Health Organ 2012;90:905–913

Workshop

# New economic models addressing antibiotic resistance

**Alexandra Waluszewski**, Professor of Business Studies, Uppsala University
**Enrico Baraldi**, Professor of Industrial Engineering and Management, Uppsala University
**Francesco Ciabuschi**, Professor of International Business, Uppsala University

Antimicrobial resistance does not only challenge public health needs worldwide, but is also a huge economic burden, for society at large and for the health care setting specifically (Nathan & Cars, 2014). While considerably reducing the efficacy of existing antibiotics, antimicrobial resistance also reduces the economic value and profitability of antibiotics. This has contributed to the progressive disengagement of the pharmaceutical industry from developing this type of drugs. Hence, the established business model for antibiotics based on maximizing sales and use is no longer viable in the face of antimicrobial resistance (Outterson *et al.*, 2015). Instead stewardship, conservation and responsible use of these very precious and increasingly scarce resources are required (Cars, 2014). This workshop is dedicated to the needs for new economic models, in the private as well as the public sector, which can facilitate the transformations necessary to confront the resistance problem, in terms of both responsible use and development of antibiotics.

**The main focus areas for the workshop are:**

- The economic forces that create barriers or possibilities in the research and development of new antibiotics, the production and provision of established and new antibiotics and the use in different settings, also emphasizing access.
- The changes in the social, economic and technical structures that are necessary in private as well as public economic models in order to facilitate the development and provision of new antibiotics, and the use of antibiotics according to responsible use and equitable access.
- The economic and political controversies that have to be tackled in order to reorganize the global supply and use of antibiotics, new ones included.

Antimicrobial resistance threatens the established role of antibiotics as being the cornerstone in the treatment of infectious diseases and of a multitude of essential healthcare practices, stretching from being used to cure rather simple infections, to being a prerequisite for advanced medical treatments based on surgery or chemotherapy (So *et al.*, 2012). Hence, the human *and* economic consequences of a decreasing antibiotic efficacy are colossal.

### Use of antibiotics in order to compensate for lacking investments

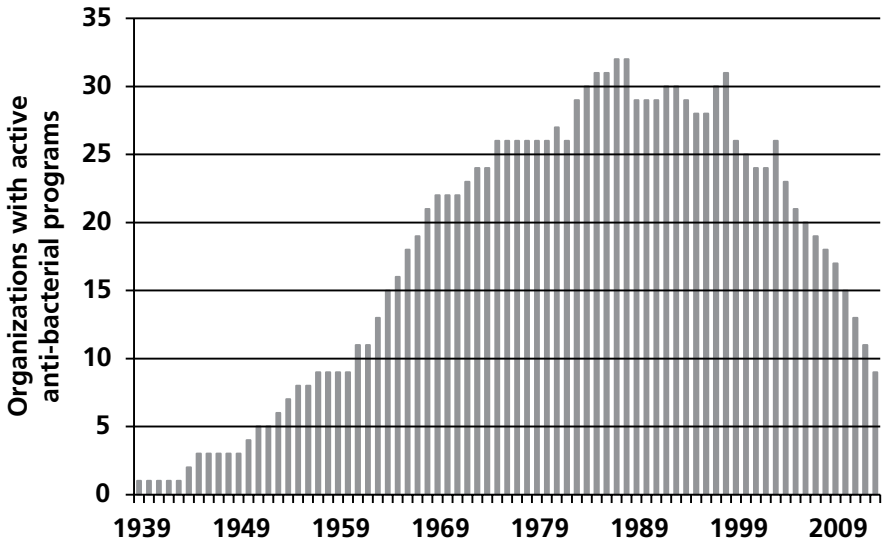
Antimicrobial resistance also challenges the use of antibiotics in order to compensate for lacking investments in social and material structures in the public and private sector. For example, instead of investing in water and sewage infrastructure in low-income countries, antibiotics are used to treat infectious diseases that could be prevented with better hygiene and, above all, affect children. Antibiotics are also used as means to decrease investments in animal farming. By treating all animals with antibiotics as a pre-cautionary measure, the investments in space and facilities can be reduced and with that the cost for individual control (Nathan & Cars, 2014). Hence, the direct and indirect economic consequences of antimicrobial resistance are huge and almost impossible to assess in detail – and so are also the economic consequences of not having effective antibiotics because of antimicrobial resistance.

### Decreased engagement

Along with the societal and economic burden generated by antimicrobial resistance goes another challenge: the radical reduction of private and public actor's engagement in the various activities related to the development and provision of new antibiotics. The common denominator among academic research, public and private research and development, large pharmaceutical companies as well as smaller pharmaceutical companies and start-ups is that all are decreasing their engagement in the antibiotic field (Outterson *et al.*, 2015). For example, in their evaluation of all US Food and Drug Administration approved new molecular entities since 1930, Kinch *et al* (2014) show that approvals for new antibacterial agents indicates an even more dramatic decrease in the number of biotechnology and pharmaceutical companies developing this class of drugs (see figure below).

### The ordinary innovation logic is broken

Over the past three decades, the number of established pharmaceutical companies that engaged in research and development activities related to new antibiotics has decreased from 25 companies to 4 companies. Of these 4 companies, only 2 companies have come so far as to actually have a drug that has reached Phase 2 of testing. Hence, the economic equation is difficult to solve: On the one side, the private and public structures that have the ability to provide research, research and development and indus-




Source: Kinch *et al.* (2014, page 1286)

trialization of new antibiotics have withdrawn from engagement in new antibiotics. On the other side, the private and public structures that are responsible for use will, if the contemporary patterns of drug use are not changed, contribute to increasing antimicrobial resistance. (See *e.g.* Boucher *et al*, 2009, Theuretzbacher, 2009, Outterson, 2014.)

In contradiction to the innovation pattern common to most products successfully introduced to market, the use of any new antibiotic has to be restricted or somehow controlled. This implies that the ordinary innovation logic is broken (Outterson *et al*., 2015). A simple 'sales-maximization' model can no longer cover investments in private research and development and industrialization. Instead, there is an urgent need for rethinking both business and socioeconomic models related to the provision and use of new and established antibiotics.

**Loss of expertise**

The fact that many organizations with a successful track record have abandoned research and development on antibiotics means that the institutional knowledge is lost as experienced personnel are generally let go or reassigned. Over time this becomes increasingly important since people retire and new expertise is not recruited. This loss also includes that thousands of interfaces between for example public and private interests have disappeared. These are structures that need to be systematically rebuilt.

**De-linking models**

The traditional incentives and reward mechanisms to stimulate antimicrobial R&D still rely on expectations of return on investment based on a high sales model, which collides with the need to contain sales due to antibiotic resistance. There is a debate as to the relevance of these mechanisms as they may lead to development of new antibiotics but not to curb resistance as companies are still motivated to sell as many products as possible (this is the case for instance of product development grants, faster approvals from European Medicines Agency/Food and Drug Administrations and longer patents). Therefore reward mechanisms and incentives also have to de-link product development efforts from sales of antibiotics, as a way to support antibiotics conservation and responsible use (Outterson *et al*., 2015).

An example of de-linking models are "Patent buy-out prize funds", whereby governments buy patents from innovators and directly control sales of an antibiotic: however an incentive such as this is complex to implement due to difficulties in negotiating adequate prices for buying patents and the risk that other antibiotics not covered by government control remain on sale (see *e.g.*, Outtersson 2014).

Furthermore, most of the reviewed economic incentives intervene with subsidies to product developing companies to cover part of their R&D expenses or with promises to purchase predefined amounts of newly developed products, while maintaining the existing economic and organizational structure of the antibiotic field. Therefore, this workshop aims to stimulate discussions over truly transformative new models, including a more far-reaching reorganization of this field.

A related example is the public procurement model. It is one of the most well proven models in other fields like IT, aerospace technology and the defence industry. The most central shift in this model compared to traditional incentive models, is that the buyer assumes the risk and the economical responsibility (So *et al*, 2012). It is important to remember that somebody, somewhere is going to have to pay for the increased need for development and provision of new antibiotics *and* for stewardship in use. The challenge is to find a way forward that is acceptable for all important parties and that supports development, provision, responsible use *and* equitable access.

**To recreate the foundations needed for renewed engagement**

There is a need to recreate renewed engagement in research and development of antibiotics. How this may look is an issue to be discussed in the workshop. Often a large part of the responsibility is laid on the pharmaceutical industries. However, Kinch *et al* (2014) argue that there might, in the short term, be a need for governmental and/or non-governmental support to recreate the foundations needed for renewed engagement. Incentives that they mention are for example tax advantages, clear guidance on trials required for approval, or intellectual property considerations for companies entering or re-entering the field.

## Joint responsibility from all important stakeholders

To avoid the risk that increasing drug resistance will cause a re-emergence of trends regarding morbidity and mortality from infectious diseases equivalent to those seen in the early 20th century, creative and active engagement together with a productive discussion and the participation of public and private organizations is necessary, concludes Kinch *et al.* (2014). Resources, risks and rewards will need to be shared across several groups of public and private organizations (So *et al.*, 2012). This discussion needs to take the broad pictures of what socioeconomic structures are needed in addressing the problem of antimicrobial resistance as a *whole* (Cars, 2014). The discussion shall not only include what relevant stakeholders' responsibilities are but which stakeholders are needed, locally, nationally and internationally.

**References**


This text is, besides the specific sources presented below, based on experiences from an on-going multidisciplinary and multi-stakeholder research project: DRIVE-AB consortium (see http://drive-ab.eu/).

Boucher, HW, Talbot, GH, Bradley JS, *et al*. 2009, *Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America*. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America, 2009;48:1–12

Cars, O., 2014, *Securing access to effective antibiotics for current and future generations. Whose responsibility?* Upsala Journal of Medical Sciences. 2014; 119: 209–214

Kinch, M.S., Patridge, E., Plummer, M. and Hoyer, D., 2014, *An analysis of FDA-approved drugs for infectious disease: antibacterial agents*, Drug Discovery Today, 19/9: 1283–1287

Nathan, C., & Cars, O., 2014, *Antibiotic Resistance — Problems, Progress, and Prospects*, New England Journal of Medicine, 371:1761–1763

Outterson, K., 2014, *New Business Models for Sustainable Antibiotics*, Chatham House, Center on Global Health Security Working Group Papers, 2014, page 21–22

Outterson, K., Powers, J.H., Daniel, G W., & McClellan, M B., 2015, *Repairing The Broken Market For Antibiotic Innovation*, Health Affairs, 34, no.2 (2015): 277–285

So, A D., Ruiz-Esparza Q., Gupta N., Cars O., 2012, *3Rs for innovating novel antibiotics: sharing resources, risks, and rewards*, The BMJ, 344: e1782

Theuretzbacher U. 2009, *Future antibiotics scenarios: is the tide starting to turn?* International journal of antimicrobial agents 2009;34:15–20

Workshop

# The environmental dimension of antibiotic resistance

**D G Joakim Larsson**, Professor in Environmental Pharmacology, Department of Infectious Diseases, Institute of Biomedicine, University of Gothenburg
**Linus Sandegren**, Associate Professor, Department of Medical Biochemistry and Microbiology, Uppsala University

**The aim of the workshop**
In this workshop our aim is to stimulate different stakeholders to realise and take into account the environmental dimensions of antibiotic resistance within their respective fields of influence, including national and international policy documents and action plans. After an introduction presenting the risk scenarios and need for measures, the workshop participants will work collectively to identify; what can be done, barriers that might prevent action, incentives and potential costs involved. A common goal is to reduce emissions of antibiotics and antibiotic resistant bacteria in the environment and thereby reduce the risk for development and dissemination of bacteria resistant to present and future antibiotics. We hope that this workshop will lead to a more comprehensive understanding of the "one health concept" among the participants and the organizations and countries they represent.

**The three focus areas for the workshop are:**
1. Risk management regarding emission of antibiotics from pharmaceutical manufacturing.
2. Risk management regarding emission of human sewage/municipal wastewater.
3. Emission from agricultural sources.

### A one-health concept for antibiotic resistance needs to include environmental dimensions

It is recognized that the most important driver for the development of antibiotic resistance is the use, misuse and overuse of antibiotics. A "one-health concept" has been more and more widely recognized as overarching strategy to efficiently address the challenge, including both humans, animals and the interaction with the external environment. Without seriously considering environmental dimensions, global antibiotic resistance dissemination is expected to be fuelled even further, especially in those parts of the world that still suffer from inadequate sanitation and poor water quality (Graham *et al*, 2014). Thus, to curb increasing antibiotic resistance worldwide, we need to recognize that antibiotic resistance is not exclusively an issue of inappropriate antibiotic use in humans and animals, but is also connected to how we manage our wastes.

### The environment plays two important roles with regard to antibiotic resistance

The environment plays two important roles with regard to antibiotic resistance; The first is as a vector for transmission of several human pathogens, including resistant bacteria. The second role is in the emergence of resistance in pathogens. Almost all classes of antibiotics are of natural origin and resistance mechanisms exist in both the natural producers and in bacteria that have been exposed to natural antibiotics. These harmless environmental bacteria are an important source or reservoir for novel resistance factors that under an increased selection pressure from antibiotic pollution can be recruited into human pathogens through horizontal gene transfer. The major clinical resistance mechanisms present today originate from environmental bacteria. Reducing the risk for both these processes are imperative parts to develop new tools, policies and regulations to counter antimicrobial resistance, in line with for example the strategic agenda of the JPIAMR (2013).

The WHO currently considers antibiotic resistance one of the greatest threats to public health. The global and multifaceted problem of antimicrobial resistance demands comprehensive and creative solutions, which require action from many sectors of society. However, in comparison with, for example, the JPIAMR strategic research agenda (2013), the draft global action plan on antimicrobial resistance only briefly touches the environmental dimensions of antibiotic resistance. Hence, there will likely be a need to increase the awareness of the environmental aspects among stakeholders that have the possibility to take environmental responsibility, thereby reducing the risks for antibiotic resistance promotion.

### Environmental exposure to antibiotics and antibiotic resistance genes from pharmaceutical manufacturing

An environmental hot-spot for the emergence of resistance are related to discharges from antibiotic manufacturing. To reduce risks here, and to create incentives for improvement, attention is needed from a variety of stakeholders worldwide. Identifying existing and possible contributions is a core part of this workshop.

Direct emission from pharmaceutical manufacturing is a source of much, much higher environmental discharges than that excreted from humans (Larsson, 2014). The magnitude of the discharges has a major impact on the risk scenario, as it is clear that selective concentrations of antibiotics are spread through these industrial discharges, which in some cases have led to massive proliferation of multi-resistant bacteria (Bengtsson-Palme *et al*, 2014). Risk management also differs between production and excretion in terms of accountability, incentive creation, legal opportunities, substitution possibilities and costs (Larsson, 2014). For example, two products are most often exchangeable from a clinical point of view if they contain the same active pharmaceutical ingredients in the same quantities. The use of one or the other will therefore not affect the amounts of excreted active pharmaceutical ingredients in urine and faeces. Importantly, however, is that the two products may be associated with substantially different pollution loads at the manufacturing stage. Regulation and monitoring of antibiotics-emission from production sites, as well as greater transparency through the supply chain, are urgently needed in order to facilitate improvements, including informed choices of products.

Pruden *et al* have in a recent review focused on identifying management options that may be put into effect immediately, which include policy measures to restrain the spread of antimicrobial resistance from hot-spots (Pruden *et al*, 2013).

FOTO: JOAKIM LARSSON.

Large purchasers of medicines, such as pharmacies and hospitals are important stakeholders and as such they could assume greater responsibility; as an example, Swedish county councils have started to require some degree of control over environmental emissions from production when they procure pharmaceuticals for the hospitals. Action in this area is critical because most governments are focusing on cost as the primary driver of policy decisions. Accordingly, the Swedish government has proposed a change in the system for generic substitution and reimbursement of pharmaceutical costs, where not only price but also control over environmental emissions from production will be taken into account. Extending the framework of *Good Manufacturing Practices* to include environmental considerations could also be an important tool, as proposed by the Swedish government and the Swedish Medical Products Agency (MPA) to the EU.

**Risk management regarding emission of human sewage/municipal wastewater**

Another important focus regarding environmental dimensions of antibiotic resistance relates to the spread of antibiotics and resistant pathogens via human sewage. Here, we deal with situations ranging from *no treatment* to *highly advanced treatment*. Limiting resistance transmission via sewage in one part of the world, will likely benefit all at the end of the day. But, what are the obstacles for improvement, and how do we get around them?

The need for improved sanitation and sewage treatment in the developing world is a key component. The WHO estimates that 2.6 billion people today lack access to basic sanitation. This by itself results in direct releases of antibiotic resistant bacteria and pathogens into the environment and ambient waters. Furthermore traditional wastewater treatment plants are not designed for the removal of antibiotics or antibiotic resistance genes. Although still an open question, it is suspected that low levels of residual antibiotics in sewage select for antibiotic resistant strains (Gullberg *et al*, 2011). Wastewater treatment plants therefore represent a critical node for control of the global spread of antibiotic resistance. Wastewater reuse is becoming a worldwide strategy for water sustainability. Regarding sludge/biosolids and other solid wastes the main management options being discussed are incineration and an appropriate use of landfills.

### Emission from agricultural sources

Agricultural usage of antibiotics represents a large proportion of the overall consumption of antibiotics worldwide, although the amounts of antibiotics used vary extensively among countries. Antibiotics use in animals is within the scope of another workshop at the Uppsala Health Summit, here we are primarily concerned with how the wastes generated are handled. Notably, it is not only the issue of animal keeping, how and if they are treated with antibiotics, that varies greatly between different countries but also the management of animal faeces and urine. In some contrast to the human situation, one challenge is that there are more diverse exposure pathways from agricultural sources. Overall, the dissemination directly to the soil environment is greater, for example through spreading of manure on arable land. The direct link with the human food chain is thereby stronger. Legislation and stakeholders involved also differ.

### There is still little or no legislation

One important question that is highlighted is; do we have the regulation and legislation that is needed? There are still no regulations regarding surface water levels for any active pharmaceutical ingredient (Larsson, 2014). There are, however, operational tools like the European Water Framework Directive that could be used, where threshold values could be defined. Three pharmaceuticals were recently added to the so-called 'watch list' within the European Water Framework Directive. Moreover, for example regional authorities, have the possibility to state which chemicals cannot be discharged, but there is no equivalent for pharmaceuticals. The conclusion is that effective measures *can* be taken if the issue is considered sufficiently important. Clearly, initiatives to further the development of adequate regulations are needed.

### A global problem that demands local action

Although antibiotic resistance is a global challenge, local action is necessary to reduce its spread via the environment. Studies have shown that regional management regimes for agricultural and clinical use of antibiotics, together with good hygiene, in many cases are successful in minimizing resistance on a national basis (Pruden *et al*, 2013).

The challenge is further complicated by the fact that the question of responsibility is unclear or shared. For example, who is responsible for emissions from wastewater treatment plants and from animal keeping? Which government agency is responsible, or is it the responsibility of regional authorities or municipalities? The definition of responsibility is a prerequisite for success and should be addressed country-wise and the various responsibilities should be clarified.

### Risk reduction at little or no cost

Pruden *et al* (2013) have identified several management options across agriculture, wastewater treatment and pharmaceutical manufacturing that could aid in mitigating risks of antimicrobial resistance in the environment. Many of the options highlighted are practical strategies that are economically feasible and that can be synergistically implemented with other benefits. Selected recent proactive measures demonstrate that such actions are possible and that they add momentum to the development of new policies and regulations. *Outreach*, *education*, *communication*, *monitoring*, and *transparency* are all vital to the success of management schemes for limiting the spread of antibiotic resistance via environmental pathways.

The important next step is to identify key stakeholders in relation to the management options. The driving force of incentives – both economic and social – should not be underestimated.

**References**


Bengtsson-Palme J, Boulund, F., Fick, J., Kristiansson, E. and Larsson, D.G.J., (2014) *Shotgun metagenomics reveals a wide array of antibiotic resistance genes and mobile elements in a polluted lake in India.* Front. Microbiol. 5:648.

Gullberg E, Cao S, Berg OG, Ilbäck C, Sandegren L, *et al.* (2011) Selection of Resistant Bacteria at Very Low Antibiotic Concentrations. PLoS Pathog 7(7):e1002158

Graham, D.W., (2014) *Underappreciated Role of Regionally Poor Water Quality on Globally Increasing Antibiotic Resistance*, Environ. Sci. Technol. 2014, 48, 11746–11747

JPIAMR (2013) *Strategic Research Agenda, Joint Programming Initiative on Antimicrobial Resistance*, 5th December 2013

Larsson, D.G.J. (2014) *Pollution from drug manufacturing: review and perspectives,* Phil. Trans. R. Soc. B 369:20130571

Pruden, A. *et al,* (2013) *Management Options for Reducing the Release of Antibiotics and Antibiotic Resistance Genes to the Environment*, Environmental Health Perspectives, vol 121, number 8

**Workshop**

# Research and innovation for new therapies

## – collaborative models

**Anders Karlén**, Professor in Computer-aided drug design, Uppsala University
**Diarmaid Hughes**, Professor of Medical Molecular Bacteriology, Uppsala University
**Gunnar Sandberg**, PhD, Programme Director, Swedish Agency for Innovation Systems
**Bengt Guss**, Professor in Microbiology, Swedish University of Agricultural Sciences
**Cecilia Nilsson** , PhD, Project leader SciLifeLab, Uppsala University Innovation

The pipeline of new antimicrobials is today almost dry. Very few antimicrobial drugs have been approved by the Food and Drug Administration in the USA, or the European Medicines Agencies during the last decade, and none of those approved has useful activity against multidrug-resistant pathogens. There is a need to boost development and innovation and recently several public and private investments have been made in the areas of antimicrobials, vaccines and diagnostics. For example, collaborative research initiatives such as the Innovative Medicines Initiative's programme New Drugs for Bad Bugs and India's Open Source Drug Discovery programme have recently been launched. But will these efforts be enough? How do we best promote research to support the development of new antimicrobials, vaccines, and diagnostics to ensure that we have effective treatment and prevention options also in the future, and improved ways to rapidly and accurately diagnose antimicrobial resistance?

**The focus areas for the workshop are:**

- How do we make best use of available funding at the national, regional and global levels, to stimulate discovery and development of new antimicrobials, vaccines and diagnostics?
- What models would engage the best academic researchers, and at the same time attract industry, to meet the needs for new antimicrobials, vaccines and diagnostics from a public health perspective?
  - How do we stimulate the creation of Public-Private Partnerships (PPP) and participation in PPP's from both the public and the private side?
  - How do we stimulate creation of and investment in alternative innovation models (*e.g.* charity, open innovation, or other) to promote the development of new antimicrobials, vaccines and diagnostics?

The WHO Global Action Plan on antimicrobial resistance urges member states and other stakeholders to invest in basic scientific research as well as in collaborative partnerships for research and innovation. "To ensure sustainable investments in countering antimicrobial resistance" is presented as one of the five strategic objectives in the plan.

### Challenges in discovering new antibiotics

The antibiotic pipeline is running empty and we face a global challenge in fighting resistance and delivering novel antibiotics to the market. Antibiotic drug discovery is scientifically challenging. The problem begins with finding novel hits or starting points and continues through development and clinical testing where problems of toxicity often kill projects at the late stage. As a result the discovery of effective and novel antimicrobials is both challenging and expensive. Addressing the initial hit identification problem requires access to suitable compound collections and this motivates, among other approaches, a thorough investigation of biodiversity to develop natural product libraries. There are also potential alternatives to antibiotics that might form part of a portfolio of approaches to address the need for effective infection therapies. These include developing inhibitors of bacterial virulence, repurposing or potentiating neglected or shelved compounds, and investigating the potential of monoclonal antibodies to clear infections.

Academic researchers and SMEs can contribute to the early stages of drug discovery, tackling problems across a very broad range of potential targets, but usually lack the financial and technical resources to take a project through to completion of clinical trials. In contrast large pharmaceutical companies are typically focused on particular areas of strategic interest and are less inclined to engage in broad programs of early discovery. It would clearly be beneficial for the future success of antibacterial drug discovery to identify and exploit new models that better align the scientific and financial interests and capabilities of academic researchers, SMEs and large pharmaceutical companies.

### Collaborative models

The current drug discovery and development model is constrained by the need for IP protection and confidentiality that places severe limitations on collaboration and sharing of resources or expertise from diverse fields. Could collaborative models be a better way to meet the challenges of developing new antibiotics (So *et al.*, 2011)?

In the field of neglected diseases different collaborative models have proven very successful. Some examples of these include the Medicines for Malaria Venture (MMV), the Drugs for Neglected Diseases Initiative (DNDi), and GSK´s Diseases of the Developing World Center at Tres Cantos (Hunter *et al.*, 2011). These organisations work in partnership with academia, the pharmaceutical industry and non-governmental institutions to build R&D portfolios for delivering medicines for neglected diseases.

The Open Source Drug Discovery (OSDD) project, initiated by the Council of Scientific and Industrial Research (CSIR) in India, has adopted an open source model in an attempt to drive collaboration in drug discovery across geographical borders. OSDD emphasizes integrative science that encompasses various disciplines and open-sharing of data (Bhardway *et al.*, 2011). The intention is that any new chemical entities developed by OSDD should be taken into clinical trials with the participation of multiple companies. The aim is to ensure the availability of drugs for diseases afflicting resource poor areas (Bhardway *et al.*, 2011).

The European Joint Programme Initiative on Antimicrobial Resistance (JPIAMR) also recognizes the importance of involving different stakeholders in addressing this serious problem.

Novel models and partnerships have also been built up outside the neglected disease area which might also serve as an inspiration for antibacterial drug discovery. They include for example the Phenotypic Drug Discovery Initiative set up by Lilly to foster collaboration with the research community in the area of Alzheimer's, cancer, diabetes etc. Many of the models described above rely on open collaborations often via Public Private Partnerships (PPPs).

### Public Private Partnerships

PPPs use public and philanthropic funds to engage the pharmaceutical industry and academic research organisations in undertaking R&D for diseases that they would normally be unable or unwilling to pursue independently, without additional incentives. These collaborations can

also involve small companies, patient advocacies and healthcare providers. A recent notable example is the New Drugs for Bad Bugs (ND4BB) programme, a PPP launched by the Innovative Medicines Initiative (IMI) with support from the European Commission and major pharmaceutical companies (through EFPIA, the European Federation of Pharmaceutical Industries and Associations).

### New Drugs for Bad Bugs – combating antibiotic resistance

ND4BB spans seven research topics including antibacterial drug discovery, antibacterial drug development, economics of antibiotic development, and antibiotic stewardship. Each project is a PPP in which pharmaceutical companies, academic researchers and small-to-medium-sized biotechnology companies collaborate under a framework that encourages data sharing between the partners with the aim of developing novel antibiotics (Rex 2014).

One of the programmes within ND4BB, ENABLE, has been set up specifically to drive early stage development of novel Gram-negative antibacterial drugs, with the aim of taking at least one compound through Phase I clinical trials.

Although, still in development, stakeholders see a bright future for the ND4BB campaign. One important consequence of ND4BB is an increased awareness from the pharmaceutical industry side that this type of PPP initiative might be something useful to engage in, showing that there are areas where competitors can usefully collaborate. Such a broad level of teamwork might be the best hope – maybe the only hope – for fighting the growing threat from antibiotic resistant bacteria argues May in the article *Time for teamwork* (May, 2014).

### The way forward

Are cooperative models the best way forward, and if so, how do we build up the necessary competence to exploit this concept within academia and industry? How do we construct models to engage the best academic researchers knowing that the incentives in terms of individual recognition when working in a collaborative model may not always align with the academic system and at the same time attract industry, so as to meet the needs from a public health perspective? Although obtaining funding for such collaborations will be critical we need to ask whether other elements need to be put in place to ensure that we obtain the best outcome. A successful model will need strong leadership and governance, clear IP rules, and should align with the underlying interests of both the public and private partners.

The aim of this workshop is to propose how to best set up collaborative models that can help overcome the obstacles responsible for the current shortage of new antimicrobials, vaccines, and diagnostics in the developmental pipeline, and to identify the specific stakeholders that need to act on this problem in both the short term and the long term. The question is, what is the best balance of models to ensure a healthy pipeline of new antibiotics into the future?

**References**


Bhardwaj, A., Scaria, V., Raghava, G.P.S., Lynn, A.M., Chandra, N., Banerjee, S., Raghunandanan, M.V., Pandey, V., Taneja, B., Yadav, J., Dash, D., Bhattacharya, J., Misra, A., Kumar, A., Ramachandran, S., Thomas, Z., Open Source Drug Discovery Consortium, and Brahmacharia, S.K., *Open source drug discovery – A new paradigm of collaborative research in tuberculosis drug development*, Tuberculosis 91 (2011) 479–486

Hunter, J., *Challenges for pharmaceutical industry: new partnerships for sustainable human health*. Philosophical transactions. Series A, Mathematical, physical, and engineering sciences, 369 (2011) 1817–1825

May, M., *Drug development: Time for teamwork*, Nature 509 (2014) S4–S5

Rex, J.H., *ND4BB: addressing the antimicrobial resistance crisis*, Nature Reviews Microbiology, 12 (2014) 231–232

So, A.D., Gupta, N., Brahmachari, S.K., Chopra, I., Munos, B., Nathan, C., Outterson, K., Paccaud, J.P., Payne, D.J., Peeling, R.W., Spigelman, M. and Weigelt, J., *Towards new business models for R&D for novel antibiotics*, Drug Resistance Updates 14 (2011) 88–94

**Workshop**

# Improved diagnostics for public health and surveillance

**Anna Zorzet**, PhD, coordinator ReAct, Uppsala University
**Jonas Lundkvist**, PhD, Associate professor in Health Economics, Uppsala University
**Martin Sundqvist**, MD, PhD, Dept. of Laboratory Medicine, Clinical Microbiology, Örebro University Hospital
**Johan Struwe**, MD, PhD, Expert, Public Health Agency of Sweden

Whenever antibiotic resistance is discussed, access to better diagnostics is often emphasized as an important tool to help manage the problem. The need for new diagnostics is highlighted in most strategic documents on antibiotic resistance such as the draft Global action plan on antimicrobial resistance, the European Commission's action plan, the Joint Programming Initiative on Antimicrobial Resistance's strategic research agenda and national action plans.

However, the discussion is often focused on an optimal diagnostic tool that will be able to deliver both identification of species and antimicrobial susceptibility pattern for any disease in around 30 minutes, without advanced technology and at a low cost. While it would certainly be valuable to have such a test, it is not likely that it will be developed in the near future (*e.g.* Goosens 2013). Nevertheless, there are still many advances to be made in the diagnostics area, in the absence of such an optimal test, although the demands of diagnostic tools will certainly be quite different depending on their intended usage. Improved diagnostics are key both in resource-limited and more well-equipped settings. In this workshop we will highlight three focus areas where diagnostics are critically needed:

- Diagnosing multi-resistance – focus on patient safety
- Diagnostic tests to optimize antibiotic therapy – focus on reducing antibiotic use
- Diagnostic tools for surveillance

Within the focus areas, the challenges of financing, access and uptake and a process for needs assessment will be discussed. The aim of the workshop is to have answered two questions for each area:

- Which steps should be taken next?
- Who can and will take responsibility for taking the next step?

There are many reasons why diagnostics are high on the agenda today. There is strong evidence that minimisation of time from test to treatment decreases mortality and morbidity. RAND Health concludes that the high incidence of deaths from for example tuberculosis, malaria, HIV/AIDS and bacterial pneumonia is due in part to the shortcomings of existing diagnostic methods. An appropriate point-of-care test could also identify those patients who would benefit from antibiotic treatment from those who would not, thereby supporting prudent use of antibiotics. Diagnostics are also an important component in collecting surveillance data that can influence decision-making.

### Diagnosing multi-resistance – focus on patient safety

The most advanced tests and logistics for diagnostics of infectious diseases and susceptibility testing are predominantly available in high-income countries with comparatively low or moderate prevalence of multi-resistant bacteria. In these settings, it has been shown that rapid species identification and antibiotic susceptibility results lead to better antibiotic therapy in sepsis patients as well as to decreased hospital costs. Most of today's antibiotics are available in these countries, giving the potential for a successful modification of therapy and increased likelihood of therapeutic success. Achieving both a rapid species identification and susceptibility profile also requires more complicated tests, probably best suited for hospital settings.

However, in large parts of the world the range of available antibiotics as well as the diagnostic infrastructure and knowhow are quite limited. Additionally it costs less to treat than to test in many low-income settings (WHO 2014). The diagnostics of infectious diseases will then typically be based on algorithms of clinical signs leading to a guidance of therapy. The data, so far available, indicates that at the same time the levels of antibiotic resistance in these areas are alarmingly high. Therefore, it seems of great importance to increase the diagnostic activity in proximity to the patient. Ideally the diagnostics (including susceptibility testing) should be made available for the direct treatment of the patient. But increased diagnostic activity could also lead to a better validation of clinical algorithms and improve local resistance data resulting in a better chance of choosing an effective antibiotic empirically.

RAND health emphasizes that access to correct treatment is critical to accessing the full benefits of a new diagnostic test. If only three antibiotics are available in a certain area, do we need to know if the bacteria are susceptible to other drugs than those three available? If so, can we provide these areas with those effective antibiotics? It is of great importance that the diagnostics developed are adapted to the questions asked locally and that these questions are based on an updated epidemiology of infectious diseases and prevalence of resistance in relevant pathogens.

### Diagnostic tests to optimize antibiotic therapy – focus on reducing antibiotic use

Antibiotic policies in the primary health care setting focus on avoiding overuse of antibiotics. The diagnostic question is often "Is it a bacterial infection or not?" This question is still valid and needs better diagnostic tools to enable an answer. However, the increase in multi-resistant bacteria also in primary health care, increases the demand for rapid diagnostic tests, as the relevant question now would be "Is it a bacterial infection, will it benefit from treatment and if so what treatment is effective?" A strategy based on rapid detection of respiratory viruses could in a community setting lead to a reduction in the need for antibiotics in upper respiratory tract infections as the tendency to use a "wait and see" approach would increase. This assumption is, however, based on a setting with a well-functioning health care system.

So far, no studies have been conducted on what kind of diagnostic tests that would be most beneficial in low-income countries, or what kind of test that would be feasible (both related to knowhow and economics) to implement. To provide the majority of the world's population with at least basic diagnostic tools to determine the cause of an infection and an idea of the antibiotic susceptibility calls for an open-minded discussion on the use of new and existing tests but also covering logistics and implementation strategies.

### Diagnostic tools for surveillance

Surveillance of antimicrobial resistance is one of the cornerstones needed to inform actions in the Global Action Plan that WHO has prepared together with partners, which will be presented to the World Health Assembly in May 2015. Still, according to the WHO 2014 global report on surveillance of antimicrobial resistance, there

are many knowledge gaps about the magnitude of the problem in bacteria causing some of our most common infections, particularly in areas where health systems are weak. Clinical microbiology may not be used, or available, for a number of reasons. And if samples are sent to the laboratory, they are often biased towards the most severely ill patients who have not responded to first line treatment because of infections caused by resistant bacteria. Furthermore, due to lacking capacity, methodology and performance, laboratories may not comply with standard protocols and consequently compilation of resistance data is not done and fed back to clinicians. When data are summarized they often describe a proportion of resistant bacteria without patient information. To be more useful for public health purposes, it would be better to have measures of the proportion of resistance in bacteria causing a specific clinical condition.

Appropriate surveillance requires samples from defined populations and patient groups in different settings processed with assured quality. Also, some of the data desired for surveillance may not be the same data that is collected for clinical management. Easy-to-use and stable standardized tools for antimicrobial susceptibility testing and analysis are urgently needed, particularly to support surveillance in low-resource settings where know-how, electricity, water and other supplies may be scarce. Grundmann emphasises that considering the potential demands and the gaps in the diagnostic service landscape especially in low- and middle-income countries, a step-wise approach edging towards a complete international surveillance initiative is the most likely scenario. Not all regions need to move at the same pace.

### Challenges to discuss in relation to focus areas

*Needs assessment*

As stated above, the need for new diagnostics is highlighted in most strategic documents on antibiotic resistance. However, Goossens states that today, very few companies have technologies in their pipelines that can meet the requirements that are often put forward; the tests should be accurate, easy-to-use, give rapid responses and preferably function in situations with a low level of infrastructure.

Many companies, Goossens further argues, are struggling to align their business goals with the technology solutions because the diagnostic needs have not been clearly defined. A technology roadmap on rapid diagnostic tests for infectious diseases is needed to help calculate, plan, and coordinate technology developments that meet real medical needs. For the individual patient as well as from a public health perspective, we need to assure that recommended and prescribed antibiotics really are effective. Furthermore, rapid and simple diagnostics can increase the value of larger stewardship polices.

*Access to and uptake of diagnostic tests*

There are diagnostic tests available today which could improve the use of antibiotics, but they are not always used correctly, or at all. This is true for both low- and middle-income and high-income countries. It is important to identify the barriers to access and use of those antibiotic resistance diagnostics currently available, and to discuss if the barriers are mainly due to test characteristics (*e.g.* the right kind of tests do not exist) or not (*e.g.* regulatory, financial). The path to the use of diagnostics involves passing several steps involving different stakeholders, *e.g.* national or regional authorities, distributors, healthcare providers, pharmacies, clinicians and patients, and the requirements and expectations of these stakeholders often vary.

Budgetary incentives for healthcare personnel to test for antimicrobial susceptibility are also complicated by large external benefits, which occur outside the healthcare system and potentially also many years into the future. There are also other non-financial-related barriers, including patent protection concerns in many emerging markets, a need for harmonized and predictable regulatory landscape, increasing evidence requirements, lack of trained and skilled workforce etc. In addition, in many parts of the world, patients pay for diagnostic tests out of pocket. These barriers to uptake also influence the global incentives to develop new diagnostics and potentially contribute to higher cost for those diagnostics used. To improve the use of diagnostics, it will be important to ensure that the broader and important global long-term clinical and economic implications of antibiotic resistance are recognised.

*Financing*

The way development of new tests and improvement of old tests are financed will contribute to

the ultimate success of these tests. A few different examples of new financing models, which do not rely solely on market forces have come to light, such as awarding prizes to diagnostic tests that fulfil a range of criteria. The largest is the GBP 10 million Longitude prize. There is also a EUR 1 million EU prize for a "low cost, rapid, easy to use and minimal invasive test that can identify at the point of care patients with upper respiratory tract infections that can safely be managed without antibiotics".[1]

In September 2014, President Obama launched a USD 20 million prize sponsored by the National Institutes of Health and the Biomedical Advanced Research and Development Authority to facilitate the development of a rapid diagnostic test, to identify highly resistant bacterial infections at the point of care. Another way of trying to stimulate uptake of diagnostic tests in low-resource settings is to subsidise the final product. An example is the TBXpert tuberculosis diagnostic project, a three-year UNITAID-funded collaboration for roll-out of this technology to 21 recipient countries.[2]

However, prizes and subsidized end-products are just examples, and it is likely that different financing models could be used, depending on the exact nature of the test, as well as the setting where it is meant to be used.

[1] https://longitudeprize.org
http://ec.europa.eu/research/horizonprize/index.cfm?prize=better-use-antibiotics

[2] www.whitehouse.gov/the-press-office/2014/09/18/fact-sheet-obama-administration-takes-actions-combat-antibiotic-resistan
www.who.int/tb/laboratory/mtbrifrollout/en/

**References**


*Ad hoc consultation on rapid methods for antimicrobial susceptibility testing at point-of-care in lower- and middle-income countries,* 8-9 April 2014 Geneva, Switzerland, WHO

*Estimating the Global Health Impact of Improved Diagnostic Tools for the Developing World*, (2007) RAND Health, Research Highlight

*https:///longitudeprize.org*

*http://ec.europa.eu/research/horizonprize/index.cfm?prize=better-use-antibiotics*

*www.whitehouse.gov/the-press-office/2014/09/18/fact-sheet-obama-administration-takes-actions-combat-antibiotic-resistan*

*www.who.int/tb/laboratory/mtbrifrollout/en/*

Goossens, H., (2013) *Antibiotic resistance—the need for global solutions, Part 3: Minimising the time to effective treatment—rapid diagnostic testing*, Lancet Infect Dis 2013; 13: 1057–98

Grundmann, H., (2014) *Towards a global antibiotic resistance surveillance system: a primer for a roadmap*, Upsala Journal of Medical Sciences. 2014; 119: 87–95

**Workshop**

# Antibiotics in animal production

In this workshop we will focus on how to align our efforts with the WHO Global Action Plan's clear strategy on the use of antibiotics in animal production: "A reduction in the consumption of antibiotics used in food production (terrestrial and aquatic livestock, and other agricultural practices) and reduction in the use in animals of antibiotics critically important for human health. Progressive reduction (to zero) in the use of medical and veterinary antimicrobials for applications other than human and animal health." This combined with the threat of increasing resistance among animal pathogens that may render currently available antibiotics ineffective in the future, means that there is an urgent need to reduce the use of antibiotics in animal production.

**The main focus areas for the workshop are:**

- What measures need to be taken and who has the mandate to do it?
- Who should initiate a reduction in use of antibiotics in animal production?
- How should (potential) costs for this be distributed within the food chain?
- What would be the consequences for global food security?

Global livestock production is increasing rapidly. To satisfy the increasing and changing demands for animal food products, while at the same time sustaining the natural resource base, is a major challenge to agriculture today, particularly in low-income countries. Despite measures taken by some countries, antibiotic use in humans, animals and agriculture is still increasing, and the projected increase in demand for animal food products may have a consequent impact on antibiotic use.

Antibiotics are used in livestock production to treat sick animals, protect healthy animals in contact with sick ones and during periods of transport or similar stresses. They are also used, in the absence of clinical disease, as growth promoters in some countries and production systems, which is controversial and has led to a number of countries limiting or banning use of antibiotics in this way.

**There is an undeniable need for action**

Available data do not allow us to quantify the contribution of antibiotics used in livestock to the development of resistance in human pathogens. Rushton *et al* conclude in their report for the OECD on *Antimicrobial Resistance – The use of antimicrobials in the livestock sector* that there is a trade-off between the current use of antibiotics in livestock and the potential risks to human health. Some would argue that this is becoming more critical, yet to assess this trade-off requires much stronger datasets on antibiotic use in livestock, resistance gene exchanges and transmission dynamics into humans than is currently available.

However, it is clear that the use of antibiotics in livestock affects the prevalence of resistant bacteria in animals. The WHO:s statements on reduction of this use indicates that it is also of critical importance to human health. De Briyne *et al* conclude that considerable attention is being given to antibiotic resistance regarding public and animal health, with the European Commission, the Heads of Medicines Agencies, the Federation of Veterinarians of Europe and a number of Member States and veterinary organisations all issuing strategies and/or action plans.

The aim of the workshop is not to try to quantify the risk. A premise for the discussion is, like the WHO states, that there is a problem which is *critically important* for human health. Moreover, it is just as critical for animal health, due to increasing resistance among animal pathogens and restrictions on what antibiotics will be available for the treatment of animals. The aim of the workshop is to discuss what measures need to be taken to reduce the use of antimicrobials and who has the mandate to put them into action.

**What do we know of prescribing behaviour?**

Antibiotics in livestock are, as stated above, used for three purposes: disease therapy, disease prevention and growth promotion. In some regions of the world, antibiotics are only available on veterinary prescription while in other parts of the world this is not needed (FAO, 2014). Moreover, antibiotics for growth promotion are mixed in the feed and regarded as a feed additive. The different reasons of use in animals require different approaches for promoting a reduction in the use of antibiotics.

Given that a reduction of the use of antibiotics is a clear target today, we need to know more about what influences veterinary prescribing habits. De Briyne *et al* have studied factors influencing antibiotic prescribing habits amongst veterinarians in Europe, in order to find the best strategies to achieve the desired change. Their findings showed that the factors which most strongly influenced prescribing behaviour were sensitivity tests, own experience, the risk for development of antibiotic resistance, and ease of administration. They also identified clear differences in the preferences between countries regarding what antibiotic classes were being used and that national guidelines help to drive the responsible use of antibiotics and reduce the extent of use of critically important antibiotics. They conclude that a more widespread implementation of veterinary antibiotic prescribing policies, and monitoring of adherence to these, should ensure more responsible use.

De Briyne *et al* also conclude that there is evidently a need for future innovation and development of practical sensitivity tests that provide rapid and meaningful results, at a reasonable cost.

**Increased demand for livestock products**

According to the FAO the demand for pork products has increased over the last decades,

leading to a doubling of pig production in the last 20 years. Rushton *et al* state that this is partly due to the increase of the world's population but also a consequence of increased urbanisation. There have been several responses to the greater demand for livestock products, for example a general increase in the global livestock populations, an intensification of livestock production systems relying on diets of concentrate feeds, indoor housing and use of specialised breeds with greater output per animal and greater densities of livestock populations clustered in areas with access to transport and processing systems.

As stated by the FAO, the intensification of pig production and the objective to produce more at reduced costs raise important questions regarding disease management. In many regions of the world, control of infectious diseases is often based on the use of antibiotics, without appropriate supervision by veterinary authorities. In addition, antibiotics can be obtained without prescription in many countries.

Rushton *et al* state that from an economic perspective it is important to recognise that low-level antimicrobial use in livestock influences the efficiency of feed inputs and hence the overall productivity of a system. This is the theory behind antibiotics for growth promotion. However, a recently published report from the OECD demonstrates that the effect is reduced in good production systems (OECD, 2015). There are clearly trade-offs in terms of animal health. Rushton *et al* also conclude that there are significant knowledge gaps in areas such as the economic contributions of antimicrobials through their reduction in livestock disease burdens and their estimated impacts on hunger and poverty

alleviation. This is an important aspect regarding global food security.

### Prevention is essential

It is not the *preventive use* of antibiotics, but *prevention* that is essential. De Briyne *et al* argue that key points for disease prevention are; to limit animal-to-animal contact, reduce stress, and to ensure good hygiene and good nutrition. These recommendations are relevant to all animal production systems. Sometimes limitations are highlighted when animal production involves animals that graze outdoors, but it is possible to create infectious disease control barriers even in these cases. Another challenge is that farmers are sometimes not granted loans for building systems that reduce the risk of infectious diseases. Prevention of infectious diseases in livestock production carries additional costs.

### Alternative measures need to be explored

The FAO highlights that many alternative disease management approaches are being investigated in order to restrict the use of antibiotics for growth promotion, and to a lesser extent for disease prevention. These include, for example, vaccination against specific bacterial diseases, feed supplementation with probiotics, with herb extracts, with clays or minerals, etc. The FAO has also noted that there is increasing interest in East and Southeast Asia to identify alternatives to antibiotics in order to prevent the occurrence of antibiotic resistance and avoid the presence of antibiotic residues in meat.

### Joint responsibility from all stakeholders

Antibiotic resistance has spread worldwide and there are today many and well documented examples of this (Lancet, 2013). Whilst the use of antibiotics for promoting growth has been banned in Europe since 2006, it is still common practice in East and Southeast Asia, South America and the US. This highlights the need for joint responsibility from all stakeholders and underscores the importance of global consensus, both regarding the scope and the gravity of the problem.

The importance of joint responsibility does not only apply in a global context, it is equally important at each step along the supply-chain. Consumers are powerful stakeholders on the demand-side. But producers, the food industry and food retailers are equally powerful stakeholders on the supply-side. They can create new markets for food that are not based on a perfunctory use of antibiotics. Herein lies a joint problem and a joint responsibility that transcends the issue of whether animal production based on an over-use of antibiotics is *literally* dangerous for human beings. The use of antibiotics has to be reduced for the welfare of generations to come.

**References**


Where no reference is made the information presented above is derived from an interview with the workshop leader, Susanna Sternberg Lewerin, Professor in Epizootiology and Disease Control, the Swedish University of Agricultural Sciences.

*Antibiotic resistance—the need for global solutions,* (2013) The Lancet Infectious Diseases Commission, Lancet Infect Dis 2013; 13: 1057–98

De Briyne, N., Atkinson, J., Pokludová, L., Borriello, S. P. and Price, S. (2013) *Factors influencing antibiotic prescribing habits and use of sensitivity testing amongst veterinarians in Europe*, Veterinary Record 2013 173: 475

De Briyne, N., Atkinson, J., Pokludová, L. and Borriello, S. P., (2014) *Antibiotics used most commonly to treat animals in Europe*, Veterinary Record 2014 175: 325

OECD Working Party on Agricultural Policies and Markets, (2015) *Global antimicrobial use in the livestock sector,* TAD/CA/APM/WP(2014)34/FINAL

*REPORT on Antimicrobial Usage and Alternatives for Prophylaxis and Performance Enhancement in Pig Populations in East and Southeast Asia*, Food and Agriculture Organization of the United Nations Regional Office for Asia and the Pacific, Bangkok, 2014

Rushton, J., Pinto Ferreira, J. and Stärk, K.D. (2014), *Antimicrobial Resistance: The Use of Antimicrobials in the Livestock Sector*, OECD Food, Agriculture and Fisheries Papers, No. 68, OECD Publishing

# GE Healthcare

GE Healthcare is one of the sponsors of the Uppsala Health Summit 2015. GE Healthcare works to develop innovative, high quality products and services that protect the health of workers, customers, and the environment.

To gain further perspectives and insights about how existing technologies for producing vaccines and general capacity building in resource poor parts of the world can contribute in efforts to address antibiotic resistance, we have interviewed Dr Daria Donati, senior director, Enterprise Solutions, GE Healthcare.

**Voices have been raised regarding the lack of focus on integration of vaccination programmes into broader antimicrobial resistance control strategies.**
**How important is this?**
– The importance of this cannot be overstated. In many, many cases, what we see today is the effect of insufficient preventative measures.

That is the case for many, not all, but many cases of antimicrobial resistance. If you have a population that has not been vaccinated, the probability that they will be exposed to a disease that can become chronic is very high. A good vaccination programme, especially in certain countries, can really help control the number of instances of antimicrobial resistance. Most likely, we will not be able to eliminate the problem, but it will be an important step in the right direction. In many countries vaccination programmes are insufficient for two reasons: (1) authorities do not have the capacity to organise or carry out vaccination programmes and (2) they may not have access to the effective drugs that other countries do.

– GE Healthcare has been working in the past trying to support governments, NGO:s and other stakeholders, enabling them to rapidly deploy capacity for vaccine productions in countries that are less capable of doing this themselves. However, it is essential that this is done delivering the same quality and safety capabilities that you will have in high-income countries. The aim is to aid the capacity building, in terms of manufacturing, in order to improve access to vaccines and other essential medicines. With the help of organisations such as WHO, countries can implement vaccination programmes that will have a direct effect on actions against antibiotic resistance.

**What are the most important issues in addressing the antimicrobial resistance crises?**
– From our perspective, we can see that enabling manufacturers to meet unmet needs is crucial in addressing the antimicrobial resistance crisis. Globally, we see a movement in the market with a clear tendency in the set up of localized manufacturing solutions, to supply for local essential medicines needs.

– How do these manufacturing solutions look like? Smaller facilities footprint, flexible manufacturing and cost control are the key factors. The ability to control biopharmaceutical costs has become more and more important. Stakeholders want to know in advance all the factors influencing final cost given the high competition on the market. Providing effective and innovative solutions in manufacturing, supports the stakeholders position in the key medicines supplies and helps them to deliver the same quality, no matter where.

– So, we work in the pre-phase of addressing the antimicrobial resistance, which aims to support the prevention of the resistance itself.

**GE Healthcare has developed technologies to be able to rapidly build up production facilities where access to treatment is limited. How can that technology be used to fight antimicrobial resistance?**
– Capacity building is a very important part of the fight against antimicrobial resistance. In a global overview of bio manufacturing, it can be noted that knowledge of manufacturing and manufacturing support is localized to industrialized countries. In emerging economies however, it is not only funding and the ability to intervene quickly that is lacking; there is also a shortage of people with the qualifications needed to enable manufacturing and delivery. Often, what these countries need is capacity building, from the first phases all the way to manufacturing and management.

**Why does GE sponsor an initiative like the Uppsala Health Summit?**
– Our company is built on technical solutions, discovered at Uppsala University, and it is here in Uppsala that we have the heart of our manufacturing activities. We really believe that an event like the Uppsala Health Summit is a great forum to connect stakeholders and policymakers, both nationally and internationally, fostering an environment of open exchange. From the outset, we envisioned that GE Healthcare would be a good partner for this activity, given our strong presence in Uppsala and our global engagement with a strong link to Global health.

# Uppsala Monitoring Centre

Uppsala Monitoring Centre (UMC) is one of the sponsors of the Uppsala Health Summit 2015. UMC is an independent foundation and a centre for international service and scientific research that was established in 1978. UMC is a WHO Collaborating Centre and is responsible for the scientific and technical operations of WHO's international drug monitoring program. The foundation's priorities are the safety of patients and the safe and effective use of medicines in every part of the world. To gain further perspectives and insights on how pharmacovigilance can contribute in the efforts to tackle antibiotic resistance we have interviewed Dr Marie Lindquist, Director of UMC.

*Pharmacovigilance* means the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem (WHO). However, Dr Marie Lindquist emphasizes the broader perspective on pharmacovigilance – "Yes, it is about science and methodology, but it is primarily about people, it is for people. If we lose that, we haven't achieved anything." The purpose of UMC's work in pharmacovigilance is to support good therapeutic decision-making regarding the benefits and risks of treatment options for patients taking medicines.

**How can pharmacovigilance be understood in a broader public health and patients' well-being context?**
– The theme for the Uppsala Health Summit is antibiotic resistance, which is a huge global problem. If we do not have effective treatment for infections, millions of lives will be at risk in every country. So there is no doubt that global action needs to be communicated through educational campaigns about how we use antibiotics wisely. We also need to improve ways to detect signals of emerging antimicrobial resistance so that we can prevent it from spreading. This is exactly the kind of work that we do at the UMC and that is pharmacovigilance.

**How can pharmacovigilance contribute to tackling antibiotics resistance?**
– Some people may argue that antimicrobial resistance is not part of pharmacovigilance, but I argue that it is. We have worked actively here at the UMC to broaden the scope of pharmacovigilance to actually consider everything related to how drugs are used. This includes not only antimicrobial resistance, but also medication errors, bad quality drugs etc.

– At the UMC, we have developed scientific methods for collecting and analysing information. The same reporting channels and analytical tools can be applied when looking for signals of emerging antimicrobial resistance problems.

**The challenges must vary greatly. What are the main challenges in low- and middle-income countries compared to high-income countries?**
– Countries are at different levels of maturity regarding the systems that they have in place to monitor the safety of medicines. UMC is now working with over 120 member countries globally. Very crudely speaking, we can talk about three levels of maturity. The entry level entails a country where the process has started to consider not only getting better access to medicines in the country, but also how to ensure safe and effective use of medicines and how a system can be set up for this. UMC provides teaching and training efforts to support these countries and we help them with basic data collection tools.

– Then we have countries with the basic structures in place. We try to help them to turn the data that they have into useful information and knowledge that benefits healthcare professionals and patients. It is a more sophisticated method for structuring and analysing the data. Furthermore, we initiate discussions on good communication practices and how to integrate pharmacovigilance into healthcare and not treat it as an isolated project.

– The final stage includes countries that have been doing this for many years, that have effective systems and good analytical methods in place. Here we focus on partnerships to develop more advanced research methods and on how to make use of new data sources like social media, and Smartphone applications where people record their own progress and measures etc. It is a huge and interesting field that we are just starting to tap into with E-health and patient engagement.

**What methodology does UMC work with in combating antibiotics resistance?**
– We have developed methodologies that can be used to actually track emerging signals of antimicrobial resistance. It is a type of cluster analysis that is used, but without the data we cannot find the signals, so we very much rely on active participation from healthcare professionals and patients in pharmacovigilance. Pharmacovigilance is a concern for everyone and it has to be part of healthcare delivery.

**You are about to launch VigiAccess, what is that? And how can VigiAccess help patients?**
– For the first time ever we can make data from a global database available publicly. It is a web application that allows anyone to search VigiBase, the global WHO database with data from 120 member countries on suspected adverse reactions from medicines and vaccines. It is important to keep in mind that this is not *the* answer. It is not hard evidence, but it can point us in the right direction and it can indicate that we need to investigate matters further to see if a reaction was actually caused by a specific drug. It is up to us in the pharmacovigilance community to communicate what this data tells us and what it does not. However, it is important to remember, that this is about people's health and it is about suffering, which makes the data protection aspect very important. In addition to VigiAccess, we have also launched an online pharmacovigilance campaign "Take & Tell". "Take & Tell" delivers a very simple message about the importance of monitoring and talking to our doctors about our own well-being in relation to medicines. It is a small change in our behaviour with a big impact on our health.

**Why does UMC sponsor an initiative like the Uppsala Health Summit?**
– For us, it is a very important to have a platform where we can engage partners so that we can act *now* to prevent a looming disaster. We see Uppsala Health Summit as an excellent space for dialogue and ideas, where we can interact, network and partner with others who share the same desire to do something and the same vision of patient safety and well being, globally.

# AstraZeneca

AstraZeneca is one of the sponsors of the Uppsala Health Summit. To gain further perspectives and insights on the subject of antibiotic resistance we have interviewed Dr John Rex, Senior Vice President and Head of Infection, Global Medicines Development at AstraZeneca.

Dr John Rex describes how the challenges in addressing antimicrobial resistance can be related to three different phases of a linear process.

1. Discovering new antibiotics is hard.
2. Developing antibiotics has been and can be difficult.
3. Antibiotics are unfavourable, from an economic perspective, in a classic market-based system.

The transformation, over the past 60 years, of our ability to treat patients with infectious diseases has been dramatic. The prospect that we might not have antibiotics to treat infection in the future in the way that we want and need requires us to break the problem down and try to resolve the challenges in each phase.

**Why is developing new antibiotics so difficult?**

– It is easy to presume that given the widespread resistance that we see today, it would be easy to develop new drugs for bad bugs. On the contrary. It is relatively hard to do clinical studies of a new drug against resistant bacteria. Large-scale trials must have a sufficient number of infected patients which, in practice, means the epidemic is upon us before we can actually do the development program. That is not satisfactory.

**Do we have to develop new approaches or are there existing approaches that can be used?**

– This is an area where we have made rather a lot of progress. We – the international development community – have spent the last six or seven years talking about how we can solve this problem. By making really good use of all the scientific knowledge we have, it is possible to reduce the required size of the development program to a smaller core, which doesn't require quite as many people being infected with the resistant bacteria before we can get the drug registered. We have made huge progress here, and the FDA and the EMA have issued guiding documents that describe *streamlined*

*focused pathways*, which companies are now testing and refining. They are actually being tried right now – real products are going down these pathways and we are learning as we go along. This is really big progress.

**How do we attack the challenge of the economics being unfavourable?**
– The tension is obvious. The message to pharmaceutical companies is: please discover them, but we do not want to have to use them. It is a tension that cannot be reconciled with traditional market forces. We need to be good stewards, which means not using antibiotics when we do not need to given that even their correct use drives resistance. This is a problem that requires us to take a step back and rethink the business model of antibacterials. There are multiple stakeholder conversations going on at the moment, all focused on the need for new models.

**Could Public Private Partnerships (PPP) be one model?**
– It could be. For discovery and development, absolutely. The problem you have to solve at the end of the day is that the management of a drug on the market presumes the existence of a defined owner who takes the responsibility for additional studies, the manufacturing supply chain, import drug licences, pharmacovigilance etc. It probably costs 15–20 million dollars per year, per drug, just to keep the drug available. A PPP could take on the development of a drug, but would it actually take the responsibility, for the next ten years? It has not really registered within the community – the magnitude and the depth of this third problem, ***i.e.*** that the economics are unfavourable.

**How can we make sure that companies do get return on investment?**
– The type of model that comes up over and over again is an insurance-like model. Take, for instance, life insurance as a concept – you pay it, expecting never to have to use it, but you know that one day it might be important for your family. The model is not exactly the same, since you will actually be using antibiotics. However, a variation of this concept does seem appropriate here. If, for example, a meaningful number of territories around the world were willing to buy access to a new agent whether used or not, the company would be able both to recover its development costs and to maintain the supply chain needed to make the drug available.

**How is the current discussion?**
– We have a well-informed conversation now. About five years ago, the need for engagement with the pharmaceutical industries was discussed for the first time, because of the need to make it attractive for them to work in this space. The idea that something needs to be done to incentivise pharma to develop products is not the first thing that people think of, but once you develop the conversation, people see the urgency. I believe that we now are in a phase where we will see the conversation take a step forward over the next 18 months, in terms of understanding what it takes to carry a new pharmaceutical down the road for ten years. We need to talk rationally about good approaches.

**How do we keep from excess use?**
– Best use has to be based on the education of patients and healthcare providers. You want to avoid best use being based on what you can afford. You want to use the right drug for the right person. We have to take away the pressure on the sales side and we want to measure variables that are good control of process by the users, for example, over what percentage of time that antibiotics were given to a patient was a culture done? We need metrics that drive the behaviour of the system and give feedback to the providers who, by reading cultures over time, are learning their resistance patterns locally and how to better choose treatments.

**Why does AstraZeneca sponsor an initiative like the Uppsala Health Summit?**
– We believe that antibiotics are fundamental to enabling modern medicine and this kind of conversation is critical. We are committed to research and development in this important area of public health, which is why we recently chose to create a stand-alone subsidiary company, focused exclusively on the research and development of early-stage antibiotic pipeline. We need to find business models that provide us with the antibiotics that are needed globally. I think the science is going to get cracked. I think the regulatory part has been cracked. I think the economic part is the big problem still outstanding.

# Governance

## Steering committee

**Chairman: Professor Anders Malmberg**
Deputy Vice-Chancellor of Uppsala University

**Dr Johanna Adami**
Director Health, VINNOVA, Sweden's Innovation Agency

**Dr Jens Mattsson**
Director General, National Veterinary Institute (SVA)

**Professor Johan Schnürer**
Pro Vice-Chancellor at the Swedish University for Agricultural Sciences (SLU)

**Yvonne Näsström**
Director Economic Development, City of Uppsala

**Christer Svensson**
Regional Director, Nordea

**Börje Wennberg**
Chairman, Uppsala County Council Executive Committee

**Professor Bengt Wittgren**
Director, Swedish Medical Products Agency

## Advisory Board

**Chairman: Peter Egardt**
Governor, Uppsala County

**Nicola Bedlington**
Director General, European Patients' Forum

**Göran Bexell**
Senior Professor of Ethics, The Pufendorf Institute, Lund University

**Anders Olauson**
Founder of the Ågrenska Centre; Member of United Nations' ECOSOC; Member of Swedish National Board of Health and Welfare's Advisory Board; President of European Patients' Forum

**Dr Ingrid Wünning Tschol**
Senior Vice President, Health and Science, Robert Bosch Stiftung

**Sireesha Perabathina**
Associate Director, Access Health International

**Prof. Florence Haseltine**
Founder Society for Women's Health Research; Former Director NIH Center for Population Research

**Joy Phumaphi**
Executive Secretary ALMA, former Minister of health Botswana

## Project manager

**Madeleine Neil**
MSc Ba and Econ., Uppsala University

## Program committee

**Chairman: Thomas Tängden**
Assistant Professor, Uppsala University, Dept of Medical Sciences, ReAct

**Stefan Peterson**
Professor Uppsala University, Dept of Women's and Children's Health

**Anna Zorzet**
PhD, Uppsala University, Dept of Medical Sciences, ReAct

**Susanna Sternberg Lewerin**
Professor, Swedish University of Agricultural Sciences, Dept of Biomedical Sciences and Veterinary Public Health

**Joakim Larsson**
Professor, University of Gothenburg, Dept of Infectious Diseases

**Anders Karlén**
Professor, Uppsala University, Dept of Medicinal Chemistry

**Alexandra Waluszewski**
Professor, Uppsala University, Science and Technology Studies Center

## PARTNERS

UPPSALA UNIVERSITET

SLU

WORLD CLASS UPPSALA!

LÄKEMEDELSVERKET
MEDICAL PRODUCTS AGENCY

SVA NATIONAL VETERINARY INSTITUTE

Landstinget i Uppsala län

VINNOVA

Uppsala Kommun

## SPONSORS

AstraZeneca

Uppsala Monitoring Centre

LIF

MEDA

Livsmedelsverket

Jordbruks verket

jpiamr
Joint Programming Initiative on Antimicrobial Resistance

PRODUCTION: GRAPHIC SERVICES, UPPSALA UNIVERSITY 2015.

# www.uppsalahealthsummit.se

**Uppsala Health Summit**
c/o Uppsala University
P.O. Box 256
SE-751 05 Uppsala, Sweden
info@uppsalahealthsummit.se
www.uppsalahealthsummit.se
#uhs_2015