



A world without antibiotics

Conclusions from Uppsala Health Summit
2–3 June 2015



About Uppsala Health Summit

Uppsala Health Summit is an international arena for dialogue on how to make better use of knowledge and innovations to improve health and healthcare over the world. Dialogue between selected leaders, opinion formers and experts is at the centre of the summit. Different aspects, different perspectives help us to understand the complexity of the challenge, and help us to propose workable

solutions, step by step, and to identify key stakeholders.

Uppsala Health Summit is a collaborative effort from a group of not-for-profit Swedish partners – universities, local government, national authorities – initiated by the network Worldclass Uppsala and coordinated by Uppsala University.

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Uppsala Health Summit 2015 – A world without antibiotics



Introduction

Antibiotic resistance is a major public health threat that has to be met with multifaceted actions and global collaboration. In June 2015, about 200 stakeholders and experts from all parts of the world met at Uppsala Health Summit, to discuss in dialogue how to meet this challenge.

The summit's starting point was the global action plan on antimicrobial resistance, adopted the week before by the World Health Assembly.

This document includes the conclusions and recommendations from the workshops held during the summit on the following topics:

- A. Access not excess
- B. New economic models addressing antibiotic resistance
- C. The environmental dimension of antibiotic resistance
- D. Research and innovation for new therapies – collaborative models
- E. Improved diagnostics for patient safety and surveillance
- F. Antibiotics in animal production

The outputs from the different workshop groups were presented and discussed at the summit in plenum. A draft report has also been circulated among the delegates for comments.

General observations

This was one of the very first arenas gathering stakeholders from different sectors and geographies where operationalization of the global action plan was in focus for the dialogue, especially during the workshops.

Despite discussing different topics, some general observations were recorded from several workshops.

- It was highlighted in most workshops that national governments and international organisations, like the European Union or the United Nations, need to increase their level of commitment to the struggle against antibiotics resistance. Many mentioned that governments' commitment and capacity of leadership are crucial for the issue.
- The need for information and education of healthcare professionals, consumers, farmers and other stakeholders was stressed. The message and format must be tailored to the target group. Governments or organizations, like the WHO, can coordinate and secure the quality of the information used at a national or international level. Many workshops discussed the need to visualize antibiotic resistance, to give it a "face and a name". Responsible communication can help maintaining the issue high on the political agenda, as well as stakeholders' awareness on



Antibiotics are the cornerstones in any health system. The pyramid of health systems is built on these miracle drugs. But today, these pillars are rapidly crumbling, potentially causing a collapse of our entire modern medicine.

Otto Cars,
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Dr Gilles Forte,
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how they can and should favour prudent use of antibiotics.

- Too many actors are today dependent on sales of antibiotics to secure their income, including healthcare workers, pharmacies, veterinarians, and the pharmaceutical industry. Delinking incomes from sales of antibiotics is a recurring proposal from the workshops that will require new regulations and business models. Those whose incomes will be threatened will need support.
- Governments should use trade agreements, regulations, and public procurement policies as tools to promote a rational use of antibiotics. For example, growth promoters in food production could be banned and environmental criteria included in legislation pertaining to pharmaceuticals in the framework of good manufacturing practices (GMP).
- Rational use of antibiotics in humans implies access to effective antibiotics as well as sufficient skills of healthcare professionals, appropriate diagnostic tools and surveillance data on antibiotic resistance. Non-prescription sales should be avoided, without putting access to antibiotics at hazard, and perverse incentives for overuse must be explored and targeted.
- Development of new treatments, vaccines and diagnostics is not only depending on financial resources but poses a great scientific challenge. Several workshops pointed out the need for intensified academic research, collaborations between academia, SMEs and big pharmaceutical companies, and sharing access to existing data. Healthcare professional and experts must set up target product



The global action plan per se is a plan and the resolution urges the member states to implement the plan, to mobilize financial resources to realize the plan's actions...

There is a need for urgent action!

Dr Gilles Forte,
Department of Essential
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profiles for new antibiotics that meet the most urgent medical need. Long-term investments are needed for the field to be attractive for scientists.

- There is too little knowledge of the cost of non-action. More studies on the burden of antibiotic resistance, in terms of financial as well as human costs, are needed to incentivise governments and other stakeholders to take action.
- Surveillance is deemed crucial for success. Thus, the need to gather reliable data re-occurred in several workshops and plenum discussions.
- Access to finance is key to many of the actions in the global action plan, as well as to many of the proposals from the summit's workshops. It is important that existing and upcoming initiatives are communicated and well coordinated, to avoid dispersion of funds and lost opportunities.

These and other observations and recommendations are further developed in the following sections reporting conclusions from all six workshops.

Together with the Pre-Conference report, available here, this report form a dense overview of the current situation as well as of proposals on how we can start controlling the development of resistant bacteria.

We hope that this report will help and inspire decision makers in policy, industry, NGOs, healthcare and academia to initiate change. Some proposals will require financial investments to be realized, others are more dependent on the will to take necessary decisions.

We invite you who participated in the discussions to use the report in your own work as a source of inspiration and of good arguments for taking the necessary steps. We invite all others – decision makers, opinion formers and experts – to read, comment and act on these proposals.

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Workshop conclusions and suggestions

Reports from Workshops

- Workshop A** Access not excess – rational use of antibiotics
- Workshop B** New economic models addressing antibiotic resistance
- Workshop C** The environmental dimension of antibiotic resistance
- Workshop D** Research and innovation for new therapies – collaborative models
- Workshop E** Improved diagnostics for public health and surveillance
- Workshop F** Antibiotics in animal production



Workshop A

Access not excess

– rational use of antibiotics

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Karin Abbor-Svensson, Programme Administrator, Dag Hammarskjöld Foundation

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Workshop goal

A discussion on what happens when a new class of antibiotics becomes available in a low-income country. How do we balance issues of access and excess?

Background

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

The workshop

The main focus areas for the workshop were:

- 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?

The workshop was run as a scenario, where participants were assigned the role of a defined stakeholder group, based on their professional background.

- *AXEX* is the name given to the fictive country, in which the scenario takes place.
- *BACTERM* is the name given to a fictive new drug described below.

Each stakeholder group was assigned the task to define which actions they deemed necessary for their stakeholder group to take in order to maximize the use of an opportunity presented to the country AXEX, and to suggest actions they would like other stakeholder groups to take.

An opportunity presented to AXEX, and a challenge

- BACTERM, is the first example of a new class of antibiotics which has become available.
 - Effective against respiratory pathogens
 - International subsidy mechanism brings wholesale price down to 1 USD/dose
 - There is wide international concern for irrational use and resistance development
- AXEX must decide how to arrange a distribution system for BACTERM balancing concerns of cost and resistance development with good access to this life-saving drug.

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Otto Cars, Professor Uppsala University;
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The scenario

The workshop was premised on the following scenario:

- A country, called AXEX, predominantly rural with a population of 25 million and a 2 per cent growth rate.
- GDP per capita 400 USD, economic growth of 4 per cent per annum, mostly subsistence agriculture, but a growing capital with a well-to-do middle class and rural migrants.
- Annual public health expenditure 15 USD/capita + private out of pocket 15 USD/capita.
- No national health insurance system but some primarily urban work-related schemes covering formal sector employees.
- Public healthcare system:
 - Based on dispensaries and healthcare centres, supported by district hospitals as well as regional and national referral hospitals
 - Drug supply is primarily through a “push” system with pre-packaged boxes to lower level facilities (dispensary and health centre) and a “pull” system whereby drugs are ordered from district hospital and up. Drug stock-outs are frequent
 - An essential drugs list exists and usage is free by policy, but in practice patients often have to buy missing items and drugs

- Private healthcare system:
 - Strong and diverse
 - Ranges from private medicine vendors, to unregistered and registered drug shops and formal medical staff’s afternoon/evening clinics
- Health seeking and quality of care:
 - Pneumonia and malaria are the major causes of death among children
 - Care seeking studies for childhood febrile illness incidents indicate that half the care sought outside the home is to public providers and half to private providers
 - In theory antibiotics require prescriptions, but in practice it is available over the counter
 - Quality of care studies indicate extensive use of antibiotics and antimalarials in presumptive treatment, but also that there is evidence of both low level of use of antibiotics and mistreatment with other drugs, e.g. antimalarials and antipyretics, among children dying from pneumonia
 - Also indications of resistance to widely available and affordable antibiotics



The promising developments we have seen in many parts of the world in relation to the fulfilment of the Millennium goals have in many ways been underpinned by the use of antibiotics. Without effective antibiotics, some of the progress made can become undone. Therefore, I think it’s surprising and alarming that access to effective antibiotics or antimicrobials are so far not mentioned in the process of the new sustainable goals.

Otto Cars,
Professor Uppsala University;
Senior Advisor and Founder,
ReAct



Conclusions and suggestions

Priority actions self-reported by stakeholder groups:

Regulators and government

- Develop best practices (similar to what already exists for TB/malaria/HIV/narcotic control) including pharmacovigilance.
- Develop legislation on appropriate antibiotic use.
- Develop a policy platform involving civil society organizations, academia and industry.
- Ensure surveillance is developed (drug use, antimicrobial resistance).

Clinicians

- Establish clinical guidelines for appropriate use of new antimicrobials – including use of rapid diagnostic tests.
- Develop and support education and communication strategies.
- Develop surveillance monitoring for resistance related to new drugs, as well as use and clinical failures.

Civil society and NGOs

- Reduce demand through massive information sharing.
- Disseminate best practices.
- Contribute to surveillance and monitoring

(from more accurate assessment of AMR² to use/misuse at the local level).

- *Caution: Don't treat AMR as an infectious disease or microbes as "enemies".*

Pharmacists and private providers

- Ensure that prescriptions are evidence-based (general) and needs-based (individual).
- Develop methods for self-regulation and accreditation.

Industry

- Forecast demand for the new drug.
- Ensure sufficient stocks.
- Keep records of product flow and distribution channels.

Academics

- Raise awareness of AMR at all levels.
- Develop a sensitive algorithm to differentiate bacterial versus viral fevers, include use of rapid diagnostics, and ensuring malaria is ruled out first.
- Develop surveillance methods.
- Assist with social acceptance of new drugs, monitoring use, distribution, follow-up of side-effects.

² AMR=Antimicrobial resistance

Actions asked of other stakeholder groups

Regulators and government	Clinicians	Civil society and NGOs	Pharmacists and private providers	Industry	Academics
<ul style="list-style-type: none"> • Build surveillance systems in partnership between high-income and low-income countries • Proper monitoring of who receive antibiotics, including sanctions for inappropriate use • Rationalize and streamline the private sector supply chain: manufacturing – distributor – wholesaler – retailer – patient • Require disclosure of information for procurement • Restrict distribution to public providers (in the context of overall strengthening of health systems) • Set frameworks (regulation guidelines for action) • Classification of method of sale • National action plan 	<ul style="list-style-type: none"> • Prescribe according to evidence • Develop clinical guidelines and algorithms • Look for side-effects • Identify persons and populations with reduced access • Separate prescribing from financial incentives and dispensing 	<ul style="list-style-type: none"> • Education and public awareness on: <ul style="list-style-type: none"> a) quality care b) correct antibiotics use c) antimicrobial resistance • Participation in policy platforms, feedback mechanisms 	<ul style="list-style-type: none"> • Restrict over the counter sales of new antibiotics • Monitor availability of medicines • Monitor use of medicines • Provide data on stock-outs • Separate dispensing from financial incentives • Adhere to professional standards • Stringent control and monitoring by regulatory bodies • Education on antimicrobial resistance 	<ul style="list-style-type: none"> • Develop a code of ethics for new drugs promotion • Manage waste from drug production into the environment • Information disclosure • Develop rapid diagnostic tests for organisms and antibiotic resistance • Monitor and evaluate use and resistance • Increase investment into antibiotic stewardship • Quality stamp for generics (at the international level) • Look at the contracts that industry has • Uphold the subsidy 	<ul style="list-style-type: none"> • Education on antimicrobial resistance for all • Curriculum review and training • Track resistance prevalence patterns • Identify research gaps • Develop rapid diagnostic tests • Pharmacovigilance • Evaluation of AMR program implementation • Platform for information sharing and collaboration

Panel discussion on proposals

Following the stakeholder groups' presentations of actions needed, the whole workshop gathered for a summarizing panel discussion on the suggestions made.

The importance of accountability

The importance of accountability was raised, with differences between being accountable (producing reports) and being held to account (punishment, enforcement of legislation). Accountability is everybody's responsibility, in particular when there is potential for numerous conflicts of interest. Governments could include progress on AMR in their annual performance review. In Ghana, the civil society is able to set an agenda for government through an aide-mémoire each year.

Government must take overall responsibility and leadership

It is clear that stakeholders must take responsibility for their respective parts of the system that will deliver this new class of antibiotics to patients. However, the sentiment emerged that government must take overall responsibility and leadership. Universal healthcare would be an important first step for governments to strengthen the health system., but governments must also work to counter financial incentives that promote overuse.

There is also a need for a due diligence involving academics to answer the question "should this antibiotic be used at all?". A government led review panel could be responsible for this.

Clinicians requested that governments ensure that the whole population has access to smartphones, an increasingly powerful device for health information.

Financial implications

The financial implications were briefly discussed, particularly in the context of the recently adopted global action plan, which lacks clear financial planning. The AMR community knows that funding must be used to strengthen healthcare systems, but global funding does not yet prioritise this. Many funders see such actions as diluting impact, compared to targeted

intervention. There is a need for discussions on what should be funded, when, and by whom. Taxation can be effective in OECD countries, particularly of corporations, but there is little domestic flexibility in low-income countries like this. In the specific case of the fictive new antibiotic discussed, could the drug be too competitively priced?

Further reading

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We will not succeed without strengthening the world's weakest health systems.

Otto Cars,
Professor Uppsala University;
Senior Advisor and Founder,
ReAct



Martha Gyansa-Lutterodt,
Director of pharmaceutical services,
Ministry of Health, Ghana



Data speaks, and
speaks very loudly...

I think political commitment to
access can be achieved if politicians
and key stakeholders are engaged
right from the beginning.

Martha Gyansa-Lutterodt,
Director of pharmaceutical
services, Ministry of Health,
Ghana

Main take home messages

- Strategies of controlled distribution and use will need to be adapted to weak health systems and include both public and private providers, as well as consumers and NGOs. A holistic strengthening of health systems will be required to provide effective access while minimizing excess use.
- Ethical issues will need to be considered and addressed as interventions to promote rational drug use and give access to effective antimicrobials are constructed.
- Accountability is everybody's responsibility, in particular when there exists potential for many conflicts of interest.
- Governments must take overall responsibility and leadership.
- Country regulators to develop national policy platforms for Antimicrobial Resistance and rational use of drugs as part of the Universal Health Care agenda.
- Surveillance of antimicrobial use as well as resistance must be established.
- Inclusion of rapid diagnostic tests in clinical guidelines.
- Development of methods for accreditation and self-regulation for (private as well as public) providers.
- Governments must prepare plans for distribution systems for new and effective antibiotics.



Workshop B

New economic models addressing antibiotic resistance

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Workshop goal

The ambition of the workshop was to move from a macro abstract level, at which several economic models have been formulated so far, to a more micro concrete socio-economic level of antibiotic development, supply and use.

Background

The awareness of the challenges that antibiotic resistance puts on society is increasing, with the WHO action plan (2015) leading the way. However, there is still a lack of consensus on specific models, interventions and regulations outlining how to create economic conditions that facilitate the development and production of new drugs *while* guaranteeing equitable access and stewardship.

If conservation of and access to new antibiotics are to be achieved, the traditional innovation model does not work, i.e. covering the costs for development of new antibiotics by maximizing future sales or price can no longer be the standard financing model (Outterson et al., 2015, Cars, 2014, So et al., 2012). Instead, different kinds of ‘de-linked’ models are being discussed (see e.g. the O’Neill report 2015). These de-linked models are intended to separate the profitability of the drug from the volume of sales and propose that the cost of development and supply is covered by other arrangements than user maximization.

The workshop

The workshop was dedicated to discussions of what types of new economic models and structural changes in the antibiotics field that are necessary to simultaneously solve the two difficult equations:

1. Development of new antibiotics, which have to be used restrictively and whose R&D costs cannot be covered by maximizing sales and price.
2. Reduction of overuse of antibiotics in high- and middle-income countries and access to antibiotics in low-income countries.

The ambition of the workshop was to move from a macro abstract level, at which several economic models have been formulated so far, to a more micro concrete socio-economic level of antibiotic development, supply and use. To achieve this purpose, the workshop relied on the participants’ direct experiences from the following three areas:

- A. the health sector (in high-, middle- and low-income areas),
- B. industry (SME⁵ and big pharma) and,
- C. policy (national and transnational).

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⁴ R&D=Research and Development

⁵ SME=Small and medium size enterprises



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Thailand

Conclusions and suggestions

Two main discussion themes were proposed. The first focused on the *changes necessary in the supplying setting*. Such changes included all the a) activities and resources, b) stakeholders and c) financial arrangements required to guarantee the development/production/global distribution of new antibiotics, considering the broken innovation logic.

The second theme concerned the *changes necessary in the user setting* and included all the a) activities, b) stakeholders and c) financial arrangements on national and transnational levels required to tackle over-use of while also guaranteeing equitable access to antibiotics. On both these themes, the participants were asked to identify possibilities as well as obstacles to realizing the required changes.

Challenges and solutions related to the supply of new antibiotics

The challenges related to the supply of new antibiotics were seen as consisting of two different but related questions: *How to secure the development of new compounds* and *how to guarantee the scaling-up and production of new antibiotics*.

There are probably only three new drugs in the pipeline with the ability to attack the majority

of today's most resistant bacteria, as estimated among others in the O'Neill report (2015). There was a shared understanding among representatives for healthcare, industry and policy that there is an urgent need to *radically increase investments in basic research, i.e. research that has a long-term and open-ended approach*, above all in the academic, but also in the SME setting, in order to provide society with new compounds effective on Gram-positive and especially Gram-negative bacteria.

The challenge is not only that big pharma has reduced engagement in R&D related to the antibiotic field. Also within academia, research related to this field has lost the ability to attract talented researchers due to a lack of large research programs on this topic that can both secure funding and offer attractive career opportunities. Several of the participants did even use the word 'brain-drain' to illustrate the seriousness of the problem in the academic setting. Instead, a significant share of R&D related to antibiotics was seen as taking place in the SME setting, which was considered both an opportunity and an obstacle. In the long run, the innovative work taking place is dependent on input from academic research. Also, in order to contribute to a significant output in terms



of approved substances that are also scaled up, produced and globally marketed, connections must be maintained between the SME's and pharmaceutical firms, which were still seen as the main actors possessing the capacity necessary to carry out these important but resource-demanding activities.

A related obstacle was identified in the conflicting interests between academic researchers, who seek to publish, and the industry's need to retain secrecy and ensure intellectual property protection. Furthermore, compared to other diseases, AMR is relatively 'faceless', with the public unlikely to identify it as an important area of research. This makes attracting funding more difficult. This was also seen as an explanation



for the fact that AMR⁶ still has not attracted support in terms of the establishment of patient organizations engaged in fundraising for research.

The solution suggested was the establishment of significant long-term financing of *academic* antibiotic-related research in a varied and wide sense: from the discovery of new compounds, to prevention and diagnostics. In order to make the field attractive for a new generation of talented

researchers, very visible and long-term commitments must be made by public as well as private research funding bodies, on national as well as transnational levels.

A number of possible sources of increased research funding were suggested, such as a small tax on antibiotic products for the human and veterinary sector, a re-orientation of existing research funding, crowd-funding, and insurance-based funding. A related aspect suggested was the possibility to reduce time for approval, where the FDA and other regulatory agencies could play a key role. If a significant increase of investments in academic research would be achieved, a positive side-effect was identified in terms of increased input of solutions which SMEs could then develop further.

The challenge of getting pharmaceutical companies to engage in R&D, scaling-up and production was also considered. As one of the participants expressed it: "Big Pharma used to be the big driver of development – but not anymore." Big pharma's reduced activities in the antibiotic field was seen as reducing the capacity of these companies to receive and further develop compounds, due to quickly decreasing knowhow of scaling-up and producing potential antibiotic drug candidates.

The suggested solutions were that political and policy actors, on national as well as transnational levels, together with the healthcare sector, take the lead and utilize their joint power to mobilize funding. Not only for basic research, but also for testing, approval and scaling-up of new antibiotics. New reward systems and principles were considered as essential for development and production: these new systems should be varied in order to adequately compensate the efforts of

a variety of companies, from CROs⁷ and SMEs to pharmaceutical firms. The shared understanding was that neither politicians/policy nor the healthcare sector can passively wait for a new engagement from big pharma and most of the discussions centred on the need for different kinds of public initiatives and investments. If public investments in basic research and commercial R&D related to AMR increase, it could constitute an important signal to pharmaceutical firms to reengage in the field – and a support to the forces within large companies that fight for increased engagement in the antibiotic field.

⁶ AMR=Antimicrobial resistance

⁷ CRO=Contract Research Organizations

In Thailand we believe in the strategies of triangles that move the mountains. Tri-Angles. The three angles are power of wisdom; social power and political and policy power. We need to strengthen all three powers and link them to be a powerful triangle to move the mountain of antimicrobial resistance.

Dr Suwit Wibulpolprasert,
Senior advisor to the Minister of
Public Health, Thailand

One type of solution discussed entails having producers invest a certain percentage of their earnings to a global fund. Such a fund could be utilized by public bodies for different types of long-term innovation procurements, which could involve combinations of SMEs and pharmaceutical firms. The participants underlined that there are a lot of experiences made in relation to the development and production of vaccines and HIV drugs that could be utilized in the development of new types of ‘hybrid’ models, inspired by the GAVI Alliance and PEPFAR, (*President’s Emergency Plan for AIDS Relief*) but adapted to the antibiotic field. Political/policy bodies have a key role to play in this process: rules have to be set, e.g. concerning governance of intellectual property rights, on global and national levels.

Furthermore, governmental bodies could also reduce the burden of AMR by selecting suppliers of antibiotics based on an increased awareness of their production equipment and, above all, their degree of pollution. By choosing producer responsible for large effluents, for example some producers of generics, governmental bodies can be a part of the problem.

Challenges and solutions related to the use of antibiotics

The problem related to the use of antibiotics has two sides: overuse *and* underuse – and both are the result of weak healthcare systems. This understanding was shared by the participants, who also underlined the need for global governmental awareness of AMR and global governmental surveillance of the use of antibiotics. A particular challenge related to overuse/underuse is the great variety in usage patterns among low-, middle- and high-income countries, but also within countries. Misuse of antibiotics derives from among other things: selling over the counter, selling of counterfeited drugs, self-medication and lack of diagnostics – and can result in both overuse and underuse. Furthermore, although the use of antibiotics in the veterinary sectors was the focus of another workshop, the participants still wanted to underline the importance of including this area in attempts to create responsible user systems.

The suggested solutions have to be global but still possible to adapt to the challenges posted by specific national contexts. They have to include



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the use of all kinds of antibiotics, from new ones to generics. Solutions also have to include the handling of residuals from the use of antibiotics. The initiative has to come from the more affluent part of the world, but the design of the solutions needed has to emerge in interaction with representatives from low- and middle-income countries. This implies that the use of antibiotics has to be put at the top of the political agenda, on national as well as transnational levels. However, besides the political and policy bodies, with the regulators in the forefront, also the producing companies and distributing organisations have to be involved in the design of appropriate user systems.

The importance of both regulating and supporting healthcare providers was emphasized. Above all, physicians have to explain to patients when and how to use antibiotics – and when not to. It was further stressed that the doctors’ incomes cannot be based on the prescription of drugs. A related problem is that when a drug is in the trial stage, the potential effects of changes in



Don’t fall in love with ONE specific economic model in advance. If we do that, it will overshadow many other possible solutions. Don’t try to create ONE huge organization responsible for global use. We may end up with a “FIFA-syndrome”.

Alexandra Waluszewski,
Professor of Business studies,
Uppsala University

Main take home messages

- We need significant long-term financing of *academic* antibiotic-related research in a varied and wide sense: from the discovery of new compounds to prevention and diagnostics.
- Possible sources of increased research funding could be a small tax on antibiotic products for the human and veterinary sector, a re-orientation of existing research funding, crowd-funding, and insurance-based funding.
- Reduce time for approval, where the FDA and other regulatory agencies could play a key role.
- Political and policy actors, on national as well as transnational levels, should work together with the healthcare sector, take the lead and utilize their joint power to mobilize funding for basic research, for testing, approval and scaling up of new antibiotics.
 - New reward systems and principles for development and production must de-link
 - These new systems should be varied to adequately compensate the efforts of a variety of companies, from CROs and SMEs to pharmaceutical firms.
 - Doctors' incomes cannot be based on the prescription of drugs.
- Producers to invest a certain percentage of their earnings to a global fund. Such a fund could be utilized by public bodies for different types of long-term innovation procurements, which could involve combinations of SMEs and pharmaceutical firms.
- Regardless if the system is tax or insurance based, it has to be possible to adapt to the economic situation of different user contexts and countries.
- The establishment of systems for controlling the overuse has to be combined with the establishment of infrastructure for creating equitable access to drugs in regions with underuse.

the user dose on resistance are not being investigated. This complicated user question has to be addressed as part of the research on antibiotics but it also has to be on the agenda in the healthcare delivery systems. Hence, the establishment of a system that can affect both overuse and underuse has to go hand in hand with education in a wide sense.

The financing of a stewardship use system has to be made in a way that does not cause underuse, that is, lack of access to patients truly needing a treatment. This implies that, regardless if the system is tax or insurance based, it has to be possible to adapt to the economic situation of different user contexts and countries. Furthermore, several of the participants emphasized that the establishment of systems for controlling overuse has to be combined with the establishment of infrastructure for creating equitable access to drugs in regions with underuse.

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Workshop C

The environmental dimension of antibiotic resistance

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Workshop goal

The ambition of the workshop was to identify actions that need to be taken by various stakeholders in response to contamination of antibiotics and antibiotic-resistant bacteria into the environment from antibiotic production facilities, human usage and animal usage.

Background

The total exposure of bacteria to antibiotics is recognized as the main driver behind the development and spread of antibiotic resistance. The environment plays two key roles in this process: The first is as a vector for transmission of many human pathogens, including resistant bacteria. The second role is in the emergence of resistance in pathogens, since almost all classes of antibiotics are of natural origin and resistance mechanisms exist in the environment in both the natural producers and in bacteria that have been exposed to natural antibiotics before they were adopted into human medicine. The major clinical resistance mechanisms present today originate from environmental bacteria. They are therefore an important source for novel resistance factors that, under an increased selection pressure from antibiotic use and pollution, can be recruited into human pathogens through horizontal gene transfer.⁹

The situations where bacteria are exposed to medical antibiotics and hence a potential selection pressure can be divided into three categories: i) before clinical use – by exposure from contaminated waste water from production facilities, ii) during clinical use – by exposure to antibiotic dosing of humans and animals, and iii) after clinical use – by antibiotics excreted from

treated humans and animals or by incorrect disposal of residual medicines.

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 the production of these antibiotics and our waste.

The workshop

During the workshop the discussions focused on three areas, namely contamination of antibiotics and antibiotic-resistant bacteria to the environment from:

1. antibiotic production facilities,
2. human usage and
3. animal usage.

These three areas pose different risks for selection and spread of resistant bacteria and also require different actions to reduce the risks (Pruden et al, 2013). Specific recommendations listed are compiled from the workshop discussions.

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⁹ Horizontal gene transfer is the transfer of genes between organisms through other ways than reproduction.



Conclusions and suggestions

Contamination from antibiotic production facilities

Pharmaceutical production facilities represent defined point sources for environmental emissions, thereby providing opportunities for resource-efficient pollution control. Production sites for active pharmaceutical ingredients (APIs) are, on the other hand, spread throughout different regions of the world, with China and India being two of the most important suppliers. Emissions that take place far away from where products are sold and used provide special challenges for management. Strong price-pressure, lack of specified emission standards, lack of transparency together with a wide-spread ignorance or lack of awareness of the problem have been counterproductive with regard to actions to reduce pollution. *The main challenge is not primarily to find technical solutions, but to incentivize change.* To achieve this, attention is needed from a variety of stakeholders worldwide.

Actions needed

- Awareness of the environmental challenges connected with pharmaceutical production needs to increase among key stakeholders and the public through efficient information campaigns.

- Demand full transparency on where, by whom and under what environmental conditions pharmaceuticals are produced. This should be applicable to the entire production chain, down to and including the production of the active pharmaceutical ingredients and third parties dealing with waste streams.
- Include environmental emission criteria in public procurement policies for pharmaceuticals and lift those aspects above lowest possible price.
- Refine the generic substitution system present in many countries by including environmental pollution control during manufacturing when companies/products are competing for reimbursement.
- Within European legislation pertaining to pharmaceuticals and in the framework of good manufacturing practices (GMP), manufacturers of medicinal products should be required to comply with specific requirements limiting discharges and emissions of APIs into the water environment. This would force all companies importing active pharmaceutical ingredients in the EU and the US to apply the same level of emission control.
- Support research aimed at defining concentrations of antibiotics that are not promoting resistance development.



The global action plan mentions the environment in a few places, but it's not a large part of the plan. They raise the awareness issue, but there are a number of other points that could be done today.

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- Define discharge limits for antibiotics. Acceptable concentrations should not select for resistant bacteria, hence not promote the emergence and spread of resistance. Such discharge limits can be applied both when setting emission standards for individual factories, and as part of a revision of present Environmental Risk Assessment Guidelines (Ågerstrand et al, 2015).
- Require emission control of antibiotics and antibiotic-resistant bacteria from manufacturing sites.
- Microbial treatment should, when possible, be avoided for wastewater contaminated with high levels of antibiotics in order to reduce the risk of resistance promotion during the treatment process. When applicable, wastewater should be sterilized.
- Support research aimed at defining concentrations of antibiotics that are not promoting resistance development (same as above).
- Define environmental quality criteria for antibiotics that tend to be found in concentration at or near those that are expected to promote resistance. This can be applied within for example the European Water Framework Directive.
- Municipal sewage treatment plants need to be developed to reduce antibiotics as well as antibiotic resistant bacteria and resistance genes to safe levels. Implementation of advanced treatment options (ozonation, activated carbon filtration, thermophilic anaerobic sludge digestion) should be considered when either an unacceptable risk is identified or in order to follow the precautionary principle.
- Special measures should be considered to treat hospital wastewater before discharging it to communal wastewater treatment plants.
- Support research on wastewater treatment and the effects on the reduction of antibiotic residues and pathogens.

Contamination from human antibiotic use

Release of antibiotics from human consumption occurs because a large fraction of many drugs is excreted in active form through urine and faeces. Emission from human use is highly context dependent and the need for improved sanitation and sewage treatment in the developing world is a key component to preventing the spread of resistant pathogens. The WHO estimates that 2.6 billion people currently lack access to basic sanitation. This, by itself, results in direct releases of antibiotic resistant bacteria and pathogens into the environment and ambient waters.

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 and this may pose a risk when biological treatment is used (Gullberg et al, 2011). Wastewater treatment plants therefore represent a critical node for control of the global spread of antibiotic resistance.

Actions needed

- Improving sanitation and wastewater treatment in the developing world would be greatly beneficial for reducing both the spread of antibiotics as well as the spread of resistant and non-resistant pathogens. The effect on human health would be most noticeable in this part of the world and measures are urgently needed.

Contamination from animal antibiotic use

Agricultural/animal usage of antibiotics is more extensive than human usage globally, although the relative proportions vary substantially between countries. Overall, however, emission of antibiotics into the environment from agricultural use is substantial. Limiting the general use of antimicrobials, in particular critically important antimicrobials, is therefore the most efficient way of also reducing the release of such compounds into the environment. As with human waste, excreted antibiotics end up together with potential pathogens from agricultural settings. One challenge is the more diverse set of pathways for exposure from agricultural sources.

Actions needed

- Treatment of stored manure can reduce the amount of antimicrobials. Composting and storage are simple ways to eliminate some antibiotics.
- Removal of antibiotic resistant bacteria and resistance genes may prove more difficult since they are known to exist both in animals and in manure. Composting and biological treatment of manure can reduce the load but more research is needed.



It's important that even if you, as a stakeholder or regulator, may only be able to make a small difference, it's important to dare take the lead, and show that things are possible, even if your little action only makes a small difference.

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- Containment of manure and urine from animals is important to prevent uncontrolled spread to the environment and measures to control surface runoff and seeping from storages and protection against flooding problems should be implemented.
- Application of manure to arable soil should be done in ways that minimizes uncontrolled surface runoff.
- Monitoring the presence of antibiotics and antibiotic resistant bacteria in soil and setting international standard limits for contamination should be implemented.
- Aquaculture is at particular risk of releasing antibiotic contaminated water into the environment and should be regulated by special legislation.
- Legislation on waste management in many regions needs to be improved, including microbial risk assessments of manure storage and use of antibiotics in aquaculture.
- Thresholds for the levels of antimicrobials in soil that is considered safe should be determined and regulations for the control of emissions should be implemented, in the same way as for pesticides.
- Resistant pathogens in crops and food should be monitored more extensively to prevent the spread to humans.

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Main take home messages

Although antibiotic resistance is a global challenge, local action is necessary to reduce its spread via the environment. The definition of responsibility is a prerequisite for success and should be addressed country-wise and the various responsibilities should be clarified.

Contamination from antibiotic production facilities

- Demand full transparency on where, by whom and under what environmental conditions pharmaceuticals are produced.
- Define discharge limits for antibiotics and emission controls at manufacturing sites.
- Increase awareness of the environmental challenges connected with pharmaceutical production among key stakeholders and the public through efficient information campaigns. Include environmental emission criteria in public procurement policies for pharmaceuticals and lift those aspects above lowest possible price.
- Refine the generic substitution system present in many countries by including environmental pollution in the evaluation criteria when competing for reimbursement.
- Within the framework of good manufacturing practices (GMP), manufactures of medicinal products should be required to comply with specific requirements limiting discharges and emissions of APIs into the water environment.

Contamination from human antibiotic use

- Improve sanitation and wastewater treatment.
- Support research aimed at defining concentrations of antibiotics that are not promoting resistance development.
- Define environmental quality criteria for antibiotics that tend to be found in concentration at or near those that are expected to promote resistance.
- Municipal sewage treatment plants need to be developed to reduce antibiotics as well as antibiotic resistant bacteria and resistance genes to safe levels.
- Special measures should be considered to treat hospital wastewater.
- Support research on wastewater treatment and the effects on the reduction of antibiotic residues and pathogens.

Contamination from animal antibiotic use

- Legislation on waste management in many regions needs to be improved.
- Treatment of stored manure can reduce the amount of antimicrobials.
- Containment of manure and urine from animals is important to prevent uncontrolled spread to the environment and measures to control surface runoff and seeping.
- Application of manure to arable soil should be done in ways that minimizes uncontrolled surface runoff.
- Set international standard limits for antibiotics and antibiotic resistant bacteria in soil and develop strategies for monitoring them.
- Aquaculture should be regulated by special legislation.
- Resistant pathogens in crops and food should be monitored to prevent the spread to humans.



Workshop D

Research and innovation for new therapies

– collaborative models

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Peter Brandt, Associate professor, Department of Medicinal Chemistry, Uppsala University

Workshop goal

The ambition of the workshop was to discuss how to make best use of current funding and where new funding should be directed, given that there is an urgent need to find means to boost the development of new antibiotic drugs.

Background

Research on new antimicrobial therapies is associated with high risks and low to negligible profitability. This has led to a dramatic decline of antimicrobial drug discovery efforts conducted and sponsored by the pharmaceutical industry. As a result, the pipeline of new antimicrobials is starting to dry up.

A recent paper issued by the Review on Antimicrobial Resistance discusses this mismatch between global needs and the size and quality of the current pipeline.¹¹ The conclusion is that there is an urgent need to find means to boost the development of new antibiotic drugs. This view is shared by WHO in its Global action plan on antimicrobial resistance.¹² The Global action plan further states that there is a knowledge gap that needs to be filled in “basic research [. . .] to support the development of new treatments, diagnostic tools, vaccines”.

The workshop

Whereas the WHO Global action plan on antimicrobial resistance sets out as one of five objectives to “increase investment in new medicines, diagnostic tools, [and] vaccines”, the aim of this workshop was to discuss *how* to make best use of *current* funding and *where* new funding should be directed.

Some of the questions discussed were:

- In what sort of organisation will new antimicrobials, vaccines, and diagnostics be discovered?
- How can alternative innovation models for new antibiotics be created and supported?
- Who should develop the products?
- Who should select which projects will be sponsored?
- How should the current knowhow in antimicrobial drug discovery and development best be preserved and advanced?

While some of the questions failed to be resolved during the workshop, for others consensus was reached.

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¹¹ O’Neill, J. Securing new drugs for future generations: The pipeline of antibiotics. (May 2015)

¹² Ref to WHO Global action plan on antimicrobial resistance.

Conclusions and suggestions

A joint knowledge (data)base

Performing successful antimicrobial research requires bright scientists knowledgeable in the field with a long-term financial support. Currently, the knowledge base is diminishing as big pharma is moving its attention away from this field. Therefore, processes should be initiated to capture and secure knowledge from historical antimicrobial research performed by big pharma.¹³ A database of targets, projects, compounds, and related data will facilitate future antibiotic drug discovery. This action is urgent and needed before the knowhow of experienced researchers in the field is lost. The lessons learnt by the industry should be made public knowledge, searchable and accessible to all current and future stakeholders. Excitingly work is on-going in this direction within the IMI TRANSLOCATION project where this type of information is presently being captured.¹⁴

Improved communication and marketing

To attract the most brilliant academics to work with antimicrobial research and to interest young talent to the field, there is a need for improved communication, marketing and branding. We can learn from the successful work done in other disease areas, such as breast cancer, cystic fibrosis (CF), and amyotrophic lateral sclerosis (ALS). However, the patients affected by antimicrobial resistance are often elderly individuals who also suffer from other medical conditions and there is a lack of patient organisations that work to raise awareness about antimicrobial infections and that can advocate on behalf of those affected. Thus, to promote the field of antimicrobial research and to recruit capital and skilled scientists more resources need to be allocated to storytelling and communicating the challenges and needs as well as to make antibiotic drug discovery an exciting field to work in.

Reduce risk in early drug discovery

SMEs are playing an increasingly important role in antimicrobial research, not least by acting as a sanctuary for antimicrobial scientists who have left big pharma. To facilitate their work, it will be important to use current funding to reduce

the risks associated with early drug discovery for SMEs. One way to achieve this is through the use of public-private partnerships, such as is done by IMI/ENABLE.¹⁵ The goal of the ENABLE project is to progress at least one compound into preclinical and phase 1 clinical studies. This will not come close to meeting global needs, estimated in the O'Neill report¹⁶ to be on average 1.5 new licenced antibiotic therapies every year.

There are more public-private partnerships, as well as other initiatives, that target AMR, e.g. the BARDA BSA programme, the European Joint Programme Initiative on Antimicrobial Resistance (JPIAMR) and the IMI project Translocation. During the workshop, it was also suggested that Product Development Partnerships, like the Medicines for Malaria Venture and Drugs for Neglected Diseases initiative, should be used as models for establishing similar structures in the AMR field. Open Innovation models, like the OSDD model in India, could play an important role in this area.



Unless you have a sustained way to communicating to people, in a way that captures their attention, the danger is at this stage that political interests shift on to something else...

You focus on mortality, but how many people know someone whose life has been put at risk by a resistant infection? When you start to look at that, you start to get a larger population who have a stake in the outcome of this process.

Brendan Barnes,
Director IP and Global Health,
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¹³ For a good example of this, see for example Payne, D. J.; Gwynn, M. N.; Holmes, D. J.; Pompliano, D. L. *Nature Rev. Drug Disc.* 2007, 6, 29–40.

¹⁴ www.nd4bb.eu/index.php/myarticles/15-workpackage6n7-2

¹⁵ Rex, J. H. *Nature Reviews Microbiology* 2014, 12, 231–232.

¹⁶ The probability of success for an antibiotic compound entering a Phase I clinical trial is on average about 12%.



Broad and diverse funding

Historically, most breakthrough research in the antimicrobial field has been performed by academia, which might be explained by the curiosity inherent to academic research. Funding academic research can be done in various ways; either by supporting individually selected PIs or by funding centres of excellence or university incubators, which bring together top scientists from various fields for antimicrobial research to promote and support innovation. As it is not possible to know where breakthrough research will originate, it is recommended that the allocation of funds for academic research should have a broad and diverse approach. It was generally agreed that academia and SMEs are the most appropriate place for the discovery of new antimicrobial compounds. However, incorporating the expertise and experience of the pharmaceutical industry, to help with the allocation of funding and to avoid repeating work on failed targets and compound series, will be important to increase the probability of success.

Better defined therapeutic needs

To further stimulate innovation and development of new antimicrobials, vaccines and diagnostics, specific therapeutic needs and targets must be clearly defined, as to ensure that early discovery programmes are focused on developing the right therapies. No single target product profile (TPP) can cover all aspects of AMR. Thus, there is a need for multiple TPPs and thereby leading scientists in a similar vein as the original Longitude Prizes encouraged scientists to find methods for navigating the oceans.

References and further reading

O'Neill, J. Securing new drugs for future generations: The pipeline of antibiotics. (May 2015)

Payne, D. J.; Gwynn, M. N.; Holmes, D. J.; Pompliano, D. L. *Nature Rev. Drug Disc.* 2007, *6*, 29–40.

Rex, J. H. *Nature Reviews Microbiology* 2014, *12*, 231–232.

The Pew Charitable Trusts: Tracking the Pipeline of Antibiotics in Development: www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development

Main take home messages

- Attract the most brilliant academics to work with antibiotics.
 - Create a centre of excellence with input from industry.
 - Long term funding needed.
- One pot model for funding to focus and combine sources.
- Establish a database of unsuccessful drug discovery programs in AMR. Lessons learnt by the industry should be made public knowledge, searchable and accessible.
- To promote the field of antimicrobial research and to recruit capital and skilled scientists more resources need to be allocated to storytelling and communicating the challenges and needs as well as to make antibiotic drug discovery an exciting field to work in.
- To achieve this, long term funding is required to ensure stability and prosperity in the field.
- Draw upon experiences made by other Product Development Partnerships like the Medicines for Malaria Venture and Drugs for Neglected Diseases initiative.
- Allocation of funds for academic research should have a broad and diverse approach. It was generally agreed that academia and SMEs are the most appropriate place for the discovery of new antimicrobial compounds.
- Incorporate the expertise and experience of the pharmaceutical industry, to help with the allocation of funding and to avoid repeating work on failed targets and compound series, to increase the probability of success.
- Develop global but flexible Target Product Profiles (TPPs) to stimulate innovation and development of new antimicrobials, vaccines and diagnostics.



It's a global problem. It should be a global solution. At the same time, if you wait to have every member of the WHO on board, you wait a long time...

You have to start with the people that have some of the resources and the willing!

Brendan Barnes,
Director IP and Global Health,
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Workshop E

Improved diagnostics for public health and surveillance

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Johan Struwe, MD, PhD, Expert, Public Health Agency of Sweden

Workshop goal

Propose actions to improve the development, availability and uptake of diagnostic tests defining when/if antibiotics is needed; defining the right treatment for improved patient safety and as a tool to improve general surveillance of antibiotic resistance.

Background

Diagnostics play a crucial role for establishing what constitutes appropriate use of antibiotics, and for controlling development of resistance. We need diagnostics to provide patients and doctors with information to ensure correct treatment as a matter of patient safety, but also as tools to reduce unnecessary use of antibiotics. Rapid and simple diagnostics is one important tool to improve antibiotic stewardship policies. Diagnostics is also needed to aid mapping and resistance surveillance.

Even though its importance is known, the world still lacks technologies that can respond to needs and there are issues with uptake and use of available diagnostics. Prizes have been launched, e.g. the £10 million Longitude Prize or the €1 million prize announced by the European Commission, to spur the development of simple, rapid and low cost tests. However, little has been said about how to stimulate uptake and if we have the necessary infrastructure in place.

The workshop

The discussions in the workshop were built around six different topics, which together build the broad issue of the need for improved diagnostics. The workshop focused on diagnostics for human use, though the need for diagnostics in veterinary medicine is recognized. A group of experts with different experiences and perspectives was formed around each topic, to suggest the next steps to be taken to move their issue forward.

The six focus areas of the discussion were:

1. How do we secure financing of discovery and development of diagnostics for use in both high- and low-resource settings? What parts of the diagnostic discovery and development chain are most critical? Which needs could be met by the market forces, and when is support from governments or philanthropists necessary?
2. How do we meet the challenges of financing and building infrastructure to combine patient diagnostics with surveillance, in low-resource settings? The group was specifically invited to take into consideration how currently available tests can be better used with improved infrastructures, such as laboratories, trained personnel, collection of data.

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3. How can we set up a process to define so-called Target Product Profiles, TPPs, for diagnostics, *i.e.* defining the intent of products and under which conditions they must work? A sustainable process must account for changed prioritized alterations in resistance, and should address both high and low resource settings.
4. As more diagnostic tests are developed, we risk having a plethora of different methods, demanding different tools for taking samples, performing tests, evaluating the results, etc. How can we create a process towards an open diagnostics platform with common standards, transparent output data, thus minimizing the needs for different tools, processes and making sure that results from testing are comparable?
5. Assume we have a good working tool to support decisions for optimal treatment. How shall we promote access to and uptake of this tool in high-resource settings?
6. Assume we have a good working tool to support decisions for optimal treatment. How shall we promote access to and uptake of this tool in resource-poor settings?



Dr Manica Balassegaram, Executive Director, Médecins sans Frontières, Access Campaign

Conclusions and suggestions

All the six topic groups identified a need for improved awareness, *i.e.* increased communication efforts, on why the use of diagnostics is vital for patient safety and public health. Likewise, coordination of all efforts was a recurring theme in the propositions, not least of different financing mechanisms. It was emphasized that initiatives should be donor *supported*, not donor driven. Several groups raised the need for improved communications, to redefine diagnostics as a life-saving and cost-saving measure. The need to make the economic case was another recurring theme, also recognized in the WHO Global action plan.¹⁸

Finance development of new diagnostics

To finance development of new diagnostics, we need to *advocate* for and *pool* funds for the three stages of development: early stage research; development; and clinical trials. To support communication, we need data on the costs for

not employing diagnostics. Early stage funding could potentially come from existing initiatives like JPIAMR, IMI, Medical Research Councils etc. Crowd funding could potentially be utilized as a source for early stage funding, along the lines of the iCancer initiative.¹⁹ For the development stage, philanthropic and country development funds could be utilized, potentially creating a joint development fund for diagnostics. The European and Developing Countries Clinical Trials Partnership (EDCTP) was mentioned as a potential source of funding for clinical trials.

The group suggested that organisations like ReAct and the recently announced Uppsala Antibiotics Centre collaborate with WHO and others to raise awareness among the funding organizations and to enable the necessary pooling of resources. WHO could convene donors to create the necessary development funds.

¹⁸ WHO, Draft global action plan on antimicrobial resistance, A68/20, March 2015.

¹⁹ <http://icancer.org.uk/>



An important point raised was the benefit of showing the costs of *not* using diagnostics. The ongoing Review on Antimicrobial Resistance, chaired by Lord Jim O’Neill, will be publishing a paper on diagnostics in October, which will discuss the benefits of using diagnostics, the problems in the market, and possible incentives to encourage uptake.

Finally, the group suggested that pools of intellectual property (IP) could be created, and made available, from IP created for other purposes, for other regions or simply left in drawers, and today owned by diagnostics companies.

Infrastructure in low-resource settings

Before starting any new investment schemes, the workshop suggested that the WHO establish a framework for, and coordinate a mapping of, existing national capacities of infrastructure in low-resource settings. The ministries of health, supported by consultants if needed, should carry out the gap analyses. The newly announced Fleming Fund²⁰ could provide initial financing, but this will need to be matched by other countries to set up a Global fund for capacity building in low resource settings.

The analyses made will help select the best-suited centres to which training programs and

other capacity building initiatives should be concentrated. Already existing training programs can be the starting point for capacity building. The workshop proposed the creation of a new initiative, “Microbiologist without borders”, a voluntary group that could travel to help countries set up labs with assured quality.

The group suggested that the WHO should coordinate efforts of training and financing. This could be coordinated with the development of the global antimicrobial surveillance system in support of the global action plan against antimicrobial resistance, work which has already been initialised in a collaboration between WHO and the Public Health Agency of Sweden.

Develop the target product profiles

To develop the target product profiles, i.e. what kinds of diagnostics are most urgently needed, the workshop suggested a four-step process based on a bottom-up approach and the Delphi methodology:

1. Workshops at local and national levels to define needs, relevance, and conditions of work.
2. Collect results and discuss them in different fora, also using internet and social media, following Delphi methodology.
3. Global prioritization meeting.
4. Political endorsement of outcome.



Make it really clear from the innovation perspective, that if we want to talk about tackling antimicrobial resistance, we must have diagnostics and vaccines integrated into that picture.

Dr Manica Balassegaram,
Executive Director, Médecins
sans Frontières, Access Campaign

²⁰ www.wellcome.ac.uk/News/Media-office/Press-releases/2015/WTP058933.htm



The group suggested that the WHO should govern the process, but assigning management to suitable NGOs. The first workshops and prioritization process should involve clinicians, laboratories, healthcare workers, researchers, policy makers, donor organization, pharma and diagnostics industry, etc. This does not need to be a very costly venture, with costs estimated in the range of 1–2 M USD. Implementation ultimately needs to be the responsibility of health ministries, which is why political endorsement of the prioritization process is essential.

In addition, the group saw a need for an inventory of tests already in use, including investigating if these can be applied to different areas. Funding needed: A quick estimate by workshop participants put the cost for 3 pilot studies at 3 million USD. The WHO was urged to make sure that the on-going infrastructure and capacity building in the wake of the Ebola epidemic is used to strengthen healthcare systems and laboratory capacity in general, so that another vertical program is not created. This capacity could then also be utilized for ABR²¹ needs.

Open platform for diagnostics

The bottom-up approach, to understand needs, was also proposed by the group discussing the creation of an open platform for diagnostics. Such infrastructure would require governmental support. To argue for such platform, health economic analyses showing the economic value of diagnostics are needed. Likewise, the full support of the diagnostics industry is needed.

The WHO could create an “Essential diagnostics programme” to coordinate the technical

aspects. However, the operation of the platform will require a sustainable business model, involving additional actors.

Promote access to and uptake of diagnostics

To promote access to and uptake of diagnostics, many needs in high- and low-resource settings turned out to be rather similar. Both groups mentioned the need to ensure and implement clinical and economics evidence and to look at financial incentives for using diagnostics.

In high-resource settings, guidelines for usage should be issued and promoted by Health Technology Assessment agencies to ensure that all the benefits of using diagnostic tests are taken into account. In contexts where such agency or similar actors are not present, governments must ensure that policies and guidelines are developed and observed in these contexts.

In both settings, the issues of communication and education are important. Target groups are healthcare workers and patients. The groups proposed the WHO to develop general guidelines and content for communication. Format and channels must however be adapted to the local setting.

In both high and low resource settings, mechanisms for payment and reimbursement must be part of the overall policy. In high resource settings, the group suggested incentives directed to healthcare providers spurring the use of tests and to act on the outcome of the test. Incentives must be adapted to local mechanisms, but the workshop suggested that the WHO initiate a benchmark for increased transparency and as a way to stimulate increased use of test.

In low-resource settings, a decoupling of healthcare providers’ earnings from prescriptions issued was proposed. Instead, standard reimbursement packages were suggested, e.g. a “fever fee” involving the same amount regardless what the cause of the fever is, in line with the idea of universal health coverage.

Low-resource settings will likely need subsidies to secure access and use of diagnostics. Thus, this issue should also be part of funding packages discussed previously.



The public doesn’t really know how much guess-work is going on, and how great the needs for diagnostics are. We need the public engaged and seeing the need for diagnostics and funding!

Dr Anna Zorzet, Coordinator ReAct, Uppsala University

21 ABR=Antibiotic resistance

Further reading

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

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

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Main take home messages

- More knowledge is needed.
 - Adopt a bottom-up approach to gain knowledge needed for Target Product Profiles and open source platforms.
 - We need more health economic data to understand the economic gains that come from improved use of diagnostics.
 - Create an essential diagnostics program within WHO, to integrate the lessons learned from e.g. the Ebola crisis.
 - Map existing national capacities of infrastructure in low-resource settings. Such mapping, “checklists” will be part of WHO’s global antimicrobial resistance surveillance system.
- Funding for diagnostics is needed, but more urgently, funding must be pooled and well coordinated. The WHO or one or several of its member states can organize such funding conference.
 - Coordination of funding must have a holistic approach, including all stages from early research to securing access and use of diagnostics, as well as of infrastructure and capacity building.
 - Donors’ role is to support the case, not to drive it.
- Reimbursement mechanisms and other incentives must be developed to promote, not punish, the use of diagnostics.
 - Decouple healthcare providers’ earnings from prescriptions issued.
 - Develop incentives for healthcare providers to use tests and to act on the outcome of the test
 - Health technology agencies or health ministries, depending on setting, must develop policies and guidelines for use of diagnostics.
- We need communication campaigns to increase awareness of the need for diagnostics, and its role in controlling antibiotic resistance.
 - Target groups are patients, healthcare workers, donor organizations, health authorities, industry
 - WHO to develop general guidelines and content for communication. Format and channels must however be adapted to the local setting. NGO:s or other local champions to carry out campaign.



Workshop F

Antibiotics in animal production

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Workshop goal

The workshop's aim was to produce proposals for actions to achieve a reduction in the use of antibiotics in animal production, but not discourage prudent use of antibiotics, i.e. to treat sick animals when needed.

Global livestock production is increasing rapidly. Satisfying increasing and changing demands for animal food products, while protecting natural resources, constitutes a major challenge for agriculture today, particularly in low-income countries.

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. Some countries have also taken action to reduce the use of other antibiotic use in livestock. The Netherlands is a good example, where the therapeutic use of antibiotics in animal production has been halved thanks to broad interventions throughout the production chain.

It has been estimated that the global yearly antimicrobial consumption by livestock is over 60 000 tonnes. Additionally, the projected increase in the demand for animal food products may have a consequent impact on antibiotic use.

The workshop

In this workshop the focus lay on how to align stakeholders' efforts with the WHO Global action plan's clear strategy on antibiotics in animal production. This combined with the threat of increasing resistance among animal pathogens, which 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 workshop aims were to produce proposals for actions to achieve this goal, while also aiming for a global discontinuation of using antimicrobials for growth promotion and prophylaxis, but not discourage prudent use²³ of antimicrobials, i.e. to treat sick animals when needed.

²² Correspondence to be addressed to Professor Susanna Sternberg Lewerin, susanna.sternberg-lewerin@slu.se

²³ The concept "Prudent use" means no prophylactic, subtherapeutic or growth promoting use of antimicrobials. Therapeutic use of antimicrobials to treat infections is however part of prudent use.



Conclusions and suggestions

Education and awareness

A prerequisite for the realisation of many actions is education and awareness among consumers, farmers, policymakers and food industry.

There is insufficient easily available and easily applicable information for the public/consumers. The public needs to be aware of how and where antimicrobials are used in animal production to realise how it affects them. Generally, knowledge about animal production is low and this must be improved if changes are to be made.

Information campaigns via social media, with the support of consumer organisations were proposed. Why not recruit a famous chef as a role model/spokesperson? Authorities, scientists, veterinarians and farmers' organisations should provide the information. Consumers need to understand what is the real problem, not ask for "antibiotic-free" food. They must understand that this is mainly an issue of safe production, not safe food.

There must also be a feedback mechanism in place for monitoring data on use and resistance. Information and monitoring must be linked to political decisions, taking local aspects into account.

Moreover, the general public is not aware of the environmental effects caused by waste from animal production. This must be addressed.

Additionally, farmers need education to increase their awareness of antibiotic usage, antimicrobial resistance and how to properly manage waste from antibiotic use. Benchmarking is useful to make farmers aware of individual usage and what to do about it. Biosecurity is important to prevent infectious diseases and thus reduce the need for antimicrobial treatment of the animals, which is a point to be emphasised. Both veterinarians and farmers need to be educated in disease prevention.

Policymakers and authorities should provide some information, however, it must also come from farmers' organisations, farm advisors and veterinarians.

Disease prevention, Best practice

A crucial part of reducing the use of antibiotics in animal production is to reduce disease prevalence in livestock production. This can be achieved, e.g. through improved farm constructions that would lead to lower animal density, minimised injuries as well as reduced stress and aggressions. Lower animal density means more

space per animal and hence higher costs for housing but also reduced stress, less injuries and, for some diseases, interrupted disease transmission. Moreover, improved hygiene, nutrition and genetics will render antibiotic growth promoters (AGPs) and mass prophylactic use of antimicrobials obsolete.

Farm advisors and veterinarians must provide clear and justified advice to facilitate a change. Good examples should be used to convey messages (individual farmers, regions, countries with successful management systems that don't require routine use of antibiotics). It is necessary to define best production practices, which may vary somewhat depending on region and animal production system/sector. A standard for best practice must be manageable. It does not imply a total ban of antimicrobials, but rather prudent use, and disease prevention measures must be an integral part of it.

Procurement mechanisms

Pressure from consumers and politicians should be used to make retailers and the food industry address the issue. Market demands justify the introduction of production standards as regards use of antibiotics in animal production. Retailers must see the marketing opportunities for prudent use of antimicrobials in food production and make it easier for the consumers to choose food produced under best practice. Although there are large global differences, these mechanisms can be used and adapted to local contexts.

Retailers manage food safety issues by placing requirements on producers' production standards etc. Compliance is requested from farmers all over the world as it relates to multiple food safety issues. This issue could be handled via the same mechanisms, which have been used before for e.g. Fairtrade labelling that demonstrates that the mechanism of procurement from retailers is very powerful. The supplier has to provide documentation; this may be an added benefit as it is a driving force for data gathering.

GFSI (Global Food Safety Initiative) could be used to add the aspect of prudent antibiotic use in animal husbandry to existing guidelines. Although cultural differences make it difficult to find international agreement, with many countries wanting their own standards, a common international guidance document would be



Dr. Hetty van Beers-Schreurs, Director General, SDa Autoriteit Diergeenmiddelen, Netherlands

useful as minimum requirement, which can be complemented by country-specific aspects. A basic requirement that everyone has to fulfil would be desirable and provide a level playing field for producers. Rules and standards should be equal on the market. In addition, retailers could provide incentives to reduce antibiotic use e.g. via premium prices and a globally standardised label. Such a label would help consumers make informed choices, thus putting pressure on food producers via the retail industry.

Ultimately, it will be the consumers and farmers that will pay the costs. Farmers will benefit in the long run but in the short term many may go out of business. However, there are different pressures on different producers in different markets (local, regional, global). Moreover, large producers may adapt more easily, small producers will not need to, while medium size producers will incur high costs and may have difficulties adjusting.

Education of consumers and farmers will have to precede consumer demand so that retailers will be forced to act and farmers having to respond to their demands. When the procurement mechanism works, imposing a global ban on antimicrobial growth promoters will be the next natural step and, subsequently, other actions towards prudent use of antimicrobials.



I want to share with you today the key factors on why we were successful. The first one, one that has been mentioned several times today, is "awareness, awareness, awareness".

Dr. Hetty van Beers-Schreurs,
Director General,
SDa Autoriteit Diergeen-
middelen, Netherlands

(On how Netherlands gained political commitment for reducing use of antibiotics for animal production.)



New economic models

There must be incentives for veterinarians to be more restrictive in prescribing antibiotics. At the moment many depend on prescription and sales of antibiotics as part of their income. Farmer consortia, regulators, and veterinarians themselves must impose and apply new economic models for veterinary services.

Ultimately, the farmer will benefit by an economic model that does not rely on antibiotics. Therefore, farmer organisations should drive the process. Veterinarians need to communicate that a good advice is as valuable for the farmers as a prescription for drugs, perhaps even more valuable. Professional organisations (farmers, veterinarians) can build case studies (the good examples), but regional development of business models may also be needed. Policymakers can use taxes and subsidies to achieve good farming practice with prudent use of antibiotics.

Regulatory aspects

Regulations must be part of the global actions. A ban on antimicrobial growth promoters, restrictions on prophylactic use and herd treatments, prescription requirements, regulating profit from sales of antibiotics, and waste man-

agement rules are all part of the regulatory options that must be explored. An iterative process where demands are increased stepwise may be practical.

Improved farm constructions, with more space for the animals as well as mandatory health plans with requirement for regular veterinary visits could be part of animal health legislation. Demands for animal welfare, biosecurity and prudent use of antibiotics could be included in regulations as well as in trade agreements. A global ban on AGP should be negotiated within the WTO as a technical agreement. It is important that the issue of prudent use is included and settled in trade agreements. Food safety standards are not enough, trade agreements must achieve more.

In the absence of absolute consumer awareness, many drivers are needed, such as new legislation and enforced compliance with rules that are already in place. It is necessary to follow up to ensure that rules are followed. Moreover, there is a need for data on farm level, country level, different suppliers etc. for benchmarking. Data should include antibiotic usage as well as prevalence of resistance. Monitoring must be applied



For highly optimized systems, such as the ones we are approaching in Europe or in the US, the added value of antibiotics as growth promoters is probably very small or approaching that level.

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and goals for reduction set. This principle is applicable in all countries but could vary between countries, depending on context. This could prove costly for some countries and low-income countries will need support.

To control and regulate import and marketing of antibiotics is important. Aspects such as availability of antibiotics without veterinary prescription and profits from sales of antibiotics must be addressed within a regulatory framework. Cooperation between the different stakeholders and fair warning of upcoming legal changes will help in introducing such changes. A strategy for how to deal with potential production and income loss for farmers and other stakeholders must be in place and information on alternatives to general use of antibiotics must be available. Regulations on use of antibiotics should include ban of AGP and antibiotics available on prescription only.

Further reading

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Main take home messages

- Education and awareness campaigns are needed among consumers, farmers, policymakers and food industry for many of the other proposed actions to succeed.
 - On the supply side, farmers need education on antibiotics, antibiotic resistance and disease prevention. Examples of best practice must be conveyed to farmers.
 - On the demand side, consumers and retailers can drive change if better informed and educated.
- Retailers and the food industry should demand prudent use of antibiotics in animal production as part of the procurement mechanism.
- International guidelines for standards on how to label food produced with prudent use should be introduced to support consumers' informed choice.
- Veterinarians must start charging for advice and not only prescriptions or medicines.
- Policymakers must turn to regulatory means to achieve a new economic model for veterinary services.
- Prudent use of antibiotics should be part of trade agreements on animals and animal products, including a global ban on antibiotics for growth promotion.
- Governments must develop strategies to deal with the initial potential income loss among e.g. farmers following a ban on AGPs.
- Collection of data on antibiotic usage and antimicrobial resistance should be mandatory and used for benchmarking and all potential legislative tools should be explored.

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Uppsala Health Summit 2016

The role of diet for obesity and non-communicable diseases

Non-communicable diseases, NCD:s, are the largest killers globally, and its burden is expected to increase in all parts of the world, in high-income, middle-income and in low-income countries. Advancements in medicine have permitted us to handle, sometimes even cure, these NCD:s, which is positive but with increasing burden on healthcare and health-care systems.

Risk factors related to lifestyle, such as diet and physical activity, account for a large share of the increasing incidence of NCD:s. Obesity plays an important role for the development of diabetes, cardio-vascular diseases and some cancers.

Obesity, due to malnutrition and lack of physical activity, increase globally and is thus often referred to as "epidemic". According to the WHO data for 2014, 13 % of the world's population is obese, and 39 % of all adults were overweight. The prevalence of diabetes in sub-Saharan Africa is expected to increase by 100 % by 2035. These countries still suffer from the burden of infectious diseases, which causes a double pressure on frail health systems. But also in high-income countries, obesity lays a heavy burden on health systems.

At Uppsala Health Summit 2016, we will focus on the role played by diet, both as a cause to obesity but also as a means for changing the trend, on individual and on population levels, and discuss which are the next steps to take to reach the goals set up in international strategies.

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