



CHATHAM HOUSE

Chatham House, 10 St James's Square, London SW1Y 4LE

T: +44 (0)20 7957 5700 E: contact@chathamhouse.org

F: +44 (0)20 7957 5710 www.chathamhouse.org

Charity Registration Number: 208223

Global Health Security Summary

Antimicrobial Resistance: Incentivizing Change towards a Global Solution

3–4 October 2013

The views expressed in this document are the sole responsibility of the author(s) and do not necessarily reflect the view of Chatham House, its staff, associates or Council. Chatham House is independent and owes no allegiance to any government or to any political body. It does not take institutional positions on policy issues. This document is issued on the understanding that if any extract is used, the author(s)/ speaker(s) and Chatham House should be credited, preferably with the date of the publication or details of the event. Where this document refers to or reports statements made by speakers at an event every effort has been made to provide a fair representation of their views and opinions, but the ultimate responsibility for accuracy lies with this document's author(s). The published text of speeches and presentations may differ from delivery.

INTRODUCTION

This conference was held at Chatham House to initiate a series of meetings organized by the Centre on Global Health Security to address the problem of antimicrobial resistance. The conference and series of roundtables aim to address, in particular, the following key issues:

- What new efforts by governments and stakeholders in the developing and developed world are needed for global antimicrobial conservation? What obstacles constrain effective action? How can they be addressed?
- What are the most efficient ways of stimulating new drug development for long-term sustainability? What has been tried? What is most likely to work? What does this mean for government policies?
- How do we address antibiotic use in the food and agriculture sector (including fisheries)? How do we promote cross-sectoral collaboration? What are the obstacles? How can they be overcome?

The underlying purpose of these consultations is to influence actions by governments and policy-makers in global and multilateral fora such as the World Health Organization (WHO), the World Organization for Animal Health (OIE), the Food and Agriculture Organization (FAO) and the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR), and in national governments (e.g. through policies to promote long-term sustainability). Possible outcomes include contributing to the content of agreements in the WHO, the OIE, the FAO and other organizations on global actions to combat resistance and recommendations to national governments on stewardship and incentives for drug development.

The conference, which brought together a broad range of senior participants from industry, regulators, research organizations and civil society, was organized to provide the foundation for the roundtables by presenting an overview of the problem and proposed solutions, and exploring key issues to be selected for discussion in the roundtables. These included:

- Maintaining antibiotic effectiveness,
- Stimulating drug development and innovation and the role of diagnostic tests and vaccines,
- Use of antibiotics in food and agriculture, and
- Fostering global commitment to combat the problem.

Most of the discussion was held under the Chatham House Rule, which states that when a meeting, or part thereof, is held under the Chatham House Rule, participants are free to use the information received, but neither the identity nor the affiliation of the speaker(s), nor that of any other participant, may be revealed.

KEYNOTE OVERVIEW

UK Chief Medical Officer Professor Dame Sally Davies opened the conference by outlining the key issues around tackling antibiotic resistance. She drew parallels between antibiotic resistance and climate change, in terms of the apparent reluctance to face the threat and the assumption that the medical community should prove that use of antibiotics in animals is harmful to human health, rather than the veterinary and livestock community having to prove their need for antibiotics.

She noted that antimicrobial resistance kills an estimated 25,000 people a year in Europe – about the same death toll as for traffic accidents – and one child every five minutes in Southeast Asia. Global travel, and the ability of antibiotic-resistant bacteria to transcend national borders, makes it a global responsibility. She argued that political commitment to addressing the problem has been insufficient because next-line antibiotics have thus far been available. However, with the pipeline drying up, the problem has now become urgent and in a step that takes the issue more seriously, the UK government is moving to add antimicrobial resistance to the its risk register, next to terrorism, pandemic flu and climate change.

She outlined a multi-pronged solution that includes stewardship of current antibiotics through better infection control and antibiotic conservation, development of effective diagnostic tests, global surveillance of antibiotic use and resistance in people and animals, intergovernmental cooperation, research to overcome scientific challenges in drug development, and incentives for industry to replenish the antibiotic pipeline. She declared she is on a mission to raise awareness of the urgency of the problem in order to bring it to a tipping point of action.

In discussion, the following issues were raised.

- As with climate change, the rate of change and the magnitude of the effect on patients is unknown, and some territories will be more adversely affected and more quickly than others. However, unlike climate change, antimicrobial resistance science is undisputed, which should make it easier to make the case.
- It may make sense to withhold some new antibiotics from the general market to reserve them for emergency use only, in which case new funding mechanisms will need to be found so that pharmaceutical company revenues are not dependent on sales volume.
- Efforts need to be made to step up developing country engagement in the issue. Problems that need to be addressed in such countries include irrational use by patients, overprescribing by doctors, companies overselling to doctors and heavy use of antibiotics in animal feed for growth promotion. However, Dame Sally said she was not in favour of imposing plans on developing countries, but that experts from those countries should be encouraged to develop their own plans, with appropriate support.
- The fact that veterinarians make money from selling antibiotics is an issue that needs addressing.

PROPOSED SIX-POINT OVERALL PLAN FOR ADDRESSING THE PROBLEM

Before the conference discussions moved onto specific aspects of the challenge, a six-point plan for what needs to be done to tackle antimicrobial resistance was presented. The presenter acknowledged the 2001 WHO Global Strategy for Containment of Antimicrobial Resistance as one of the best initiatives to date for promoting policy for addressing the issue, but argued that a major flaw was that it listed too many things for countries to do and that lessons can be learned from other global health initiatives that propose a few universally acceptable essential actions. The six elements of an effective country response to the antimicrobial resistance problem were outlined as follows.

1. Reduce the need for antibiotics by improving public health through measures such as immunization, infection control and sanitation

The presenter noted that antibiotics are being introduced into developing countries where clean water, sanitation, immunization and the other basic public health measures that reduce the need for antibiotics are often not in place. Therefore the burden of infection is higher. Essentially, antibiotics are being used as a substitute for hygiene and other measures that should be in place, which was not the burden placed on them when they were introduced in developed countries. It is clear that public health needs to be improved and antibiotics cannot be relied upon to be the primary response to infections. This has been recognized and steps are being taken, but the pace of change is too slow.

2. Phase out antibiotic use for growth promotion in agriculture

To illustrate the scale of the problem, the presenter cited a study in Kenya that found that 82% of farmers administered drugs without the input of veterinary personnel. It was noted that when the use of antibiotics for livestock growth promotion was phased out in Sweden almost 28 years ago, most farms did not have a problem complying, and the 3% that did were those without modern practices and hygiene. The European Union has taken the lead on this issue while efforts in the United States, for example, have lagged. Meanwhile, in developing countries such as India, Kenya, South Africa and Vietnam, agricultural use of antibiotics is rising rapidly, as a result of both greater demand for meat and increased availability of antibiotics. The presenter argued that if steps are not taken now to curtail this, the political pressure opposing it in five or 10 years time, when there will be a large constituency of people who believe agricultural use is necessary, is likely to be insurmountable.

3. Change incentives for prescribing antibiotics and non-prescription sales

It is not clear that physicians in many countries are acting as adequate gatekeepers for antibiotics because they are driven by other motives, such as payment linked to antibiotic prescriptions, fear of malpractice suits, or retention of patients. Rising income in developing countries is a major pressure increasing antibiotic consumption. Regulatory capacity to enforce rules regarding the over-the-counter sales of antibiotics is weak in several countries. Conservation efforts must not block access to life-saving drugs and it must be remembered that although resistance is an important cause of death in some populations, lack of access to antibiotics still kills more people in developing countries than resistance does.

4. Invest in resistance surveillance, for clinical decision-making and for policy

Several new initiatives are aimed at improving surveillance of antibiotic use and resistance. Policy-makers need aggregate-level information on antibiotic use, resistance and trends in order to make

decisions. To get policy-makers' attention, it is not enough solely to discuss levels of resistance affecting specific individual antibiotics. Lessons can be learned from the simplicity of the messaging around this issue in tuberculosis and HIV.

5. Invest in new vaccines, drugs, and diagnostics

Thought needs to be given to whether all new drugs should be made affordable for everyone, because if the question of how new drugs should be used has not been addressed, investing in new drug development alone will not solve the problem. Diagnostic tests are also needed, and vaccines have significant potential to reduce the need for antibiotics.

6. Ensure political commitment to the threat of resistance

Political commitment is important because it drives decision-makers to take action. Steps have been taken in this area, with several national and regional declarations, but political commitment and coordination at the global level is inadequate. There needs to be global coordination of the response, global surveillance and global agreement of what countries will do progressively, given that, like climate change, this is a problem where antibiotic resistance that emerges in one country has consequences for others.

MAINTAINING ANTIBIOTIC EFFECTIVENESS

This discussion focused on what can be done to maintain antibiotic effectiveness, what particular issues developing countries face, what strategies are successful for controlling the spread of resistant infections and how those can be applied in developing countries, and what the barriers to behaviour change are. It was reiterated that a careful balance has to be struck between controlling antibiotic use in order to preserve drug effectiveness and ensuring access for those who need it. But it was argued that responsible access to medicines, especially antibiotics, must be encouraged. There is a need for local champions, as well as international champions, to ensure that all involved parties are engaged.

The 2001 WHO global strategy for containment of antimicrobial resistance was considered to offer good guidance for maintaining antibiotic effectiveness, but it was agreed that its uptake was hampered by it being published on the same day as the 9/11 terrorist bombings. More recently, World Health Day in 2011 was devoted to the issue, with the publication of a six-point policy package for countries. The points were as follows:

- Develop and implement a comprehensive, financed national plan;
- Strengthen surveillance and laboratory capacity;
- Ensure uninterrupted access to essential medicines of assured quality;
- Regulate and promote rational use of medicines;
- Enhance infection prevention and control; and
- Foster innovation and research and development for new tools.

It was reported that an on-going WHO study is finding that within countries, there is a lack of coordination within and beyond the health sector, there is a lack of surveillance capacity, particularly in low- and middle-income countries, (20% of which have a national action plan, compared with half of high-income countries), and that there is a lack of information to guide strategies. The global magnitude of the antibiotic resistance remains unknown, as does the impact in terms of illness, death and cost. However, WHO research has shown some evidence that policy implementation does result in more rational antibiotic use.

Developing country challenges

The particular issues developing countries face were also outlined. For instance, in Ghana, monitoring of use of antibiotics is weak, as is recording of treatment failures, regulation, the control of counterfeit medicines, and the linking of laboratory findings with prescribing. Capacity is being built to provide evidence for decision-making, but policy is not translating into action and there is irrational prescribing and a weak gatekeeper system. Funding would be necessary to bolster surveillance and drug use monitoring.

In another example, it was reported that in Malaysia in private clinics and hospitals, doctors are prescribing powerful antibiotics to women with menstrual pain because incentives such as drug company payments, gifts and travel motivate them to increase prescriptions.

The development of and rationale behind the Chennai Declaration, a roadmap for tackling antimicrobial resistance drafted by the medical societies in India in 2012, was outlined. In response to controversy surrounding government action in the wake of the emergence of the NDM-1 antibiotic-resistant enzyme in India, the declaration took a stepwise approach to tackling the problem. In recognition that it is not feasible to control over-the-counter sales of all antibiotics, the declaration produced a list of 24 second- and third-line antibiotics and 11 tuberculosis drugs that can now only be purchased with a prescription. The Indian government took up the list and enacted a new rule bringing those drugs listed under prescription-only from 1 March 2014. Usage will be monitored. The Chennai Declaration was praised as a major step in tackling antibiotic resistance in the developing world.

Changing prescribing behaviour

Human behaviour was considered to have a significant influence on the effectiveness of antibiotics, and it was argued that social scientists might need to be recruited to help develop strategies for reducing patient demand and overcoming resistance to change.

One strategy suggested for moderating antibiotic use was to reserve certain last-resort antibiotics solely for human medicine. This has not been applied in any country and it is unclear what the criteria would be for prioritizing which antimicrobials should never be used in animals. It was further suggested that consideration should be given to whether all antibiotics, whether used in animals or humans, should come under prescription control globally, as a step toward responsible use, given that about 50% of antibiotics used globally are obtained without a prescription.

However, prescribing behaviour was considered to have a major influence on antibiotic effectiveness. It was noted that this is influenced by many factors, and that this means policy is not everything. One important factor is that in hospital acute care there is a culture of non-interference with colleagues' prescribing. It is senior members of the hospital team that influence this, so it is important to include them, rather than solely technical experts such as microbiologists, infectious disease specialists and pharmacists, on review boards and stewardship groups. It was suggested that to foster wider ownership of the issue in hospitals an even broader stakeholder group be recruited, such as haematologists, surgeons and oncologists.

Prescribing behaviour could also be improved by framing antibiotic stewardship as an aspect of quality of care and patient safety and by engaging specifically with the wider healthcare workforce, including nurses. Incentives could be developed to link adherence to guidelines to medical education, performance appraisals and merit awards, perhaps even parking spaces. Mobile phone apps for prescribers – m-health – also have the potential to influence prescribing behaviour.

Several participants favoured delinking financial gain for doctors and hospitals from prescribing antibiotics. Strategies for influencing prescribing behaviour would need to be country-specific because the incentives differ. For instance, in China the best strategy may be to address how hospitals are reimbursed, given that a study suggested that one quarter of hospital revenues come from antibiotic sales, while in India it may be better to focus on how doctors are paid, and in the United States emphasis may need to be shifted from reimbursing antibiotics prescriptions to reimbursing investments in infection control measures.

Surveillance

Finally, surveillance was widely considered to be a cornerstone of any plan for maintaining antibiotic effectiveness and it was agreed that this is weak in many countries. It was noted that several countries would not be able to establish adequate surveillance and monitoring without external support, and that even in countries that have surveillance systems, there is no consistency in how to measure resistance and in what is measured, or how to interpret results. Surveillance data was considered important not only for taking the guesswork out of current prescribing, but also for guiding the use of any new drugs and for convincing political leaders and funders to invest in money in the problem. The Danish Denmap surveillance system, which publishes annual reports on the use of antibiotics in animals, humans, and the extent of resistance in animals, food and humans, was heralded as an example to be followed.

However, beyond national surveillance, the development of a global surveillance system was also considered important. One presenter proposed the creation of a global database of the genetic code of all microorganisms, dubbed the Global Microbial Identifier. This would enable real-time surveillance of the spread of antibiotic resistant bacteria across the globe and users to rapidly identify the organism, discover precisely where it has been found before, and determine how to treat the infection based on the level of documented resistance to certain antibiotics. There are at least three significant regional databases that could serve as a starting point.

STIMULATING DRUG DEVELOPMENT: PIPELINES AND INCENTIVES

Presentations and discussion focused on the nature of the shortfall in the pipeline of new drugs, how market models for making new antibiotics can be improved, what new mechanisms have been tried and what other approaches should be explored.

It was agreed that the antibiotic pipeline is drying up and that the two major barriers to reinvigorating it are scientific challenges and the lack of financial incentives for the pharmaceutical industry. It was noted that within Europe, statistics indicate there may have been a slight improvement in the pipeline in the last five years; some new companies have entered the market, but some major players have withdrawn. Several participants argued that the success of HIV/AIDS innovation and political mobilization sets a precedent for thinking differently in anti-infectives.

New scientific approaches

Drug developers reported experiencing challenges with the current scientific paradigm of developing small molecules to kill bacteria and said new scientific approaches are needed. Some examples of what is being tried were discussed. One presenter described experience with development of a tuberculosis drug that targets a new mechanism of action, to demonstrate that new types of drugs can be developed, regulatory agencies can support an accelerated process, and the drug can make a difference to patients. Another presenter outlined new approaches to treating bacterial infections being explored in Europe, particularly by small and medium-sized companies. These approaches include bacteriophages, nanomedicine, new delivery systems and drugs that modulate the immune system. Several participants noted that the discovery of biomarkers and the development of diagnostic tests are important for new antibiotic development.

It was contended that the potential of antibiotic-producing microbes and other natural products has not been exhausted, although much of the expertise needed to screen such compounds and process them has probably been lost.

Several participants said making the regulatory approval process faster, smoother and more predictable would help. It was contended that most of the important antibiotics now in use would not have been approved in the current regulatory climate. Antibiotics are more likely to fail to gain European regulatory approval than other types of drugs are, often because of issues with the study design, but developers are increasingly working with regulatory agencies in advance of their applications and that this is expected to lead to a higher success rate for marketing approval. It was

noted that another step regulatory agencies can take is to align their principles, in order to reduce the number of clinical trials necessary for approval globally and to overcome other hurdles. Steps toward regulatory convergence are being taken, with the US Food and Drug Administration and the European Medicines Agency in ongoing dialogue aimed at harmonizing recommendations and requirements for antibiotics.

Incentives for antibiotic development

It was agreed that another major challenge in antibiotic development is how developers can make a financial return when the new drug they produce is used frugally. It was contended that unless overall reimbursement for the sector increases by billions, and conservation is simultaneously introduced, progress would be difficult.

One of the significant challenges is that better antibiotic stewardship depresses pharmaceutical sales, essentially fighting against the current drug development business model, making the development of new antibiotics relatively unattractive to companies. It was agreed that incentives for innovation are needed for academia, biotechnology and pharmaceutical companies.

Public-private partnerships were proposed as part of the solution to the financial return challenge. One presenter described a new strategy being considered that entails a limited development package where the drug is labelled and poised for use only as a last resort, when there is an unmet medical need. This approach would only be feasible in the context of a public-private partnership, and would allow changes in resistance and epidemiology to dictate the use of the drug.

It was reported that the most recent call for proposals under the Innovative Medicines Initiative New Drugs for Bad Bugs programme sought proposals for a new sustainable commercial model for antibiotic development.

Many participants mentioned a need to disconnect return on investment and profit from the volume of antibiotic sales. A proposal for severing the link between antibiotic revenues and sales volume was outlined as a way to overcome the problem. Four principles of 'delinkage', explored in a recent study of potential incentives, were described. These include disconnecting revenues from sales volumes, increasing total company revenues from antibiotics, coordinating drug development efforts with conservation measures, and ensuring that patients can gain access to the new drugs, regardless of their ability to pay. The study concluded that given that there is a large gap between the value to pharmaceutical companies in producing new antibiotics and the value to society in having new antibiotics available, society should be investing in the sector. It was further contended that coordination between public funders and regulators and other relevant bodies could make the field more predictable, and therefore more affordable.

The study also concluded that patent extensions would have a small effect, while changing the cost of capital would have a significant effect, as would speeding up regulatory approval. Drug development prize money would have to be substantial – hundreds of millions, or billions, of dollars – in order to act as an effective incentive. The design of incentives, and the point at which they are applied during the drug development process, makes a difference.

Other ideas suggested for separating revenues from sales include:

- Transferable exclusivity, where exclusive marketing rights can be transferred from a new antibiotic to a new drug of another type, and
- Antibiotics pricing based on GDP, so that patients in richer countries pay more than those in poorer countries.

Outlook for drug development

One presenter expressed optimism over steps being taken in this area. Some governments are seriously engaged with the problem, but more governments need to take the issue up. It could well

need public funding, and perhaps legislation, and that is unlikely to be politically palatable without public understanding of the threat that antibiotic resistance poses. Companies engaged in this area are open to working differently, but not many companies are engaged; there is much work to be done in making antibiotic development a more attractive area for investment for biotechnology firms, pharmaceutical companies and academics. Focusing on the small number of companies already engaged is not going to be enough.

Another presenter argued that the pharmaceutical industry needs more predictability in the antibiotic market. One participant proposed that the current pipeline stimulation model is not necessarily broken, and that consideration must be given to the fact that efforts to fight antimicrobial resistance intensified only a few years ago and it takes time for the pharmaceutical industry to react. However, the interests of companies, investors and public health need to be aligned through practical measures that will address flaws in the current market and bring new products in the next few years. Current efforts should be intensified and lessons learned from other markets. For instance, it was noted that lessons can be learned from the response to HIV/AIDS, where regulatory review was accelerated, prices for the drugs were high, a biomarker was discovered and rapidly approved and 20 new drugs were produced in 20 years, extending the life of patients by about 30 to 40 years. Similar success with antibiotics could be possible if incentives and organizations are aligned.

One presenter concluded that the industry will have to move step-wise, with the first step being to pool what it has, use the Innovative Medicines Initiative, and engage with regulatory agencies and payers. The level of activity would need to be stepped up beyond that, to bring back product ideas that were dropped long ago and significant expand the number of companies active in the field.

THE ROLE OF DIAGNOSTIC TESTS AND VACCINES

Diagnostic tests

The development of diagnostic tests was considered important for addressing antibiotic resistance. It was agreed that diagnostic tests, particularly rapid ones, would reduce the inappropriate use of antibiotics, which may be given on guesswork to a patient with a viral rather than bacterial infection in the absence of a diagnostic test.

They were also considered important for conducting clinical trials. Patients are often enrolled in trials before investigators identify the organism causing the disease. Greater diagnostic certainty would allow researchers to analyse the organism and test its susceptibility to specific drugs, and help them select the right patients for their trials, which would enable studies to be smaller, saving money and time.

Recent advances in diagnostic test development, challenges faced in introducing them, and current efforts to overcome barriers to development, market entry and deployment were outlined.

It was argued that the ideal diagnostic test is cheap, accurate, fast and simple. However, it is not possible to achieve all of those at the same time, so trade-offs are necessary.

Progress has been made in developing tests that are simple and fast, for instance for HIV and malaria. The Grand Challenges Canada initiative is investigating several promising technologies, including the possibility of generic detection platforms that could be used with a menu of tests from different companies, as well as basic tests for use at lower levels of the health system that would simply distinguish between bacteria and viruses, and whether gram-positive or -negative if bacteria. Moves are underway to harmonize approval of diagnostic tests across countries. Other gaps include discovery of diagnostic biomarkers and research to improve the processing of sputum samples. It was argued that a new model of public-private sector collaboration is needed and that development prizes, which so far have not been successful in producing products, need reassessment.

Vaccines

It was also agreed that vaccines can contribute to the fight against antibiotic resistance. The following points were made on this topic.

- Existing vaccines prevent antibiotic resistance and reduce the circulation of resistant strains. For instance, after the introduction of the pneumococcus vaccine in the United States in 2000, the incidence of antibiotic-resistant pneumococci dropped 81% in infants, who were vaccinated, and by 41% in the elderly, who were not vaccinated.
- It is possible today to develop vaccines against most antibiotic-resistant bacteria. Technology advances over the last 30 years, such as combining genomics with the use of novel adjuvants, have made it possible to produce vaccines that were previously impossible. It was proposed that combining such technologies would enable the development of vaccines against most antibiotic-resistant bacteria.
- Bacterial resistance to vaccines has not been reported.

USE IN FOOD AND AGRICULTURE

Discussions on this issue focused on to what extent the use of antibiotics in agriculture contributes to development of resistance in humans, what has been done to reduce the use of antibiotics in animals and what new approaches should be tried.

The presenter giving an overview of the topic noted that demand for animal protein is expected to increase more than 50% before 2020 as incomes continue to rise in emerging economies. Intensification of animal production is considered inevitable and this will probably mean agricultural use of antibiotics will increase. Antibiotics are essential for human and animal health, as well as for food security and the human health, livestock and even plant sectors have a shared responsibility to minimise the development of antimicrobial resistance.

A second presenter outlined the evidence on antibiotic use in food animals in the United States and its effect on human health, noting that in 2011, more than 80% of antibiotics used in the country were given to livestock, and that 60% of those drugs are important for treating infections in humans. It is estimated that use in animals is six times higher in the United States than it is in Denmark, and that about 90% of the time, the antibiotics are added to feed or drinking water in sub-therapeutic doses without a prescription. The speaker cited a US FDA study that found 36 years ago that the use of penicillins and tetracyclines in animals posed a threat to human health. Since then, approval has not been withdrawn for the use of antibiotics in animal feed, but a recently proposed veterinary feed directive would place the use of medically important antibiotics under closer veterinary supervision and limit approved uses. A second initiative in the United States, known as Draft Guidance 213, would provide a framework for the pharmaceutical industry to voluntarily gradually cease sales of medically important antibiotics for livestock growth promotion and require veterinary oversight of the therapeutic use of antibiotics in animals.

Another presenter outlined the application of antibiotics control to the US pork production industry. Guidelines for animal care and antibiotic use have been incorporated into the US Pork Quality Assurance Program and regulators are starting to introduce third-party audits of adherence to the guidelines, which are voluntary. The guidelines include having a veterinarian giving input as the basis for all medication decision-making, regardless of what channel the antimicrobials or other animal health products may be purchased through; appropriate clinical diagnosis; limiting treatment; and using antibiotics that are important for treating resistant infections in either humans or animals only after careful review and justification.

Several challenges to addressing the use of antibiotics in animals, and current efforts to tackle them, were identified and discussed. Discussion focused on the following.

Surveillance: It was widely agreed that surveillance of the use of antibiotics and monitoring of resistance was critically important to the rational use of antibiotics in animals and for combatting resistance. An international survey of 178 countries showed that only 27% of countries have a

surveillance system that collects data on the use of antibiotics in animals, which means there is a need for countries to build capacity in surveillance of the use of antibiotics and the scale of resistance.

It was argued that statistics should be reported and that reporting should be broken down according to whether antibiotics are being added to feed or drinking water, or injected, and by animal type. Such statistics standards should be propagated globally.

More controlled use: There is no control of the use of antimicrobial drugs in more than 120 countries, where antibiotics circulate as an everyday commodity and they are purchased and used without veterinary supervision. The availability of counterfeit or falsified antibiotics is a significant problem, and they are increasingly being traded internationally. Addressing Internet sales of antibiotics was considered a priority.

It was also noted that more controlled use could be facilitated if veterinary education were to address the issue of antimicrobial resistance. International agencies have produced guideline standards for veterinary curricula.

One participant argued that Africa, much of which is experiencing rapid economic growth, can leapfrog over other countries by learning from the mistakes other countries made and developing from the outset a smarter system for using antibiotics. It was contended that this could be done with scarce resources if planned correctly.

A few participants warned that care should be taken in addressing use of antibiotics in food production so as to avoid unintended consequences, such as the replacement of antibiotics with heavy metals. They urged that both risks and benefits of reducing the use of specific antibiotics be considered. For instance, there is some evidence that if animals are allowed to get sick and recover with lesions, their carcasses are more likely to be contaminated with campylobacter and salmonella than those of animals that have never been sick. Consideration should be given to whether there is a place for targeted brief use of antimicrobials to prevent infections in animals, to avert the need to treat large herds with larger amounts of antibiotics for a longer period of time to cure illness.

One presenter also questioned whether all livestock production systems are at equal risk of selection and dissemination of antimicrobial resistance, arguing that resistance is most likely to occur in systems that are in transition from simple to highly sophisticated intensive operations, which tend to manage to maintain animal health without heavy use of antibiotics because they have more rigorous infection control measures and vaccination programmes in place.

It was also argued that antibiotic resistance of most concern to public health is associated with therapeutic use of antibiotics, rather than to preventive use in animal feed, and that care should be taken to target interventions precisely so that they address the specific use patterns that are associated with the greatest harm.

Antibiotic sales linked to veterinarians' income: The fact that veterinarians' income is linked to sales of antibiotics was considered a problem. One presenter likened veterinarians in most countries to drug dealers, as much of their income comes from supplying antibiotics. Several participants recommended reducing the profit motive for veterinarians to prescribe antibiotics. However, one warned that if ensuring that antibiotics are used under the supervision of a veterinarian is a priority, as many agree it should be, there is a danger that farmers might be more likely to turn to the Internet to buy antibiotics if it becomes too difficult for them to obtain the drugs from veterinarians.

Use of antibiotics as livestock growth promoters: It was noted that the use of antibiotics for livestock growth promotion is widespread. Only 51 countries have banned the practice. Several participants said controlling this use should be a priority, but it was argued that one challenge will be that what is considered growth promotion in one country may be seen as disease prevention and control in another.

A case study presented on action taken in Denmark showed that banning the use of antimicrobials for livestock growth promotion reduced use by 30%, and rather than reducing productivity,

increased production efficiency. It was argued that productivity increased because the role of veterinarians changed so that instead of primarily prescribing antibiotics, they spent more time visiting farms and assisting with infection control and other aspects of animal health management. Most of the Danish guidelines were developed in consultation with, and with partial funding from, livestock producers. One participant argued, however, that while the Danish model of antibiotic control in farming is to be highly regarded, many developing countries do not have the resources to achieve such level of control at the moment, although that could be a long-term target.

Role of veterinary vaccines: It was considered that veterinary vaccines have an important role to play in reducing demand for antibiotics and that there is a need for better vaccines. A case study of vaccine use in aquaculture in Norway was presented and showed that after fish vaccines were introduced, production increased while the use of antimicrobials decreased. Similar to the Danish case study on the banning of antibiotic growth promoters, the productivity boost was attributed not only to the introduction of vaccines but also to simultaneous improvements in management and infection control.

Coordination within countries and globally: Several participants argued that within countries, cooperation and coordination between ministries and authorities involved is inadequate. It was proposed that national committees on antimicrobial resistance could be made a priority in all countries. While standards are an important step, implementation and monitoring of compliance is crucial. Compliance evaluations are currently voluntary.

However, one presenter argued that while coordination between the relevant sectors was important, it would not be enough on its own. Likewise, national policies, while essential, will never fully address the problem and the global nature of it demands action on a globally coordinated level. Antimicrobial resistance is a priority area of collaboration between the WHO, FAO and OIE. Priorities at the global level are at the moment to aim to reduce non-therapeutic use of antimicrobials in plants and as growth promoters or preventive medicine in animals.

FOSTERING GLOBAL COMMITMENT

It was broadly agreed that political will to tackle the problem on a global level is lacking, despite there being WHO guidance on what needs to be done, and that there is a need to understand and address the barriers in order for global commitment to be stepped up and progress to be made. It was argued that to achieve that, a clear message that frames the issues appropriately and incorporates a plan for antibiotic stewardship, ideas for stimulating new drug development, including for developing different financial models for different markets, is needed, along with robust surveillance and monitoring data of the scale of the problem and efforts to address it. Several participants mentioned that champions at both the national and global levels are needed to raise antibiotic resistance up the political and public agenda.

It was proposed that, to foster global commitment, the G8 and G20, as global agenda-setters, should be targeted to harmonise their positions and adopt common recommendations to set an example for the rest of the world. The Organization for Economic Co-operation and Development should be targeted likewise. Meanwhile, regulators, perhaps through the International Conference of Drug Regulatory Authorities, should also be lobbied to make a special case of antibiotics.

Another participant argued that there is work to be done in systematically connecting the issue of antibiotic resistance to existing global agendas such as immunization, hospital hygiene, children's health, access to medicine, the post-2015 development agenda and universal health coverage. Notably, the universal health coverage movement is likely to expand access to antibiotics in many countries and leaders of the effort to combat antibiotic resistance need to determine how best to integrate the issue into that agenda and agree what messages need to be communicated about antibiotics in the context of universal health coverage.

It was noted that there is currently no mechanism for holding countries accountable for what they do with respect to antibiotic resistance. Perhaps approaches taken in other areas, such as the Montreal Protocol for phasing out the use of chlorofluorocarbons, or the Code of Conduct for Responsible Fisheries, could be used as models for developing a framework for national

accountability in combatting antibiotic resistance. One participant noted that the antibiotic resistance problem should be able to achieve a similar level of global engagement as climate change, perhaps with a similar intergovernmental panel that drives the science and action. Several participants favoured consideration of an international convention to address antibiotic resistance through prudent use and drug pipeline reinvigoration.

One participant argued that there is no need for a new international bureaucracy to replace the current system that links the WHO, FAO and OIE. Addressing the problem in stages, starting with targeting the non-therapeutic use of antibiotics in animals and plants, was thought to be an important strategy for building global political support. One of the priorities could be to convince governments and other stakeholders that there is already international consensus on what needs to be done, that eligibility for public resources is clear given that combatting antibiotic resistance fits the definition of a global public good, and that the global priority should be to implement existing standards.

Another speaker noted that progress has been made on a few basic concepts that can enhance global commitment, such as the recognition that incentives for pharmaceutical companies to invigorate the drug pipeline need to be tied to incentives for antibiotic conservation.

Communication and framing

However, several participants argued that one of the major barriers to gaining sufficient political will is the way the issue has been framed and that poor communication and messaging is one reason why efforts to foster global commitment to the issue have largely failed thus far.

It was broadly agreed that a critical gap is simple, clear and concise messaging around the issue. Examples mentioned as models included the 'ABC' messaging for HIV prevention and the six-point package of messages used for promoting tuberculosis control. Furthermore, messages need to be aligned between advocates but tailored to each audience group, such as doctors, hospital administrators, governments, pharmaceutical companies, international agencies and the general public, in order to cultivate commitment and incentivise behaviour change.

For instance, to convey the long-term negative consequences of antibiotics overuse or misuse to the general public, would focusing on the potential health effects of eating antibiotics-treated food be a more effective motivator than focusing on how doctors overprescribe? Similarly, might it be effective to frame the problem for hospitals and health officials in terms of every use of antibiotic representing a failure of the chain of hygiene, vaccination, and infection control?

Other communication ideas proposed for fostering political will and general commitment to the issue included:

- Articulating the cost of inaction;
- The need for an overall vision (For instance, every country needs to have an antibiotics survival plan whose objectives are to minimize the infectious disease burden and enable infections to remain treatable.);
- Using language that avoids the phrase 'antibiotic resistance'; and
- Drafting specialists with skills in communication, behavioural science and anthropology into the effort.

CONCLUSION

It was concluded that tackling antibiotic resistance is something that has to move ahead in a coordinated manner across many sectors on many different levels, from the local to the global. Key areas of need were identified as follows.

- A shared vision that is well articulated and includes action aimed at humans, animals and food.
- Robust surveillance and reporting to better understand the scale of the problem and monitor the use of antibiotics and patterns of resistance.
- The fostering of political commitment and recruitment of champions.
- The application and sharing of what is known to work.
- Incentives to stimulate the antibiotic pipeline, diagnostic tests and vaccines, and the behaviour change needed for antibiotic conservation.