

Stimulating innovation, sustainable use and global access to antibiotics

2016 DRIVE-AB Conference
CONFERENCE REPORT



Introduction

On 2 June, 2016, decision makers and policy influencers engaged in tackling antimicrobial resistance (AMR) gathered at the Royal Netherlands Academy of Arts and Sciences in Amsterdam for the conference, Stimulating innovation, sustainable use and global access to antibiotics, which was organized by the Innovative Medicines Initiative (IMI) DRIVE-AB consortium and funded by the Government of the Netherlands.

The main goal of the meeting was to identify key policies that could be implemented globally to stimulate the innovation of critically needed new antibacterial treatments and ensure their availability and sustainable use. Input from the conference will inform DRIVE-AB's final policy recommendations, which are an important contribution to global initiatives to manage the looming public health threat of AMR.

As part of the conference, DRIVE-AB presented the preliminary results of its research and sought feedback from stakeholders regarding the feasibility and implementation of the incentive policies and reward models that the consortium is considering. The conference also explored how on-going European and international initiatives addressing AMR may complement each other and identified opportunities for greater global coordination and sharing of best practices.

The conference was structured around four sessions, each featuring a keynote address followed by a panel discussion and questions and answers. At the end of each panel discussion participants worked together on an 'agenda for future action', highlighting concrete steps to address current gaps in policy at the national level.

The topics covered in the four sessions were as follows. A full agenda can be found in the appendix.

Session 1: Setting the scene

This session reviewed global initiatives in the fight against AMR and identified key gaps in action, policy or its implementation. The

keynote discussed lessons learned from Dutch interventions to decrease antibiotic use and future actions that will be taken.

Session 2: Addressing antibiotic innovation together with sustainable use

This session explored how antimicrobial stewardship and sustainable use policies can be integrated into new policy interventions, including new economic models, and how current and anticipated trends in AMR are influencing public health priorities and antibiotic innovation. The keynote described the current status of global activities on surveillance, responsible use, and new treatments for bacterial infections.

Session 3: New economic models for antibiotic innovation

This session explored a range of incentives and policies designed to stimulate the discovery and development of new antibiotics while ensuring both sustainable use of and appropriate access to them. Potential challenges to implementing such policies were considered and discussed. The keynote discussed new economic models to stimulate antibiotic innovation, including barriers to and opportunities for integrating sustainable use and access policies.

Session 4: The way forward

This session aimed to define priority actions for more effectively addressing incentives for innovation while ensuring sustainable use of and appropriate access to antibiotics. It opened with a brief outline of the final recommendations of the UK Review on Antimicrobial Resistance.

Overview: A Wicked Problem

Otto Cars, Founder and Senior Advisor of ReAct-Action on Antibiotic Resistance, framed the day's discussions by recognizing that AMR is a "super wicked problem" and that DRIVE-AB's task of driving reinvestment in research and development (R&D) for antibiotics and providing new ways to ensure their access and sustainability will be difficult, but that there is a moral responsibility to do so. Policy responses must be proportional to the magnitude of the public health threat and will require concerted, international solutions and a global perspective. Cars reminded participants that while high-income countries

fear a post-antibiotic era, many places still lack access to basic antibiotics; therefore, society must promote innovation while striving to balance access and excess. During the conference, panelists and participants called for several actions to ensure the availability of effective antibiotics (see text box). DRIVE-AB will incorporate these suggestions into its final reward model recommendations to the extent possible. The precise mechanisms for implementation and suggestions for measuring feasibility and outcomes will be informed by the varied experiences relayed by the panelists and captured within this report.

Agenda for the future

Essential components of the global response

- Encourage social and technological innovation
- Implement and improve surveillance systems for AMR
- Establish public health priorities across settings (human and veterinary, etc.) as the basis of policy efforts, including targets for new drug development
- Coordinate action and build on successful models of stewardship, incentives and access

Encourage responsible use of antibiotics

- Increase awareness and demand accountability at all levels regarding the prescribing and use of antibiotics
- Invest in AMR education for all health professionals, including veterinarians
- Establish infrastructure and use data to promote optimal prescribing
- Educate children to reduce demand for antibiotics in future generations
- Increase vaccine development and usage to decrease dependence on antibiotics

Bring new antibiotics to patients

- Develop and pilot new reward models for antibiotic innovators, including push and pull incentives, and encourage private investment to fund antibiotic innovation
- Ensure the value of antibiotics is captured in reward models
- Ensure supra-national coordination and increased public funds

Other highlights from the conference discussions

While the conference was organized into four separate sessions, common themes emerged throughout the day's discussions. The following summarizes conversations around these themes, outlines current policies and describes regional infrastructure and capacities that DRIVE-AB must consider in its final recommendations.

Balancing access and excess

Marie-Paule Kieny of the World Health Organization asserted that resistance is not the result of market failure for antibiotics. The culprit, she explained, is the improper use of antibiotics, so spurring research and development is only part of the solution. Science alone will not solve this complex problem, agreed Martin Seychell from the European Commission. Panelists said that a "One Health" approach—addressing antibiotic use in human and animal health as well as the environment—is necessary.

Regarding agriculture, UK Chief Medical Officer Dame Sally Davies predicted that antibiotic use will rise with increased meat consumption in low-income countries, and added that while eliminating the use of antibiotics for growth promotion may be a goal, monitoring antibiotic sales and consumption and measuring residues in food and milk are good interim objectives. Agricultural practices can be improved in high-income countries such as England, where she estimated that 280,000 chickens contaminated with resistant organisms reach market shelves every year.

With respect to human health—the main focus of the conference—panelists cited opportunities to improve antibiotic use, given the wide variation in prescribing within and across countries that cannot be entirely explained by resistance patterns. On how to ensure compliance with stewardship, Inge Gyssens, from Radboud University Medical Center, Netherlands, cited the example of the Netherlands, where the national Health Care Inspectorate has started to enforce compliance with national antibiotic

prescription guidelines in hospitals. However, others noted a lack of resources and basic laboratory capacity in some regions. Yehuda Carmeli, from Tel-Aviv Medical Center, Israel, suggested that strict regulations should be enacted, saying: "We don't allow surgeons to operate if they don't have sterile operating rooms. Why should we allow people to prescribe antibiotics if there is no control, if there is no thinking, if there is no science behind it?"

The discussion of diagnostic tests highlighted regional differences in health care systems. Suwit Wibulpolprasert of the International Health Policy Program, Ministry of Public Health, Thailand, favoured improving clinical training, while Seychell called for improved infection control infrastructure, clean water and better sanitation in resource-limited regions. Further, antibiotics may be too readily available where health care infrastructure is weak, said Wibulpolprasert, who estimated that close to 400,000 grocery stores sell antibiotics without a prescription in Thailand.

Conference attendee Folasade Ogunsola, from the University of Lagos, Nigeria, reminded participants that stewardship must be tailored to the specific health care environment and reflect local capacities, citing Nigeria, where antibiotics are generally given in the community by non-physicians, as an example. Betuel Sigauque, from the Working Group for the Global Antibiotic Resistance Partnership GARP—CISM, Ministry of Health, Mozambique, spoke about his country's experience, where a working group was formed to evaluate usage practices and a national action plan developed to tackle AMR. He also talked about the need to increase vaccination.

Outcomes and Implementation

Individual governments are taking action, said Angelique Berg, Director-General of Health at the Ministry of Health, Welfare and Sport, The Netherlands, who explained that her country mandates stewardship programmes in hospitals and that “A-teams” help ensure adherence to guidelines. To prevent the spread of resistance to important last-resort and future new antibiotics, Dominique Monnet of the European Centre for Disease Prevention and Control (ECDC) suggested that patients being treated with such drugs should be isolated.

European-wide efforts are also underway and Seychell noted that the EU is reviewing its 2011 Action Plan against AMR. ECDC is drafting, for the European Commission, antibiotic stewardship guidelines for release in 2016 that will echo some recommendations made by the United States Centers for Disease Control and Prevention (US CDC), according to Monnet. Further, the EU is considering using e-prescriptions and requiring diagnostic tests to improve antibiotic prescribing. Kieny noted that health care providers can treat infections more effectively using diagnostics, but panelists acknowledged that it is hard to bundle the development and/or use of diagnostics and drugs due to current regulations and that other factors currently limit the use of diagnostics as a stewardship tool.

Arjun Srinivasan from the US CDC described efforts in the US to define the optimal tools and infrastructure to promote antibiotic stewardship in acute care hospitals, nursing homes and long-term care facilities. Stewardship is required in nursing homes and soon will be mandatory in hospitals receiving

government funding through the US Centers for Medicaid & Medicare Services. Monnet said that hospitals could be rewarded for proper use of antibiotics, and noted that Spain is one country providing such financial incentives.

The US CDC intends to collect antibiotic prescribing data from hospitals and report risk-adjusted benchmarks to help monitor antibiotic usage and make comparisons across facilities. Auditing and feedback-type approaches have been effective for individual prescribers, according to Davies. In the UK, where Public Health England informs community doctors about their prescribing compared with other providers, there has been a reduction in outpatient antibiotic use. Through monitoring and feedback on prescribing and other measures, the Netherlands experienced a 10 percent reduction in antibiotics use in a hospital urology department over one year and surgical infections are down by 60 percent as a result of tackling staphylococcus nasal colonization in carriers prior to procedures, according to a study. Hospital costs have also been reduced, according to Berg, who attributed success to political will and empowerment at the hospital level.

But usage information alone is inadequate, according to panelists, who stressed that stewardship should focus on patient outcomes and that incentives must be linked to appropriate use, not only reduced use.

Societal champions needed to catalyse action

To Wibulpolprasert, the world has recognized AMR as a threat thanks to prominent champions and leaders, but more of them are needed at all levels of society. He advocated for “social innovation”, and asserted that “action without planning is better than planning without actions”. Kieny proposed that civil society should demand accountability from health care facilities, while Dominique Monnet advocated for educating children about antibiotics to change society’s attitudes.

From Policy to Action: Setting priorities, coordinating efforts

There is currently no international framework to tackle AMR, and without one, Seychell explained, there is a risk of well-meaning but uncoordinated actions. Goals and targets for action need to be better defined. On that front, the World Health Assembly is establishing a list of public health threats to guide efforts, while the ECDC will issue a resistance burden report in 2018. Priorities should be re-evaluated over time against the antibiotic pipeline. Panelists offered other suggestions for coordinated and immediate action, including creating a market for off-patent antibiotics using a joint procurement model and piloting new economic models for innovative products. Jean-Pierre Paccaud from the Drugs for Neglected Diseases initiative and Global

Antibiotic Research and Development Partnership suggested that a global fund may stimulate innovation that is in line with public health priorities.

Government commitment, sound policies and financing are needed to support action on AMR and that is why the UN is important, said Davies. While she would like to see a global treaty on actions to fight resistance, the chances of that happening are low, in her estimation. With a coalition of countries, however, Davies believes it might be possible to ban antibiotics for growth promotion in farming, stop internet sales of antibiotics and develop a logo to let consumers know that antibiotics are a valuable resource that should be used with care.

New economic models for antibiotic innovation: Convergence and balance

Anja Schreijer reminded participants that generating new antibiotics and trying to extend the useful lifespan of these critical drugs are both needed. Not doing both, she explained, “will be like mopping up the floor without also turning off the faucet.” This balance is something that DRIVE-AB partner Ramanan Laxminarayan believes is critical for discussions about incentives.

According to John-Arne Røttingen from the Norwegian Institute of Public Health, policy makers are now converging on both “push” and “pull” incentives with a focus on reward models that “de-link” revenues from the volume of drugs sold and systems to ensure access and sustainable use. The strength of DRIVE-AB compared with other efforts, Røttingen said, is that it will recommend reward models that balance innovation with sustainable use and equitable access.

He described DRIVE-AB’s preliminary reward models and explained the types of innovation that each model might stimulate. He noted that sustainability would require local policies

for antibiotic use, transparency on consumption, and contractual agreements between governments and companies that impose requirements on developers bringing new antibiotics to market.

Panelists from industry described rewards that are attractive to corporate decision makers, with Florence Séjourné from the BEAM Alliance (representing European Small and Medium Enterprises) noting that push initiatives need to be available and should apply to small-molecule and other antibacterial products. John Rex from Astra Zeneca noted that research and development are unpredictable and that effort follows reward. He also noted that any reward model needs to acknowledge that antibiotic development requires “care and feeding” over many years and that manufacturing can be difficult. Séjourné and Rex asserted that antibiotic rewards are not currently aligned with the value they bring to individual patients and public health.

Financing innovation

Any incentives would require funding and some panelists suggested that innovators in therapeutic areas that benefit from antibiotics indirectly should contribute to their development. For example, since cancer patients suffer infections frequently, perhaps companies selling oncology products might assume some of the costs for antibiotic development.

Shiva Dustdar from the European Investment Bank (EIB) discussed how to help raise private capital for antibiotic development given the low perceived return on investment for antibiotics. One way

she proposed is a blended financing approach that helps de-risk investment for private players; for example, providing funding for research and development, with the expectation that some will be paid back upon achievement of specified milestones. According to Dustdar, the EIB is now involved in a pilot programme with the European Commission called the Infectious Diseases Financing Facility that serves as a bridge between granting institutions and the capital markets via such a mechanism.

Public versus private funding

Kieny highlighted that if society agrees that AMR is an urgent public health threat, it is a state responsibility to invest money to address it. She further suggested that an international binding agreement might help ensure both access to new antibiotics and their preservation. It might also foster agreement on who invests in what aspect of the antibiotic pipeline.

Others, including Joe Larsen from the U.S. Biomedical Advanced Research and Development Authority (BARDA) countered that relying entirely on government financing is a disadvantage. Raising sufficient government funds and making it available consistently over long time horizons is challenging because there is a tendency for officials to lose focus and reduce the investments over time.

Larsen also noted the challenge that predicting “winners” posed for government funders, recognizing that it is not assured that the drugs invested in with public funds will ultimately best serve the public. Larsen also cautioned that, “...markets don’t like it when governments do experiments on them,” and said that pilot studies of proposed reward models should be tested to avoid unintended consequences. In fact, pilot projects are planned, said Rex, who added that trade associations and individual companies are now negotiating at least two innovative reward models in Europe. While adherence to strict requirements and processes poses downsides, government programmes such as those offered by BARDA might serve as a good foundation for an innovative reward model, given the government’s significant experience in administering research contracts.

Sustained response and long-term investment

David Heymann from Chatham House reminded participants of the need for a sustained response to AMR, as previous efforts have lost momentum in the face of other pressing concerns. Examples of global public health success include the WHO framework convention on tobacco control, which has reduced the demand and supply of tobacco and could be translated to antibiotics, according to Heymann.

Reducing unnecessary demand is an important component of recommendations from the UK AMR Review, explained Jeremy Knox, who was part of this team. Demand-side interventions in the UK's ten-point plan include the mandatory use of diagnostics where available and the implementation of market incentives for tests. Some panelists asserted that the impact of low prices for generic antibiotics on the market for, and usage of, antibiotics should be studied as an area for intervention.

On the supply side, a two-pronged approach consisting of a global innovation fund to spur development should be paired with lump-sum payments in the order of \$1-1.5 billion for priority antibiotics. According to Knox, this level of investment over a decade could fundamentally transform the marketplace for antibiotics. The UK recommendations may not work in other countries, said Christian Brun-Buisson from the Ministry of

Social Affairs and Health of France. His government is currently exploring a range of incentive models that could work at the national level, other than a market-entry reward, which might be unfeasible. France is contemplating a special designation and incentive system for products linked to public health needs, according to Brun-Buisson.

Knox asserted that while the governments of the G20 could afford to fund incentives, taxes could be levied on the sales of antibiotics used in agriculture, or innovators could be required to “pay or play,” whereby pharmaceutical companies working in therapeutic areas where patients rely on effective antibiotics (such as oncology) help fund incentives for their development, unless they choose to conduct the R&D themselves. Julie Gerberding of MSD noted that some developers are investing in antibiotics and other products to address resistance, including diagnostics and vaccines because of the significant unmet need. More than 90 companies and 11 industry groups from 21 countries signed the Davos declaration¹ – a call for collaboration on reward models and commitment by companies to increase research and development and ensure access to therapies. Gerberding recommended that targeted incentives help unleash private investment by de-risking basic science.

Keeping up momentum

The UK AMR Review is now discussing its final report with policy makers around the globe and hopes to see AMR on the agenda at the G7. The UN General Assembly meeting in September 2016 will be a useful venue for discussions and it is hoped it will drive action, panelists said. Gerberding expressed scepticism about the political will for sustained changes to reward models. Marc Mendelson, Chairperson of the South African Ministerial Advisory Committee on AMR, was more optimistic, citing interest at the highest levels in his country, which is reflected in an increase in infectious disease specialists. What is lacking, according to Mendelson, is public engagement. Manica Balasegaram,

representing the Médecins Sans Frontières' Access Campaign, concurred, calling for a dedicated organization like UNAIDS and massive public awareness campaigns on AMR.

Ursula Theuretzbacher, of the Center for Anti-Infective Agents, Austria, and DRIVE-AB partner, noted that the consortium is trying to engage all stakeholders in discussions. The consortium hopes to reconcile the diverse opinions reflected at the conference and plans to issue final recommendations on balanced reward models in 2017.

¹ <http://amr-review.org/industry-declaration>

Appendix

0830 - 0900 **Registration and Refreshments**

0900 - 0905 **Welcome Address**

Judy Hackett, AstraZeneca and DRIVE-AB coordinator, and Jos van der Meer, President European Academies' Science Advisory Council, Royal Netherlands Academy of Arts and Sciences

Chair – *Stephan Harbarth, Geneva University Hospitals and Faculty of Medicine and DRIVE-AB coordinator*

Session 1: Setting the scene

Moderated by Professor Otto Cars, ReAct and DRIVE-AB partner

This session will discuss the global landscape in the fight against antimicrobial resistance and identify key gaps in action, policy or its implementation.

0905 - 0910 **Introductions**

Otto Cars, Founder and senior adviser, ReAct-Action on Antibiotic Resistance, DRIVE-AB partner

0910 - 0930 **Keynote: Lessons learned from Dutch interventions to decrease antibiotic use, and future actions that will be taken**

Angelique Berg, Director-General of Health at the Ministry of Health, Welfare and Sport, The Netherlands

0930 - 1015 **Panel Discussion**

Martin Seychell, European Commission, Directorate-General for Health and Food Safety

Marie-Paule Kieny, World Health Organization

Suwit Wibulpolprasert, International Health Policy Program, Ministry of Public Health, Thailand

Lynn Marks, GSK, Senior Clinical Advisor to the Infectious Disease Therapy Area Unit

1015 - 1030 **Agenda for Future Action**

1030 - 1100 **Refreshments**

Session 2: Addressing antibiotic innovation together with sustainable use

Moderated by Anja Schreijer, Independent Consultant in Antimicrobial Resistance, WHO/Europe

This session will explore how antimicrobial stewardship and sustainable use policies can be integrated into new policy interventions, including new economic models, and how current and anticipated trends in antibiotic resistance are influencing public health priorities and antibiotic innovation.

1100 - 1105 **Introductions**

Anja Schreijer, Independent Consultant in Antimicrobial Resistance, WHO/Europe

1105 - 1125 **Keynote: Current status of global activities on surveillance, responsible use, and new treatments for bacterial infections**

Dame Sally Davies, Department of Health, England

1125 - 1215 **Panel Discussion**

Inge Gyssens, Radboud University Medical Center and DRIVE-AB partner

Yehuda Carmeli, Tel-Aviv Medical Center and DRIVE-AB partner

Marc Sprenger, World Health Organization

Dominique Monnet, European Centre for Disease Prevention and Control

Arjun Srinivasan, U.S. Centers for Disease Control and Prevention

Betuel Sigauque, Manhica Health Research Centre, Mozambique

1215 - 1230 **Agenda for Future Action**

1230 - 1330 **Lunch Break**

Session 3: New economic models for antibiotic innovation

Moderated by Ramanan Laxminarayan, Center for Disease Dynamics, Economics and Policy, Strathclyde University and DRIVE-AB partner

This session will explore a range of incentives and policies designed to stimulate the discovery and development of new antibiotics while ensuring both sustainable use of and appropriate access to antibiotics. Potential challenges to implementing such policies will be considered and discussed.

1330 - 1335 **Introductions**

Ramanan Laxminarayan, Director, Center for Disease Dynamics, Economics and Policy, Strathclyde University and DRIVE-AB partner

1335 - 1400 **Keynote: New economic models to stimulate antibiotic innovation, including barriers to and opportunities for integrating sustainable use and access policies**

John-Arne Røttingen, Norwegian Institute of Public Health and DRIVE-AB partner

1400 - 1445 **Panel Discussion**

Jean-Pierre Paccaud, Drugs for Neglected Diseases initiative and Global Antibiotic Research and Development partnership

Shiva Dustdar, European Investment Bank

Florence Séjourné, BEAM Alliance

Joe Larsen, Biomedical Advanced Research and Development Authority

John Rex, AstraZeneca, Senior VP and Chief Strategy Officer, Infection Business Unit

1445 - 1500 **Agenda for Future Action**

1500 - 1530 **Refreshments**

Session 4: The way forward

Moderated by David Heymann, Chatham House and DRIVE-AB partner

This session aims to define priority actions for more effectively addressing incentives for innovation while ensuring sustainable use of and appropriate access to antibiotics.

1530 - 1535 **Introductions**

David Heymann, Chatham House and DRIVE-AB partner

1535 - 1545 **Update: Brief outline of the final recommendations of the UK Review on Antimicrobial Resistance**

Hala Audi, Review on Antimicrobial Resistance, United Kingdom

1550 - 1655 **Panel Discussion**

Marc Mendelson, Federation of Infectious Diseases Societies of Southern Africa

Manica Balasegaram, Médecins Sans Frontières Access Campaign

Wiebke Löbker, Federal Joint Committee (G-BA), Germany

Christian Brun-Buisson, Ministerial Delegate on AMR, Ministry of Social Affairs and Health, France

Julie Gerberding, MSD, Executive Vice President for Strategic Communications, Global Public Policy and Population Health

Ursula Theuretzbacher, Center for Anti-Infective Agents, Vienna and DRIVE-AB partner

1655 - 1700 **Agenda for Future Action**

1700 - 1710 **Closing Address**

John-Arne Røttingen, Norwegian Institute of Public Health and DRIVE-AB partner



This conference was generously supported by the Dutch Ministry of Health, Welfare and Sport.

Antimicrobial Resistance is a threat that is evolving slowly but progressively, jeopardizing the health of all people. Antimicrobial Resistance is therefore a top priority on the Health Agenda during the Dutch EU-presidency in the first half of 2016. In February, the Netherlands organized the first One Health Ministerial conference on AMR. Because the Netherlands believes the One Health approach, when all disciplines work together, is crucial in combating Antimicrobial Resistance.

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