

CURRENT STATUS ON AMR FROM A ONE HEALTH PERSPECTIVE

POSTSCRIPT: INTERNATIONAL SYMPOSIUM ON ANTIMICROBIAL RESISTANCE

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AMR - A Call for Action

The Royal Danish Embassy in the UK, the Danish Health Authority and the Novo Nordisk Foundation, convened a cross-sector international symposium on Antimicrobial Resistance (AMR). The symposium brought together multi-stakeholder experts from more than 65 organisations to share current international experiences, facilitate an update on research, clinical, innovation, policy and social programmes, address the challenge of AMR through a One Health approach with integrated actions across human, animal and environmental health sectors, critically important to achieve the Sustainable Development Goals (SDGs).

The symposium and postscript clearly articulate the role of the international community and national initiatives in addressing current AMR challenges with the solutions available. It is an important reminder that the international community do have the tools, solutions and means available, but lack the strategic and systematic implementation of relevant and effective interventions at scale.

The AMR symposium experts recommend joint policy development and implementation targets, expanded research collaboration, clinical and diagnostics development and further incentivising of investments and AMR diplomacy, including:

- **Policy:** Promote political value and ROI from One Health investments in AMR – both human, animal, environment and broader societal determinants
- **Stewardship:** Advocate for appropriate treatments through reliable diagnostics, surveillance systems and implementation of infection prevention and control
- **National Action Plans:** Ensure that countries have National Action Plans on AMR with adequate funding
- **Program implementation:** Facilitate adaptation and adoption of AMR interventions in different country contexts by using Implementation Research
- **Antibiotics:** Ensure incentives to stimulate R&D, introduce public-private partnerships in the use of data sharing and clinical modelling, and to keep new and existing antibiotics on the market
- **Payment Models:** Explore innovative payment and subscription models, leveraging real world data and high degree of digitalization in society for relevant reimbursement models



KEY MESSAGES

- Antimicrobial Resistance is a global health crisis, and must be dealt with urgently.
- An estimated 1.2 million deaths globally are caused by bacterial AMR. This number is predicted to rise to 10 million annual deaths by 2050, and be accompanied by high global GDP losses, in the absence of proper action.
- There is an urgent need for better global One Health surveillance of both antimicrobial consumption and resistance.
- We need to strengthen antimicrobial stewardship in both the human and animal sector under the One Health Approach. The current efforts are not sufficient to stem AMR development globally.
- There is a need to raise public and political awareness of AMR, involving civil society and patient organizations etc.
- Prevention of infections, both resistant and non-resistant, must be a priority as infections drive antibiotic use. To this end, infection prevention and control programmes and, in low- and middle-income countries, access to clean water and sanitation should be improved. Also, existing vaccine programs should be strengthened, and new vaccines developed.
- The pipeline for new antibiotics is drying out due to a lack of economic incentives for developing new antibiotics. There is a need for both national and supra-national cooperation to create innovative economic incentive models for pharmaceutical companies to develop and marketize new antibiotics.
- Public health interventions to tackle AMR are a cost-effective - and very often cost-saving - investment.



An Emerging Health Crisis

WHO has ranked Antimicrobial Resistance (AMR) as one of the top 10 global public health threats faced by humanity. In 2019 an estimated 1.3 million deaths could be attributed directly to bacterial AMR[1], and without radical action this number is predicted to rise to 10 million annual deaths by 2050 – making infections with antibiotic resistant bacteria a bigger killer than cancer.

In addition to the human cost of AMR leading to morbidity and deaths, the crisis has vast economic consequences. By 2050, AMR is predicted to result in more than 568 million extra hospital days each year in the EU/EEA region alone[2], and the annual global GDP is predicted to fall with as much as 3.8% in a high-impact AMR scenario[3].

This postscript captures prioritised themes, discussion points and recommendations from the symposium. This is for the purpose of contributing to future policy development, continued research dialogue, clinical collaboration activities and investments.

AMR IN NUMBERS



5 million deaths associated with bacterial AMR in 2019



80% of AMR deaths occur in developing countries



20% of AMR deaths occur in children aged under five years

Source: GRAM Report, The Lancet, 2022

[1] <https://www.healthdata.org/news-release/lancet-estimated-12-million-people-died-2019-antibiotic-resistant-bacterial-infections>

[2] <https://www.oecd.org/health/health-systems/AMR-Tackling-the-Burden-in-the-EU-OECD-ECDC-Briefing-Note-2019.pdf>

[3] <https://www.worldbank.org/en/news/press-release/2016/09/18/by-2050-drug-resistant-infections-could-cause-global-economic-damage-on-par-with-2008-financial-crisis>



The main driver behind the AMR crisis is an increased use of antimicrobials in humans and animals. Between 2000 and 2015[4] the global consumption of antibiotics in the human sector rose by 65%, with most of the increase happening in low- and middle-income countries. As total global consumption rises, we also see a worrying relative increase in antibiotics with higher resistance potential.

There are multiple and interconnected causes underlying this increase. In low- and middle-income countries a range of factors contribute to a high burden of communicable diseases driving antimicrobial consumption and thus AMR, including a lack of clean water and sanitation along with resource constraints on infection prevention and control (IPC) programmes in the health care sector. In high-income countries the consumption of antibiotics has been relatively stable for several years but the consumption per capita is high, and like the rest of the world, high-income countries see a rise in the use of last-resort broad spectrum antibiotics following an upward trend in resistant infections.

Inappropriate and excess use of antibiotics in both human and animal health contributes significantly to AMR. Globally almost 50% of human antibiotic treatments[5] are initiated without a proper diagnosis and with the wrong drug. Inappropriate use can be avoided by regulations on prescribing and purchase of antimicrobials and by good stewardship practices among medical doctors and veterinarians, but especially low- and middle-income countries face resource constraints in implementation of these measures. Paradoxically, many low- and middle-income countries simultaneously face challenges in both avoiding inappropriate treatment and ensuring access to appropriate treatment with antimicrobials.

These challenges are exacerbated by insufficient wastewater management, allowing residues of antibiotics and resistant pathogens to enter the environment from homes, hospitals, pharmaceutical industries, and livestock farms. When water sources, soil and crops for human consumption are contaminated, it may contribute to spread of resistant bacteria to animals and humans.

The multiple factors behind the rapidly accelerating AMR crisis underlines the need for international collaboration and a cross-sector approach, involving sectors such as human, animal, environment, education and social science sectors, government, NGOs, research, industry, and civil society.

[4] <https://www.pnas.org/doi/10.1073/pnas.1717295115>

[5] <https://www.bcg.com/publications/2022/model-for-tackling-antimicrobial-resistance>



Challenges and Solutions Discussed

Challenges of AMR – The Patient Perspective

While the Covid-19 pandemic was countered worldwide with immediate action and new allocated resources, the AMR crisis – often described as a pandemic in slow-motion – does not yet attract the necessary political interest and commitment. There is a limited awareness of the urgency and potential consequences of insufficient action not only among policymakers but throughout society. Highlighting and communicating the consequences of AMR for patients today and in the near future is pivotal to create the necessary political momentum for AMR action.

According to the Union for International Cancer Control, one of the largest cancer-fighting organisations globally, drug-resistant infections have the potential to undermine all progress made in cancer treatment. As many as 1 in 5 cancer patients undergoing treatment are hospitalised due to infections, and antibiotics are the main line of defence. Infections are already the second leading cause of death in patients with cancer, and this share is expected to rise with AMR. People with cancer are more susceptible to infections due to the underlying disease and a compromised immune system as a result of treatments for cancer like bone marrow transplants, radiotherapy and chemotherapy.

Furthermore, AMR can challenge almost all aspects of modern medicine, increasing the mortality on everything from major surgery to banal pneumonias and urinary tract infections. AMR also threatens people with common chronic conditions, such as diabetes and chronic lung disease, who are more susceptible to infections.

Strengthening of Antimicrobial Stewardship under a One Health Approach

Effective antimicrobial stewardship (AMS) requires better training, increased awareness of AMR, access to appropriate antimicrobials and not least access to adequate diagnostic tools that are both affordable and quick, making it possible to rapidly determine appropriate drug and dosage for an infection.

AMS-programs can include updated clinical guidelines, education, and regulation. The same principles apply to the use of antimicrobials in the animal and agriculture sectors.

The effects of AMS-programs are well documented, but as with many other efforts to combat AMR, they require resources difficult to allocate in low- and middle-income countries, and currently the necessary groundwork is often not being done. High-income countries have a responsibility to share knowledge and experience of best practice.



Improved Infection Prevention and Control (IPC)

To reduce antibiotic consumption worldwide it is critical to improve infection prevention and control, using all tools available.

One third of the world's population is living without access to improved sanitation[6], and two billion people are without safely managed water sources[7]. This increases the level of infections, which in turn increases the use of antibiotics and development of AMR.

Water, sanitation, and hygiene (WASH) have been priorities for WHO for many years, but the number of people without access to washing their hands and safely discard human waste is still high. There is an urgent need to improve these conditions to stem the AMR-crisis. It is also important to improve hygiene standards in health care settings to prevent the spread of infections, especially resistant infections and the development of new resistant strains within and from hospitals. Other infection prevention measures include expanding vaccine coverage of already existing vaccines and development of new ones.

Importantly, improved infection prevention measures will have implications far wider than AMR, as they will improve prevention of a broad range of communicable diseases and strengthen pandemic preparedness.

Driving Better Surveillance

To establish informed policies on AMR, there is a need for global surveillance of antimicrobial consumption and antimicrobial resistance, but today the only human global surveillance in place – the WHO program GLASS – is fragmented, including only partial data from 109 countries. Data is especially lacking from low- and middle-income countries, but even OECD-countries are challenged in delivering relevant and reliable data. The lack and poor quality of data limits its use in guiding policy makers to efficiently mitigate antimicrobial resistance. There is an urgent need to establish better global surveillance and effective systems for analysing and sharing data across sectors, and borders[8].

National Action Plans – and Implementation in OECD Countries

It was discussed that there was a gap between the existing knowledge about AMR and effective policies. Even though there is a need for more surveillance, we know enough about what works to start acting on the multiple challenges with antimicrobial resistance.

[6] <http://resistancecontrol.info/2017/prevention-first-tackling-amr-through-water-sanitation-and-hygiene/>

[7] <https://www.who.int/news-room/fact-sheets/detail/drinking-water>

[8] <https://aricjournal.biomedcentral.com/articles/10.1186/s13756-021-00931-w>
<https://www.who.int/publications/i/item/9789240027336>



In 2015 the World Health Assembly called on countries to develop and implement the Global action plan on antimicrobial resistance (AMR). This work is lacking, not only in low- and middle-income countries but also in OECD countries. As of 2020, just 43% of OECD countries[9] had implemented national action plans, 47% had a plan but had either just started or not implemented anything and 10% had no plan at all. The groundwork – converting the plans to relevant activities – is often not being done. The political focus on AMR has in part been halted by the COVID19 pandemic, and to make it a political priority, there is a need to build public awareness and activate civil society organizations, including patient organizations, in this work.

A sustained One Health approach is necessary to protect human health from AMR. Antimicrobial use in both humans, animals and plants and environmental factors all contribute to AMR. Thus, effective solutions require actions and coordination across all relevant sectors. At the same time, AMR must be contextualized and integrated within a broader global health agenda, such as in the context of the Sustainable Development Goals. In this context, it is important to note the threat that AMR constitutes to general health and well-being, as well as to treating complications to non-communicable diseases such as cancer and diabetes.

Given the complexity of the AMR challenge, there is a risk of policy paralysis and losing momentum. An overarching AMR agenda should target actions along a critical path both high-impact and feasible actions.

Countermeasures – Fixing a Broken Market Model

As AMR soars the need for new antibiotics on the market becomes more urgent, but very few are under development. Since the 1980's the number of new antibiotics entering the market has been reduced by half each year, and pharmaceutical companies and researchers are hesitant to enter the field with the necessary funding and expertise. The main reason for the lack of innovation in new antibiotics is the absence of a global market that ensures the sustainable revenues necessary to finance research, commercialization, and production at scale.

The cost of developing a new antibiotic is between 1.3-1.7 billion dollars, while the expected revenue is only 500 million dollars throughout the patents period[10].

[9] Tripartite AMR-Self Assessment Survey 2020-2021

[10] <https://jamanetwork.com/journals/jama/article-abstract/2762311>



To develop lifesaving new drugs, there is a need to create the necessary economic incentives to bring the pharmaceutical companies back in the race. Both push and pull-factors are being discussed, and especially two models are of interest and are currently being tested in UK, Sweden and the US. A subscription model, with a fixed annual payment or minimum revenues in return for an antimicrobial product supply guarantee, delinked from the volumes sold. And exclusivity extension, where patent extensions are granted to the successful antimicrobial innovator with transferability to already approved drugs[11].

Both models require strong private-public partnerships when new models are being explored, and both national and supra-national solutions are required to put new models to optimal use. Today the G7 countries, the EU, and China are responsible for 80% of global pharmaceutical sales. Focusing on these markets provides the best odds for implementing a sustainably sized subscription model.

Economic Impact of Inactivity

By promoting prudent use of antibiotics in humans, strengthening AMR awareness and One Health policies, and preventing the spread of resistant infections, OECD estimates that OECD countries would save 4.8B USD/year to the budget of healthcare systems, making the interventions cost effective[12].

Because of the huge economic impact of inadequate action against AMR both on a national and a global level, there is an urgent need for political commitment not only within healthcare and agriculture but from finance ministers, making it possible to allocate the necessary resources and public investments.

[11] <https://www.bcg.com/publications/2022/model-for-tackling-antimicrobial-resistance>

[12] OECD. *Stemming the Superbug Tide: just a few dollars more*. 2018. [oe.cd/amr-2018](https://www.oecd.org/amr-2018)



AMR - The Danish Approach

Denmark has for more than twenty years actively worked on reducing the use of antibiotics in both healthcare and the animal and food sector, and the level of AMR infections is low in both a European and international context.

The relative success in curbing AMR in Denmark can be attributed to a constant focus on stewardship, promoting a restrictive and prudent use of antibiotics in both human and animal health, improving infection prevention and control in hospitals, and a systematic surveillance of antibiotic consumption and resistance in both humans and animals. In 2017 this work was reinforced with a One Health Strategy against antibiotic resistance, with a focus on cross sector and cross border cooperation adjoined by a national action plan on antibiotics for human healthcare and a national action plan for antibiotic resistance in production animals and food.

The combined efforts have resulted in an overall reduction in the use of antibiotics for pigs by 29,4% since 2010. There has also been a decrease in antibiotic consumption in humans but with a relative increase in the use of broad-spectrum antibiotics in primary care. This – along with a steady rise in the number of infections in Danish hospitals overall, and an increasing number of certain resistant infections – demonstrates that there is a continuing need for further initiatives and action in the field both nationally and internationally.

Denmark, like all other countries, is affected by the development of resistant bacteria in other parts of the world. AMR knows no borders, and many of the resistant bacteria in Danish hospitals have travelled across the border via humans, animals, or food. The challenge of AMR is by nature a global challenge calling for global collaboration fuelled and inspired by national experiences and best practice.

PRIORITIES FOR FUTURE ACTION IN HUMAN HEALTHCARE IN DENMARK

- Continued efforts to strengthen antimicrobial stewardship
- Enhance efforts to prevent and control spread of infections
- Improve infection prevention and control programs in both hospitals and primary care
- Investigate possibilities for prevention in schools, daycare, workplace, home etc.
- Strengthen vaccination programs, especially for influenza and pneumococcal disease
- Development of new antimicrobials, but also new/improved vaccines



INITIATIVES IN THE DANISH ANIMAL AND FOOD PRODUCTION

1999: Ban on antimicrobial growth promoters

2010: The 'Yellow Card Initiative' regulating the use of veterinary antimicrobials at pig farms

2016: Restrictions on veterinary use of antibiotics important for human health

Reduction target for the use of antibiotics since 2010

RESULTS IN THE DANISH ANIMAL AND FOOD PRODUCTION

29,4 % reduction in total use of antimicrobials for pigs from 2010-2021[13]