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EPILOGUE

Securing access to effective antibiotics for current and future generations. Whose responsibility?

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Antibiotic resistance—the tip of the iceberg

Access to effective antibiotics is essential in all health systems. The following quote from Charles Fletcher, a Research Fellow who in 1941 helped Howard Florey conduct the first clinical trials of penicillin, predicted the revolution of medicine brought about by penicillin and other antibiotics:

> "It is difficult to convey the excitement of actually witnessing the amazing power of penicillin over infections for which there had previously been no effective treatment. I could not then imagine the transformation of medicine and surgery that penicillin would produce. But I did glimpse the disappearance of the chambers of horrors which seems to be the best way to describe those old septic wards, and could see that we should never again have to fear the streptococcus . . . or the more deadly staphylococcus (1)."

Today, more than 70 years later, antibiotic resistance (ABR) is increasingly undermining the effective treatment of infections and posing one of the biggest threats to health care. Bacterial strains, resistant also to colistin, which is one of the few remaining therapeutic options available to treat infections due to carbapenem-resistant Enterobacteriaceae, are now spreading globally (2,3).

Although many achievements in modern medicine are now obviously at stake, the burden of ABR is most likely falling disproportionally on low- and middle-income countries (LMICs), where high intestinal colonization with multiresistant Gram-negative is reported more frequently (4,5) and where these bacteria are causing a significant mortality (5-8). The consequences of ABR in LMICs are aggravated by poor sanitation and infection control. A recent review showed that health care-associated infections in neonatal intensive care units in LMICs might be up to nine times more common than in the US (9). Lack of access to and affordability of newer antibiotics are other critical factors associated with ABR in LMICs. Already in 2005, experts warned that, because of the development of resistance to first-line antibiotics, 70% of hospital-acquired neonatal infections could not be successfully treated by using the regimens recommended by the World Health Organization (WHO) (10).

Without effective antibiotics, the rate of postoperative infections in patients with hip replacement is 40%–50%, and about 30% of those with an infection will die (11). In 2010 in Thailand, nosocomial infections due to five major bacteria (Escherichia coli, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and methicillin-resistant Staphylococcus aureus) resulted in an additional 38,481 deaths (12). Although data on the health and economic burden of ABR are still scarce, costs are probably underestimated (11), and existing information should be sufficient to generate a strong global policy response. Furthermore, the consequences of ABR stretch far beyond the health sector. A return of untreatable infections would cause large effects on global security, economy, and development.

Why has there been a lack of concerted response to antibiotic resistance?

This question has been asked repeatedly over the past years, and unfortunately, there is no simple answer.

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Certainly, there has been no lack of warnings; in fact, such warnings were raised many years ago. Both Alexander Fleming and Howard Florey addressed the issue of ABR in their speeches at the Nobel Prize ceremony in 1945[1], and as early as 1942 the microbiologist René Dubos predicted that bacterial resistance to antibiotics should be expected, insisting that the relative protection from disease afforded by antibiotics was being 'bought at the cost of a huge ransom' (13). Recent years have witnessed an exponential increase in the number of scientific papers dealing with this problem. Searching for 'antibiotic resistance' in the PubMed database yields 184 articles written in 1990; the corresponding figure in 2013 was 1552, i.e. an eight-fold increase.

Of the many possible reasons for the weak policy response, I think the following may be the most important: 1) Although antibiotic resistance is undermining the ability to treat common infectious diseases effectively, it is not in itself a disease. Accordingly, it has not received the same visibility as the three major global infectious diseases (tuberculosis, malaria, and HIV/AIDS). 2) Since the discovery of penicillin, there has been the belief that as current antibiotics become ineffective because of resistance the pharmaceutical industry will continuously develop new ones. This is a dangerous self-deception. It is now abundantly clear that the development of new antibiotics is not happening. In fact, no new classes of antibiotics have been discovered since 1987, and the pipeline of new antibiotics is empty (14). 3) The above factors have resulted in a lack of incentives to describe and quantify health, environmental, safety, and economic consequences of the resistance problem, leading to a vicious cycle in which neither the WHO nor national governments have prioritized the issue.

Bridging the gap between science and policy: the Swedish experience

Increasing the use of antibiotics and a rapid increase in resistance to penicillin among pneumococci in southern Sweden in the early 1990s alarmed the medical profession and authorities in Sweden, and was the incentive for the foundation of Strama, the Swedish Strategic Programme against Antibiotic Resistance (15,16). Strama was established in 1995 as a voluntary network organized at two levels: a national level comprising governmental authorities and professional organizations, including the animal sector; and a regional level with nodes of independent local groups in all counties of Sweden, co-ordinated by the department for communicable disease control. The local groups are typically made up of specialists in communicable diseases, infectious diseases, clinical microbiology, infection control, general practice, and pharmacy. Paediatricians as well as ear, nose, and throat specialists are common additional members. From 2000, financial support has been provided by the Swedish Government. Since its inception as a voluntary network, Strama has undergone several structural changes. Today, the national level is organized within the Public Health Agency of Sweden, and the local Strama groups are supported by the county councils. The guiding principle underlying local Strama activities is to promote the rational use of antibiotics by providing prescribers with feedback on local or individual data on prescription for comparison with other prescribers and prevailing therapy recommendations. Local data on ABR are provided by the clinical microbiology laboratory. Other important activities include developing and adopting local treatment guidelines and organizing courses and lectures for local physicians and other health care workers at different levels of training. While initially focusing on general practice, parallel groups targeting hospital care have been established in an increasing number of counties and regions (17). After almost 20 years, I am impressed by the continued energy and innovative capacity of the local Strama groups. Strama's multidisciplinary and multisectorial programme has developed into a co-ordinated national effort that has contributed to a decrease in antibiotic use without measurable negative consequences. Antibiotic use in Sweden is among the lowest in Europe, and resistance levels are still comparatively low in Sweden[2]. Some factors that have been instrumental for this success were the utilization and early involvement of pre-existing structures and resources, such as the communicable disease officers, the multidisciplinary approach, collaboration with the local drug and therapeutics committees, microbiology laboratories, and, not least, strong political support. The Strama project also became the impetus for the first EU initiative on ABR, which was initiated by a Swedish member of the European Economic and Social Committee[3].

[1]http://www.nobelprize.org/

[2]http://www.folkhalsomyndigheten.se/pagefiles/12861/swedres-svarm-2012.pdf

[3]http://eescopinions.eesc.europa.eu/EESCopinionDocument.aspx?identifier=ces\anciennes_sections\envi\envi471\ces1118-1998_ac.doc&language=EN

WHO and antibiotic resistance

In 2000, the WHO published a report on infectious diseases. In the foreword, the Director-General at the time, Dr Gro Harlem Brundtland, stated the following:

> "By developing a global strategy to contain resistance and building alliances involving all health care providers—countries, governments, international organizations, non-governmental organizations and both the private and public health care sectors—we have an opportunity to launch a massive effort against infectious diseases that perpetuate poverty. Used wisely and widely, the drugs we have today can be made available to the world's poorest to prevent the health catastrophes of tomorrow[4]."

The global strategy was launched in 2001[5], but sufficient financial and human resources to implement the strategy were never satisfactorily provided. Member states recognized this gap and initiated a new resolution, adopted by the World Health Assembly in 2005, which urged member states to ensure the development of a coherent, comprehensive, and integrated national approach to implementing the strategy for containment of antimicrobial resistance. This new resolution also requested the Director-General to strengthen WHO's leadership role in containing antimicrobial resistance and to increase the provision of technical support[6]. I was personally involved in the process leading to this resolution as an expert to the Swedish Ministry of Health and Social Affairs and was convinced from the many interventions (primarily from LMICs) in the debate that the lack of global attention to ABR was a significant problem already then. In 2011, antimicrobial resistance was the theme of the World Health Day, which created a new momentum for the issue. However, human and financial resources within the WHO are still scarce.

Bridging the gap between science and policy: Action on Antibiotic Resistance (ReAct)

The evident difficulties of enforcing global recommendations and the weak links between well-formulated strategies and the acceptance and capacity for implementation by national policymakers caused concern. A dialogue had already taken place in 2002 between Strama, the Division of Global Health at Karolinska Institutet, Stockholm, and the Dag Hammarskjöld Foundation, Uppsala, regarding the need for a concerted global action on ABR. This dialogue included the WHO and other stakeholders and led to meetings in 2004 and 2005 and, subsequently, to the creation of ReAct (Action on Antibiotic Resistance) as an independent international network[7]. ReAct aims for profound change in awareness and action to manage the interacting social, political, ecological, and technical forces that drive the rising rate of antibiotic-resistant human and animal infection and the rapid spread of resistance within and between communities and countries. The underlying strategy of ReAct has been to broaden the debate and connect people to transform a scientifically and technically complex issue into social and political action. ReAct is not a formally organized network; rather, it has been growing organically through many powerful individuals with experience from global health policy, social movements, and work on indigenous issues. ReAct has contributed in raising the profile of ABR in the global health debate and is supporting growing networks on ABR in Latin America, South-East Asia, and Africa. ReAct believes that access to effective antibiotics should be part of every person's right to health and that globally sustainable models for the development, distribution, and use of new antibiotics need to be developed.

ReAct operates an international secretariat with its administration based within Uppsala University. ReAct is funded by a number of agencies but predominantly by the Swedish International Development Co-operation Agency (Sida), the Swedish Ministry of Health and Social Affairs, and Uppsala University.

Innovative incentives for effective antibiotics

At the time of the inception of ReAct, there was already an increasing concern among physicians and scientists globally regarding the low investments in research and development (R&D) for novel antibiotics. New business models and pathways to stimulate R&D for the needed technology became an important part of our agenda. ReAct was invited to write a background paper for the WHO project 'Priority Medicines for Europe and the World'[8], and when Sweden hosted its presidency of the

[4]http://apps.who.int/iris/handle/10665/66672

[5]http://www.who.int/csr/resources/publications/drugresist/en/EGlobal_Strat.pdf

[6]http://www.searo.who.int/entity/medicines/topics/wha_58_27.pdf

[7]http://www.reactgroup.org/

[8]http://www.reactgroup.org/uploads/publications/react-publications/antibacterial-drug-resistance.pdf

European Union in the fall of 2009 it was decided to arrange an expert conference to analyse the causes and possible solutions to the shortfall of new antibiotics in development[9].

The conference called on a unique mix of experts representing the European Commission, EU agencies, governments, academia, the European Federation of Pharmaceutical Industries and Associations, civil society organizations (CSOs) and other organizations, as well as regulators of pharmaceutical products. The conference was preceded by a workshop session addressing the possibilities of regulatory, financial, and legislative options and research strategies to enhance the possibilities of getting new and much-needed products to the patients.

ReAct was part of the planning committee and initiated a collaboration with the European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) to carry out the first scientific study to visualize the gap in the availability of new antibiotics in relation to the burden of infections[10]. The study entitled 'The bacterial challenge—time to react: A call to narrow the gap between multidrug-resistant bacteria in the EU and the development of new antibacterial agents' contained the strong evidence required to make it obvious that incentives from the public sector were needed to reinvigorate innovation. The results of the conference formed the basis for conclusions by the health ministers at the meeting of the Employment, Social Policy, Health and Consumer Affairs Council (EPSCO)[11].

These conclusions were adopted on 1 December 2009 and called upon the European Commission to 'within 24 months, develop a comprehensive action-plan with concrete proposals concerning incentives to develop new effective antibiotics, including ways to secure their rational use; and ensure that these proposals take account of the economic impact on the financial sustainability of healthcare systems'.

As a continuation of the preparatory work for shaping a new business model, the Swedish Ministry of Health and Social Affairs supported ReAct to arrange a global conference in Uppsala in 2010 (18). This meeting became a tipping point in confirming ABR as a serious global health issue and in understanding that a broad set of issues was involved in a solution.

In late 2011, the EU Commission announced its action plan[12]. This plan is a comprehensive set of proposals for a first 5-year period in the human and animal fields. One of its 12 action points deals with development of new antibacterials and includes a specific antibiotic programme 'New Drugs for Bad Bugs' (ND4BB) within the Innovative Medicines Initiative (IMI). One of the projects that have been launched within this initiative is ENABLE[13], a consortium with 32 partners, led by Uppsala University. This project will create and manage a drug discovery platform for testing and optimizing molecules that are still in the earlier stages of drug discovery but have the potential to become future drug candidates capable of treating resistant Gram-negative infections.

The way forward

The world is accountable for the present-day crisis of ABR by a failing public policy, global governance, research prioritization, and market system. A radical rethink of current policies and the establishment of new norms of antibiotic use are critical if we wish to avoid the risk of humanity losing control of the ability to manage bacterial infections. Securing access to effective antibiotics for current and future generations must therefore be everyone's responsibility, from consumers to politicians. We need to stop looking at ABR as a technical problem and redefine it by incorporating it into a health systems perspective (19). The issue can only be solved if it is considered from a global perspective in which effective antibiotics are viewed as a 'global public good'.

The ultimate responsibility to support and co-ordinate actions lies with national governments, in which political leadership naturally falls on ministries of health. However, the issue is cross-cutting and must involve many sectors, including agriculture, research and education, security, trade, development aid, and finance. To preserve the dwindling resource of effective antibiotics, co-ordinated efforts are also needed on the global level. There is still no global system for surveillance of ABR (20) or a standardized procedure that would allow us to measure the global disease burden caused by ABR. There is an obvious need for better diagnostic tools to identify those patients that really need an antibiotic. New antibiotics are urgently needed, but the innovative capacity is

[9]http://www.lakemedelsverket.se/upload/nyheter/2009/Rapport%20fr%C3%A5n%20m%C3%B6tet.pdf

[10]http://www.ecdc.europa.eu/en/publications/Publications/0909_TER_The_Bacterial_Challenge_Time_to_React.pdf

[11]http://www.consilium.europa.eu/uedocs/cms_data/docs/pressdata/en/lsa/111608.pdf

[12]Action plan against the rising threats from Antimicrobial Resistance, 2011. European Union. http://ec.europa.eu/dgs/health_consumer/docs/communication_amr_2011_748_en.pdf

[13]http://www.nd4bb-enable.eu/

dangerously low (21). Whatever policies are used to solve the lack of innovation, they must foster development of antibiotics with a novel mechanism of action, be based on public health needs analysis, and consider the question of global access at affordable prices. Another critical issue, raised by Julian Davies in the prologue of this special issue of Uppsala Journal of Medical Sciences, is how new drugs can be kept active without stringent controls of their clinical use (22). This will require a drastic behavioural change at all levels of society (23), as well as regulatory, policy, and financing options in which de-linking return of investments from sales is a key component (24). New ways for controlled distribution of antibiotics to balance access against the risk of inappropriate use must be sought (25).

The frustration with the worlds paralysis to address this problem, as well as with the expectation that the WHO must shoulder global leadership, is continuously increasing. Building a new global system for sustainable and equitable access to effective antibiotics is needed and will require large financial commitments from research funders, aid agencies, other donors, and philanthropists. Are the world leaders prepared to face the costs of non-action? Will a coalition of concerned governments take leadership in collaboration with the WHO, other UN agencies, international bodies, and civil society organizations to break ground for the global agreements/regulations and other actions needed? The window of opportunity is rapidly closing.

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I feel greatly honoured by the initiative from the editors of Upsala Journal of Medical Sciences for devoting this entire issue to antibiotic resistance. I also would like to thank all authors for their excellent articles. They will provide significant contributions to the global debate and offer constructive solutions to the serious crisis caused by antibiotic resistance. Antibiotics and antibiotic resistance have been an important part of my life during the last 30 years. My thanks go to my first teachers in infectious diseases in the 1960s who had worked in an era before penicillin and who wisely taught us to use antibiotics with respect. I am also very grateful to my colleagues at the Department of Infectious Diseases, my PhD students, my co-workers in the lab and abroad, and all friends in the Strama Network and in ReAct. You have all given me energy to continue this journey. But above all my thanks go to my wife for her continued support and understanding all these years. A major driver for me has been to help secure a future free from fear of untreatable infections for my children, grandchildren, and all other children in the world. Although there are very worrying trends, I am much more optimistic today that just a few years ago.

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