Tackling the threat of antimicrobial resistance: from policy to sustainable action

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Antibiotics underpin all of modern medicine, from routine major surgery through to caesarean sections and modern cancer therapies. These drugs have revolutionized how we practice medicine, but we are in a constant evolutionary battle to evade microbial resistance and this has become a major global public health problem. We have overused and misused these essential medicines both in the human and animal health sectors and this threatens the effectiveness of antimicrobials for future generations. We can only address the threat of antimicrobial resistance (AMR) through international collaboration across human and animal health sectors integrating social, economic and behavioural factors. Our global organizations are rising to the challenge with the recent World Health Assembly resolution on AMR and development of the Global Action plan but we must act now to avoid a return to a pre-antibiotic era.

1. Introduction

Antimicrobial resistance (AMR) existed long before antimicrobials were harnessed for use by humans. It develops through a Darwinian process of natural selection: those microbes which are resistant to an antimicrobial continue to thrive in its presence, and hence gain a selective advantage. Many forms of resistance are dependent on enzyme action; those microbes with resistance pass the genes encoding for the enzymes to the next generation, and so forth. The picture is complicated, and the process hastened, by the intra-generational genetic sharing mechanisms which some bacteria possess.

Antibiotics have been used to treat bacterial infections since the mid-twentieth century, and resistance of human bacterial infections to antibiotics has been described ever since. When giving his Nobel lecture following the discovery of penicillin, Fleming sounded a warning about resistance [1, p. 93]

It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body.

Antibiotics contributed to a major shift in patterns of mortality, both in the UK and worldwide. In 1900, before the discovery of penicillin in 1928, respiratory and gastrointestinal infections accounted for an estimated one-third of total deaths. In less than a century, there has been a major decline in deaths from infectious diseases, although respiratory tract infections such as pneumonia and influenza still feature in the top 10 leading causes of death in high-income countries [2]. One of the primary reasons for this continued medical success despite the growth of resistance has been the continuous development of new classes of antibiotics, which have different mechanisms of action. Bacterial infections that have developed resistance to one or multiple classes of...
antibiotics can still be treated by using antibiotics with a different mechanism of action, either alone or in combination with other antibiotics.

Provided there is a continued supply of new antibiotics, we may be able to keep pace with the emergence of drug-resistant strains. However, discovery of new classes of antibiotics stalled in the mid-1980s and few have been discovered over the last quarter of a century [3]. Partly as a consequence of this, isolates are now appearing which are resistant to all antibiotics in our armoury, raising the spectre of untreatable infection even at the world’s most advanced medical centres [4]. Excitingly, within the last month, a new antibiotic called teixobactin has been developed, using novel methods to cultivate soil bacteria [5]. Teixobactin has good activity in vitro against gram-positive bacteria including drug-resistant strains, but it is yet to be trialled in humans.

In the UK, national surveillance of resistance comprises routine testing of bacterial samples for resistance to a wide panel of antibiotics. This includes testing samples for resistance to the carbapenem class of antibiotics, widely regarded as the class of last resort for drug-resistant infections. Until 2003, carbapenem-resistant strains were extremely rare in both the UK and Europe. Since then, there has been an exponential rise in the number of carbapenem-resistant infections in the UK (figure 1), and these are hard to treat. Most worrying of all, surveillance has recently identified half a dozen clinical isolates within the UK which are resistant to all tested antibiotics: that is, infections which are effectively untreatable because of resistance are now present in the UK, albeit at an extremely low prevalence.

2. Responding to the threat of antimicrobial resistance

While AMR has long been recognized as a threat to human health, in recent years many countries have focused on reducing healthcare-acquired infections such as methicillin-resistant Staphylococcus aureus (MRSA) and Clostridium difficile infection (CDI) (figure 2). This has led to a significant reduction in the incidence of both MRSA and CDI within hospitals in the UK and a major decline in prescribing of cephalosporins and fluoroquinolones. Arguably, this success has shifted attention away from AMR, allowing it to escalate. Despite concerted efforts from 1998 onwards, through a series of World Health Assembly (WHA) resolutions and the 2001 WHO global strategy for containment of AMR, the need to accelerate progress on AMR has been widely acknowledged by the WHO, the USA and the European commission.

In 2012/2013, the publication of several landmark reports from organizations and individuals including the World Economic Forum [7], the US Centers for Disease Control [8] and the Chief Medical Officer for England [9] has led to a renewed international focus on AMR. The CMO’s report highlighted infections and the rise of resistance, drawing national and global attention to this problem. A new UK-wide cross-government AMR strategy was developed and published in 2013 [10], building on the previous 2001 strategy with some important refinements. The ‘One Health’ approach was interpreted more broadly to encompass collaboration not only across human and animal sectors but also economic, social and behavioural components with a focus on collaborative action in this area. The new strategy had a major focus on measuring outcomes alongside an innovative combination of policy approaches to stimulate research and development, improve surveillance, prevent and control infection, optimize antimicrobial use and relay key AMR messages to public and professional audiences. AMR was quickly placed on the risk registers of both the Department of Health and the Department for Environment, Food and Rural Affairs and the CMO called for inclusion on the Government risk register as part of the national security risk assessment making AMR a cross-government priority.

Though important for the UK, this action alone could not drive the collaborative response and commitment that was required from governments across the world. This demanded a strategic approach: maximizing political influence, engaging with the public and working to develop the scientific evidence-base to deliver new antimicrobials.

The UK maximized its influence by working across government to raise AMR on the political agenda worldwide. The CMO capitalized on her high-profile position as
independent advisor to the UK Government to convey a compelling narrative on the threat of AMR and reach out to civil society through activities such as her TEDx talk, ‘The Drugs Don’t Work’, and Penguin book of the same name. The scientific case was apparent: the burden of drug-resistant infections was increasing with no new antibiotics in the pipeline. Nonetheless, it has been essential to build the evidence-base by obtaining an accurate global picture of the magnitude of AMR and national surveillance capacity through the WHO 2014 report on global surveillance, highlighting the need for capacity building.

While there was global recognition of the importance of AMR, including a number of separate national initiatives, in the period immediately after publication of the CMO’s report in 2011 there was no clear mechanism for collaborative international efforts. Driven by the UK and Sweden, a resolution on AMR was drafted and ratified at the 67th WHA in 2014. This gave the WHO a mandate to develop a global action plan, legitimizing action on behalf of member states. The draft action plan acknowledges that member states will have different priorities in relation to AMR so it has been devised as a series of building blocks [11]. Member states are encouraged to develop action plans that focus interventions on where nationally they are most needed.

Under the influence of the UK, the broader interpretation of the ‘One Health’ concept has been more widely adopted. The UK continues to provide leadership in this area, as was evident from the recent One Health Conference at The Hague (June 2014) in which the UK was one of the few countries to send representatives from both human and animal health sectors, the Chief Medical and Veterinary Officers and Ministers, respectively. This broader approach has led to recognition in government that this is not solely a health issue, but that AMR encompasses economic, social and security considerations. In response to this, the Prime Minister, David Cameron, established an economic review by Jim O’Neill on AMR with the recent publication of the first paper focusing on the macroeconomic impact of increasing AMR [12]. This suggests that drug-resistant infections will cost the world 10 million extra deaths per year and up to 100 trillion dollars by 2050 if action is not taken to reduce AMR (figure 3).

The success of the AMR strategy and action plan depends on strong practical support, infrastructure and high-quality data. While the UK has taken a strong leadership role, other countries have also demonstrated leadership. The USA-led Global Health Security Agenda includes a programme, co-led by the UK, specifically focused on AMR in order to provide support for countries to build infrastructure to work towards the goals outlined in the action plan. Alongside this work, a meeting in Stockholm was convened to discuss WHO-led coordination of surveillance data to ensure that the impact of action against the plan can be monitored.

The world is looking to the UK for leadership on AMR. Our leadership can be shown not just through our action on the international stage, but also through the domestic action we are taking. We need to put our own house in order if we are to advocate vigorously in the international arena. By publishing an annual progress report, we are holding ourselves to account: highlighting our successes to share our learning, and also identifying areas of weakness where we must do more [13]. The UK now has one of the world’s most effective surveillance systems for monitoring AMR and prescribing [14]. This is great progress, but surveillance is still limited, particularly in relation to antimicrobial use in hospitals. The uniformity of antimicrobial policies across NHS Trusts for the treatment of common infections needs to be improved, but without driving selection pressure for resistance by overreliance on a few key drugs. This is being addressed through the development of short syndromespecific guidance on the management of common infections in hospitals, coordinated by the Governmental Advisory Group on AMR and healthcare-associated infections (ARHAI) and the National Institute of Healthcare Excellence (NICE). These guidelines will sit in the context of a prescribing framework to promote antibiotic stewardship including prescribing diversity, lessening the risk of AMR associated with intensive use of a few antibiotic classes. This will build on existing stewardship initiatives such as ‘Start Smart then Focus’ and the soon to be published antimicrobial stewardship guidance from NICE.

We have established an AMR Research Funders’ Forum, led by the Medical Research Council, which brings together major research funders and government to ensure evidence is developed to better understand the relationship between AMR in animals and humans, laying a solid foundation for policy. This is essential because understanding of the AMR ecosystem is limited, and although progress has been made in collecting data from the human and animal health sectors, methods for linking and interpreting this combined data are yet to be developed.

The UK has played a pivotal role in galvanizing international action on AMR and we must continue to demonstrate leadership in this area. By supporting international partnerships and coalitions, we can facilitate the development of new antibiotics and other treatments. We can seek assurance from the WHO and the EU of their commitment to accelerate progress on AMR and work with the WHO to support the development of the global action plan on AMR.

Most clinicians recognize the importance of antimicrobial stewardship but there is an intrinsic tension between balancing the risk to an individual patient thought to have an infectious disease and the need to protect the population through
prevention of the development of AMR. An abundance of clinical caution can drive practitioners towards inappropriate antibiotic use and this may be mitigated by the use of robust, evidence-based clinical guidelines; rapid diagnostics could also play a key role of targeting antibiotic use. Without clinical leadership across specialties, it will prove difficult to have an impact on antibiotic prescribing in hospitals through initiatives such as ‘Start Smart then Focus’ [15].

There is good evidence that public campaigns around antibiotics lead to reduction in use. The individual impact of various public campaigns in Europe between 1997 and 2007 has been estimated to be equivalent to a 6.5–28.3% drop in the mean level of antibiotic use [16,17]. The response of the public to European Antibiotic Awareness Day in November 2013 saw unprecedented levels of online access to educational materials, with more than 12,000 people pledging to become an antibiotic guardian when the campaign was refreshed in November 2014 [18]. Whether the recent actions of many health leaders to raise public awareness of this issue through depicting a post-antibiotic era can be considered equivalent to a public campaign is unclear, but it seems likely that they will have had some impact.

Public support for action to tackle AMR is crucial, as many measures to mitigate the effects of resistance will incur substantial financial and societal costs, which will ultimately be borne by the public, both through taxation and, probably, through higher purchase costs of products whose manufacturing methods are altered. For example, a pricing paradox exists in farming whereby antibiotics, an increasingly scarce natural resource, cost less than implementation of more rigorous hygiene practices. Reversal of this paradox may lead to higher food prices. While these costs are undoubtedly less than the long-term cost of unmitigated antibiotic resistance, they are also more immediate and, superficially at least, discretionary.

If AMR is allowed to continue unchecked, we may enter a ‘post-antibiotic era’ of medicine, in which treatments from minor surgery to major transplants could become impossible, mortality will rise, and healthcare costs will spiral as we resort to newer, more expensive antibiotics and sustain a greater number of longer hospital admissions. Indeed, infection-related mortality rates may increase to a level comparable with those in the Victorian era.

The threat of AMR is grave; but there are glimmers of hope. Examples of healthcare-associated infections show that concerted, sustained and unwavering action can deliver results. Cases of MRSA in hospitals in England have declined by 87.3% from their peak in 2003, and C. difficile infections have fallen by over 60% from their peak in 2007. Yet, these successes lie against a background of a sustained increase in mortality attributable to infections caused by antimicrobial resistant bacteria as a whole.

The Royal Society can play a key role in helping to tackle AMR. Strong scientific support for this agenda, targeting AMR research and development of the basic science is badly needed. The scientific challenge is both broad and deep. We require discovery or creation of new drugs with different antimicrobial properties at the molecular level; invention of rapid diagnostic tests on the broader technological level and improved understanding of ways to influence antibiotic practice in the medical community and beyond on the social level; as well as new vaccines to prevent infection. We need to further improve surveillance systems on a global level and facilitate data sharing. And we need to develop new economic models to ensure that development of new antibiotics and technologies is a viable prospect for industrial partners. All such endeavours require sustained high-level scientific support, in terms of action and funding in addition to rhetoric.

If we are to protect the world’s population today and for generations to come, then there is much more work to be done.

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Reference


