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Antimicrobial resistance: are we at the dawn of the post-antibiotic era?

DN Williams
Retired Professor of Medicine, University of Minnesota Medical School, Minneapolis, MN, USA

In 2014 the World Health Organization (WHO) addressed the concern that antimicrobial resistance (AMR) had increased to the degree that we may no longer have effective antimicrobial treatments and are at the dawn of a post-antibiotic era.[1] This re-affirmed the need for the urgent implementation of approaches to address AMR advocated by national organisations.[2,3] The final Review on Antimicrobial Resistance details initiatives, solutions and financial strategies to avoid the potentially devastating consequences of AMR.[4] AMR has major societal and financial consequences and successful implementation will require support and leadership from the WHO, the United Nations, the G20 group of leading industrial nations, and others. Antimicrobial use is the main driver of AMR and is a shared societal responsibility. If we are to use these precious resources wisely, antibiotic stewardship principles need to be applied to human and animal use.

INTRODUCTION

AMR is a long-standing health concern that has recently garnered increased attention because of the emergence of microbes that are resistant to very many of the therapeutic agents currently available. The term 'AMR' applies to resistance in viruses, bacteria, fungi and parasites but in this Perspective the focus is on bacterial resistance to antibiotics. Gram negative bacteria in particular have developed multidrug resistance and are a global health threat. Other major threats to world health include the emergence of resistance in strains of Plasmodium species (malaria), Mycobacterium tuberculosis and HIV, and the lack of access to antibiotics. All these issues disproportionately impact the lives of people living in the developing world.[5] AMR knows no geographic borders hence the need to develop comprehensive global strategies to address the root causes and implement solutions.

Many organisms have intrinsic resistance mechanisms that preceded the discovery of antimicrobial agents. The widespread use of antibiotics in humans and animals has exerted selective pressure favouring the emergence of resistant isolates. Sir Alexander Fleming in his 1945 Nobel Prize acceptance speech was prescient in warning of the dangers of the inappropriate use of penicillin and the emergence of resistance.[6] He drew attention to the dangers of unregulated access to penicillin and the risk of penicillin-resistant organisms resulting from under-dosing the drug.

From the 1950s to the late 1990s, concerns about AMR were alleviated by the development of a steady stream of new antimicrobials which has now virtually ceased.[7,8] Common gram negative bacteria and other organisms have genetic mechanisms of developing resistance that can evade the effects of antibiotics. These include genes that enable organisms to produce enzymes such as extended spectrum beta lactamases and various carbapenemases, efflux pump mechanisms and plasmids carrying resistance genes. Recent reports of the development of colistin resistance in *Escherichia coli* mediated by a plasmid carrying the mcr1 gene have caused great concern.[9] Colistin is generally considered to be one of the antibiotics of last resort. The broader global implications of AMR are underscored by the fact that several highly resistant bacterial isolates were first reported in Asia and linked to the animal use of antibiotics.

There are many urgent aspects of AMR to address, some of which are reviewed herein, drawing from a number of resources but especially from the O'Neill Review and from personal clinical experience.[1–4,10]

The over- and mis-use of antibiotics are the main drivers in the selection of resistant bacteria. While a great deal of attention has recently been focused on the failure to develop new antibacterial drugs, this is of secondary importance to the judicious use of agents we already have. The successful development of new antibiotics and novel treatments such as monoclonal antibodies, antitoxins, probiotics and bacteriophage therapies have to be accompanied by a commitment to use them with great care to ensure their long term effectiveness.[11] The O'Neill Review outlines ways to address these and other concerns.

THE O'NEILL REVIEW ON ANTIMICROBIAL RESISTANCE

The final O'Neill Review, published in May 2016, was the culmination of a series of eight reports over 19 months[4] and was commissioned by the UK government and the Wellcome Trust. The Review clearly articulated the importance of AMR, its potentially devastating effect on

health, and its economic and security consequences. The impact of AMR is already alarming with an estimated 700,000 deaths worldwide each year but this is dwarfed by the estimate that, by 2050, 10 million people will die each year at a cumulative cost of 100 trillion US dollars of economic output, unless solutions are found.

The Review details some of the economic aspects of AMR including estimated costs of proposed solutions with country or region-specific timelines and targets for implementation. Lord Kelvin is famously quoted as saying: 'if you cannot measure it, you cannot improve it'. European Union (EU) countries have been ahead of the rest of the world in having centralised systems for collecting surveillance data of antibiotic use and resistance on a country by country basis.[12,] There are wide variations in antibiotic use between and within countries and the EU tracks use in community and hospital settings by drug class.[12,] It has now been recommended that these same surveillance systems be replicated worldwide with oversight by WHO. The global consumption of antibiotics for human use increased by 36% between 2000 and 2010; Brazil, Russia, India, China and South Africa accounted for 76% of the increase.[13] Use of the two classes of antibiotics of last resort, carbapenems and polymixins, also increased.

Antibiotic use for animal growth promotion was eliminated in the EU in 2006, starting with bans in Sweden in 1986.[14] In 2015 the USA's Food and Drug Administration introduced similar regulations on eliminating antibiotics for animal growth promotion and recommended veterinary oversight of all aspects of animal antibiotic prescribing with full implementation by December 2016.[15] In many countries, about twice as many antibiotics are used for animal, agricultural or aqua-cultural purposes than for humans.[16]

In the Review's executive summary the recommended action steps to curb AMR are laid out in terms of 'supply and demand '. Simply put, our demand for effective antibiotics for human and animal use has outstripped the supply and we must urgently address both aspects. Responsible antibiotic use is a shared responsibility hence the interest in a 'one Health' approach recognising the impact of AMR on humans, animals and the environment. There have been calls for the measurement of the impact of antibiotic use invoking the concept of an 'antibiotic footprint' of a given treatment.

AN ABBREVIATED SUMMARY OF THE O'NEILL 10 POINT PLAN TO ADDRESS AMR

A) STEPS TO REDUCE DEMAND

1. A massive global public awareness campaign.

Develop a global and sustained plan, coordinated via WHO and others to: increase awareness of AMR; support behavioural change regarding antibiotic use; and prevent over- the-counter dispensing of antibiotics without a prescription. The messages should be delivered at a country-specific level and tailored to local norms.

2. Improve hygiene and prevent the spread of infection.

- Governments, regulators and others should embed infection prevention and control practices as a top priority with targeted reduction goals for healthcare associated infections with incentives and targets by country.
- Public health and philanthropic funding bodies should support studies demonstrating the effectiveness of novel infection prevention and control interventions.
- For low and middle income countries the first step is to improve public health infrastructure, including clean water and sanitation.

3. Reduce unnecessary use of antimicrobials in agriculture and their dissemination into the environment.

- The G20, UN, WHO and other agencies would lead in the global effort to improve the collection of surveillance data regarding antibiotic use in agriculture and the spread of resistant microbes among animals. Starting in 2018, the goal is to reduce unnecessary antibiotic use in animals.
- Undertake an economic analysis of the costs associated with lowering antibiotic use in farming.
- Get an international agreement on a list of antibiotics most critical to human health to help determine which antibiotics should be banned or restricted from use in agriculture.
- Improve labelling of meat products regarding antibiotic content.
- Establish defined targets at a country level to reduce unnecessary use of antibiotics in agriculture. Targets could be set with milestones over 10 years.
- Reduce the discharge of antibiotics into the environment and monitor progress.

4. Improve global surveillance of drug resistance and treatment in humans and animals.

- This would be coordinated through the WHO's new Global AMR surveillance initiative to monitor the emergence and spread of drug-resistant infections.
- National governments and others would ensure that data be shared.

5. Promote new rapid diagnostics to cut unnecessary use of antibiotics.

- High income countries would support the use of rapid point-of-care diagnostics and facilitate their mandatory use. The aim is to inform antibiotic prescribing using patient-specific data.
- Develop a 'diagnostic market stimulus' system to ensure use in low and middle income countries.

6. Promote the development and use of vaccines and alternatives.

- Promote the uptake and use of existing vaccines for human and animal use.
- Sustain a viable market for vaccines that have the greatest potential for tackling drug resistance such as conjugated pneumococcal and *Haemophilus influenzae* Type B vaccines.
- Explore alternative treatments to antibiotics.

7. Improve the numbers, pay and recognition of people working in infectious disease.

- improve funding and training opportunities to increase the number of healthcare workers on the front line of fighting resistance and of academic scientists working in the field.
- In the US, infectious disease physicians are the lowest paid of 25 medical specialties leading to many training positions going unfilled.

B) STEPS TO INCREASE SUPPLY

8. Establish a Global Innovation Fund for early stage and non-commercial research.

- Government, public and philanthropic research organisations should collaborate on funding research into new antimicrobials and other related products (including vaccines and diagnostics).
- The goal for the Global Innovation Fund is to invest $2 billion per year over 5 years.

9. Better incentives to promote investment for new drugs and improve existing ones.

- Returns on investment to develop new antibiotics are unattractive for the pharmaceutical industry despite the very high medical need. The goal is to better align the public health needs with commercial incentives by reducing the link between profit and volume of sales through 'market entry rewards '. Upfront funding would reduce the dependence on drug sales.
- Initially the goal would be to target high need drugs to treat highly resistant *Neisseria gonorrhoeae,* Mycobacterium tuberculosis, gram negative bacteria and some fungal organisms.
- A $1 billion grant would be paid for a successful product through levies to pharmaceutical companies and other funding sources.

10. Build a global coalition for real action via the G20 and the UN

- G20 to take leadership on defined aspects of the global response to AMR, including work to develop new antibiotics, diagnostics and vaccines

In his foreword, Lord O'Neill lists four interventions for early implementation that are of particular importance for tackling AMR:

1. A global public awareness education campaign;
2. Investing in new drug development;
3. Using antibiotics parsimoniously in humans;
4. Reducing antibiotic use in agriculture.

There is general agreement by all parties on the steps to take to reduce AMR. Some members of the public misunderstand the concerns about antibiotic use and AMR, including the belief that antibiotics are effective against viruses and that the term 'antibiotic resistance' refers to the patient being 'resistant' rather than the microorganism. While many of the initiatives detailed in the Review have been articulated in the recent past and adopted by some countries, it should be pointed out that no single country can tackle and implement the necessary steps alone.[17]

SELECTED CLINICAL APPROACHES

There are many recent publications, guidelines, recommendations, and best practices[18–22] to help inform decision making on the judicious use of antibiotics together with some recently proposed regulations on their use.[23]

STEPS TO CONSIDER BEFORE PRESCRIBING AN ANTIBIOTIC

In most countries, far more antibiotics are prescribed in outpatient settings than in the hospital. Accurate and timely diagnosis of an infection requiring an antibiotic is generally more challenging in the doctor's surgery and other outpatient settings because of patient expectations, time pressures and the lack of rapid point of care diagnostic tools. It is estimated that between 30% and 50% of the antibiotic use in these settings is unnecessary. Despite major educational efforts for patients and healthcare professionals, antibiotics continue to be unnecessarily prescribed for many viral respiratory infections such as the common cold, acute pharyngitis, acute bronchitis and sinusitis.[21,24–26]

Many factors have been identified that influence antibiotic prescribing, including the patient's educational and socioeconomic status, seasonal factors, and physician behaviour and practice patterns. Feedback of an individual physician's antibiotic prescribing practices, comparisons with colleagues locally and nationally, and targeted education can help reduce unnecessary antibiotic treatment.[24–26] Sharing data that support no or delayed treatment for many respiratory infections may be helpful as physicians often cite ' fear of complications' as the reason to prescribe. Long term follow up data from a national programme in Sweden showed no correlation between a reduction in outpatient antibiotic prescriptions for respiratory infections and selected complication rates.[27] Recent publications have highlighted the potential benefit of delayed antibiotic strategies in uncomplicated acute respiratory infections in adults.[28,29] These strategies are a compromise between the clinician's desire (and the patient's request) to 'do something' and to allay fears of missing potential complications on the one hand and the goal of reducing the possible consequences of antibiotic misuse on the other.[29] While such strategies are imperfect, they can result in reducing antibiotic use without reducing patient satisfaction.

The treatment of asymptomatic bacteriuria should be avoided, except during pregnancy and at the time of urological instrumentation. Some experts also recommend treatment for patients receiving immunosuppressive agents shortly after renal transplantation. Recent data have shown that the treatment of asymptomatic bacteriuria is associated with subsequent acute symptomatic urinary infection with more resistant bacterial isolates.[30]

ANTIBIOTIC PRESCRIBING STEPS

Before prescribing an antibiotic, make sure that treatment is warranted and ask the following:

- Do the patient's symptoms suggest a bacterial or other treatable infectious process?
- Are there specific patient exposure risks to consider such as occupation; outside activities; human, animal or insect bites and contacts; travel – especially to the developing world; the consumption of unsafe food or water; sexual activity; intravenous drug use and so on?
- Is the patient in a special risk category such as a recent hospital stay or having an immunocompromising condition?
- Is the likely anatomic site of infection known? This may influence your antibiotic choice.
- Where was the infection acquired (hospital, other healthcare facility or community)?
- What is your assessment of the clinical severity of the infection?
- Does the patient have a history of a drug allergy? The history needs to be carefully reviewed and not accepted at face value as the term may erroneously be ascribed to a variety of events such as 'the antibiotic upset my stomach' or 'I immediately felt worse after I took it'. Patients with an immediate allergic reaction such as airway obstruction or hypotension should not receive the same or a closely related drug. The reaction history should be carefully documented and the patient told to remind medical staff of it at future encounters.
- Is the prescribed antibiotic known to be effective in treating the targeted infection?
- Other important factors to review include: possible drug interactions; cost; route and frequency of administration; the patient's antibiotic prescription history over the preceding three months; the drug's toxicity profile and side effects

Antibiotics account for almost 20% of emergency room visits for drug-related side effects. Co-trimoxazole and clindamycin are the most frequently implicated agents.[31] When prescribing an antibiotic the patient should be informed of possible side effects (such as rash; diarrhoea and specifically the risk of *Clostridium difficile*; gastrointestinal symptoms and fever) and provided with written materials and contact information to report concerns. Routine monitoring with laboratory tests that are tailored to the prescribed drug is important, e.g. renal function in patients receiving gentamicin or vancomycin; electrolytes, platelet and white blood cell counts in patients receiving high dose or prolonged treatment with co-trimoxazole. A longer duration of therapy can result in more side effects and this is an important consideration for patients receiving linezolid (bone marrow suppression and neurotoxicity) and metronidazole (peripheral neuropathy).

THE 'FIVE DS' OF ANTIBIOTIC PRESCRIBING

There are recommendations by the NHS and other authorities to promote antibiotic stewardship programs that include documenting the reason for antibiotic use (indication), periodically reviewing the need for ongoing antibiotic treatment and a prompt to consider a switch from intravenous to oral use.[19–22] The '5 Ds' should be reviewed 72 hours after the initiation of therapy when culture and sensitivity results may be available:

1. Discontinuation. Do you still believe that the patient has an infection? If not, discontinue treatment.

2. De-escalation. Do the microbiology results and the patient's clinical progress enable you to narrow, change or stop the initial antibiotic regimen?

3. Duration of therapy. The optimal duration of therapy for common infections has been arbitrary, typically ranging from 7 to 10 to 14 days. A recent comprehensive review of the duration of antibiotic therapy for a broad range of infections in paediatric patients gave guidance on the duration of both the initial intravenous and the total course of therapy.[32] Other examples of studies that provide guidance on treatment duration include:

a) in 'uncomplicated cellulitis', 5 days of treatment is as effective as 10 days.[33]
b) in community-acquired pneumonia, national guidelines from the UK and the USA recommend 5 days for uncomplicated mild community-acquired pneumonia with longer courses in selected circumstances. There are differences between the guidelines in the recommended drug choices.[34,35]
c) in uncomplicated urinary infections (cystitis) in women aged from 18 to 65 years, guidelines from the USA and Europe endorse short course treatments.[36,37] While details of the specific drug recommendations differ, generally one can treat for:

- 5 days with nitrofurantoin (caution in the elderly and avoid in renal insufficiency)
- 3 days with co-trimoxazole (avoid if the known local resistance to *E. coli* is > 20% or if it has been used to treat infection in the previous three months)
- a single 3 gram dose of fosfomycin
- fluoroquinolones and beta lactam antibiotics are reserved for situations where the therapeutic choice is limited by resistance or drug allergies

In the absence of complicating factors, many infections can be treated with shorter courses of antibiotics than have traditionally been used. There are controlled studies on the effectiveness of shorter courses of treatment for pyelonephritis;[36] ventilator-associated and hospital-acquired pneumonia[38,39] and intra-abdominal infection.[40]

In terms of days of therapy, if '5 could become the new 10' the result would be a lower likelihood of the emergence of antibiotic resistant bacteria, a reduced incidence of *Clostridium difficile* infection, fewer antibiotic-related drug side effects and lower costs to the healthcare system. Determining the duration of therapy depends on factors such as the host (e.g. immunocompromising condition); the clinical assessment (severity of the illness; extent of the infection; and complications); response to treatment and careful follow up.

4. Dose and dosage form. The treatment dose of an antibiotic may need to be modified for a number of reasons including renal function and the severity and site of infection. Antibiotics, particularly in paediatrics, have to be dosed by body weight and, for oral drug administration, bioavailability and factors that could affect drug absorption such as bowel disease and drug–drug interactions need to be evaluated. For sick hospitalised patients, the intravenous route is frequently preferred initially.

When can you switch from an intravenous to an oral formulation? This should be based on your assessment of the patient's overall clinical progress and the patient's ability to tolerate an oral formulation of the intravenously administered drug or an acceptable alternate. Ideally the selected drug should have favourable bioavailability characteristics.

5. Discussion/Disposition. Can you begin to formulate a plan for discharge? This should include a discussion about where the patient will be discharged to, e.g. home or to a care facility, and whether he or she will require additional medical and supportive resources.

THE ROLE OF THE LABORATORY

Not all laboratory tests are created equal and results have to be interpreted in the clinical context. Determining whether a bacterial isolate is a pathogen, a contaminant or a commensal requires clinical input. 'Positive' culture results may lead to treatment, even if it is unwarranted (e.g. treating asymptomatic bacteriuria). Results of laboratory tests are only as good as the quality of the specimen submitted for analysis and culture.[41] For example:

- Collecting cultures at the time of the clinical presentation and before antibiotics have been started will increase the likelihood of isolating a pathogen.
- The likelihood of isolating an organism from an aspirate of pus is much greater than isolating one from a swab.
- The ability to isolate an organism from a blood culture improves when testing blood volumes of 10 ml or more
- Requests to culture specimens of expectorated sputum should be rejected if the specimen does not meet accepted criteria (> 5 WBCs and less than 10 epithelial cells/HPF) as the culture results could lead to inappropriate treatments.
- Testing stool for the presence of *Clostridium difficile* toxins, should only be undertaken if 'the specimen conforms to the collection container' (i.e. loose stool).

Various biomarkers have been used to help guide whether or not to initiate antibiotic therapy such as C-reactive protein levels in pneumonia or to help decide when to stop antibiotics as in the use of serial procalcitonin levels. Matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) systems enable

the rapid identification of organisms following isolation from clinical specimens and, when coupled with ASP initiatives, have been shown to decrease the time to effective and optimal antibiotic therapy and to improve patient outcomes (30 day all cause mortality and length of stay in ICUs.[42]

Microbiology tests using techniques such as antigen detection and molecular methods can facilitate rapid detection and identification of organisms and antibiotic susceptibilities from blood and other specimens.[43] Newer rapid point of care tests can, in a matter of hours, detect:

- PBP2a allowing a methicillin-resistant *Staphylococcus aureus* diagnosis to be made or excluded.
- *Streptococcus pneumoniae* and *Legionella pneumophila* type 1 by urinary antigen testing.
- Cryptococcus neoformans, herpes simplex virus and enterovirus antigens in cerebrospinal fluid.

Multiplex PCR assays are now able to detect an increasing array of pertinent pathogens from selected tissue sources. Other technologies, such as the ability to link information from the electronic medical record at the time of medical decision making, are important. Displaying updated microbiology and other key tests at the time of order entry can get 'the right information to the right person at the right time'.

CONCLUSIONS

AMR is a reality which, according to Dame Sally Davies, the Chief Medical Officer for England[2] is 'a catastrophic threat'. Without effective antibiotics our ability to safely perform major surgeries, administer chemotherapy and undertake organ transplantation will be severely compromised. While concerns about AMR have been discussed for many years they have only recently received the attention they deserve. The WHO, the Centres for Disease Control in Europe and the USA as well as many national health systems have advocated for action. The steps are broadly agreed upon by all the key participants responsible for managing human and animal health. More work needs to be done to ensure that the public at large and physicians in general have a better understanding and acceptance of the dangers of AMR. The key now is to reduce the inappropriate use of antibiotics by the deployment of rapid point-of-care diagnostics and ongoing education. The O'Neill Reviews have made a powerful economic case of how to fund the key steps. We must all hope that world bodies will urgently agree to provide the funds to implement the recommendations.

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