ANTIBIOTICS and AMR

a global perspective

Antibiotic resistance is at a crossroad. In the world today, deaths in low income countries from Antimicrobial Resistance (AMR) are predicted to rise dramatically by 2050. We know how to stop this disaster, and some steps are being taken in the right direction. Will these steps be enough? Antibiotics for Critical Priority bacterial Pathogens are in the clinical trials stage, but, overall, the pipeline is described by the WHO as inadequate. Combinations of antibiotics and rejuvenation of old antibiotics are appearing in development and have potential alongside new chemical entities and new classes. The AMR report, chaired by Jim O'Neill, has recommended what we need to do. The actions in response to this report are, at best, patchy. Universal access to new antibiotics by both the rich and the poor may be feasible, but universal stewardship will be a difficult problem to solve. Long-term solutions, particularly for antibiotic development by the pharmaceutical industry are proposed here.

By Professor Anthony Coates and Dr Yanmin Hu

It is predicted that 10 million people will die each year from Antimicrobial Resistance (AMR O'Neil report 2016) if the present well-described inertia continues. These deaths will be predominantly in low income countries. A limited number of brave, mostly small antibiotic companies are developing new antibiotics against Critical Priority Pathogens (WHO 2017) which are Carbapenem-resistant Gram-negative bacteria. But, this alone is not enough. These new antibiotics need to become available to the poor in low income countries. Furthermore, all countries need to use antibiotics in a responsible way (for example, not via the internet or 'over the counter') – so-called Stewardship, which will reduce the emergence of resistance. New fast, cheap diagnostic tests will help this process when they become available in all countries. Since systemic antibiotics give rise to resistant bacterial mutants in the large intestine, AMR will continue to spread unless the use of antibiotics is substantially reduced, or some other solution is found. This review will discuss the WHO list of Antibacterials in Clinical Trials (2017) and will then address the difficult issues of universal access, universal stewardship and long-term antibiotic development by the pharmaceutical industry.

Table 1: WHO list of antibacterials in clinical development which are active against all three WHO Critical Priority Pathogens which are carbapenem resistant

Enterobacteriaceae (CRE)	Pseudomonas (CRPA)	Acinetobacter (CRAB)

Antibiotics which are in clinical development (WHO Antibacterial Agents in Clinical Development 2017)

The WHO has identified three Critical Priority pathogens (**Table 1**) which threaten to significantly contribute to the increase in annual global deaths from 0.7 million now, to 50 million by 2050. These are common bacteria which are highly resistant to antibiotics, including the most sophisticated penicillins, namely the carbapenems. The most dangerous of these are the Carbapenem-resistant *Enterobacteriaceae* because they are epidemic. This means that they spread rapidly with a doubling time of two years. They are also rapidly acquiring resistance to the last resort antibiotic colistin. There are six antibiotics in clinical trial development which are active against all three WHO Critical Priority Pathogens (**Table 2**).

Compounds in clinical development which are active against all three Critical Priority Pathogens

As shown in **Table 2**, of these compounds two have a new target. Five were in Phase I and one in Phase III (as reported by the WHO in 2017). Interestingly, four compounds were in combinations of which two use a beta-lactamase inhibitor plus an old antibiotic. If the beta-lactamase inhibitor has only weak antibacterial action on its own, it is unlikely to reduce the emergence of mutant beta-lactamase which results in resistance. Some betalactamase inhibitors are not active against all carbapenemases. Of the other two compounds, the mechanism of action of the synergy appears to involve increased membrane permeability.

The likelihood of the Phase I compounds reaching the market is 14%. (The Helperby compound may have a higher chance of reaching the market because it is a combination of two already marketed antimicrobials.) The Phase III compound is more likely to reach the market.

This pipeline is inadequate because it is uncertain that these compounds will eventually reach the market. Furthermore, according to the WHO this pipeline will not be sufficient to tackle the impending AMR threat.

Helperby Therapeutics has developed a new combination with Azidothymidine (a new class of anti-bacterial with a new target, **Figure 1**) and colistimethate sodium (colistin). The mechanism of

ANTIBIOTIC	CLINICAL TRIAL PHASE	COMPANY	NEW TARGET
ARB-002 (Azidothymidine) + CMS	I	Helperby Therapeutics Ltd	Yes
VNRX 5133 + cefepime	I	VenatoRx Pharmaceuticals	Yes
SPR-741 + β-lactams	I	Spero Therapeutics, Inc	No
AIC 499 + BLI	I	AiCuris GmbH	No
GSK334280	I	GlaxoSmithKline plc	No
Cefiderocol	3	Shionogi Inc	No

Table 2: Six companies with compounds active in all three WHO Critical Priority Pathogens

action of azidothymidine is to bind to the end of the replicating DNA strand (**Figure 1A**) which blocks DNA strand elongation. Eventually the block can be relieved by the cleavage of azidothymidine from the strand (**Figure 1B**) which allows elongation to resume. The combination is synergistic against colistin-carbapenem resistant CRE. The synergy opens up the development of Low Dose colistin regimen.

The combination is faster acting than colistin alone. It is also active against CRAB and CRPA. Because the two compounds are already in clinical use, the FDA and EMA allow facilitated clinical development paths (such as 505(b)2 by FDA), GMP supply, is established and most preclinical/toxicity work has been completed, so the development time should be quicker than for NCEs. Importantly, the two compounds are both antibacterial, therefore the enhanced combination of the two should be able to reduce the emergence of resistance. An outline of the pharmacokinetics in 27 healthy volunteers of the combination of azidothymidine and colistin is shown in **Figure 2**.

VenatoRX Pharmaceuticals is developing a boranate-based beta-lactamase inhibitor which is active against serine- and metallo-betalactamases. This is a new class/target. It is combined with cefepime.

Spero Therapeutics, Inc has completed a Phase Ib drug-drug interaction trial of SPR741 which is a novel non-antibacterial polymyxin. It is thought to increase permeability of bacterial membranes, and to enhance the action of beta-lactam antibiotics. In the clinical trial it was combined with piperacillin/tazobactam, ceftazidime and aztreonam.

AiCuris GmbH. There is limited availability of information about the structure, activity or partner beta-lactamase inhibitor.

GlaxoSmithKline. GSK-3342830 is siderophore-cephalosporin. The siderophore uses the bacterial iron transport pathway to enhance uptake of the compound through the outer membrane of Gram-negative bacteria. A Phase I trial was suspended in March 2017.

Shionogi Inc. Cefiderocol is a siderphore-cephalosporin. It has completed Phase III clinical trials for hospital-acquired and ventilator-associated pneumonia and critical Gram-negative pathogens.

Further compounds in clinical development which are active against one or two Critical Priority Pathogens

There are a further 12 compounds in clinical trials which are in this category. Of these, seven are combinations, all of which are beta-lactamase inhibitors. Clinical trial stage compounds: three are in Phase III, two in Phase II and six in Phase I and information about one is not available. These compounds will be particularly useful in situations where the susceptibility of the pathogen is already known, for example after conventional or rapid diagnostic tests. Where the pathogen is unknown, these new compounds could be useful in combination with other antibiotics if it is suspected that the spectrum needs to be broadened.

The case for the development of combinations of antibiotics – rejuvenation with combinations and reduction of resistance emergence

Combinations of antibiotics are used to rejuvenate old antibiotics. The classic example is the combination of a beta-lactam and a beta-lactamase inhibitor, such as amoxicillin plus clavulanic acid. Of the 18 compounds in clinical development, with activity against one of more Critical Priority Pathogens, half are combinations with beta-lactamase inhibitors. Companies such as Spero and Helperby Therapeutics are developing non-beta-lactamse combinations which rejuvenate old antibiotics against all of the WHO Critical Priority pathogens by permeabilising the bacterial membrane.

Another important impact of combinations is to prevent the emergence of bacterial resistance to antibiotics. In 1948, streptomycin was used to treat tuberculosis patients. Although improvement occurred initially, resistance developed and many died. In 1952, the British Medical Research Council completed a landmark trial in which they treated tuberculosis patients with a combination of streptomycin and para-amino-salacylic acid. Resistance did not develop and all the patients survived.

This showed that combinations can prevent the emergence of resistance in patients with tuberculosis. This finding has led to the development of the standard four-drug combination regimen which is used to treat tuberculosis today. Unfortunately, if this standard TB regimen has not been used properly, for example, patients fail to follow the course of medication, resistance emerges. The way that combinations prevent the emergence of resistance is thought to be through the mutation frequency of the individual drugs in the combination. For instance, if we consider the combination of old antibiotics A and B which act on different targets, if A has a mutation frequency of 10^{-6} and B also has a mutation frequency of 10^{-6}, the mutation frequency of the combination should be 10^{-12}. In

Figure 1
The mechanism of action of Azidothymidine (AZT): AZT is incorporated into the replicating DNA strand (A) and blocks further replication. In humans, AZT also blocks DNA replication, but is quickly cleaved off the end of the DNA strand (B) and replication is restored

other words, a combination of the two drugs is much less likely to lead to the emergence of resistance than one drug which is used on its own. Combinations have also been developed for infections due to Helicobacter pylori and Human Immunodeficiency Virus. These regimens also prevent the emergence of resistance.

However, combinations have not been well explored for common Gram-positive and Gram-negative bacterial infections. Here, I describe a small number of examples. While, a combination of trimethoprim and sulfamethoxazole was developed, resistance did develop, probably because the drugs targeted different enzymes in the same metabolic pathway. Combinations of beta-lactam antibiotics and beta-lactamase inhibitors are widely used, but resistance has also arisen to these, possibly because most betalactamase inhibitors are not themselves antibacterial, and so the accompanying beta-lactam antibiotic is, in effect, monotherapy, which quickly leads to resistance.

In my view, the way forward is to re-explore the combination of two or more antibacterial agents, each of which acts on a different mechanism against the target bacterium. In the WHO list of antibiotics which are active against Critical Priority Pathogens, Helperby Therapeutics is developing a Phase II ready combination of azidothymidine and colistin. Both of these compounds are active against Enterobacteriaceae. Azidothymidine is a bacterial DNA chain replication inhibitor (see **Figure 1**) and is a new class of antibacterial compound.

The Review on Antimicrobial Resistance (chaired by Jim O'Neill, published in 2016)

This review recommended 10 interventions, sometimes called the Ten Commandments:

1. A massive global public awareness campaign. There has been some progress in some countries, but much more needs to be done.
2. Improve hygiene and prevent the spread of infection. There is already a wide range in standards between different countries. Although some new efforts are under way, there is a long way to go. For example, the spread of colistin resistance seems to be faster than expected, particularly in bacteria which are also resistant to carbapenems.
3. Reduce the unnecessary use of antimicrobials in agriculture and their dissemination into the environment. Some good progress in some countries, but still a long way to go.
4. Improve the global surveillance of drug resistance in humans and animals. There has been some progress in some countries.
5. Promote new, rapid diagnostics to cut unnecessary use of antibiotics. Significant progress has been made in the development of new fast diagnostic tests for antibiotic resistant bacteria. Some of these tests are already in the market and improved, even faster, tests are in development. The AMR report suggested that rapid diagnostic tests should be a prerequisite for all antibiotic prescribing, but no government is enthusiastic about this idea. But, for new diagnostics to reduce unnecessary antibiotic usage and provide effective therapy to those

most in need, they must be embedded in clinics throughout the world.

6. Promote the development and use of vaccines and alternatives. Some progress is being made, but the absence of enough interest by big pharmaceutical companies and the lack of market entry rewards, will slow this important area.

7. Improve the numbers, pay and recognition of people working in infectious disease. Following the increase in AMR publicity and financing, the number of researchers in the area seem to be increasing.

8. Establish a Global Innovation Fund for early-stage and non-commercial research. The news is encouraging because the financing for early stage research and development is increasing. For example, the Chinese and British governments, the Wellcome Trust and the US Biomedical Advanced Research and Development Authority (BARDA) and the Danish pharma company Novo have announced significant new joint funding initiatives.

9. Better incentives to promote investment for new drugs and improving existing ones. Although representatives of the 25 largest pharmaceutical companies are thought to have discussed AMR (at Davos 2018), they agreed to remain engaged on the issue. This is very disappointing. For example, serious interest in AMR by big pharma and market entry rewards, as suggested by the O'Neill report would stimulate and facilitate new drugs, vaccines and diagnostic tests.

10. Build a global coalition for real action-via the G20 and the UN. Progress is slow. On the one hand, governments tend to move slowly. On the other, if all the people who die from AMR in one year were to die in one day (for example in plane crashes or fires), governments would move much faster than they have done over the past two years.

Overall, progress during the past two years has been patchy. Some areas, such as the return of big pharmaceutical companies and the introduction of market entry rewards have not occurred. This means that new drugs, vaccines and diagnostic tests will struggle in the development and marketing stages. In my view, at the present slow rate of progress, the O'Neill projections for 10 million deaths per year by 2050 may be an underestimate.

Universal access- – supply to the rich and to the poor

Antibiotics are life-saving drugs. Antimicrobial resistance means that many antibiotics are no longer effective amongst the poor. New antibiotics are going to be discovered and developed mainly in high-income countries, such as the US. But most of the burden of AMR disease is already falling upon lower income countries, and will continue to do so. In the 1980s, new drugs for AIDS were developed in high income countries, but were too expensive for the poor. Indian companies such as Cipla, led by Yusuf Hamied, produced AIDS drugs which were affordable by the poor for a fraction of the cost. This is a somewhat extreme commercial model. In the AMR field, there is a not-for-profit model, called the Global Antibiotic Research and Development Partnership (GARDP). WHO was the midwife, DNDi the mother and GARDP the baby, born in 2016. It has a remit to ensuring universal access. In addition, GARDP aims to develop antibiotics and antibiotic combinations which are not commercially viable, such as treatments for sepsis in babies and children, and for highly-resistant gonococcal infection. This model is not suitable for commercial development, although GARDP does partner with companies. An example of a commercial model (there are many) is Helperby Therapeutics which has a partner in India which co-develops combinations of antibiotics and supplies to India and Africa at prices which are affordable by the poor, while Helperby sells into high income countries.

Stewardship

Antibiotic stewardship is co-ordinated intervention which reduces inappropriate use of antibiotics by helping the selection of the optimal antibiotic regimen (the dose, duration and route). The global reduction of inappropriate antibiotic use is important because the administration of an oral antibiotic to humans results in antibiotic resistance in the large intestine within seven days. The length of time that the resistant bacteria are detectable in the individual is up to one year. This means that each individual who has been treated with an oral antibiotic is defaecating resistant bacteria for up to a year. Since many people in low income countries do not have access to toilets, contamination of the environment with highly-resistant bacteria occurs. It has even been recorded that up to half of visitors from a low-level resistance country who spend time in a country with a high level of antibiotic resistance, return home carrying highly-resistant bacteria in their large intestine. In high-income countries, where water flushing toilets are usually available, the antibiotic treated individual carries resistant bacteria in the intestine, may transmit them to their household and may be a risk to themselves – for example, if they require surgery or become immunosuppressed. Furthermore, sewage systems sometimes break down and release raw

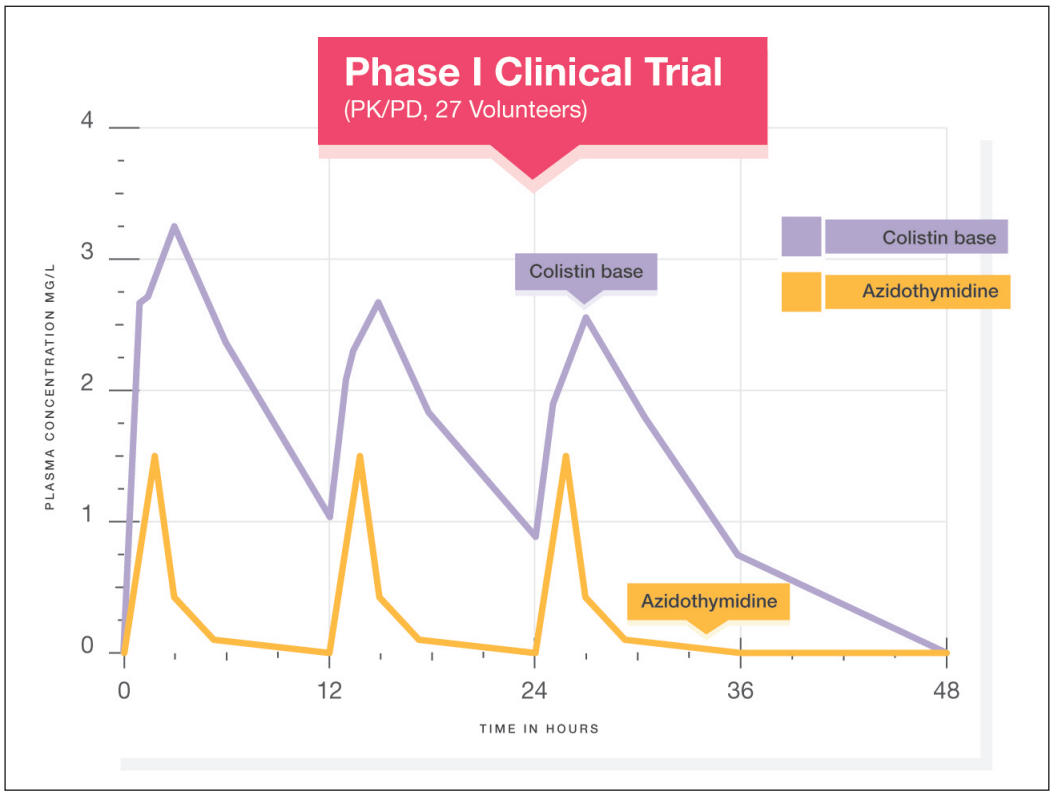

Figure 2
Phase I clinical trial of a combination of azidothymidine and colistin: Helperby Therapeutics is in clinical development with a combination of two antimicrobials, namely azidothymidine(a new antibacterial class in clinical development) and an old antibiotic colistin which is considered to be the last resort for Gram-negative bacterial infections. This combination is active against all three WHO Critical Priority pathogens. The figure is a cartoon of the serum levels in a Phase I Pharmacokinetics Clinical Trial in 27 volunteers. Doses of the drugs were no higher than approved doses in the case of AZT, and were lower than doses which are often used in the clinic for colistin. Concentrations in sera were observed which, in combination, are bactericidal

effluent into river systems, thus contaminating the environment.

Stewardship requires local guidelines and teams of trained professionals. In UK, for patients with life-threatening infections, prompt, effective antibiotic treatment must be started within one hour, or as soon as possible. Broad-spectrum antibiotics should be avoided and careful documentation should be recorded in the patient's clinical records. For prophylaxis, a single dose is recommended, or more doses in special circumstances.

Once susceptibility is known, switch to the correct antibiotic. Ultra-rapid antibiotic sensitivity tests which give results in less than one hour would be helpful. National and local stewardship guidelines and regular reviews will be needed. Education of patients, and their clinical and non-clinical care givers, should be a priority in the fight against AMR.

The United Nations has recommended that every country plays its part in the control of AMR, and improved stewardship is an important component of these efforts.

A global stewardship regulatory authority is a logical next step. However, at the present time it is unlikely to be a practical solution. For example, internet purchase of antibiotics, particularly by people with poor access to these drugs, sale of antibiotics over the counter, provision of antibiotics by people who are not medically qualified, poor sanitation, poor education, war and inadequate infrastructure are significant hurdles. Whether countries will adopt effective stewardship schemes by 2050 is an open question. In the first two years since the UN resolution, there has not been an obvious slowing of, for example, the epidemic spread of colistin resistance. This does not bode well for the global control of the spread of AMR.

What should the pharmaceutical industry do to tackle the AMR problem?

It is easy to blame the large pharmaceutical companies for failing to develop new antibiotics. However, it costs huge sums of money to discover, develop and then market an antibiotic. It is well known that the unit price for a course of treatment for a life-threatening infection with a new antibiotic is lower (from 10-1,000 fold) than other new drugs, such as new cancer or immunologic treatments. Big pharmaceutical companies are not charities and answer to shareholders who require profits. What is clear now is that they will not come to the rescue (with a small number of exceptions), unless the financial rewards are realistic.

What they should do, in my view, is to make a joint effort to persuade governments to introduce market entry rewards. A prize of $1 billion or more (as suggested by Jim O'Neill's AMR report) for the development of new treatments to combat AMR would make a significant difference.

Nevertheless, the present situation is quite positive. In spite of all the challenges, a handful of mainly small companies have antibiotic treatments in clinical trials against all three of the WHO Critical Priority Pathogens. A further 12 companies have compounds which are active against one or two of these dangerous pathogens. There are increased levels of grants and fast track regulatory support. The first global public private partnership has been founded and has raised substantial sums of money for the development of antibiotic treatments for infections which the commercial sector is unlikely to cover.

New antibiotics which are effective against the Critical Pathogens will reach the market. How the market will respond is not clear. The optimistic view is that several of these will be blockbusters like Cubicin, in other words will earn a billion dollars or more per year. The pessimistic view is that they will struggle because it is fashionable to pay a low price for antibiotics. It is my view that some of these drugs will attain universal access for the poor, particularly for companies which have partners in low income countries. Whether these new antibiotics will be used in accordance with good stewardship is unknown at the present time.

What is the 100-year plan for a pharmaceutical industry which faces the complete destruction of the current repertoire of available antibiotics? The simple answer is that there is no plan. Unfortunately, bacteria do have a plan. This is to become resistant as quickly as possible to all new antibiotic threats. It has served them well for billions of years.

My view is that industry should have a long-term plan. The plan must be to find treatments for AMR as quickly as bacteria do. For example, to focus on developing new monotherapies for AMR, and then throwing them away, is unsustainable for a 100 years. The plan should include old antibiotics. The rejuvenated old antibiotic would only be used in combination with another antibiotic in order to reduce the emergence of resistance.

Combinations could be two, three or even four drugs, as is the case in tuberculosis therapy. Ultrafast diagnostics would be used to choose the correct combination. The current regulatory framework is much too slow to deal with AMR, which can arise in a few days. In order to populate a new range of antibiotic combinations of old and new antibiotics, ultra-fast clinical trials are needed. For example, Phase I/II PK/PD with less patients than at present. In this way, it could be envisaged that a single old antibiotic could be rejuvenated several times in a 100-year period by combination with different antibiotics (sometimes called antibiotic resistance breakers). That half of the 18 drugs in clinical development against Critical Priority Pathogens are combinations with betalactamase inhibitors supports the idea that rejuvenation of old drugs is feasible in the long term.

Conclusion

Antibiotic discovery and development for resistant Gram-positive bacteria has been successful. For Critical Priority carbapenem-resistant Gram-negatives, the pipeline is inadequate, although the prospects are reasonably good for some drugs, even if they do not cover all of the problem bacteria. DDW

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