Introduction to Antibiotic Resistance

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Abstract The inexorable rise in multidrug-resistant Gram-negative bacteria has been widely reported. Multiple modes of resistance often present in a single strain of bacteria, and this may also be combined with an increase in virulence, both of which are leading to a significant increase in morbidity and mortality in patients. Against this background, the absolute number of new antibiotics licensed has declined especially for Gram-negative multidrug-resistant pathogens. The reasons for this failure are presented here: market issues, big pharma changes, regulatory constraints, difficulties in finding drugable targets and, lastly, suitable compounds worthy of full development.

Keywords Antibiotic resistance • Gram-positive bacteria • Gram-negative bacteria • Regulatory

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Antibiotics have saved millions of lives and eased the suffering of patients of all ages for more than 60 years. These "wonder drugs" deserve much of the credit for the dramatic increase in life expectancy in the United States and around the world in the twentieth century. They prevent amputations and blindness, advance our ability to perform surgery, enable new cancer treatments to be used and protect the lives of our military men and women. A famous infectious disease expert once noted that the discovery of penicillin in the early 1940s gave more curative power to a lone provider than the collective talent of all the physicians in New York City at that time. Unfortunately, it is inevitable that, over time, bacteria develop resistance to existing antibiotics, making infections more difficult to treat.

Antibiotic resistance is not a new phenomenon. National surveillance data and independent studies show that drug-resistant, disease-causing bacteria have multiplied and spread at alarming rates in recent decades. A diverse range of patients is affected. The Institute of Medicine (IOM), Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH) and Food and Drug Administration (FDA) warn that drug-resistant bacteria are a serious public health threat, especially considering that there are a few novel drugs in the pipeline to combat them.

Infections that were once easily curable with antibiotics are becoming difficult, even impossible, to treat, and an increasing number of people are suffering severe illness—or dying—as a result. This year, nearly two million people in the United States will acquire bacterial infections whilst in hospital, and about 90,000 of them will die, according to CDC estimates. More than 70% of the bacteria that cause these infections will be resistant to at least one of the drugs commonly used to fight them. In a growing and frightening number of cases, these bacteria are resistant to many approved drugs, and patients have to be treated with new, investigational compounds or older, possibly more toxic alternatives. For many patients, there simply are no drugs that work.

Furthermore, some strains of resistant bacteria are no longer confined to hospitals and are occurring in otherwise healthy individuals in communities across the United States and other countries.

In 1998, Bax and others noted the increase in MDR pathogens leading to antibiotics in general losing their effectiveness. According to IOM and FDA, only two new classes of antibiotics have been developed in the past 30 years, and resistance to one class emerged even before the FDA approved the drug. Nalidixic acid launched in 1962 and then daptomycin launched in the USA in 2003, these are the last two systemic antibiotics with a completely new mode of action introduced to the market (Bax et al. 1998). The recommendations include researching and developing new antibiotics, clarifying the strengths and weakness of clinical trials with the aim of improving their relevance. This included measuring the precise impact of the use of antibiotics on the prevalence of resistance, the effect of resistance on a range of clinical outcomes and the effect of outcomes on costs.

As resistant bacteria multiply, so does the burden they place on our healthcare system. The economic cost has reached billions of dollars annually in the United States, according to estimates from IOM and the former Congressional Office of Technology Assessment. The human cost in terms of pain, grief and suffering, however, is incalculable.

1 What Is Happening to Antibiotic Resistance?

Multidrug resistance (MDR) is increasing (Arias and Murray 2012; So et al. 2012). Amongst Gram-negative bacteria, the increasing incidence of bacteria which carry carbapenemases, such as New Delhi metallo-beta-lactamase (NDM-1) and extended-spectrum beta-lactamases (ESBL) (Pitout and Laupland 2008), is particularly worrying because very few antibiotics remain that are effective against such MDR bacteria. In addition, for some MDR strains there may be an increase in virulence (Walsh 2011; Poirel et al. 2007).

The phenomenon of more than one resistance mechanism occurring in one mutant strain of bacteria is increasing the threat. For example, enzymes which destroy antibiotics, porin defects, alteration in cell wall structure, changes in RNA and efflux pumps can all occur in MDR strains (Taubes 2008). Plasmids which encode MDR genes are an important part of the rapid transfer of resistance between bacteria within a species and even between species. In Gram-negative bacteria, beta-lactamases in the periplasmic space destroy beta-lactams including, in some cases, carbapenems. Overexpression of transmembrane efflux pumps can reduce the efficacy of beta-lactams including meropenem, aminoglycosides, quinolones and tetracyclines. Antibiotic-modifying enzymes can blunt the activity of aminoglycosides and ciprofloxacin, and mutations of the DNA gyrase and topoisomerase IV genes induce resistance to quinolones (Giamarellou 2009).

Other mechanisms of antibiotic activity include ribosomal mutation or modification which reduces the effect of tetracyclines and aminoglycosides, mutations in lipopolysaccharide structure which affects the efficacy of polymyxin and loss of porins which reduces the efficacy of carbapenems. Bypassing of dihydrofolate reductase leads to resistance to trimethoprim, and bypassing dihydropteroate synthase results in sulphonamide resistance (Livermore 2009).

The traditional way of developing a broad-spectrum, blockbuster, antibacterial drug is probably a thing of the past, and targeted treatments are now required. This requires different regulatory routes and these are currently being considered but need significant development (Livermore 2004). The current considerations include a greater use of PK/PD to support clinical trials and conditional approval for compounds with a high medical need to risk ratio. Pathogen-specific indications require significant discussion and development with regulatory authorities and experts in the field. Pathogen-specific clinical studies may be more scientifically valid than indication studies because an anti-infective targets infecting organisms and the clinical expression of disease varies by pathogen, site of infection, virulence and host response. Perhaps the orphan drug route could be used for rare life-threatening infections such as those caused by NDM-1? Should surrogate markers be developed? What is the place of rapid diagnostics? Another question is whether approval, which is based on extrapolations, could be arranged for compounds with similar microbiological, pharmacological and disease characteristics, for example, intra-abdominal sepsis and gynaecological infections.

Drug-resistant pathogens are responsible for more and more infections. Indeed, it is impossible to study even a single MDR species in all indications. An indication-only

approach may frustrate wider application, and the corollary will follow: that a pathogen-only licence may actually extend use. Importantly, the ratio of benefit-risk is the basis of medical need and of regulatory support. Both individual benefit and public health need to be considered. The licensed indications of recently marketed antibacterials (since 2000) are helpful, but many are not indicated for infections caused by Gram-negative bacteria. The exceptions are gemifloxacin and tigecycline which are also active against certain MDR pathogens. All remaining antibiotics, except ertapenem, were licensed for MRSA (Livermore et al. 2003).

The licensed indications of antibiotics since 2000 are useful for indications such as acute bacterial skin and skin structure infections (ABSSSI) and Gram-positive community-acquired pneumonia (CAP) but not indications in which MDR Gram-negative bacteria cause the infection. And this is where medical need is highest.

2 Epidemiology of Resistance

MDR organisms are now present in every continent and in virtually every hospital in the world. There is a marked regional variation in the incidence of MDR strains, and indeed, the number of clinically significant infections caused by them fluctuates between each hospital. In other words, the intra-hospital infection rate due to MDR Gram-negatives varies (Gopalakrishnan and Sureshkumar 2010). Some countries have higher levels of resistance than others. For example, the incidence of MRSA in Greece is higher than that in Sweden (Sader et al. 2006).

The species of MDR bacteria which are most prevalent and are responsible for two-thirds of all healthcare-associated infections (HIAs) are conveniently described by the acronym, ESKAPE (Bouchett et al. 2009). The six pathogens that make up this acronym are *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter spp*.

Intensive care units (ICUs) are an important focus of antimicrobial resistance because patients there are particularly vulnerable to infection. Recent data from ICUs in Europe (Vincent et al. 2009) show that the incidence of Gram-positive infections, such as MRSA, has either decreased or remained stable and the prevalence of bacteria resistant to vancomycin, daptomycin or linezolid has remained at a low level. Unfortunately, the prevalence of MDR Gram-negative bacteria is increasing, and this is creating a particularly serious situation in ICUs. MDR *Escherichia coli* and *Klebsiella pneumoniae* are a special problem; these organisms have transferable resistance genes residing on plasmids and produce enzymes such as extended-spectrum β-lactamases and carbapenemases. Carbapenemase-expressing bacteria, such as *Klebsiella pneumoniae* (EMA/ECDC Joint Technical Report, the bacterial challenge: time to react http://ecdc.europa.eu/), are a particular problem because carbapenems are the antibiotics of last resort for some MDR Gram-negative infections. The alternatives, such as polymyxins, are quite toxic and are associated with a less favourable outcome for the patient (Falagas et al. 2005).

This problem is currently such a major public health threat that the British Health Protection Agency (HPA) and the Advisory Committee on Antimicrobial Resistance

and Healthcare Associated Infection (ARHAI) have issued an advisory note on the detection of carbapenemases, infection control and treatment which is available at. http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/CarbapenemResistance/GuidanceOnCarbapenamProducers/.

NDM-1, the New Delhi metallo-carbapenemase, has been observed in Enterobacteriaceae since 2008 (Yong et al. 2010). In 2010, Kumarasamy 2010 described 29 cases in the UK, 17 of which were associated with visits to India and Pakistan. This was supported by data showing that NDM-1-carrying Enterobacteriaceae are widespread across the Indian subcontinent (http://www.ncbi.nlm.nih.gov/pubmed/20705517). Street water in New Delhi is contaminated with NDM bacteria, which suggests that travellers become colonised and then carry these MDR organisms to other countries (http://www.channel4.com/news/drug-resistant-superbug-threatens-ukhospitals). Also, it is reported that in a hospital in Mumbai, 5–7% of Enterobacteriaceae carry NDM-1 (http://www.ncbi.nlm.nih.gov/pubmed/20964525).

Not only does NDM-1 destroy the main group of last-resort antibiotics but it can also be transferred between different species of bacteria (Potron et al. 2011).

The emergence of NDM-1 marks a serious deterioration in the range of effective antibiotics which are currently available to treat MDR-resistant Gram-negative bacteria.

Recent data suggest that dissemination of antibiotic resistance amongst MDR Gram-negative bacteria is associated with high-risk clones (Woodford 2008). In some cases, it is thought that single clones spread; for example, multilocus sequence typing has shown that KPC carbapenemase-positive *Klebsiella pneumoniae* ST258 spread from Greece to northwest Europe. In other cases, clones may repeatedly and independently acquire resistance. Woodford and colleagues looked at the interplay between clone and resistance for *E. coli, K. pneumoniae, Acinetobacter baumannii* and *Pseudomonas aeruginosa* and observed that high-risk clones play a major role in the spread of resistance. These clones seem to accumulate and switch resistance.

3 Concerns and Activities Occurring to Reduce This Threat

In September 2001, WHO launched the first global strategy for combating the serious problems caused by the emergence and spread of antimicrobial resistance. Known as the WHO Global Strategy for Containment of Antimicrobial Resistance, it recognised that antimicrobial resistance is a global problem that must be addressed in all countries. No single nation, however effective it is at containing resistance within its borders, can protect itself from the importation of resistant pathogens through travel and trade. Poor prescribing practised in any country now threatens to undermine the potency of vital antimicrobials everywhere.

The WHO strategy recommends interventions that can be used to both slow the emergence and reduce the spread of resistance in a diverse range of settings. These interventions are organised according to groups of people whose practices and behaviours contribute to resistance and where changes are judged likely to have a

significant impact at both national and international levels. These include consumers, prescribers and dispensers, veterinarians and managers of hospitals and diagnostic laboratories, as well as national governments, pharmaceutical industry, professional societies and international agencies (http://www.who.int/mediacentre/factsheets/fs194/en sourced 15th Jan 2011).

4 US Congress

Until recently, research and development (R&D) efforts have provided new drugs in time to treat bacteria that became resistant to older antibiotics. That is no longer the case. Unfortunately, both the public and private sectors appear to have been lulled into a false sense of security based on past successes. The potential crisis at hand is the result of a marked decrease in industry R&D, government inaction and the increasing prevalence of resistant bacteria. Infectious disease physicians are alarmed by the prospect that effective antibiotics may not be available to treat seriously ill patients in the near future.

The Infectious Disease Society of America report in July 2004 published the report entitled "Bad Bugs, No Drugs" with a subtitle: "As Antibiotic Discovery Stagnates. . . A Public Health Crisis Brews" (Infectious Disease Society of America 2004). This report discussed possible incentives most likely to spur R&D within major pharmaceutical companies. The committee also considered the FDA as pivotal partners along with their "critical path" initiatives. Other groups who needed to invest new resources include the congress, the administration, CDC, NIAID and public-private research efforts.

5 European Medicines Agency (EMA) Activities

MDR bacteria remain a major issue in hospital-associated infections, and new reservoirs for such organisms have arisen both in the community and in animals (Dufour et al. 2002; Cuny et al. 2010).

Alarmingly, the number of infections that now require treatment with either carbapenems or polymyxin is increasing (Meyer et al. 2010). In contrast, the number of new antibiotic applications has decreased, and the level of R&D within Europe has declined over the last few years (ECDC EMA Joint Report 2009).

Several requests have been made to the EMA to provide more detailed guidance on the requirements to support issues such as patient selection and primary endpoints. For some indications, there is no established position on data required because either they are rarely studied or because existing guidance does not cover such issues.

In February 2010, the EMA released, for comment, revised draft guidelines for the evaluation of medicinal products indicated for the treatment of bacterial infections (CPMP/EWP/558/95 rev2). In preparation for the next revision of these guidelines (rev3), the EMA Efficacy Working Party (EWP) organised a meeting on

7th–8th February 2011 with key European opinion leaders, industry representatives and the FDA. The objectives of this meeting were to receive comment on the Rev2 guidelines, to debate ways to improve the regulatory process so that the decreasing rate of new antibiotic applications and declining R&D within Europe might be reversed and to discuss important differences between the EMA and FDA opinions on clinical trial design with a view to achieving harmonisation.

Meeting participants included members of the EMA, European regulatory authority experts, the Anti-Infective Scientific Advisory Group (SAG), selected experts from the European Federation of Pharmaceutical Industries and Associations (EFPIA) and other experts including RB.

The report of the workshop was published on the EMA website on the 17th March 2011 (EMA/257650/2011) as a concept paper, and an addition to the note for guidance on evaluation of medicinal products published on 22nd September 2011 (EMA/CHMP/EWP/736904/2011) proposed the development of the addendum.

Many issues were discussed including non-inferiority/superiority studies, bacteraemia, febrile neutropenia and MDR bacteria. These activities and related documents are a genuine attempt by the EMA to address some major issues that antibiotic developers have experienced including changes in goalposts, unrealistic expectations, increased bureaucracy and increases in complexity and size of clinical trials. Regulators are oblivious to the increasingly limited resources and financial burden of most of the antibiotic developers. Added to this is that many of the primary endpoints required by the EMA for indications such as pneumonia and skin and soft tissue bacterial infections are different to those required by the FDA. This state of affairs is bad for the regulators, bad for the antibiotic developers and bad for patients!

Williams and Bax (2009) state that regulatory activities have had a major negative impact on the R&D and availability of new antibiotics. Pharmaceutical companies have abandoned investment in this area. Mass redundancies have resulted with no large pharmaceutical companies now working in antibacterial research. This has now resulted in significant loss of expertise in antibiotic R&D.

6 React

React (reactgroup.org) is an independent global network for concerted action on antibiotic resistance which is funded by the Swedish government and Uppsala University. React acts as a forum for ideas, debate and collaboration between diverse stakeholders in order to manage concerted global action on antibiotic resistance.

There are numerous other groups involved.

TATFAR comprise of European and US members of the Transatlantic Task Force for Antimicrobial resistance (ecdc.europa.en/activities/diseaseprogrammes/tatfar). TATFAR are looking at challenges and solutions in the development of ways to manage the increasingly difficult issue of antimicrobial resistance. These activities are funded via the European Centre for Disease Prevention and Control (ECDC) located in Stockholm, Sweden. Their mission includes the strengthening of

Europe's defences against infectious diseases. Specific activities include the European Antimicrobial Resistance network (EARS-NET).

The Infectious Disease Society of America (IDSA) (http://www.idsociety.org) represents 9,000 physicians and healthcare professionals who specialise in infectious diseases. Initiatives to address the growing antimicrobial resistance problem include proposals to build sustainable antibiotic R&D included in the short term to produce the 10 × 20 initiative, whereby leading to the delivery of ten new systemic antibiotics by 2020. This has led to detailing the US Congress and Food and Drug Agency (FDA). In fact, this has resulted in over 60 communications. Included in these are efforts to provide the input into the FDA in order to bring regulatory clarity to the antibiotic approval pathway. The IDSA also lobbied US Congress to advance the adaption of statutorily defined incentives with sufficient power to encourage manufacturers to engage in antibiotic and related diagnostic R&D.

The British Society for Antimicrobial Chemotherapy (BSAC) with 700 members exists to facilitate the acquisition and dissemination of knowledge in the field of antimicrobial therapy. The BSAC (http://www.bsac.org.uk) in Urgent Need initiative identified the barriers discouraging participation in antibacterial R&D and considered what opportunities exist to stimulate interest in the field looking at three major components required to bring antibacterial agents to the market.

7 Present State of Antibiotic Research Constraints

Generally, infections caused by Gram-positives such as methicillin-resistant Staphylococci (MRSA) are still susceptible to a range of old and new antibiotics (Boucher et al. 2009).

Two new novel antibiotic classes active against multi-resistant Gram-positive infections were commercialised in the decade starting in the year 2000. Unfortunately, this is not the same situation for multi-resistant Gram-negative bacillary bacteria. The last truly novel active antibiotic against Gram-negative bacteria was nalidixic acid, the forerunner of the plethora of quinolone antibiotics. The development of resistance of common bacteria including *Staphylococcus aureus* and Gram-negative bacteria such as *Pseudomonas aeruginosa* has been rapid. A large number of analogues have been developed in each class of antibiotics although market delivery of analogues has been more feasible for some classes, such as cephalosporins and quinolones, than others, for example, the macrolides.

New analogue development, however, has not been able to keep up with the rise in MDR Gram-negative organisms for the last decade or so. New antibiotics must attack multiple targets within each bacterial species which also are increasing over time. These bacteria are now expressing multiple-resistant determinants against a large number of established antibiotic classes such as beta-lactams and beta-lactam inhibitors, aminoglycosides, quinolones and tetracyclines. In addition, the acquisition of multidrug resistance determinants by bacteria appears to increase the pathogenicity of the bacteria. Part of the problem of the lack of new novel agents is because in the

1990s big pharma companies adopted a strategy of R&D which was beguiling opportunity of the new techniques in molecular biology which included bacterial genomics, combinatorial chemistry and high-throughput screening enabling the identification of lethal targets and virulence factors. Unfortunately, this led to a wasted decade or more with no new useful classes of antibiotics being identified (Silver 2011). Perhaps the antibiotic researchers confused activity with progress!

Economic barriers to the development of new novel antibiotics have increased. A large part of this problem is that, unlike any other classes of medicines, significant use of antibiotics leads to development of resistance to those agents and, therefore, increasing clinical failure. Antibiotics that are highly effective against more resistant bacteria will, by definition, be used only when the causative bacteria have been identified, thus limiting its use very significantly as most antibiotics are prescribed empirically. Because of the lack of novel new agents, the great majority of available antibiotics are now generic, resulting in low prices. Launching a new, expensive antibiotic, including one with high activity versus MDR Gram-negative bacteria, is not to be recommended!

Prescribing doctors are constantly urged to use antibiotics appropriately and prudently so as to optimise patient outcomes and minimise the acquisition and spread of antibiotic resistance (Bax et al. 1998). But the evidence base expected to be derived from clinical trials usually fails to give them the guidance required to achieve this end. Unfortunately, many calls for appropriate use merely mean a non-specific reduction in use (Bax et al. 1999).

Since the amalgamation of large pharmaceutical companies such as GlaxoSmithKline, Sanofi-Aventis and Pfizer Wyeth, the research groups of large pharma have generally left Europe to set up anew in the USA. Indeed, only a few large pharmas have now significant research in the antibacterial area, most are concentrated in the USA, and Pfizer has considered moving to China; unfortunately, this decision was reversed. In the meantime, most of the US-based research has left Pfizer.

Progress in R&D for new novel agents active against Gram-negative pathogens has been dire. Currently, there are no new agents active against these key pathogens in phase 3 or phase 4 clinical studies (Williams and Bax 2009).

Regulatory guidelines for clinical development have a major impact on decisions regarding research and development. Approval of new antibacterials in Europe and the USA has decreased significantly in recent years along with a large increase in development costs largely through the requirement for increasingly larger clinical trials and often complicated guidelines. Antibiotic clinical development is extremely complex and onerous but with the prospect of a small market return! Criticisms of regulatory agencies, largely by the pharma industry, include the ever increasing stringency in the licensing requirements: a licensing process that is bureaucratic, costly and also inconsistent in its requirement, consequent upon the lack of international harmonisation, notably between the Food and Drug Agency and the European Medicine Agency (Finch 2011).

It is possible that no new, novel, broad-spectrum antibiotics active against a broad range of MDR Gram-negative bacteria will be available in the next 10 years. Even after discovery, it takes 8–10 years before an antibiotic becomes generally available for use!

Antibiotics active against selected resistant Gram-negative bacteria include beta-lactamase inhibitors such as Novexel 104 and Bas 30072 which are active against KPC and NDM-1 beta-lactamase, respectively (Livermore et al. 2011; Page et al. 2012).

Unfortunately, they will have specific activity against bacteria which produce those specific beta-lactamases but not against other carbapenemases. They will, therefore, become narrow-spectrum antibiotics even though Novexel 104 is to be combined with ceftazidime and BAL30072 is to be combined with meropenem.

8 Proposals on Co-development of Antibiotics

In many conditions, developing narrow-spectrum antibiotics creates difficulties if the causative organism might not be covered with the novel compound (e.g. a Gram-positive antibiotic monotherapy for CAP treatment).

Recent FDA draft guidelines outline methods for the co-development of novel antibiotic agents and help address certain scientific and regulatory issues that will arise during co-development.

It is intended where there is:

- The need to treat a serious condition
- A rationale for combination of agents to be used
- Preclinical data suggesting synergistic effects in either efficacy or preventing resistance development
- Compelling reason why the agents cannot be developed individually, for example, increased risk or resistance or limited activity as monotherapy

In many cases, co-development would facilitate trial design where monotherapy would prove difficult. Targeted treatment will require methods for quick, cheap and accurate methods of diagnosis, which currently are not available. Currently, blood cultures are initially taken but can take up to five days to be returned, and so blind treatment is required in most cases for all likely organisms.

Due to advances in "lab on a chip", starting targeted treatment within the first hour of presentation will increasingly be possible. Rates of detection in a sample of blood of biotin (vitamin B7) at a concentration of about 1 part per 40 billion were achieved in 10 minutes (http://www.sciencedaily.com/releases/2011/03/110318102243.htm) (Peleg and Hooper 2010; van Duijn et al. 2011; Woodford et al. 2011).

9 Abstracts

"High-risk clones" play a major role in the spread of resistance, with the risk lying in their tenacity—deriving from poorly understood survival traits—and a flexible ability to accumulate and switch resistance, rather than to constant resistance batteries (Woodford et al. 2011).

As numbers of published results from national/international surveillance studies rise rapidly, the amount of new information may be overwhelming. Therefore, the

authors reviewed recent trends in antibiotic resistance in ICUs across Europe over 18 months (Woodford et al. 2011).

Antibiotic resistance in ICUs is rapidly increasing in both epidemics and endemicity of multi- and panresistant Gram-negative pathogens. Better infection control and improved diagnostics will become even more important than before (Woodford et al. 2011).

10 Conclusion

At least 10 years are required after compound selection to achieve regulatory approval. It follows therefore that the prospects for the delivery to the market in the next 10 years for general use of a new important antibiotic active against even a moderate range of MDR Gram-negative pathogens are not good. Many proposals have been made by governments, academics, non-government organisation, companies and researchers, but in spite of this, little has been achieved so far.

It remains to be seen if the world can combine its vast resources to combat the bacterial challenge which is increasing daily.

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