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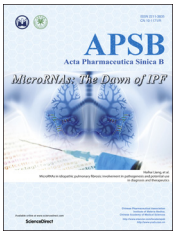

PERSPECTIVE

A review of global initiatives to fight antibiotic resistance and recent antibiotics' discovery

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Abstract Data from across the world have shown an overall decline in the antibiotic pipeline and continually rising resistance to all first-line and last-resort antibiotics. The gaps in our knowledge of existing prevalence and mechanisms of antibiotic resistance (ABR) are all too well known. Several decades of antibiotic abuse in humans, animals, and agricultural practices have created health emergency situations and huge socio-economic impact. This paper discusses key findings of the studies conducted by several national and international collaborative organizations on the current state of affairs in ABR. Alongside, a brief overview of the antibacterial agents' discovery in recent years approved by the US FDA is discussed.

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1. Introduction

It is essential to understand the international scope of antibiotic resistance (ABR) which is no longer an impending threat in any one part of the world; in fact, it is happening globally and poses unimaginable risks to animal health. Currently, there is no systematic international surveillance of ABR, but leading organizations and governments across the world are developing coordinated action plans to effectively control and manage the risks involved, many of which are discussed here. However, an accurate determination of the magnitude of ABR on a global scale is a complex and multidimensional task which is nearly impossible to achieve using currently invested resources. Nevertheless, there have been encouraging developments[1–4] in last few years. The developed world seems to have woken to the perils of ABR and accordingly formulated stiff policies and stimulated surveillance methods, but the developing world is yet to show a hard line systematic approach in their fight against ABR. As a comparison, available reports have estimated a per annum death toll of 23,000 in the US[4], 25,000 in EU[3], and 58,000[1] in India from various drug resistant bacterial infections.

The 2013 World Health Organization's (WHO) report[2] was the first most comprehensive and closest to ground-zero analysis on ABR. The European Union[3] and the Centers for Disease Control and Prevention (CDC)[4] reports also provide their territorial overview of the situation. The latest of all is a 2015 report by Global Antibiotic Resistance Partnership (GARP)[1].

2. Global antibiotic resistance partnership (GARP) report—2015[1]

GARP fostered the initiation of a dialog for coordinated antibiotic policy in eight countries which led to the development of a comprehensive world antibiotics report that discusses global patterns in ABR and use, policy interventions and state of R&D pipeline for new drugs. Not surprisingly, according to their 2015 report—The State of World's Antibiotics, resistance patterns differ country wise and mirror the use of antibiotics and disease patterns. The good news is, US, Europe, Canada, and South Africa have reported a decline in methicillin-resistant *Staphylococcus aureus* (MRSA) infections over the past few years, while on the reverse, sub-Saharan Africa, Australia, Latin America (90%) and India (47%) have reported increase in MRSA infections. Across the world, third and fourth generation cephalosporin resistant *Escherichia Coli* are becoming difficult to treat due to their ability to secrete extended-spectrum β-lactamase (ESBLs). In 2013, 17 out of 22 European countries reported 85% to 100% of ESBL positive *E. coli* isolates (European Antimicrobial Resistance Surveillance Network, EARS-Net, 2014). In 2009 and 2010, 28% of the *E. coli* family (Enterobacteriacae) from 11 Asian countries was reported to be ESBL producers, and their resistance to third- and fourth-generation cephalosporins ranged between 26% and 50%.

There are wide variations in global data for carbapenem-resistant enterobacteriacae (CRE) family. Carbapenems are last-resort antibiotics used against bacteria resistant to first-, second- and third-line antibiotics. CRE resistance seems to have remained stable in Canada (2015), in EU some countries have reported an increase, but largely limited to 10% for *Klebsiella pneumoniae* and under 1% for *E. coli* (2013–2014). The US reported 11% resistance for *Klebsiella* spp. and 2% of *E. coli* isolates (2013). India reported a steep increase in *K. pneumoniae* resistance, from 29% (2008) to 57% (2014) and for *E. coli* resistance increased from 10% (2008) to 13% (2013). Overall, the GARP data suggests higher risks of ABR in developing countries due to higher numbers of immunocompromised patients, inaccessibility to second- and third-line drugs, poor hygiene, unreliable quarantine measures and policy implementation issues.

However, the positive strategic and policy developments on a global scale have persuaded various countries to adopt strict measures. Plans are being formulated to control, prevent and monitor ABR. For example, in 2015, the World Health Assembly endorsed the Global Action Plan on Antimicrobial Resistance and invited all countries to adopt national strategies for ABR control, prevention, and monitoring within two years. The same year, US President formulated a National Action Plan for Combating Antibiotic-Resistant Bacteria. The European Union and Southeast Asian WHO countries have also committed to addressing the issue. Countries like China, India, South Africa, Vietnam, Philippines, Australia, and New Zealand have also set up national surveillance bodies which collect, track and report ABR trends.

3. World Health Organization—2014[2]

WHO's report—Antimicrobial Resistance, Global Report on Surveillance—provides an extensive global review of ABR including surveillance and resistance data for bacteria that are classified as "bacteria of international concern". A detailed review of health and economic burden of ABR, the challenges in surveillance, and proposed future directions for its control and prevention are discussed. Not so surprisingly, the key findings in this report are largely influenced by the availability of data and different surveillance methodologies used in various regions. The European region (74%) and east Mediterranean region (32%) are the best and worst suppliers of ABR data, while others fall in between. The data contributions for other regions are: Americas (60%), west pacific (70%), south-east Asia (55%) and Africas (49%). As a result, the key findings, when viewed in light of the differences in data availability from various regions, provide an inconclusive picture. This is due to the added challenge of identifying the extent to which such differences in reported data reflect real differences in resistance patterns for drug-antibacterial agents, or are attributable to differences in sampling of patients, laboratory performance and methodology, etc. However, it is important to rest our focus on the findings which are insightful. The WHO has classified seven bacteria of international concern; their identification and resistance overview is given below:

- *E. coli*: resistant to third-generation cephalosporins, extended spectrum β-lactamases (ESBLs), and fluoroquinolones;
- *K. pneumoniae*: resistant to third-generation cephalosporins, including ESBLs, and carbapenems;
- *S. aureus:* resistant to β-lactam antibacterial drugs (methicillin, MRSA);
- *Staphylococcus pneumoniae*: resistant or nonsusceptible to penicillin (or both);
- Non-typhoidal *Salmonella* (NTS): resistant to fluoroquinolones;
- *Shigella* species: resistant to fluoroquinolones; and
- *Neisseria gonorrhoeae*: decreased susceptibility to third-generation cephalosporins.

It is worth noting that for *E. coli*, *K. pneumoniae* and *S. aureus*, the proportion of bacteria resistant to commonly used specified

antibacterial drugs exceeded 50% in many WHO regions. All WHO regions found *K. pneumoniae* resistant to carbapenems, usually the last line of available treatment, with reports in European and Mediterranean region exceeding 50%. Most WHO regions reported MRSA proportions exceeding 20%, and some exceeding 80%. Non-susceptibility to penicillin has been detected in all WHO regions.

4. European Center for Disease Prevention and Control (ECDC)—2014[3]

ECDC is the European Union's main surveillance system on antimicrobial resistance. It has led the efforts and created a European antimicrobial resistance surveillance interactive database (EARS-Net) that provides annually updated information on the occurrence and spread of resistance in European countries and releases annual reports. Their 2014 report—Antimicrobial Resistance Surveillance in Europe—summarizes the resistance patterns for the following challenging bacteria: *E. coli, K. pneumoniae, Pseudomonas aeruginosa, Acinetobacter* species, *Streptococcus pneumoniae, S. aureus, and Enterococci.*

ECDC reported an "especially worrying" situation for Gram-negative bacteria due to high and increasing resistance percentages reported from many parts of Europe. High resistance increase to third generation cephalosporins (often in combination with fluoroquinolone and aminoglycoside resistance) was observed in *K. pneumoniae* and *E. coli* between 2011 and 2014. A 7.4% increase in carbapenem resistance in *K. pneumoniae* was observed in 2014, although carbapenem resistance *in E. coli* remained rare. In *K. pneumoniae*, the most common resistance phenotype was found resistant to three key antimicrobial groups: fluoroquinolones, third-generation cephalosporins and aminoglycosides.

For Gram-positive bacteria such as for MRSA, the resistance trends have decreased from 18.6% in 2011 to 17.4% in 2014. The resistance percentages for *S. pneumoniae* have remained stable from 2011 to 2014, and it remained less susceptible to macrolides than penicillin. In 2014, an increase in vancomycin-resistant *Enterococci* was reported since 2004. *P. aeruginosa* isolates also showed resistance, with a majority of countries reporting resistance percentages above 10% for all antimicrobial groups under surveillance, including carbapenems, fluoroquinolines and aminoglycosides. Carbapenem resistance in *P. aeruginosa* was recorded to vary between 4.4% and 58.5% in 2014. Resistance patterns for MRSA showed wide intercountry variations in Europe, ranging from 0.9% to 56.0%. Notably, the weighted mean MRSA percentage decreased from 18.6% in 2011 to 17.4% in 2014. However, 7 out of 29 countries reported MRSA percentages above 25%, and despite the overall positive development on MRSA front, EU classifies MRSA as a public health priority in Europe. Notably, vancomycin resistance in *Enterococcus faecium* showed an increase from 2011 to 2014 due to which it remains a major infection control challenge.

5. US Centre for Disease Control and Prevention (CDC)—2013[4]

In 2013, the CDC in their report—Antibiotic Resistance Threats in the United States—classified ABR as a complex problem having potentially catastrophic consequences of inaction. CDC provided what they called "conservative and minimum" estimates of more than two million people sickened every year with ABR infections in the US causing at least 23,000 deaths.

The US's premier health agency prioritized bacteria according to the concern-levels, namely: urgent, serious, and concerning.

Urgent bacteria are defined as those with high-consequence antibiotic-resistant threats because of significant risks identified. These may not be currently widespread but have the potential to become so and therefore require urgent public health attention. These include *Clostridium difficile*, Carbapenem-resistant *Enterobacteriaceae* (CRE), and drug-resistant *Neisseria gonorrhoeae.*

C. Difficile requires urgent and aggressive actions and causes 14,000 deaths, 250,000 infections per annum, resulting in more than one billion excess medical costs. It spreads quickly being naturally resistant to a large number of antibiotics and has developed resistance to fluoroquinolones. CREs, such as *Klebsiella* species and *E. coli*, have become resistant to all or nearly all antibiotics, including carbapenems, causing 600 deaths and sickening 9000 people every year in the US. *N. gonorrhoeae* causes 246,000 drug-resistant infections every year and is showing resistance to antibiotics usually used to treat it, including cefixime (an oral cephalosporin), ceftriaxone (an injectable cephalosporin), azithromycin, and tetracycline.

Serious bacteria are recognized as significant antibiotic resistant threats having low/declining incidences and reasonable availability of drugs, but if left unmonitored may become urgent in near future. These include various drug resistant strains of *Acinetobacter*, *Campylobacter*, fluconazole-resistant *Candida* (a fungus), extended spectrum β-lactamase producing *Enterobacteriaceae* (ESBLs), vancomycin-resistant *Enterococcus* (VRE), *P. aeruginosa*, non-typhoidal *Salmonella, Salmonella typhi*, *Shigella*, MRSA, *S. pneumoniae*, and *Sternoclavicular tuberculosis.*

Concerning bacteria are those with low ABR having multiple drug options available for resistant strains, but cause severe illness and require monitoring. These include vancomycin-resistant *S. aureus* (VRSA), erythromycin-resistant Group A *Streptococcus*, and clindamycin-resistant Group B *Streptococcus*.

Importantly, within the US, multidrug-resistant and extensively drug-resistant tuberculosis (MDR and XDR TB) infections are not an immediate and urgent threat, unlike developing countries in south-east Asia, because such infections are uncommon due a robust prevention and control program. Same is true for MRSA because at present there are multiple effective antibiotics for treating infections but if the strains become more resistant then MRSA may change from a serious to an urgent threat.

The above discussion provides an overview of the ABR threat on a global scale as recorded by the leading health agencies across the world. Below, let us put this information in perspective and look at the antibacterial drugs approved in last five years by the United States' Food and Drug Administration (US FDA).

6. Antibacterial agents/antibiotics approved by the US FDA from 2011 to 2016[5]

Table 1 shows a list of drugs approved by the US FDA for sale in the United States from 2011 to 2016. Effectively targeting drug resistance requires use of antibacterial agents with novel mechanism of action. Between 1930 and 1962, the antibiotic industry was fertile and twenty new classes of drugs made it to the market. Since 1960s, only three entirely new classes of drugs were approved; however, numerous analogs have made it to the market. Consequently, drugs have become less effective and bacteria more

Table 1 Drugs approved by FDA from 2011–2016.

Drug	Indication	Company (year)
Avycaz (ceftazidime–avibactam)	For complicated intra-abdominal and urinary tract infections caused by *E. coli*, *K. pneumoniae*, *C. koseri*, *E. aerogenes*, *E. cloacae*, *C. freundii*, *Proteus* spp., and *P. aeruginosa*	Actavis (February 2015)
Dalvance (dalbavancin)	For acute bacterial skin and skin structure infections caused by *S. aureus* (including methicillinsusceptible and methicillin-resistant strains), *S. pyogenes, S. agalactiae*, and *S. anginosus*	Durata Therapeutics (May 2014)
Metronidazole 1.3% Vaginal Gel	For the treatment of bacterial vaginosis caused by anaerobic bacteria and protozoa	Actavis, Inc. (April 2014)
Orbactiv (oritavancin)	For acute bacterial skin and skin structure infections *S. aureus* (including methicillin-susceptible and methicillin-resistant isolates), *S. pyogenes, S. agalactiae, S. dysgalactiae, S. anginosus group* (including *S. anginosus, S. intermedius, and S. constellatus*), and *E. faecalis* (vancomycin-susceptible isolates only).	The Medicines Company (August 2014)
Sivextro (tedizolid phosphate)	For acute bacterial skin and skin structure infections. *S. aureus* (including MRSA and methicillin-susceptible [MSSA] isolates), *S. pyogenes, S. agalactiae, S. anginosus* Group (including *S. anginosus, S. intermedius, and S. constellatus*), and *E. faecalis.*	Cubist Pharmaceuticals (June 2014)
Sirturo (bedaquiline)	For multi-drug resistant tuberculosis	Janssen Therapeutics (December 2012)
Abthrax (raxibacumab)	For Anthrax	GlaxoSmithKline (December 2012)
Dificid (fidaxomicin)	For *C. difficile*-associated diarrhea	Optimer Pharmaceuticals (May 2011)

C. difficile, *Clostridium difficile*; *C. freundii*, *Citrobacter freundii*; *C. koseri*, *Citrobacter koseri*; *E. coli*, *Escherichia coli*; *E. faecalis*, *Enterococcus faecalis*; *E. aerogenes*, *Enterobacter aerogenes*; *E. cloacae*, *Enterobacter cloacae*; *K. pneumoniae*, *Klebsiella pneumoniae*; *P. aeruginosa*, *Pseudomonas aeruginos*; *S. agalactiae*, *Streptococcus agalactiae*; *S. anginosus*, *Streptococcus anginosus*; *S. aureus*, *Staphylococcus aureus*; *S. constellatus*, *Streptococcus constellatus*; *S. intermedius*, *Streptococcus intermedius*; *S. pyogenes*, *Streptococcus pyogenes*; *S. agalactiae*, *Streptococcus agalactiae*; *S. anginosus*, *Streptococcus anginosus*; *S. constellatus*, *Streptococcus constellatus*; *S. dysgalactiae*, *Streptococcus dysgalactiae*; *S. intermedius*, *Streptococcus intermedius*.

infective. According to one estimate, twenty novel classes of drugs are needed for antibiotics to be working effectively for next fifty years[5,6]. At present, not even enough analogs are making it through FDA approvals. In last five years, a meager eight antibiotics were approved as discussed below:

6.1. *Avycaz*

A third generation cephalosporin combination drug having two components, ceftazidime and avibactam. Ceftazidime is an antibacterial drug which binds to penicillin binding proteins and works against certain Gram-negative and Gram-positive bacteria. Avibactam is a non-betalactam beta-lactamase inhibitor which inactivates β-lactamases and protects ceftazidime from degradation.

6.2. *Dalvance (dalbavancin)*

This is indicated for adult-use only, those having acute bacterial skin infections. It works against several Gram-positive bacteria including *S. aureus* (including methicillin-susceptible and methicillin-resistant strains). Dalbavancin, is a semisynthetic lipoglycopeptide that binds to the D-alanyl-D-alanine residues interfering with cell wall synthesis and preventing cross-linking.

6.3. *Metronidaozle*

This is a nitroimidazole antibiotic used for treatment of anaerobic bacteria and protozoa causing bacterial vaginosis in non-pregnant women.

6.4. *Orbactiv (oritavancin)*

It is semisynthetic lipoglycopeptide antibacterial drug having bactericidal activity against *S. aureus*, *Streptococcus pyogenes*, and *Enterococcus faecalis* including MRSA.

6.5. *Sivextro (tedizolid phosphate)*

This belongs to oxazolidinone class and is indicated for the treatment of adults with acute bacterial skin and skin structure infections. Tedizolid binds to the 50S subunit of the bacterial ribosome resulting in inhibition of protein synthesis.

6.6. *Sirturo (bedaquiline)*

It is a diarylquinoline antimycobacterial drug that inhibits mycobacterial ATP (adenosine 5′-triphosphate) synthase in *Mycobacterium tuberculosis*. This is used in combination therapy in adults with pulmonary multi-drug resistant tuberculosis.

6.7. *Abthrax (raxibacumab)*

Abthrax is a monoclonal antibody approved for the treatment and prevention of inhalational anthrax when alternative therapies are not available or appropriate.

6.8. *Dificid (fidaxomicin)*

A narrow spectrum macrocyclic antibiotic used for treating adults having *Clostridium difficile*–associated diarrhea. It works by inhibition of RNA synthesis.

7. Conclusions

The currently available estimates of ABR burden in each country point to an evident conclusion that it is in the self interest of each country to prolong antibiotic effectiveness within their territories. The pipeline of new antibacterial agents is especially discouraging and it has been so for the last few decades. Several reasons are attributed to this grim scenario of drug discovery for new antibiotics. The major one however is the lacking interest of pharma companies. Finding it hard to recoup drug discovery costs from antibiotics which develop resistance within a decade or so, pharmaceutical companies preferably choose to invest in safer types of drugs, such as antidepressants, statins, and anti-inflammatory medications, which can bring steady flow of revenue, even when off-patent. Although, academic laboratories appear to continue their research efforts in looking for new drug leads, their efforts are inadvertently quashed by their inability to collaborate with the pharma companies for conducting high level pre-clinical research, and also their failure to transfer/license such technologies beyond academic laboratories. Such setbacks cost dearly to the new antibiotic discovery, because academic laboratories lack the resources and funding to carry out top gear research on their own. This symbiotic relationship of academic labs and pharma industry needs to be lessened by increasing the amount of federal funding to the universities. It so appears that the government has begun efforts to lure pharmaceutical companies back into the antibiotic research by facilitating fast-track FDA approvals, providing extended drug-patent exclusivity of five years, which is evidenced by the Generating Antibiotic Incentives Now (GAIN) Act, a new law brought about in 2012 by the US government; although, the results of it remain to be seen in coming years.

For now, the future of antibiotic discovery is uncertain, and therefore we need to lessen our anticipation of a robust antibacterial drug pipeline and with that our hopes for a drastic upsurge in ABR drug discovery trends in near future. In fact, preventive measures can go a long way in tackling ABR effectively and appear to be a reasonable solution to the problem until some radical innovation transforms the antibacterial drug pipeline towards betterment.

All countries, especially the developing ones, in the context of antibiotics, need to institute methods for the appropriate choice of drug treatment—a complex problem involving prescribers, dispensers, and consumers. The most necessary component, the diagnostic aspect of drug prescription, is often ignored in many countries. It is important that bacterial culture and susceptibility testing before antibacterial prescription are mandated. Drug quality plays an important role too and needs serious enforcement measures. This is a particularly common problem with generic drug makers in developing countries. Sub-optimal amounts of drug invariably lead to drug resistance; therefore quality control measures of drug labels are important. At the same time, educational interventions at the patient level play a critical role. Most importantly, controlling the spread of resistant organisms using proper quarantine measures will have a tremendous additive effect on the prevention of ABR dissemination. For example, in case of outbreaks, countries must be ready with pre-specialized task forces to prevent the introduction and transmission of infective agents, especially amongst mobile population. The "search and destroy" policy involving patient pre-screening, isolating, quarantining, staff member screening, has been proven effective in many countries. Similar approaches should be tailored specific to the needs of each region and outbreak type, and must be pre-instituted and ready-at-use at the eleventh hour. It is also important to realize that each country faces its unique challenges in ABR and therefore needs to proactively review their own precise problems and find solution applicable within their boundaries.

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