

The dearth of new antibiotic development: why we should be worried and what we can do about it

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Antibiotic resistance is a natural phenomenon — resistant strains of *Staphylococcus aureus* were encountered soon after the introduction of penicillin into clinical medicine in 1941 by Florey, Chain and colleagues.¹⁻³ The story of penicillin's discovery and then manufacture in sufficient quantities to treat injured troops at the D-Day landing in 1944 is also notable, because it was probably the last time an antimicrobial was developed to such an initial extent by anyone other than a large pharmaceutical company.⁴ To our knowledge, since the time of Florey, no government (regardless of its rhetoric) has developed a single new antimicrobial, and, while many clinicians criticise the activities of the big drug manufacturers, it is these companies that have been responsible for almost all new antimicrobial research and development during the past half-century.⁵ Although antibiotic development was rapid between the 1950s and the 1970s, with multiple new drugs being developed, many of these gains have been eroded over the past 30 years because of the rapid emergence of and spread of resistance to antimicrobials.⁶ Here, we explain what lies behind the developing resistance and why, despite a seemingly crowded current antibiotic market, the true picture is that our antibiotic development pipeline has been reduced to a trickle. We propose some problem-based solutions that could help prevent, or at least delay, a return to the dangers of the pre-antibiotic era.

ABSTRACT

- The emergence and spread of multidrug-resistant pathogens has increased substantially over the past 20 years.
- Over the same period, the development of new antibiotics has decreased alarmingly, with many pharmaceutical companies pulling out of antibiotic research in favour of developing “lifestyle” drugs.
- Reasons given for withdrawing from antibiotic development include poor “net present value” status of antibiotics, changes in regulations requiring larger drug trials and prolonged post-marketing surveillance, clinical preference for narrow-spectrum rather than broad-spectrum agents, and high new-drug purchase costs.
- Major improvements in infection control in Australia are needed to prevent further spread of resistant clones, buying some time to develop urgently needed new antibiotic agents.
- Perpetuating a culture of “pharma bashing” will simply lead to more pharmaceutical companies withdrawing from the market. A change in the health and research culture is needed to improve cooperation between public, academic and private sectors.

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Why do we need new antibiotics?

Burgeoning resistance

The increasing prevalence of resistant pathogens is mainly related to either the emergence of new strains or the spread of existing resistant clones. The specific mechanisms of drug resistance are important in determining its likely reversibility. For instance, plasmid-mediated resistance (eg, ampicillin resistance in *Escherichia coli*) is more likely to be reversible when exposure to the relevant antibiotic is withdrawn than chromosomally mediated resistance (eg, fluoroquinolone resistance in gram-negative bacteria), which is often a “one-way street”, with reversal much less likely.⁷

Although the emergence of resistant clones is crucial, the factor responsible for most resistance problems is patient-to-patient spread of existing resistant clones, usually on the hands of healthcare workers or on shared equipment in hospitals,⁸⁻¹¹ aided by the increasing immunological frailty of many hospital inpatients.⁷

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Inappropriate antibiotic use is a key driver of resistance, but the reasons for such use can be complex.⁷ In developed countries, the obsession with “zero risk” has distorted the decision-making process for many clinicians, with broad-spectrum antibiotics being used even when not indicated. Pharmaceutical marketing often targets such clinician insecurity, and rational debate is not always helped by the growing band of “microbiology accountants”, who report the percentage of resistant strains among their laboratory collections of pathogens rather than the likelihood of resistant pathogens among patients presenting with a particular disease.

Appropriate antibiotic prescribing has also been affected by the threat of bioterrorism.¹² For instance, although the anthrax strain used in the 2001 US anthrax attacks was susceptible to both tetracyclines and penicillin, 32 000 government workers and other contacts were treated with oral ciprofloxacin for up to 60 days as prophylaxis, just in case the strain was capable of producing β -lactamase.¹³

Underpowered response?

The current antibiotic market is fairly crowded with agents, but many of these are “me-too” antibiotics — drugs from the same class developed by competing companies (eg, fluoroquinolones and third-generation cephalosporins). There has been a decline in registration of new antibiotics. A summary of new antibiotics and older antibiotics with new indications or treatment options is given in Box 1.

1 New antibiotics, and older antibiotics with new indications or treatment options

Antibiotic	Drug class	Initial development period	Antibacterial spectrum	Limitations/adverse effects or new issues	Current status*
New agents					
Gemifloxacin, garenoxacin, sitafloxacin	Fluoroquinolone	Early 1960s	Variety of gram-positives (not VRE, MRSA) and gram-negatives	Resistance already established in some places, due to widespread ciprofloxacin use. Role uncertain, given availability of older agents	NAv Aust. Garenoxacin development halted
Ramoplanin	Glycolipodeptide	Early 1980s	Gram-positives, including VRE	Not absorbed orally — used for temporary suppression of faecal VRE colonisation	NAv Aust. Not US FDA-approved. In Phase III trials
Daptomycin	Lipopeptide	Late 1980s	Gram-positives: VRE, MRSA, SA-RVS	Myalgia at high doses	NAv Aust. US FDA-approved Sep 2003
Linezolid	Oxazolidinone	Late 1980s	Gram-positives: VRE, MRSA, SA-RVS, some <i>Mycobacteria</i> spp., <i>Nocardia</i> spp.	Haematological toxicity, especially thrombocytopenia; peripheral neuropathy (rare)	RAc Aust
Quinupristin, dalbavancin	Streptogramin	Early 1990s	Gram-positives: VRE (not <i>Enterococcus faecalis</i>), MRSA, SA-RVS	Infusion site pain, arthralgia, myalgia	RAc Aust
Oritavancin, dalbavancin	Novel glycopeptide	Late 1990s	Gram-positives: VRE (oritavancin only), MRSA, SA-RVS	Toxicity uncertain	NAv Aust. Not US FDA-approved. In Phase III trials
Telithromycin, cethromycin	Ketolide (related to macrolides)	Late 1990s	Typical and atypical respiratory pathogens, including <i>Mycoplasma</i> , <i>Chlamydia</i> spp.	Hepatotoxicity, blurred vision, QT changes on ECG	NAv Aust. Available in Europe and the United States.
Tigecycline	Glycylcycline (semisynthetic derivative of minocycline)	Late 1990s	Gram-positives: VRE, MRSA, SA-RVS; some gram-negatives	Nausea, vomiting, headaches	NAv Aust. Not US FDA-approved. In Phase III trials
Older agents					
Penicillin G	β -Lactam	Late 1930s	Gram-positives: streptococci, enterococci, <i>Clostridium</i> , <i>Listeria</i> spp.	Continuous infusion provides high serum levels for intermediate-resistant strains (eg, some VRE). Suitable for hospital-in-the-home treatment in some cases ^{14,15}	Av Aust
Colistin, polymyxin B	Cationic peptides	1950s	Gram-negatives, including <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter baumannii</i> , <i>Klebsiella pneumoniae</i>	Renal toxicity, neurotoxicity	Av Aust
Amphotericin B	Polyene	Late 1950s	Most fungi	Preliminary data suggest that continuous infusion may reduce renal toxicity and hence reduce the need to switch to newer, more expensive liposomal analogues ^{16,17}	Av Aust
Gentamicin	Aminoglycoside	Early 1960s	Many gram-negatives	Meta-analyses suggest a once-daily dose of 4–6 mg/kg daily [†] is associated with reduced renal and ototoxicity, but efficacy is similar to multidose regimens	Av Aust

ECG = electrocardiogram. FDA = Food and Drug Administration. MRSA = methicillin-resistant *Staphylococcus aureus*. SA-RVS = *Staphylococcus aureus* with reduced vancomycin susceptibility. VRE = vancomycin-resistant enterococci.

* Availability: Av Aust = available in Australia; RAc Aust = restricted access in Australia; NAv Aust = not available in Australia.

† Recommended dose for an adult with normal renal function.

Several of the “new” antibiotics were actually discovered in the 1980s. Their development stalled because of poor initial results or problems with toxicity, but, more recently, desperation has led to renewed research interest in these drug classes, especially agents for treating gram-positive pathogens (Box 2). For example, dapto-

mycin was initially studied in the early 1990s but was “shelved” due to toxicity, especially its potential to cause myositis. Its use at a lower dose has now been reassessed.^{18,19}

Oritavancin, tigecycline and ramoplanin are the only truly new antibiotic agents that are likely to enter the Australian market in

2 Multiresistant bacteria for which there are currently few available treatment options

Gram-negatives

- *Acinetobacter baumannii*
- *Pseudomonas aeruginosa*
- *Stenotrophomonas maltophilia*
- Some *Klebsiella pneumoniae*

Gram-positives

- Methicillin-resistant *Staphylococcus aureus*
- *S. aureus* with reduced susceptibility to vancomycin and/or linezolid
- Methicillin-resistant coagulase-negative staphylococci
- Vancomycin-resistant enterococci
- Multidrug-resistant *Mycobacterium tuberculosis*, rapidly growing mycobacteria, *Mycobacterium avium* complex

the next 5 years, with only tigecycline likely to be active against gram-negative bacteria.^{20,21} Because of this and the worsening problem of multiresistant *Acinetobacter* spp., *Pseudomonas aeruginosa* and *Klebsiella* spp., clinicians have been forced to use more toxic older agents such as colistin (Box 1).²²

Why is the new-antibiotic pipeline running dry?

Large pharmaceutical companies are primarily responsible for new antibiotic development, with 93% of new agents developed between 1980 and 2003 coming from this source, rather than small biotechnology companies or small pharmaceutical manufacturers.⁵ The cost of researching and developing any new drug is generally in excess of US\$500 million, and it usually takes about 8–10 years from the time a drug is first developed to the time it is released for sale.^{5,6} Naturally, pharmaceutical companies will only take this risk if there is reasonable likelihood of recouping development costs and making a profit. The pharmaceutical industry is under considerable financial pressure, with many companies believing they need to get bigger to survive and to afford the research needed for drug licensing. However, with more than 40 companies merging and consolidating over the past 20 years, there are now only about eight companies still undertaking some antibiotic research and development.^{23,24} This is because, during the past 10–15 years, a number of key factors (discussed below) have combined to reduce pharmaceutical companies' interest in antibiotic development.

Relatively low "net present value"

For an increasing number of pharmaceutical companies, antibiotics are financially less attractive to develop than drugs for other indications (Box 3). Antibiotics are generally used for short periods for specific, relatively narrow indications. In comparison, other agents (eg, lipid-lowering agents) are often commenced at a relatively young age, are taken by a large proportion of the population for many years without much restriction, and are not subject to the emergence of resistance. Further, in contrast to the restrictions placed on antibiotics, there are few guidelines (or physician experts) advising against widespread use of these agents.²⁵

Conducting clinical trials is one of the major expenditures in developing any new drug, and a separate clinical trial is needed for

each potential indication for a drug. The complexity of conducting clinical trials for antibiotics adds to the costs associated with their development and licensure.

Such financial considerations are often summarised by a drug's "net present value" (NPV). This is what the drug's future is worth in today's money. Usually, the NPV is then risk-adjusted (rNPV), based on the extent to which the drug has been developed. For instance, an antibiotic in Phase III trials carries less risk than one early in development (most antibiotics in Phase III trials have an 87% "success rate").²⁴ Thus, it is no surprise that antibiotics have a lower rNPV than many other drug classes. In fact, in some industry estimates, injectable antibiotics rank well behind musculoskeletal, neuroscience and oncology agents and vaccines in terms of rNPV.²⁴

Stricter standards for equivalence

Most antibiotic trials are "equivalence" trials, whereby the new drug is required to have equivalent or similar efficacy to an older, comparator agent that is already licensed for the relevant indication. The amount to which the efficacy of the new agent can differ from the comparator and still be considered sufficiently similar to be "equivalent" is called the "delta" value. Until recently, the standard for most antibiotic trials in which a drug's efficacy was estimated to be 80%–90% was a delta value of 15% — that is, as long as the new antibiotic was within 15% of the efficacy of the comparator (ie, no more than 15% better or worse) it was considered statistically equivalent. Such trials would generally be used to support the licensure of the new drug for the studied indication. Because of concerns about possible "downward" drift in efficacy over time, some regulatory authorities have proposed that the delta value be reduced to 10%. The effect of this proposal would be to more than double the number of patients who need to be enrolled in antibiotic trials to demonstrate the new standard of "equivalence" (eg, for a study of community-acquired pneumonia, 1500–2200 patients would be required instead of 600–1000).²⁵ Increased patient recruitment would add to trial costs.

Further, for some relatively uncommon, but important, indications, this increase in required patient recruitment would be unachievable from a clinical perspective, or would result in the trial becoming so prolonged that the comparator drug may no longer be considered appropriate due to the emergence of antibiotic resistance. It is believed that the proposed change in the trial delta value was a key reason for at least two major manufacturers withdrawing from antibiotic research prior to 2002.²⁶

3 Number of publicly disclosed new molecular entities currently undergoing research and development by the world's 15 largest pharmaceutical companies*

Indication or agent type	Number of new entities
Depression/anxiety	23
Bladder hyperactivity	8
Osteoporosis	7
Antibiotics	5
Erectile dysfunction	4
Obesity	3

*Adapted from Spellberg et al.⁵

Risk of rapidly emerging antibiotic resistance

While the presence of antibiotic resistance among key clinical pathogens can be an important driver of new antibiotic development, it can also be a disincentive. This is especially the case if resistance to a new agent is emerging quickly, so that clinical trials cannot be completed without a substantial number of the enrolled patients being infected with new, highly resistant strains. This mostly affects trials associated with relatively rare clinical conditions (eg, bacterial meningitis or endocarditis), for which trials may take many years and require many enrolment sites to complete. However, it is often these uncommon, clinically devastating diseases that most require the development of new antibiotics to overcome the reduced efficacy of older agents.

Cross-class resistance can be a particular problem, as the development of resistance to either the new agent or the older comparator during a trial can make the assessment of either equivalence or superiority clinically irrelevant, and thus devalue the trial.

Clinical preference for narrow-spectrum agents

Given the costs associated with drug development, many companies attempt to design agents with a broad antibacterial spectrum to make them more suitable for a wide variety of indications. However, to avoid rapid emergence of resistance, many infectious disease experts often prefer that new antibiotics be used for specific, narrow indications for which the efficacy of older agents has become a problem. Thus, while pharmaceutical companies are pressing for multi-indication use to recoup their development costs, regulatory authorities frequently limit a new drug's indications.

Varying licensure regulations

Conducting clinical trials to obtain multi-indication licensure is complicated by the fact that licensing requirements can vary between the United States, the United Kingdom, Europe, Australia and South America. Although there have been attempts to streamline these regulatory requirements, differences remain, so that pharmaceutical companies invariably target their most profitable market (generally the United States) when designing trials, even though other markets may have a greater disease burden and clinical need for the new agent.⁷ The World Health Organization and other agencies have tried to help standardise regulatory requirements, but progress has been slow.

Relatively high purchase price

Invariably, new agents are more expensive to users than their older comparators, as they are still under patent protection, and companies attempt to recoup their development costs during the patent period. In Australia, the initial high cost of some agents often leads to restrictions on their use both in hospitals and by the Pharmaceutical Benefits Scheme. In some developing countries, this high cost of a new drug encourages pharmaceutical companies that make generic drugs to ignore patent law and produce the drug at reduced cost, thereby often further eroding the new drug's market.⁷

Increased post-marketing surveillance

Post-marketing surveillance of new drugs has been a growing requirement of most regulatory authorities over the past 20 years.

For some agents, this has been vital in identifying important toxicities (eg, hepatotoxicity associated with trovafloxacin), but, for others, it has identified potential adverse effects that, although important, would not overly limit use of the drug if the clinical indication were sufficiently worthy (eg, the possibility of elevated liver enzyme levels and some blurred vision associated with use of telithromycin).^{23,24} However, the requirement for companies to maintain detailed post-marketing surveillance programs adds to a drug's development costs and reduces its NPV, as some commercial risk persists after a drug is licensed.

How can we improve the situation?

In the near future, there appears to be little that can be done to overcome the current and impending shortage of new agents. Instead, there must be a greater focus on appropriate infection control measures to limit the spread of resistant clones within hospitals and reduce the emergence of new resistant strains by restricting unnecessary antibiotic use in humans and in agriculture.^{7,27}

In Australia, the current hyperendemic spread of methicillin-resistant *S. aureus* within most large hospitals is a reflection of past apathy and woeful infection control measures in the 1970s and 1980s. The same mistakes must not be repeated with vancomycin-resistant enterococci, *S. aureus* with reduced vancomycin susceptibility, and multiresistant *Acinetobacter*.²⁸⁻³⁰ Governments need to prioritise funding for effective infection control measures, such as patient cohorting and isolation (ie, greater access to single rooms) and improved hand hygiene among healthcare workers through the use of alcohol/chlorhexidine-based handrub to minimise transmission of resistant pathogens.¹¹ Neglecting these issues will inevitably undermine current healthcare gains.

To encourage renewed interest in antibiotic research and development, a number of approaches have been suggested, many of which we believe could be effective:

- **Standardise regulation and licensure.** Standard requirements for drug regulation in the United States, United Kingdom, Europe and other regions could have substantial benefits by reducing the number of clinical trials needed to obtain widespread licensure.
- **Specify appropriate antibiotic comparators.** The proposal for a 10% delta value arose in response to concerns about downward drift in comparator efficacy. An alternative way of reducing the likelihood of inadequate efficacy would be for regulatory agencies to specify the appropriate antibiotic comparator required for each indication. This approach would allow the 15% delta value (and thus the current number of patients required for each trial) to be maintained.
- **Broaden the funding base for drug research and development.** To reduce the financial risk of developing new drugs, antibiotic research and development could be co-funded by pharmaceutical companies, governments and public academic institutions.²⁷ Tax incentives for companies to perform work in identifying new drugs might help.⁷
- **Increase cooperation between academic institutions and pharmaceutical companies.** More research into the mechanisms of antibiotic resistance and bacterial physiology would allow the development of antimicrobials with new mechanisms of action, as occurred with the recently discovered CBR703 class of molecules, which inhibit bacterial RNA polymerase.³¹
- **Fast-track drug licensure when needed.** For high-priority diseases, where resistance is a major clinical problem, a new

system of fast-tracking licensure of potential agents is necessary to enhance clinical availability while continuing to monitor potential adverse reactions. The current system of fast-tracking drugs for treating HIV could serve as a useful model.⁷

Extending the duration of patent protection (so-called "exclusivity") has also been proposed as a way of encouraging antibiotic research and development. However, we believe this is unlikely to be particularly effective, as the later years of a drug's patent are heavily discounted in the NPV calculation because of the emergence of resistance and higher likelihood of generic pharmaceutical companies ignoring patent regulations and producing the drug at lower cost.

Conclusion

Declining antibiotic research and development at a time of increasing emergence and spread of resistant pathogens poses a major challenge to our society if we are to avoid a return to the pre-antibiotic era for many infections. Perpetuating a culture of "pharma bashing" will simply lead to more pharmaceutical companies withdrawing from the market. Crucial to success will be a change in the health and research culture towards greater cooperation between the public, academic and private sectors. Improving infection control initiatives will buy some time, but, given the lag between antibiotic development and eventual availability, we need to develop a sensible strategy soon to avoid problems in the next one to two decades.

Competing interests

None identified.

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