POLICY RESPONSES TO THE GROWING THREAT OF ANTIBIOTIC RESISTANCE

POLICY BRIEF 6 MAY 2008

THE ANTIBIOTIC PIPELINE

Effective antibiotics for severe infections caused by resistant bacteria are needed urgently. The speed with which bacteria develop resistance to antibiotics, in contrast with the slow development of new drugs, has led some experts to warn of a "post-antibiotic era."[1,2] Compared to the pace 30 years ago, few novel antibiotics have been added to pharmacy shelves in recent years, and the R&D pipeline will, at best, continue its slow trickle of new agents. Judicious use of the antibiotics currently available—particularly through better infection control in hospitals and more rational prescribing—may help conserve their effectiveness. However, even if we improve these practices, resistant bacteria will continue to develop, and new and better drugs will be needed.

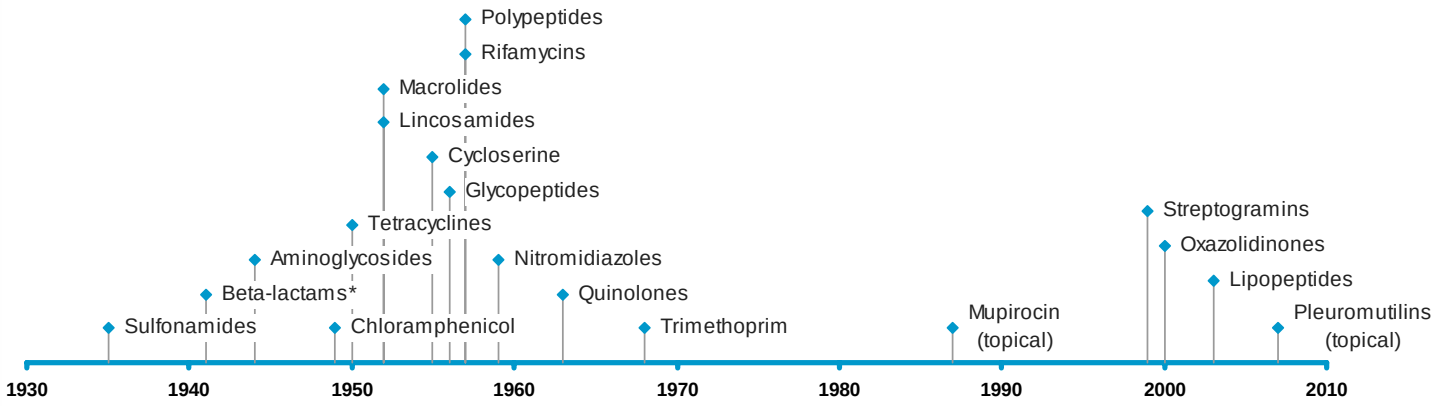
A Brief History of Antibiotic Development

The story of Alexander Fleming's discovery of penicillin in 1928—the bread mold that killed his *Staphylococcus aureus* cultures—is well known. Just a few years later, the antibacterial properties of sulfonamides were noted, and the first antibiotic drugs to fight infections in humans were developed in the 1930s. The next three decades were boom times for antibiotic research: 14 different "classes" of antibiotics—representing novel mechanisms of action—became available for human use (see Figure 1). As bacteria developed resistance against one type of antibiotic—penicillins, for example—drugs in a new class filled the treatment void. More recently, the discovery of unique antibiotic classes has slowed. Since 1970, only five new classes have been introduced for human use, and two of those are limited to topical use (see Box).

The Diversity of Recent Antibiotics

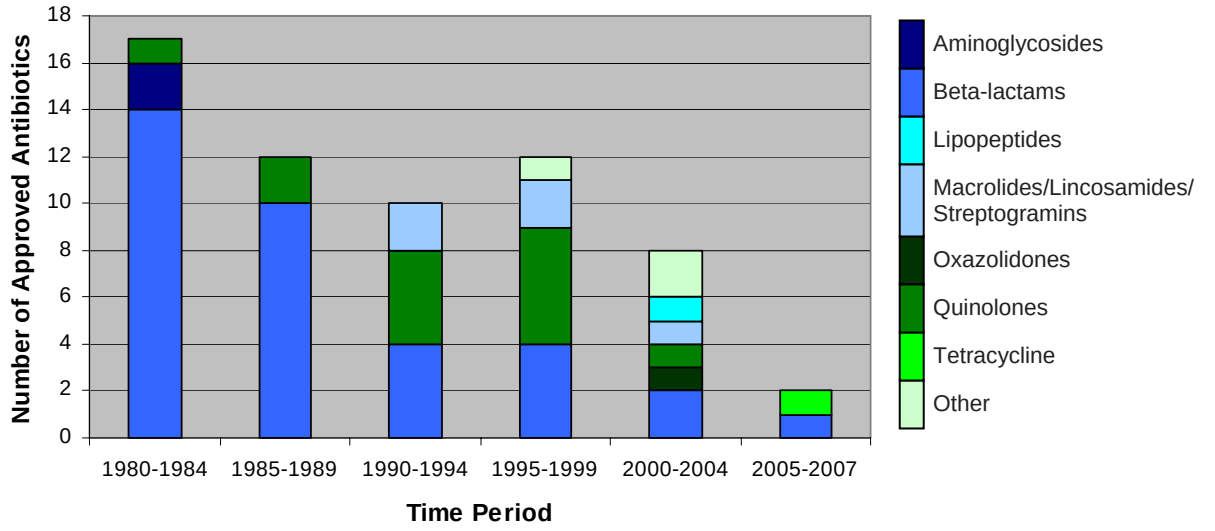
The number of new antibiotics—not just new formulations of existing ones—to be approved by the FDA each year has fallen steadily since 1980 (see Figure 2), a trend that holds for all drugs. This has left few treatment options for the most stubborn forms of MRSA (methicillin-resistant *Staphylococcus aureus*). The picture is even bleaker for infections caused by Gram-negative bacteria, which are occasionally resistant to all the antibiotics now on the market.

Figure 1: 14 classes of antibiotics were introduced for human use between 1935 and 1968; since then, 5 have been introduced.



* Beta-lactams include three groups sometimes identified as separate classes: penicillins, cephalosporins, and carbapenems.

Figure 2: The number of new systemic antibiotic agents has declined since 1980, and most (75%) of these drugs are in two classes, beta-lactams and quinolones.



Box: Topical Antibiotics

Most discussion of antibiotics focuses on the pills or injectable forms used to treat infections inside the body. While improved antibiotics in these forms are necessary, topical antibiotics are also needed to treat skin infections—especially the growing number of methicillin-resistant *Staphylococcus aureus*) MRSA skin infections (see Counting MRSA Cases and Which MRSA is It?).

At the same time that the number of new antibiotics to reach the market is declining, new antibiotics are also declining in diversity—more than three-quarters of the new drugs are in two classes. [3] Despite this grim picture, in fact, novel developments since 2000 have ended the antibiotic drought of the late 20th century (see Figure 1). And although most new antibiotics still come from existing classes, there is now more diversity. The new drugs may also be more effective and safer than earlier drugs in their class.[4]

The current antibiotic pipeline also lacks diversity in the range of diseases at which new drugs are aimed. Several different antibiotics (or different formulations of existing antibiotics) may be needed to combat a single type of bacteria if it causes very different types of infections (for example, the same bacteria can cause both skin and blood infections). Of the 13 new antibiotics approved by the FDA in the past 10 years, only three target the most serious conditions: blood infections and hospital-acquired pneumonia (see Figure 3). The others are effective only for less severe, often self-limited conditions (meaning the infection would resolve on its own even if not treated), such as bronchitis or skin infections.

A task force created by the Infectious Disease Society of America evaluated the antibiotic pipeline based on a third type of diversity: the diversity of new drugs' target organisms and the diseases they cause. The task force identified six high-priority pathogens they consider most in need of new antimicrobials (see Figure 5).[5] New antibiotics have recently been approved to combat diseases due to MRSA-, VRE-, and ESBL-producing bacteria, but little progress has been made against infections with *Acinetobacter* and *Pseudomonas* bacteria.

Antibiotics in Development and the Future

Some new products are on the horizon. Manufacturers have filed six New Drug Applications (NDAs) for new antibiotics, the last step before the FDA approves a product for marketing and sales (see Figure 4). The FDA must approve an NDA for each indication of a drug. The pending NDAs would not allow the new drugs to be used by the most seriously

Figure 3: The FDA approved 13 new antibiotics in the past 10 years (those with novel mechanisms of action are shaded).

Year Approved	Compound Name (Brand Name)	Indications	Targeted Organisms
1998	**Rifapentine** (Priftin)	tuberculosis	Mycobacterium tuberculosis
1999	**Quinupristin/ dalfopristin** (Synercid)	VRE infections	
		skin and skin structure infections	methicillin-susceptible *S. aureus* and *Streptococcus pyogenes*
1999	**Moxifloxacin** (Avelox)	bronchitis and sinusitis; community-acquired pneumonia; skin and skin structure infections	G+ and G-, including multi-drug resistant *Streptococcus pneumoniae*
1999	**Gatifloxacin** (Tequin)	Discontinued in 2006 due to severe side effects.	
2000	**Linezolid** (Zyvox)	VRE infections	
		pneumonia, hospital- and community-acquired	G+, including MRSA, and multi-drug resistant *Streptococcus pneumoniae*
		skin and skin structure infections	G+; including MRSA
2001	**Cefditoren pivoxil** (Spectracef)	bronchitis; community-acquired pneumonia	G+ and G- (not effective against bacteria already showing resistance to drugs in this class)
		uncomplicated skin and skin structure infections	methicillin-susceptible *S. aureus* and *Streptococcus pyogenes*
		pharyngitis/tonsillitis	*Streptococcus pyogenes*
2001	**Ertapenem** (Invanz)	intra-abdominal infections; community-acquired pneumonia; urinary tract infections; skin and skin structure infections; acute pelvic infections	G+ and G- (typically reserved for ESBL-producing G-)
2003	**Gemifloxacin** (Factive)	community-acquired pneumonia; bronchitis	G+ and G-; including multi-drug resistant *S. pneumoniae*
2003	**Daptomycin** (Cubicin)	skin and skin structure infections; bacteremia	G+, including MRSA; may be used in combination therapies for G- (*in vitro* activity against VRE demonstrated, but no clinical data)
2004	**Telithromycin** (Ketek)	community-acquired pneumonia	G+ and G- (including multi-drug resistant *S. pneumoniae*)
		FDA approval was withdrawn in 2007 for bronchitis and sinusitis because the threat of serious side effects did not justify the drug's use for these self-limiting infections.	
2005	**Tigecycline** (Tygacil)	skin and skin structure infections; intra-abdominal infections	G+ and G- (including MRSA, and ESBL-producing G- bacteria; *in vitro* activity against VRE demonstrated, but no clinical data)
2007	**Retapamulin** (Altabax, topical)	impetigo	G+ (*in vitro* activity against MRSA demonstrated, but no clinical data)
2007	**Doripenem** (Doribax)	intra-abdominal infections; urinary tract infections	G+ and G- (effective in lower concentrations than current drugs in its class)

Notes: G+: Gram-positive bacteria
G-: Gram-negative bacteria
VRE: vancomycin-resistant *Enterococci*
MRSA: methicillin-resistant *Staphylococcus aureus*
ESBL: extended spectrum beta-lactamase

Figure 4: Six new antibiotic applications are pending with FDA (none have novel mechanisms of action).

Antibiotic	NDA Filed	Indications Sought	Targeted Organisms	Status of Application
Dalbavancin	12/2004	skin and skin structure infections (catheter infections, phase 2)	G+ (including VRE and MRSA)	12/2007: FDA issued approvable letter requesting additional information.
Faropenem medoxomil	12/2005	sinusitis, bronchitis, and community-acquired pneumonia	G+ and G-	4/2008: new clinical trials (begun in response to an FDA non-approvable letter) halted due to financial concerns.
Telavancin	2/2007	skin and skin structure infections (hospital-acquired pneumonia, phase 3)	G+ (including MRSA)	3/2008: Theravance provided FDA with the requested additional information; final decision expected by 7/21/2008.
Ceftobiprole	5/2007	skin and skin structure infections (all pneumonia, phase 3)	G+ and G- (including MRSA, which is unique for this class)	3/2008: FDA says approval is dependent on an inspection of the study sites and a review of the clinical data.
Oritavancin	2/2008	skin and skin structure infections (bacteremia, phase 2)	G+ (including MRSA)	
Iclaprim	3/2008	skin and skin structure infections (all pneumonia, phase 2)	G+ (including MRSA)	

Figure 5: These six pathogens were identified by IDSA's Antimicrobial Availability Task Force as priority targets for antimicrobial research.

Name	Type of Organism
Acinetobacter baumannii	G-
Aspergillus spp.	Fungi
ESBL-producing *E. coli* and *Klebsiella* spp.	G-
VRE	G+
Pseudomonas aeruginosa	G-
MRSA	G+

ill patients, those with bacteremias or hospital-acquired pneumonias. Four of the drugs are still being studied in clinical trials for those indications. If the trial results are favorable, additional NDAs can be filed later to get the drug approved for more conditions.

At least five additional antibiotic candidates are in the final stage of clinical testing, which should lead to FDA approval within a few years, if no problems arise. Twenty-five or more other antibiotic candidates are in *earlier stages of clinical testing.*

Antibiotic development has not stopped, but its slow pace and narrow scope is worrying physicians and public health specialists. Rational use of available drugs is an important component for the future, but policies encouraging the research and development of new drugs are also needed. Our recent report—*Extending the Cure: Policy Responses to the Growing Threat of Antibiotic Resistance*— outlines some policy options, and current research from the Extending the Cure project group is exploring those options in more detail.[6] A future policy brief will highlight some new insights into how society can encourage antibiotic development and stewardship.

References

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