

ReAct facts

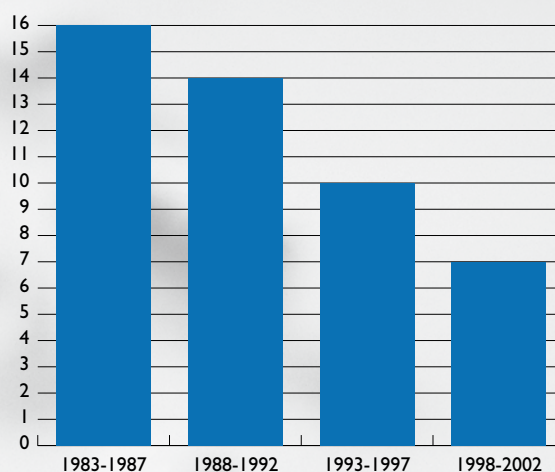
A fact sheet from ReAct – Action on Antibiotic Resistance, www.reactgroup.org

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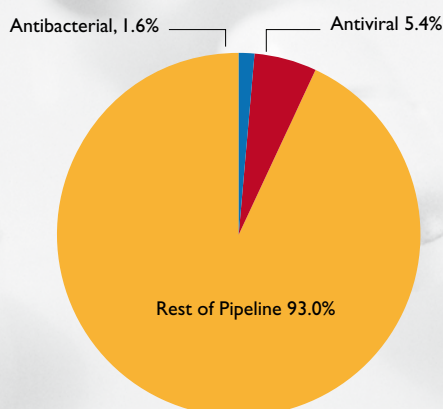
Decline in Antibacterial Innovation

Despite the increasing risk of antibacterial resistance, the number of new antibiotics has actually decreased in the past couple of decades. In the four five-year periods between 1983 and 2002, the number of new drugs introduced has fallen by 56%, from 16 new antibiotics between 1983 and 1987 to 7 new antibiotics between 1998 and 2002.¹

The R&D pipeline for the near future does not appear to reverse this trend. In a study of the pipelines of the 15 largest pharmaceutical companies, which were responsible for 93% of antibiotics introduced between 1980 and 2003, there were only 5 antibacterials, or 1.6% of the pipeline for these companies. This contrasts to 5.4% of the pipeline that is dedicated to antiviral drugs.¹



New antibacterial agents approved in the United States, 1983-2002. Source: Adapted from Spellberg (2004)



R&D Pipeline of 15 Largest Pharmaceutical Companies. Source: Data from Spellberg (2004)



Major Pharmaceutical Companies Exiting the Market

At the same time that the number of antibacterials in the pipeline is decreasing, a number of major pharmaceuticals have abandoned or sold off their antibiotic units: “Aventis and Roche spun off their anti-infective business. BMS, Eli Lilly, Wyeth and Procter & Gamble ended discovery of anti-infectives. GlaxoSmithKline downsized its anti-infective discovery.”²

As of 2004, the antibacterial discovery programs of half of large pharmaceutical companies in the United States and Japan had been discontinued or decreased since 1985.²

Lack on Innovative New Drugs

Combating antibiotic resistance requires more than just new drugs. Resistance to antibiotics frequently leads to resistance to the whole class of drugs, thus new classes of drugs are required to treat resistant bacteria, not just new drugs in existing classes.

Since the discovery of the first antibacterial drugs in the 1930’s, over a dozen classes of antibiotics have been discovered, all but two of which were developed prior to 1970. No new classes were discovered in the 1970’s, 80’s or 90’s, and only recently have two new classes become available: Oxazolidinones (in 2000) and Lipopeptides (in 2003).^{2,3}

A more in-depth analysis of the entire industry in 2005 paints a more optimistic picture. White found 70 drug candidates in the pipeline ranging from preclinical to pre-registration, 13 of which were in 5 new classes of antibiotics.⁴ However, of the 44 candidates whose targets were available, most target gram-positive bacteria.

Year Introduced	Class of Drug
1935	Sulfonamides
1941	Penicillins
1944	Aminoglycosides
1945	Cephalosporins
1949	Chloramphenicol
1950	Tetracyclines
1952	Macrolides/ Lincosamides/ Streptogramins
1956	Glycopeptides
1957	Rifamycins
1959	Nitroimidiazoles
1963	Quinolones
1968	Trimethoprim
2000	Oxazolidinones
2003	Lipopeptides

Antibacterial Pipeline by Bacterial Target ⁴

Bacterial Target	# of candidates in pipeline
Gram +Positive including Methicillin-resistant Staphylococcus aureus (MRSA), Glycopeptide/Vanomycin-intermediate Staphylococcus aureus (GISA/VISA), Vanomycin-resistant Enterococci (VRE)	31
Respiratory Tract Infections, Multidrug-resistant streptococcus pneumoniae (MDRSP) + H.influenzae	16
Gram Negative including Extended Spectrum Beta-Lactamase (ESBL), cefotaxime, quinolone-resistant	7
Non-fermenters / Pseudomonas including carbapenem-resistant	5
Anaerobes	1

* Sum does not equal 44 as some drugs have multiple targets



◆ ReAct links a wide range of individuals, organisations and networks around the world taking concerted action to respond to antibiotic resistance.

◆ Our vision is that current and future generations of people around the globe should have access to effective treatment of bacterial infections.

◆ ReAct believes that antibiotics should be used appropriately, their use reduced when of no benefit and their correct and specific use increased when needed.

◆ ReAct believes that awareness of ecological balance is needed as part of an integral concept of health.

Additionally, all the drug candidates for new classes of drugs, when targets were disclosed, targeted only Gram Positive and RTI bacteria. There are no new class candidates for gram-negative bacteria.

The contrast of White’s data with that of Spellberg, which was restricted to the 15 largest pharmaceutical companies, suggests that smaller companies may be playing a larger role in developing new antibiotics. Of the 36 companies that White identifies as ‘current discoverers’ of antibacterials, only 6 are among Spellberg’s top 15 largest pharmaceutical companies.

Little Incentive to Innovate

The priority given to an R&D project is determined, in part, by the net present value (NPV) of the drug, which weighs the expenses against the expected revenues in the future.⁵ The higher the potential revenue of the drug, the higher the NPV and the resources a company is willing to risk in developing a treatment.

Antibacterials stack very poorly against other therapeutic classes in terms of NPV:⁵

Project therapeutic class	Risk-adjusted NPV × \$1,000,000
Musculoskeletal	1,150
Neuroscience	720
Oncology	300
Vaccines	160
Injectable antibiotic (Gm+)	100
Oral contraceptive	10

Several reasons can account for the relatively weak NPV of antibacterials:^{5,6}

- Drug discovery for chronic diseases is more favorable because long-term treatment generates more revenue than the short-term treatment of antibiotics.
- A large number of old antibiotics already exist, resulting in a high level of therapeutic competition for newly developed drugs.
- R&D programs focus on broad-spectrum antibiotics, which may be counter to public health efforts to encourage narrow spectrum use of such drugs. Discouraging first-line use of new drugs can negatively impact sales.

Creating Incentives for Innovation

A number of interventions have been proposed for improving innovation in neglected diseases. Several of these mechanisms may also have potential in priming R&D for antibacterials as well.

Generally, ‘push’ mechanisms pay for inputs into the R&D process – whether financial, transactional or time-wise--that are required to bring a new drug to market, increasing the attractiveness of investing in neglected inno-

vation. Some push mechanisms that have been proposed for neglected disease include:

- *Public compound libraries* – provide access to compound libraries to screen for potential antibacterial activity, reducing R&D costs^{7,8}
- *Patent pooling* – the collective management on intellectual property reduces transactional costs and IP barriers to innovation⁹

While push mechanisms focus on the inputs to R&D, ‘pull’ mechanisms focus on the outputs by paying for completed projects. Some proposed pull mechanisms have included:

- *Advanced Market Commitments* – creates a fund which establishes an agreement with countries and NGOs to pay a pre-determined per-unit price innovations that address a particular need¹⁰
- *Prize Funds* – provides a financial reward for new therapies addressing a specific health threat^{11,12}

Product Development Partnerships. While push and pull mechanisms manipulate the current system of innovation, product-development partnerships (PDP) have had an important role in developing the pipeline for neglected diseases.¹³ PDPs characteristically leverage the respective expertise of the public and private sectors to create and deliver innovative medicines in neglected diseases.

While there were only 16 new drugs developed between 1975 and 1999 for tropical diseases and tuberculosis,¹⁴ a recent study noted that there are currently 63 drug candidates in the pipeline.¹³ Fifty percent of the projects were developed by multinational pharmaceutical companies under ‘no profit, no loss’ models, half of which were developed with PDPs. However, 45% of the 63 projects were developed by PDPs in conjunction with small-scale business. These businesses, which required smaller possible returns on investment, operated under commercial, for-profit models.

Drugs with novel mechanisms of action are needed to combat antibiotic resistance, and PDPs have proven effective in targeting such “breakthrough” therapies.¹³ Only 8% of projects developed solely by industry focused on breakthrough therapies, while 49% of PDP projects and 63% of industry projects developed in conjunction with PDPs targeted breakthrough therapies.

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