Antibiotics and challenges in the wake of superbugs

www.biochemj.org/bj/330/0581/bj3300581.htm

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"When I woke up just after dawn on September 28, 1928, I certainly didn't plan to revolutionise all medicine by discovering the world's first antibiotic, or bacteria killer," ....would later say, "But I suppose that was exactly what I did."

Who said this and what was the antibiotic?
• Widespread use of antibiotics after WWII to improve global health

• Increasing antibiotic resistance in bacterial pathogens coupled with a lag in the development of additional antibiotics by pharmaceutical companies poses an escalating problem in the 21st century

2005: ~19,000 deaths from bacterial infections.
Today: 2 million people infected; ~23,000 deaths/year in US from bacterial infections!!! (from cdc.gov)

• Challenge to design effective new generation antibiotics among the growing impact of superbugs, overuse of antibiotics, and decline in research and development of new prospects

• Use of structure-based drug design to develop novel drugs based on high resolution structures of drug targets and their resistance mutants
Antibiotics

- Natural or synthetic compounds that either kill (bactericidal) or inhibit growth (bacteriostatic) of bacteria (or other microorganisms)

- Antibiotics may be classified in several ways. Most common classification schemes are based on chemical structure of the antibiotic
Antibacterial agents, suitable for therapy:

**Natural –**
Derived from natural sources such as fungi and soil bacteria.
Penicillin as the classic example, derived from the fungus *Penicillium*
Pharmaceutical industry produces penicillin from cultures of *Penicillium chrysogenum* that are adapted for high yield
Others: many aminoglycosides from soil bacteria (e.g., streptomycin)

**Semi-synthetic -**
Natural products that have been chemically modified to improve effectiveness of the product or to reduce side effects, etc
Examples include the β-lactams ampicillin, amoxicillin, etc, derived from fungi

**Completely synthetic –**
Products are synthesized completely in the laboratory
Sulfa drugs, folic acid analogs are examples
Antibiotic Targets in Bacterial Cells

Cell Wall Synthesis
- D-cycloserine
- Vancomycin
- Bacitracin
- Penicillins
- Cephalosporins
- Cephamycins

Cell Wall Integrity
- β-lactamases

DNA Synthesis
- Metronidazole

DNA Gyrase
- Quinolones

RNA Polymerase
- Rifampicin

Cell Wall

DNA Replication

Ribosomes
- 50S
- 30S

Translation
- Protein Synthesis
  - (50S Inhibitors)
  - Erythromycin
  - Chloramphenicol
  - Cindamycin
  - Lincomycin

- Protein Synthesis
  - (30S Inhibitors)
  - Tetracyclines
  - Streptomycin
  - Spectinomycin
  - Kanamycin

Cytoplasmic Membrane

Phospholipid Membranes
- Polymyxins

Essential Biochemistry
www.wiley.com
Resistance to Antibiotics can occur through two general genetic mechanisms:

1. Intrinsic resistance
   Some bacteria are naturally more resistant to certain classes of antibiotics than others.
   Examples:
   • certain bacteria may lack a transport system for an antibiotic
   • bacteria may lack the target of the antibiotic molecule
   • the cell wall is covered with an outer membrane blocks entry of the antibiotic (as in the case for Gram negative bacteria).

2. Acquired resistance
   Bacteria acquire resistance to antibiotics for which they were previously susceptible through
   • spontaneous gene mutation (rate of $10^{-8}$–$10^{-9}$) and fixation of mutation in the population through rapid cell division (vertical evolution)
   • horizontal gene transfer mechanisms, such as conjugation, transformation, or transduction. Impact of this can be significant. For example, in 10 years' time between 1985 and 1995, the percentage of ampicillin-resistant *Shigella* (causes intestinal illness) grew from 32% to 67%! 
How do bacteria become resistant to antibiotics?

Bacteria acquire genes that encode proteins that shield or protect them from the effects of the antibiotic.

These genes may have arisen by mutation of existing genes OR they may have been acquired from other resistant bacteria through the transfer of genetic information between bacteria.

Antibiotic resistance genes are often carried on plasmids and can be exchanged between bacteria.
Several mechanisms (shown in red) exist to inactivate an antibiotic. Mechanism(s) used depend on the genes found in the resistant bacteria of interest, such as:

1. **Synthesis of enzymes that breakdown the antibiotic:**
   - Penicillinase (a type of β-lactamase, breaks the β-lactam ring, thereby destroying the antibiotic). Other enzyme types are also prevalent (e.g., cephalosporinases). New Delhi metallo-beta lactamase (NDM-1), an enzyme that makes bacteria resistant to a broad range of beta-lactam antibiotics (creating resistant “superbugs”)

   ![Penicillin G](Penicillin.png)

2. **Modification of their own enzymes that would normally be targets of the antibiotic** (e.g., DNA gyrase)
Mechanisms, continued:

3. Synthesis of “pumps” inserted into the cell membrane to remove the antibiotic from the interior of the cell.

4. Addition of chemical groups onto the target so that the antibiotic does not recognize the target. (e.g., erythromycin resistance)

5. Modification of the antibiotic so that it no longer recognizes its target (e.g., kanamycin resistance)

6. Modification of the peptidoglycan cell wall to avoid the antibiotic effect
What can government to help solve the antibiotic crisis?

Three main components to the report (2014):
• improve surveillance of antibiotic-resistant bacteria and stop outbreaks;
• increase the life of current antibiotics and develop new ones, as well as promote research accelerating clinical trials;
• increase economic incentives to develop new antibiotics.
SUMMARY:

• Bacterial antibiotic resistance is an increasingly serious global health problem

• Global scientific research imperatives:
  Development of new derivatives of antibiotics
  Discovery of new classes of antibiotics with novel mechanisms of action
  Development of new approaches to treating bacterial infections

• Government and industrial partnerships are essential to foster new antibiotic drug development