Bacterial Biochemistry

Mechanism of Bacterial resistance

Antimicrobial resistance - a threat to public health and patient safety

- Infections with resistant organisms are associated with increased morbidity and mortality
- Extended stays in hospitals
- Reduced treatment options
- Untreatable infections
- Increased healthcare costs

Gram-negatives

- **Penicillinase identified in the laboratory, 1940**

  Penicillin entered clinical use

- **Penicillinase quickly spread in clinical isolates**

  Broad-spectrum antibiotics became available in 1950-60's

- **Beta-lactamases with increasing spectrum 1950-1970**

  Cephalosporins became available in the 1970's

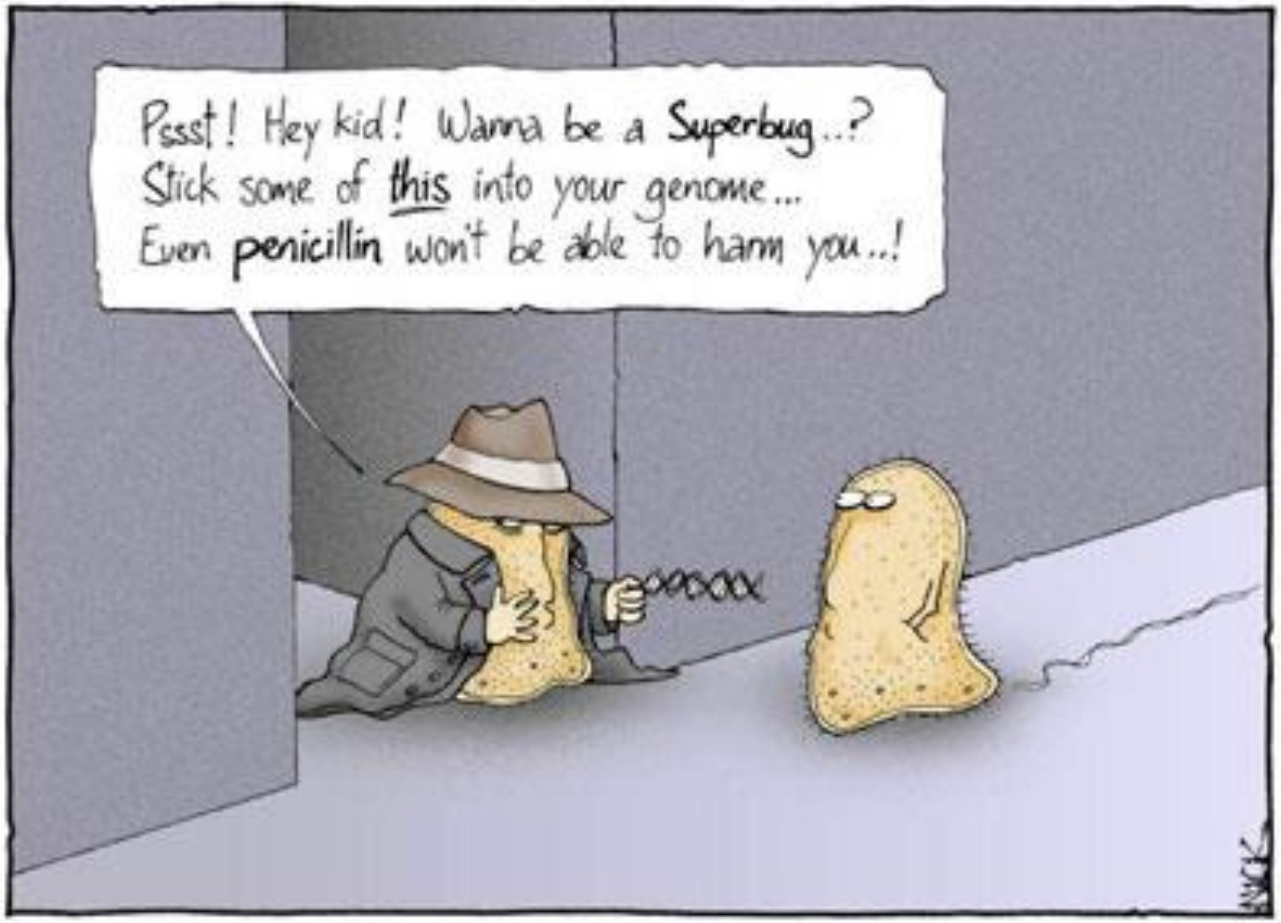
- **Extended spectrum beta-lactamases, ESBLs, 1980-1990 (TEM, SHV,**
  Carbapenems became available 1985

- **1996 (2003 EU) carbapenemases (KPC, VIM, OXA, NDM-1)**

- **2009- carbapenem-non-susceptible *Enterobacteriaceae* (CSNEs) –**
- **"UNTREATABLE"!**

Evolution of antibiotic resistance is a consequence of selective pressure

Antibiotic Resistance: Mechanisms, Prevalence, and Strategies for Treatment

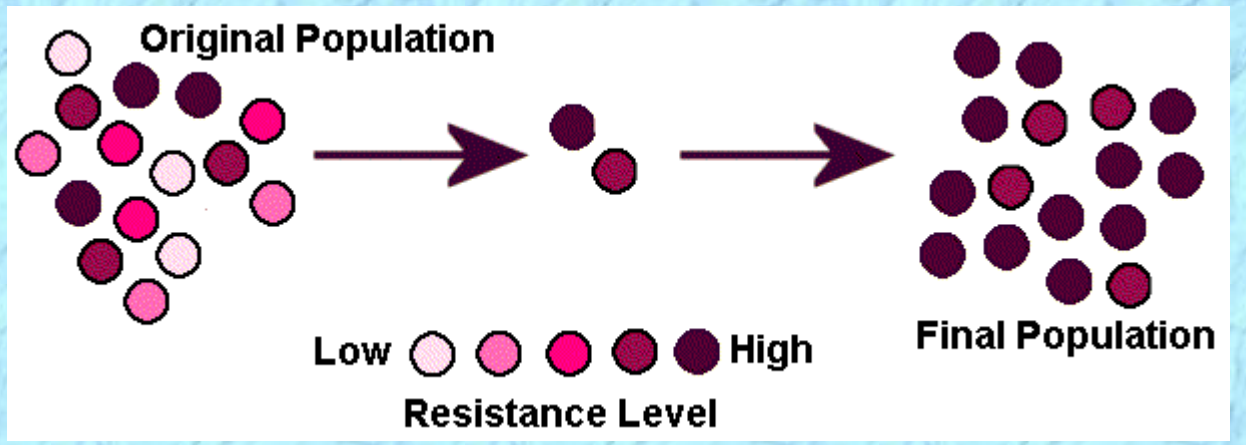


It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

Selection for resistance

antibiotic

Antibiotic not effective



Antibiotic Resistance

- The ability of a microorganism to avoid the harmful effects of an antibiotic by destroying it, transporting it out of the cell, or undergoing changes that block its effects.

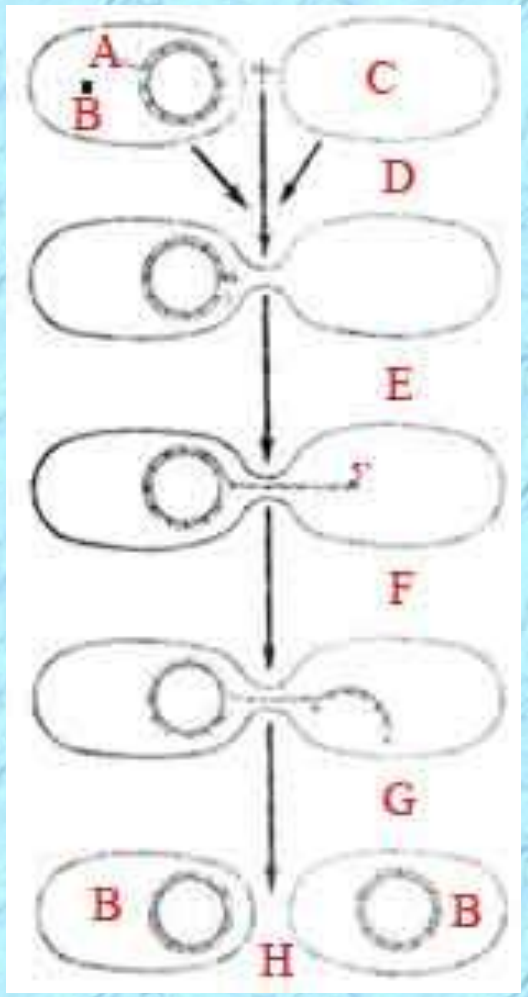
- Cellular stress results in selective pressures on a microorganism, leading to the development and eventual prevalence of resistance within a population

- Three possible outcomes when antibiotics are introduced:

    1. Death (Bactericidal)
    2. Growth Inhibition (Bacteriostatic)
    3. Resistance

- Bacteria can develop resistance to multiple drugs and antibiotics, further facilitating their spread.

Bacterial Processes Leading to Resistance

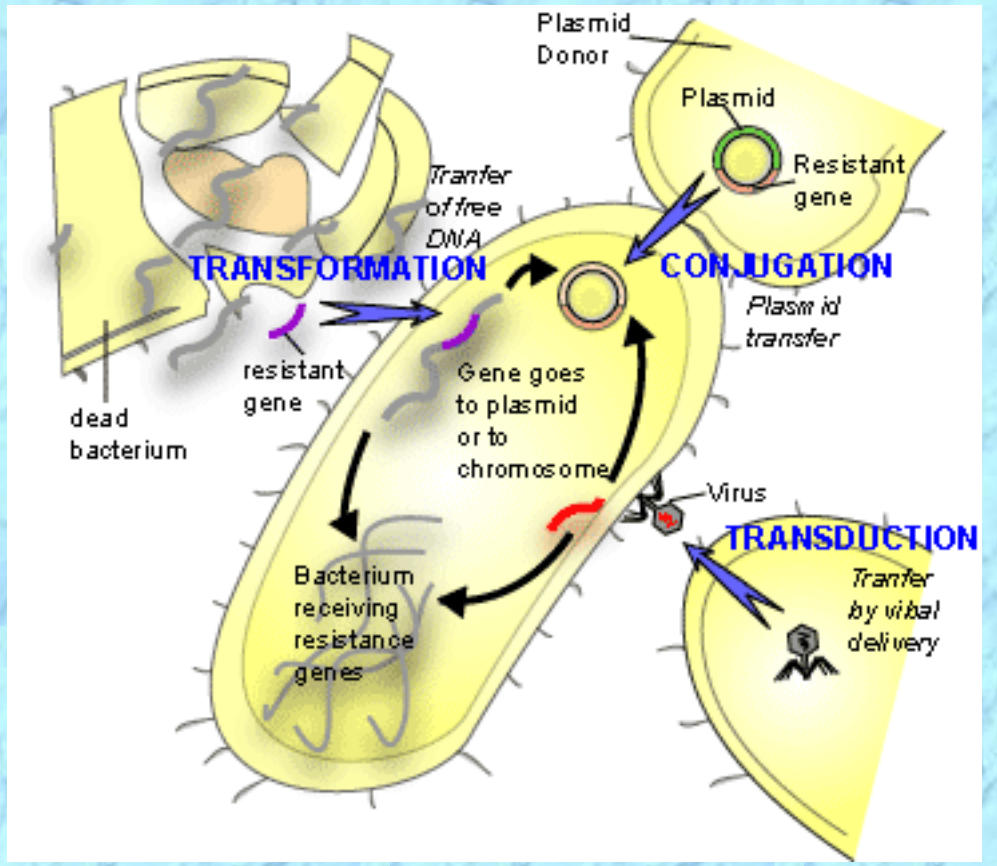


- Conjugation: Transfer of a plasmid through direct cell contact.
  - R Plasmids confer resistance.

- Rolling circle:
  - Conjugation bridge is made between cells
  - Plasmid begins to replicate as a rolling circle
  - Travels across bridge in a linear fashion
  - Re-circularizes in recipient cell

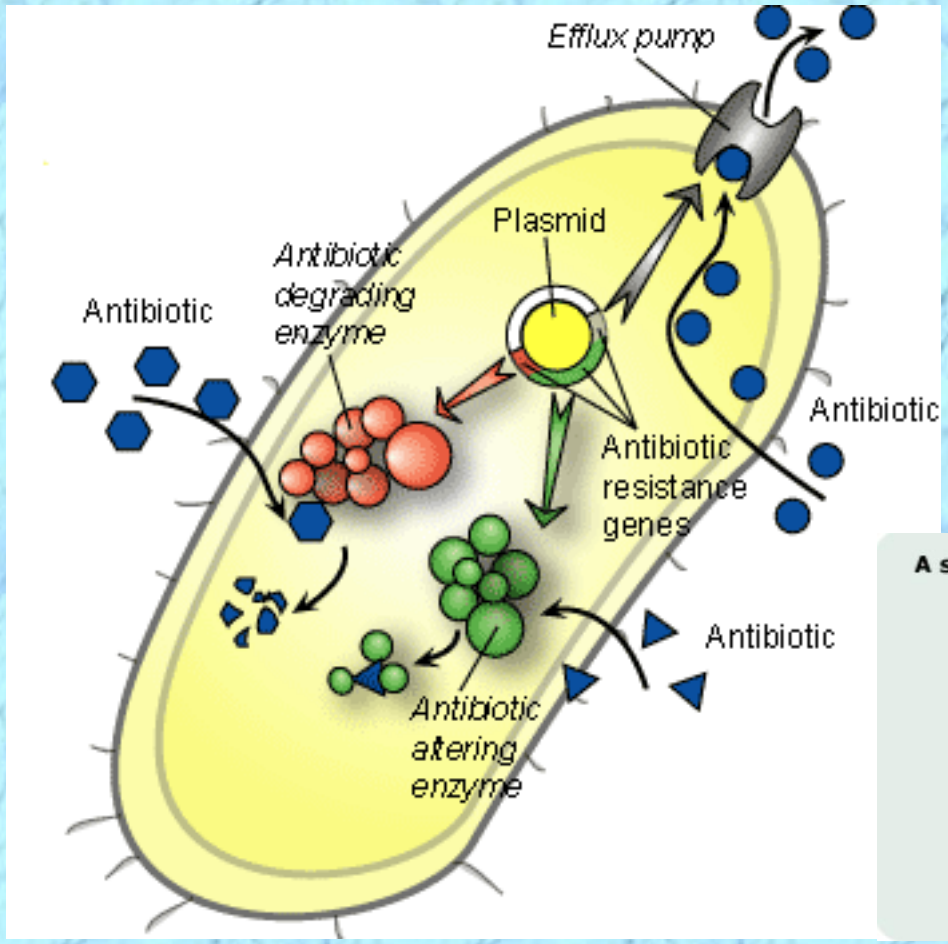
- Horizontal gene transfer- Transfer of genes without production of offspring.

Bacterial Processes Leading to Resistance

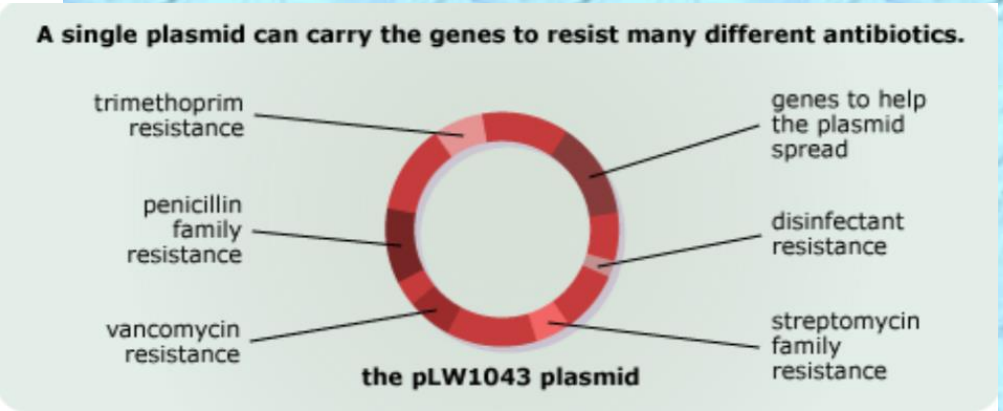


- **Transformation:** Uptake of DNA from the environment, incorporation into the genome, and gene expression.
- **Transduction**- The insertion of genetic material from a virus (Bacteriophage), and incorporation into the genome.
- **Vertical Gene Transfer**: Transfer of genetic material from parent to daughter cell (Generational Inheritance)

Mechanisms of Resistance



- **Change the antibiotic structure so that it is no longer able to perform its function**
- **Break down the antibiotic**
- **Pump the antibiotic out of the cell**



Mechanisms of Resistance

Antibiotic	Method of resistance
Chloramphenicol	reduced uptake into cell
Tetracycline	active efflux from the cell
β-lactams, Erythromycin, Lincomycin	eliminates or reduces binding of antibiotic to target
β-lactams, Erythromycin	hydrolysis
Aminoglycosides, Chloramphenicol, Fosfomycin, Lincomycin	inactivation of antibiotic by enzymatic modification
β-lactams, Fusidic Acid	sequestering of the antibiotic by protein binding
Sulfonamides, Trimethoprim	metabolic bypass of inhibited reaction
Sulfonamides, Trimethoprim	overproduction of antibiotic target (titration)
Bleomycin	binding of specific immunity protein to antibiotic

Table 1. Mechanisms of antibiotic resistance.

http://www.scq.ubc.ca/attack-of-the-superbugs-antibiotic-resistance/

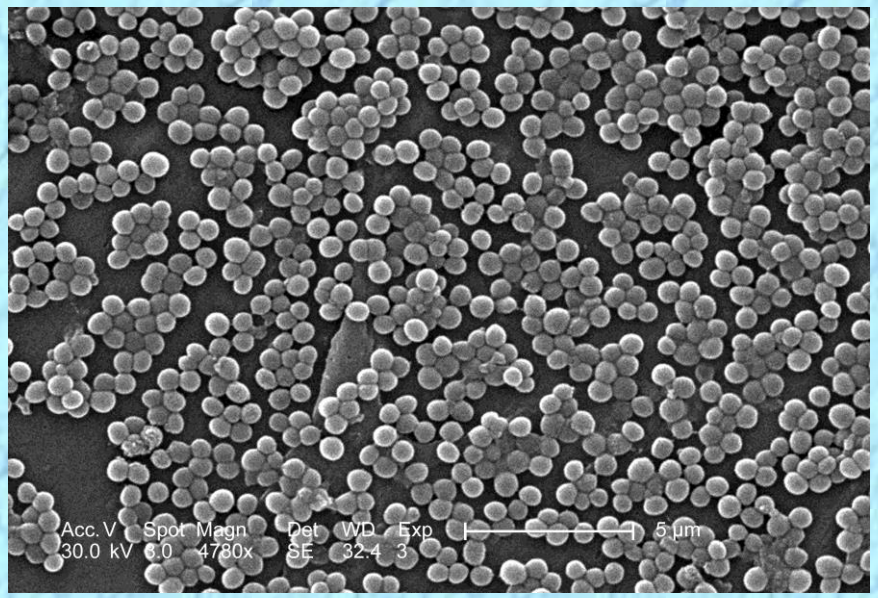
MRSA

- Methicillin-Resistant *Staphylococcus aureus*
  - Also Vancomycin Resistant (VRSA)

- Infects the nostrils, respiratory tract, wounds, and urinary tract.

- Symptoms:
  - Red bumps
  - Large boils
  - Can later infect vital organs, leading to sepsis, toxic shock syndrome, and necrotizing pneumonia.

- Commonly found and contracted within hospitals and healthcare centers (Nosocomial Infection)



Tuberculosis

- *Mycobacterium tuberculosis*

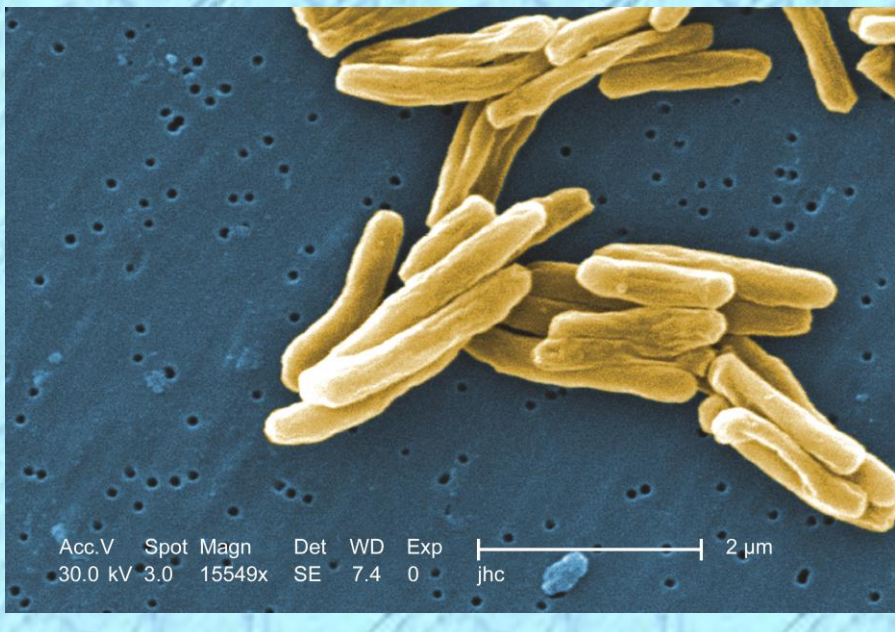
- Can survive long exposures to acids, detergents, oxidative bursts, and antibiotics.

- Treatment typically takes over six months, allowing the bacteria ample time to adapt and mutate.

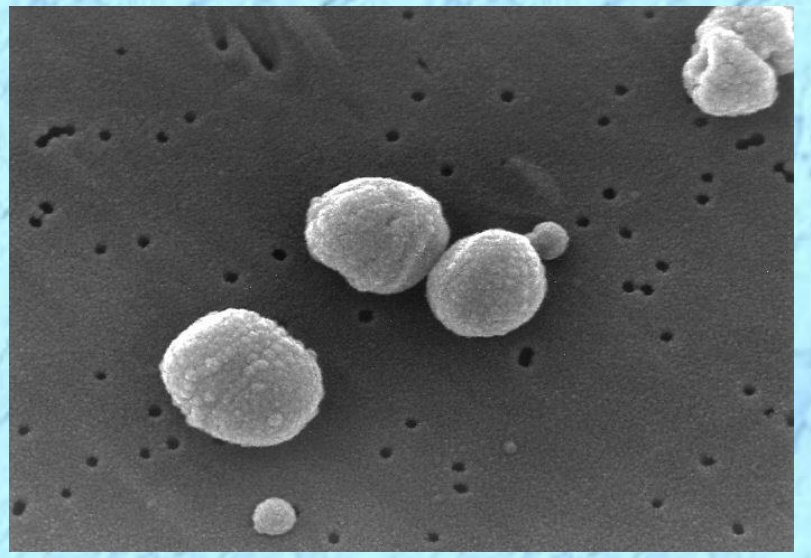
- Four antibiotics used: isoniazid, rifampicin, pyrazinamide, and ethambutol.

- Most of the antibiotics are aimed at inhibiting the synthesis of mycolic acids, a major component of the cell wall.

- Multi–drug-resistant tuberculosis is resistant to two antibiotics, Extensively drug resistant tuberculosis is resistant to three, with a cure rate of only 30%.



Pneumonia



http://upload.wikimedia.org/wikipedia/commons/2/20/Streptococcus_pneumoniae.jpg

- ***Streptococcus pneumoniae and Klebsiella pneumoniae*** **(CRKP)**
- **Several strains of pneumonia that is resistant to at least one antibiotic.**
- **There are seven strains of resistant pneumonia, the most well known of which is the 19A strain.**
- **In 2000, 40% of pneumonia infections in the USA were resistant to at least one antibiotic. 11% were resistant to at least three drugs.**
- **This has dropped significantly since the introduction of the 7-valent pneumococcal conjugate vaccine.**

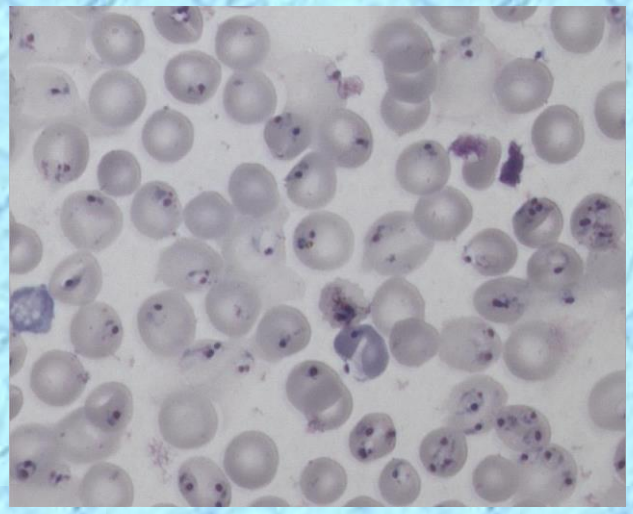
Malaria

- Caused by *Plasmodium falciparum*, a eukaryotic protist.

- Malarial infections are almost always a mix of resistant and non-resistant strains.

- Treating malaria with a large dose of antibiotics results in competitive release
  - Susceptible strains were wiped out, resistant strains were able to spread more readily than when they had never had a competitor.

- Lower doses were found to be more effective at reducing symptoms, while avoiding positive selection.



Mouse erythrocytes infected with *Plasmodium chabaudi*

Potential Solutions

- **Vaccines:**

➢ **Many scientists are looking into manufacturing vaccines for resistant strains of bacteria.**

➢ **Don't suffer the same fate as antibiotics, as they stimulate the body's immune system to eradicate the infection.**

- **Cytokines:**

➢ **Several government organizations are experimenting with adding cytokines to animal feed rather than antibiotics.**

➢ **Have been found to enhance the growth of the animals, without the use of antibiotics.**

Potential Solutions

- **Bacteriophage therapy:**

➢ **The therapeutic use of lytic bacteriophages to treat bacterial infections.**

- **Responsible use of antibiotics:**

➢ **Only use when prescribed for a bacterial infection.**

➢ **Use exactly as instructed, do not stop treatment early.**

➢ **Industries must research ways of making products safe while reducing the use of antibiotics.**

Misuse/Overuse of Antibiotics

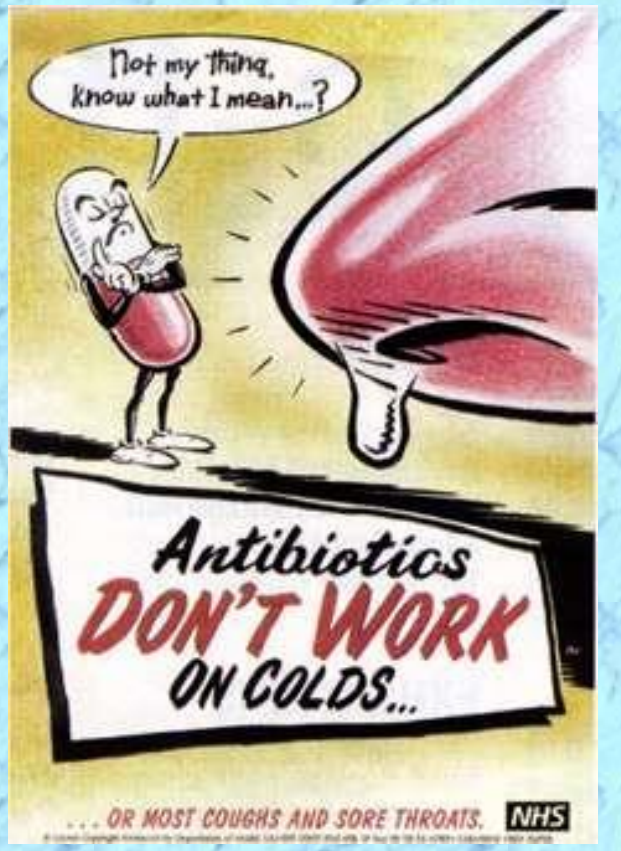
- Plays a substantial role in the emergence of resistant strains of bacteria.

- Although resistance is natural, the proportion of resistant bacteria multiply when antibiotics are used carelessly.

- Millions of people take antibiotics unnecessarily every year.

- Antibiotics have no effect on viral illnesses such as:
  - Colds
  - Flu
  - Sore Throats
  - Bronchitis

- Use of antibiotics for feed animals and livestock also a major factor.



http://www.lowdensitylifestyle.com/FREE,%20flexibility,%20fluidity/antibiotics/