Why Don’t These Drugs Work Anymore?

Biosciences in the 21st Century
Dr. Amber Rice
November 17, 2014
Estimates of Burden of Antibacterial Resistance

**European Union**
- Population: 500m
- 25,000 deaths per year
- 2.5m extra hospital days
- Overall societal costs: €900 million, hosp. days
- Approx. €1.5 billion per year
- Source: ECDC 2007

**Thailand**
- Population: 70m
- >38,000 deaths
- >3.2m hospital days
- Overall societal costs: US$ 84.6–202.8 mill. direct
- >US$1.3 billion indirect
- Source: Pumart et al 2012

**United States**
- Population: 300m
- >23,000 deaths
- >2.0m illnesses
- Overall societal costs: Up to $20 billion direct
- Up to $35 billion indirect
- Source: US CDC 2013

Global information is insufficient to show complete disease burden impact and costs
Why don’t these drugs work anymore?

• Drug resistance: a case study
• How does resistance evolve?
  – Three mechanisms of evolution
• Examples of “superbugs”
• Avoiding more widespread resistance
Drug resistance: a case study

- AZT (azidothymidine) approved as a treatment for HIV in 1987.
Drug resistance: a case study

- After several months of treatment, higher concentrations of AZT were needed.
Drug resistance: a case study

• In most cases, patients became resistant to AZT within 6 months!
What happened?

Why might a drug stop working so quickly?
Why don’t these drugs work anymore?

• Drug resistance: a case study
• How does resistance evolve?
  – Three mechanisms of evolution
• Examples of “superbugs”
• Avoiding more widespread resistance
Back to our case study: the evolution of resistance

Susceptible
Reverse Transcriptase

Resistant
Reverse Transcriptase

Copyright © 2004 Pearson Prentice Hall, Inc.
Mechanisms of evolution

1. **Natural selection**: differential reproductive success
   - Non-random
   - Not forward-looking, can only work with existing variation
   - Only adaptive mechanism of evolution

Figure: Univ. of Calif. Mus. of Paleontology’s Understanding Evolution Site
Back to our case study: the evolution of resistance by natural selection.
Mechanisms of evolution: sources of variation

2. **Mutation**: a change in DNA sequence, gene order, or chromosome number
   - Random
   - Increases genetic variation within populations
   - Types of mutations:
     • Point mutations
     • Insertions
     • Deletions
     • Gene duplications
     • Chromosomal inversions
     • Polyploidy

Figure: Univ. of Calif. Mus. of Paleontology's Understanding Evolution Site
Mechanisms of evolution: sources of variation

3. **Gene flow (or migration):** movement of genes between populations
   - Increases genetic variation within populations
   - Makes populations more similar to each other

Figure: Univ. of Calif. Mus. of Paleontology's Understanding Evolution Site
• Bacteria can also pick-up resistance genes through horizontal gene transfer

Evolution of resistance: gene flow introduces variation
Are the necessary “ingredients” present for the evolution of antimicrobial resistance by natural selection?
Evolution of resistance

• Heritable variation for resistance
  – 30,000 year-old bacterial DNA recovered from Yukon permafrost
  – Genes for resistance to several antibiotics, including tetracycline and vancomycin (D’Costa et al. 2011, Nature)
  – So, resistant strains:
    • can pre-date use of the antimicrobial drug.
    • may arise by random mutation or even gene transfer after the drug is in use.
Evolution of resistance

• Differential reproduction
  – Widespread use of antibiotics creates strong selection for resistant strains.
    • Antibiotics over-prescribed by doctors
    • Antibiotics used in agriculture and commercial products
  – Use of any anti-microbial drug, not only antibiotics, creates strong selection for resistance.
Back to our case study: new treatments informed by evolution

- By understanding how resistance evolves, researchers could design new treatments.
Why are drug cocktails more effective?

- With a single drug, only 1 mutation can confer resistance.
  - Easy. HIV has large populations, a short generation time, and a high mutation rate.
- For resistance to drug cocktails,

- More mutations needed for resistance → lower probability the mutations will occur together in one virion.
Why don’t these drugs work anymore?

• Drug resistance: a case study
• How does resistance evolve?
  – Three mechanisms of evolution
• Examples of “superbugs”
• Avoiding more widespread resistance
MRSA
Methicillin-resistant *Staphylococcus aureus*

- Spread in hospitals and with close physical contact (e.g., among inmates, athletes)
- 33% worldwide have Staph, ~1% MRSA
- Painful skin conditions, even bacterial pneumonia and blood infections
- Can be fatal
- Resistant to entire class of penicillin-like antibiotics
- In 2002, vancomycin-resistant strain found
MDR-TB
Multidrug-resistant Tuberculosis

• TB is major cause of death worldwide.
  – 2 million TB-related deaths each year
• 440,000 MDR-TB cases each year
  – 150,000 deaths
• 2\textsuperscript{nd} line drugs have more side-effects, cost up to 100x more!

U.S. National Institute of Allergy and Infectious Diseases (NIAID)
Malaria

- Caused by *Plasmodium spp.* protozoan
- Transmitted by mosquito
- Tropical and sub-tropical regions
- Fever, muscle & back pain, vomiting, anemia…
- Brain damage in children
- Nearly 1 million deaths each year
- Drugs used for treatment and for prevention
- Resistance to cheapest and most commonly used drugs is widespread
- Resistance to newer drugs is emerging

World Health Organization (WHO)
U.S. National Institute of Allergy and Infectious Diseases (NIAID)
Why don’t these drugs work anymore?

• Drug resistance: a case study
• How does resistance evolve?
  – Three mechanisms of evolution
• Examples of “superbugs”
• Avoiding more widespread resistance
Avoiding more widespread resistance

1. Avoid contracting infections
2. Minimize transmission of resistant microbes
3. Improve use of antimicrobial drugs
   - Take only when appropriate (i.e., don’t take an antibiotic for the flu!)
   - Use antibacterial soaps/cleaners ONLY around people with weakened immune systems
   - Avoid broad-spectrum antibiotics if possible.
   - Take ALL of the medication
   - Reduce agricultural use of antibiotics
Why can reducing inappropriate use of antimicrobial drugs combat resistance?

- Resistance is sometimes costly for microbes.
Why can reducing inappropriate use of antimicrobial drugs combat resistance?

• Use of specific antibiotics (not broad-spectrum)
  – Some antibiotics target a greater number of bacterial species.
  – Often used when diagnosis is unclear.
  – Why is it better to prescribe an antibiotic that targets fewer species?
    • Selection for resistance will act only on the species that are targeted by the drug.
Why can reducing inappropriate use of antimicrobial drugs combat resistance?

• Taking ALL of the medication increases the chance of exterminating the microbial population before resistance evolves.
  – If you stop early, you may get sick again or stay sick for longer.
  – Longer illness → more bacterial generations → greater chance of mutation for resistance arising
  – Even if resistant microbes DO arise, immune system may successfully fight them if population is small.
    • Stopping the drug lets the population grow larger.
Why can reducing inappropriate use of antimicrobial drugs combat resistance?

- Resistant bacteria escape livestock, spread to humans
Current research aims

- What is the mechanism of resistance?
- How do microbes acquire and pass on resistance genes?
- Development of better diagnostic tests to avoid the need for “broad spectrum” antibiotics
- Development of new drugs/vaccines

Over the last 30 years, no major new types of antibiotics have been developed

World Health Organization (WHO), 2014