Why Don't These Drugs Work Anymore?

Biosciences in the 21st Century

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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

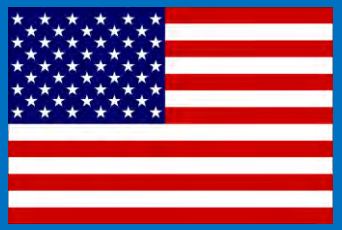
Source: Pumart et al 2012

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

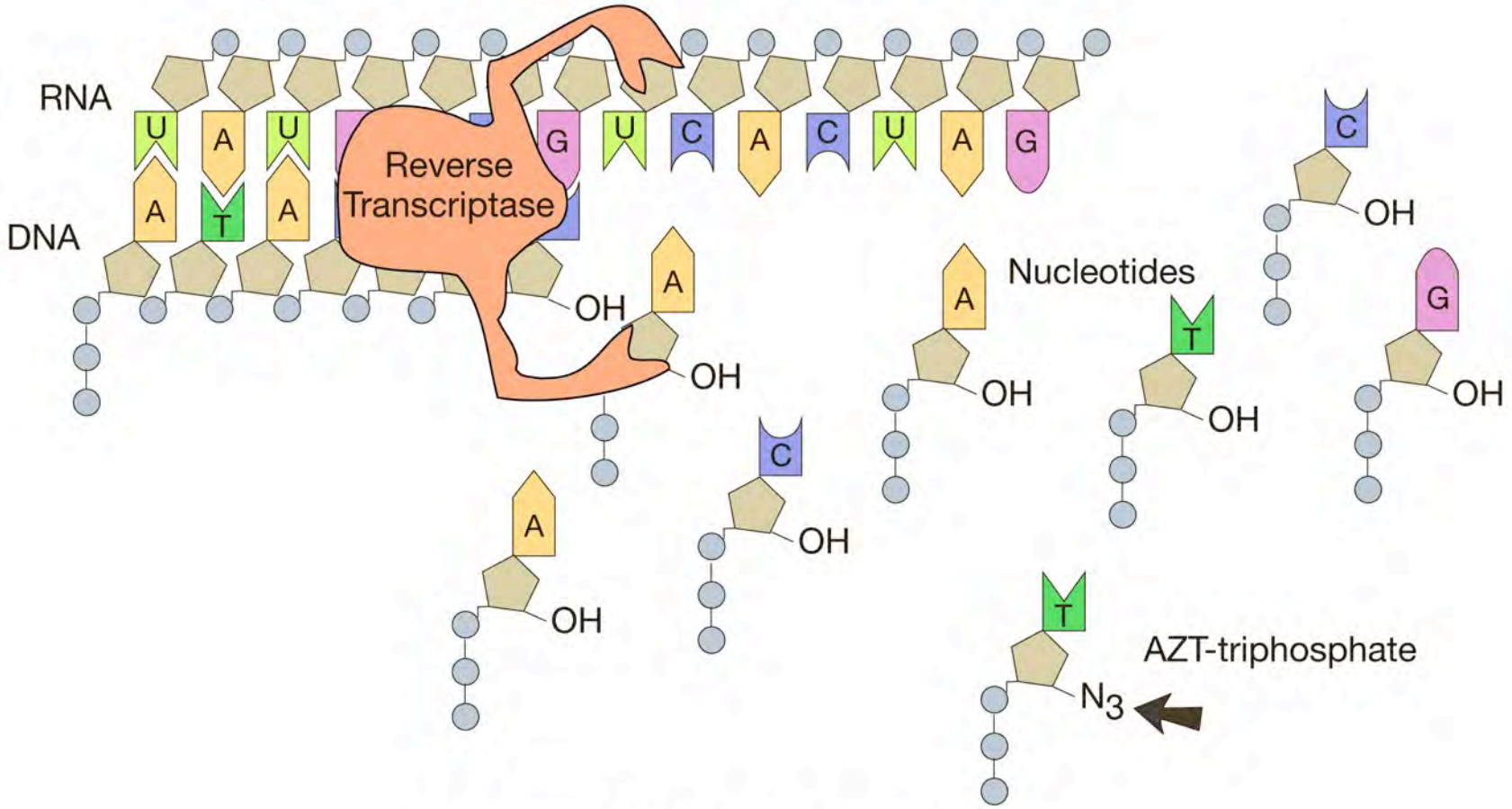
Global information is insufficient to show complete disease burden impact and costs

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

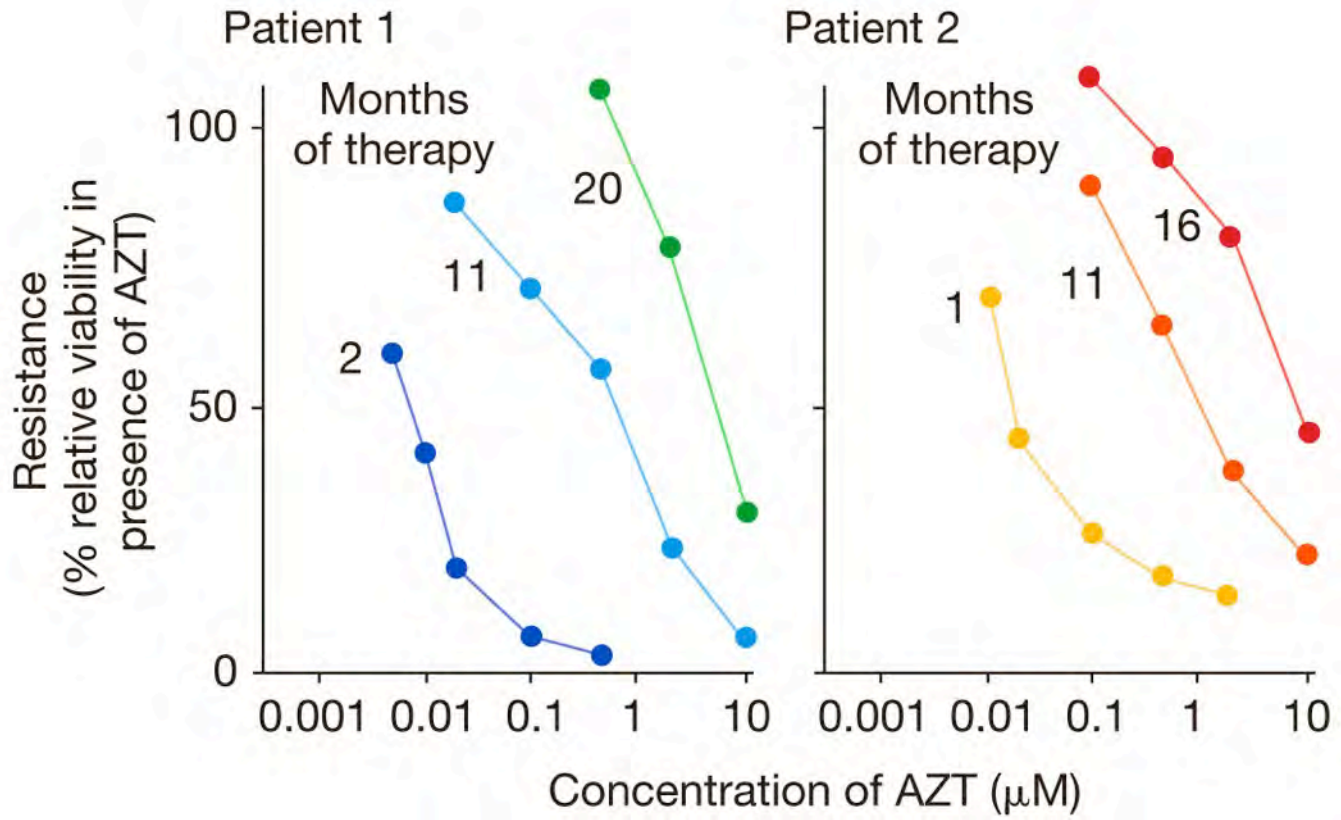
Drug resistance: a case study

- AZT (azidothymidine) approved as a treatment for HIV in 1987.



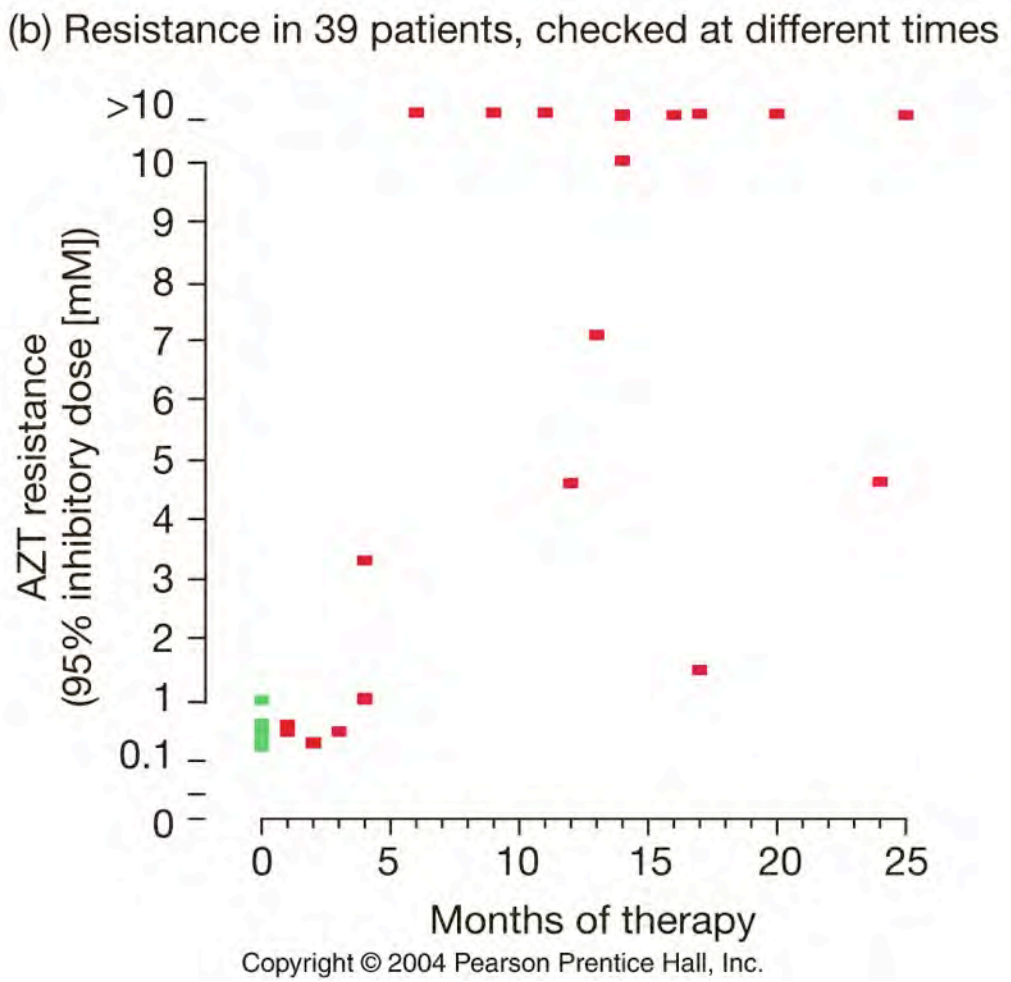
Drug resistance: a case study

- 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?

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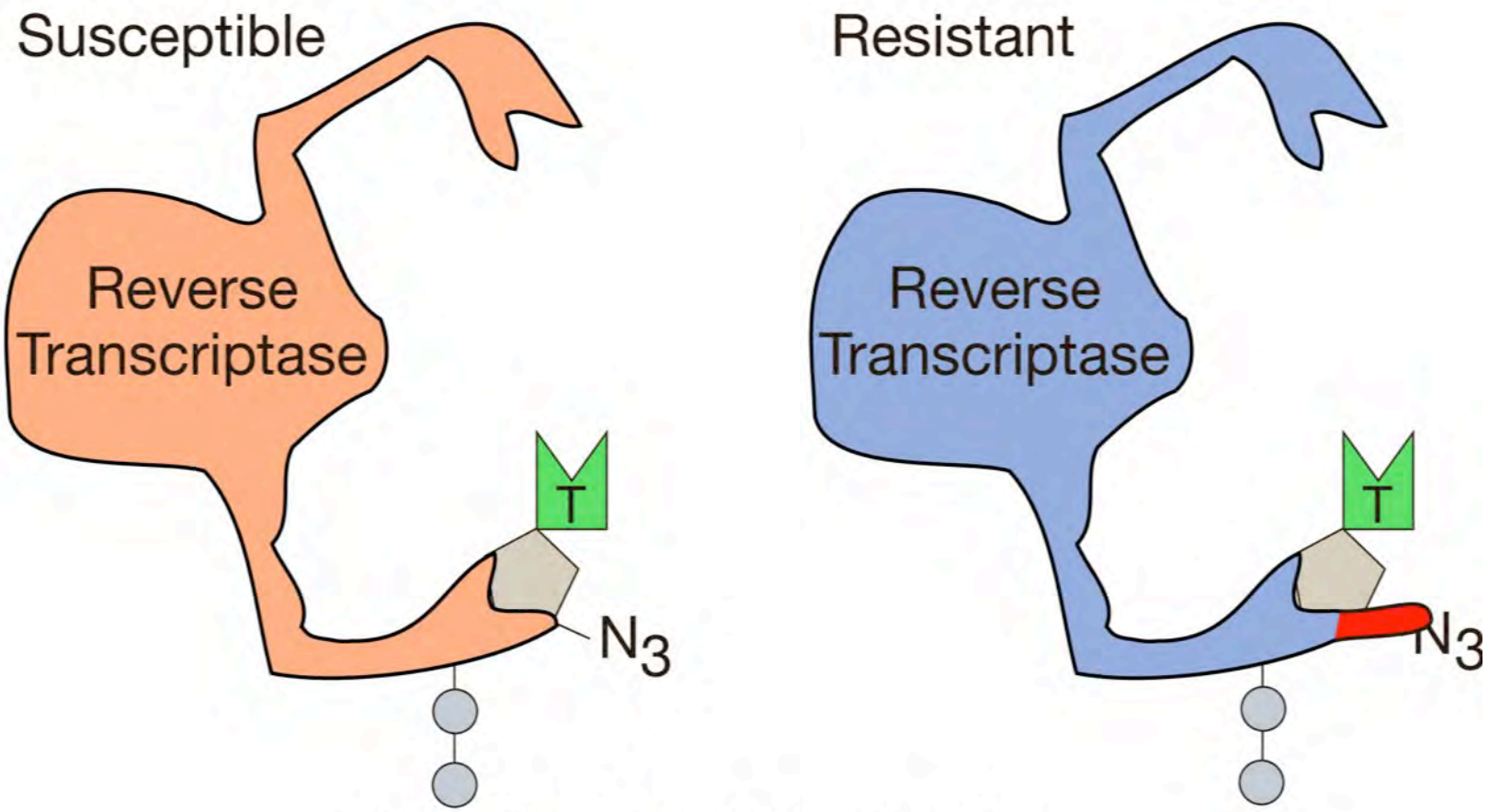
Back to our case study: the evolution of resistance

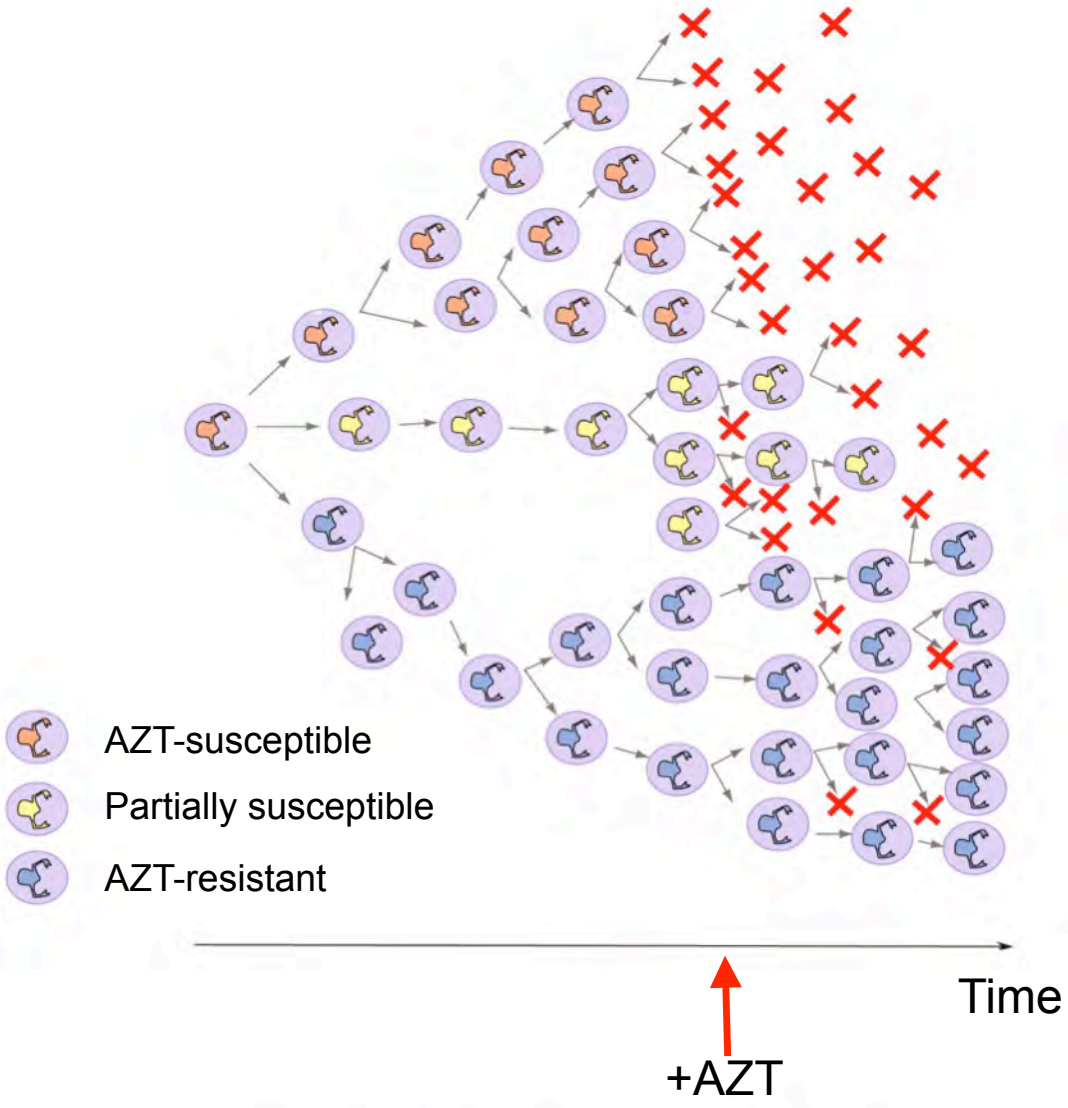


Mechanisms of evolution

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

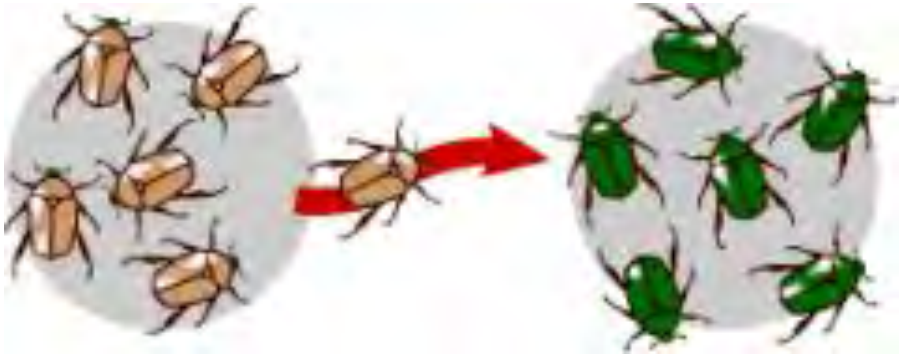
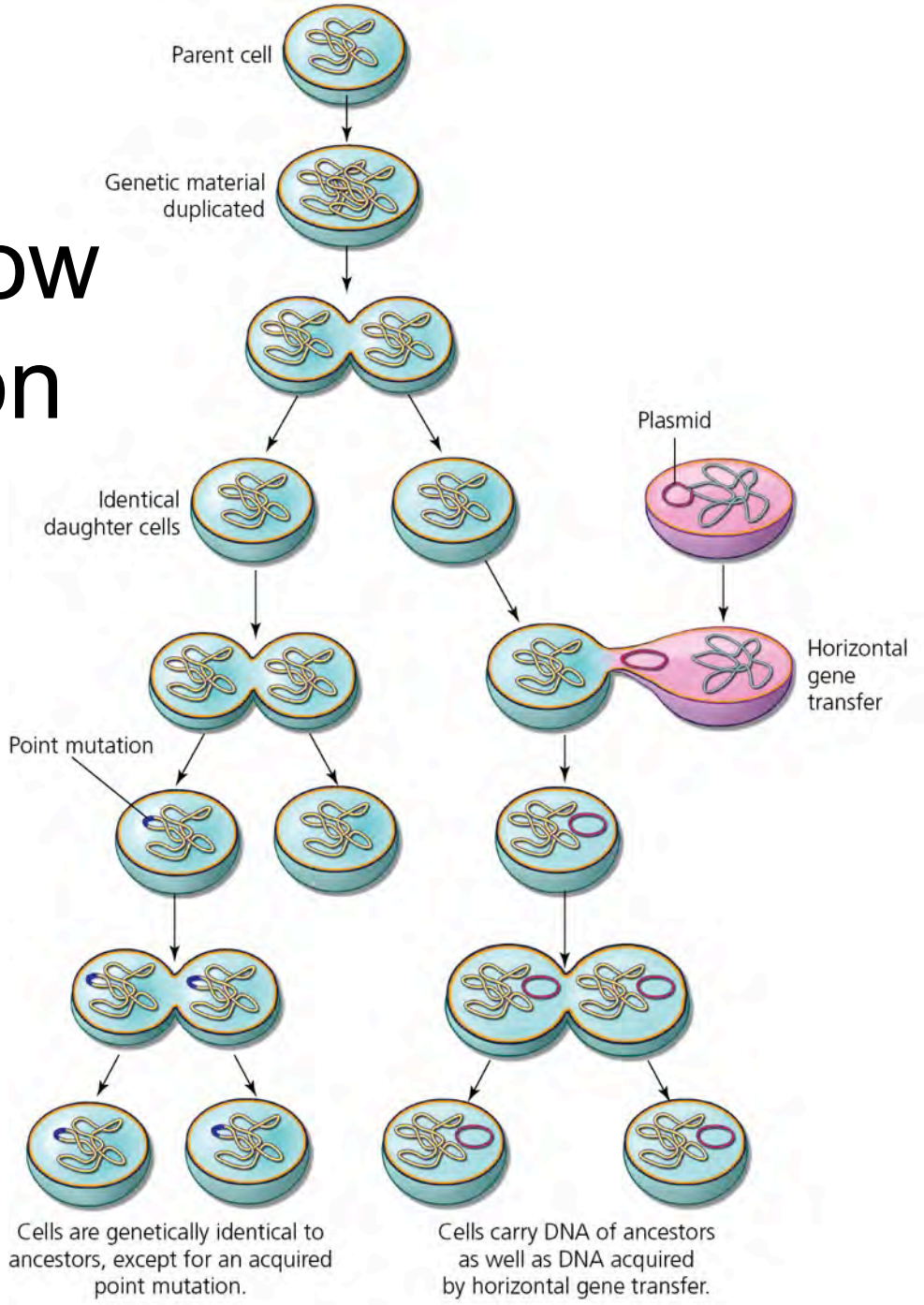


Figure: Univ. of Calif. Mus. of Paleontology's Understanding Evolution Site

Evolution of resistance: gene flow introduces variation

- Bacteria can also pick-up resistance genes through **horizontal gene transfer**



Are the necessary “ingredients” present for the evolution of antimicrobial resistance by natural selection?

Evolution of resistance

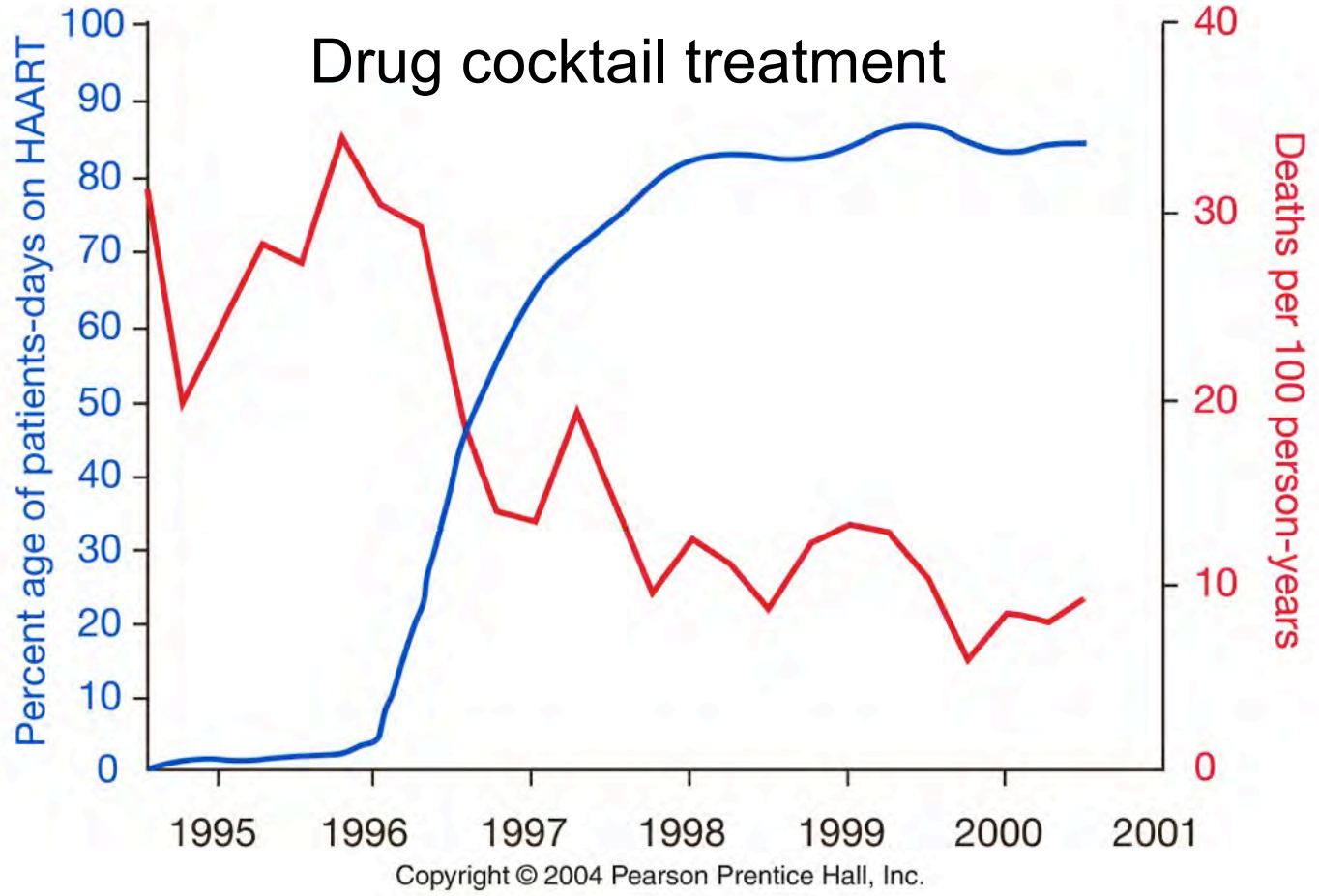
- Heritable variation for resistance
  - 30,000 year-old bacterial DNA recovered from Yukon permafrost
  - Genes for resistance to several antibiotics, including tetracycline and vancomycin (D'Costa et al. 2011, Nature)
  - So, resistant strains:
    - can pre-date use of the antimicrobial drug.
    - 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

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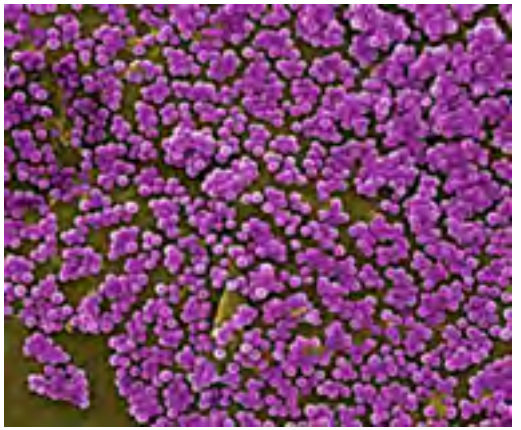
MRSA

Methicillin-resistant *Staphylococcus aureus*

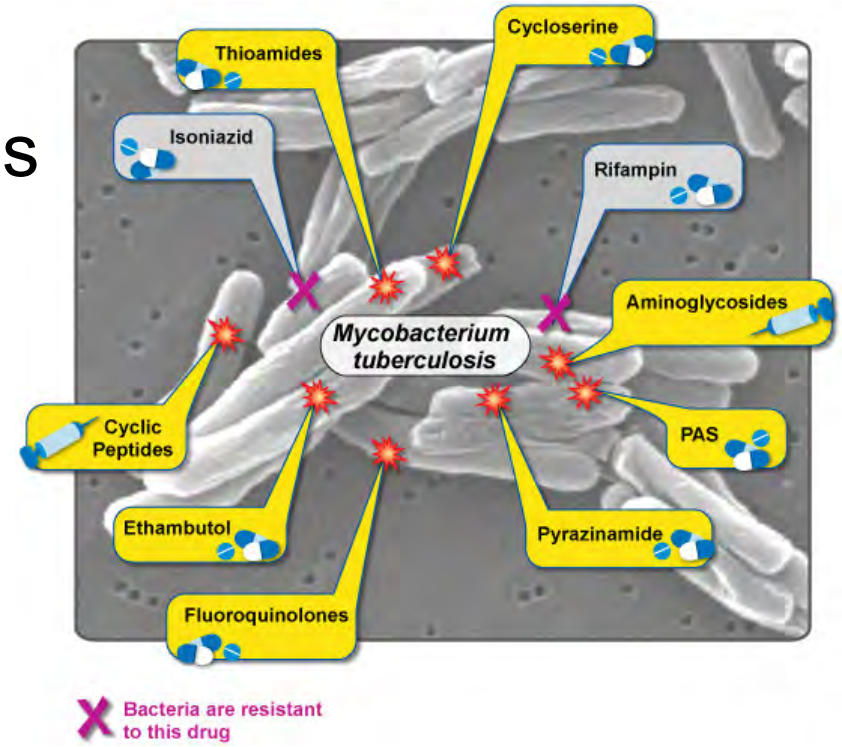
- Spread in hospitals and with close physical contact (e.g., among inmates, athletes)
- 33% worldwide have Staph, ~1% MRSA
- Painful skin conditions, even bacterial pneumonia and blood infections
- Can be fatal
- Resistant to entire class of penicillin-like antibiotics
- In 2002, vancomycin-resistant 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
- 2nd 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)

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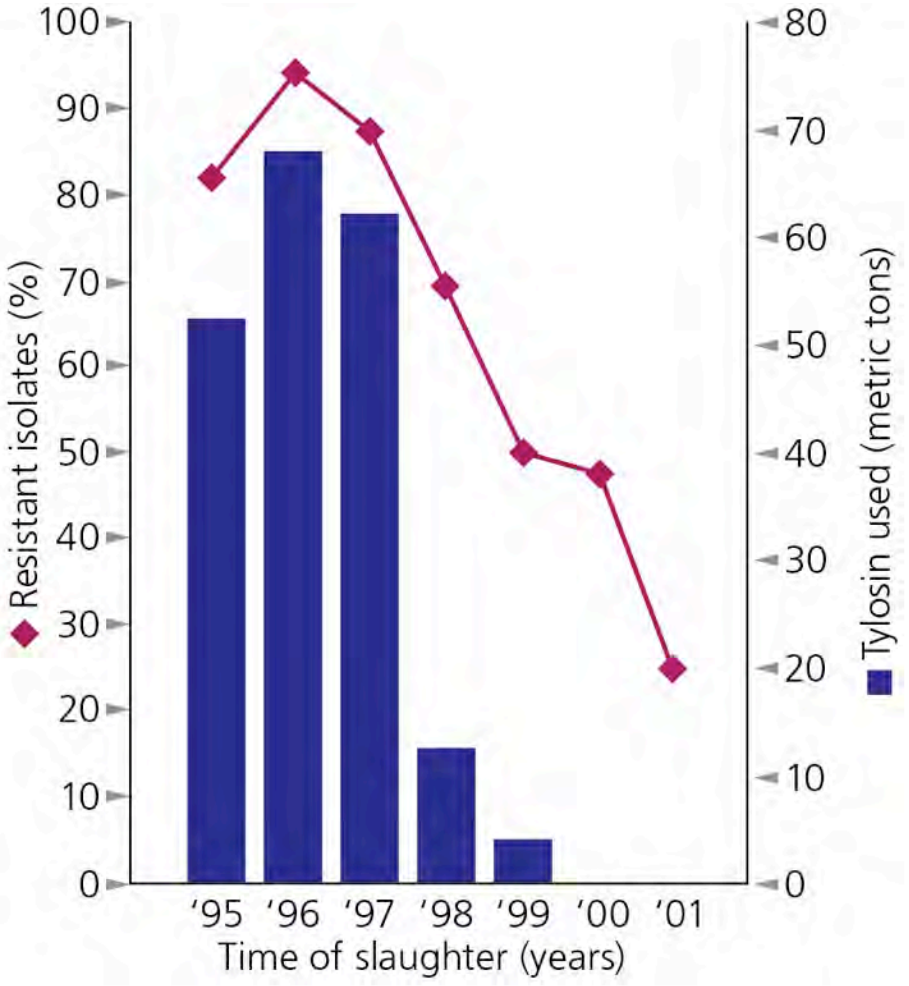
Avoiding more widespread resistance

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.



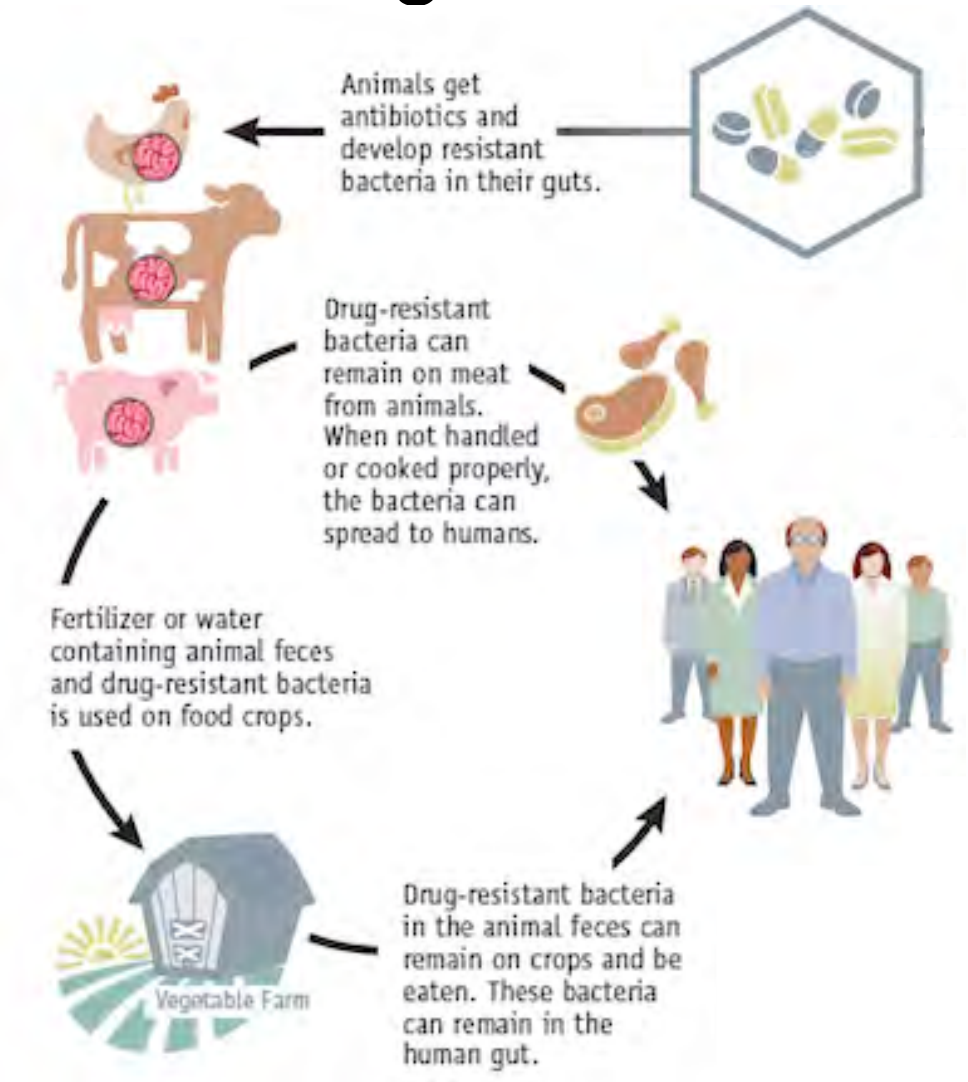
Why can reducing inappropriate use of antimicrobial drugs combat resistance?

- 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.

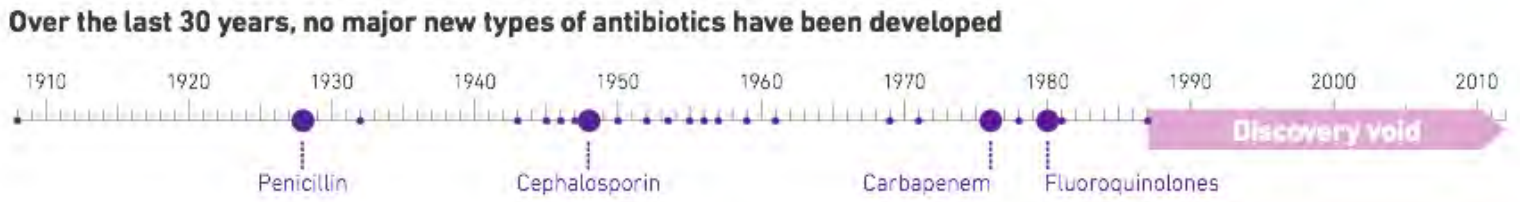
Why can reducing inappropriate use of antimicrobial drugs combat resistance?



- 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



World Health Organization (WHO), 2014