Preparing for the Battle

Antibiotic Resistance

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resistance to common bacteria has reached alarming levels. Few, if any, of the available treatments options remain effective for common infections.

World Health Organization Global Report on Antibiotic Resistance, 2014:

Analysis: Humans Losing War Against Antibiotic-Resistant 'Superbugs'

A prominent researcher says humans have "fallen way behind" in the war against superbugs.

Europe 'losing' superbugs battle

Infections have reached epidemic proportions and now outstrip our ability to treat them. Infections are warning.

More than 25,000 people die of bacterial infections every year, and bacteria are able to outsmart existing drugs, experts are warning.

Fighting superbugs

The most urgent global public health problems is the growing capability of bacteria to resist antibiotic drugs. The crisis of microbial resistance is particularly acute in hospitals, where it is often able to resist multiple drugs have spawned. More than 70 percent of the bacteria that cause hospital-related infections are already resistant to at least one type of antibacterial drug.
Battle Plan

1. Understand the enemy
2. Attack and counterattack
3. Intelligence from the frontlines
4. Join the fight
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Meet your microbes
Bacteria are very small

Human Skin Cell

H
1 μm

E.coli
They outnumber us >10:1 on our bodies

They can be helpful

*S. epidermidis* inhibits *S. aureus*\(^1\) colonization

Iwase et al, Nature 2010

Skin Cells
They can be helpful

Bacteria in the large intestine help us digest food, and produce useful compounds such as vitamins.
They can be **helpful**

Bacteria in the gut are important for training the immune system.
Not all bacteria are good

CLOSTRIDIUM DIFFICILE
250,000 Infections/year

ENTEROBACTERIACEAE
9,000 Infections/year

NEISSERIA GONORRHOEAE
246,000 Infections/year

THREAT LEVEL
URGENT

This bacteria is an immediate public health threat that requires urgent and aggressive action.
Not all bacteria are good

Each year, antibiotic resistant microbes cause at least

2,049,442 illnesses

23,000 deaths
Battle Plan

1. Understanding the enemy

2. Attack and counterattack
   - History of antibiotics
   - How antibiotics work
   - What causes antibiotic resistance?

3. Intelligence from the frontlines

4. Join the fight
Antibiotics revolutionized medicine

Alexander Fleming discovered Penicillin in 1928

Photo: http://en.wikipedia.org/wiki/Penicillin
Plate image adapted from: http://www.smccd.edu/accounts/case/graphics/staph.jpeg
Antibiotics target critical processes in the cell.
Antibiotics target critical processes in the cell

DNA Replication

Fluoroquinolones

Adapted from http://en.wikipedia.org/wiki/Quinolone
Antibiotics target critical processes in the cell.

Adapted from http://en.wikipedia.org/wiki/Rifamycin
Antibiotics target critical processes in the cell

Protein Synthesis

Tetracycline

Adapted from http://en.wikipedia.org/wiki/Tetracycline
Antibiotics target critical processes in the cell

Cell Wall Synthesis

Penicillin

Adapted from http://en.wikipedia.org/wiki/Penicillin_binding_proteins
Our antibiotics are losing effectiveness against *Neisseria Gonorrhoeae*. 

[CDC Report on antibiotic resistance, 2013](#)
How did this happen?
How did this happen?

EVOLUTION
Replication errors create diversity within a population
Replication errors create diversity within a population

Resistant mutant
Bacteria “share” genes via horizontal gene transfer

Many important genes for antibiotic resistance can be found on PLASMIDS, mobile DNA elements that can easily jump between species.
Antibiotics kill off the sensitive cells, allowing resistant cells to take over.

Initial **sensitive** population with rare **resistant** cell.
Antibiotics kill off the sensitive cells, allowing resistant cells to take over.
Antibiotics kill off the sensitive cells, allowing resistant cells to take over the population.

Initial sensitive population with rare resistant cell

Antibiotics kill sensitive cells, but not resistant cells

Resistant cells take over the population
Questions?
Battle Plan

1. Understanding the enemy

2. Attack and counterattack

3. Intelligence from the frontlines
   - Better Stewardship
   - New antibiotics
   - Diagnostics

4. Join the fight
Conserve what we have left: better Stewardship

~90% of antibiotics used in the US are for agricultural production¹

Antibiotics used as growth promoters in livestock production:

- Bambermycin
- Lasalocid
- Monensin
- Salinomycin
- Virginiamycin
- Bacitracin

¹ Union of Concerned Scientists. 2001
² Reinhardt, Merck Veterinary Manual, 2012
Conserve what we have left: better Stewardship

Antibiotic use in agriculture has been shown to generate resistant bacteria which can then spread to humans.

In 2013, the FDA imposed voluntary guidelines for phasing out certain antibiotics in livestock feed.
Conserve what we have left: better Stewardship

As much as

50% of antibiotics prescriptions are unnecessary or misused

Hospitals are working to:
• Make sure to culture bacteria for identification before starting antibiotic treatment
• Give clear dosage and duration instructions
• Reassess effectiveness in 2-3 days

CDC Report on antibiotic resistance, 2013
Battle Plan

1. Understanding the enemy

2. Attack and counterattack

3. Intelligence from the frontlines
   - Better Stewardship
   - New antibiotics
   - Diagnostics

4. Join the fight
We are discovering fewer and fewer antibiotics

Graphics and data adapted from CDC Report on Antibiotic Resistance, 2013
Sorting through dirt for new antibiotics

- Through millenia of microbial warfare, soil bacteria have developed the majority of antibiotics
- Many microbes need “support” from the soil community to grow and are difficult to grow in the laboratory
- The “iChip”, introduced in 2010, can grow previously uncultured bacteria

Teixobactin, 2015
New diagnostics for fast detection

- Many pathogens grow very slowly in the lab
- Knowing what antibiotics they are resistant to is time-sensitive
  - Don’t waste time using the wrong antibiotics
  - Don’t allow further resistance to develop
- New methods for fast diagnosis based on detection of microbial DNA can significantly speed up this process
Battle Plan

1. Understanding the enemy
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The CDC recommends:

**Tactic #1**

Prevent infections by practicing good hand hygiene
The CDC recommends:

**Tactic #2**

DO NOT ask for antibiotics when your doctor thinks you do not need them (ex. viral infections)

http://www.cdc.gov/features/antibioticresistance/
Antibiotics cannot kill viruses

Bacteria: complex cell with DNA replication, transcription, translation

Virus: a packet of DNA
The CDC recommends:

**Tactic #3**

Always use antibiotics for full duration prescribed

http://www.cdc.gov/features/antibioticresistance/
What doesn’t kill you makes you more resistant

Initial sensitive population with rare resistant cell
What doesn’t kill you makes you more resistant

Initial **sensitive** population with rare **resistant** cell

**Antibiotics** kill **sensitive** cells quickly, and **slightly resistant** cells slowly. Therapy eventually eradicates all cells.
What doesn’t kill you makes you more resistant

Premature end of antibiotics therapy allow slightly resistant cells to take over, and possibly gain increased resistance

Initial sensitive population with rare resistant cell
**Battle Plan**

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<tr>
<th>1</th>
<th>Understand the enemy</th>
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<td>2</td>
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1. **DO** Wash your hands
2. **DON’T** take antibiotics for viral infections
3. **DON’T** skip prescribed antibiotics

<table>
<thead>
<tr>
<th>Livestock</th>
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<td>90%</td>
<td>50%</td>
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![Graph showing new antibiotics over years](image)
Thank you!

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Harvard Integrated Life Sciences

addgene
The nonprofit plasmid repository