Objectives

Antibiotics Past
- Review discovery of antibiotics and the impact of antibiotic use on treatment of infections

Antibiotics Present
- Discuss current challenges associated with antibiotic usage, resistance, and drug development

Antibiotics Future
- Explore opportunities for preservation of antibiotics and the development of new antibiotics
Life Before Antibiotics

- **Syphilis**
  - 1360’s
  - Mercury was applied to the skin, taken orally, or injected

- **Malaria**
  - 1600’s
  - Cinchona tree bark from South America
  - Later found to have quinine

- **General Wounds**
  - 2000 BC
  - Honey was applied to wounds
  - Sugar can dehydrate bacteria and acid can prevent growth
History of Penicillin

Dr. Alexander Fleming discovered Penicillin in 1928

In early 1942, 400 million units of penicillin were manufactured

At the end of WWII, 650 billion units/month were being produced
Outpatient Antibiotic Prescriptions per 1,000 Population by State - 2016

Source: CDC
Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:

At least **2,049,442** illnesses, **23,000** deaths

*bacteria and fungus included in this report

Antibiotic resistance threats in the United States, CDC 2013
‘The storms we’re seeing now, people thought this was decades in the future’
Antibiotic Resistance
How Antibiotic Resistance Happens

Many bacteria and a few are drug-resistant

Antibiotics kill bacteria that are not resistant

The drug-resistant bacteria now take over

Some bacteria can share their drug-resistance
Resistance Timeline

1943 Penicillin
1967 Gentamicin
1972 Vancomycin
1979 Gentamicin Resistance
1988 Vancomycin Resistance
1996 Levofloxacin Resistance
1996 Levofloxacin
2000 Linezolid Resistance
2001 Linezolid

Adapted from: https://www.cdc.gov/drugresistance/about.html
# MGH Resistance

## KLEBSIELLA PNEUMONIAE

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Interpretation</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>Resistant</td>
<td>&gt;=64</td>
</tr>
<tr>
<td>Ampicillin</td>
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<td>Aztreonam</td>
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<td>Cefazolin</td>
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<tr>
<td>Cefepime</td>
<td>Resistant</td>
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<tr>
<td>Ceftriaxone</td>
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<tr>
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<td>Ertapenem</td>
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<td>Gentamicin</td>
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<tr>
<td>Imipenem</td>
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<td>8</td>
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<tr>
<td>Levofloxacin</td>
<td>Resistant</td>
<td>&gt;=8</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Resistant</td>
<td>&gt;=16</td>
</tr>
<tr>
<td>Piperacillin-tazobactam</td>
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<td>&gt;=128</td>
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<tr>
<td>Tetracycline</td>
<td>Resistant</td>
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</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>Resistant</td>
<td>&gt;=320</td>
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</tbody>
</table>

**Comments**: KLEBSIELLA PNEUMONIAE
Few KLEBSIELLA PNEUMONIAE
ARE WE LOSING THE FIGHT AGAINST SUPERBUGS?
And: Is it already too late?
Stewardship

Financial Stewardship

Environmental Stewardship

Antimicrobial Stewardship
Antimicrobial Stewardship Goal

Improve clinical outcomes by:
- Optimizing antimicrobial utilization
- Decreasing antimicrobial resistance

CDC Core Elements of Hospital Antibiotic Stewardship Programs. 2018.
Antimicrobial Stewardship Core Elements

- Leader Commitment
  - Financial and personnel support from hospital leadership

- Drug Expertise and Action
  - Physicians and Pharmacists
  - Implement policies

- Tracking & Reporting
  - Monitor antibiotic prescribing and antibiotic use

- Education
  - Provide updates and educational programs to learners
Percentage of Hospitals Meeting all 7 Core Elements of Hospital Antibiotic Stewardship Programs* by State, 2017

Nationally, 76.4% of hospitals have met all 7 Core Elements (3,816 of 4,992); the national goal is 100% of hospitals by 2020.

*More information on CDC’s Core Elements of Hospital Antibiotic Stewardship Programs can be found at: https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html

Source: CDC’s National Healthcare Safety Network (NHSN) Survey
What can you do to help?

Decrease Antibiotic Use

- Only use antibiotics when appropriate
- Use shortest duration of antibiotics

Use Better Antibiotics

- Antibiotics need to be tailored to treat the infection
Do I really need antibiotics?

SAY YES TO ANTIBIOTICS when needed for certain infections caused by bacteria.

SAY NO TO ANTIBIOTICS for viruses such as colds and flu, or runny noses, even if the mucus is thick, yellow or green. Antibiotics also won’t help for some common bacterial infections including most cases of bronchitis, many sinus infections, and some ear infections.

Antibiotics are only needed for treating certain infections caused by bacteria. Antibiotics do not work on viruses.

To learn more about antibiotic prescribing and use, visit www.cdc.gov/antibiotic-use.
Antibiotics can save lives but aren’t always needed

Antibiotics do not work on viruses

Any time antibiotics are used they can cause side effects

Taking antibiotics can cause resistance

If you take antibiotics, take them exactly as prescribed

Clean your hands, cover your mouth, and get vaccinated
Risk factors and mitigation strategies

• Use of antibiotics is the single most important risk factor leading to AR around the world
  • Up to 80% of all antibiotics used in animals

• Core strategies for prevention of spread of MDRO:
  • Preventing infections and the spread of resistance
  • Tracking resistant bacteria
  • Improving the use of today’s antibiotics
  • *Promoting the development of new antibiotics and developing new diagnostic tests for resistant bacteria*
Antimicrobial Innovation and Market Forces
Current Antimicrobial Market Model

- **Current model is:**
  - High R&D risk
  - Limited, and not guaranteed, ROI
  - Small window of opportunity to recoup investment cost/profit
  - Success = restricted agent

This market model is **unsustainable** and does not incentivize **innovation** in antimicrobial development.

R&D: Research & Development
ROI: Return on investment

Number of New Antibiotics Approved by the FDA

<table>
<thead>
<tr>
<th>Years</th>
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<tbody>
<tr>
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</tr>
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<td>10</td>
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<tr>
<td>1998-2002</td>
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<tr>
<td>2003-2007</td>
<td>6</td>
</tr>
<tr>
<td>2008-2012</td>
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Future Antimicrobial Market Models

- **Current model is:**
  - High R&D risk
  - Limited, and not guaranteed, ROI
  - Small window of opportunity to recoup investment cost/profit
  - Success = restricted agent

- **A new model should:**
  - Share risk of R&D
  - Prioritize regulatory review
  - Guarantee (some) return on investment
  - Better re-imbursement models
Current Efforts to Support Antibiotic Development

**CARB-X:**
- Launched in 2016 by U.S. HHS Department
- Later joined by U.K. government and private partners
- Non-profit public-private partnership
- $500 million in initial assets

**Innovative Medicines Initiatives:**
- Funded by E.U. and European pharmaceutical industry
- Over €3.27B in initial investment

**The Indo-Pacific Centre for Health Security:**
- Established by Australian government
- Over $300 million in public commitment to research and development
Prioritize Regulatory Review

• GAIN title of FDA Safety and Innovation Act of 2012 authorized:
  • QIDP: qualified infectious diseases product
  • Offers priority review and approval
  • Also qualifies for an additional 5 years of patent protection

• Limited Population Pathway for Antibacterial and Antifungal Drugs (LPAD)
  • Authorized by 21st Century Cures Act of 2016
  • FDA beginning to implement – draft guidance recently published
  • Streamlines review process for novel antimicrobial agents
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<td>2008-2012</td>
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<td>2013-2018</td>
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<th>Sponsor</th>
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<th>Novel Abx Class</th>
<th>New Non-traditional Product</th>
<th>New Target</th>
<th>Description</th>
<th>Priority</th>
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<td>✓</td>
<td>✓</td>
<td>Pseudomonas elastase inhibitor</td>
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<td>Bugworks Research</td>
<td>GVR0X</td>
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<td>Gyrase-topoisomerase inhibitor</td>
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<td>Sulopenem</td>
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<td>Gram-negative activity</td>
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<td>✓</td>
<td>Virulence modifier</td>
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<td>✓</td>
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<td>Seres Therapeutics</td>
<td>SER-155</td>
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<td>✓</td>
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<td>Potentiator</td>
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<td>Microbiome</td>
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<td>C. difficile</td>
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</table>
Preventing Future Antibiotic Resistance

Antimicrobial Preservation & Stewardship

- ID Specialist
- Microbiology
- Infection Control
- Administration
- Nursing & Providers
- ID Pharmacist
Non-Human Antimicrobial Use
Antimicrobial Use in Animal Feed

- Used to prevent, treat or control spread of disease in animals, as well as promote growth

- Limited data to characterize use and appropriateness (i.e. mostly done without veterinary prescriptions)

- Estimated 9.7 million Kg consumed in 2015
  - 26% increase over 2009 levels

- Directly linked to antimicrobial resistance in animals

- Documented cases of transmission to humans
Sales of Medically-important Antimicrobials in U.S. Animal Feed

Annual Sales (2009-2016)

Millions of Kg

Year


Source: U.S. Food and Drug Administration
Antimicrobial Use in Animal Feed: International Response

• World Health Organization Recommendations (2017):
  
  • Overall reduction in use of all classes of medically important antimicrobials in food-producing animals
  
  • Complete restriction of use for growth promotion
  
  • Complete restriction of use for prevention of infectious diseases that have not yet been clinically diagnosed
  
  • Restrict use for control of the dissemination of a clinically diagnosed infectious disease identified within a group of food-producing animals
Antimicrobial Use in Animal Feed: International Response

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Antimicrobial Use in Animal Feed: International Response

• U.S.A FDA 2012-2013 Guidance for Industry

  • Limit medically important antimicrobial drugs to uses in animals that are considered necessary for assuring animal health

  • Limit medically important antimicrobial drugs to uses in animals that include veterinary oversight or consultation

  • Phase-in regulations to ensure oversight by veterinarians

  • All recommendations are voluntary
Antimicrobial Use in Animal Feed: International Response

• As of 2017 FDA announced:
  • All affected drug applications have either aligned with the recommendations, or their approvals have been voluntarily withdrawn
  • Products cannot be used for production (e.g. growth promotion) purposes and may only be used under the authorization of a licensed veterinarian
Sales of Medically-important Antimicrobials in U.S. Animal Feed

Annual Sales (2009-2016)

- **Source**: U.S. Food and Drug Administration

**Graph Details**
- **Years**: 2009 to 2016
- **Sales Units**: Millions of Kg
- **Trend**: Linear increase from 2009 to 2014, followed by a 14% decrease from 2015 to 2016
Antimicrobial Animal Use in Europe

• European Union:
  • Use for growth promotion banned since 2006
  • Most members reported veterinary oversight as of 2018
  • E.U. strategies and initiatives to:
    • Monitor use of antimicrobial in livestock
    • Monitor resistance related to antimicrobial use in livestock
    • Monitor sales data in farming industry
‘The storms we’re seeing now, people thought this was decades in the future’
Response from Scientific Community

• Stakeholder Forum on Antimicrobial Resistance (S-FAR):
  • Convened by Infectious Diseases Society of America
  • Currently ~135 member organizations
  • Goal to:
    • Bring partners together to discuss individual policy priorities and to identify mutual areas of interest and collaboration
    • Keep partners informed about developments in federal policy
    • Encourage and enable partners to engage on U.S. policies to drive action and achieve results
Response from Government Agencies

• White House National Strategy For Combating Antibiotic-resistant Bacteria 2014
  • Identified 6 areas of national importance

• CDC national commitment to combat antimicrobial resistance
  • Public and private sector commitments
  • Over 110 organizations pledging support

• CDC agencies
  • National databases for antimicrobial use (human and non-human use) and resistance
Final Thoughts

• Antimicrobial resistance is a *global* emergency that will require a *global* response

• Public and private sectors collaboration is key

• Incentives to encourage private sector innovations are necessary

• Continued preservation of current and future antimicrobial agents can sustain our success
Conclusion

**Past**
- Antibiotics are crucial for the treatment of countless infections

**Present**
- Antibiotic resistance is growing and leaving us with infections that we cannot treat

**Future**
- New drug development strategies have increased new antibiotics to help combat resistance and stewardship is helping to preserve current antibiotics
Ghosts of Antibiotics Past, Present, and Future

Meagan Adamsick, PharmD

Ramy Elshaboury, PharmD, BCPS-AQ ID