Is the Antibiotic Era Over? An Overview of Antimicrobial Resistance

Research!America

Presented by Elaine Larson, PhD, RN, CIC
What we will discuss....

• What is antimicrobial resistance and why does it matter?

• What is the current status of global antimicrobial resistance and what are the causes?

• Implications for
  – individuals and the public
  – health care systems and institutions
  – government
Microbes/Humans

- **Microbes:** $5 \times 10^{31}$
  $(50,000,0000,000,000,0000,000,0000,000,000,000)$

- **Humans:** $6 \times 10^9$
  $(6,000,0000,000)$

- Microbiology in the 21st century, ASM, 2004
**Microbial Adaptability (Blaser)**

- **Without \( O_2 \)**
- **Boiling water**
- **Ice**
- **Crushing Pressure & No Sun**
- **Rocks**
- **Us**
“The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily under-dose himself and by exposing his microbes to non-lethal quantities of the drug, make them resistant”

Alexander Fleming in his Nobel Prize acceptance speech in 1945.
Fleming was right:
“At the beginning of the 21st century, antimicrobial resistance is common, has developed against every class of antimicrobial drug, and appears to be spreading into new niches.”

http://www.cdc.gov/ncidod/EID/vol11no06/05-0167.htm
In the US...

Each year, more than 2.8 million antimicrobial-resistant infections occur among hospital inpatients and more than 35,000 people die as a result.

2022 National and State Healthcare-Associated Infections Progress Report, CDC
Financial Burden of Antimicrobial Resistance to Healthcare Systems

Estimated $4.6 billion in health care costs annually


Additional costs of resistant vs sensitive strains

<table>
<thead>
<tr>
<th></th>
<th>Healthcare-Acquired</th>
<th>Community-Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charges</td>
<td>$18,990</td>
<td>$32,400</td>
</tr>
<tr>
<td>Length of stay</td>
<td>2.2 days</td>
<td>4.2 days</td>
</tr>
<tr>
<td>Deaths</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>

Outbreaks in the Community

- Sports participants
- Inmates in correctional facilities
- Military recruits
- Daycare attendees
- Native Americans / Alaskan Natives
- Men who have sex with men
- Tattoo recipients
- Hurricane evacuees in shelters
- Longterm care residents
Characteristics of Microbes that Enhance Resistance

- **Speed.** Bacterial populations can double ~ every 20 mins
- **Exchangeability.** Bacteria can exchange genetic material
- **Mutation.** Under antibiotic pressure, resistant mutants emerge
Effect of antibiotic prescribing on resistance

- Analysis of 24 studies in primary care;
- Risk of resistance in respiratory and urinary tract infections was about 2.5 times greater with more antibiotic use;
- Effect greatest in month immediately after treatment, but persisted up to 12 months

Costelloe, et.al. BMJ 2010; 340:c2096
Antibiotics in Agriculture

- In 2020, >230 million pounds of antibiotics were approved for use in food-producing animal; many times more than the amount sold to humans who were sick*
- Many of the antibiotics used in this setting are of the same class as those used to treat human infections

Antibiotic consumption in animals

At the same time, the arsenal of antibiotics peaked in 2000 and is still declining.
The number of new antibiotics developed and approved has steadily decreased in the past three decades, leaving fewer options to treat resistant bacteria.

*Intervals from 1980–2009 are 5-year intervals; 2010–2012 is a 3-year interval. Drugs are limited to systemic agents. Data courtesy of FDA’s Center for Drug Evaluation and Research (CDER).
As of 2020...

- 23 antibiotics in development
  - 15 in Phase 1 clinical trials,
  - 13 in Phase 2,
  - 13 in Phase 3,
  - 2 have had new drug applications submitted.

- Historically, about 60% of drugs that enter Phase 3 will be approved.

Development of new antibiotics will not solve the problem alone

- No new classes of antibiotics have been discovered since the 1980s; antibiotics brought to market in the past three decades are variations of drugs that have been previously discovered.

- Discovering and developing new antibiotics is challenging; the science is tricky and R&D is time-consuming, expensive, and often fails. It generally requires 10-15 years and over $1 billion to develop a new antibiotic.

- Developing antibiotics to treat highly resistant bacterial infections is less likely because:
  - Few patients contract these infections and meet the requirements to participate in traditional clinical trials.
  - There is little incentive for industry to develop such drugs because of the high cost.
Implications for...

Individuals and the public

Health care institutions and systems

Government
INDIVIDUALS AND THE PUBLIC
Public Knowledge/Attitudes

- 2,386 people in NYC interviewed
- 88% thought colds were caused by bacteria
- Only 29.8% agreed that most colds and flu would improve without medication
- 89.9% stated that antibiotics are usually or sometimes needed to treat viral throat infections
- 27.6% stated that antibiotics were usually or sometimes indicated for asthma attacks.

- Emerg Infect Dis 2003; 9:1096-1102
Antibiotics sold without prescription

Survey of three NYC neighborhoods

- 1 in 5 stores in Hispanic neighborhood had antibiotics on the shelves
- Antibiotics available upon request in all stores: ampicillin, amoxicillin, tetracycline, erythromycin
- Offered as single doses individually wrapped and in larger quantities.

- Larson & Figueroa, J Urban Health 2004; 81:498-504
For the public...

- Get vaccinated to prevent infections when possible
- Be informed about appropriate use of antimicrobials
HEALTHCARE INSTITUTIONS AND SYSTEMS
Outpatient U.S. Antibiotic Use

• 80-90% of human antibiotic use and >60% of antibiotic expenditures are in the outpatient setting
• In 2014, 266.1 million courses of antibiotics were dispensed to outpatients, equivalent to >5 prescriptions/year for every 6 people
• At least 28-50% of prescriptions are unnecessary
• Antibiotic prescribing in the outpatient setting varies by state and health plan
• Local outpatient prescribing practices contribute to local resistance patterns

https://www.cdc.gov/antibiotic-use/data/outpatient-prescribing/index.html
Community Prescribing Patterns

- Rates of prescribing antibiotics for viral URI range from 25-56%
- When presented with clinical scenarios of viral pharyngitis, 81% of 948 clinicians used an inappropriate treatment strategy
- 22% of emergency room visitors reported that their physician routinely prescribed Abs for a cold
- >800 physicians rated the issue of resistance as the lowest of seven determinants of their choice regarding antibiotic prescribing

Inpatient Antibiotic Prescribing 2021

NEW CDC DATA

MORE THAN HALF OF ANTIBIOTIC PRESCRIBING FOR SELECTED EVENTS IN HOSPITALS WAS NOT CONSISTENT WITH RECOMMENDED PRESCRIBING PRACTICES

ANTIBIOTIC PRESCRIBING WAS NOT SUPPORTED IN:

- 79% of patients with community-acquired pneumonia
- 77% of patients with urinary tract infections
- 47% of patients prescribed fluoroquinolone treatment
- 27% of patients prescribed intravenous vancomycin antibiotic

HOSPITAL PRESCRIBERS & PHARMACISTS CAN IMPROVE PRESCRIBING:

- Optimize antibiotic selection
- Re-assess antibiotic treatment when the results of diagnostic testing are available
- Use the shortest effective duration of therapy

FIND RESOURCES ON HOW TO IMPROVE HOSPITAL ANTIBIOTIC USE AND HELP FIGHT ANTIBIOTIC RESISTANCE: https://bit.ly/HospitalCoreElements
Antibiotic Use in 3 Pediatric Units

- 38% of babies in 3 pediatric units received ≥1 antibiotic that violated CDC recommendations

- Pediatr Infect Dis J. 2009; 28(12)1047-1051
Longterm Care Facilities

- 50-70% of nursing home residents are prescribed an antibiotic each year

- 25-75% of antibiotic prescribing in nursing homes is inappropriate

# Three Primary Prevention Strategies

<table>
<thead>
<tr>
<th>CDC Recommendations*</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent infections in the first place</td>
<td>Infection Prevention</td>
</tr>
<tr>
<td>Improve antibiotic and antifungal use and minimize misuse to slow the development of resistance</td>
<td>Antimicrobial Stewardship</td>
</tr>
<tr>
<td>Stop the spread of resistance when it does develop</td>
<td>Infection Control</td>
</tr>
</tbody>
</table>

*https://www.cdc.gov/drugresistance/actions-to-fight.html*
GOVERNMENT
External Influencers

- CMS reimbursement
- Public reporting
- Legislation
- Big business
Key U.S. Actions to Combat Antimicrobial Resistance

- 2013: CDC released the first *Antibiotic Resistance Threats Report*


- 2015: The White House hosted the *Forum on Antibiotic Stewardship* and released the first *U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria*

- 2016: CDC established the *Antimicrobial Resistance Laboratory Network*

But progress has been slow

- For example, in 2011 FDA did not approve two long-pending petitions from consumer and other groups to limit the use of several antibiotics in farm animals, saying a voluntary approach would lead to more "judicious use" of the drugs in agriculture.
- Unfortunately, that approach has not worked

Center for Infectious Disease Research and Policy (http://www.cidrap.umn.edu/cidrap/content/fs/food-disease/news/nov1011petitions.html)
Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria (PACCARB)

- Established 2015 using One Health framework
- Includes experts in human and animal health, agriculture, environment
- Produced 11 national reports and recommendations to federal government
Trends in Legislation: 2011-19

- PACCARB members analyzed pieces of antimicrobial legislation; 4/28
- (14%) passed
- Common themes: incentivizing new drug development, biodefense, expanded scope of use, stewardship, stricter veterinary oversight
“...the current balance between guidelines vs legislation does not seem to have adequately addressed the rise in antibiotic resistance....Striking the right balance will require more effective dialogue between policy makers, public health experts, and the agricultural industry.”

Will Legislation Work?

- In settings (e.g., Netherlands, Denmark) where hospital stringent policies regarding antibiotic stewardship are in place, rates of resistant organisms have dropped precipitously.
- The U.S. is slower than Europe with regard to legislation.

References:
- JAC Antimicrob Resist. 2023; 5(6):dlad111. PMID: 38021039;
- Lancet Infect Dis. 2016; 16(7):847-856. PMID: 26947617
PACCARB Recommendation: Two Key Research Actions

- Maintain or increase funding for the CDC's Antibiotic Resistance Solutions Initiative and AHRQ healthcare-associated infection and antibiotic-resistance programs.
- Stress importance of continued funding for AMR research in agriculture provided by the U.S. Department of Agriculture's National Institute of Food and Agriculture.

- Website: hhs.gov/paccarb  E-mail: carb@hhs.gov

**NIH Funding for AMR**

<table>
<thead>
<tr>
<th>Grants/projects with ‘Antimicrobial Resistance’ in the title</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/1/13-12/1/15</td>
<td>2</td>
</tr>
<tr>
<td>1/1/16-12/1/19</td>
<td>10</td>
</tr>
<tr>
<td>1/1/20-12/1/13</td>
<td>39</td>
</tr>
</tbody>
</table>

[https://reporter.nih.gov/](https://reporter.nih.gov/)
What is needed for truly sustainable solutions?

--Robert Skov, International Centre for Antimicrobial Resistance Solutions

Political will

Ownership throughout the whole stakeholder chain

Understand people’s behavior

Specific to context

Cost-effective

Evidence based

Span the One Health spectrum/be cross-sectoral
Germs Are Us

“We are an endlessly variable stew of essential microbes and they are working in ways we have not yet understood. Antibiotics are so miraculous that we have been lulled into a belief that there is no downside. But there is: they kill good bacteria along with the bad bacteria.”

(New Yorker, Oct 22, 2012)

So we must live with respect for the microbial world we share
Thanks to...

- M. Blaser, F. Lowy, R. Weinstein, M. Marx, A. Ratner, S. Patel from whom slides were used with permission

- Elaine Larson, ell23@columbia.edu
Impact of COVID on AMR
US Impact

Because of pandemic impacts, 2020 data are delayed or unavailable for 9 of the 18 antimicrobial resistance threats.

- Clostridioides difficile (C. diff)
- Drug-resistant Neisseria gonorrhoeae
- Drug-resistant Campylobacter
- Drug-resistant nontyphoidal Salmonella
- Drug-resistant Salmonella serotype Typhi
- Drug-resistant Shigella
- Drug-resistant Streptococcus pneumoniae
- Erythromycin-resistant group A Streptococcus
- Clindamycin-resistant group B Streptococcus

Available data show an alarming increase in resistant infections starting during hospitalization, growing at least 15% from 2019 to 2020.

- Carbapenem-resistant Acinetobacter (+78%)
- Antifungal-resistant Candida auris (+60%)*
- Carbapenem-resistant Enterobacteriales (+35%)
- Antifungal-resistant Candida (+26%)
- ESBL-producing Enterobacterales (+32%)
- Vancomycin-resistant Enterococcus (+14%)
- Multidrug-resistant P. aeruginosa (+32%)
- Methicillin-resistant Staphylococcus aureus (+13%)

https://www.cdc.gov/drugresistance/covid19.html
Global Impact

Bacterial and fungal infections in COVID-19 patients
- Nosocomial and secondary bacterial infections/coinfections
- Prolonged hospital/ICU stay

Inappropriate prescribing and use of antimicrobials
- Part of COVID-19 treatment regimen
- Difficulty in distinguishing the symptoms of COVID-19

Increased use of biocides
- Biocide-resistant microbes
- Change of organisms in viable but not cultivable state

Impact of compromised healthcare services on the rise of COVID-19
- Disrupted antibiotic stewardship programme and surveillance
- Encumber diagnostic laboratory services

COVID-19 pandemic and emergence of AMR

Focus of PACCARB
PACCARB Reports to Date

- Initial assessment of US National Action Plan to Combat AMR
- Preparing for the next pandemic in an era of antimicrobial resistance (AMR)
- Advancing interprofessional education and practice to combat AMR
- Improving antimicrobial access and use across One Health
PACCARB Reports (cont)

- Key strategies to enhance infection prevention and control and antimicrobial stewardship
- Priorities for the US National Action Plan to Combat AMR
- Incentivizing the development of vaccines, diagnostics, and therapeutics to combat AMR
PACCARB Current Mandate

- To be completed by May 2024
- Provide recommendations on “how US government agencies can lead AMR efforts for sustained action domestically and internationally”*
- Public hearing on 2/22 will focus on Global AMR

*DHHS Sec Becerra task letter to PACCARB
Latest discoveries
Recent Scientific Discovery

• “A novel antibiotic class targeting the lipopolysaccharide transporter”


• Identified tethered macrocyclic peptide (MCP) antibiotics with potent antibacterial activity against carbapenem-resistant A. baumannii (CRAB)
Recent Governmental Initiative

• CDC’s Antibiotic Resistance Solutions Initiative (ARSI)*

• Provides grants to state and local health departments, public health partners, and private sector to prevent infections across healthcare settings and communities and sustains an AMR Laboratory Network for up to 7 regional labs.

• * https://www.cdc.gov/drugresistance/solutions-initiative/index.html