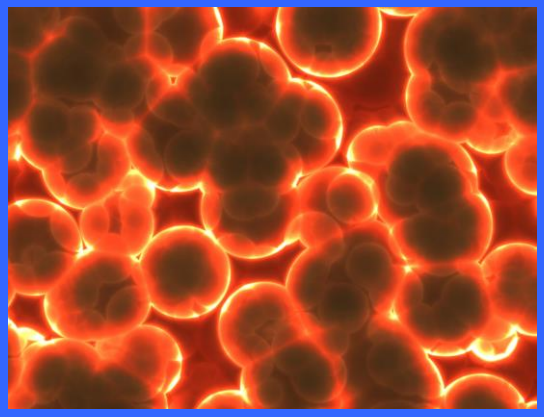
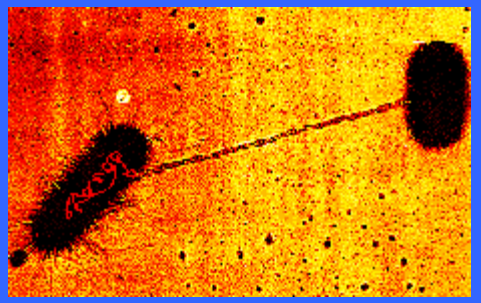
Is the Antibiotic Era Over? An Overview of Antimicrobial Resistance

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:** 5×10^{31}
  (50,000,0000,000,000,0000,000,0000,000,000)

- **Humans:** 6×10^{9}
  (6,000,000,000)

- **Microbiology in the 21st century, ASM, 2004**

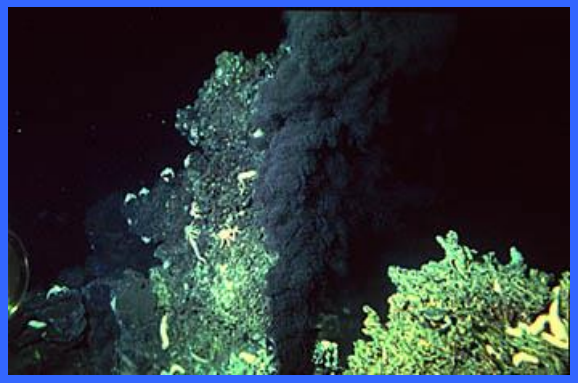
Microbial Adaptability (Blaser)

Without 0_2

Boiling water

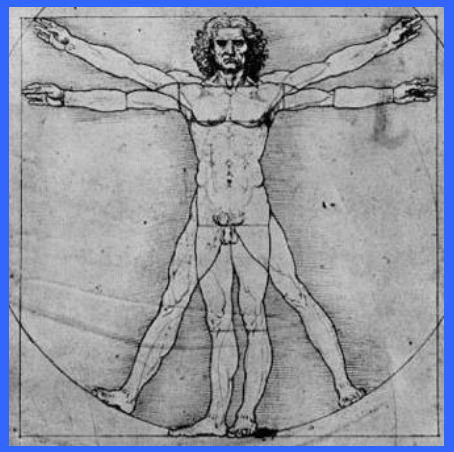
Ice

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

https://arpsp.cdc.gov/profile/antibiotic-resistance?tab=antibiotic-resistance

Financial Burden of Antimicrobial Resistance to Healthcare Systems

Estimated $4.6 billion in health care costs annually

https://www.cdc.gov/drugresistance/solutions-initiative/stories/partnership-estimates-healthcare-cost.html

Additional costs of resistant vs sensitive strains

	Healthcare-Acquired	Community-Acquired
Charges	$18,990	$32,400
Length of stay	2.2 days	4.2 days
Deaths	4%	3%

J Clin Infect Dis 2012; 55:807-815.

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**

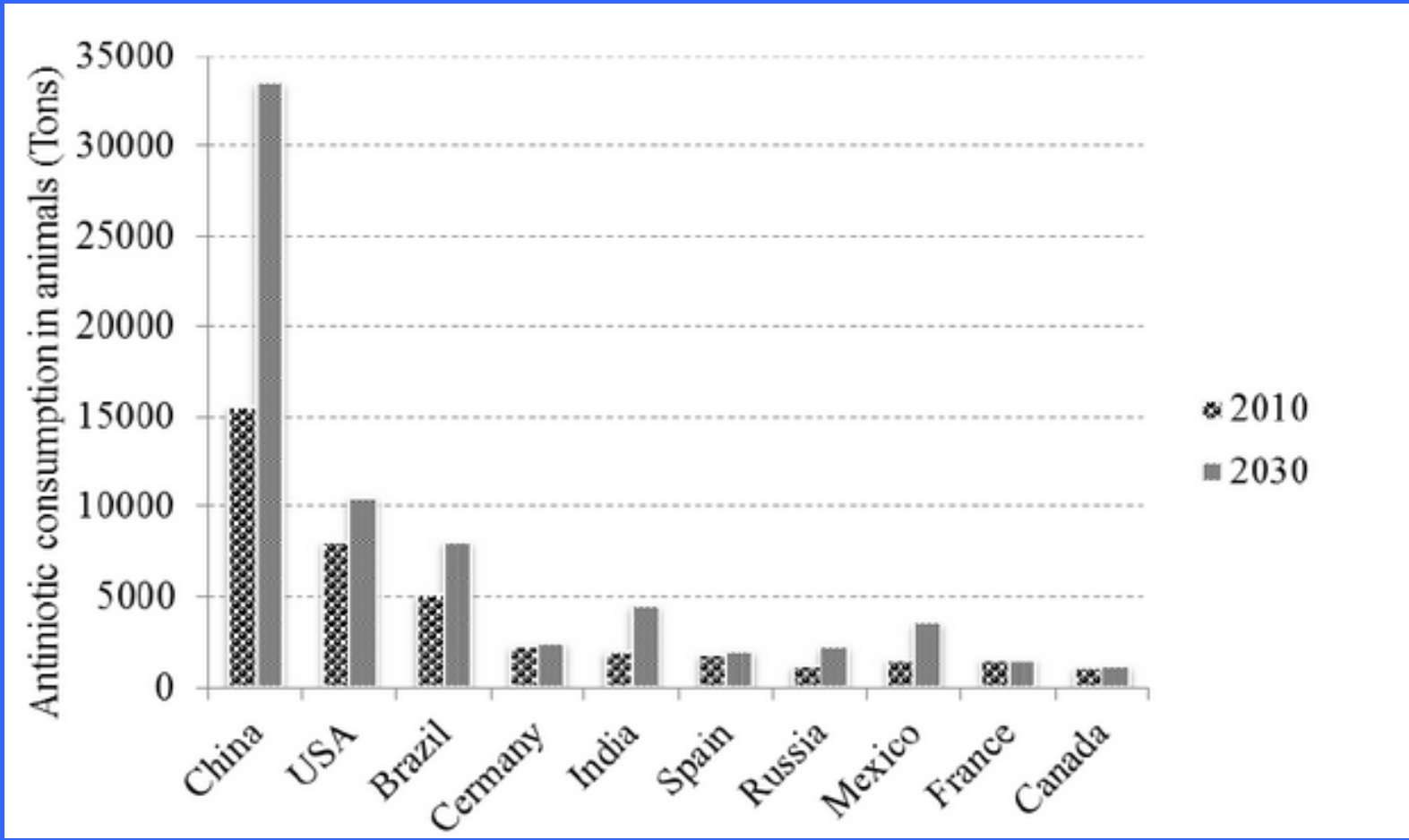
Effect of antibiotic prescribing on resistance

- **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**

***https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-annual-summary-report-antimicrobials-sold-or-distributed-2020-use-food-producing**



Antibiotic consumption in animals

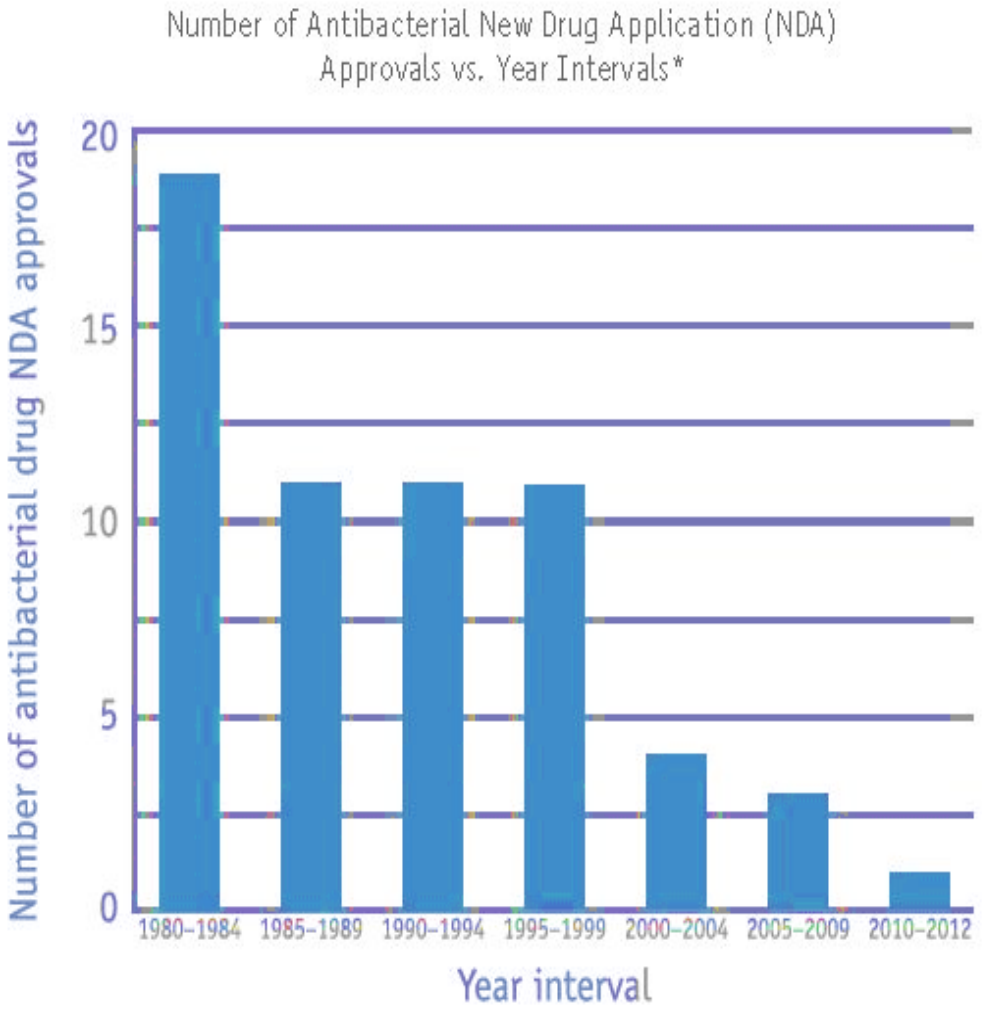
Sarkar DJ, et al. IJEPP 2018; 4(1):4-18.

At the same time,

The arsenal of antibiotics peaked in 2000 and is still declining

Tomorrow's Antibiotics: The Drug Pipeline

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.**

https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/tracking-the-global-pipeline-of-antibiotics-in-development

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 $1billion 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

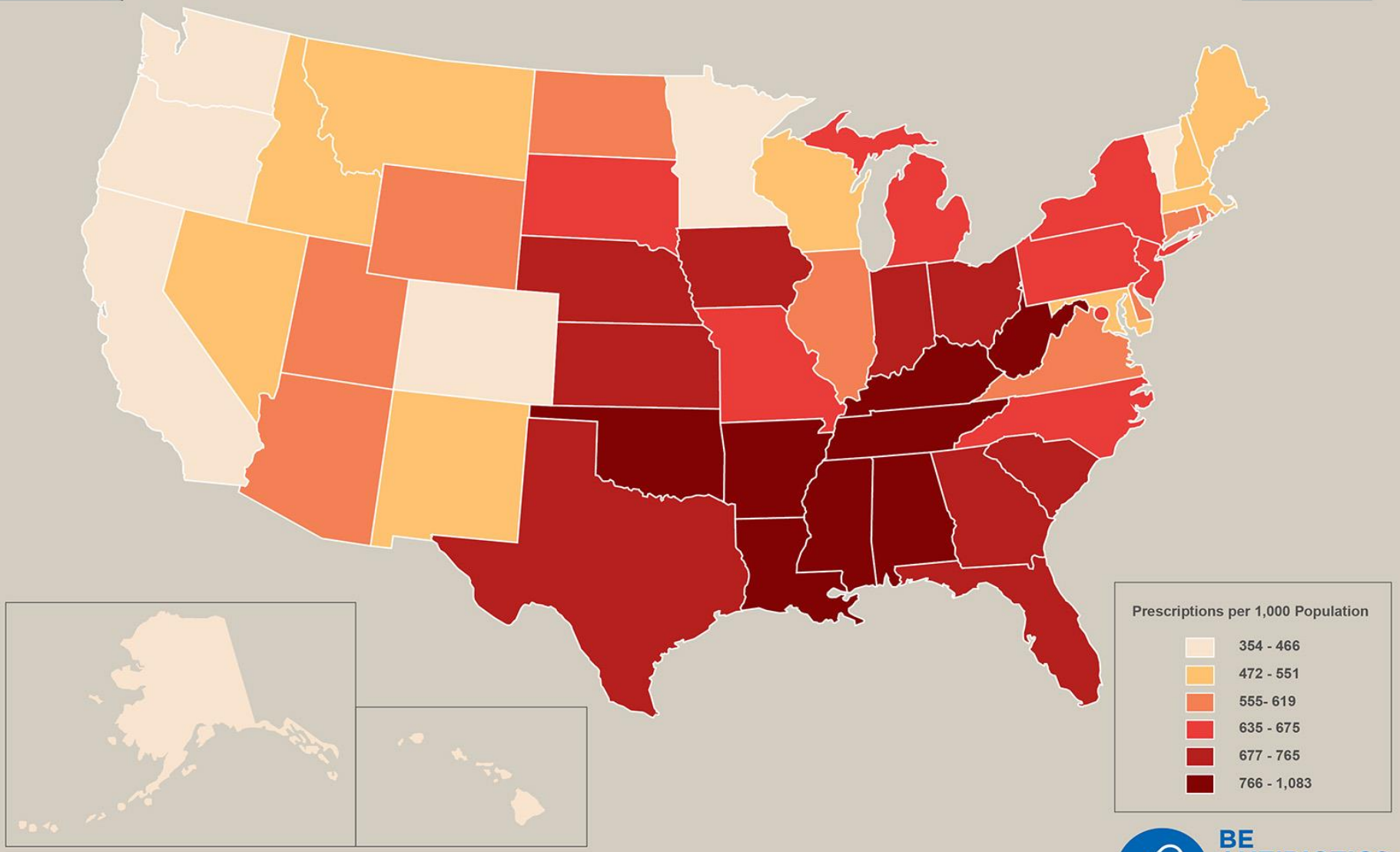
https://www.cdc.gov/antibiotic-use/data/outpatient-prescribing/index.html

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**

Open Forum Infect Dis, 7/20, 7(7), ofaa244, https://doi.org/10.1093/ofid/ofaa244; https://www.ama-assn.org/delivering-care/public-health/physicians-antibiotic-resistance-problem-not-my-office

Antibiotic Prescriptions per 1,000 Population by State - 2021

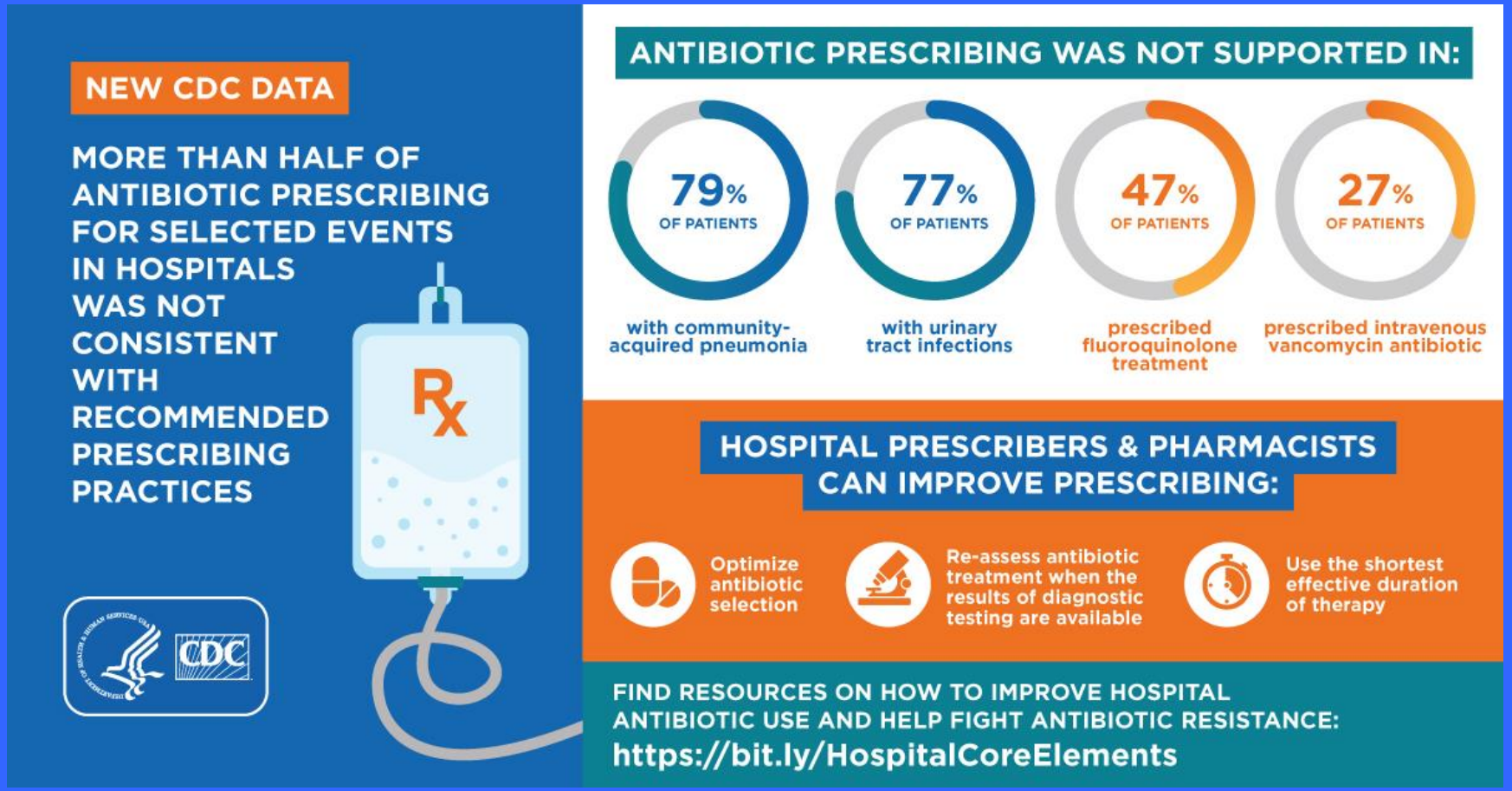


Data source: IQVIA Xponent 2021

CS334840-A

BE ANTIBIOTICS AWARE
SMART USE, BEST CARE

Inpatient Antibiotic Prescribing 2021



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

  - Reister MR, et.al. J Infect Dis 2023 Aug 16; 228(4):464-468.

Three Primary Prevention Strategies

*CDC Recommendations**	*Strategy*
•**Prevent infections** in the first place	Infection Prevention
•**Improve antibiotic and antifungal use and minimize misuse** to slow the development of resistance	Antimicrobial Stewardship
•**Stop the spread** of resistance when it does develop	Infection Control

****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***
- ***2014:* The White House released the *U.S. National Strategy for Combating Antibiotic-Resistant Bacteria*, established *The Interagency Task Force for Combating Antibiotic Resistant Bacteria*, and the *Presidential Advisory Council on Combating Antibiotic Resistant Bacteria***
- ***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***
- ***2020:* The White House released the second *U.S. National Action Plan for Combating Antibiotic-Resistant Bacteria* for 2020-2025**

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**

PACCARB

PRESIDENTIAL ADVISORY COUNCIL ON COMBATING ANTIBIOTIC-RESISTANT BACTERIA

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."

McClelland S, Lamoureux B, Larson E. *Am J Infect Contr* 2021; 49:813-817.

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 legislation**

JAC Antimicrob Resist. 2023; 5(6):dlad111. PMID: 38021039;
Lancet Infect Dis. 2021;21(11):1549-1556. PMID: 34303417;
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**

https://www.hhs.gov/ash/advisory-committees/paccarb/reports-and-recommendations/recommendation-report-3/index.html

NIH Funding for AMR

Grants/projects with ‘Antimicrobial Resistance’ in the title	Number
1/1/13-12/1/15	2
1/1/16-12/1/19	10
1/1/20-12/1/13	39

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

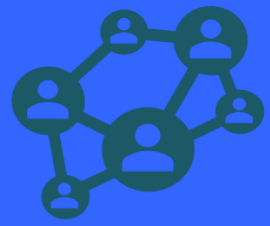
Specific to context

Evidence based

Country Capacity

Understand people's behavior

Cost-effective



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.

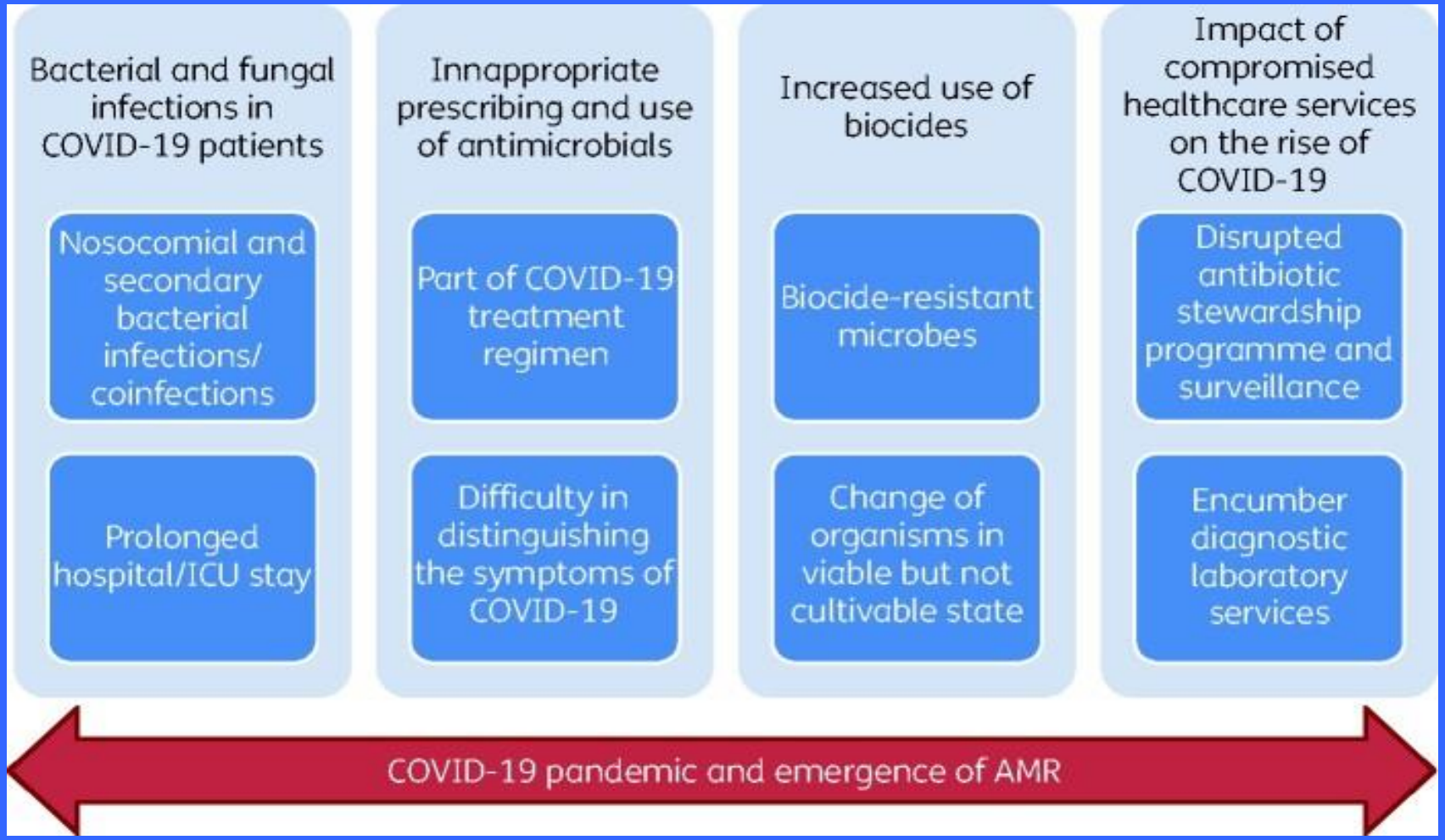
- *Clostridioides difficile (C. diff)*
- Drug-resistant *Neisseria gonorrhoeae*
- Drug-resistant *Campylobacter*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- Drug-resistant *Streptococcus pneumoniae*
- Erythromycin-resistant group 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 Enterobacterales (↑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



Ansari S, et.al. JAC Antimicrob Resist. 2021 Jun; 3(2): dlab038. Published online 2021 Apr 8. doi: 10.1093/jacamr/dlab038

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”**
- **Zamploni E, et.al., Nature 2024, 625(7995):566-571. doi: 10.1038/s41586-023-06873-0. Epub 2024 Jan 3.**
- **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**