

BAD BUGS, WHICH DRUGS

A Review of Drug-Resistant Pathogens and Pharmacotherapy



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Disclosures

- This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand or drug.
- The presenter has no personal conflicts of interest to disclose.

Overview

- Epidemiology
- Microbiology background
- Methicillin Resistant *Staphylococcus aureus*
- Extended Spectrum Beta-Lactamases
- Carbapenem Resistant Enterobacteriaceae
- Pharmacokinetics

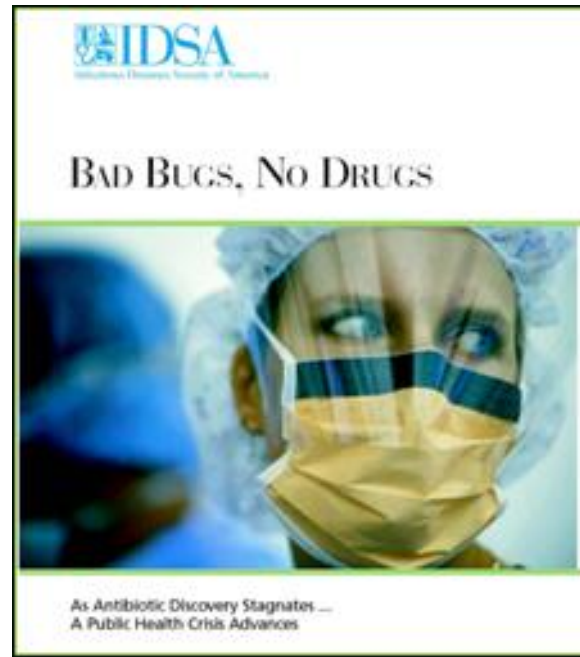
Definitions

- MRSA methicillin resistant *Staphylococcus aureus*
- VRE vancomycin resistant *Enterococcus*
- CRE carbapenem resistant Enterobacteriaceae
- KPC *Klebsiella pneumoniae* carbapenemase
- ESBL extended spectrum beta-lactamase

EPIDEMIOLOGY

Epidemiology

- International problem
 - 2004: IDSA made statement to FDA → “Bad Bugs, No Drugs” born
 - Outlines the crisis of growing antibiotic resistance



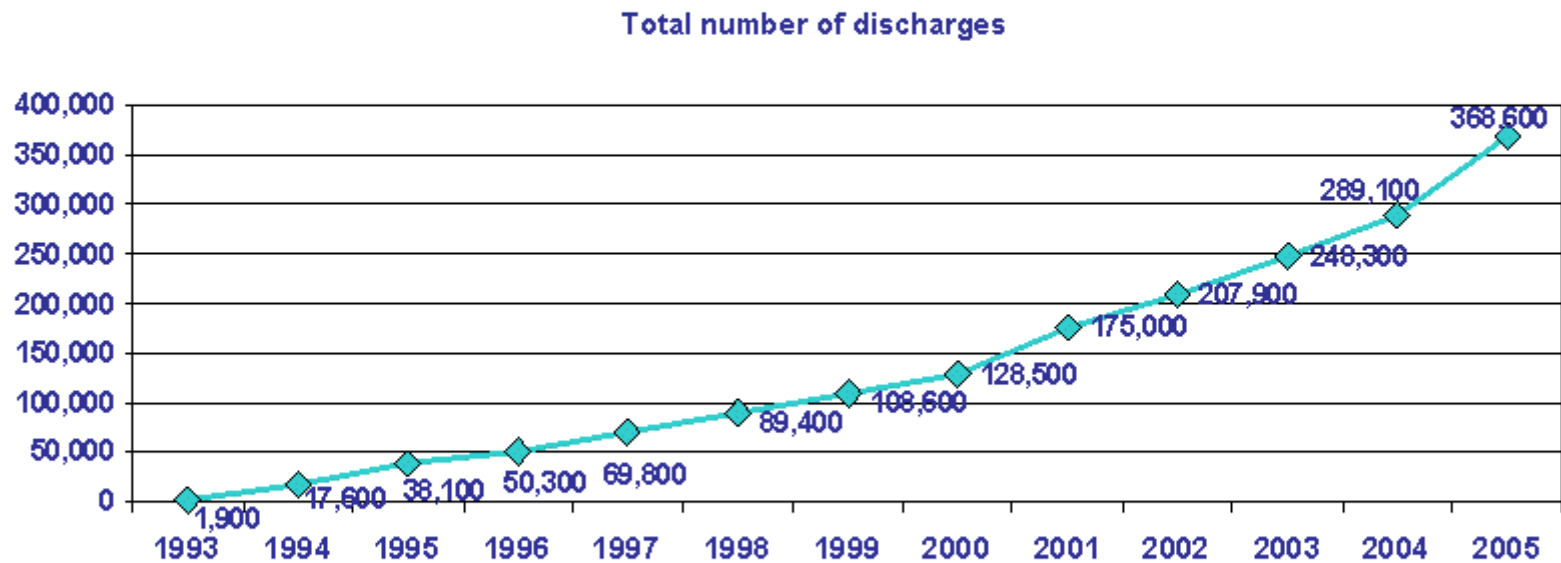
Sources: IDSA. Bad Bugs No Drugs. 2004.

Image from:

http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Antimicrobial_Resistance/10x20

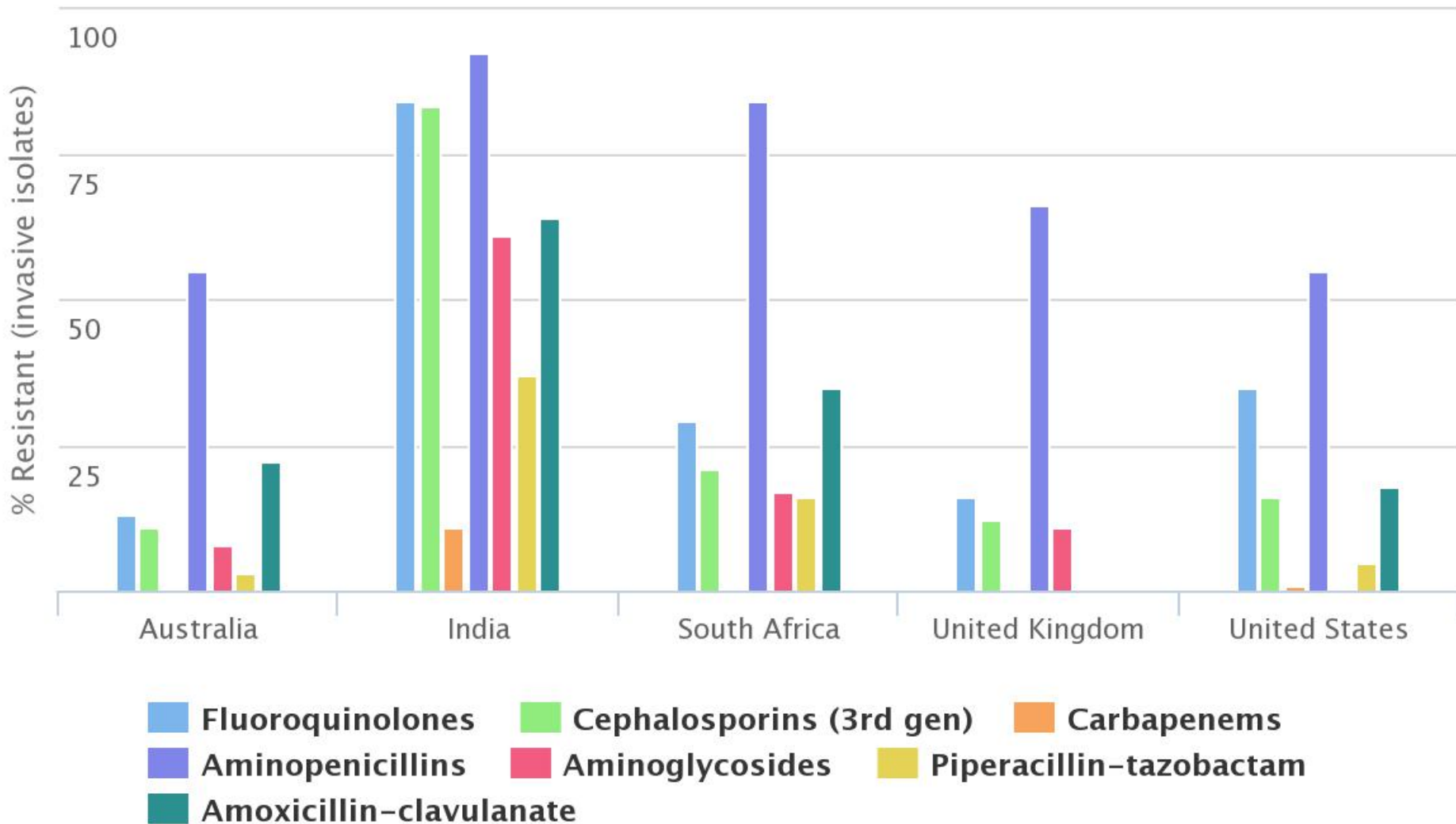


Figure 1. Hospital stays with methicillin-resistant Staphylococcus aureus (MRSA) infections, 1993–2005

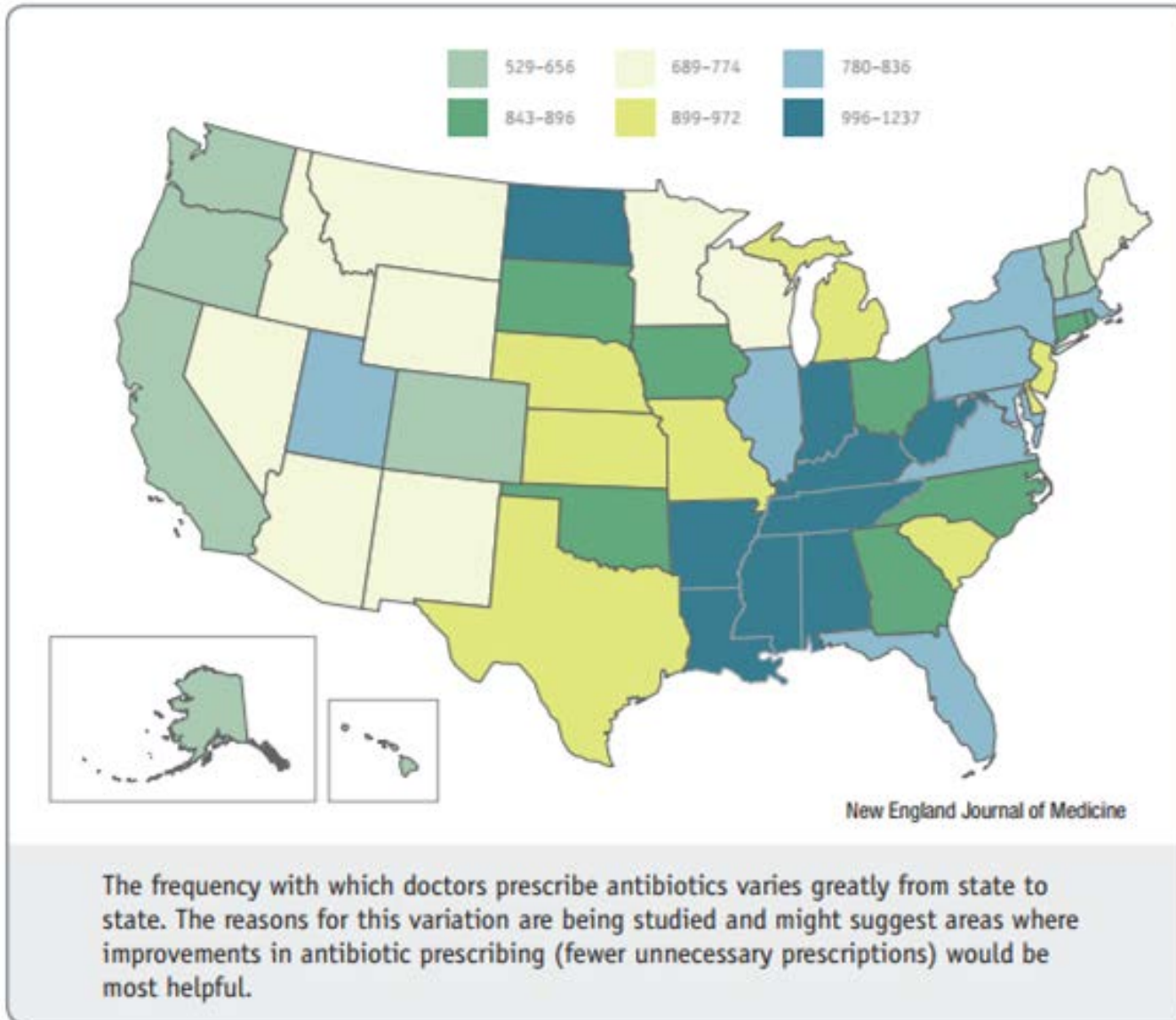


Source: AHRQ, Center for Delivery, Organization, and Markets, Healthcare Cost and Utilization Project, Nationwide Inpatient Sample, 1993-2005

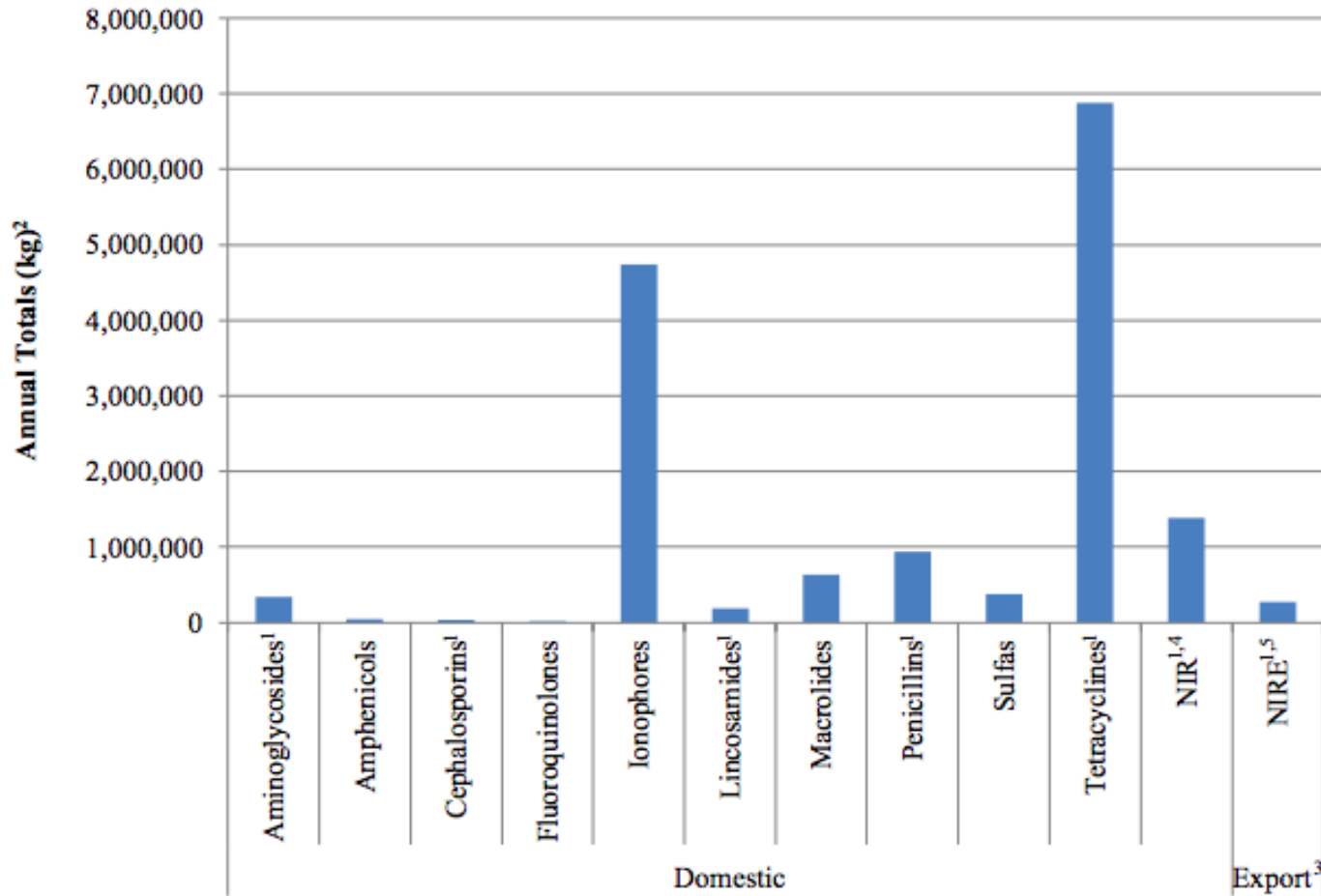
Antibiotic Resistance of *Escherichia coli*



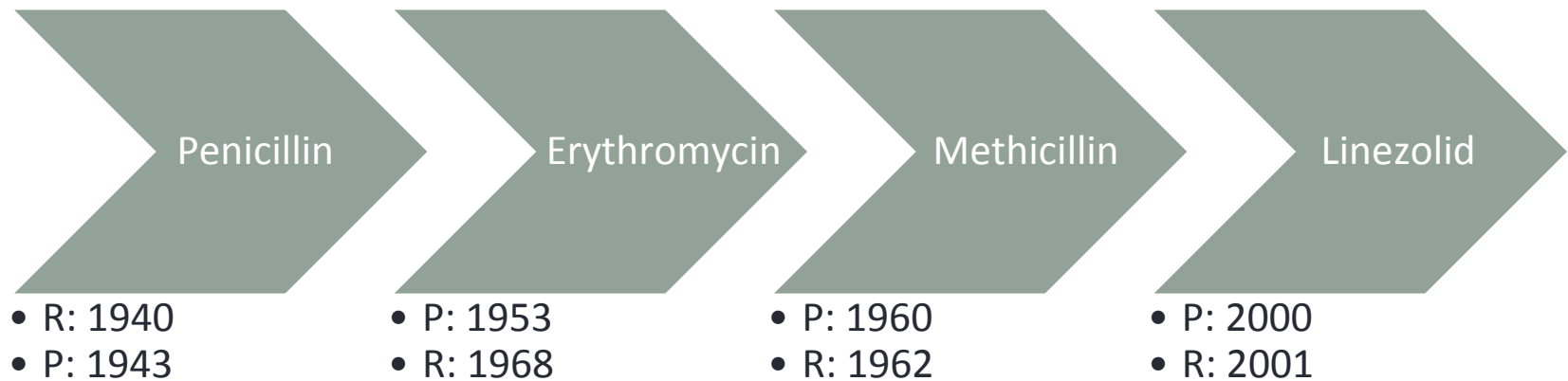
Antibiotic Prescriptions per 1000 Persons of All Ages According to State, 2010



**ANTIMICROBIAL DRUGS APPROVED FOR USE IN FOOD-PRODUCING ANIMALS¹
 ACTIVELY MARKETED IN 2015
 SALES AND DISTRIBUTION DATA
 REPORTED BY DRUG CLASS**



Brief History of Resistance



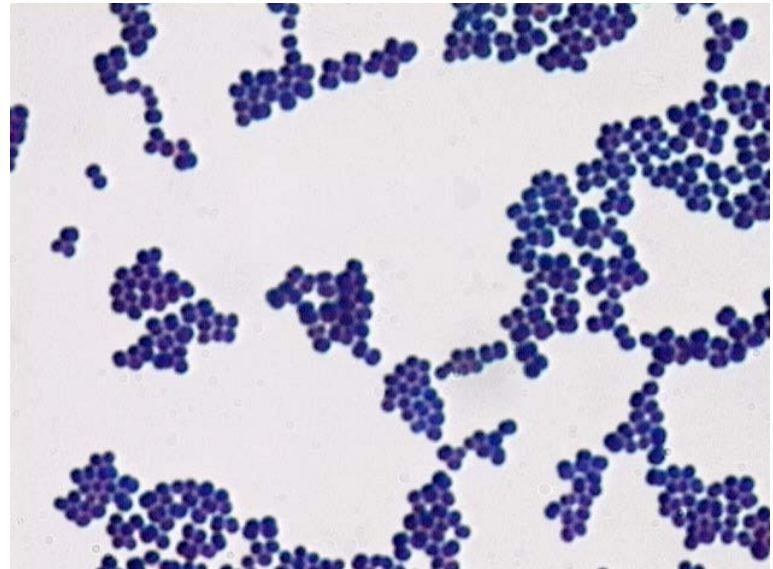
MICROBIOLOGY REVIEW

Background

- Bacteria classifications
 - Gram positive vs. gram negative
 - Aerobe vs. anaerobe
 - Typical vs. atypical

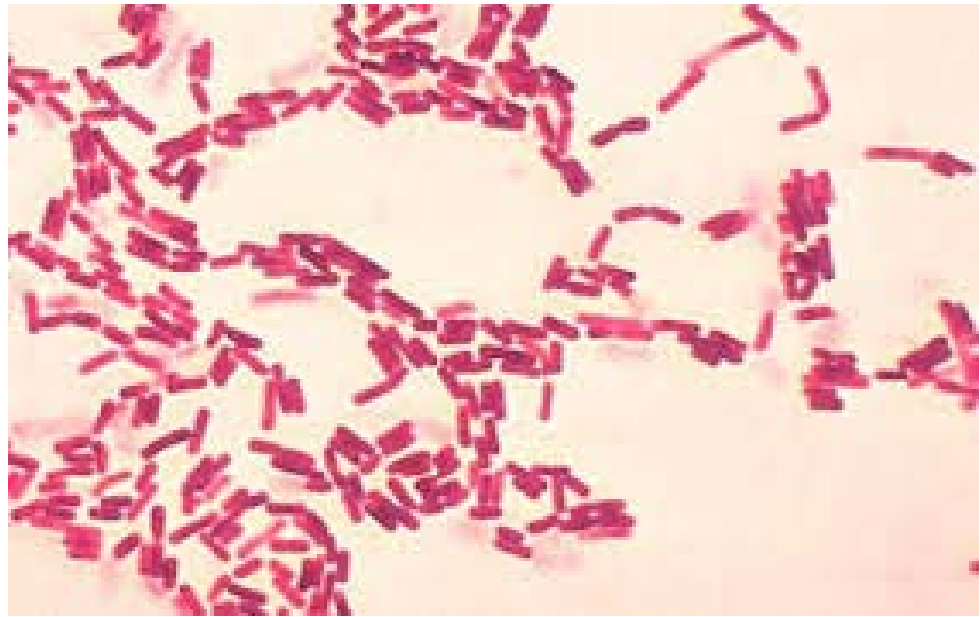
Background

- Gram positives (focus on these today)
 - *Staphylococcus*
 - *Streptococcus*
 - *Enterococcus*



Background

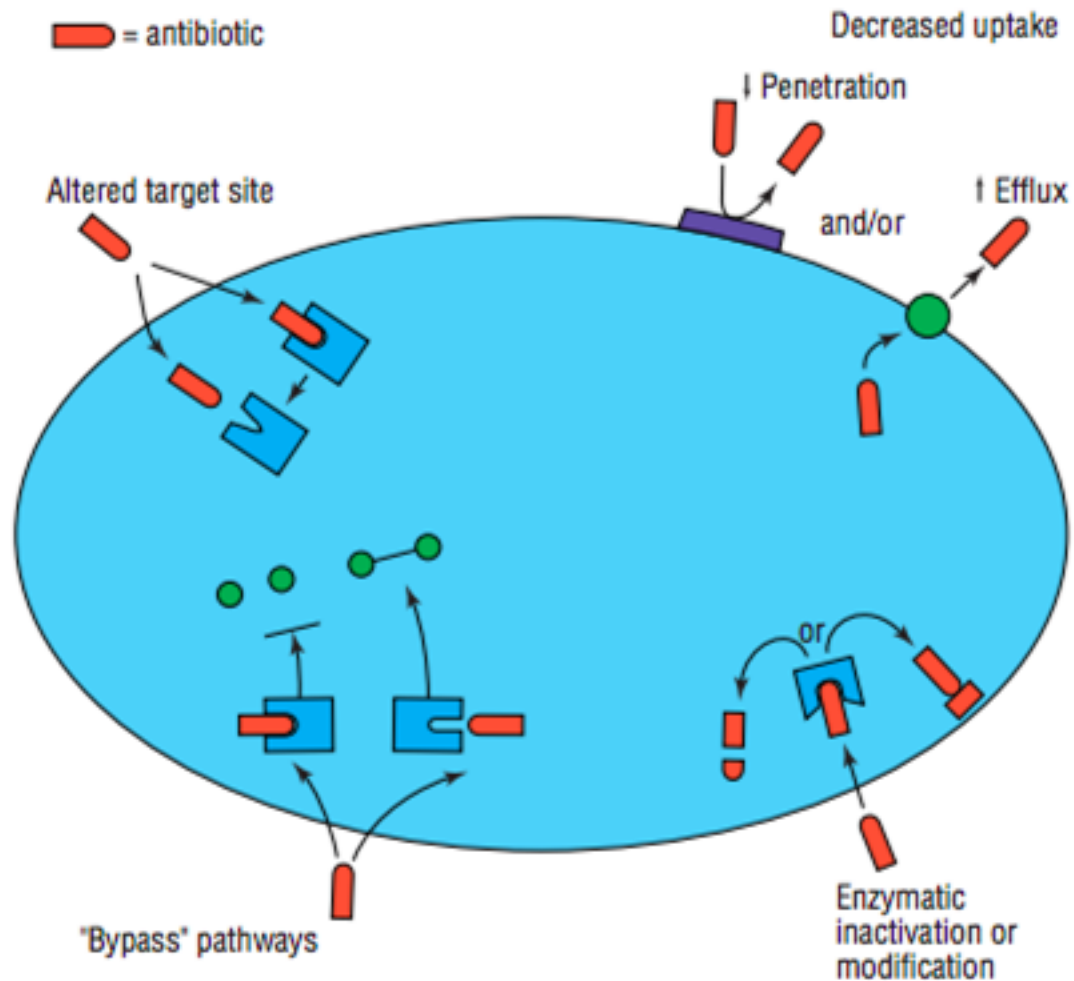
- Gram negatives (focus on these today)
 - *E. coli*
 - *Klebsiella*
 - *Pseudomonas*



Mechanisms of Resistance

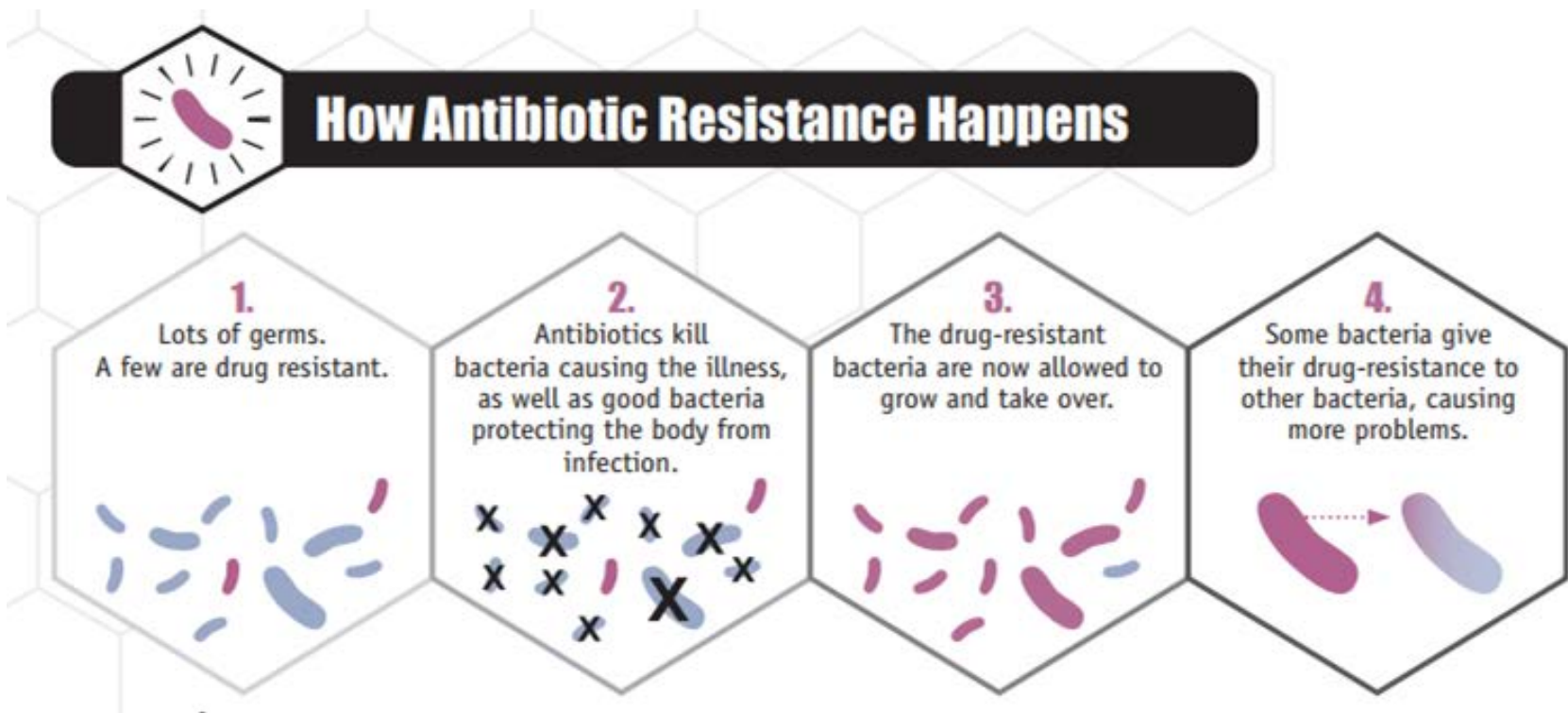
- Efflux pumps
- Competitive inhibition
- Change in binding site
- Drug inactivation

Mechanisms of Resistance



Background

- Concept: selective pressure



Background

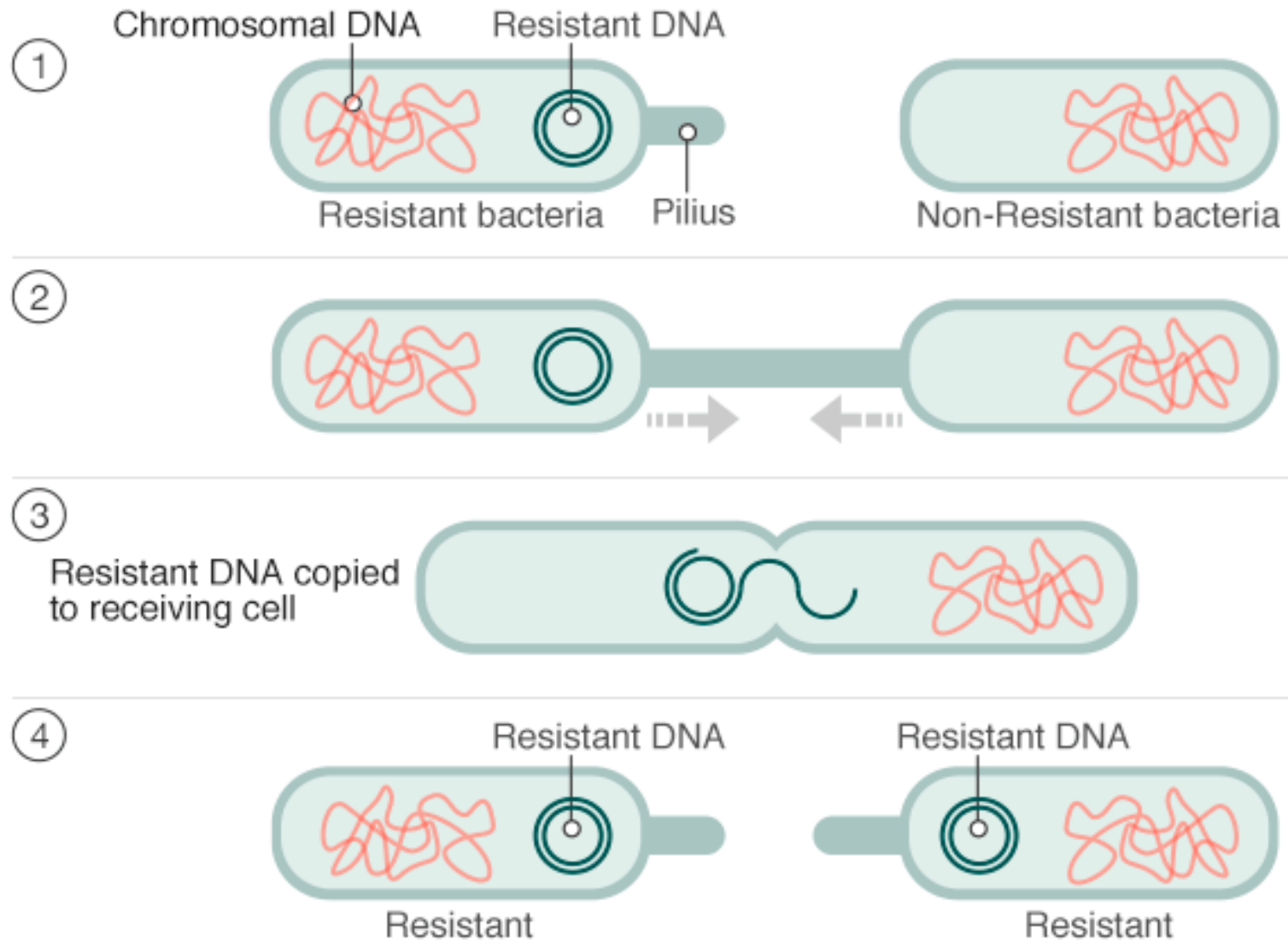
- Genetic mutation
- Bacterial genetic transfer
 - Plasmid mediated
 - Transposon mediated



Sources: Bradford. Clin Microbiol Rev. 2001.

Image from: <https://www.twenty20.com/photos/2436b635-9ee9-448b-9ad4-e47d824a07fa>

How antibiotic resistance spreads



SPECIFIC PATHOGENS

MRSA

- Well-studied pathogen
- Encoded by the *mecA* gene
 - *mecA* is encoded on a mobile genetic element
 - *mecA* encodes for a protein that is not bound by antibiotics well so cell wall remains intact
- Confers resistance to:
 - Nafcillin, oxacillin, dicloxacillin

MRSA

- Optimal treatment choices:
 - Vancomycin
 - TMP/SMX
 - Doxycycline
 - Linezolid
 - Daptomycin
- Future directions

Dalbavancin

- DISCOVER-1 and DISCOVER-2 trials
 - Compared dalbavancin vs. vancomycin transition to linezolid
 - Dosing strategy: 1000mg IV on day 1, 500mg IV on day 8
 - Found to be noninferior for skin/soft tissue infections
- Offers unique dosing strategy

Oritavancin

- SOLO-1
 - Compared oritavancin to vancomycin
 - Dosing strategy: 1200mg IV x 1
 - Found to be noninferior for skin/soft tissue infections
- SOLO-2
 - Same trial design as SOLO-1
 - Again noninferior

Patient Case—Poll Question

- JK is a 48-year-old female presenting to the emergency department with cellulitis. She has failed outpatient oral antibiotic therapy, but does not appear clinically unstable. If available at your institution, which of the following could be appropriate?
 - A) Dalbavancin 1000 mg IV x 1 today, then 500 mg on day 8
 - B) Oritavancin 2000 mg IV x 1 today
 - C) Daptomycin 500 mg IV every 12 hours
 - D) Linezolid 600 mg PO every 24 hours

Patient Case—Poll Response

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ESBL

- Encoded by variety of genes:
 - TEM
 - SHV
 - CTX-M
 - AMP-C
- Confers resistance to:
 - Cephalosporins
 - Aztreonam
 - Piperacillin/tazobactam (?)

ESBL

- Ambler classification
 - Based on structure
- Other classifications
 - Based on function
- Plasmid or chromosome mediated

ESBL

- Optimal treatments
 - Carbapenems
- Future directions
 - Ceftazidime/avibactam
 - Ceftolozane/tazobactam

RECLAIM

- Compared ceftazidime/avibactam to meropenem for complicated intraabdominal infections
 - Found to be noninferior with combination
 - Used 5-14 days of therapy
 - Allowed for addition of gram positive coverage as needed
- Completed microbiological comparison

RECAPTURE

- Comparison of ceftazidime/avibactam to doripenem for complicated urinary tract infections
 - Found to be at least noninferior, and superior in some subsets of patients
 - 10-14 days total therapy
- Completed microbiological comparison
 - Similar pathogens and cure rates

REPRISE

- Comparison of ceftazidime/avibactam with best available therapy for complicated intra-abdominal infections or urinary tract infections
 - Pathogens were required to be resistant to ceftazidime alone
 - 5 to 14 days of therapy
 - Included: meropenem, imipenem, doripenem, colistin
 - Intra-abdominal infections only: tigecycline
 - Combination therapy permitted
- Found to be noninferior to best available therapy for both indications

ASPECT-cIAI

- Compared ceftolozane/tazobactam + metronidazole to meropenem for complicated IAI
 - Found to be noninferior
 - Allowed for 5-10 days of IV therapy, extension if criteria met
- Microbiological evaluation done, noninferior

ASPECT-cUTI

- Compared ceftolozane/tazobactam to levofloxacin for complicated UTI
 - 7 days of therapy used
 - No other therapy permitted
- Results: ceftolozane/tazobactam was superior per the combined primary endpoint
 - Microbiological cure was superior, but clinical cure rates were not different

CRE

- Encoded by a few genes:
 - KPC
 - NDM
- Confers resistance to:
 - Carbapenems

CRE

- Optimal treatments:
 - Typically combination therapy
 - Colistin/polymyxin
 - Tigecycline
 - Aminoglycosides
 - Fosfomycin
 - Urinary tract infections only, specific pathogens
 - Carbapenems
 - Potentially as extended infusions

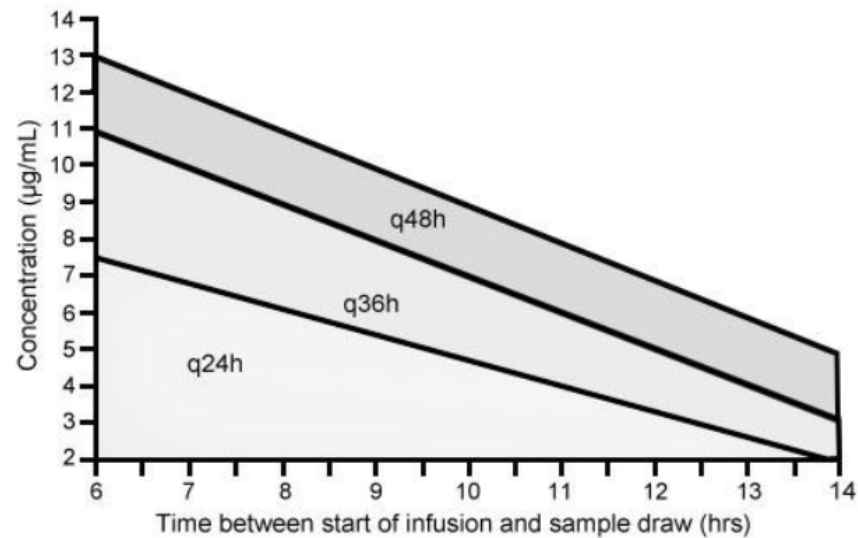
Colistin Resistance

- Found in case reports
- *mcr-1* gene
- Usually changes lipopolysaccharide
- Ideal treatment unclear

PHARMACOKINETICS

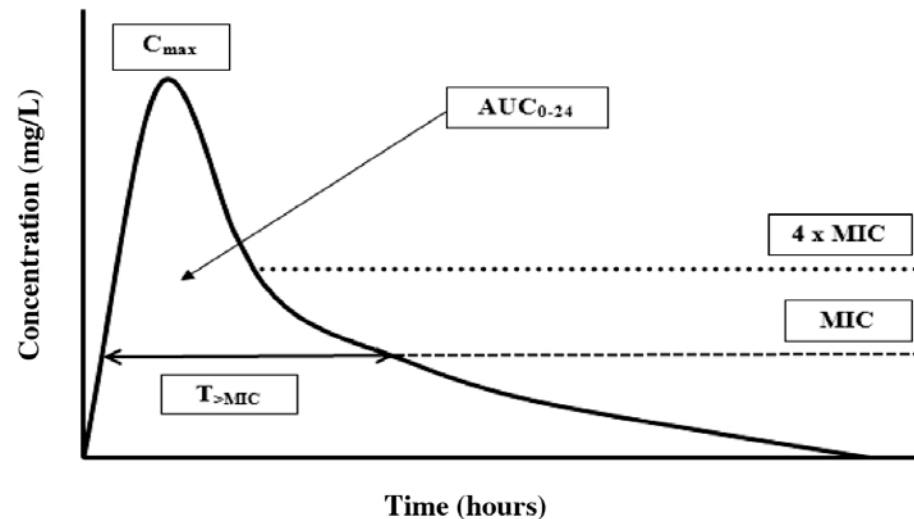
PKPD

- High dose extended interval aminoglycosides
 - Concentration dependent antibiotic
 - Typical dosing 7mg/kg every 24 hours
 - Achieves post-antibiotic effect



PKPD

- Extended infusion beta lactams
 - Piperacillin/tazobactam
 - Meropenem
 - Cephalosporins?



Sources: Vardakas. Lancet Infect Dis. 2017.

Image from: <https://annalsofintensivecare.springeropen.com/articles/10.1186/2110-5820-2-37>

PKPD Patient Case–Poll Question

- Patient DY is growing *Pseudomonas aeruginosa* from a blood culture. It is found to be resistant to fluoroquinolones. Which antibiotic option could be appropriate for this patient?
 - A) Ceftriaxone 2g IV Q 12 hours
 - B) Piperacillin/tazobactam 3.375g IV Q 8 hours over 4 hours each
 - C) Cefepime 2g IV Q 12 hours over 15 minutes each
 - D) Levofloxacin 750mg IV Q 24 hours

PKPD Patient Case–Poll Response

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PKPD

- Inhaled options for pneumonia/cystic fibrosis
 - Tobramycin
 - Colistin
 - Others



Source: Image from: <http://www.haydenspharmacy.com/nebulizer-medications/>.

Where do we go from here?

- CDC's Four Core Actions
 - Prevent the spread of infection
 - Track drug resistance
 - Improve antibiotic stewardship
 - Develop new drugs/diagnostic tests

Where do we go from here, *continued*

- Practice appropriate containment
 - Hand hygiene
 - Isolation appropriateness
- Antimicrobial stewardship
 - Less pressure on organisms will decrease resistance emergence
 - Right drug, right bug, right spectrum, right dose, right duration

Summary

- Antibiotic resistance is a growing problem
- Many pathogens exhibit resistance
- Optimal treatment may include new medications or alternate dosing strategies
- Pharmacists can be impactful in drug choice, dosing and monitoring

Resources

- CDC CRE Toolkit:
<https://www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html>
- CDC Antimicrobial Resistance Information:
<https://www.cdc.gov/drugresistance/index.html>
- FDA NARMS:
<https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/NationalAntimicrobialResistanceMonitoringSystem/default.htm>
- CDDEP Resistance Maps:
<https://resistancemap.cddep.org/index.php>

QUESTIONS

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