



Antibiotic Resistance and the Evolution of Superbugs

W. Kemper Alston, MD, MPH

Community Medical School

April 4, 2017

Woman died from superbug resistant to all available antibiotics in U.S.

CDC estimates 2 million infections and 23,000 deaths per year in the U.S. caused by antibiotic-resistant bacteria.



Carbapenem-resistant Enterobacteriaceae (CRE) bacteria is pictured in this medical illustration provided by the U.S. Centers for Disease Control and Prevention. / **REUTERS/CDC**

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A Nevada woman has died from an infection resistant to all available **antibiotics** in the United States, public health officials report.

According to the Centers for Disease Control and Prevention, the woman's condition was deemed incurable after being tested against 26 different antibiotics.

Though this isn't the first case of pan-resistant bacteria in the U.S., at this time it is still uncommon. Still, experts note that antibiotic resistance is a growing health concern globally and call the newly reported case "a wake up call."



Patients' bodies had super bugs

More than 100 people who died at hospitals in south-west London in the last three years were carrying deadly super bugs, figures show.

At St. George's NHS Trust 95 people had C. difficile listed on their death certificate and the bug was cited as a cause of death for 14 of those.

A further 21 people died where MRSA was listed as a related cause.

Urgent Threats

- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

Serious Threats

- Multidrug-resistant *Acinetobacter*
- Drug-resistant *Campylobacter*
- Fluconazole-resistant *Candida* (a fungus)
- Extended spectrum β -lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant *Enterococcus* (VRE)
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant Non-typhoidal *Salmonella*
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning Threats

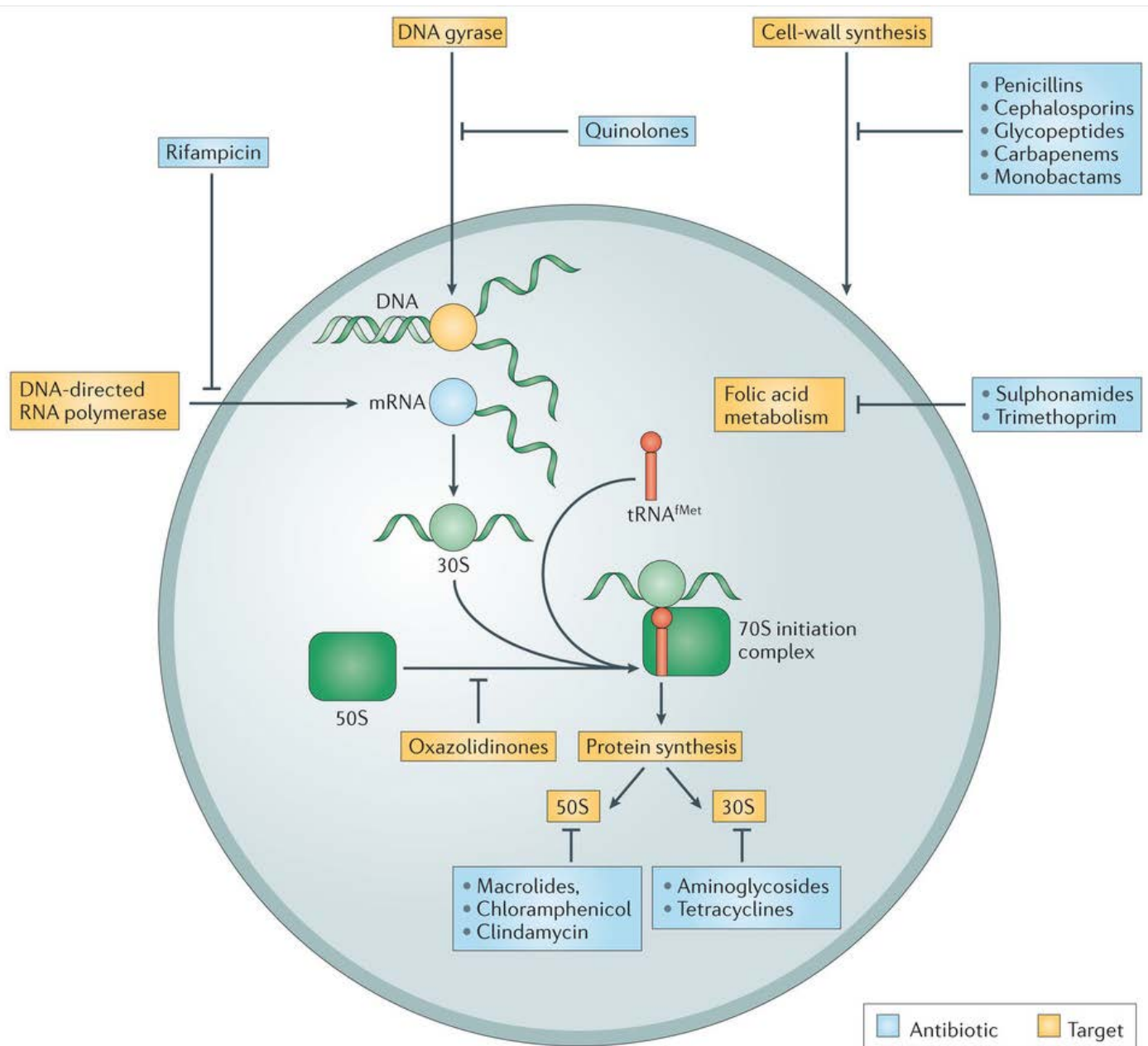
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*

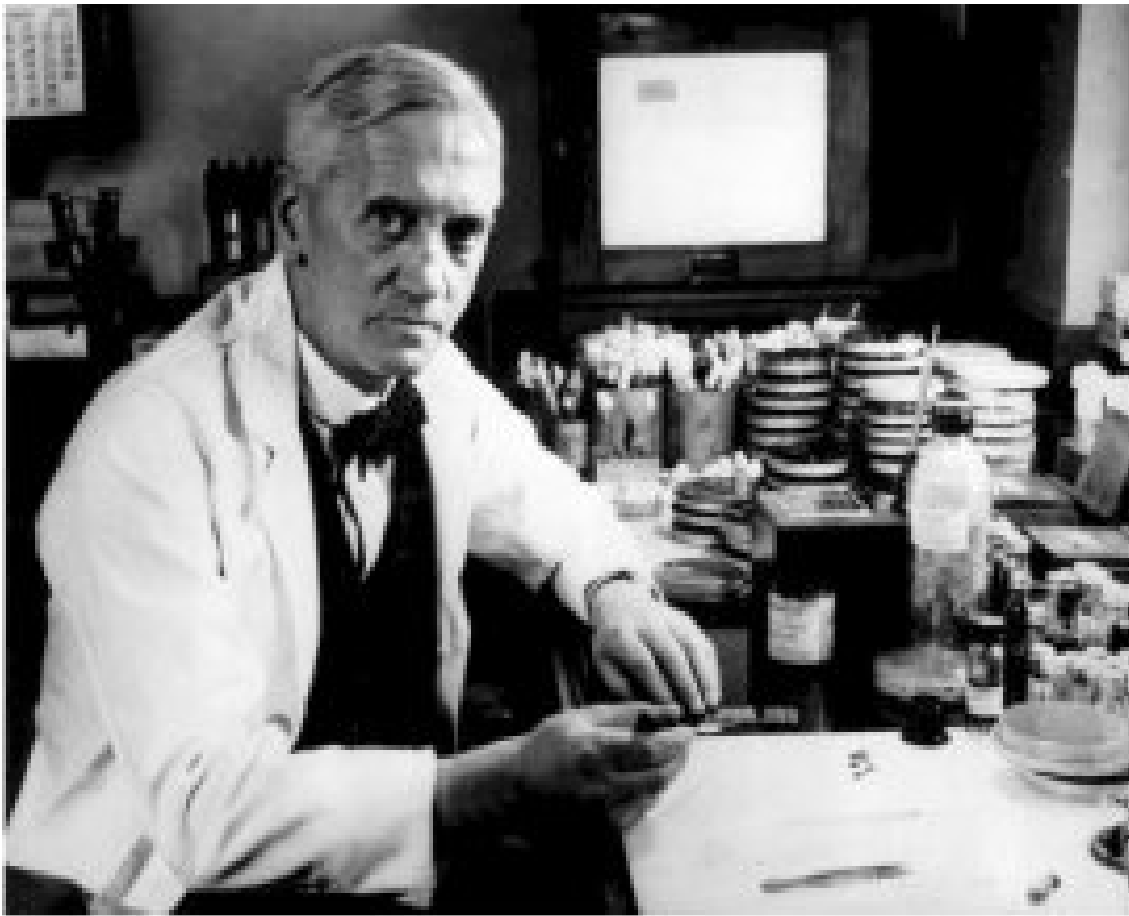
Objectives

- **How antibiotics work**
- **How microbes become antibiotic-resistant**
- **A case study: MRSA**
- **Basic approaches to controlling antibiotic resistance**

How Antibiotics Work

- Antibiotics bind to specific targets on or within bacteria. Different types of antibiotics have different targets. Common targets include the bacterial cell wall and the genetic machinery inside the bacteria.**
- Once bound to its target, the antibiotic kills, or at least inhibits growth of, the bacteria.**
- Antibiotics do not work alone to cure infections; you still need a functioning immune system, drainage of abscesses, and the removal of dead tissue and infected foreign bodies (metal, plastic, cement, etc.).**



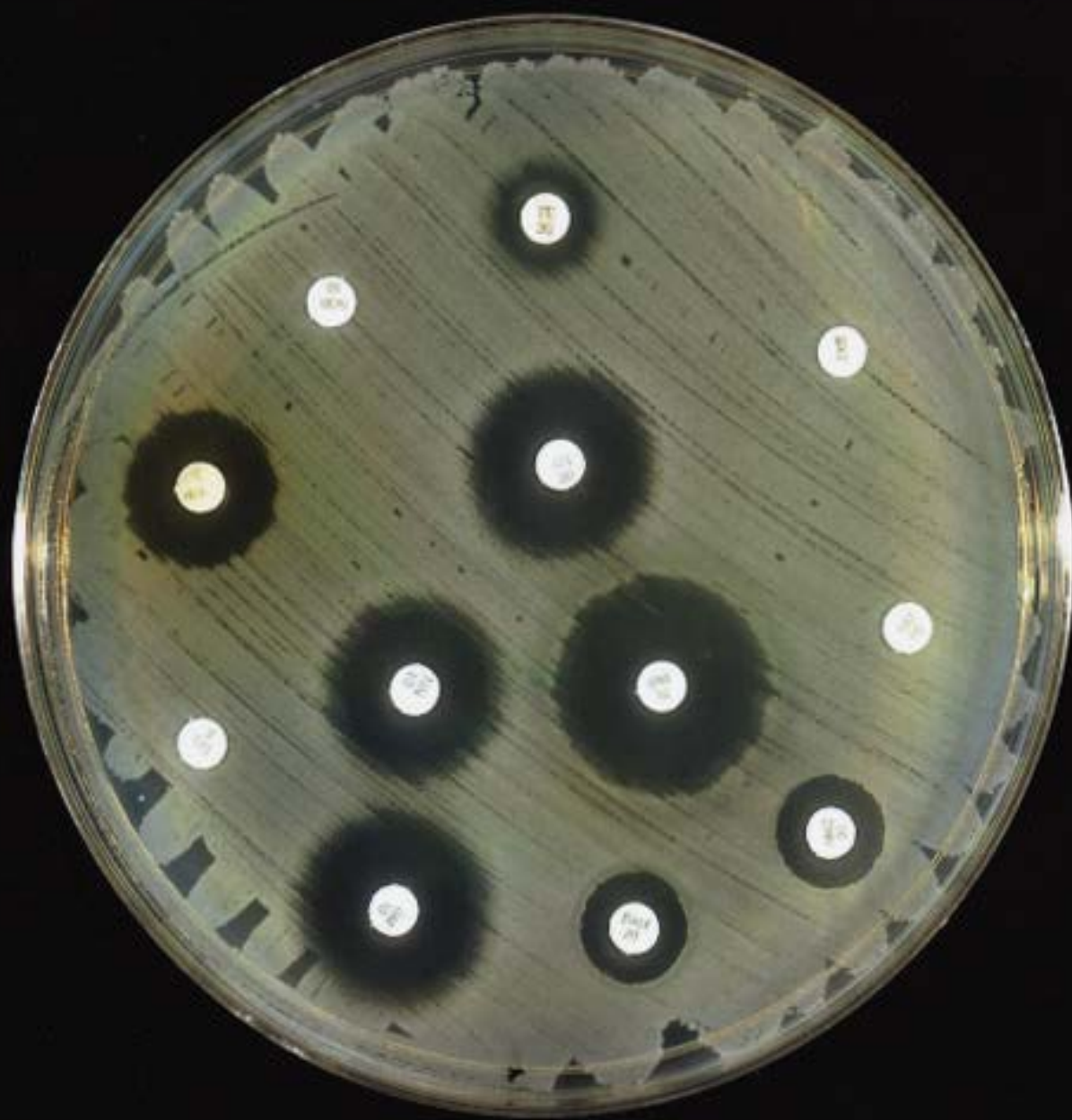


Alexander Fleming (1881 – 1955), Scottish. Discovered penicillin at St. Mary's Hospital in London in 1928.





Fleming's photograph



Our bodies are home to many more microbial cells than human cells. We are natural reefs, or scaffolding, for microbes. These microbes are vital to our development and survival. An increasing number of illnesses have been attributed to alterations in this microbiome. Occasionally a pathogenic microbe takes up residence among the normal flora, invades, and makes us ill.

None of the antibiotics we use are able to target a single type of bacteria and leave our normal flora undamaged. The antibiotics we prescribe attack bacteria we know, or suspect, to be causing infection, but also kill or inhibit many other types of harmless bacteria that comprise our microbiome.

Antibiotics do not “sterilize” us.

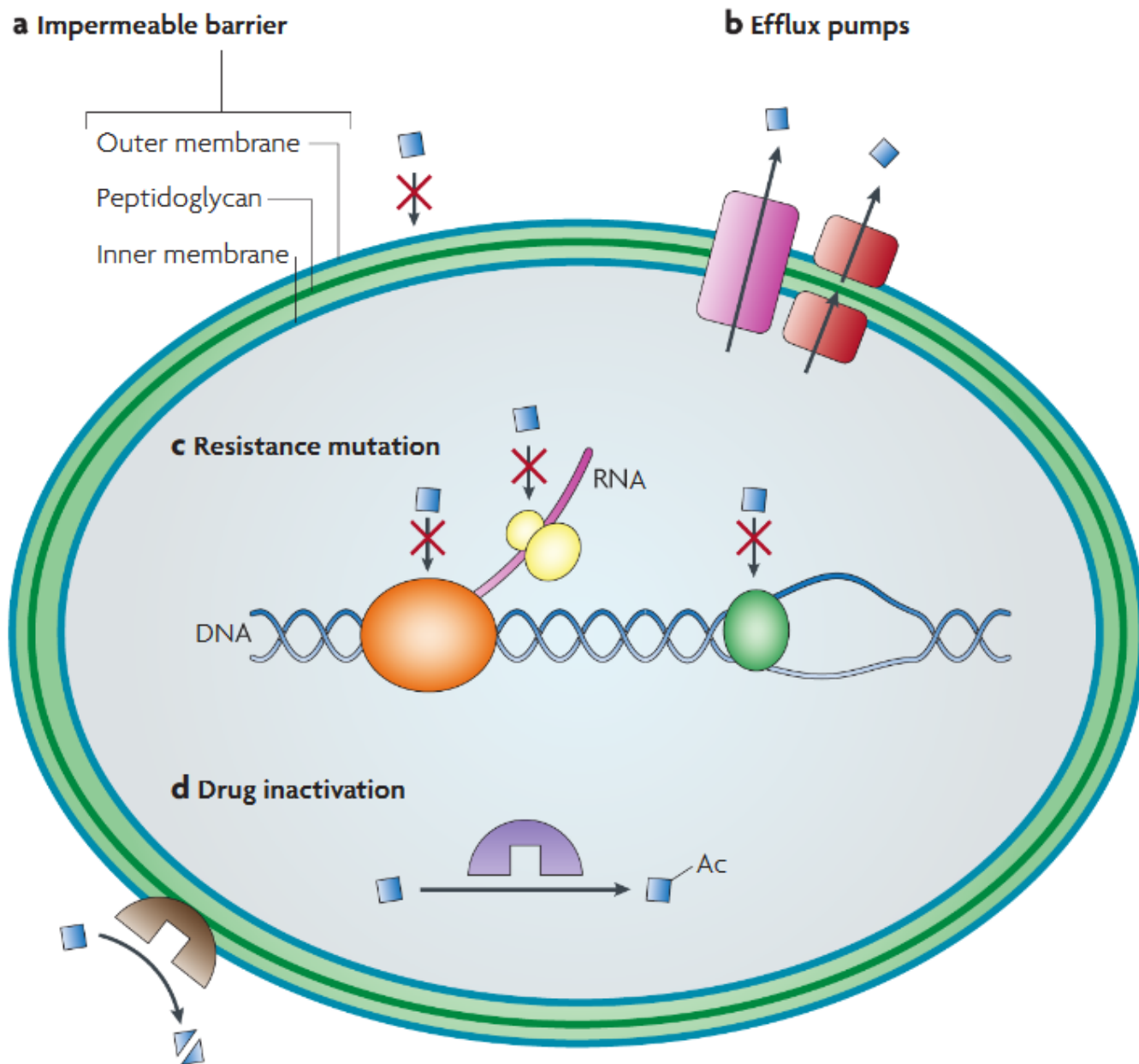
Hopefully they eradicate a pathogenic invader, but at the same time they damage our microbiome and make us more likely to be colonized with antibiotic-resistant organisms.

**Our diagnostic testing is limited.
Many of the antibiotics we prescribe,
both in the clinics and the hospital,
treat a disease (pneumonia or urine
infection for example) without our
knowing which specific bacteria are
actually the cause or what antibiotics
they are susceptible to.**

All antibiotics we use are have a limited duration of utility. Some antibiotics are more durable than others, but each dose of an antibiotic, ever so slightly, contributes to their demise.

Basic Mechanisms of Antibiotic Resistance

- **Enzymatically destroy the drug before it binds the target**
- **Alter the drug target so it cannot bind**
- **Reduce access of the drug to the target:**
 - **Block entry**
 - **Pump drug out of the cell**



Antibiotic Resistance Concepts (1)

- **Antibiotics, and the genetic elements which confer resistance to antibiotics, existed in nature long before they were developed for medicinal use.**
- **Microbes are more adaptable than we are. Microbial evolution depends on genetic variability in response to selective pressure. In human terms, they divide quickly, mutate often, and promiscuously share DNA.**

Antibiotic Resistance Concepts (2)

- **Antibiotic resistance correlates with antibiotic use. The frequency of resistance reflects the degree to which antibiotic use exerts selective pressure.**
- **Resistance may be a local phenomenon, on a hospital ward or in a community, or may reflect the global spread of resistance genes.**

Antibiotic Resistance Concepts (3)

- **Bacteria have a finite number of mechanisms by which they become resistant to antibiotics, but resistance has developed with each new class of drug.**
- **There are no antibiotics to which resistance has not been demonstrated.**

Antibiotic Resistance Concepts (4)

- **Resistance to a class of antibiotics may occur rapidly or may not occur for decades. The emergence of resistant strains may be accelerated in closed, stressed populations, such as animal farms, daycare centers, or intensive care units.**

Thanks to PENICILLIN ...He Will Come Home!





The good old days...



**“It is time to close the book on
infectious diseases”**

William Stewart, Surgeon General, 1967

2017: MDR Everything

(multidrug resistance)

- The Big Three:
 - Tuberculosis
 - HIV
 - Malaria
- Staph aureus (MRSA)
- Pseudomonas
- Pneumococcus
- Klebsiella & E. coli (CRE)
- Enterococcus (VRE)
- Enterobacter
- Gonorrhea
- Acinetobacter
- Influenza

Totally drug-resistant TB emerges in India

Discovery of a deadly form of TB highlights crisis of 'mismanagement'.

Katherine Rowland

13 January 2012

Physicians in India have identified a form of incurable tuberculosis there, raising further concerns over increasing drug resistance to the disease¹. Although reports call this latest form a “new entity”, researchers suggest that it is instead another development in a long-standing problem.

The discovery makes India the third country in which a completely drug-resistant form of the disease has emerged, following cases documented in Italy in 2007² and Iran in 2009³.

Malaria Patients in UK Show Resistance to Treatment for First Time

Malaria is developing resistance at rates that could potentially overwhelm modern treatments

By Michael Sainato • 01/31/17 12:30pm

NEWS

Malaria's Drug Miracle in Danger

Like many others before it, the latest generation of malaria drugs is losing its punch. This time, can global disaster be averted?

BANGKOK—Malaria rates are plummeting in many places, and scientists are optimistically talking about ridding entire countries of the disease—or even, in the long run, eradicating it worldwide. But in Southeast Asia, a new threat is looming—one that so far has received little attention but that could wipe out the recent advances and set back the global fight by decades.

Along the border between Thailand and Cambodia, *Plasmodium falciparum*, the most dangerous of malaria parasites, is showing unmistakable signs of becoming resistant to artemisinin derivatives, the group of powerful drugs that—as part of so-called

India or Africa could unleash the resistant parasites there.

Plans are under way to minimize the risk of that happening. The idea is to control malaria as aggressively as possible in the border area, making sure patients don't pass resistant parasites on to mosquitoes, and keeping parasites from being exposed to nonlethal drug levels that could fuel more resistance. Already, large numbers of insecticide-treated bed nets have been distributed in the area, and Cambodia has enacted a ban on the sale of so-called monotherapies, pills that contain artemisinin but lack the double whammy provided by the second drug in an ACT.

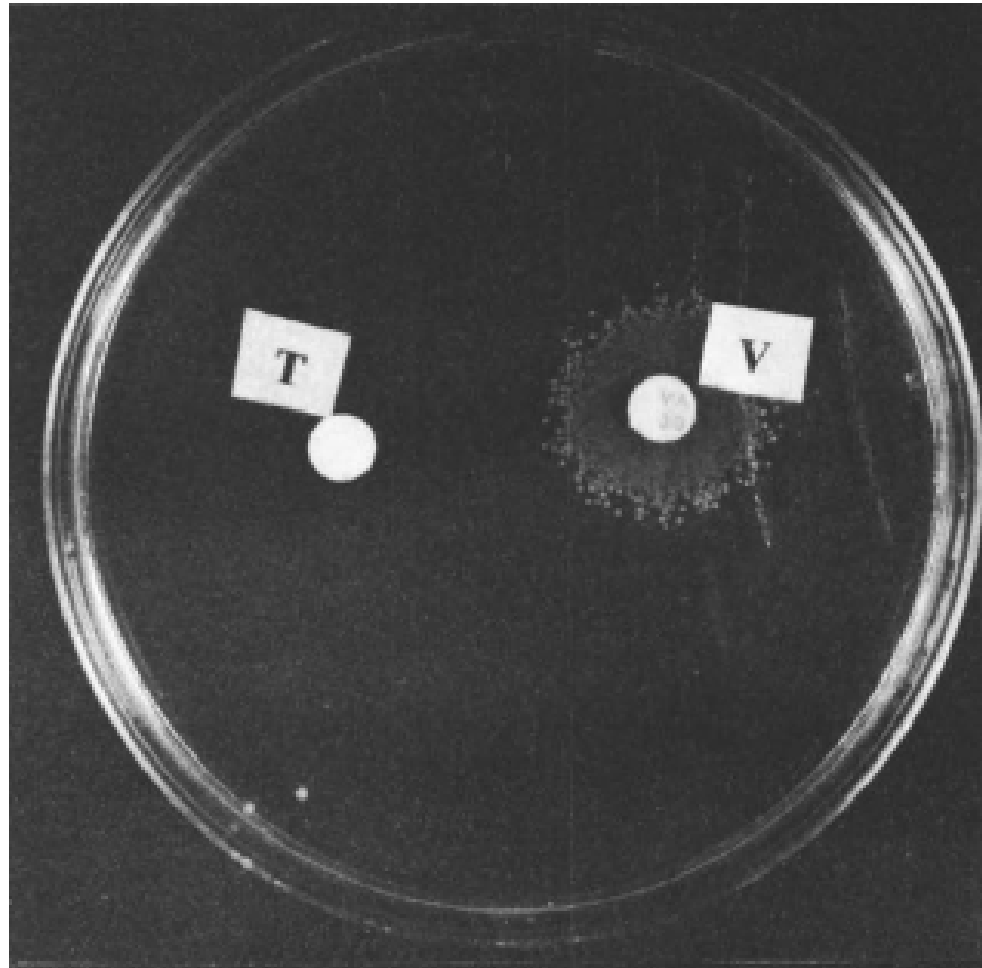
Bacteria Subsisting on Antibiotics

Gautam Dantas,^{1*} Morten O. A. Sommer,^{1,2*} Rantimi D. Oluwasegun,¹ George M. Church^{1†}

Antibiotics are a crucial line of defense against bacterial infections. Nevertheless, several antibiotics are natural products of microorganisms that have as yet poorly appreciated ecological roles in the wider environment. We isolated hundreds of soil bacteria with the capacity to grow on antibiotics as a sole carbon source. Of 18 antibiotics tested, representing eight major classes of natural and synthetic origin, 13 to 17 supported the growth of clonal bacteria from each of 11 diverse soils. Bacteria subsisting on antibiotics are surprisingly phylogenetically diverse, and many are closely related to human pathogens. Furthermore, each antibiotic-consuming isolate was resistant to multiple antibiotics at clinically relevant concentrations. This phenomenon suggests that this unappreciated reservoir of antibiotic-resistance determinants can contribute to the increasing levels of multiple antibiotic resistance in pathogenic bacteria.

Urinary Tract Infection with an *Enterococcus faecalis* Isolate that Requires Vancomycin for Growth

Henry S. Fraimow, MD; Donald L. Jungkind, PhD; David W. Lander, MS; Dawn R. Delso, BS; and James L. Dean, MD



The Strange Case of Staph aureus

- Penicillin introduced in mid-1940s. It is active against Staph aureus.



- Penicillin introduced mid-1940s.
- **Penicillin-resistant Staph aureus due to enzymatic destruction (β -lactamase) is common by the 1950s.**

570

THE NEW ENGLAND JOURNAL OF MEDICINE

Apr. 7, 1955

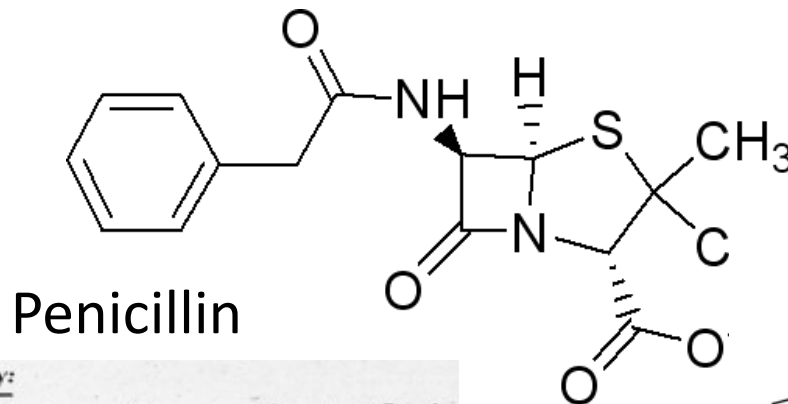
SPECIAL ARTICLE

CHANGING PATTERNS OF RESISTANCE OF CERTAIN COMMON PATHOGENIC BACTERIA TO ANTIMICROBIAL AGENTS*

MAXWELL FINLAND, M.D.†

BOSTON

- Penicillin introduced mid-1940s.
- Penicillin-resistant Staph aureus due to β -lactamase common by the 1950s.
- In 1959, penicillin was modified to create methicillin in order to resist β -lactamase.



Penicillin

Physicians Hail Medical Discovery:

British Scientists Develop 'Super Penicillin'

LONDON (AP) — British doctors today hailed the “outstanding achievement” of medical research in developing a new drug, celbenin, described as a super - penicillin soon to be available all over the world.

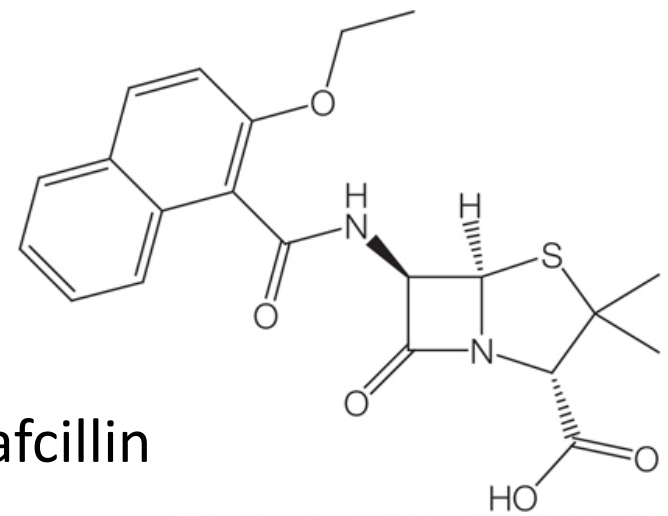
THE BRITISH Medical Journal cautioned that much more experimentation will be necessary before the full capabilities of the drug can be assessed, but it has already proved

capable of killing germs that are resistant to ordinary penicillin.

“Celbenin is completely absorbed into the bloodstream when injected and its use is entirely free from toxic side-effects,” said a spokesman for Beecham Research Laboratories, developers of the drug.

The medical journal describes in detail clinical results of tests.

One hospital found that only



Nafcillin

- Penicillin introduced mid-1940s.
- Penicillin-resistant *Staph aureus* due to β -lactamase common by the 1950s.
- In 1959, penicillin was modified to create methicillin in order to resist β -lactamase.
- **By 1961 *Staph aureus* had evolved a different target (penicillin-binding protein), creating MRSA.**

Staphylococci Resistant to Methicillin (“Celbenin”)

SIR,—In the earlier period of clinical usage of methicillin (“celbenin”) some experiments indicated that there were no strains of staphylococci resistant to it.^{1 2} Eventually further research in England proved that there might be some resistant strains.³ In Turkey, thus far, methicillin has not been used clinically. In spite of this, in our experiments three strains of *Staphylococcus pyogenes aureus* have been found resistant to this antibiotic.

- **Penicillin introduced mid-1940s.**
- **Penicillin-resistant Staph aureus due to β -lactamase common by the 1950s.**
- **In 1959, penicillin was modified to create methicillin in order to resist β -lactamase.**
- **By 1961, Staph aureus changes penicillin-binding protein target for β -lactams, creating MRSA.**
- **Vancomycin rushed to market. Heavy use begins in the 1980s.**

REASSESSMENTS OF VANCOMYCIN—A POTENTIALLY USEFUL ANTIBIOTIC

Based on Symposia Held in
Atlanta, Georgia, November 1-2, 1978;
San Francisco, California, November 16-17, 1978; and
Chicago, Illinois, July 19-20, 1979

Guest Editors: ROBERT I. WISE and MITCHELL KORY

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- Vancomycin rushed to market. Heavy use begins in 1980s.
- **1988: Vancomycin-resistant enterococci (altered vancomycin target).**

MEDICAL INTELLIGENCE



New England Journal of Medicine,
7/21/88

**PLASMID-MEDIATED RESISTANCE TO
VANCOMYCIN AND TEICoplanin IN
*ENTEROCOCCUS FAECIUM***

ROLAND LECLERCQ, M.D., ELIANE DERLOT,
JEAN DUVAL, M.D., AND PATRICE COURVALIN, M.D.

- Penicillin introduced mid-1940s.
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- By 1961, *Staph aureus* changes penicillin-binding protein target for β -lactams, creating MRSA.
- Vancomycin rushed to market. Heavy use begins in 1980s.
- 1988: Vancomycin-resistant enterococci described.
- **2002: Vancomycin-resistant *Staph aureus* described.**

BRIEF REPORT

Infection with Vancomycin-Resistant
Staphylococcus aureus Containing
the *vanA* Resistance Gene

Soju Chang, M.D., M.P.H., Dawn M. Sievert, M.S., Jeffrey C. Hageman, M.H.S.,
Matthew L. Boulton, M.D., Fred C. Tenover, Ph.D., M.P.H.,
Frances Pouch Downes, Dr.P.H., Sandip Shah, M.S., James T. Rudrik, Ph.D.,
Guy R. Pupp, D.P.M., William J. Brown, Ph.D., Denise Cardo, M.D.,
and Scott K. Fridkin, M.D., for the Vancomycin-Resistant
Staphylococcus aureus Investigative Team*

- **Penicillin introduced mid-1940s.**
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- **1988: Vancomycin-resistant enterococci described .**
- **1994: Vancomycin-dependent enterococci.**
- **2002: Vancomycin-resistant Staph aureus described.**
- **Quinupristin-dalfopristin, daptomycin, & linezolid approved (1999 – 2003) to meet challenge of vancomycin resistance.**

Characterization of isolates associated with emerging resistance to quinupristin/dalfopristin (Synercid®) during a worldwide clinical program

M. Dowzicky^{a,*}, G.H. Talbot^a, C. Feger^b, P. Prokocimer^a, J. Etienne^c, R. Leclercq^d

^aRhône-Poulenc Rorer Pharmaceuticals, Collegeville, PA, USA;

^bRhône-Poulenc Rorer Pharmaceuticals, Antony, France;

^cMicrobiology, Hôpital Edouard Herriot, F-69437 Lyon, France;

^dMicrobiology, CHU Côte de Nacre, F-14033 Caen, France.

Quinupristin-dalfopristin resistance

BRIEF REPORT

Daptomycin resistance

Daptomycin-Resistant, Methicillin-Resistant *Staphylococcus aureus* Bacteremia

A. Mangili, I. Bica, D. R. Snyderman, and D. H. Hamer^a

Division of Geographic Medicine and Infectious Diseases, Department of Medicine, Tufts–New England Medical Center and Tufts University School of Medicine, Boston, Massachusetts

Massachusetts, area (hereafter referred to as the “outside hospital”) on 5 January 2004 with hyponatremia, hyperkalemia, confusion, and worsening edema of the lower extremities. On the day of admission, he reported chronic back pain, suprapubic tenderness, occasional chills, and frequent bowel movements but no fever or sweating. At examination, he was disoriented with regard to date and time and appeared to have jaundice, but, otherwise, he was not in acute distress. His temperature was 35.7°C, blood pressure was 109/58 mm Hg, pulse

Clinical Outbreak of Linezolid-Resistant *Staphylococcus aureus* in an Intensive Care Unit

Miguel Sánchez García, MD, PhD

María Ángeles De la Torre, MD

Gracia Morales, PhD

Beatriz Peláez, PhD

María José Tolón, MD

Sara Domingo, MD

Francisco Javier Candel, MD, PhD

Raquel Andrade, PhD

Context Linezolid resistance is extremely uncommon in *Staphylococcus aureus*.

Objective To report an outbreak with linezolid and methicillin-resistant *S. aureus* (LRSA) in an intensive care department and the effective control measures taken.

Design, Setting, and Patients Outbreak study of consecutive critically ill patients colonized and/or infected with LRSA at an intensive care department of a 1000-bed tertiary care university teaching hospital in Madrid, Spain. Patients were placed under strict contact isolation. Daily updates of outbreak data and recommendations for the use of linezolid were issued. Extensive environmental sampling and screening of the hands of health care workers were performed.

Linezolid resistance

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- **Vancomycin rushed to market. Heavy use begins in 1980s.**
- **1988: Vancomycin-resistant enterococci described.**
- **2002: Vancomycin-resistant Staph aureus described.**
- **Quinupristin-dalfopristin, daptomycin, & linezolid released (1999 – 2003) to meet challenge of vancomycin resistance. Resistance to all 3 reported.**
- **Telavancin, dalbavancin, oritavancin and ceftaroline approved since 2009....**

PBP2a Mutations Causing High-Level Ceftaroline Resistance in Clinical Methicillin-Resistant *Staphylococcus aureus* Isolates

S. Wesley Long,^a Randall J. Olsen,^a Shrenik C. Mehta,^c Timothy Palzkill,^c Patricia L. Cernoch,^a Katherine K. Perez,^{a,b} William L. Musick,^b Adriana E. Rosato,^a James M. Musser^a

Center for Molecular and Translational Human Infectious Diseases Research, Department of Pathology and Genomic Medicine, Houston Methodist Hospital and Houston Methodist Research Institute, Houston, Texas, USA^a; Department of Pharmacy, Houston Methodist Hospital, Houston, Texas, USA^b; Department of Pharmacology, Baylor College of Medicine, Houston, Texas, USA^c

Ceftaroline is the first member of a novel class of cephalosporins approved for use in the United States. Although prior studies have identified eight ceftaroline-resistant methicillin-resistant *Staphylococcus aureus* (MRSA) isolates in Europe and Asia with MICs ranging from 4 to 8 mg/liter, high-level resistance to ceftaroline (> 32 mg/liter) has not been described in MRSA strains isolated in the United States. We isolated a ceftaroline-resistant (MIC > 32 mg/liter) MRSA strain from the blood of a cystic fibrosis patient and five MRSA strains from the respiratory tract of this patient. Whole-genome sequencing identified two amino acid-altering mutations uniquely present in the ceftaroline-binding pocket of the transpeptidase region of penicillin-binding protein 2a (PBP2a) in ceftaroline-resistant isolates. Biochemical analyses and the study of isogenic mutant strains confirmed that these changes caused ceftaroline resistance. Thus, we identified the molecular mechanism of ceftaroline resistance in the first MRSA strain with high-level ceftaroline resistance isolated in the United States.

That's It For the Good News

Superbug found at suburban hospital

Lutheran General, health officials taking steps to prevent spread of CRE

By [Robert McCoppin](#) and [Cynthia Dizikes](#), Tribune reporters

January 10, 2014

A north suburban hospital made a public plea Thursday that any patient who underwent a specific endoscopic procedure between January and September 2013 return for a free screening after a highly drug-resistant strain of bacteria was found on some of the scopes.

So far, Advocate Lutheran General Hospital in Park Ridge has identified 38 patients who have tested positive for an emerging strain of carbapenem-resistant Enterobacteriaceae, or CRE, which are bacteria that are resistant to a class of antibiotics used as a last-resort treatment for seriously ill people.

Over the course of the last year, the Centers for Disease Control and Prevention has identified a total of 44 people in northeastern Illinois with this particular strain, making it the largest such outbreak in the United States to date.

Fear of a “Post-Antibiotic Era”

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STAT

PUBLIC HEALTH

Superbug Resistant to Last-Resort Antibiotic Arises in China

China has been using colistin to speed growth of farm animals

By Helen Branswell, STAT on January 27, 2017

Component
Source & Organism ID

Urine

Comment:

KLEBSIELLA PNEUMONIAE

MIC, Aerobic Bacteria

FINAL 08/07/14 1618

Comment:

(Note)

SOURCE: URINE, Urine KLEBSIELLA PNEUMONIAE

SUSCEPTIBILITY, AEROBIC, MIC

FINAL

KLEBSIELLA PNEUMONIAE COMPLEX

Organism identified by client.

Organism KLEBSIELLA PNEUMONIAE COMPLEX
Antibiotic MIC (mcg/mL) Interpretation

Ampicillin	>16	R
Amp/Sulb	>16/8	R
Pip/Taz	>64/4	R
Ticar/Clav	>64/2	R
Cefazolin	>16	R
Oral cephalosporins		R
Cefepime	>16	R
Ceftazidime	>16	R
Ceftriaxone	>32	R
Ertapenem	>1	R
Meropenem	>8	R
Ciprofloxacin	>2	R
Levofloxacin	>4	R
Amikacin	32	I
Gentamicin	>8	R
Tobramycin	>8	R
Nitrofurantoin	>64	R
TMP/SMX	>2/38	R

Oral cephalosporins: The interpretation applies to uncomplicated urinary tract infections only. The oral cephalosporins category includes cefdinir, cefuroxime and cephalexin.

S=SUSCEPTIBLE I=INTERMEDIATE R=RESISTANT
N=NOT SUSCEPTIBLE D=DOSE DEPENDENT SUSCEPTIBLE

Performed or Referred by: Mayo Clinic Labs: Rochester Main Campus, 200
First ST SW, Rochester, MN 55905, Lab Dir: Franklin R. Cockerill III,
MD

8/26/14

Specimen: Trachea. Specimen submitted on a swab.

Gram Smear Result: Mod Polys, Mod Mixed gram positive and gram negative organisms

Result KLEBSIELLA PNEUMONIAE CRE

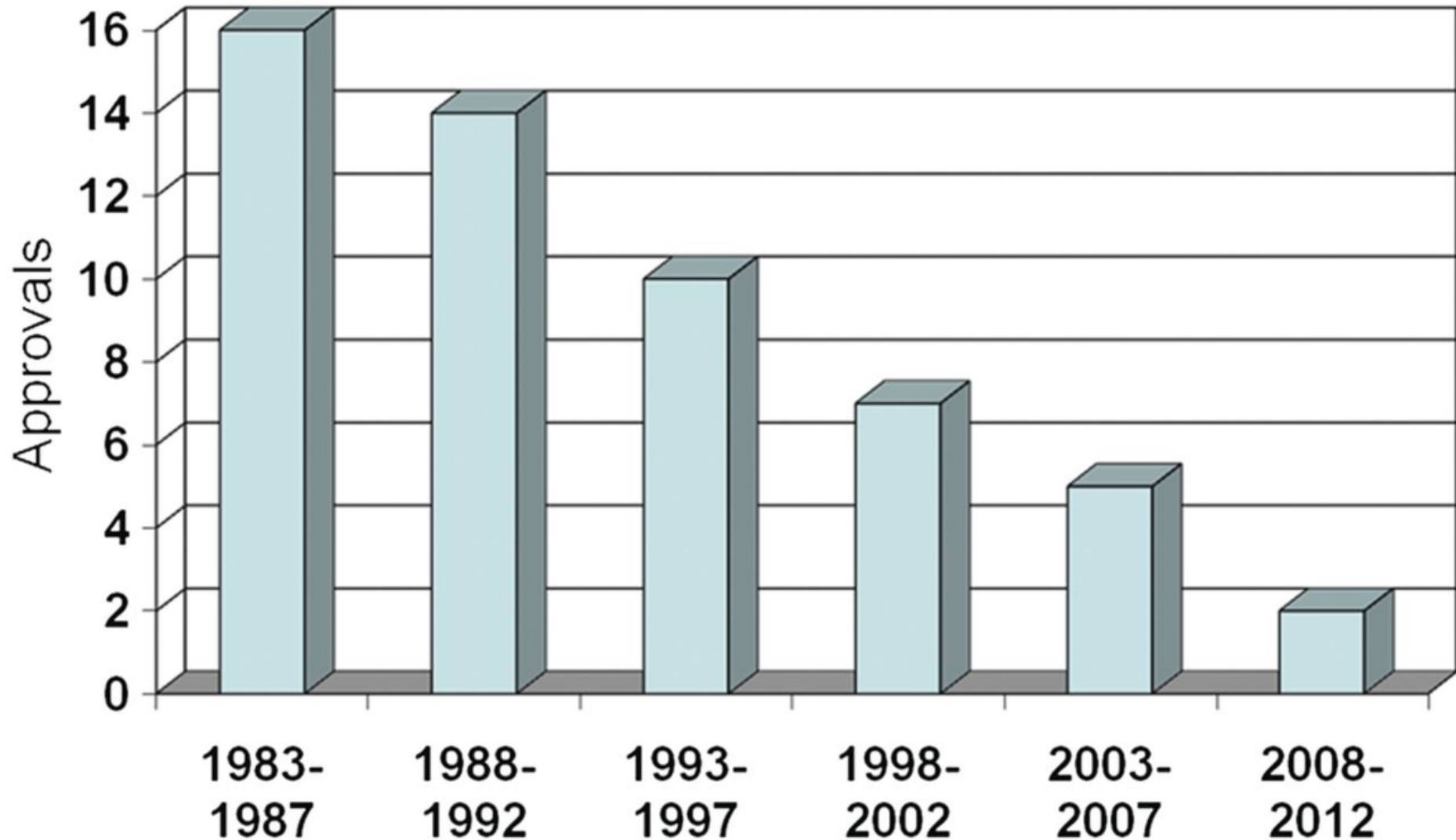
<u>Antibiotic</u>	<u>Interpretation</u>
Amikacin	Intermediate
Ampicillin	Resistant
Amp-Sulbactam	Resistant
Ceftazidime	Resistant
Ceftriaxone	Resistant
Ciprofloxacin	Resistant
Colistin	Resistant
Ertapenem	Resistant
Gentamicin	Resistant
Meropenem	Resistant
Pip-Tazobactam	Resistant
Polymyxin B	Resistant
Tobramycin	Resistant
Trim-Sulfa	Resistant

Final Thoughts

- **There is no evidence that antibiotic resistance is slowing. Everywhere you look it is increasing.**
- **Physicians and patients need to think about antibiotics as a unique, time-limited drug class, with each dose contributing to their demise.**
- **We cannot assume that the pharmaceutical industry will successfully bring novel antibiotics to the market faster than we burn them out.**
- **Industry needs incentives to develop these drugs which are *not* traditionally big money-makers. Drugs for incurable diseases (hypertension, lipids, diabetes, HIV, etc.) are more profitable than drugs for diseases which either kill you or are cured in the first week.**

Declining Antibiotic Approvals

United States



The GAIN Act

TITLE VIII—GENERATING ANTIBIOTIC INCENTIVES NOW

SEC. 801. EXTENSION OF EXCLUSIVITY PERIOD FOR DRUGS.

(a) IN GENERAL.—Chapter V (21 U.S.C. 351 et seq.) is amended by inserting after section 505D the following:

“SEC. 505E. EXTENSION OF EXCLUSIVITY PERIOD FOR NEW QUALIFIED INFECTIOUS DISEASE PRODUCTS.

“(a) EXTENSION.—If the Secretary approves an application pursuant to section 505 for a drug that has been designated as a qualified infectious disease product under subsection (d), the 4- and 5-year periods described in subsections (c)(3)(E)(ii) and (j)(5)(F)(ii) of section 505, the 3-year periods described in clauses (iii) and (iv) of subsection (c)(3)(E) and clauses (iii) and (iv) of subsection (j)(5)(F) of section 505, or the 7-year period described in section 527, as applicable, shall be extended by 5 years.

Passed in the U.S. Senate June 26, 2012, by a vote of 92 – 4
President Obama signed into law on July 9, 2012

Final Thoughts(2)

- **As soon as a new antibiotic is released, infectious disease specialists try to limit it's use. This makes for a poor business plan.**
- **Physicians need to do a better job at preserving our existing drugs:**
 - **Reduce inappropriate use, restrict use, rotate use, combination use.**
 - **Treat only as long as is necessary. Shorter durations.**
- **Healthcare workers need to reduce the transmission of resistant bacteria in the hospital:**
 - **Hand hygiene.**
 - **Contact isolation.**
- **We need to resolve the controversy over the use of antibiotics in farming. Animal use accounts for about 75% of the antibiotic market in the U.S.**

Final Thoughts(3)

- **We need more comprehensive surveillance systems both in the community and in hospitals. Ignorance breeds complacency.**
- **We need more research about what really works to slow the development of resistance, rather than relying on dogma and anecdote.**
- **We need vaccines**
- **We need rapid, accurate diagnostic tests to allow physicians to focus treatment, rather than relying on a “shotgun” approach**
- **President Obama signed Executive Order 13676 on 9/18/14: Combating Antibiotic-Resistant Bacteria**

A detailed microscopic image of various bacteria. In the upper left, there are large, pink, rod-shaped bacteria with many fine, hair-like appendages. To their right, there are several smaller, purple, spherical bacteria, some with long, thin, wavy appendages. In the center, there are long, blue, chain-like structures made of small, round bacteria. In the lower left, there are more pink, rod-shaped bacteria. In the lower right, there are large, brownish, spherical bacteria with many long, thin, wavy appendages. The background is black with a faint, light-colored hexagonal grid pattern.

ANTIBIOTIC RESISTANCE THREATS in the United States, 2013



U.S. Department of
Health and Human Services
Centers for Disease
Control and Prevention

NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2015



GLOBAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE



**World Health
Organization**

2015

REX MORGAN M.D.

