# A Perspective on Methicillin-Resistant *Staphylococcus aureus* (MRSA) and Other Multi-Drug-Resistant Organisms

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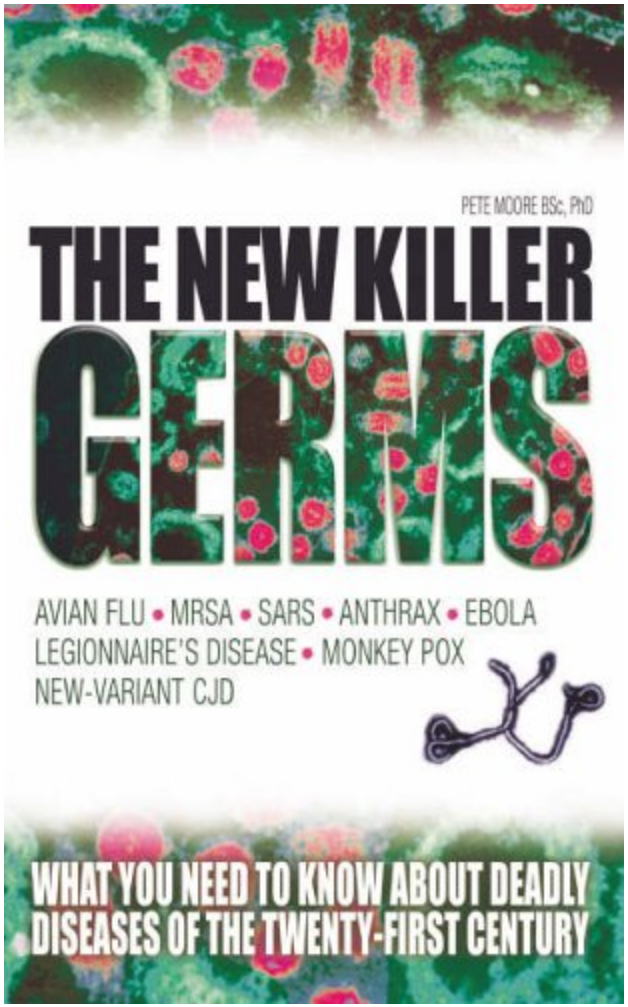

PETE MOORE BSc, PhD
THE NEW KILLER
GERMS
AVIAN FLU • MRSA • SARS • ANTHRAX • EBOLA
LEGIONNAIRE'S DISEASE • MONKEY POX
NEW-VARIANT CJD
WHAT YOU NEED TO KNOW ABOUT DEADLY
DISEASES OF THE TWENTY-FIRST CENTURY

# Facts About Antibiotic Resistance

- About 2 million people acquire bacterial infections in U.S. hospitals each year, and 90,000 die as a result.
- About 70% of those infections are resistant to at least one drug, according to the Centers for Disease Control and Prevention (CDC).

# Facts About Antibiotic Resistance

- A 2000-2001 analysis of U.S. hospitalizations found that *Staph aureus* infections caused 12,000 deaths and $9.5 billion in hospital costs each year (Noskin, *Archives of Internal Medicine*).
- In 2002, 57.1% (approx.102,000 cases) of *Staph aureus* in U.S. hospitals were MRSA (CDC).
- Although MRSA used to be limited primarily to hospital patients, it is becoming increasingly common in the broader community.
  - A study of children with community-acquired staph infections at the University of Texas found nearly 70% infected with MRSA.

Klevens, R. M. et al. JAMA 2007;298:1763-1771.

## Observed Incidence Rates of Invasive Methicillin-Resistant Staphylococcus aureus (MRSA) by Active Bacterial Core Surveillance Site and Epidemiologic Classification, United States, 2005a

**Table 2.** Observed Incidence Rates of Invasive Methicillin-Resistant *Staphylococcus aureus* (MRSA) by Active Bacterial Core Surveillance Site and Epidemiologic Classification, United States, 2005[a]

| | | Incidence per 100 000 | | | |
|---|---|---|---|---|---|
| | | | Health Care–Associated | | |
| Surveillance Site No. (Location)[b] | No. of Cases | Community-Associated | Community-Onset | Hospital-Onset | Total |
| 1 (Connecticut) | 952 | 2.7 | 15.6 | 8.4 | 27.1 |
| 2 (Atlanta, GA, metropolitan area) | 1165 | 5.1 | 16.7 | 10.3 | 33.0 |
| 3 (San Francisco, CA, Bay Area) | 936 | 4.5 | 15.9 | 7.7 | 29.2 |
| 4 (Denver, CO, metropolitan area) | 480 | 2.8 | 12.3 | 6.0 | 21.2 |
| 5 (Portland, OR, metropolitan area) | 305 | 4.7 | 11.4 | 3.6 | 19.8 |
| 6 (Monroe County, NY) | 307 | 2.7 | 22.2 | 16.8 | 41.9 |
| 7 (Baltimore City, MD) | 742 | 29.7 | 62.9 | 19.7 | 116.7 |
| 8 (Davidson County, TN) | 305 | 6.8 | 30.4 | 13.9 | 53.0 |
| 9 (Ramsey County, MN) | 95 | 1.6 | 11.5 | 6.1 | 19.2 |

[a] Epidemiologic classification of disease consisted of health care–associated (either hospital-onset cases with a culture collected >48 h after hospital admission or community-onset cases with health care risk factors but a culture collected ≤48 h after hospital admission) and community-associated cases (no health care risk factors).
[b] Site numbers were assigned in descending order of population size.

***Conclusions*** *Invasive MRSA infection affects certain populations disproportionately. It is a major public health problem primarily related to health care but no longer confined to intensive care units, acute care hospitals, or any health care institution*.



JAMA

# Numbers and Incidence Rates of Invasive Methicillin-Resistant Staphylococcus aureus (MRSA) Infections and Deaths, by Selected Demographic Characteristics and Epidemiologic Classifications, Active Bacterial Core Surveillance, United States, 2005a

**Table 4.** Numbers and Incidence Rates of Invasive Methicillin-Resistant *Staphylococcus aureus* (MRSA) Infections and Deaths, by Selected Demographic Characteristics and Epidemiologic Classifications, Active Bacterial Core Surveillance, United States, 2005[a]

| | Invasive MRSA Infections | | | | | | Invasive MRSA Deaths | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Incidence per 100 000 | | | | | | Incidence per 100 000 | | | |
| | | | | Health Care–Associated | | | | | | Health Care–Associated | | |
| Demographic | Actual No. | Estimated No. | Community | Community-Onset | Hospital-Onset | Total | Actual No. | Estimated No. | Community | Community-Onset | Hospital-Onset | Total |
| Sex | | | | | | | | | | | | |
| Male | 3066 | 54 790 | 6.1 | 20.6 | 10.1 | 37.5 | 571 | 10 840 | 0.8 | 3.9 | 2.7 | 7.4 |
| Female | 2220 | 39 360 | 3.2 | 14.7 | 7.9 | 26.3 | 417 | 7820 | 0.3 | 2.6 | 2.2 | 5.2 |
| Age, y | | | | | | | | | | | | |
| <1 | 60 | 950 | 3.5 | 4.7 | 14.7 | 23.1 | 5 | 80 | 0 | 0.3 | 1.6 | 2.0 |
| 1 | 9 | 160 | 2.9 | 0.0 | 1.0 | 3.8 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2-4 | 18 | 290 | 0.8 | 1.0 | 0.6 | 2.4 | 1 | 10 | 0 | 0 | 0.1 | 0.1 |
| 5-17 | 47 | 730 | 0.6 | 0.4 | 0.3 | 1.4 | 3 | 60 | 0 | 0 | 0.1 | 0.1 |
| 18-34 | 434 | 7050 | 3.2 | 4.2 | 2.4 | 10.1 | 31 | 460 | 0.1 | 0.2 | 0.3 | 0.7 |
| 35-49 | 1082 | 16 100 | 6.3 | 11.9 | 5.3 | 24.3 | 92 | 1400 | 0.4 | 0.8 | 0.9 | 2.1 |
| 50-64 | 1327 | 22 120 | 6.7 | 23.9 | 12.1 | 43.9 | 224 | 3640 | 0.9 | 3.2 | 2.9 | 7.2 |
| ≥65 | 2308 | 46 970 | 8.9 | 78.2 | 39.1 | 127.7 | 632 | 13 000 | 2.1 | 19.7 | 13.4 | 35.3 |
| Race | | | | | | | | | | | | |
| White | 2716 | 66 590 | 3.8 | 15.3 | 8.1 | 27.7 | 596 | 14 270 | 0.4 | 3.1 | 2.4 | 5.9 |
| Black | 1794 | 25 980 | 10.9 | 37.2 | 16.6 | 66.5 | 263 | 3900 | 0.2 | 4.8 | 3.7 | 10.0 |
| Other | 139 | 1790 | 1.6 | 5.4 | 3.3 | 10.4 | 38 | 480 | 0.1 | 1.3 | 1.2 | 2.8 |
| Total (interval estimates) | 5287 | 94 360 (72 850-104 000) | 4.6 (3.6-4.4) | 17.6 (14.7-18.2) | 8.9 (6.1-11.8) | 31.8 (24.4-35.2) | 988 | 18 650 (10 050-22 100) | 0.5 (0.3-0.6) | 3.2 (1.7-3.7) | 2.5 (1.2-3.1) | 6.3 (3.3-7.5) |

[a] Epidemiologic classification of disease consisted of healthcare-associated (either hospital-onset cases with a culture collected >48 hours after hospital admission or community-onset cases with healthcare risk factors but a culture collected ≤48 hours after hospital admission) and community-associated cases (those with no healthcare risk factors). There were 638 cases and 91 deaths with unknown race.

**Klevens, R. M. et al. JAMA 2007;298:1763-1771.**



JAMA

The New York Times

# Dead Student Had Infection, Officials Say

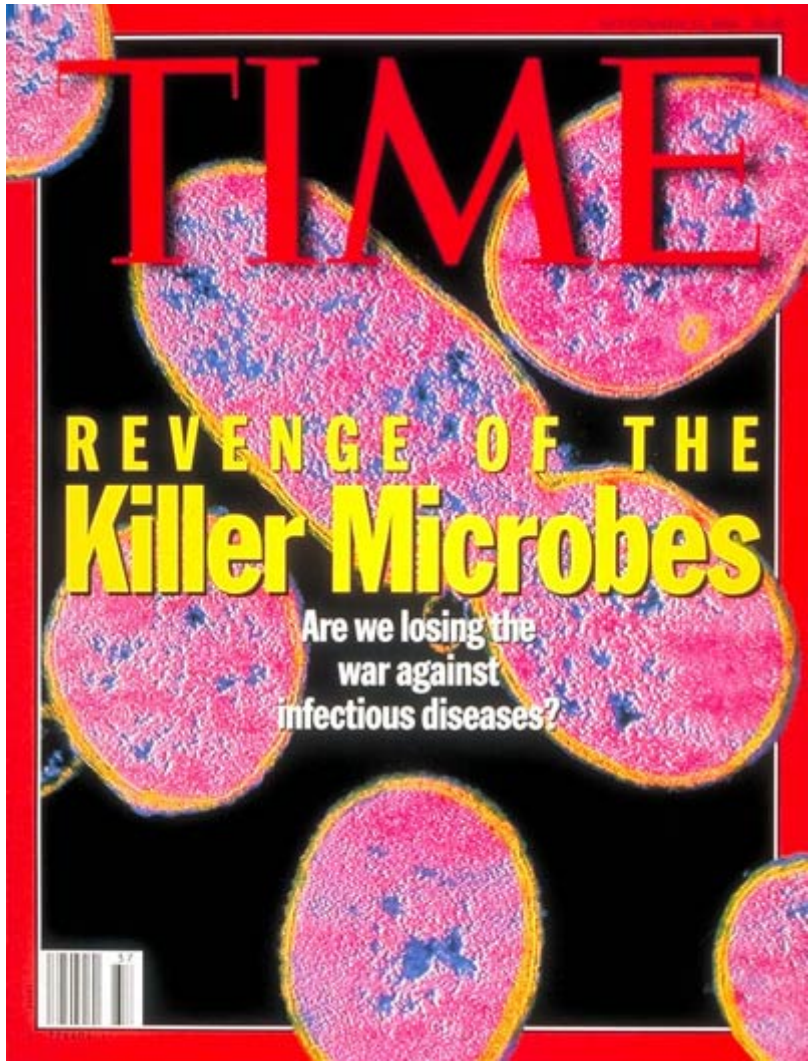
By WINNIE HU and SARAH KERSHAW

October 26, 2007

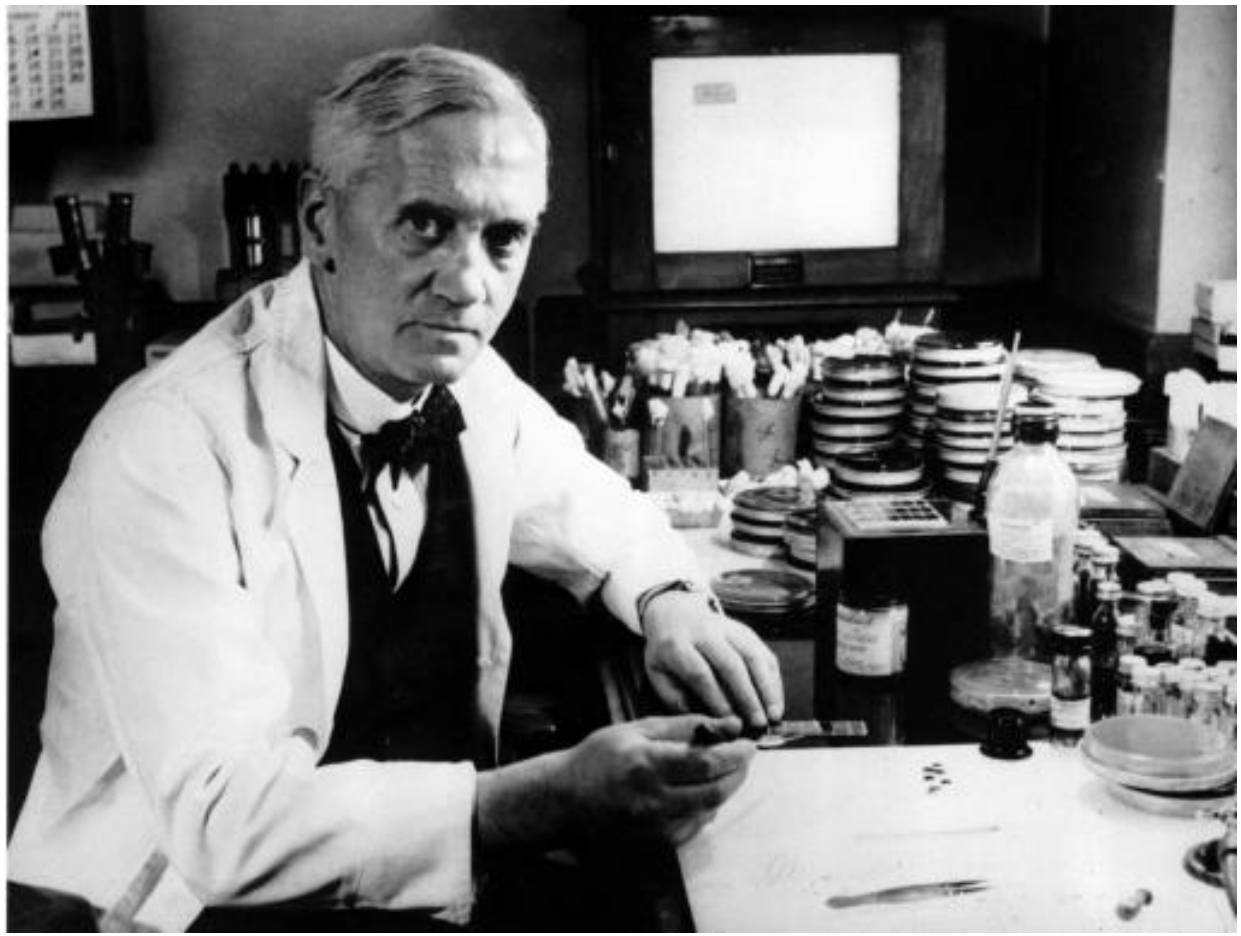
# Health Officials Try to Calm Parents About Staph

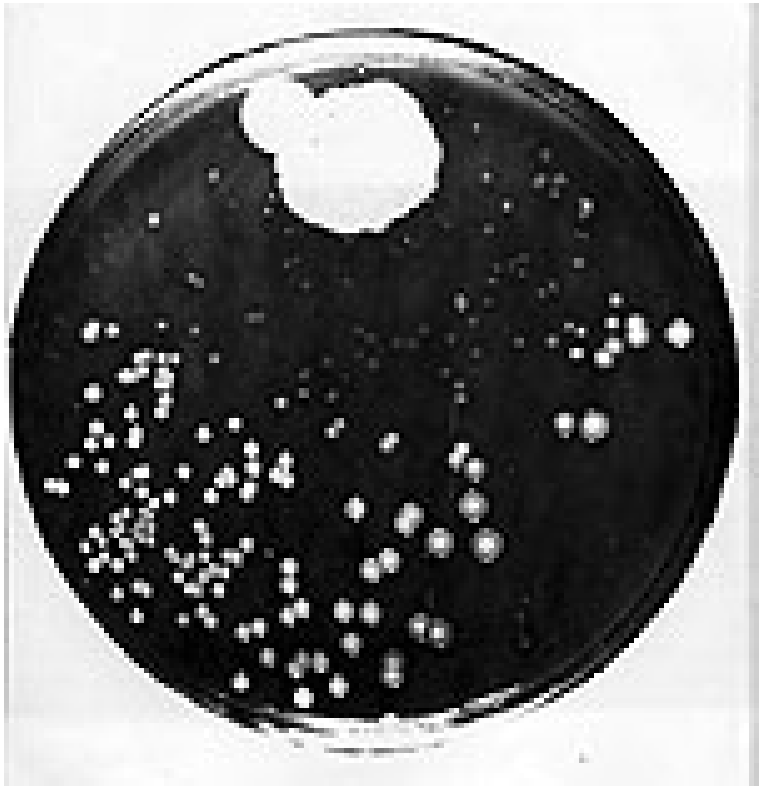
Wednesday, October 27, 2007


**Amirah Brown, 12, a seventh grader at Intermediate School 211 in Canarsie, going home early Friday so she could get a medical checkup.**


TIME
REVENGE OF THE
Killer Microbes
Are we losing the
war against
infectious diseases?

Satan Smiting Job with Sore Boils  circa 1826

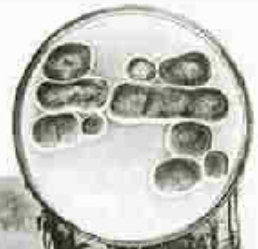




**“…. the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out… In such cases the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope this evil can be averted.”**

**- Sir Alexander Fleming, June 1945**

# Thanks to PENICILLIN
## ...He Will Come Home!



### FROM ORDINARY MOLD—
*the Greatest Healing Agent of this War!*

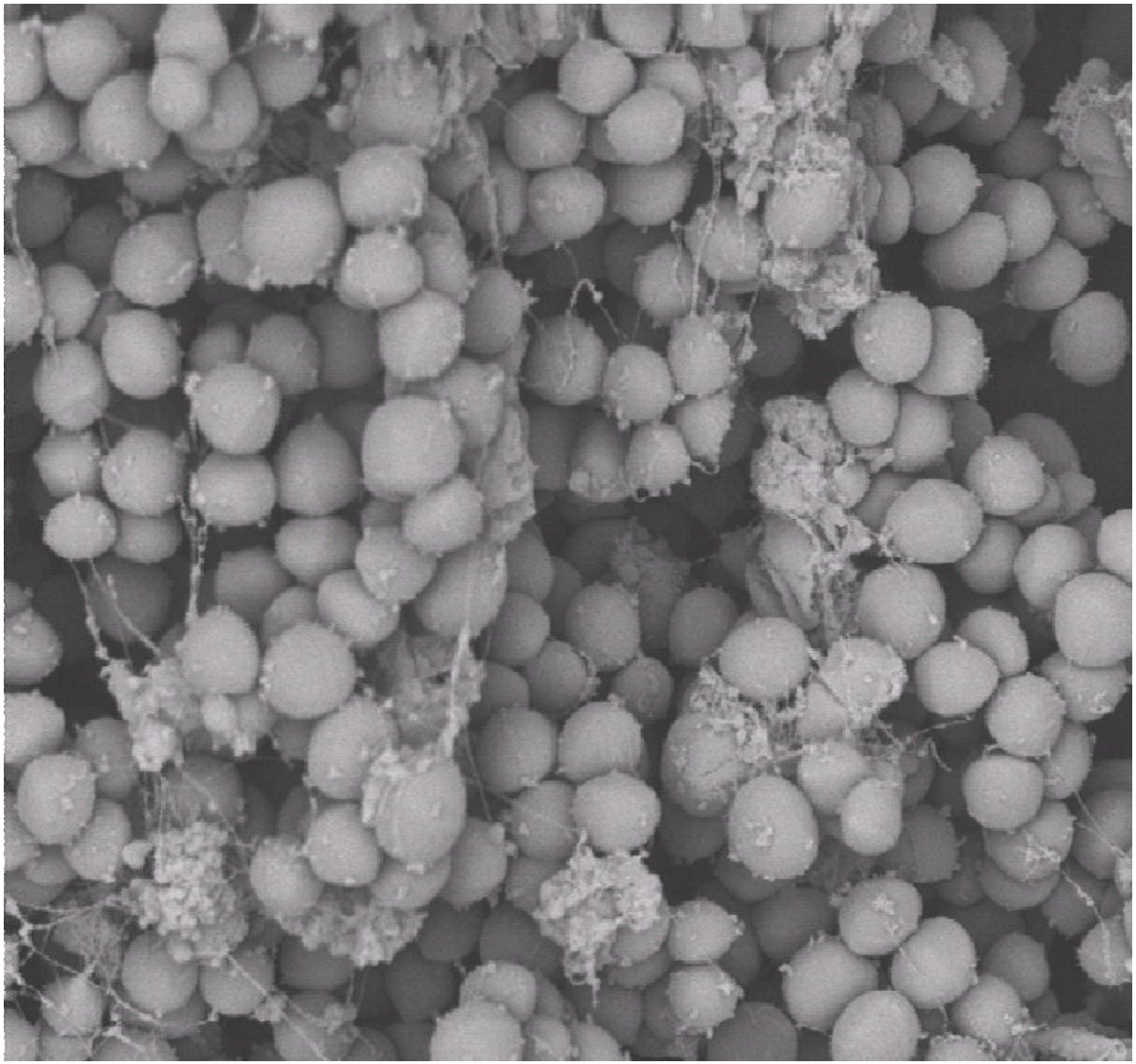
When the thunderous battles of this war have subsided to peace-time echoes from history books, the greatest achievement of World War II may well be the discovery and development — out of many valuable wonder weapons that destroy — but of a weapon that saves lives. That weapon, of course, is penicillin.

Every day, penicillin is performing some unbelievable acts of healing on scores of battlefronts. Thousands of men will return home who otherwise would not have had a chance. Sooner still, more and more of this precious drug is to be available for civilian use... to save the lives of patients of every age.

A few years ago, production of penicillin was difficult, costly. Today, due to specially developed methods of mass-production, as one by Schenley Laboratories, Inc., and the 20 other firms designated by the government to make penicillin, it is available in ever increasing quantity, at progressively lower cost.

Listen to "THE DOCTOR TALKS" starring RAYMOND MASSEY, U.S.A. Saturday evenings, C.W.S. See your paper for time and station.

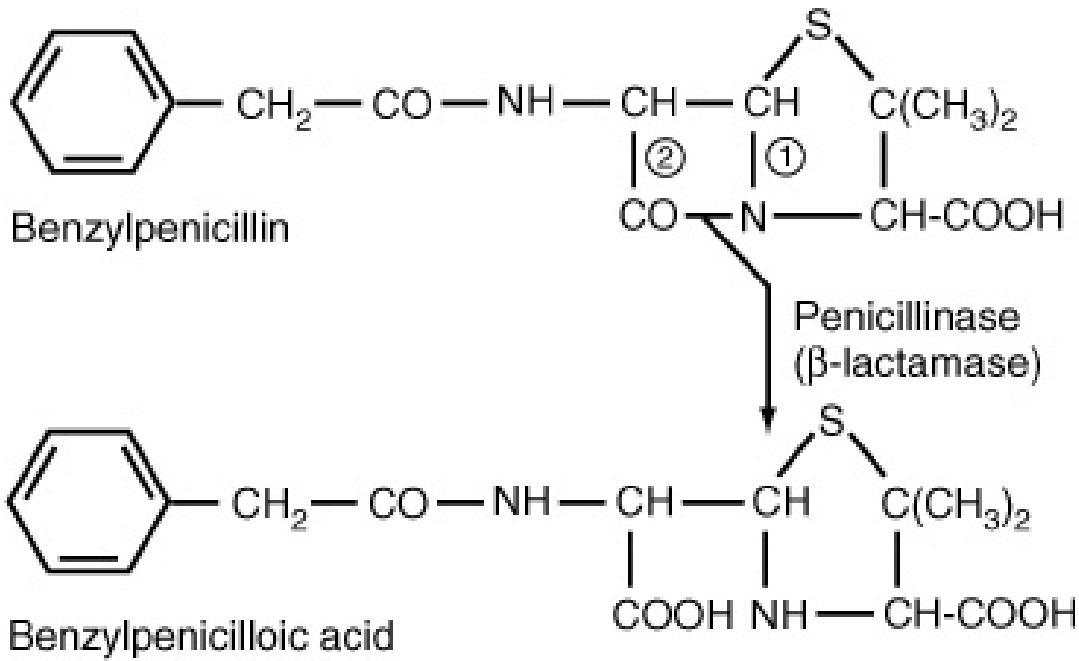
Producers of PENICILLIN



# Toxins Produced by *S. aureus*

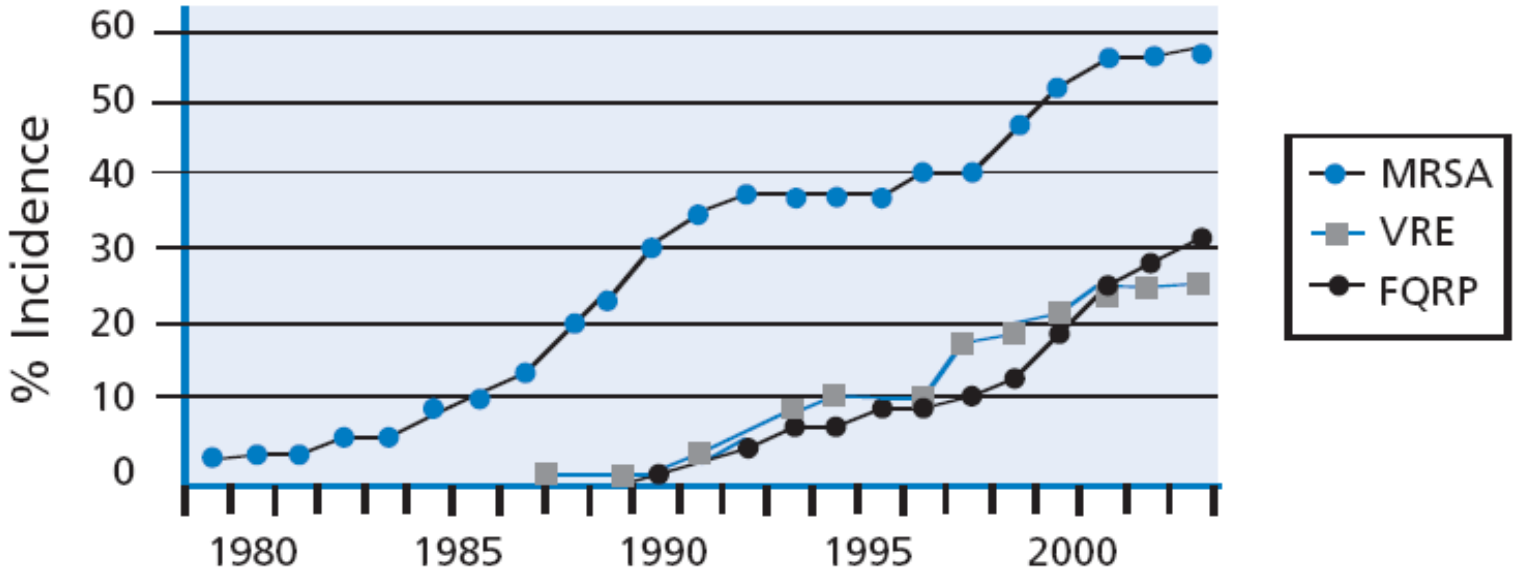
- Catalase: Converts hydrogen peroxide into water & oxygen
- Coagulase: Enzyme-like protein that causes clotting. May deposit fibrin on the surface of staphylococci, possibly altering their ingestion by phagocytic cells or their destruction within such cells.
- Hyaluronidase, staphylokinase, proteinases, lipases, ß-lactamases
- Exotoxins: $\alpha$-toxin (hemolysin), $\beta$-toxin, $\gamma$-toxin, $\delta$-toxin
- Leukocidin
- Exfoliative toxin
- Toxic shock syndrome toxin
- Enterotoxins

Courtesy of Doug Black Pharm D

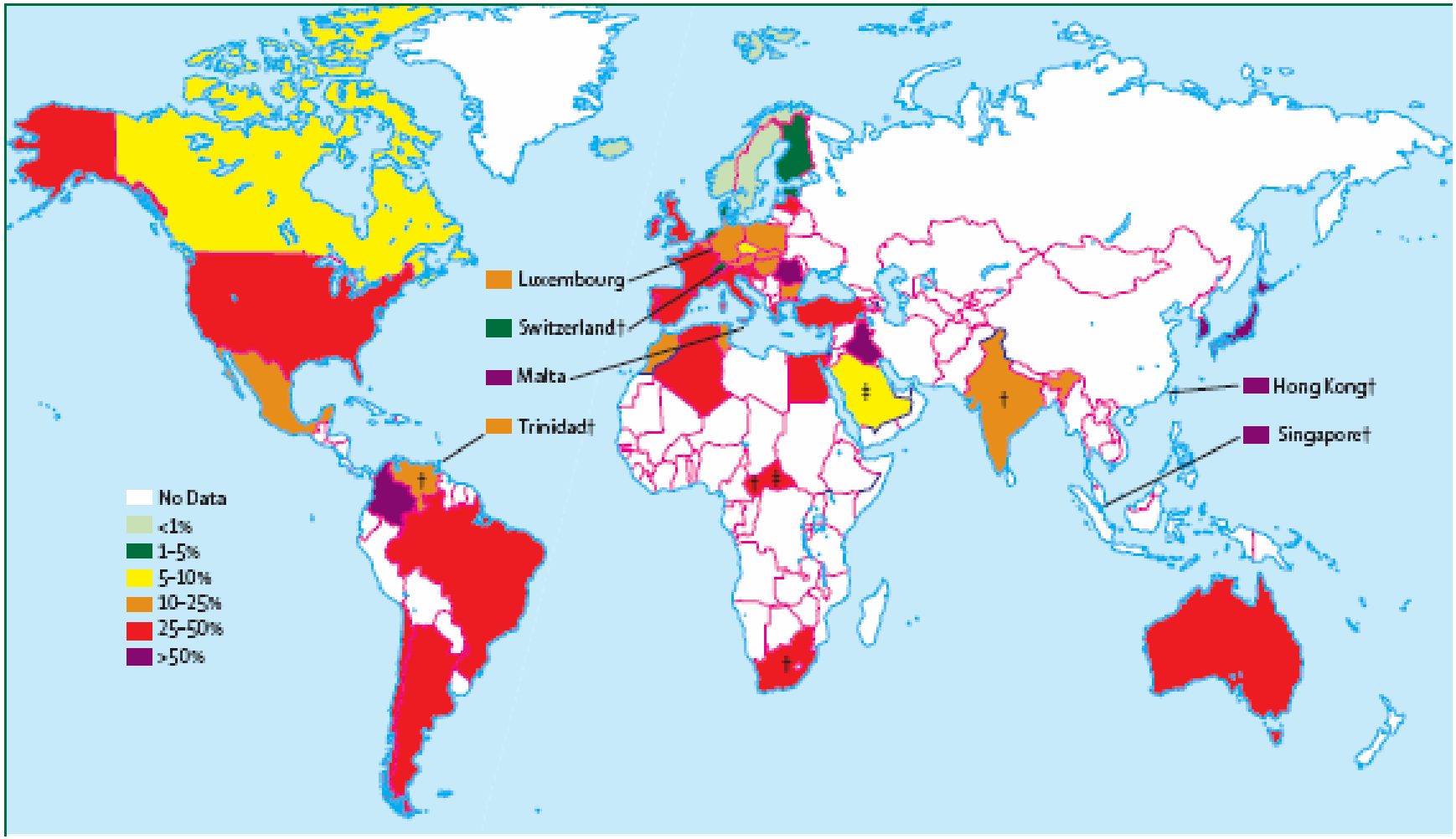



1 Thiazolidine ring
2 β-lactam ring

## Chart 1: Resistant Strains Spread Rapidly




**Source:** Centers for Disease Control and Prevention




Grundmann, H. Lancet 2006. 368:87485

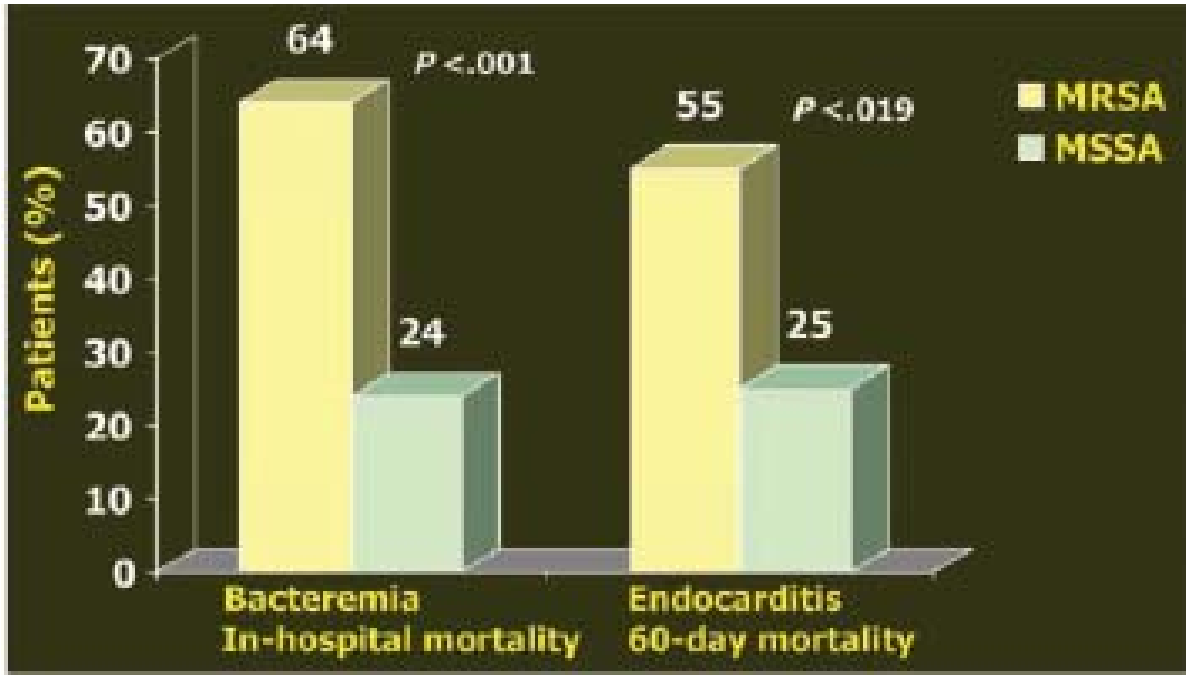
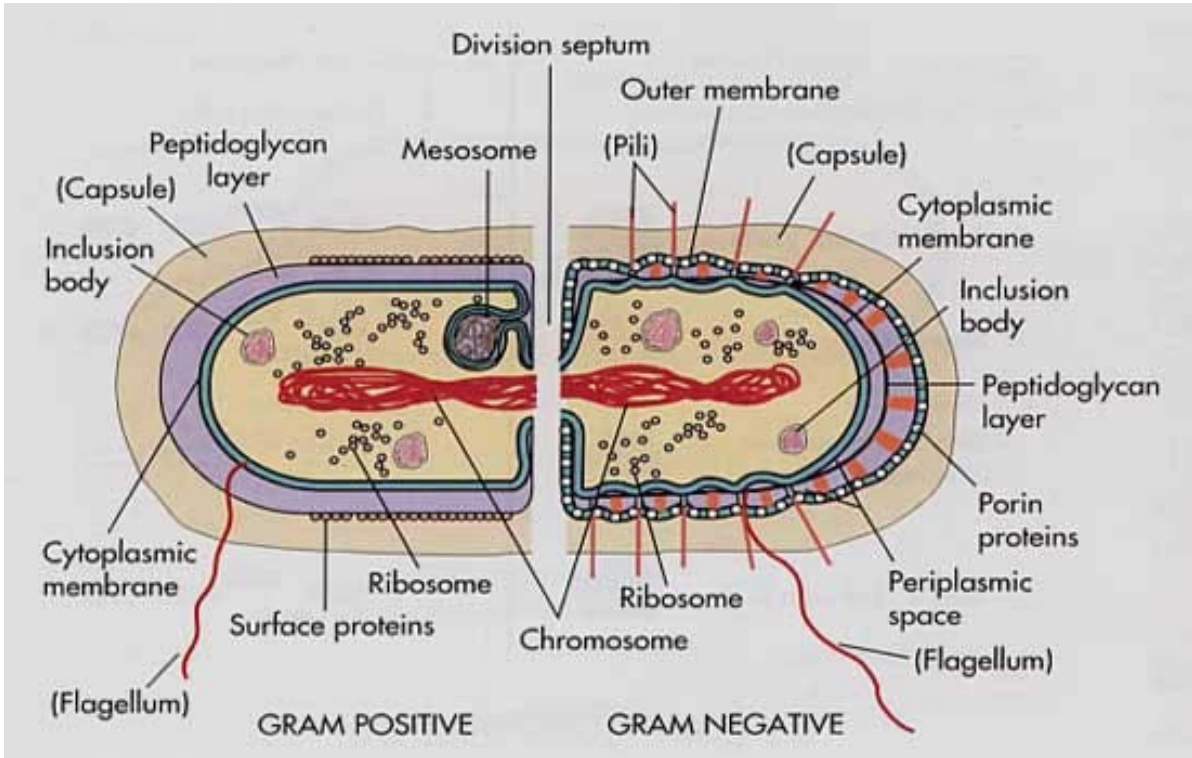
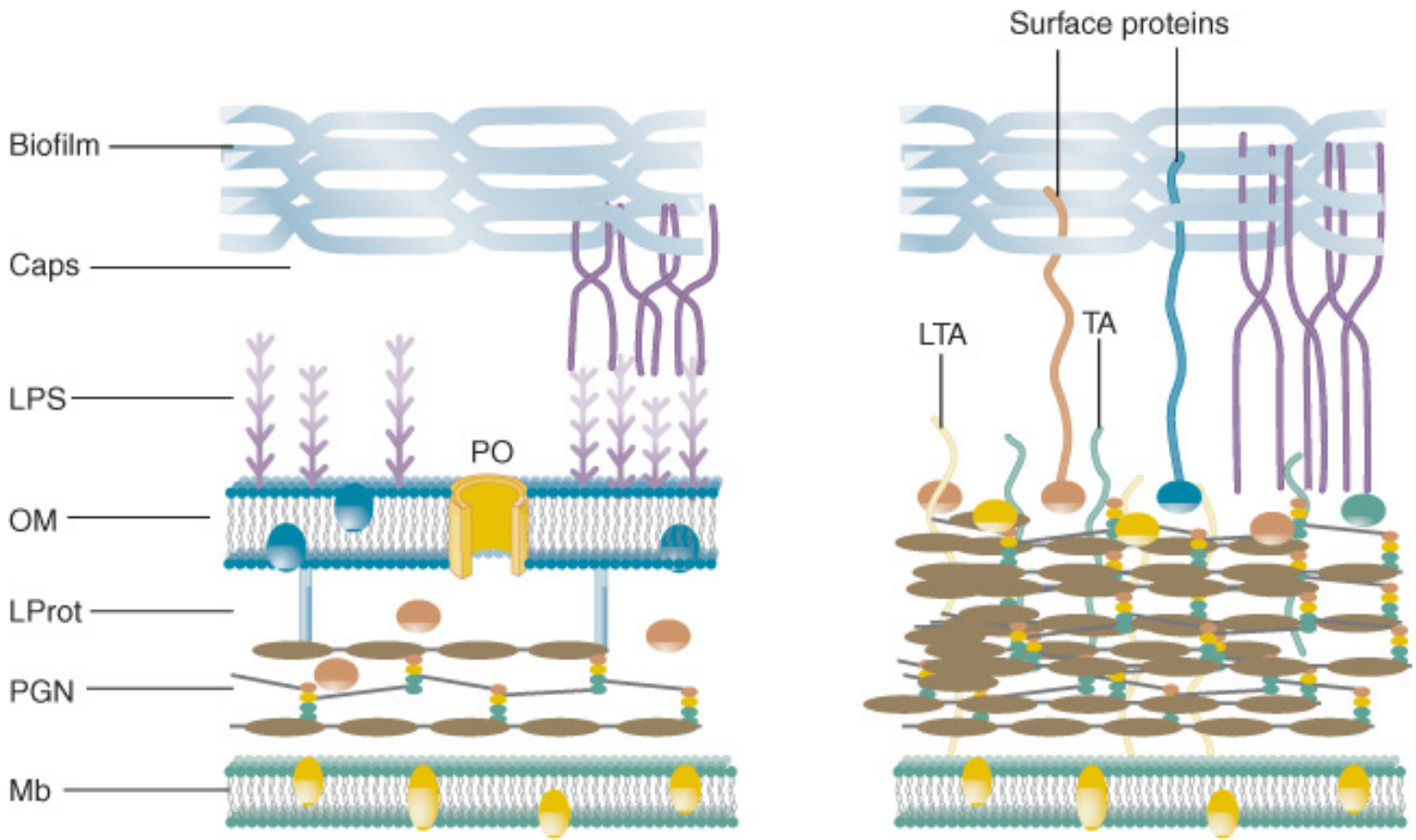
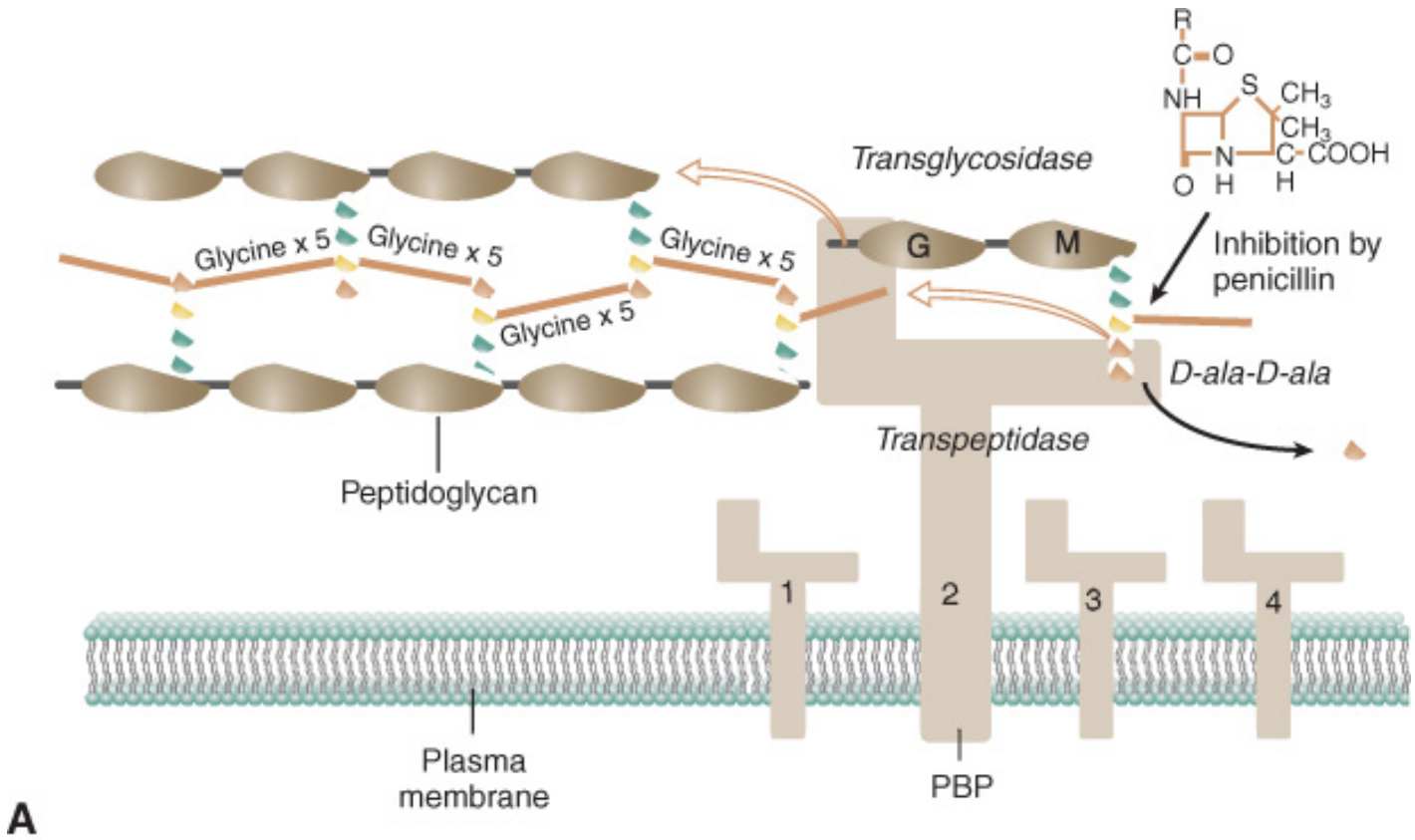


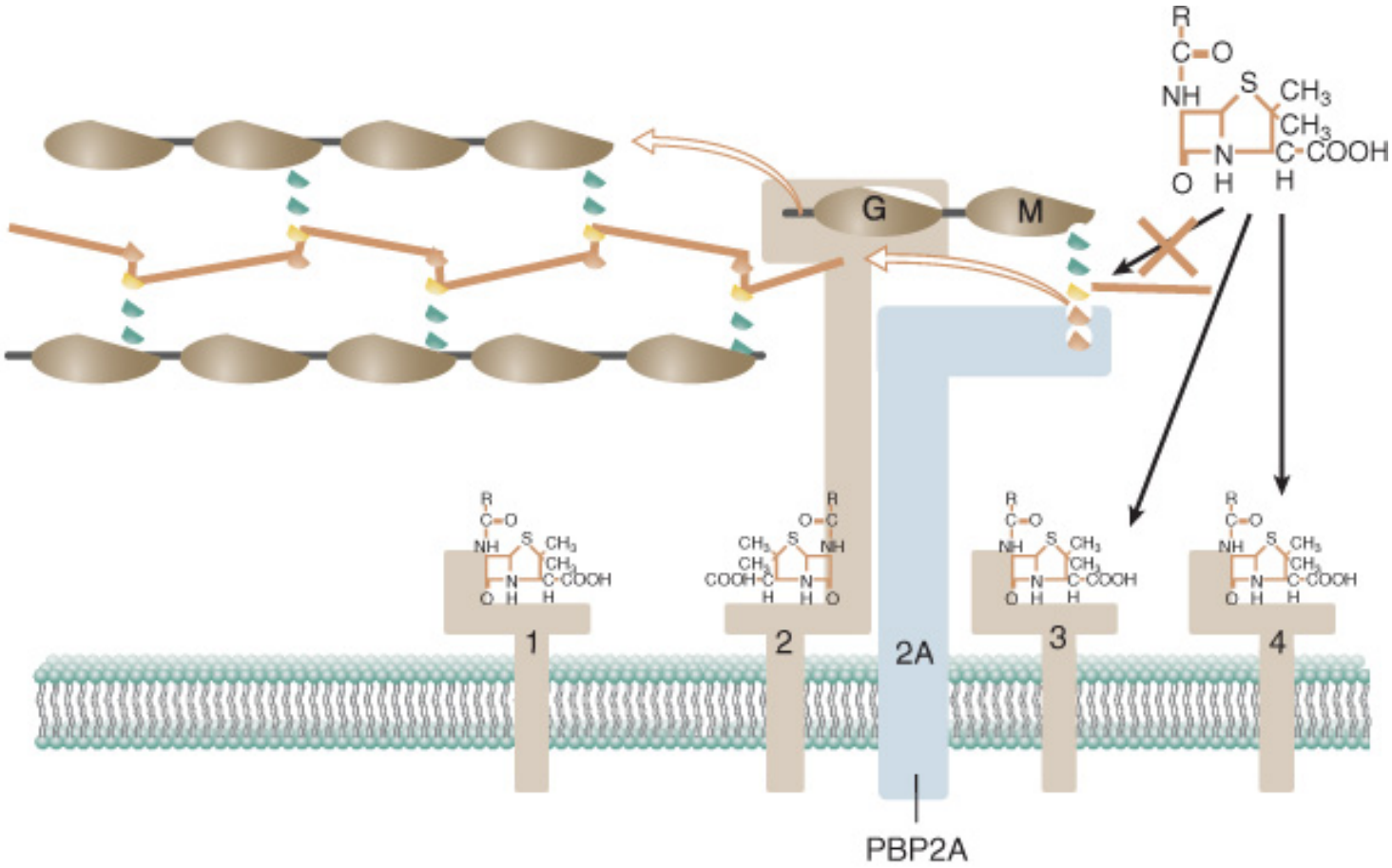

**Figure 2.** Clinical impact of methicillin-resistant *Staphylococcus aureus* (MRSA). *A,* Effect of MRSA on mortality. *B,* Effect of MRSA on length of hospital stay. MSSA, methicillin-susceptible *S. aureus;* NS, nonsignificant. Adapted from Appelbaum [23], with permission from Blackwell Publishing *(A),* and Shorr et al. [19] *(B).*


Division septum
Outer membrane
Peptidoglycan layer
Mesosome
(Pili)
(Capsule)
(Capsule)
Cytoplasmic membrane
Inclusion body
Inclusion body
Peptidoglycan layer
Porin proteins
Cytoplasmic membrane
Ribosome
Surface proteins
Ribosome
Chromosome
Periplasmic space
(Flagellum)
(Flagellum)
GRAM POSITIVE
GRAM NEGATIVE

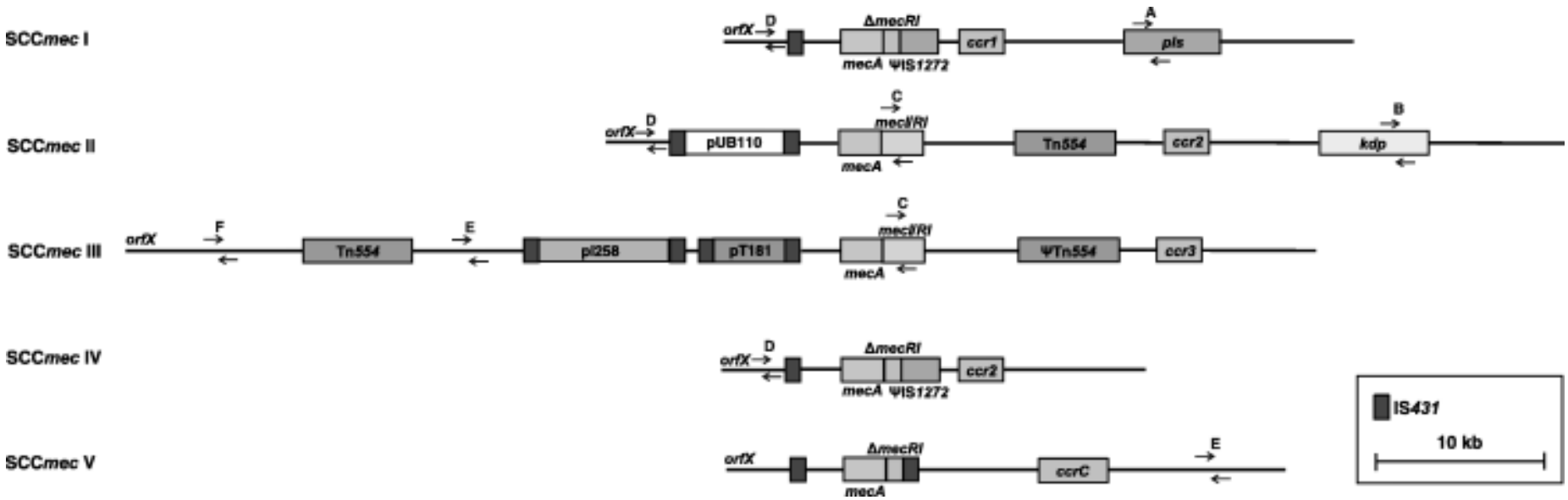



**Gram Negative** **Gram Positive**






B




Schematic arrangement of SCC*mec* types I–V [7–9,131]. The major elements of the five SCC*mec* types (*ccr* genes, IS*431*, IS*1272*, *mecA*, *mecI*/*RI*, *orfX*, pI258, pT181, pUB101 and Tn*554*) are shown, as are the six loci (A–F) used for SCC*mec* typing according to the method of Oliviera *et al*.

*Clinical Microbiology and Infection* **13** (3), 222-235

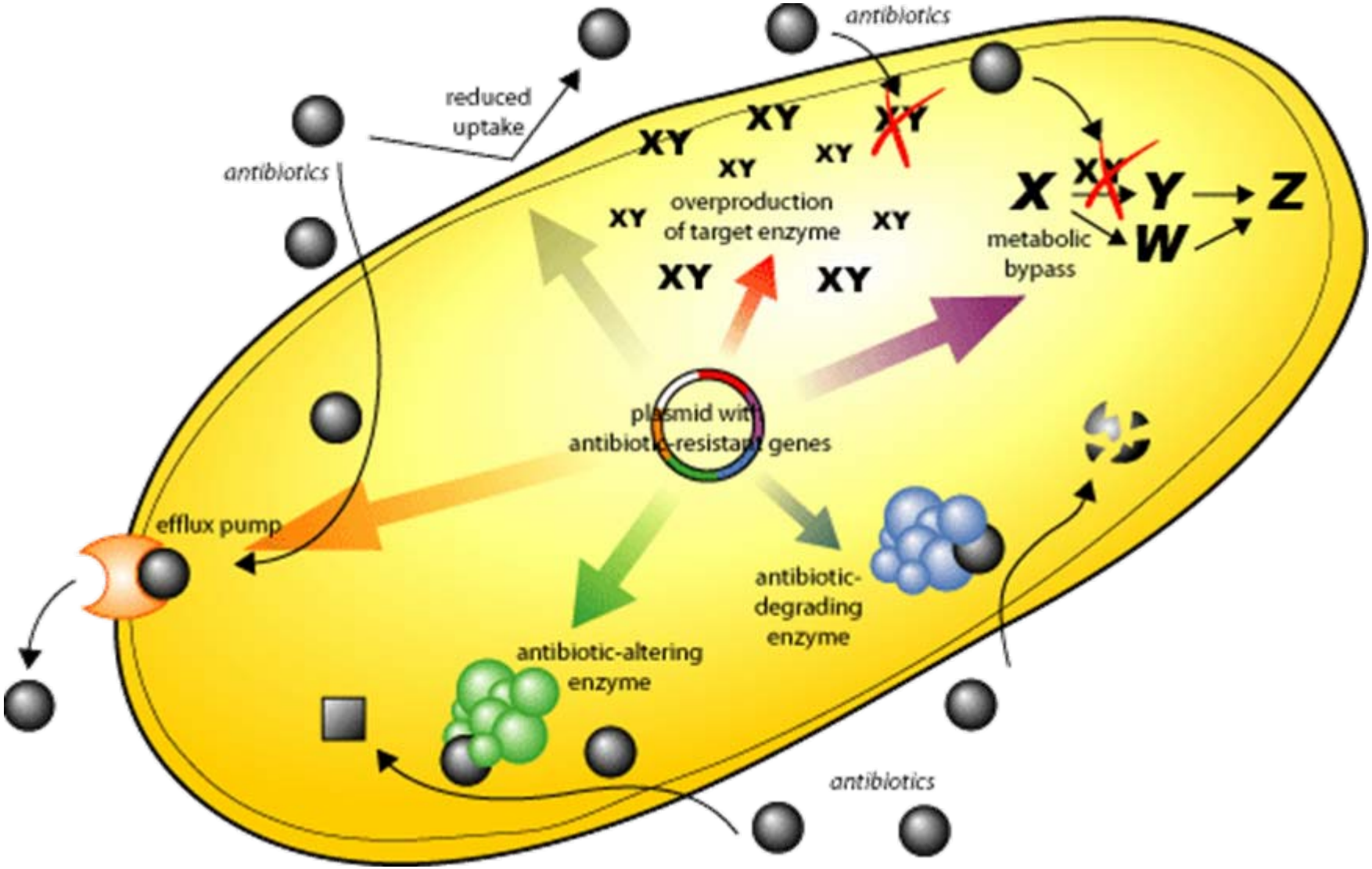
# Mechanisms of Resistance in *S. aureus*

- Genetic variation in *S. aureus* is very extensive
- Lateral gene transfer has played a fundamental role in the evolution of *S. aureus.*
- The *mec* gene has been horizontally transferred into distinct *S. aureus* chromosomal backgrounds at least five times, demonstrating that methicillin-resistant strains have evolved multiple independent times, rather than from a single ancestral strain.

M. Kuroda. Lancet, V. 357, Issue 9264, Pages 1225-1240

# Mechanisms of Antimicrobial Resistance

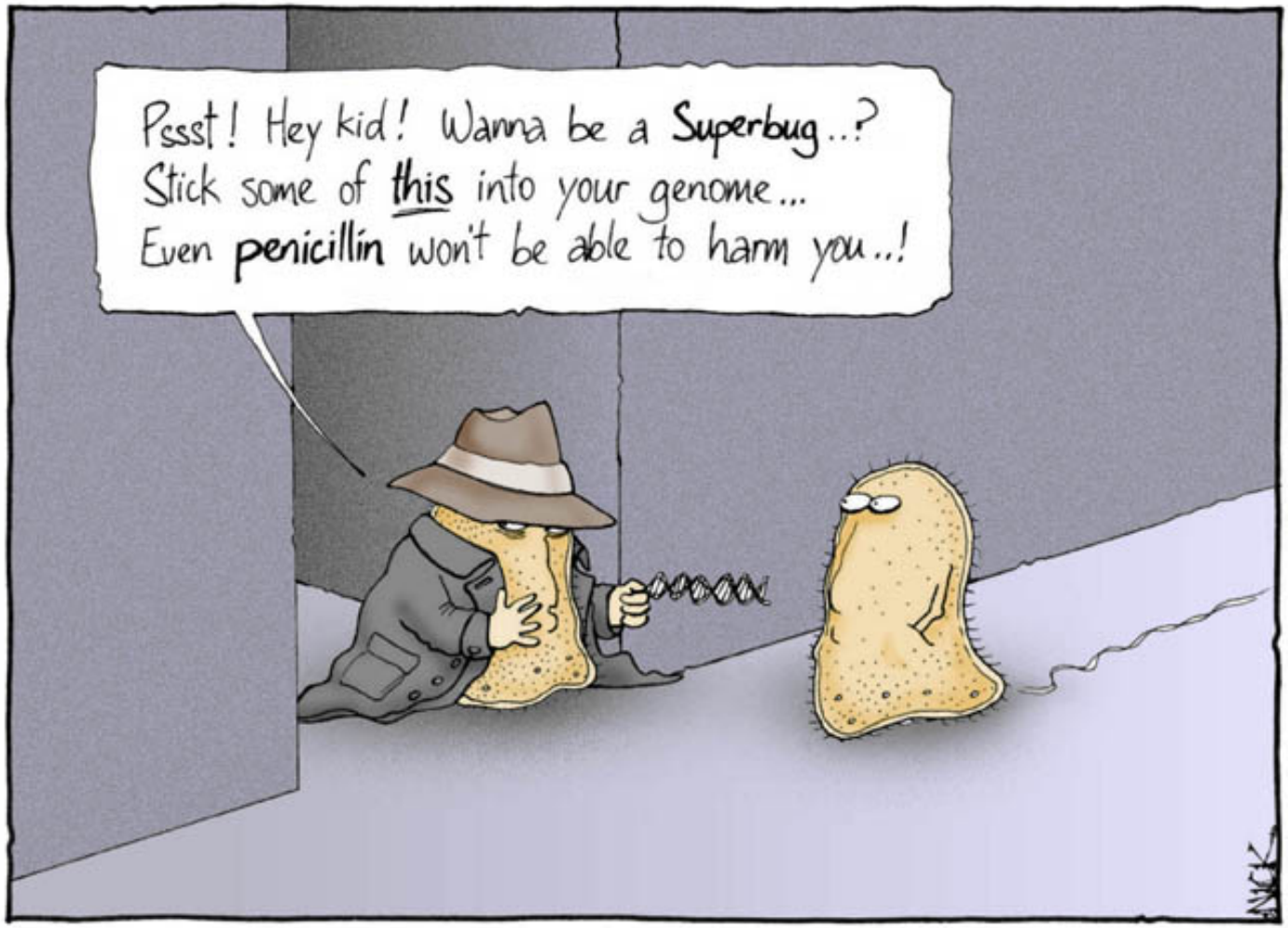
- Infectious organisms adapt quickly to new environmental conditions.
- Bacteria, compared with higher life forms, have small numbers of genes.
- Even a single random genetic mutation can greatly affect the ability to cause disease.
- Because most microbes reproduce by dividing every few hours, bacteria can evolve rapidly.
- A mutation that helps a microbe survive exposure to an antibiotic will quickly become dominant throughout the microbial population.
- Microbes also often acquire genes from each other, including genes that confer resistance.



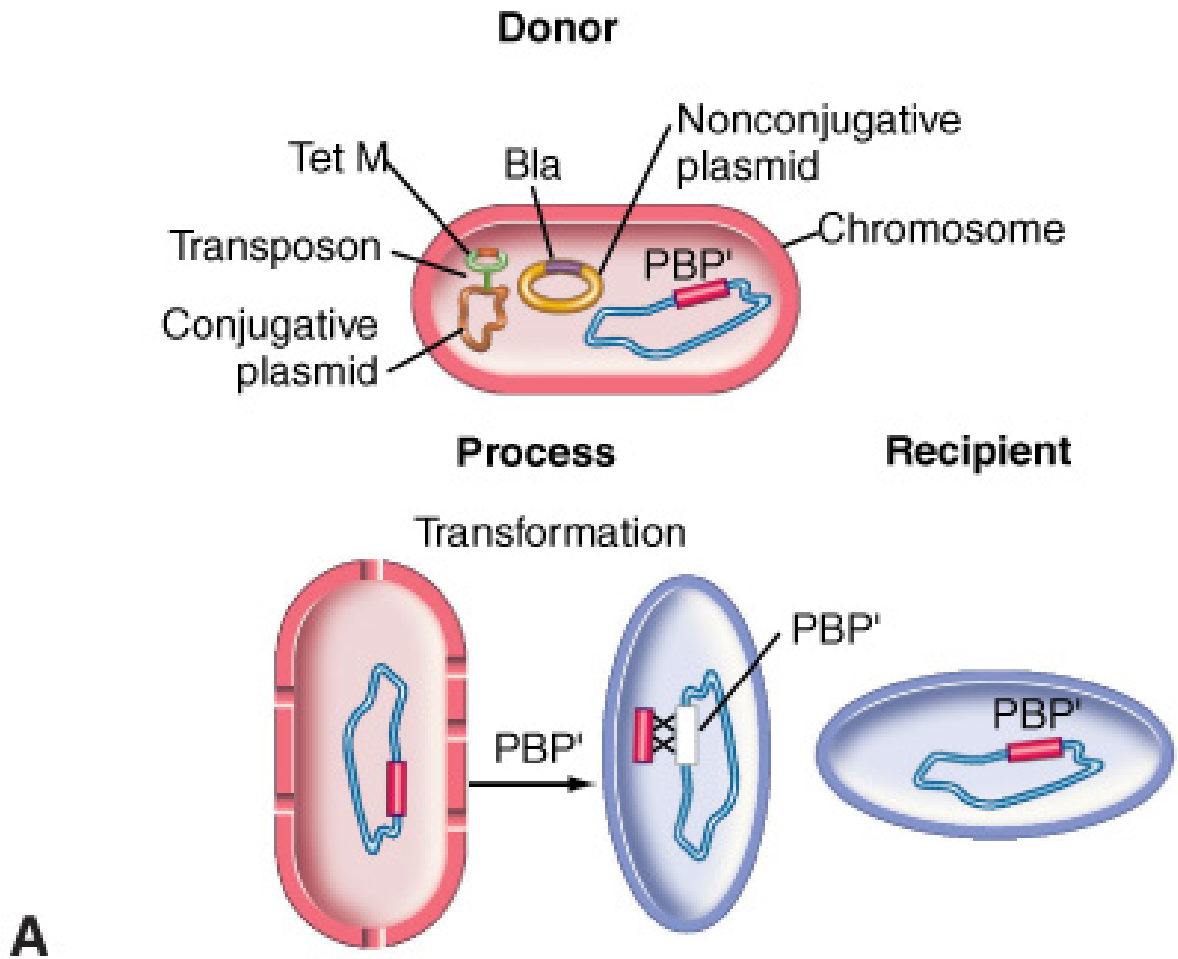

Sara Wilcox www.scq.ubc.ca/cationic-peptides-a-new-hope/

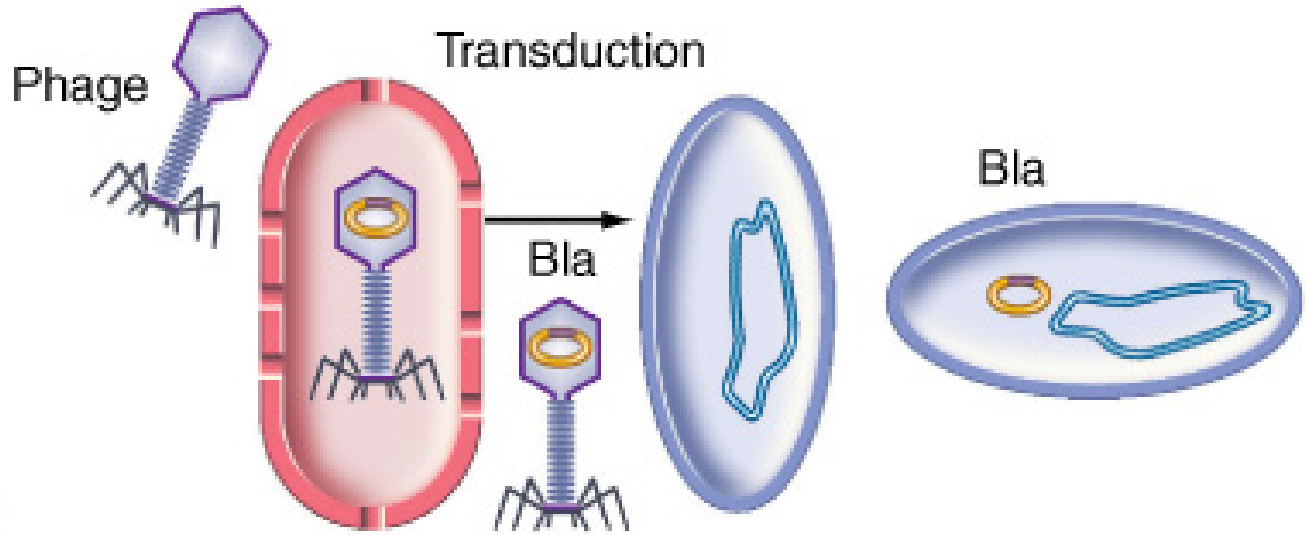
# Mechanisms of Antimicrobial Resistance

- Enzymatic inhibition
  - Modification or destruction of the antibiotic
- Decreased permeability of bacterial membranes
  - Reduced uptake of antibiotic
- Increased efflux of antibiotic
  - ATP binding proteins, membrane located efflux proteins and diffusion are 3 mechanism for increasing the efflux of antibiotic from the bacterial cell.
- Altered target sites
  - Alteration in penicillin binding protein; Production of a new cytoplasmic membrane protein; Altered target enzymes; Altered ribosomal RNA binding site
- Overproduction of the drug target
- Auxotrophs
  - Altered growth factor requirements




It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.



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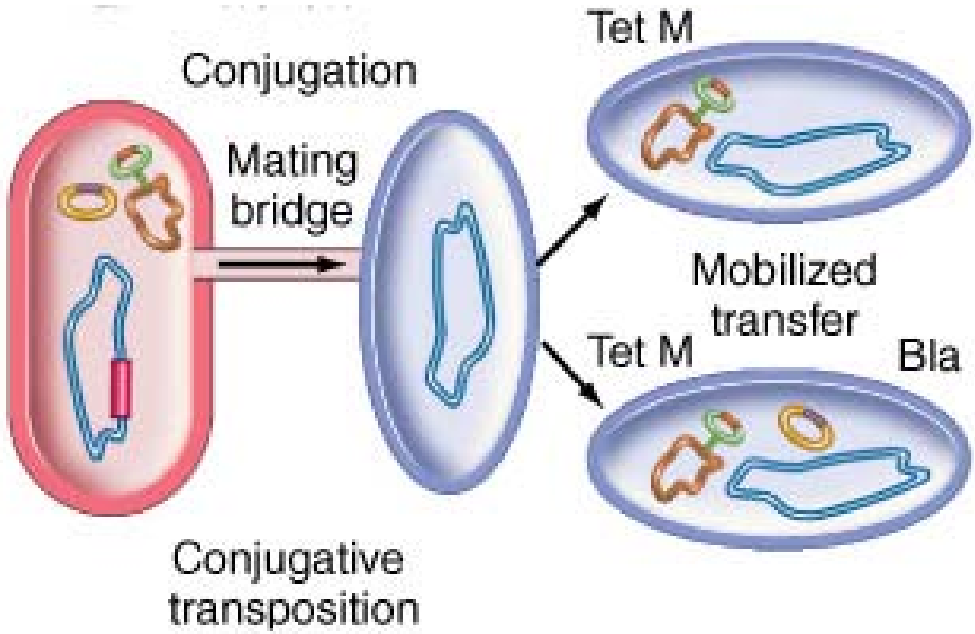


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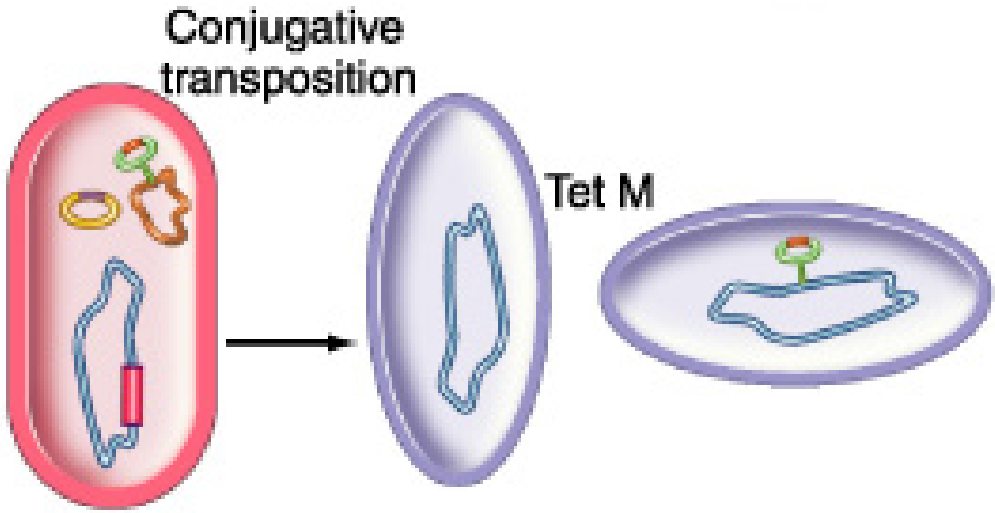


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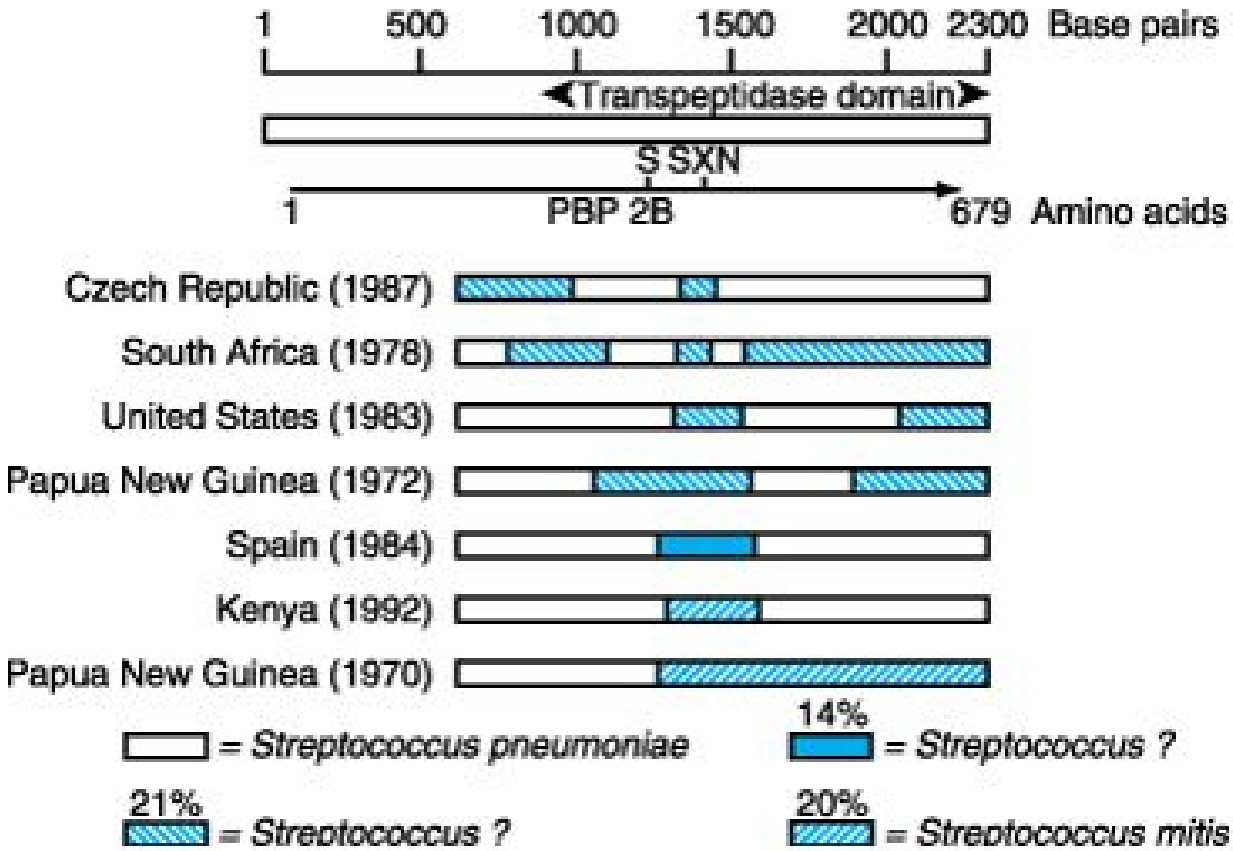


Source: Brunton LL, Lazo JS, Parker KL: *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 11th Edition: http://www.accessmedicine.com


BUY BONDS
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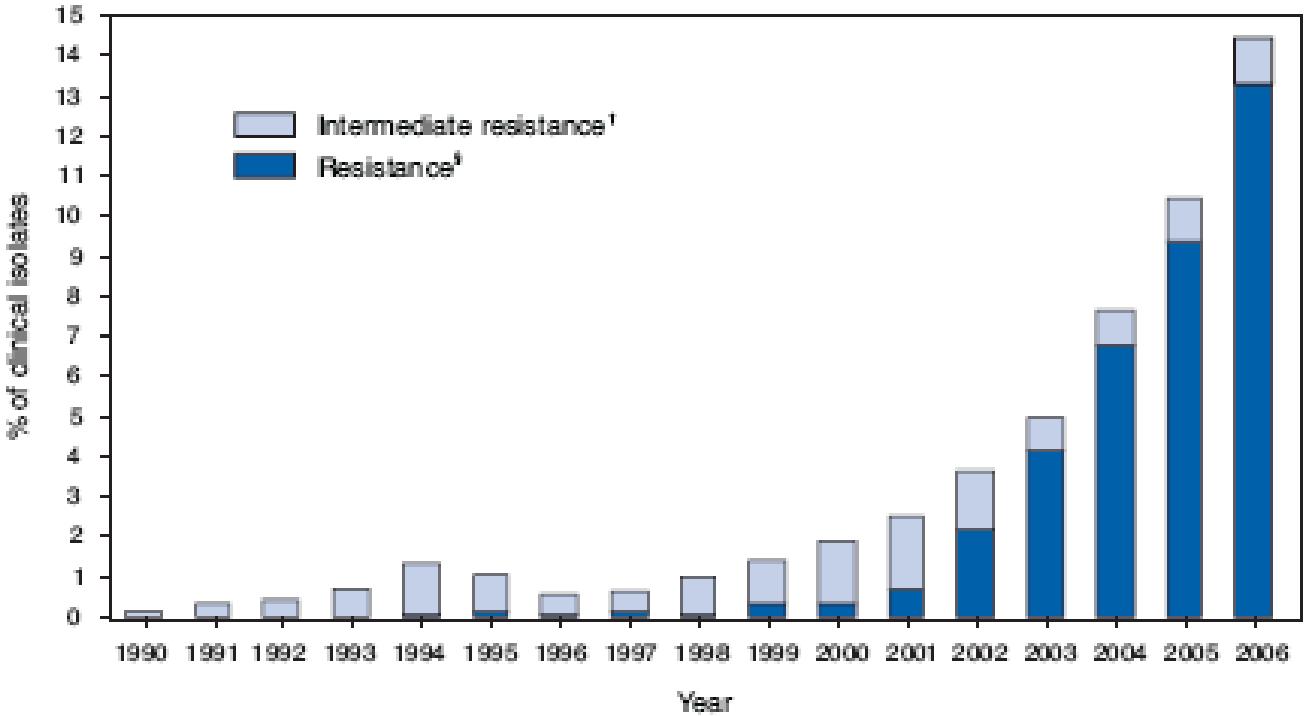
CURES
GONORRHEA
THE GREAT CRIPPLER—STERILIZER
IN 4 HOURS
SEE YOUR DOCTOR TODAY
HE NOW HAS PENICILLIN
FOR YOUR TREATMENT

**FIGURE. Percentage of *Neisseria gonorrhoeae* isolates with intermediate resistance or resistance to ciprofloxacin, by year — Gonococcal Isolate Surveillance Project, United States, 1990–2006***




* Data for 2006 are preliminary (January–June only).
† Demonstrating ciprofloxacin minimum inhibitory concentrations (MICs) of 0.125–0.500 μg/mL.
§ Demonstrating ciprofloxacin MICs of ≥1.0 μg/mL.

**TABLE 2.** SELECTED CURRENT PROBLEMS WITH ANTIMICROBIAL DRUGS, ACCORDING TO ORGANISM.

| ORGANISM | PROBLEM |
|---|---|
| Gram-positive cocci | Methicillin-resistant *Staph. aureus* and coagulase-negative staphylococci; penicillin-resistant pneumococci; macrolide-resistant streptococci; vancomycin-resistant enterococci |
| Gram-negative cocci | Penicillin-resistant meningococci; quinolone-resistant gonococci |
| Gram-negative bacilli | Enterobacter and other Enterobacteriaceae with chromosomal β-lactamases; multidrug-resistant *P. aeruginosa, Stenotrophomonas maltophilia;* acinetobacter species with novel β-lactamases, aminoglycoside-modifying enzymes, and other resistance mechanisms; Enterobacteriaceae with extended-spectrum β-lactamases; multidrug-resistant diarrheal pathogens (shigella species, salmonella species, *Escherichia coli,* campylobacter species) |
| Acid-fast bacilli | Multidrug-resistant *Mycobacterium tuberculosis;* multidrug-resistant *M. avium* complex |

Gold. N Engl J Med 335:1445, November 7, 1996

**TABLE 1.** SELECTED CURRENT PROBLEMS WITH ANTIMICROBIAL-DRUG RESISTANCE, ACCORDING TO DRUG CLASS.

| ANTIBIOTIC CLASS | MECHANISM OF RESISTANCE |
|---|---|
| Cephalosporins | Extended-spectrum β-lactamases, chromosomal cephalosporinases |
| β-Lactamase inhibitors | Hyperproducers of β-lactamases, new β-lactamases resistant to inhibitors, chromosomal cephalosporinases |
| Carbapenems | Zinc metalloenzymes and other β-lactamases |
| Vancomycin, teicoplanin | Modified cell-wall precursors with decreased affinity for vancomycin |
| Quinolones | Alterations in DNA topoisomerase, efflux mechanisms, permeability changes |
| Trimethoprim–sulfamethoxazole | Resistant enzymes in folate-synthesis pathway |
| Erythromycin, new macrolides | Methylation of the bacterial ribosome producing resistance to macrolides, clindamycin, and streptogramin B antibiotics |
| Aminoglycosides | Aminoglycoside-modifying enzymes |

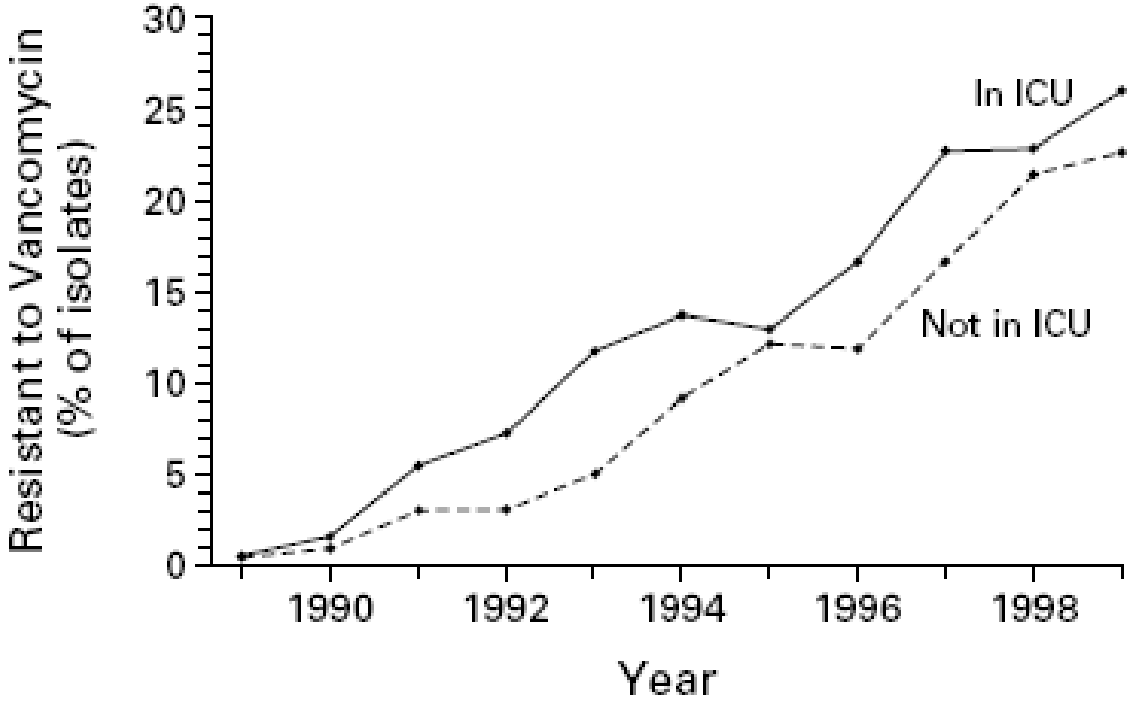
Gold. N Engl J Med 335:1445, November 7, 1996

# Facts About Antibiotic Resistance

- The total cost of antimicrobial resistance to U.S. society is nearly $5 billion annually, according to the Institute of Medicine. Treating resistant pathogens often requires more expensive drugs and extended hospital stays.

# Facts About Antibiotic Resistance

- Vancomycin-resistant enterococci (VRE) can cause wound infections, infections in blood, the urinary tract and heart, and life-threatening infections for hospital patients.
- In 2002, 27.5 percent (an estimated 26,000 cases) of tested enterococci samples from ICUs were resistant to vancomycin, according to CDC.




Resistance of Nosocomial Isolates of Enterococci to Vancomycin (NNIS), 1989 through June 1999.

Murray BE.N Engl J Med 342:710, March 9, 2000

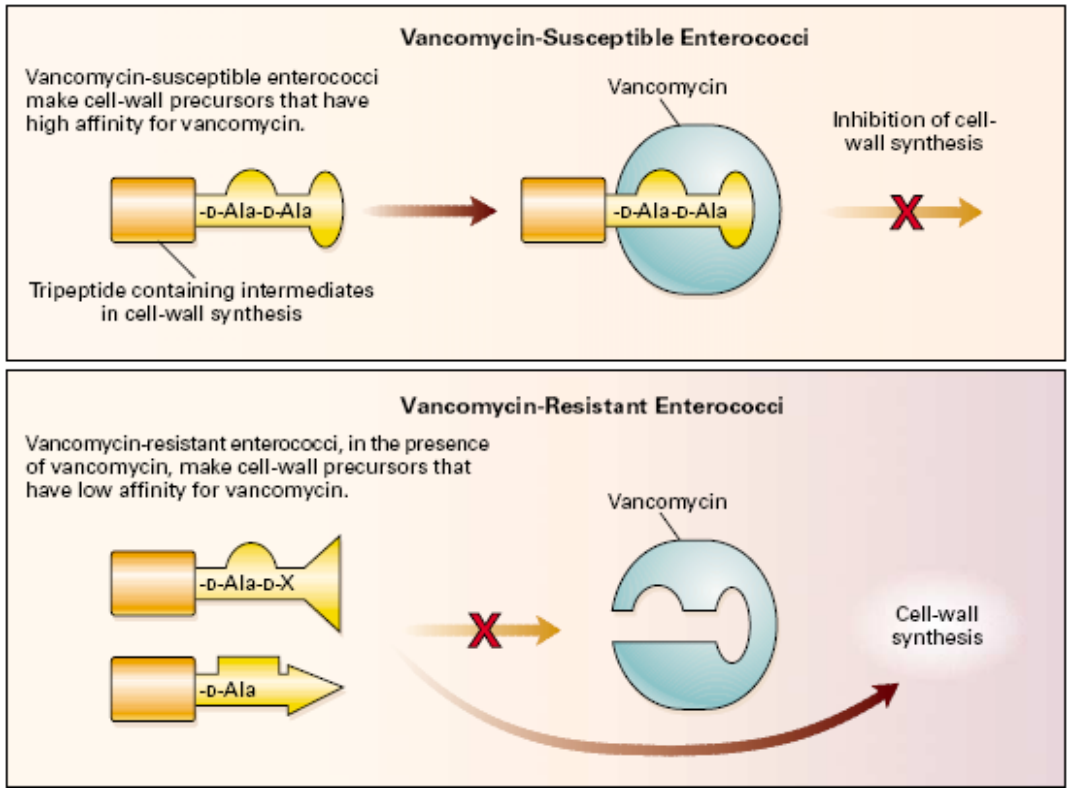



**Figure 1.** Schematic Diagram of the Mechanism of Resistance to Vancomycin.

Murray BE.N Engl J Med 342:710, March 9, 2000

# Facts About Antibiotic Resistance

- *P. aeruginosa* causes infections of the urinary tract, lungs, and wounds and other infections commonly found in intensive care units.
- The percentage of *Pseudomonas aeruginosa* resistant to either ciprofloxacin or ofloxacin, two common antibiotics of the fluoroquinolone class , has increased dramatically.
- Recent CDC data show that in 2002, nearly 33% of tested samples from ICUs were resistant to fluoroquinolones.

## Table 3: Percent of Drug Resistance in Hospital-Acquired Infections in 2002

| Drug/Pathogen | Resistance (%) |
|---|---|
| Methicillin/*S. aureus* | 57.1 |
| Vancomycin/enterococci | 27.5 |
| Quinolone/*P. aeruginosa* | 32.8 |
| Methicillin/CNS | 89.1 |
| 3rd-gen. Ceph./*E. coli* | 6.3 |
| 3rd-gen. Ceph./*K. pneumoniae* | 14.0 |
| Imipenem/*P. aeruginosa* | 22.3 |
| 3rd-gen. Ceph./*P. aeruginosa* | 30.2 |
| 3rd-gen. Ceph./*Enterobacter spp.* | 32.2 |
| Penicillin/*S. pneumoniae* | 11.3 |

## Table 1: Estimated Cases of Hospital-Acquired Infections Caused by Selected Resistant Bacteria in the United States in 2002

| Antibiotic-Resistant Bacteria | Estimated Cases |
|---|---|
| Methicillin/*S. aureus* | 102,000 |
| Methicillin/CNS | 130,000 |
| Vancomycin/enterococci | 26,000 |
| Ceftazidime/*P. aeruginosa* | 12,000 |
| Ampicillin/*E. coli* | 65,000 |
| Imipenem/*P. aeruginosa* | 16,000 |
| Ceftazidime/*K. pneumoniae* | 11,000 |

**Source:** Centers for Disease Control and Prevention, Division of Healthcare Quality Promotion

# Factors Contributing to Resistance

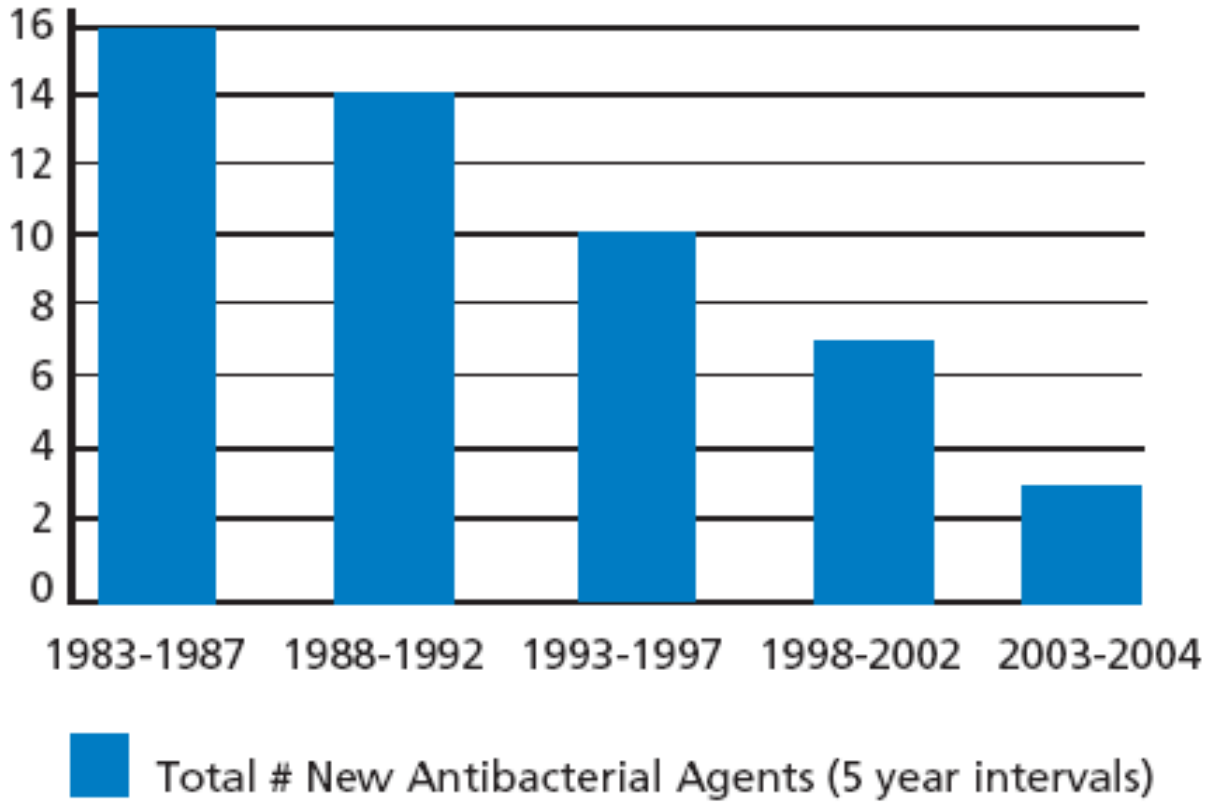
- Evolution / Selective pressure
- Misuse of antimicrobials
  - Patient expectations
  - Self-medication, poor compliance with therapy
  - Inappropriate prescriptions
- Hospital environment
  - Highly susceptible patients
  - Intensive and prolonged antimicrobial use
  - Cross-infection
- Agricultural/veterinary use of antimicrobials
  - In North America and Europe, an estimated 50% in tonnage of all antimicrobial production is used in food-producing animals and poultry as supplements for prophylaxis or growth promotion

## Table 2: History of Antibiotic Discovery and Approval

| Year Introduced | Class of Drug |
|---|---|
| 1935 | Sulfonamides |
| 1941 | Penicillins |
| 1945 | Cephalosporins |
| 1944 | Aminoglycosides |
| 1949 | Chloramphenicol |
| 1950 | Tetracyclines |
| 1952 | Macrolides/ Lincosamides/ Streptogramins |
| 1956 | Glycopeptides |
| 1957 | Rifamycins |
| 1959 | Nitroimidiazoles |
| 1962 | Quinolones |
| 1968 | Trimethoprim |
| 2000 | Oxazolidinones |
| 2003 | Lipopeptides |

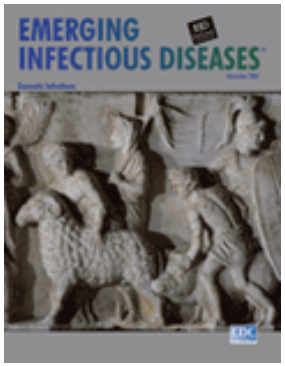
**Source:** Food and Drug Administration (modified)

# Chart 2: Antibacterial Agents Approved, 1983-2004




**Source:** Spellberg et al., *Clinical Infectious Diseases*, May 1, 2004 (modified)


What's going on?
Tell us about these new liners that are kinder to our teats and improve milk quality.




**Volume 13, Number 12–December 2007**

# *Research:* Emergence of Methicillin-Resistant *Staphylococcus aureus* of Animal Origin in Humans.

**Inge van Loo et al.**

*Abstract*

In 2003 in the Netherlands, a new methicillin-resistant *Staphylococcus aureus (*MRSA) strain emerged that could not be typed with *Sma*1 pulsed-field gel electrophoresis (NT-MRSA)…The frequency of NT-MRSA increased from 0% in 2002 to >21% after intensified surveillance was implemented in July 2006. A case–control study showed that carriers of NT-MRSA were more often pig or cattle farmers (pig farmers odds ratio [OR] 12.2, 95% confidence interval [CI] 3.1–48.6; cattle farmers OR 19.7, 95% CI 2.3–169.5). Molecular typing showed that the NT-MRSA strains belonged to a new clonal complex, ST 398. ***This study shows that MRSA from an animal reservoir has recently entered the human population and is now responsible for >20% of all MRSA in the Netherlands.***

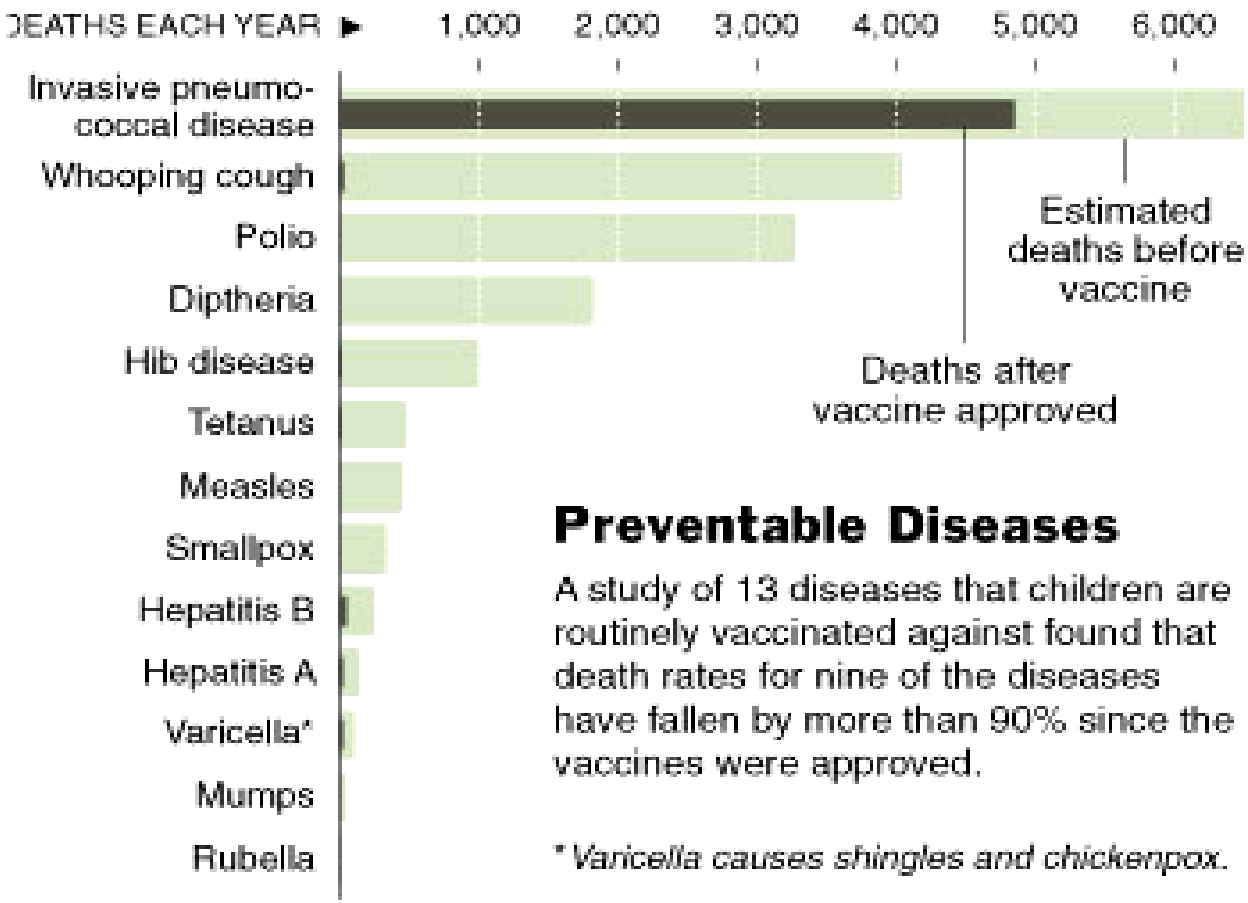
# FDA Rules Override Warnings About Drug

## Cattle Antibiotic Moves Forward Despite Fears of Human Risk

By Rick Weiss Washington Post Staff Writer Sunday, March 4, 2007

The government is on track to approve a new antibiotic to treat a pneumonia-like disease in cattle, despite warnings from health groups and a majority of the agency's own expert advisers that the decision will be dangerous for people.

The drug, called cefquinome, belongs to a class of highly potent antibiotics that are among medicine's last defenses against several serious human infections. No drug from that class has been approved in the United States for use in animals. *The American Medical Association and about a dozen other health groups warned the Food and Drug Administration that giving cefquinome to animals would probably speed the emergence of microbes resistant to that important class of antibiotics, as has happened with other drugs.*




*Source: JAMA; Centers for Disease Control and Prevention*

THE NEW YORK TIMES

# HIGHLIGHTS OF H.R. 3697 STRATEGIES TO ADDRESS ANTIMICROBIAL RESISTANCE (STAAR) ACT

*SEPTEMBER 27, 2007*

- Reauthorizing the Antimicrobial Resistance Task Force, establishing an Advisory Board of outside experts and an Office of Antimicrobial Resistance reporting to the Secretary of Health and Human Services whose director will oversee government efforts to combat antimicrobial resistance;
- Creating a joint blueprint for antimicrobial resistance research at the NIH and CDC and establishment of a Clinical Research and Public Health Network;
- Collecting available and relevant data to allow government to better assess the antimicrobial resistance problem including how antibiotic use triggers the development of resistance; and
- Establishing demonstration projects to encourage more appropriate use of existing antibiotics.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