The evolution of antibiotic resistance

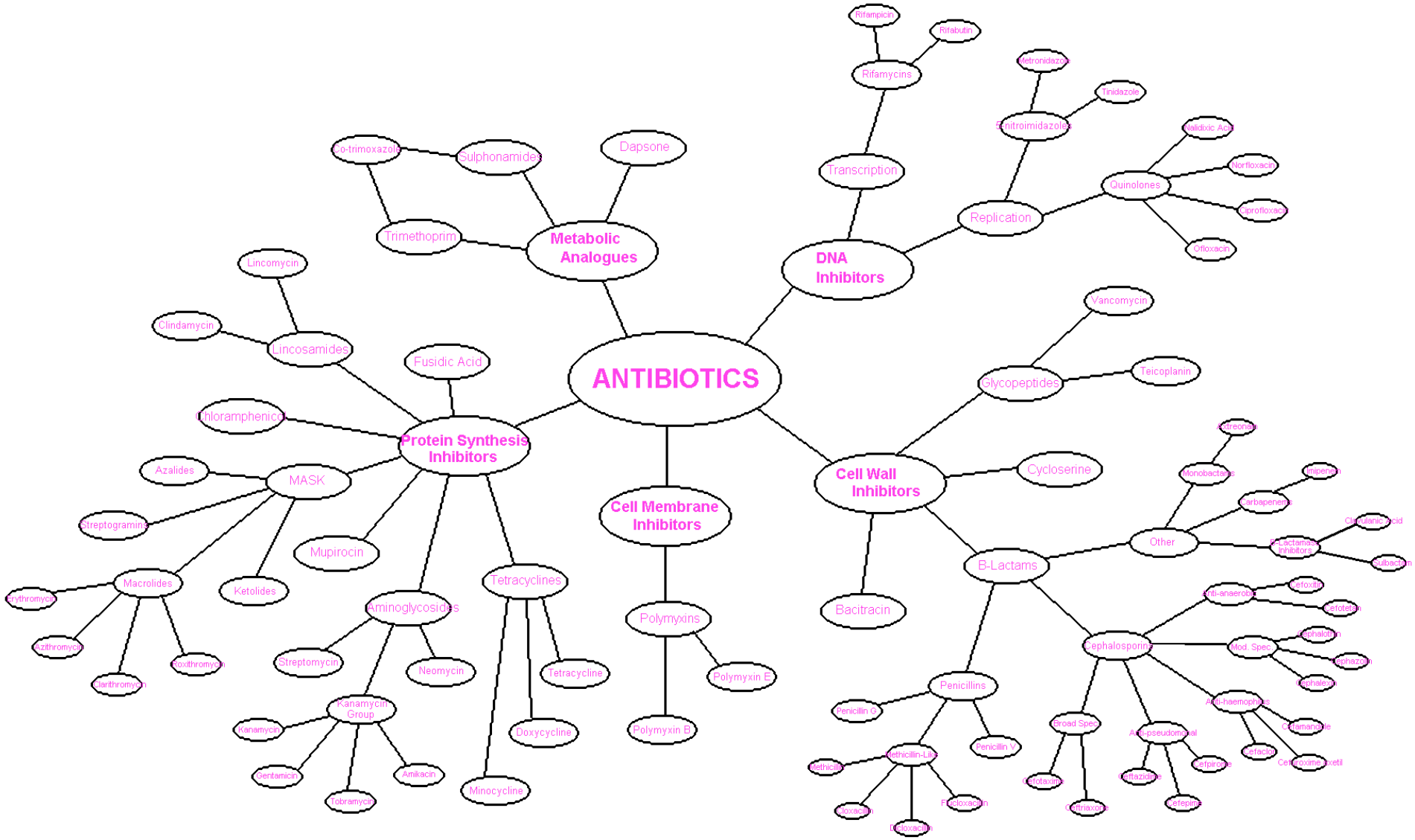
Are we learning the lesson?

- What are antibiotics?
- The problem of antibiotic resistance
- The social economy of antibiotic resistance
- The evolution of resistance
- The ecology of resistance
- Resisting resistance

What are antibiotics?

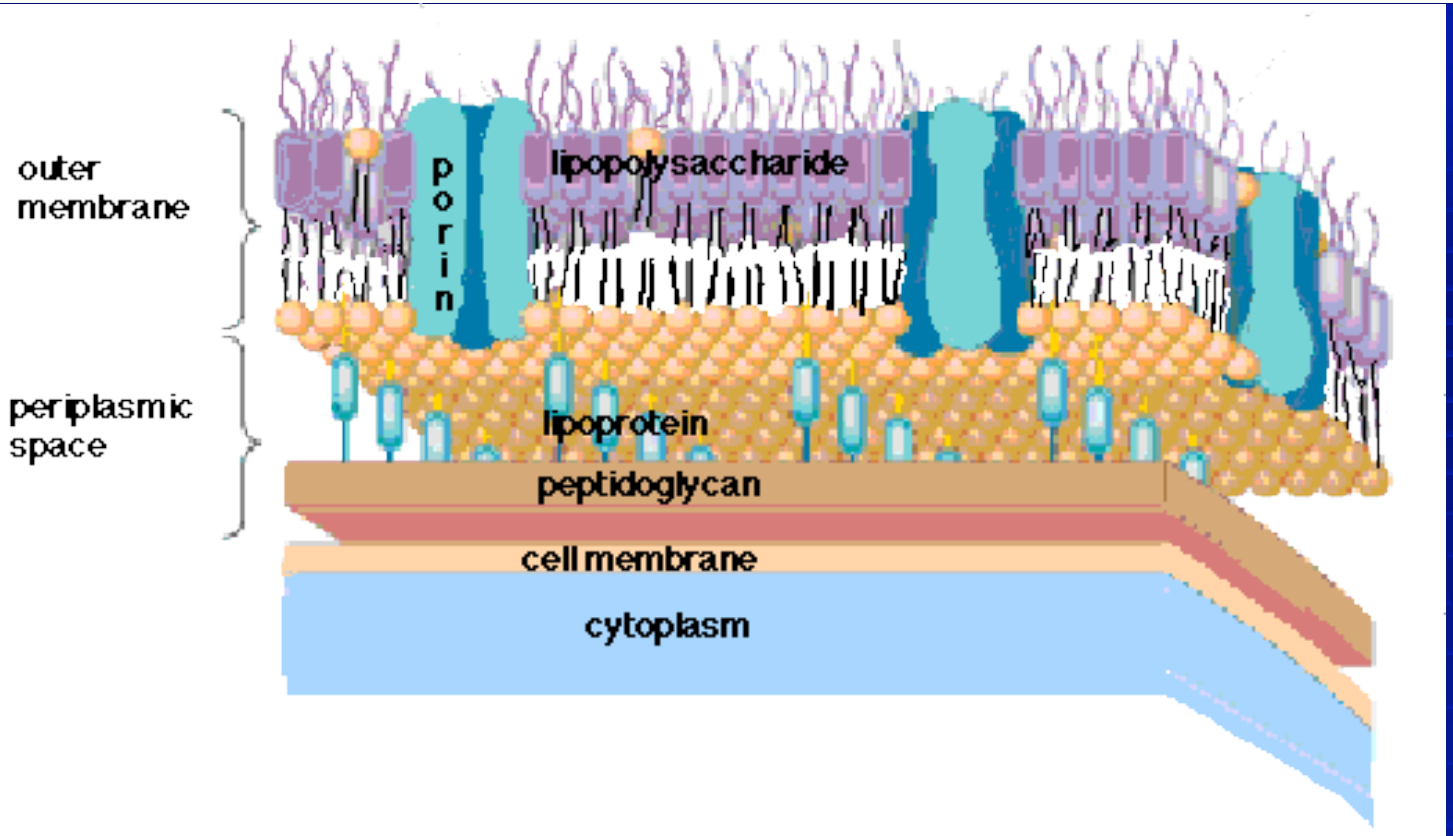
- Antibiotics are a heterogeneous class of molecules that interfere with the growth of bacteria.
- Many antibiotics are naturally occurring, and are isolated from a variety of bacterial, fungal or eukaryotic sources.
- Frequently, naturally occurring antibiotics are modified to make them more effective.
- Some antibiotics are synthetic, and may have no natural counterpart

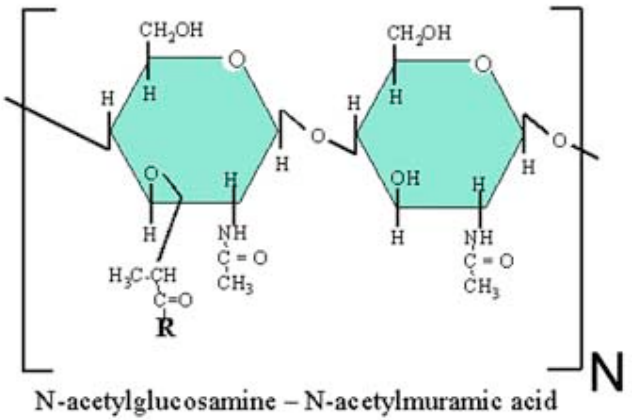
	Event	Country
1929	penicillin discovered	England
1932	sulfonamides (Prontosil) discovered	Germany
1939	gramicidin discovered	United States
1942	penicillin introduced	England and United States
1943	streptomycin discovered	United States
1943	bacitracin discovered	United States
1945	cephalosporins discovered	Italy
1947	chloramphenicol discovered	United States
1947	chlortetracycline discovered	United States
1949	neomycin discovered	United States
1950	oxytetracycline discovered	United States
1952	erythromycin discovered	United States
1956	vancomycin discovered	United States
1957	kanamycin discovered	Japan
1960	methicillin introduced	England and United States
1961	ampicillin introduced	England
1961	spectinomycin reported	United States
1963	gentamicin discovered	United States
1964	cephalosporins introduced	England
1966	doxycycline introduced	United States
1967	clindamycin reported	United States
1971	tobramycin discovered	United States
1972	cephamycins (cefoxitin) discovered	United States
1972	minocycline introduced	United States


ANTIBIOTICS
Metabolic Analogues
Co-trimoxazole
Sulphonamides
Dapsone
Trimethoprim
DNA Inhibitors
Transcription
Rifampicin
Rifabutin
Rifamycins
Replication
Nitroimidazoles
Metronidazole
Tinidazole
Quinolones
Nalidixic Acid
Norfloxacin
Ciprofloxacin
Ofloxacin
Protein Synthesis Inhibitors
Lincosamides
Lincomycin
Clindamycin
Fusidic Acid
Chloramphenicol
MASK
Azalides
Streptogramins
Macrolides
Erythromycin
Azithromycin
Clarithromycin
Roxithromycin
Ketolides
Mupirocin
Aminoglycosides
Streptomycin
Kanamycin Group
Kanamycin
Gentamicin
Tobramycin
Amikacin
Neomycin
Tetracyclines
Tetracycline
Doxycycline
Minocycline
Cell Membrane Inhibitors
Polymyxins
Polymyxin B
Polymyxin B
Cell Wall Inhibitors
Glycopeptides
Vancomycin
Teicoplanin
Cycloserine
Bacitracin
B-Lactams
Other
Aztreonam
Monobactams
Imipenem
Carbapenems
Clavulanic Acid
B-Lactamase Inhibitors
Sulbactam
Penicillins
Penicillin G
Penicillin V
Broad Spec
Ampicillin-Like
Methicillin
Oxacillin
Flucloxacillin
Cloxacillin
Anti-pseudomonal
Ticarcillin
Piperacillin
Anti-haemophilus
Cephalosporins
Anti-anaerobic
Cefoxitin
Cefotetan
Mod. Spec
Cephalothin
Cephazolin
Cephalexin
Broad Spec
Cefotaxime
Ceftriaxone
Anti-pseudomonal
Ceftazidime
Cefepime
Anti-haemophilus
Cefamandole
Cefaclor
Cefuroxime Axetil

Mode of action

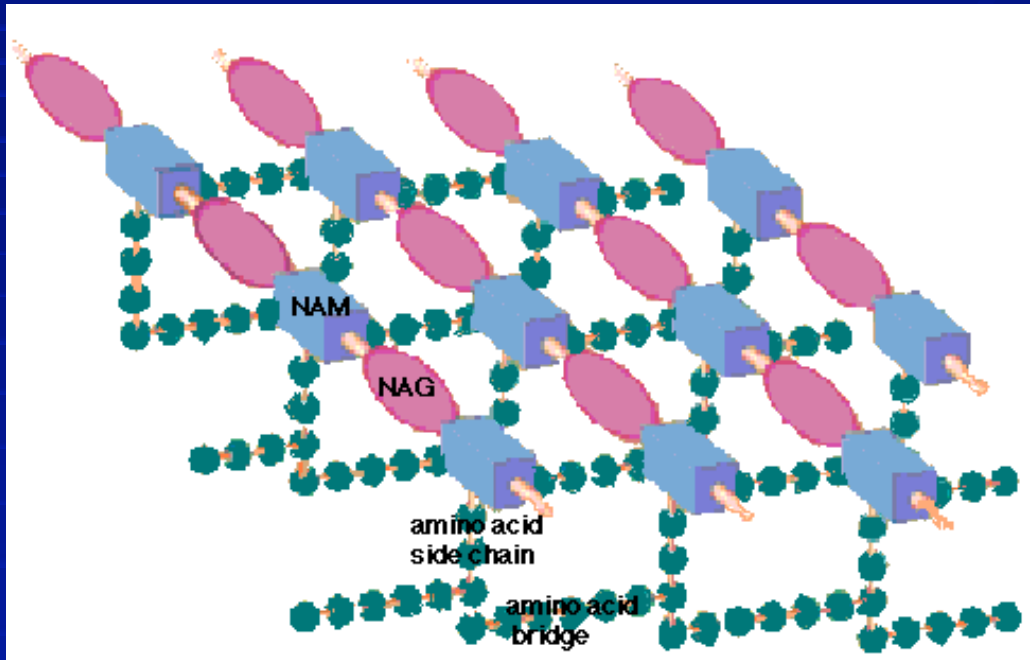
- Antibiotics work in a variety of ways, but generally depend on their ability to:
- Mimic an critical molecule
- Bind irreversibly to an active site
- Compete with a naturally occurring molecule for binding, passage or transport.

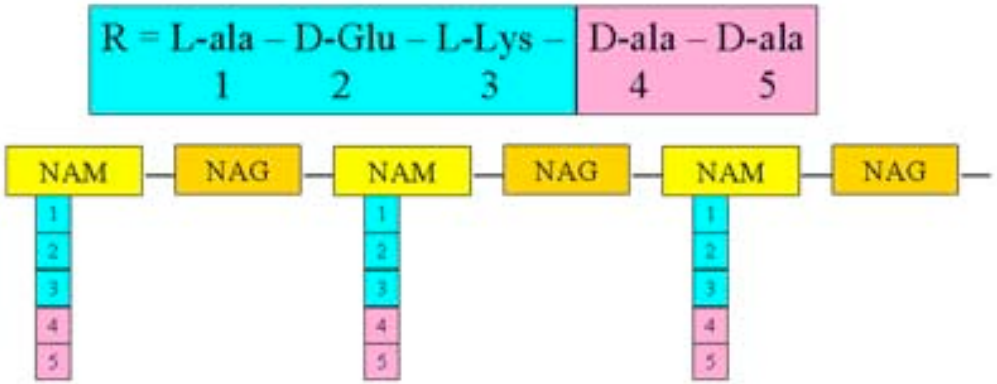




N-acetylglucosamine – N-acetylmuramic acid

The pentapeptide





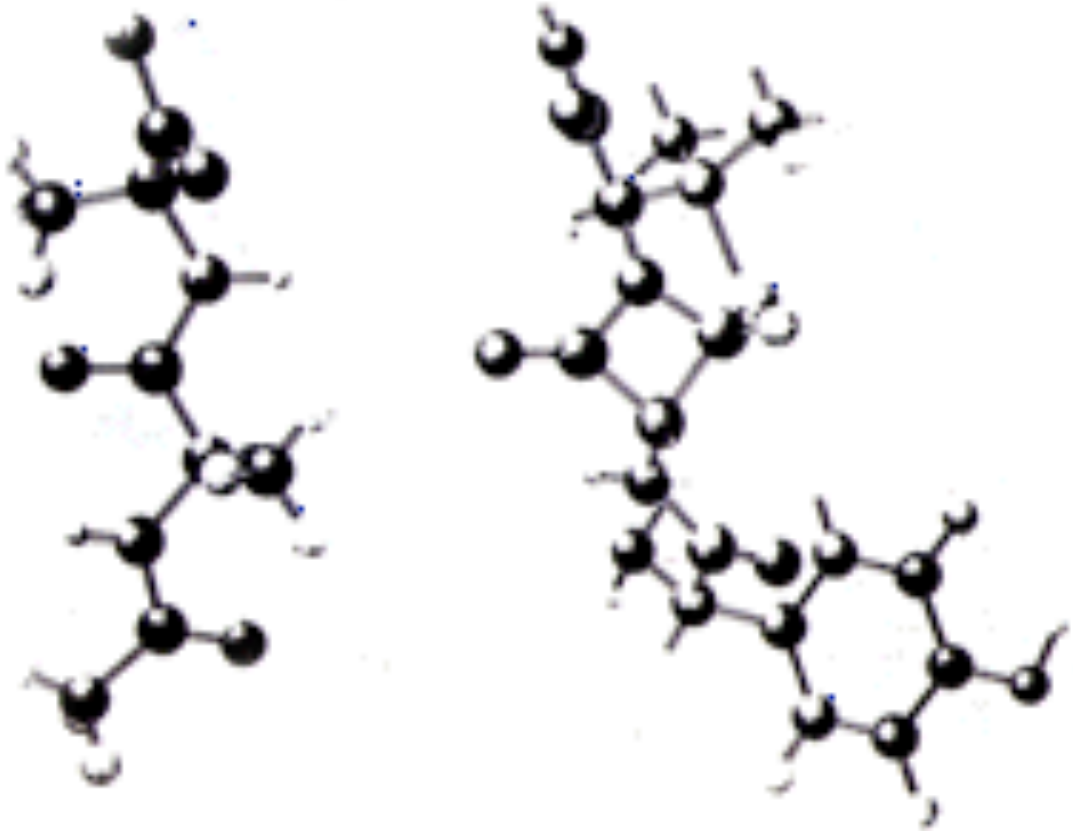


Figure5: Comparison of the structures of the D-Ala-D-Ala terminus of the pentapeptide component of the cell wall (left)and amoxicillin (right). As one can see, the two appear very similar.

The objective

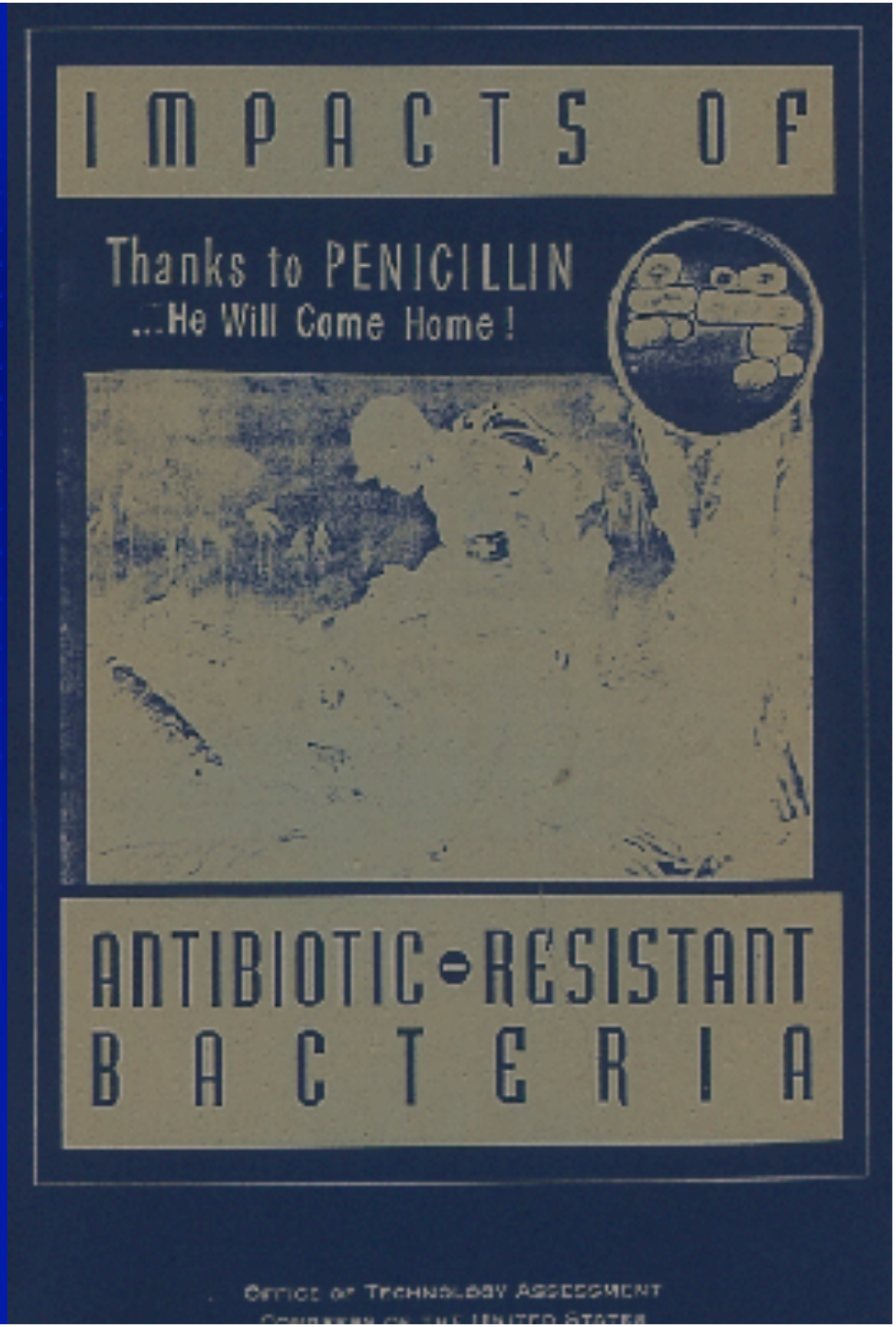
- Antibiotics are designed to slow the growth, or to kill target organisms.
- A therapeutic antibiotic needs to do this with minimal toxicity to the host
- This is usually accomplished by directing the antibiotic at a phylogenetically unique feature of the bacterial target (e.g. cell wall, ribosome, etc…)

- What are antibiotics?
- The problem of antibiotic resistance
- The social economy of antibiotic resistance
- The evolution of resistance
- The ecology of resistance
- Resisting resistance

The evolutionary effect

- Why are antibiotics naturally occurring?
- Surely not for us to find and refine them
- They play a role in microbial ecosystems (more on this later)
- Important to remember that the selection for resistance does not begin with the discovery of penicillin.

- But it sure gets worse.
- Antibiotic resistance emerges in response to antibiotic use.



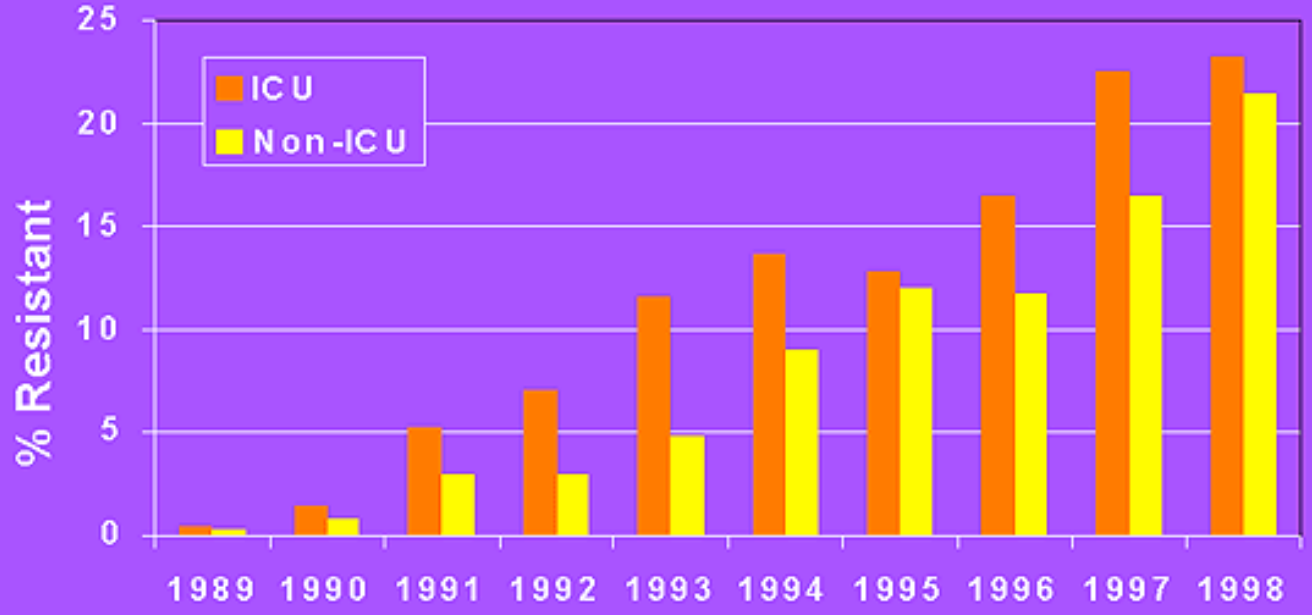
Just how important is the problem?

- In terms of public health, one of the central public health issues of our age.
- The problem is simple: every human bacterial pathogen harbors resistance to all currently known antibiotics.

Emerging antibiotic resistance

- A tremendously important public health problem:
  - 10-50% of incoming infections in clinical settings are resistant to one or more frontline antibiotics.
  - 3 million deaths worldwide due to diarrhea-causing infections, most of them antibiotic resistant
  - A prevalent cause of complications or death in immuno-compromised individuals.

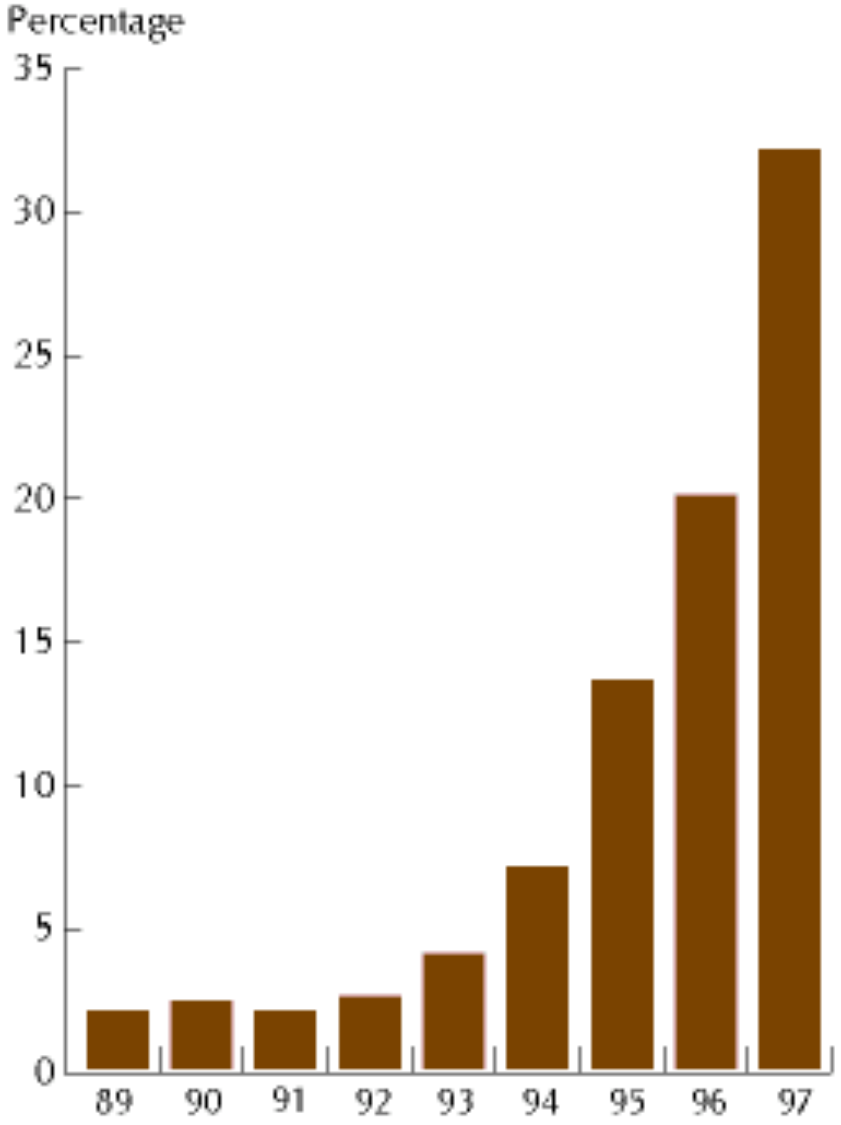
Emerging Vancomycin-resistant Enterococcal Infections*



* in U.S. NNIS Hospitals

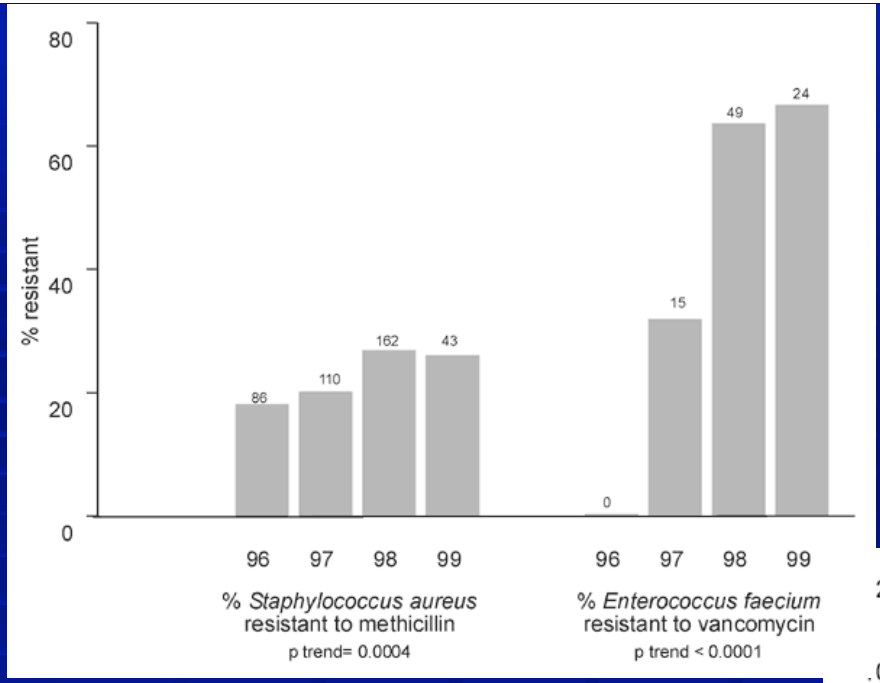
CDC
CENTERS FOR DISEASE CONTROL

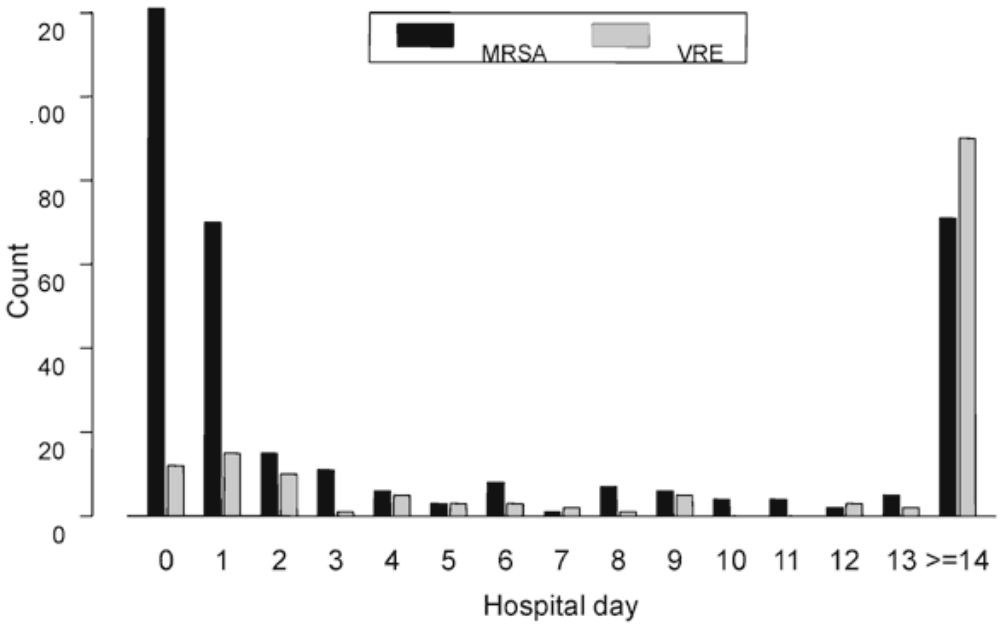
STAPHYLOCOCCUS RESISTANCE TO METHICILLIN IN UK HOSPITALS



Source: ReacherMH et al. BMJ 2000;320: 213-215

Some scary stuff

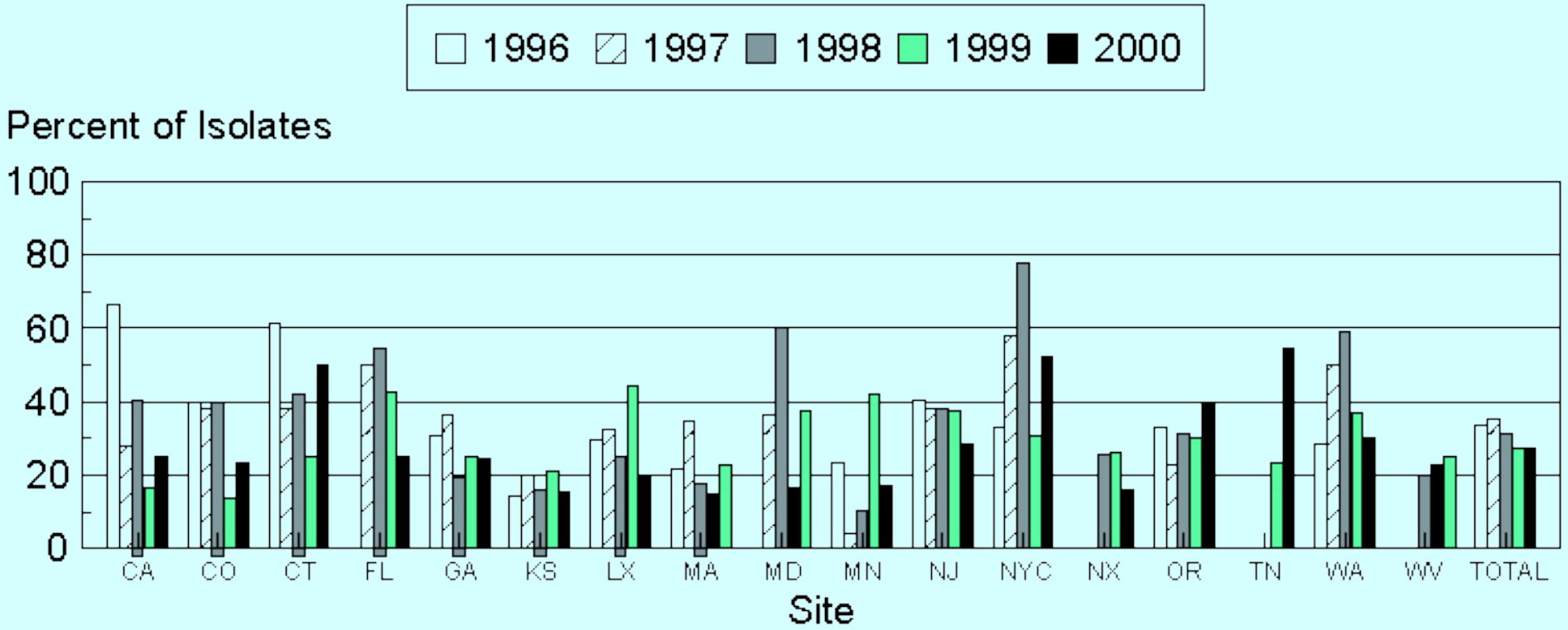




Methycillin resistant *S. aureus* and Vancomycin resistant *Enterococcus* infections

S.S. Huang et al, EID **8**(2):195-201

Multidrug resistance

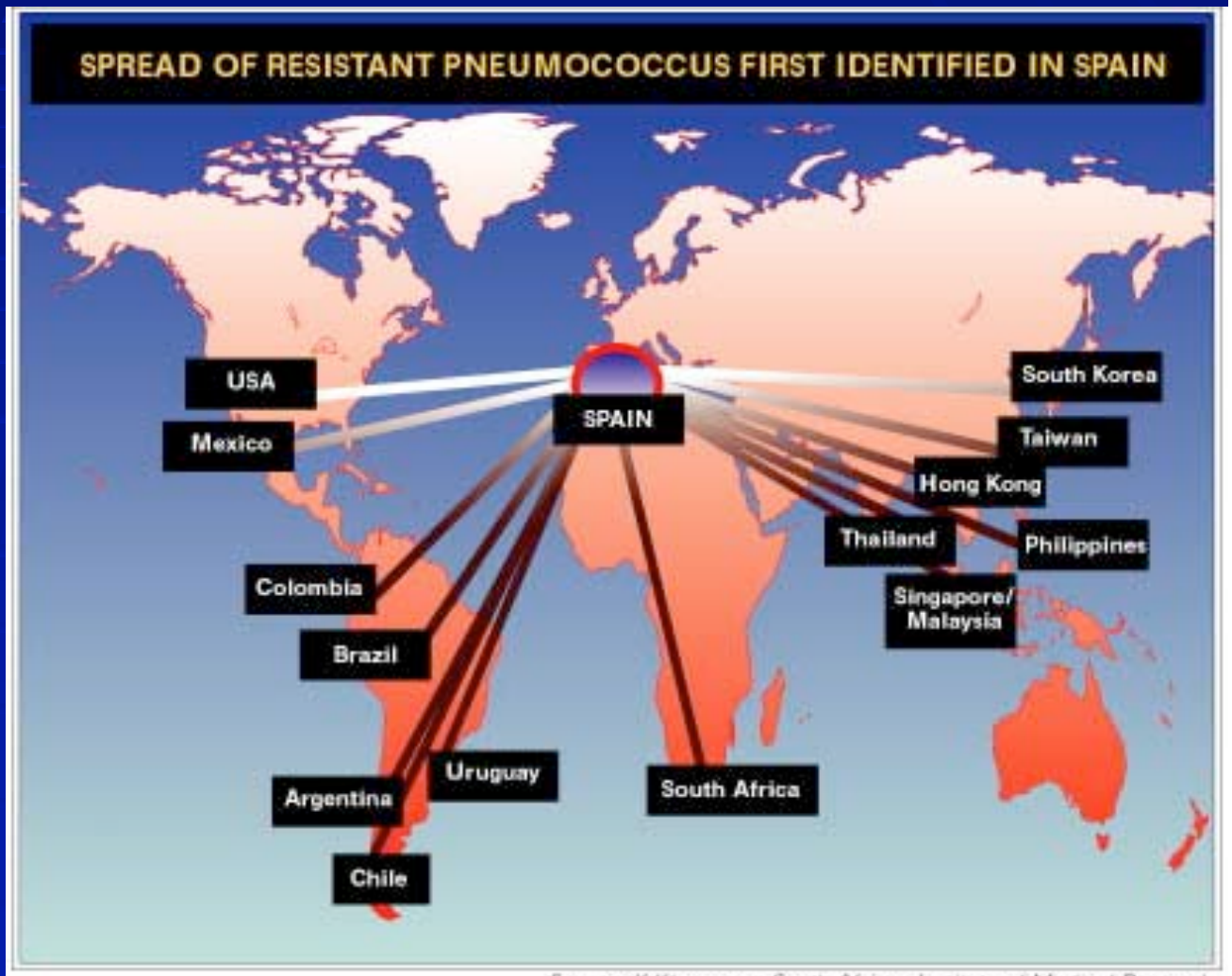


Percent Typhimurium with at least ACSSuT pattern for all sites:
1996 - 103/306 = 34% 1997 - 115/326 = 35% 1998 - 120/380 = 32%
1999 - 102/362 = 28% 2000 - 84/303 = 28%

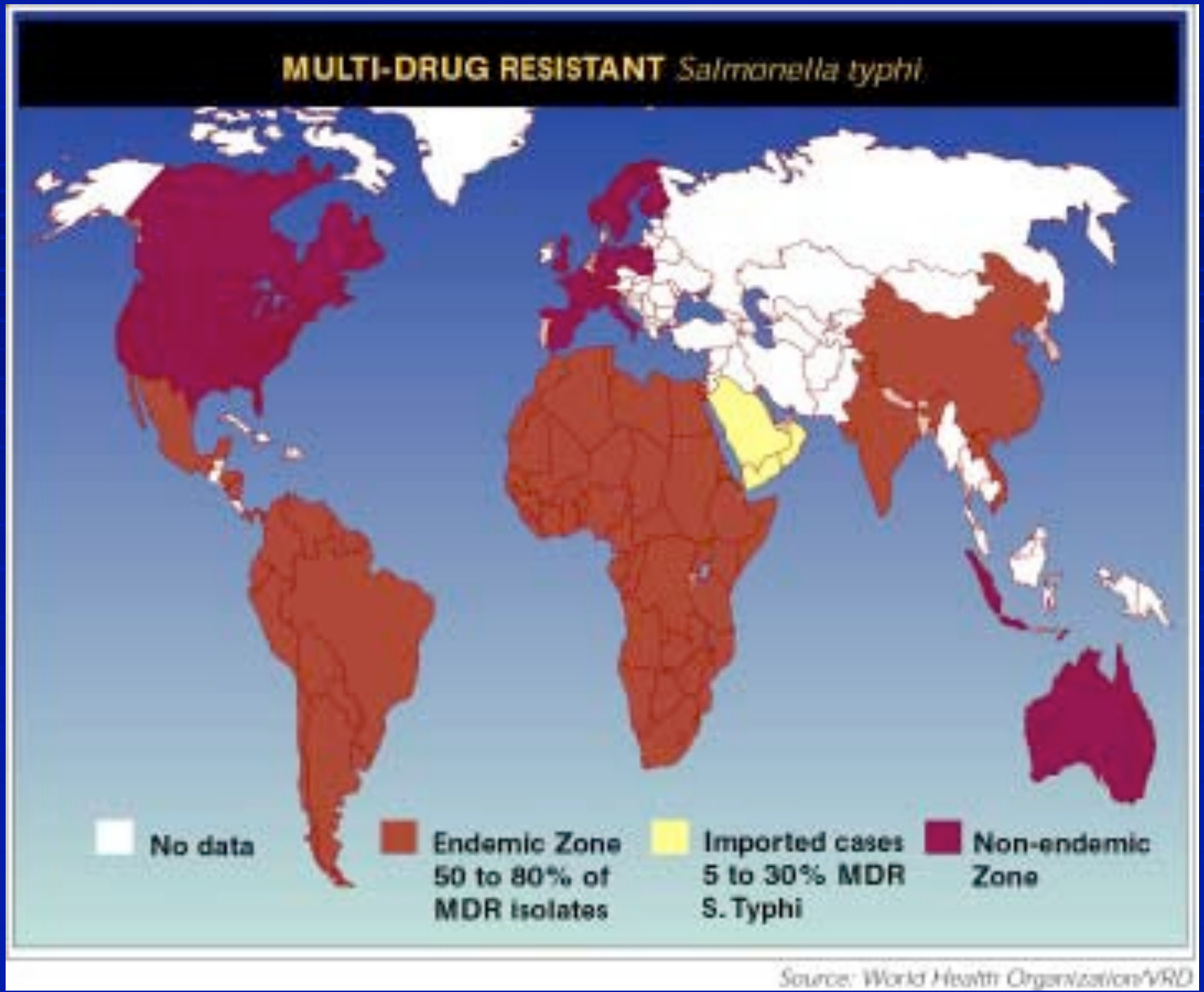
CA=Alameda, Contra Costa, and San Francisco counties
NX=excluding New York City

LX=Los Angeles County
NYC=New York City

A global problem

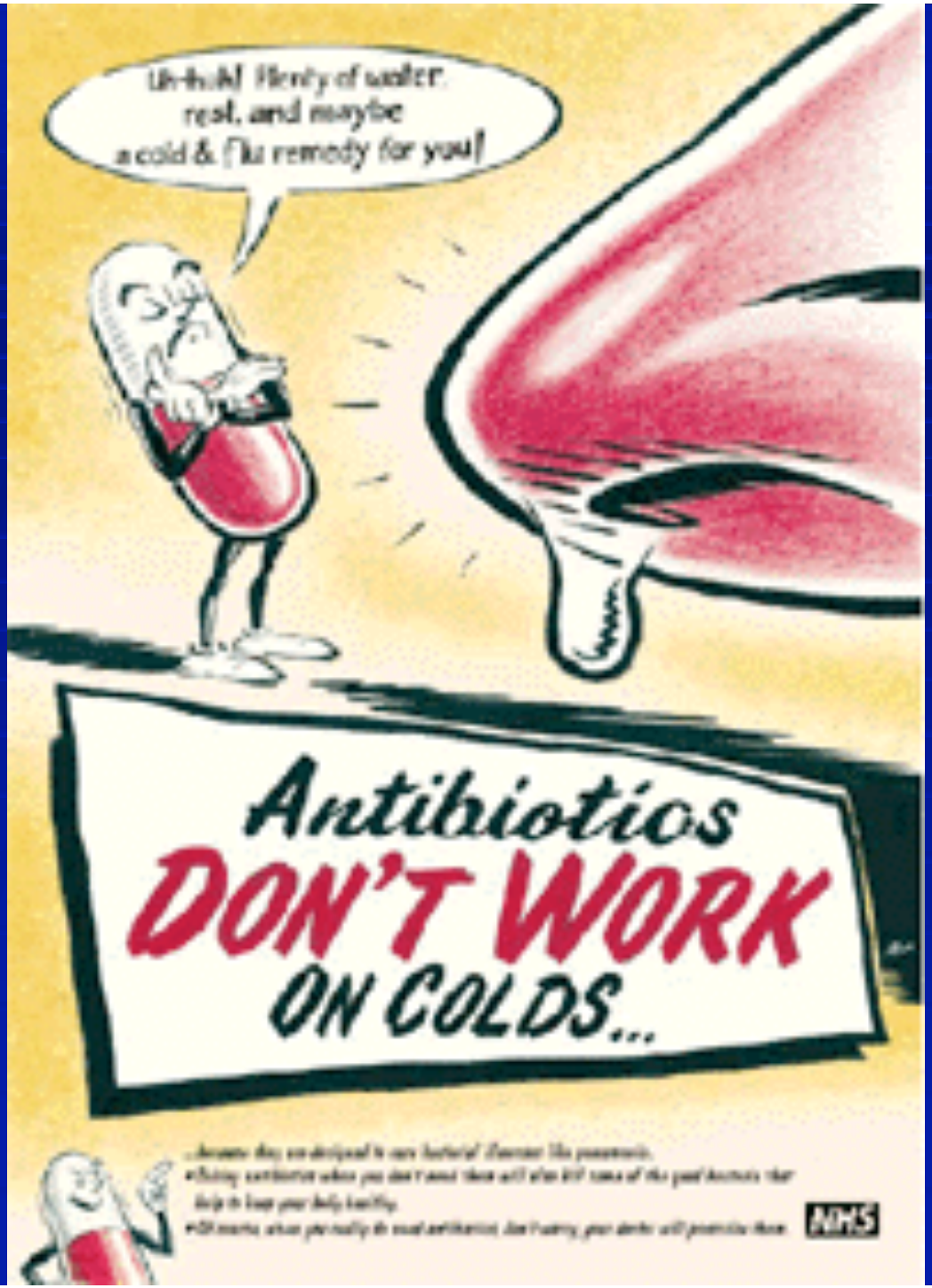


Source: K.Klugmann, South African Institute of Medical Research


MULTI-DRUG RESISTANT Salmonella typhi
No data
Endemic Zone
50 to 80% of
MDR isolates
Imported cases
5 to 30% MDR
S. Typhi
Non-endemic
Zone
Source: World Health Organization/VRD

Why is resistance so rampant?

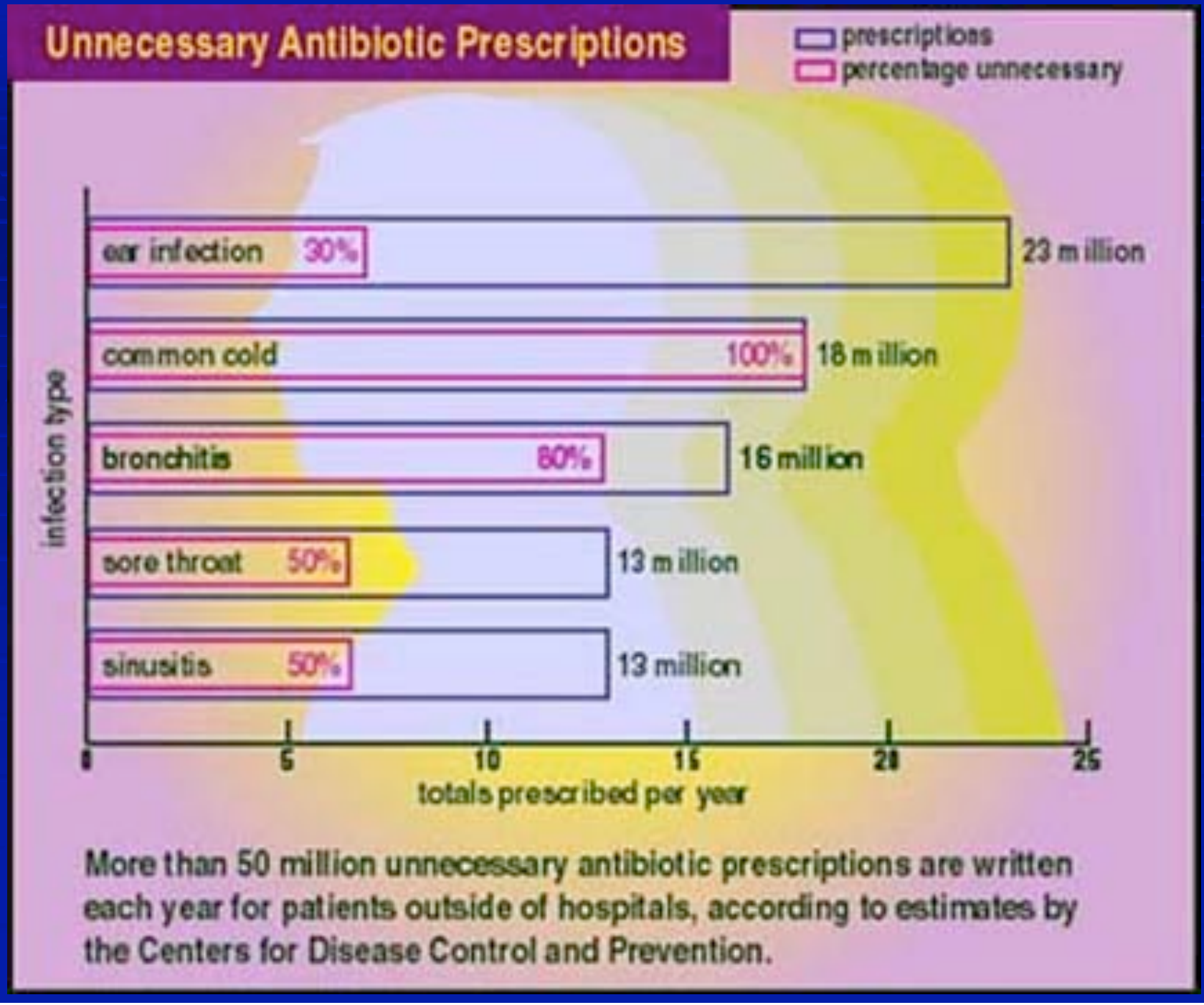
- Overuse
- Misuse
- Misprescription
- Environmental hazard


Uh-huh! Plenty of water, rest, and maybe a cold & flu remedy for you!
Antibiotics
DON'T WORK
ON COLDS...
NHS

National Ambulatory Medical Care Survey (USA, 1998)

	N° (mill.) of visits	Presence (%) of bacterial pathogens	% treated with AB
Rhinitis	25	5	30
Otitis media	13	65	76
Pharyngitis	14	25	62
Bronchitis	13	10	59
Sinusitis	11	40	70

Gonzales et al., CID, 2001, **33**, 757


Unnecessary Antibiotic Prescriptions
prescriptions
percentage unnecessary
ear infection
30%
23 million
common cold
100%
18 million
bronchitis
80%
16 million
sore throat
50%
13 million
sinusitis
50%
13 million
infection type
0
5
10
15
20
25
totals prescribed per year
More than 50 million unnecessary antibiotic prescriptions are written each year for patients outside of hospitals, according to estimates by the Centers for Disease Control and Prevention.

Use of antibiotics[3]

Where antibiotics are used	Types of use	Questionable use
Human use (50%)	20% Hospital	20-50% Unnecessary
	80% Community	
Agricultural use (50%)	20% Therapeutic	40-80% Highly questionable
	80% Prophylactic/growth promotion	

The scope of antibiotic use

- 50 million pounds of antibiotics are produced annually in the US
- 190 million hospital prescriptions/year in the US, 133 million outside prescriptions.
- 50% of the latter category may be unnecessary.