ANTIBIOTICS

Use & Misuse

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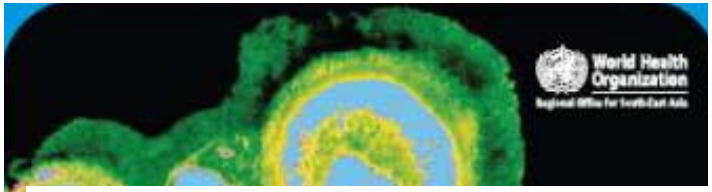
FAQs



ON ANTIMICROBIAL RESISTANCE

USE ANTIBIOTICS RATIONALLY

Q: What are antibiotics and how do they differ from antimicrobial agents?

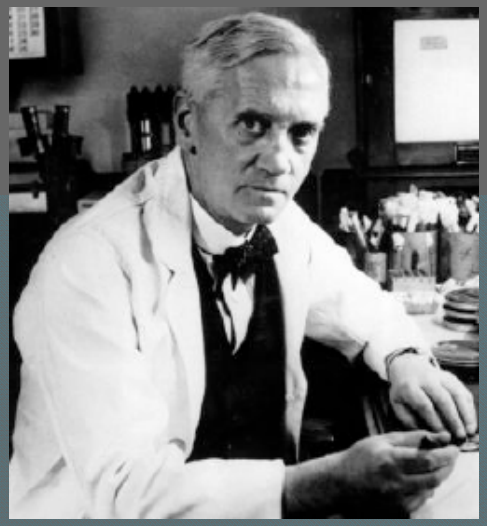
Representative Sources of Antibiotics

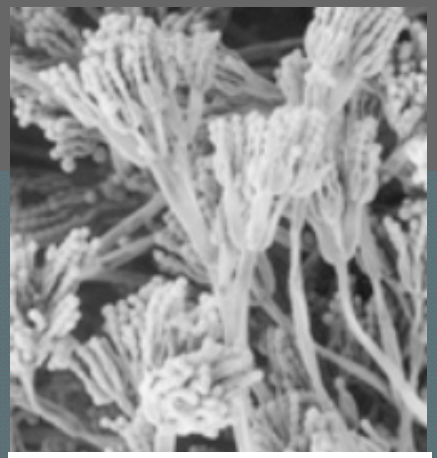
Microorganism	Antibiotic
Gram-Positive Rods	
Bacillus subtilis	Bacitracin
Bacillus polymyxa	Polymyxin
Actinomycetes	
Streptomyces nodosus	Amphotericin B
Streptomyces venezuelae	Chloramphenicol
Streptomyces aureofaciens	Chlortetracycline and tetracycline
Streptomyces erythraeus	Erythromycin
Streptomyces fradiae	Neomycin
Streptomyces griseus	Streptomycin
Micromonospora purpureae	Gentamicin
Fungi	
Cephalosporium spp.	Cephalothin
Penicillium griseofulvum	Griseofulvin
Penicillium notatum	Penicillin

Antibiotics

- are antimicrobial agents or medicines
- used to treat infections caused by microbes
  - bacteria, viruses, fungi or parasites.
- ***prepared from other living organisms***.

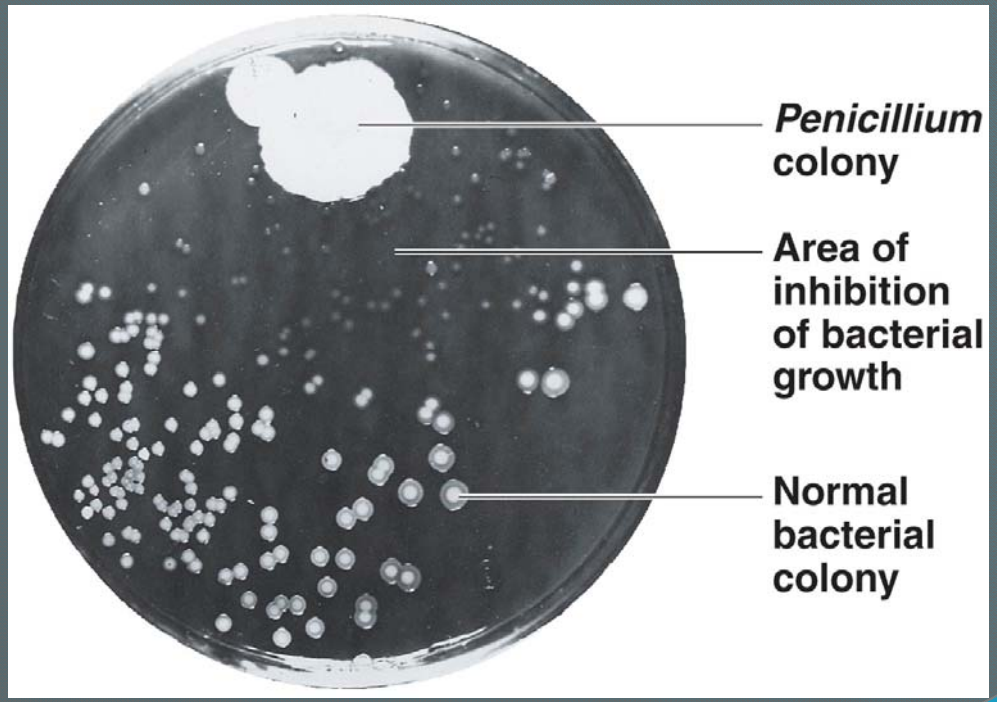
- **1928:**





Penicillium notatum

- **1940**: – Howard Florey & Ernst Chain performed *first clinical trial* of penicillin.



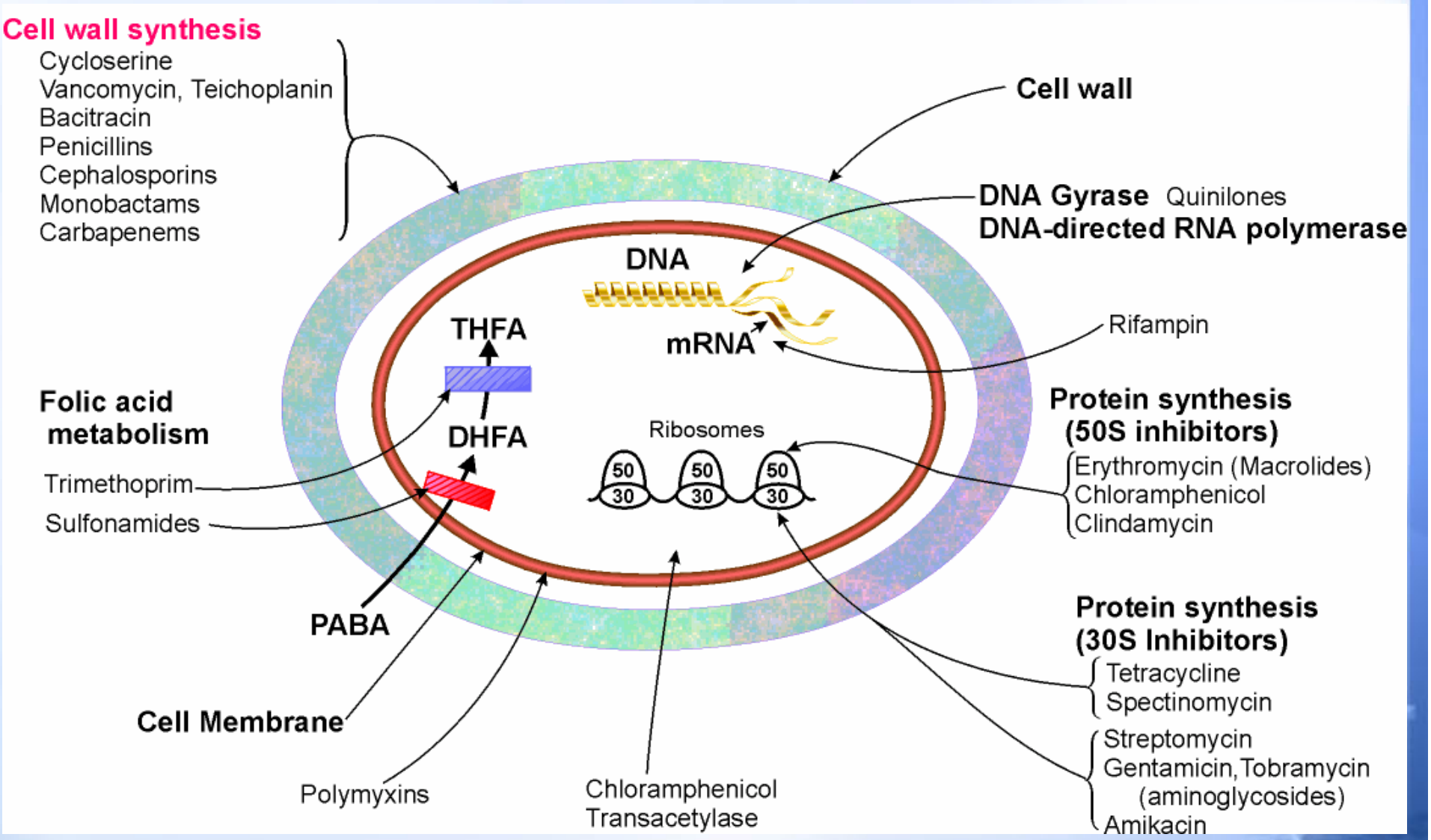
- However, Not all antimicrobial agents are antibiotics
- because **some are synthesized** chemically and not obtained from a living organism.

- Nevertheless, for ease of communication, "antibiotics" & "antimicrobial agents" are used ***interchangeably***.

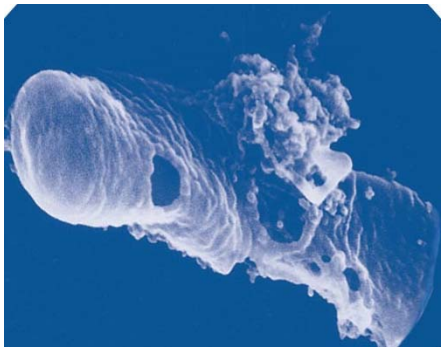
Antimicrobials Developed

Synthetic Molecules	Natural Products	
• Sulfonamides • Trimethoprim • Quinolones • Nitroimidazoles • Nitrofurans • Oxazolidinones	• ß-lactams – Penicillins – Cephalosporins – Carbapenems – ß-lactamase inhibitors • Tetracyclines • Chloramphenicol • Aminoglyosides • Glycopeptides	• Lincosamides • Macrolides • Streptogramins • Polymyxins • Rifampicins • Lipopeptides • Mupirocin

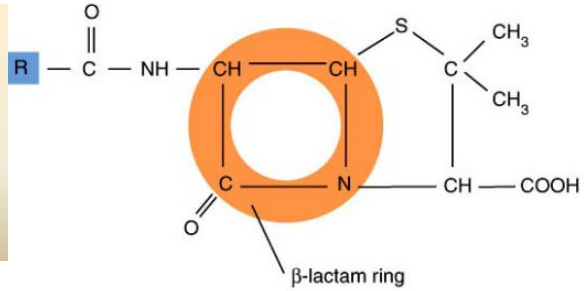
Sites of Antimicrobial Actions



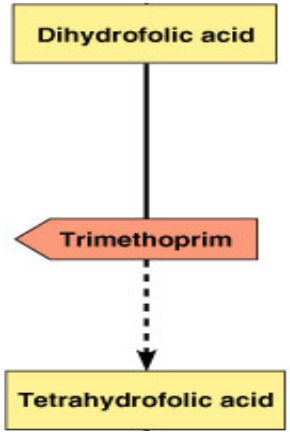
Selective toxicity - A drug that kills harmful microbes without damaging the host



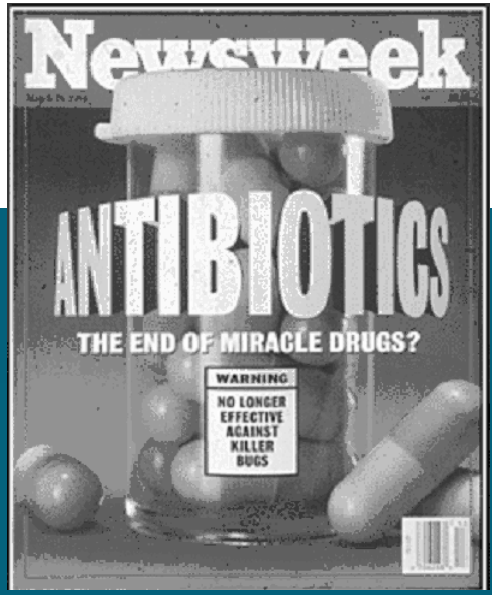
This bacterium is lysing because an antibiotic disrupted its cell wall. Why doesn't the antibiotic lyse human cells?



Specificity of inhibitors of dihydrofolate reductase			
DHFRI	**IC_{50}(μmol/l) for dihydrofolate reductase**		
	Human	***Protozoal***	***Bacterial***
Trimethoprim	**260**	**0.07**	**0.005**
Pyrimethamine	0.7	0.0005	2.5
Methotrexate	0.001	~0.1	Inactive



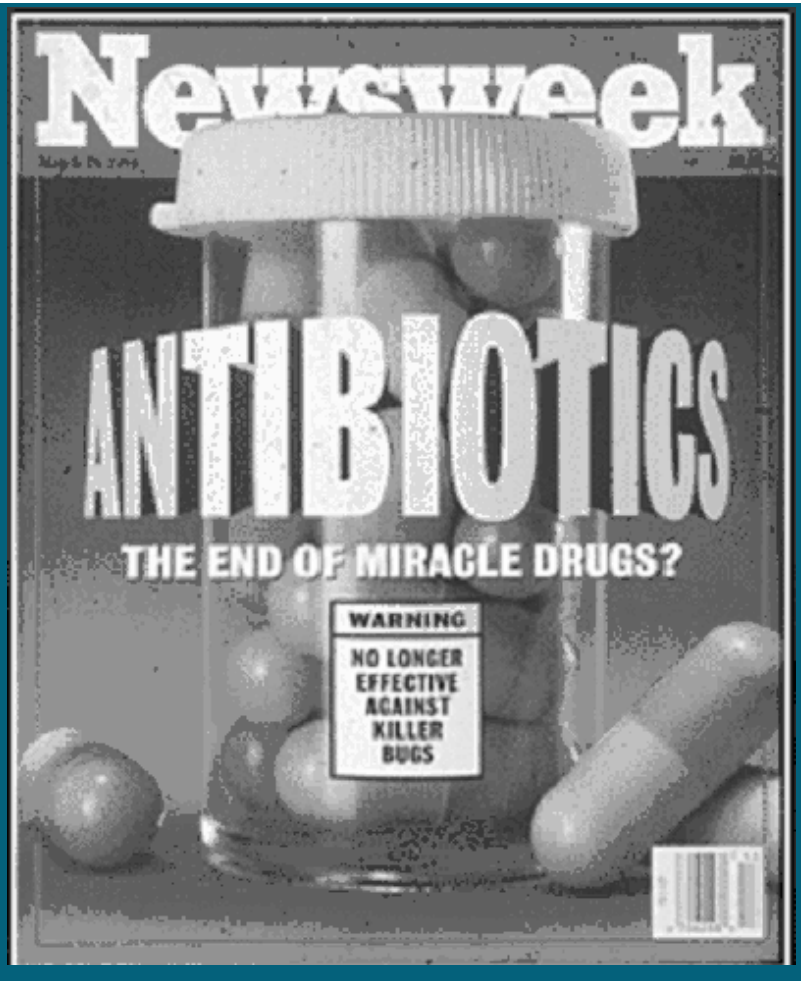
Antibiotics: Roadway



Tyrothricine
Gramicidin
Tyrocidine
Streptomycin
Bacitracin
Neomycin
Penicillin
Erythromycin
Spectinomycin
Lincomycin
Oleandomycin
Spiramycin
Gentamicin
Josamycin
Novobiocin
Cycloserine
Tobramycin
Fusidic acid
Rosaramycin
Cephalosporins, 3G, 4G
Oxazolidinone
Daptomycin
1930
1940
1950
1960
1970
1980
1990
2000
2010
Tigecycline
Fluoroquinolones
Chloramphenicol
Polymyxin
Framycetin
Oxytetracycline
Nystatin
Chlortetracycline
Cephalosporin
1G, 2G
Paromomycin
Nebramycins
Rifamycin
Kanamycin
Vancomycin
Ribostamycin
Butirocin
Sissomycin

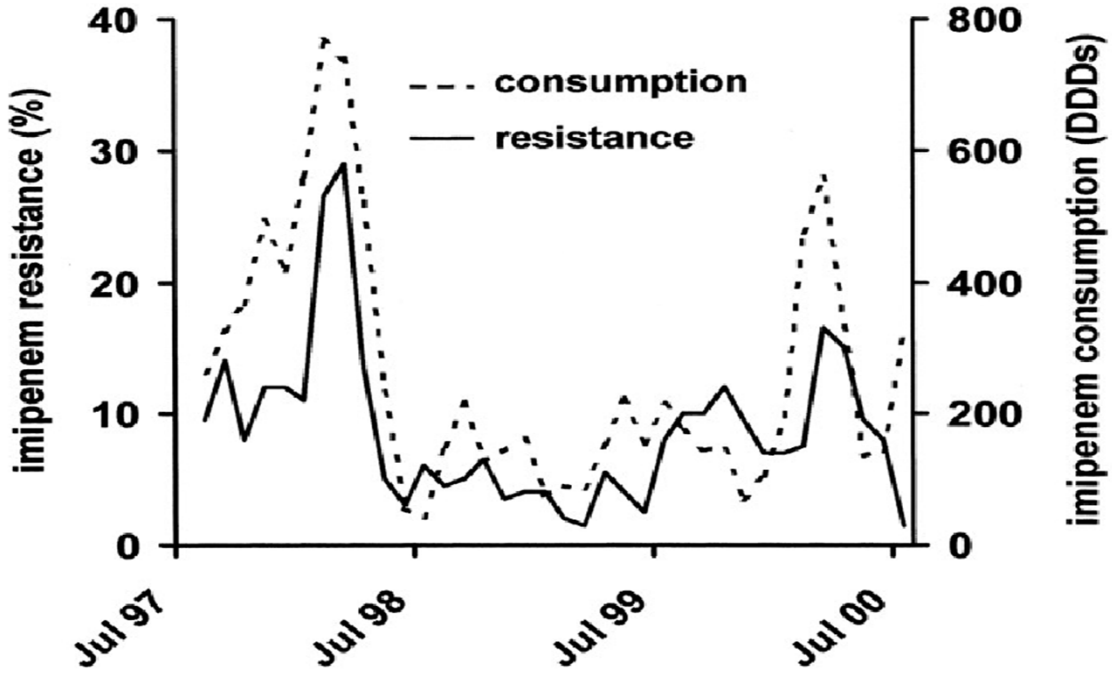
Are we running out of new class of antibiotics

Antibiotic class	Year of launch
Sulphonamides	1936
Penicillins	1940
Tetracyclines	1949
Chloramphenicol	1949
Aminoglycosides	1950
Macrolides	1952
Glycopeptides	1958
Streptogramins	1962
Quinolones	1962
Oxazolidinones	**2001**
Glycylcyclines	**2005**



Q: What do we understand by the term antimicrobial resistance?

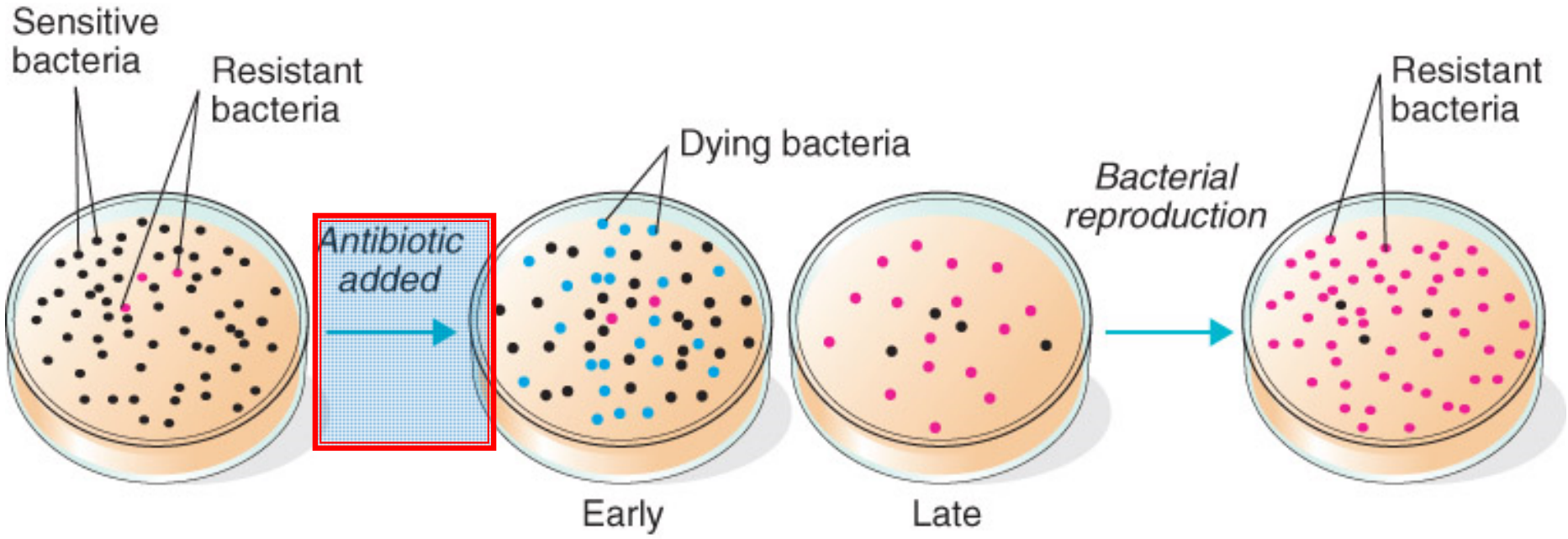
- A *natural biological phenomenon*
- **Use of antibiotics** for any infection, in any dose or for any period of time, **causes a *selective pressure*** on microbial population.

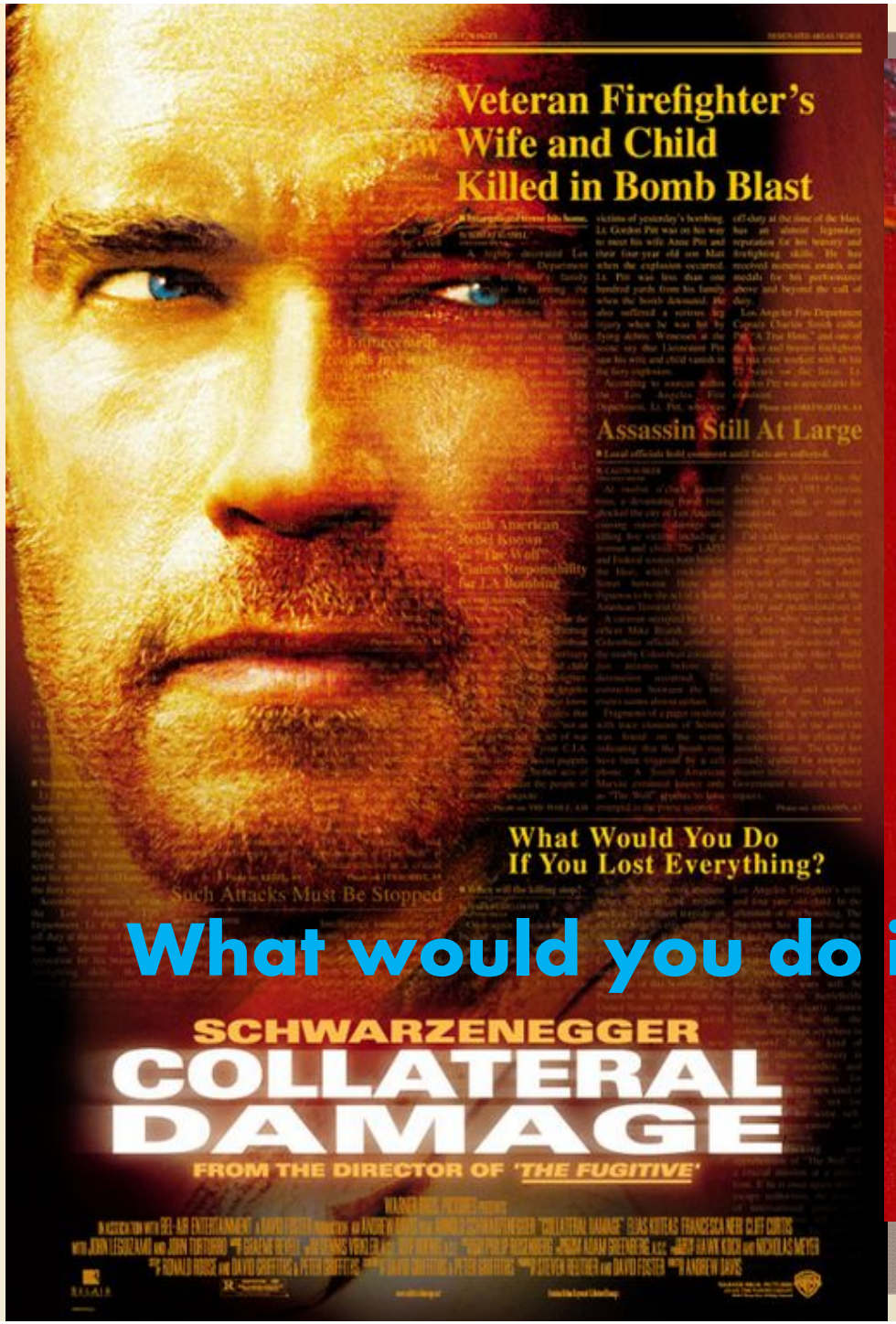


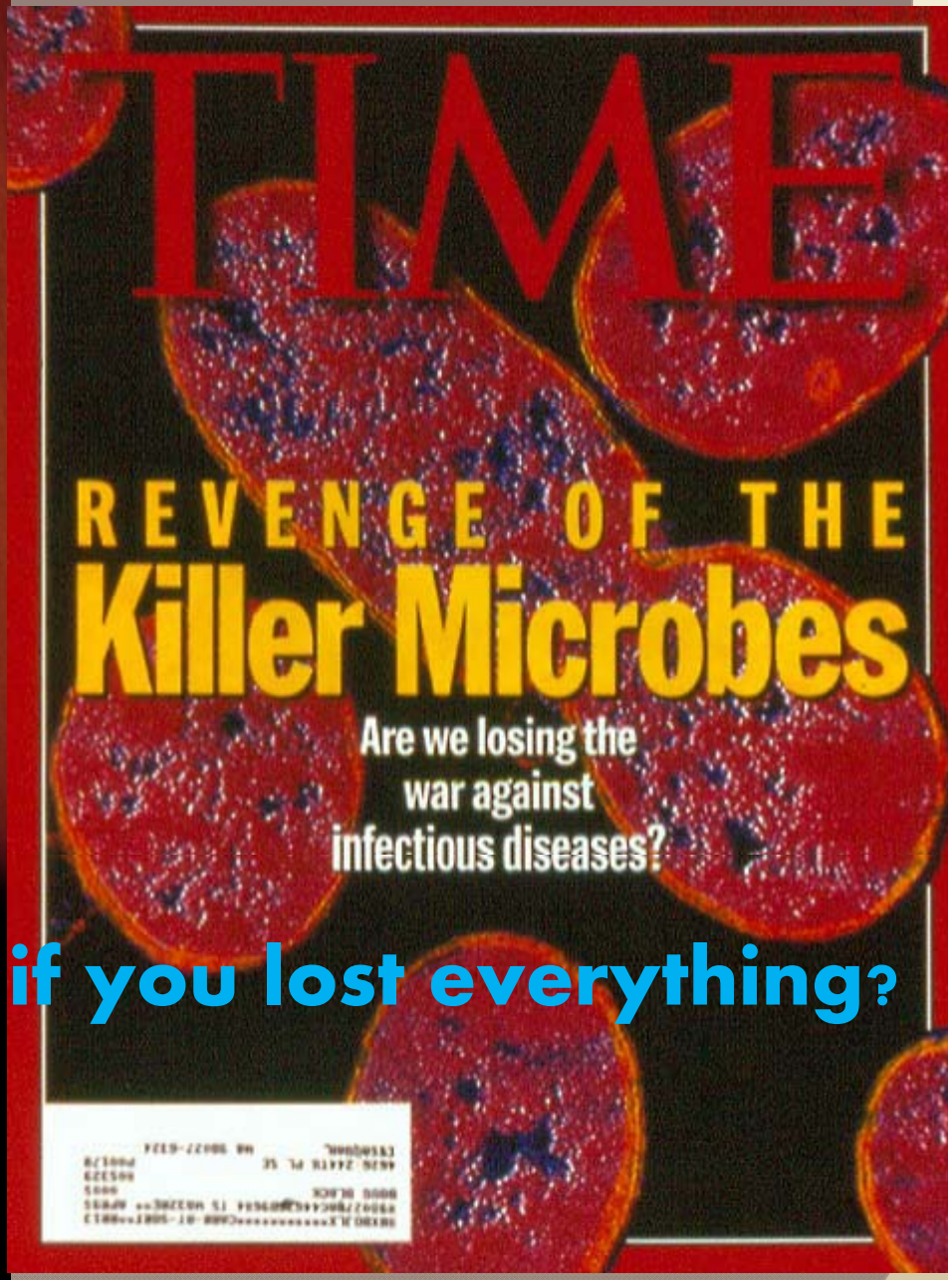
Antimicrobial Resistance

- Under optimal conditions, the majority of the infecting microbes will be killed.

- However, if a *few resistant mutants* **exist** in the population, & the treatment is insufficient or the patient is immunocompromised, the mutant can **flourish**.

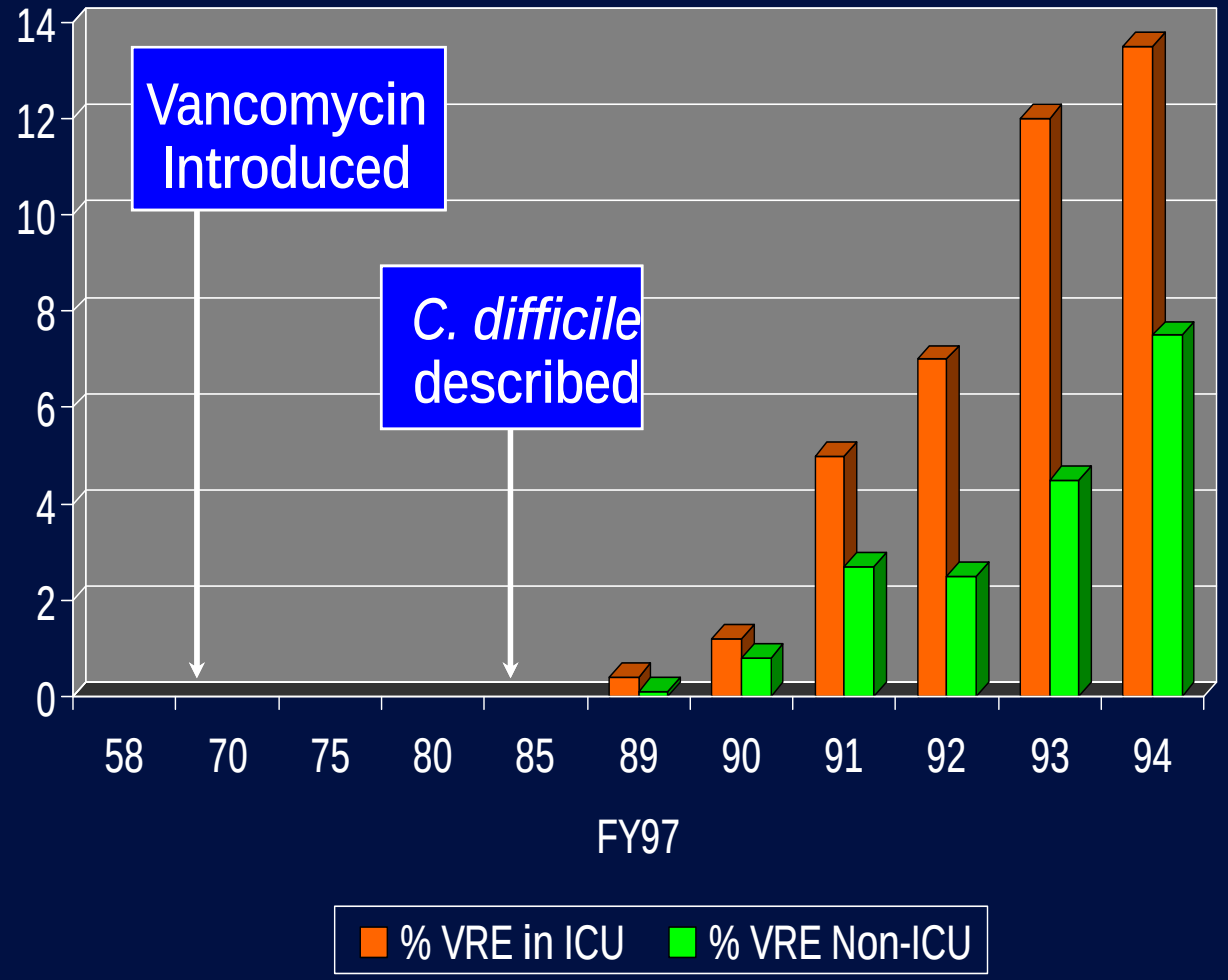




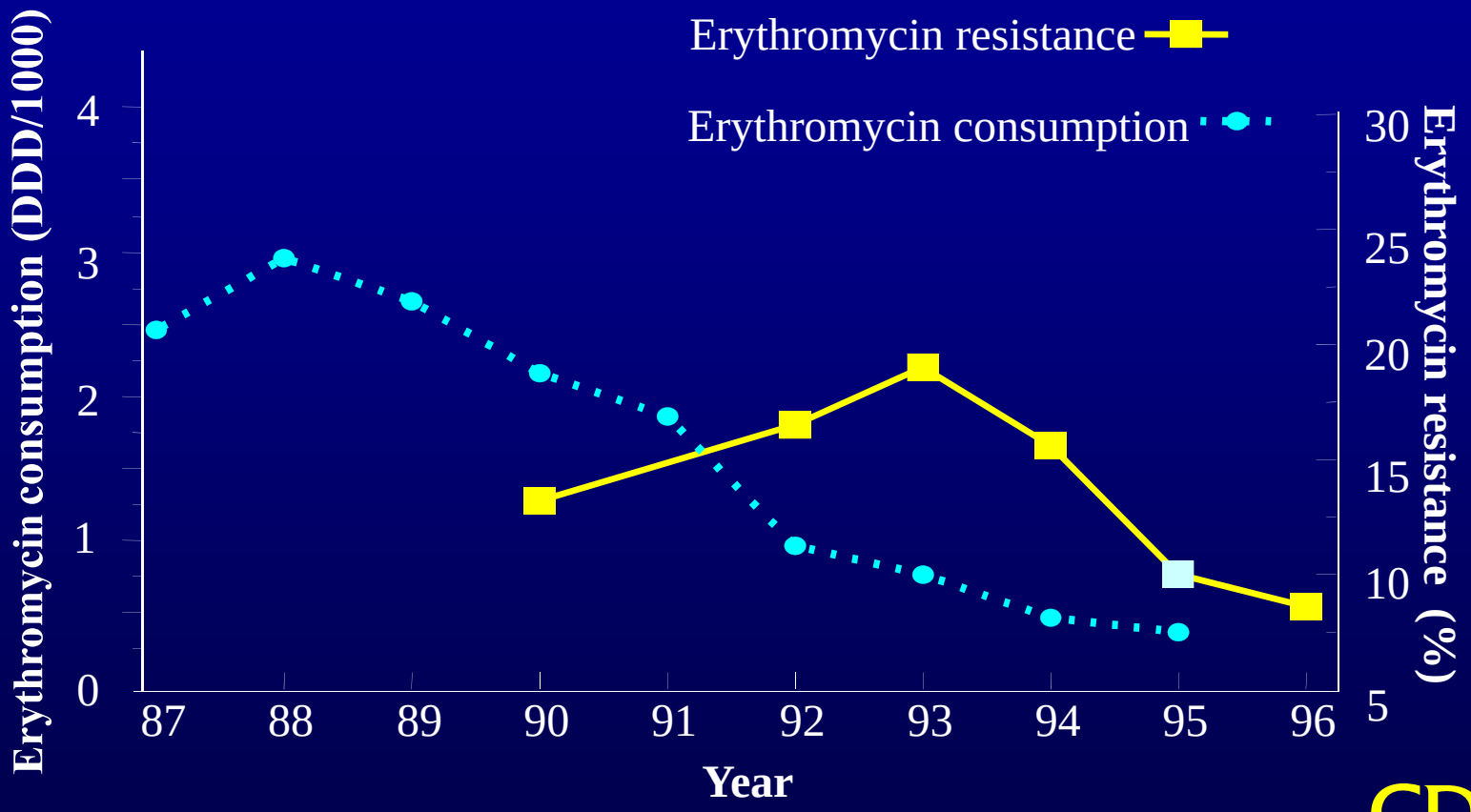


What would you do if you lost everything?

Increasing VRE Over Time



Controlling Erythromycin Resistance in Group A Streptococci - Finland



CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Seppala, NEJM 1997;337:441

Q: When was the first resistance to antibiotics noted & how have we progressed since then?

Agent	Year of FDA Approval	First Reported Resistance
Penicillin	1943	1940
Streptomycin	1947	1947
Tetracycline	1952	1956
Methicillin	1960	1961
Nalidixic Acid	1964	1966
Gentamicin	1967	1969
Vancomycin	1972	1987
Cefotaxime	1981	1981 (AmpC β-lactamase) 1983 (ESBL)
Linezolid	2000	1999

- **Problem has increased & today is a global issue.**
- **MDR-O, including the newly discovered agents.**
- **A worrisome situation.**

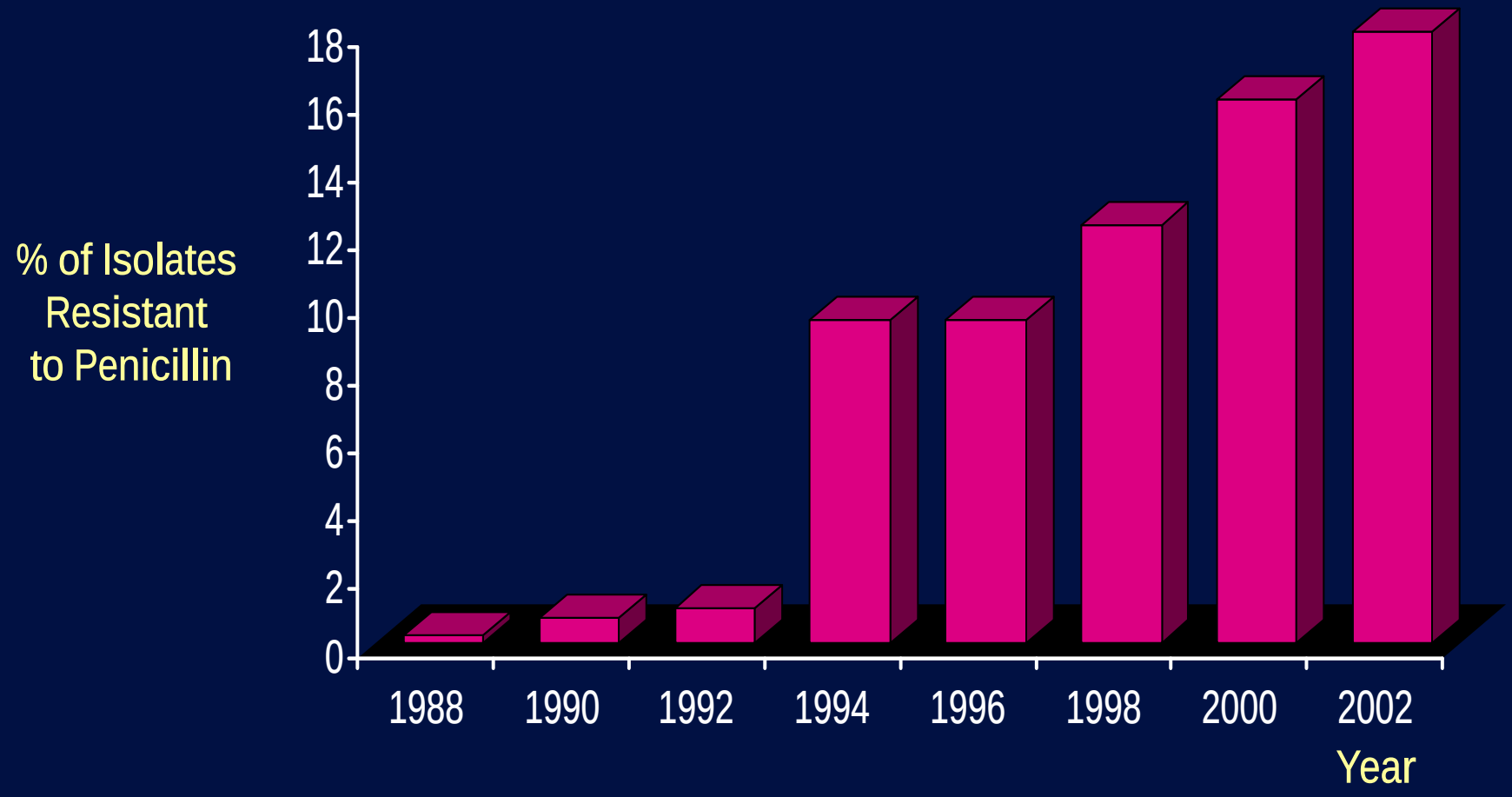
Q: Why is resistance to antibiotics a problem?

- serious threat to mankind
- prolonged hospital stay
  - treatment failures & secondary complications
  - require constant intensive cares
- increased cost
- higher mortality
- spread of MDR organisms
- outbreak of health-care-associated infections
- a challenge for treatment

EMERGING RESISTANT PATHOGENS: COMMUNITY

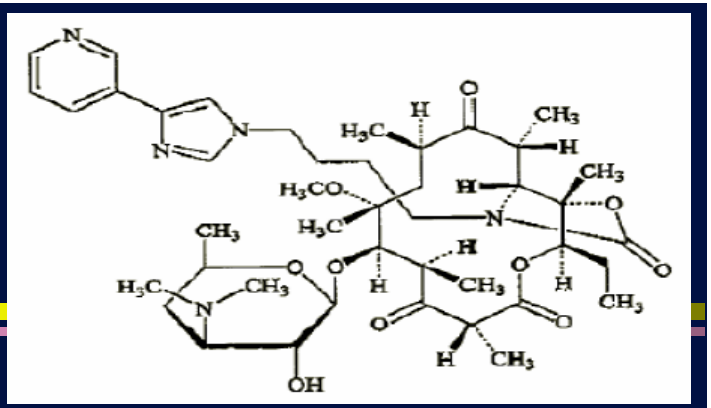
- HIV : Multiple agents
- *Pneumococcus* : Penicillin/cephalosporins, erythromycin
- *Mycobacterium tuberculosis* : INH, rifampin
- *Neisseria gonorrhoeae* : Penicillin, quinolones
- *Staphyloccus aureus* : Oxacillin
- *Plasmodium falciparum* : Chloroquine, mefloquine, others

Trend for Penicillin-Resistant (MIC ≥ 2 mg/ml) *S. pneumoniae* in the US (1988-2002)



Breiman RF, et al. *JAMA*. 1994;271:1831-1835. Doern GV, et al. *AAC*. 1996;40:1208-1213. Thornsberry C, et al. *DMID*. 1997;29:249-257. Thornsberry C, et al. *JAC*. 1999;44:749-759. Thornsberry C, et al. *CID* 2002;34(S1):S4-S16. Karlowsky, et al. *CID*. 2003;36:963-970. Sahm, et al. IDSA 2003, abstract 201. Data on file, Ortho-McNeil Pharmaceutical, Inc. In vitro activity does not necessarily correlate with clinical results.

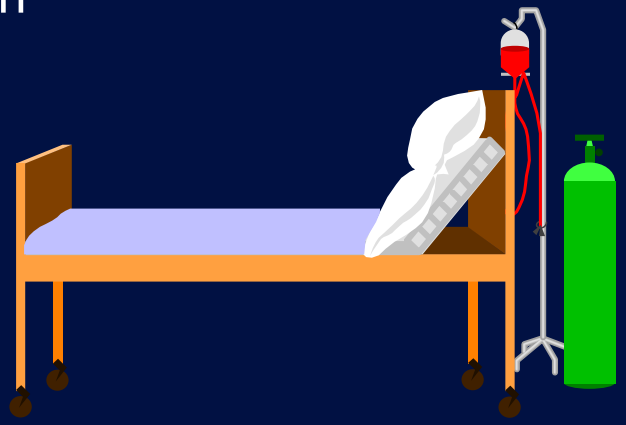
Telithromycin (Ketek®)



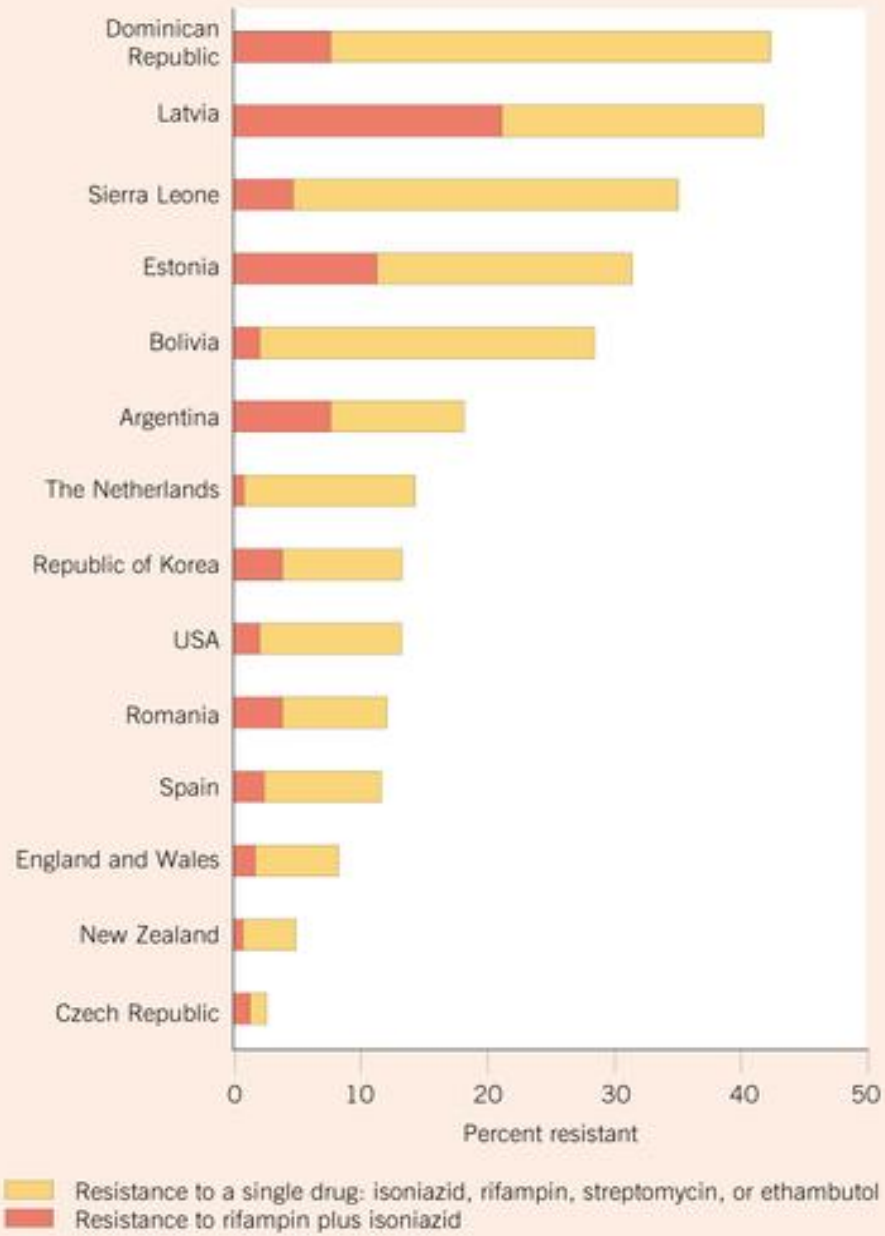
- A ketolide (structurally related to macrolides)
- Spectrum of activity
  - Group A, B, C and G Streptococci, Streptococcus pneumoniae (including multidrug resistant strains), MSSA
  - Listeria monocytogenes, Neisseria meningitidis, Moraxella catarrhalis, Haemophilus influenzae
  - Legionella, Chlamydia, Mycoplasma
  - No activity vs. MRSA, GRE, or any enteric gram-negative bacteria
- Indications
  - Mild to moderate community acquired pneumonia

EMERGING RESISTANT PATHOGENS:
HEALTH CARE FACILITIES

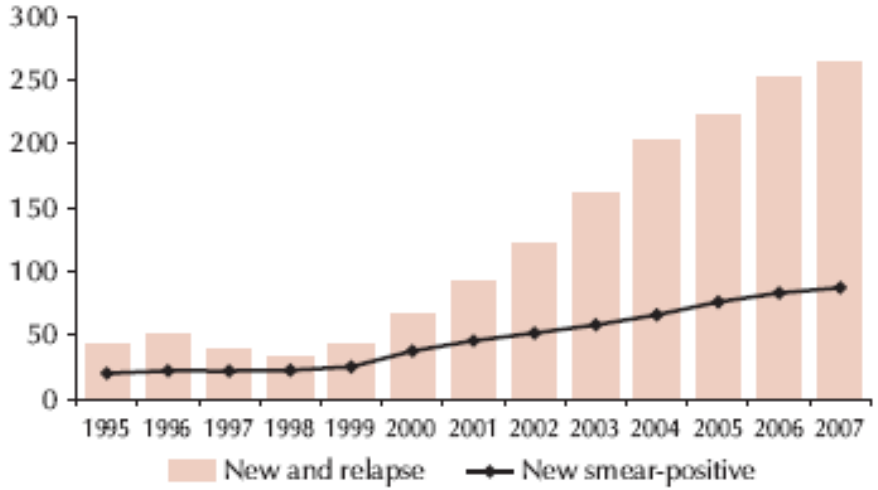
- *Staphylococcus aureus* : Oxacillin, vancomycin, linezolid
- *Enterococcus* : Penicillin, aminoglycosides, vancomycin, linezolid, dalfopristin-quinupristin
- *Enterobacteriaceae* : ESBL producers, carbapenems
- *Candida spp.* : Fluconazole
- *Mycobacterium tuberculosis* : INH, rifampin



GLOBAL DISTRIBUTION OF RESISTANCE TO ANTITUBERCULOSIS DRUGS



TB notification rate (per 100 000 population)



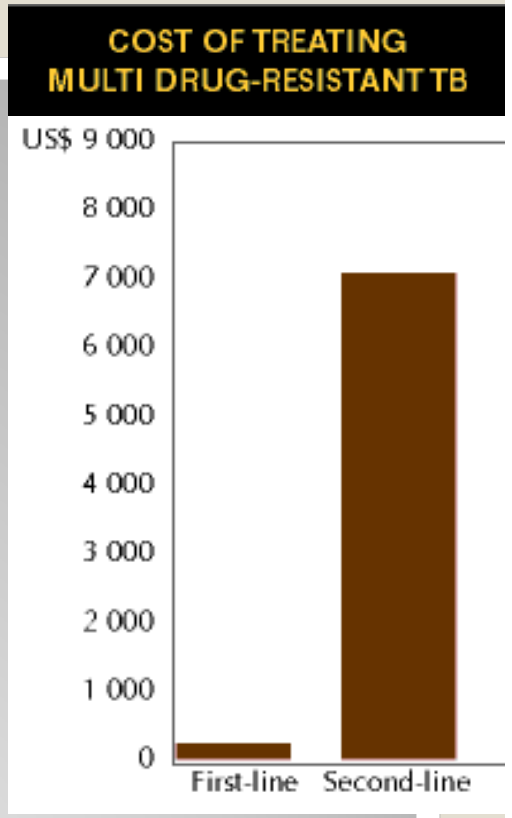
THE "DOTS" APPROACH IS THE CURE FOR TB
AND PROLONGS THE EFFECTIVENESS OF TB DRUGS

MDR-TB: "Multi-Drug-Resistant"

- Resistant to at least INH & Rifampin (first line drugs)

XDR-TB: "Extensively-Drug-Resistant Mtb"

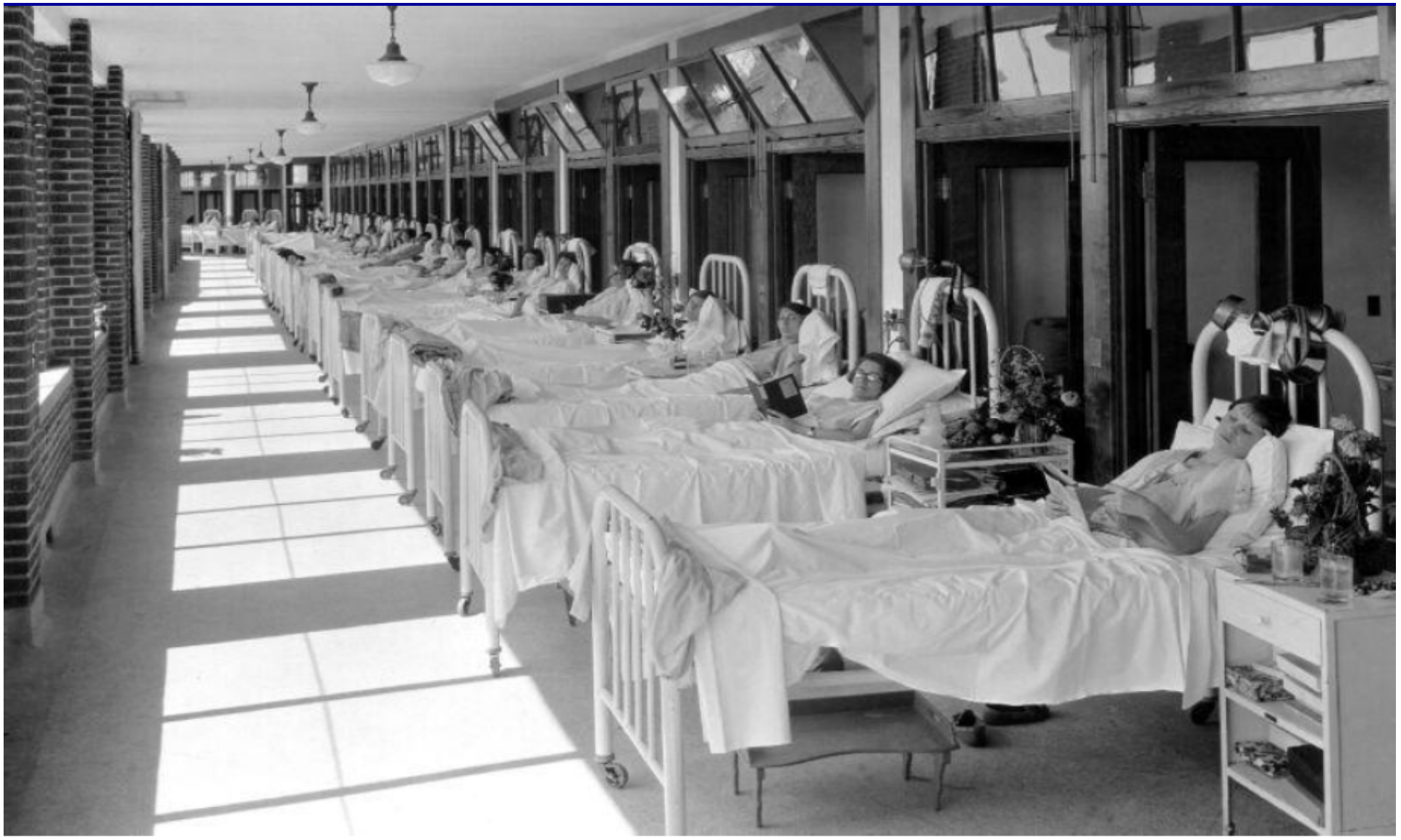
- Resistant to INH & Rifampin, **AND**
- Resistant to any Fluoroquinolone , **AND**
- Resistant to at least one of three injectable 2nd-line abx (capreomycin, kanamycin, and amikacin)



WHO estimate (2004) ½ million MDR-TB. Also estimated that 15-20% of the MDR-TB is actually XDR-TB.

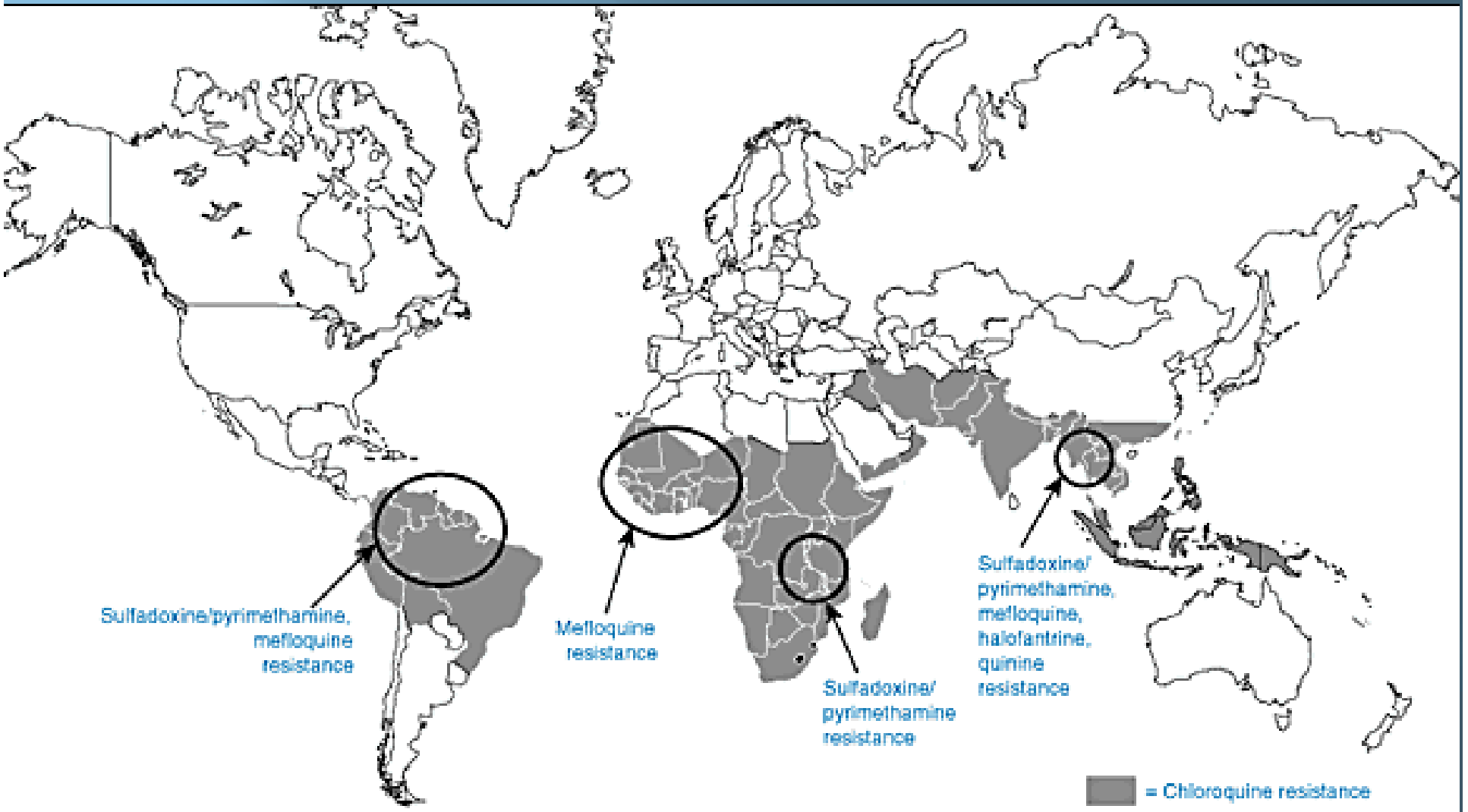
Drug Resistance!! Any Surprise?

- Resulted from overuse of abx
- Patient non-compliance
- Lack of adequate drugs in some parts of the world



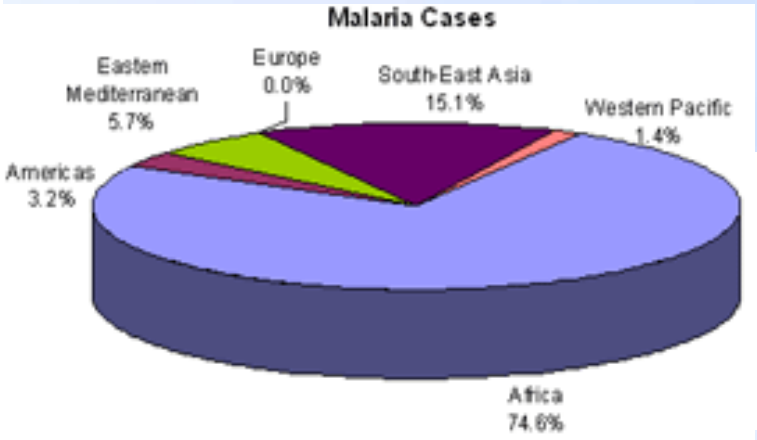
'We are back in the nineteenth century.'

Mario Raviglione, in charge of TB for WHO in 2007

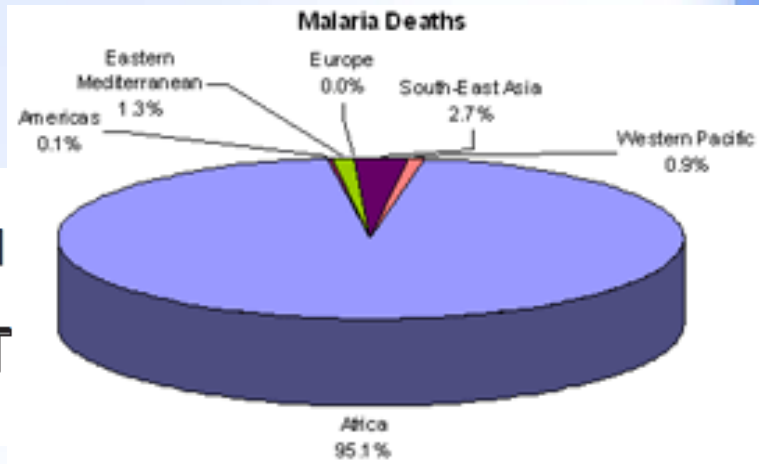

Sulfadoxine/pyrimethamine, mefloquine resistance
Mefloquine resistance
Sulfadoxine/ pyrimethamine resistance
Sulfadoxine/ pyrimethamine, mefloquine, halofantrine, quinine resistance
= Chloroquine resistance

25 April 2011
Achieving Progress and Impact

WORLD MALARIA DAY



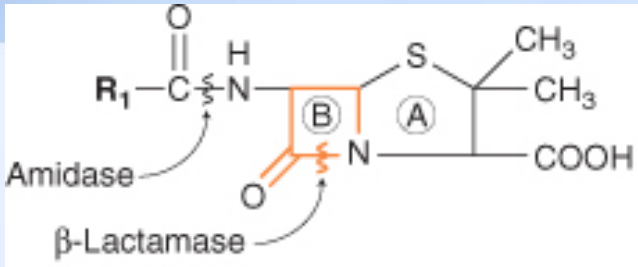
GLOBAL PLAN FOR ARTEMISININ RESISTANCE CONTAINMENT (GPARC)



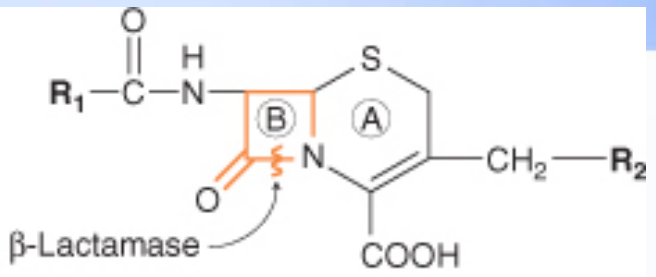
DRUG-RESISTANT MALARIA WOULD BE A GLOBAL CATASTROPHE.
TAKE THE RIGHT DOSE FOR THE RIGHT DURATION,
AND SUPPORT VECTOR CONTROL AND OTHER MEASURES.

β-lactam antibiotics

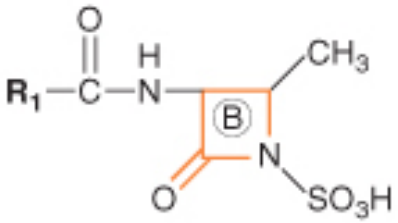
β-lactam ring: A hetero-atomic ring structure, consisting of 3 carbon atoms and 1 nitrogen atom. A lactam is a cyclic amide.



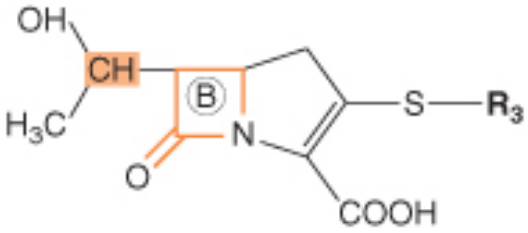
Penicillin nucleus



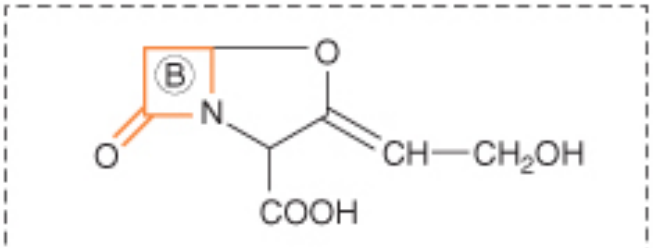
Cephalosporin nucleus



Monobactam nucleus
(β-lactamase resistant)

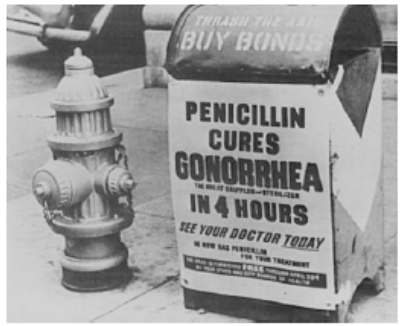


Carbapenem nucleus
(high resistance to β-lactamases)



Clavulanic acid
(inhibits many β-lactamases)

Doctors Prescribe PCN

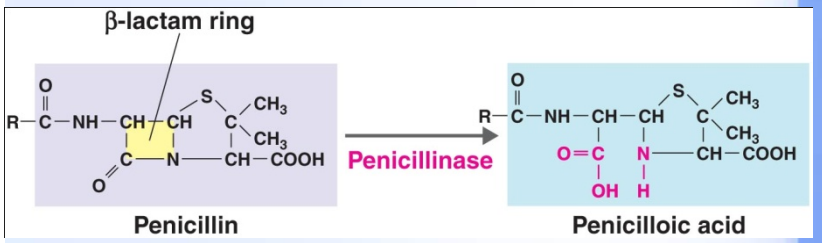


Bugs' Response:

Penicillinase

⇪PCN use ⇒ rapid emergence of Staph aureus w/plasmid-encoded Penicillinase

∴PCN ineffective

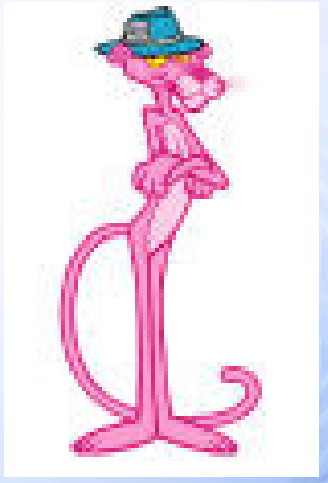


Doctors Now Prescribing 1st & 2nd Generation Cephalosporins:

- Cephalosporins became widely used for treatment of serious infections due to GNR in the 1980s

Bugs' Response:

Cephalosporinase



Doctors Now Prescribing 3rd Generation Cephalosporins:

- Resistance to these expanded-spectrum β-lactam abx quickly emerged.
- Because of their increased spectrum of activity, these enzymes were called ESBL
- >150 ESBLs

Bugs' Response:

ESBL

Antibiotic Profile

E. Coli (ESBL)

Antibiotic	MIC
Ampicillin	>=32 Resistant
Aztreonam	16 Resistant
Cefazolin	>=64 Resistant
Ceftazidime	16 Resistant
Ceftriaxone	>=64 Resistant
Cefuroxime	>=64 Resistant
Ciprofloxacin	>=4 Resistant
Gentamicin	<=1 Susceptible
Imipenem	<=1 Susceptible
Piperacillin	>=128 Resistant
Piperacillin/Tazobac	<=4 Susceptible
Tobramycin	<=1 Susceptible
Trimethoprim/Sulfa	>=320 Resistant
Levofloxacin	>=8 Resistant
Cefepime	2 Resistant

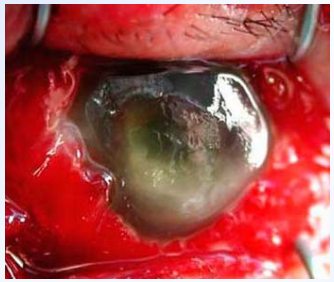
Doctors Now Prescribing Carbapenems:

Bugs' Response:

Carbapenemase (CRE / KPC)

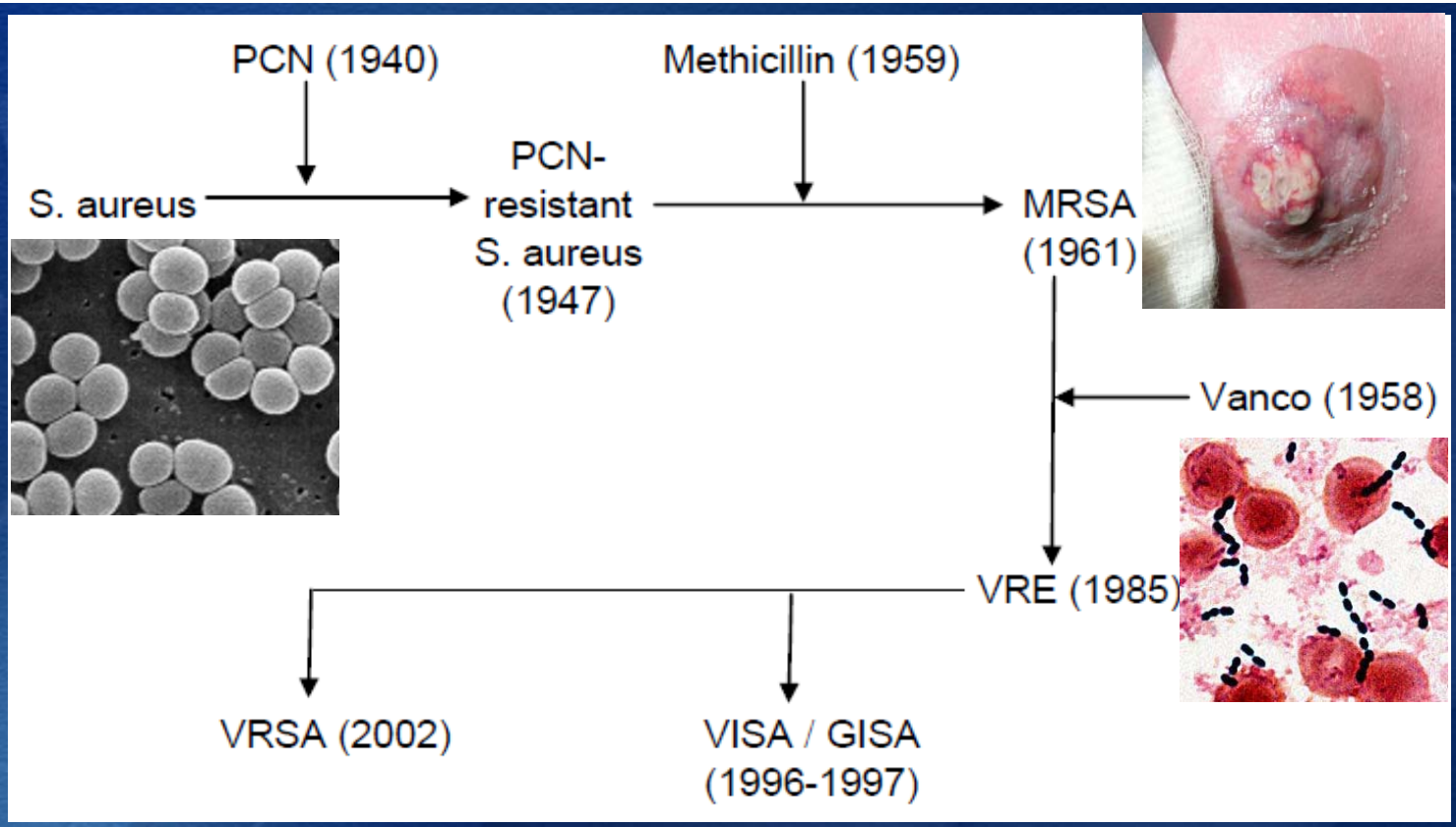
Carbapenemase **R**esistant **E**nterobacteriaceae

- First found to be produced by
  Klebsiella pneumoniae (KPC)
- Other GNR also produce carbapenemase
  (Serratia, Enterobacter, E.coli, Salmonella)



The future of antibiotic resistance… NDM-1

- **NDM-1- New Delhi Metallo-beta-lactamase gene confers resistance to all antibiotics except colistin and tigecycline**
- **Originally identified in December 2009 in *Klebsiella pneumoniae* from patient in New Delhi, India**
- **Currently found in *K. pneumonia, E. coli*, & Enterobacteriaceae in India, Pakistan, UK, US, Canada, & Japan**



VRSA & VISA (GISA)

(Glycopeptide-Intermediate Staph aureus)

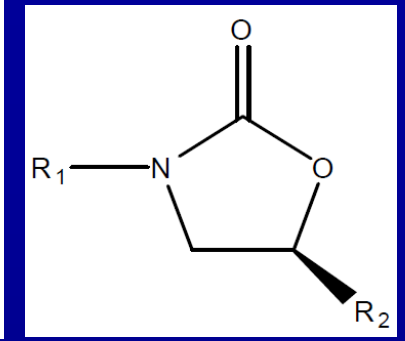
- 1992: **in vitro** passing of β-lactam-resistant plasmid from VRE to Staph aureus = GISA
- 2002: 1st documented case of **in vivo** transfer of high-level vanco resistance from VRE to Staph aureus. VRSA isolated from renal dialysis cath tip (Michigan).

CDC definition

- VISA: vancomycin MIC is 4-8 µg/ml
- VRSA: vancomycin MIC is ≥16 µg/ml

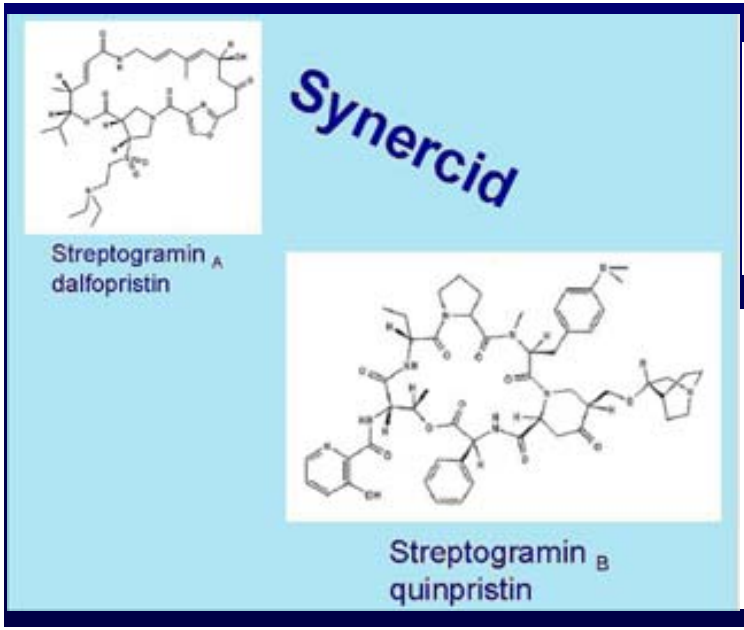
Oxazolidinones

- Linezolid (Zyvox) was approved by the FDA in 2000
- Effective against Vancomycin Resistant *Staph. aureus* (VRSA) and *Enterococci* (VRE)



Semisynthetic streptogramins

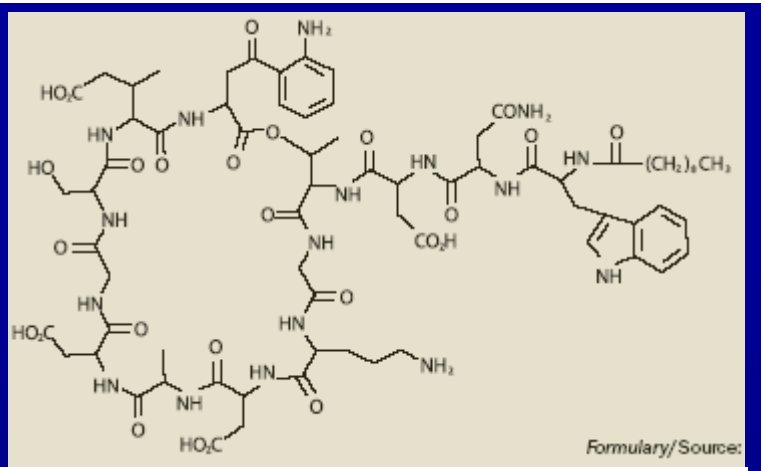
- Quinupristin/dalfopristin (Synercid) was approved by the FDA in 1999
- Effective against Vancomycin Resistant *Staph. aureus* (VRSA) and *Enterococci* (VRE)



They act by inhibiting bacterial protein synthesis. Individually, quinupristin and dalfopristin exhibit only very modest bacteriostatic activity, but combined together as an intravenous injection they are active against many Gram-positive bacteria.

action is to inhibit protein formation by binding to the 50S subunit of the bacterial ribosome. Dalfopristin changes the structure of the ribosome so as to promote the binding of quinupristin, which probably explains the improved effectiveness of the drugs when administered together.

Daptomycin (Cubicin®)

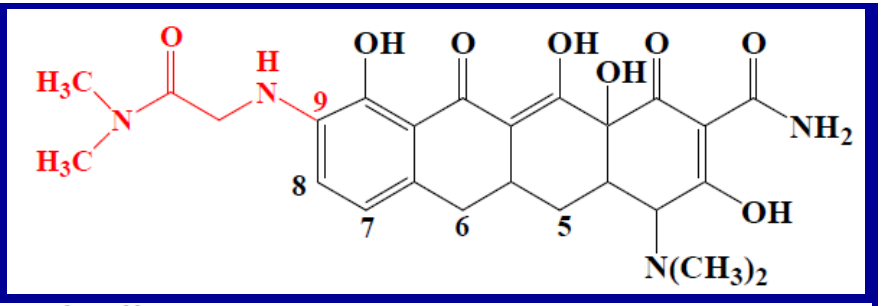


Lipopeptides

- Daptomycin (Cubicin) was approved by the FDA in 2003

- Cyclic lipoglycopeptide
- Spectrum of activity
  - MSSA, MRSA, Streptococcus pyogenes, Streptococcus agalactiae
  - Enterococcus faecalis (vancomycin-susceptible isolates only)
- Indications
  - Complicated skin and skin structure infections caused by susceptible Gram-positive microorganisms
  - Staphylococcus aureus bloodstream infections including those with right-sided infective endocarditis (MSSA and MRSA) (native valve)

Tigecycline (Tygacil®)



- Active against methicillin-resistant *S. aureus* and probably VRE (*in vitro*)
- Broad spectrum
- Approved for complicated intra-abdominal and skin and skin structure infections
- Not a substrate for tetracycline antiporters or ribosome protection proteins
- Intravenous administration
- Bacteriostatic

Glycylcyclines

- 9-Aminotetracyclines acylated with N-dimethylglycine
- Tigecycline was approved by the FDA in 2005

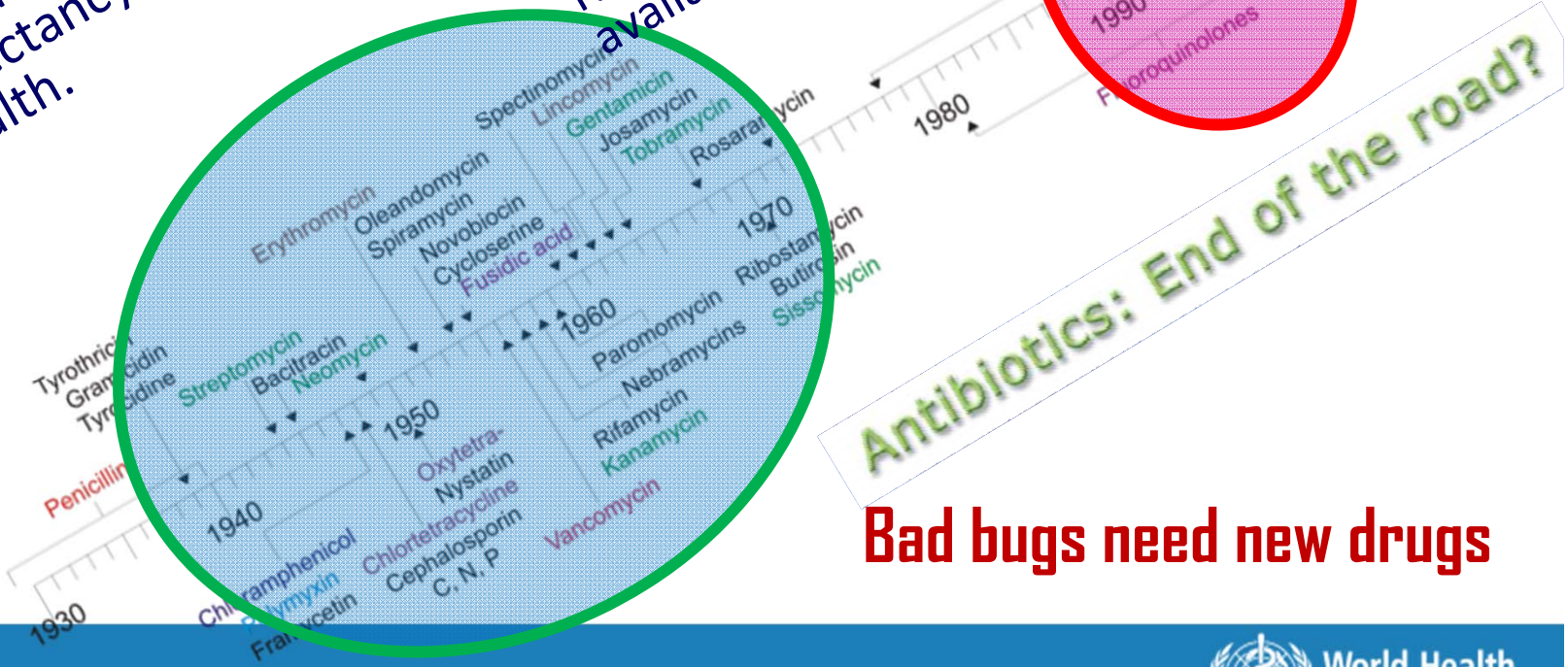
- Indications
  - Complicated skin infections by
    - Escherichia coli
    - Enterococcus faecalis (vanco-S isolates only)
    - Staphylococcus aureus (Methi-S or Methi-R)
    - Streptococcus agalactiae
    - Streptococcus pyogenes
    - Bacteroides fragilis
  - Complicated intra-abdominal inf: by
    - Citrobacter freundii
    - Enterobacter cloacae
    - E. coli, K. oxytoca, K. pneumoniae
    - Enterococcus faecalis (Vanco-S isolates only)
    - Staphylococcus aureus (Methi-S or Methi-R)
    - Bacteriodes fragilis
    - Clostridium perfringens
    - Peptostreptococcus micros

Superbugs* are visible manifestations of our prolonged failure to preserve antibiotics

** Methicillin resistant *Staph aureus*, MDR-& XDR Mycobacteria, ESBL producing Gram negative bacteria, NDM-1 producing enterobacteriaceae bacteria are few examples of superbugs

Q: Is this problem a serious one?

- Yes.
- Discovery of antibiotics in the **last 40–50 years**, bringing **gains** in life expectancy and human health.
- However, all these gains have been threatened because of MDR organisms emerged over the **last 20–30 years**.
- This has almost reached a dead end. Not many of newer agents would be available in the next 10 years.



Bad bugs need new drugs

World Health Organization
Regional Office for South-East Asia

Q: How can a MDR-O spread from one patient to another?

- **Most - through the hands**
  of doctors, nurses and other staff.
- accounts for ***majority*** of serious health-care associated infections.

Other modes of transfer

- Weak **infection control practices** &
  poor **general hygiene**

- overcrowding
- poor sanitation

- Wrong **prescription practices**
- **irrational use of antibiotic combinations**
  to treat minor or nonexistent infections,

  for the fear of losing the patient to another professional colleague
  (esply in the private sector)

The Chain of Infection

1. Infectious agent

4. Susceptible person

2. Reservoir

3. Means of transmission

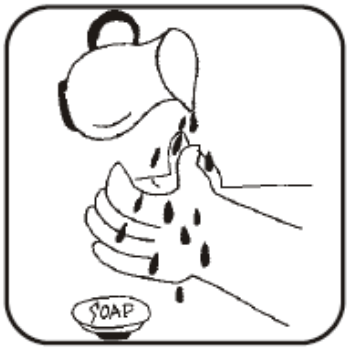
Hand Washing is Key!

It takes the whole village

…to break the chain.

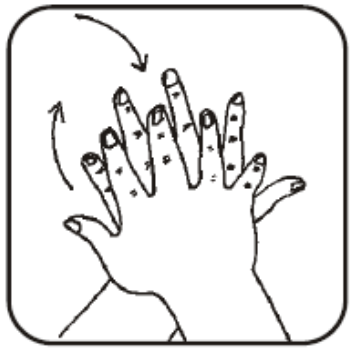
Do your part!

How to wash your hands well



Use soap all over your hands

Rub hands palm to palm



Clean the backs of your hands too

Clean between all fingers including thumb

Alcohol Based Hand Sanitizers

- CDC hand antiseptic agents of choice
  - Recommended by CDC based on strong experimental, clinical, epidemiologic and microbiologic data
  - Antimicrobial superiority
    - Greater microbicidal effect
    - Prolonged residual effect
  - Ease of use and application

Quick

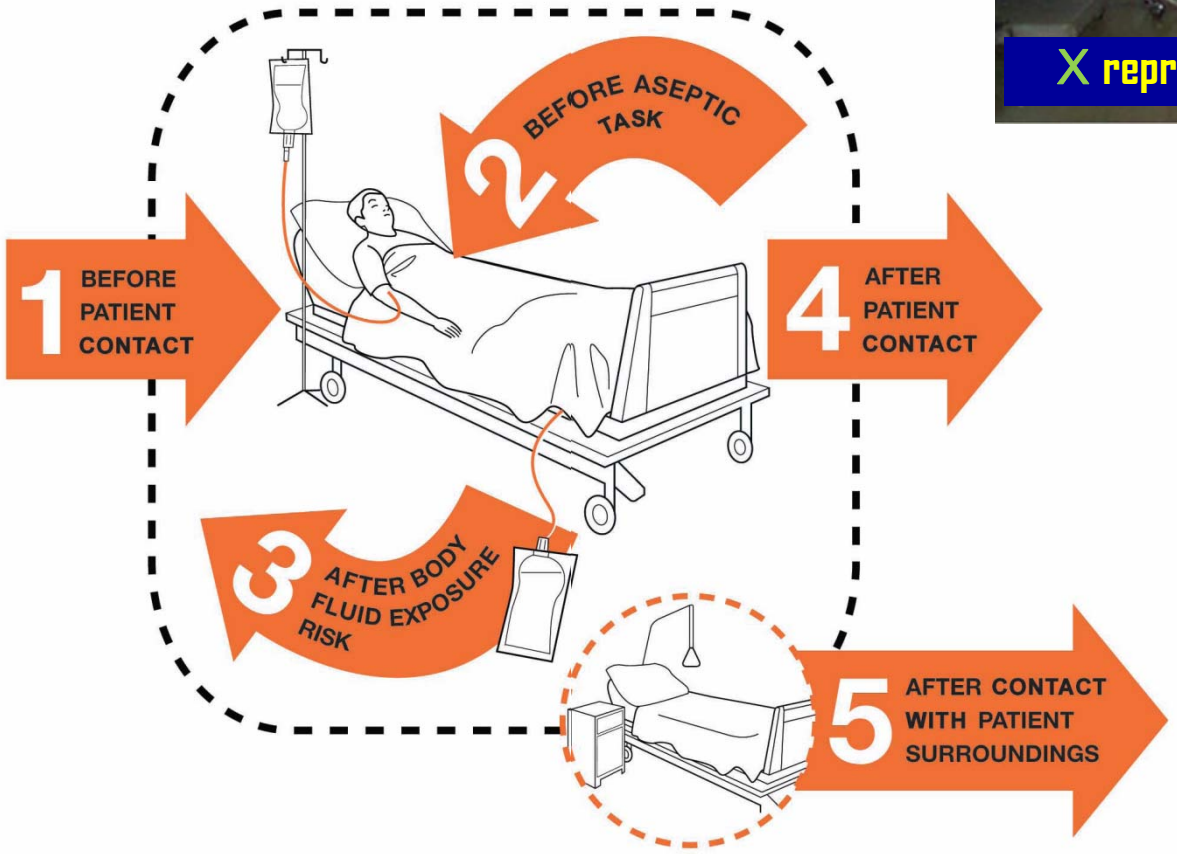
Easy to use

Very effective antisepsis due to bactericidal properties of alcohol

Hand-washing

By far the single most important aspect of controlling of HAI is hand washing.

X represents a positive *Enterococcus culture*



Q: “Inappropriate use of antibiotics” is an oftenheard term in the media. What does this mean?

- **Incorrect antibiotic being prescribed for a condition**.
  - Some conditions do not even warrant an antibiotic.

- **Wrong doses, incomplete schedules & inadequate timing of an antibiotic**
  - abuse by medical practitioners.

- **High-end** (& expensive) **antibiotics**
  (for patients with serious illness, admitted to ICU)
  being treated for a minor ailment on an outpatient basis in a clinic.

Q: Do people themselves contribute to the emergence of antibiotic resistance & to the abuse of antibiotics?

- Yes.
- Some patients hope to get rid of their ailment, however minor it may be, almost *instantly*.
- *Anxiety & impatience* prevail upon them to pressure or even “window shop” for a physician or doctor who would prescribe a “strong” antibiotic to rid of their condition in record time.

- A little knowledge is a dangerous thing,
- eg. people asking for **half a strip of ciprofloxacin or azithromycin** without having a proper diagnosis or prescription.

People themselves contribute to the abuse of antibiotics

- Pharmacy practices in developing countries are also partly responsible for the abuse, as it is possible to purchase any antibiotic, OTC.

- In the past, it was erroneously thought that **socioeconomic status** of a patient had a lot to do with **OTC sales** of antibiotics.
- It is now understood that patients belonging to **all strata** of society have been known to buy antibiotics in improper or *inappropriate ways*.

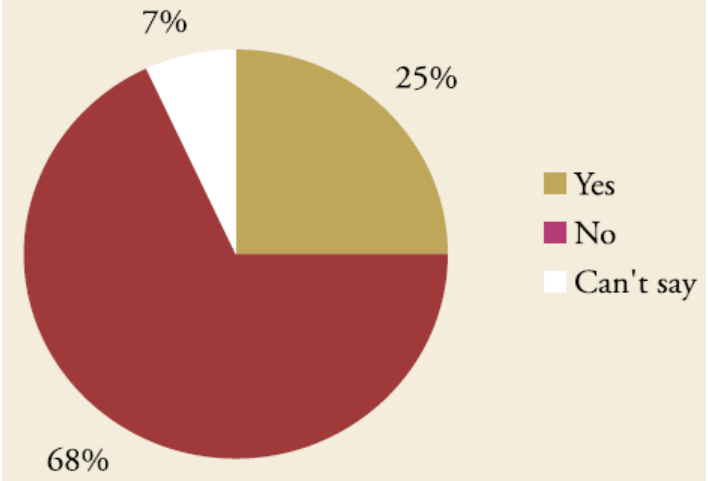
economic status – not taking full course of antibiotics

- economic burden compels
  "<u>cannot afford</u>" to buy the full schedule of an antibiotic
  patients **abort their treatment half way** & stop taking

- patients who are not economically disadvantaged are also known to stop treatment before the schedule ends
  since they "**<u>feel better</u>**"

Q: Should antibiotics be discontinued by the patient when he starts feeling better, even before completion of recommended course?

25% of responders said Yes



But stopping antibiotics before the course is finished leads to antibiotic resistance

Q: What is the role of the pharmaceutical industry in propagating antibiotic resistance?

- **Incorrect marketing strategies**

  giving incentives to the doctor who writes the *maximum number of antibiotic prescriptions*, pharmacists and other dealers for personal gain and profit

- Production of **quality drugs** with recommended antibiotic potency is also critical in preventing resistance.

- **Effective regulatory mechanisms** can ensure that pharmaceutical industry produces high-quality drugs.

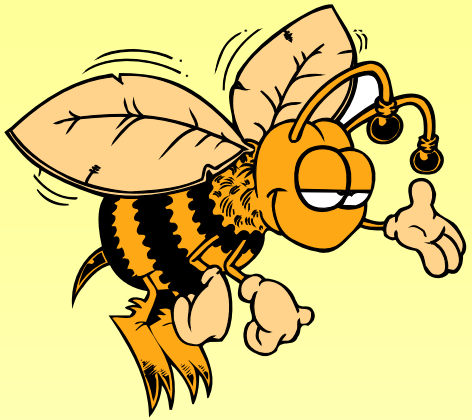
Q: How has poverty and lack of awareness aggravated the problem of antibiotic resistance in developing countries?

- Poverty
  - — buy whatever antibiotic sold to them OTC
  - — also do not finish a full course

- in addition, a majority of the population
  - — may not have access to good health-care facilities
  - — do not have means or opportunity to see a qualified physician

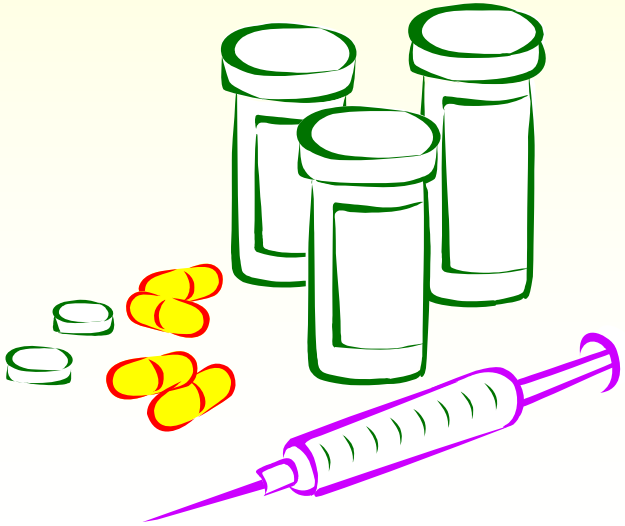
- This has led to the emergence of unqualified doctors, who are
  - — not aware of the basics of medicine.
  - — may prescribe suboptimal doses & schedules of antibiotics.

RATIONALIZE PRESCRIPTION AND USE OF ANTIBIOTICS



Rational Use of ED plays a crucial role in prevention & control of diseases!

- **ESSENTIAL DRUGS CONCEPT &**
- **RATIONAL PRESCRIBING PRACTICE**



Essential Drugs (ED) Concept

- **in countries with financial constraint, all drugs cannot be made available**

- a list of minimum medicine needs for a basic health care system

- **most needed for the health care of the majority of population**
  - generic (non-proprietary) preparations, less expensive

- list is different in different countries, different situations
- s/b **updated every 3 years**

- priority conditions are selected on the basis of current & estimated future public health relevance.

Essential Drugs (ED)

Efficacy proven

Acceptable quality & safety

Available at all time

Affordable price by patient

Complementary Drugs (CD)

- to supplement Essential Drugs
- as alternatives when resistance develops to ED
- made available as fund permits

e.g., Erythromycin (E), Azithromycin (C)

Gentamicin (E), Amikacin (C)

- 2002 MEDP (Myanmar Essential Drugs Programme)

ESSENTIAL AND COMPLEMENTARY DRUGS (Myanmar Essential Drug Project, Ministry Of Health, 2002)

6. Anti-infective Drugs

Anthelmintics

Intestinal anthelmintics

Mebendazole (E)
Niclosamide (E)
Albendazole (E)

Antifilaria

Diethylcarbamazine (citrate) (E)
Ivermectin (E)

Antibacterials

Penicillins &Cephalosporins

Amoxicillin (trihydrate/sodium) (E)
Amoxicillin with Clavulanic acid (Co-amoxiclav) (E)
Benzathine penicillin(E)
Benzyl penicillin G (sodium/potassium) (E)
Flucloxacillin (sodium) (E)
Cloxacillin (E)
Phenoxymethyl penicillin(potassium) (E)
Procaine penicillin G (E)
Fortified procaine penicillin G (E)
Cephalexin (E)
Cephradine (E)
Cefuroxime(sodium)(C)
Cefaclor (C)
Ceftriaxone(sodium)(C)
Ceftazidine (pentahydrate) (C)

Other Antibacterials

Chloramphenicol (palmitate/ sodium succinate) (E)
Co-trimoxazole (E)
Doxycycline (hydrate) (E)
Erythromycin (stearate/ ethylsuccinate/ lactobionate) (E)
Gentamicin (sulphate) (E)
Metronidazole (benzoote) (E)
Neomycin (sulphate) (C)
Azithromycin (dihydrate) (C)
Amikacin (sulphate) (C)
Norfloxacin (E)
Ciprofloxacin (E)
Clindamycin (C)

Rational Prescribing Practice

- ✓ - appropriate drug
- ✓ - effective
- ✓ - acceptable quality & safety
- ✓ - affordable
- ✓ - correct dose, interval & duration
- ✓ - not irrational

Irrational prescribing

(a) **Extravagant prescribing**

(b) **Over prescribing**

(c) **Under prescribing**

(d) **Incorrect prescribing**

Q: Which common ailments for which antibiotics are prescribed should not usually be treated in this way?

- **respiratory illnesses** (common cold, cough, bronchitis, wheezing, a running nose, sore throat)

  (usually symptoms of viral infections, often seasonal)

- **diarrhoeas**

  (most are self-limiting & may be caused by viruses)

Antibiotics are misused.

- Almost every episode of GE is treated with varying doses of antibiotics for different lengths of time.

- Antibiotics have *no effect* on these viruses.

FREQUENCY OF ANTIBIOTIC USE

Diagnosis	Children	Adult
Common cold	44%	51%
URI	46%	52%
Bronchitis	75%	66%

Nyquist A-C, et al. JAMA 1998;279:875
Gonzoles R, et al. JAMA 1997;278:901

Common cold and flu do NOT need antibiotics

Take only fluids and paracetamol

Q: If the mucus from a running nose turns yellow, does the infection need an antibiotic?

- **not necessarily**

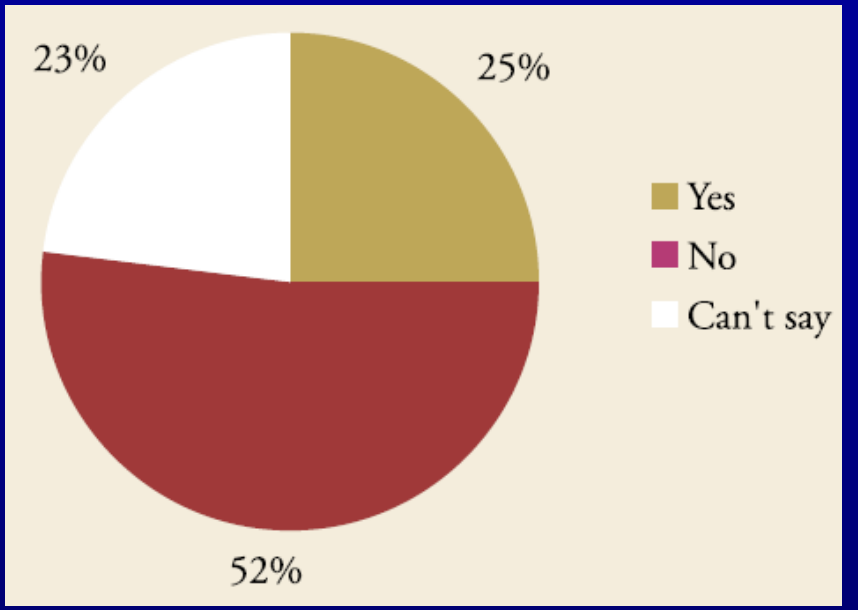
- It is *possible* that the mucus has thickened & it could also change colour during a cold.

Perceptions of communities and physicians in use of antibiotics

Q: Should antibiotics be given to a child with any fever?

25% said Yes

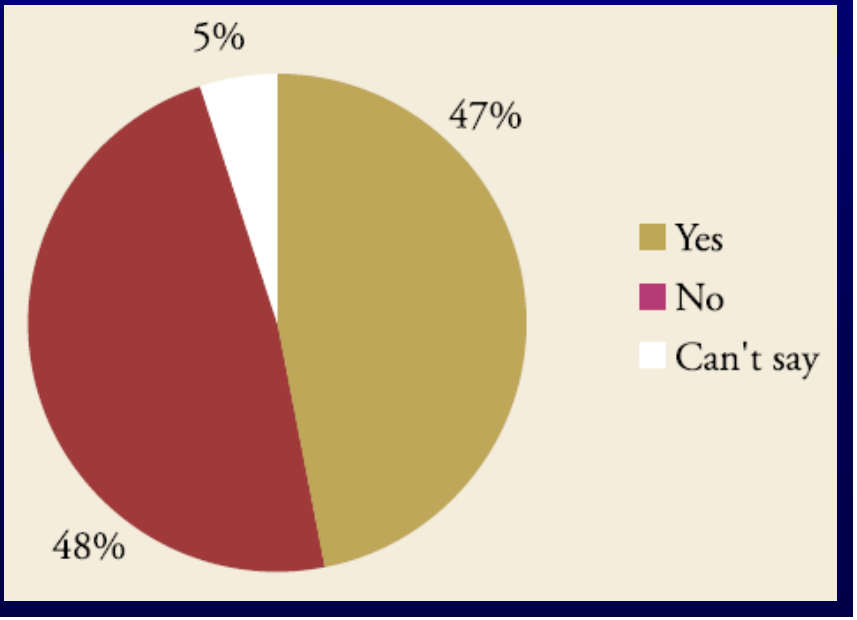
But antibiotics have no effect on viral fevers



Q: Will you wish to change your doctor if he fails to prescribe antibiotics for your common cold?

47% of patients said Yes

But antibiotics cannot cure the common cold!



Q: Antibiotic are used in animal industry for various purposes. Does this have an impact on antibiotic resistance?

- Antibiotics have been used in animals
  as a growth-promoting agent as well as for treating infections
- such as tetracyclines, quinolones
- accumulate in the tissues of animals

- Bacteria exposed to these low concentrations of antimicrobial agents tend to develop resistance.

- passed on from animals to humans
  - through food and unhygienic practices.
  - directly from animals by contact.

- salmonella, campylobacter

Antibiotics in Meat

To boost the growth of closely confined swine, U.S. farmers buy feed containing subtherapeutic doses of any of 21 antibiotics.

Shooting Antibiotics into Cattle

Antibiotic misuse

- Cheaper/easier than cleanliness
- Agricultural use
- Incorrect use
- Inappropriate prescription
- Water contamination

Antimicrobial Resistance

World Health Day 2011

Use antibiotics rationally

- Antibiotic resistance is a major problem world-wide
- Resistance is inevitable with use
- No new class of antibiotic introduced over the last 2 decades
- Appropriate use is the only way of prolonging the useful life of an antibiotic

ANTIBIOTIC

RATIONAL USE & MISUSE

The first consideration in selecting an antibiotic is whether it is even indicated.

16% of physicians will prescribe antibiotics to a patient with non-specific fever

17% of physicians feel that all patients with cough need antibiotics

18% of physicians recommend antibiotic therapy for diarrhoea

Overprescribing and overuse of antibiotics leads to antibiotic resistance.

The reflex action
to associate fever with treatable infections and
prescribe antibiotics
without further evaluation is
irrational and potentially dangerous.

Clinical Use of Antibiotics

Selection of an Antimicrobial Agent

requires clinical judgment and

detailed knowledge of pharmacological and

microbiological factors.

Antibiotics have 3 general uses:

empirical therapy

definitive therapy

prophylactic therapy

Empiric (or presumptive) therapy

- Use of antibiotic ***before*** the pathogen responsible for a particular illness or the susceptibility to a particular antimicrobial agent is *known*.

- Justification is the hope that early intervention will improve the outcome. *In critically ill patient, a delay could prove fatal.*

- Eg. acutely ill patients with infections of unknown origin
  (eg. symptoms characteristic of *meningitis*)
  febrile episodes in *neutropenic* cancer patients
  certain episodes of *community-acquired pneumonia*

  for public health reasons
  eg. *urethritis* in a young sexually active man usually requires treatment for *N gonorrhoeae* & *Chlamydia*

Empirical therapy

should cover all the likely pathogens,

preferably, a single broad-spectrum agent.

Once the infecting microorganism is identified,

empiric therapy is optimally modified to

Definitive therapy, which is

typically narrower in coverage, low-toxicity drug, is

given for an appropriate duration

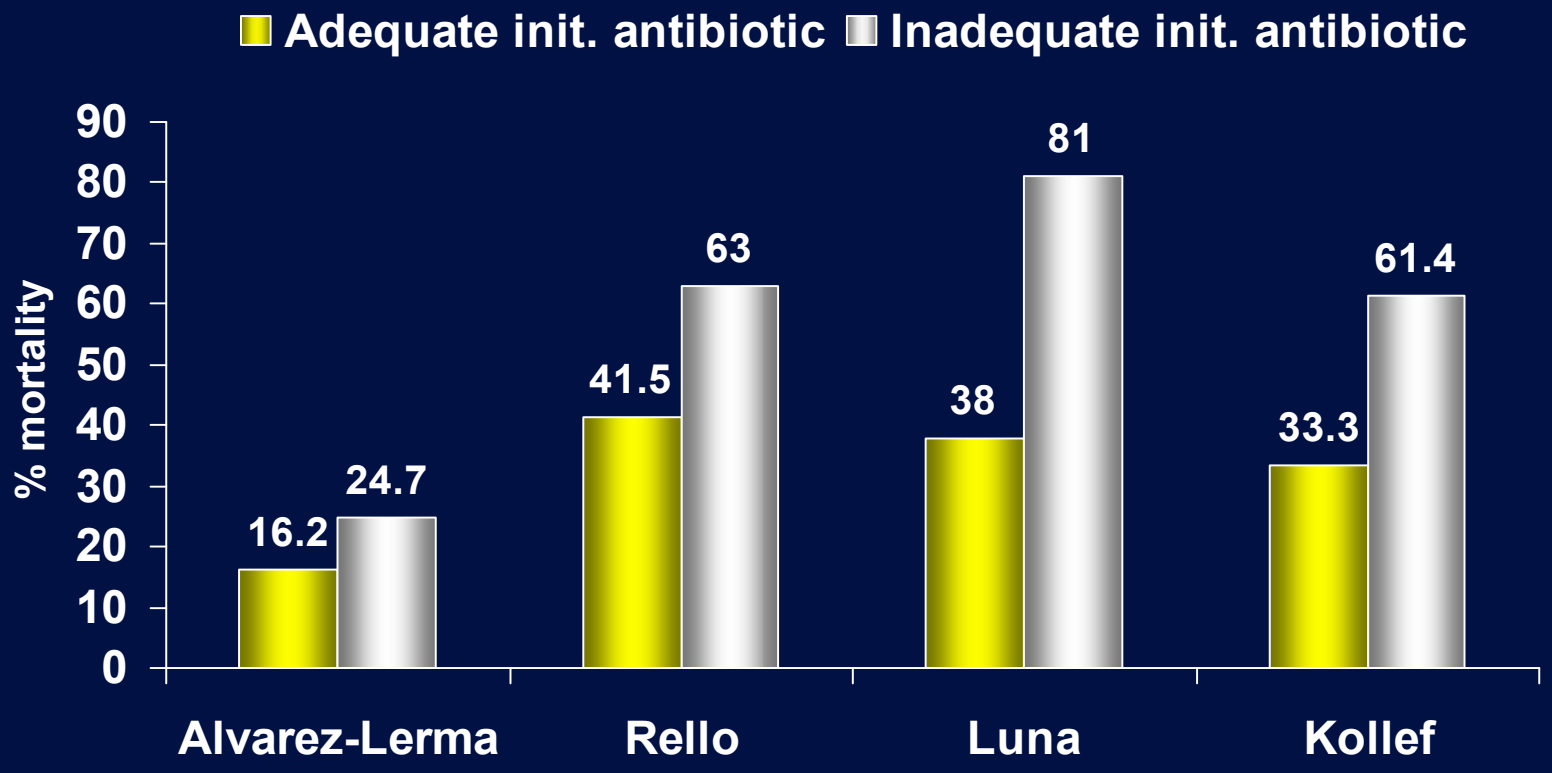
- based on the results of clinical trials or experience.

Failures to identify the infecting microorganism and

to narrow the antibiotic spectrum thereafter

are ***common misuses*** of antibiotics.

Importance of Initial Empiric Antibiotic Selection



Alvarez-Lerma F. *Intensive Care Med* 1996 May;22(5):387-94.

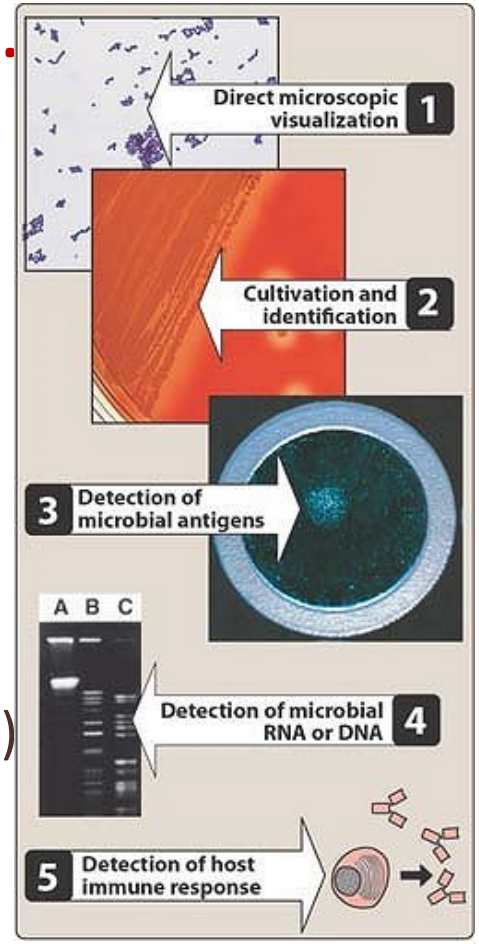
Rello J, Gallego M, Mariscal D, et al. *Am J Respir Crit Care Med* 1997 Jul;156(1):196-200.

Luna CM, Vujacich P, Niederman MS et al. *Chest* 1997;111:676-685.

Kollef MH and Ward S. *Chest* 1998 Feb;113(2):412-20.

Initiation of empiric therapy

should follow a specific & systematic approach.



Formulate a Clinical Diagnosis

(eg, pneumonia, cellulitis, sinusitis)

Obtain Specimens for Laboratory Examination

microscopy or simple examination (urine)

cultures (blood, sputum, urine, CSF, stool)

non-culture methods (antigen testing, PCR, serology)

Formulate a Microbiologic Diagnosis

History, physical examination, & immediately available laboratory results (eg, Gram stain of urine or sputum) may provide highly specific information.

Choice of Antibiotic: **patient factors**:

1.**Immune system**:

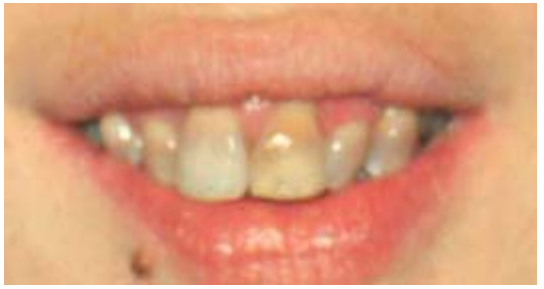
- alcoholism, diabetes, HIV infection, malnutrition, advanced age, immunosuppressive therapy

Higher-than-usual doses of bactericidal agents or longer courses of treatment are required.

2. **Age**:

Neonates particularly vulnerable to the toxic effects of **chloramphenicol** & **sulfonamides**.

Young children should not be treated with **tetracyclines**, which affect bone growth.



Choice of Antibiotic: **patient factors**:

(3) **renal dysfunction**

(4) **hepatic dysfunction**

Dosage Adjustment Needed in Renal Impairment	Acyclovir, amantadine, **aminoglycosides**, aztreonam, **cephalosporins**,[1] clarithromycin, cycloserine, daptomycin, didanosine, doripenem, emtri-citabine, ertapenem, ethambutol, famciclovir, fluconazole, flucytosine, foscarnet, ganciclovir, imipenem, lamivudine, meropenem, penicillins,[3] quinolones, rimantadine, stavudine, telbivudine, telithromycin, tenofovir, terbinafine, trimethoprim-sulfamethoxazole, valacyclovir, vancomycin, zalcitabine, zidovudine
Contraindicated in Renal Impairment	Cidofovir, methenamine, nalidixic acid, nitrofurantoin, sulfonamides (long-acting), **tetracyclines**[2]
Dosage Adjustment Needed in Hepatic Impairment	Amprenavir, atazanavir, chloramphenicol, clindamycin, **erythromycin**, fosamprenavir, indinavir, metronidazole, rimantadine, tigecycline

[1]Except cefoperazone and ceftriaxone.

[2]Except doxycycline and possibly minocycline.

[3]Except antistaphylococcal penicillins (eg, nafcillin and dicloxacillin).

Choice of Antibiotic: **patient factors**:

5. **Pregnancy**

US FDA categories of antimicrobials & fetal risk.

CATE-GORY	DESCRIPTION	DRUG
A	No human fetal risk or remote possibility of fetal harm	
B	No controlled studies show human risk; animal studies suggest potential toxicity	β-Lactams β-Lactams with inhibitors Cephalosporins *Aztreonam* *Clindamycin* *Erythromycin* *Azithromycin* *Metronidazole* *Nitrofurantoin* Sulfonamides
C	Animal fetal toxicity demonstrated; human risk undefined	*Chloramphenicol* Fluoroquinolones *Clarithromycin* *Trimethoprim* *Vancomycin* *Gentamicin* *Trimethoprim-sulfa-methoxazole*
D	Human fetal risk present, but benefits outweigh risks	Tetracyclines Aminoglycosides (except *gentamicin*)
X	Human fetal risk present but does not outweigh benefits; contraindicated in pregnancy	

6. prior adverse drug effects

7. epidemiologic exposure

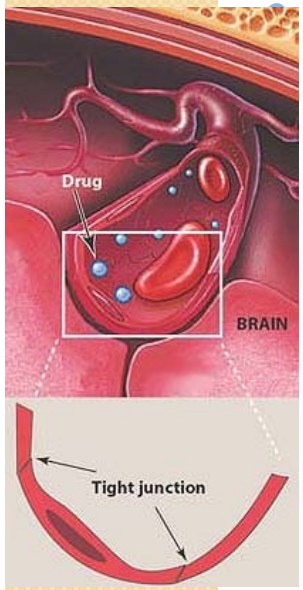
(eg, exposure to a sick family member or pet, recent hospitalization, recent travel, occupational exposure, or new sexual partner)

Choice of Antibiotic: **pharmacologic factors**:

pharmacokinetic properties & drug delivery to the site of infection

- Ideal drug for ambulatory patient
- **good oral bioavailability** & a long plasma half-life so that
- **taken only once or twice a day**.

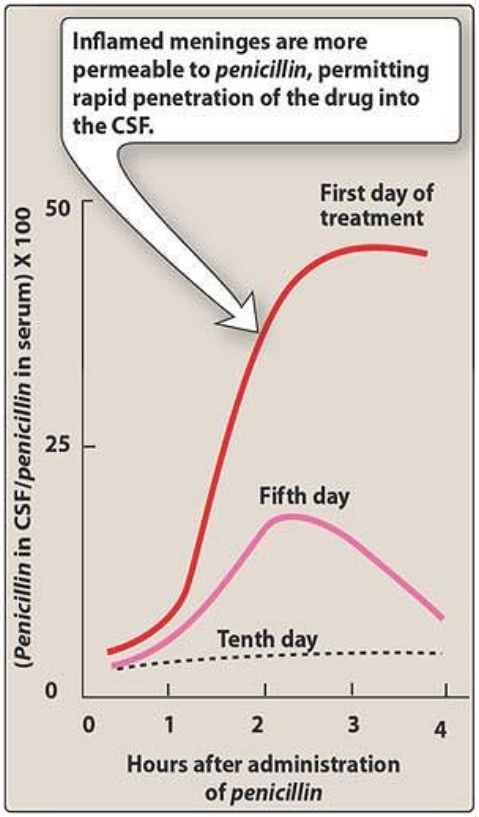
- Site of infection & antibiotic penetration
- **<u>CSF penetration</u>**



quinolones, metronidazole,
- significant CNS penetration

β-lactam antibiotics, such as penicillin G,
intact BBB - limited penetration
meningitis (inflamed) - permeability ↑.

aminoglycoside - poor penetration.
(can be given intrathecally)



Choice of Antibiotic: **pharmacologic factors**:

pharmacokinetic properties & drug delivery to the site of infection

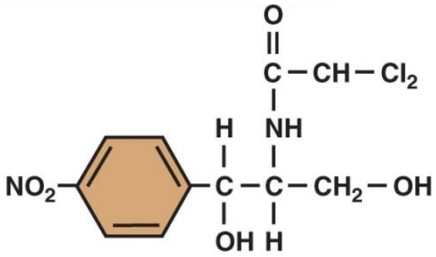
- Because antibiotic concentrations are low in bone, patient with **osteomyelitis** must usually be treated with antibiotics for several weeks.
- Urine concentration of an antibiotic can be 10 to 50 times the peak serum concentration. For this reason, **UTI** can be easier to treat than infections at other sites.

- **Route of elimination** affects both selection & use of antibiotics.
- Drugs that are eliminated by **renal** excretion are more effective for **UTI** than drugs largely metabolized or undergo biliary excretion.

Choice of Antibiotic: **pharmacologic factors**:

Adverse effect profile

- important to consider **risk-to-benefit ratio**
- **β-lactam & macrolide** antibiotics cause a relatively **low incidence of organ system toxicity** & are often used to treat minor infections, including infections in pregnant women.
- In contrast, **aminoglycosides** cause relatively **high incidence of severe adverse effects** & are usually reserved for serious or life threatening infections.
- **Chloramphenicol**
  because of potential for serious toxicity to the patient, reserved for life-threatening infections.



- [Note: Safety is related not only to the **inherent nature of the drug** but also to **patient factors** that can predispose to toxicity.]

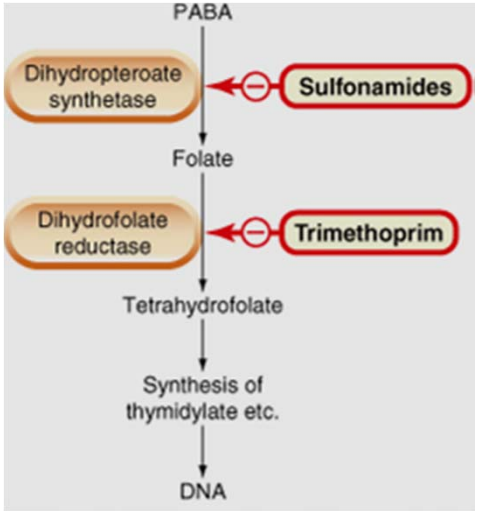
Genetic polymorphisms

- important factor in inter-individual differences in toxic effects of antibiotics

Choice of Antibiotic: **pharmacologic factors**:

Drug interaction: Synergism in antibacterial combinations

- Sequential inhibition of successive steps in metabolism
  (eg. sulphonamide + trimethoprim)



- Sequential inhibition of protein synthesis (eg. Syncercid®)
- Facilitation of drug entry of one antibiotic by another
  (eg. β-lactam + aminoglycoside)
- Inhibition of inactivating enzymes
  (eg. ampicillin + clavulanic acid)

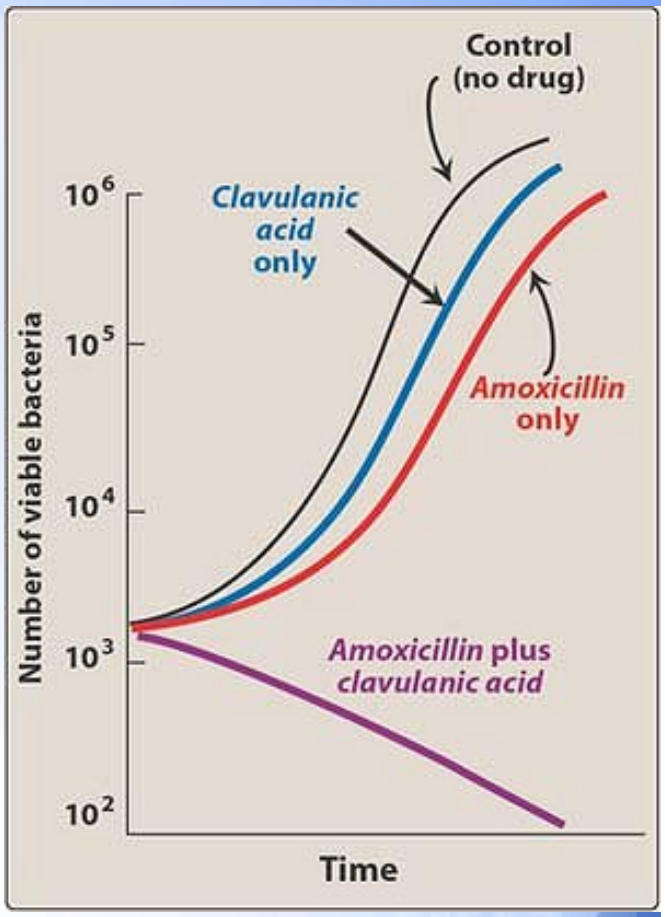
Penicillin + β-lactamase inhibitor

AUGMENTIN® (Amoxicillin + Clavulanic acid)

TIMENTIN® (Ticarcillin + Clavulanic acid)

UNASYN® (Ampicillin + Sulbactam)

ZOSYN® (Piperacillin + Tazobactam)



Choice of Antibiotic: **pharmacologic factors**:

Drug interaction: Antagonism in antibacterial combinations

- a bacteriostatic drug prevents bactericidal activity of another (eg. Tx of meningitis)

- Competition for drug binding sites
  eg. macrolide – chloramphenicol combinations

- Inhibition of cell wall permeability mechanisms
  eg. chloramphenicol – aminoglycoside combinations

- Induction of β-lactamases by β-lactam drugs such as imipenem & cefoxitin combined with *older* β-lactam drugs that are β-lactamase unstable

Choice of Antibiotic

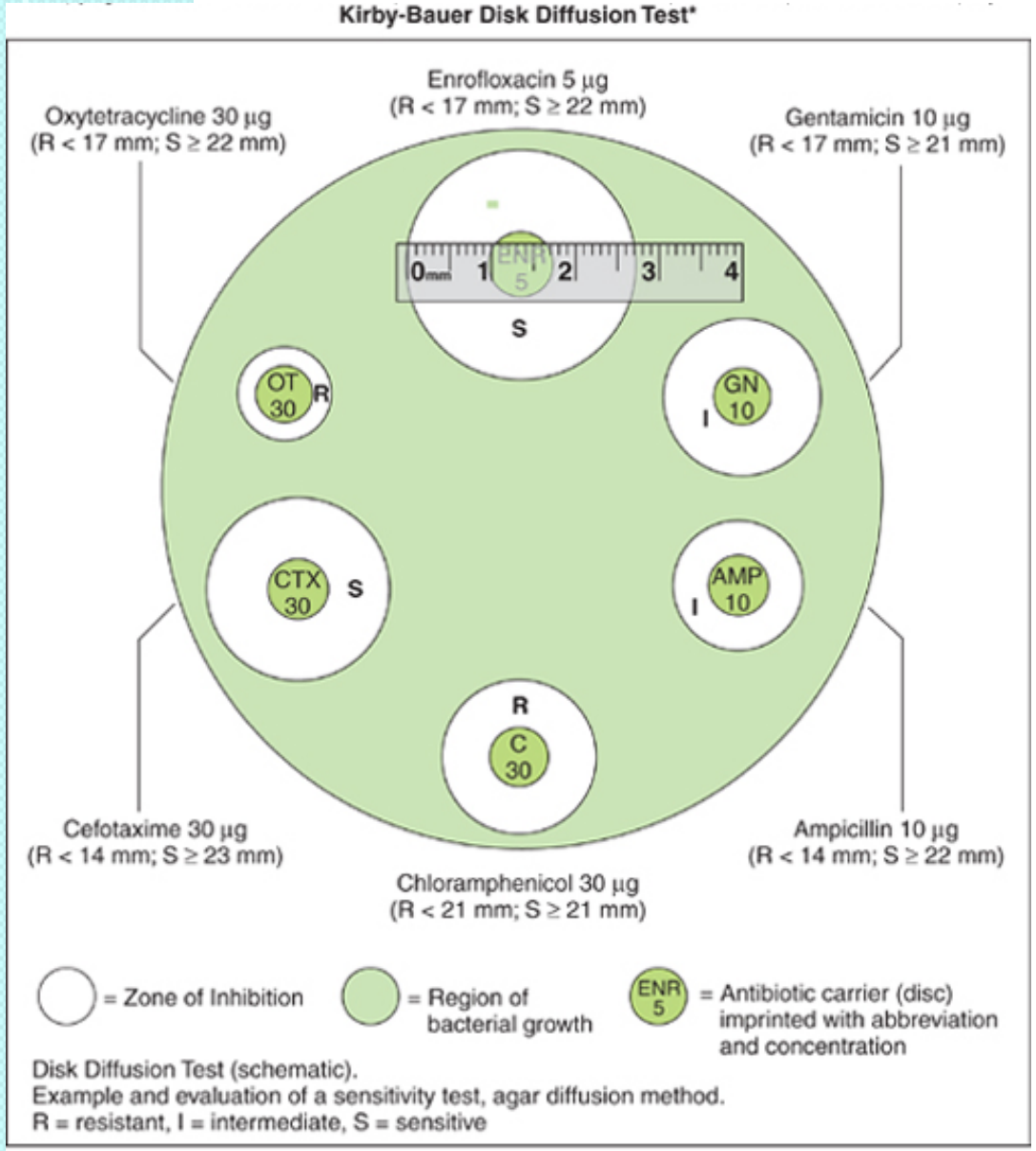
Antimicrobial susceptibility of infective organisms

- Some pathogens, such as Strept. pyogenes & Neisseria meningitidis, usually have **predictable** susceptibility patterns.

In contrast, most G (-)ve bacilli, enterococci, staphylococcal species often show **unpredictable** susceptibility patterns and *require susceptibility testing.*

Choice of Antibiotic

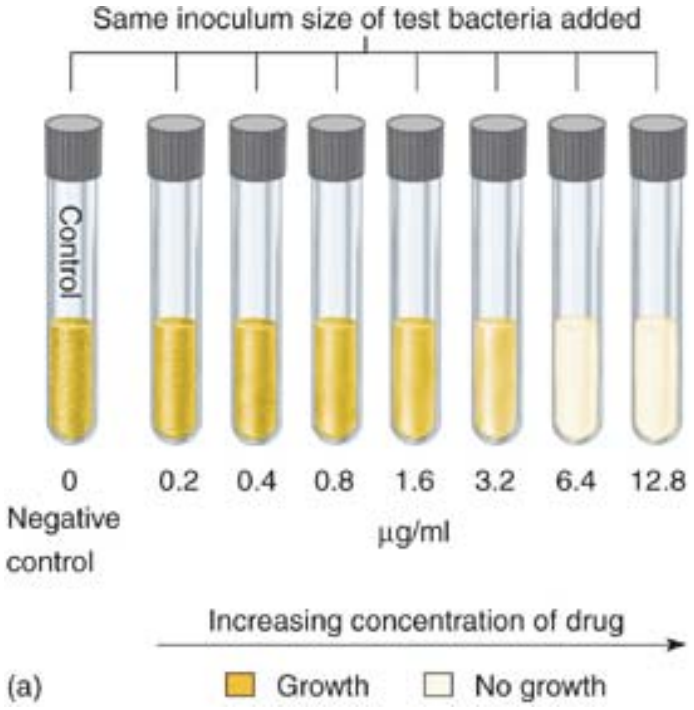
Testing for microbial sensitivity



*R and S values differ from table 12.8 due to differing concentrations of the antimicrobials.

Various methods are used, including disk-diffusion, dilution test, and automated broth dilution.

The results are either reported on a semi-quantitative scale (i.e., **resistant**, intermediate, or **susceptible**) or in terms of **MIC**.

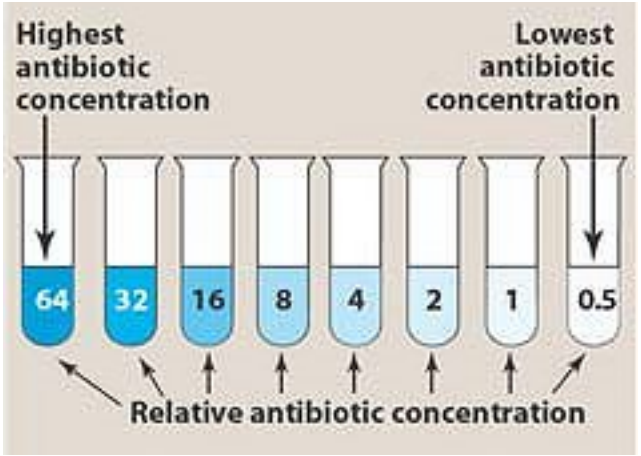


Choice of Antibiotic

Determination of antimicrobial susceptibility

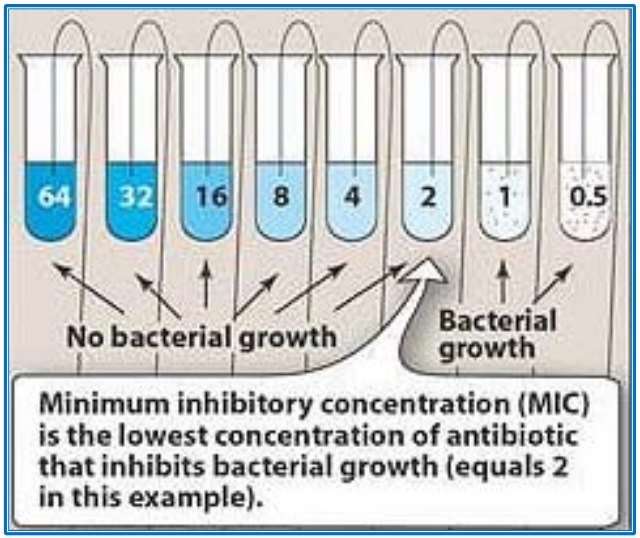
Minimum **I**nhibitory **C**oncentration:

- serial dilutions of an antibiotic
- inoculated with the organism
- tubes are incubated



MIC is the **lowest concentration of antibiotic that inhibits bacterial growth.**

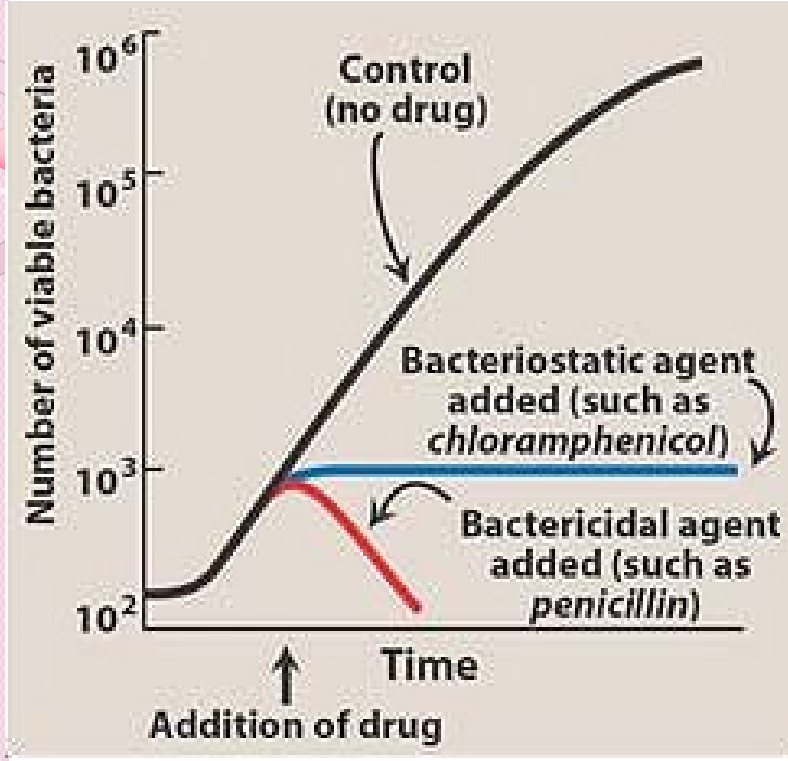
To provide effective antimicrobial therapy, clinically obtainable antibiotic concentration in body fluids should be greater than MIC.



MICs are important **to confirm antimicrobial resistance** and also **to monitor the activity of new antimicrobial agents.**

Choice of Antibiotic

Effects of **bactericidal** & **bacteriostatic** drugs



Bactericidal agents	Bacteriostatic agents
Aminoglycosides	Chloramphenicol
Bacitracin	Clindamycin
β-lactam antibiotics	Ethambutol
Daptomycin	Macrolides
Isoniazid	Nitrofurantoin
Ketolides	Novobiocin
Metronidazole	Oxazolidinones
Polymyxins	Sulfonamides
Pyrazinamide	Tetracyclines
Quinolones	Tigecycline
Rifampin	Trimethoprim
Vancomycin	

Cidal ↔ Static immunocompetent host

Cidal > Static immunocompromised host
seriously ill patient

B'cidal agents
endocarditis, meningitis, &
infections in neutropenic cancer patients.

Choice of Antibiotic

Effects of **bactericidal** & **bacteriostatic** drugs

- **Has limitations.**

Eg. chloramphenicol – b'static against G (-)ve rods

– b'cidal against others, such as S. pneumoniae

On the other hand, enterococci are inhibited but not killed by vancomycin, penicillin, or ampicillin used as single agents.

Choice of Antibiotic

Lesser frequency of **Dosing** (among agents with similar antimicrobial spectrums)

(eg, ceftriaxone may be conveniently given once every 24 hours)

	IV/IM preparations	Dose
3rd generation Cephalosporins	Cefotaxime	1-3 g 6-12 H
	Cefoperazone	2 g 12 H
	Ceftriaxone	1 g 24 H
	Ceftazidime	1 g 8 H

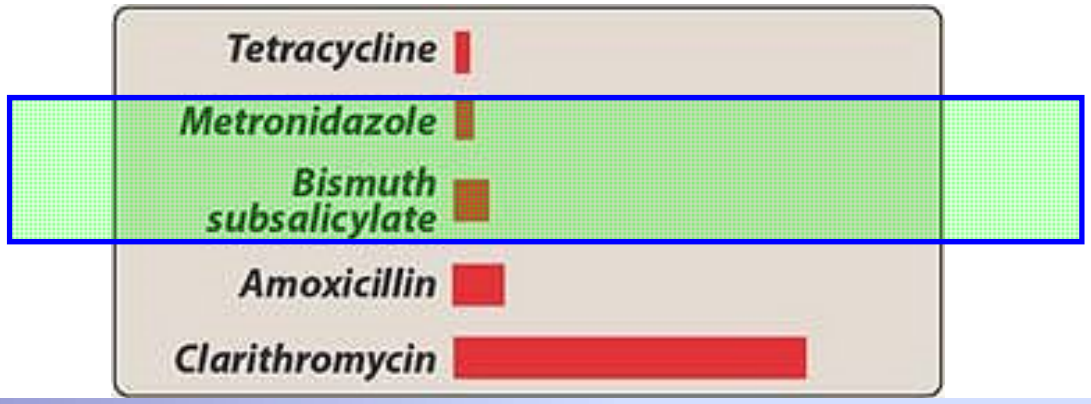
Recommended minimum durations of treatment

Infection	Minimum duration
Tuberculosis	4 - 6 months
Empyema/lung abscess	4 - 6 weeks
Endocarditis	4 weeks
Osteomyelitis	4 weeks
Atypical pneumonia	2 - 3 weeks
Pneumococcal meningitis	7 days
Pneumococcal pneumonia	5 days

Choice of Antibiotic

Cost of antimicrobial therapy

(esply when multiple agents with **comparable efficacy & toxicity** are available)



Relative cost of some drugs used for treatment of PU caused by H. pylori.

None of these agents shows a clear therapeutic superiority.

Selecting clarithromycin instead as the drug of choice would clearly make a considerable cost impact.

Local factors

Antibiotic activity may be reduced significantly in pus. Low pH found in abscess can markedly ↓ activity of aminoglycosides.

Prosthetics such as cardiac valves, artificial joints, pacemakers, vascular grafts, promote formation of a bacterial biofilm that impairs phagocytosis. Successful therapy usually requires removal of foreign material.

As a general rule, when pus, necrotic tissue, or a foreign body is present, an **antimicrobial agent given in adequate dose plus a properly performed surgical procedure.**

Intracellular pathogens

(*eg. Salmonella, Brucella, Toxoplasma, Listeria, M. Tuberculosis)*

Certain antibiotics

(*eg.* fluoroquinolones, isoniazid, cotrimoxazole, rifampin) penetrate cells well & can achieve intracellular concentrations.

Route of Administration

Oral route

- chosen for mild infections
- an outpatient basis
- economic pressures

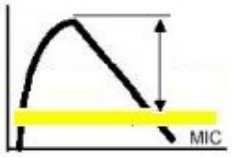
Parenteral administration

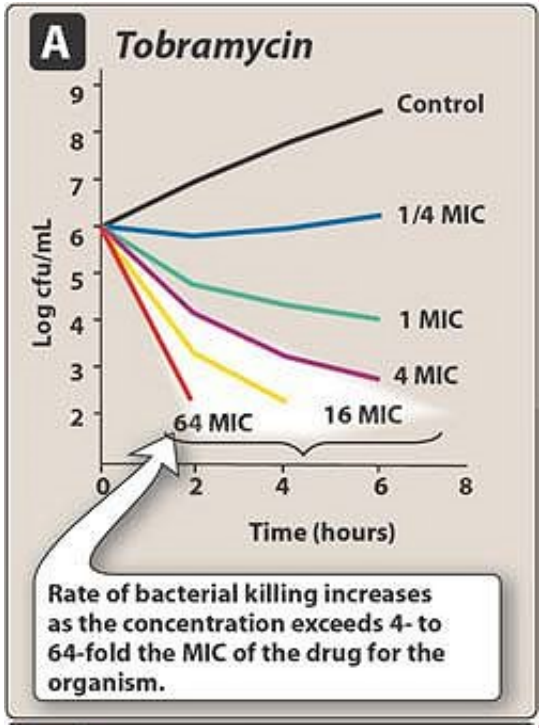
- for drugs poorly absorbed from GI tract
  (such as vancomycin, aminoglycosides, & amphotericin B)
- for treatment serious infections.

Determinants of **Rational Dosing**

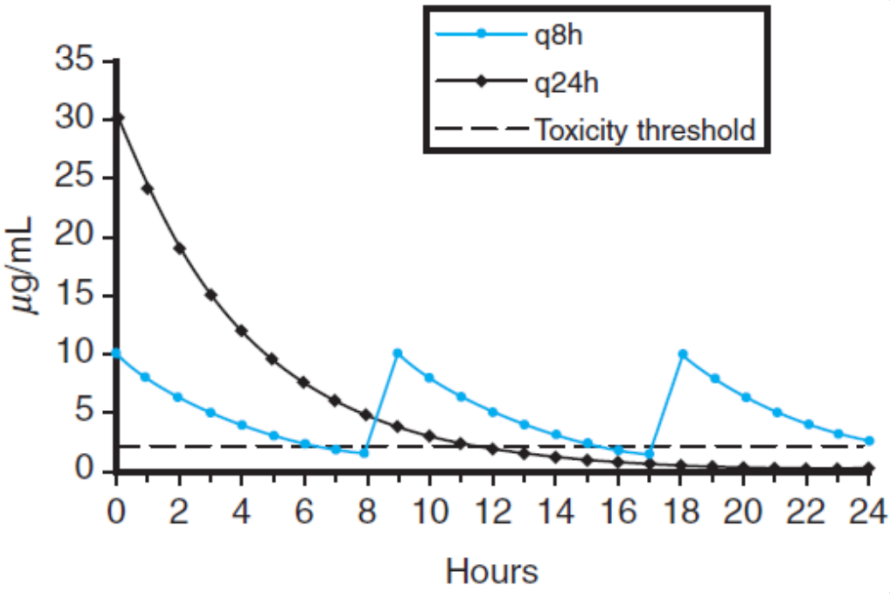
1. **Concentration-dependent killing**

Eg. aminoglycosides, fluoroquinolones, & carbapenems show a significant ↑ in rate of killing as antibiotic concentration ↑ from 4 to 64 **fold MIC**.





Once-daily aminoglycoside
(= efficacy, less toxic)
achieves high peak levels, favoring rapid killing of infecting pathogen.

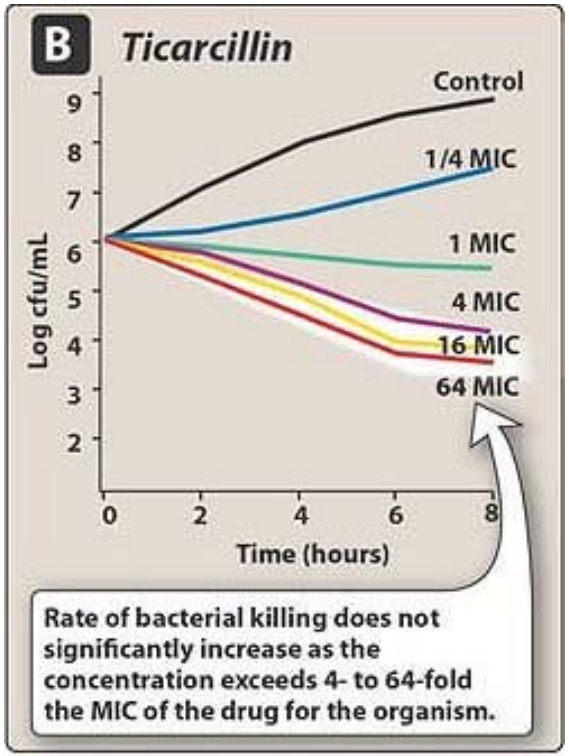


Determinants of Rational Dosing

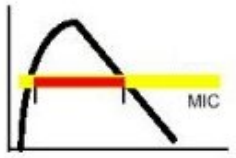
2. Time-dependent killing

Eg. β-lactams, glycopeptides, macrolides, clindamycin, & linezolid

increasing the antibiotic concentration to higher multiples of MIC does not significantly ↑ the rate of kill. (concentration-independent)



Clinical efficacy is best predicted by % of time that blood concentrations of a drug remain above MIC.



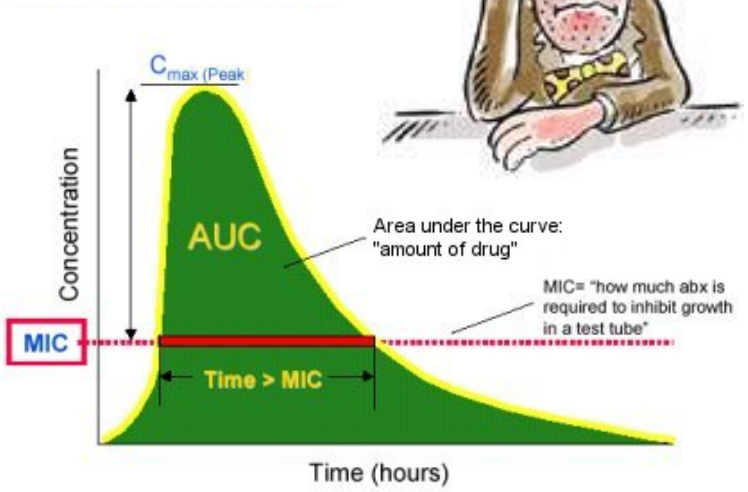
Eg. for penicillins & cephalosporins, dosing schedules that ensure <u>blood levels > MIC 60 to 70% of the time</u> → clinically effective.

Some suggest that some severe infections are best treated by continuous infusion of these agents rather than by intermittent dosing.

Determinants of Rational Dosing

3. Post-Antibiotic Effect (PAE)

- **Persistent suppression of microbial growth that occurs after levels of antibiotic have fallen below the MIC.**

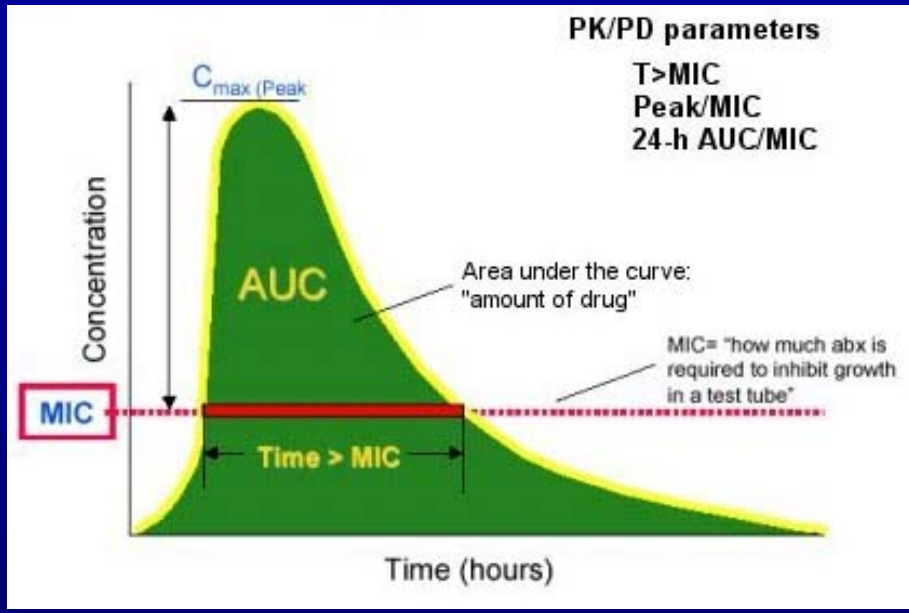


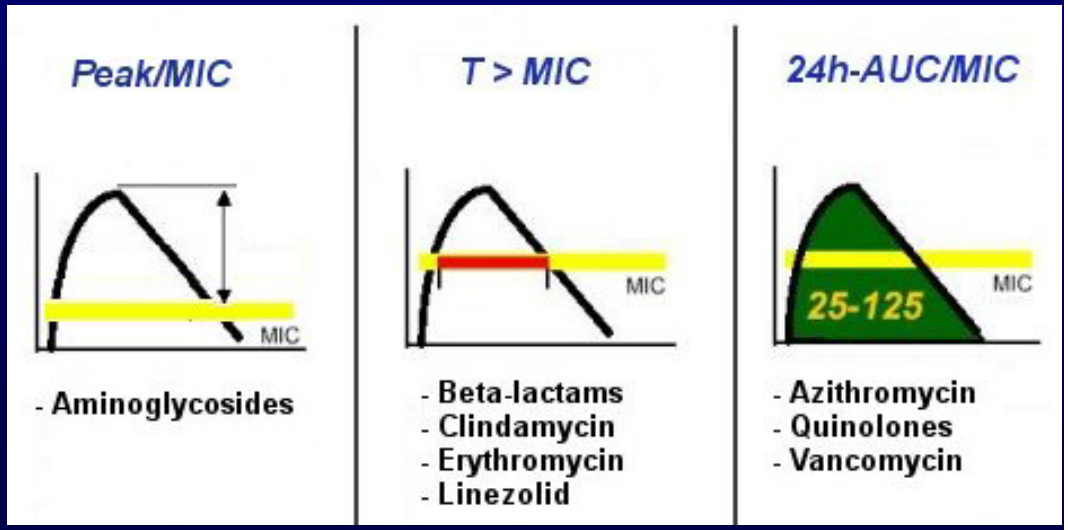
Antimicrobial drugs exhibiting a long PAE (several hours) often require only **one dose per day**.

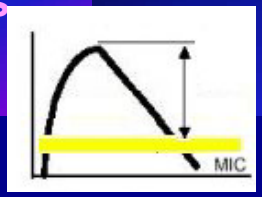
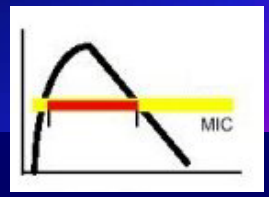
Eg. aminoglycosides & fluoroquinolones, exhibit a long PAE, particularly against G (-)ve bacteria.

PK/PD approach to antibiotic therapy

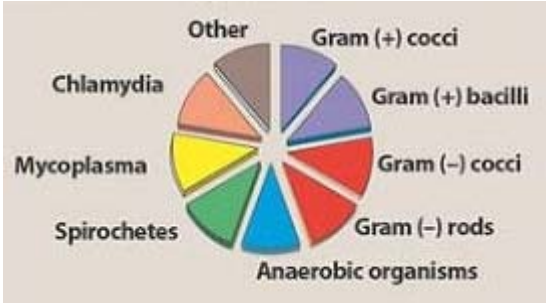
- (PK) is concerned with the time course of antimicrobial concentrations in the body.
- (PD) is concerned with the relationship between those concentrations and the antimicrobial effect.
- Integrating PK parameters with MIC gives us 3 PK/PD parameters which quantify the activity of an antibiotic:





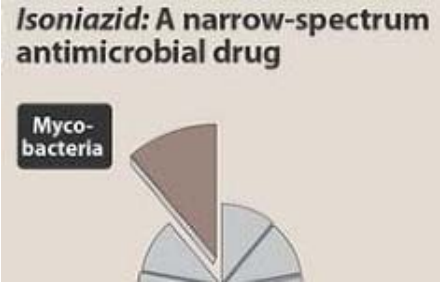
Pattern of Activity	Antibiotics	Ideal Dosing Regimen	PK/PD Parameter (antibiotic efficacy)
Type I Concentration-dependent killing & prolong PAE	Aminoglycosides Daptomycin Fluoroquinolones Ketolides	Maximize concentrations	Peak/MIC 24h-AUC/MIC  
Type II Time-dependent killing & minimal PAE	β –lactam antibiotics Clindamycin Erythromycin Linezolid	Maximize duration of exposure	T>MIC 
Type III Time-dependent killing & moderate to prolong PAE	Azithromycin Tetracyclines Vancomycin dalfo-quinupristin	Maximize amount of drug	24h-AUC/MIC 

Chemotherapeutic Spectra



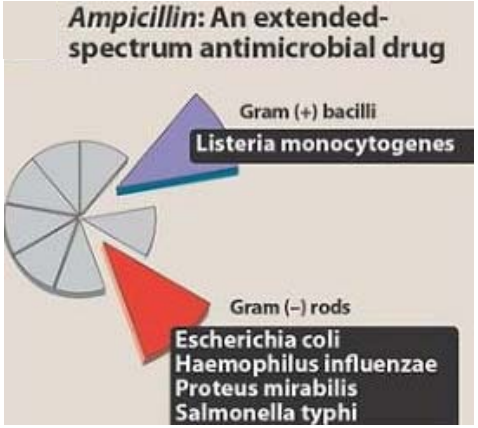
Narrow-spectrum antibiotics

acting only on a single or a limited group of microorganisms eg. *isoniazid* is active only against mycobacteria.



Extended-spectrum antibiotics

effective against G(+)ve organisms and also against a significant number of G(-)ve bacteria eg. *ampicillin*

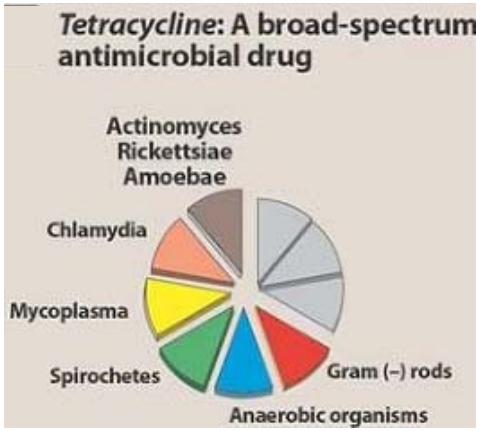


Broad-spectrum antibiotics

affect a wide variety of microbial species

eg. *tetracycline, chloramphenicol*

Administration precipitate a superinfection of an organism such as Candida albicans.



Combinations of antimicrobial drugs

It is therapeutically advisable to treat patients with the ***single agent that is most specific for the infecting organism.***

This strategy

-reduces the possibility of superinfection,

-decreases the emergence of resistant organisms, and

-minimizes toxicity.

However, situations in which combinations of drugs are employed do exist.

Eg. treatment of tuberculosis

INDICATIONS FOR COMBINATIONS OF ANTIMICROBIAL AGENTS

(1) ***for empirical therapy of an infection for which the cause is unknown***

Eg. in community-acquired pneumonia, macrolide m/b used for atypical organisms (*Mycoplasma) + cefuroxime for pneumococci & G (-)ve*.

(2) ***for treatment of polymicrobial infections***

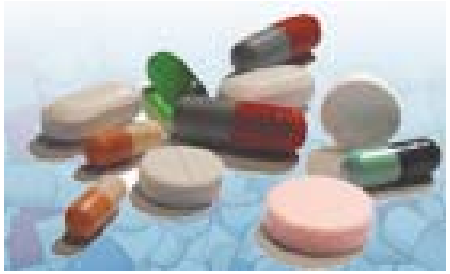
Eg. intra-abdominal, hepatic & brain abscess, & some genital infections may require drug combination to eradicate mixed aerobic-anaerobic inf$^{n:}$.

(3) ***to enhance antimicrobial activity for a specific infection (ie. for synergy)***

Eg. penicillin + strepto or gentamicin → Enterococcal endocarditis
β-lactam antibiotics + aminoglycosides → *Pseudomonas aeruginosa*

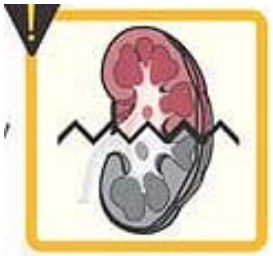
(4) ***to prevent emergence of resistance***

Eg. rifampin



DISADVANTAGES

OF COMBINATIONS OF ANTIMICROBIAL AGENTS



- ↑ risk of toxicity *(eg. vancomycin-aminoglycoside combination)*
- selection of MDR organisms
- superinfection
- ↑ cost
- antibiotic antagonism *(eg. penicillin-tetracycline combination)*

Antimicrobial Drugs Most Often Used for the Treatment of Infections Caused by Selected Bacteria

Bacteria	Antimicrobial Drugs
Gram-Positive Cocci	
***Enterococcus* species**	penicillin G or ampicillin + gentamicin; vancomycin + gentamicin; quinupristin + dalfopristin, linezolid, daptomycin, tigecycline
Staphylococcus aureus	penicillin G (if sensitive), nafcillin, oxacillin, vancomycin, quinupristin + dalfopristin, linezolid, daptomycin, tigecycline
Streptococcus pyogenes	penicillin G or V, a cephalosporin, a macrolide, clindamycin
Viridans group streptococci	penicillin G + gentamicin; vancomycin
Streptococcus pneumoniae	penicillin G (if sensitive), a cephalosporin II or III, amoxicillin + clavulanate, an advanced fluoroquinolone, azithromycin, telithromycin

Antimicrobial Drugs Most Often Used for the Treatment of Infections Caused by Selected Bacteria

Bacteria	Antimicrobial Drugs
Gram-Positive Bacilli	
Bacillus anthracis	ciprofloxacin ± clindamycin and rifampicin; doxycycline
Clostridium difficile	metronidazole, oral vancomycin
Clostridium perfringens, Clostridium tetani	penicillin G
Corynebacterium diphtheriae	a macrolide, penicillin G
Listeria monocytogenes	ampicillin, gentamicin

Antimicrobial Drugs Most Often Used for the Treatment of Infections Caused by Selected Bacteria

Bacteria	Antimicrobial Drugs
Gram-Negative Cocci	
Moraxella catarrhalis	amoxicillin + clavulanate, a cephalosporin II or III, a macrolide
Neisseria gonorrhoeae	ceftriaxone, spectinomycin, a fluoroquinolone
Neisseria meningitides	penicillin G, a cephalosporin II or III, chloramphenicol

Antimicrobial Drugs Most Often Used for the Treatment of Infections Caused by Selected Bacteria

Bacteria	Antimicrobial Drugs
Gram-Negative Bacilli	
Bacteroides species	metronidazole, penicillin + β-lactamase inhibitor, clindamycin, chloramphenicol, penicillin G (oropharyngeal strains)
Bordetella pertussis	a macrolide, cotrimoxazole
Helicobacter pylori	tetracycline, clarithromycin, amoxicillin, metronidazole, bismuth compounds, proton pump inhibitors
Haemophilus influenzae	amoxicillin + clavulanate, a cephalosporin II or III, azithromycin, a fluoroquinolone

Antimicrobial Drugs Most Often Used for the Treatment of Infections Caused by Selected Bacteria

Bacteria	Antimicrobial Drugs
Gram-Negative Bacilli	
Pseudomonas aeruginosa	an aminoglycoside, ceftazidime, a fluoroquinolone, aztreonam, a carbapenem, piperacillin + tazobactam
Most Enterobacteriaceae (*E. coli, Klebsiella, Proteus, Serratia, Enterobacter, Citrobacter, Providencia* species & others)	a cephalosporin II or III, an aminoglycoside, piperacillin + tazobactam, a carbapenem, aztreonam, a fluoroquinolone, cotrimoxazole (UTI)
Salmonella & *Shigella* species *Campylobacter jejuni*	a fluoroquinolone, ceftriaxone (*Salmonella*), ampicillin + sulbactam (*Shigella*)
Yersinia pestis, Francisella tularensis	streptomycin, a tetracycline, chloramphenicol

Antimicrobial Drugs Most Often Used for the Treatment of Infections Caused by Selected Bacteria

Bacteria	Antimicrobial Drugs
Actinomycetes	
Nocardia asteroides, N. brasiliensis	cotrimoxazole
Chlamydiae, Ehrlichiae, Rickettsiae	a macrolide or a tetracycline antibiotic
Spirochetes	
Borrelia burgdorferi	doxycycline, amoxicillin, a cephalosporin II or III
Borrelia recurrentis	a tetracycline, penicillin G
Treponema pallidum	penicillin, a tetracycline

Drug Resistance

Bacteria are said to be resistant to an antibiotic if the **maximal** level of that antibiotic that can be **tolerated** by the host does not halt their growth.

Some organisms are **inherently resistant** to an antibiotic.

Eg. G (-)ve organisms are inherently resistant to vancomycin.

A. Genetic alterations leading to drug resistance

1. Spontaneous mutations of DNA:

Eg. emergence of rifampin-resistant M. tuberculosis when used as a single antibiotic.

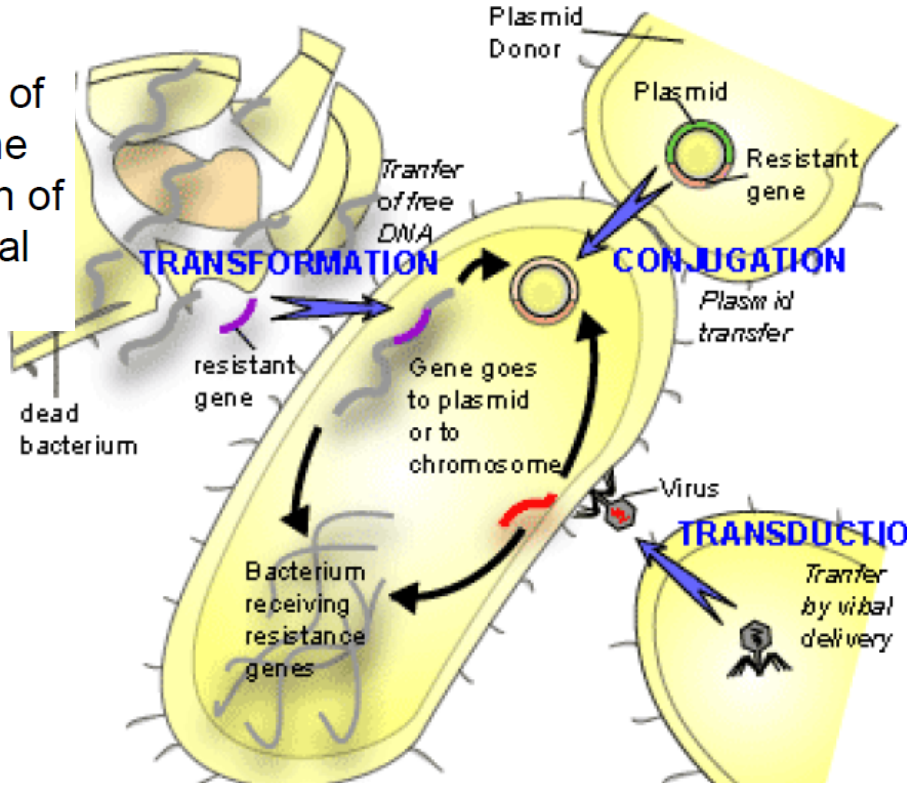
A. Genetic alterations leading to drug resistance

2. DNA transfer of drug resistance: from one bacterium to another

- Resistance properties are usually encoded in extrachromosomal R factors (resistance plasmids).

Plasmids may enter cells by processes such as transduction (phage mediated), transformation, or bacterial conjugation.

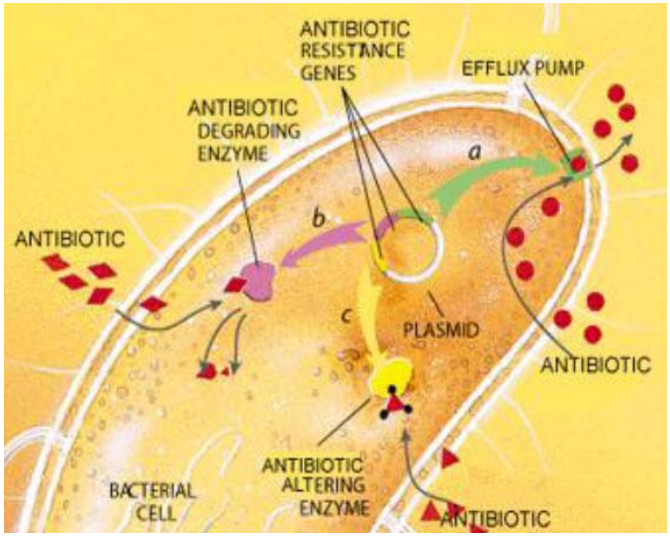
Transformation
The genetic alteration of a cell resulting from the uptake and expression of foreign genetic material (DNA).



Conjugation
The transfer of genetic material between bacteria through direct cell-to-cell contact

Transduction
The process by which bacterial DNA is moved from one bacterium to another by a virus.

B. Altered expression of proteins in drug-resistant organisms



1. **Modification of target sites**: through mutation

   eg. S. pneumoniae resistance to β-lactam antibiotics involves alterations in PBPs.

2. **↓ uptake or ↑ efflux**: drug unable to attain sufficient concentration at SOA

   eg. G (-)ve organisms can limit the penetration of β-lactam antibiotics, tetracyclines, chloramphenicol.

3. **Enzymic inactivation**: destroy or inactivate the antimicrobial agent

   eg. β-lactamases → penicillins, cephalosporins

   acetyltransferases → chloramphenicol, aminoglycosides

   esterases → macrolides

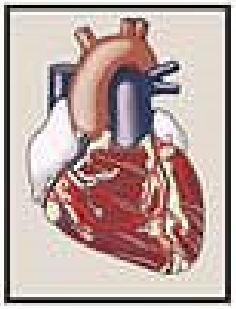
Prophylactic Antibiotics

- Prophylactic use is restricted to clinical situations in which the **benefits outweigh** the potential **risks**.

Some clinical situations in which prophylactic antibiotics are indicated.

1

Prevention of strepto-coccal infections in patients with a history of rheumatic heart disease. Patients may require years of treatment.

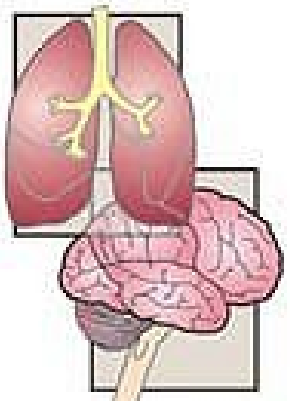


2

Pretreatment of patients undergoing dental extractions who have implanted prosthetic devices, such as artificial heart valves, to prevent seeding of the prosthesis.

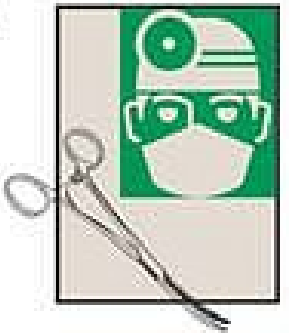
3

Prevention of tuber-culosis or meningitis among individuals who are in close contact with infected patients.



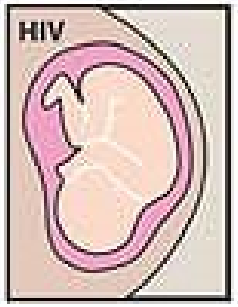
4

Treatment prior to certain surgical procedures (such as bowel surgery, joint replacement, and some gynecologic inter-ventions) to prevent infection.



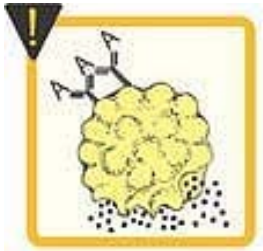
5

Treatment of the mother with *zidovudine* to protect the fetus in the case of an HIV-infected, pregnant woman.



Complications of antibiotic therapy

A. Hypersensitivity



Eg. the **penicillins**,

despite their almost absolute selective microbial toxicity, can cause serious hypersensitivity problems, ranging from urticaria (hives) to anaphylactic shock.

B. Direct toxicity

Eg. **aminoglycosides** can cause ototoxicity by interfering with membrane function in the hair cells of the organ of Corti.

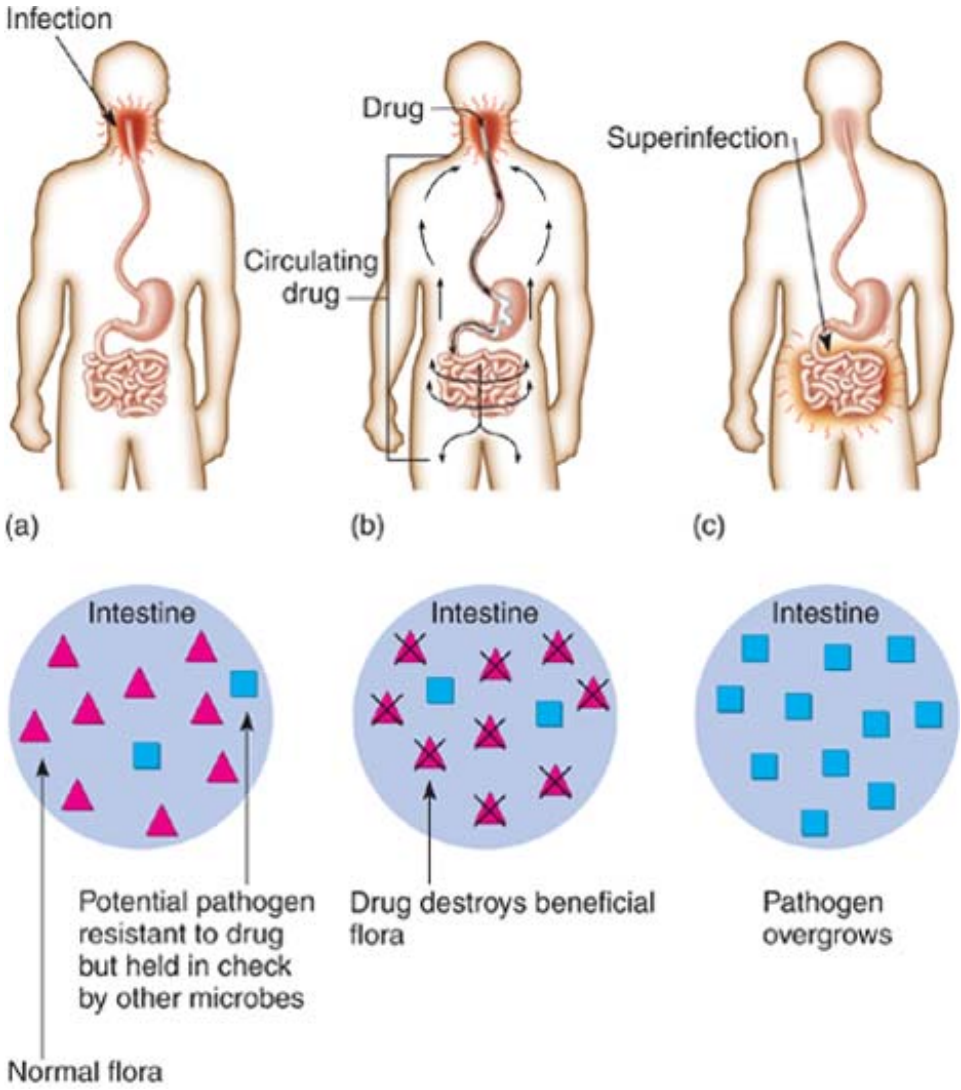
Complications of antibiotic therapy

C. Superinfections

- particularly with ***broad-spectrum antibiotics or combinations*** of agents,

alteration of normal flora, permitting the overgrowth of opportunistic organisms, especially fungi or resistant bacteria.

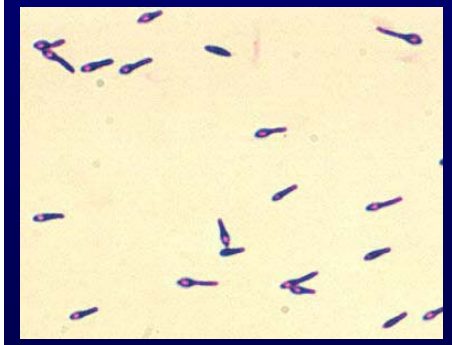
These infections are often difficult to treat.



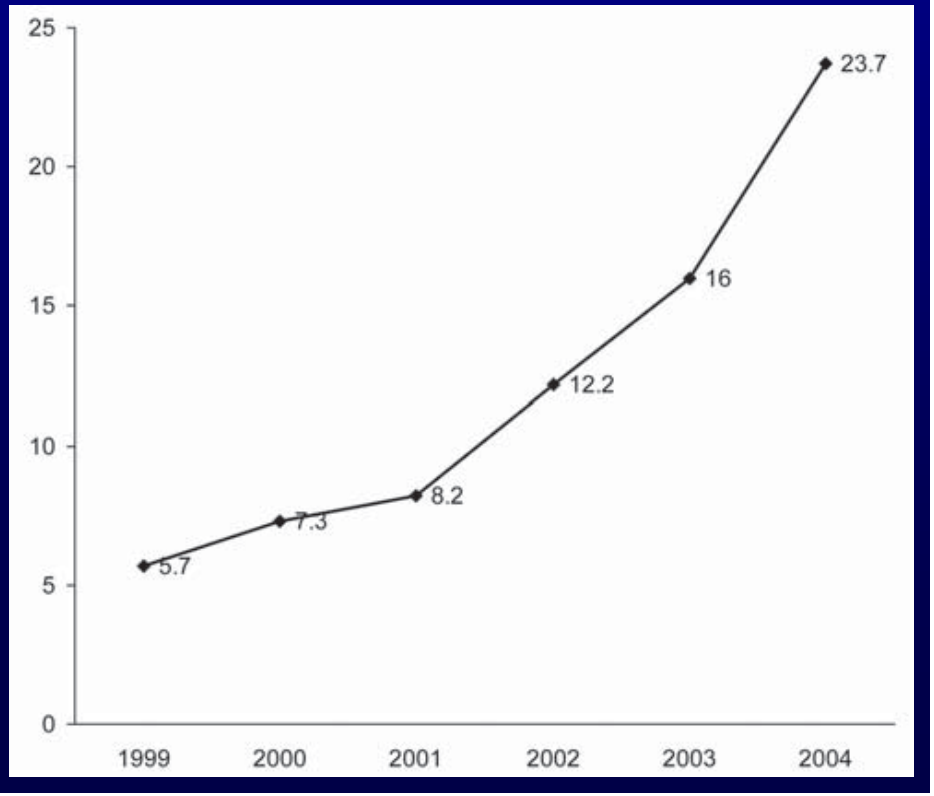
Vanco vs Flagyl for tx of CDI

	Proportion (%) of patients		
Cure	Flagyl	Vanco	*p*
Mild CDI	37/41 (90%)	39/40 (98%)	0.36
Severe CDI	29/38 (76%)	30/31 (97%)	0.02
Relapse	9/66 (14%)	56/69 (7%)	0.27

Zar, et al. CID. 2007;45:302



Yearly Clostridium difficile–related Mortality by Listing on Death Certificates, United States, 1999–2004.



Misuses of Antibiotics

TREATMENT OF NONRESPONSIVE INFECTIONS

Most viral diseases are self-limited and do not respond to any of the currently available anti-infective compounds.

Thus, antibiotic therapy of at least 90% of infections of the upper respiratory tract and many GI infections is ineffective.

Colds, coughs and most diarrhoeas don't need antibiotic treatment.

- **Instead, drink fluids and get plenty of rest.**

Misuses of Antibiotics

Therapy of PUO

Fever persisting for 2 or more weeks, *has a variety of causes;*

only about ¼ of these are infections.

Moreover, some of these infections (*eg. tuberculosis,* disseminated fungal inf$^{n:}$) may require antibiotics that are not typically used for bacterial infections.

Inappropriately administered antibiotics

may **mask** an underlying infection,

delay the diagnosis, &

prevent the identification of pathogen by culture.

Misuses of Antibiotics

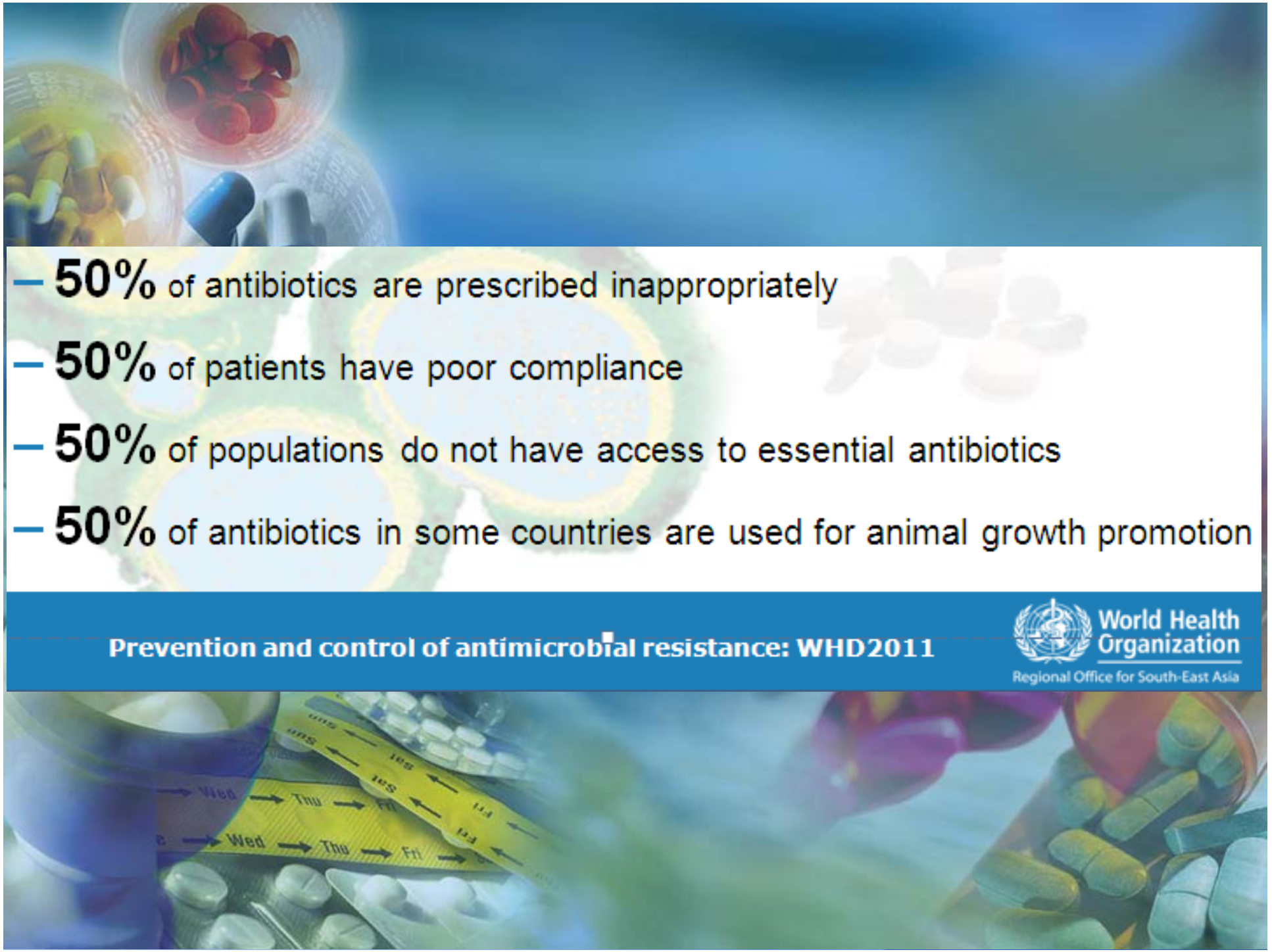
IMPROPER DOSAGE

Dosing errors with antibiotics are common.

Excessive dosing can result in significant **toxicities**, while **too low** a dose may result in **treatment failure** and is most likely to select for antibiotic **resistance**.

The greatest possibility of evil in self-medication is the use of too small doses so that instead of clearing up infection, the microbes are educated to resist penicillin and a host of penicillin-fast organisms is bread out which can be passed to other individuals and from them to other until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save.

. Sir Alexander Flemming


– 50% of antibiotics are prescribed inappropriately
– 50% of patients have poor compliance
– 50% of populations do not have access to essential antibiotics
– 50% of antibiotics in some countries are used for animal growth promotion
Prevention and control of antimicrobial resistance: WHD2011
World Health Organization
Regional Office for South-East Asia
Wed
Thu
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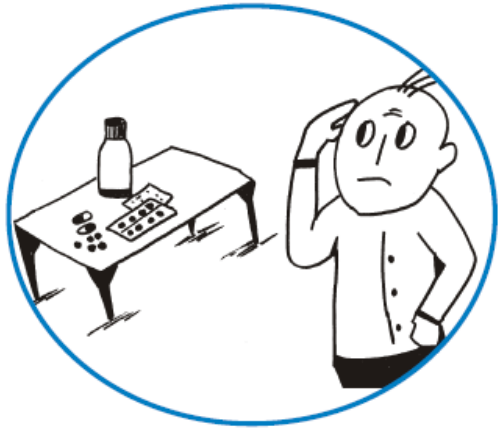
Fri

Q : How do we overcome this problem of antibiotic resistance, both in the hospital & the community?

- **Hospital antibiotic policy** &
- **standard treatment guidelines** are effective tools to encourage **rational use** of antibiotics.
  - complete **investigation**
  - to ensure proper **diagnosis** before a decision is made to the most appropriate antibiotic, dose & duration.

public contribution to fight against antibiotic resistance

- Prevent infections by observing healthy & hygienic habits.
- Always follow the advice of a doctor before you start taking an antibiotic.
- Do not store any antibiotic after its expiry or after the course is over.
- Never reuse a medicine with an old prescription on yourself or prescribe it to others. Do not try to play the role of a doctor.



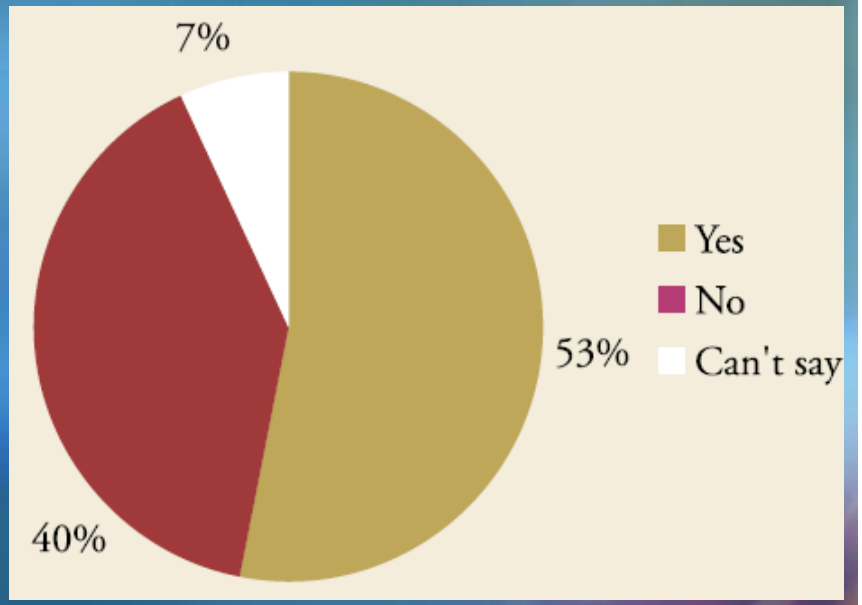
ANTIBIOTICS SAVE LIVES
THROW AWAY EXPIRED MEDICINES
AND NEVER SELF-MEDICATE

Perceptions of communities and physicians in use of antibiotics

Q: Would you prescribe antibiotics for your own use or that of your family members?

53% of people would self-prescribe antibiotics

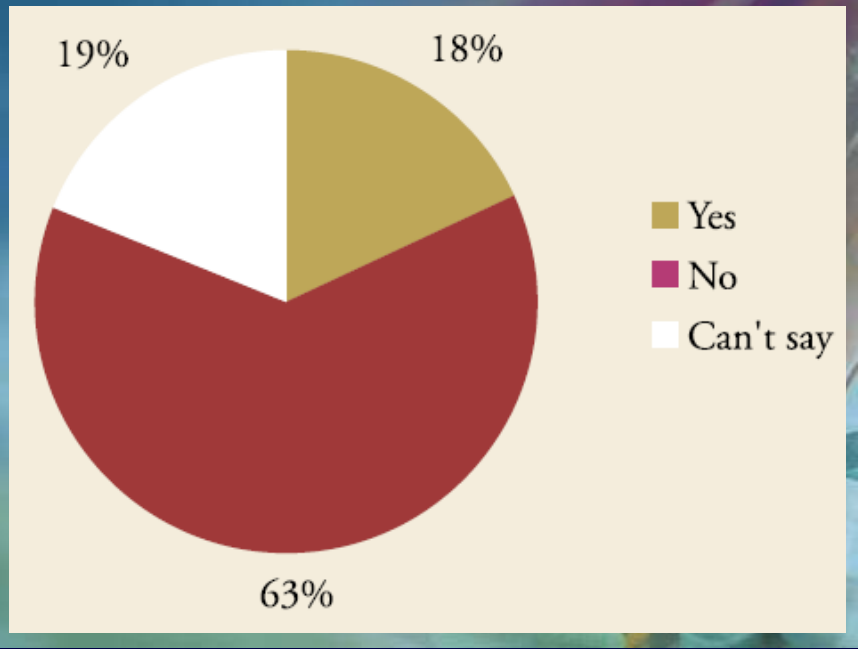
Self-medication leads to antibiotic resistance



Q: Will you save unused antibiotics for later use by yourself or by other family members?

18% of people said Yes

Re-using medicines prescribed for previous illnesses can be dangerous and leads to antibiotic resistance

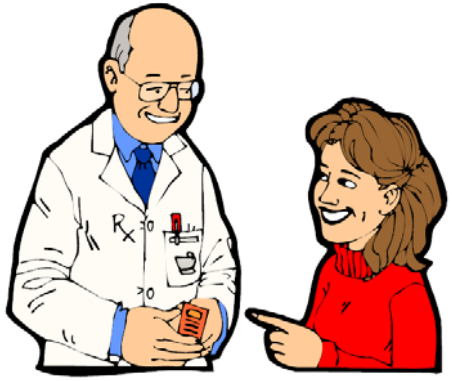


public contribution to fight against antibiotic resistance

- Do not stop an antibiotic course just because you or your child feels or looks better.

- Do not buy OTC without a valid prescription from a qualified doctor.

- Do not visit an unqualified doctor just because he claims immediate cure from all ailments & charges less.



Promote good nutrition and healthy lifestyles

Reduce infectious disease and the need for antibiotics

Vaccinate children against diseases

Minimize the need for antibiotics

Q: Who needs to take action?

- Many organizations and individuals can help — national authorities, consumers, prescribers and dispensers, veterinarians, the pharmaceutical industry, hospital administrators, professional societies and international agencies and patients.

- WHO developed & disseminated a comprehensive strategy for prevention & containment of antimicrobial resistance.
- (**http://www.searo.who.int/EN/Section10/Section17.htm**)

- This strategy addresses all issues related to resistance in antibiotics and suggests possible actions at country level.

World Health Organization
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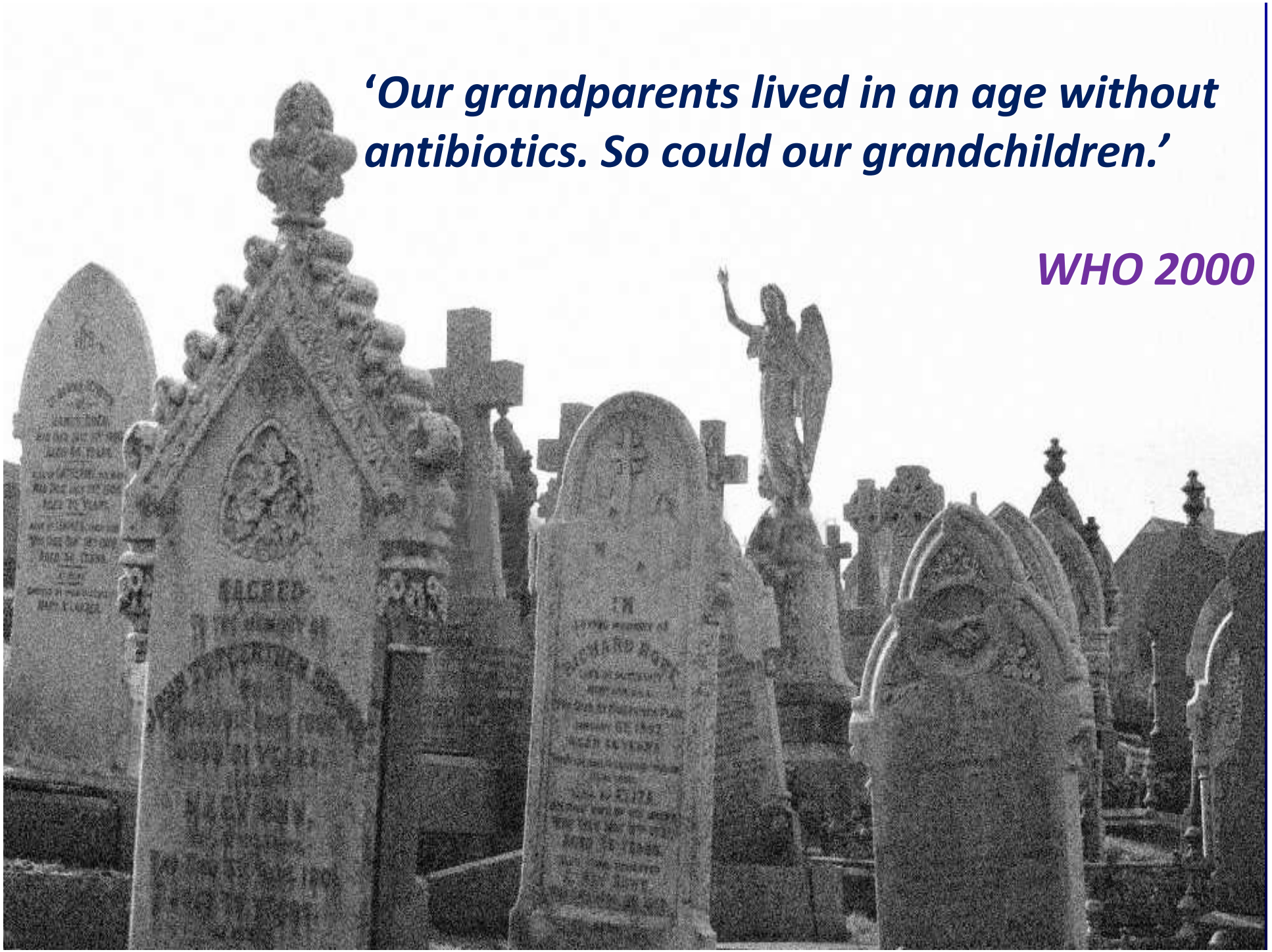
Use antibiotics rationally

Don't misuse antibiotics.

Future generations will need them too!



‘Our grandparents lived in an age without antibiotics. So could our grandchildren.’

WHO 2000

TAKE HOME MESSAGE

USE ANTIBIOTICS RATIONALLY | SAVE LIVES

QALIFIED DOCTORS

- clinical
- microbiological
- pharmacological

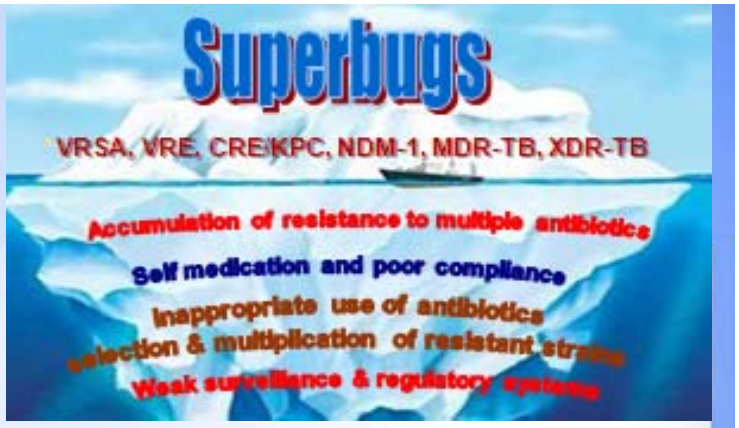
- empirical
- definitive
- preventive

ANTIBIOTIC

RATIONAL USE

- indication
- choice
  - patient factor
  - drug factor
  - sensitivity
  - dosage regimen
  - cost
  - safety & complications

ANTIBIOTIC



MISUSE

- untreatable & inappropriate conditions
- improper dosage
- incomplete course
- reuse of leftover medicines
- self medication
- use in animal feeds
- OTC sale without prescription
- latest one when older one is effective
- overprescribing

TAKE HOME MESSAGE

ANTIBIOTIC ⟷ ANTIPYRETIC

ANTIBIOTIC ⟷ ANTIDIARRHOEAL

ANTIBIOTICS DO NOT CURE ALL FEVERS

TAKE THEM ONLY FOR SPECIFIED INFECTIONS

TAKE HOME MESSAGE

USE ANTIBIOTICS RATIONALLY **SAVE LIVES**

- Antibiotic combination
- Prophylactic antibiotic
- Empirical therapy

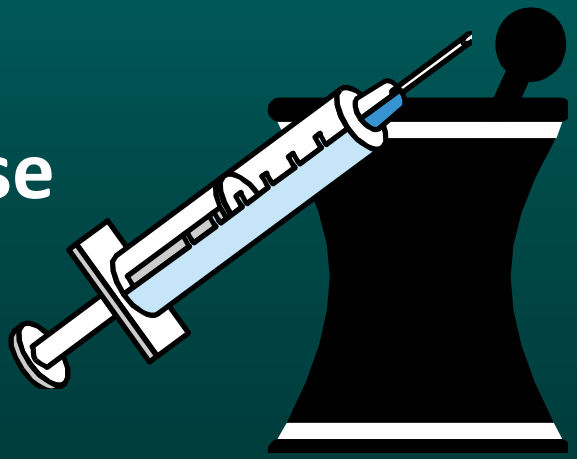
- Give only when clear indication +
- Benefit > Risk

Prevention and Control Strategies for the New Millennium

Poverty, ignorance inadequate access to drugs, poor health care delivery, have limited the control of infections.

- **Handwashing**

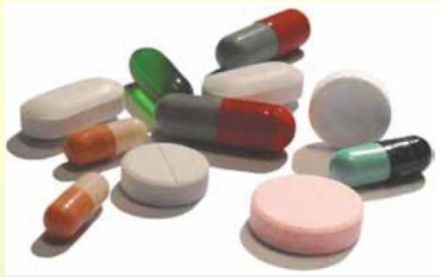
- **Antimicrobial Use**



Infection Control

↓

Antibiotic Control



Use antibiotics judiciously

Preserve their efficacy

for the next generation!

COMBAT DRUG RESISTANCE

No action today, no cure tomorrow

"…We cannot do much about the length of our life,

but we can do a lot about its width and its depth…."

Misuse of antibiotics selects for resistance mutants.

- **Misuse includes:**
  - **Using outdated or weakened antibiotics**
  - **Using antibiotics for the common cold and other inappropriate conditions**
  - **Using antibiotics in animal feed**
  - **Failing complete the prescribed regimen**
  - **Using someone else's leftover prescription**

Common misuses of antibiotics

1. the patient does not have an infection
2. the infection does not respond to antibiotics - eg viral infections
3. the latest "wonder drug" is used when an older product would be effective-
   - protecting the new product for situations where it is really needed
4. the patient "prescribes" for him/herself - using antibiotics left over from a previous illness
5. in countries with poor health care services antibiotics are sold without prescription
6. use of antibiotics for non-therapeutic purposes – eg. growth promotion or improved production in livestock

Q. What are the important points that the media can convey to general population about the antibiotic misuse and ways to prevent it?

- (a) Do not take antibiotic if it can be avoided.

- (b)
- (d) Do not use left-over medicines just because it worked the last time.

- (e) Do not give medicines to another person for what seems to be a similar illness to yours.

Antimicrobials are crucial to treating communicable diseases

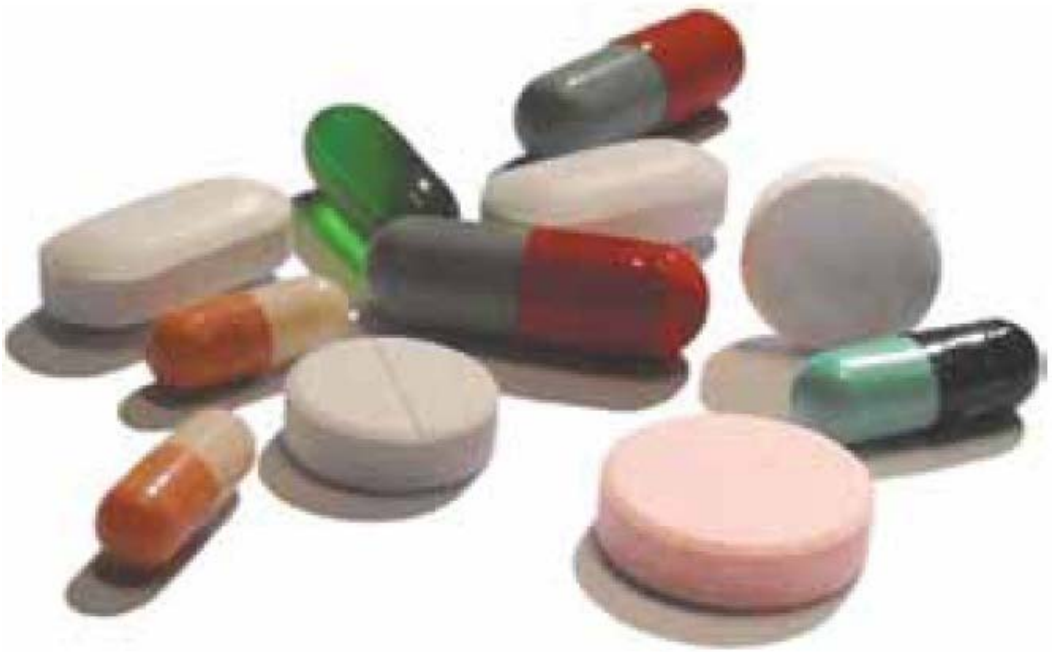
Preserve the efficacy of this irreplaceable resource

Antibiotics are a precious resource

Take them only as prescribed to prevent resistance

World Health Organization

Combat antimicrobial resistance—
No action today, no cure tomorrow



- Antibiotics save lives
- Take antibiotics as prescribed for the full duration
- Vaccinate children against preventable diseases
- Follow a healthy lifestyle and reduce the need for antibiotics
- Throw away old medicines and never self-medicate

World Health Organization
Regional Office for South-East Asia

Use antibiotics rationally

Antibiotics with In Vitro PAE > 1.5 Hours

Against G (+)ve cocci	Against G (-)ve bacilli
Aminoglycosides	**Aminoglycosides**
Carbapenems	Carbapenems
Cephalosporins	**Chloramphenicol**
Chloramphenicol	**Quinolones**
Clindamycin	Rifampin
Daptomycin	Tetracyclines
Ketolides	Tigecycline
Macrolides	
Oxazolidinones	
Penicillins	
Quinolones	
Rifampin	
Sulfonamides	
Tetracyclines	
Tigecycline	
Trimethoprim	
Vancomycin	

PAE

Proposed mechanisms include

(1) **slow recovery** after reversible nonlethal damage to cell structures;

(2) **persistence of the drug at** a binding **site** or within the periplasmic space; and

(3) the need to synthesize new enzymes before growth can resume.

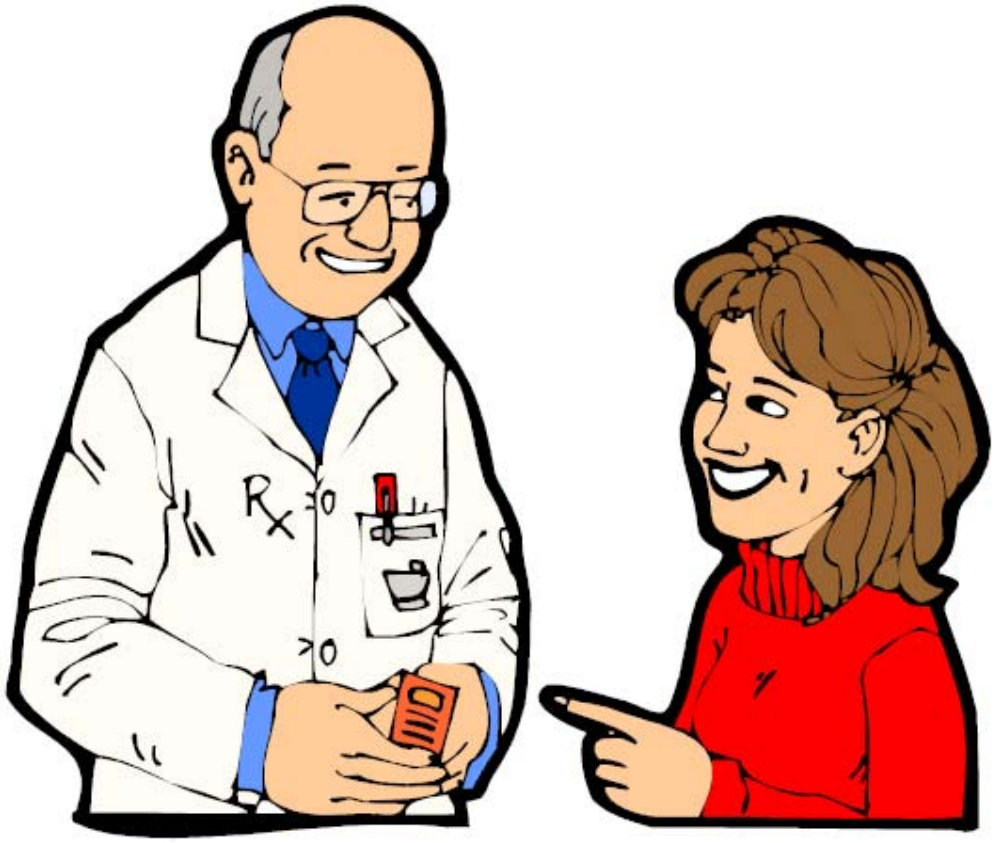
In vivo PAEs are usually much longer than in vitro PAEs.

This is thought to be due to **postantibiotic leukocyte enhancement (PALE)**

Antibiotics have no role in treatment of viral fevers.

Say NO to the use of antibiotics in cases of viral fever.

Help prevent emergence of resistance to antibiotics!



Antibiotics have no role in the treatment of seasonal flu.

Say NO to antibiotics in flu cases.

Help prevent emergence of resistance to antibiotics!

Antibiotics are not antidiarrhoeals and have no role in treatment of diarrhoeas. These are however indicated when blood is passed along with faeces (dysentery).

Do not self-medicate with antibiotics.

Help prevent emergence of resistance to antibiotics!

Q: What is the role of the doctor in preventing or curtailing antibiotic resistance?

- Patients need to be **examined** completely and the exact nature of an infection needs to be established before giving any antibiotic.
- Doctor needs to be confident about exact **dose** & **schedule**, including duration & possible side effects.
- ***Explaining what to expect to a patient*** helps prevent them from prematurely stopping antibiotic treatment.
- It is **not always beneficial** (and usually unsafe) to give two or more **antibiotic combinations**.
- It is important not to give antibiotics to cure URTI such as colds, minor coughs, bronchitis & running nose.

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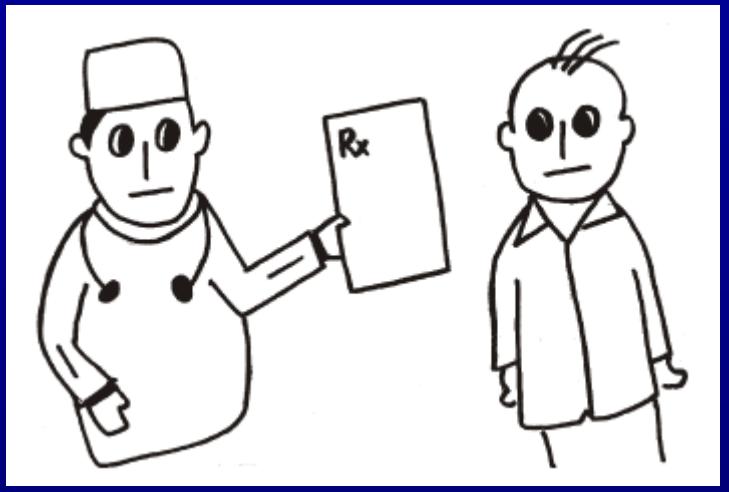
Use antibiotics rationally



Take antibiotics only as prescribed and in the recommended dose and duration.

- **Ask your doctor which prescriptions include antibiotics.**

If misused, antibiotics will lose effectiveness.

They will no longer kill germs.

This is called "antibiotic resistance".

Many germs are *already resistant* to most antibiotics.

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Use antibiotics rationally

Colds, coughs and most diarrhoeas don't need antibiotic treatment.

- **Instead, drink fluids and get plenty of rest.**

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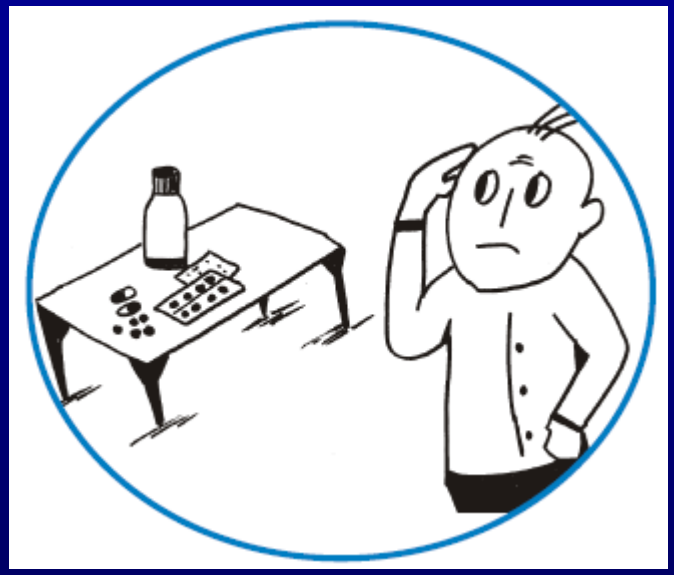
Use antibiotics rationally



Don’t reuse antibiotics that have been prescribed for previous illnesses. This is called “self-medication”. It may lead to resistance or unwanted effects.

- **See a doctor if you have fever or are sick for more than three days.**

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Use antibiotics rationally

It takes a lot of time and money to develop new antibiotics.

- **Help preserve the effectiveness of the ones we have.**

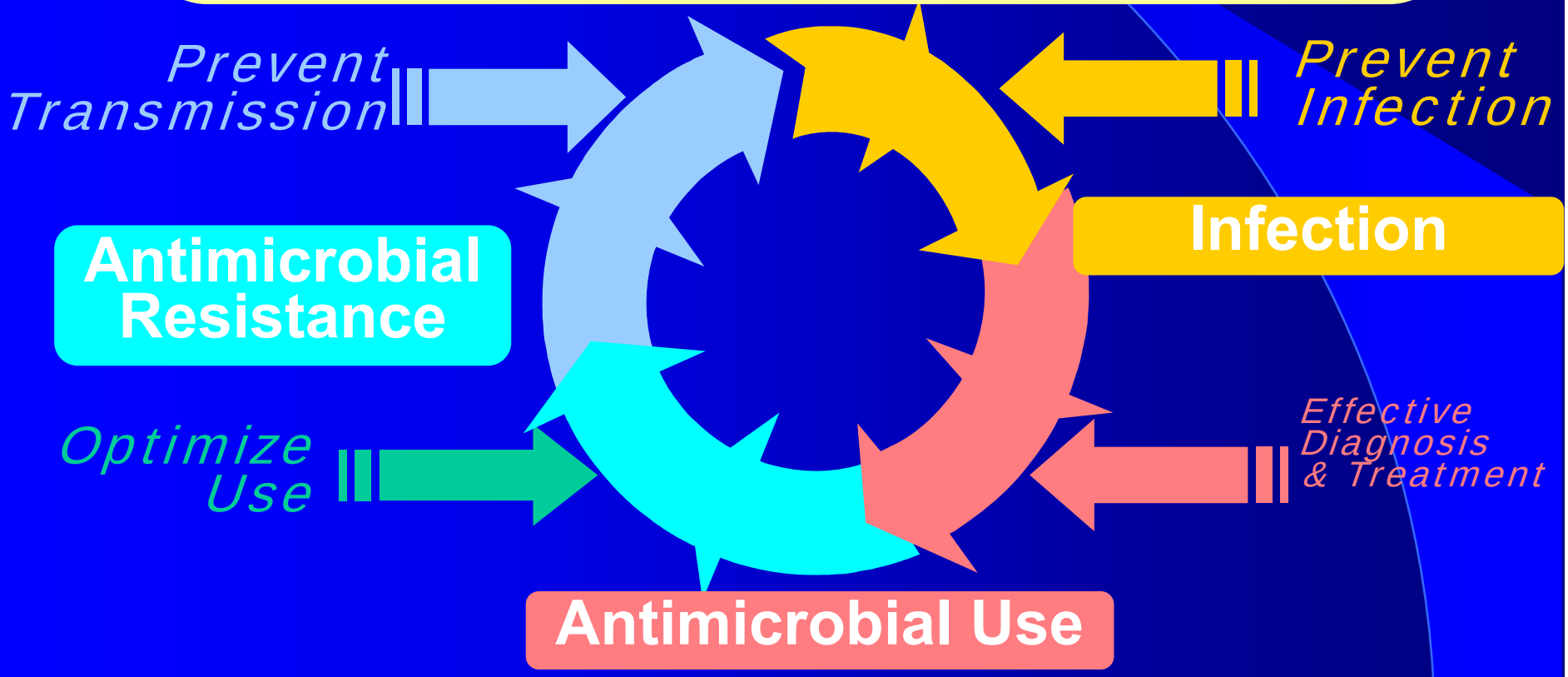
Make sure germs don't become resistant to them.

USE ANTIBIOTICS RATIONALLY

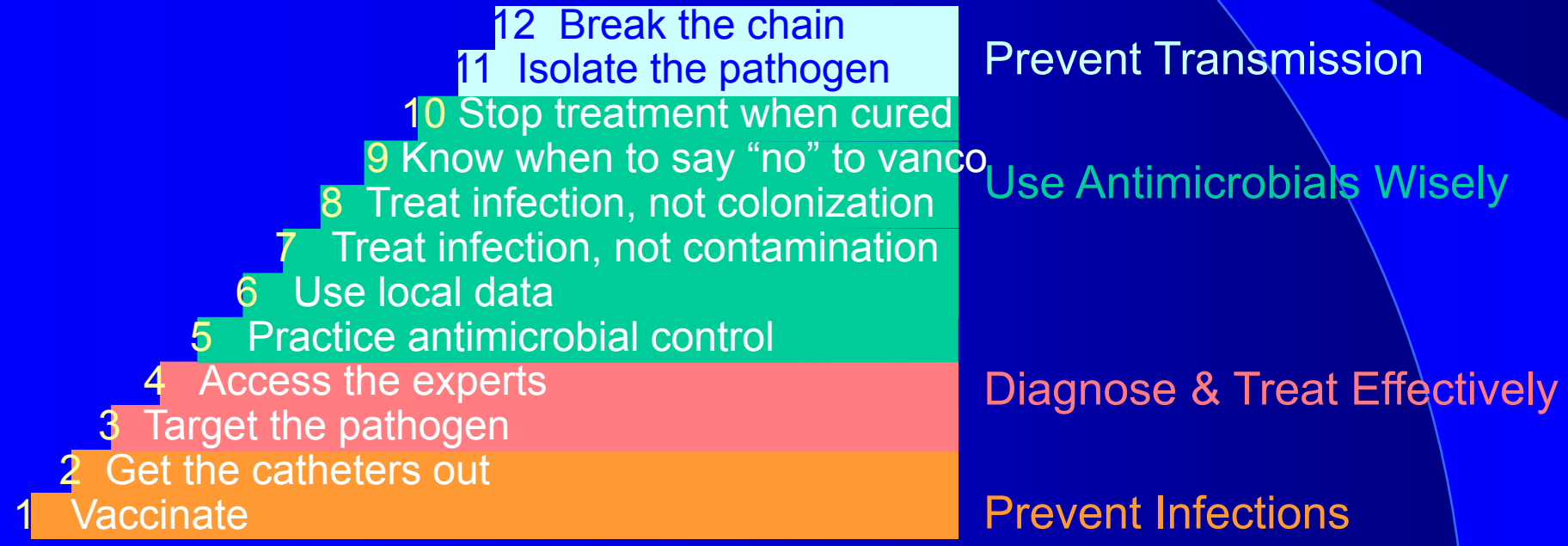
SAVE LIVES

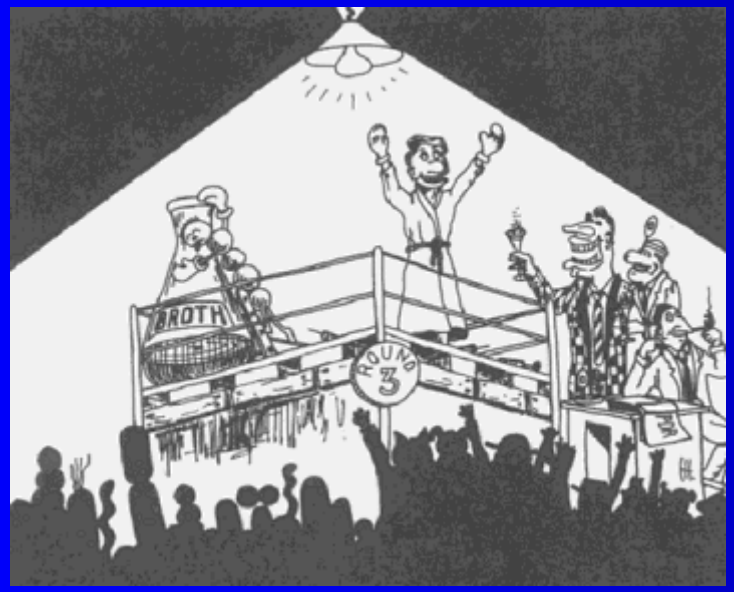
Antimicrobial Resistance: Key Prevention Strategies

Susceptible Pathogen



12 Steps to Prevent Antimicrobial Resistance




BROTH
ROUND
3


MRSA
SUPERBUG
FEARS
Srizelda
'GOOD NEWS DARLING! MY OPERATION HAS BEEN CANCELLED...'

TREATMENT OF MRSA AND OTHER ANTIBIOTIC-RESISTANT GRAM POSITIVE COCCI

Antibiotic	MRSA	MRSE	VRE *E. facium*	VRE *E. faecalis*	DR-SP
Ciprofloxacin (IV/PO)	0	0	0	0	0 to +
Levoflloxacin (IV/PO)	0	0	0	0	++
Vancomycin (IV)	++	++	0	0	++
Linezolid (IV/PO)	++	++	++	++	++
Daptomycin (IV)	++	++	++	++	++
Quinupristin-dalfopristin (IV)	++	++	++	0	++
Telithromycin (PO)	?	?	?	?	++

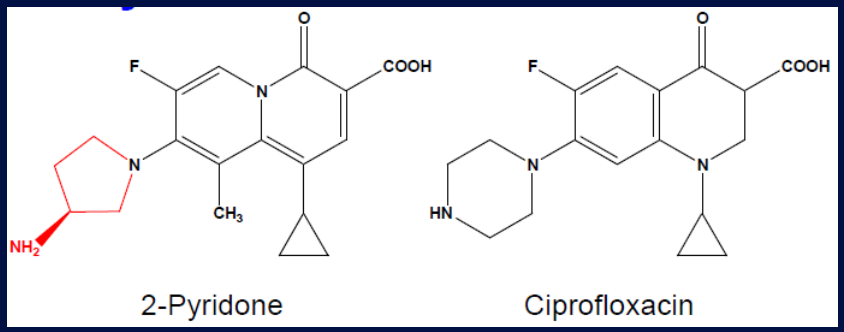
++ Drug covers >90% isolates, + drug covers 50-90% of isolates, 0 drug covers <50% of isolates

Current Status of Antibiotic Discovery

- Empiricism
  - At first highly successful
  - Now marginal
- Rational approach
  - Molecular modeling is being used extensively
  - Low yield so far, but promising
- Novel agents from non-microbial biological systems

New or Improved Antibiotics in Development

- Synthetic Vancomycins
  - A promising but unproven prospect
  - The sugar groups on the peptide backbone were modified
  - Completely synthetic drug
  - The modified drug was more efficient at killing both vancomycin-sensitive and vancomycin-resistant organisms
  - MOA is different, blocking transglycosylation rather than transpeptidation
  - Additional modifications are being tried
- For resistance to Fluoroquinolones



  - Inhibits DNA gyrase A, like quinolones
  - May be more effective against gyrAmutants

Approaches to Identify New Antibacterial Drugs

- Peptides from higher organisms
  - Magainin from frogs, reached phase III trials but never proceeded further
- Steroids from higher organisms
  - Squalamine from sharks
- Inhibitors of additional pathways
  - Block lipid A synthesis, which is an essential component of the outer membrane of gram negative bacteria

Functional Genomics

- The genomes of more than 20 microbial organisms have been sequenced
- Sequence data are used to identify essential targets by comparative genomics
- The targets are experimentally tested
- Drugs are developed to block those targets, based on structural predictions

The Future of Antibiotics

- The best long-term solution is to minimize the development of resistance
- Doctors have a critical role in accomplishing this goal

The Future of Chemotherapeutic Agents

- Antimicrobial peptides
  - Broad spectrum antibiotics from plants and animals
    - Squalamine (sharks)
    - Protegrin (pigs)
    - Magainin (frogs)
- Antisense agents
  - Complementary DNA or peptide nucleic acids that binds to a pathogen's virulence gene(s) and prevents transcription

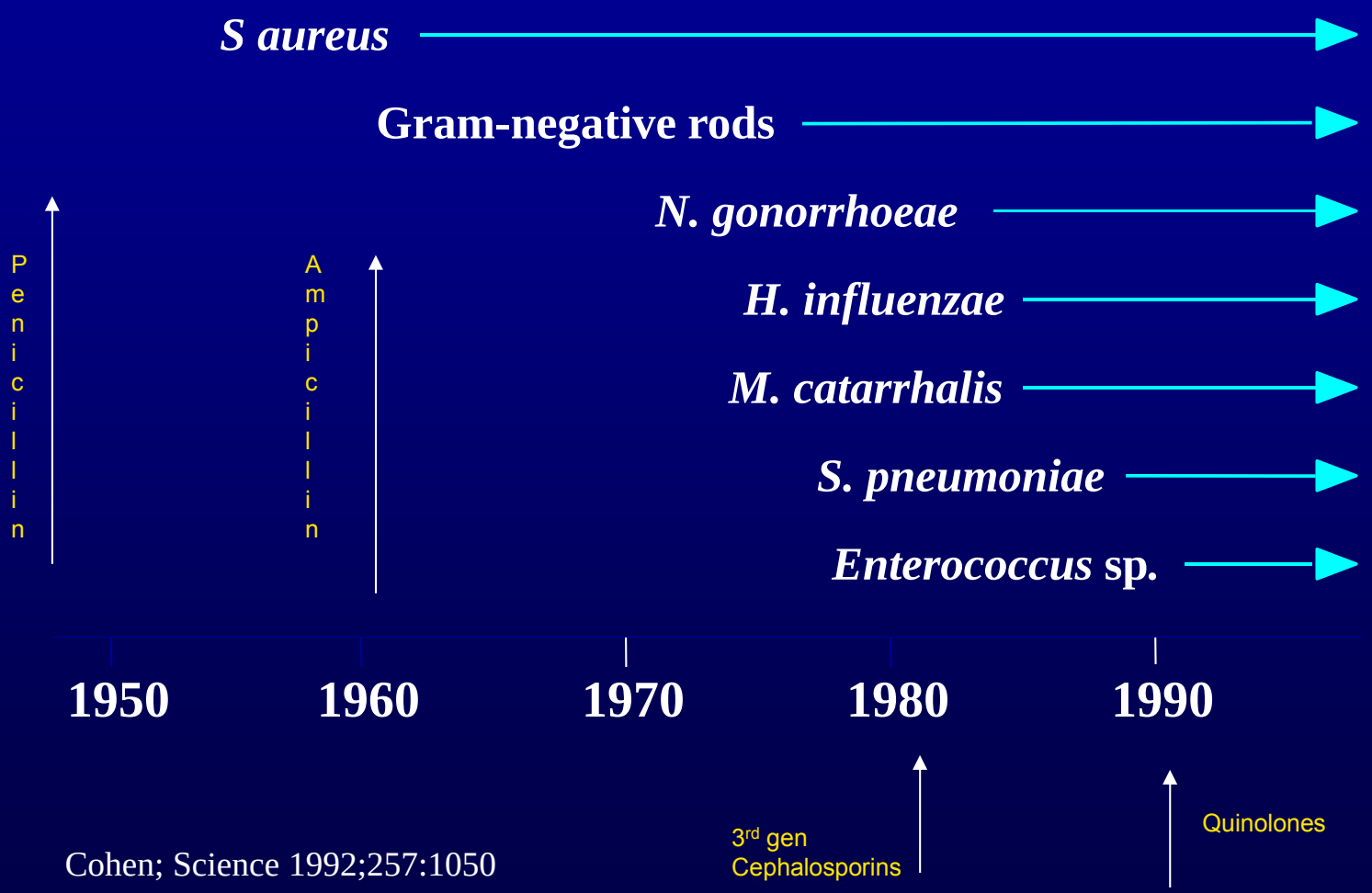
Prescribing an antibiotic

- Is an antibiotic necessary ?
- What is the most appropriate antibiotic ?
- What dose, frequency, route and duration ?
- Is the treatment effective ?

Is an antibiotic necessary ?

- Useful only for the treatment of bacterial infections
- Not all fevers are due to infection
- Not all infections are due to bacteria
  - There is no evidence that antibiotics will prevent secondary bacterial infection in patients with viral infection

Emergence of Antibiotic-Resistant Bacteria



Cohen; Science 1992;257:1050

Practices Contributing to Misuse of Antibiotics

- Inappropriate specimen selection and collection
- Inappropriate clinical tests
- Failure to use stains/smears
- Failure to use cultures and susceptibility tests

Inappropriate Antibiotic Use

- Use of antibiotics with no clinical indication (eg, for viral infections)
- Use of broad spectrum antibiotics when not indicated
- Inappropriate choice of empiric antibiotics

Inappropriate Drug Regimen

- Inappropriate dose - ineffective concentration of antibiotics at site of infection
- Inappropriate route - ineffective concentration of antibiotics at site of infection
- Inappropriate duration

Major activities

Governance	▪ Establishment of **national alliances** against AMR ▪ Designation of national focal points in MoH ▪ Constitution of multisectoral National Steering Committee
Regulatory	● Development and application of **standard treatment guidelines** in health and veterinary sectors ● Discourage non-therapeutic use of drugs in animals ● Restrictions on over-the-counter sale of antimicrobial agents
Capacity building	● **Surveillance** of antimicrobial use and resistance ● Training prescribers for rational use of antimicrobials ● Reducing disease burden and infection control ● Undertaking operational research
Community participation	● **Educating** for adherence to recommended regimens ● Discouraging self-prescription

Factors promoting emergence of resistance

- Unnecessary use (e.g. use in non-bacterial illnesses; inappropriate prophylaxis)
- Intensive use in hospital settings
- Inappropriate use: wrong choice of antimicrobial, wrong dose or duration of treatment
- Poor quality drugs
- Unregulated sales
- Self-medication

Factors promoting spread of resistance

- Prolonged illness - increases opportunity for person-to-person spread
- Poor sanitation and overcrowding
- International travel and trade, population movements
- Inadequate control of infection in health care facilities

ESSENTIAL AND COMPLEMENTARY DRUGS

(Myanmar Essential Drug Project, Ministry Of Health, 2002)

1. .	**Anaesthetics**	**GA** Ether (E) Halothane (E) Ketamine (E) Nitrous oxide (E) Thiopentone (E) Oxygen (E) Propofol (C) Isoflurane (C)	**LA** Bupivacaine (hydrochloride) (E) Lignocaine (hydrochloride) (E) Oxybuprocaine (C)
	Preoperative medication	Atropine (E) Diazepam (E) Morphine (E)	
2.	**Analgesics, Antipyretic, NSAIDs and drugs used to treat gout**	**Non-opioids** Aspirin (E) Allopurinol (E) Diclofenac (E) Ibuprofen (E) Paracetamol (E) Colchicines (C) Probenecid (C) Nimesulide (C) Naproxen (E) Celecoxib (C)	**Opioids** Codeine (E) Morphine (E) Pethidine (E) Pentazocine (C)

3.	**Antiallergic and drug used in anaphylaxis**	Adrenaline (hydrogen tartrate) (E) Chlorpheniramine (maleate) (E) Dexamethasone (sodium phosphate) (E) Hydrocortisone (acetate) (E)	Hydrocortisone (sodium succinate/ sodium phosphate) (E) Prednisolone (E) Cetirizine (hydrochloride) (E)
4.	**Antidote and other substance used in poisonings**	Non- specific Activated charcoal (E)	Specific Atropine (sulphate) (E) Dimercaprol (E) Naloxone (hydrochloride) (E) Penicillamine (E) Pralidoxime (mesilate) (E) Sodium calcium edetate (E)
5.	**Anticonvulsants, Antiepileptics**	Carbamazepine (E) Diazepam (E) Ethosuximide (C) Magnesium sulfate (E)	Phenobarbitone (sodium) (E) Phenytoin (sodium) (C) Sodium Valproate (E)

Myanmar Essential Drug List (Generic name) (INN)

Antileprosy Drugs
Clofazimine (E)
Dapsone (E)
Rifampicin (E)

Antituberculous Drugs
Rifampicin (E)
Ethambutol (hydrochloride) (E)
Isoniazid (E)
Pyrazinamide (E)
Isoniazid+Rifampicin
(combined preparation) (E)
Streptomycin (sulphate) (E)

Antifungal Drugs
Ketoconazole (E)
Amphotericin B
(SALT complex or lipid compex) (C)
Fluconazole (C)
Nystatin (E)

Antiprotozoal Drugs

Antiamoebic and Antigiardiasis Drugs
Diloxanide furoate (E)
Metronidazole (benzoate) (E)
Dehydroemetine (C)
Tinidazole (E)

Antimalarial Drugs
Chloroquine (phosphate/sulphate)(E)
Mefloquine (hydrochloride) (E)
Artemether (E)
Artesunate (E)
Doxycycline (E)
Primaquine (diphosphate) (E)
Quinine (E)
Sulfadoxine+Pyrimethamine(E)

Antiviral & Antiretroviral Agents
Acyclovir (E)
Zidovudine (E)
Lamivudine (E)
Didanosine (E)
Stavudine (E)
Indinavir (sulphate) (E)
Ritonavir (E)
Saquinavir (mesilate)(E)

7	**Antimigraine**	**(a)For Treatment of Acute Attack** **Ergotamine (tartrate) + Caffeine (C)** **Paracetamol (E)** **Aspirin (E)** **Diclofenac (potassium) (E)**	**(b) For Prophylaxis** **Propranolol (hydrochloride) (E)**
8.	**Drugs affecting the blood (Anti-anaemics)**	**Ferrous (sulfate/ fumarate) (E)** **Folic acid (sodium) (E)** **Hydroxycobalamin (E)** **Iron sorbitol (C)**	
9	**Blood products and plasma substitute**	**Plasma substitute** **Dextran 70 (E)** **Pentastarch (C)**	**Blood Preservative Solution** **Citrate Phosphate Dextrose-Adenine$_1$ (CPDA$_1$) (E)**

10 **Cardiovascular drugs**

Antianginal Drugs
Atenolol (E)
Glyceryl trinitrate (E)
Isosorbide dinitrate (E)
Isosorbide mononitrate (E)
Metoprolol (tartrate) (E)

Antihypertensive Drugs
Chlorthalidone (E)
Amlodipine(besilate)(E)
Diltiazam (E)
Prazosin (hydrochloride) (E)
Atenolol (E)
Metoprolol (tartrate) (E)
Labetolol (hydrochloride) (E)
Methyldopa (C)
Enalapril (meleate) (E)
Perindopril (erbumine) (C)
Losartan (potassium)(C)
Minoxidil (C)
Sodium nitroprusside (C)

Lipid Regulating Drugs
Simvastatin (E)
Gemfibrozil (E)
Cholestyramine (E)

Anti-arrhythmic Drugs
Lignocaine (hydrochloride) (E)
Atenolol (E)
Verapamil (hydrochloride) (E)
Metoprolol (tartrate) (E)
Disopyramide (C)
Quinidine (sulfate) (C)
Amiodarone (hydrochloride)(C)

Cardiac Glycosides
Digoxin (E)

Drugs used in shock and anaphylaxis
adrenaline (hydrogen tartrate) (E)
Chlorpheniramine (meleate) (E)
Dopamine (hydrochloride) (E)
Hydrocortisone (sodium succinate/ phosphate) (E)
Dobutamine (hydrochloride)(C)

Anti-thrombotic (Antiplatelet) Drugs
Aspirin (E)
Ticlopidine (C)
Clopidogrel (hydrogen sulphate) (C)
Fibrinolytic (Thrombolytic) Drugs
Streptokinase (E)

11	**Dermatological drugs (topical)**	**Antifungal drug** Benzoic acid + Salicylic acid (E) Clotrimazole (E) Nystatin (E) Ketoconazole (E) **Anti-inflammatory and Antipruritic drugs** Betamethasone (valerate) (E) Calamine (E)	**Anti-bacterial Drugs** Neomycin (sulphate) (E) Silver sulphadiazine (E) Povidone-Iodine (E) Metronidazole (E) Antiviral Drugs Acyclovir (E) **Keratoplastic and Keratolytic agent** Coal tar (E) Salicylic acid (E) Scabicides and pediculicides Benzyl benzoate (E) Permethrin (C)
12	**Diagnostic agents**	Amidotrizoate (iodinated sodium/ meglumine salt) (E) Barium sulfate (E)	
13	**Disinfectants and antiseptics**	**Antiseptics** Benzalkonium (chloride) (E) Cetrimide (E) Chlorhexidine (gluconate) (E) Hydrogen peroxide (E) Methylated spirit (E) Comprox AC + Parachlormetaxylenol + Dichlormetaxylenol (Aseptol) (E)	

14 **Diuretics**

- Chlorthalidone (E)
- Frusemide (E)
- Mannitol (C)
- Spironolactone (E)

15 **Gastrointestinal drugs**

Antacid

- Aluminium hydroxide (E)
- Magnesium trisilicate (E)
- Sodium bicarbonate (E)

Antiemetic drugs

- Metoclopramide (hydrochloride) (E)
- Perphenazine (E)
- Cinnarizine (hydrochloride) (C)
- Domperidone (maleate) (C)
- Ondansetron (hydrochloride) (C)
- Hyoscine (hydrochloride) (E)

Antispasmodic drugs

- Hyoscine (butylbromide) (E)
- Oxyphencyclimine (E)
- Loperamide (E)

Antiulcer drugs

- Ranitidine (hydrochloride) (E)
- Omeprazole (E)
- Bismuth subnitrate (C)
- Dimeticone (C)

Laxative & Cathartic Drugs

- Bisacodyl (E)
- Magnesium hydroxide (E)
- Magnesium sulphate (E)
- Lactulose (C)

Drugs used to treat diarrhoea

- Oral rehydration salt (E)

16. Hormone and other endocrine drugs and contraceptives

Adrenal hormone and other synthetics substitutes

Dexamethasone (sodium phosphate)(E)
Hydrocortisone
(sodium succinate/ phosphate) (E)
Prednisolone (E)

Drugs for anovulatory infertility

Clomifene citrate (E)

Female Sex Hormones Preparations for Replacement Therapy

Oestrogen (conjucated form) (C)
Oestrogen+ Medroxyprogesterone (acetate) (C)
Tibolone (E)

Insulin and other Antidiabetic Agents

Insulins (E)
- short-acting-soluble insulin
- Intermediate-
  - isophane, biphasic insulin
- long-acting-insulin zinc
  - suspension (mixed,crystalline)

Metformin (hydrochloride) (E)
Glibenclamide (E)
Gliclazide (C)
Repaglinide (E)
Acarbose (C)

Contraceptive

Hormonal contraceptive

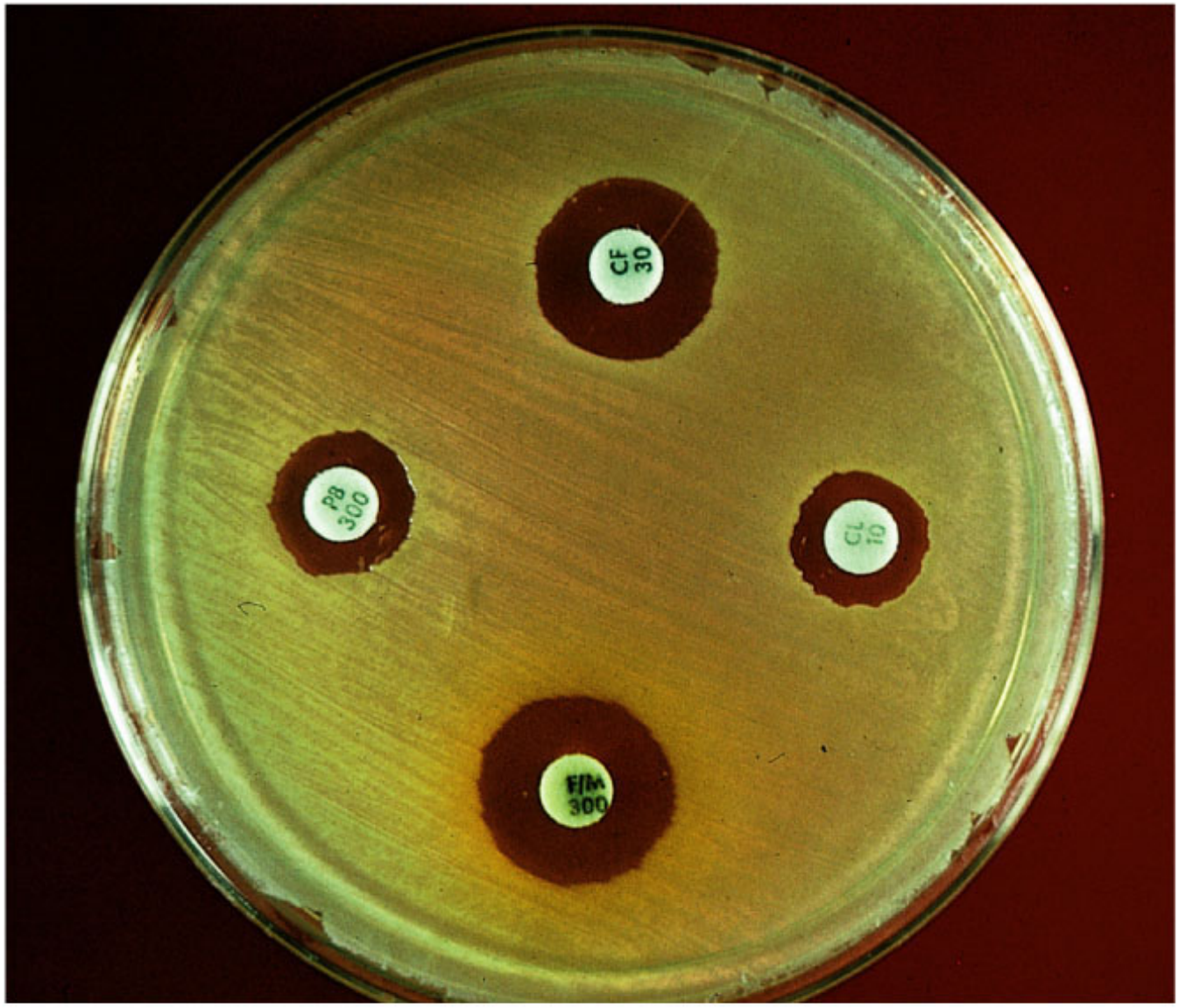
Ethinyloestradiol + Desogestrel or Levonorgestrel (E)
Levonorgestrel or Norethisterone (E)
Medroxyprogesterone (acetate) (E)
Etonogestrel (C)
Copper Intra-uterine Device (Cu-IUD) (E)
Condom (male/female) (E)
Contraceptive cap and diaphragm (C)

Thyroid hormones and Antithyroid drugs

Levothyroxine (sodium) (E)
Carbimazole (E)
Propylthiouracil (E)
Lugol's Iodine (E)
Radioactive iodine (E)

17	Immunological	Sera and Immunoglobulins Anti-snake venom for cobra bite (Cobra antivenin) (E) Anti-snake venom for viper bite (Viper antivenin) (E) Tetanus immunoglobulin (E) Rabies immunoglobulin (E)	Vaccines For universal immunization BCG vaccine (E) Diphtheria, Tetanus & Pertussis Vaccine (E) Diphtheria &Tetanus Vaccine (E) Hepatitis B Vaccine (E) Measles Vaccine (E) Poliomyelitis Vaccine (E) Tetanus Vaccine (E) For specific groups of individuals Rabies Vaccine (E) Typhoid, Paratyphoid A & B Vaccine with Vi antigen (E) Plague Vaccine (C) Haemophilus influenzae B Vaccine (HIB) (C) Measles/Mumps/Rubella Vaccine (MMR) (C) Meningococcal Vaccine (C) Yellow Fever Vaccine (C)

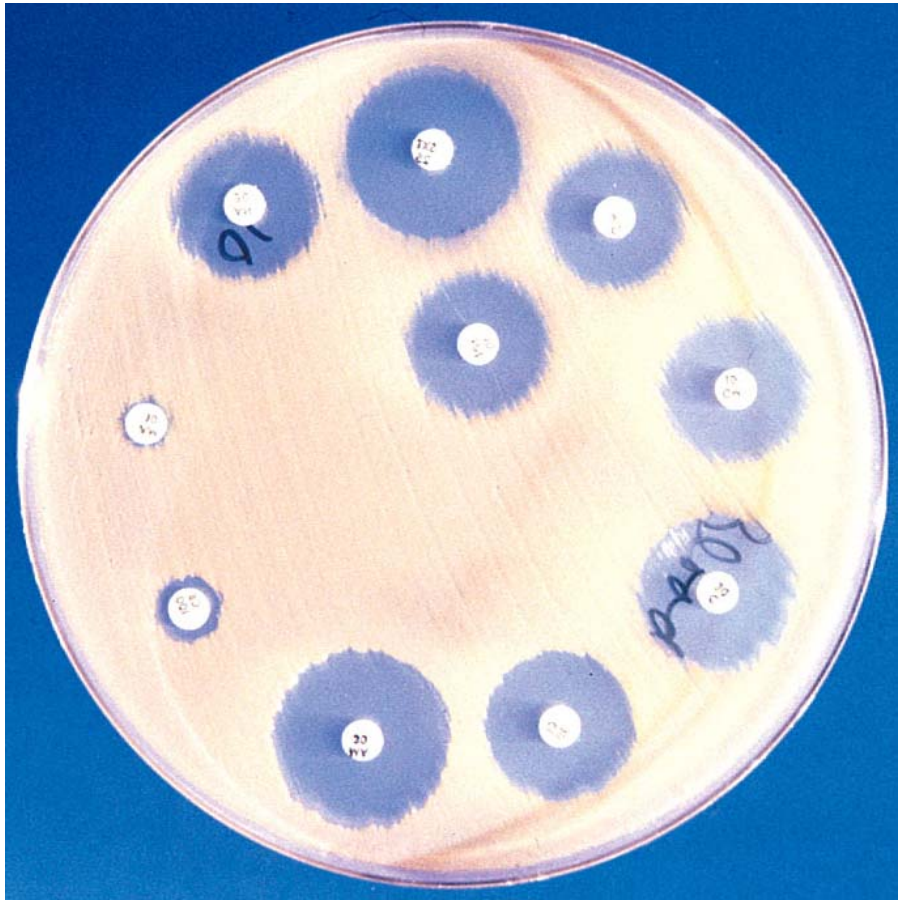
Disk-Diffusion Test



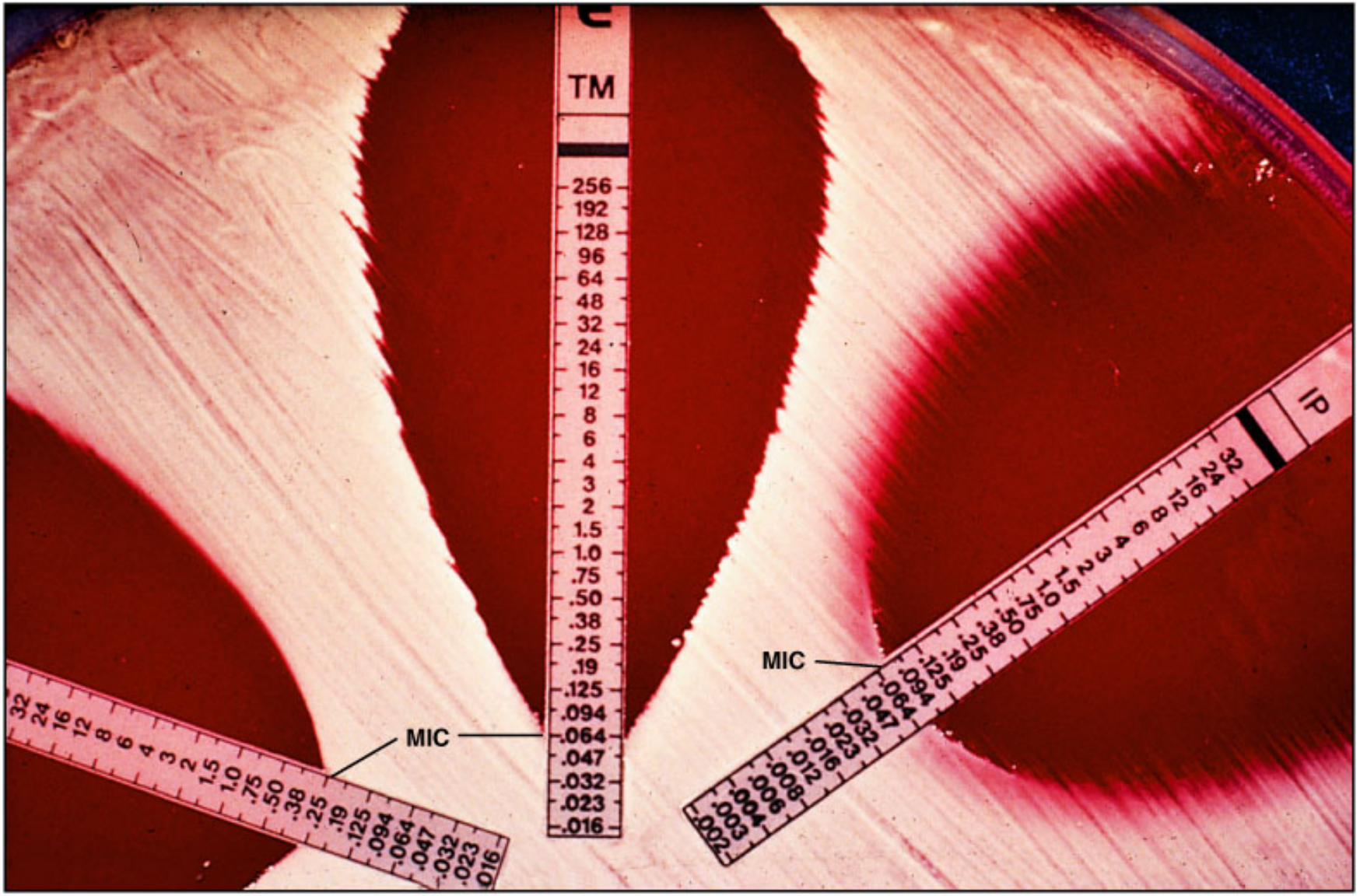
Kirby-Bauer Method

for Determining Drug Susceptibility

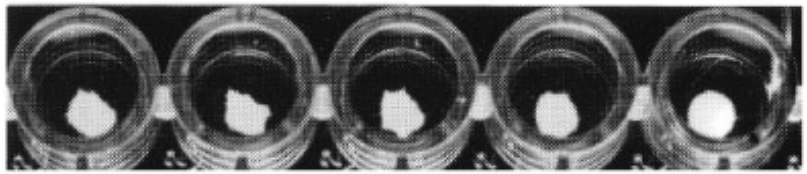
1. Bacteria spread on surface of agar plate
2. 12 disks, each with different antimicrobial drug, placed on agar plate
3. Incubated- drugs diffuse outward and kill susceptible bacteria
4. Zone of inhibition around each disk
5. Compare size of zone to chart



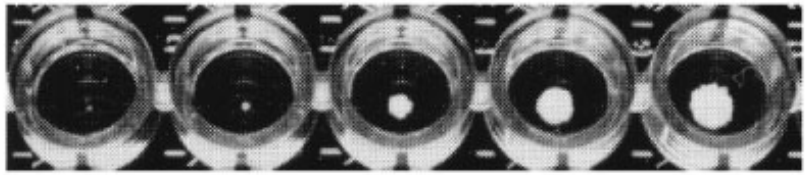
E Test



Broth Dilution Test

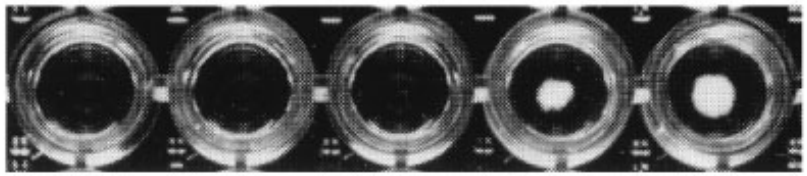


Doxycycline
(Growth in all wells, resistant)



Sulfamethoxazole
(Trailing end point; usually read where there is an estimated 80% reduction in growth)

Streptomycin
(No growth in any well; sensitive at all concentrations)



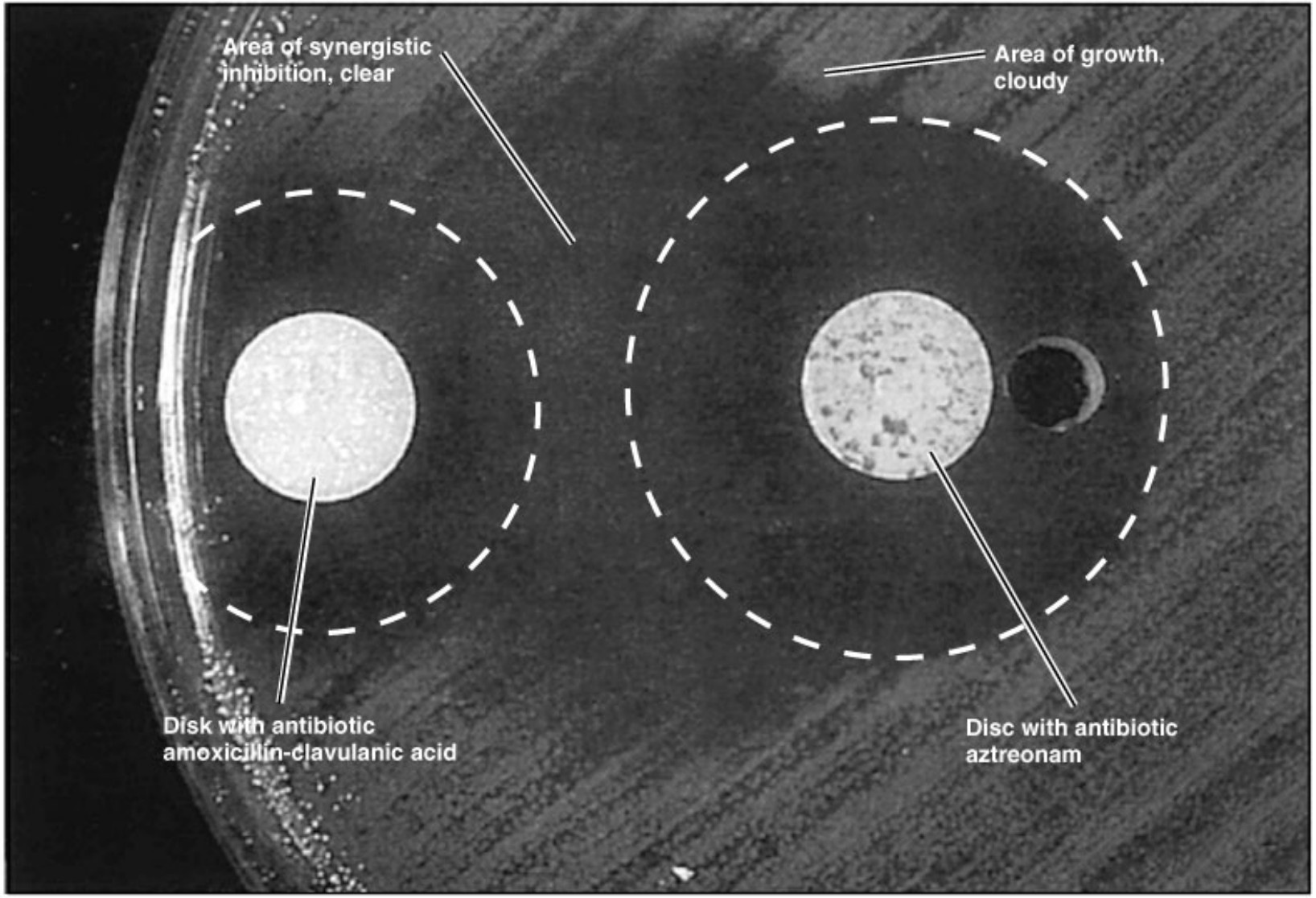
Ethambutol

Kanamycin

(Growth in second wells; ethanmbutol and kanamycin equally sensitive)

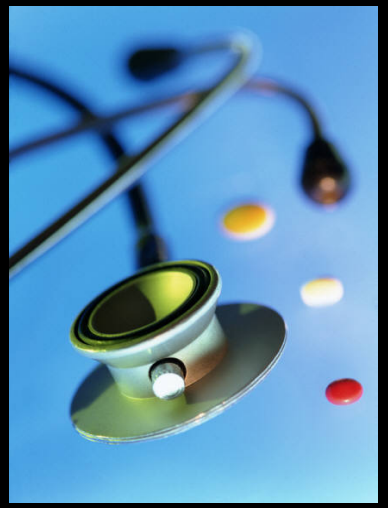
Decreasing concentration of drug →

Effects of Combinations of Drugs



The antimicrobial agent

- Narrow spectrum
- Inexpensive
- Easily administered
- Well tolerated
- Minimal side effects
- Less frequently agent is given
- More reliable adherence (compliance) of patient
- Single administration of antimicrobial agent : ideal



FEIGIN, et al. Textbook of Pediatric Infectious Diseases 2004;236:3029-3040.