Antimicrobial Stewardship

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Definition

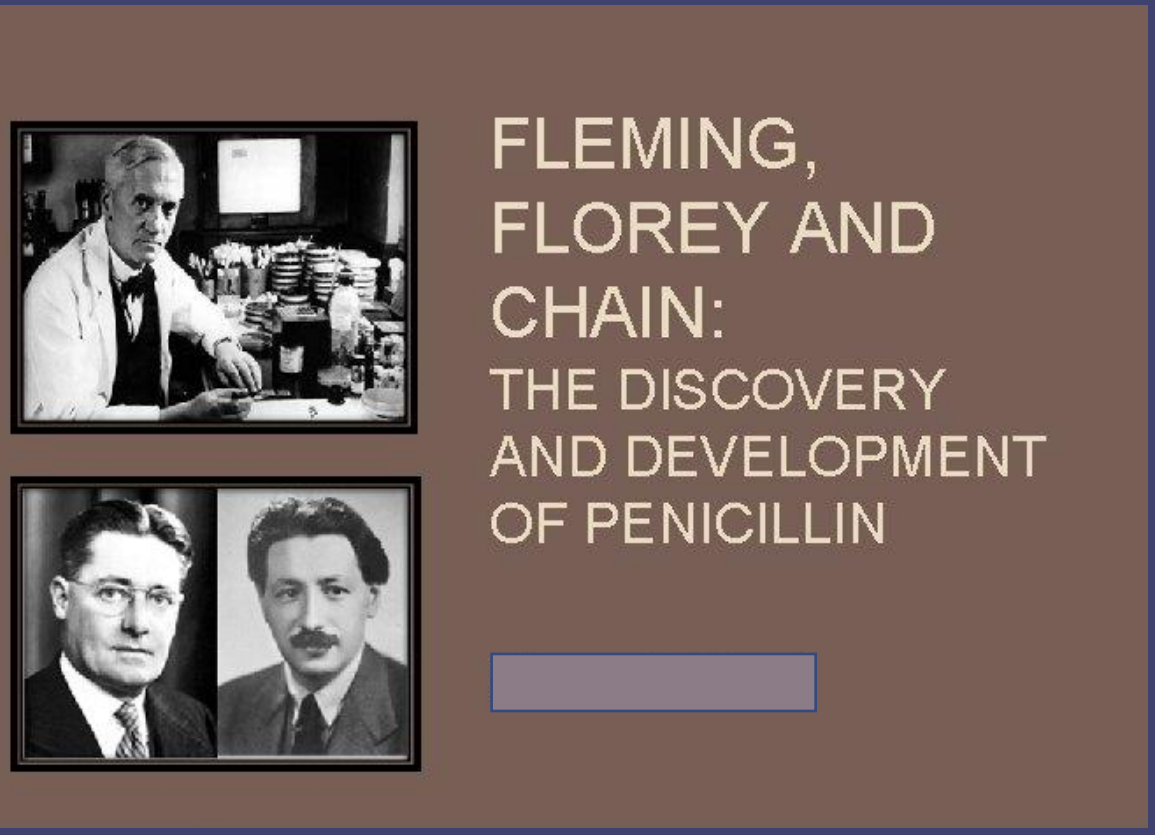
CDC has defined “Antimicrobial stewardship” as-

- The **right** antibiotic
- For the **right** patient,
- At the **right** time,
- With the **right** dose,
- **Right** route, causing
- Least harm to the patient and future patients

The Need of Antimicrobial Stewardship

Nobel Prize

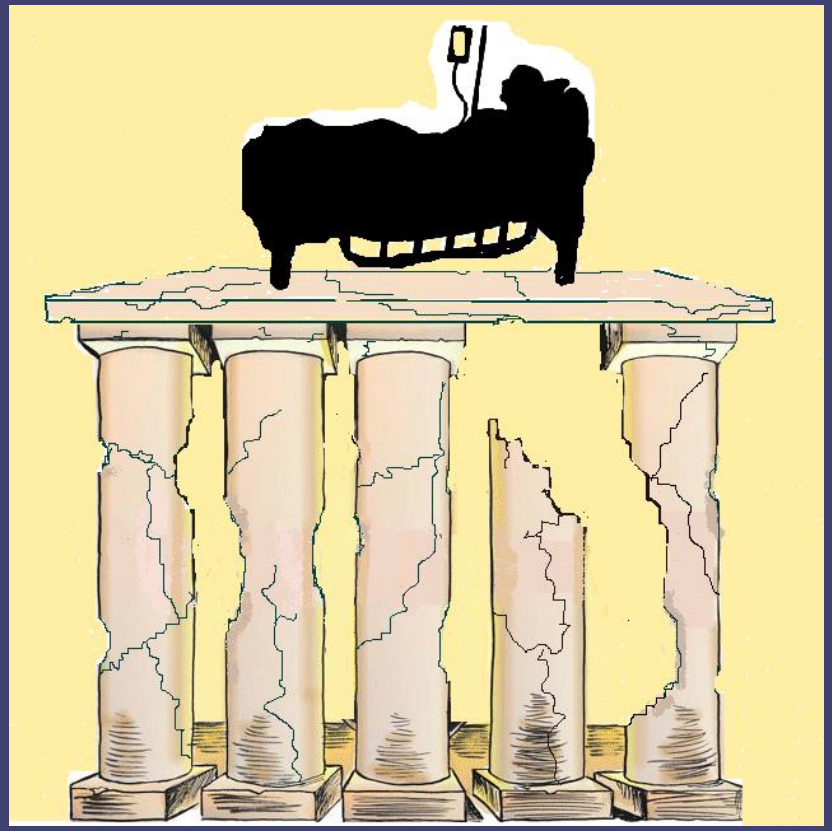
- **1945**
- **Alexander Fleming**
- **E. B. Chain**
- **H. W. Florey**
- **Discovered penicillin from Penicillium fungus**



It is not difficult to make microbes resistant to penicillin ….

…. The time may come when penicillin can be bought by anyone in the shops. Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant.

Alexander Fleming Nobel Speech 1945

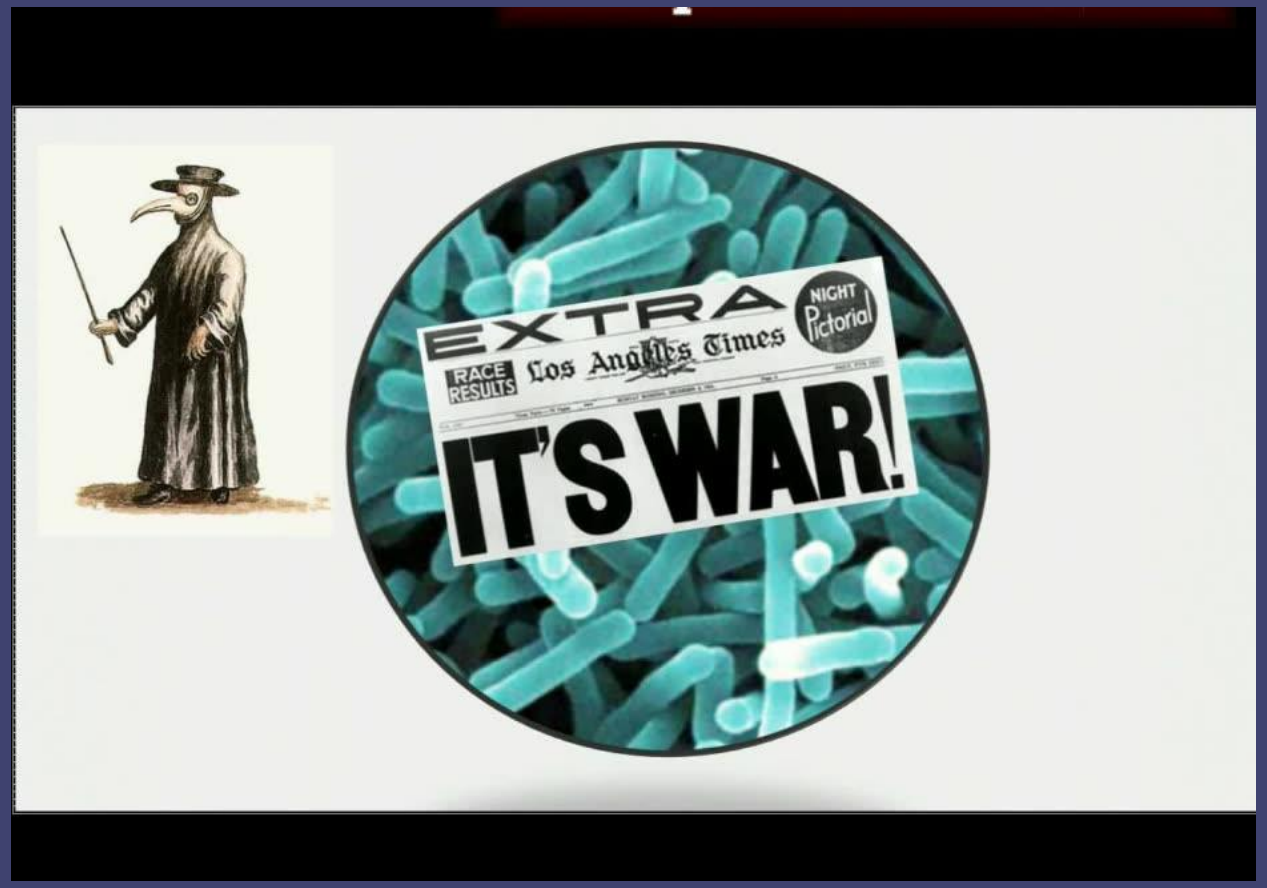


- **Modern medicine is built on access to effective antibiotics…..**

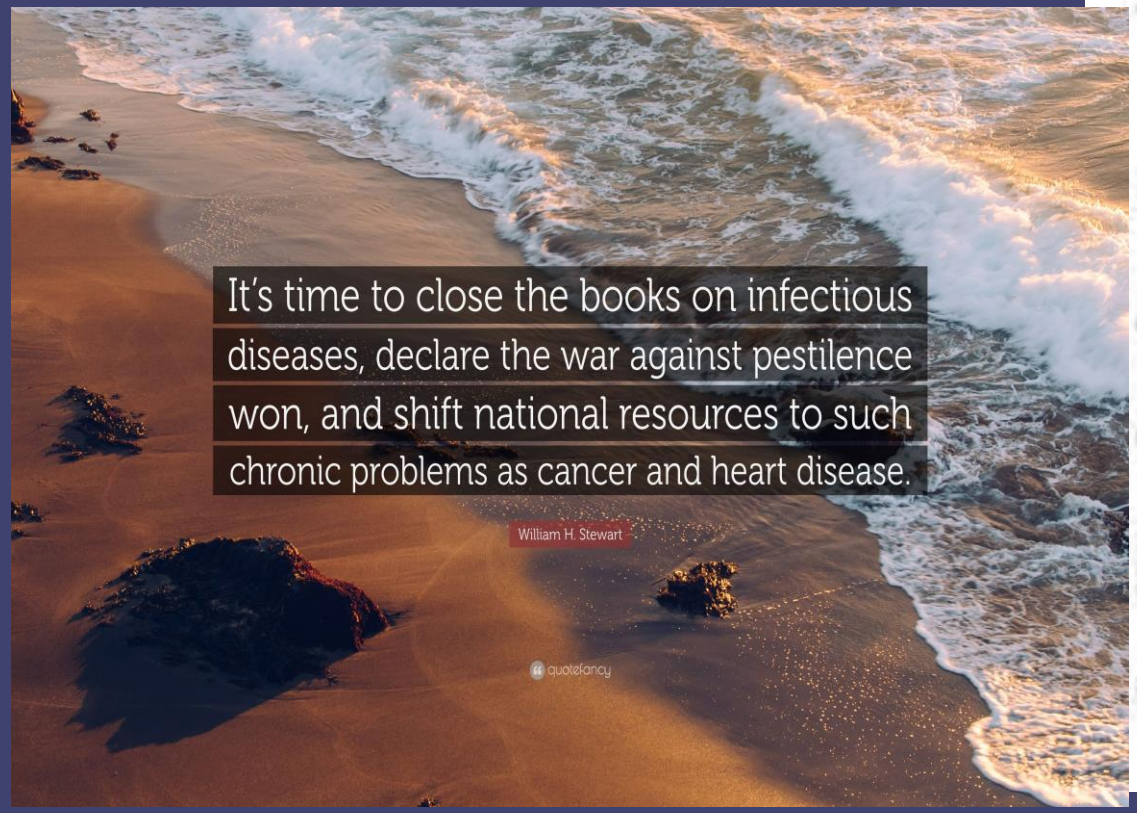
Sobering Thoughts

- The earth is 5 billion years old and bacteria have been around for 4 of those 5 billion years!
- Infectious diseases are still the most common cause of death worldwide.
- Antibiotics CANNOT distinguish between beneficial and harmful bacteria
- Antibiotics are the ONLY class of therapeutic agents that affect the environment.

- 1950-1970
- Golden age of antibiotic discovery
- About 50% of antibiotics used were discovered.

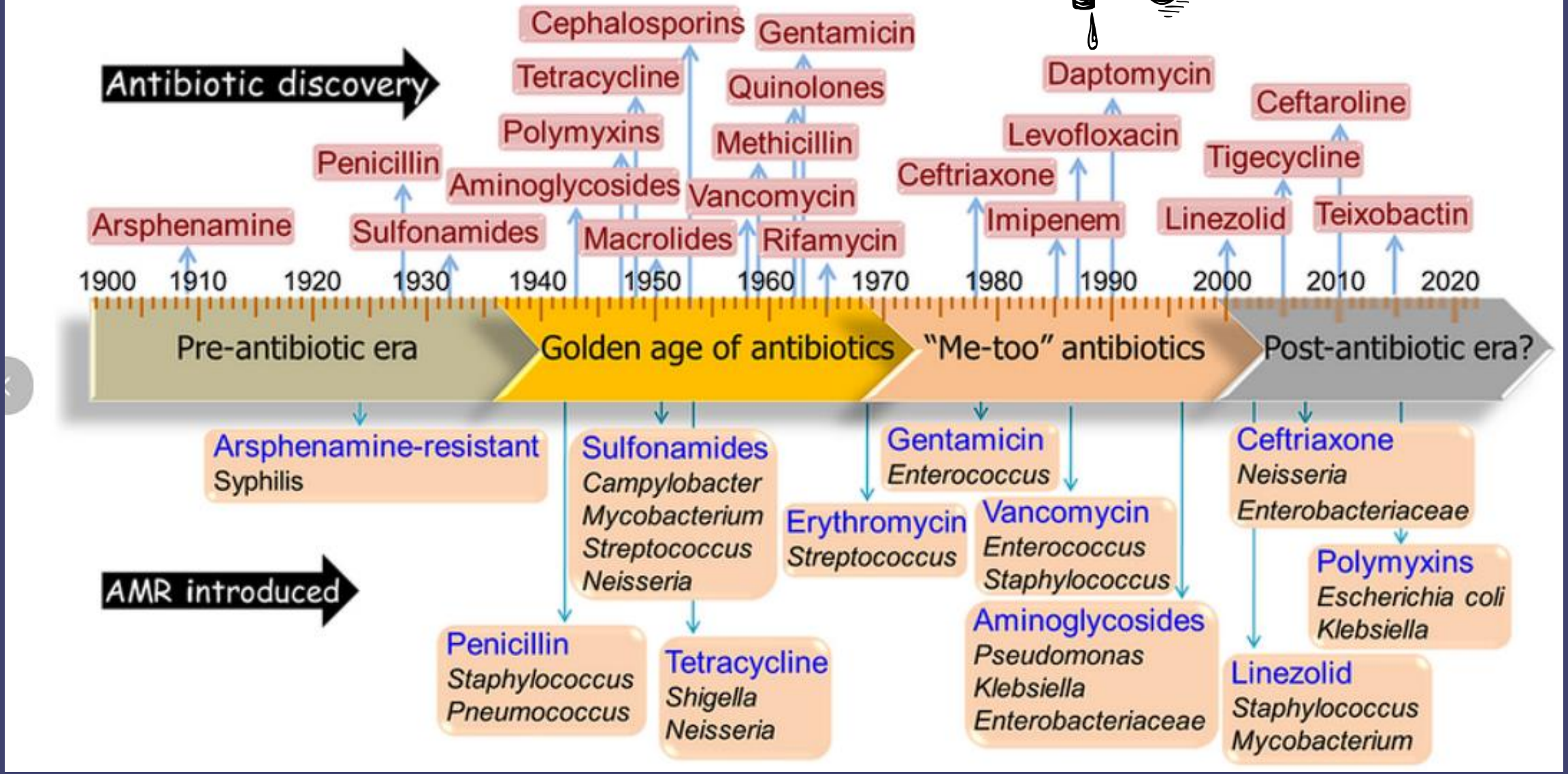


Infectious Diseases: A Premature Declaration of Victory



1967 – Surgeon General William H. Stewart testifies before the United States Congress that "the war against infectious diseases had been won" and we should focus our efforts on other areas of research and public health.

The dwindling antibiotic pipeline...



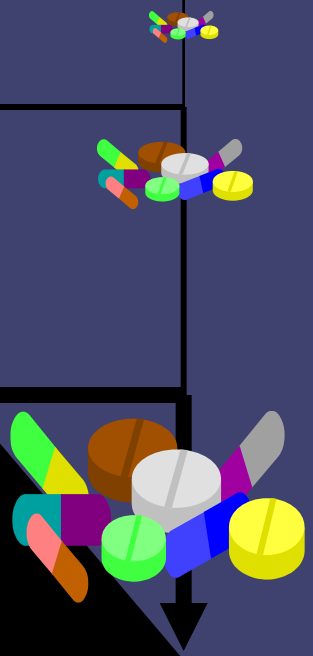
Antibiotic use in the health system

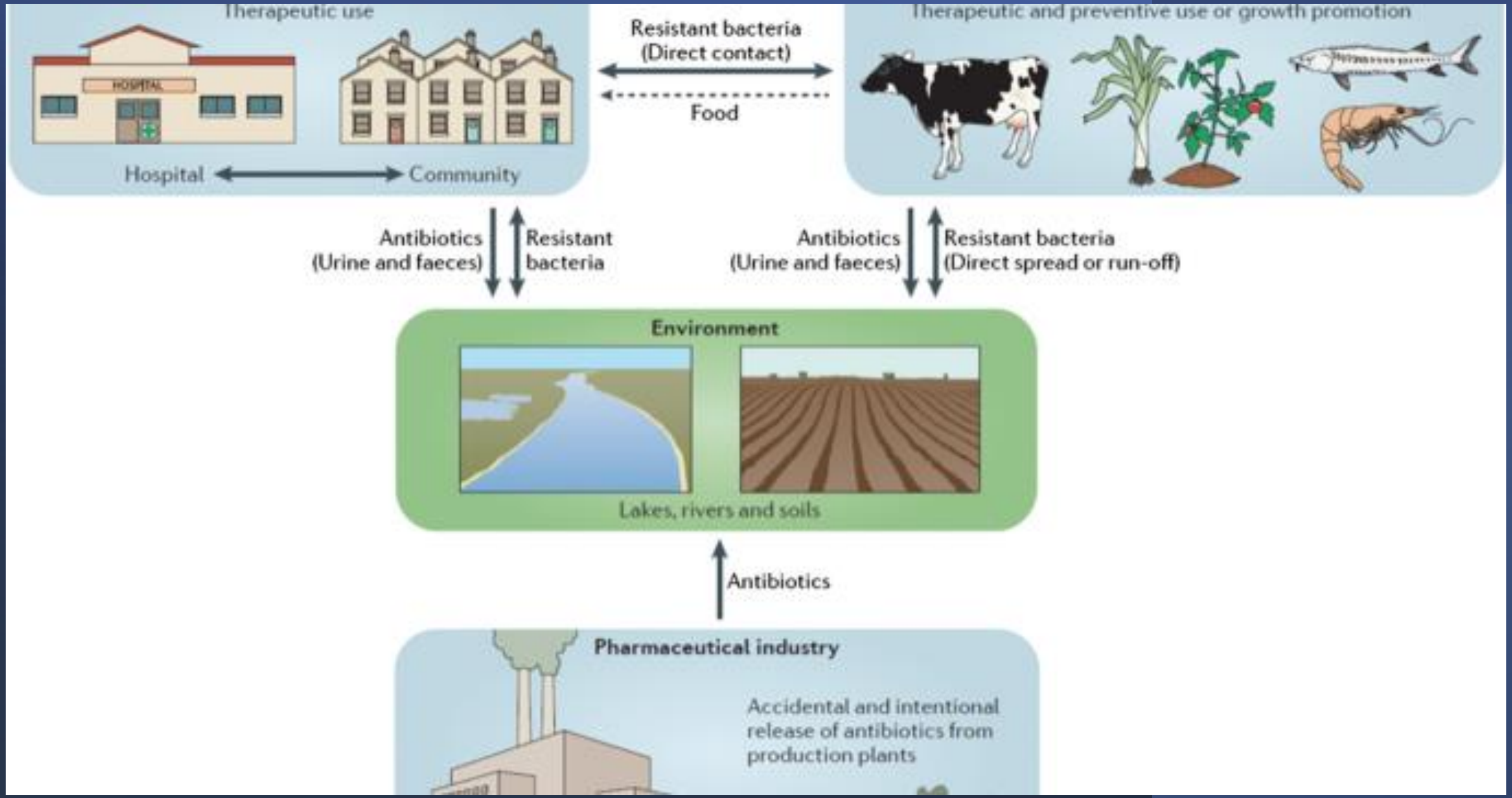
Who prescribes/ recommends?

Hospitals

Primary Health Care

Pharmacies/
drug shops

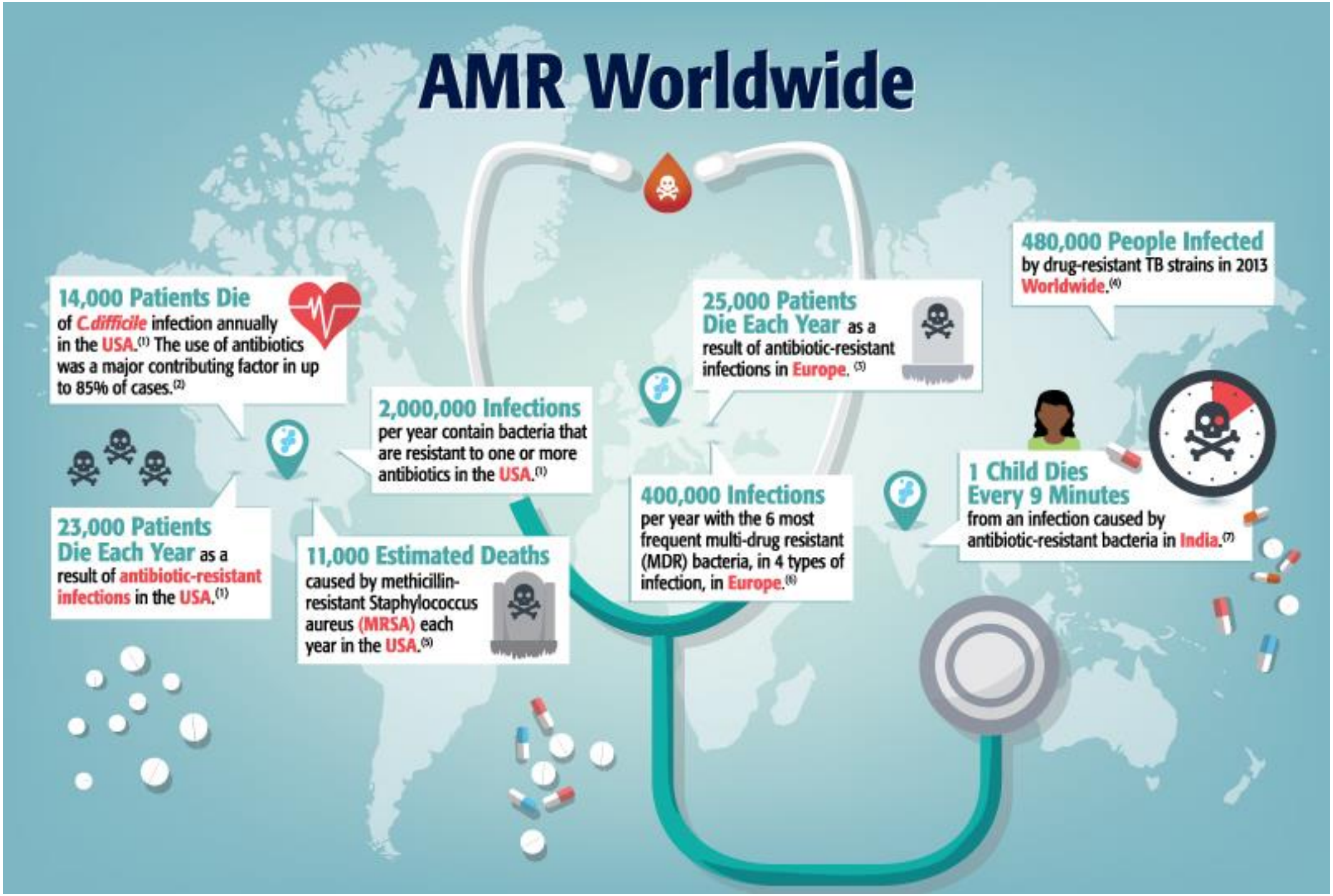



Therapeutic use
HOSPITAL
Hospital
Community
Resistant bacteria
(Direct contact)
Food
Therapeutic and preventive use or growth promotion
Antibiotics
(Urine and faeces)
Resistant
bacteria
Antibiotics
(Urine and faeces)
Resistant bacteria
(Direct spread or run-off)
Environment
Lakes, rivers and soils
Antibiotics
Pharmaceutical industry
Accidental and intentional
release of antibiotics from
production plants

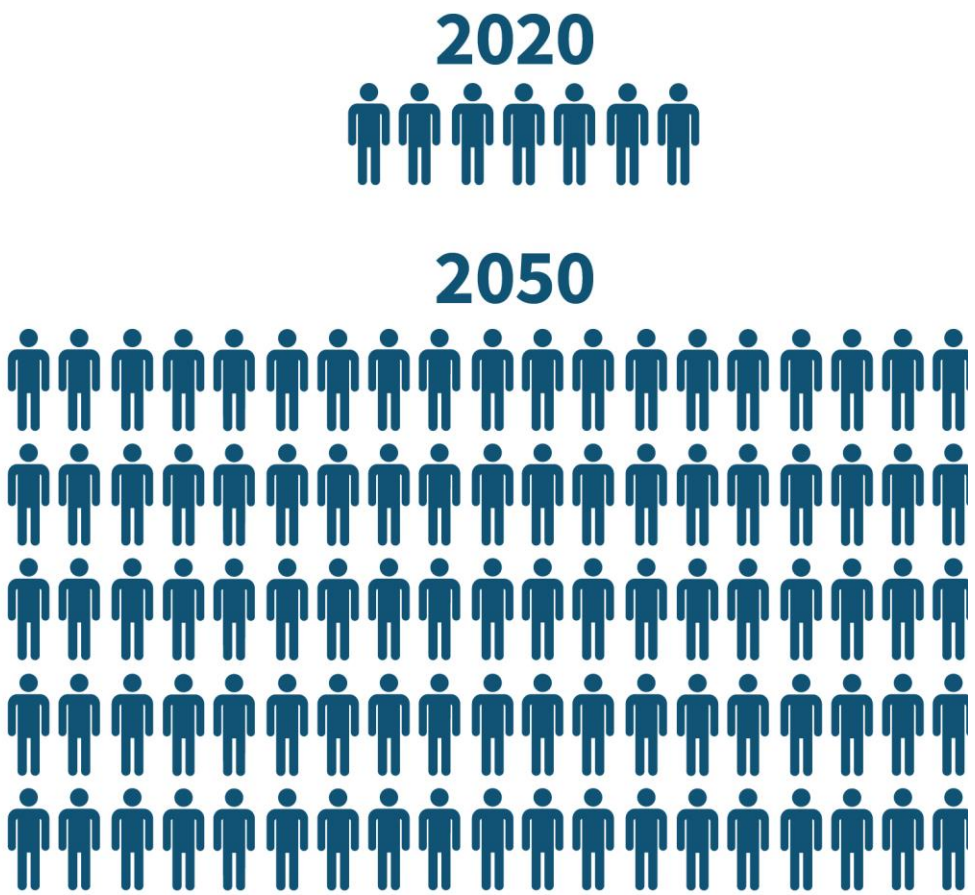
Misuse of antibiotics

Underuse	• An antibiotic is not used when it could improve health
Unnecessary use	• An antibiotic is not indicated e.g. non bacterial infections
Inappropriate use	• Incorrect timing, choice, dose, route, or duration

AMR Worldwide



ESTIMATED DEATHS DUE TO AMR IN 2020 AND 2050



= 100,000 ESTIMATED ANNUAL DEATHS BY AMR

Source: Jim O'Neill, Tackling Drug-Resistant Infections Globally: Final Report and Recommendations (London: The Review on Antimicrobial Resistance, May 2016), 4, https://amr-review.org/sites/default/files/160518_Final%20paper_with%20cover.pdf.

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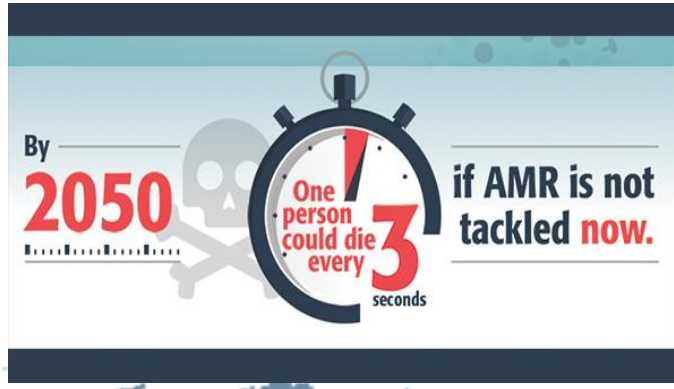
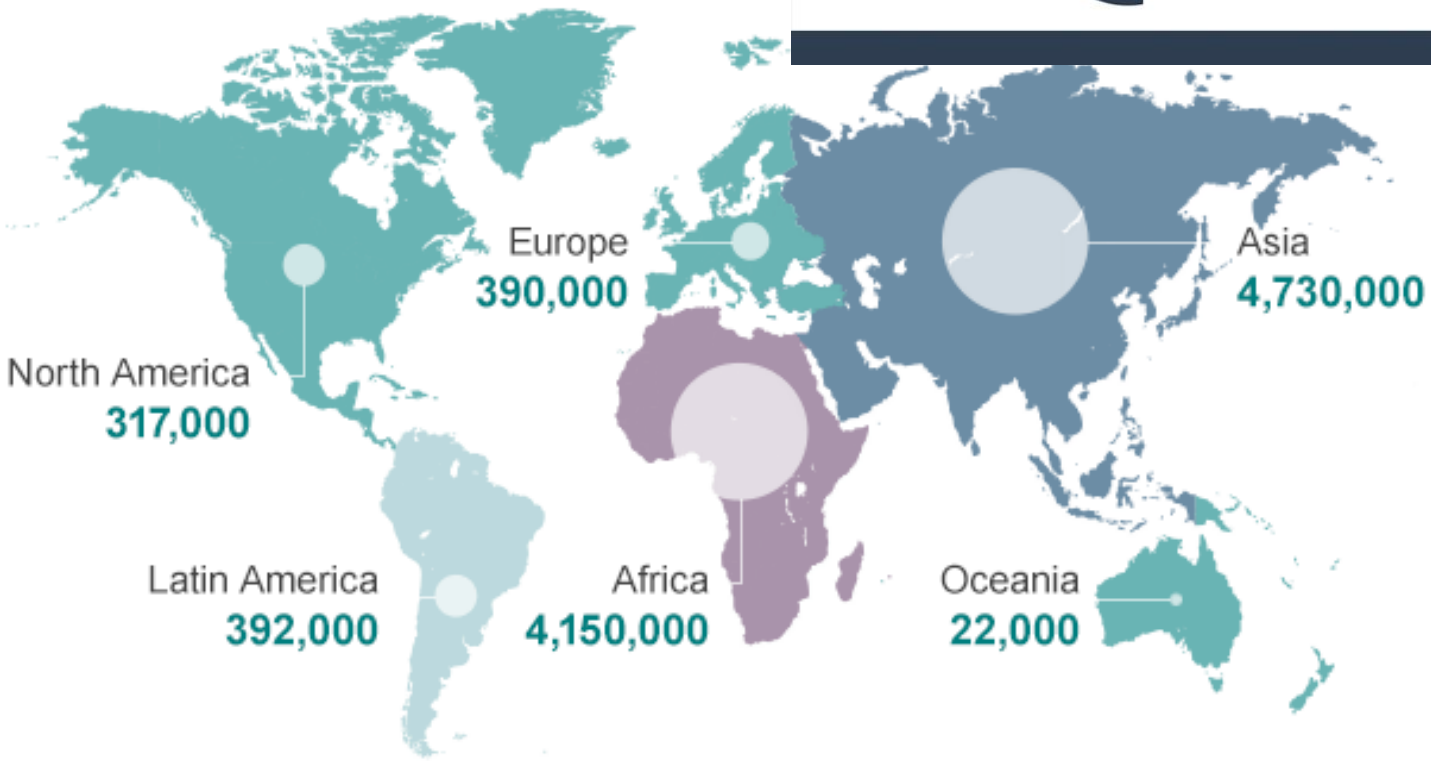
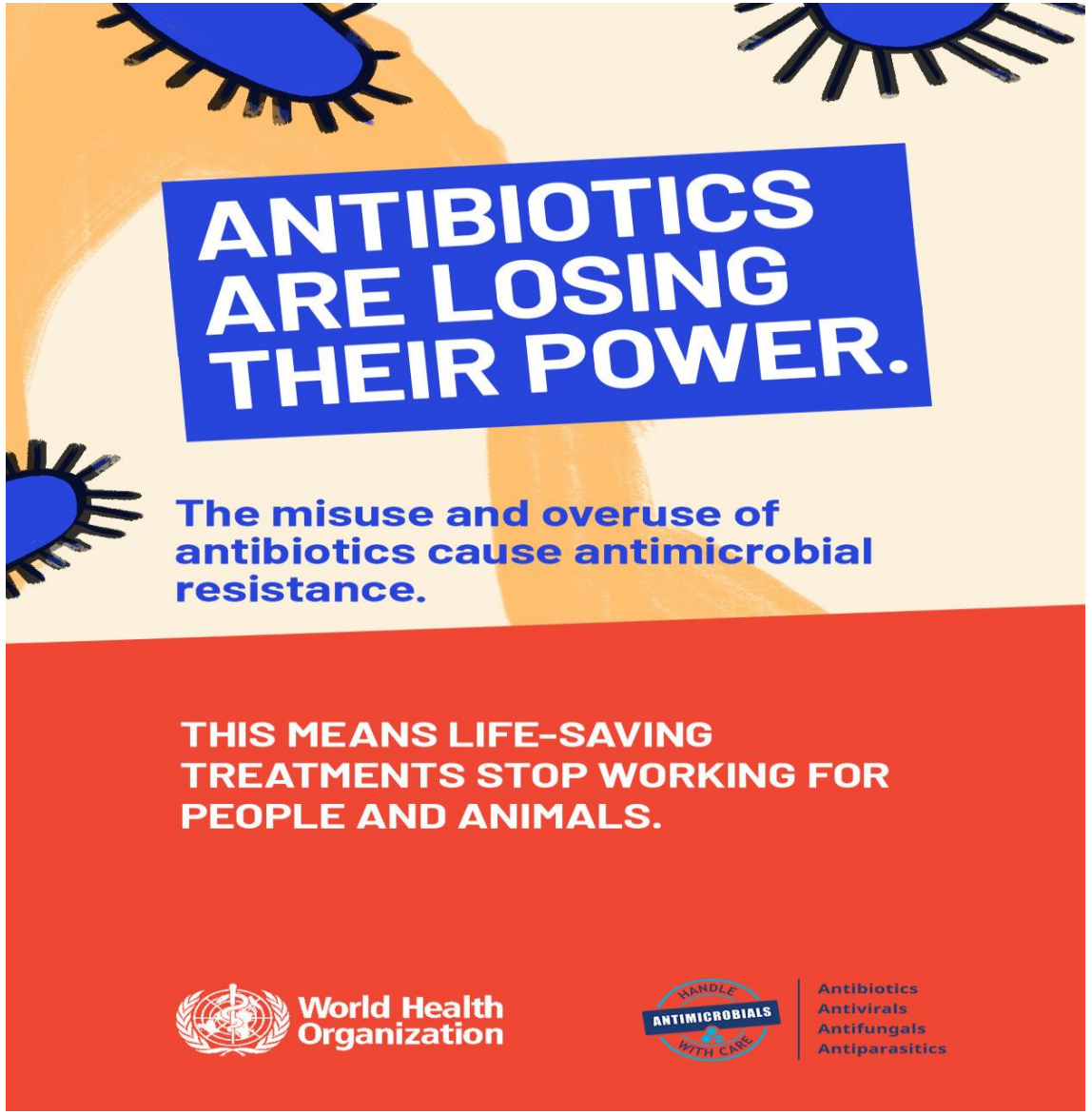




Source: Review on Antimicrobial Resistance 2014

Without action, by 2050 someone could die **every three seconds** as a result of AMR. That's **10 million people a year.**
Majority of deaths will occur in Africa and **Asia** – over 4 million in each region.


Antibiotics aren't
always the answer.
Many everyday infections get better on their own.
Misusing antibiotics, without the advice of a health worker,
makes them less effective when we really need them.


ANTIBIOTICS ARE LOSING THEIR POWER.
The misuse and overuse of antibiotics cause antimicrobial resistance.
THIS MEANS LIFE-SAVING TREATMENTS STOP WORKING FOR PEOPLE AND ANIMALS.
World Health Organization
HANDLE ANTIMICROBIALS WITH CARE
Antibiotics
Antivirals
Antifungals
Antiparasitics

Why Is AMSP Needed?

- *Antimicrobial Resistance (AMR)*
- *Misuse and Over-use of Antimicrobials*
- *Widespread Use of Antimicrobials in Other Sectors*
- *Poor Antimicrobial Research*

Antimicrobial Stewardship

Antimicrobial stewardship

Coordinated program

Promotes the appropriate use of antimicrobials (including antibiotics)

Few drugs in the pipeline

Need to conserve existing drugs

Improves patient outcomes

Decreases the spread of infections caused by multidrug-resistant organisms

Reduces microbial resistance

Goals of Antimicrobial stewardship ?

To achieve good therapeutic outcomes

To reduce drug adverse effects

To reduce treatment costs

To prevent emergence of antimicrobial resistance

AMR likely to kill 10 million people by 2050

IMPLEMENTATION OF ANTIMICROBIAL STEWARDSHIP PROGRAM

Components

- Administrative support
- Team
- Infrastructure
- Antimicrobial policy
- Stewardship strategy
- Education & training

Administrative Support (Leadership)

- Should be publicly committed to the program.
- Provide necessary funding and infrastructure support

AMSP Team

- **Multidisciplinary committee -** responsible for framing, implementing and monitoring the compliance to antimicrobial policy of the hospital.
- Led by the **antimicrobial steward -** infectious disease physician or infection control officer or clinical microbiologist.
- Other members of AMS team - stewardship nurses, clinical pharmacists and officer in-charge of pharmacy

Infrastructure

Support from Microbiology laboratory

- **Automations:**
  - Automated culture (e.g. BACTEC or BacT/ALERT),
  - Automated identification (MALDI-TOF)
  - Automated sensitivity (e.g. VITEK)
- **Biomarkers:** Procalcitonin and CRP
- **Rapid Molecular tests**
- **Emergency lab**

Antimicrobial policy

- Pocket hand book
- Prepared by AMS team
- Compliant to the standard national and international antibiotic guidelines and local antibiogram pattern

Stewardship strategy

- **Front end** strategies (formulary restriction)
- **Back end** strategies (prospective audit and feedback)

Formulary Restriction

Restricted antimicrobials	Semi restricted antimicrobials	Unrestricted antimicrobials
Pharmacy supply of >1 days requires prior approval by AMS team	Pharmacy supply of >3 days requires prior approval by AMS team	Pharmacy supply does not require AMS team approval.
Colistin Carbapenem Tigecycline	Teicoplanin, Vancomycin, Daptomycin, Linezolid, Third and fourth generation cephalosporins	First & second generation cephalosporins, Cotrimoxazole, Azithromycin, Clarithromycin, Fluoroquinolones

Back-end strategies (prospective audit and feedback)

- Difficult to perform, but it is the **most effective strategy** to implement AMSP.
- The AMS team goes for stewardship round during which they discuss with the clinical team in detail about the compliance to the antimicrobial policy.
- Mutually agreed upon constructive discussion between AMS team and clinical team.

Back-end strategies (prospective audit and feedback)

- More labor-intensive.
- More widely practiced
- More easily accepted by clinicians
- Provides a higher opportunity for educating and training the health care professionals
- Impact is delayed but sustainable

Education & Training

- Awareness campaigns
- CMEs
- Curriculum

RATIONAL USE OF ANTIMICROBIAL AGENTS

- **Prescribe Only when Indicated**
  - Conditions where antibiotics are not required – Diarrhea, URTI, when alternative diagnosis like dengue or chikungunya is suspected, as routine antibiotic prophylaxis
- **Culture of Cultures**
  - Antibiotics should be initiated only after sending site-specific cultures

Empirical vs Targeted Therapy

- **Empirical therapy –** should be based on three important elements.
  - Infective syndrome likely to be present
  - Common etiological bacterial agents for that infective syndrome
  - Local antibiogram for those organisms, indicating the AMR pattern.
- **Targeted or pathogen-directed therapy:** Empirical therapy should be modified subsequently, based on AST report (escalation or de-escalation)

Escalation vs De-escalation Approach

- For example; In hospital X, the antibiotics given for GNB such as *E. coli* are ranked according to decreasing order of susceptibility: colistin (rank-1) → tigecycline → carbapenems → piperacillin-tazobactam → cefoperazone sulbactam → amikacin → cefepime → ceftazidime → cotrimoxazole → ceftazidime → ciprofloxacin → ceftriaxone (lowest rank).
- Escalation Approach
- De-escalation Approach

[redacted]

[redacted]

ity:
nism : Escherichia coli
Site:

RINE

ments:	Colistin sensitive results must be cross checked with Broth microdilution and reported as per EUCAST & CLSI 2020 Fosfomycin results are valid only for Urinary isolates of E. coli

ification Information	**Analysis Time:**	4.90 hours	**Status:**	Final
ted Organism	94% Probability	**Escherichia coli**		
	Bionumber:	0405610454504610		
nalysis Messages				

eptibility Information	**Analysis Time:**	18.08 hours	**Status:**	Final

Antimicrobial	MIC	Interpretation	Antimicrobial	MIC	Interpretation
icillin/Clavulanic Acid	>= 32	R	Meropenem	<= 0.25	S
acillin/Tazobactam	>= 128	R	Amikacin	2	S
oxime	>= 64	R	Gentamicin	<= 1	S
axone	>= 64	R	Ciprofloxacin	>= 4	R
erazone/Sulbactam	>= 64	R	Fosfomycin	<= 16	S
ime	8	SDD	Trimethoprim/ Sulfamethoxazole	>= 320	R
enem	0.25	S			

Susceptible-dose dependent (SDD) implies that susceptibility of an isolate is dependent on the dosing regimen used. For further information, please o CLSI Performance Standards, or Product information.

S Findings

dence:	Consistent

[redacted]

Site-specific Antimicrobials

- **Lungs:** Daptomycin is not active at respiratory site(inactivated by surfactants)
- **CSF:** Any oral antibiotic, 1st & 2nd gen cephalosporins, tetracyclines, macrolides, quinolones and clindamycin are not active in CSF
- **Urine:** Antibiotics such as chloramphenicol, macrolide and clindamycin should be avoided in UTI; as they do not achieve adequate urinary concentrations

Right Dose

- Avoid Administration Errors- Antimicrobials should be administrated - correct dose (as per the age/body weight), and frequency and duration of therapy.
  - **Loading dose:** Concentration dependent- aminoglycoside, vancomycin and colistin
  - **Infusion:** Vancomycin - better when mixed with saline and given as an IV infusion
  - **Renal adjustment:** Dosage of the nephrotoxic drugs - aminoglycoside, vancomycin, and colistin - adjusted according to the creatinine clearance.

MIC-guided Therapy

- AST - performed by DD or by MIC - latter more accurate and reliable.
- Certain situations - antibiotic treatment is MIC-guided.
  - **Clinical conditions -** endocarditis, pneumococcal meningitis/pneumonia
  - **Vancomycin for *S. aureus*:** Vancomycin – avoided if MIC is >1 µg/mL.

Therapeutic index

- Ratio of susceptibility breakpoint divided by MIC of the test isolate.
- **Therapeutic index= Susceptible breakpoint/Test MIC**
- Higher the therapeutic index, better is the efficacy of the antimicrobial agent.

Therapeutic index

- For example, if a clinical isolate of *E.coli* is susceptible to both meropenem (MIC 1 µg/ml) and amikacin (MIC 8 µg/ml), **then meropenem falsely appears to be more efficacious** as its absolute MIC value is lower than amikacin.
- **MIC value** compared with standard **susceptibility breakpoint** (and not absolute MIC value) determines therapeutic efficacy

Therapeutic index

- Susceptible breakpoints of meropenem and amikacin for *E.coli* are 1 µg/mL and 16 µg/mL respectively, according to CLSI guideline 2026.
- The therapeutic index is calculated as:
  - Therapeutic index of meropenem= 1/1=1
  - Therapeutic index of amikacin= 16/8=2
  - Therefore, in this case amikacin is superior to meropenem.

Therapeutic Drug Monitoring

Therapeutic efficacy - not only relies on in vitro susceptibility result (MIC), but also dependent on in vivo activity - in turn **dependent on PK/PD parameters** of the antimicrobial agent.

- Therapeutic drug monitoring - necessary to find out how the drug behaves in vivo - important for antibiotic - vancomycin, amikacin and colistin.

PK/PD parameters

- Depending up on PK/PD parameters, antibiotics are classified as:
  - **Concentration dependent antibiotics**, e.g. aminoglycosides (better if the drug concentration in serum is much higher than the MIC of the drug)
  - **Time-dependent antibiotics**, e.g. beta-lactams: Efficacy of the drug is dependent upon **how much time the drug concentration remains higher than the MIC.** Given in frequent intervals (e.g. thrice daily)

Timely Stoppage of Antimicrobial

- Stopped at appropriate time –
- Determined by clinical improvement or
- After obtaining negative culture or
- By use of biomarkers

Biomarkers

- **P**rocalcitonin (PCT) or C-reactive protein (CRP) - used for predicting bacterial infection.
- PCT is more reliable marker than CRP.

Rational Use of Antibiotics

- **Avoid overlapping spectra**
  - Meropenem and piptaz combination therapy for double GN coverage - **avoided** as both these drugs belong to **beta-lactam** group of antimicrobials
- **Redundant antibiotic**
  - Meropenem and metronidazole combination therapy for suspected GN/ anaerobic sepsis - avoided as meropenem is active against anaerobes in addition to gram-negative bacteria.
  - Metronidazole can be withdrawn from therapy

Rational Use of Antibiotics

- **Ineffective antibiotic:** Cloxacillin in MRSA is ineffective and therefore should be avoided. Vancomycin is the drug of choice for MRSA
- **Inferior antibiotic:** Vancomycin is an inferior cell wall acting agent compared to cloxacillin for MSSA infection

HOSPITAL ANTIBIOGRAM

- Guide the clinicians in selecting the best empirical antimicrobial treatment in the event of pending microbiology culture and susceptibility results.
- Detecting and monitoring trends in antimicrobial resistance within the hospital
- Compare susceptibility rates across institutions and track resistance trends and thereby contributing to national AMR surveillance database.

Limitations of the antibiogram

- MICs not included

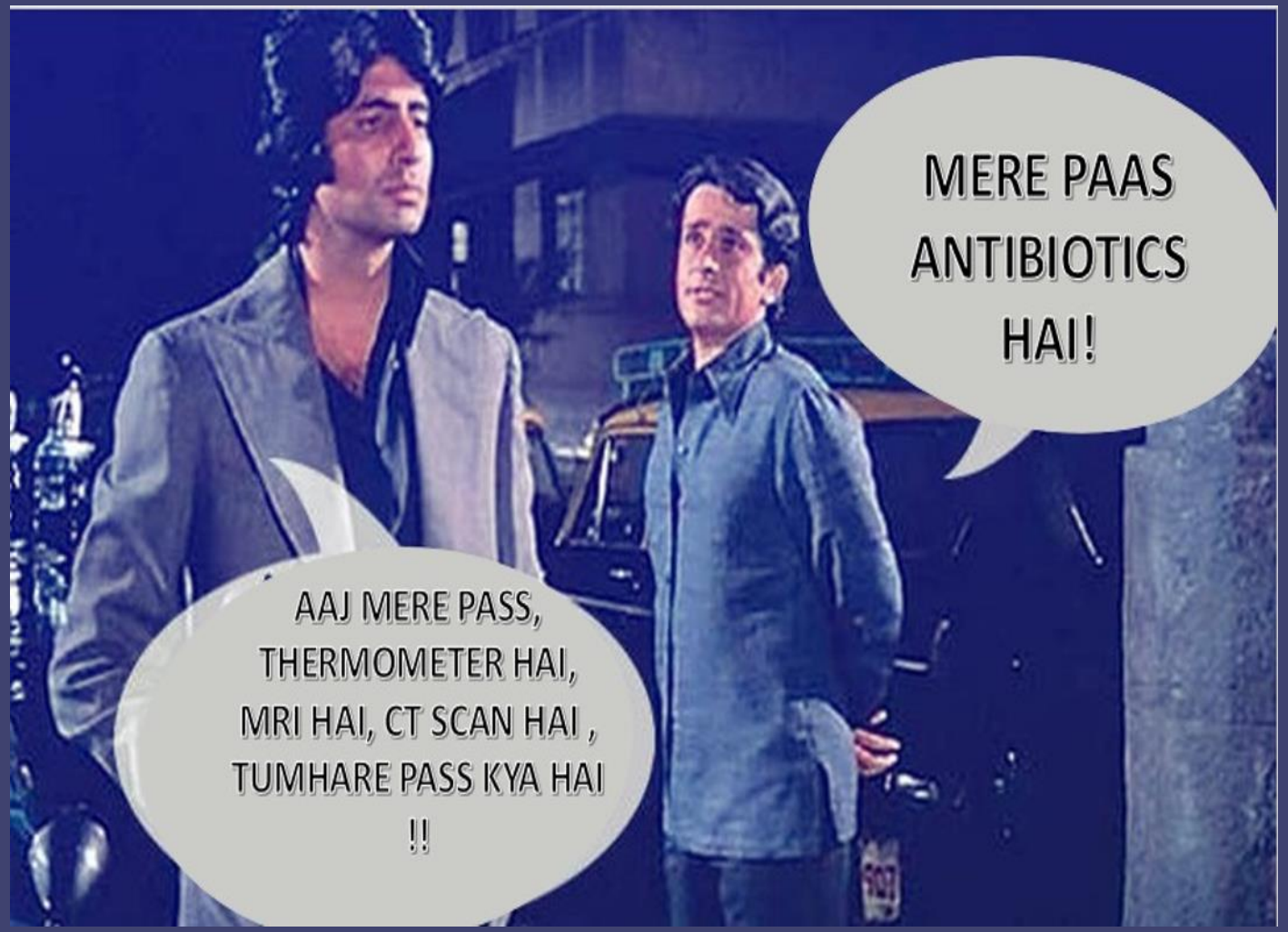
➢ Subtle trends below resistance threshold are not reflected

- Data do not take into account patient factors such as history of infection or past antimicrobial use
- Resistance patterns for certain drugs vary significantly by age, and a patient's underlying medical condition may affect how well an antimicrobial works

PUS - % Sensitivity

Isolate (No. of strains)	Ampicillin	Amox + Clav.	Gentamicin	Amikacin	Cefuroxime	Cefotaxime	Cefepime	Piperacillin-tazobactam	Aztreonam	Meropenem	Cotrimoxazole	Ciprofloxacin	Ofloxacin	Tetracycline	Ceftazidime
E. Coli (46)	8.69	39.13	56.52	76.08	15.02	13.04	28.26	41.3	23.9	65.27	39.13	19.56	21.73	41.3	NT
Klebsiella (32)	NT	NT	71.8	71.85	31.25	40.62	71.85	68.75	59.37	68.75	56.25	43.75	56.25	84.37	NT
Pseudomonas spp(28)	NT	NT	75	85.71	NT	NT	71.4	89.28	53.57	64.28	NT	78.57	82.14	NT	14.28

NT-Not Tested


MERE PAAS ANTIBIOTICS HAI!
AAJ MERE PASS, THERMOMETER HAI, MRI HAI, CT SCAN HAI , TUMHARE PASS KYA HAI !!