Bacterial toxins

Secreted by bacteria

Sometimes released upon cellular lysis

For cell killing/ Interference with normal activities

Classification of bacterial toxins

Type I – Acts from outside the cell

Type II – Acts on the cell membrane

Type III – Acts inside the cell

AB toxins are a combination of Types II and III

Type I toxins

Bacterial superantigens

Activate whole subset of T-cells
20% of total population as opposed to 0.0001 - 0.01%

Stimulated cells release pro-inflammatory cytokines
(TNF, IL-1, 6, 8)

Severe shock response

Examples - TSST of *Staph. Aureus*

Type II toxins – disrupts membranes

Alpha-haemolysin from *Staphylococcus aureus*

Gouaux JE. Science. 1996

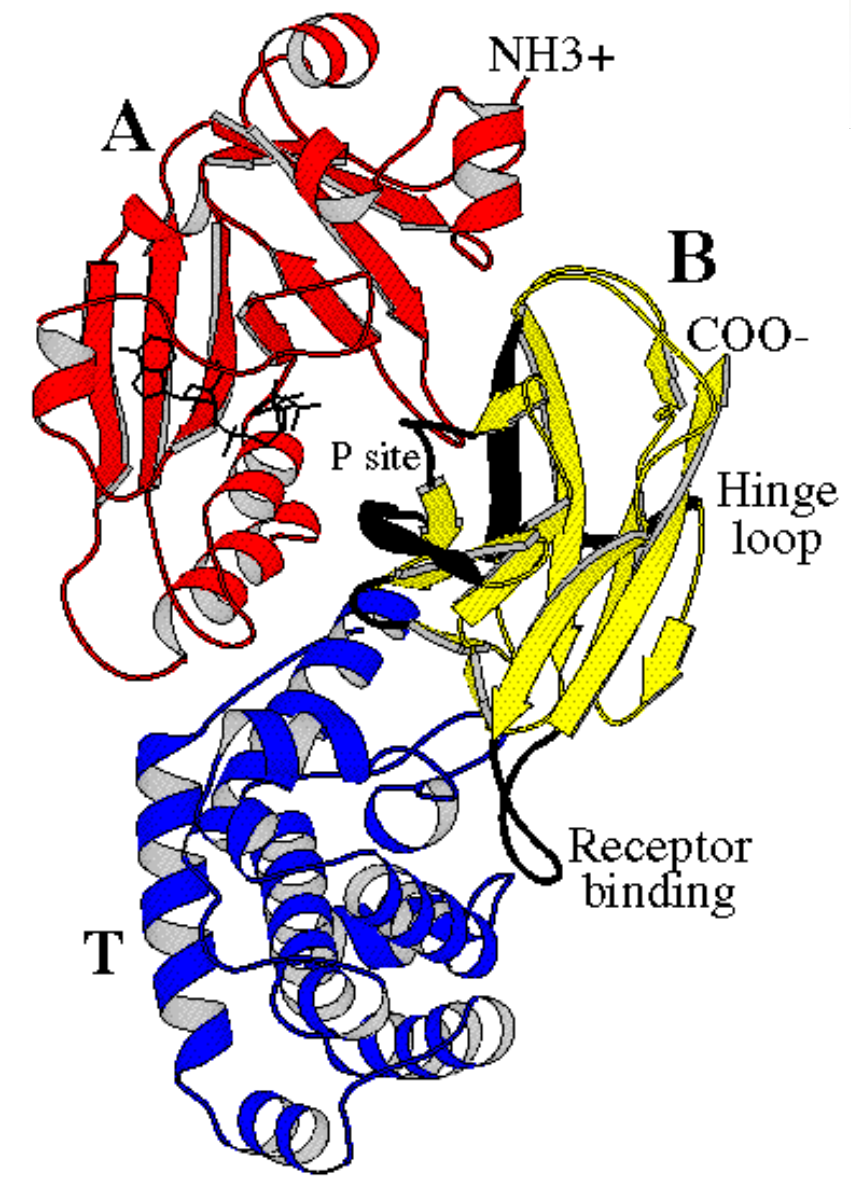
Type III toxins

1) Prevention of protein synthesis – Diptheria toxin

2) Proteolysis – Tetanus toxin

3) Alteration of signaling pathways – Anthrax toxin, Cholera toxin

Example of AB type toxin – Diptheria toxin



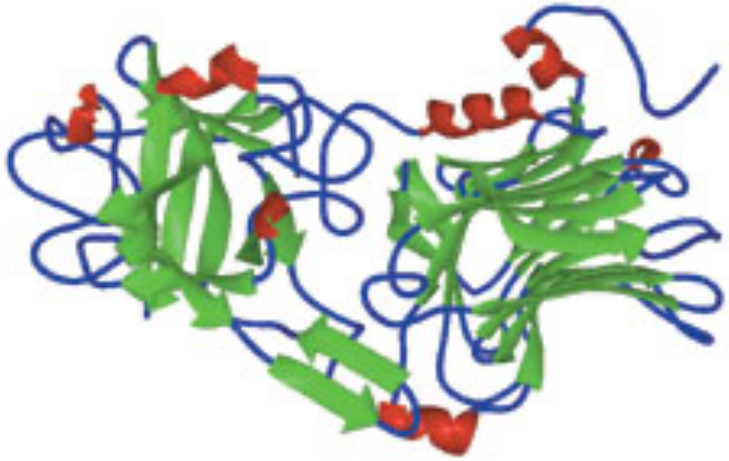
B (Translocator): Required for endosomal channel formation

A(Effector): Transfers ADP-ribose to protein synthesis initiation factor

Very effective, one toxin molecule can kill a cell

Low pH, reducing environment necessary

Example of AB type toxin – Tetanus toxin



Part B: Translocator

Channel forming component

Part A: Zinc metalloprotease

Goes to central nervous system

Cleaves synaptobrevin

Blocks release of inhibitory neurotransmitters

Hyperactivity of motor neurons

Continuous muscle contraction

(spastic paralysis)

Source: https://str.llnl.gov/

Therapeutic function of toxins

Vaccines - Formaldehyde treated toxoid preparations

Chimeric immunotoxins – For cancer therapy

Toxin bound to a targeting sequence specific for cancer cells

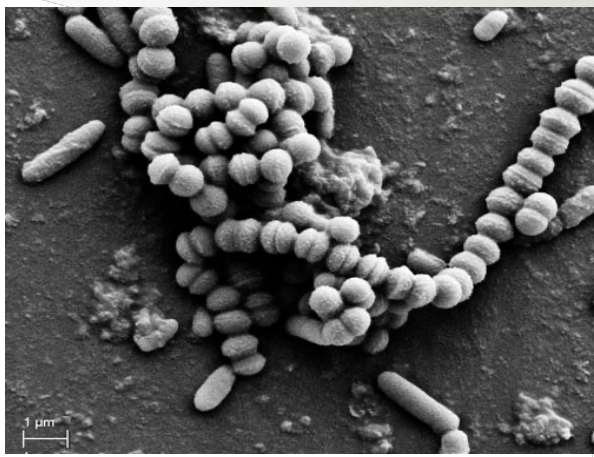
DT-IL-2 toxin (FDA approved) for treatment of cutaneous T-cell lymphoma

Cosmetic purposes - Botulinum toxin, nerve blocking, muscle relaxing activity

Quorum sensing in bacteria

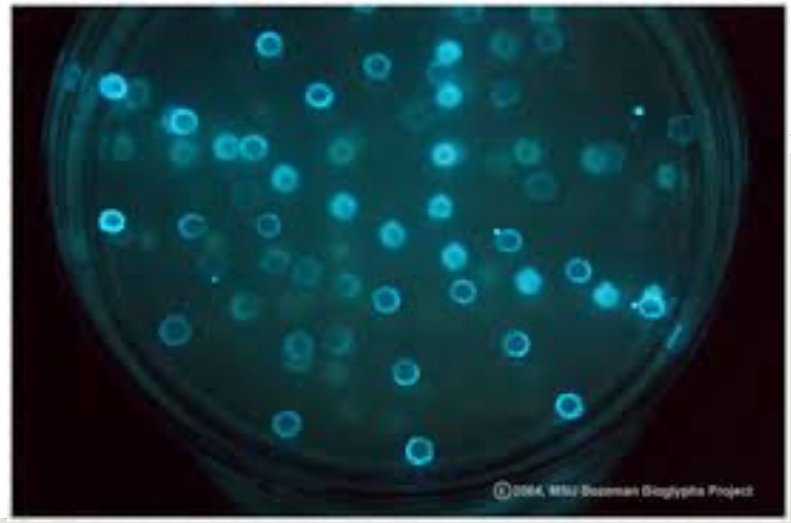
Quorum sensing - Ability of bacteria to initiate the transcription of certain genes only when a certain population density is reached

e.g. Production of luciferase by Vibrio fischeri

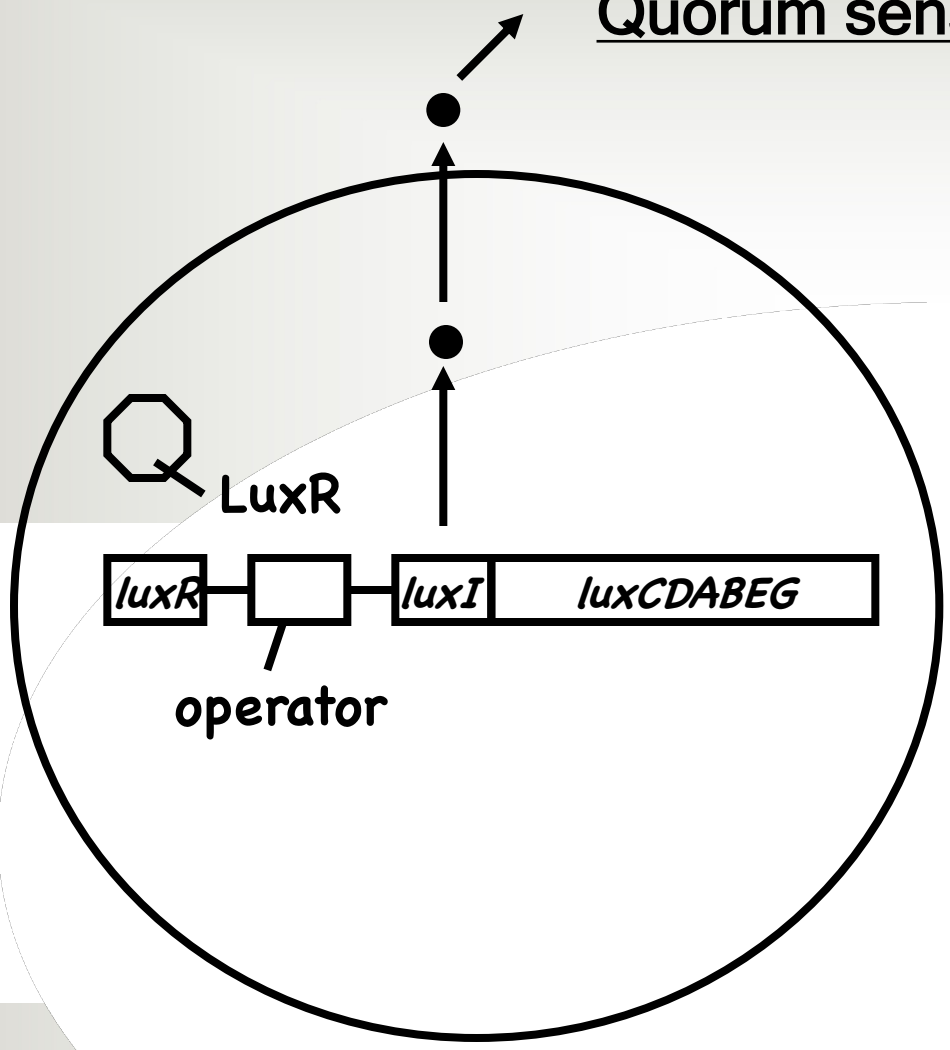


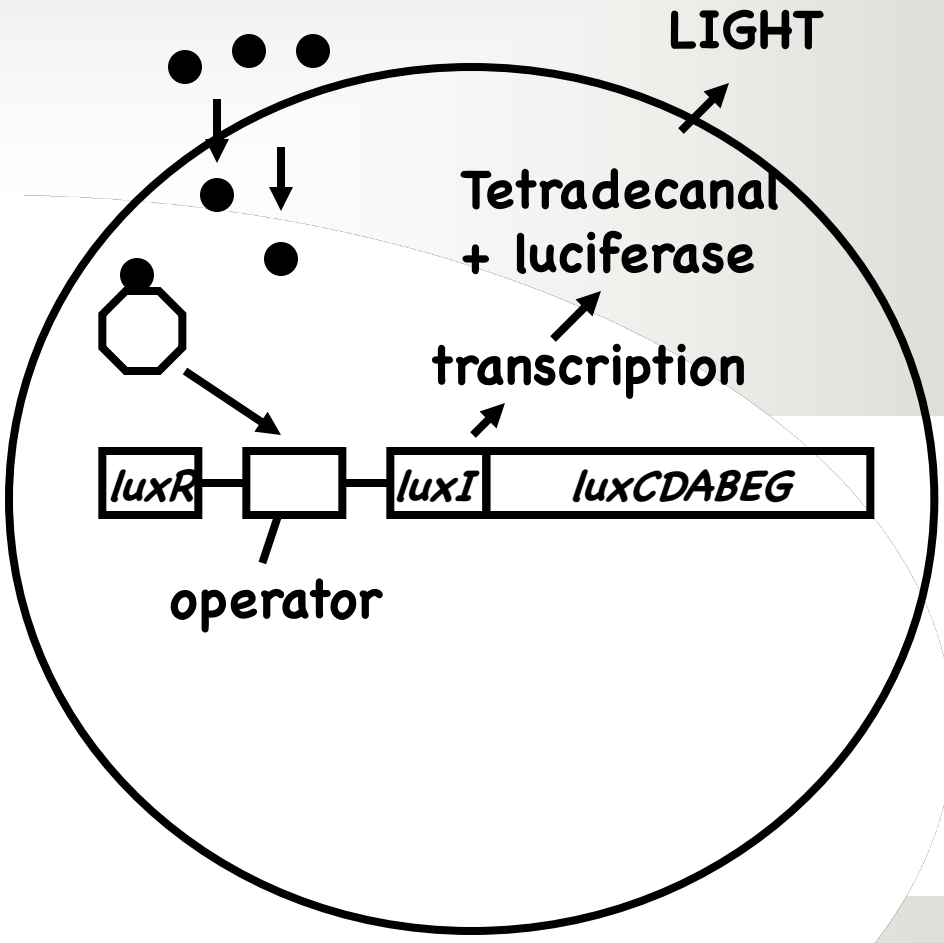
Auto inducer is a small molecule OHHL
(N-3-oxohexanoyl-L-homoserine lactone)

Threshold concentration required - 10 nM
Synthesis of luciferase genes, tetradecanal

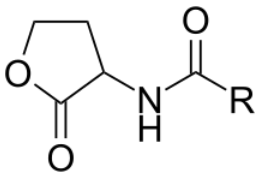


Quorum sensing in bacteria





luxI = Autoinducer (OHHL)



luxR = Transcriptional activator

luxR + luxI = activation of gene expression

Main therapy against pathogenic bacteria - antibiotics

Discovery of first antibiotic was an accident

No new discovery for several decades

Modification of old antibiotics

New drug discovery takes ~ 10-15 years, millions of $$$

Antibiotics and their role

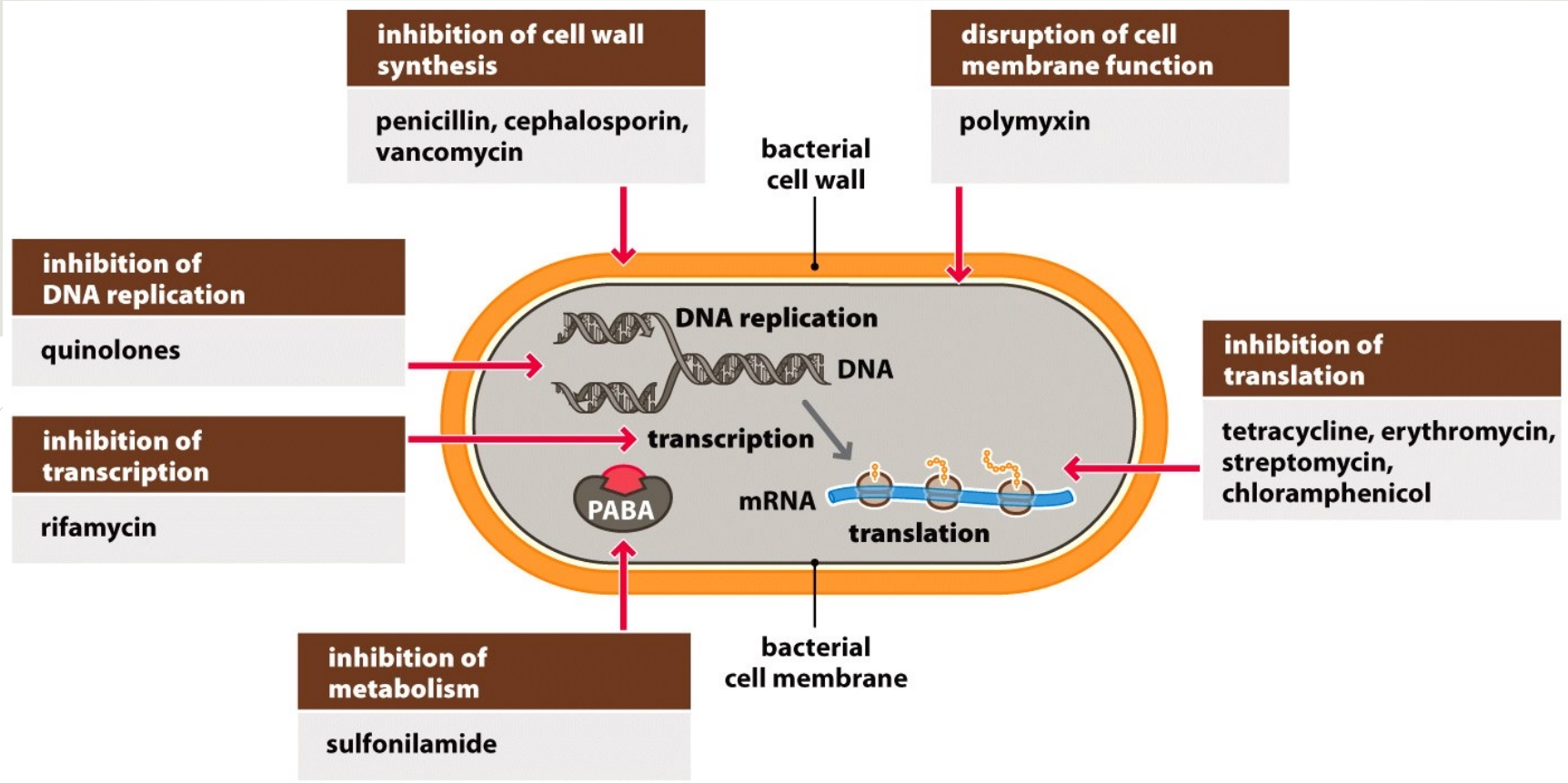


Figure 19.4 Microbiology: A Clinical Approach (© Garland Science)

Naturally produced antibiotics results of secondary metabolic processes

Semi-synthetic antibiotics – broader spectrum, increased efficiency

Antibiotics and their role

Antibiotics can be toxic!

Testing through animal studies, proper dosage

Toxicity, mutagenicity, carcinogenicity, allergic effects

Selective toxicity essential

Bacteria and antibiotic resistance

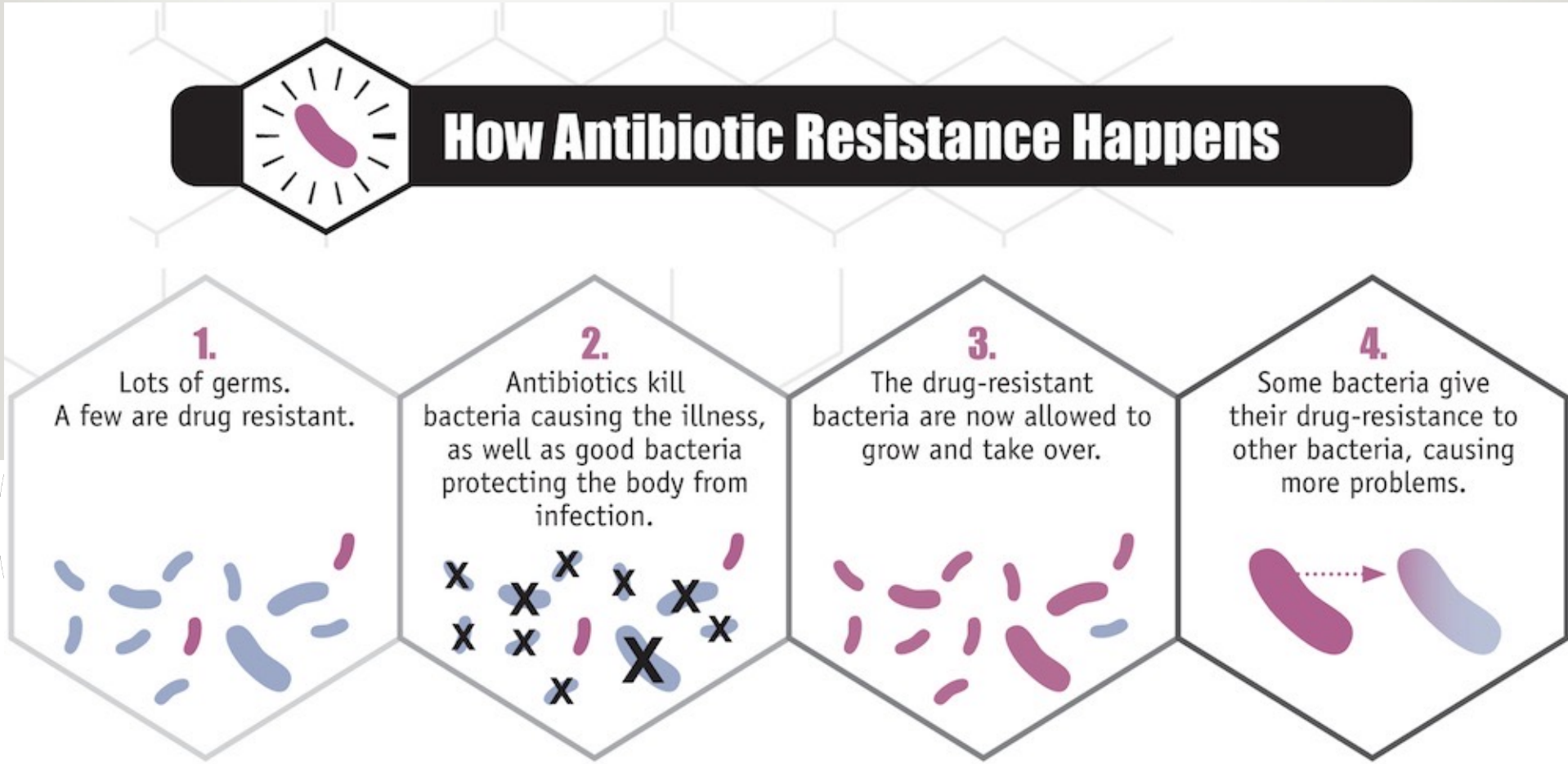
Reasons for antibiotic resistance:

Indiscriminate use –
Longer or shorter periods
Broad spectrum vs. narrow spectrum
Prescribed for “other” infections

Spread through veterinary medicine practices

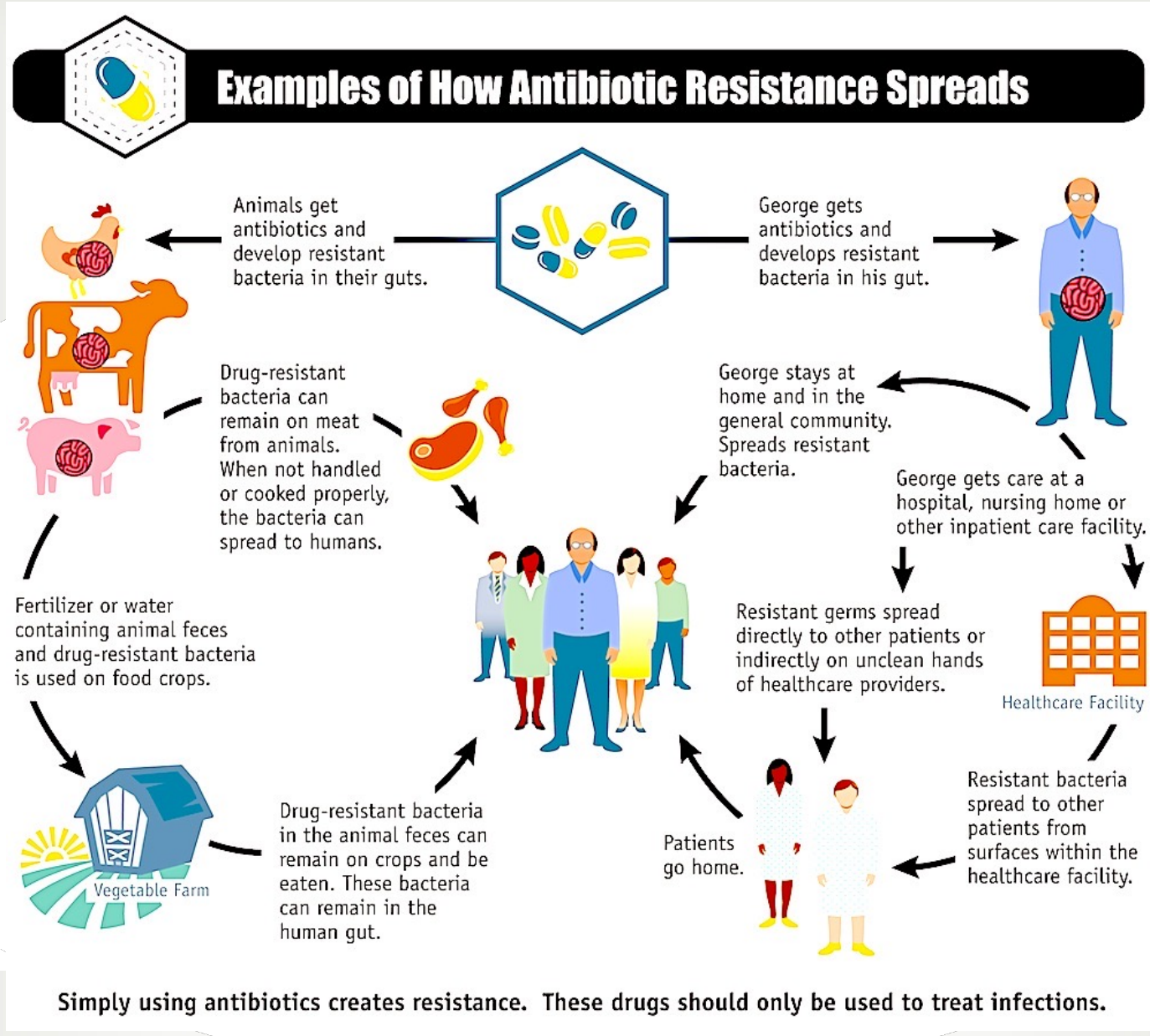
Incorrect practices at hospitals

Bacteria and antibiotic resistance



Source: CDC

Bacteria and antibiotic resistance



Source: CDC

Mechanisms for antibiotic resistance

Naturally occurring resistance (Penicillinase first discovered)

Blocking access: Blocking porins, thickened cell walls, vancomycin resistant *Staphylococcus aureus*

Blocking accumulation: Drug efflux pumps, *E.coli* against tetracyclines

Inactivation of antibiotic: beta-lactamases inactivate antiobiotics with beta-lactam rings

Alteration of target site/reduction in binding capacity/modification of metabolic pathways: mutations in RNA polymerase (rifampicin resistance), gyrase (quinolone resistance)

Mechanisms for antibiotic resistance