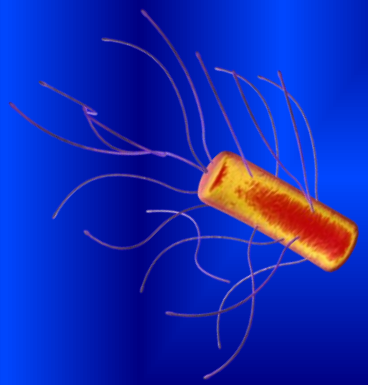
Tackling Antibiotic Resistance for Global Health: Future Challenges



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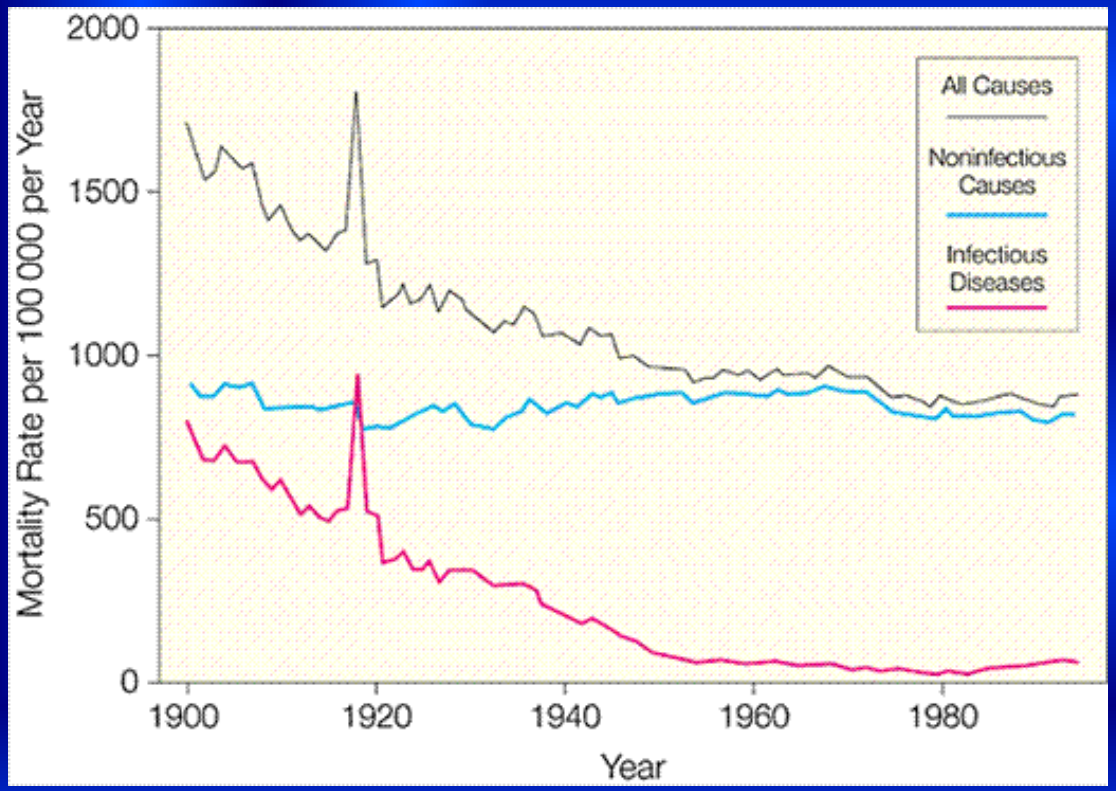
The "Miracle" of Antibiotics

- Discovery of penicillin by Sir Alexander Fleming and its subsequent development by Florey & Chain revolutionised treatment of infectious disease

- Life expectancy has ↑ due to ability to treat infection



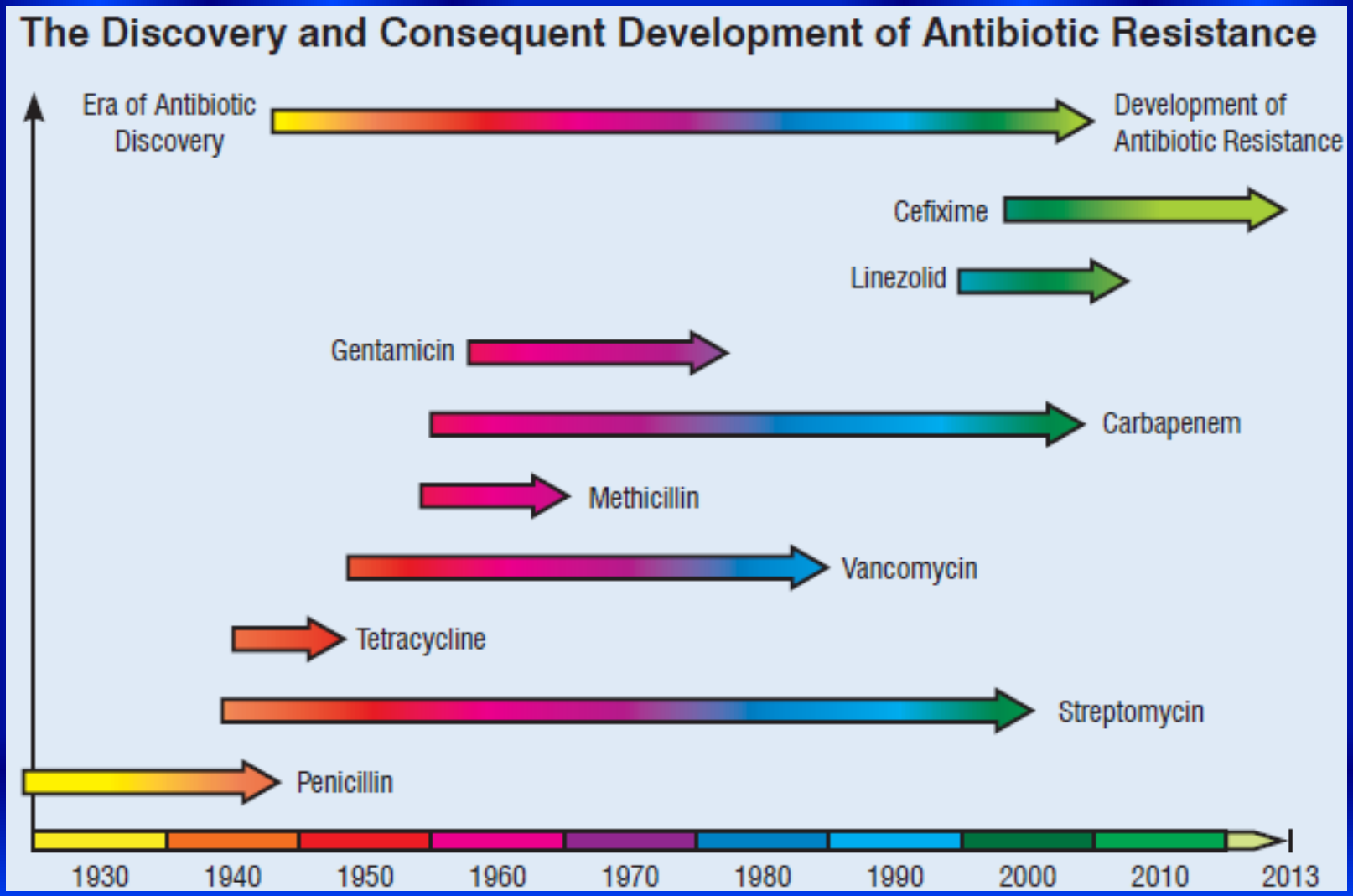
Crude mortality rates for all causes, noninfectious causes and infectious diseases over the period 1900-1996

Armstrong GL et al, JAMA 1999;281(1):61-66

Antibiotic Resistance

- It took less than 20 years for, bacteria to show signs of resistance
- *Staphylococcus aureus*, which causes blood poisoning and pneumonia, started to show resistance in the 1950s
- Today there are different strains of *S. aureus* resistant to every form of antibiotic in use

Timeline of antibiotics discovery and the evolution of antibiotic resistance

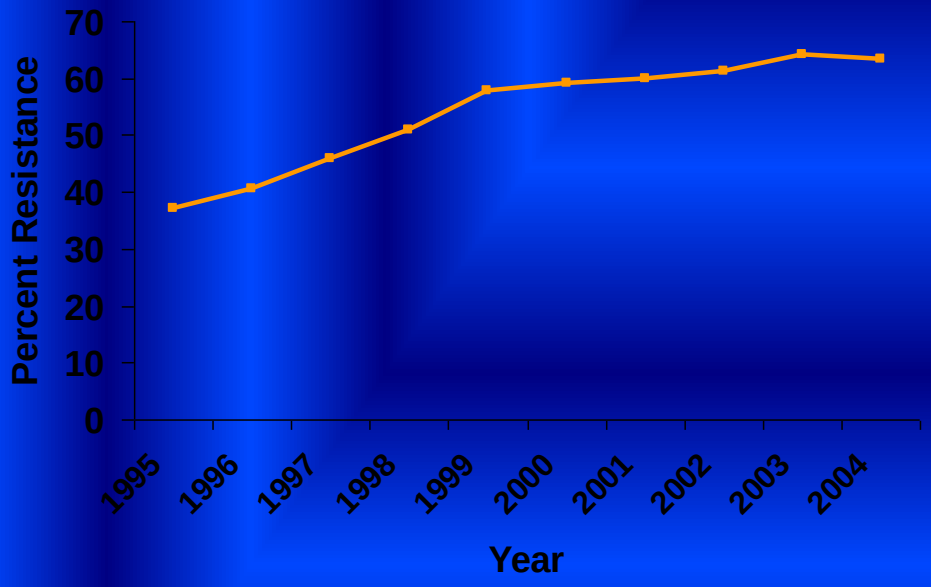


EVOLUTION OF RESISTANCE TO ANTIBACTERIALS

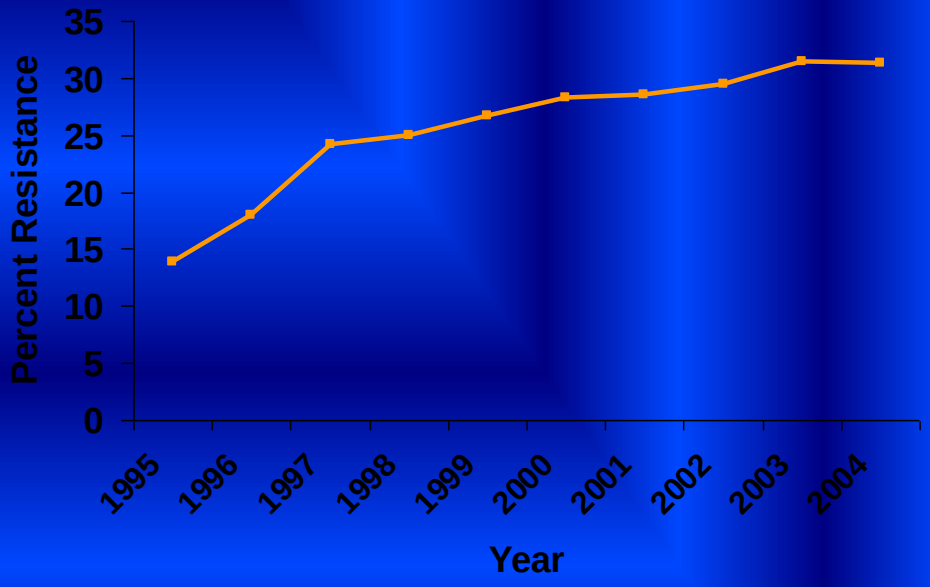
Antibiotic	Year Deployed	Resistance Observed
Sulfonamides	1930s	1940s
Penicillin	1943	1946
Streptomycin	1943	1959
Chloramphenicol	1947	1959
Tetracycline	1948	1953
Erythromycin	1952	1988
Vancomycin	1956	1988
Methicillin	1960	1961
Ampicillin	1961	1973
Cephalosporins	1960s	late 1960s

Table 20.2 Microbiology: A Clinical Approach (© Garland Science)

Gram Positive Resistance



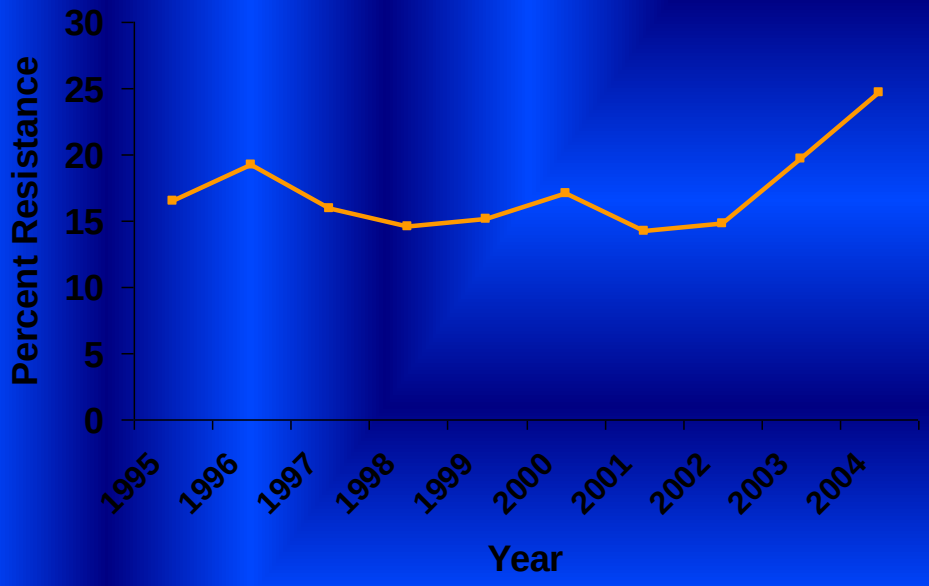
Methicillin-Resistant
Staphylococcus aureus



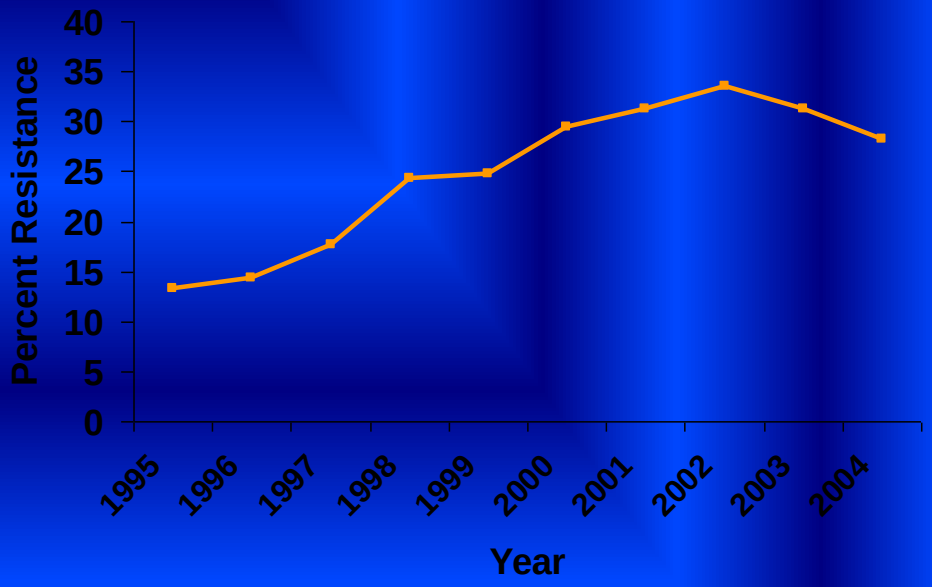
Vancomycin-Resistant
Enterococcus

National Nosocomial Infections Surveillance (NNIS) System

Gram Negative Resistance



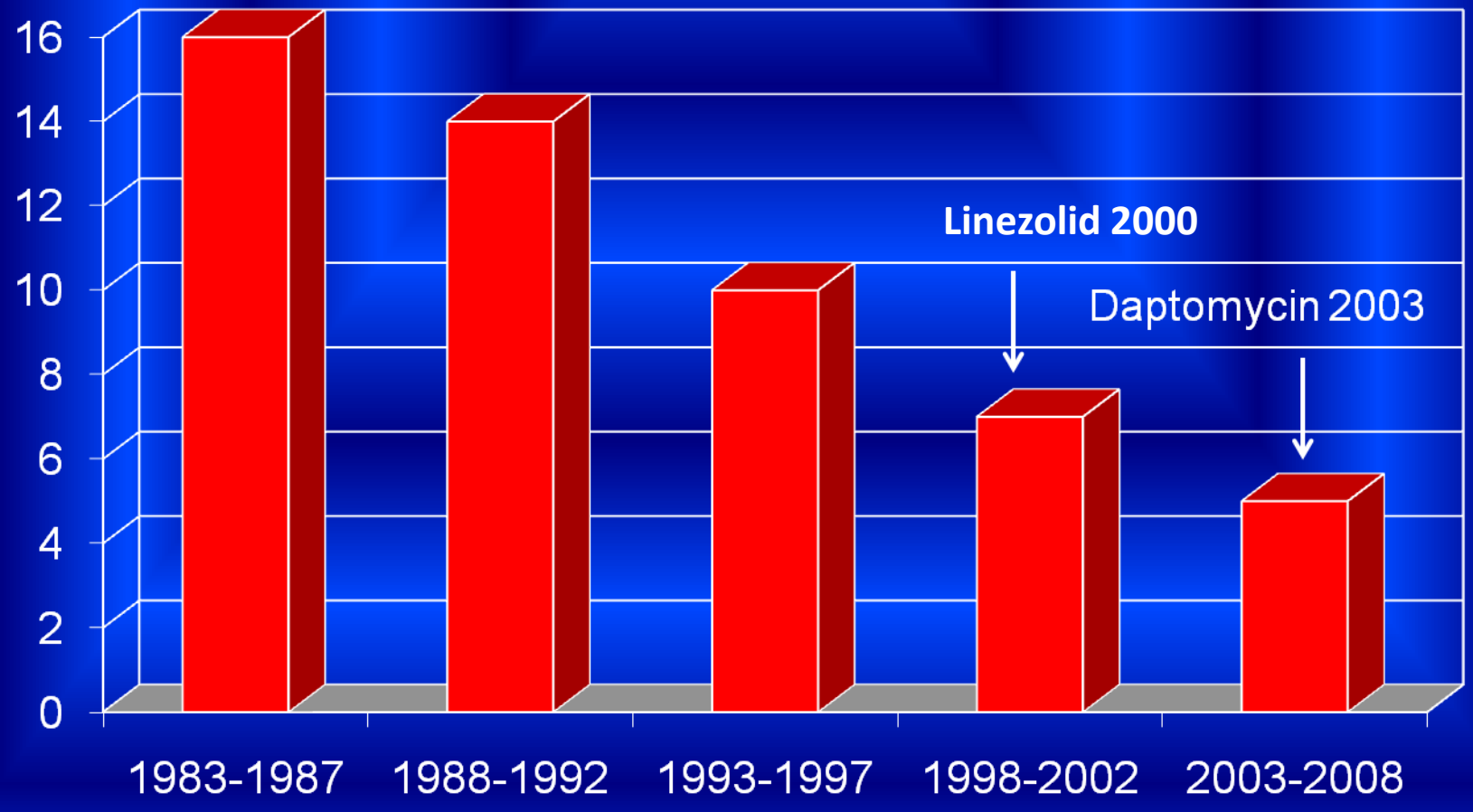
3rd Generation Cephalosporin-Resistant *Klebsiella pneumoniae*



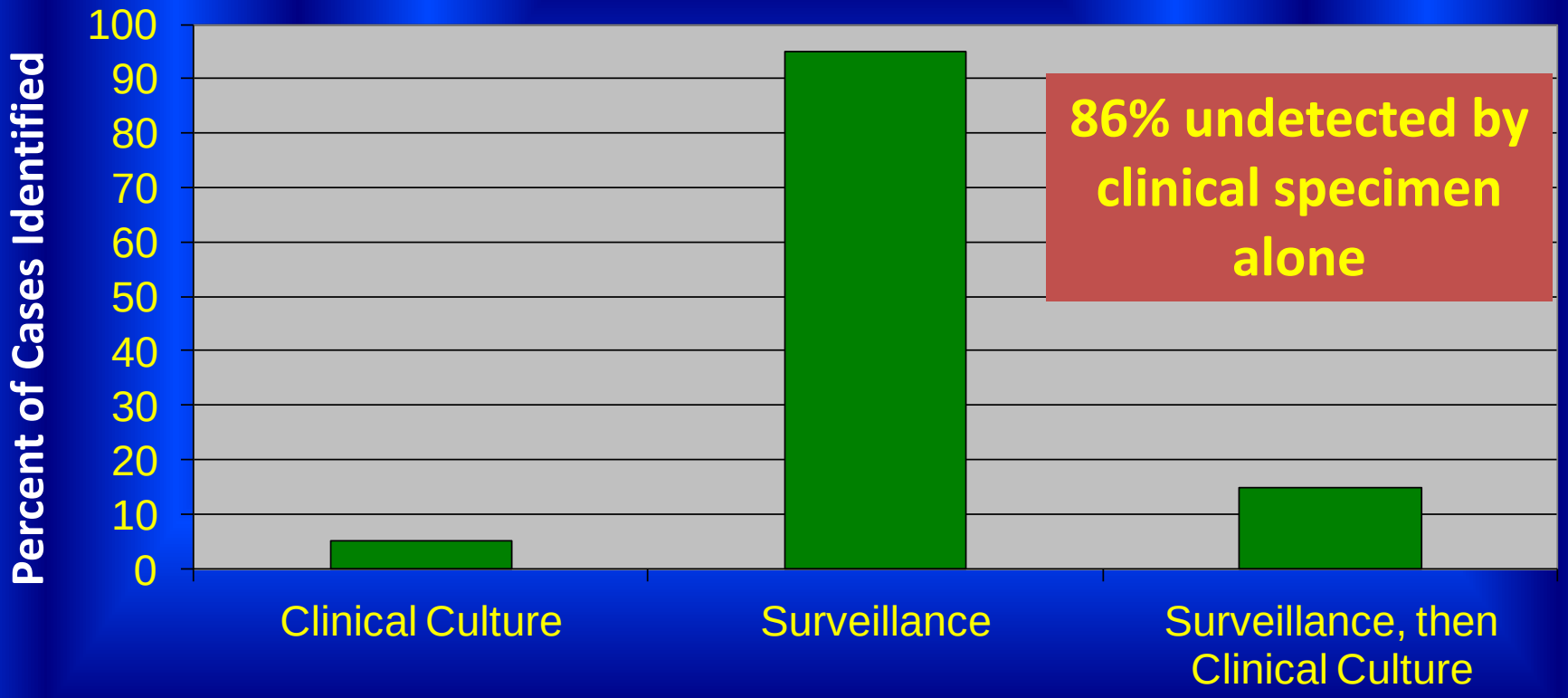
Fluoroquinolone-Resistant *Pseudomonas aeruginosa*

National Nosocomial Infections Surveillance (NNIS) System

New Antibacterial Drugs Approved By FDA



Tip of the Iceberg?

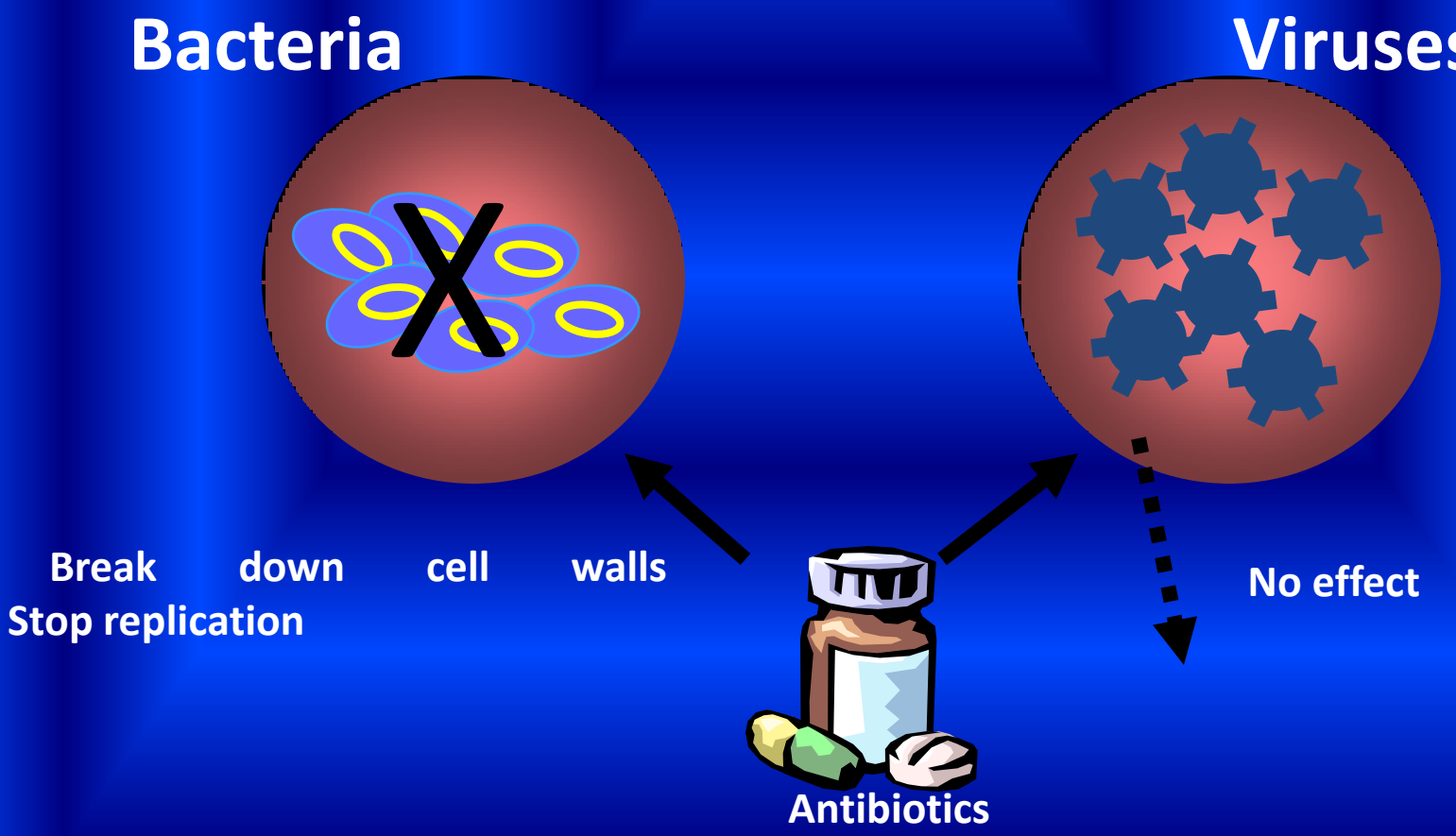


Clin Infect Dis 2003;37:326-32

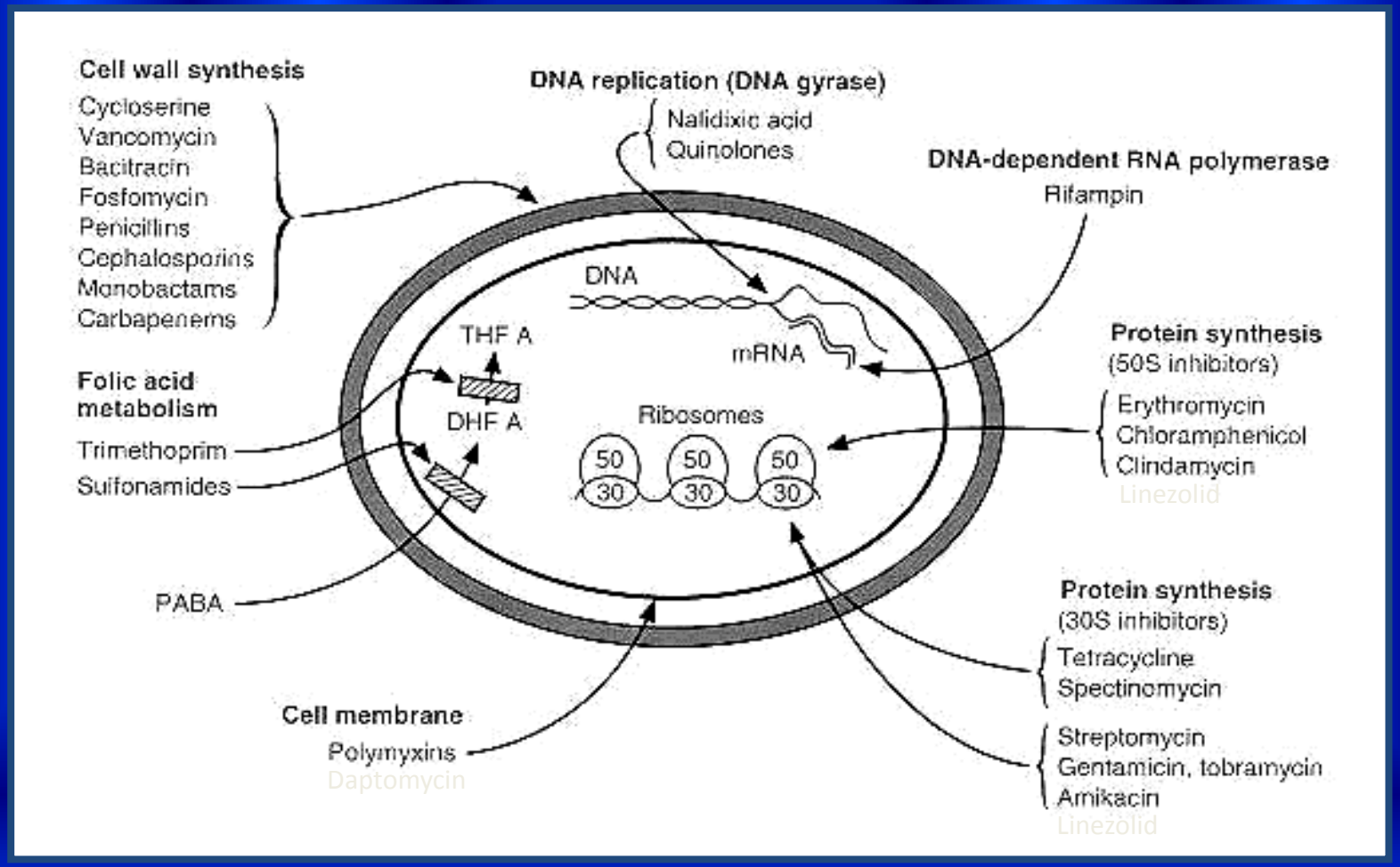
Antibiotics continue to save lives every day…

- Ability to control infection is critical to other advances in medicine
  - Neonatal care
  - Transplantation
  - Chemotherapy for malignancy
  - Immunosuppression
  - Safe surgery
  - Safe obstetric care
  - Intensive care interventions

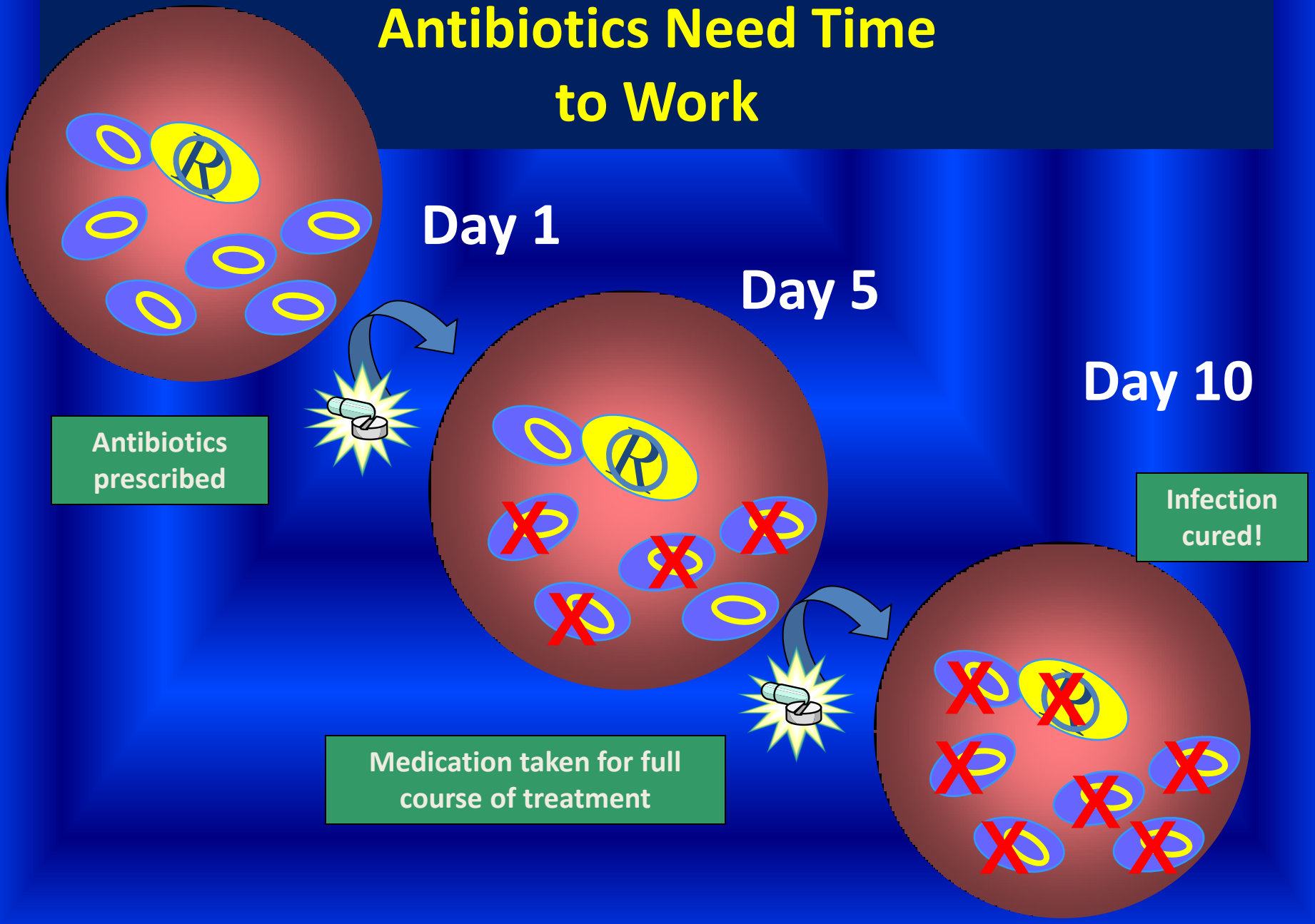
Antibacterials Kill Bacteria



Antibiotic Mechanism of Action



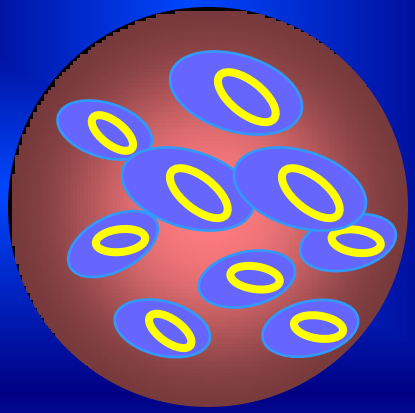
Antibiotics Need Time to Work



Case I

Jane has a sore throat. Without testing, her health care provider prescribes penicillin "just in case" it's strep.

Jane's symptoms are caused by a virus, but she also has bacteria in her sinuses.



Case II

Ashley comes home from school with a sore throat and fever.

After a positive strep test, her pediatrician prescribes penicillin.

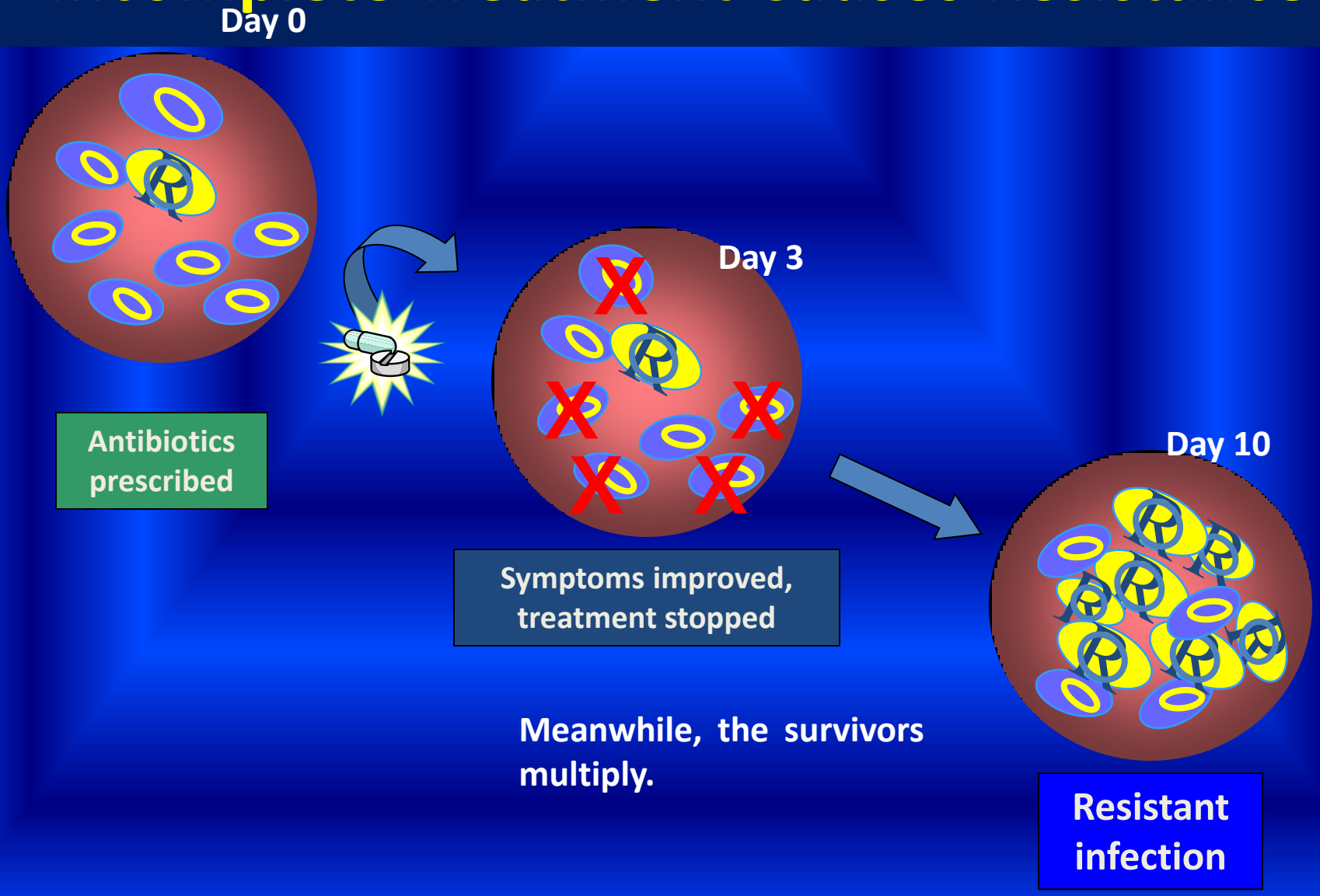
Cont'd

Ashley takes her medicine for three days.

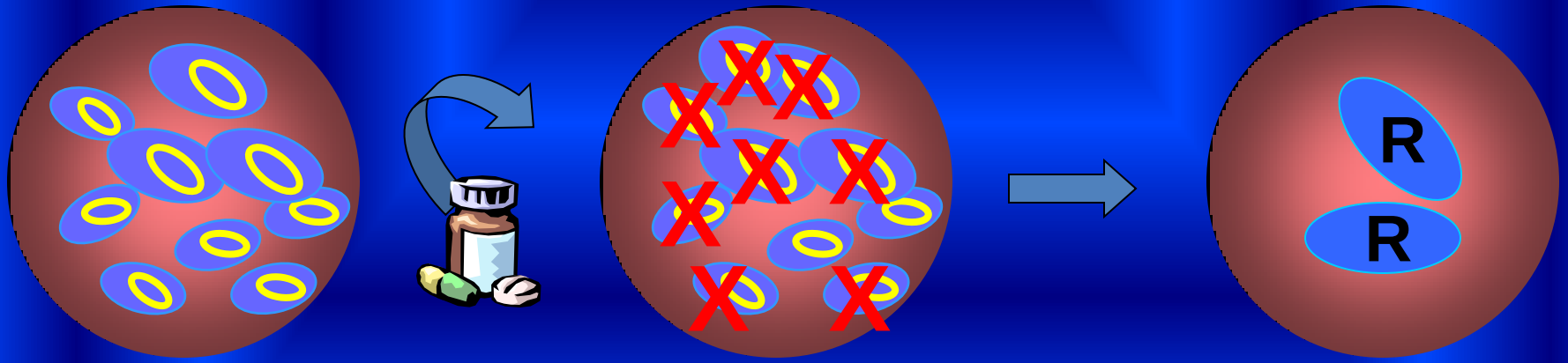
Ashley feels fine.

Her parents decide it's OK to stop.

Incomplete Treatment Causes Resistance



Unnecessary Antibiotics Cause Resistance



Jane takes penicillin.

Susceptible bacteria are killed off.

A few hardy survivors are left behind.

The survivors can withstand penicillin.

Antibiotic Overuse

Patient Concerns

- Want clear explanation
- Green nasal discharge
- Need to return to work

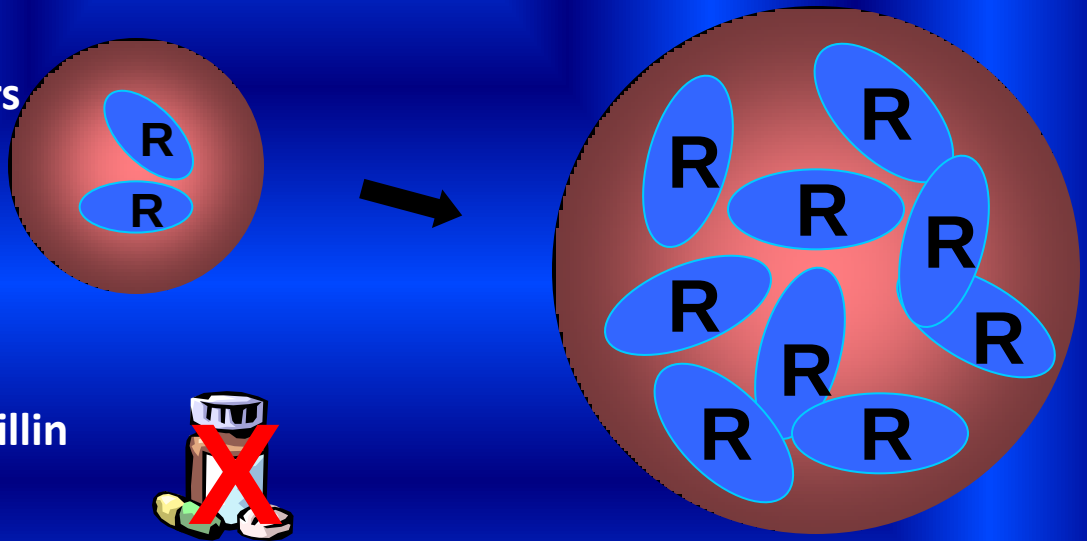
Physician Concerns

- Patient expects antibiotic
- Diagnostic uncertainty
- Time pressure

Antibiotic Prescription

Resistant Bacteria Can Multiply and Spread

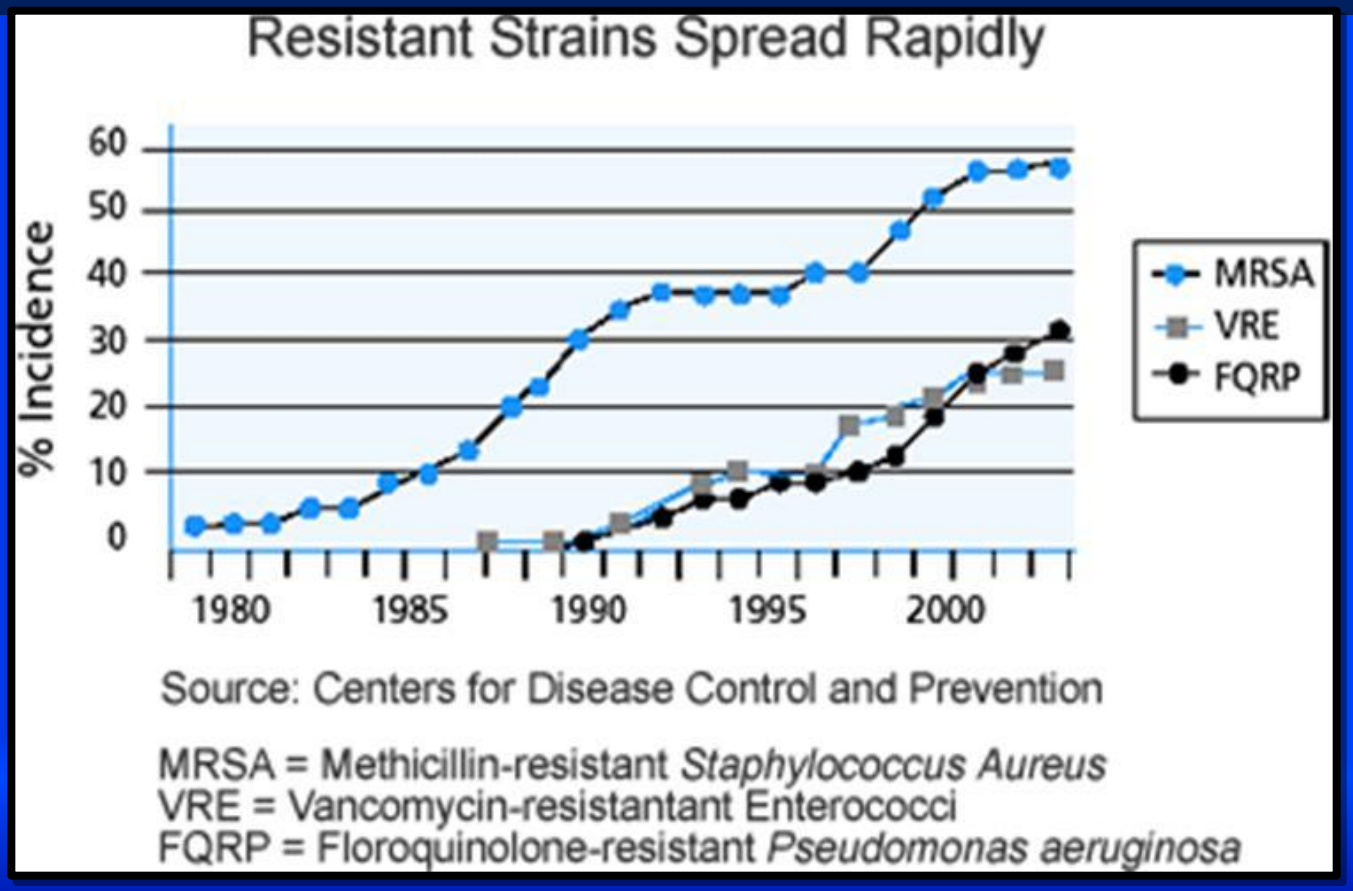
The resistant survivors multiply.



Treatment with penicillin has no effect.

Jane is now a carrier of penicillin-resistant bacteria.

Resistance spreads rapidly



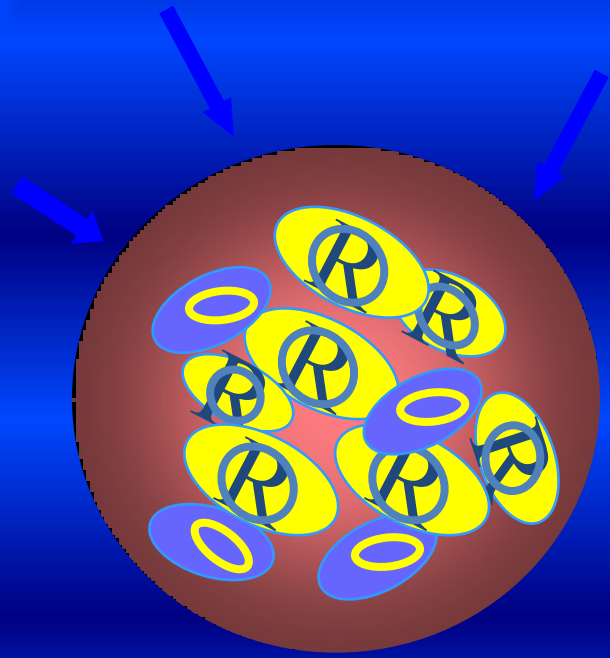
Centers for Disease Control and Prevention http://www.cdc.gov

Resistant Infections Require Special Treatment

Longer treatment

More expensive medication

Higher dosage



Intravenous (IV) medication, hospitalization

Mechanisms of Resistance

- Inactivation of drug
  - Beta-lactamases
- Alteration of the target
  - Penicillin binding proteins
  - Ribosomes
- Decreased permeability
- Drug efflux

INACTIVATION OF ANTIBIOTIC

- **Inactivation involves enzymatic breakdown of antibiotic molecules.**
- **A good example is β-lactamase:**
  - **Secreted into the bacterial periplasmic space**
  - **Attacks the antibiotic as it approaches its target**

EFFLUX PUMPING OF ANTIBIOTIC

- Efflux pumping is an active transport mechanism.
  - It requires ATP.
- Efflux pumps are found in:
  - The bacterial plasma membrane
  - The outer layer of gram-negative organisms
- Pumping keeps the concentration of antibiotic below levels that would destroy the cell
- Genes that code for efflux pumps are located on plasmids and transposons.

MODIFICATION OF ANTIBIOTIC TARGET

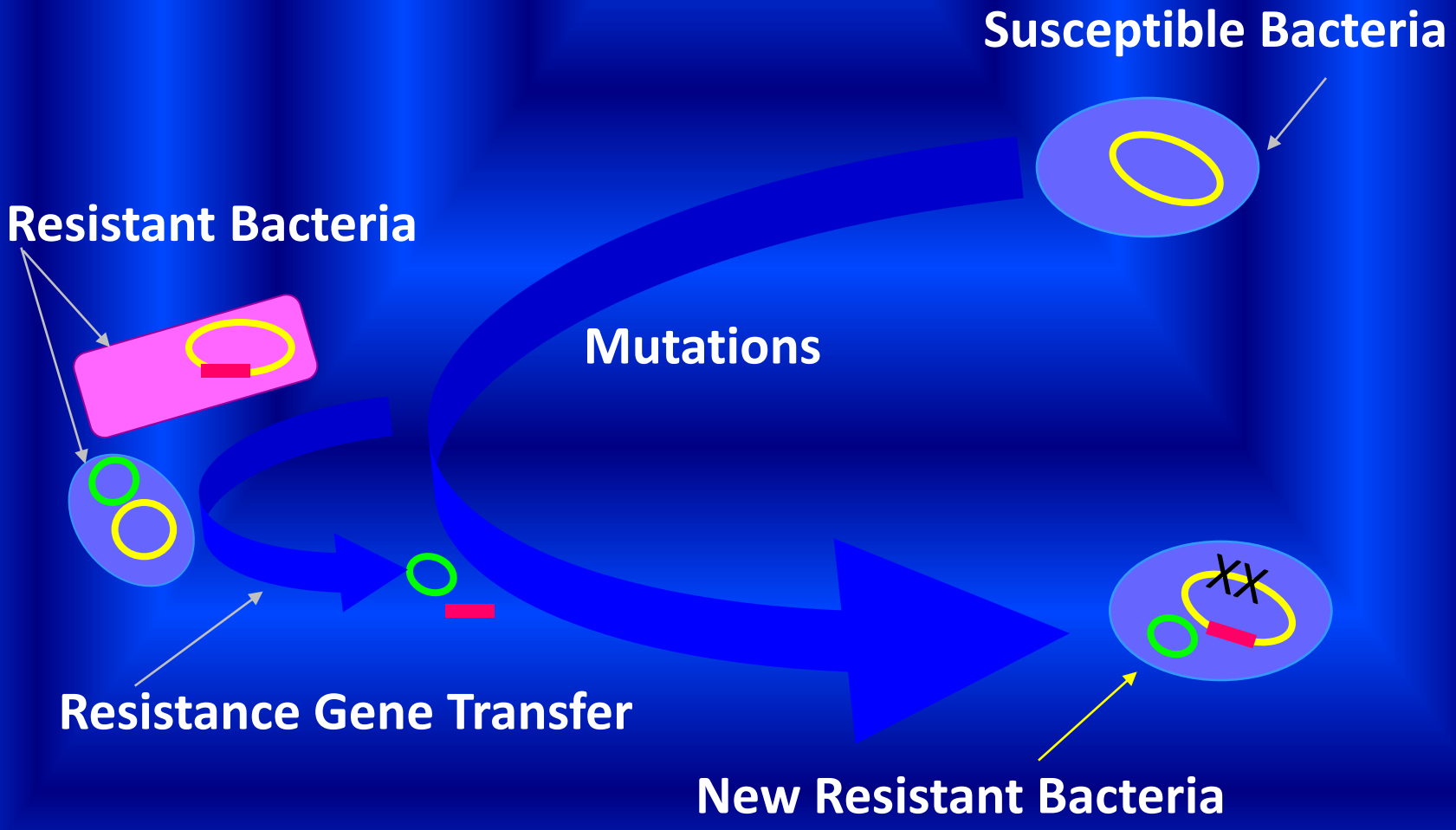
- **Bacteria can modify the antibiotic's target to escape its activity**
- **Bacteria must change structure of the target but the modified target must still be able to function. This can be achieved in two ways:**
  - **Mutation of the gene coding for the target protein**
  - **Importing a gene that codes for a modified target**

Impact of resistance

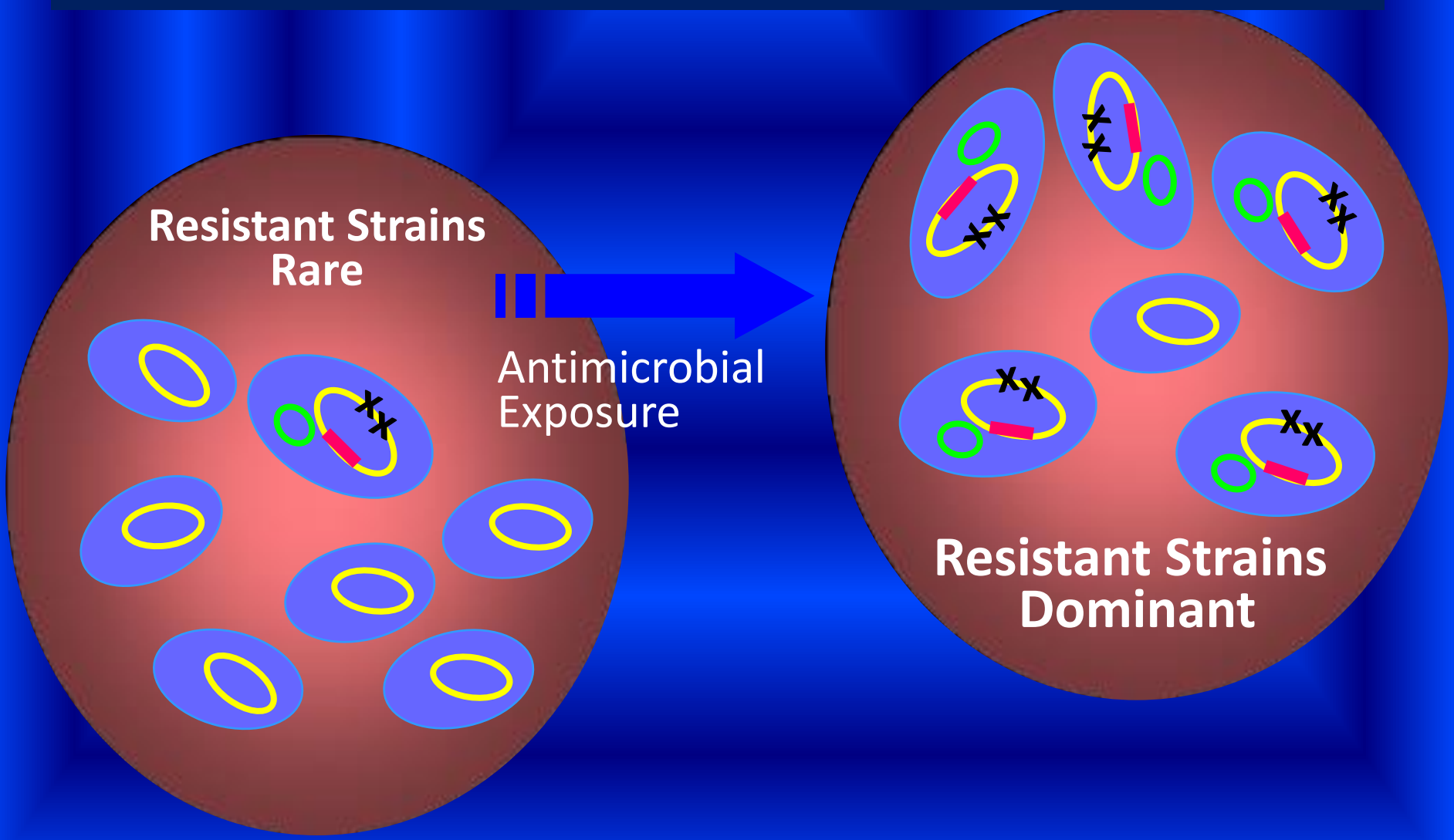
- Increased morbidity/ mortality
  - Evidence across many pathogens
- Untreatable infections
  - Now being encountered
- Increased costs
  - $18-29,000 US/patient
  - Excess length of stay 6.4 – 12.7 days/patient

Roberts RR et al. Clinical Infectious Diseases 2009; 49:1175-1184

Emergence of Antimicrobial Resistance

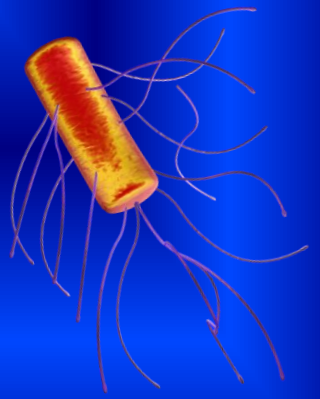


Selection for Antimicrobial-Resistant Strains

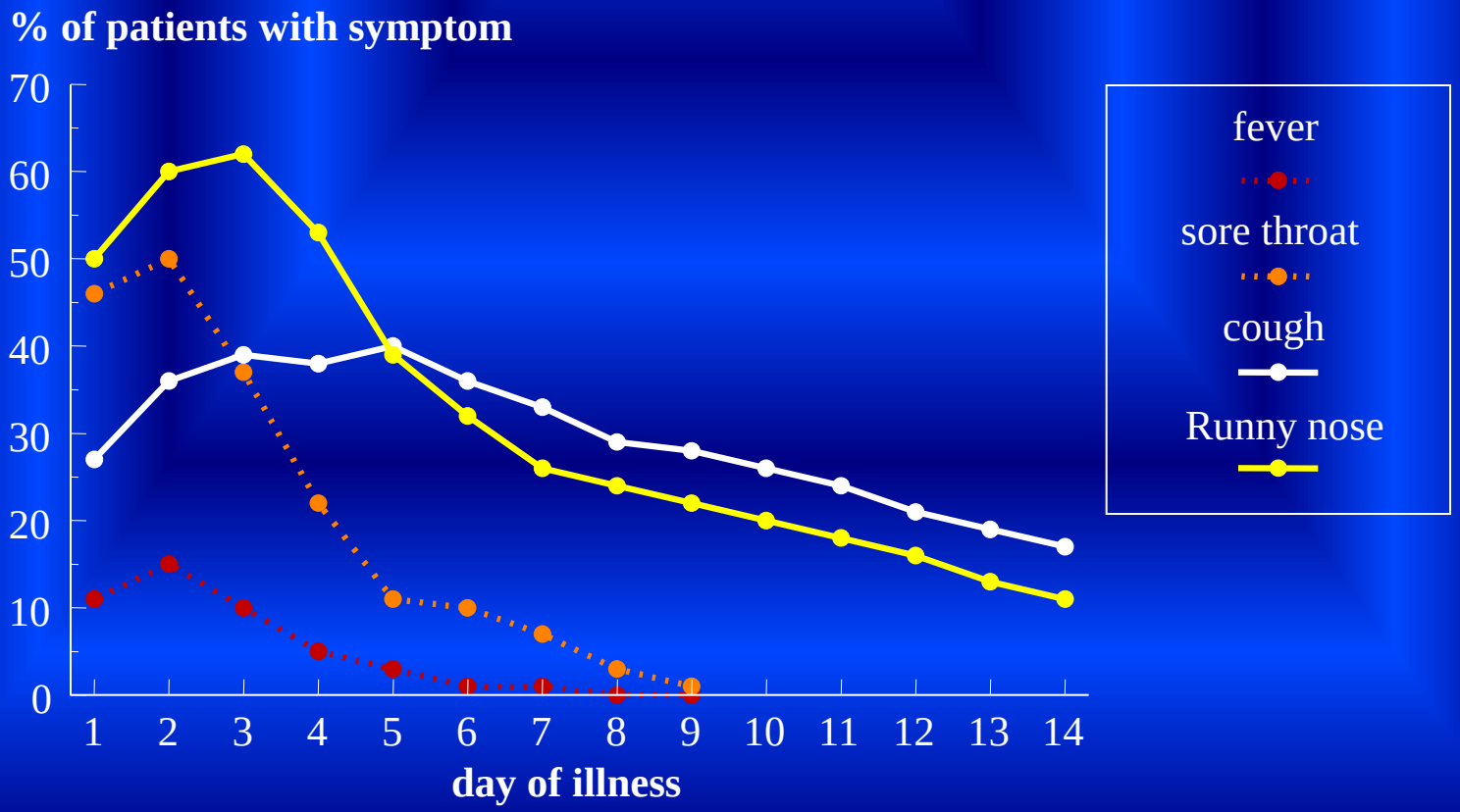


How antibiotic resistance can be prevented

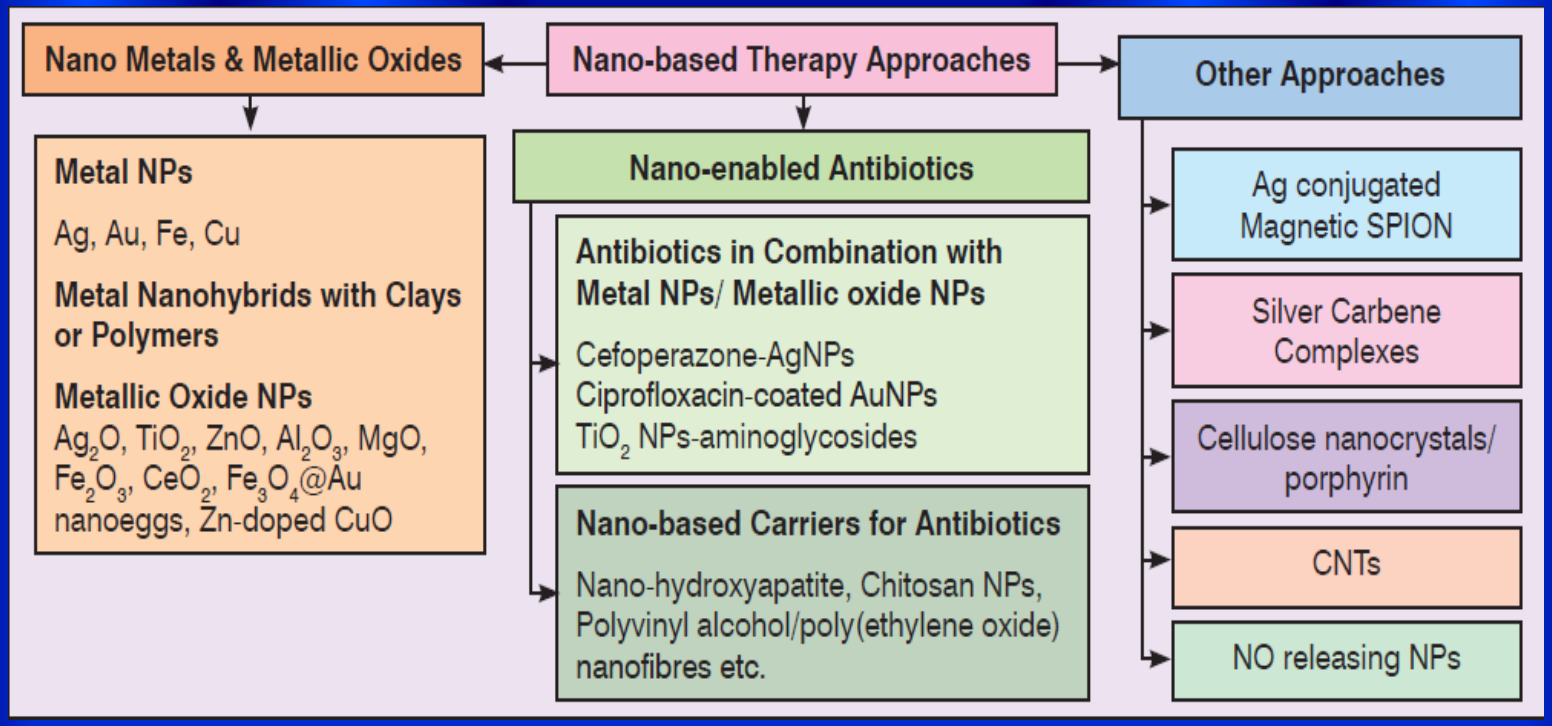
- Antibiotics should be the last line of defence NOT the first
  - Most common infections will get better by themselves through time, bed rest, liquid intake and healthy living.
- Only take antibiotics prescribed by a doctor
- If prescribed antibiotics, finish the course.
- Do not use other peoples or leftover antibiotics
  - they be specific for some other infection



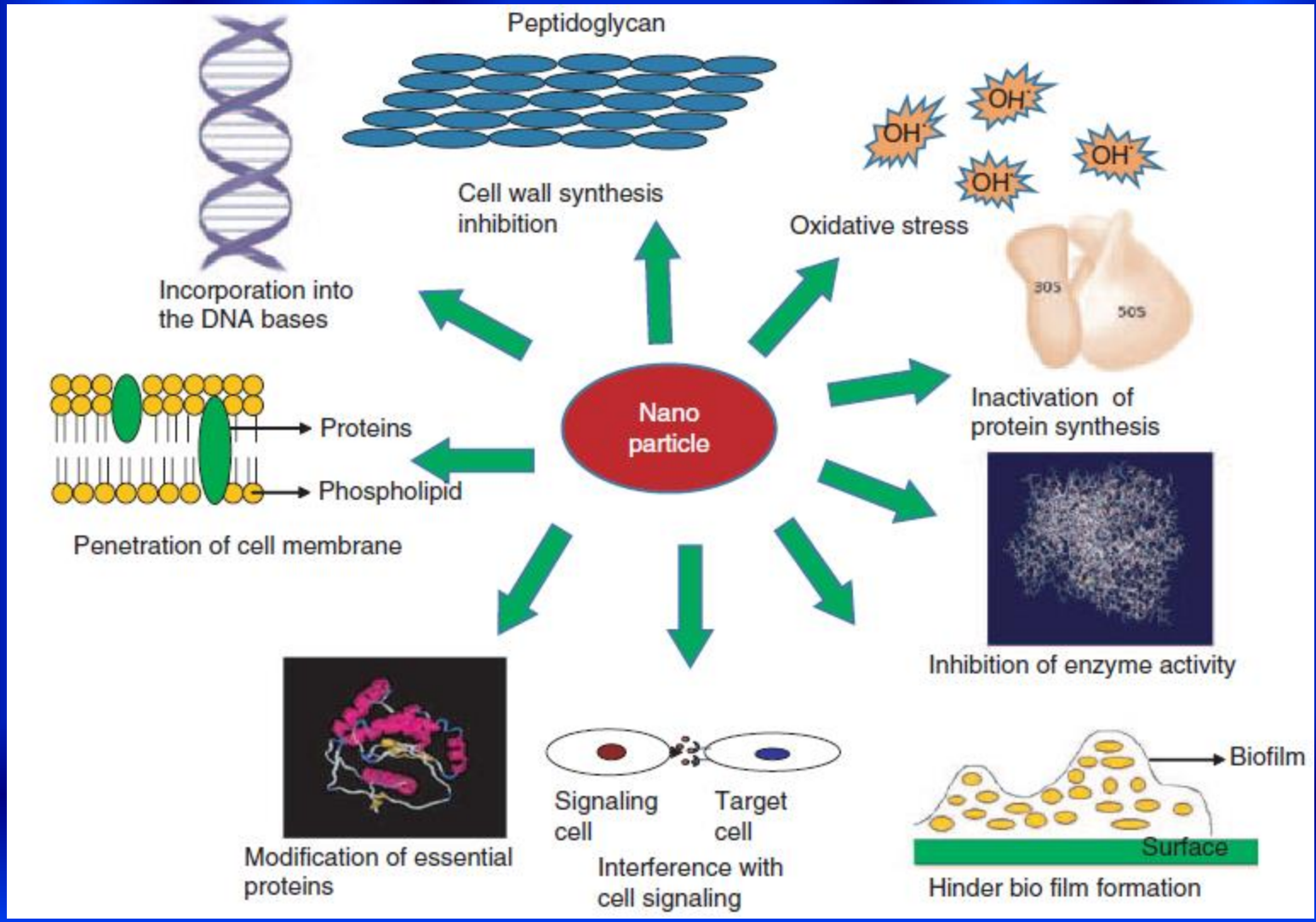
Be Realistic: It Takes Time to Get Over a Virus!



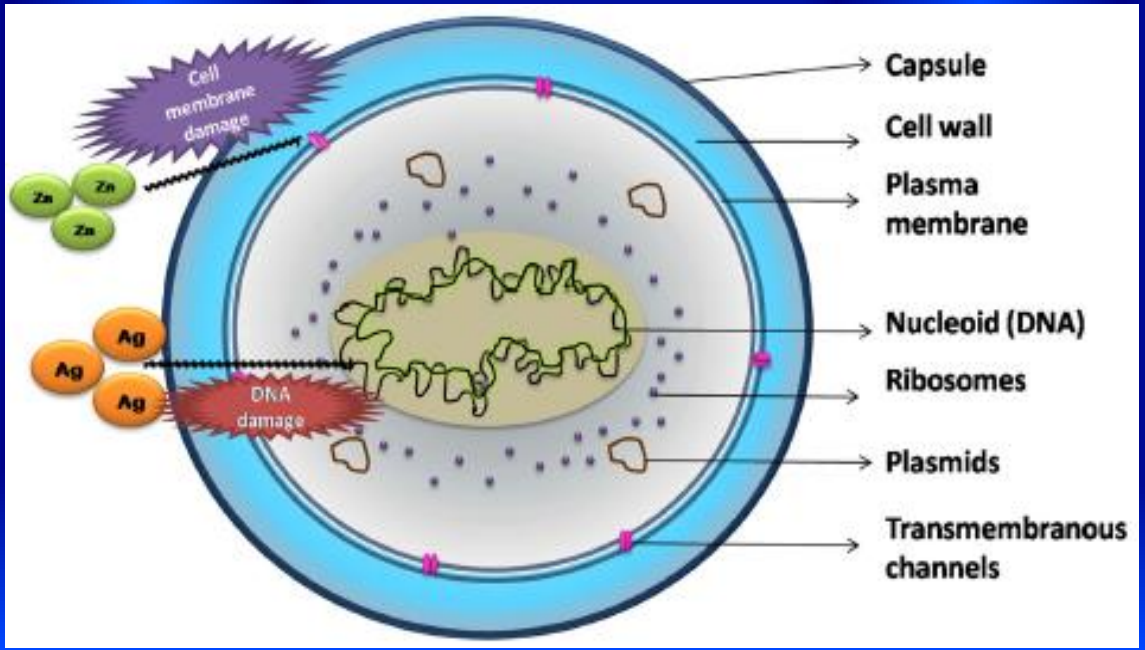
Nano-based Therapy to Combat Superbugs



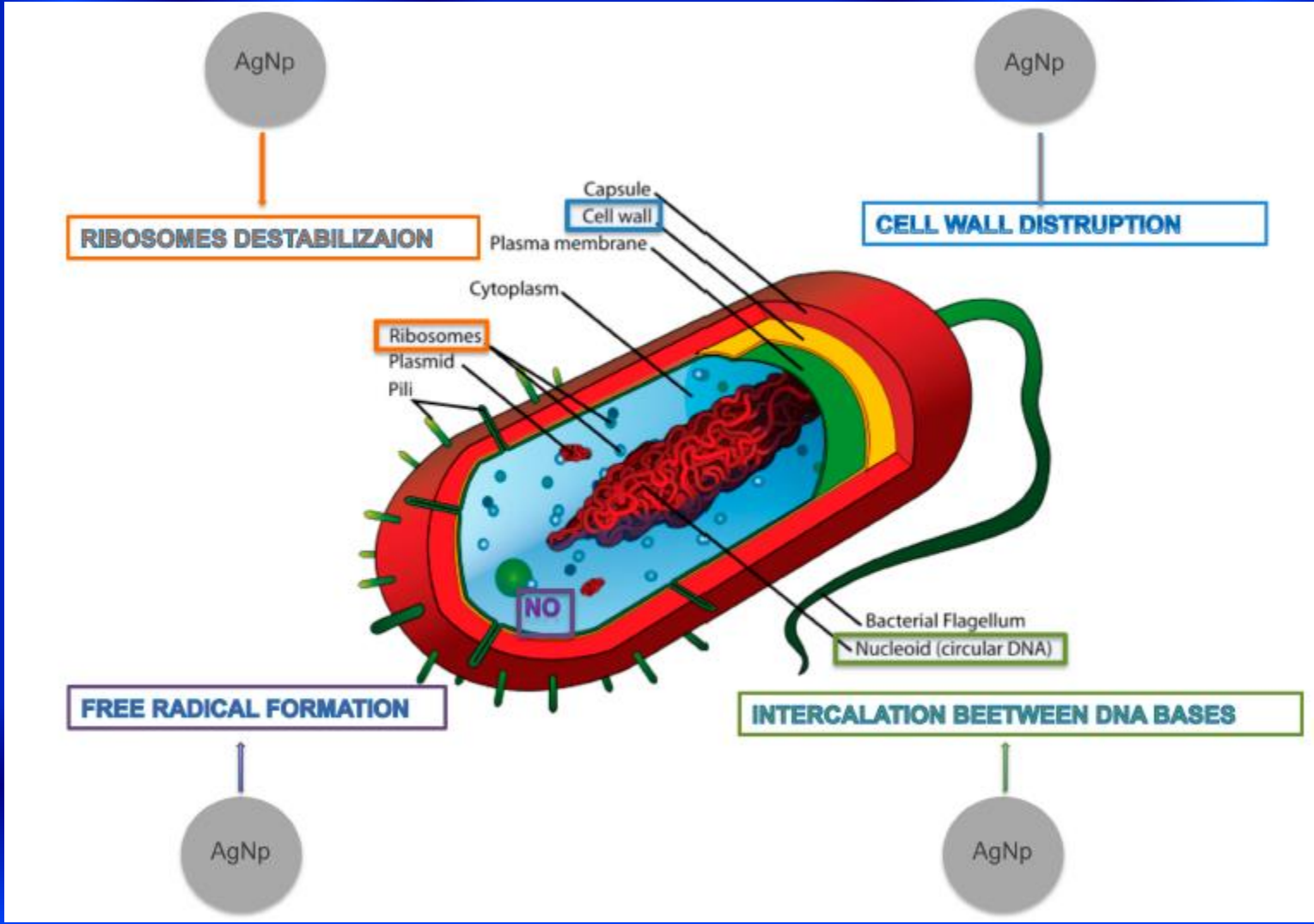
Nanoparticles in Antibiotic Resistance



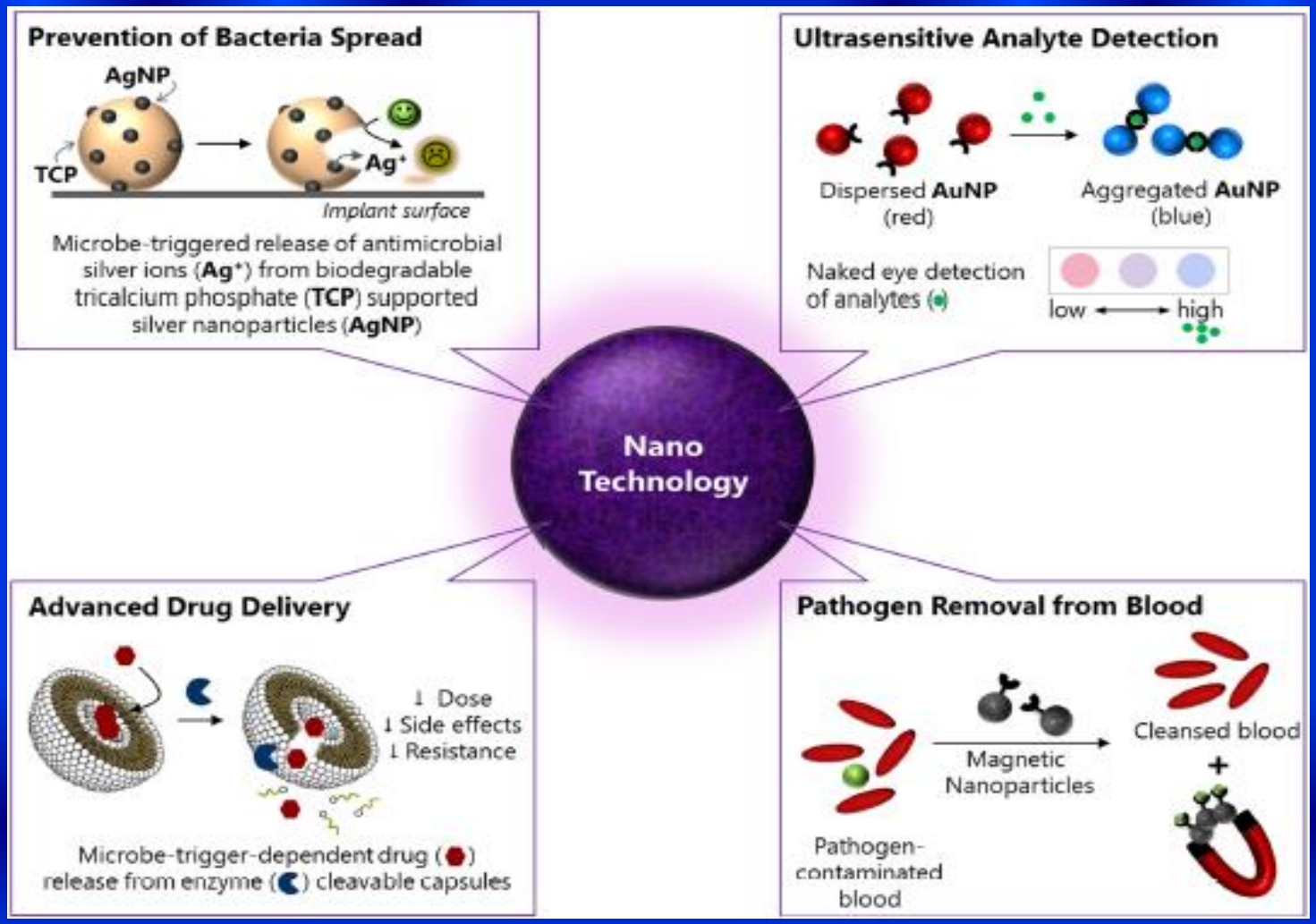
Major mechanism of action of ions



Mechanisms of AgNPs' toxic action



Nanotechnology in Antibiotic Resistance



Conclusion

- Development of antimicrobial resistance is directly related to antimicrobial usage, especially inappropriate usage
- Understanding antimicrobial kinetics & dynamics and resistance mechanisms can help guide appropriate usage
- Knowledge of local susceptibility patterns is essential
- Paucity of new antimicrobial agents in pipeline

Thank You