

Changing Patterns of Antimicrobial Resistances in Bacterial Infections

John Merlino

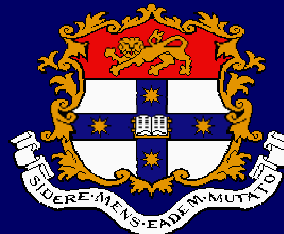
B.Sc, M.Sc. (Hons), Ph.D (Medicine) University of Sydney, FASM
Sydney, NSW Australia
JMerlino@med.usyd.edu.au

DEPARTMENT OF INFECTIOUS DISEASES AND
IMMUNOLOGY, FACULTY MEDICINE,
UNIVERSITY OF SYDNEY

SCHOOL OF BIOLOGICAL SCIENCES
MACQUARIE UNIVERSITY

DEPARTMENT OF MICROBIOLOGY AND
INFECTIOUS DISEASES
CONCORD REPATRIATION GENERAL HOSPITAL

AUSTRALIAN SOCIETY FOR MICROBIOLOGY





The Global Challenge

Antibiotics have saved millions of lives

Antibiotics are rapidly losing their effect

Bacterial Resistance: Global Problem

- Resistance to antimicrobial agents is emerging rapidly in a wide variety of organisms in various environments.



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

"The time may come when penicillin can be bought by anyone in the shops"

Alexander Fleming's Nobel Lecture, 1945

Development of anti-infectives



prontosil

penicillin G

streptomycin

chlortetracyclin

rifampin

vancomycin

methicilin

ampicillin

nalidixico ac.

cefalotina

gentamicin

cefuroxime

clavulanic ac.

cefotaxime

imipenem

norfloxacin

aztreonam

ciprofloxacin

cefepime

quinup /dalfop.

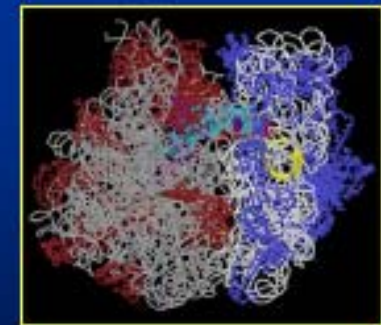
telithromicin

linezolid

daptomicin

tigecyclin

ertapenem



1920

1930

1940

1950

1960

1970

1980

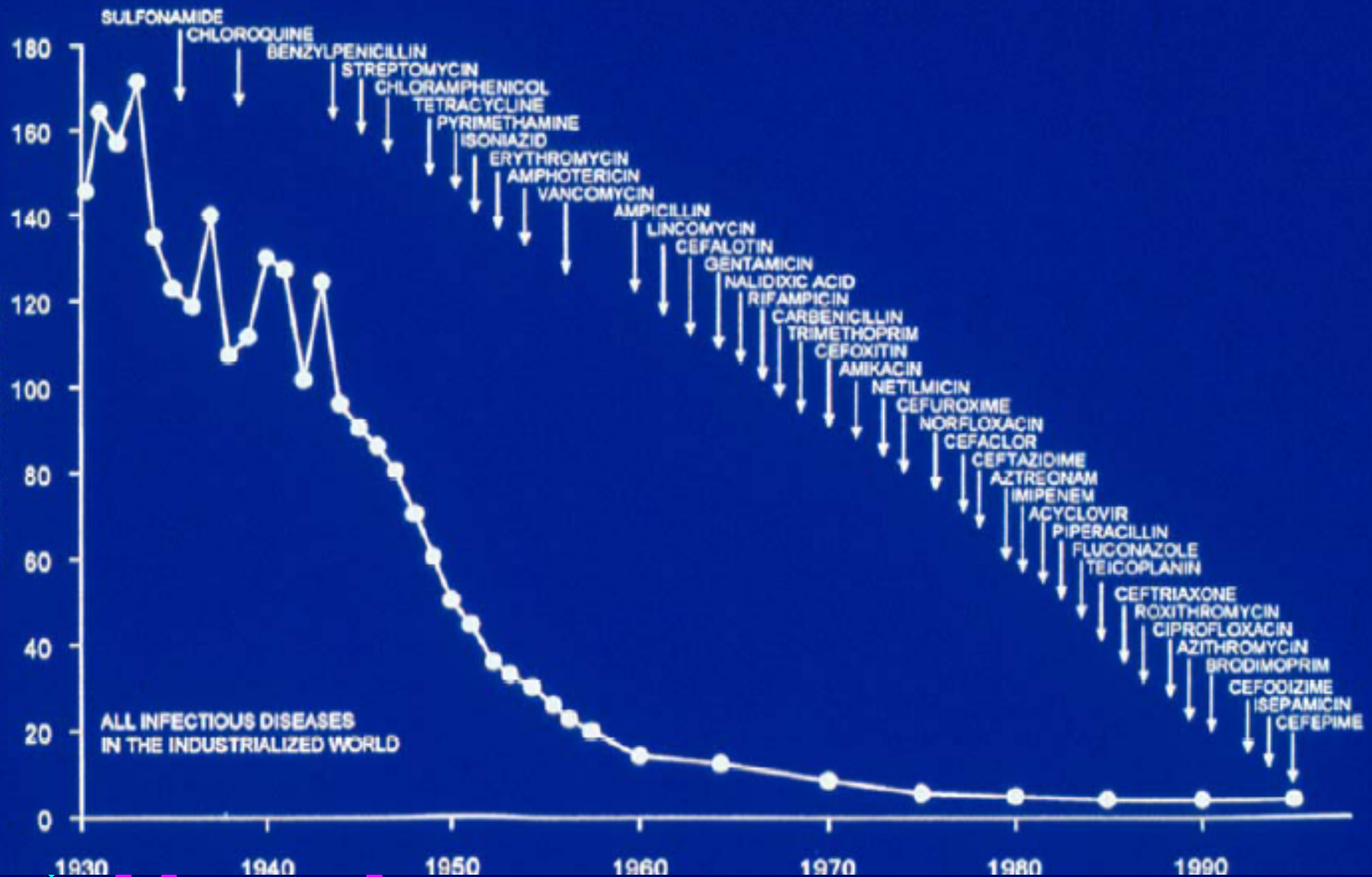
1990

2000

Emerging Resistance in Certain antibiotics

Antibiotic	Year Introduced	Reports Emergence of Resistance
Penicillin	1941	mid-1940s
Streptomycin	1944	mid-1940s
Tetracycline	1948	1950s
Erythromycin	1952	1950s
Methicillin	1957	late-1960s
Gentamicin	1964	mid-1970s
Ciprofloxacin	1988	late-1980s
Vancomycin	1958	1997

Development of Antimicrobial Agents and Paralleling Decrease in Mortality in the Industrialized World



2005 WHO & IDSA



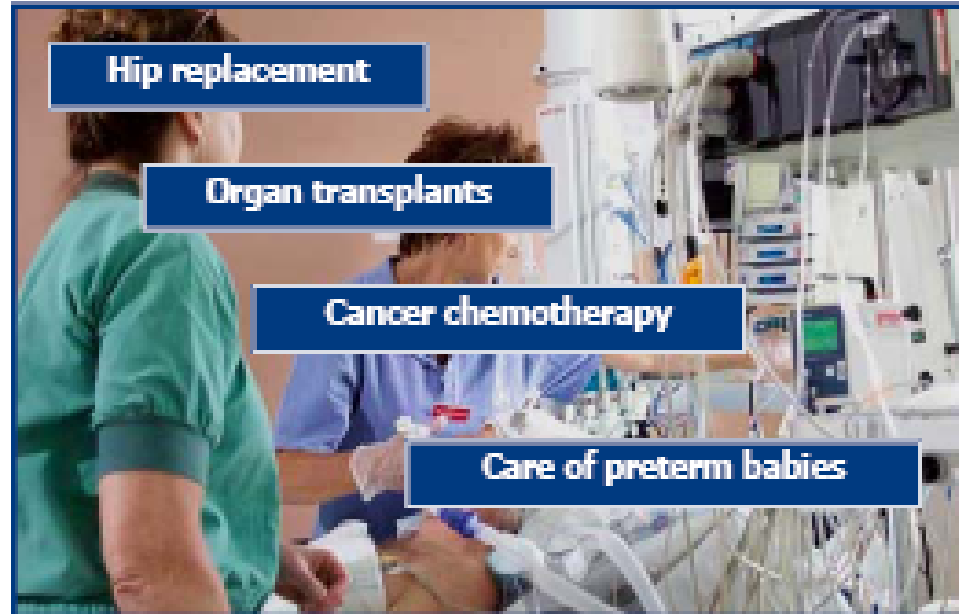
BAD BUGS, NO DRUGS



As Antibiotic Discovery Stagnates ...
A Public Health Crisis Advances

Antibiotics are Essential

Modern Medicine Is Not Possible Without Effective Antibiotics



Antibiotics are needed to fight Bacterial Infections

Reality Bacterial Resistance: Changing Patterns of Resistance

- Multidrug microbial resistance poses major challenges to the management of infections, particularly with the paucity of new drugs with activity against these bacteria.
- In the face of ever-increasing multidrug resistance, the selection of empirical antibiotic therapy is often difficult and challenging for the prescribing physician.



- It even harder for the scientist at the bench who is testing and interpreting resistance patterns CLSI, CDS, BSC standards continuously updated. – need for better phenotypic and genotypic testing methods - communication



Changing Patterns of Resistance

- Global and local data shows that resistance varies and has increased in both Gram-positive and Gram-negative pathogens, and is no longer confined to the hospital setting but the community as well.
- Numerous studies have reported a link between different classes of antibiotic use and the development of resistance in variety of organisms.
- No class of antibiotics is totally free of responsibility for resistance.

Examples: Link to AMR

- **Quinolones:** Fluoroquinolone use has been associated with the development of resistance in *Streptococcus pneumoniae* and *Enterobacteriaceae*.
- **Cephalosporins:** Ceftriaxone/Cefotaxime use has been linked to the development and spread of resistance to cephalosporins among clinical strains of *Enterobacteriaceae* eg ESBLs-CTX-M.
- **Glycopeptides & Carbapenems:** Emerging resistance to the Glycopeptides in treating MRSA & enterococcal infections (hVISA, VISA, VRSA & VRE) and Carbapenem resistance in *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter spp.* is threatening the clinical utility of these classes of antibiotics.

Examples: Difficult bugs to treat

Notable global examples include hospital and community MDR strains of:

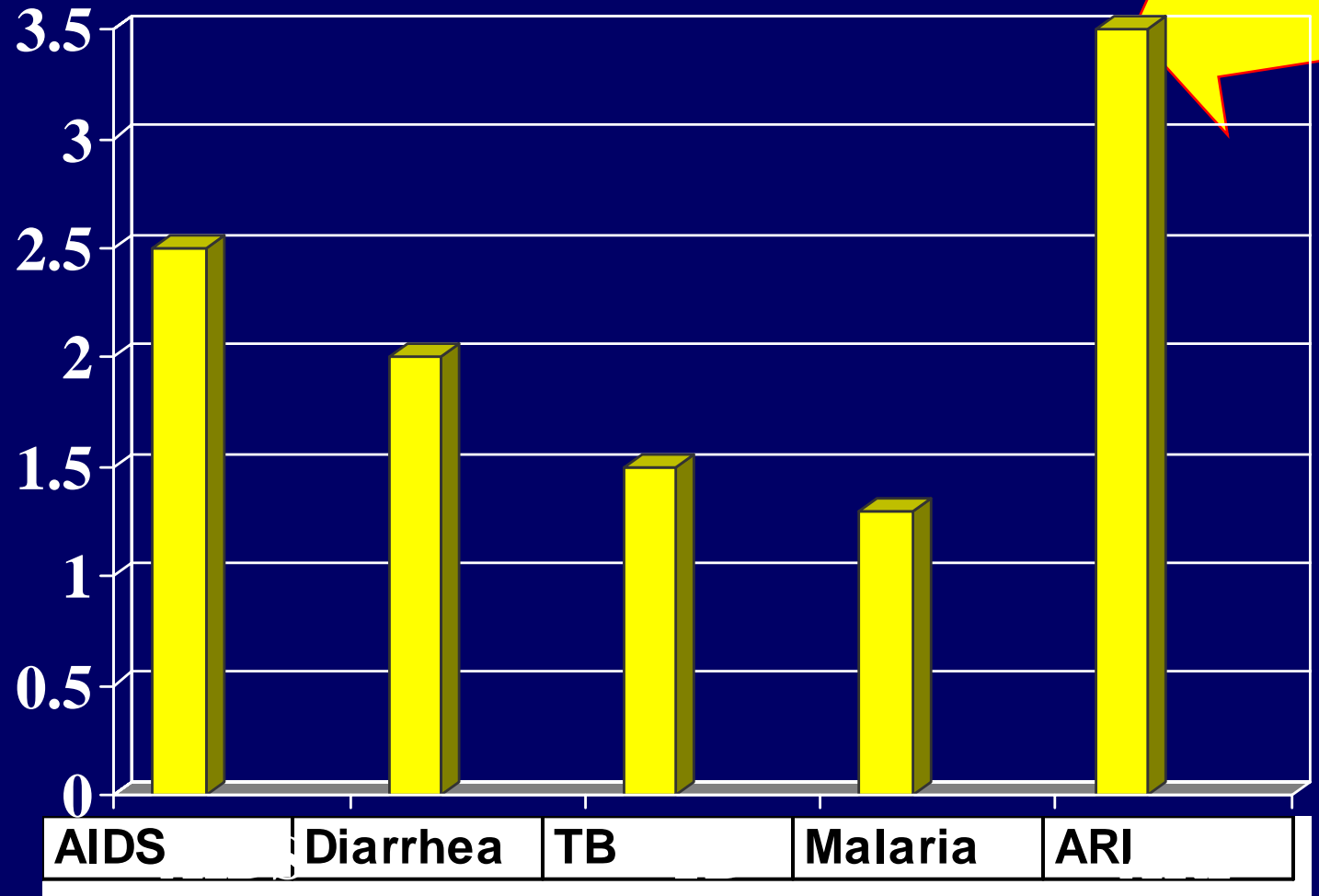
- Mycobacterium tuberculosis,
- Enterococcus faecium, (VRE)
- Enterobacter cloacae, (MBL)
- Klebsiella pneumoniae,
- S. aureus, (MRSA/hVISA)
- Acinetobacter baumannii
- Pseudomonas aeruginosa

UNUSUAL ANTIBIOTIC RESISTANCE NEEDING CONFIRMATION IN A ROUTINE LABORATORY*

Organism	Unusual Resistance
<i>S. aureus</i> CNS	Vancomycin, linezolid, quinupristin-dalfoprisitin Vancomycin, linezolid
JK coryneforms	Vancomycin, linezolid
<i>S. pneumoniae</i>	Vancomycin, meropenem, linezolid
Grp A, B, C, G beta strep.	Penicillin, vancomycin, linezolid
Enterococci	Both ampicillin and quinupristin-dalfoprisitin, linezolid
Enterobacteriaceae	Carbapenems (except <i>Proteus</i> spp.)
<i>H. influenzae</i>	Any third generation cephalosporin, carbapenem
<i>N. meningitidis</i>	High level penicillin
<i>N. gonorrhoeae</i>	Any third generation cephalosporin
<i>Acinetobacter/P. aeruginosa</i>	Colistin
Bacteroides	Metronidazole, ampicillin/sulbactam, carbapenems
<i>C. difficile</i>	Metronidazole, vancomycin

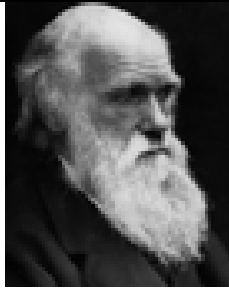
*Modified from Livermore et al. J. Antimicrob. Chemother. 2001, 48 (S1):87-102.

Millions Deaths/yr

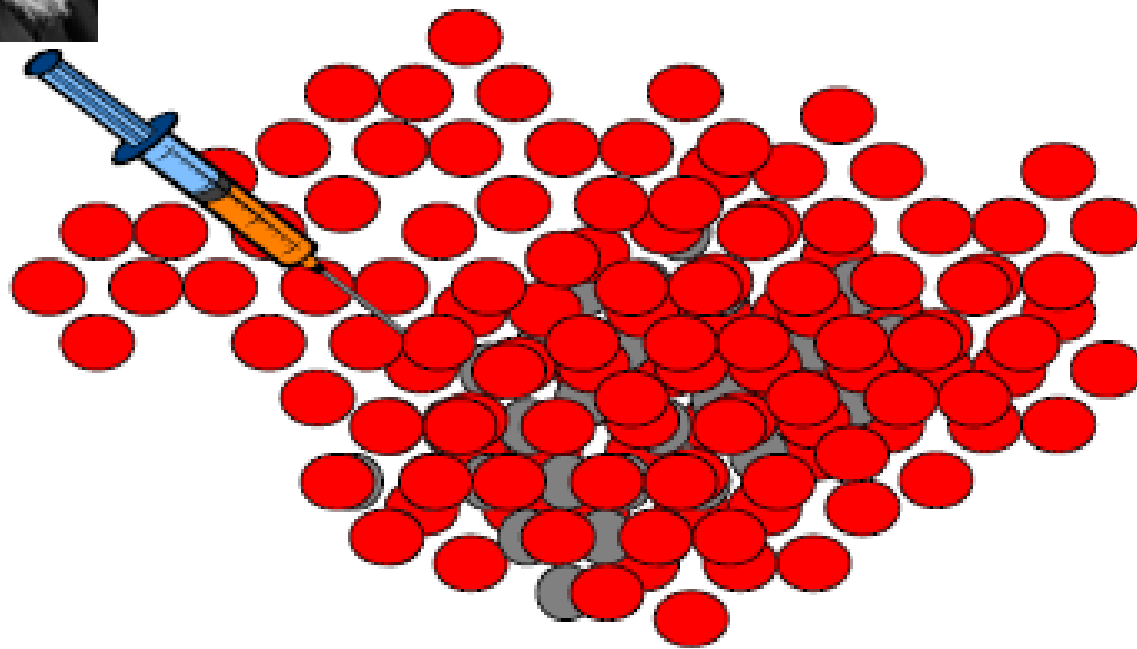


WHO

Antimicrobial Resistance: Successful Bacterial Survival Mechanisms

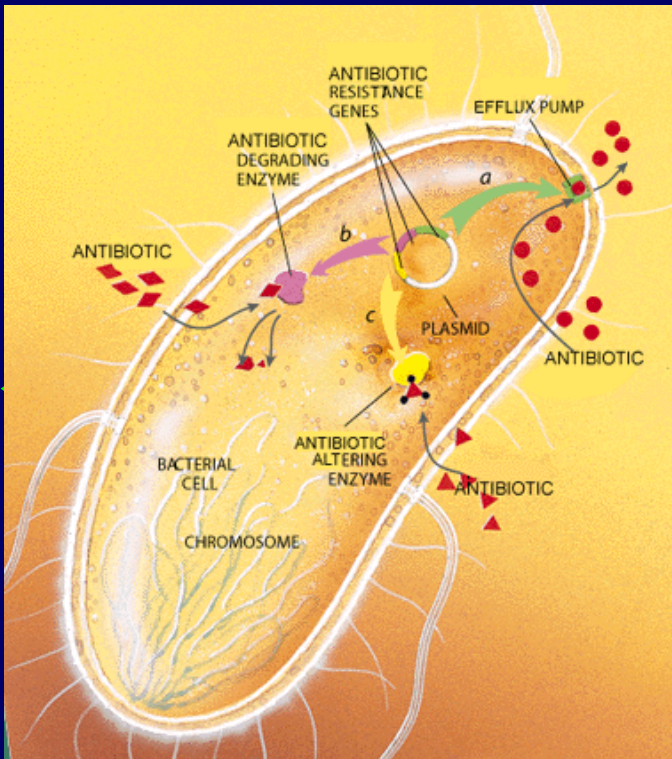


The survival of the fittest

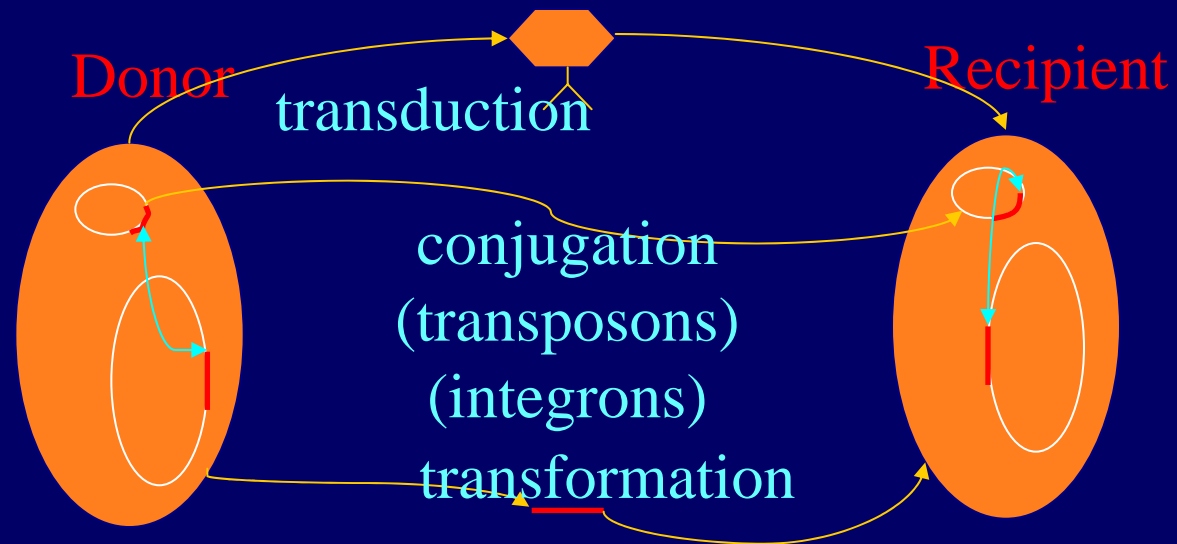


Bacterial Mechanisms of Resistance

PHYSIOLOGY CHANGES



Molecular: Acquisition of new DNA



Environmental Pressures: Antibiotic Users

“Analogy: Steroids to a Body Builder - STRONGER”

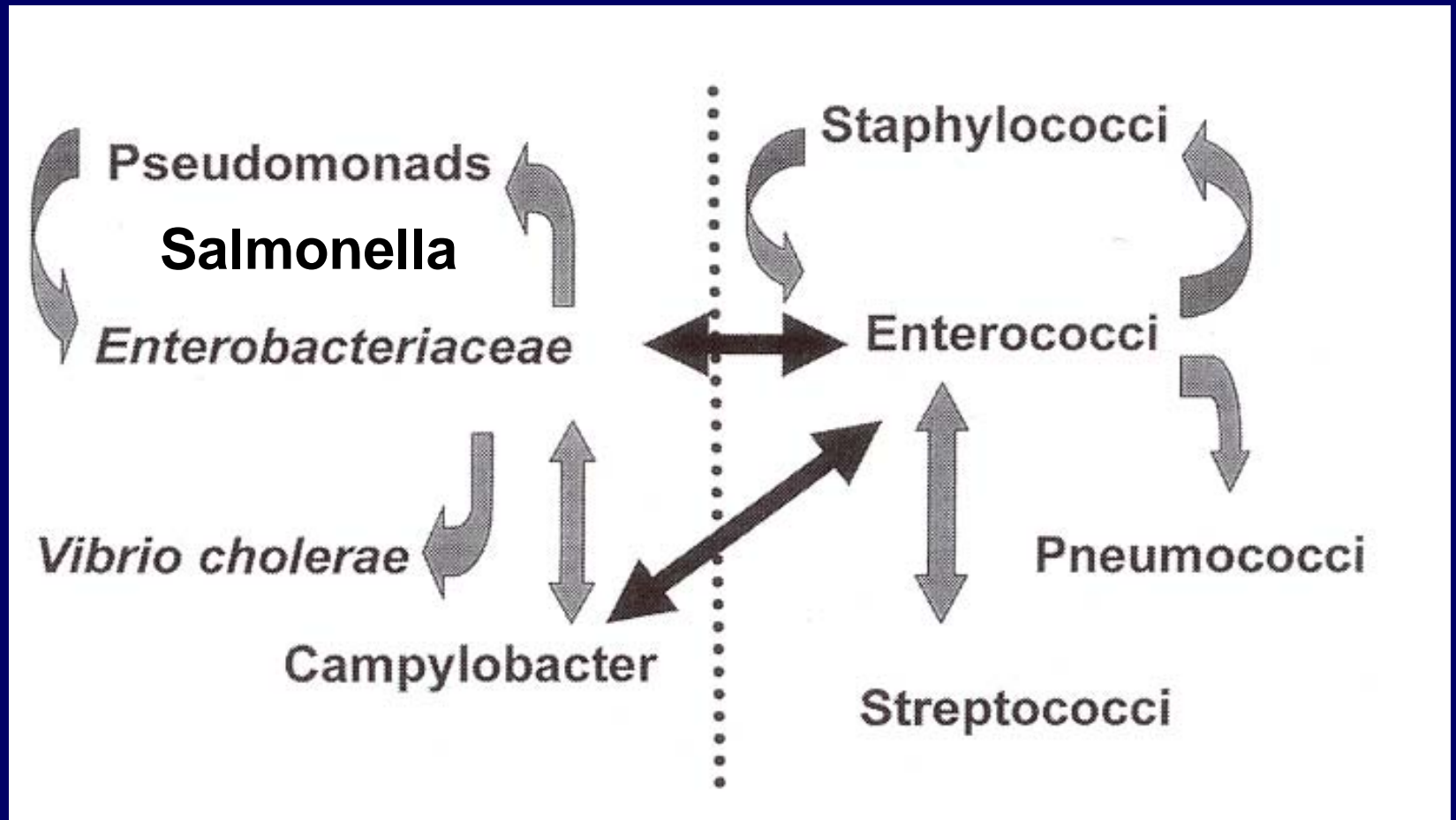
Hospital

Agriculture

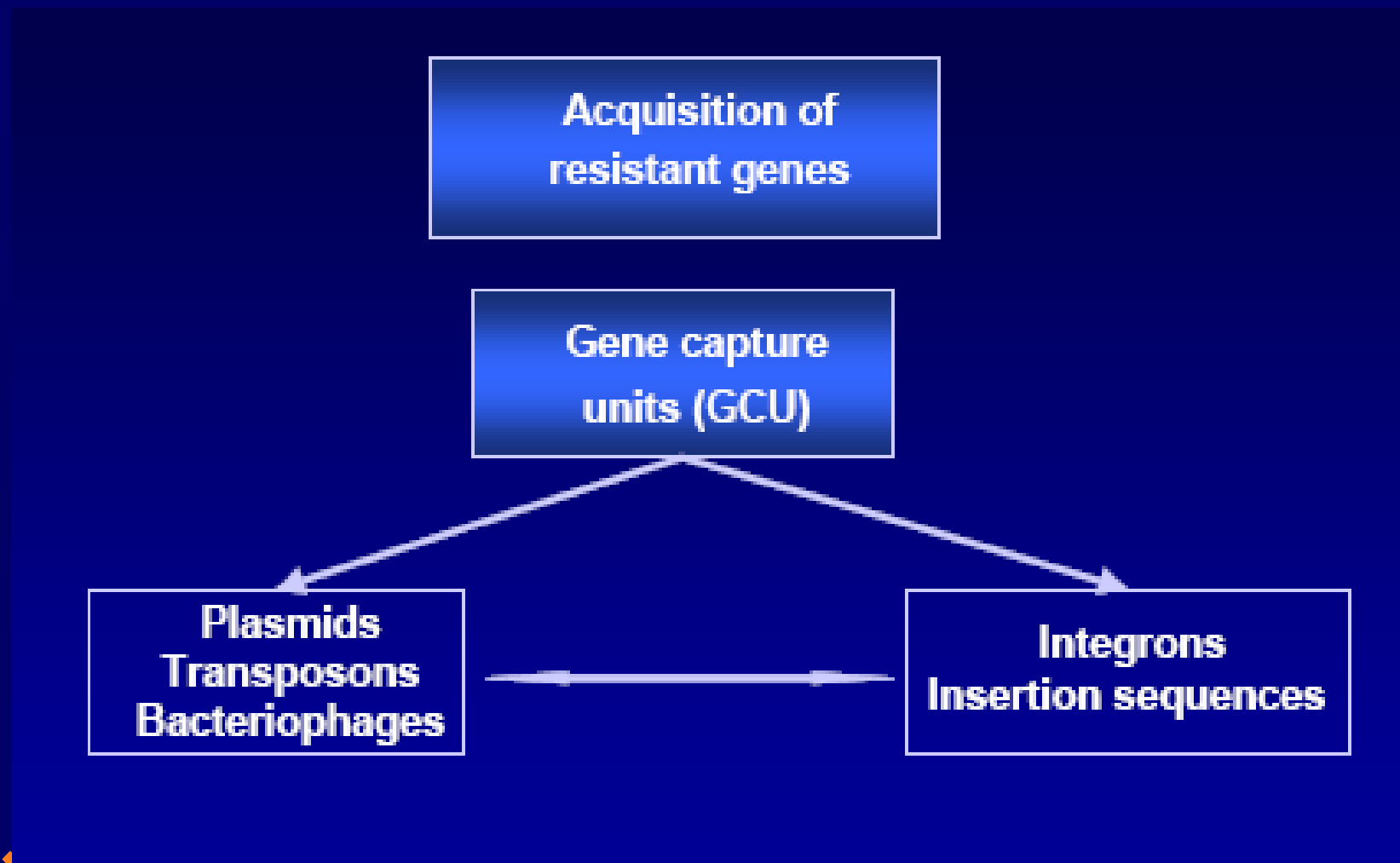
Veterinary

Community: “Normal Flora”
Commensal Environment

Lateral and Horizontal Gene Transfer (HGT)

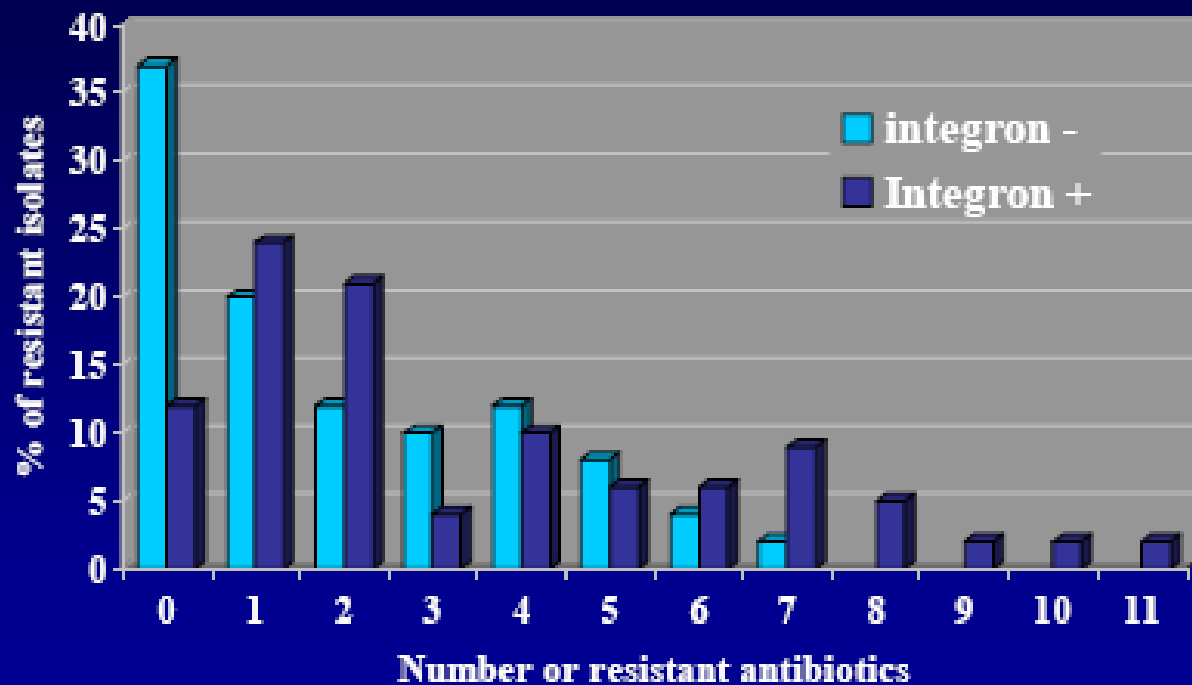


Multi-drug Resistance Genes



Link Integrons and MDR

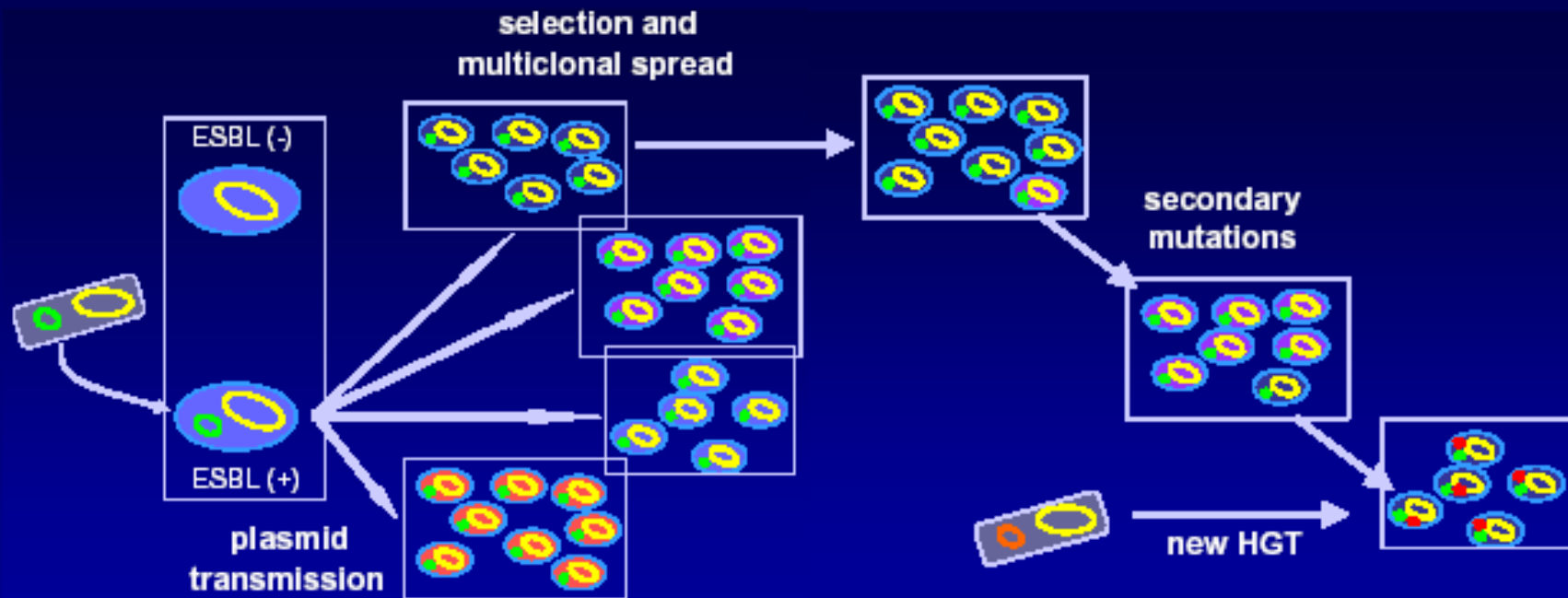
Integrons and multiresistance



Martínez-Freijó, et al.

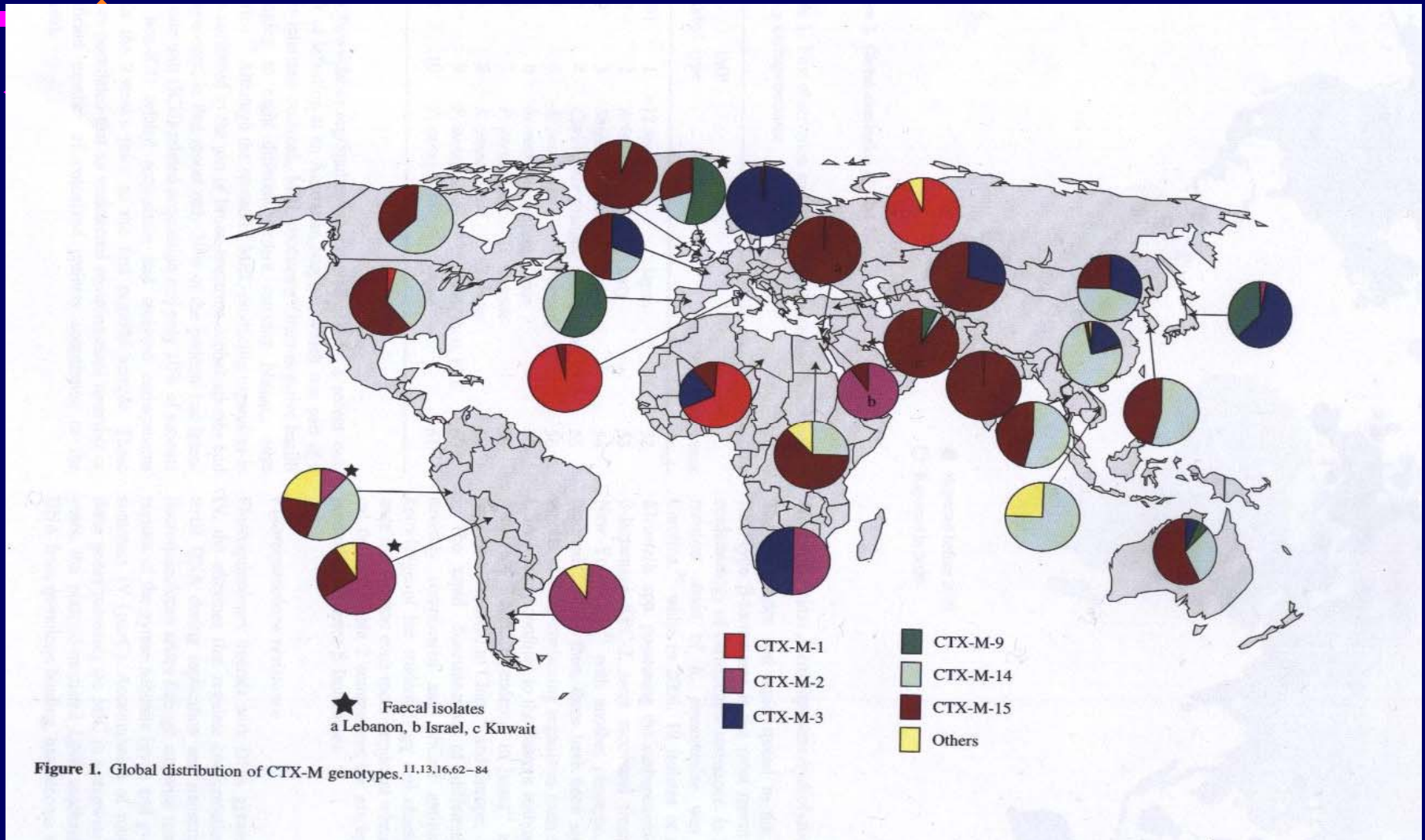
J. Antimicrob. Chemother., 1998; 42:689-696

The extended spectrum β -lactamase model... can be more complicated...



Adapted from Cantón, Coque and Baquero. Curr Opin Infect Dis 2003;16:315-25

Spread ESBL-CTXM genotypes



Hawkey & Jones JAC 2009.

Resistance mechanism:

- Decrease influx
- Increased efflux
- Enzymatic inactivation
- Sequestration
- Target modification
- Target bypass
- Target repair
- Target amplification
- Biofilm formation
- Intracellular localization

Antibiotic Action and Resistance Mechanisms

www.librainitiative.com

Mechanisms of resistance

(a) Resistance by target modification

- Example 1: **β-lactamase resistance**
- β-lactamase (β-lactamase) enzyme cleaves β-lactam ring
- Example 2: **Macrolide resistance**
- 23S rRNA methylase (erm) modifies binding of erythromycin to the 50S ribosomal subunit
- Example 3: **Streptogramin resistance**

(b) Resistance by antibiotic modification

- Example 1: **β-lactamase resistance**
- β-lactamase hydrolyzes the β-lactam ring in β-lactam antibiotics



- Example 2: **Antibiotic sequestration**
- Antibiotic sequestration (proteolysis) or active prevention binding of the modified antibiotic to the ribosome



(c) Resistance by antibiotic efflux pumps

- Antibiotic efflux is prevented either by causing the protective loss or by ATP hydrolysis
- Expression of the efflux pump can be induced by the antibiotic, or regulated by the host's DNA transcription efflux system

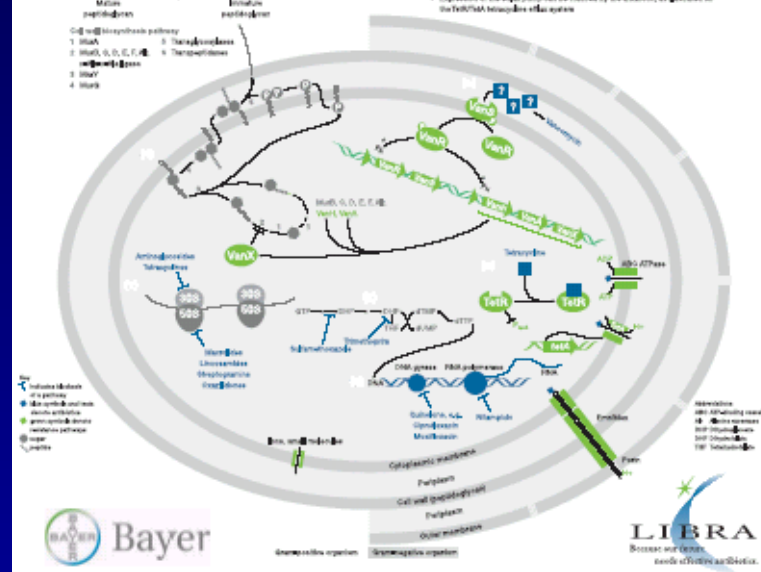
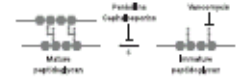
Mechanisms of action

(1) Inhibition of protein synthesis

(2) Inhibition of DNA precursor synthesis

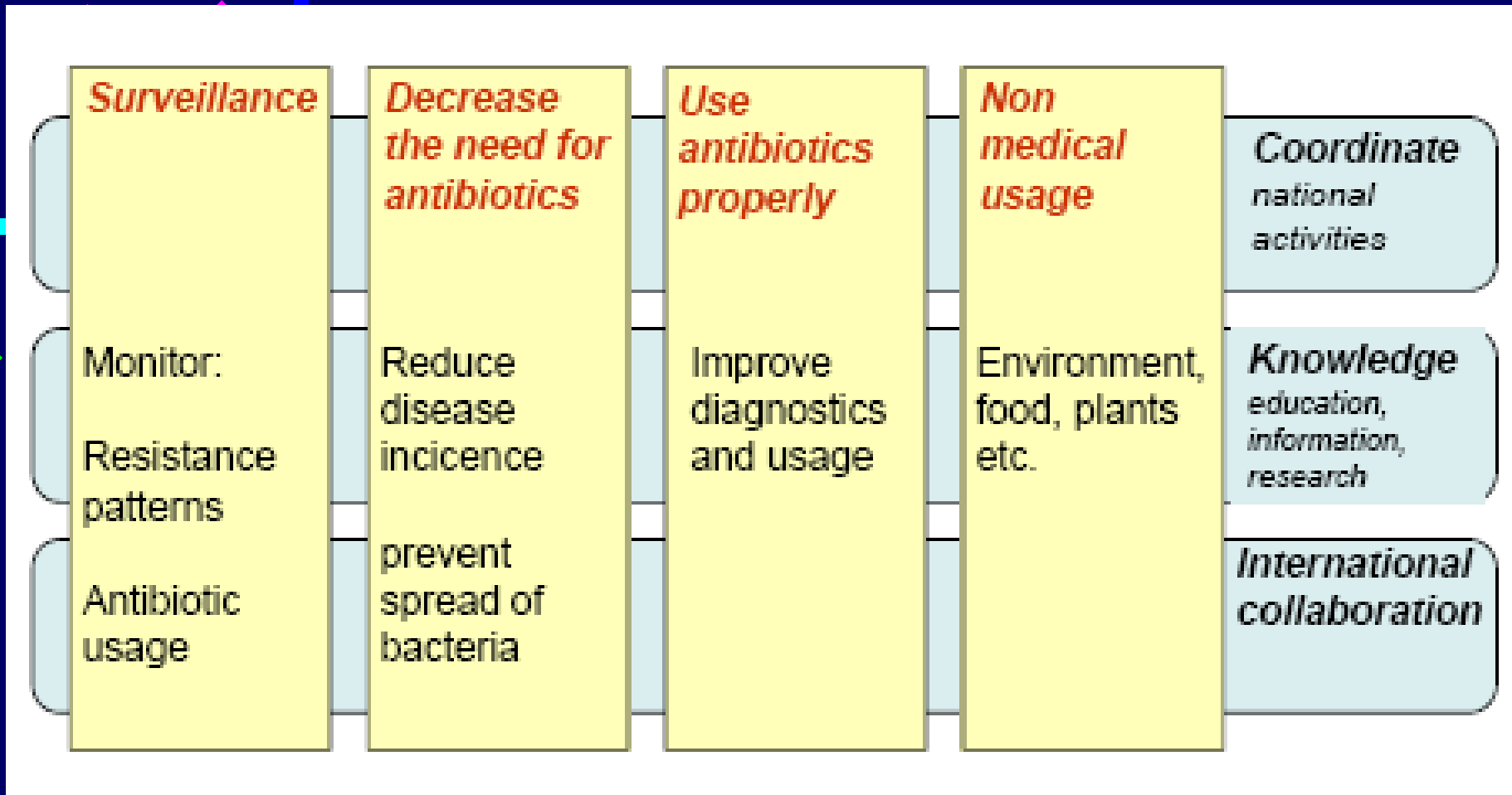
(3) Inhibition of DNA or RNA synthesis

(4) Inhibition of cell wall synthesis



...in all of them HGT has been demonstrated!

Strategies suggested in slowing down Antimicrobial Resistance Process



Summary:

- The emergence and spread of multiply resistant organisms represent the convergence of a variety of factors that include mutations within the existing host or acquisition of foreign genetic material in common resistance genes that extend their spectrum of activity.

Regulation of resistance gene expression is common in Nature and represents an efficient adjustment between energy saving and adaptation to a rapidly changing environment. Courvalin, P J. Internal Medicine 2008

- The unpredictability –

bacterial cell and “Survival Mechanisms”

Genetic diversity: the ability of bacterial organisms to acquire resistance and virulence traits in response to environmental changes

Conclusion:

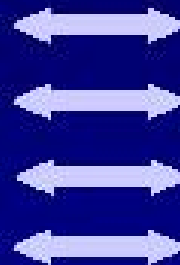
Sadly, in many cases the escalating pressures in the emergence of MDR “Superbugs” is a consequence of our own human actions.

“We want better drugs no matter what the consequences”

Future directions:

- Targets for research

- individual bacteria
- bacterial clones
- bacterial communities
- individual resistance genes
- resistance gene assemblies
- gene construction maintenance
- gene capture units



- Selective compartments
- Selective intensity:
 - total antimicrobial use
 - antimicrobial use models

Europe: TROCAR - Translational Research On Combating Antimicrobial Resistance

The gap between scientific knowledge and clinical practice in the prevention of dissemination of highly virulent multiresistant pathogen

■ The project focuses on three major strategic aims:

- Definition of the major high-risk resistant clones based on an appropriate representative collection and new clinical strains.
- Genomic and proteomic approaches to investigating specific traits associated with virulence, transmission, persistence and resistance of epidemic clones in comparison with non-epidemic clones, as well as resistance determinants and their genetic location.
- The development of bioinformatics tools to fully exploit the genomics data and allow the rapid identification of resistant strains with heightened epidemic potential.

**Thank You For Your
Attention!!**

Concord Hospital



Sydney, NSW Australia

