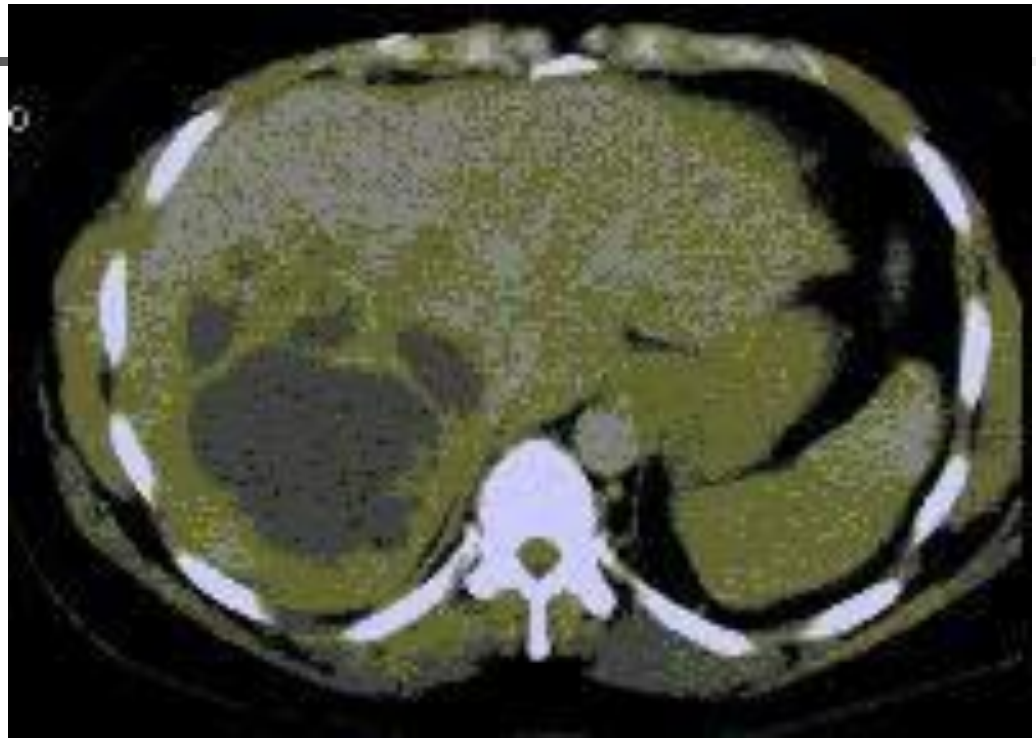
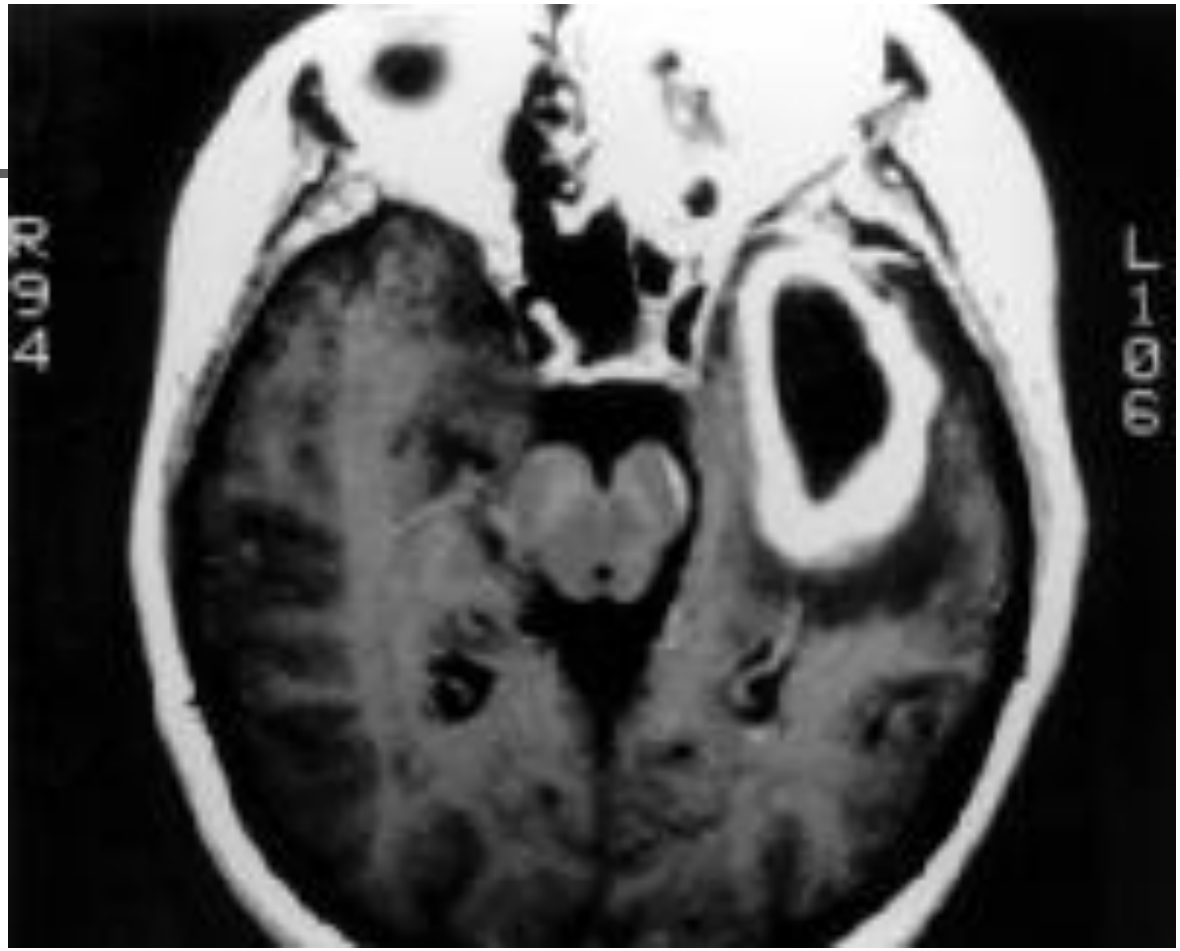
Antibiotic resistance

Faris Bakri

1-9-2008

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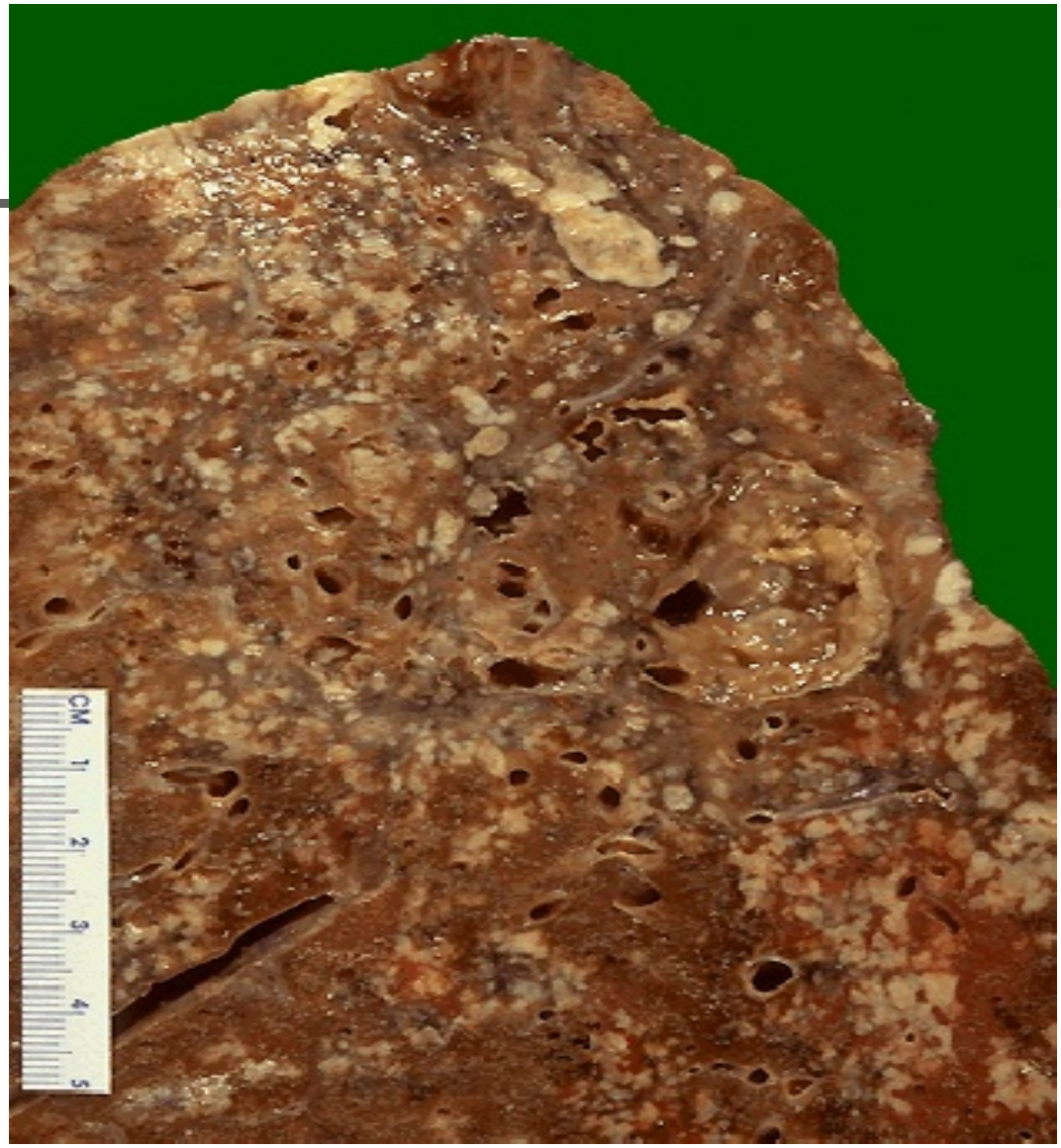
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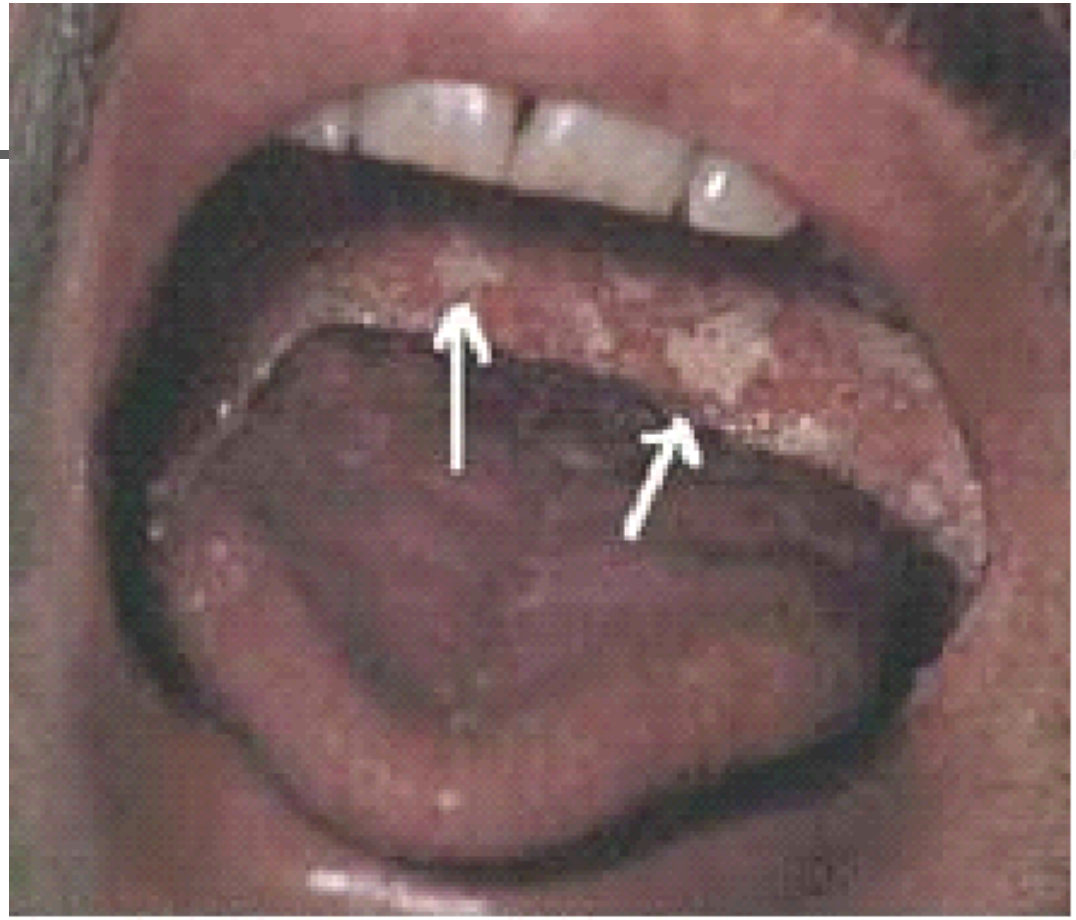


Questions, Questions, Questions

- What do we mean by resistance?
- How do we measure resistance?
- Where did resistance come from?
- What is "resistance selection"?
- How big is the problem?
- What is a surveillance system?
- What are the commonest resistant bacteria?
- Why is it a problem?
- Who is driving the problem?
- What to do?

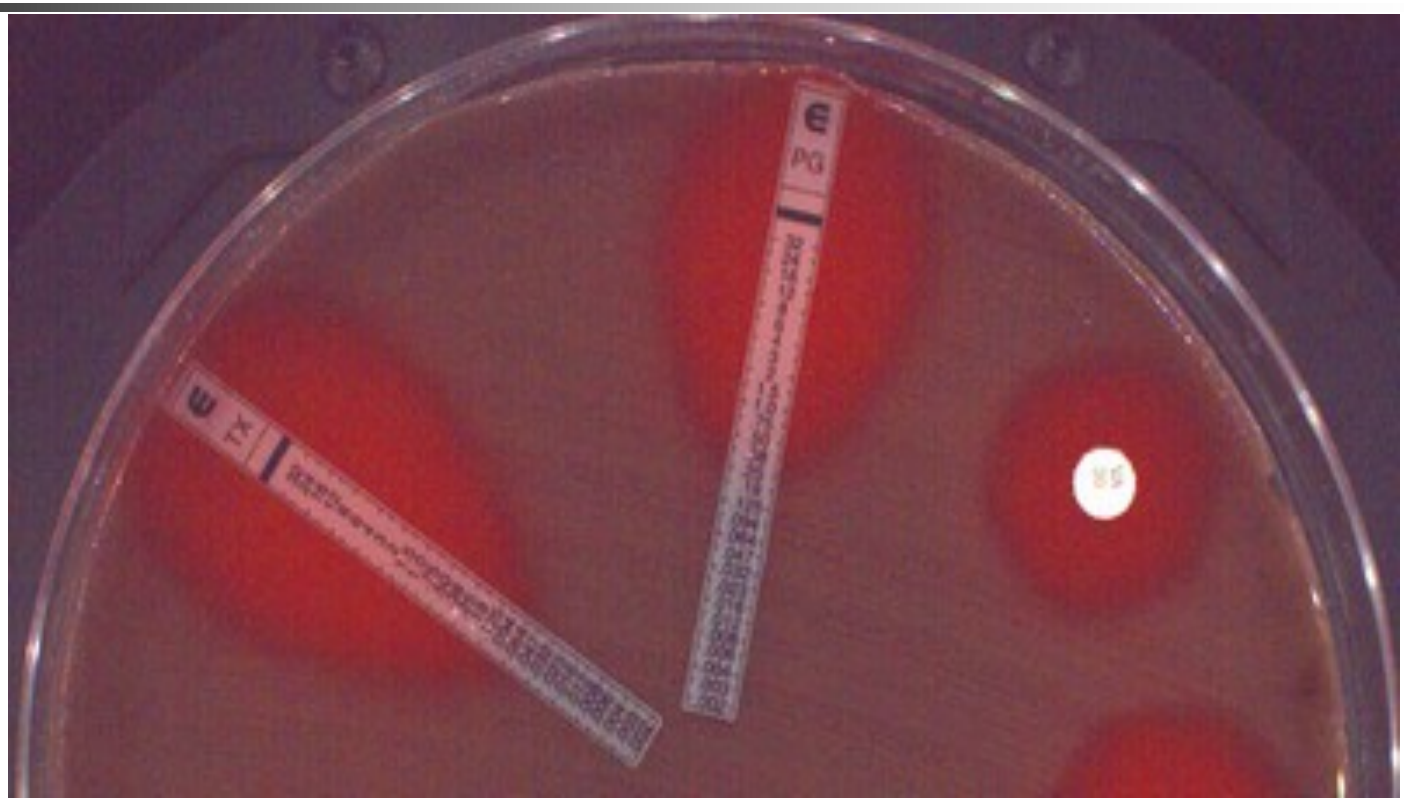
Resistant bacteria

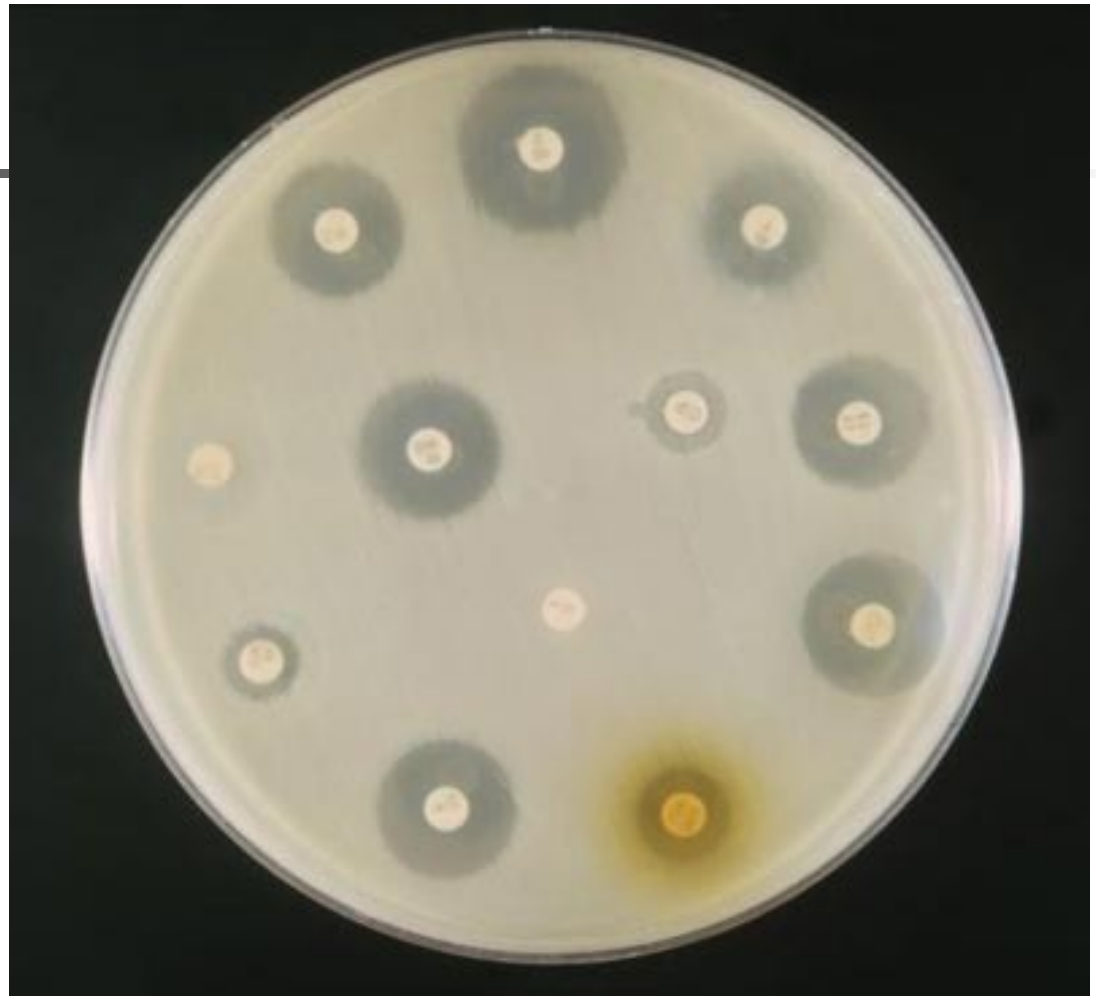
- Are not inhibited by the usually achievable systemic concentrations of the normal dosage

Testing methods

- Disk diffusion procedure
  - Sensitive, Intermediate, Resistant
- Etest
  - Quantitative (MIC) and qualitative

Etest





Intermediate strains

- MIC approaches attainable blood levels and response rate may be lower than susceptible bacteria

The in vitro dilemma

- Does the in vitro growth inhibition by a specific agent correlates with clinical response ???

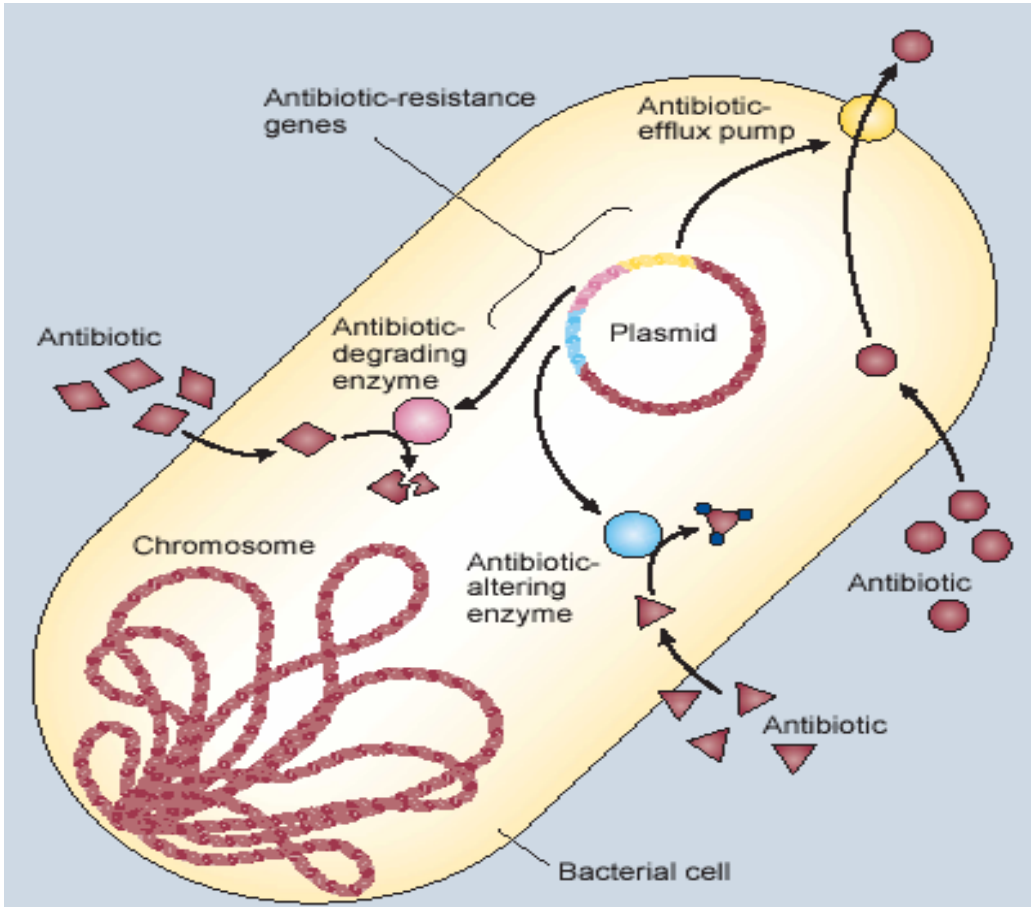
Clinical laboratory standards Institute National Committee for Clinical Laboratory Standards (NCCLS)

- Publishes the standards of testing
- Very complex documents
- Less complete for rare organisms
  - *eg. Bacillus, Corynebacterium, Leuconostoc*

NCCLS Table
eg. Streptococcus pneumonia

Antibiotic	Disc Content	Zone Diameter		
		R	I	S
*Oxacillin	1ug	-	-	≥ 20
Erythromycin	15ug	≤ 15	16-20	≥ 21
Tetracycline	30ug	≤ 18	19-22	≥ 23

Mechanisms of resistance



The origins

- Over their millennia of existence, bacteria always confronted organic structures that affected their growth
- To survive ... acquired resistant genes
  - These R genes should not have appeared in the clinical setting

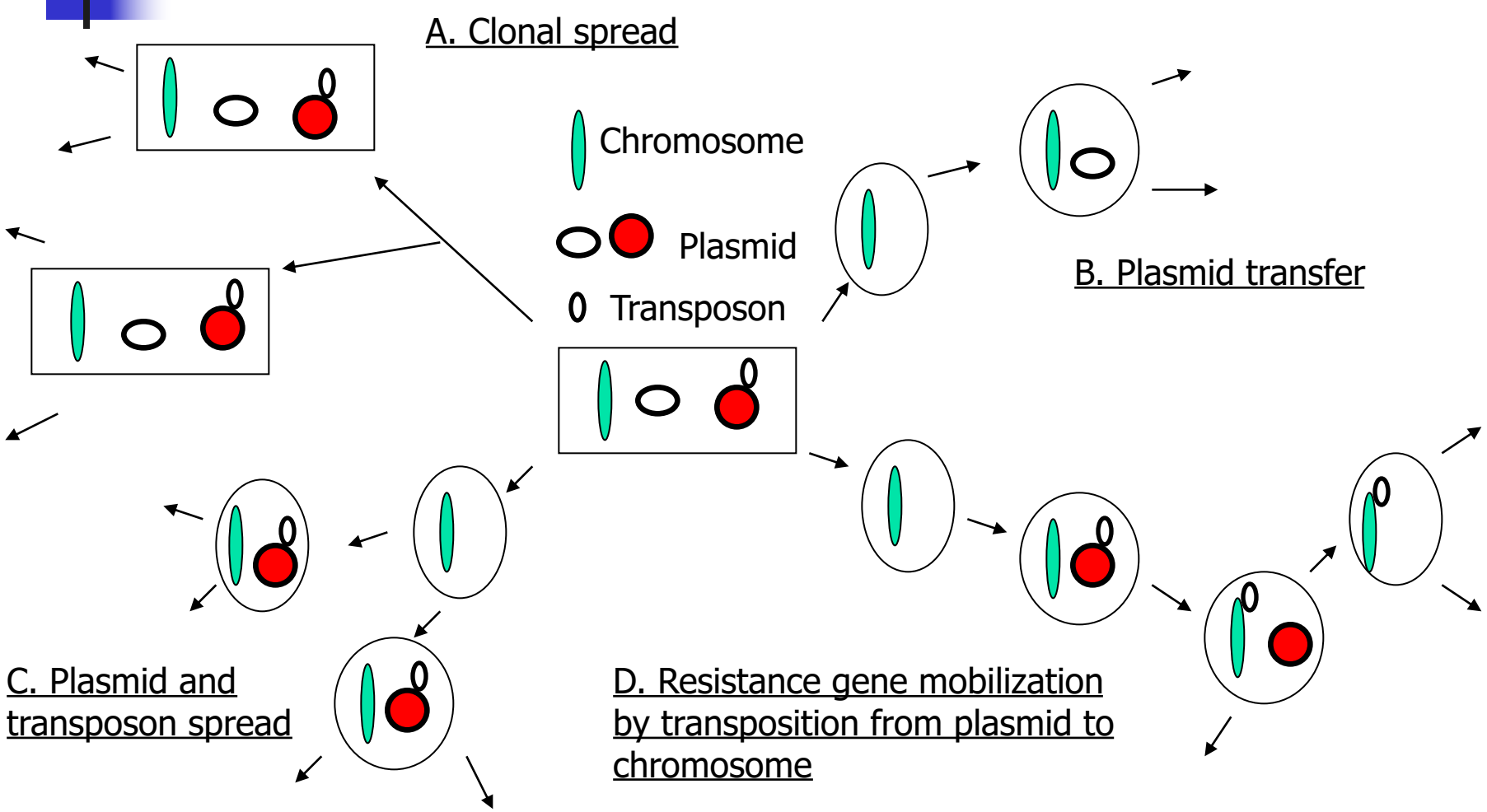
The biology of resistance
Transfer of genes

- Mutation
- Acquired

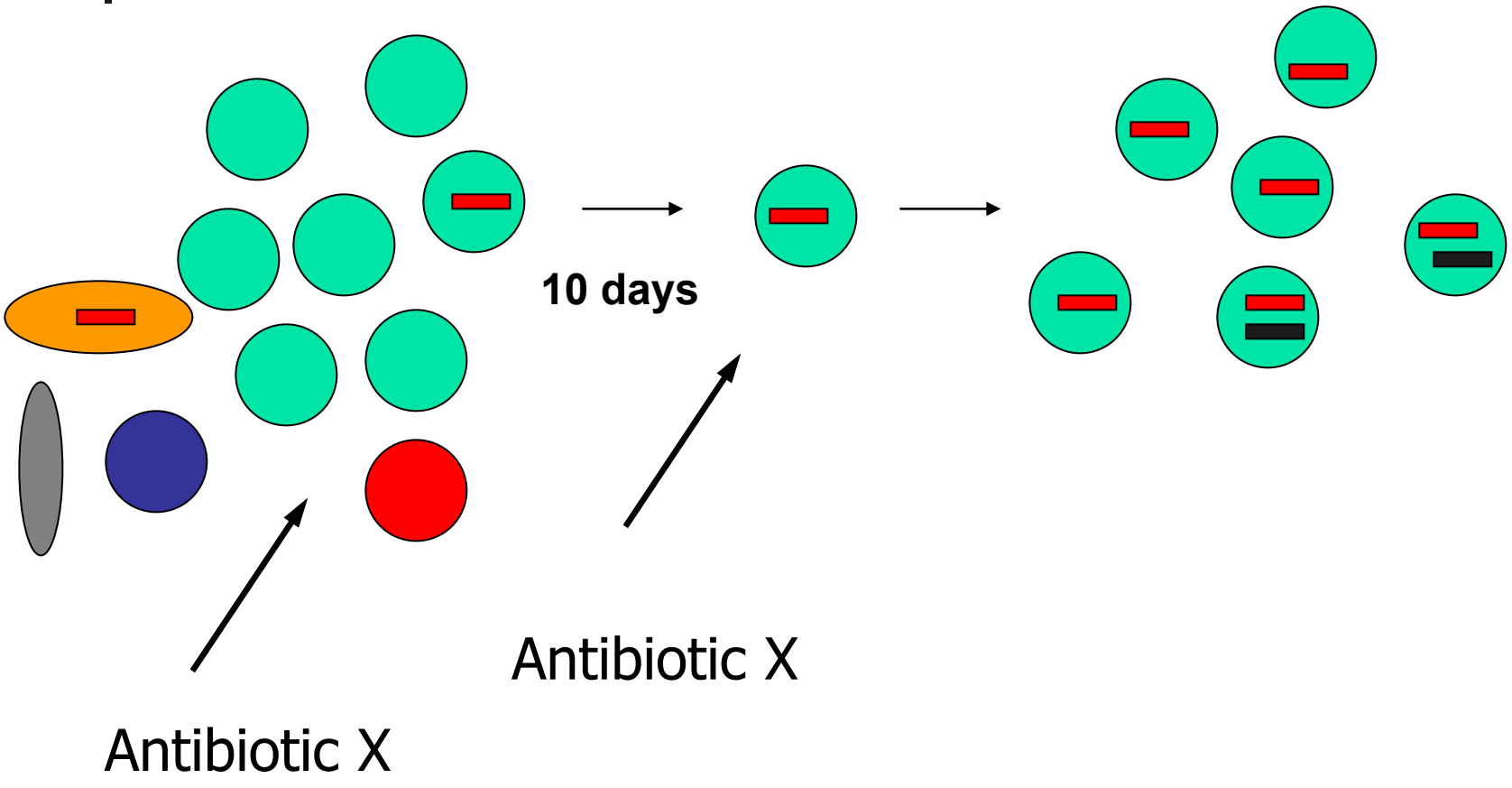
- Plasmids
- Chromosomal

- Within the same species
- Between different species

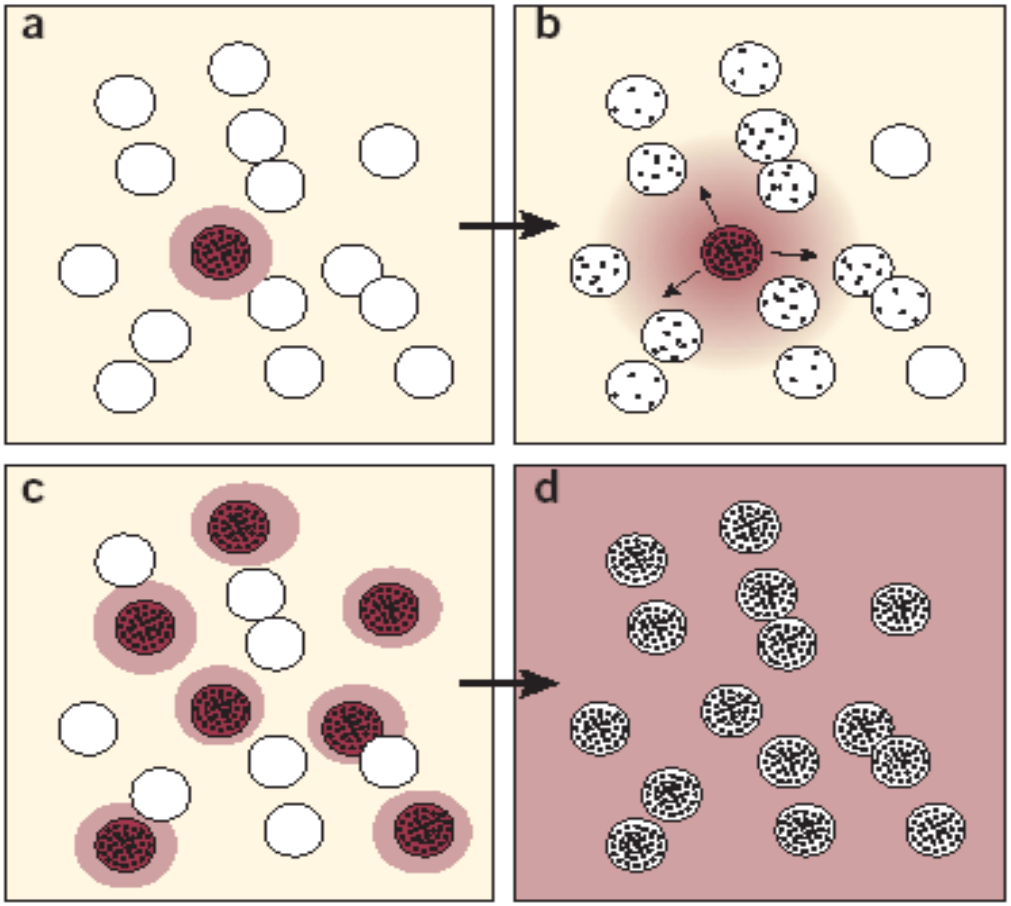
The biology of resistance



Resistance selection



Ecology of antibiotics



BRIEF REPORT

Infection with Vancomycin-Resistant *Staphylococcus aureus* Containing the *vanA* Resistance Gene

- 40 y/o lady
- HTN, DM, PVD, CRF, foot infections
- Recurrent foot infections: MSSA, MRSA
  - Vancomycin, gentamicin, levofloxacin, clindamycin,…
- April 2002: MRSA sepsis & graft infection
- June 2002: VRSA + VRE exit site infection of CV catheter

NEJM April, 2003

VRSA…

- Planter ulcer swab: VRSA + VRE
- Contacts screen: negative
- VRSA + VRE share the same v*anA* gene
- VRSA isolate was identical to:
  - MRSA from patient's nasal nares
  - MRSA from patient's close friend

NEJM April, 2003

ate of Birth: 02/07/1986 Da...
Sex:F Samp/XR Date:
Room: 55/ 1 Ins.: 10

Consultant :

CLINICA 446507
JORDAN UNIVERSITY HOSPI

Nature of S. imen :
Examin - required : 3
Charges ID 449207939528

Date - Requested : 18.10.
Physician :
Date Received :
Hr Received :

Required Information	SOURCE / SITE	DIA	NTIBIOTIC ADMINISTERED

Code No.		SUSCEPTIBILY			
106001	AFB Flourescent	AMICACIN	R	R	R
106002	Zeihl - Neelsen Stain For AFB	AMPICILLIN	R	R	R
106003	Albert Stain	CARBENICILLIN	R	R	
106004	Crybtosporidium	CEFOPERALONE			
106005	Smear / Gram Stain	CEFOTAXIME	R		
106006	Ear Culture	CEFOXITINE	R		
106007	Methylene Blue Stain	CEFTRIAXONE	R		
106008	Wound Culture	CEFUROXIME			
106009	Cerebrospinal Fluid Culture	CEPHALOTHIN			R
~~106010~~	Culture& Sensitivity	CHLORAMPHENICOL			S
106011	Pus Culture	CLINDAMYCIN			R
106012	Special Culture	CLOXACILLIN			
106013	Nasal Culture	CO. TRIMOXALOLE			
106014	Stool Culture	ERYTHROMYCINE			R
106015	Throat Culture	GENTAMYCIN	R	R	R
106016	Sputum Culture	METHICILLIN			R
106017	Aspirate Or Discharge C	NALIDIXIC ACID			
~~106018~~	Blood For Culture & Sensitivity	NETILMYCIN			
106019	Mycobacteria Culture	NITROFURANTION			
~~106020~~	Anaerobic Culture	PENICILLIN			
~~106021~~	Fungal Smear, Koh Preparation	PIPERACILLIN	R		
106022	Blood Culture For Brucella	SULPHONAMIDE			
106023	Campylobacter / Helisobacter Culture	TOBRAMYCIN			
106024	Diphtheria Culture	VANCOMYCIN			S
106025	Fungal Culture	Imipenem	S	S	
106026	Brucella Clture				
106027	Cholera Culture	Tazocin	R	R	
106028	Urine Culture				
		cefepime	R	R	

ceftazidim R R
~~Ciprofloxacin~~ R R

☐ MICROSCOPIC EXAMINATION

Blood B14
B13

☐ CULTURE RESULT ☐ NO Bacterial Growth
☐ NO ENTEROPATHOGEN ISOLATED

PATHOGENS :

Aerobic bottle
1- Klebsiella spp
Anaerobic bottle
2- Klebsiella spp
3- Enterococcus spp.

21/10/12

Date Reported Reported By

BACTERIOLOGY

Age Room: 55/ 1 Ins.: 3 ...min - required : 07

Wa... arges J.D. Fils

Consultant : .....

Physician : .....

Date Received : .....

Hr Received : .....

Required Information SOURCE / SITE

DIAGNOSIS :

ANTIBIOTIC ~~ADMINISTERED~~

Code No.	
106001	AFB Flourescent
106002	Zeihl - Neelsen Stain For AFB
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106008	Wound Culture
106009	Cerebrospinal Fluid Culture
106010	Culture& Sensitivity
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106013	Nasal Culture
106014	Stool Culture
106015	Throat Culture
106016	Sputum Culture
106017	Aspirate Or Discharge C
106018	Blood For Culture & Sensitivity
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106020	Anaerobic Culture
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106026	Brucella Clture
106027	Cholera Culture
106028	Urine Culture

SUSCEPTIBILY	S	I	R
AMICACIN	R		
AMPICILLIN	R		
CARBENICILLIN	R		
CEFOPERALONE			
CEFOTAXIME	R		
CEFOXITINE	R		
CEFTRIAXONE	R		
CEFUROXIME	R		
CEPHALOTHIN			
CHLORAMPHENICOL			
CLINDAMYCIN			
CLOXACILLIN			
CO. TRIMOXALOLE	R		
ERYTHROMYCINE			
GENTAMYCIN	R		
METHICILLIN			
NALIDIXIC ACID	R		
NETILMYCIN			
NITROFURANTION	R		
PENICILLIN			
PIPERACILLIN	R		
SULPHONAMIDE			
TOBRAMYCIN			
VANCOMYCIN			
Norfloxacin	R		
Tetracyclin	R		
Augmentin	R		

ceftazidim	R
ciprofloxacin	R
Aztreonam	R

Imipenem	S
Tazocin	R
cefepime	R

☐ MICROSCOPIC EXAMINATION

☐ CULTURE RESULT : ☐ NO Bacterial Growth .

☐ NO ENTEROPATHOGEN ISOLATED

PATHOGENS :

Acinetobacter spp.

Bact. count 5 10 lml.

21/6/2003.

Date Reported

Reported By

Consultant : [redacted]

Hr Received :

Required Information	SOURCE / SITE	DIAGNOSIS :	ANTIBIOTIC ADMINISTERED

Code No.		SUSCEPTIBILY	S	I	R
106001	AFB Flourescent	AMICACIN	R		
106002	Zeihl - Neelsen Stain For AFB	AMPICILLIN	R		
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106025	Fungal Culture	Imipenem	R		
106026	Brucella Clture	Tazocin	R		
106027	Cholera Culture	cefepime	R		
~~106028~~	Urine Culture				

Aztreonam R ceftazdim R ciprofloxacin R

☐ MICROSCOPIC EXAMINATION

B urine

☐ CULTURE RESULT ☐ NO Bacterial Growth .

☐ NO ENTEROPATHOGEN ISOLATED

PATHOGENS :

Pseudomonas aeruginosa

Bact count >10⁵/ml

21/12/22

Date Reported

Reported By

Surveillance systems

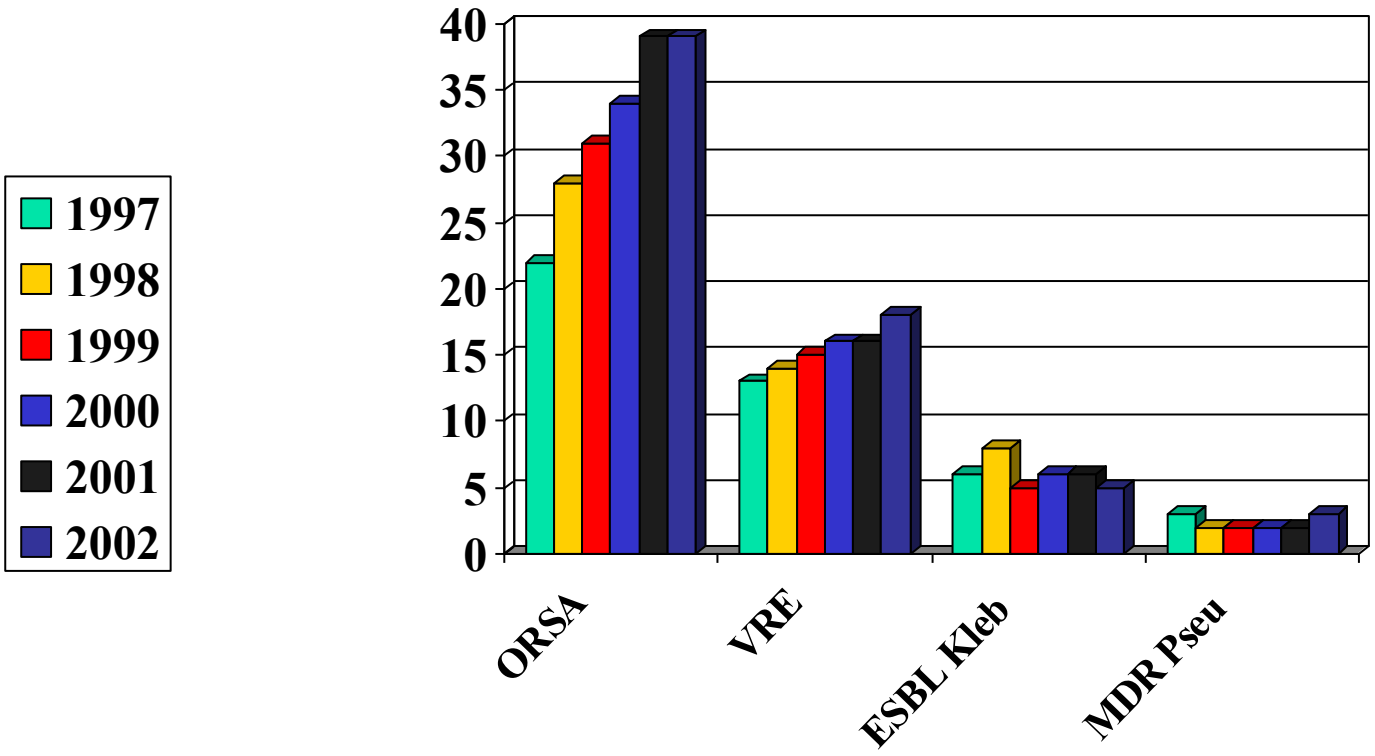
- SENTRY (Longitudinal national and international program)
- EARSS (European Antimicrobial Resistance Surveillance System)
- NNIS (National Nosocomial Infection Surveillance)
- SCOPE (Surveillance and Control of Pathogens of Epidemiologic Importance)
- ICARE (Intensive Care Antimicrobial Resistance epidemiology)

SENTRY 1997-2002

- Blood Stream Infections
- 81,213 isolates
- North America, Europe, Latin America
  - Gram +ve in US vs. Gram –ve in Europe
  - R more common in nosocomial and ICU than community settings

Diagnostic Microb Inf Dis 2004

SENTRY 1997-2002 USA

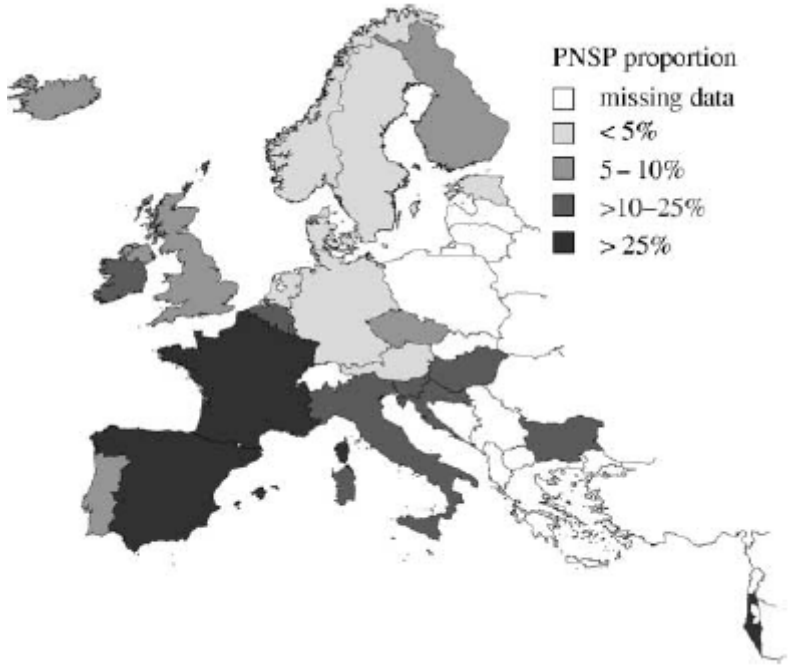


Diagnostic Microb Inf Dis 2004

EARSS Program 1999-2002

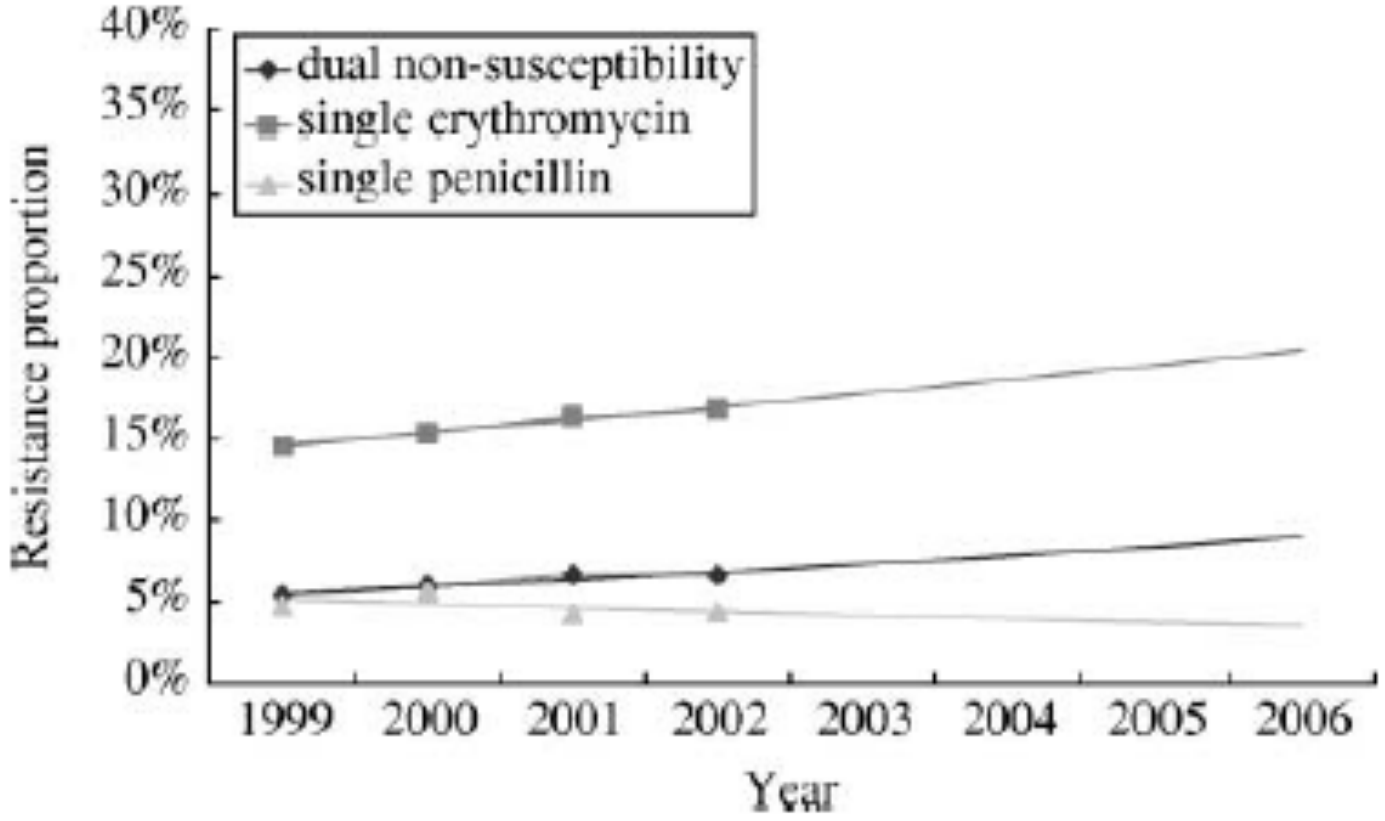
Invasive *S. pneumoniae* resistance trends

- 26 European countries
- 22 277 isolate
- Blood 93%, CSF 7%
- R highest in Mediterranean



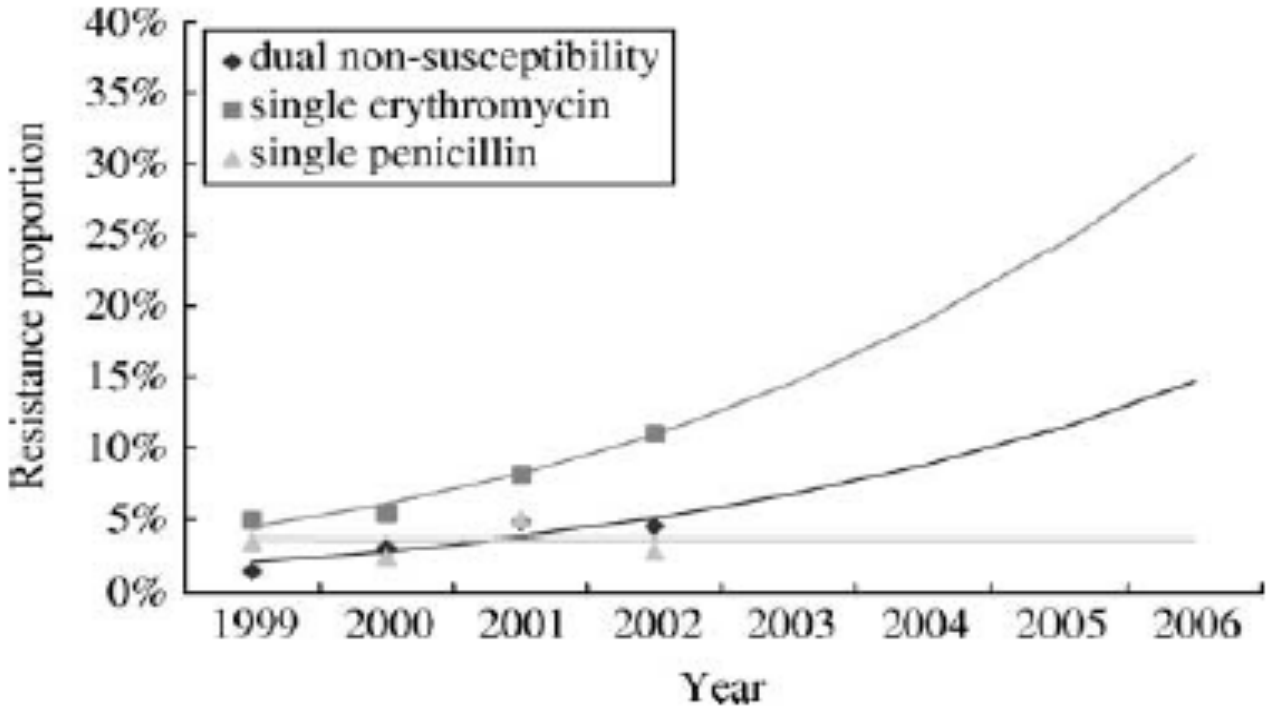
J Antim A Chem Nov. 2004

EARSS Program 1999-2002
Invasive *S. pneumoniae* resistance trends



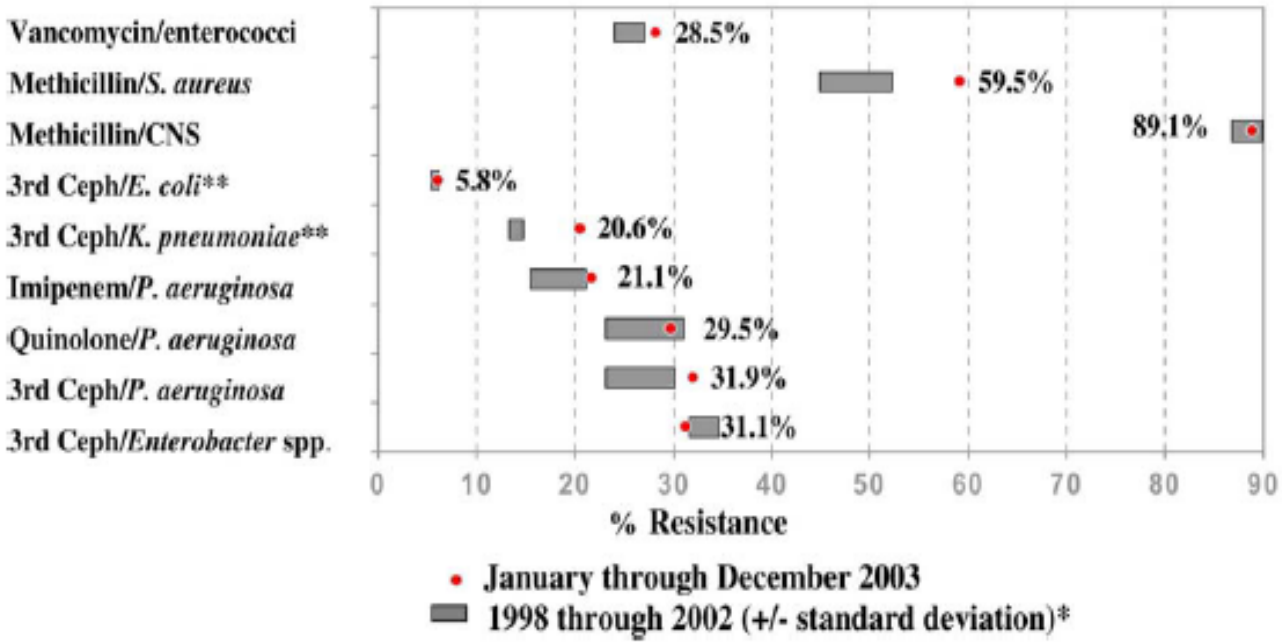
J Antim A Chem Nov. 2004

EARSS Program 1999-2002
Invasive *S. pneumoniae* resistance trends



J Antim A Chem Nov. 2004

NNIS
ICU infections and Resistance
300 hospitals in USA



Jan–Dec 2003 No. of Isolates	% increase in resistance (2003 vs 98-02*)
2048	12%
4100	11%
3336	1%
1355	0%
1068	47%
1392	15%
1825	9%
2119	20%
1411	–6%

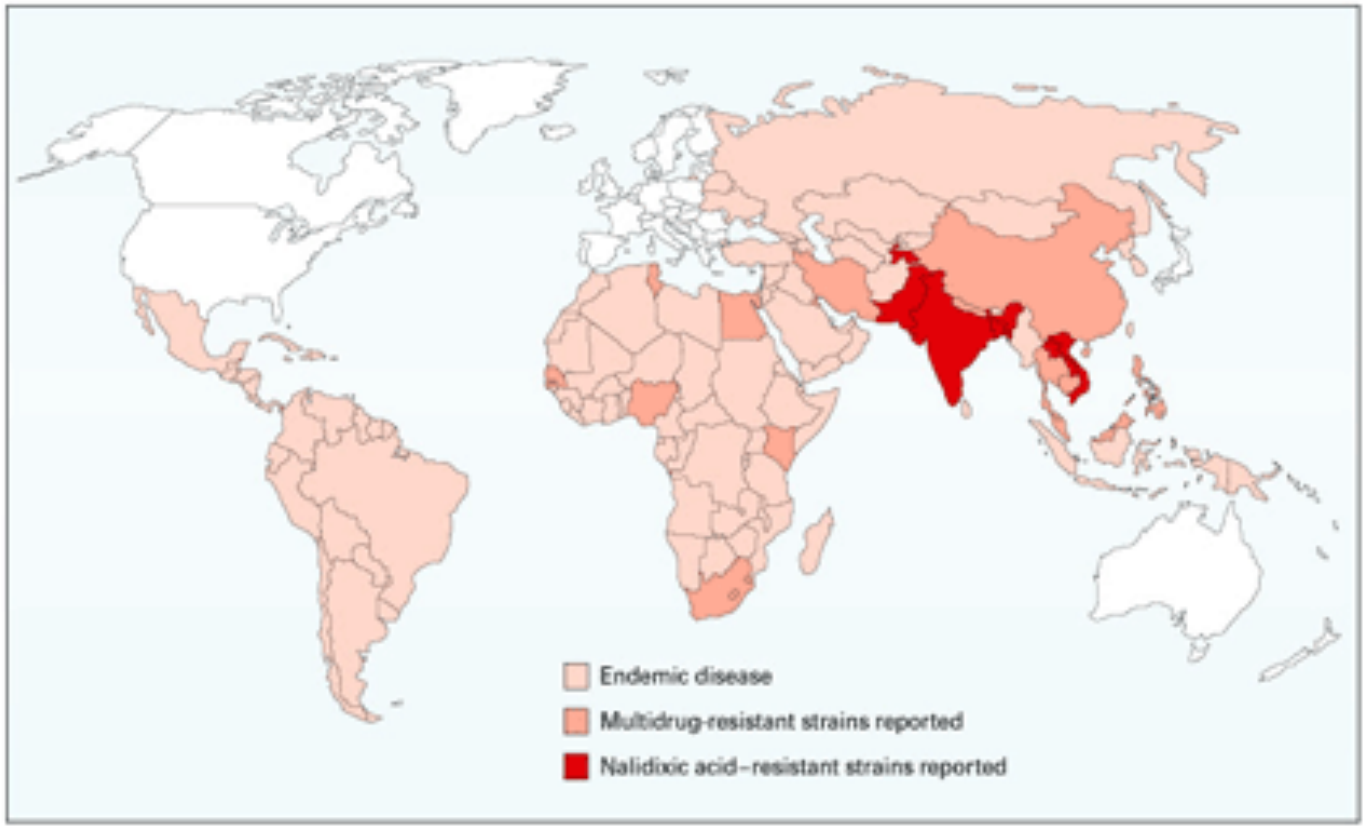
Am J Inf Control Dec 2004

Resistance to Imipenem

Strain	Patient	Ward	Source	Collection date	Previous therapy with	Outcome of hospitalization[a]
VR-143/97	NG	ICU	Pus	1 February 1997	Imi	Death
VR-146/97	GB	ICU	Bronchial aspirate	25 March 1997	Imi	Discharge
VR-155/97	SL	Surgery	Bile	27 March 1997	Czid	Death
VR-158/97	RS	ICU	Bronchial aspirate	9 July 1997	Ctri	Death
VR-170/97	RS	ICU	Bronchial aspirate	31 July 1997	Ctri	Death
VR-174/97	CE	ICU	Blood	11 September 1997	Imi, Czid	Death
VR-186/98	BC	ICU	Bronchial aspirate	5 February 1998	Amox/Clv	Death
VR-193/98	CF	Hematology	Pharyngeal swab	20 February 1998	Czid	Discharge

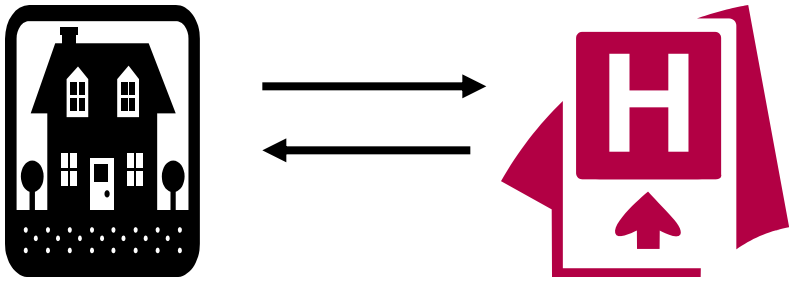
Clin Inf Dis 2000

Resistance to *S typhi*



Common resistant bacteria

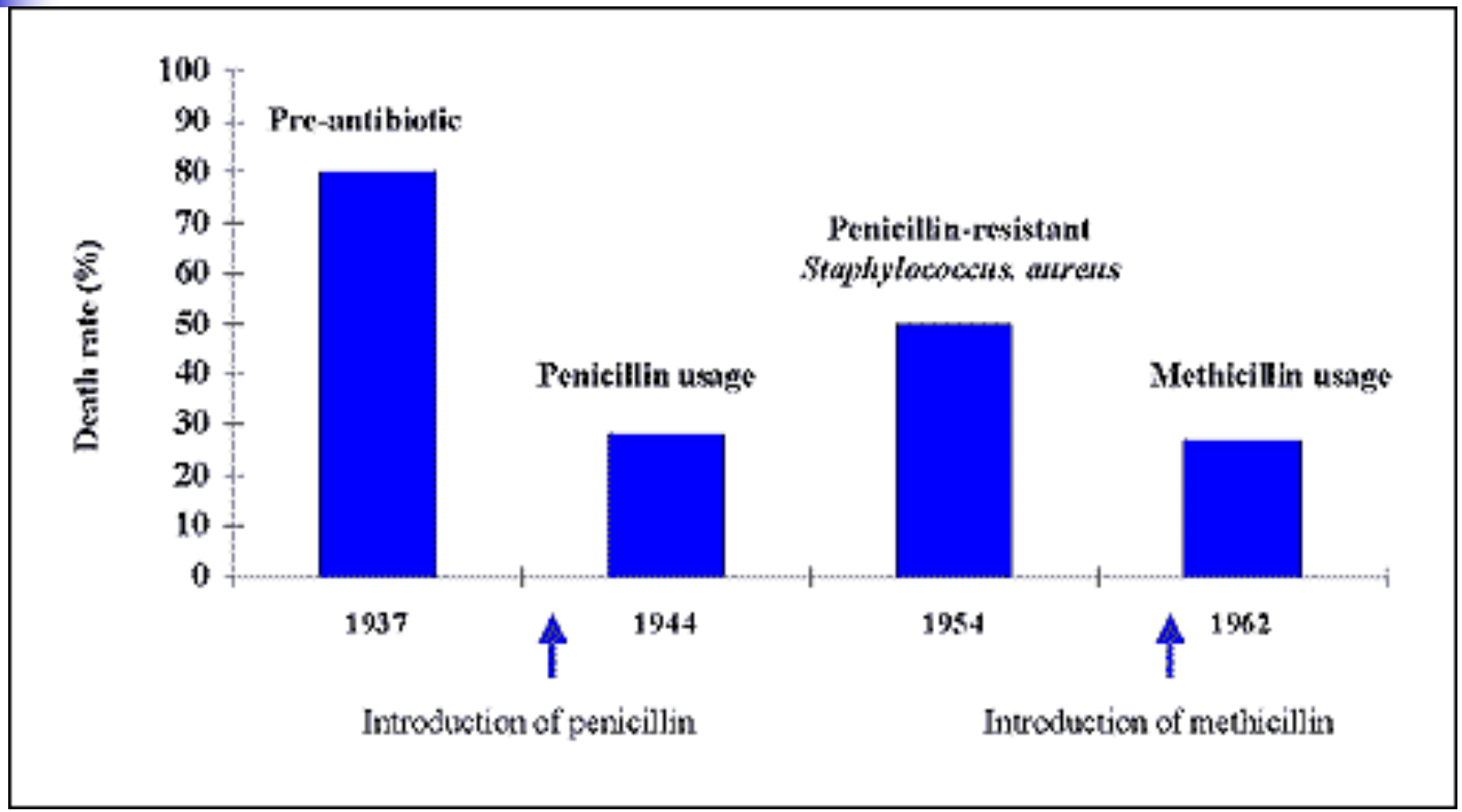
- MRSA
- CoNS
- *VRE*
- *E. coli*
- *P. aeroginosa*
- *Enterobacter* spp
- *S. pneumoniae*
- *Klebsiella* spp
- *Acinetobacter* spp
- *N. gonorrhea*
- *S. typhi*



Costs of resistance

- Double hospital stay
- Double mortality
- Double morbidity
- Higher financial cost
  - $4 billion annually-US
- Change in the ecology and flora

Mortality of *S. aureus* with time



Outcome…

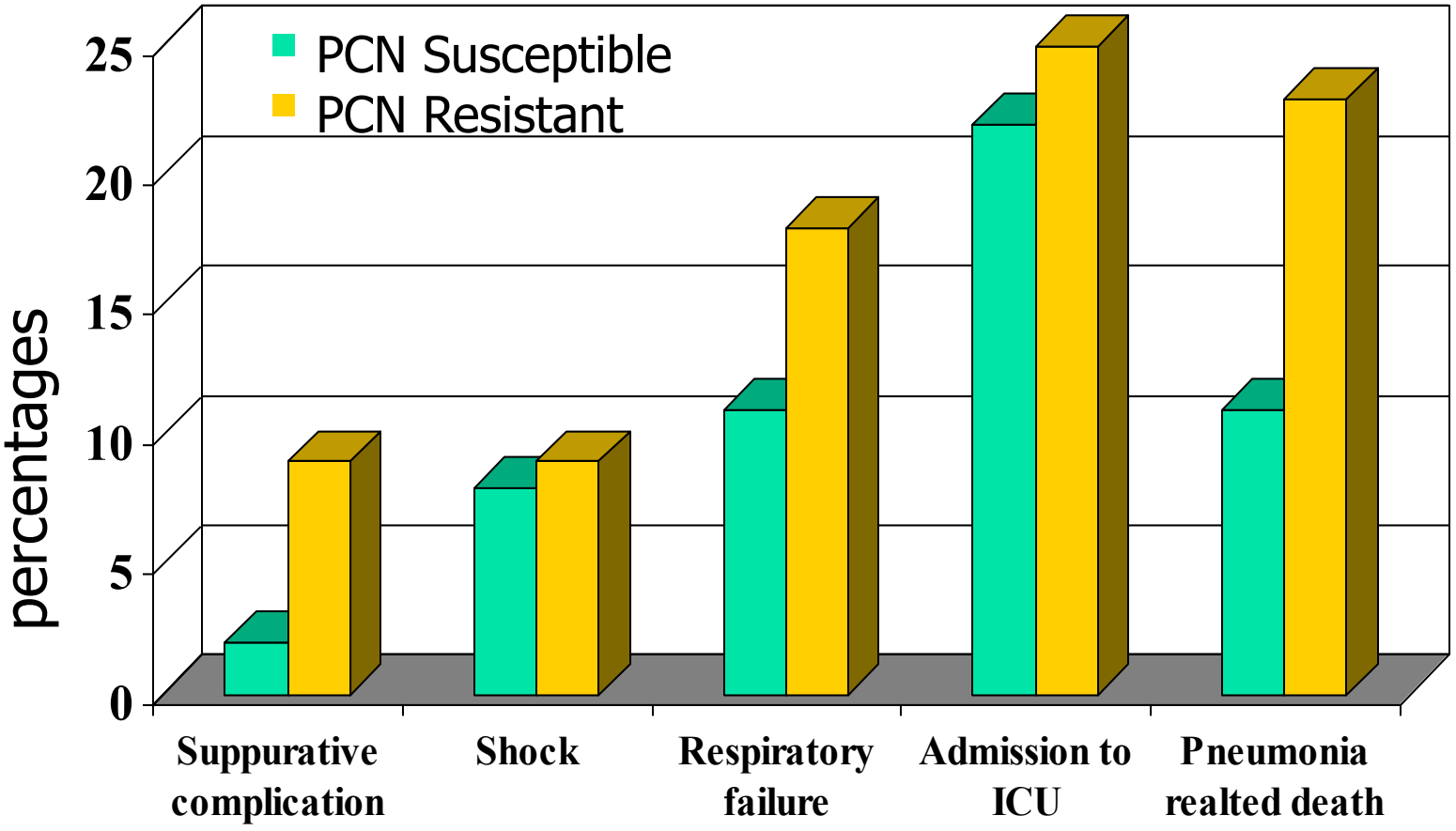
e.g. *Pseudomonas aerugenosa* infection

- 489 patients
- Emergence of R in 6.1%

Outcome	Resistance at baseline (RR)	Emergence of Resistance (RR)
Mortality	1.3	3.0
Length of hospital stay	1.0	1.7

Arch. Int. Med. May, 1999

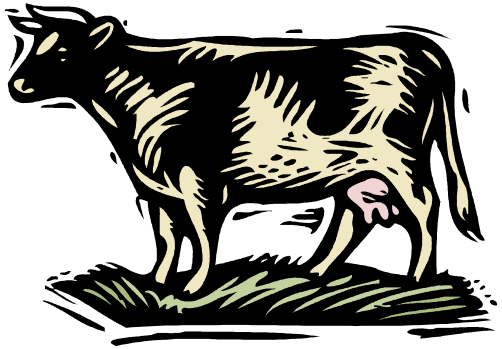
Outcome …
eg. Pneumococcal pneumonia



CID March, 2000

Antimicrobial use in agriculture

- Restricted in Europe
- Allowed in USA
- Source for resistance
- Infects humans
  - Directly
  - Indirectly (food supply)

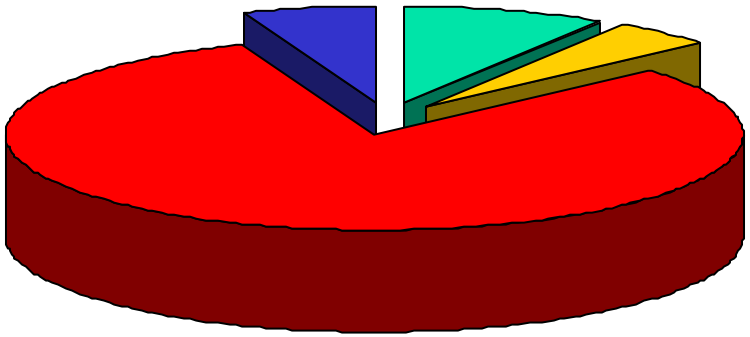


Antimicrobial consumption

Therapeutic (agricultural)
2 million lb

Humans
3 million lb

Creams-soaps-disinfectants
1.5 million lb



Non therapeutic uses
(agricultural)
27.5 million lb

Clin Infect Dis 2000

What to do?

- Surveillance systems
- Isolation
- New therapeutic approaches
  - Improve use of antibiotics
  - Develop new antibiotics
  - Better diagnostics
  - Vaccines

Control

- Restricted hospital formularies
  - Antibiotics with resistance problems
  - The best control measure

eg:

Restricted	**Not restricted**
Imipenem	Piperacillin
Gentamicin	Amikacin
Ciprofloxacin	Quinolones (except Ciprofloxacin)
Ceftazidime	3rd ceph (except ceftazidime)
Ampicillin	Cefepime

Med Clin N. Amer. Nov. 2000

Table 2. Antibacterial Pipeline (Anti–Gram Positive and Anti–Gram Negative), Big Pharma

Company	Since 1998	Phase 2/3
Abbott Laboratories	0	0
AstraZeneca	0	2
Bayer	0	0
GlaxoSmithKline	0	1
Lilly	0	0
Merck/Schering-Plough	1	1
Novartis	0	0
Ortho McNeil/Johnson & Johnson	1	0
Pfizer/Wyeth	2	0
Roche	0	0
Sanofi	0	0

Boucher, CID 2013

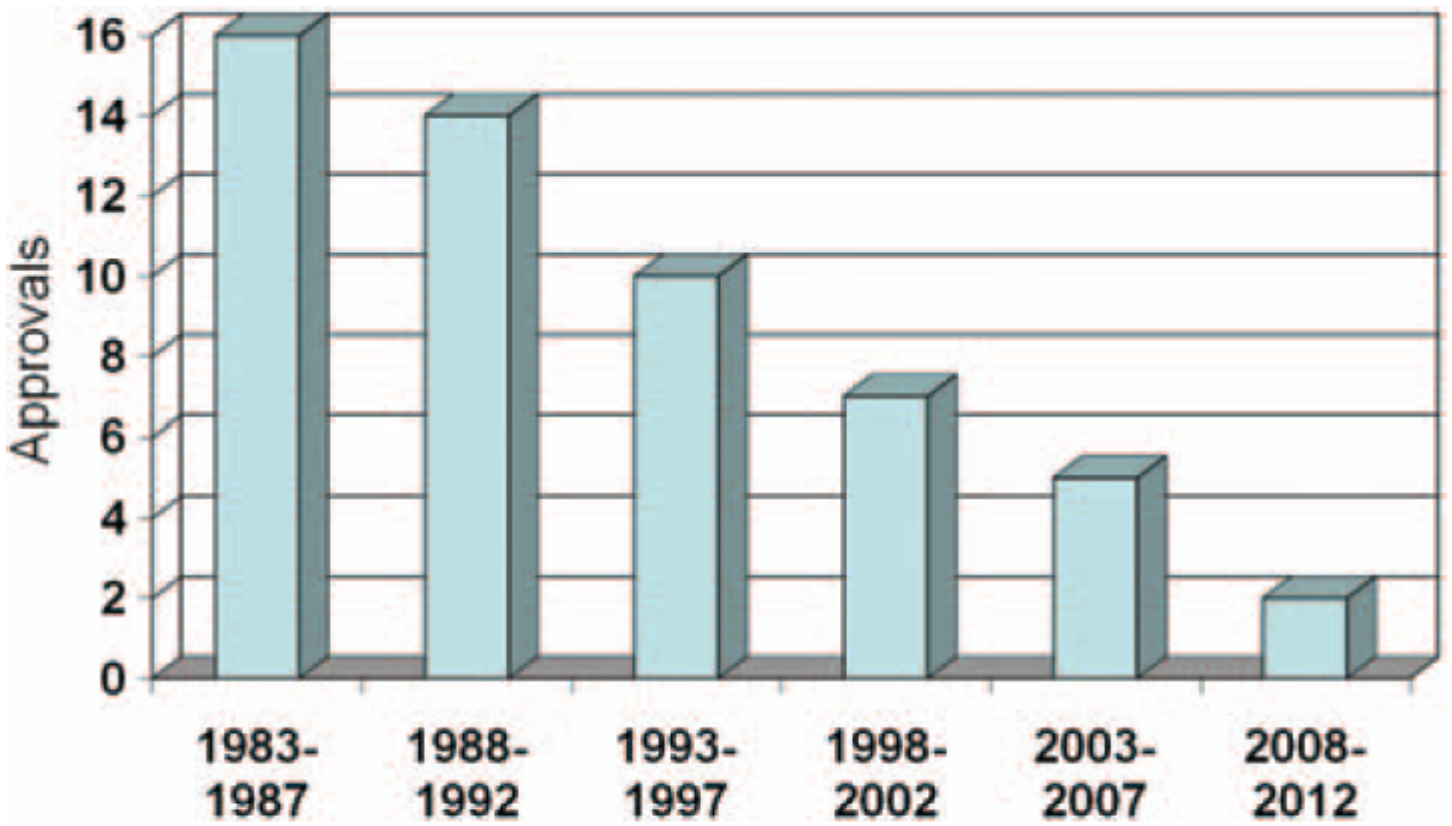
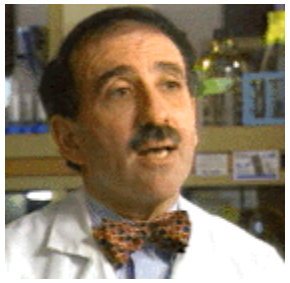


Figure 1. New systemic antibacterial agents approved by the US Food and Drug Administration per 5-year period, through 2012. Modified from Spellberg 2004 [23].

Boucher, CID 2013

Conclusion

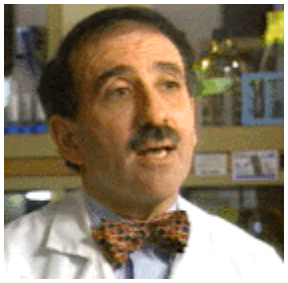


- The highly disease oriented focus of modern medicine has hindered a clear perception of the enormity nature of resistance, which suffers from an “identity crisis”. Resistance is a nameless cloud that looms over otherwise uncontrollable infections, but lacks the powerful status of a readily identifiable disease state to spur large scale efforts of control.

DR. STUART LEVY

Nature medicine, Dec 2004

Conclusion



- I think it's very, very serious. This decade has seen the emergence of bacteria that are resistant to all but one drug or even bacteria that are resistant to every drug. We've never experienced that in the history of antibiotics, …. What it means, I think, is that we're just seeing a beginning and what worries me is that there are few patients suffering from these almost untreatable infections now, that the future will show us many, many more.

DR. STUART LEVY