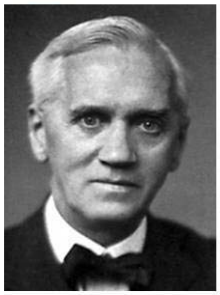
The Nobel Prize
Physiology/Medicine 1945

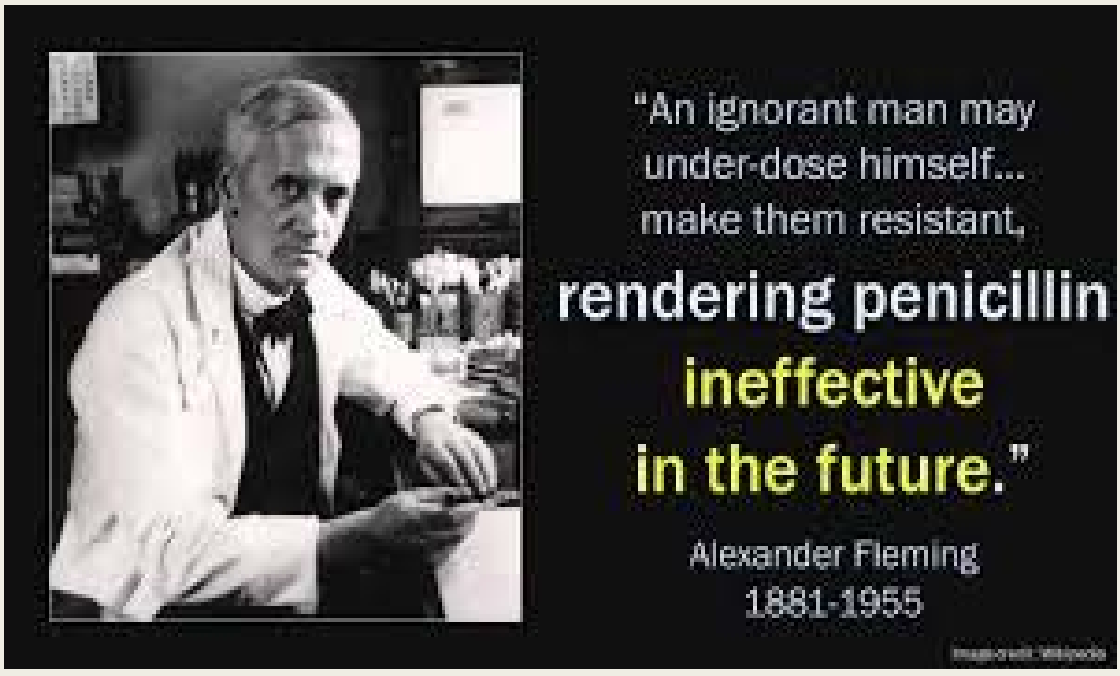


Sir Alexander Fleming
1881 - 1955

Sir Howard Walter Florey
1898 - 1968

Ernst Boris Chain
1906 - 1979

Alexander Fleming discovered the antimicrobial properties of penicillin in 1928. Twelve years later, Howard Florey and Ernst Chain developed the processes to produce penicillin in sufficient quantity for it to become widely available



1958: first pandemic of Pen–Res staphylococci

1959 development of Meticilline against Penicilline resistente Stafylococcen

first epidemics MRSA: 1965

1965: Kopenhagen 25% of Staphylococci MRSA

1965: Zurich 25% MRSA

However both in Zurich as in Kopenhagen after 5 years the percentage dropped to less than 5% Why?

First epidemic MRSA UMCUtrecht 1984,1987 (we developed protocols which are used world wide)

Martinair Crash in 1992 (Faro) determining factor for protocols

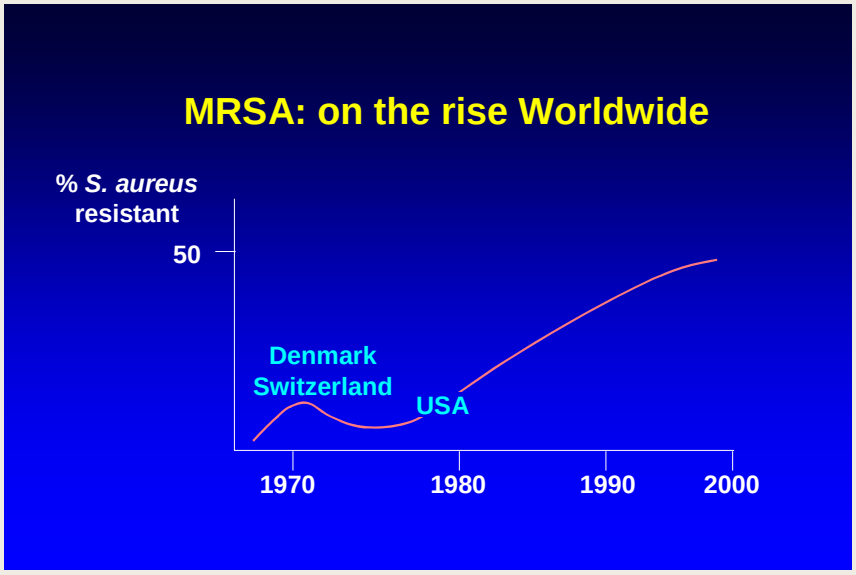
Colonization of Dutch crash victims after stay in a Portuguese hospital

No., victims	no. of days in hospital	MRSA positive
5	1	2
7	2 - 5	4
12	5 - 14	5

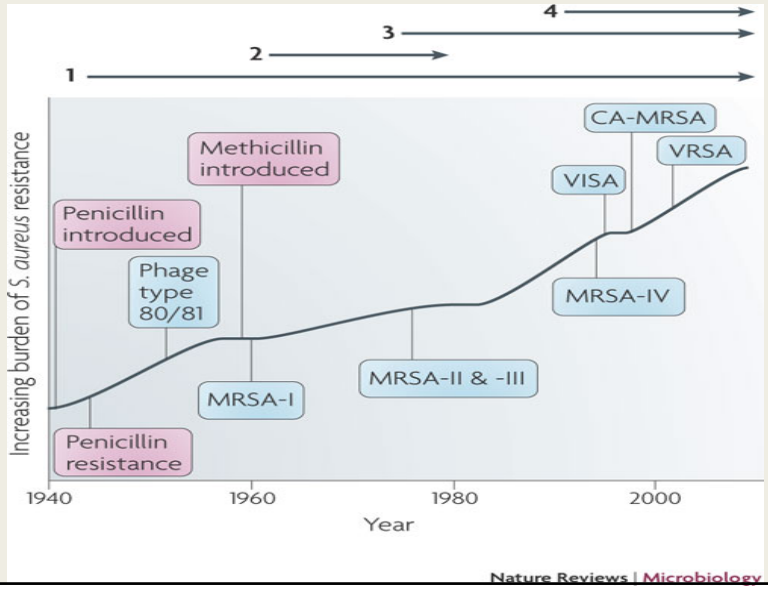
Hospitals with MRSA

Protocol Basics:

- Ward with MRSA is closed
- Patient isolated
- Search and destroy
- Staff with MRSA is send home (not allowed to work)
- Patients from a hospital abroad first in Isolation



VISA, Vancomycine Resistente MRSA (!)
The history of resistant S.aureus



DNA transfer among Staphylococci in a neonate

S. aureus methicillin susceptible

+

S. epidermidis methicillin resistant

S. aureus methicillin resistant (MRSA)

(Wielders *et al*. Lancet 2001)

Conclusion:

Staphylococcus aureus: cause of wound infections, severe life-threatening infections: lungs, osteomyelitis,post-surgery infections.

1940	**uniformly penicillin susceptible**
1960	**90% penicillin resistant**
1990	**50% methicillin resistant (MRSA)**

However MRSA at the farm (> 50% ?) "One health"

- MRSA cattle variant from cattle to farmer. However the cattle variant is less virulent
- This needs to be studied

1968
As a 23 jarige student I visited Colindale (Central Public Health (London)

Dr Anderson told me of resistent Salmonella in farmers and their cows

"One Health" concept not new

Resistance is indeed not a new phenomenon

THE LANCET

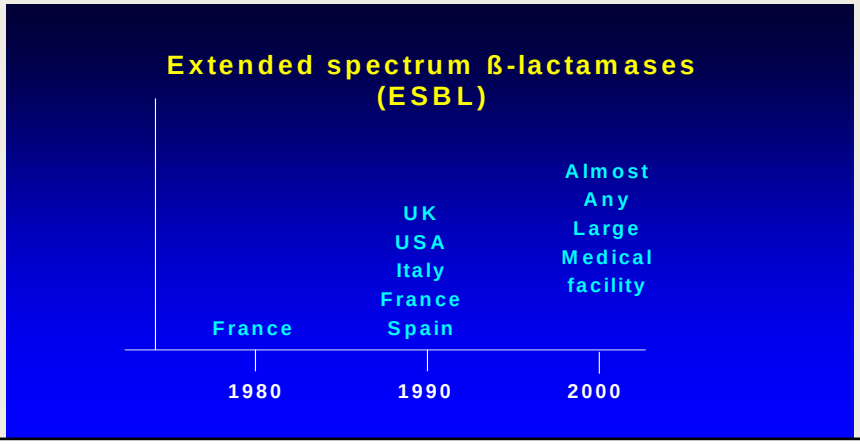
1970: Infections due to Klebsiella resistant to all available agents

"CONTROL OF INFECTION DUE TO KLEBSIELLA AEROGENES IN A NEUROSURGICAL UNIT BY WITHDRAWAL OF ALL ANTIBIOTICS"

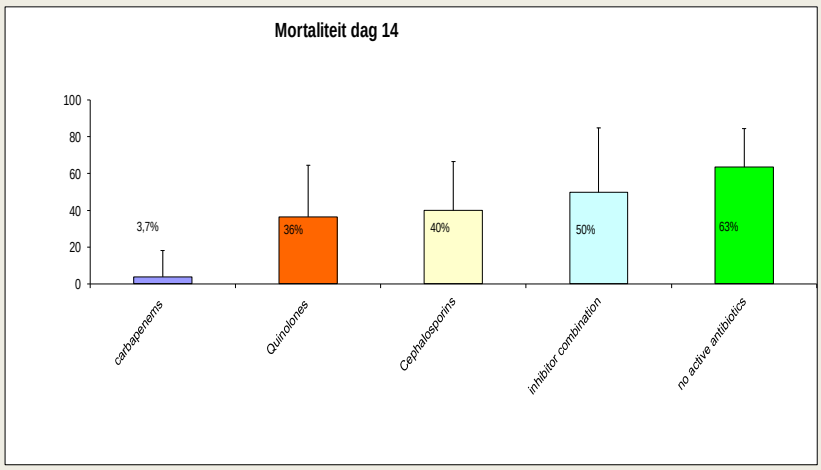
December **1970**, Pages 1213-1215 !

Resistance problem from 1960-1990 manageable; (almost every year a new antibiotic licenced)

From MRSA to the Gram negatives



Carbapenem first choice in invasive ESBL bacteremia



Paterson et al., CID, 2004

Carbapenem last resort: however the superbug is becoming resistant against Carpapenems

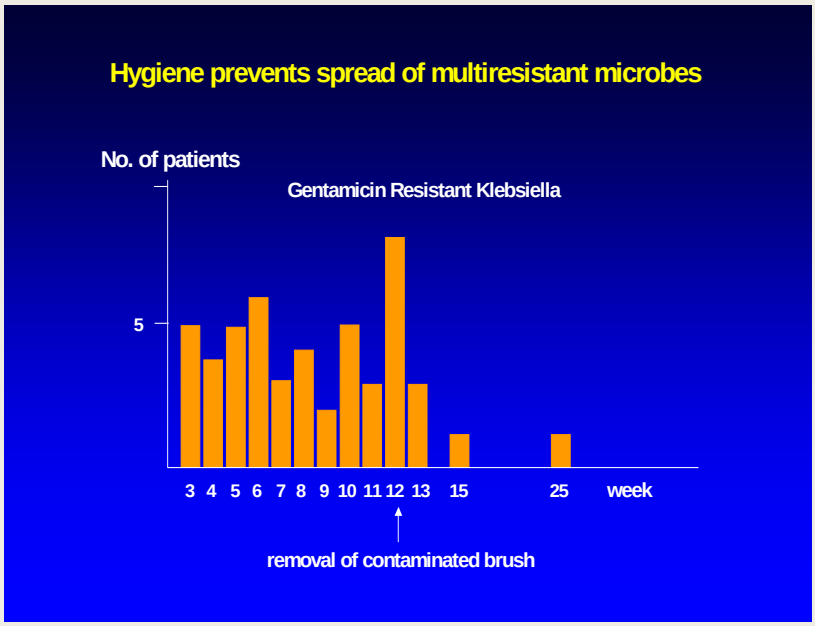
Import of ESBLs after visit abroad

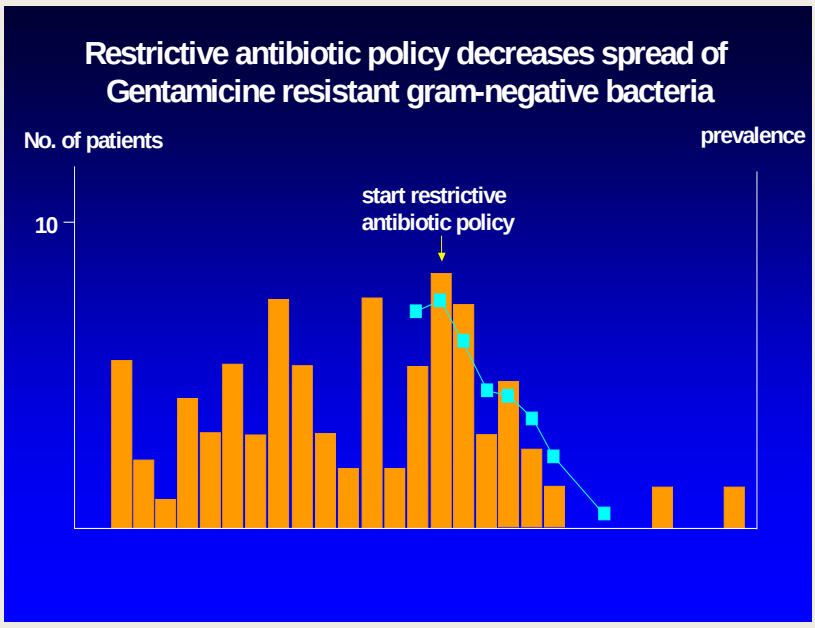
Continent or region	No. of travelers	No. (%) of travelers positive for ESBL-producing isolates
Africa	25	1 (4)
Asia (India excluded)	31	10 (32)
Central America	6	0 (0)
India	8	7 (88)
Middle East	14	4 (29)
North America	2	0 (0)
South America	1	0 (0)
Southern Europe	16	2 (13)

Asia including India: 46%

Tangden et al. AAC 2010

54% CTX-M-15


Hygiene prevents spread of multiresistant microbes
No. of patients
Gentamicin Resistant Klebsiella
5
3 4 5 6 7 8 9 10 11 12 13 15 25 week
removal of contaminated brush


Restrictive antibiotic policy decreases spread of
Gentamicine resistant gram-negative bacteria
No. of patients
prevalence
10
start restrictive
antibiotic policy

Epidemics are very expensive:

- Prevention: Hygiene extremely important
- Proper (restricted) use of antimicrobials
- Rapid diagnostics would lead to proper use of antibiotics
- A need for new antibiotics
- A new business modell for these new antibiotics
- “One Health” and the environment

New Business model for new antibiotics

- New antibiotics will be used as last resort; only when bacteria are very resistant
- Limited use of new antibiotics does not lower the ambition of teh Pharma industry to develope new antibiotics

Limitations of rapid diagnostics

- Many samples from patients carry more than one species of bacteria
- Which bacteria in the sample is the pathogen
- A resistant gene can be detected on the spot from a patient's sample
- However, how do we know that the resistance gene comes from the genome of the pathogen