Mr Ben Harris

Medical Laboratory Scientist

Honorary Lecturer, University of Otago

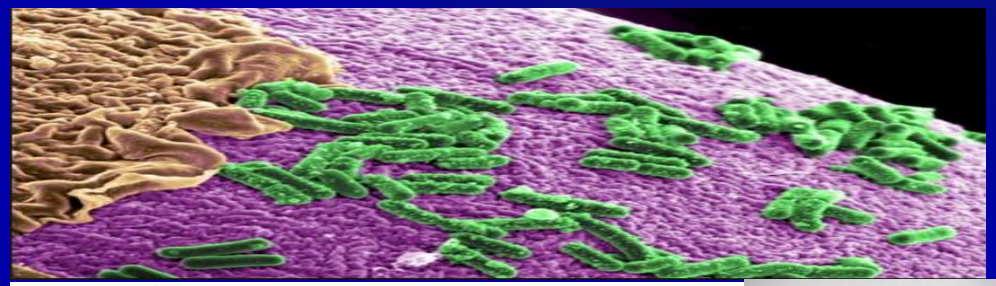
Saturday, August 13, 2016

(Room 11)

9:30 - 10:00 Antibiotic Resistance

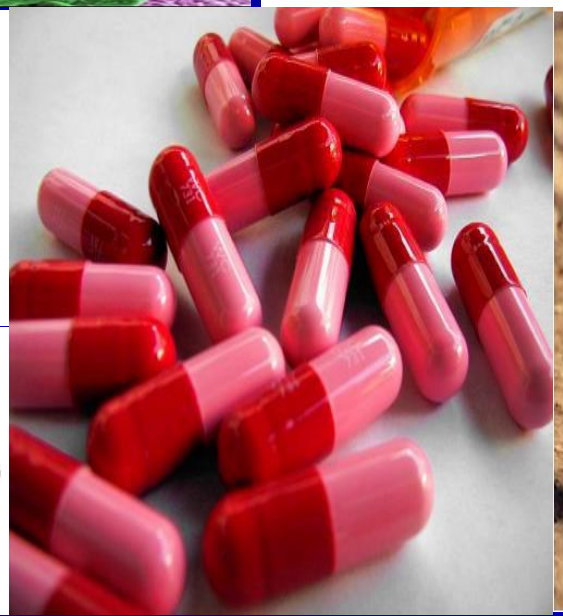
Antibiotic Resistance
Mutations or Creations?

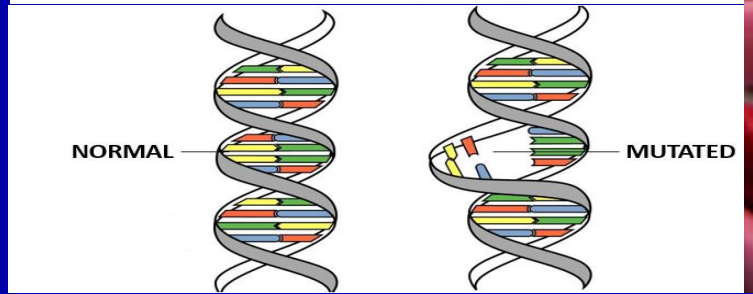
Ben Harris Med Lab Scientist Infection Prevention & Control

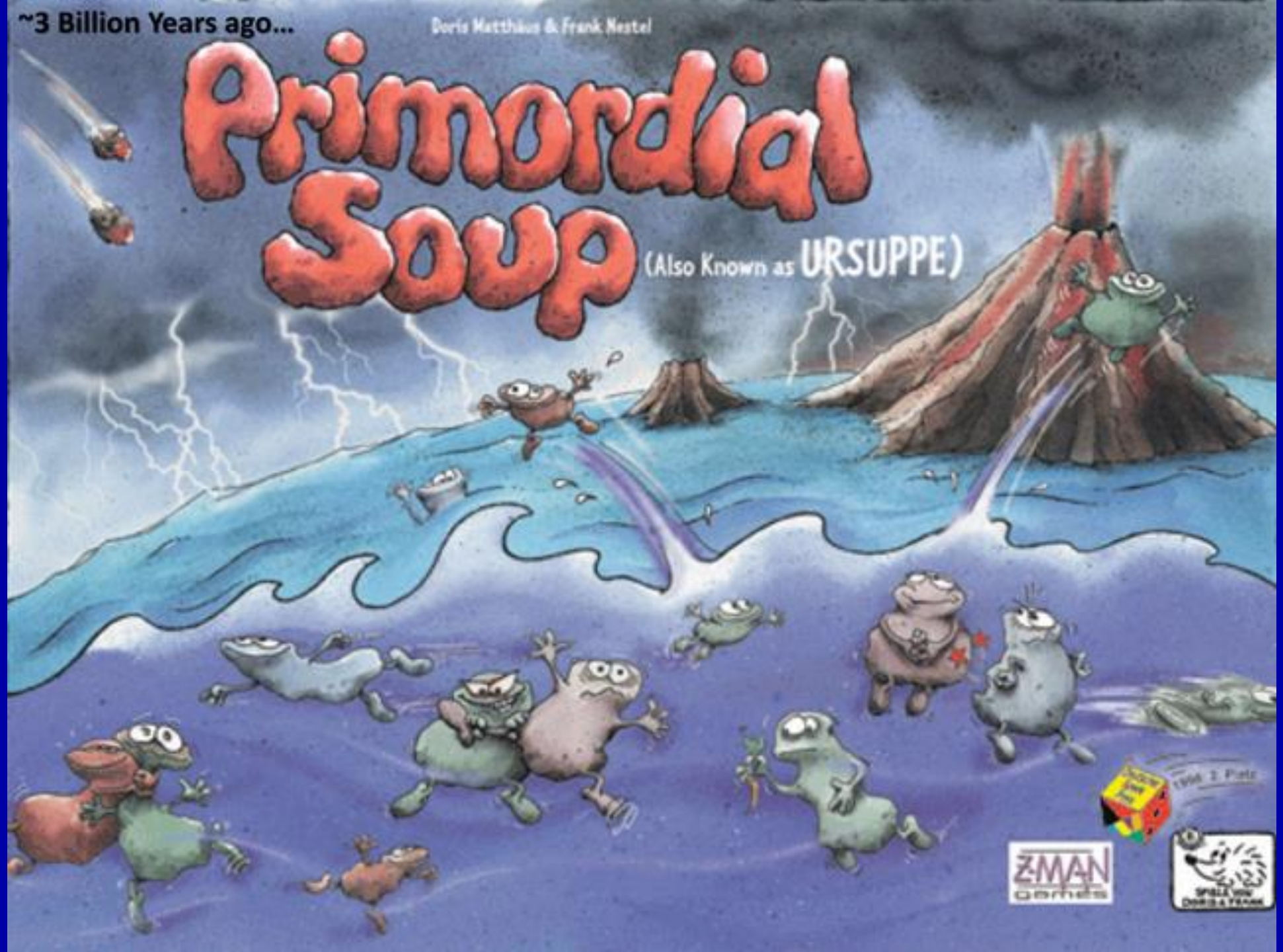


The Microbe is Nothing

The Terrain is Everything






~3 Billion Years ago...
Doris Matthäus & Frank Nestel
Primordial Soup
(Also Known as URSUPPE)
ZMAN games

Important Dates

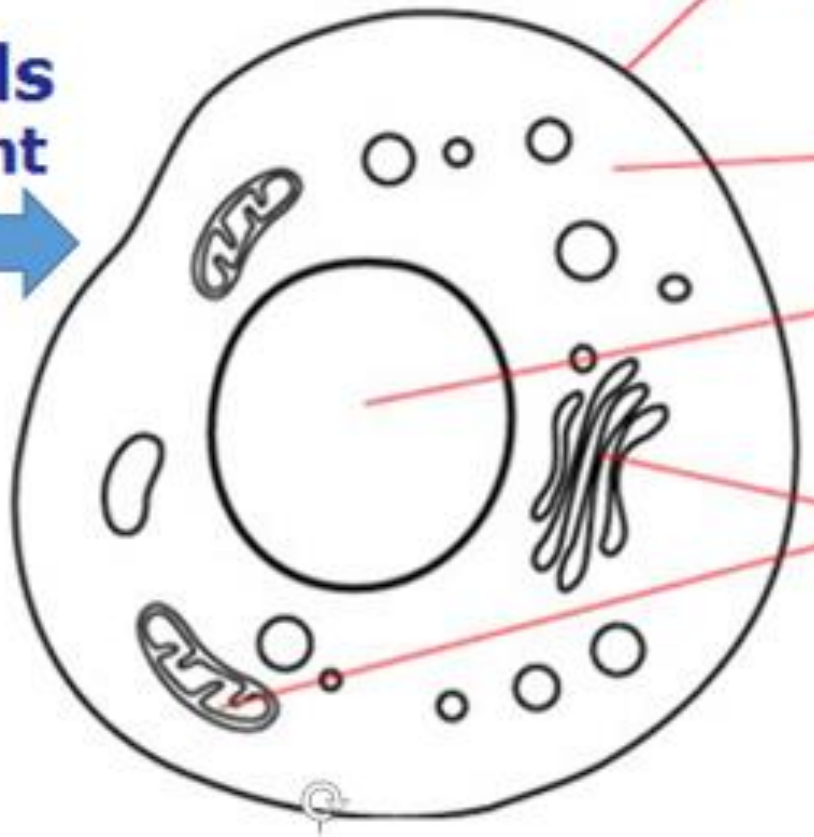
Years Ago	
• 4.5 Billion	Origin of the Earth
• 3.5 Billion	Prokaryote Bacteria
• 2.5 Billion	Oxygen in Atmosphere
• 1.5 Billion	Eukaryote cells with nucleus (animal, plant cell precursors)
• 0.5 Billion	Cambrian explosion multicelleular Eukaryote organisms, plants & animals

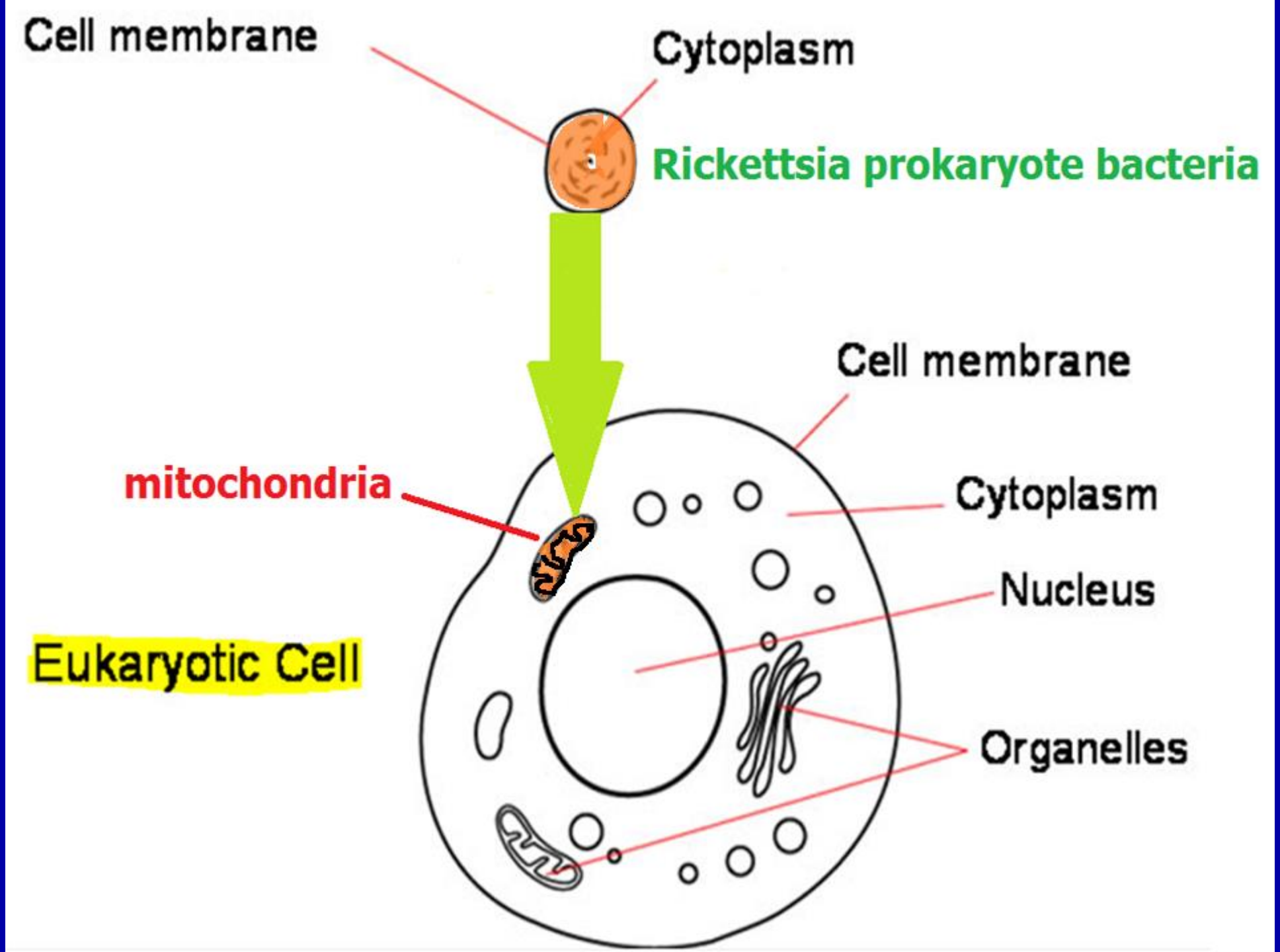
Cell membrane

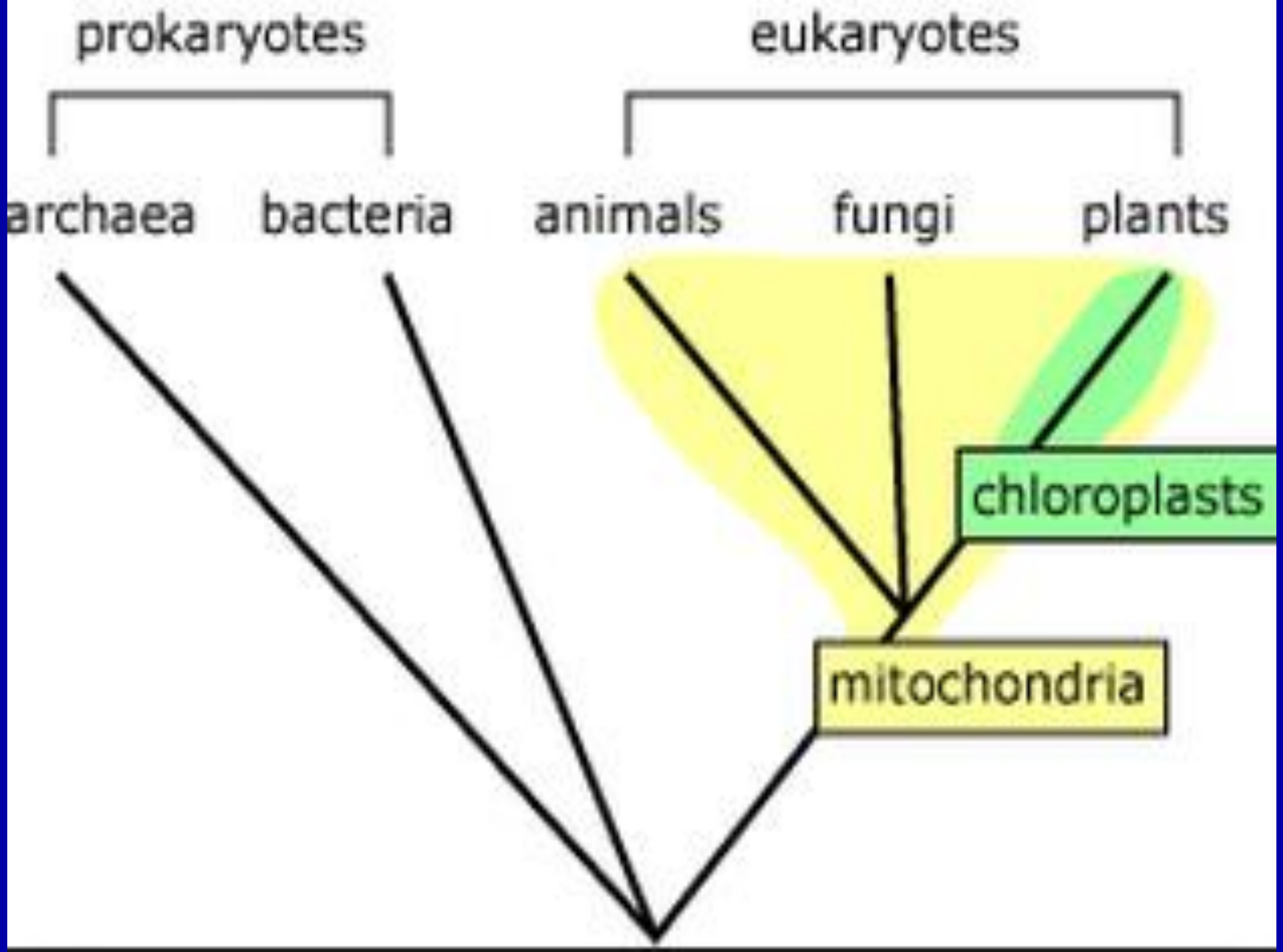
Cytoplasm

Prokaryote Cells
e.g. bacteria

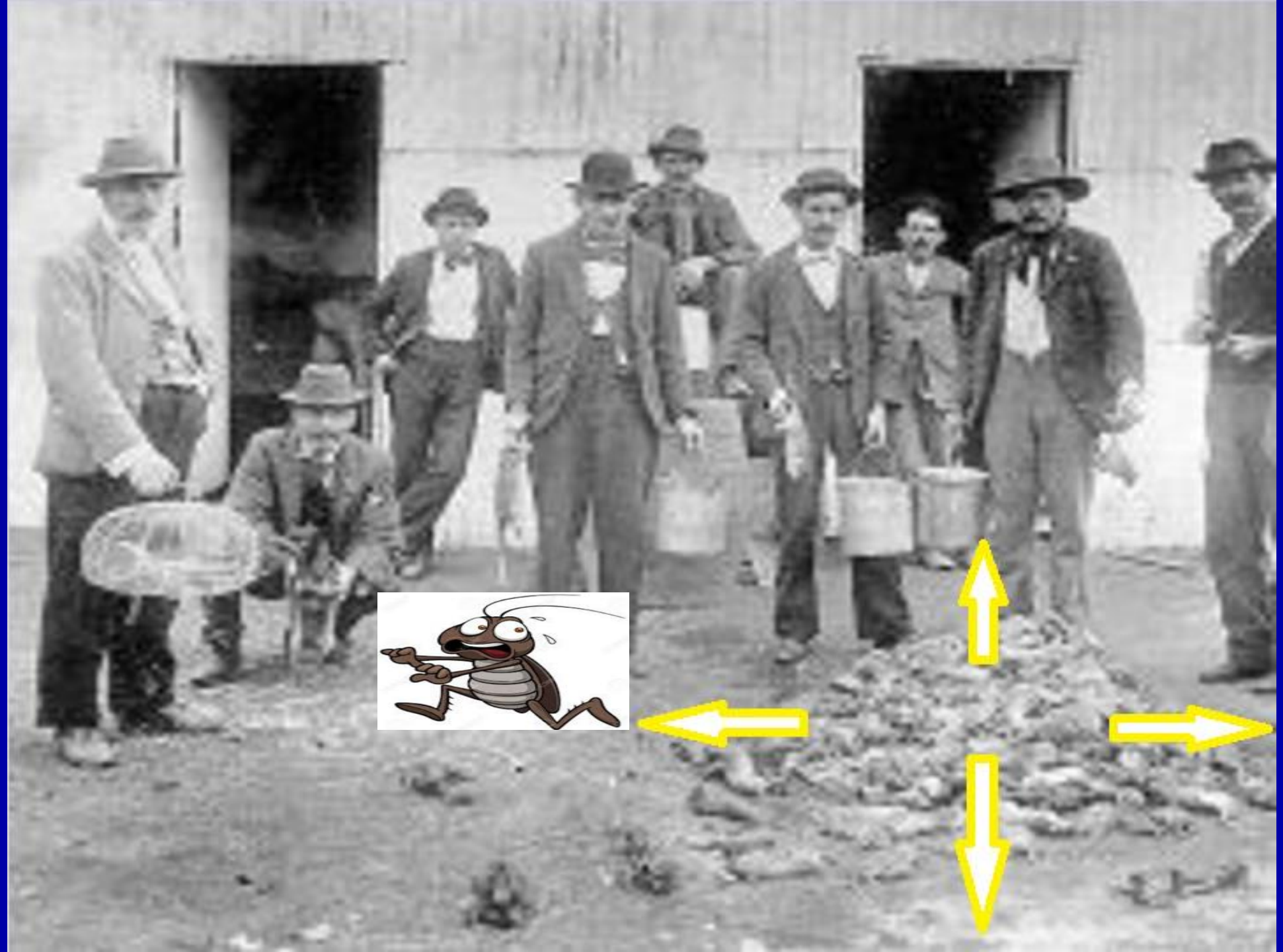
Eukaryote Cells
e.g. animal, plant




Cell membrane
Cytoplasm
Rickettsia prokaryote bacteria
Cell membrane
mitochondria
Cytoplasm
Nucleus
Eukaryotic Cell
Organelles


prokaryotes
eukaryotes
archaea
bacteria
animals
fungi
plants
chloroplasts
mitochondria


Wandern, ach wandern,
weit in die Fern',
Wandern, ach wandern,
thu' ich so gern.
Rastlos durcheilen Thäler
und Höh'n,
Welt, ach so weit,
wie bist Du so schön.
Mir ward keine Liebe,
kein heimathlich Land.
Stets weiter nur eilen,
von Niemand gekannt.
Die Sorgen und Grillen,
die kannte ich nie,
Sang und Spiel scheuchten
spät sie und früh.
Ein fahrender Sänger,
von Niemand gekannt
Ein Rattenfänger,
Das ist mein Stand.
Sch. & S.H.
AM DAGE JOHANNI ET PAULI.
Gruss aus Hameln
den 13 Juni 1902



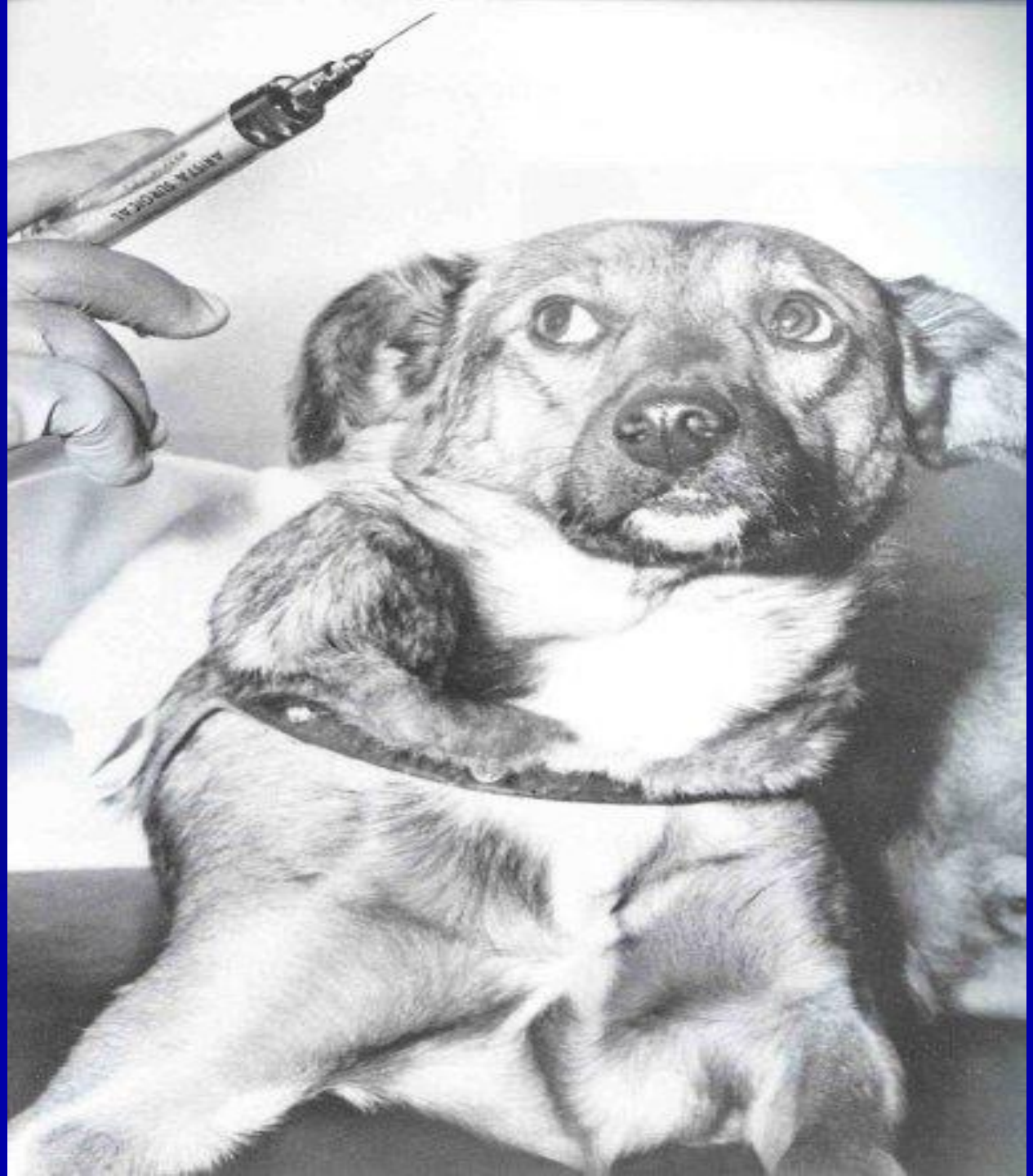
Human Infections (1)

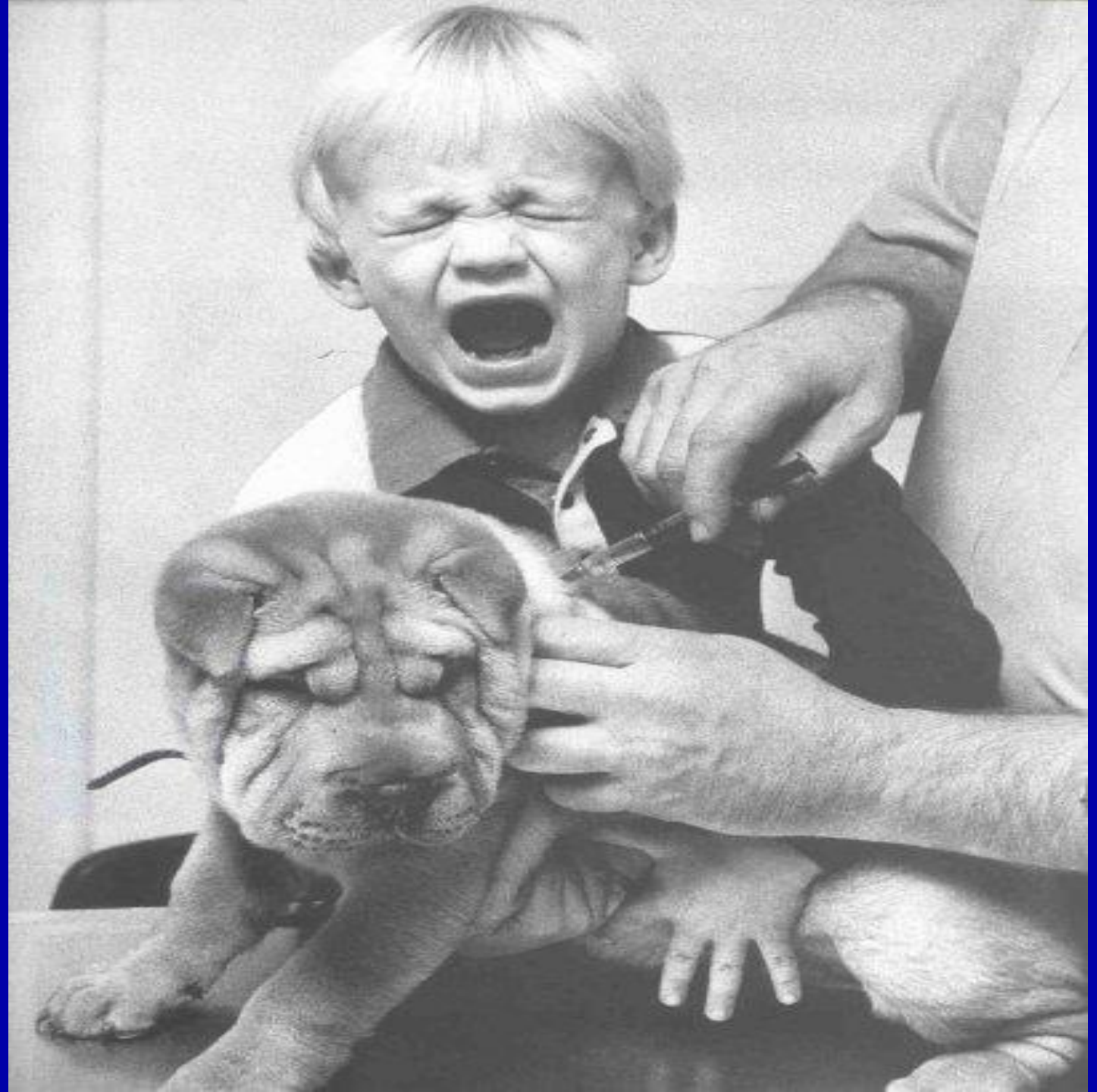
Used to be mainly epidemics:

Smallpox, plague, cholera, diphtheria, TB, syphilis, influenza, measles, etc

i.e. exogenous source

Public Health, Sanitation, Vaccinations
have largely contained or eliminated these



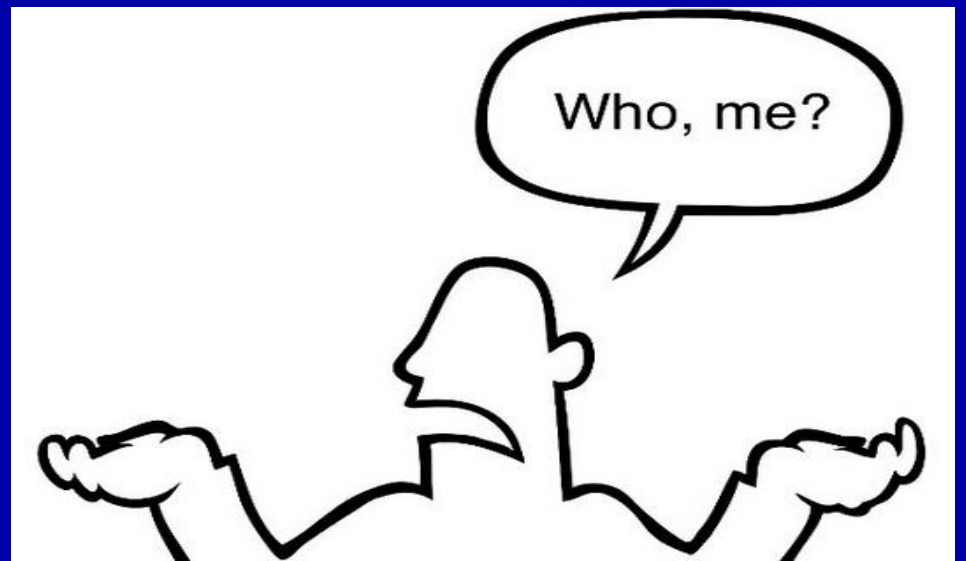


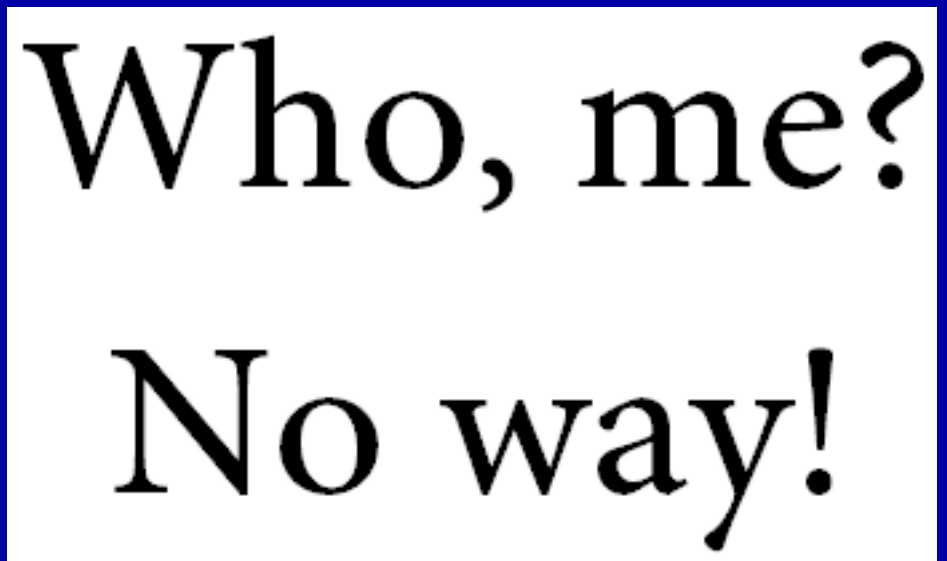
Human Infections (2)

Now mainly

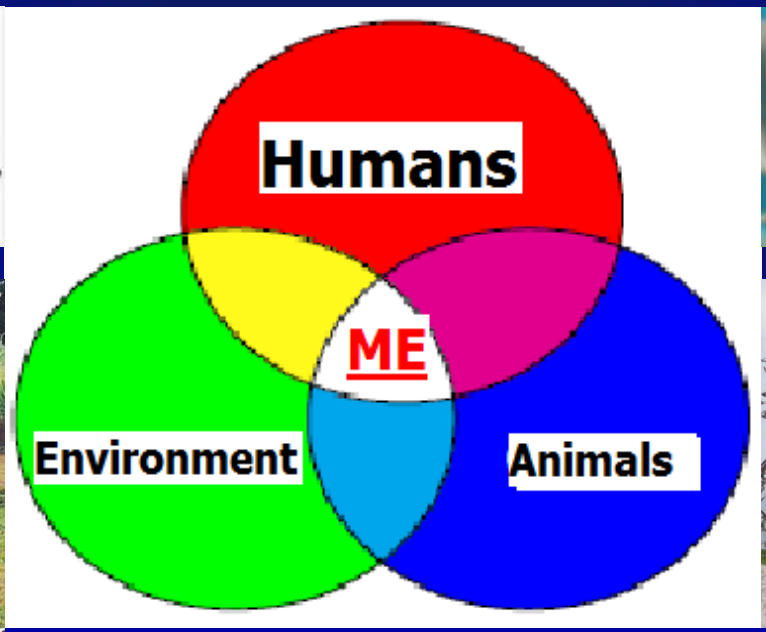
Emerge from our own microbio me

i.e. endogenous source





Sharing my microbiome



This vast microbiome is routinely shared with others + animals and environment

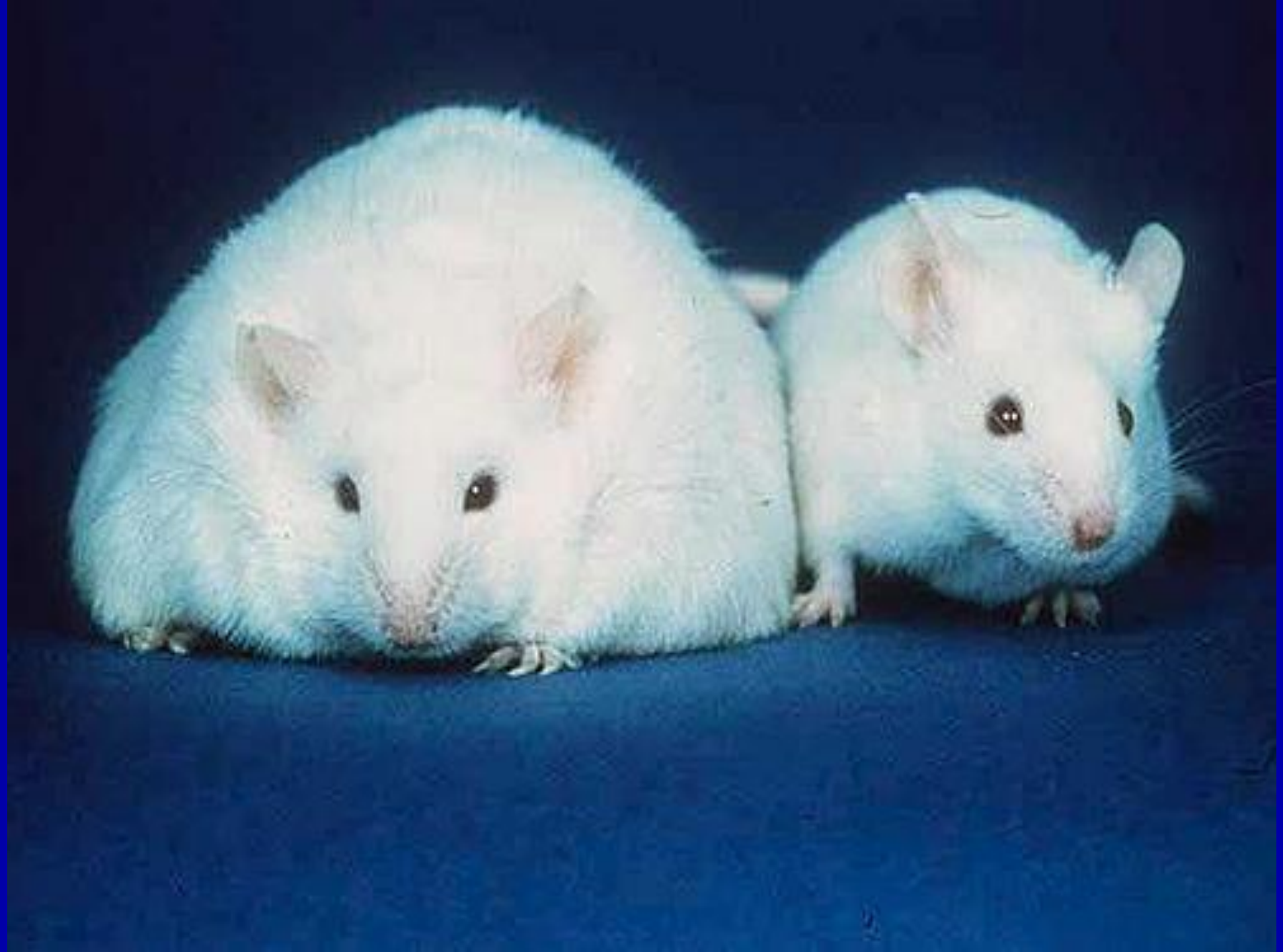
Our Microbial Garden

Emerging realisation of importance of resident microbes to our health and well-being

especially roles played in:

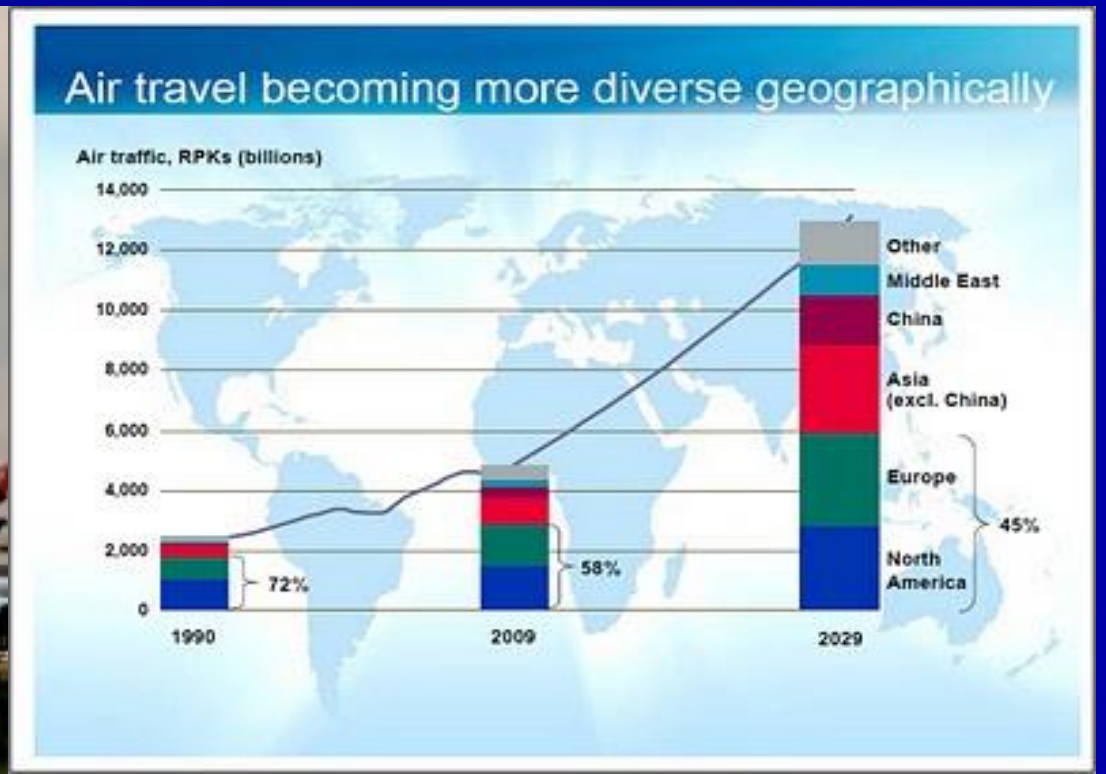
- our immune system
- contributing to food digestion
- acting as first line of defense against pathogens

Many diseases are the result of disturbed microbiomes



Global Reality Trend

Global travel people, food, animals, insects promotes rapid spread pathogenic bacteria & viruses + our shared microbiome



World Infection Trends (1)
"All Microbes are Bad"

'Old' diseases return or increase

from endemic areas

e.g. malaria, measles, dengue,
foodborne illnesses

World Infection Trends (2)
"All Microbes are Bad"

'New' diseases keep emerging

e.g. HIV/AIDS, SARS,
MERS, Ebola, Zika

H5N1 (bird flu), H7, H9

2009 H1N1 (swine)

World Infection Trends (3)

Antibiotic Use Creates These:

New forms of old diseases - endogenous

MDRO's including

- MRSA
- ESBL
- VRE
- *C. difficile*
- CRE carbapenemases

- *From our own shared microbiome*

World Infection Trends Summary

Today's emerging infectious diseases become

tomorrows endemics

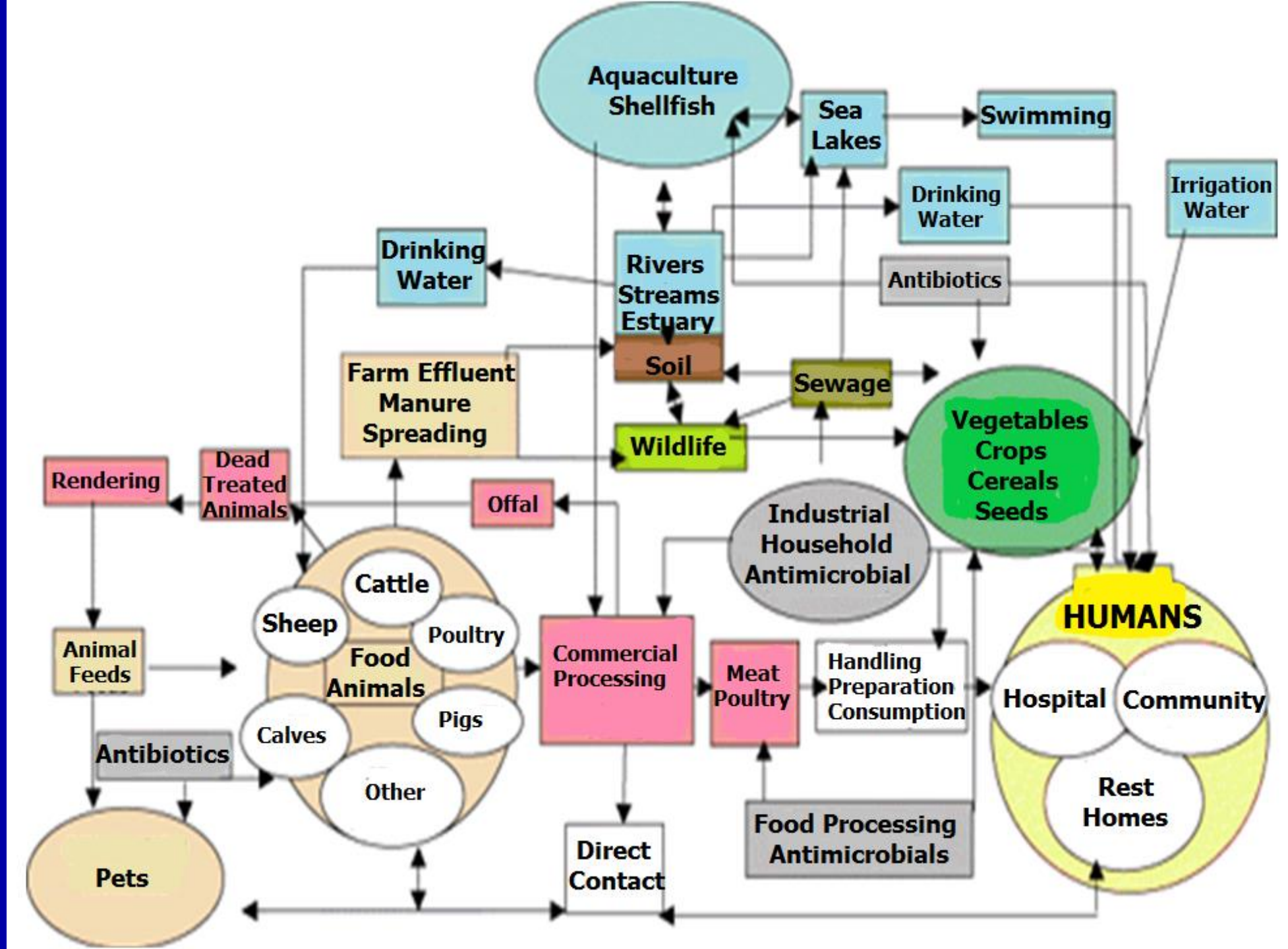

SCIENCE PHOTO LIBRARY

"…. the microbes are educated to resist penicillin …
the thoughtless person playing with penicillin is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism

I hope this evil can be averted "

-Sir Alexander Fleming, June 1945

Antibiotic Resistance Sharing


Aquaculture Shellfish
Sea Lakes
Swimming
Drinking Water
Irrigation Water
Drinking Water
Rivers Streams Estuary
Antibiotics
Soil
Sewage
Farm Effluent Manure Spreading
Wildlife
Vegetables Crops Cereals Seeds
Rendering
Dead Treated Animals
Offal
Industrial Household Antimicrobial
HUMANS
Cattle
Sheep
Poultry
Food Animals
Pigs
Calves
Other
Animal Feeds
Commercial Processing
Meat Poultry
Handling Preparation Consumption
Hospital
Community
Rest Homes
Antibiotics
Food Processing Antimicrobials
Pets
Direct Contact

Aust & NZ
Non Human Antibiotic Use

Aust

- **500 tons** for animal production (in1999)
- 300 tons human therapeutic

NZ

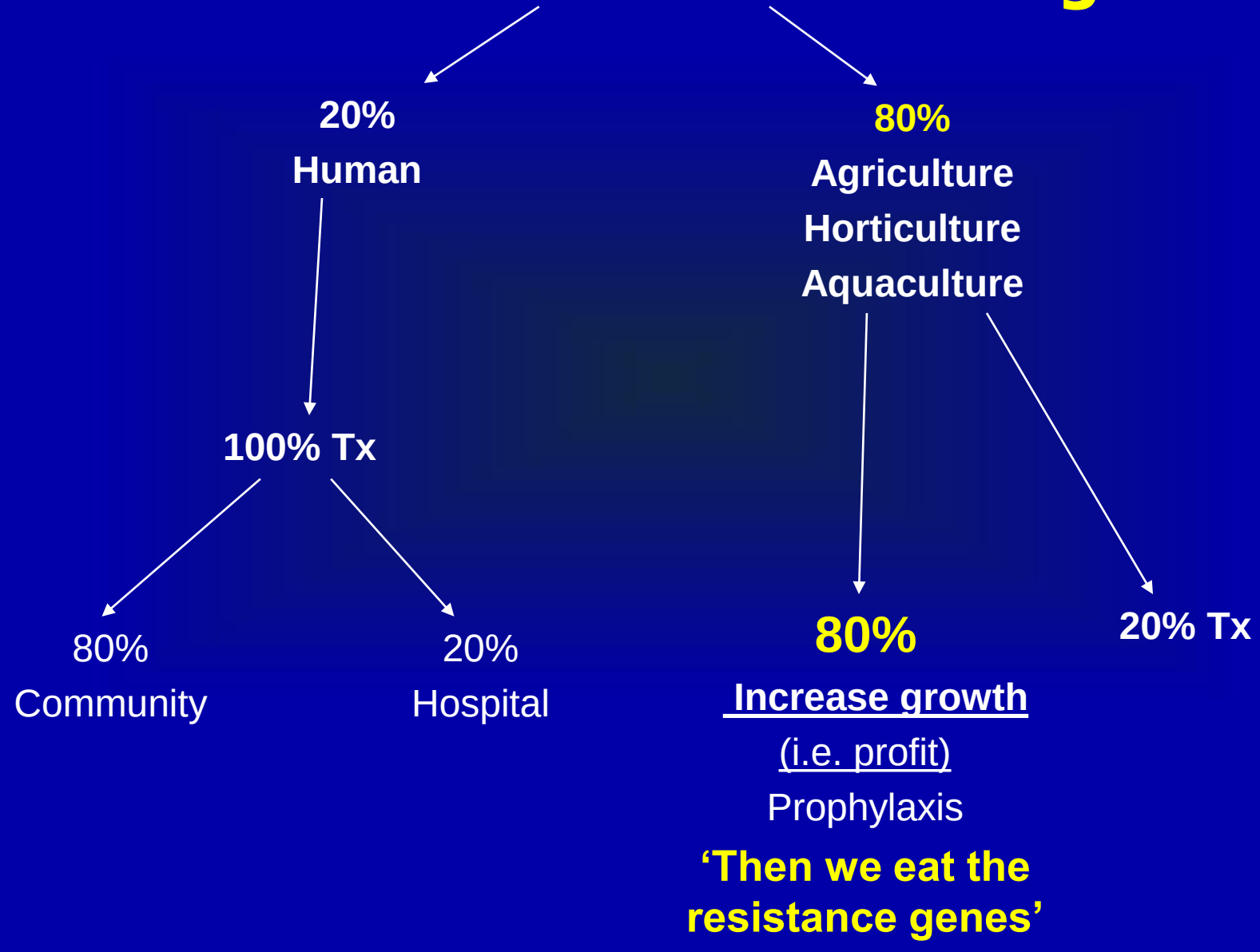
- **56 tons** for animal production (in 2009)

+ Horticulture

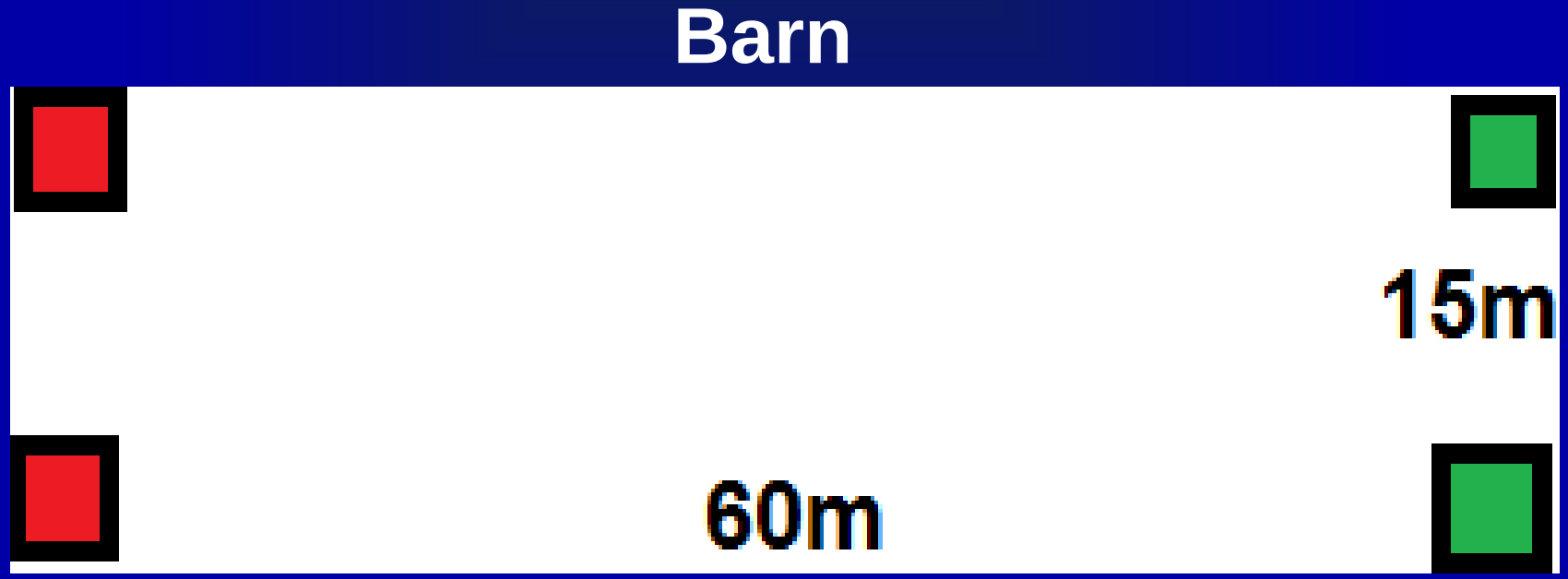
+ Aquaculture

Emerging Antibiotic Resistance

Worldwide Antibiotic Usage



Changes in Intestinal Flora of Farm Personnel after Introduction of a Tetracycline Supplemented Feed on a Farm



Stuart B. Levy, M.D., George B. FitzGerald, Ph.D., and Ann B. Macone, B.S.

N Engl J Med 1976; 295:583-588

Barn Chickens Fed Tetracycline

- 300 antibiotic free chickens in cages
- **Tetracycline feed additive in 2 cages at one end of barn only**
- Farming family of 11 (2 adults + 9)
- Gut flora: E. coli, P. mirabilis, enterococci

  \+ Kleb. pneumoniae, Ps. aeruginosa, Acinetobacter

Chickens Fed Tetracycline

Within one week most **chicken** intestinal flora **resistant to tetracycline**

(E coli, Pr mirabilis, enterococci)

Chickens Fed Tetracycline (contd)

After Tetra use for ≥ 10 weeks in chickens

> 50% E coli **also resistant to**

- **Streptomycin**
- **Ampicillin**
- **Carbenicillin**
- **Sulphonamides**

Chickens Fed Tetracycline

Farm workers then developed increased intestinal resistance

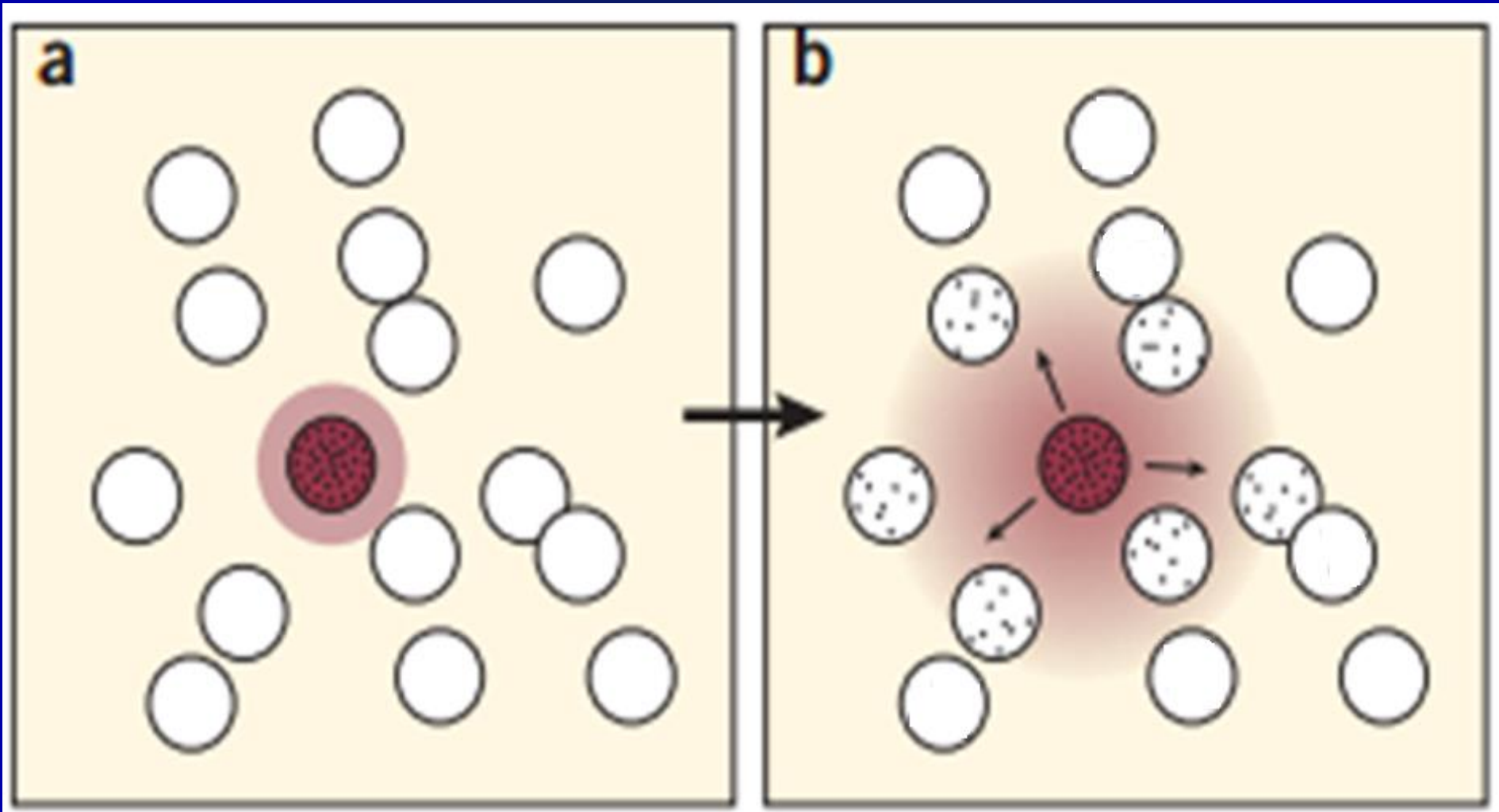
Within six months 31.3 % weekly faecal samples from farm dwellers had >80% tetracycline resistant bacteria

Key Point

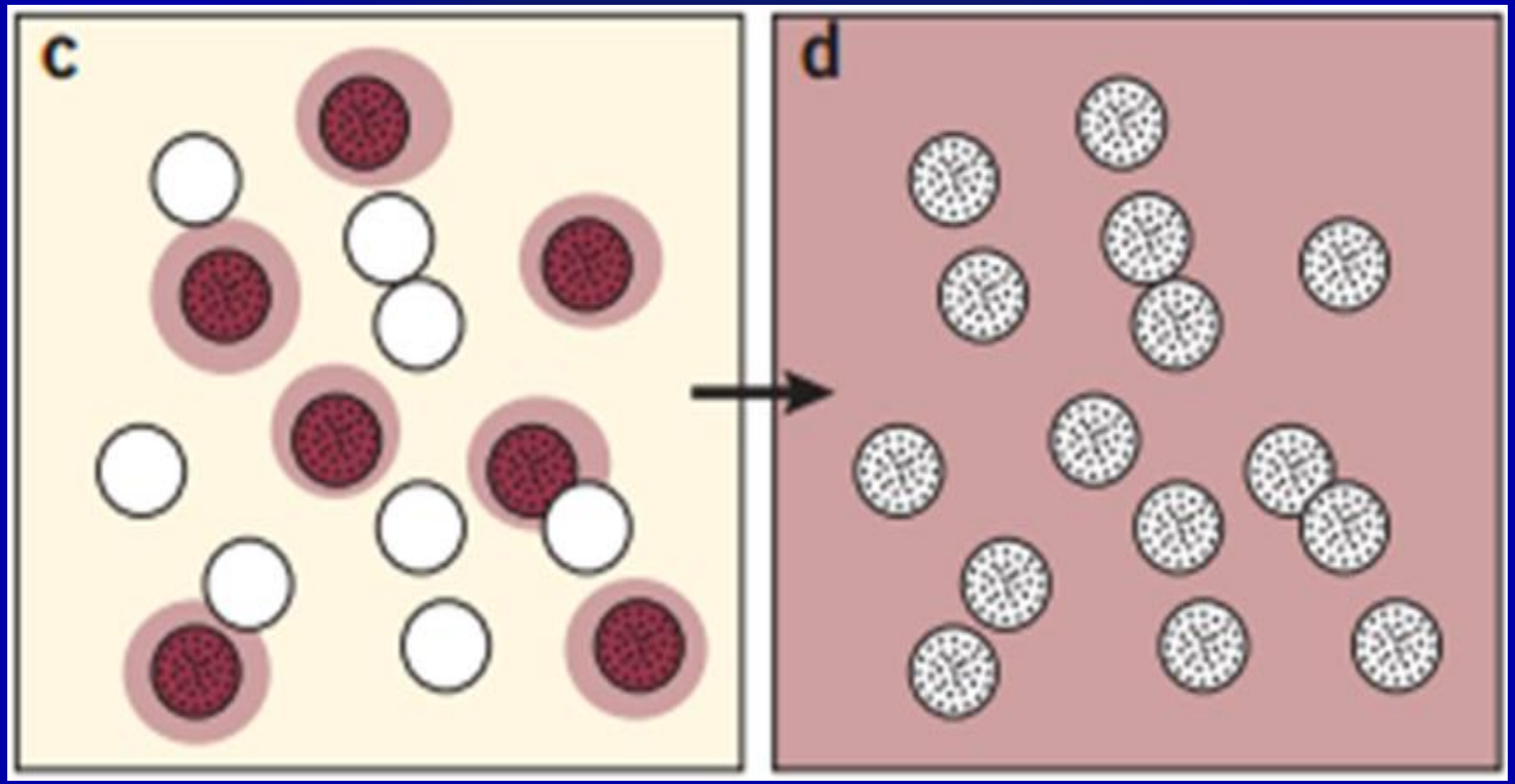
Ongoing use of a single antibiotic selects resistance for multiple structurally unrelated ABs

via linkage genes, plasmids, transposons

Antibiotic Dispersion Effect in Populations of People or Animals



Antibiotic Dispersion Effect in Populations of People or Animals




SPECIAL!
SPECIAL!

Nature 25 August 2011 vol 76, p393

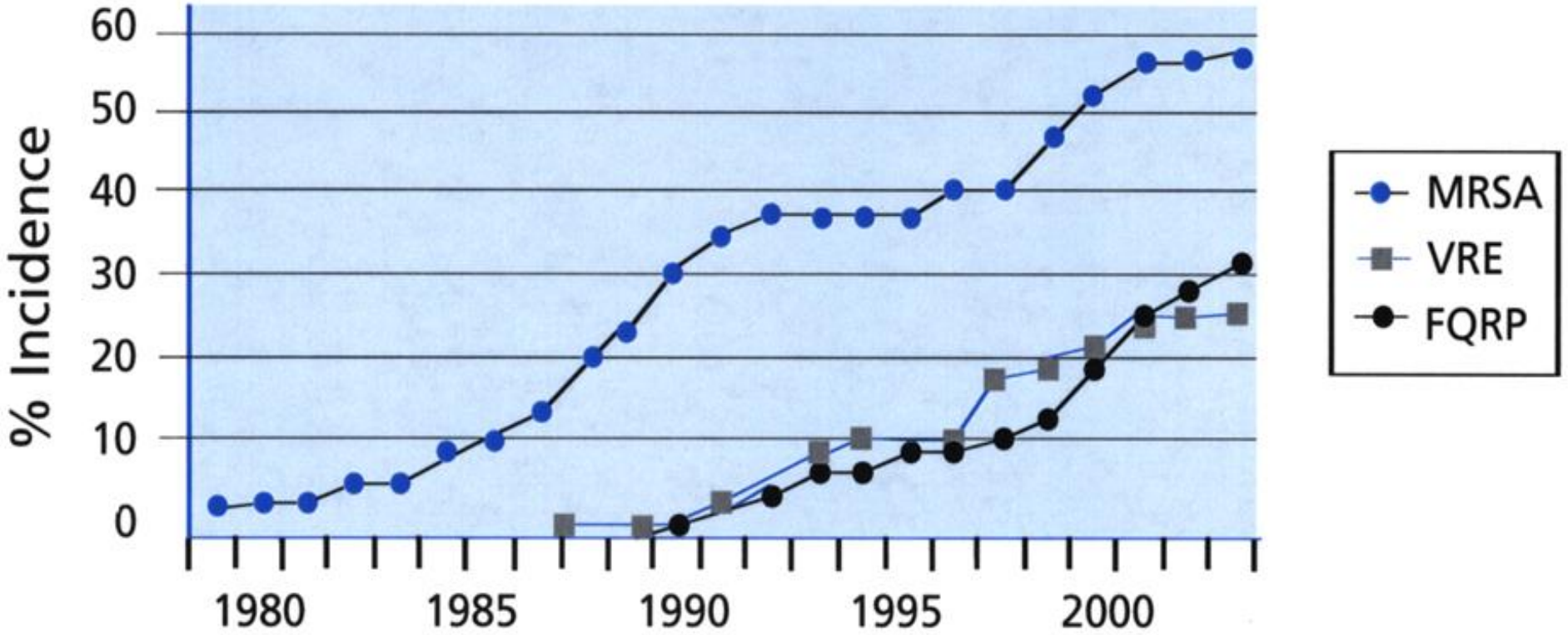
P. DUREUIL/PHOTOALTO/ALAMY

Dosed up: could excessive prescription of antibiotics be hampering children's ability to fight disease?

Stop the killing of beneficial bacteria

Increasing Frequency of Resistance

Chart 1: Resistant Strains Spread Rapidly



MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = Vancomycin-resistant *enteroccoci*
FQRP = Fluoroquinolone-resistant *Pseudomonas aeruginosa*

Source: Centers for Disease Control and Prevention

E. coli in Midstream Urine

Ampicillin	- resistant
Augmentin	- resistant
Cefotaxime	- intermediate
Ciprofloxacin	- resistant
Gentamicin	- resistant
Co-Trimoxazole	- resistant
Cephalothin	- resistant
Chloramphenicol	- resistant
Nitrofurantoin	- intermediate
Tetracycline	- resistant
Imipenem	- sensitive BUT how much longer ?

Post Antibiotic Signs - CRE

And one only of the carbapenem groups (New Delhi metallo-beta lactamase 1):

http://eurosurveillance.org/ViewArticle.aspx?ArticleId=20809

Note India 52.3%

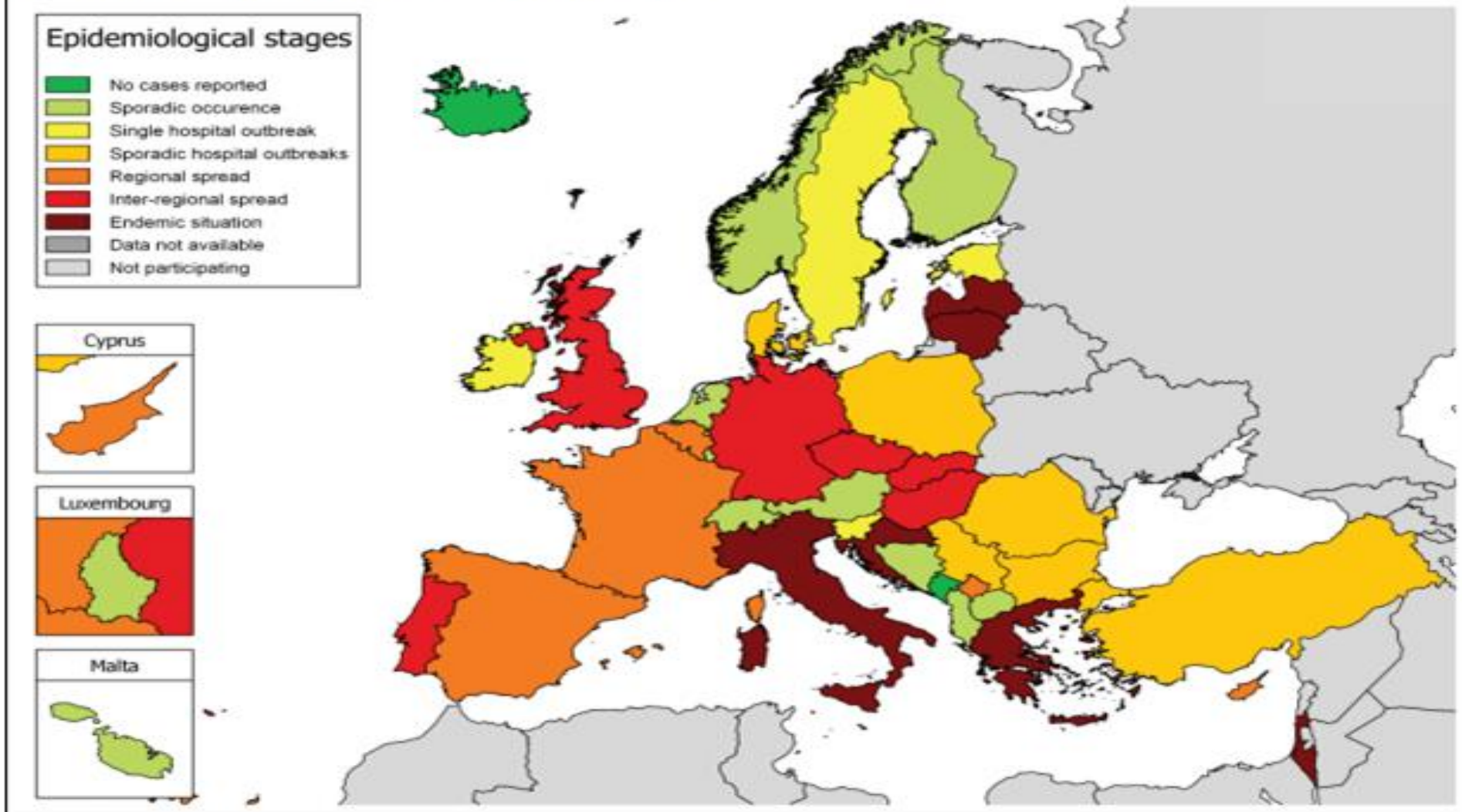
FIGURE 3

The worldwide distribution of New Delhi Metallo-beta-lactamase-1-producing bacteria 1 December 2009–31 December 2012 (n=950)

A. Worldwide distribution of autochthonous published isolates carrying the bla_{NDM-1} gene

And carbapenemase resistance in Acinetobacter species, usually more ICU associated infections :

Figure 7. Occurrence of carbapenem-resistant *A. baumannii* in European countries based on self-assessment by the national experts, March 2013



The stage designations for CRAb should be taken with caution for all 38 participating countries. Most NEs highlighted that the exact epidemiology of CRAb remains uncertain in their country, because at the time of the survey, surveillance and reporting of

Swiss Travellers Study

Kuenzli et al. BMC Infectious Diseases 2014, 14:528
http://www.biomedcentral.com/1471-2334/14/528

Only 2.8% were ESBL positive on screening pre travel, but 69.4% post travel, 86.6% ESBL positive post travel to India.
A particular risk factor was **eating ice cream or pastry (Odds Ratio increased 3.90)**

Table 4 Prospective studies on travel-associated colonization with ESBL-producing *Enterobacteriaceae* – rates and risk factors

	Travellers (n) overall	Colonization rate (%) overall	Travellers (n) India/ Indian subcontinent	Colonization rate (%) India/ Indian subcontinent	Risk factors*
Current study	170	69.4	68	86.8	Travel Destination Length of Stay Visiting Friends and Relatives Consumption of Ice Cream & Pastry
Tängden et al. [8]	100	24.0	8	88.0	Travelling to India Gastroenteritis during Trip
Kennedy et al. [9][a]	102	21.6	14	57.1	Gastroenteritis during Trip Antibiotics while Travelling
Weisenberg et al. [10]	28	25.0	7[b]	28.6	not done
Paltansing et al. [11]	370	30.5	25[c]	73.0[c]	Travelling to South and East Asia
Östholm-Balkhed et al. [12]	226	30.0	14	71.4	Travelling to Indian subcontinent, Asia, Africa north of equator

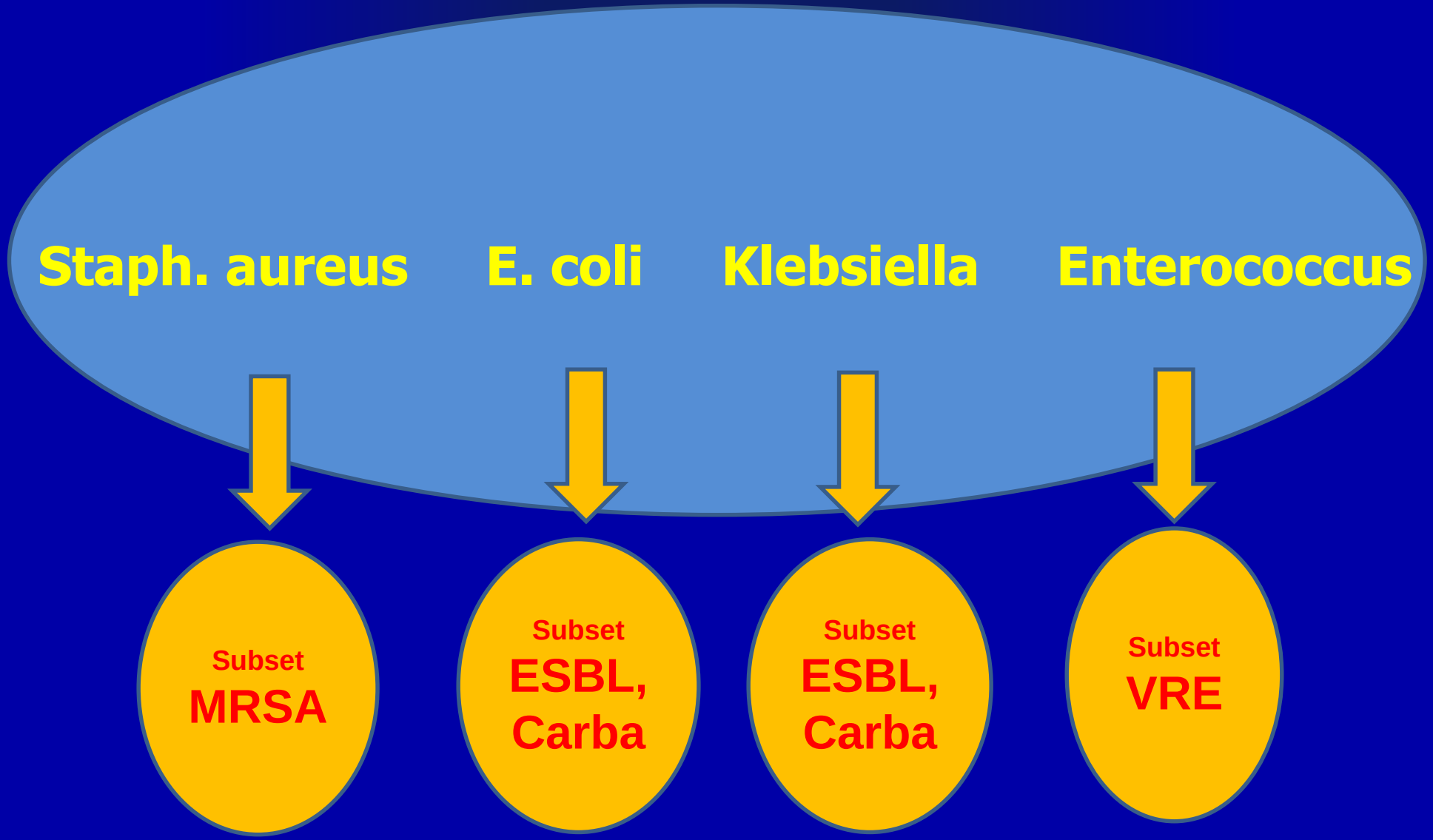
500 People with skin infection endogenous, from themselves

5% of 500 Staph aureus infection MRSA positive, which ones ???

5% MRSA + and 5% ESBL + of 500 People

3 of this 500 have swab taken should the MRSA be isolated? Benefits vs Risks of isolating??

MDRO Approach
Silo or Horizontal Required ?



Chlorhexidine Exposure Selects Antibiotic Resistance (MIC's)

Journal of Antimicrobial Chemotherapy (2008) 61, 524– 532

:

AMP ampicillin, CTX cefotaxime, VAN vancomycin, GEN Gentamicin, CIP ciprofloxacin, CEF cefuroxime
TET tetracycline, OXA oxacillin

	Hours Drying with Chlorhexidine	AMP	CTX	VAN	GEN	CIP	CEF	TET	OXA
MSSA (susceptible *Staph. aureus*)	control (no exposure)	0.06	1	1	0.25	0.25	4	0.5	0.12
	2	0.06	1	1	0.5	0.25	1	0.25	0.12
	24	0.002	1	0.002	0.25	0.002	0.002	0.002	0.002
	48	128	32	>128	2	2	64	1	128

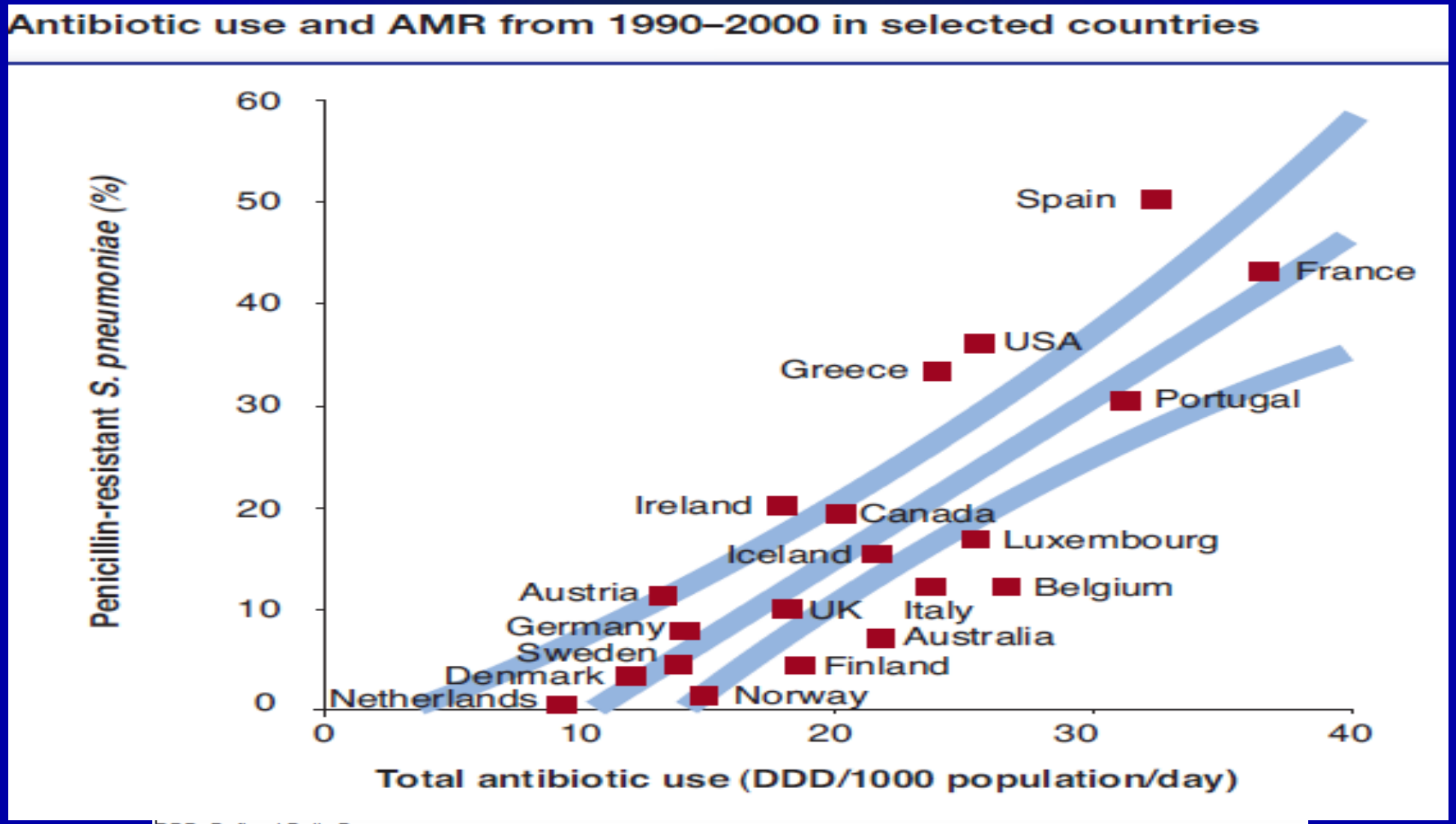
Chlorhexidine Exposure Selects Antibiotic Resistance (MIC's)

Journal of Antimicrobial Chemotherapy (2008) 61, 524– 532 :

AMP ampicillin, CTX cefotaxime, VAN vancomycin, GEN Gentamicin, CIP ciprofloxacin, CEF cefuroxime TET tetracycline, OXA oxacillin

	Hours Drying with Chlorhexidine	AMP	CTX	VAN	GEN	CIP	CEF	TET	OXA
MRSA (EMRSA 16)	control (no exposure)	>128	8	1	0.5	1	8	2	4
	2	>128	8	1	0.5	2	8	2	8
	24	>128	8	1	0.5	2	4	2	4
	48	>128	16	128	2	2	64	2	128

Antibiotic usage/resistance correlation

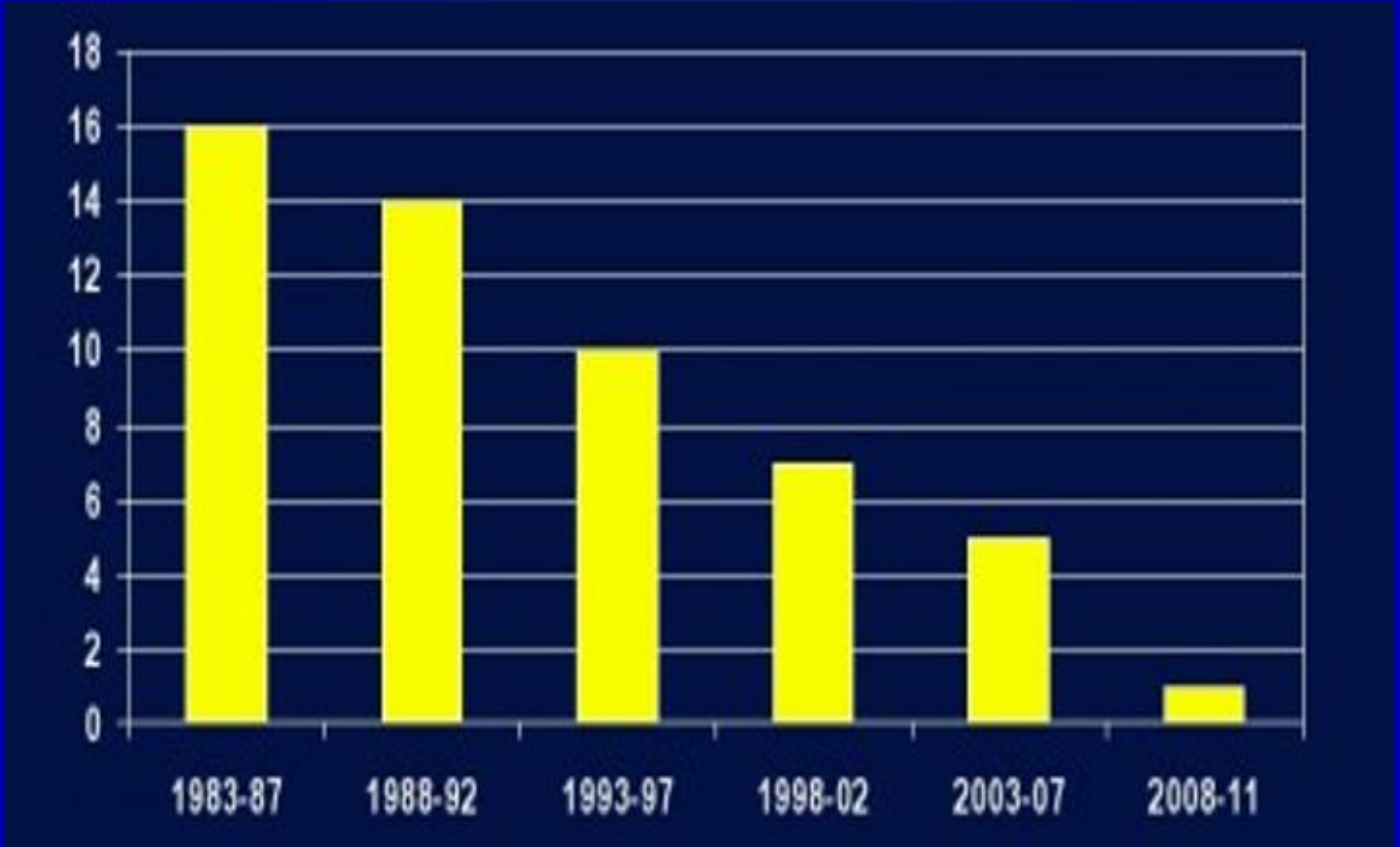


DDD: Defined Daily Doses

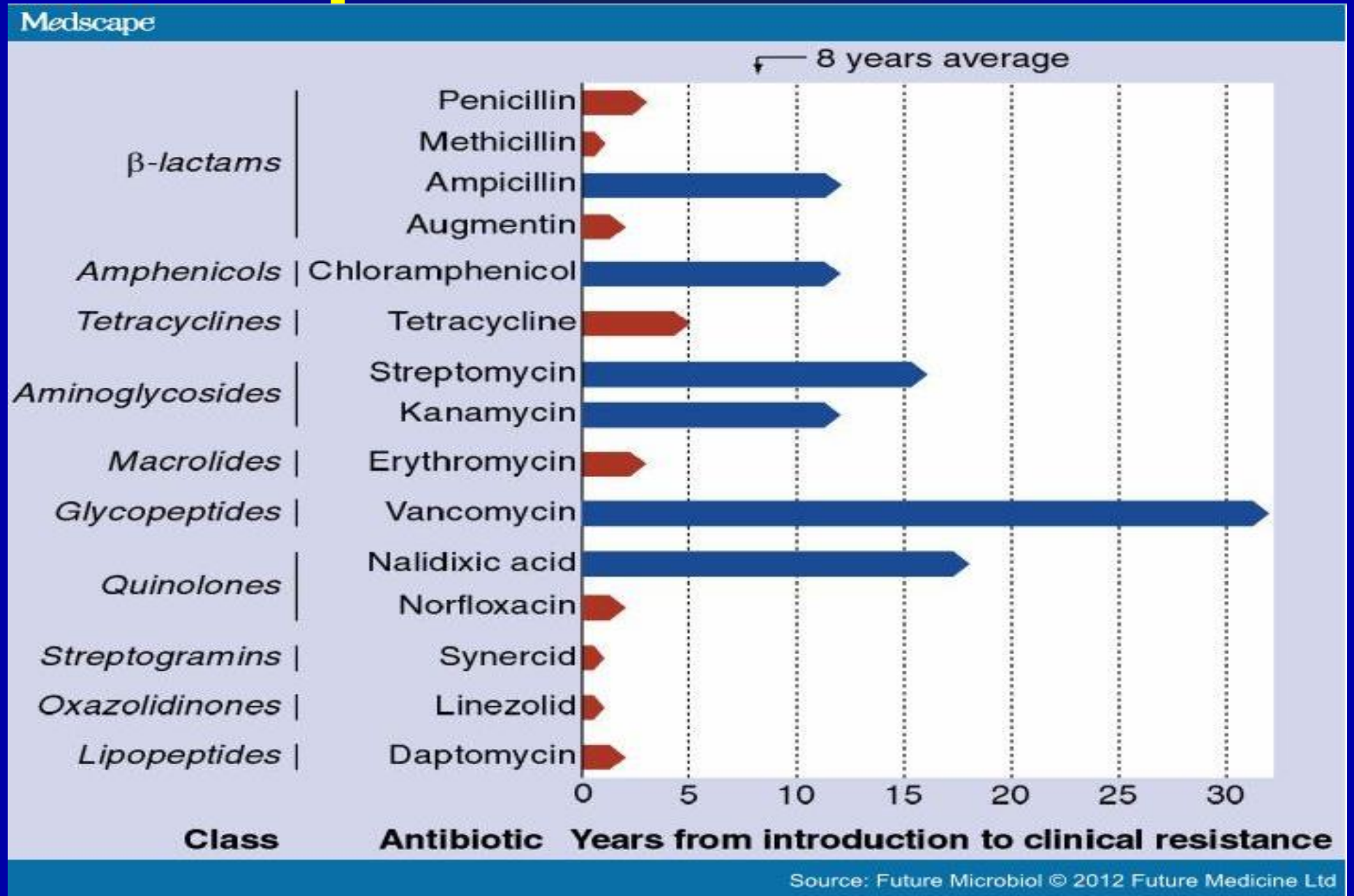
Total antibiotic use in outpatients versus prevalence of penicillin-nonsusceptible *Streptococcus pneumoniae* in 20 industrialized countries.

Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in Streptococcus pneumoniae and Streptococcus pyogenes. *Emerging Infectious Diseases*, 2004, 10(3):514-7.

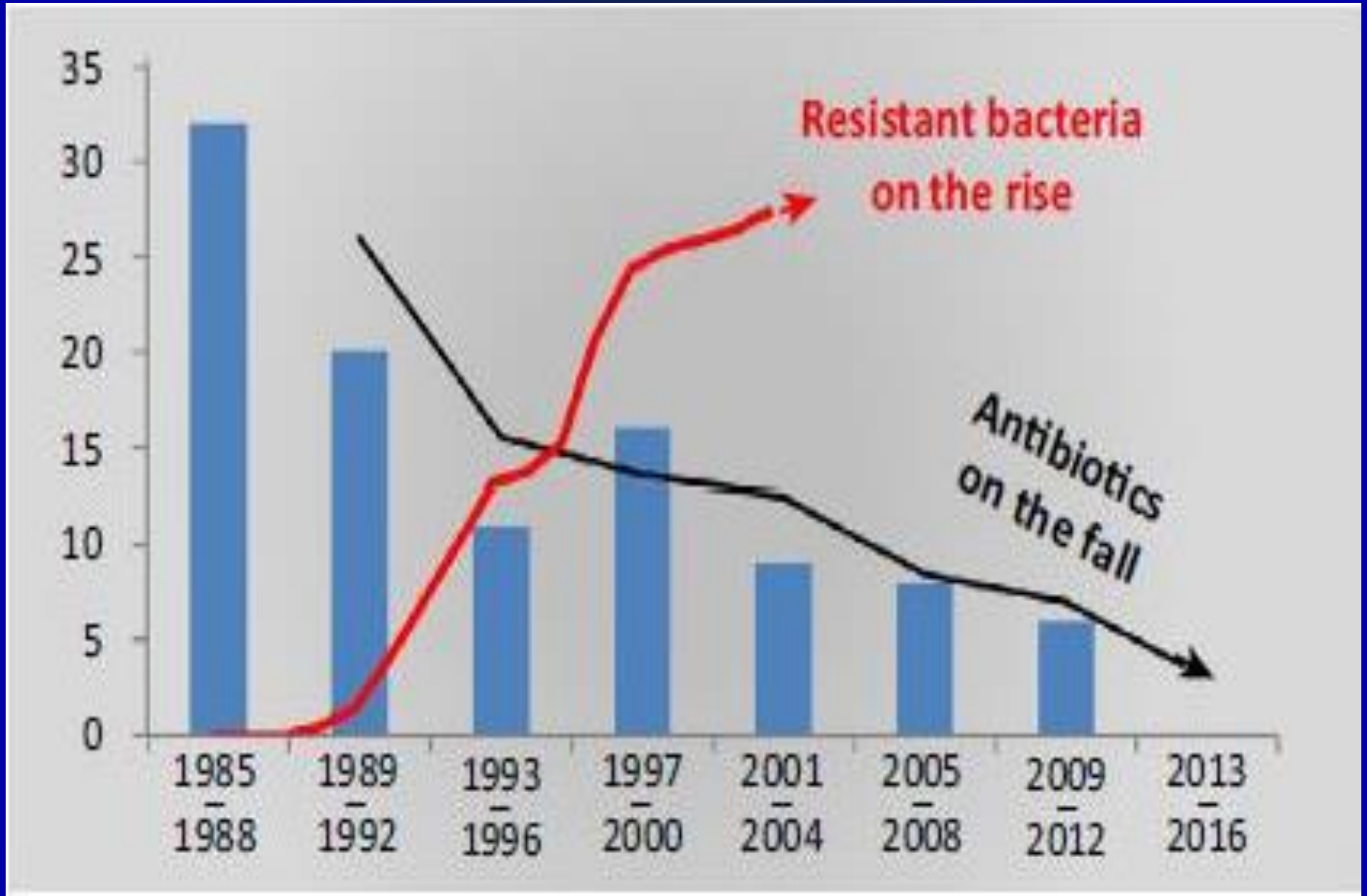
New Antibiotics each 5 years 1983-2011



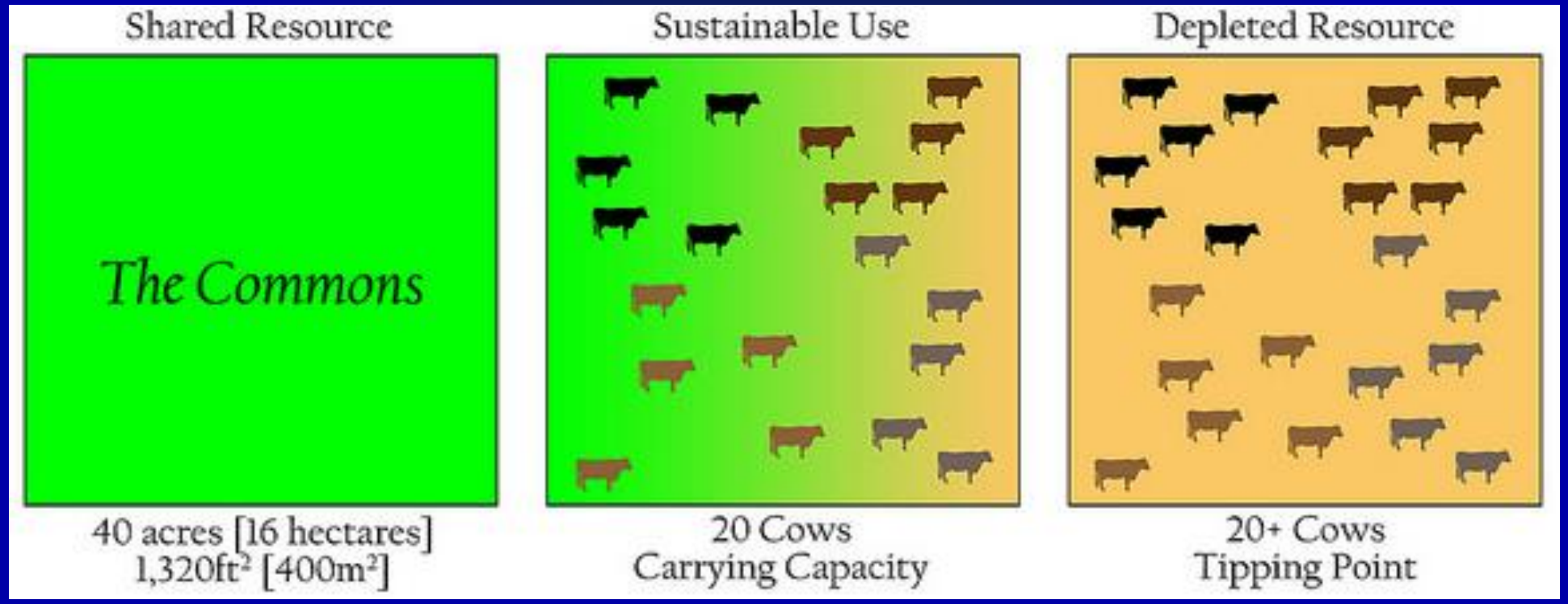
Lifespan of Each Antibiotic



Seeing the Future



Tragedy of the Commons



Refers to depletion and collapse of a common but limited resource when individuals act selfishly to maximise personal gains.

Atlantic Cod Stock Collapse
‘Get it While You Can’

NZ Antibiotic Use 2012

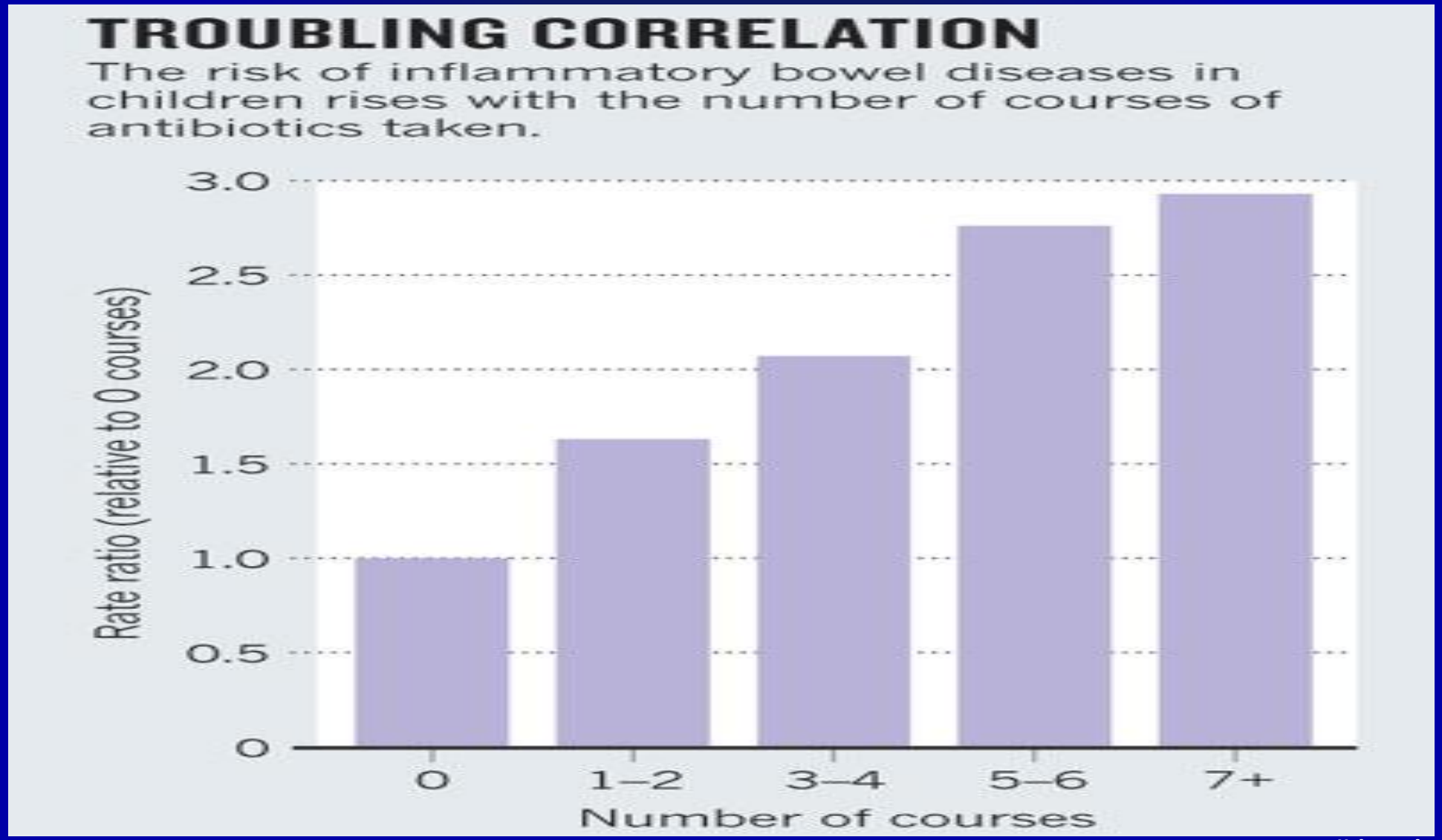
Assoc Prof Mark Thomas, University of Auckland

Annually:

- 180 AB courses per 100 children <5y
- 60 AB courses per 100 25-29yrs old

the lowest prescribing rate age group! !

IBD & Number Antibiotic courses in children correlation



Gut 60, 49-54 :2011 A Hviid et al

Imagine a World Without Antibiotics

- You know how you are FEELING better than anyone else
- Your medical practitioner knows what the CAUSE is, bacterial, viral or other and what to treat you with better than anyone else.

Listen, do not ask for or demand antibiotics – they may well cause you and others significant harm

Illness	Usual Cause		Antibiotic Needed
	Viruses	Bacteria	
Cold/Runny Nose	✓		NO
Bronchitis/Chest Cold (in otherwise healthy children and adults)	✓		NO
Whooping Cough		✓	Yes
Flu	✓		NO
Strep Throat		✓	Yes
Sore Throat (except strep)	✓		NO
Fluid in the Middle Ear (otitis media with effusion)	✓		NO
Urinary Tract Infection		✓	Yes

http://www.cdc.gov/getsmart/community/for-patients/common-illnesses/

NZ non medical AB use

2009-2011

Horticulture/Agriculture use ↓ 19%

From 70,343 kg

to 57,043 kg !

But ⬆ macrolides

⬆ aminoglycosides

⬆ cephalosporins including 3rd generation cephalosporins ↑ 26%

Sub therapeutic use to be phased out by 2030 !

BLADE OF GRASS IS RESPONSIBLE FOR LOSS OF FOOT

C. W. Jones, athletic director of the Athens Y. M. C. A. yesterday suffered the loss of his right foot, the member having been amputated just above the ankle.

Mr. Jones, it seems, recently was exercising on a plot of grass, dew on a blade of grass cutting him slightly just under the little toe. The cut did not heal as quickly as it should have and medical attention was called, but to no avail. Blood poisoning had set in, and it was imperative that the foot be amputated to prevent the poison spreading further.

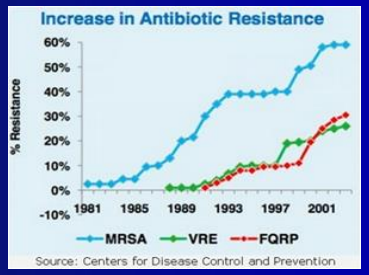
Weekly Banner, 18 July 1899, p. 2, col. 2.

Simply

- Bacteria do not become resistant

  we selectively breed resistance with every antimicrobial use

⇨



- Then we share our large bacterial microbiome mainly by our

  hands, coughing & environment

Summary

A Hospital or LTCF resistant bug is one which we HCW's gave them

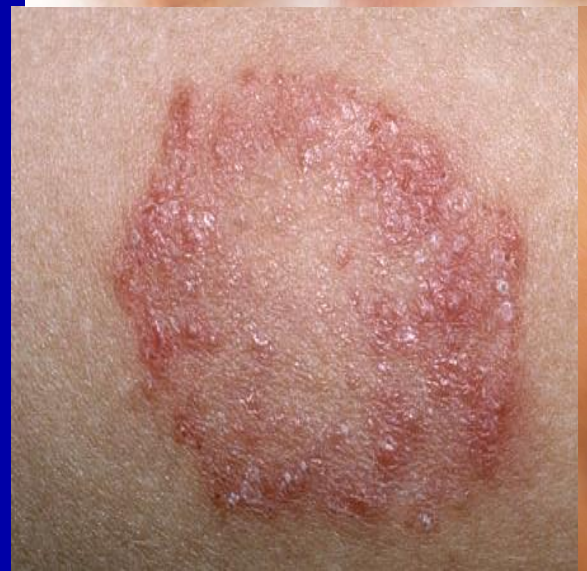
An MDRO carrier is not the problem but a symptom of a much larger issue

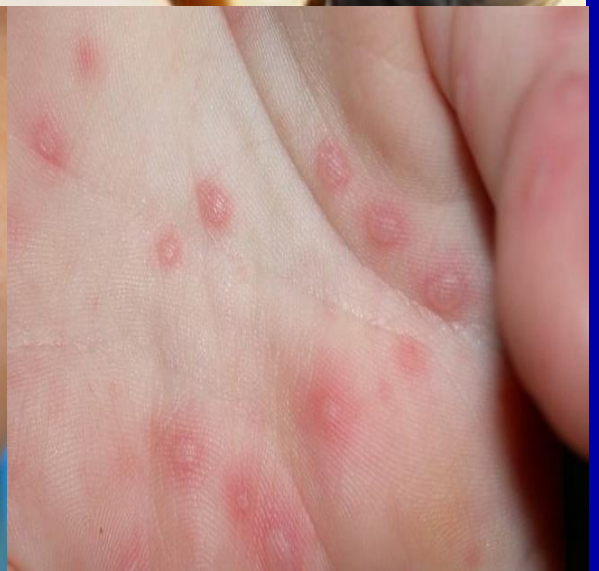
We are rapidly squandering our limited antibiotic resource


24
22
25½
24¼
27½


DO NOT Pick
your nose and
wipe it on the
walls or doors
VEOLIA
TRANSPORT

Bug Sharing



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Microbes - the SECOND lowest form of life
TERRORISTS


We're not
ALL BAD!!

Our Actions Now Are Our Future

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Simply

- Bacteria do not become resistant
  we selectively breed resistant strains

- Then we share our large bacterial microbiome mainly by our
  hands, coughing & environment

Unique, Only Antibiotics

- use of AB in one patient can compromise efficacy in another
- lose efficacy over time & must be continually replaced
- need to be used sparingly to prolong their efficacy
- for which we actively discourage use when newly approved BUT R&D/profit implications

Todays choices affect future patient outcomes

Antibiotic Summary

- Resistance emerging, increasing, evolving
- Few new antibiotics in pipeline
- Geographic variations in resistance patterns
  use & adapt to these
- Many challenges to stop transmission
  & greatly reduce AB use
- Novel treatment approaches needed

Summary

- Every Antibiotic Use helps select for microbial resistance
- HCW's (hands) are the most common vector for spreading MDRO's to patients
- A Hospital or LTCF resistant bug is one which we HCW's gave them
- An MDRO carrier is not the problem but a symptom of a much larger issue

We are increasingly rapidly squandering our limited antibiotic resource

Environmental Cleaning
& Horizontal MDRO Awareness

X7 patients in tertiary care Toronto teaching hospital with New Delhi Metallo beta lactamase-1-producing Kleb pneumonia(NDM1-Kp) acquired from x2 index patients

Acquisition risk factors:

- Index cases previously hospitalised in endemic area of India
- 4 of 7 were room mates of affected patients
- 2 of 7 were on the same ward
- 1 was admitted to the room of a discharged infected patient

Toronto Jan 2011-March 2012

Ref: International Journal of Infectious Diseases 14S4 (2010) S3–S5

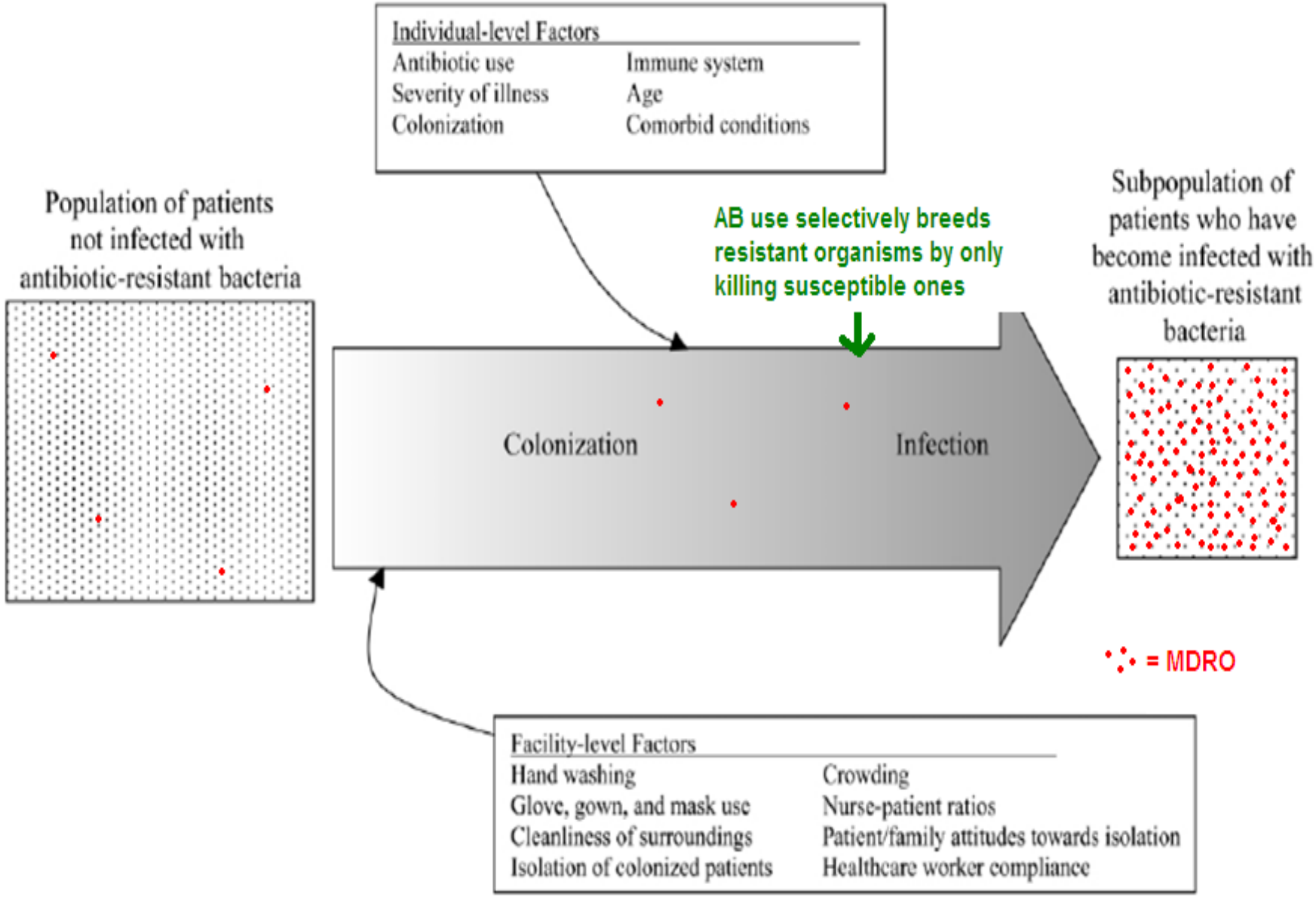


Figure 1. Factors that influence the acquisition of a nosocomial antibiotic-resistant bacterial infection

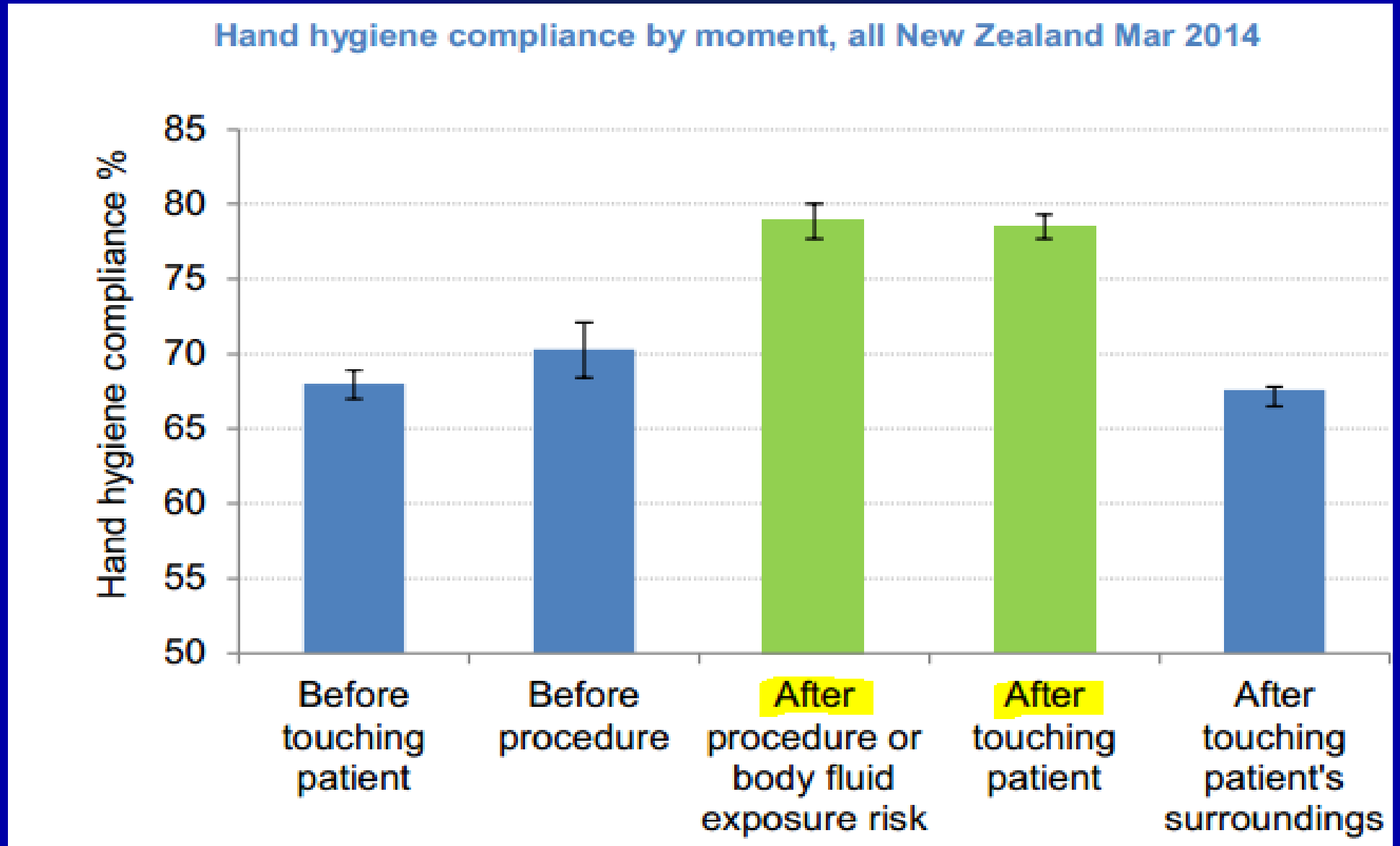
NZ Hand Hygiene Compliance Rates

80% average

X20 DHBs

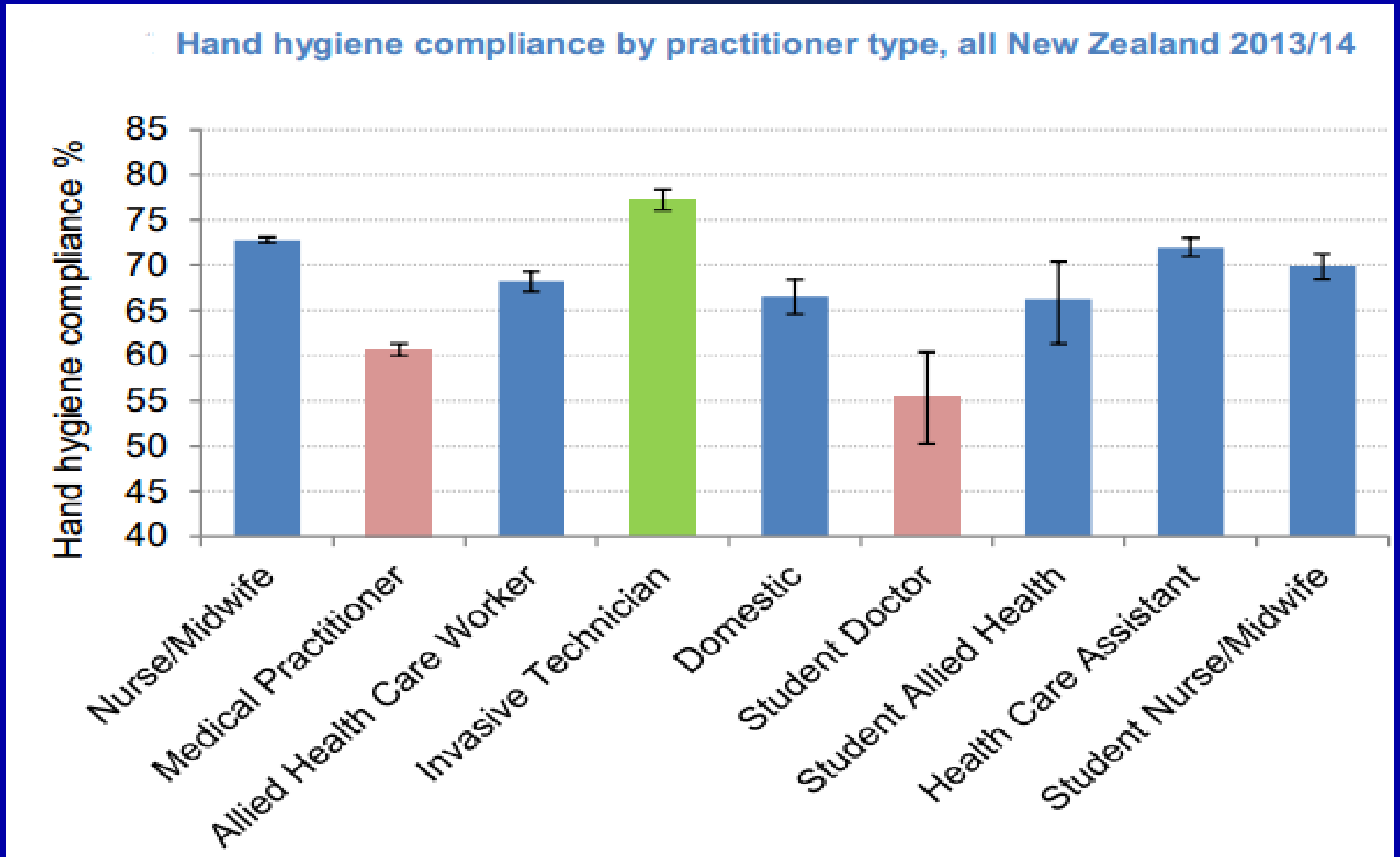
1 April – 30 June 2015

NZ DHB Hand Hygiene



Source: HHNZ

Compliance by HCW category



Source: HHNZ – average of last 4 audits

How Many HAI's?

- 1.7 million healthcare infections and 99,000 deaths in the USA annually
- NZ equivalent HAI's 24,000 infections 1,400 deaths??
- This is 4.5 infections for every 100 hospital admissions

CDC estimates effective infection control could prevent up to 70% of infections

Hospital Acquired Infection Cost Data

	Mortality %	Av. Days Stay	Av. Cost ($US)
Patients with HAI	12.2%	19.7	$191,872
Without HAI	2.0%	4.4	$35,168 (5.5x)

Pennsylvania Health Care Cost Containment Study January 2009

Evolution Adaptation Time

Humans

- In 100,000 years humans
  3,000 generations
  (assuming 30 years per generation)

- X10 is one million years human evolution

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Bacteria

- **Bacteria have 3,000 generations in 1.5 days!**
- **X10 is 15 days for equivalent one million human years evolution** but
- also vastly more bacteria to mutate/evolve/AB selected
- **Plus** swap genetic material **when alive** (species, genera)