Mr Ben Harris

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University of Otago

A/Professor David Holland

Clinical Head of the Infectious Diseases Service
Middlemore Hospital

Dr Bryan Betty

General Practitioner
Wellington

Professor Jack Heinemann

Genetics and Molecular Biology
School of Biological Sciences
University of Canterbury

A/Professor Siouxsie Wiles

Microbiologist
Head of the Bioluminescent Superbugs Lab
University of Auckland

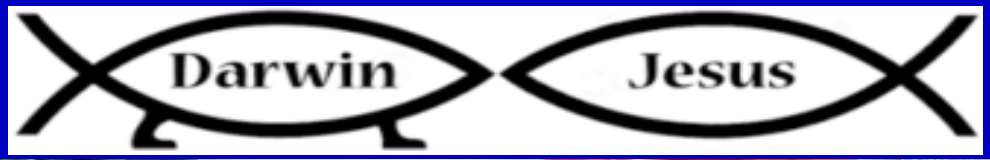
Sunday, August 11, 2019 (Room 9)

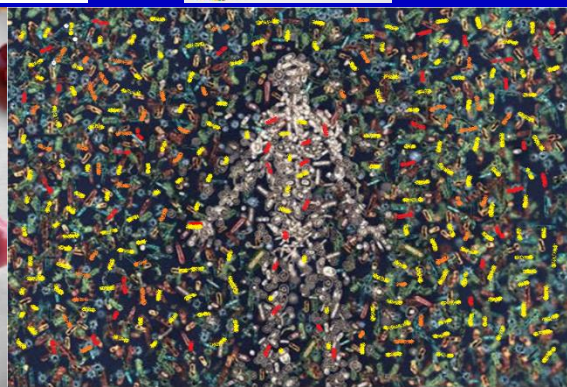
8:30 - 10:30 WS #147: Pharmac Session: Antimicrobial Resistance - Global Threat or Myth? (120mins, not repeated)

Antibiotic Resistance Mutations or Creations?

How We Squander a Miracle

Ben Harris, Medical Microbiology Scientist
NZ Infection Prevention Control Consultancy
NZIPCconsultancy@gmail.com
M: 0276273201





“We are not there to be phased by a brilliant international conference speaker

we are there because we are

gullible, ignorant & desperate”

REFERENCE:

Written comment from veteran GP regarding the didactic style that he finds most useful at GP CME

“We are not there to be phased by a brilliant international conference speaker

we are there because we are

gullible, ignorant & desperate”

Antibiotic Key Point

On NZ average

Prescribe well under 50%

antibiotics you currently prescribe

Because

- Reduce increasing MDRO endemicity
- Keep rapidly dwindling AB resource reserved for future serious infections
- Each AB use increases that patients medium to long term adverse chronic health outcomes

Tips to Achieve This

- **Respiratory - follow BPAC guidelines**
- **UTI – adults, clinical diagnosis, ban dipsticks**
- **Cutaneous**
  - **– lance abscess, no prophylactic AB unless immunocompromised, diabetic, cellulitis**
  - **- infected eczema, consider topical, bleach bathing (1:1000 dilution 5% bleach)**
- **Patient Education – waiting room AB material re MDROs and microbiome damage affects their medium to long term health outcomes**

How to Breed AB Resistance?

- The More Microbes exposed-challenged

  bowel flora > whole body skin > preop skin site

  and Oral > IV > topical

- By ANY Antimicrobial

  e.g. antibiotic, antiseptic, disinfectant, Prozac, Ibuprofen, etc

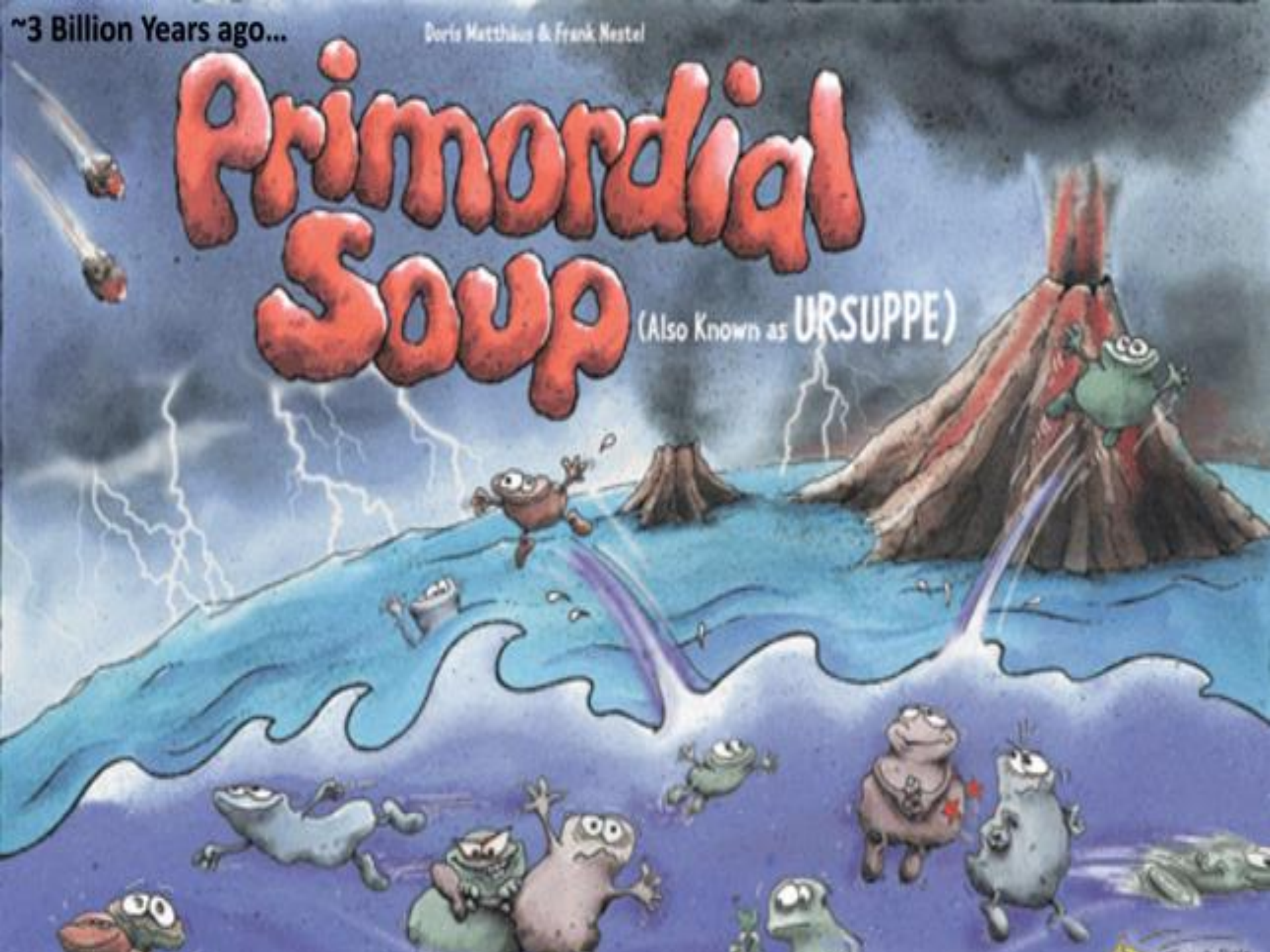
- For Longer Time

  long course ABs > short course

  residual disinfectants (e.g. chlorhexidine/Triclosan)

  > non residual (alcohol, chlorine, bleach evaporate off)

In The Beginning

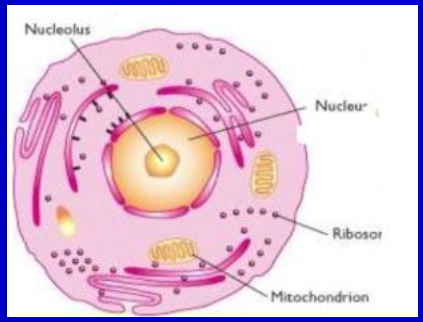

~3 Billion Years ago...
Doris Matthäus & Frank Nestel
Primordial Soup
(Also Known as URSUPPE)

Important Dates

Years Ago

- 4.5 Billion — Origin of the Earth
- 3.5 Billion  Prokaryote Bacteria – 'First Life'
- 2.5 Billion — Oxygen in Atmosphere
- 1.5 Billion — Eukaryote cells

  larger plant, animal cell precursors



- 0.5 Billion — Cambrian life 'explosion'

  multicellular Eukaryote organisms

  plant & animal species evolved

Cell membrane

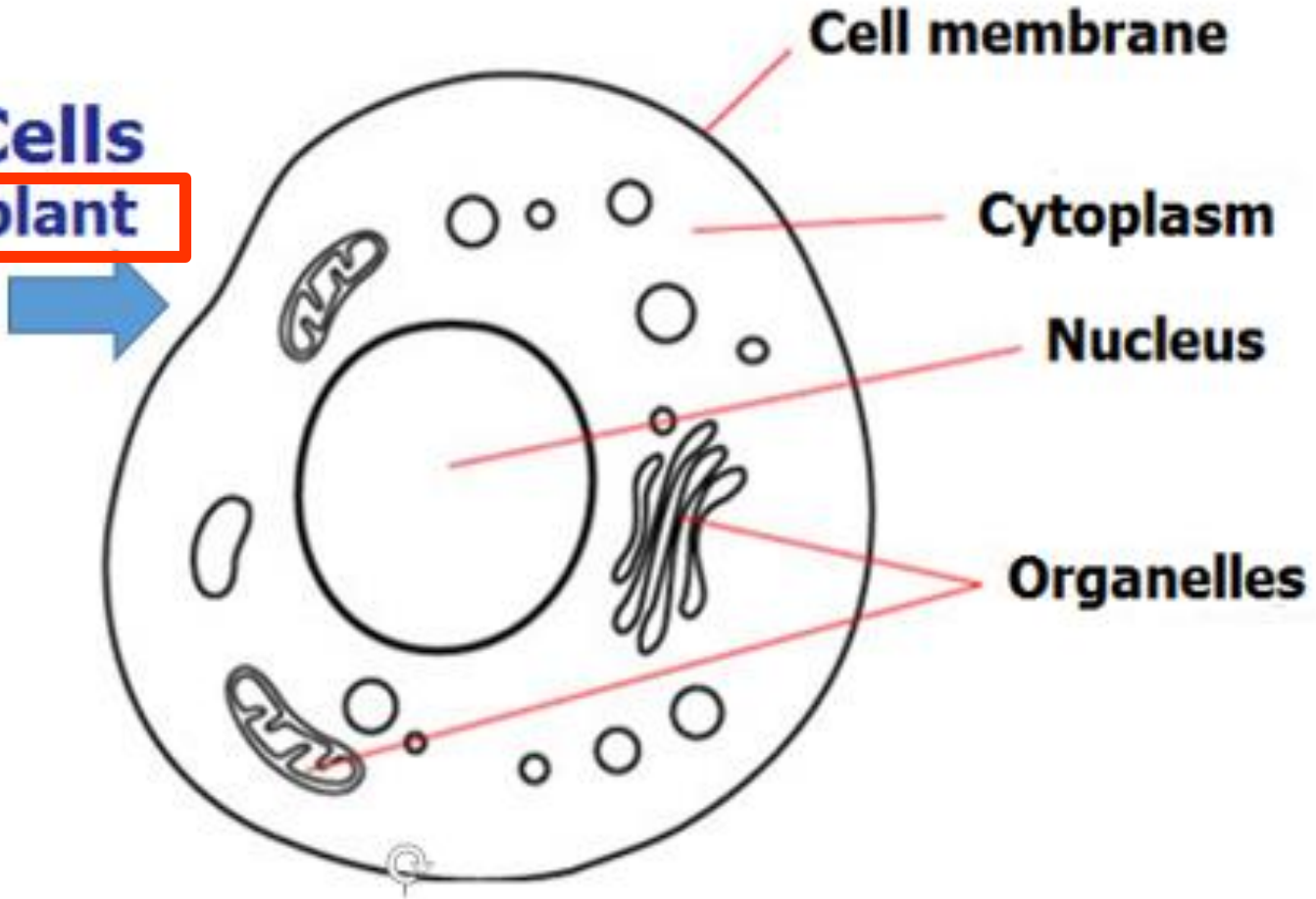
Cytoplasm

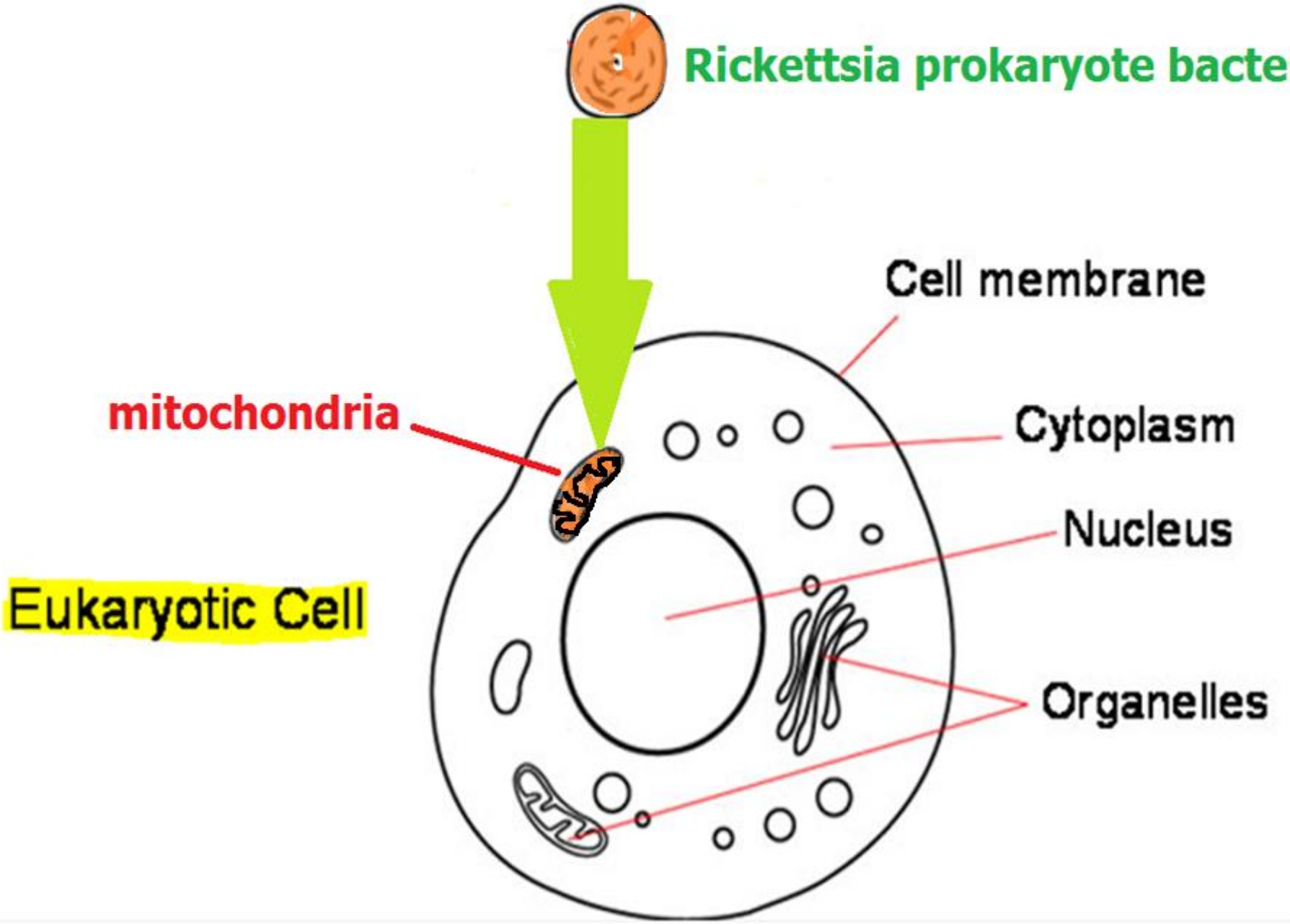
Prokaryote Cells

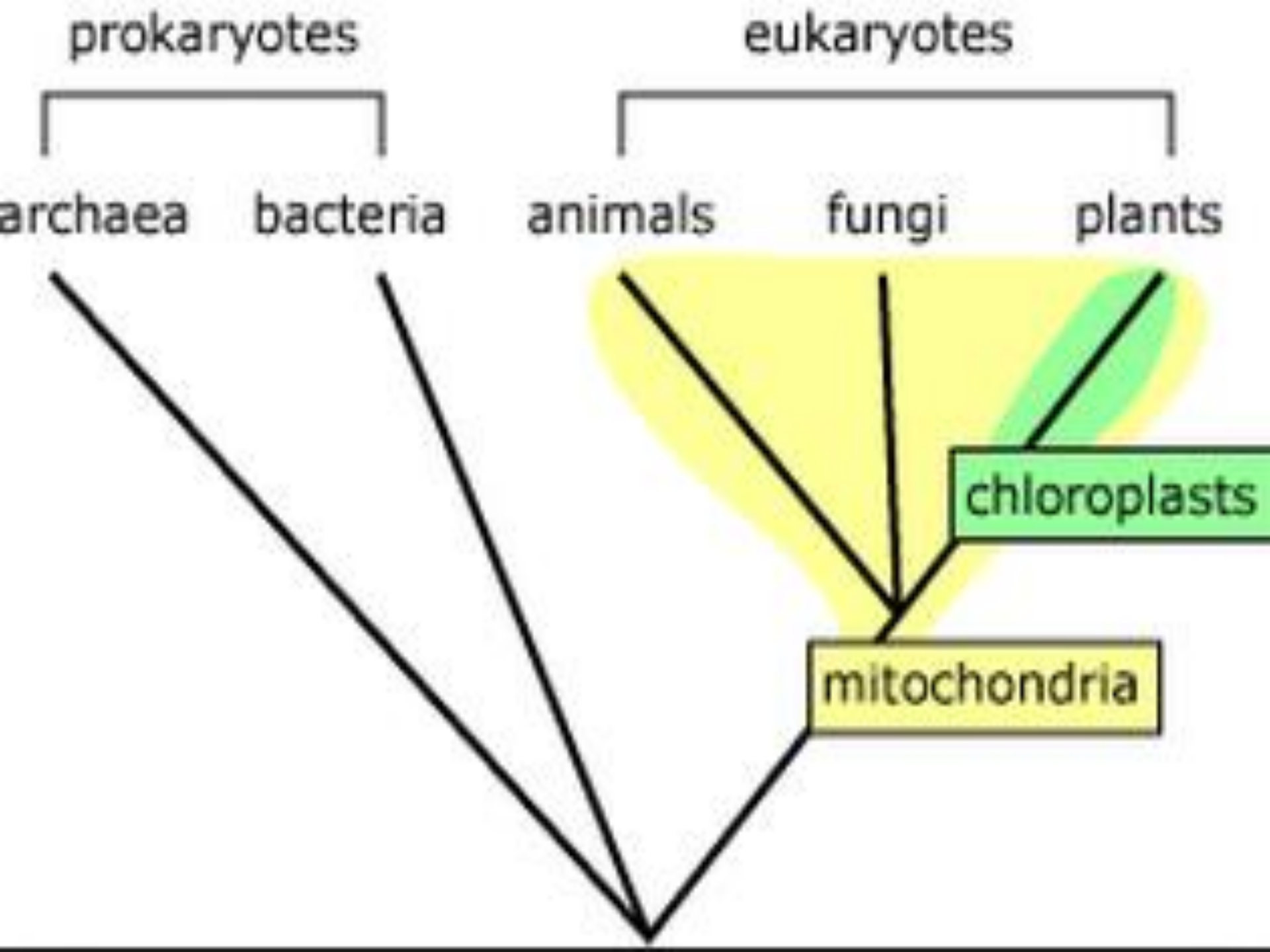
e.g. bacteria

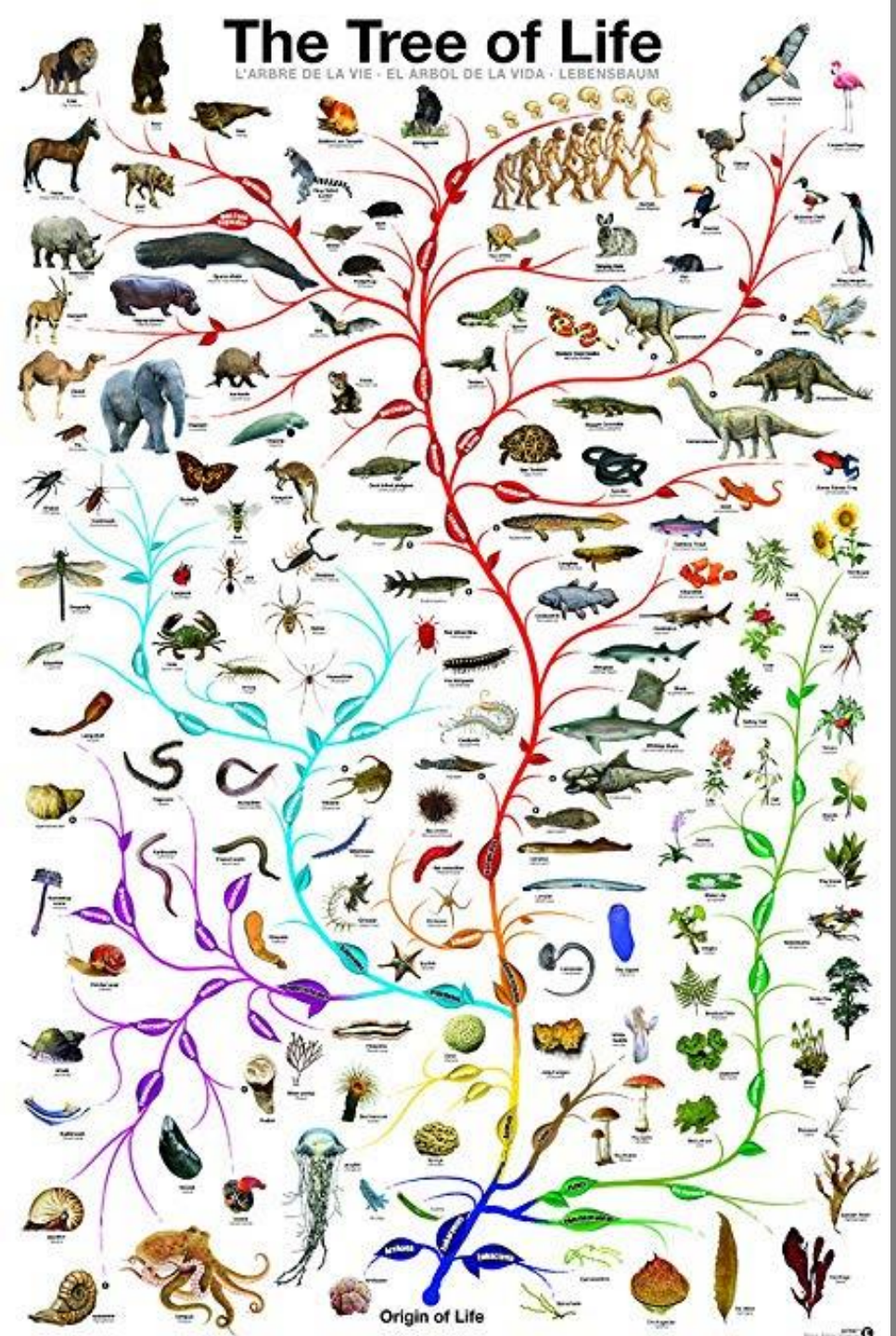
Eukaryote Cells

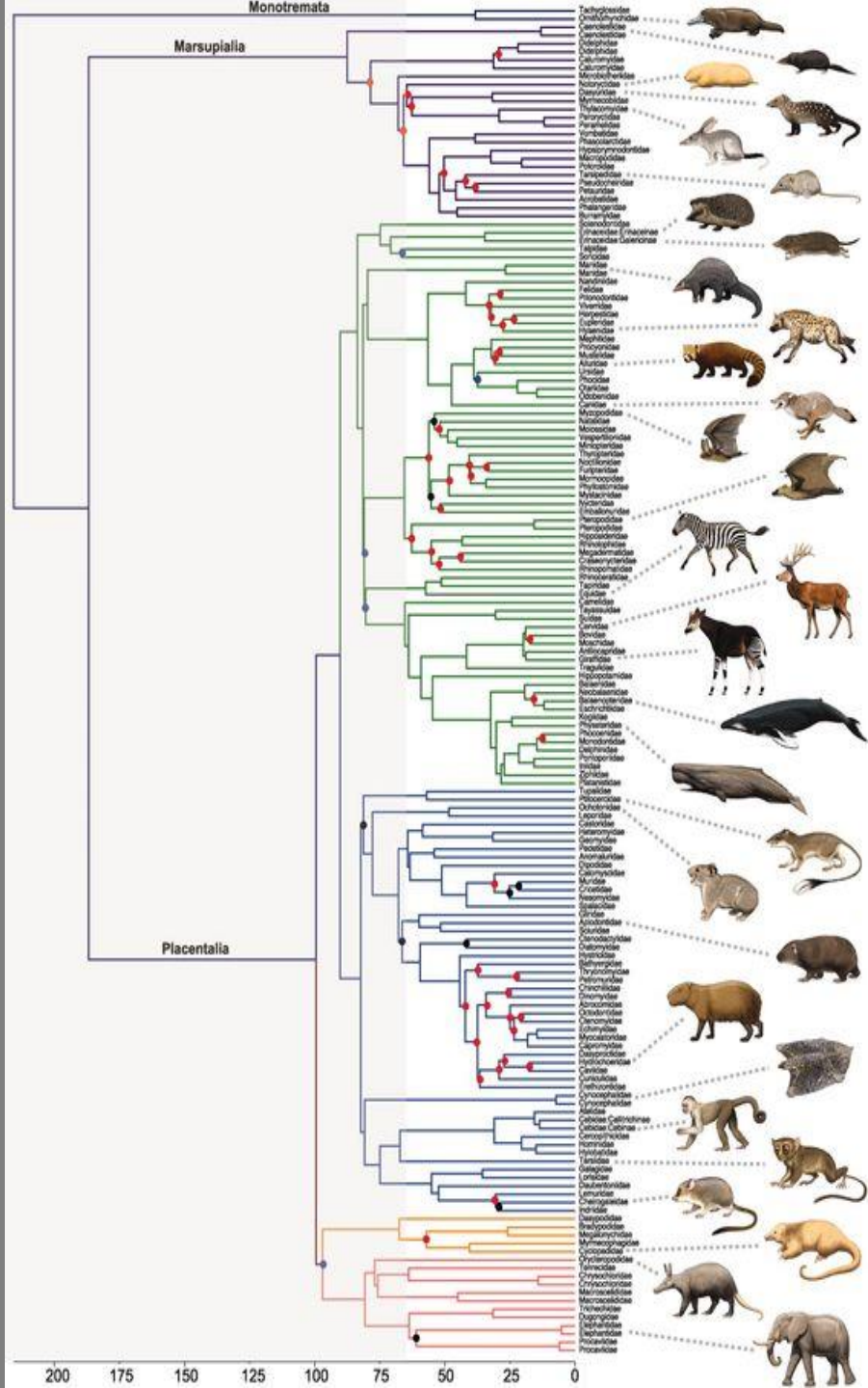
e.g. animal, plant




Rickettsia prokaryote bacteria
Cell membrane
mitochondria
Cytoplasm
Nucleus
Eukaryotic Cell
Organelles


prokaryotes
eukaryotes
archaea
bacteria
animals
fungi
plants
chloroplasts
mitochondria


The Tree of Life
L'ARBRE DE LA VIE · EL ARBOL DE LA VIDA · LEBENSBAUM
Origin of Life

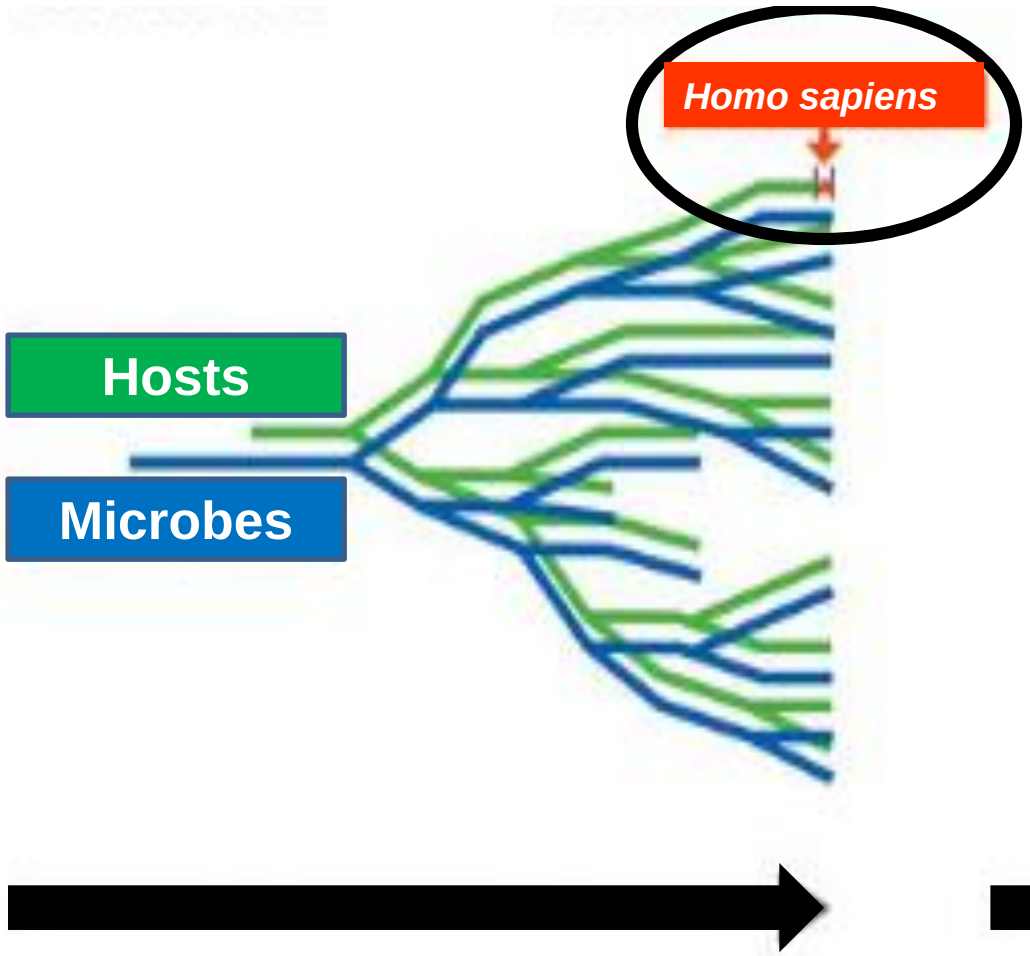

Monotremata
Marsupialia
Placentalia
200
175
150
125
100
75
50
25
0

1.5 Billion Year Co-Evolution

mutual adaptation & functional integration

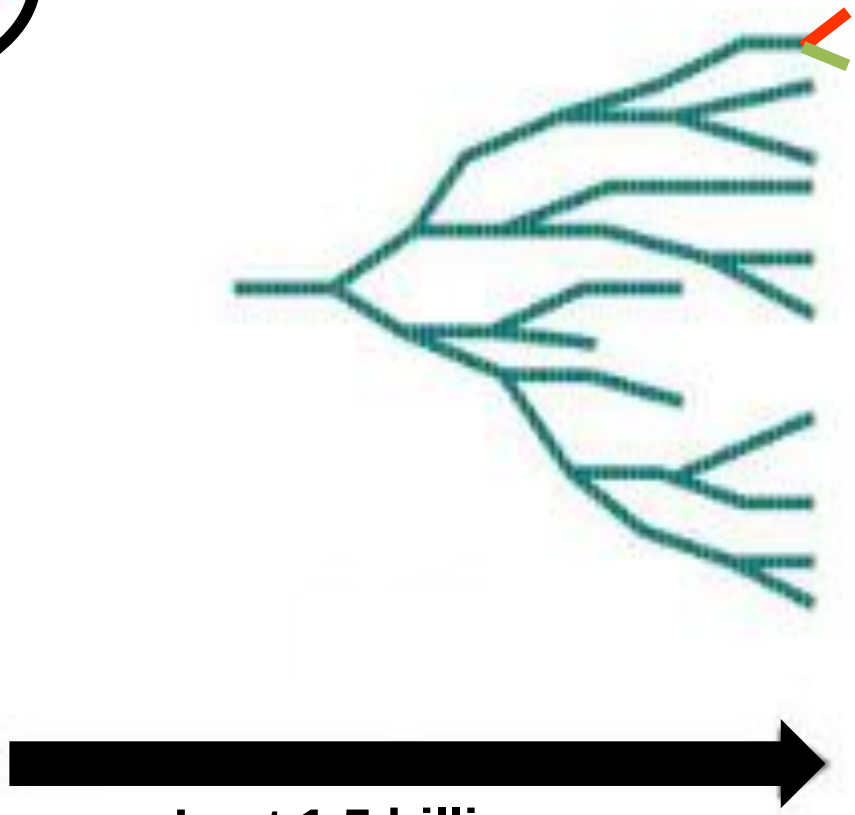
Our Microbes are 'Old Friends' – 'They Are Us'

Co-evolution of Host & Microbes



Mutual Adaptation & Functional Integration

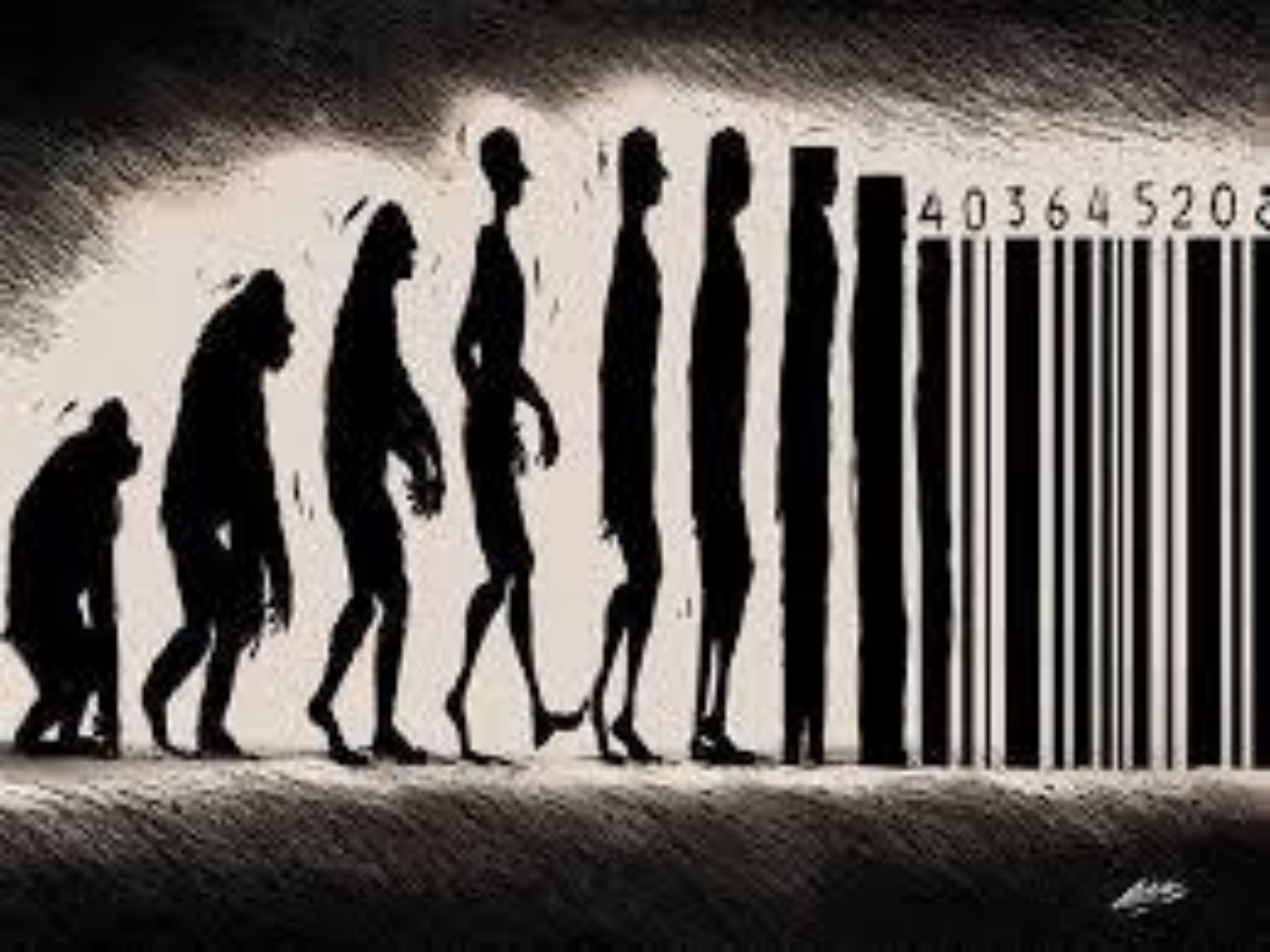
'Holobiont'



BDJ volume221, p657–666 (18 November 2016)

‘Survival of the Fittest’

or <u>most adaptable</u>


4 0 3 6 4 5 2 0

Lyn Margulis
1938-2011

Significance symbiosis in evolution

Evolution result of symbiotic mergers
e.g. of bacteria

"perhaps most important and dramatic event in the history of life"

Hurdles of Original Ideas

one grant application elicited this response:

"Your research is crap, do not bother to apply again"

her formative paper

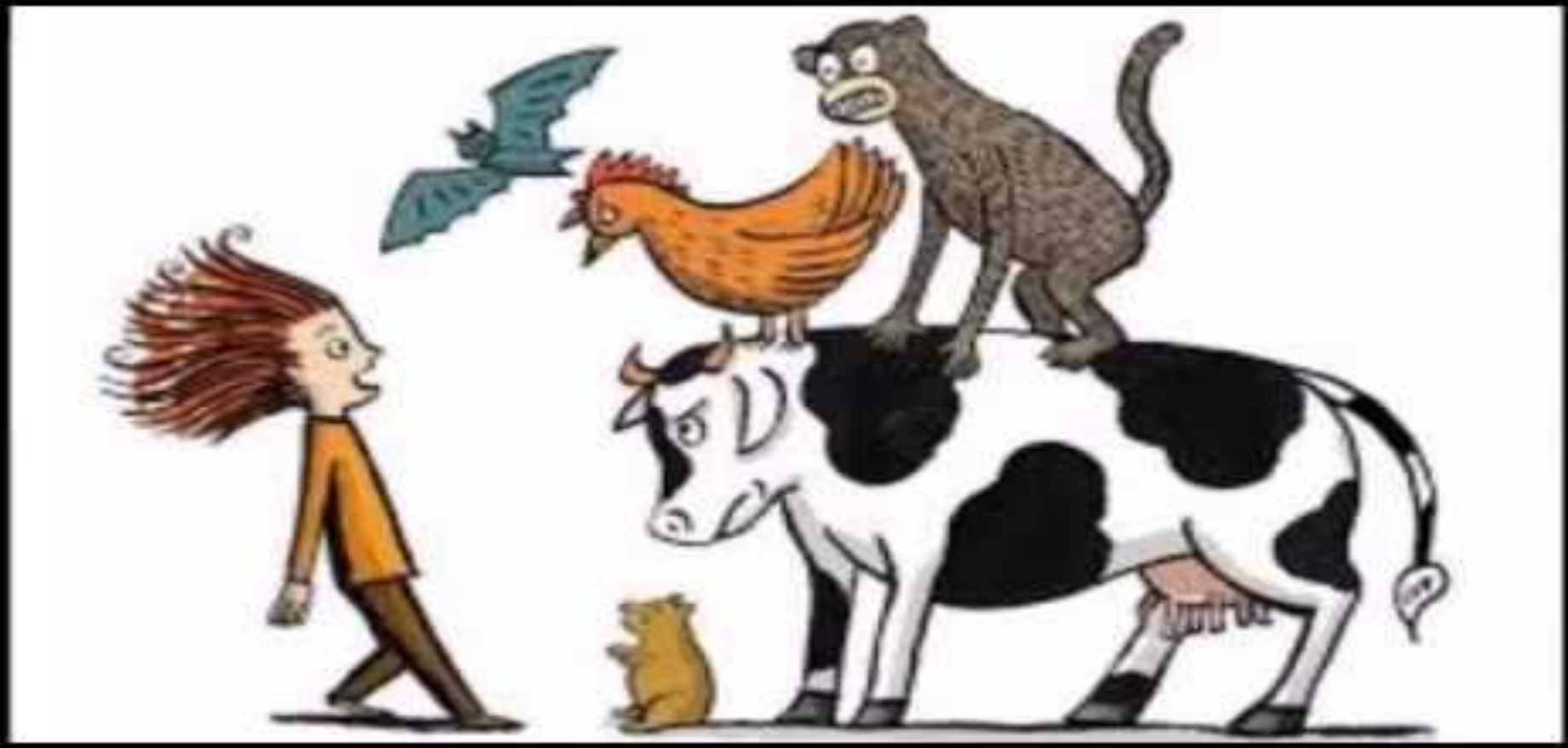
"On the Origin of Mitosing Cells" 1967

rejected by fifteen journals !

Hunter Gatherers – small groups

Paleo Diet

What Caused Most Infectious Diseases??



Rinderpest Virus infectious disease cattle

Rinderpest (German for cattle plague)

killed hundreds millions cattle over hundreds of years

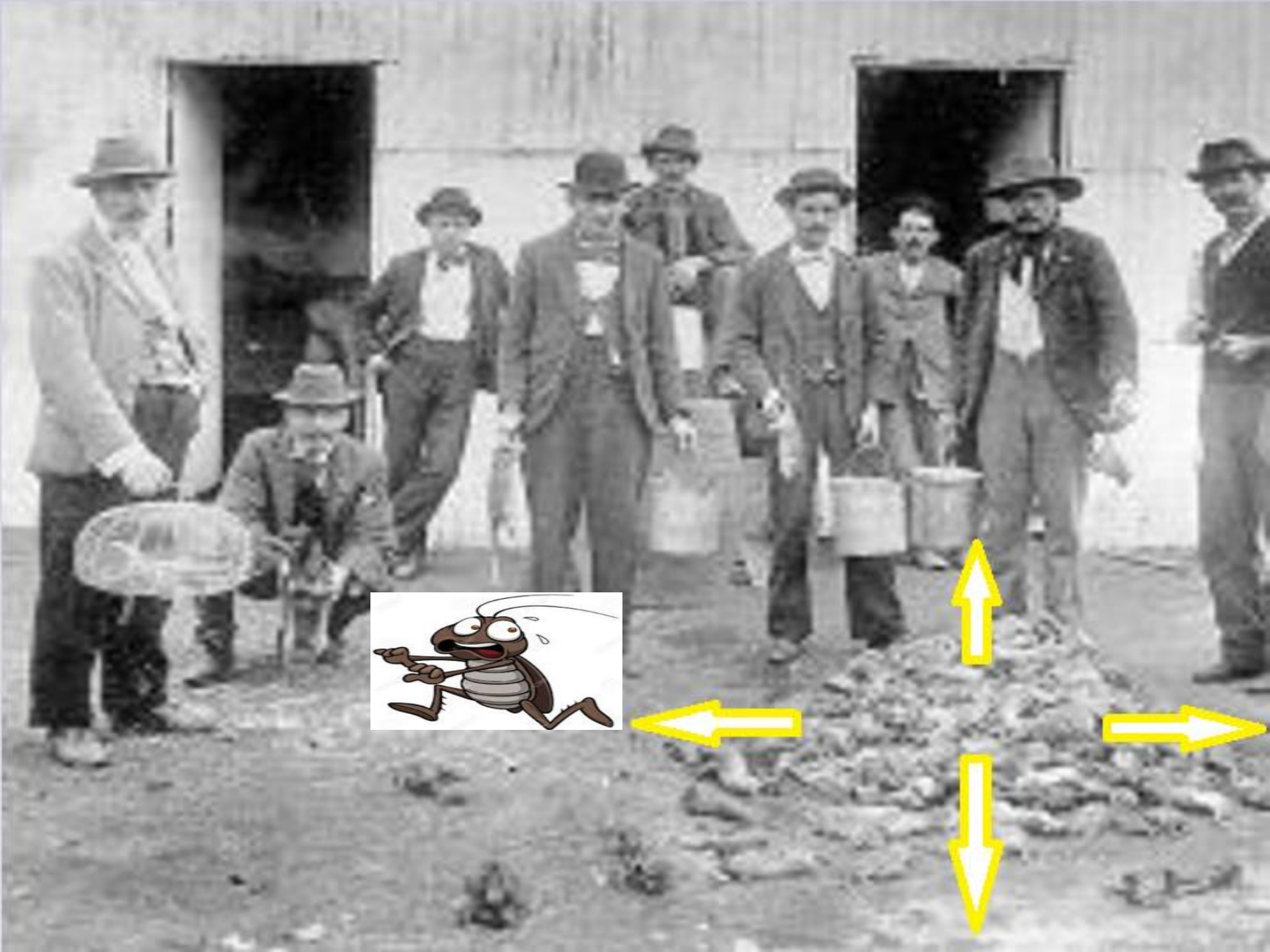
Last case 2001 **declared eradicated 2011**

Only second disease to be eradicated (after smallpox)

Rinderpest is a morbillivirus

includes virus causing measles to humans ~ 1,000 AD


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 19 Juni 1902
Geehrtes Fräulein
Freundlichen Gruß sendet Ihnen
Hochachtend



‘The Loneliest Place on Earth’

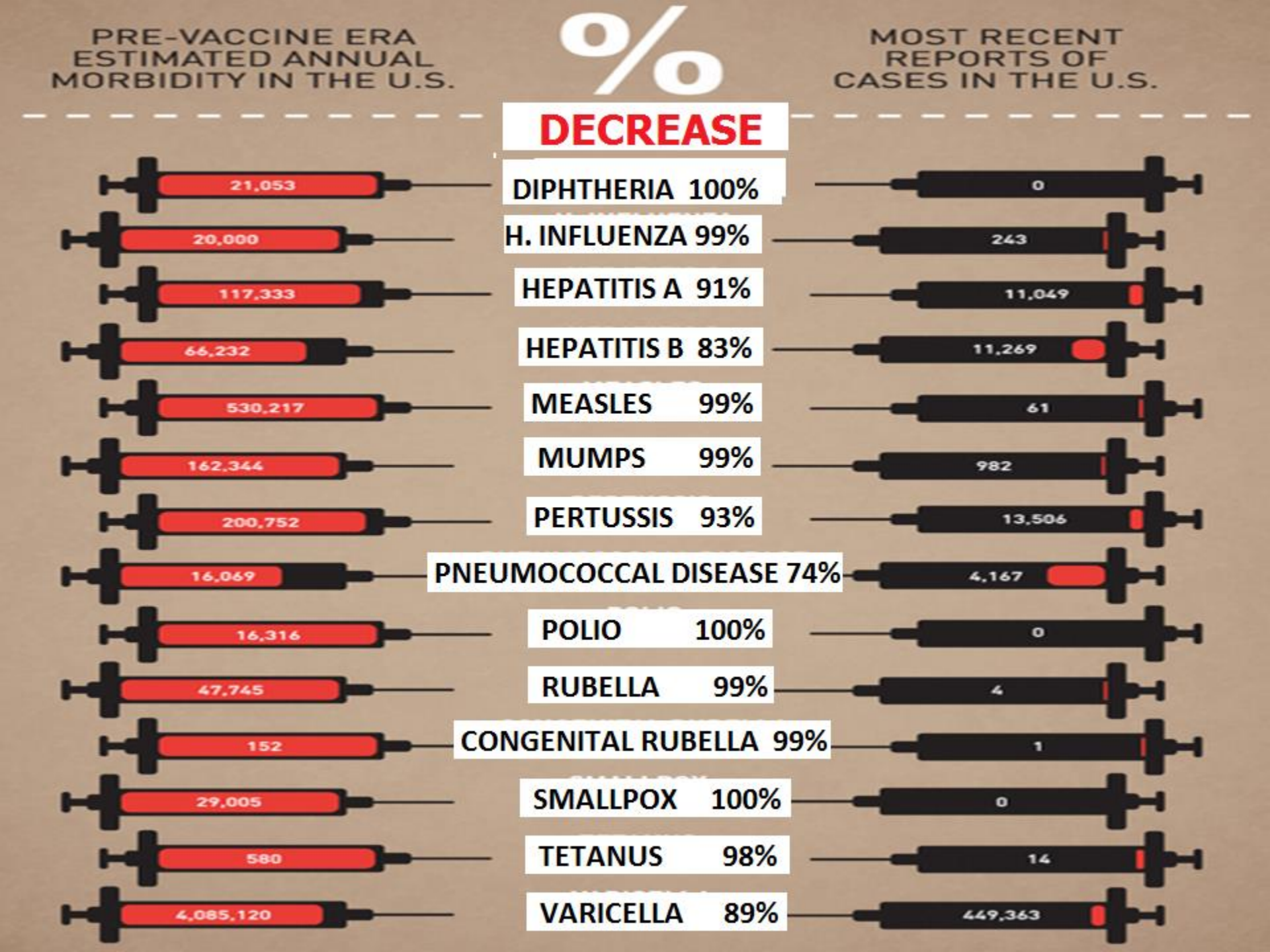
Human Infections

Used to be mainly **epidemics**:

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

i.e. exogenous source

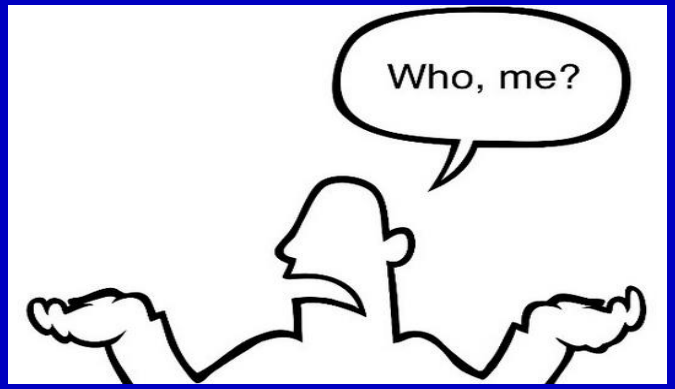
Public Health, Sanitation, Vaccinations
have largely contained or eliminated these


PRE-VACCINE ERA ESTIMATED ANNUAL MORBIDITY IN THE U.S.
%
MOST RECENT REPORTS OF CASES IN THE U.S.
DECREASE
21,053
DIPHTHERIA 100%
0
20,000
H. INFLUENZA 99%
243
117,333
HEPATITIS A 91%
11,049
66,232
HEPATITIS B 83%
11,269
530,217
MEASLES 99%
61
162,344
MUMPS 99%
982
200,752
PERTUSSIS 93%
13,506
16,069
PNEUMOCOCCAL DISEASE 74%
4,167
16,316
POLIO 100%
0
47,745
RUBELLA 99%
4
152
CONGENITAL RUBELLA 99%
1
29,005
SMALLPOX 100%
0
580
TETANUS 98%
14
4,085,120
VARICELLA 89%
449,363

Human Infections Now Mainly

Emerge from our own microbio**me**

i.e. endogenous source



Who, me?

No way!

Every Antibiotic Use Creates Endogenous MDRO Infections

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

From our own shared microbiome


SCIENCEphotoLIBRARY

"…. microbes are educated to resist penicillin …
the thoughtless person playing with penicillin is morally responsible for the deaths of those who succumb to infection with penicillin-resistant bacteria

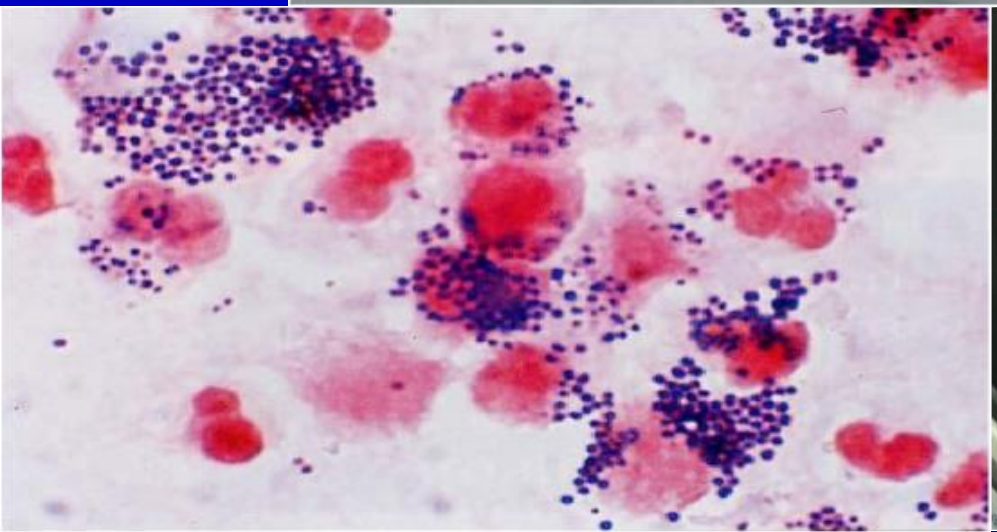
I hope this evil can be averted "

-Sir Alexander Fleming, June 1945

Staph aureus infection

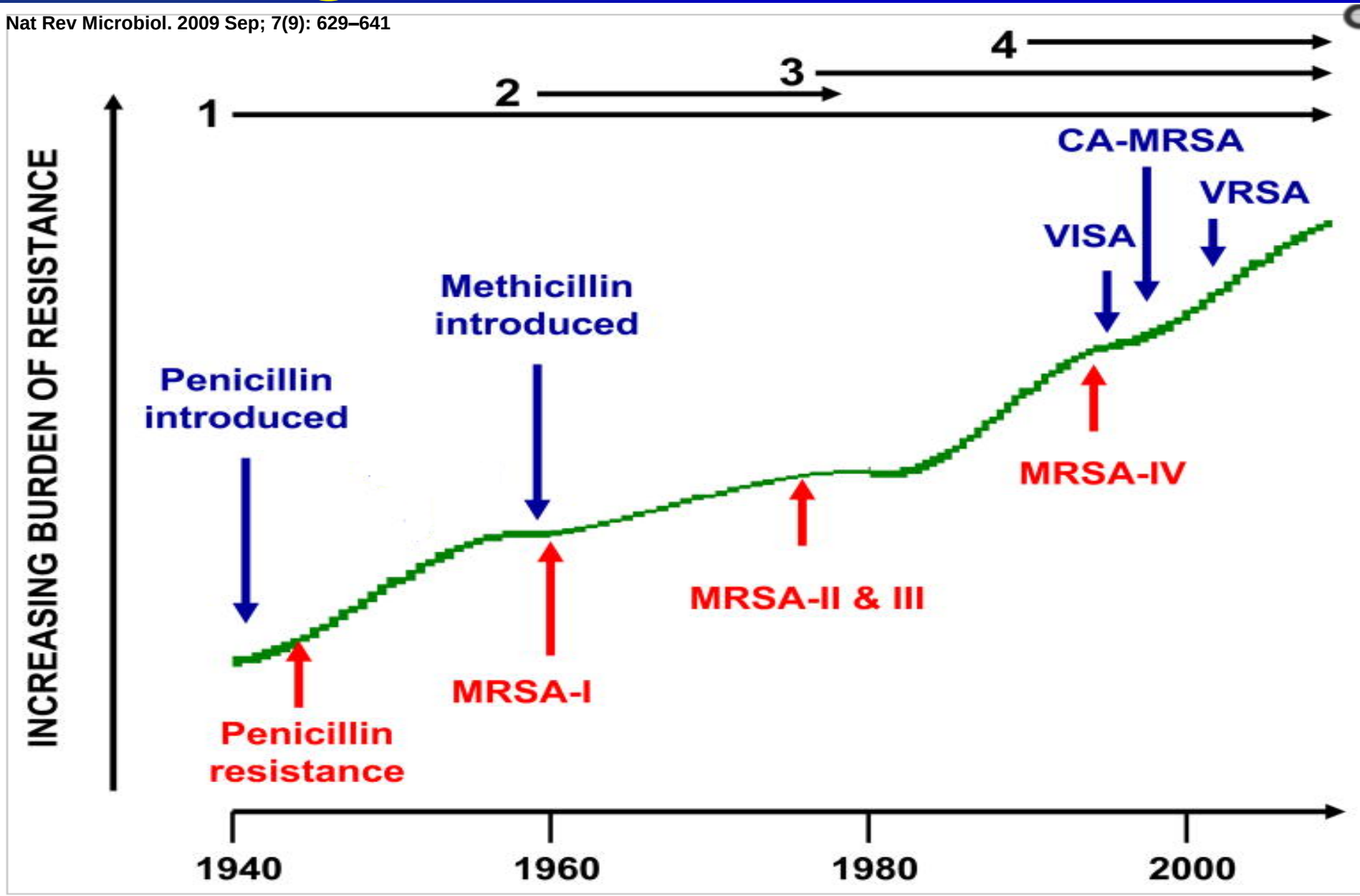
single species microbes are bad

‘eliminate them’

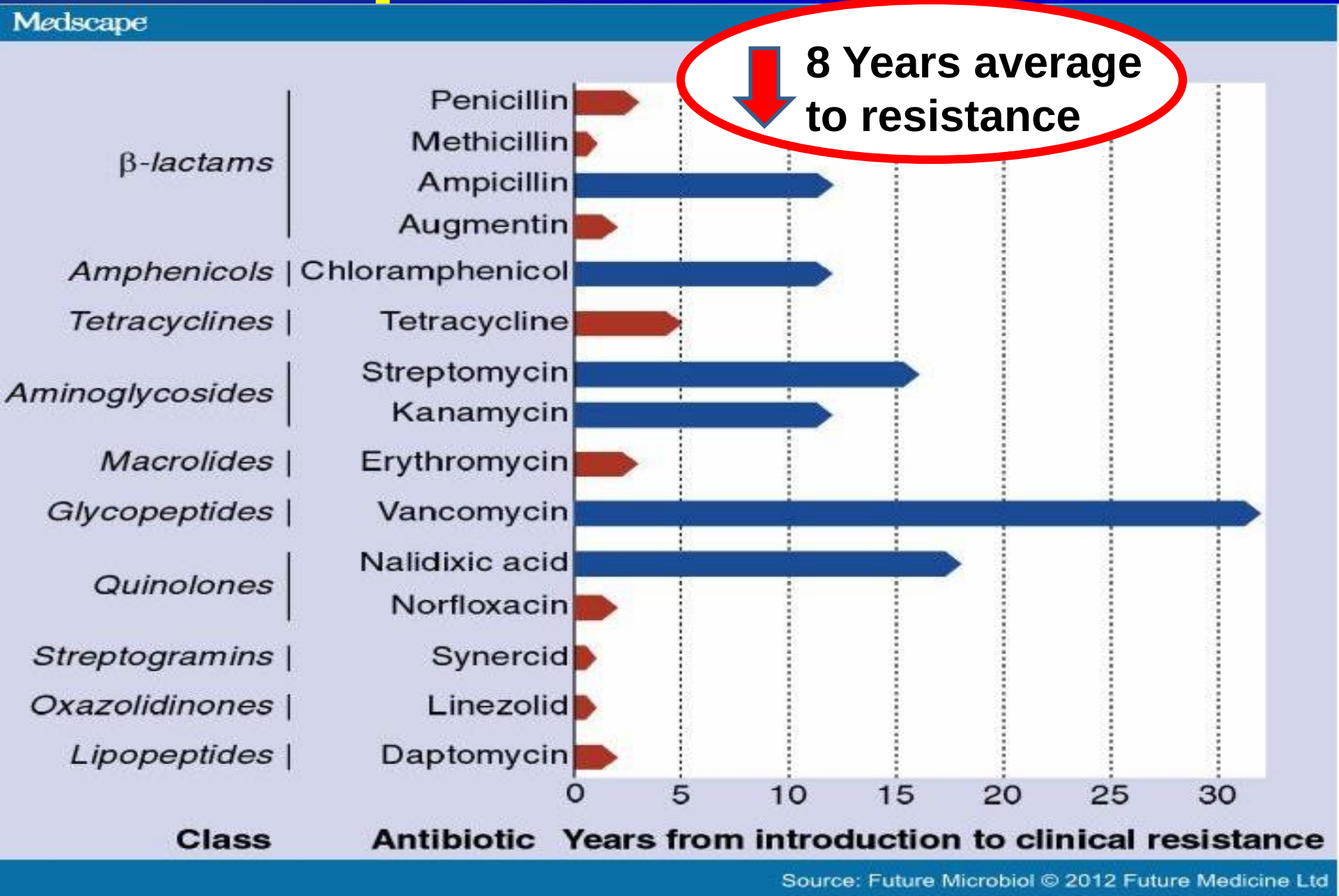


Fleming's Resistance Prediction

Nat Rev Microbiol. 2009 Sep; 7(9): 629–641



Lifespan Each Antibiotic



Evolution Adaptation Time

Humans

- **In 100,000 years humans 3,000 generations**

  (assuming 30 years per generation)

- **X10 is one million years human evolution**

Evolution Adaptation Time

Humans

- In 100,000 years humans 3,000 generations

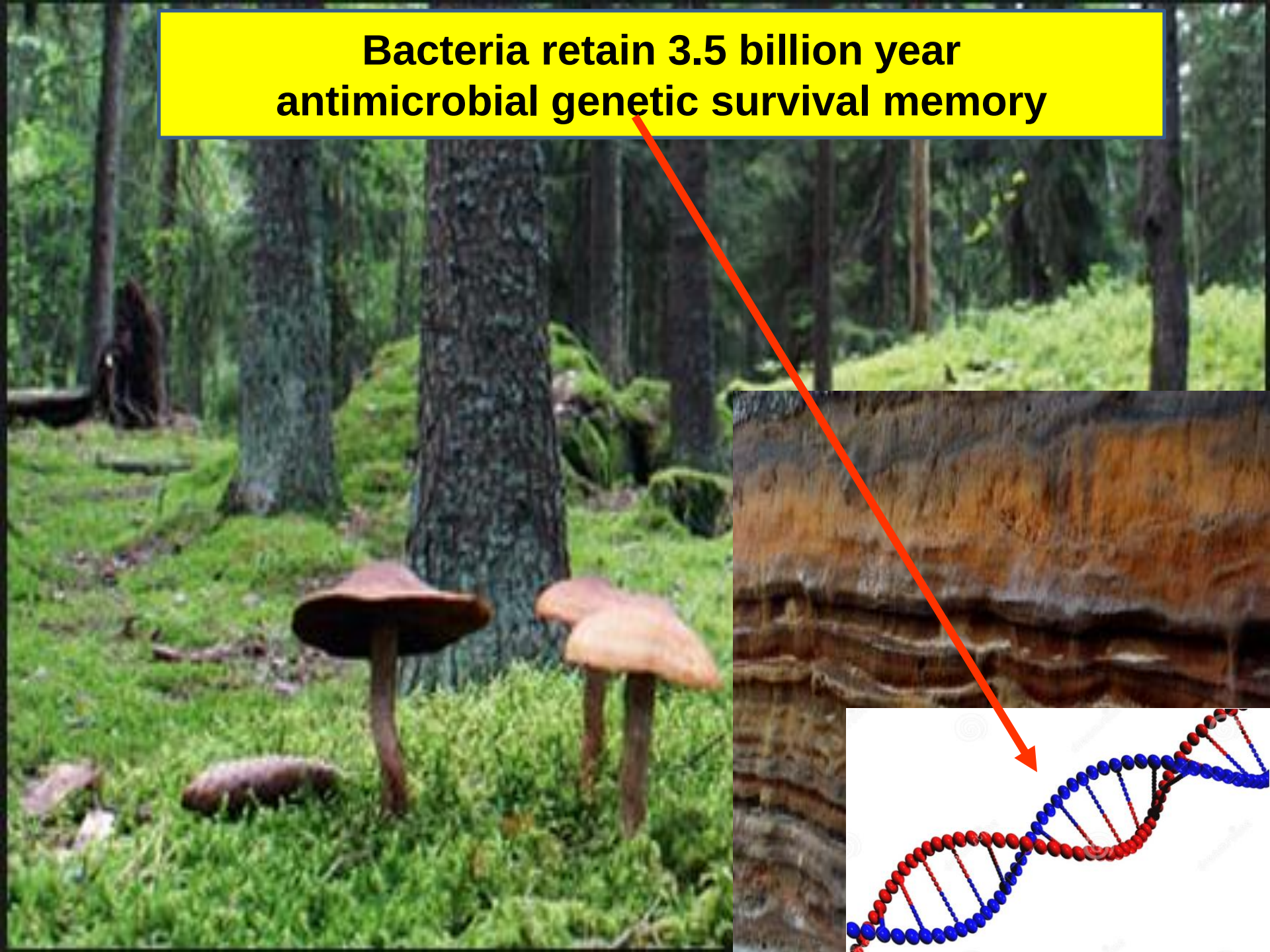
  (assuming 30 years per generation)

- X10 is one million years evolution

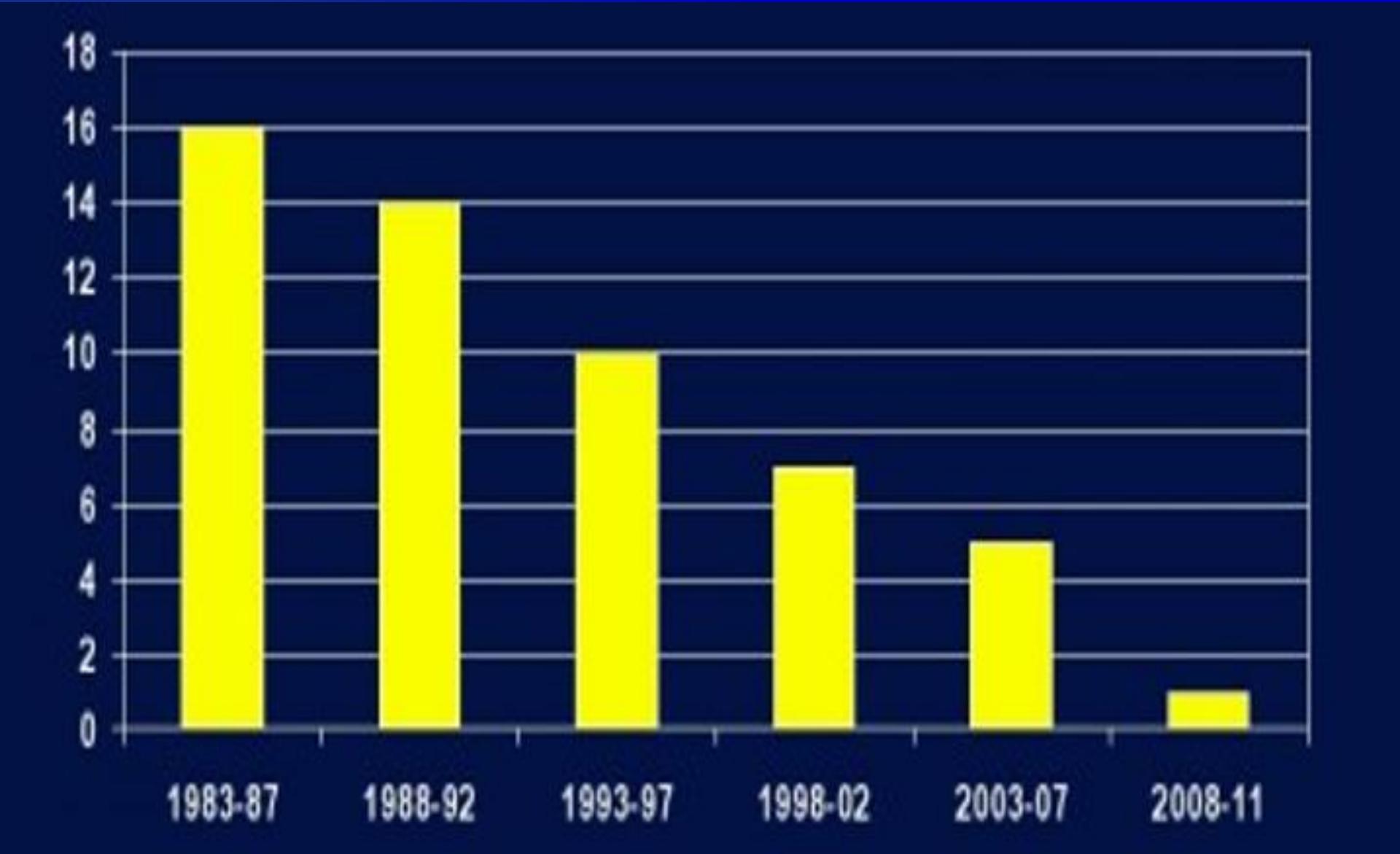
Bacteria

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

Bacteria retain 3.5 billion year antimicrobial genetic survival memory

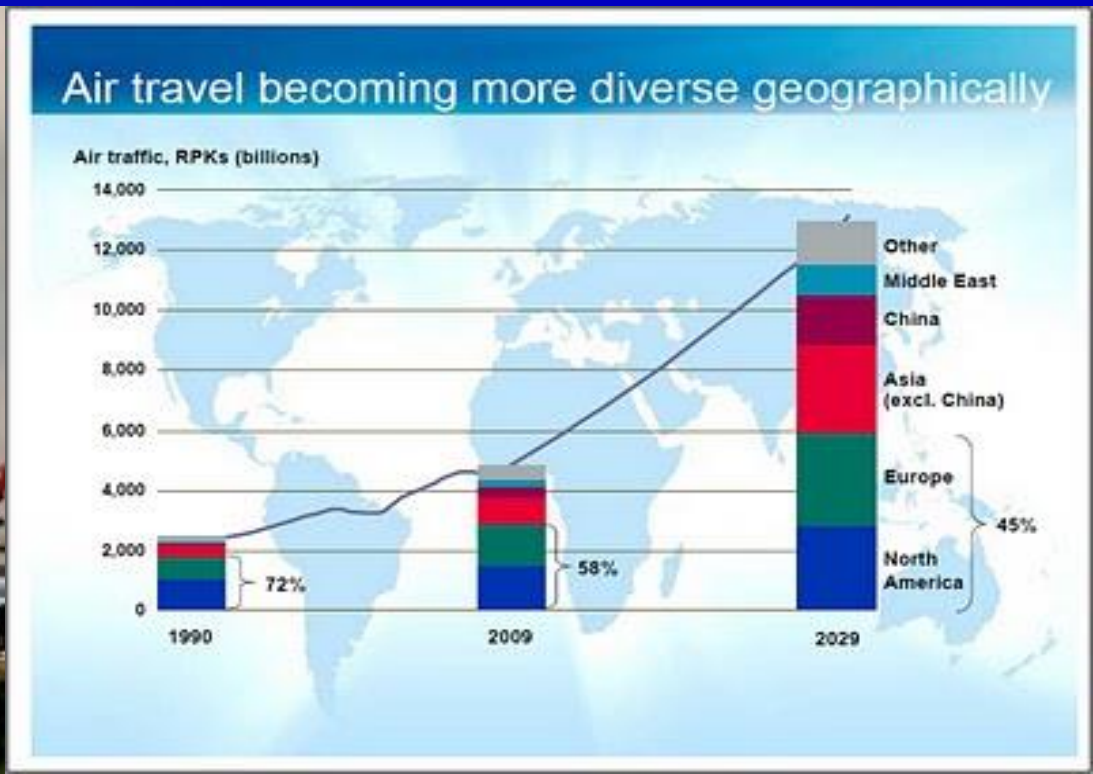


New Antibiotics each 5 years 1983-2011



Global Reality Trend

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



World Infection Trends

Todays emerging MDROs become tomorrows endemics

CPE

MDR TB

C. difficile

N. gonorrhoeae

ESBL, MRSA, VRE, Pseudomonas, Candida, Acinetobacter

Antibiotic Resistance Sharing

Our Microbial Ecosystem is Shared

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
Animal Feeds
Commercial Processing
Meat Poultry
Handling Preparation Consumption
Hospital
Community
Rest Homes
Calves
Pigs
Antibiotics
Other
Food Processing Antimicrobials
Pets
Direct Contact

Aust & NZ
Non Human Antibiotic Use

Aust

500 tons animal production

300 tons human therapeutic

+ Horticulture

+ Aquaculture

NZ

57 tons animal production

+ Horticulture

+ Aquaculture

NZ non medical AB use

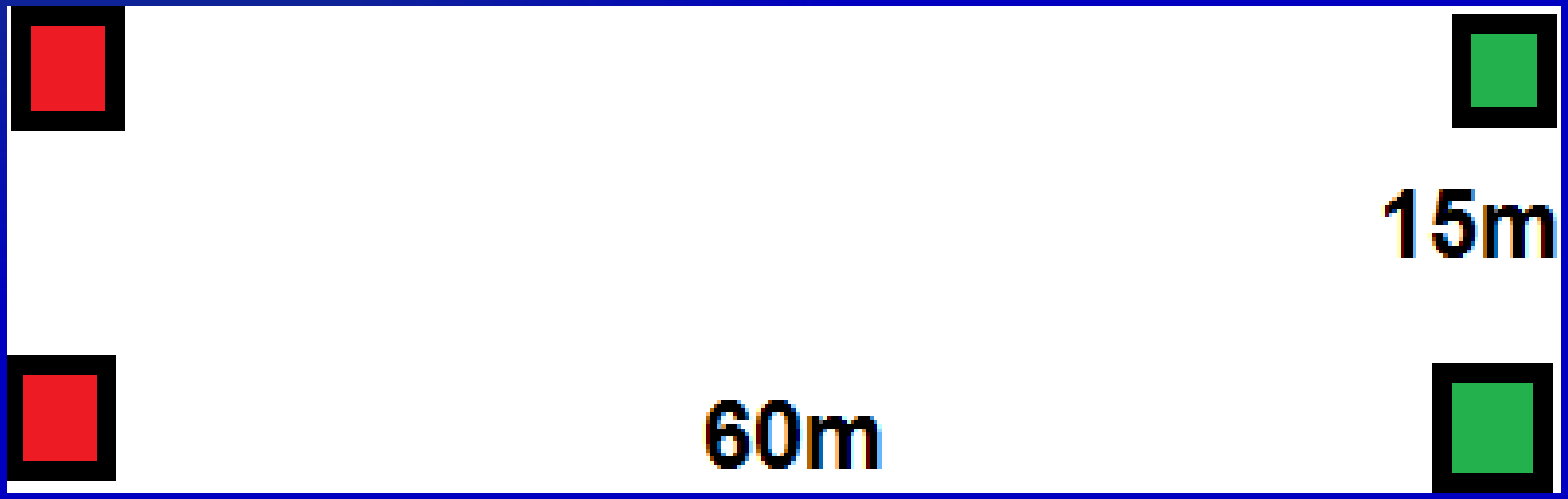
Veterinary: ~57,043 kg per year!

NZVA

Sub therapeutic use to be phased out by 2030 !

BUT ***not policy, only 'aspirational goal'!***

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**

> 50% E coli **<u>also resistant to</u>**

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

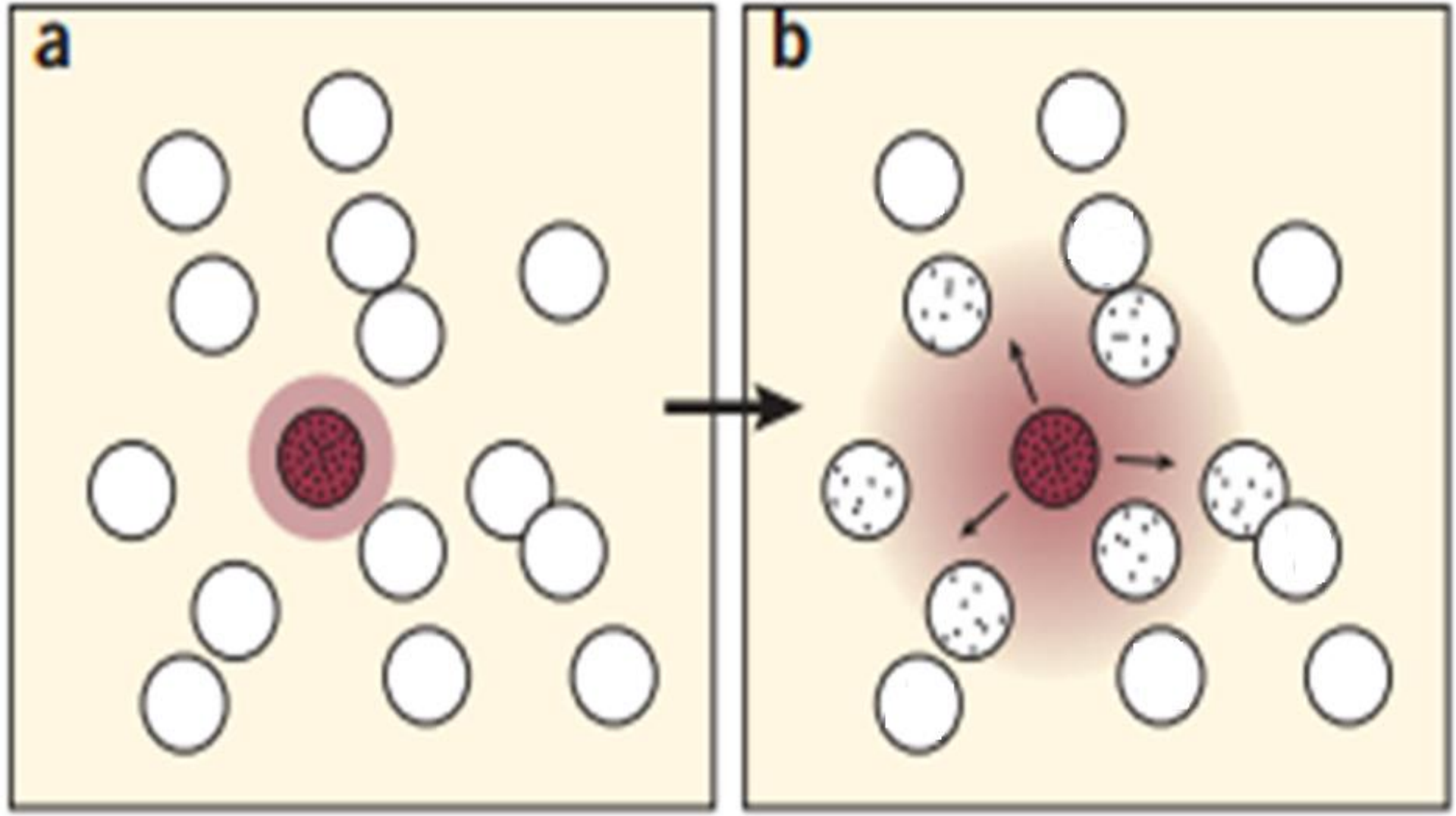
Chickens Fed Tetracycline

Farm workers then developed increased intestinal resistance

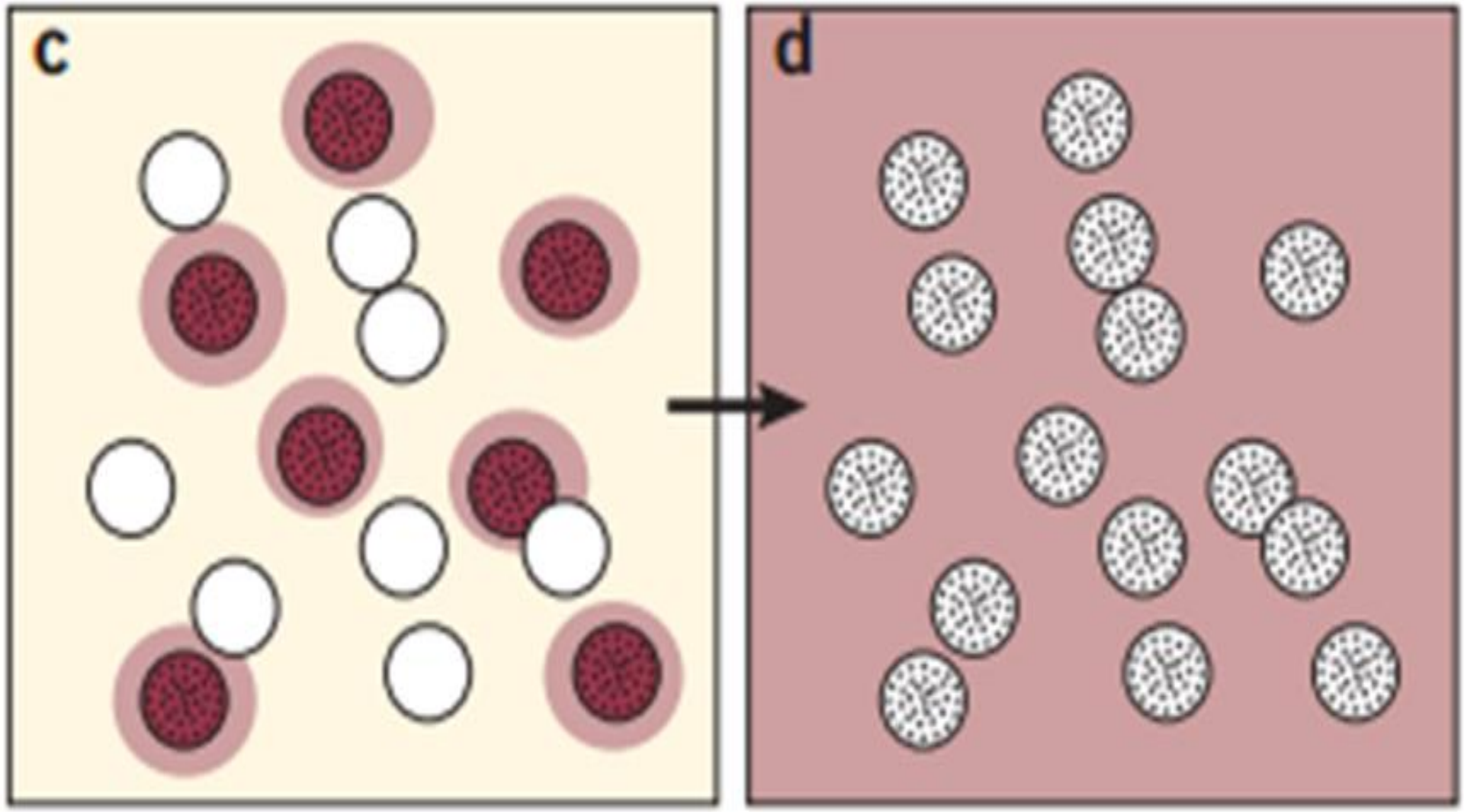
Within six months 31.3 % weekly faecal samples from farm dwellers had >80% tetracycline resistant bacteria

Antibiotic Resistance Sharing With Others

e.g. HCWs & Patients



The More on ABs the More Shared ↑ Community MDROs




SPECIAL!
SPECIAL!

2014 Swiss Travellers Study ESBL

Kuenzli et al. BMC Infectious Diseases 2014, 14:528

170 Swiss travellers, colonisation rates

- 2.8% ESBL positive pre travel
- 69.4% ESBL positive post travel

BUT

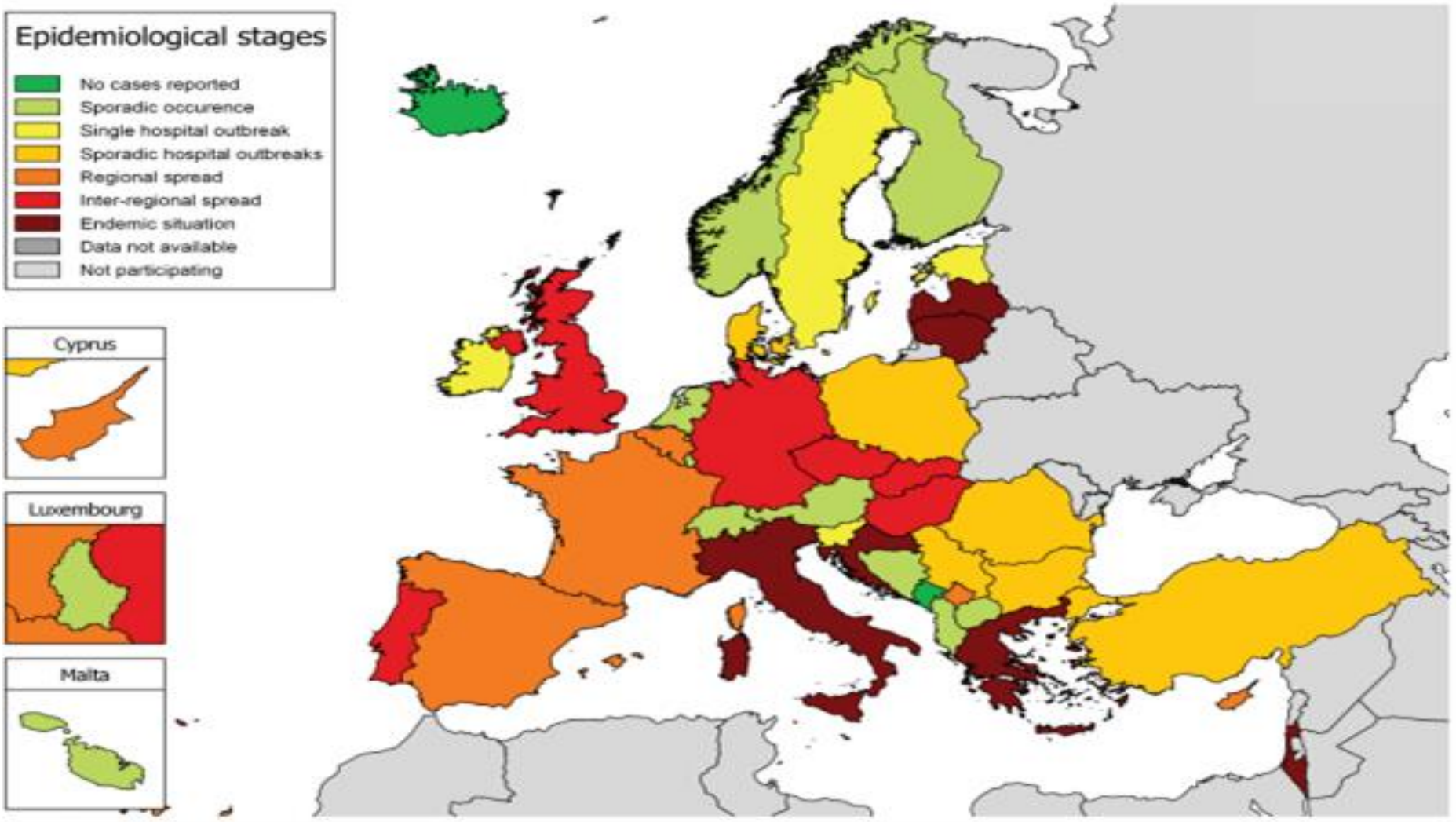
86.8% ESBL colonisation rate if travelled to India or Indian subcontinent

Risk factors included consumption ice cream & pastry (OR 3.9)
visiting friends /family, length of stay

Conclusions: High colonisation rates ESBL in travellers returning from South Asia. Environmental source best explains high colonisation

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

NZ Antibiotic Consumption

- **increased 49%** from **2006 - 2014**
- **Last year a further 9.8% increase (Pharmac)**

The increased consumption occurred

across all regions

in all ages

amongst all ethnic groups

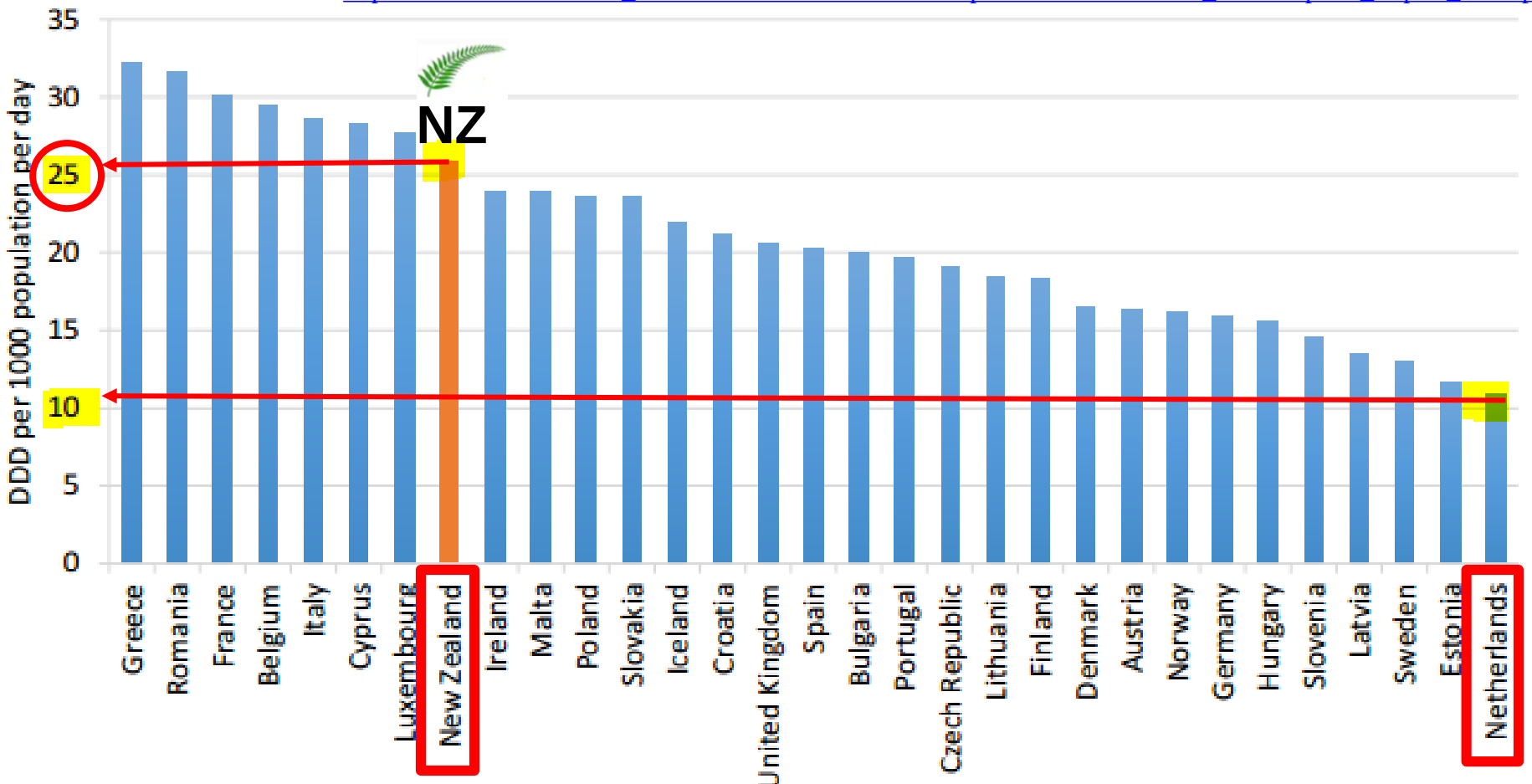
https://surv.esr.cri.nz/PDF_surveillance/AntibioticConsumption/2014/Antibiotic_Consumption_Report_Final.pdf

NZ Antibiotic Consumption

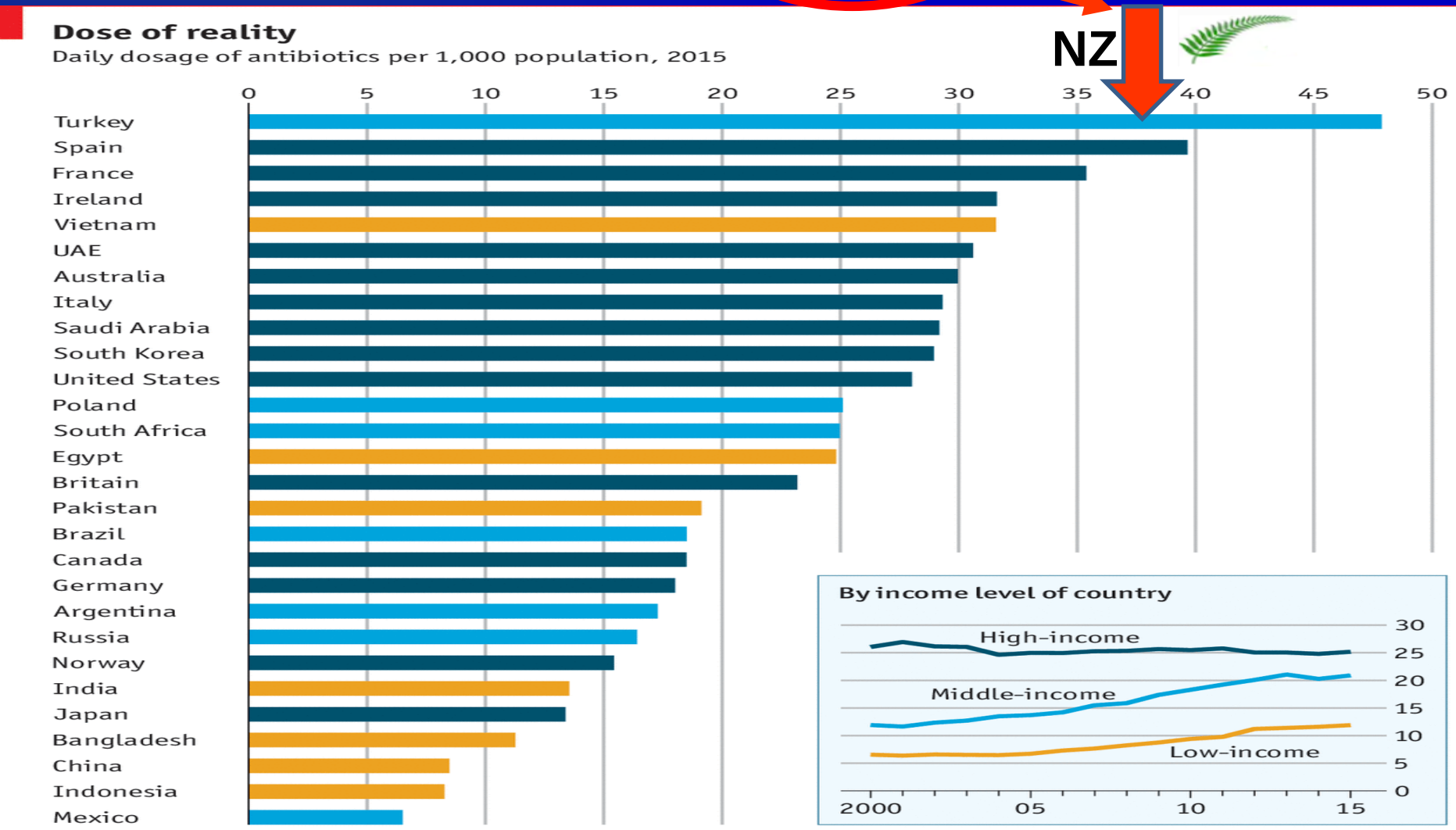
25 DDD in 2013 relative to EU countries

Figure 45. Antibiotic consumption of 29 European countries and New Zealand, 2013, expressed as DDD per 1000 population per day

https://surv.esr.cri.nz/PDF_surveillance/AntibioticConsumption/2014/Antibiotic_Consumption_Report_Final.pdf



Rising Income Rising AB Use
NZ 2016 ↑ to 38.5 DDD/10^3



Source: "Global increase and geographic convergence in antibiotic consumption between 2000 and 2015", by Eili Klein et al., Proceedings of the National Academy of Sciences, March 2016

Economist.com

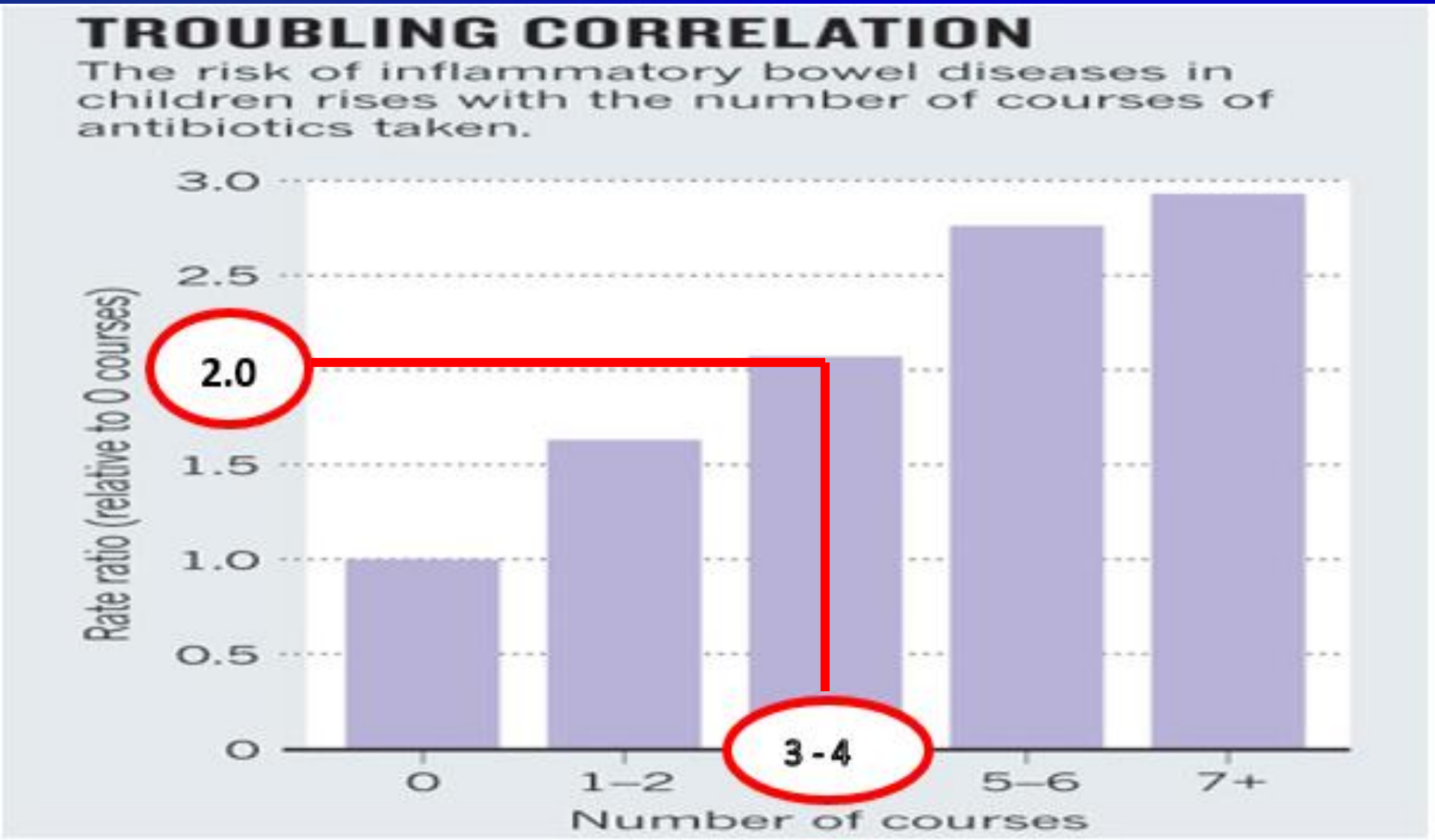
NZ Antibiotic Use 2012

Assoc Prof Mark Thomas, University of Auckland

Annually:

180 AB courses per 100 children <5y

IBD & Number Antibiotic courses in children correlation



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

Nature 25 August 2011 vol 76, p393

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

Stop the killing of beneficial bacteria


and Reading Time
Blood
pH
Negative
Trace
Strip Handle

What Role Dipsticks??

"UTI" in the Emergency Department (ED)

25.4 million U.S. adult ED visits over 8 years

where "UTI" diagnosed & treated:

- **urinary symptoms in only 32% adults**
- **24% older adults**
- **17% of ≥ 85 year olds**

UTI is a clinical diagnosis, NOT Dipstick

Acad Emerg Med 2012 Oct;19(10):1173-80

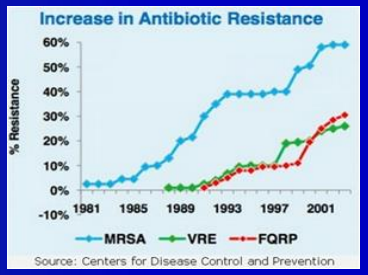

24
22
25½
24¼
27½

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

MDRO 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

Antibiotics

‘the biggest impact on post industrial medicine’

We are losing them by our own actions

Think Global, Act Local

Ethics

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.


We're not
ALL BAD!!

Our Actions Now Are Our Future

Ben Harris

Medical Microbiology Scientist

NZ Infection Prevention & Control Consultancy

NZIPCconsultancy@gmail.com

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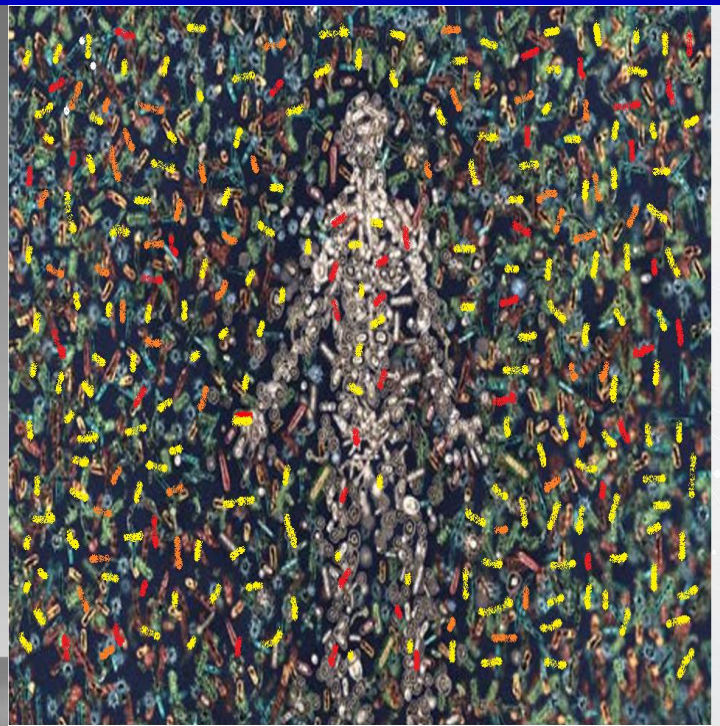
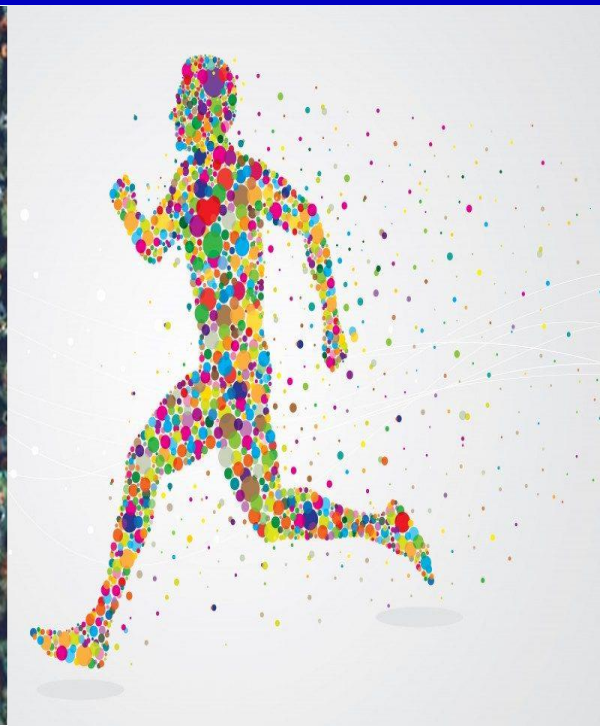




Unique, Only Antibiotics unlike other drugs

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

Todays choices affect future patient outcomes - temporal ethics

Common 'Non Antimicrobials'

Table 2. Day 1, 2, 3 growth of bacterial species against different drugs and concentrations

		S. aureus			*K. pneumoniae*			*E.coli*			*P. aeruginosa*		
	Incubation	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3	Day 1	Day 2	Day 3
Chlorhexidine	4%	0	0	0	0	0	0	0	0	0	0	0	0
	2%	0	0	0	0	0	0	0	0	0	0	0	0
	1%	1	0	0	1	0	0	6	0	0	3	0	0
	*0.5%	1	0	0	1	0	0	1	0	0	1	1	0
Triclosan	1%	1	0	0	1	0	0	1	0	0	9	TMTC	TMTC
	0.5%	1	0	0	1	TMTC	TMTC	1	0	0	9	TMTC	TMTC
	*0.25%	0	2	0	1	1	TMTC	1	0	0	TMTC	TMTC	9
	0.125%	1	5	0	1	2	TMTC	1	0	0	TMTC	TMTC	9
Ibuprofen	*50mg/ml	1	0	0	10	TMTC	9	9	6	9	9	9	10
	*25 mg/ml	0	0	0	TMTC	TMTC	10	TMTC	9	10	1	6	1
	*12.5 mg/ml	3	0	0	TMTC	TMTC	TMTC	TMTC	9	10	7	7	1
	6.25 mg/ml	9	1	3	TMTC	TMTC	TMTC	TMTC	10	9	2	6	3
Fluoxetine	20 mg/ml	0	0	0	0	0	0	1	0	0	1	0	0
	10 mg/ml	0	0	0	0	0	0	1	0	0	1	1	1
	*5 mg/ml	0	0	0	4	2	6	1	0	0	1	0	1
	*2.5 mg/ml	0	0	0	TMTC	9	7	0	0	0	1	3	1

*Asterix denotes normal therapeutic concentration

0-10 increasing bacterial growth count up to TMTC

TMTC= Too many to count, confluent growth

Control incubation plates without any drug were all confluent growth TMTC on day 1-3

The Ultimate Survivors, bacterial resistance by selection and resistance induction to antibiotics, common biocides and also commonly used drugs not usually associated with antimicrobial activity
Chris Deterling,; Ben Harris

doi: 10.5281/zenodo.2546056

Chlorhexidine Exposure Selects Antibiotic Resistance (MIC's)

MIC = Minimum Inhibitory Concentration to inhibit bacterial growth

The higher the number the more resistant the bacteria

	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

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

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

MDROs

- 1st 'superbug' Penicillin Resist Staph aureus

  1945 now 90% all Staph aureus penicillin resistant

  i.e. 'lost Penicillin resistant battle'

- 1st MRSA UK 1961

  now 5% MRSA rate all South Island Staph aureus

  14% AKL, SE Asia 24% - unless hospitalised 66%

  i.e. endemic, 'lost MRSA battle'

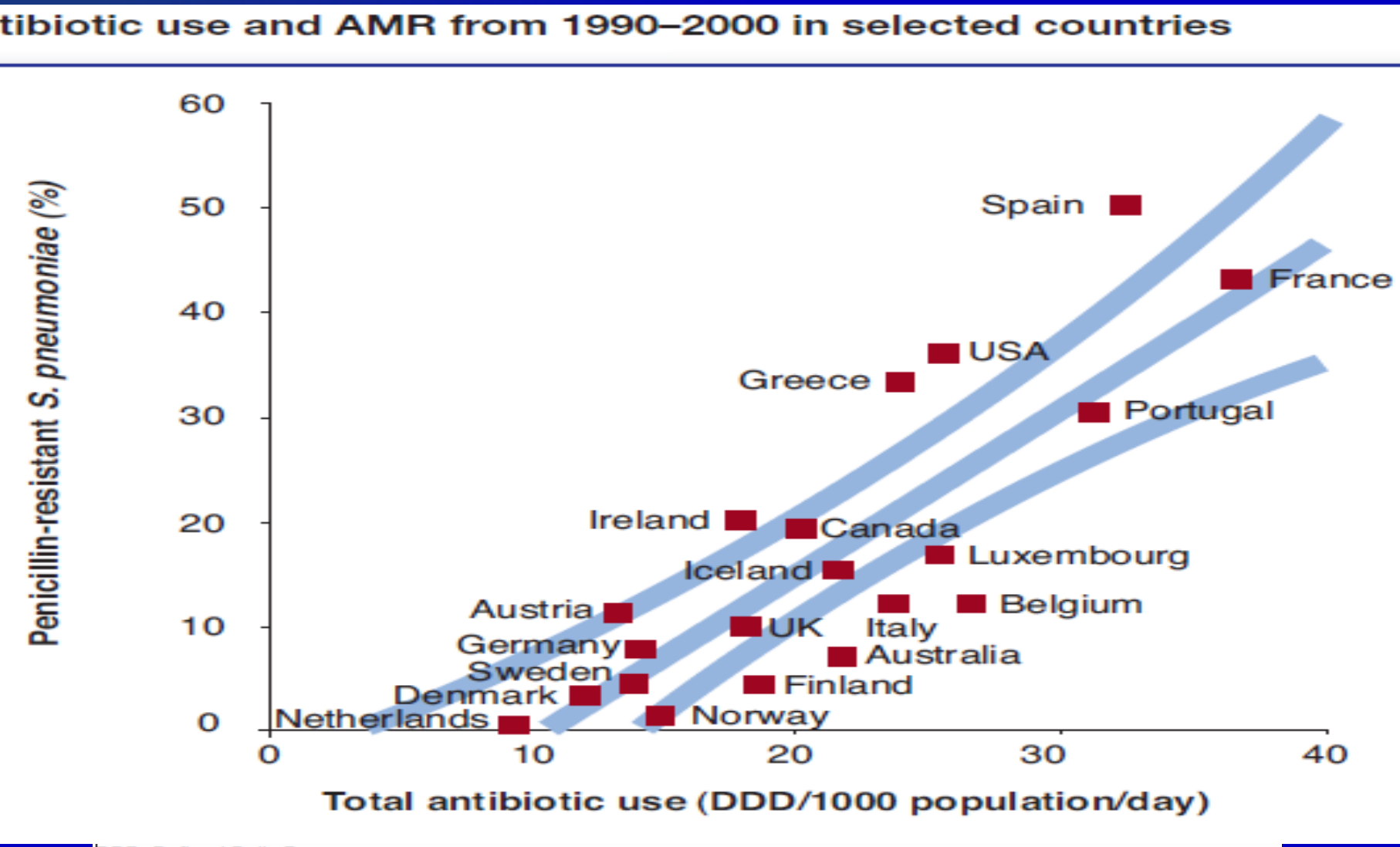
CPE, ESBL - staggeringly fast emergence and only since 2000

Behaviour Change Theory

Three Key Factors Drive Change

1. **Relevant to Self ? i.e. will it affect me**
    a. **Patient – yes, when explained, microbiome damage affects medium to long-term adverse health outcomes (obesity, mental health autoimmune illnesses, debilitation, cancer, etc)**
    b. **Prescriber - peer review comparison, business??**
2. **Interesting ?**
3. **Credible Source ?**

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.

Where is Most ABR?

Association antibiotic consumption and resistance well documented across

- **hospitals** (30-50% all patients ABs at any one time)
- **nursing homes** (NZ 40,000 residents 10% ABs per month)
- **primary care facilities** (? 10% presentations '?UTI')
- **communities** (dental, veterinary, etc)

plus between countries (people & food)

Dipsticks in Rest Homes

30-50% residents have asymptomatic bacteriuria – but no clinical infection

80% all residents have positive dipsticks

Conclusion:

No Role for DIPSTICKS

Dangerous by clinical misdirection and

Antibiotic overtreatment by 60-80%

Do Probiotics Help or Hinder Post ABs ?

Post antibiotics, probiotics cause *markedly delayed*

indigenous gut mucosal reconstitution

- composition, function, bacterial load

+ *prolonged dysbiosis ≥ 5 months*

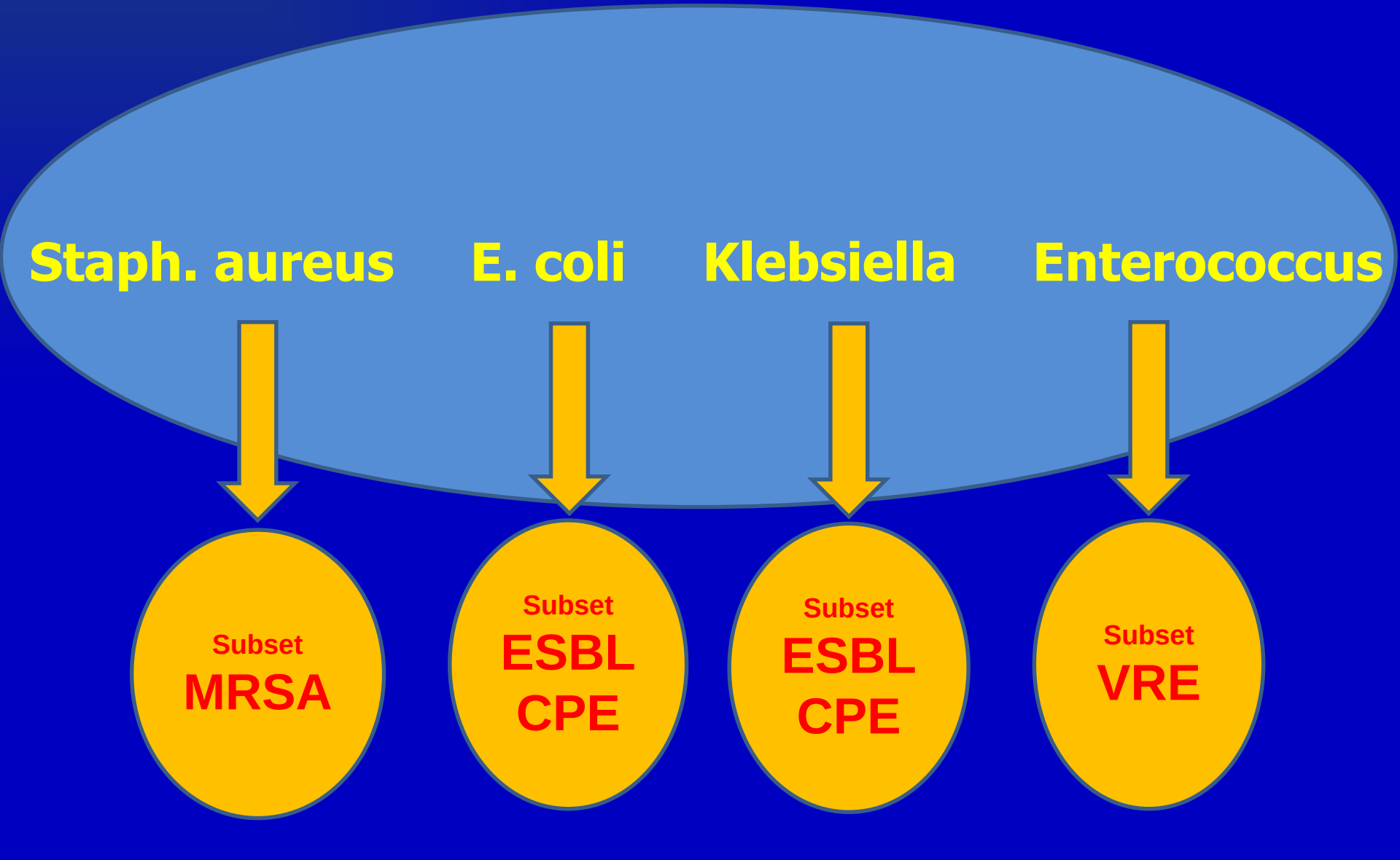
following cessation of probiotic exposure

Probiotic-induced "adverse effect" important because multiple observations link antibiotic-associated dysbiosis and lower microbial diversity with increased susceptibility to many chronic and infectious diseases

Cell Vol 174 Number 6 P1406-1423.E16, SEPTEMBER 06, 2018

Post-Antibiotic Gut Mucosal Microbiome Reconstitution Is Impaired by Probiotics and Improved by Autologous FMT

MDRO Approach
Silo or Horizontal Required ?



Biggest Threats MDROs CDC

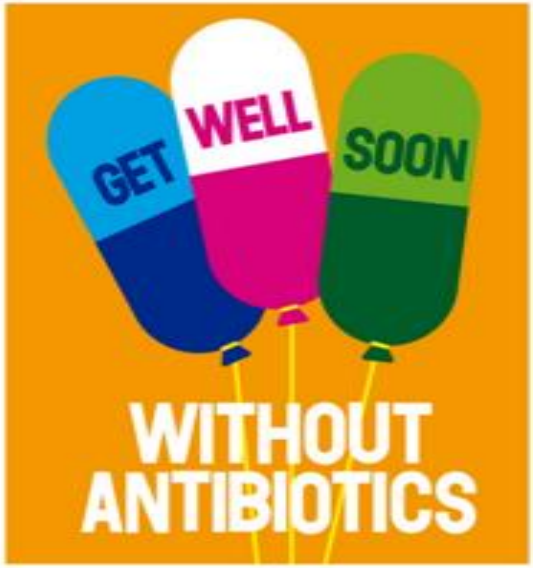
Urgent Threats – high consequence risks
- potential to become widespread

- Clostridium difficile (CDIFF)
- Carbapenem-Resistant Enterobacteriaceae (CRE/CPE)
- Neisseria gonorrhoeae

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 (CPE)	- sensitive BUT how much longer ?

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/