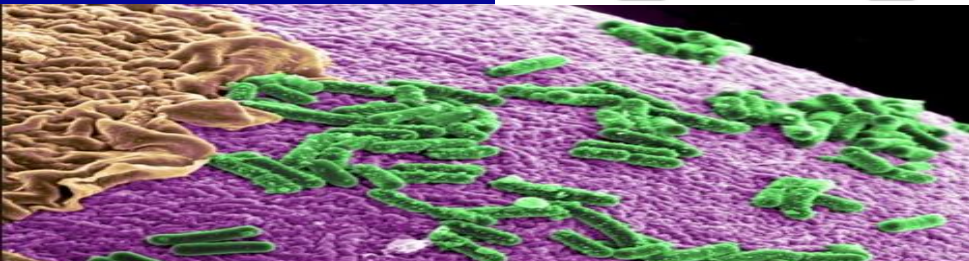


Antibiotic Resistance

Mutations or Creations?

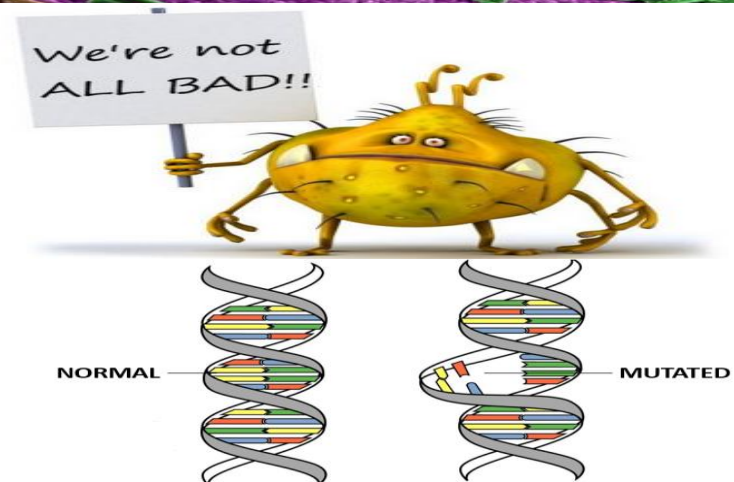
How We Squander a Miracle

Ben Harris Med Lab Scientist Infection Prevention & Control



The Microbe is Nothing

The Terrain is Everything



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
multicellular Eukaryote
organisms, plants & animals

Cell membrane

Cytoplasm

Rickettsia prokaryote bacteria



Cell membrane

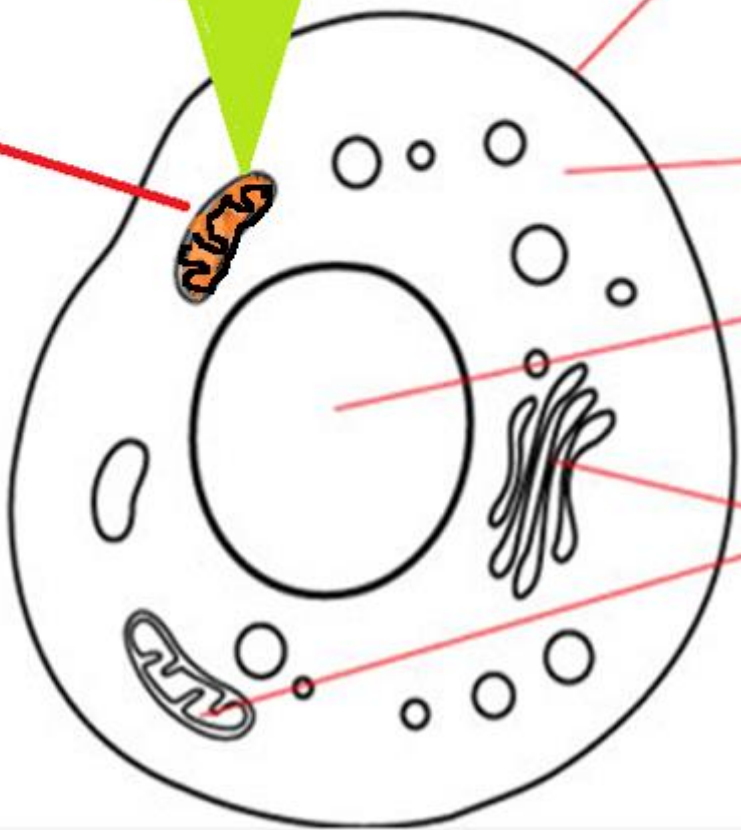
mitochondria

Cytoplasm

Nucleus

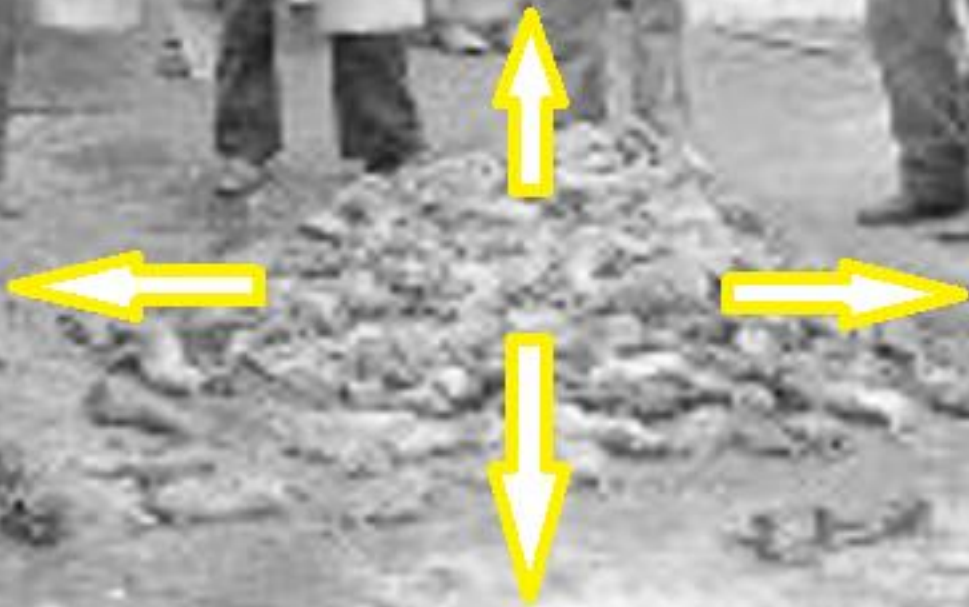
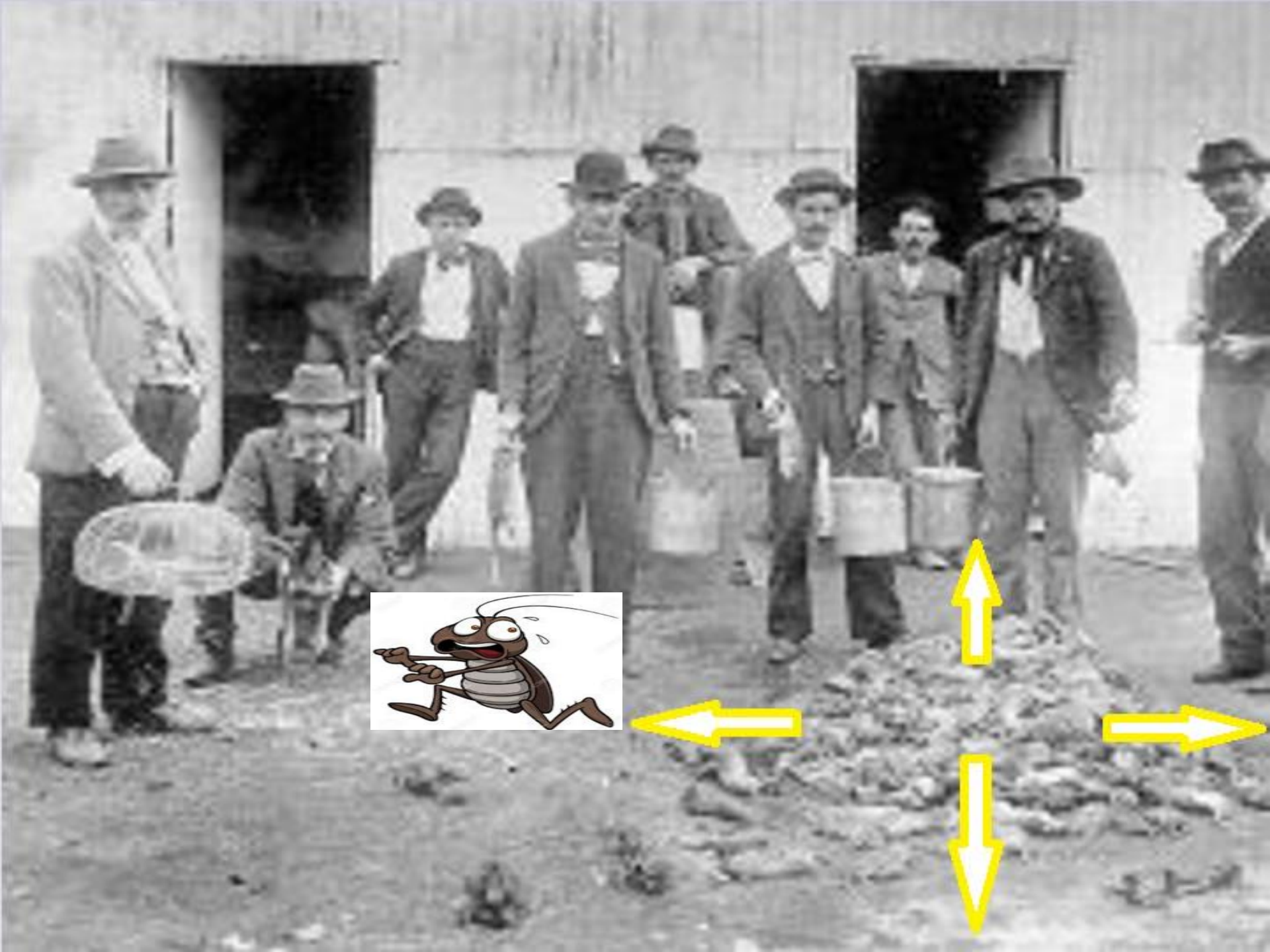
Eukaryotic Cell

Organelles









Human Infections (1)

Used to be mainly epidemics:

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

i.e. exogenous source “All Bugs Are Bad”

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



'All Bugs are Bad'

Deadliest pandemics including:



- 14th-century Black Death 75 to 200 million plague deaths in Europe
- 1492 Post Columbus South America
? 37 million population was reduced by 90%
- 1900-1977 smallpox deaths 300-500 million
- 1918–1919 Spanish influenza pandemic at least 50 to 100 million deaths
- ongoing HIV/AIDS pandemic, more than 35 million deaths

Emerging Infectious Diseases

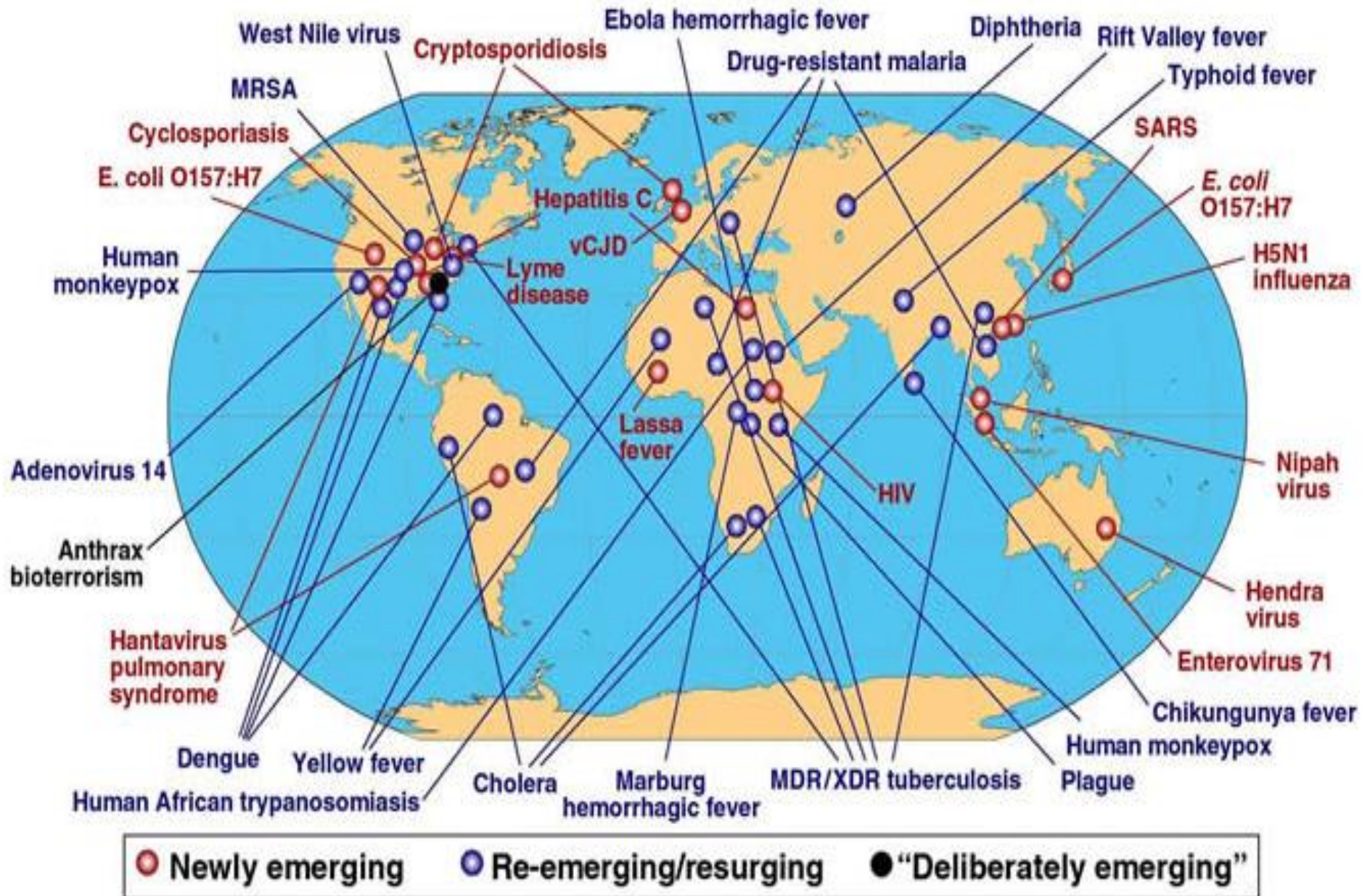
'All Bugs are Bad'

335 infectious diseases emerged globally in humans
between 1940 and 2004
nearly two-thirds originated in wildlife

Infectious Diseases cause nearly 1 in 5 deaths worldwide



Recent Emerging Diseases

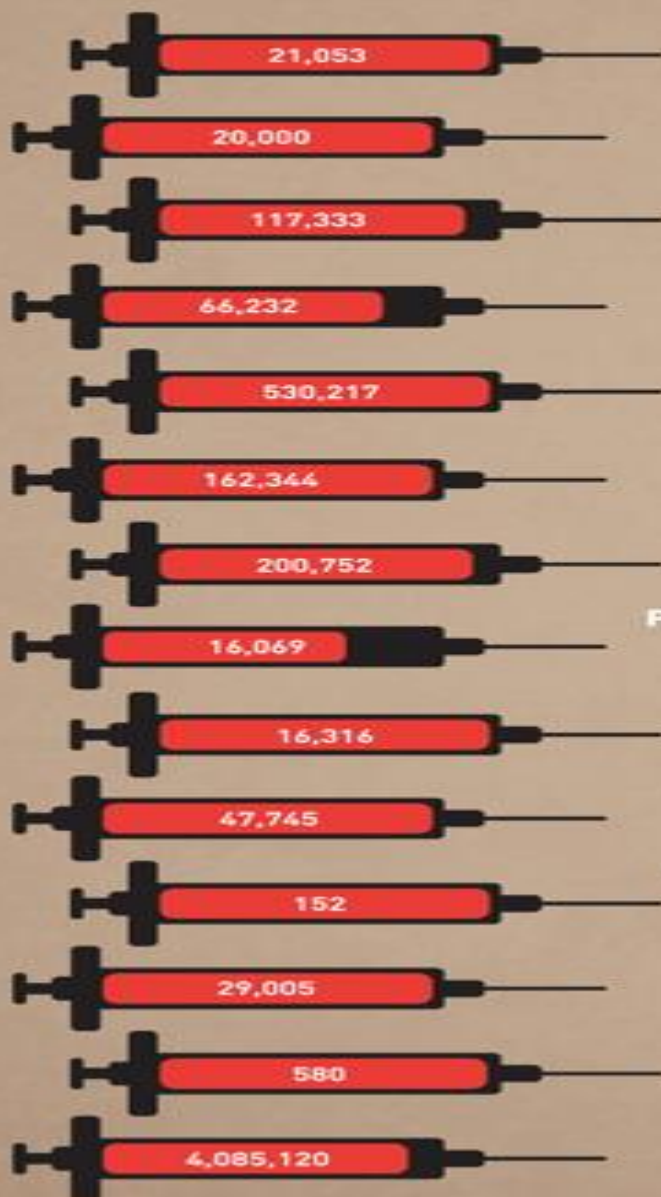


PRE-VACCINE ERA
ESTIMATED ANNUAL
MORBIDITY IN THE U.S.

%

MOST RECENT
REPORTS OF
CASES IN THE U.S.

DECREASE



DIPHTHERIA

100%

H. INFLUENZA

99%

HEPATITIS A

91%

HEPATITIS B

83%

MEASLES

99%

MUMPS

99%

PERTUSSIS

93%

PNEUMOCOCCAL DISEASE

74%

POLIO

100%

RUBELLA

99%

CONGENITAL RUBELLA

99%

SMALLPOX

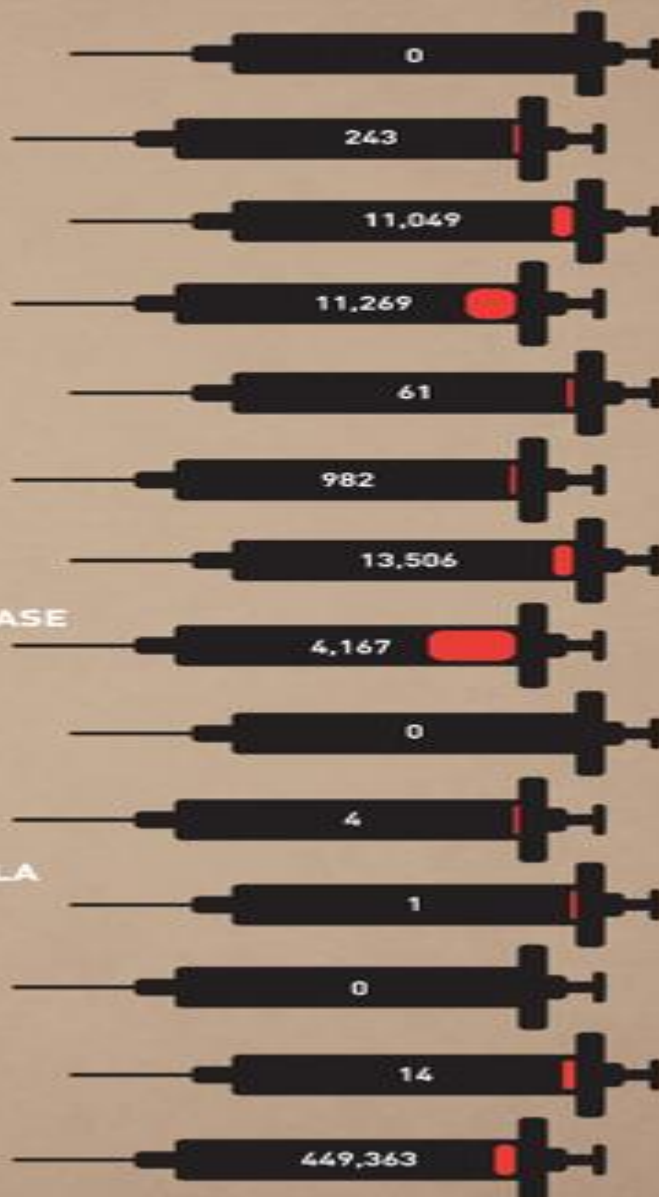
100%

TETANUS

98%

VARICELLA

89%

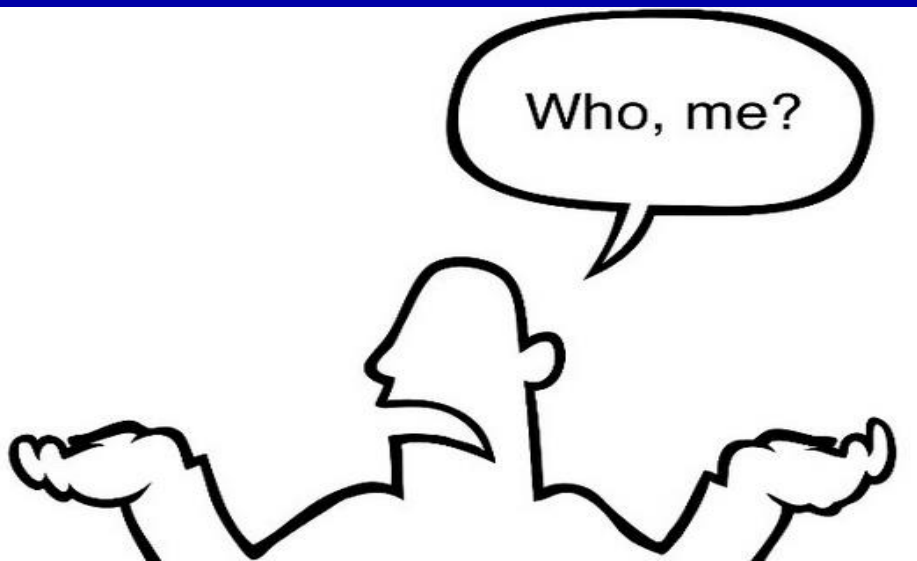


Human Infections (2)

Now mainly

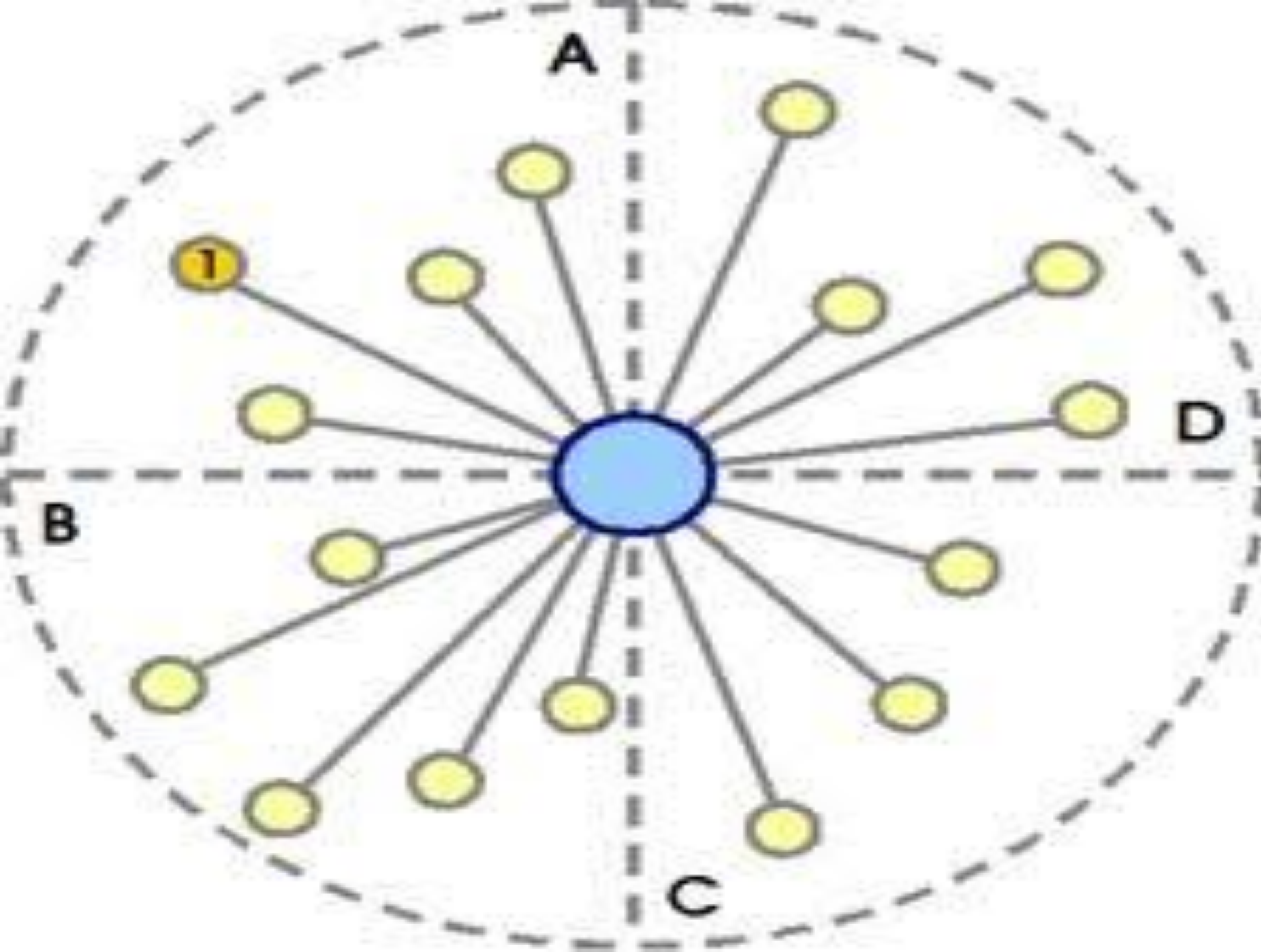
Emerge from our own microbiome

i.e. endogenous source



Who, me?
No way!











**“.... 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”**

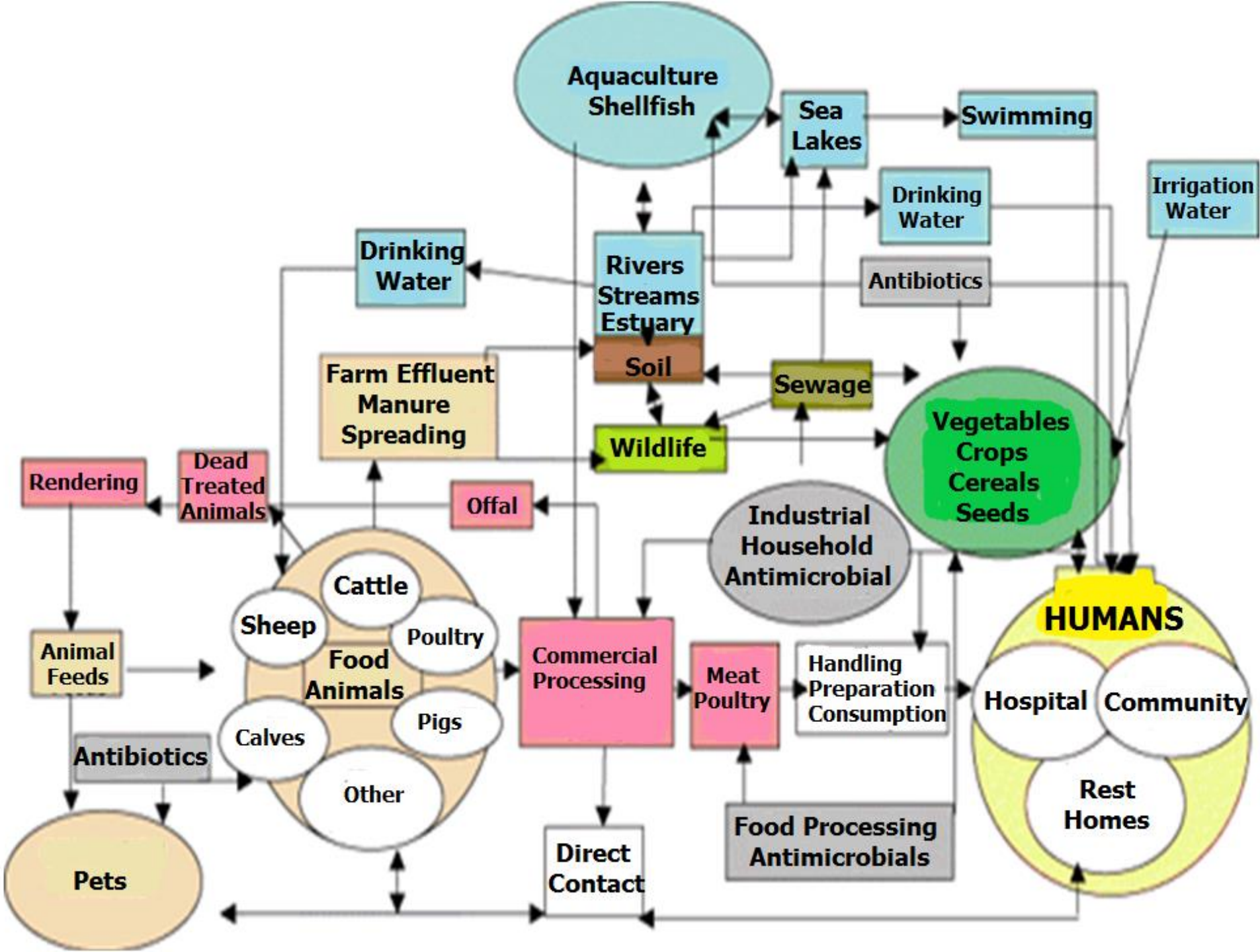
-Sir Alexander Fleming, June 1945





Antibiotic Resistance Sharing







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

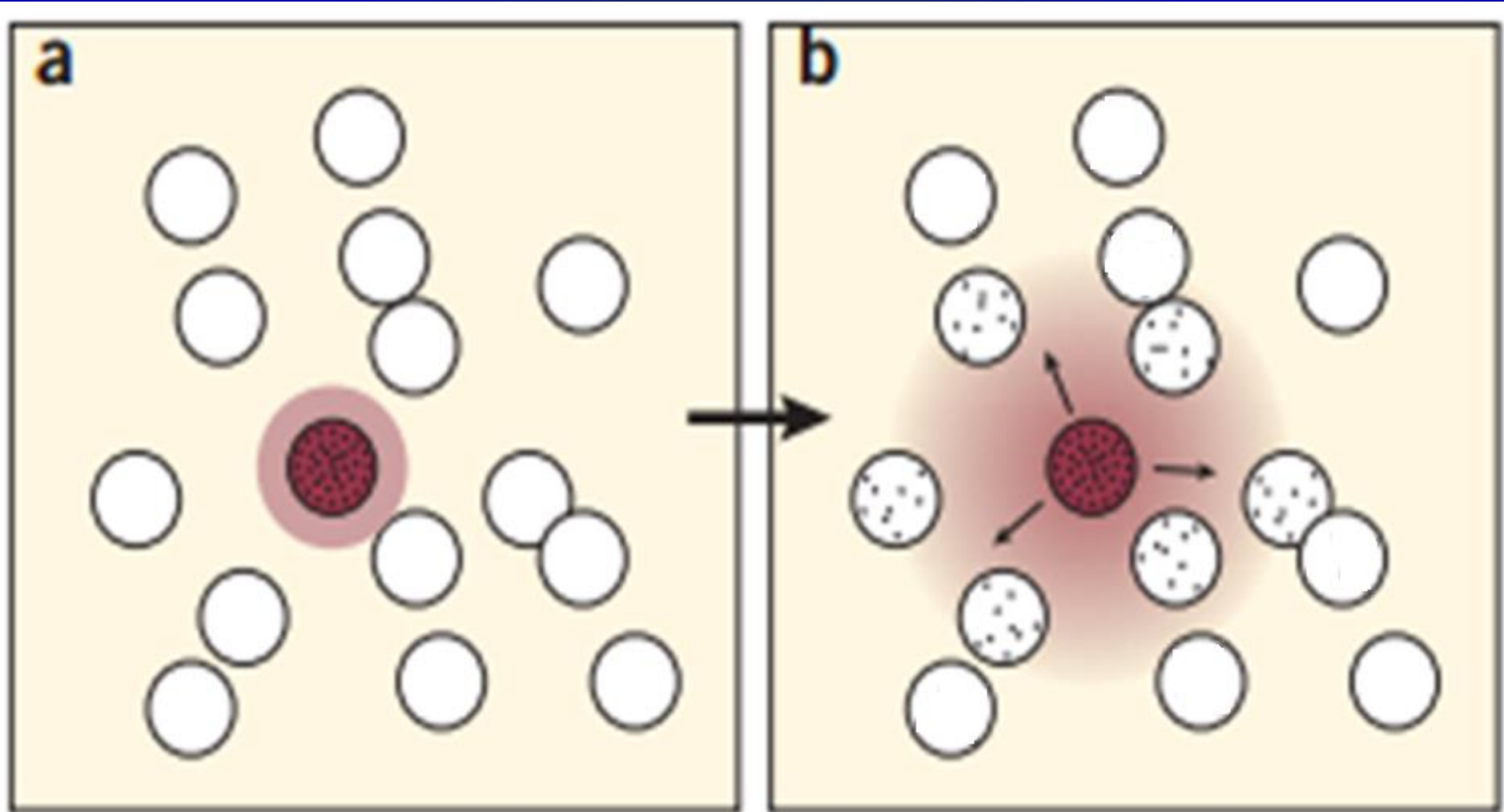
Within six months 31.3 % weekly faecal samples from farm dwellers had >80% tetracycline resistant bacteria

Key Point

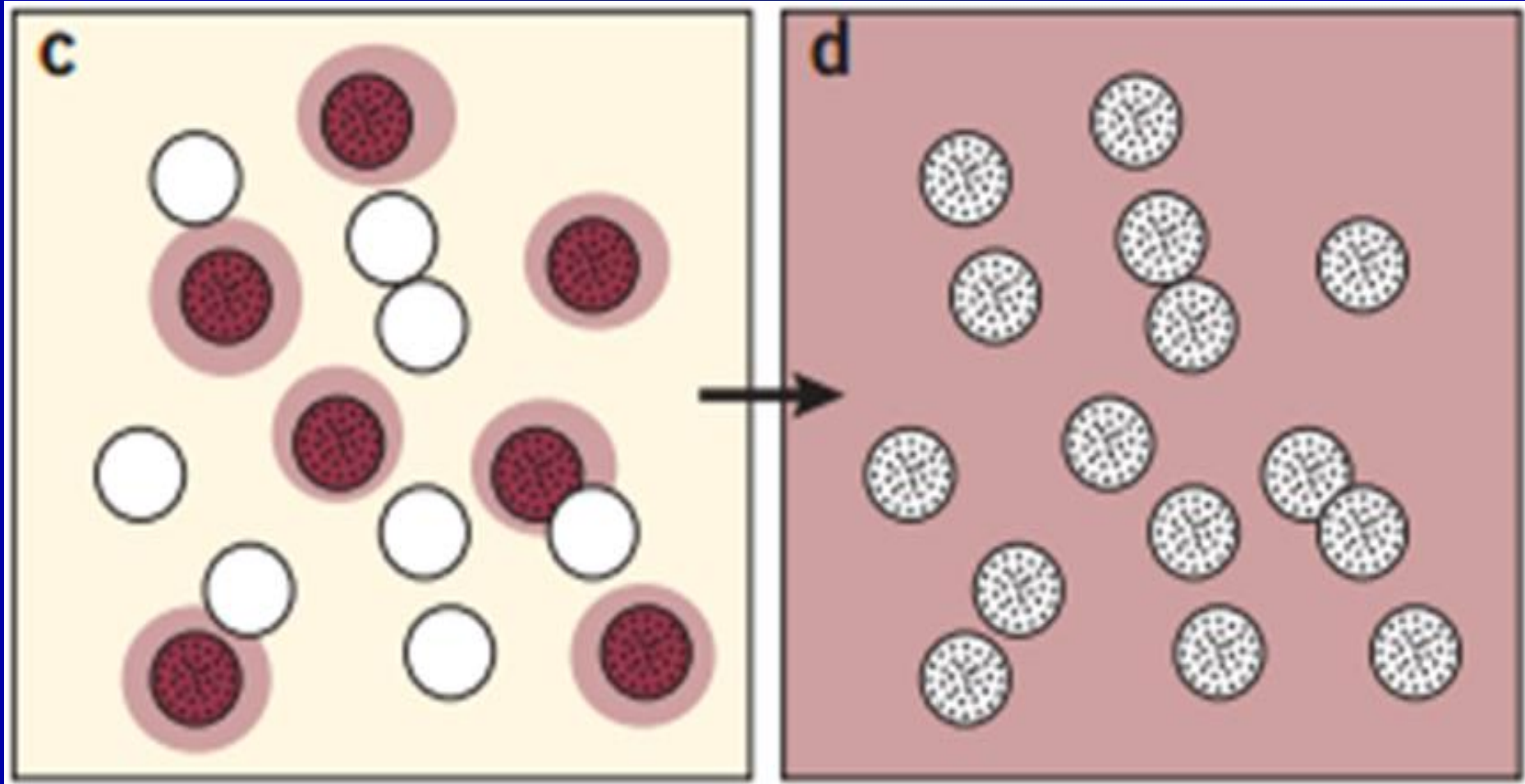
Ongoing use of a single antibiotic
selects resistance for
multiple structurally unrelated ABs

via linkage genes, plasmids, transposons

Antibiotic Dispersion Effect in Populations of People or Animals

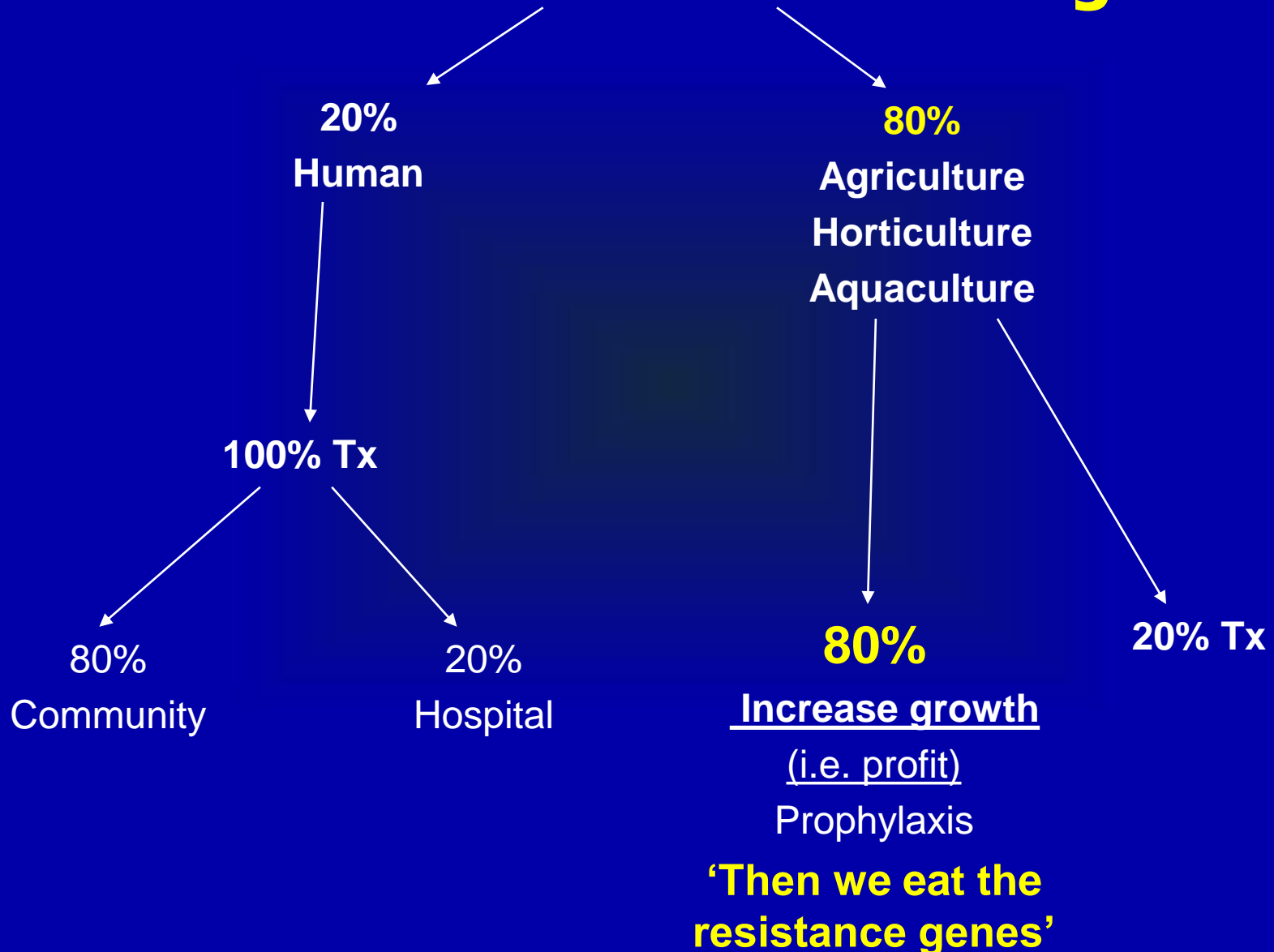


Antibiotic Dispersion Effect in Populations of People or Animals



Emerging Antibiotic Resistance

Worldwide Antibiotic Usage



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 !



NZ Antibiotic Use 2012

Assoc Prof Mark Thomas, University of Auckland

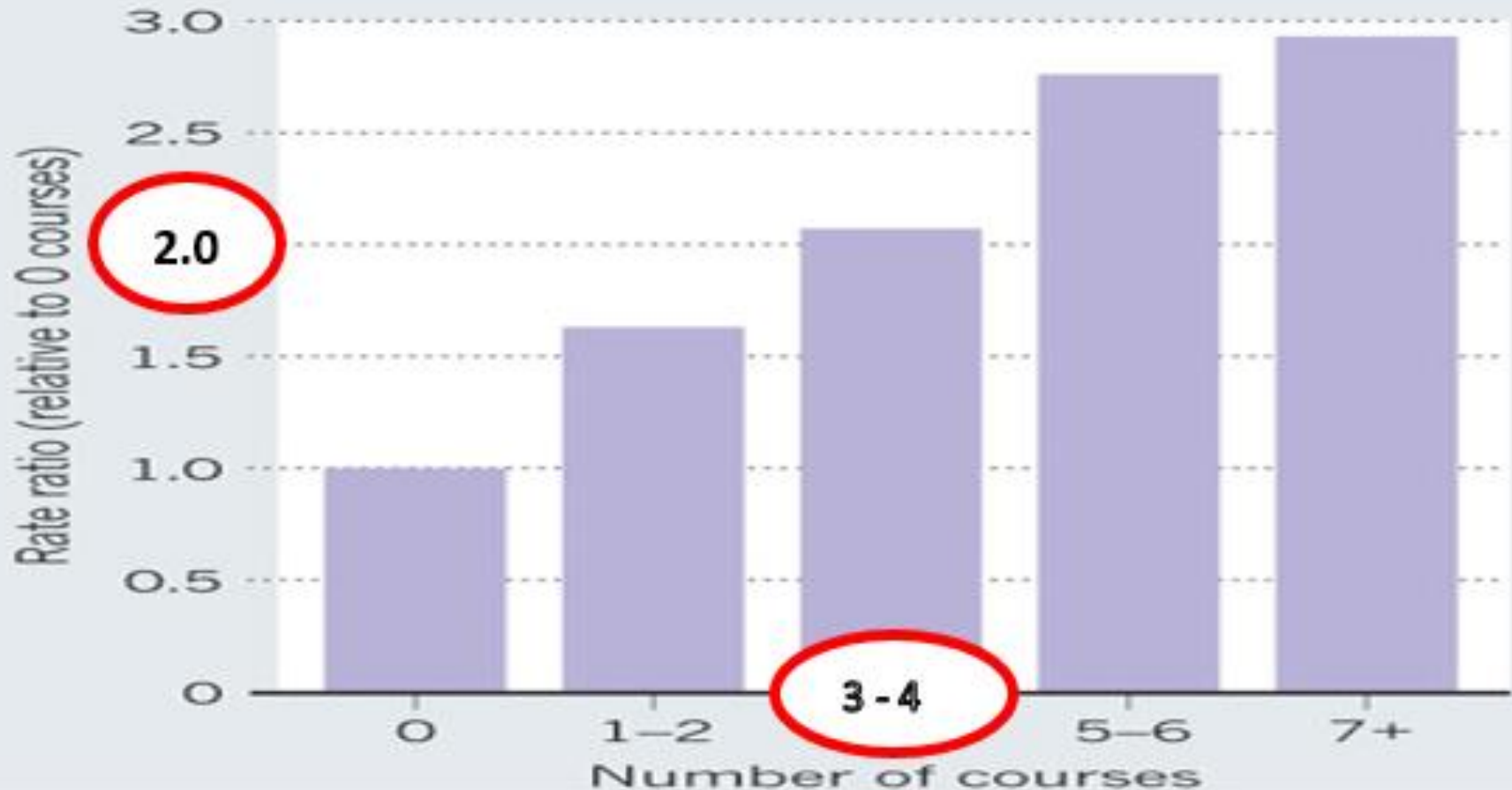
Annually:

- 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

TROUBLING CORRELATION

The risk of inflammatory bowel diseases in children rises with the number of courses of antibiotics taken.





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

Stop the killing of beneficial bacteria

Aust & NZ

Non Human Antibiotic Use

Aust

- **500 tons** for animal production (in 1999)
- **300 tons** human therapeutic

NZ

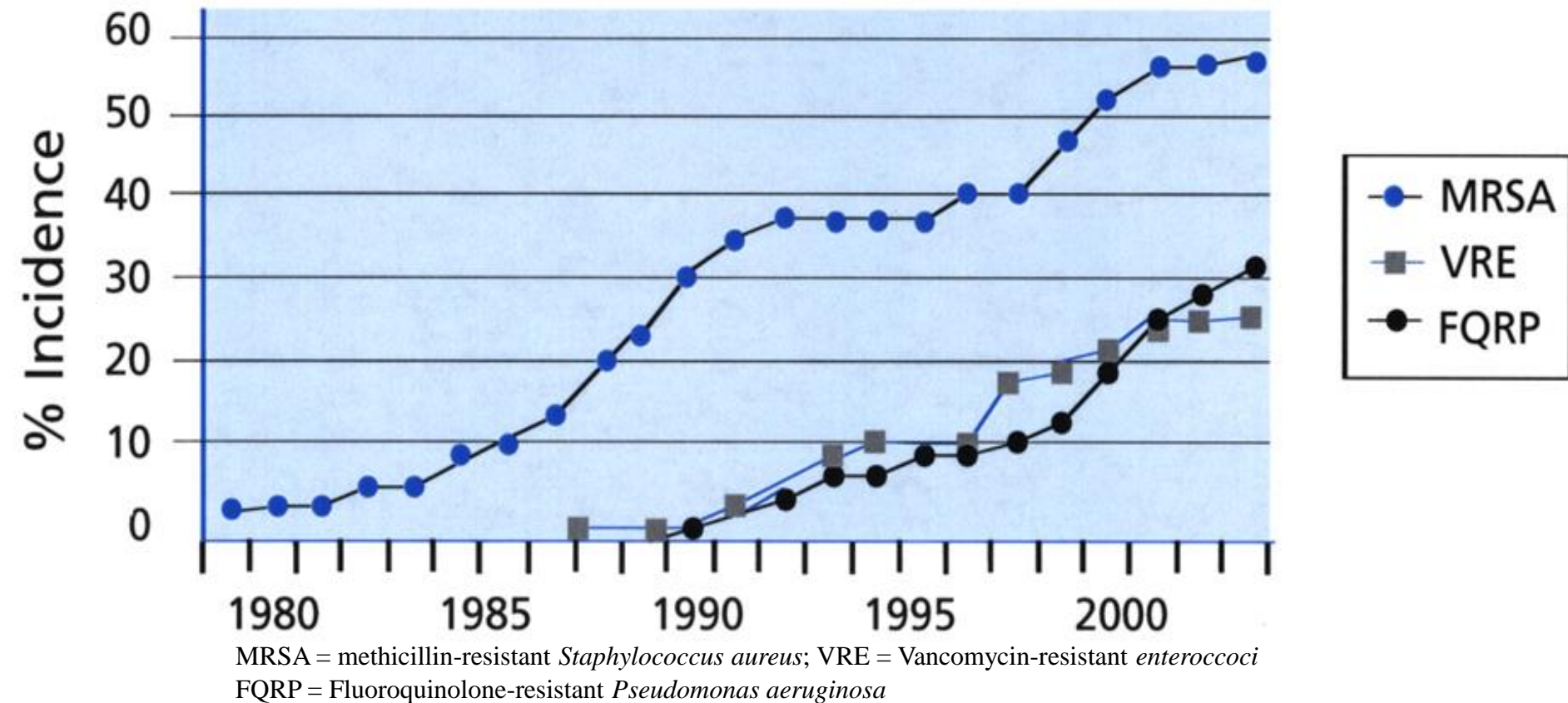
- **56 tons** for animal production (in 2009)

+ Horticulture

+ Aquaculture

Increasing Frequency of Resistance

Chart 1: Resistant Strains Spread Rapidly



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 <u>BUT how much longer ?</u>

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%

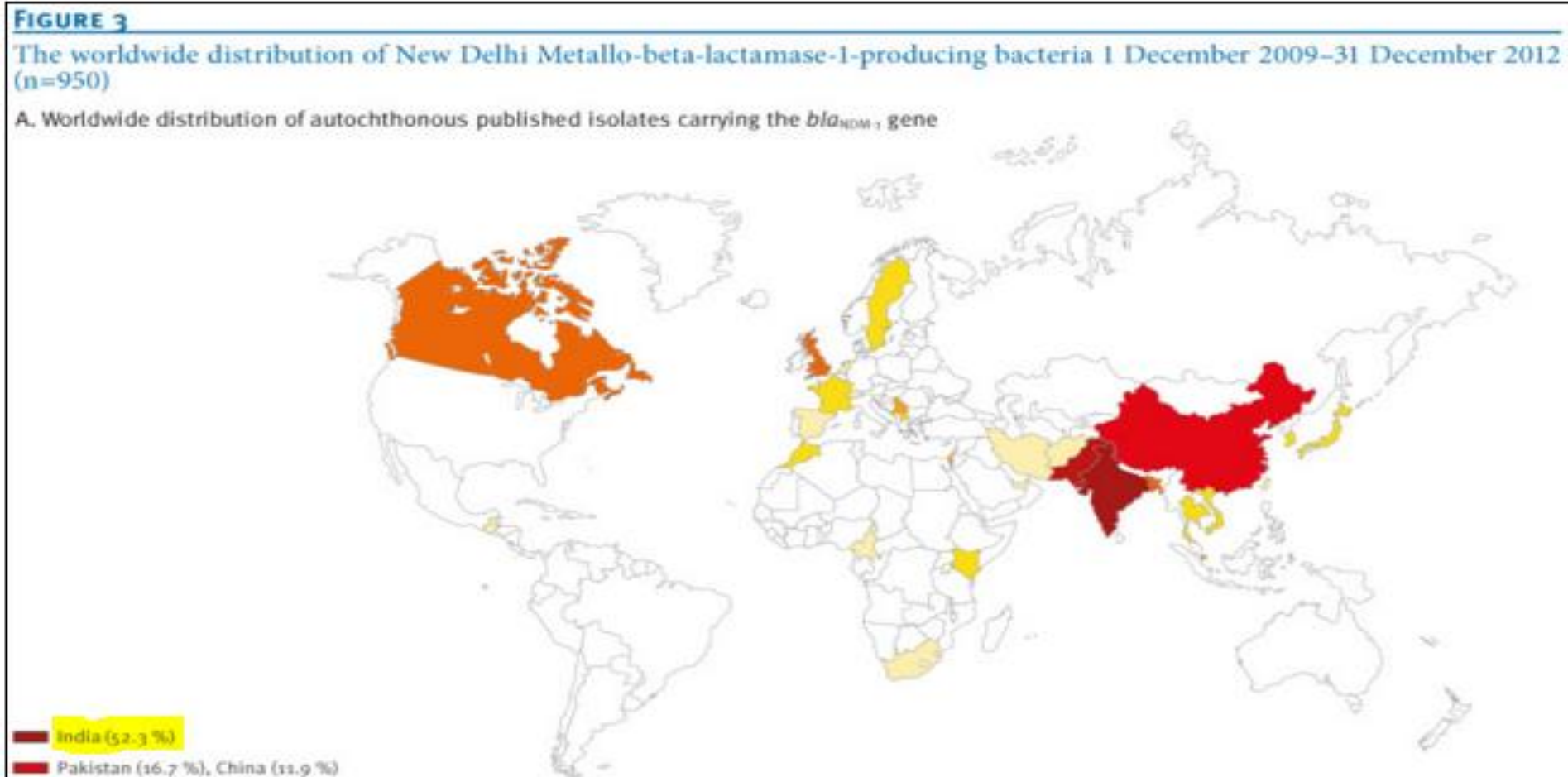
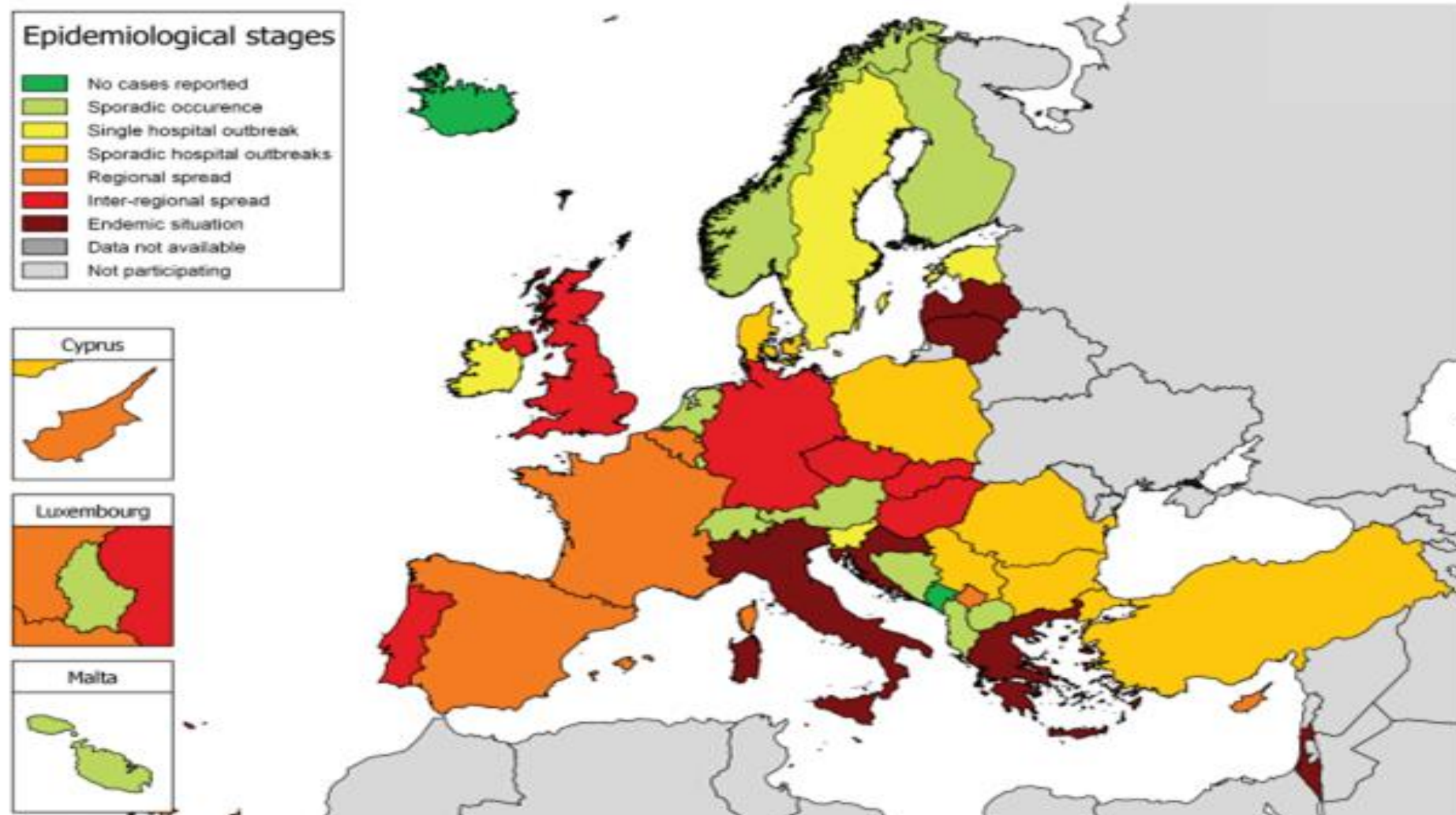


Figure 7. Occurrence of carbapenem-resistant *A. baumannii* in European countries based on self-assessment by the national experts, March 2013



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 ?

Staph. aureus

E. coli

Klebsiella

Enterococcus



**Subset
MRSA**



**Subset
ESBL,
Carba**



**Subset
ESBL,
Carba**



**Subset
VRE**

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 <i>Staph. aureus</i>)	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)

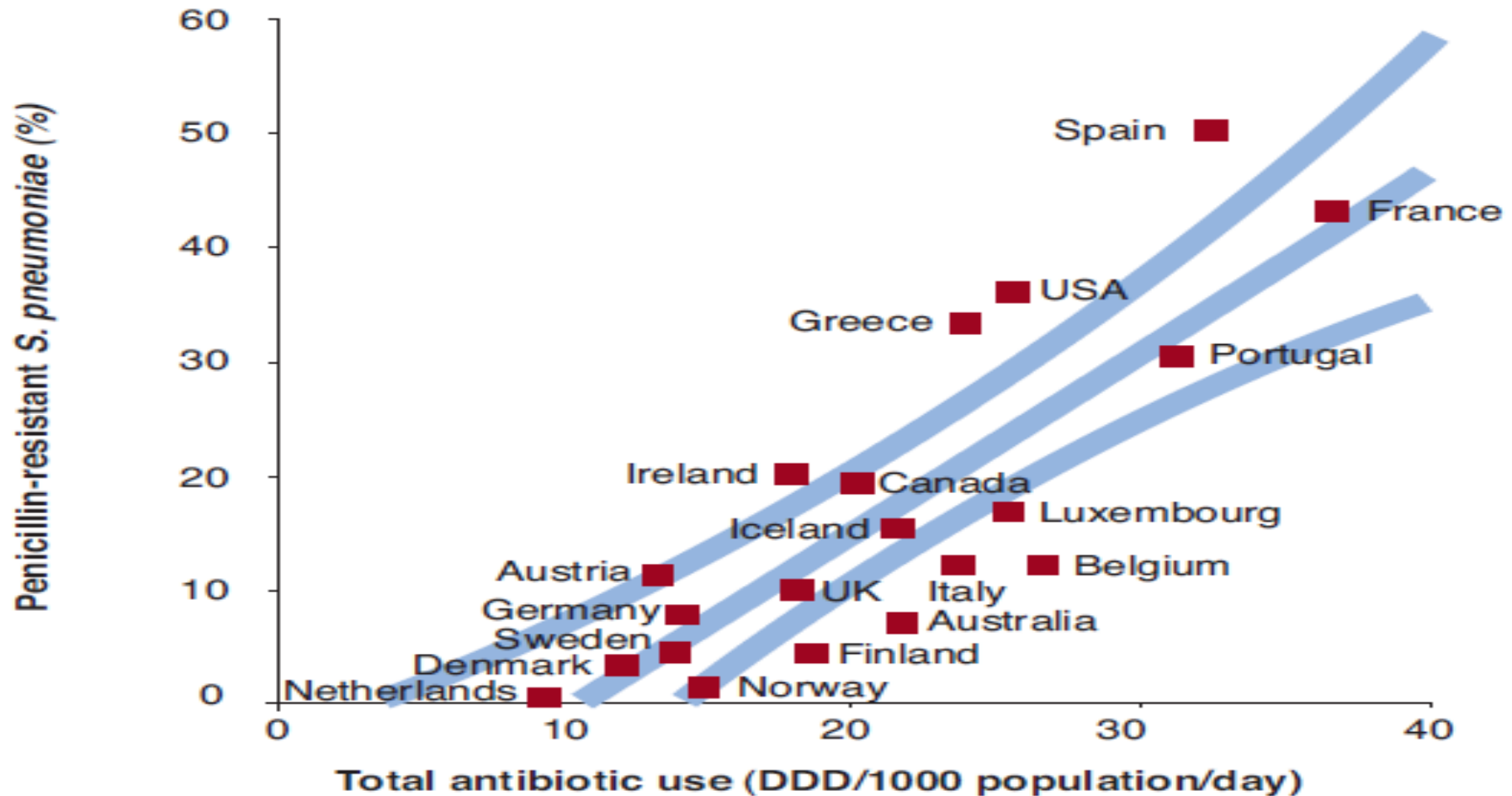
Journal of Antimicrobial Chemotherapy (2008) 61, 524– 532

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

Antibiotic use and AMR from 1990–2000 in selected countries

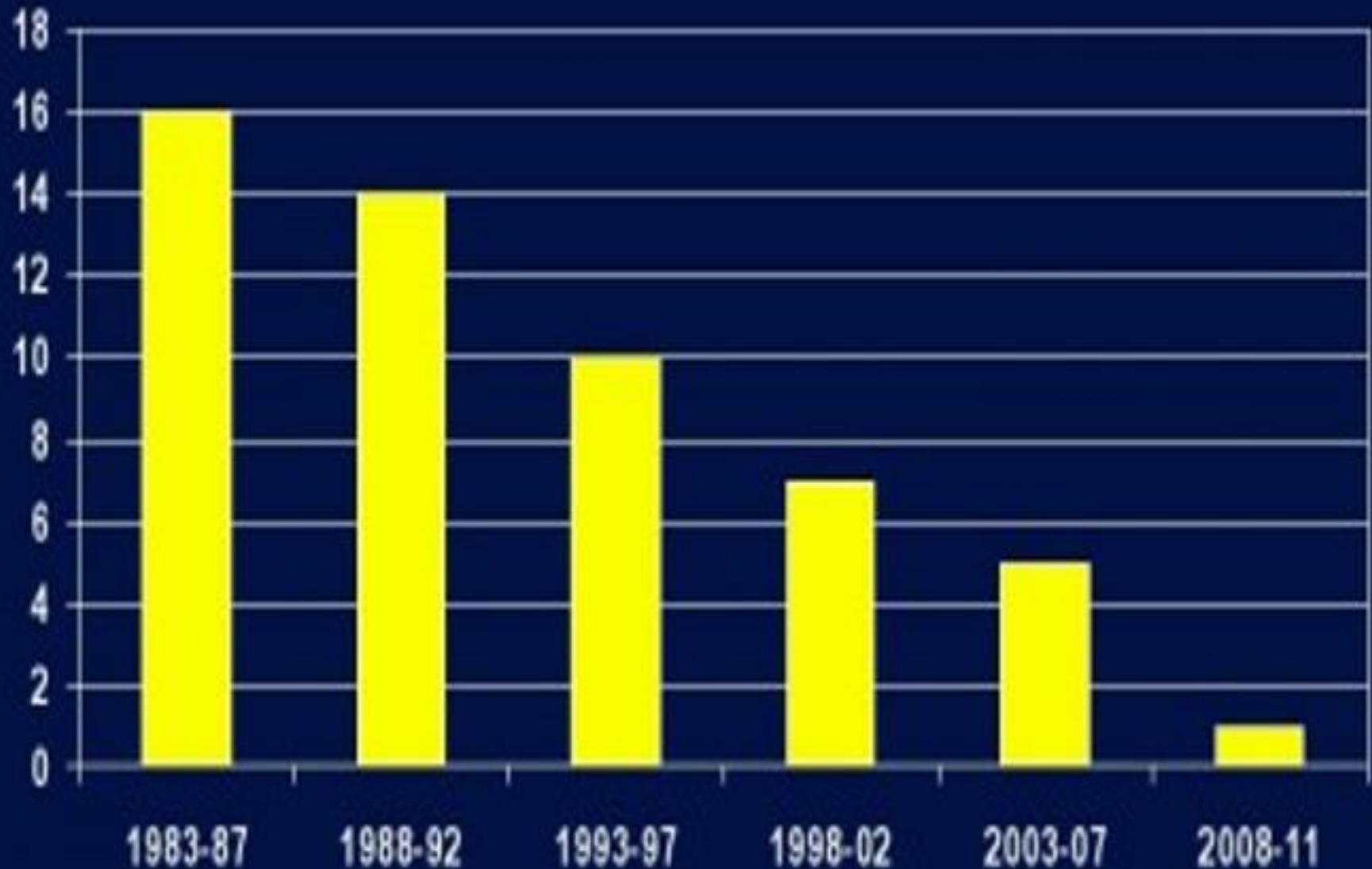


DDD: Defined Daily Doses

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

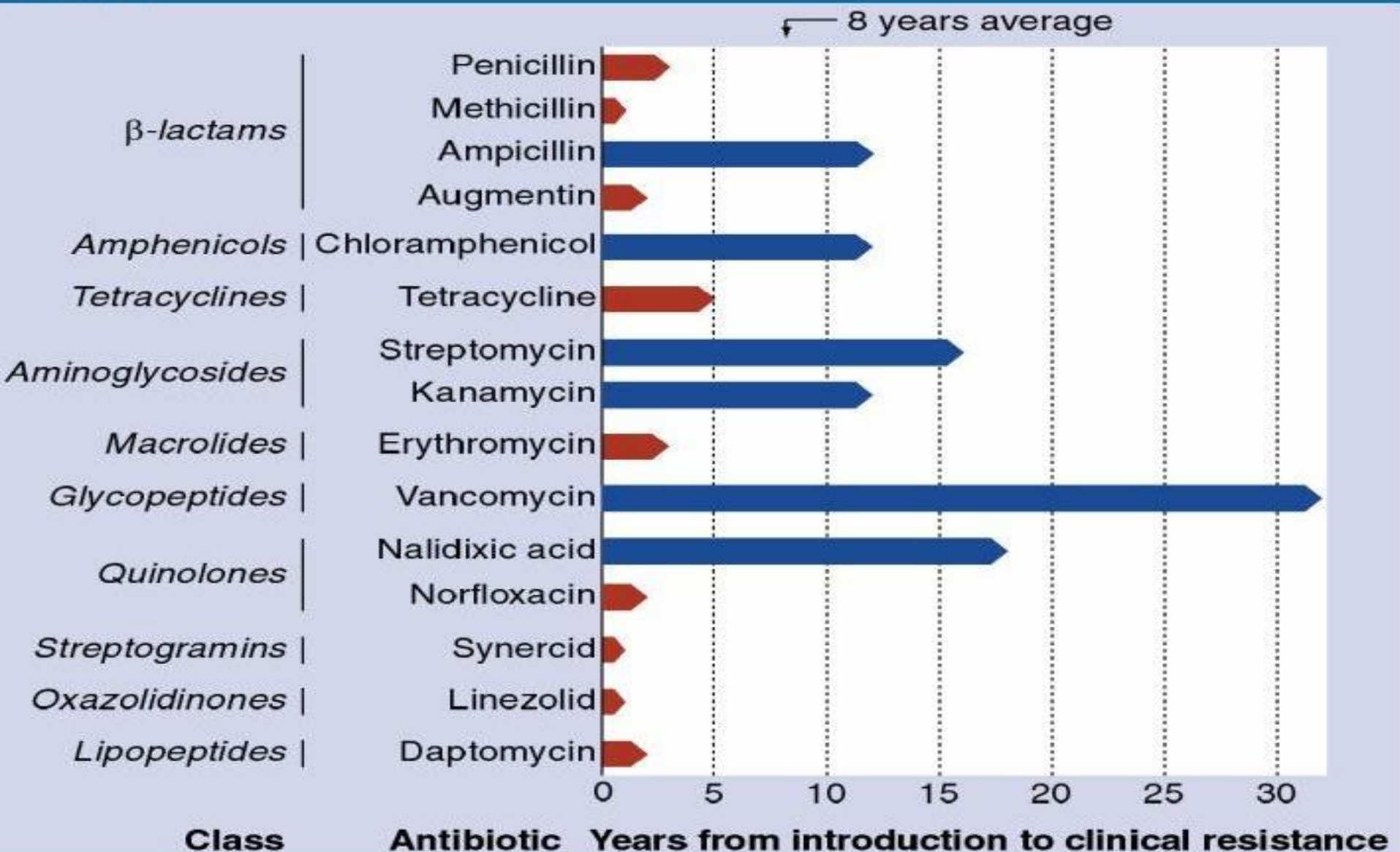
Albrich WC, Monnet DL, Harbarth S. Antibiotic selection pressure and resistance in *Streptococcus pneumoniae* and *Streptococcus pyogenes*. *Emerging Infectious Diseases*, 2004, 10(3):514-7.

New Antibiotics each 5 years 1983-2011

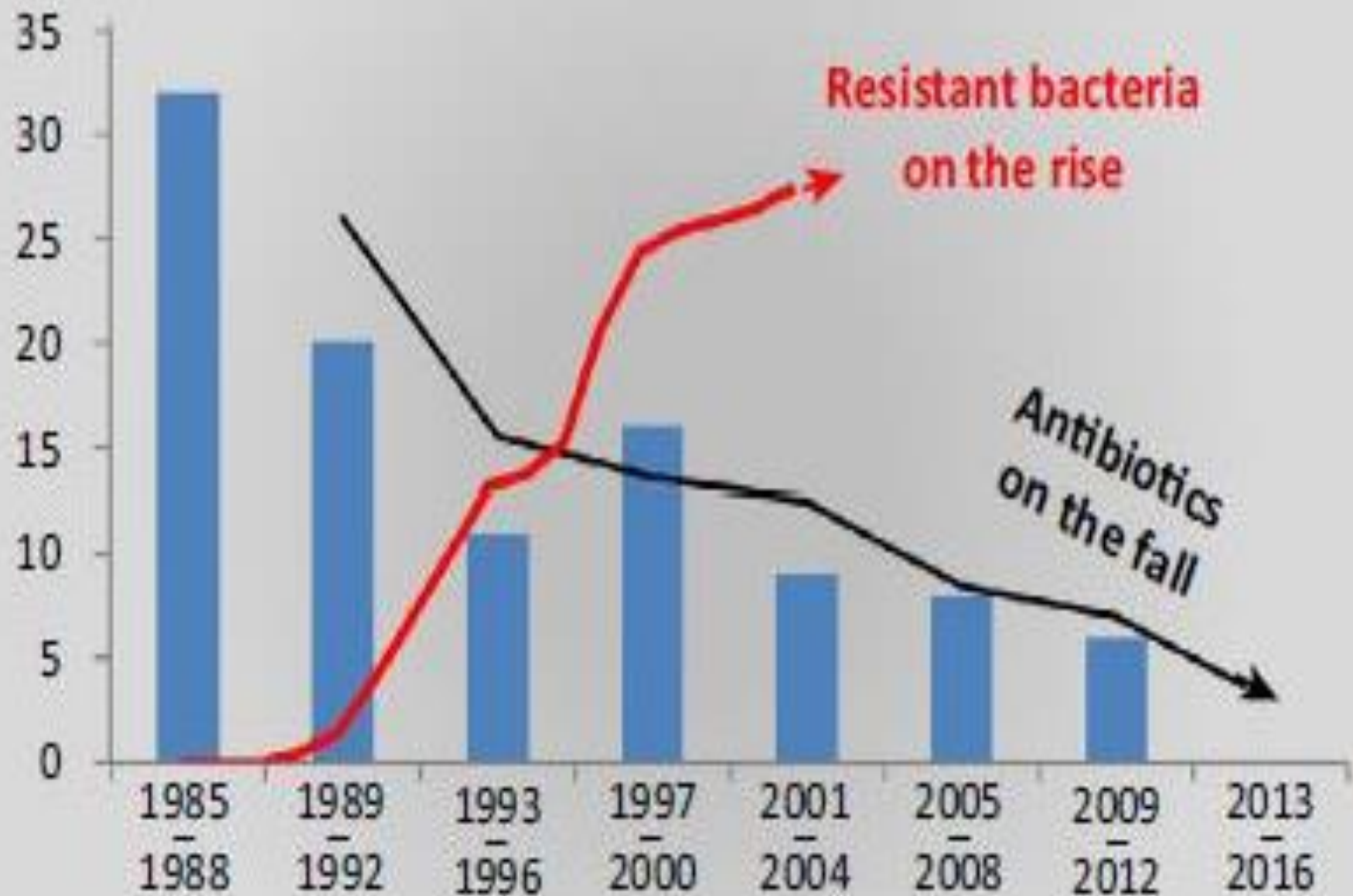


Lifespan of Each Antibiotic

Medscape



Seeing the Future



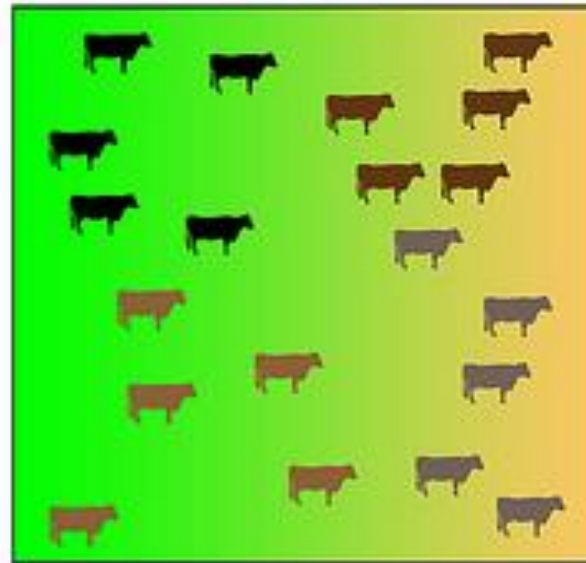
Tragedy of the Commons

Shared Resource

The Commons

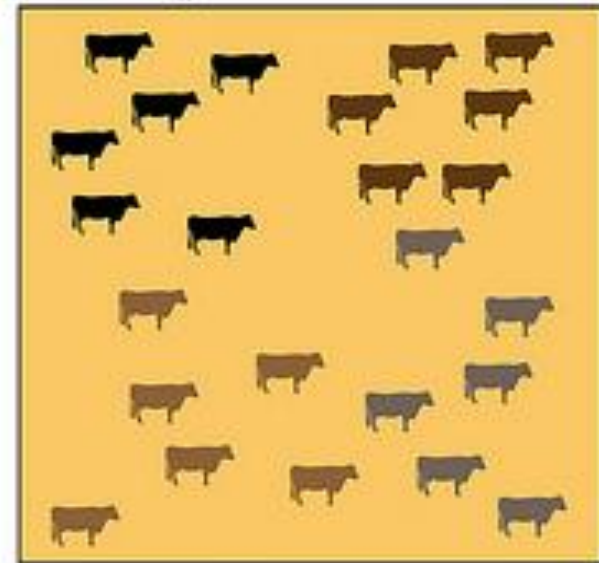
40 acres [16 hectares]
1,320ft² [400m²]

Sustainable Use



20 Cows
Carrying Capacity

Depleted Resource



20+ Cows
Tipping Point

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











Imagine a World Without Antibiotics

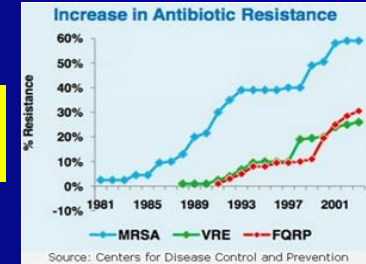


- You know how you are FEELING better than anyone else
 - Your medical practitioner knows what the CAUSE is, bacterial, viral or other and what to treat you with better than anyone else.
- Listen, do not ask for or demand antibiotics – they may well cause you and others significant harm

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

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

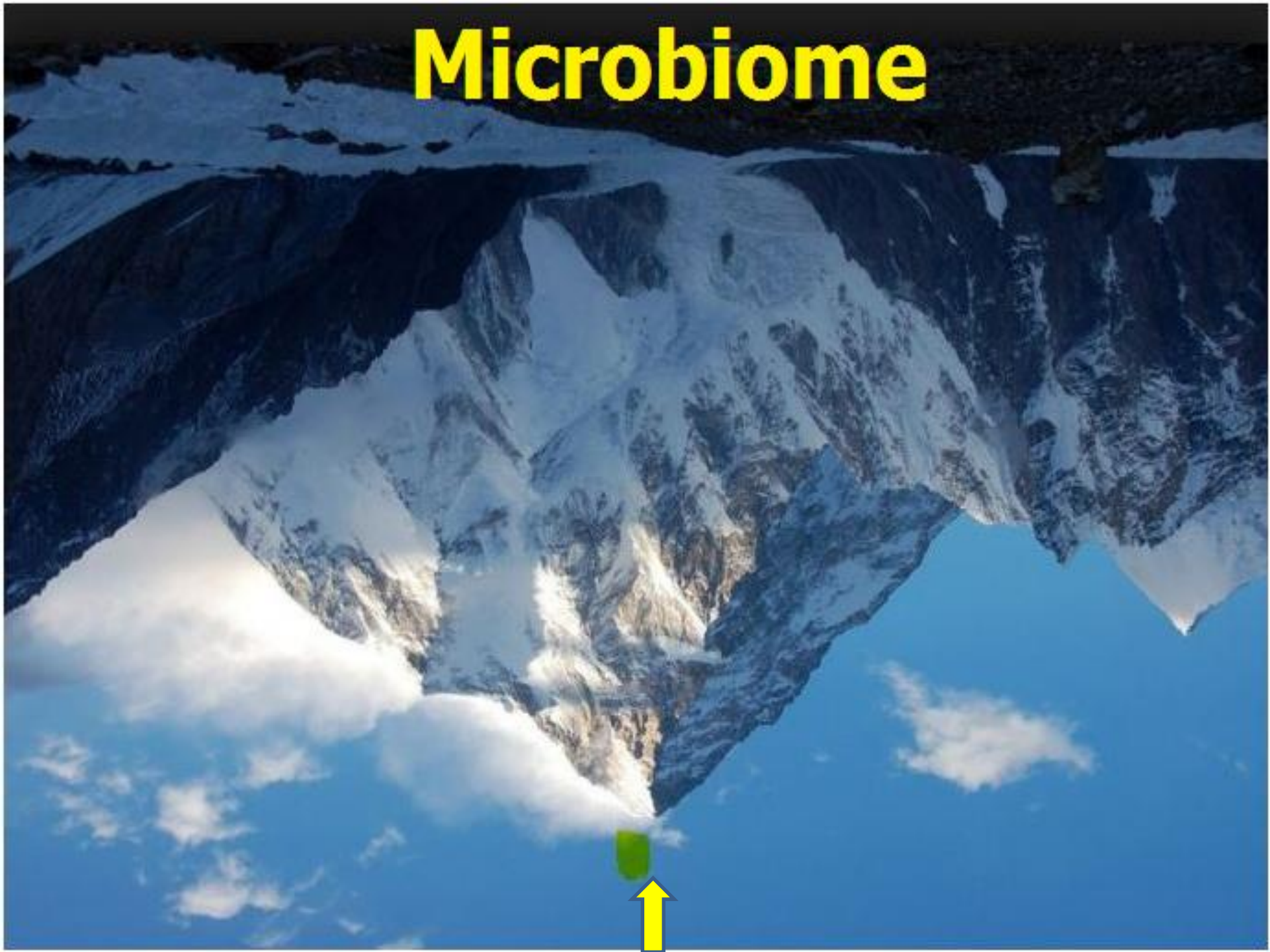




A microscopic view of various bacteria, primarily rod-shaped, against a dark background. The bacteria are illuminated with a bright blue light, giving them a glowing appearance. Some bacteria are in sharp focus, showing their textured surface, while others are blurred in the background, creating a sense of depth. The text "What's the Microbiome?" is overlaid in the center in a white, sans-serif font.

**What's the
Microbiome?**

Microbiome



Our Microbial Garden

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

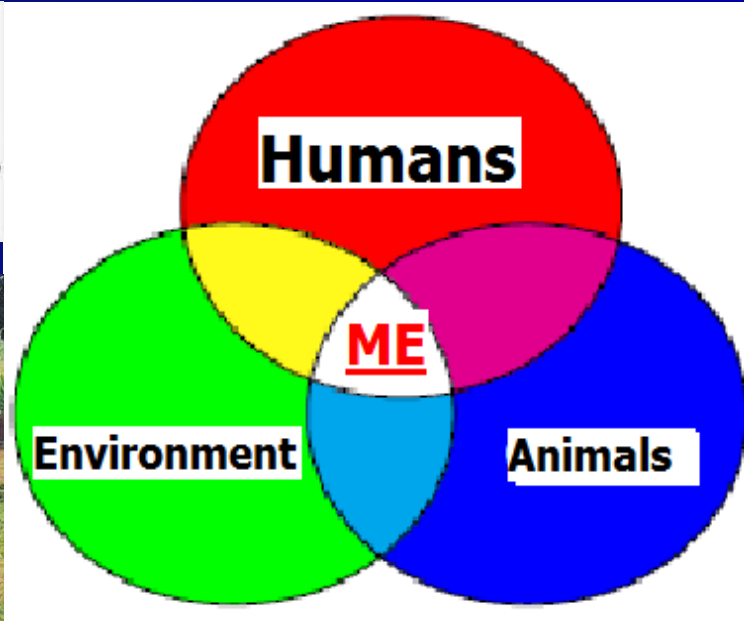
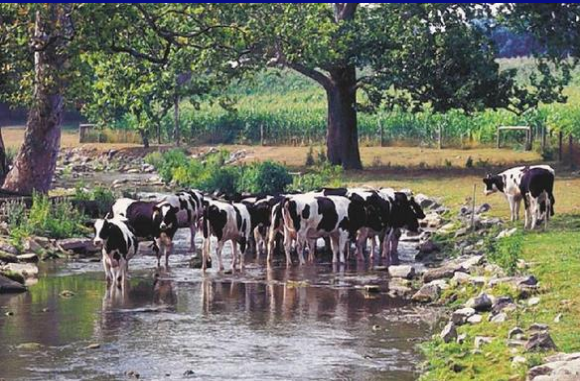
particularly with respect to roles played in:

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

Many diseases are the result of disturbed microbiomes - 'dysbiosis'



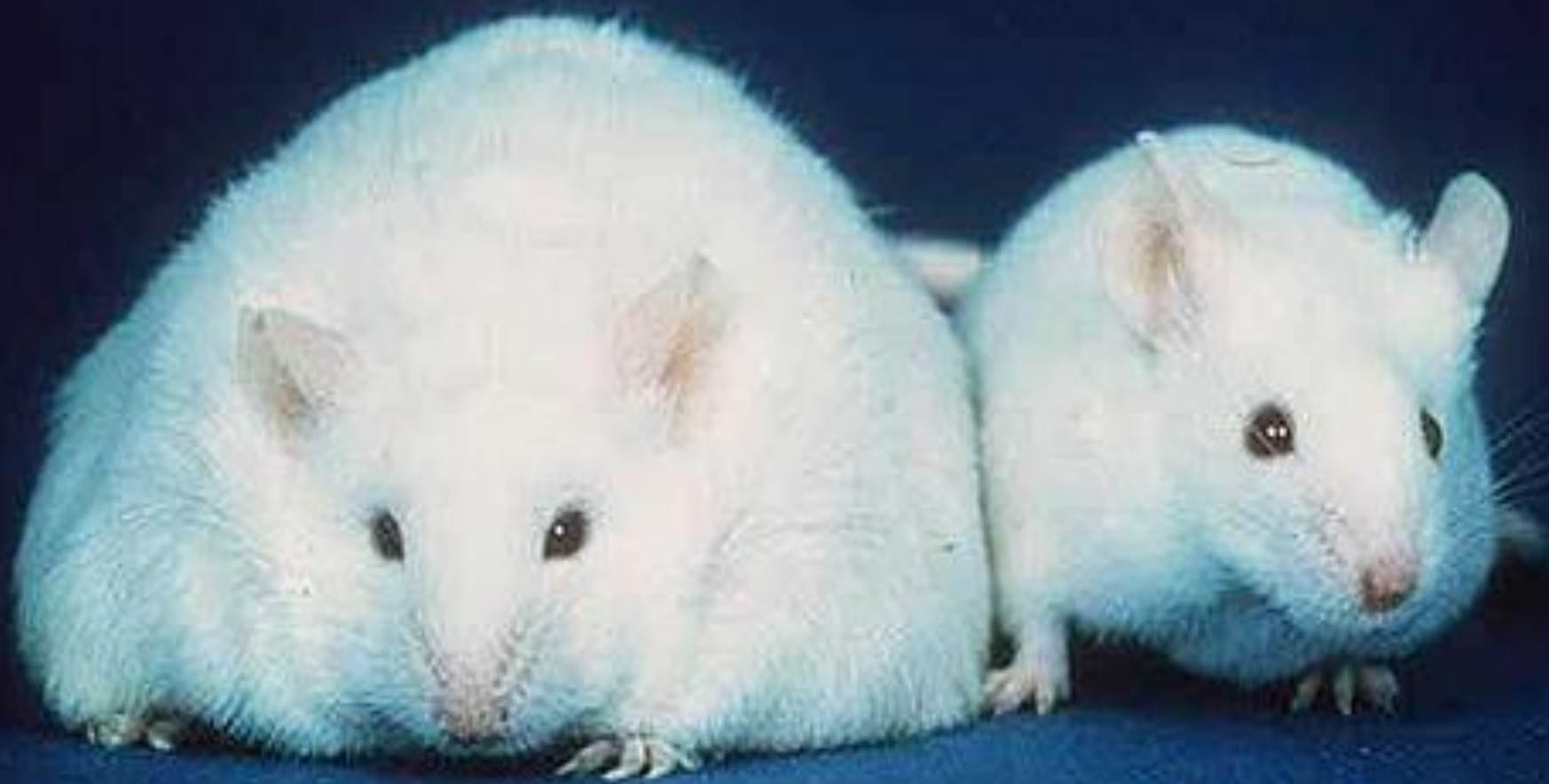
Sharing my microbiome



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



Who? Me?
I didn't do
anything!

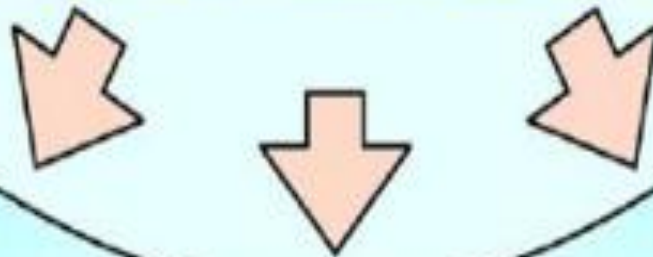




Antibiotics

Bacteria, Viruses, Hormones,
Drugs, Stress Factors

Environmental Factors



Infectious
Disease

Allergy

Cancer

Autoimmune
Disease

Cytokine Regulation

Cardiovascular
Disease

Inflammatory
Disease

Stroke

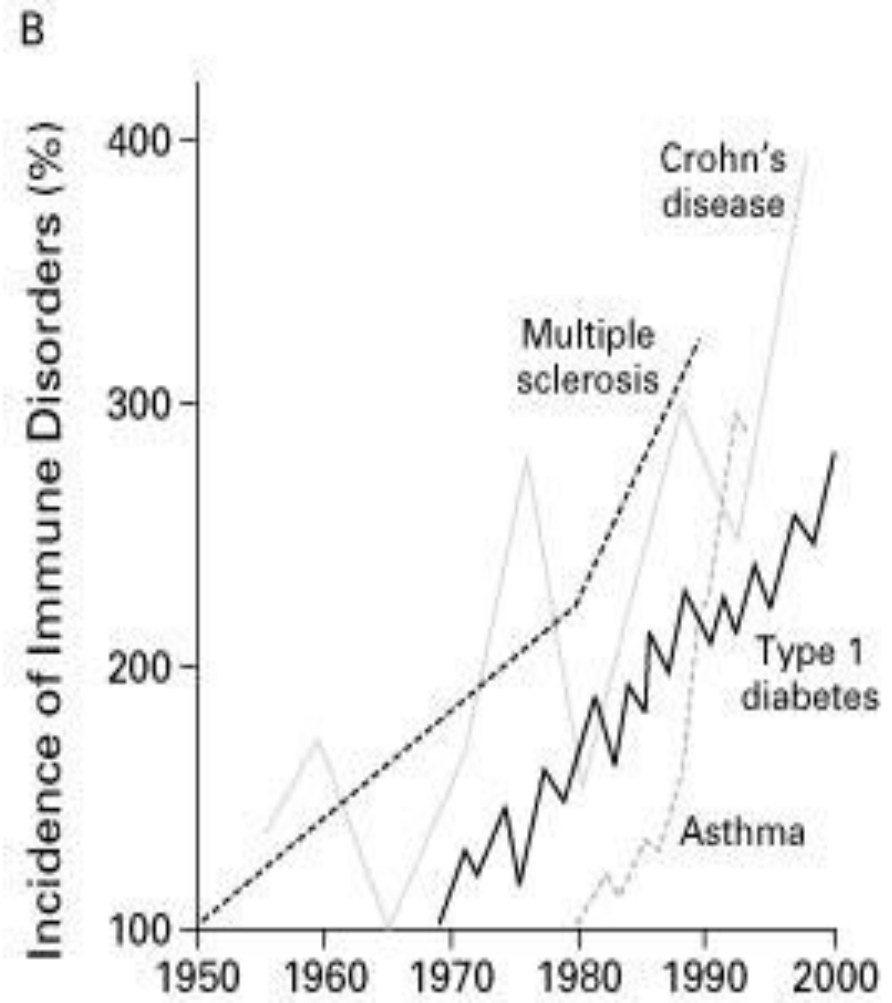
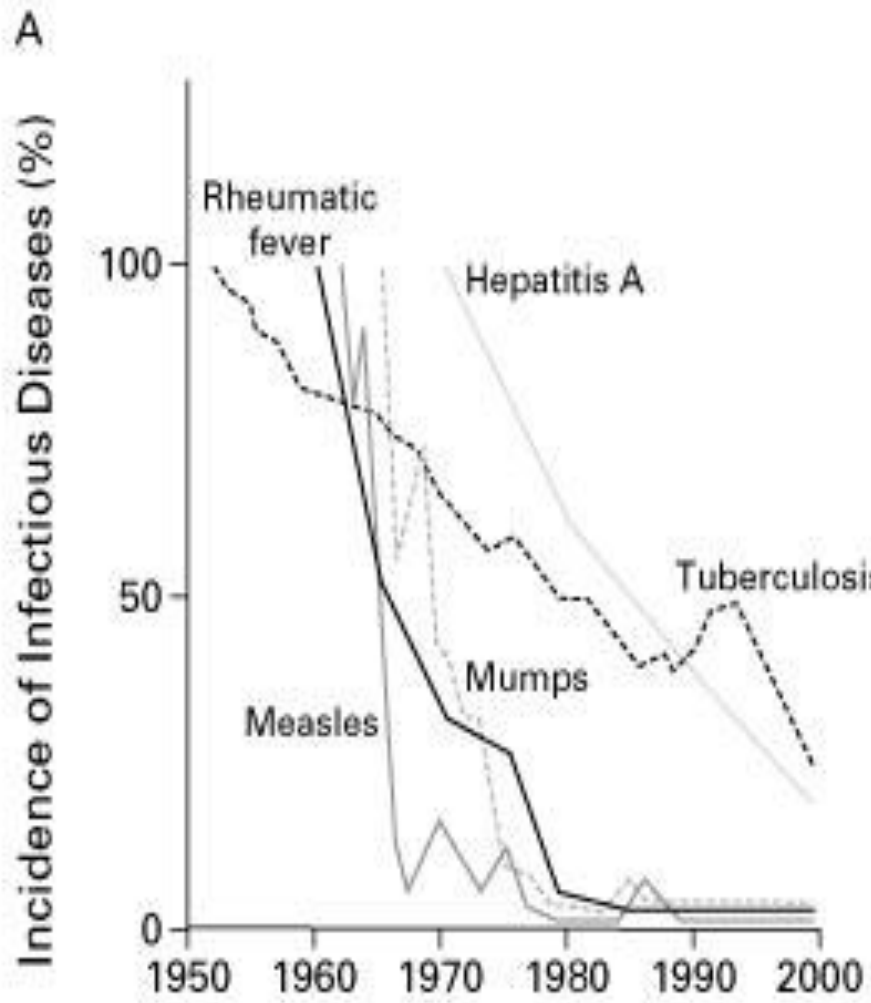
Septic Shock

Genetic Factors



Inverse Relation Incidence (1950-2000)

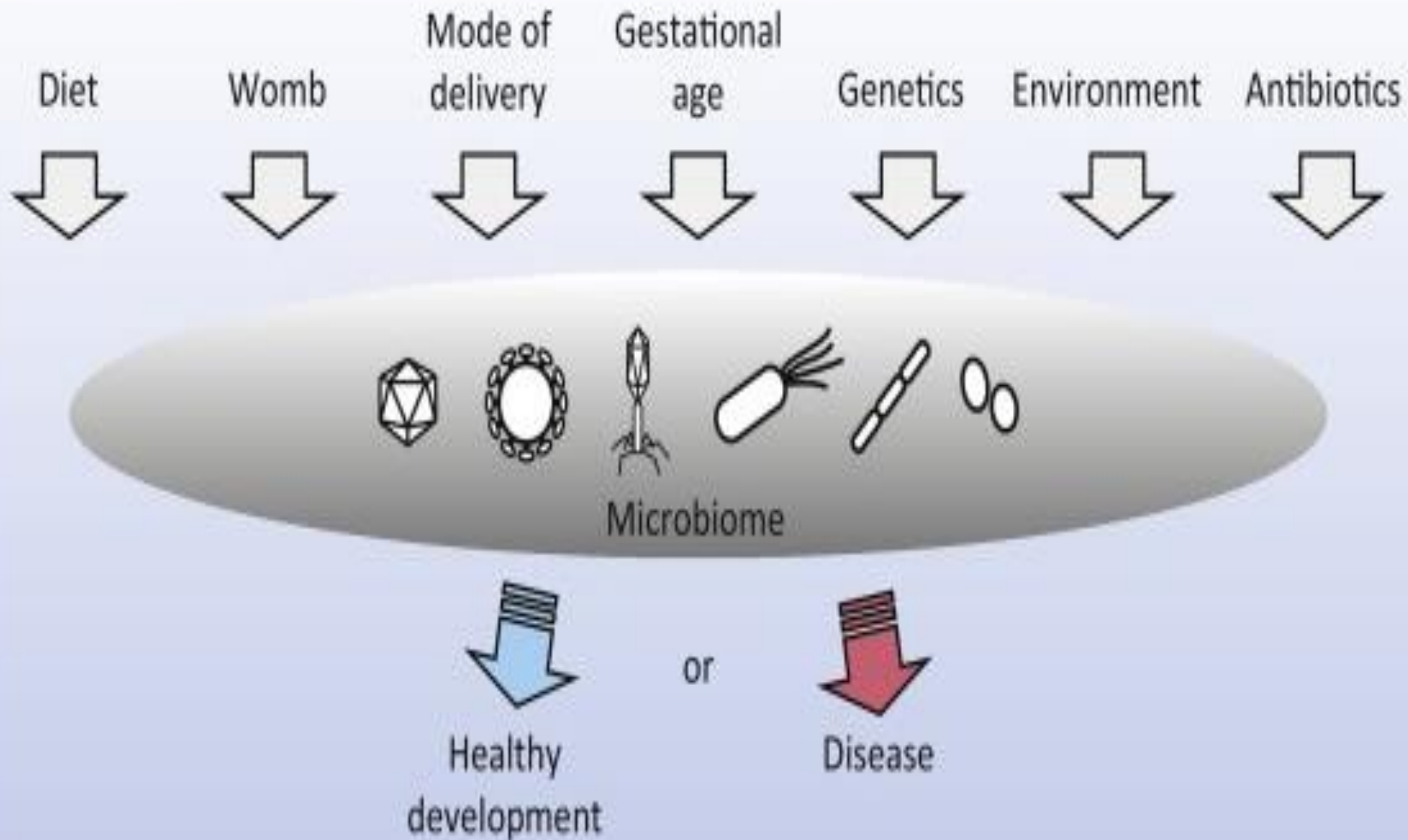
Infectious Diseases ↓ and Immune Disorders ↑



Microbiome Lifetime Dynamics



Influences on microbiome during infant development



Caesarian vs Vaginal Delivery

Associated Childhood Diseases

Josef Neu et al Clin Perinatol. 2011 Jun; 38(2): 321–331

Caesarian Delivery	Odds Ratio 95% CI versus vaginal delivery	
Allergic Rhinitis		
<i>All Caesarians</i>	1.37	(1.14 – 1.63)
<i>Repeat Caesarians only no Rupt.Mem</i>	1.78	(1.34 - 2.37)
Asthma		
<i>All Caesarians</i>	1.24	(1.01 – 1.53)
<i>Female</i>	1.53	(1.10 – 2.10)
<i>Female & Repeat Caesarians no RM</i>	1.83	(1.13 – 2.97)

Caesarian vs Vaginal Delivery

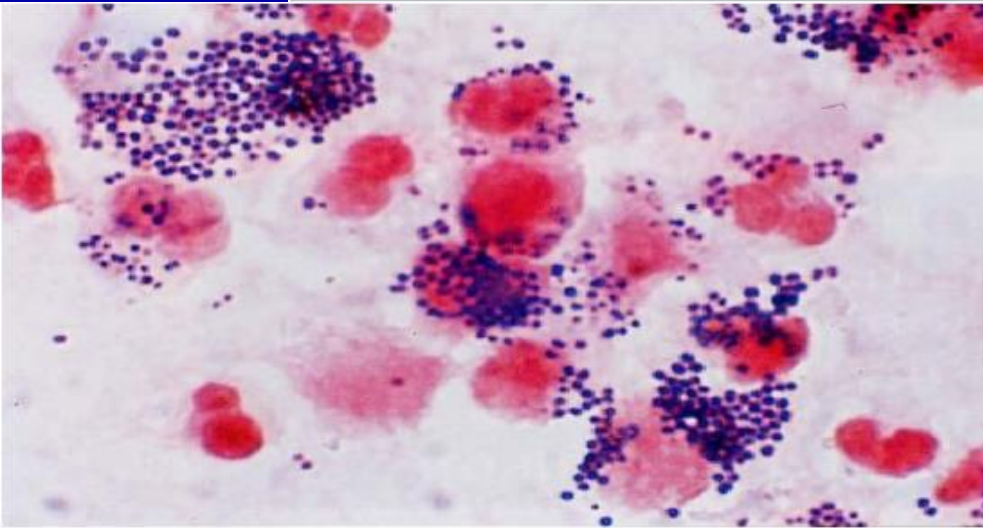
Associated Childhood Diseases

Josef Neu et al Clin Perinatol. 2011 Jun; 38(2): 321–331

Caesarian Delivery	Odds Ratio
	95% CI versus vaginal delivery
<i>Coeliac Disease</i>	1.80 (1.13 – 2.88)
<i>Diabetes Mellitus (Type 1)</i>	1.19 (1.04 – 1.36)
<i>Gastroenteritis</i> requiring hospitalisation	1.31 (1.24 – 1.38)
<i>Gastroenteritis & Asthma</i>	1.74 (1.36 – 2.23)

***Staph aureus* infection**

**single species 'microbes are bad'
eliminate them**



Newer Concepts in SSI



- Blood Sugar regulation important
- Body Temperature regulation intra op
outside 1-1.5°C core increases SSI x2
- Oxygenation - ↑ periop inspiration ↓ SSI

Future Strategies

- **Surveillance** ↑
 - ID epidemics by common & uncommon isolates
 - Correct AB prophylaxis (AB, timing, dose, duration)
 - Document costs, risk factors, readmission rates
 - Monitor post disch infections, 2^o consequences
 - Typing all isolates (?? + staff) for cross infection
- **Preventing Emerging Resistance**
 - AB necessary ?, choice, route, time, evidence??
 - Hand + Environmental Hygiene

Wound Infection Risk Balance

Relative Infection Risk



β Strep (grp.A)
Staph. aureus
Pseudomonas
Coliforms
Anaerobes
Skin commensals

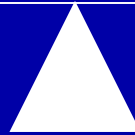
$\geq 10^5$
bacteria/gram

Host Immunity



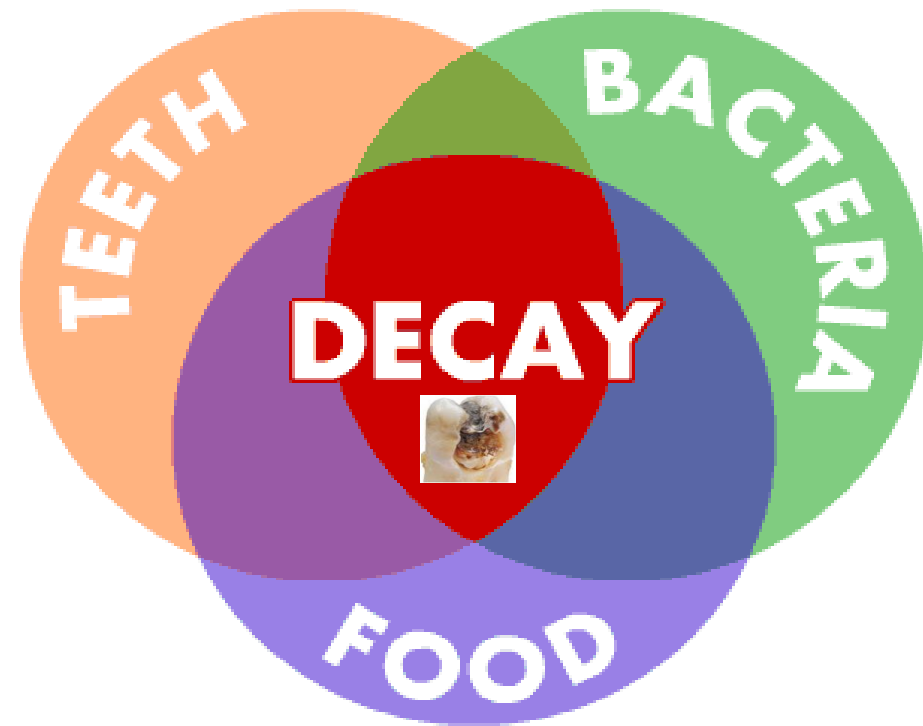
Tissue perfusion
WBC
Oxygen

Wound
depth, site, type
contamination

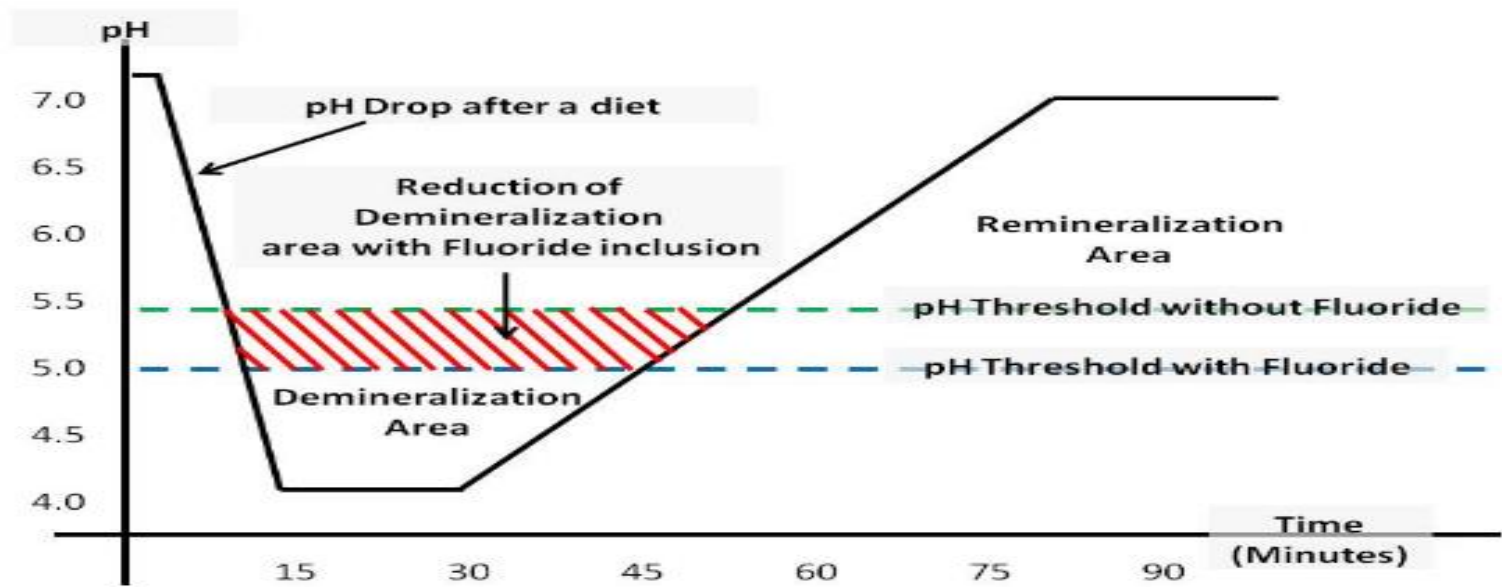


Sweet Tooth Diet Emerged





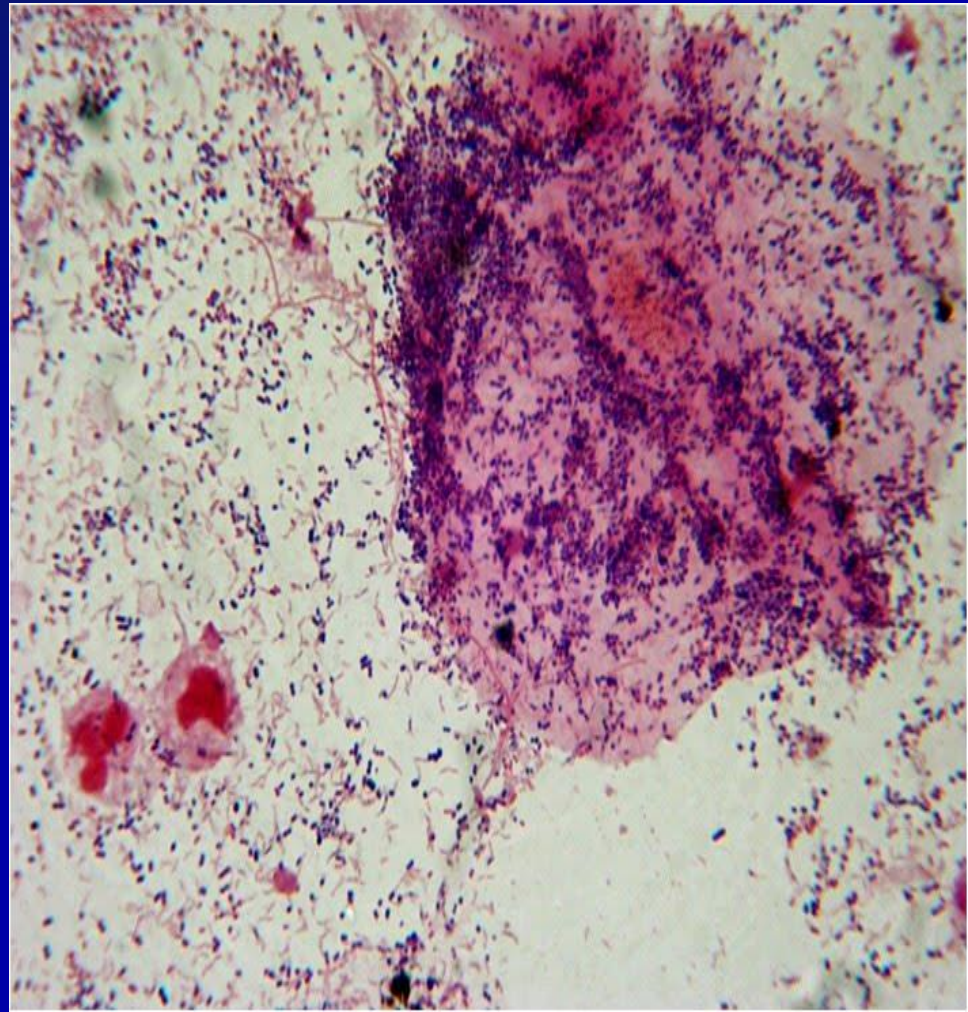
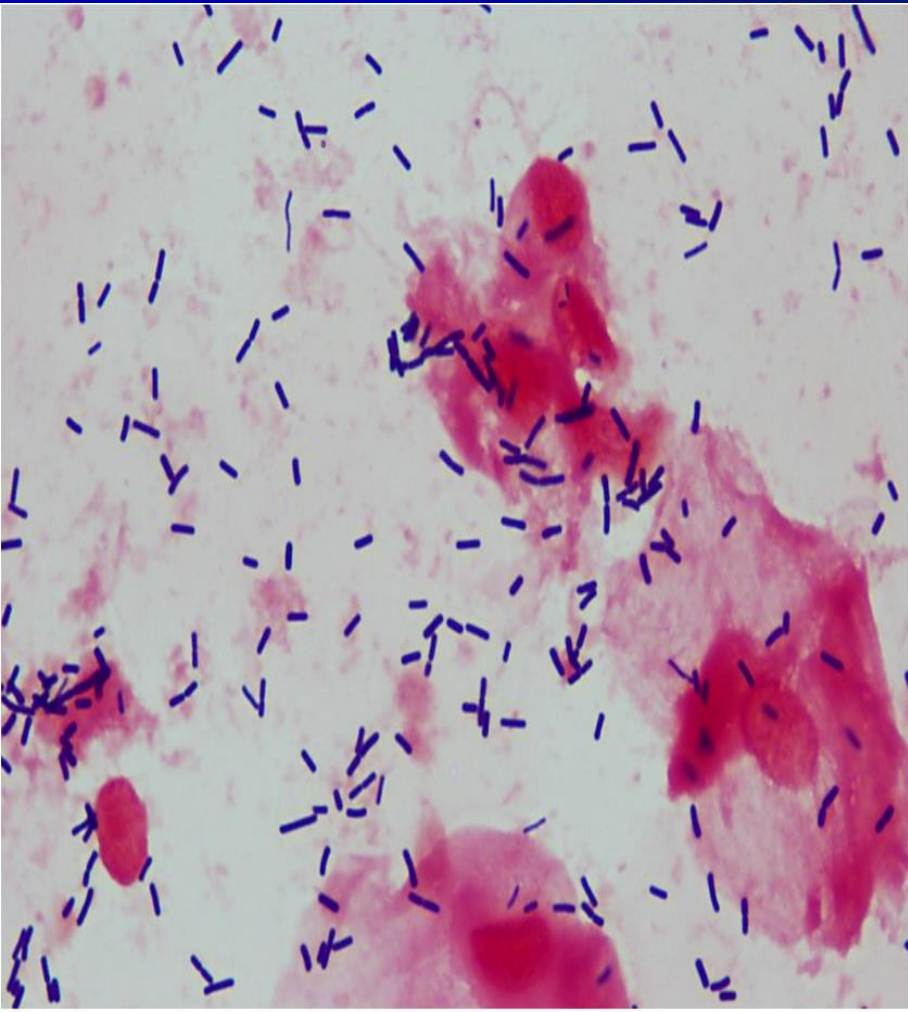
Re/ De mineralization Vs. pH



Vaginal Gram Stain

Normal

⇒ **Bacterial Vaginosis**



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



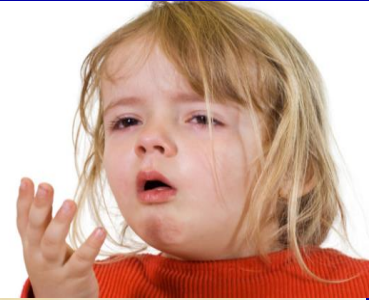
➤ From our own shared microbiome

World Infection Trends Summary

Today's emerging infectious diseases
become
tomorrows endemics



Bug Sharing





Our Actions Now Are Our Future











ben.harris@sclabs.co.nz

www.canterburyscl.co.nz

Key Points

Every antimicrobial use either

- Selects for resistant strains already present e.g. in low numbers and/or
- Induces microbial genetic memory resistance which was not apparent or expressed prior

these resistances are then cumulatively shared by all in any healthcare facility, community, region, country, ultimately worldwide (tourism, food, immigration, etc)

“My Bugs are Your Bugs”

Key Points

- Any individual known to be a carrier of a resistant microbe (MDRO e.g. MRSA, ESBL) is not the problem but an indicator of a much much larger issue (however if that individual happens to develop an infection there will be fewer treatment options for them)
- We catch most infections from ourselves i.e. endogenous e.g. *Staph aureus*
- Routine community swab isolates
 - *South Island 5% all Staph MRSA positive*
 - *Wellington community 8% MRSA positive*
 - *AKL community 13% MRSA positive*
 - *SE Asia community 24% MRSA positive*

Key Points

Any individual that happens to be a carrier of MDRO (e.g. MRSA, ESBL, CRE)

spontaneously loses that carriage in 1-12 months 90% of the time (often 1-3 months) so long as they do not use any antimicrobials (e.g. antibiotics or antiseptic body washes) within that time, which both reselect for and/or induce antibiotic resistances.

Anyone that is or has been on recent past antimicrobials also has less normal flora to help hold back unwanted strains

Key Points

- Antibiotic resistance is a very real shared emerging concern that we are creating
- The damage every antibiotic use does to our normal vast microbial microbiome which is integral for many health parameters (including obesity, moods, depression, autoimmune illnesses – Crohns, IBD, MS, arthritis, etc) may well be an even larger medium term outcome concern