Thank you Argentina!


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Woensdagavond na de wedstrij


BRAZIL

Antibiotics and intestinal dysbiosis: a place for probiotics?

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‘s-Hertogenbosch, The Netherland

Disclosures

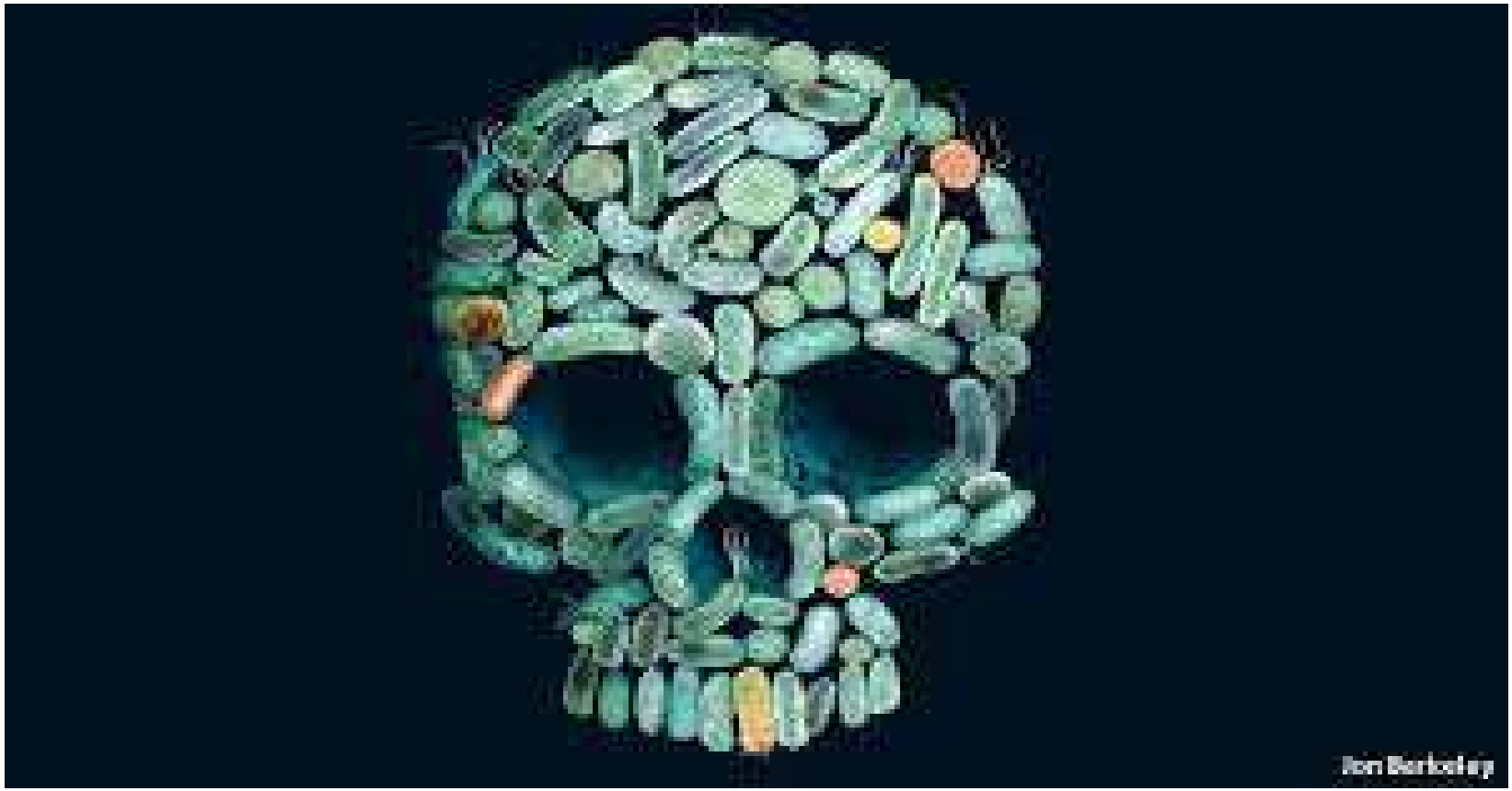
Biocodex

- Speaker
- Support of the Asia Pacific Probiotics Committee

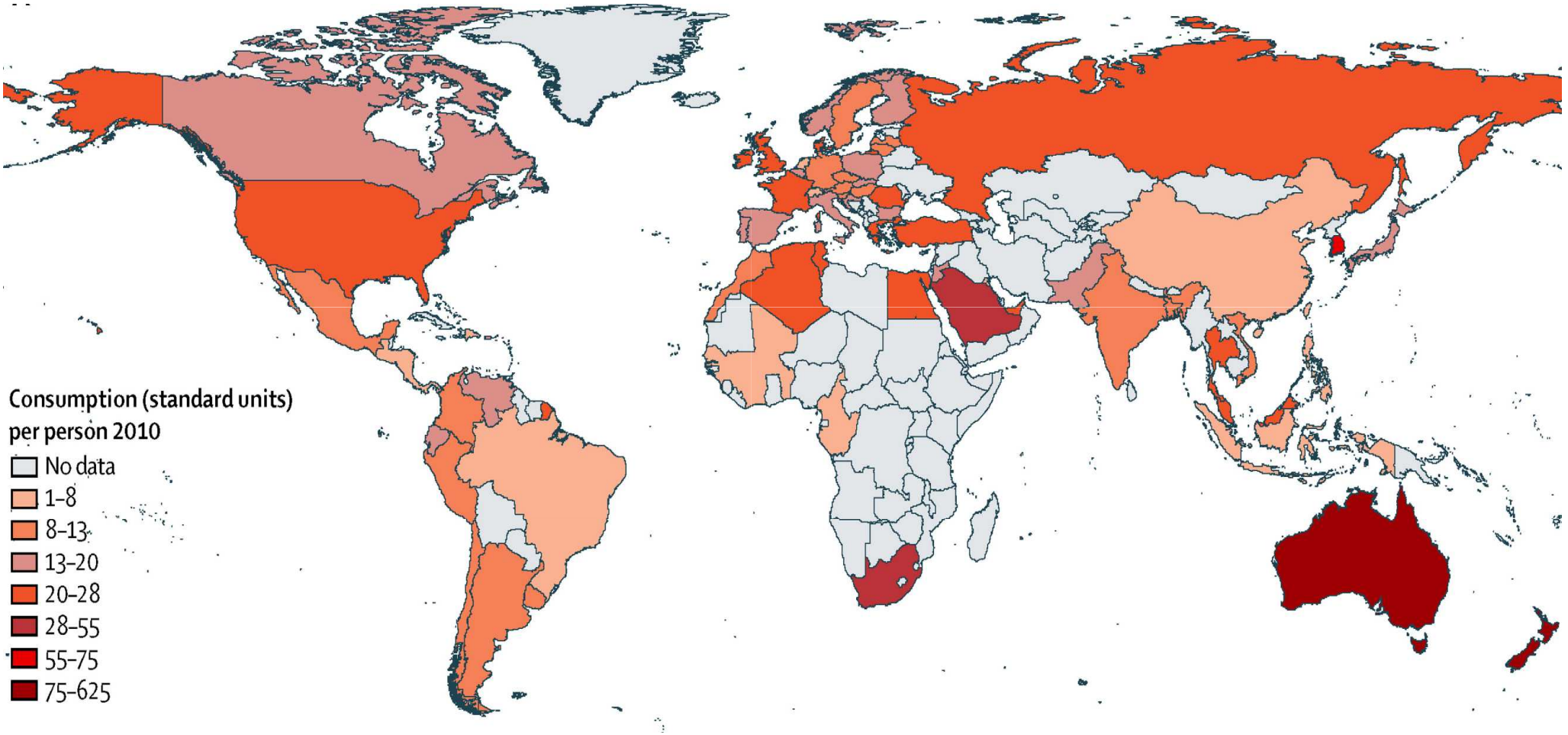
Abbott

- Speaker

Antibiotics are the Most Commonly used Drugs in Western Countries

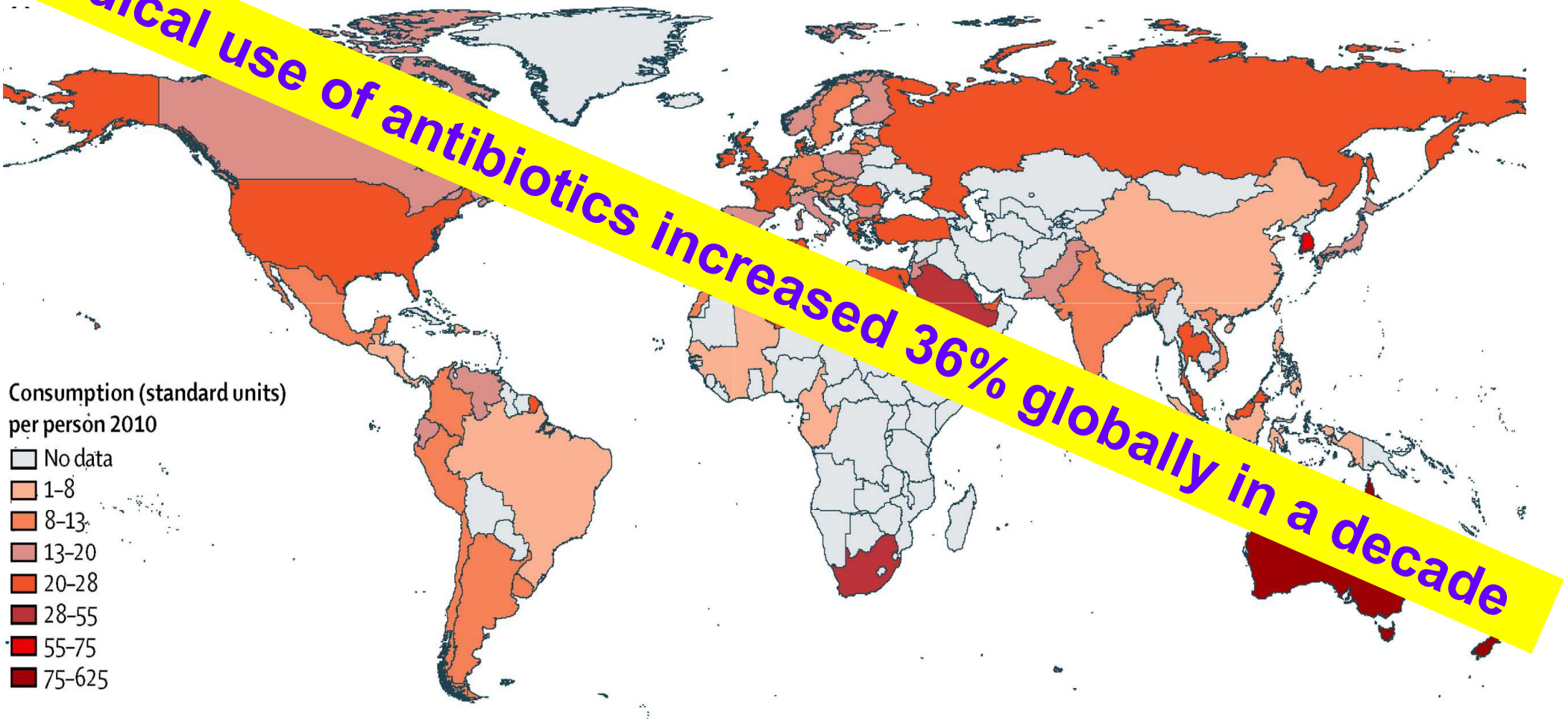


Global Consumption of Antibiotics



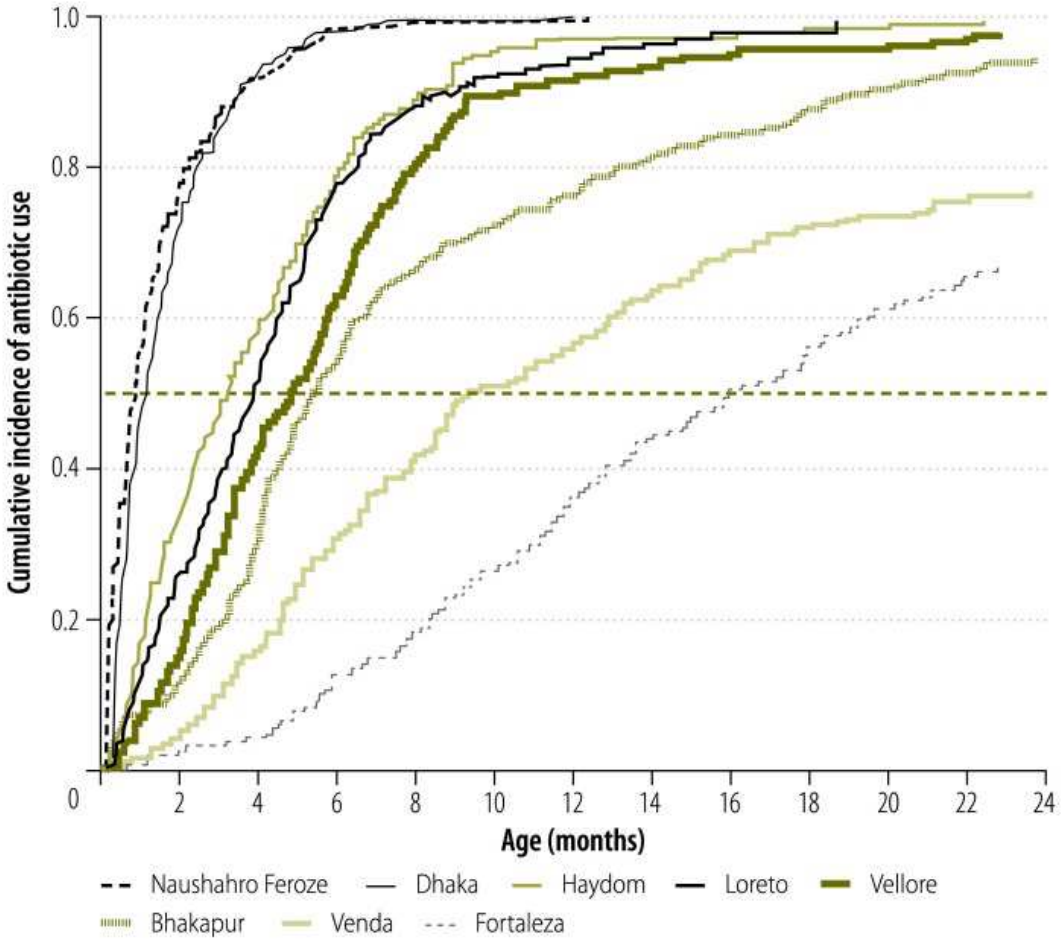
oeckel, Lancet Infect Dis.2014 742–750,

Global Consumption of Antibiotics



oeckel, Lancet Infect Dis.2014 742–750

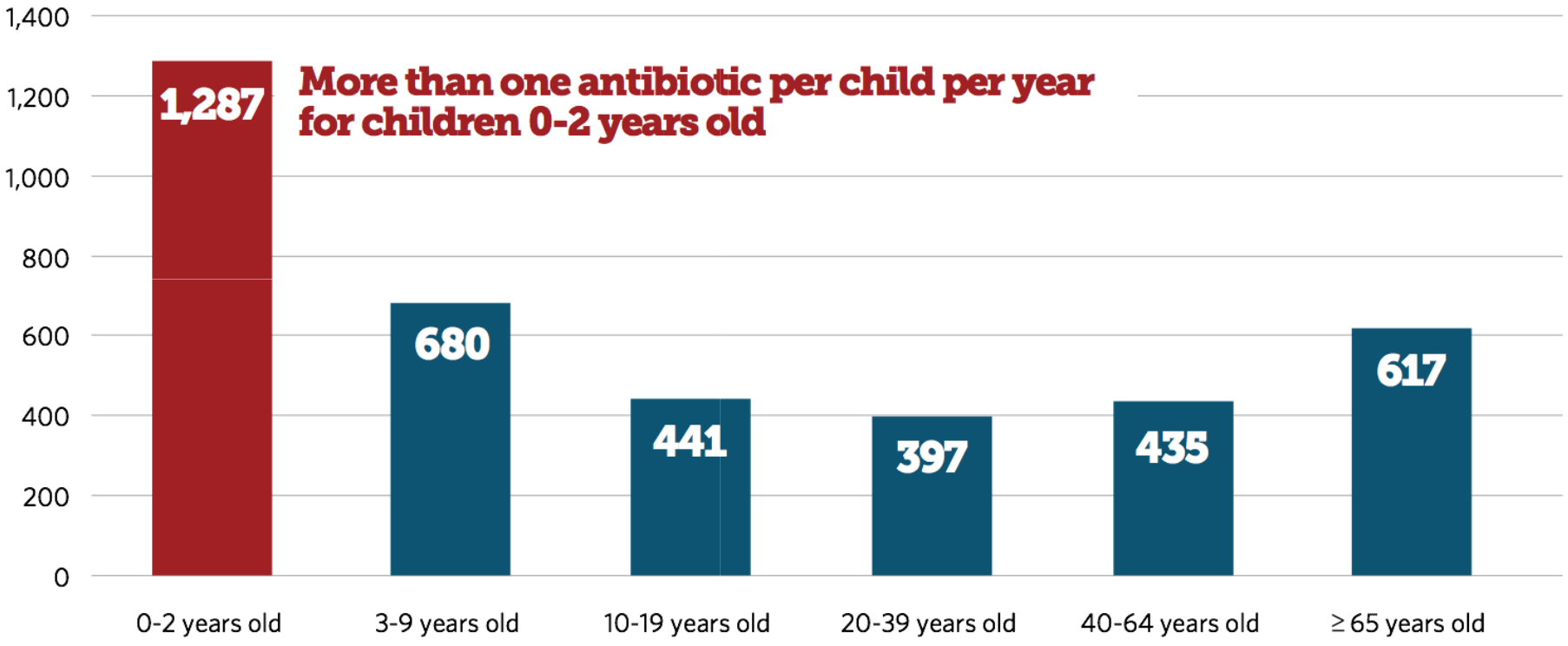
Use of antibiotics age in low resource settings



First antibiotic us
age <2 years

Rogawski ET et al. Bull World Health Organ 2017;95:49-61

Antibiotic prescription (age groups; 1000 individuals)



Source: Analysis of NAMCS and NHAMCS data on U.S. antibiotic prescribing, 2010-2011

Antibiotic consumption in lifestock

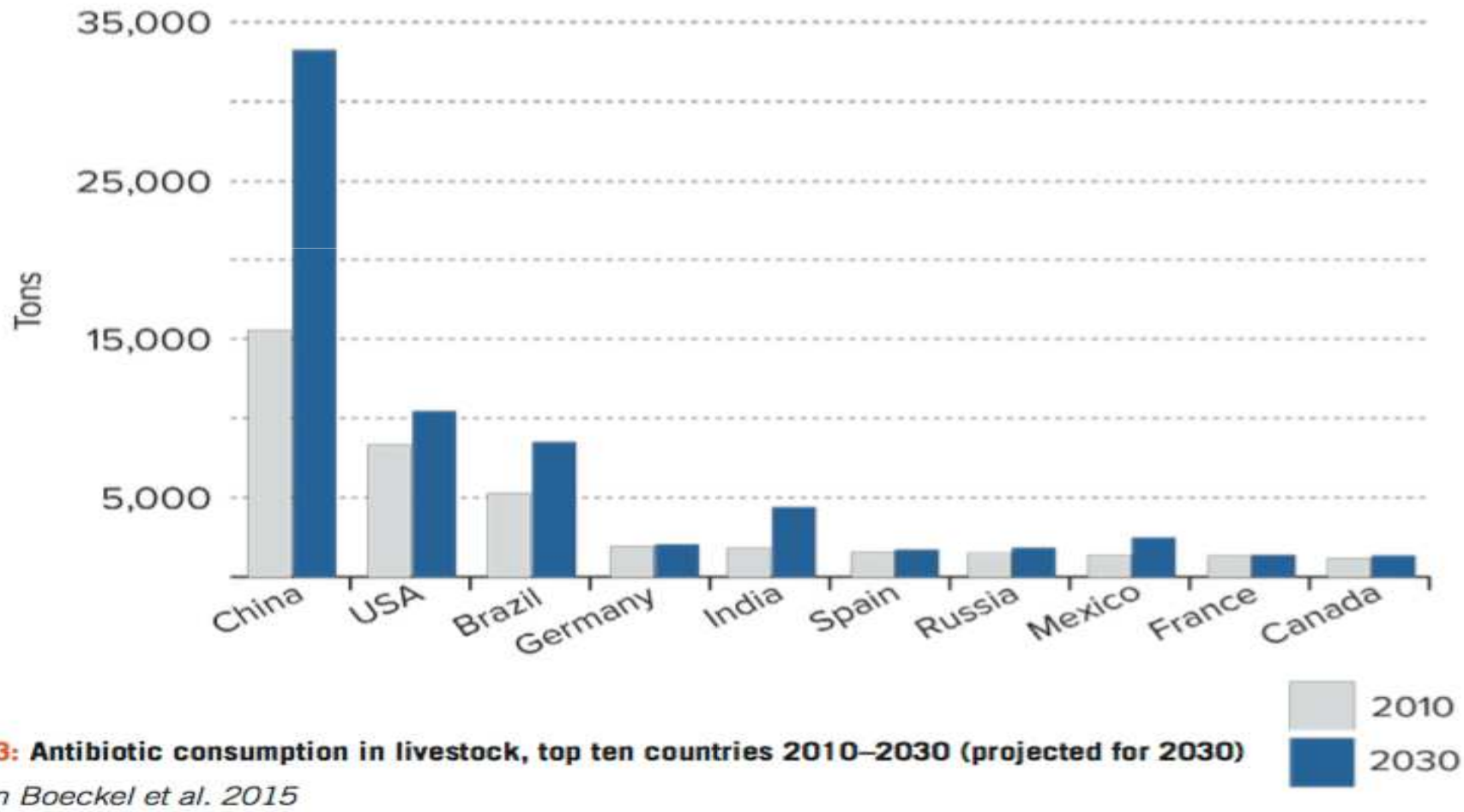


FIGURE ES-3: Antibiotic consumption in livestock, top ten countries 2010–2030 (projected for 2030)

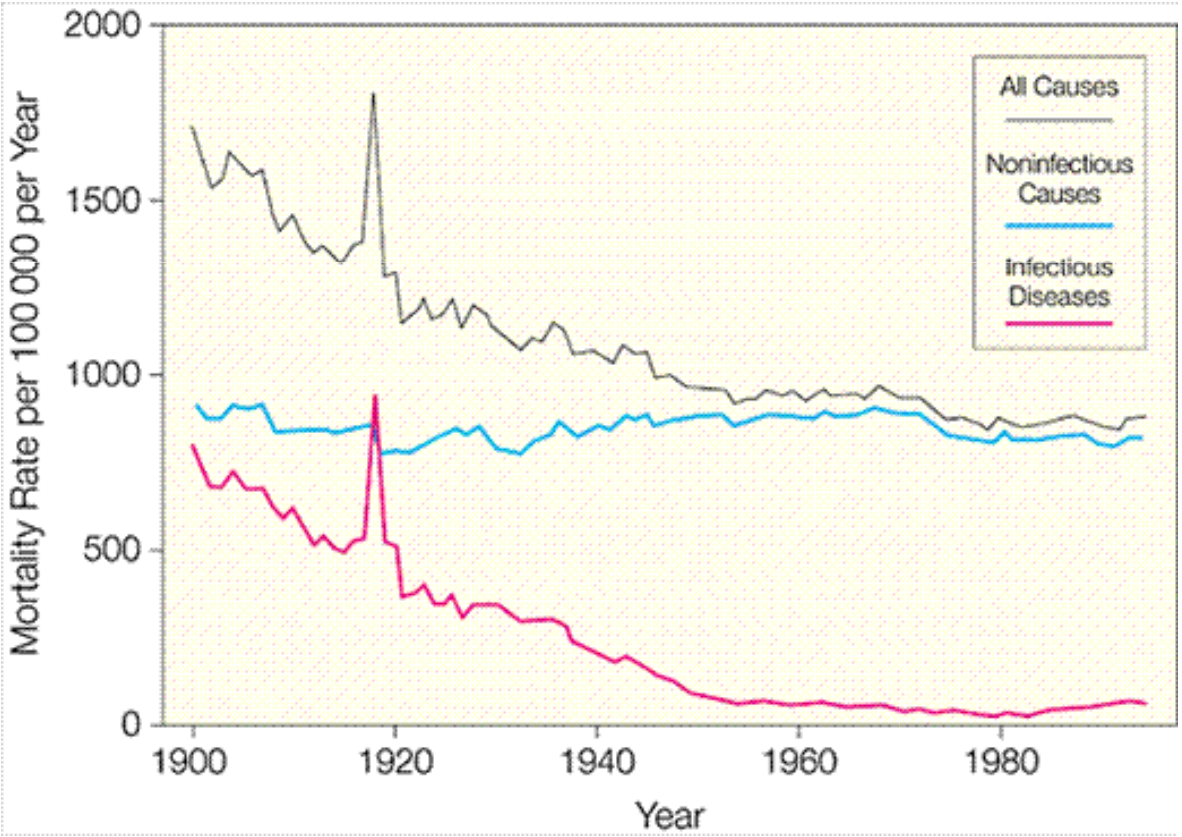
Source: Van Boeckel et al. 2015

The ‘miracle’ of antibiotics

- Discovery of penicillin revolutionised treatment of infectious disease
- Increased life expectancy due to ability to prevent and treat infection

1. Armstrong GL et al, JAMA 1999;281

The ‘miracle’ of antibiotics



Crude mortality rates for all causes, non infectious causes and infectious diseases over the period 1900-1996.

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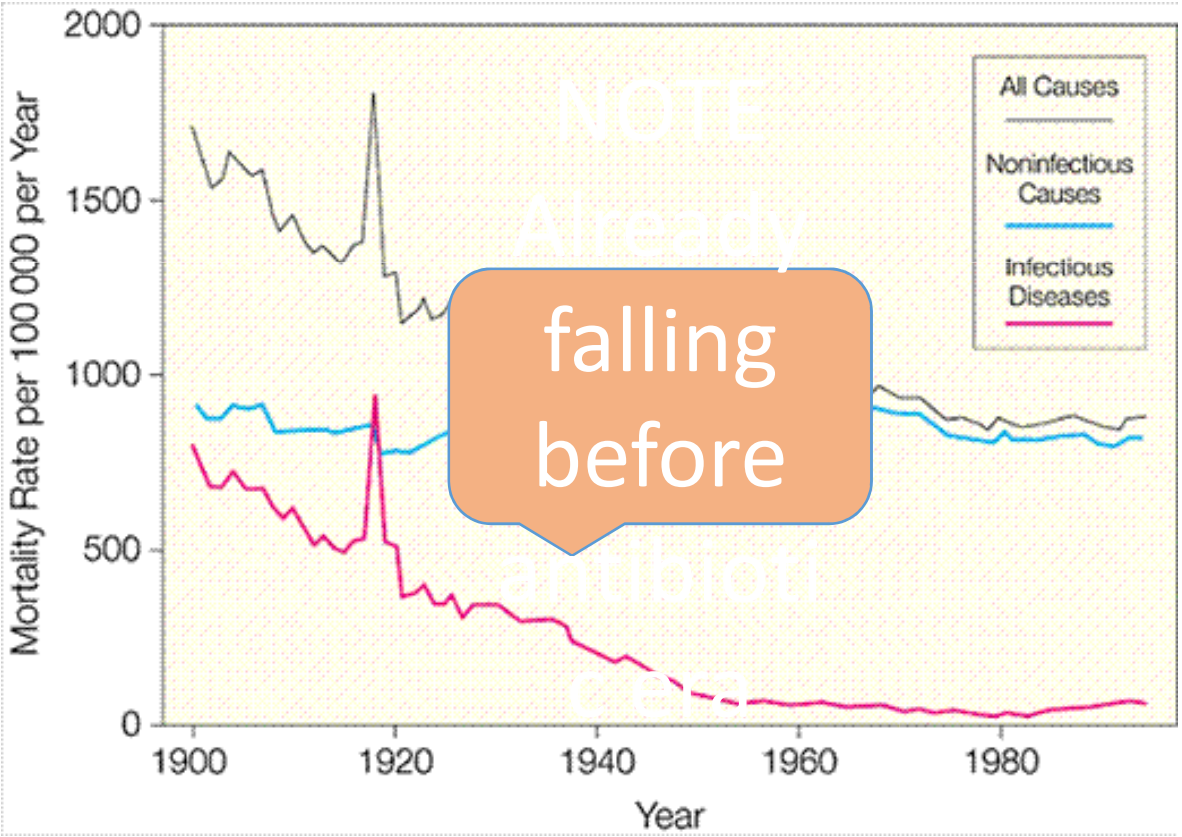

Crude mortality rates for all causes, non infectious causes and infectious diseases over the period 1900-1996.

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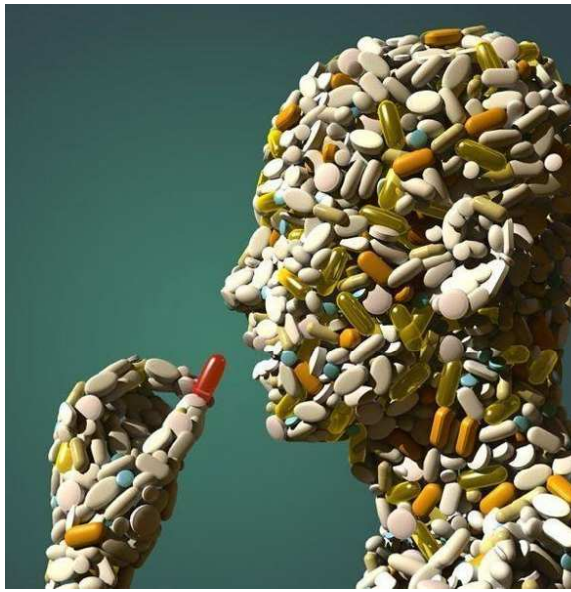
Consequences of Antibiotic (Mis)use

- Antibiotic resistance
- Disruption to microbiome
- Adverse drug events
  - Drug side effects
  - *Clostridium difficile* infection
  - Antibiotic associated diarrhea/colitis
  - Increased hospital readmissions
  - Increased health-care costs

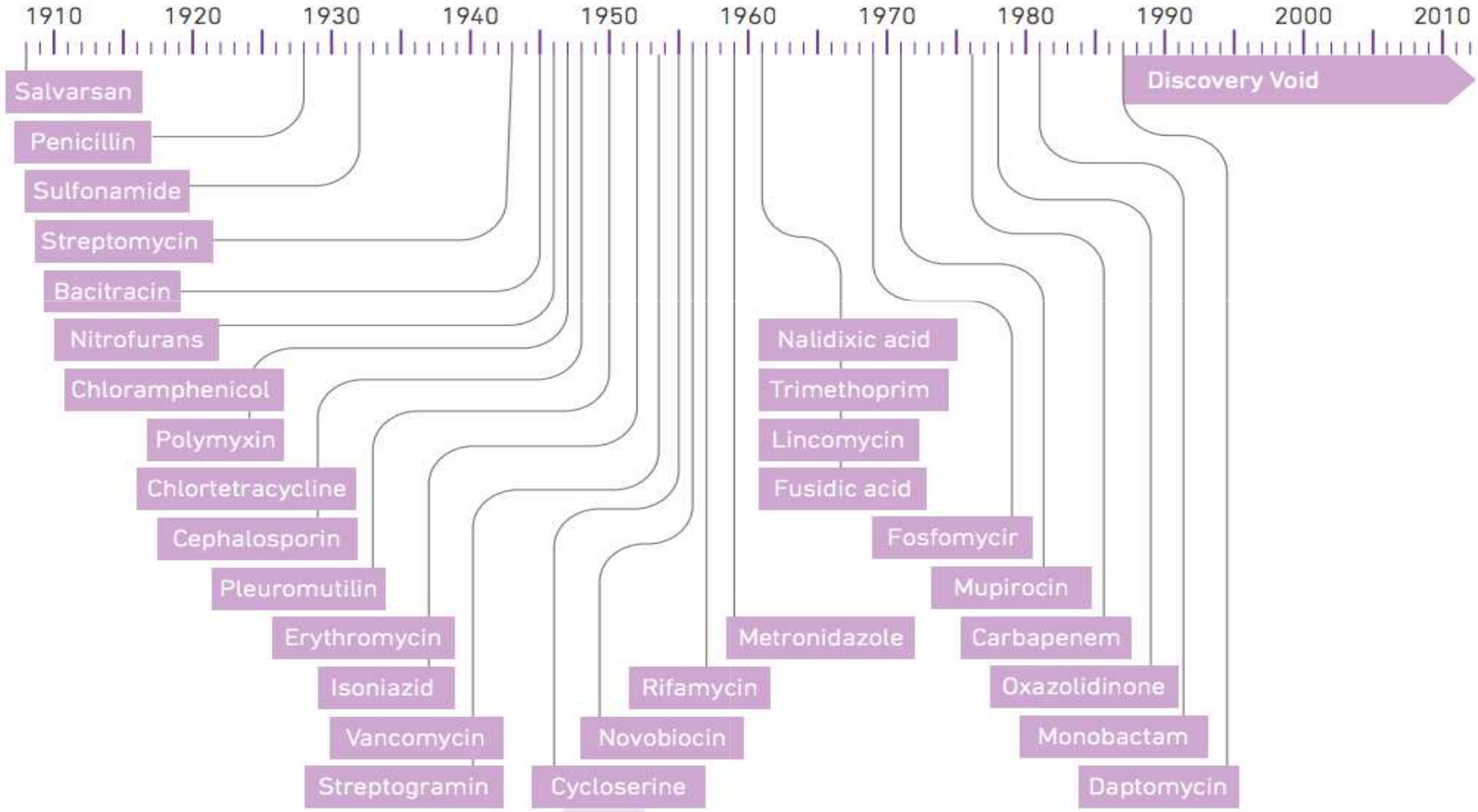


Ohl CA, Luther VP. J. Hosp. Med 2011;6

No significant new antibiotic discoveries for 30 years!

Figure 1 **Dates of discovery of distinct classes of antibacterial drugs**

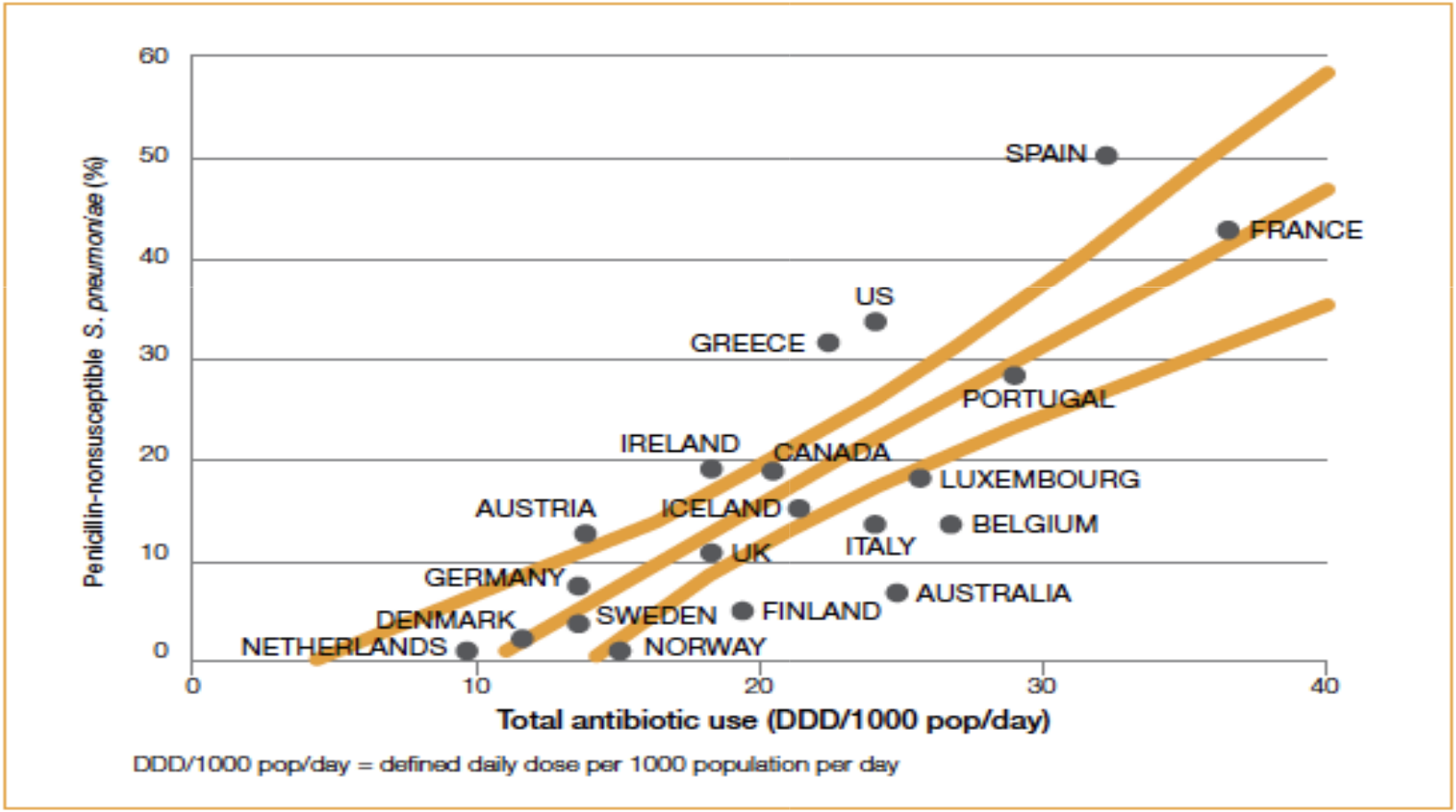
Illustration of the "discovery void." Dates indicated are those of reported initial discovery or patent.



Adapted from Silver 2011 (1) with permission of the American Society of Microbiology Journals Department.

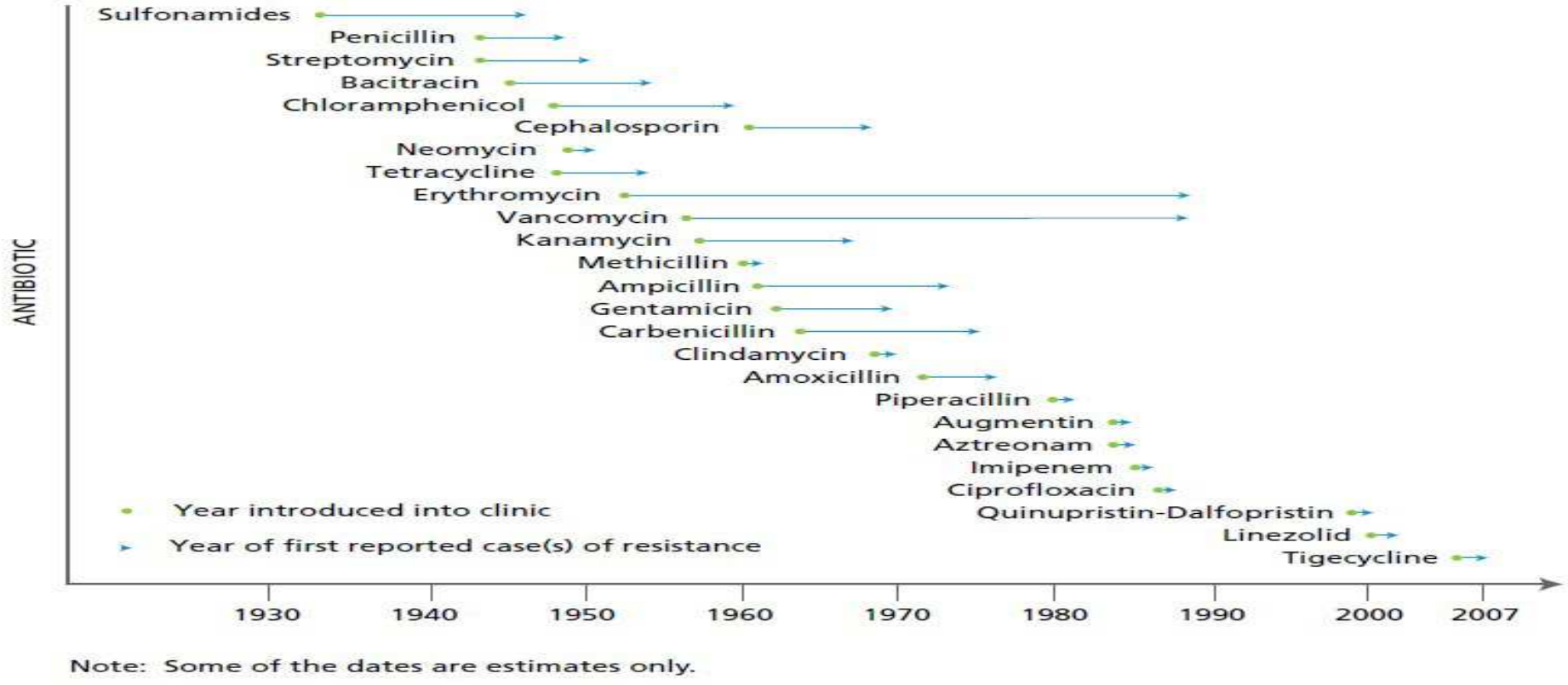
Antibiotic use and antibiotic resistance

Relationship between total antibiotic consumption and *Streptococcus pneumoniae* resistance to penicillin in 20 industrialised countries



18. Shaban RZ, Cruickshank M, Christiansen K & the Antimicrobial Resistance Standing Committee (2013), p. 6. National Surveillance and Reporting of Antimicrobial Resistance and Antibiotic Usage for Human Health in Australia. Antimicrobial Resistance Standing Committee, Australian Heath Protection Principal Committee: Canberra.

Emergence of antibiotic resistance

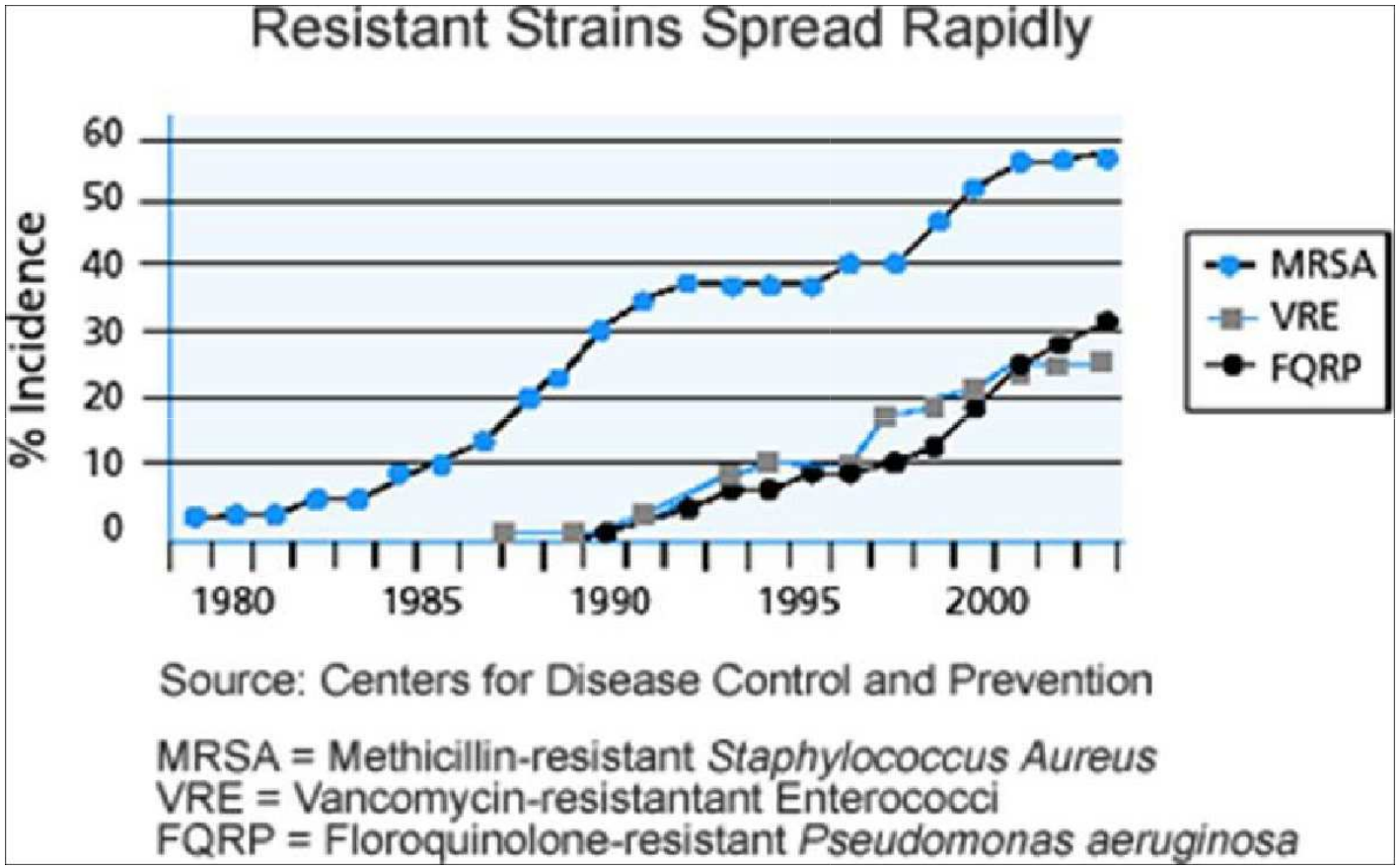


is not difficult to make microbes resistant to penicillin in the laboratory by exposing em to concentrations not sufficient to kill them, and the same thing has occasionally ppened in the body."

Alexander Fleming, 1945

4. Sir Alexander Fleming, Nobel Lecture, December 1945
5. Pray LA Insight Pharma Reports 2008, in Looke D 'The Real Threat of Antibiotic R

Resistance spreads rapidly



Natural selection
Horizontal transfe
International trav

6. Centers for Disease Control and Prevention http://www.cdc.gov/ha

“The magnitude of the problem is now accepted.

We estimate that by 2050, 10 million lives a year and a cumulative 100 trillion USD of economic output are at risk due to the rise of drug resistant infections if we do not find proactive solutions now to slow down the rise of drug resistance.

Even today, 700,000 people die of resistant infections every year.”

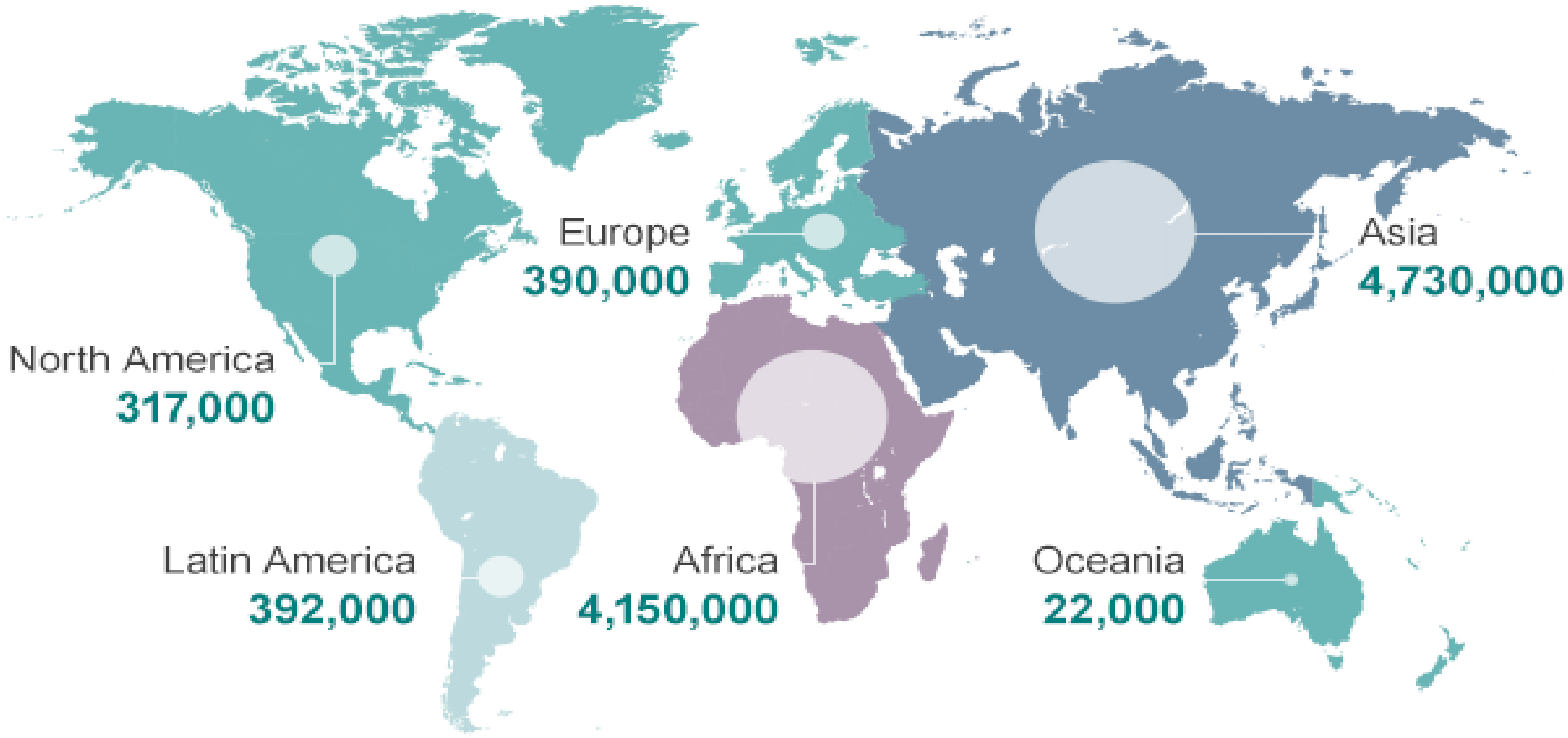
https://amr-review.org/home.html

Closed 2016

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

Deaths attributable to antimicrobial resistance every year by 2050



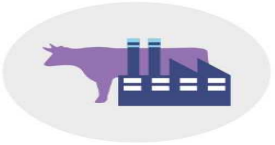
Source: Review on Antimicrobial Resistance 2014

www. weforum.org consulted on February

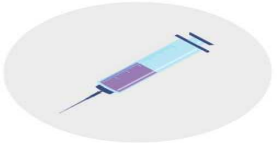
TACKLING ANTIMICROBIAL RESISTANCE ON TEN FRONTS

Public awareness

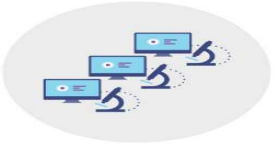
Sanitation and hygiene



Antibiotics in agriculture and the environment



Vaccines and alternatives



Surveillance

Rapid diagnostics

Human capital

Drugs

Global Innovation Fund

International coalition for action

Review on Antimicrobial Resistance

Antimicrobial stewardship

Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen, dose, duration of therapy, and route of administration.

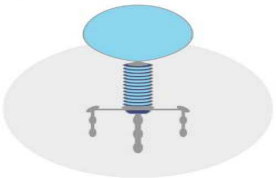
Antimicrobial stewards seek to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity and other adverse events, reduce the costs of health care for infections, and limit the selection for antimicrobial resistant strains.

ALTERNATIVE PRODUCTS TO TACKLE INFECTIONS

A selection of alternative products that are under development, which could be used for prevention or therapy.

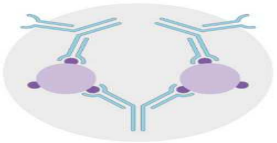
Phage therapy

Natural or engineered viruses that attack and kill bacteria



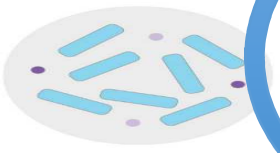
Lysins

Enzymes that directly and quickly act on bacteria



Antibodies

Bind to particular bacteria or their products, restricting their ability to cause disease

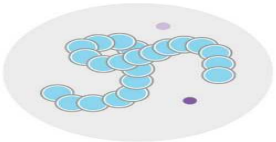


Probiotics

Prevent pathogenic bacteria colonising the gut

Immune stimulation

Boosts the patient's natural immune system

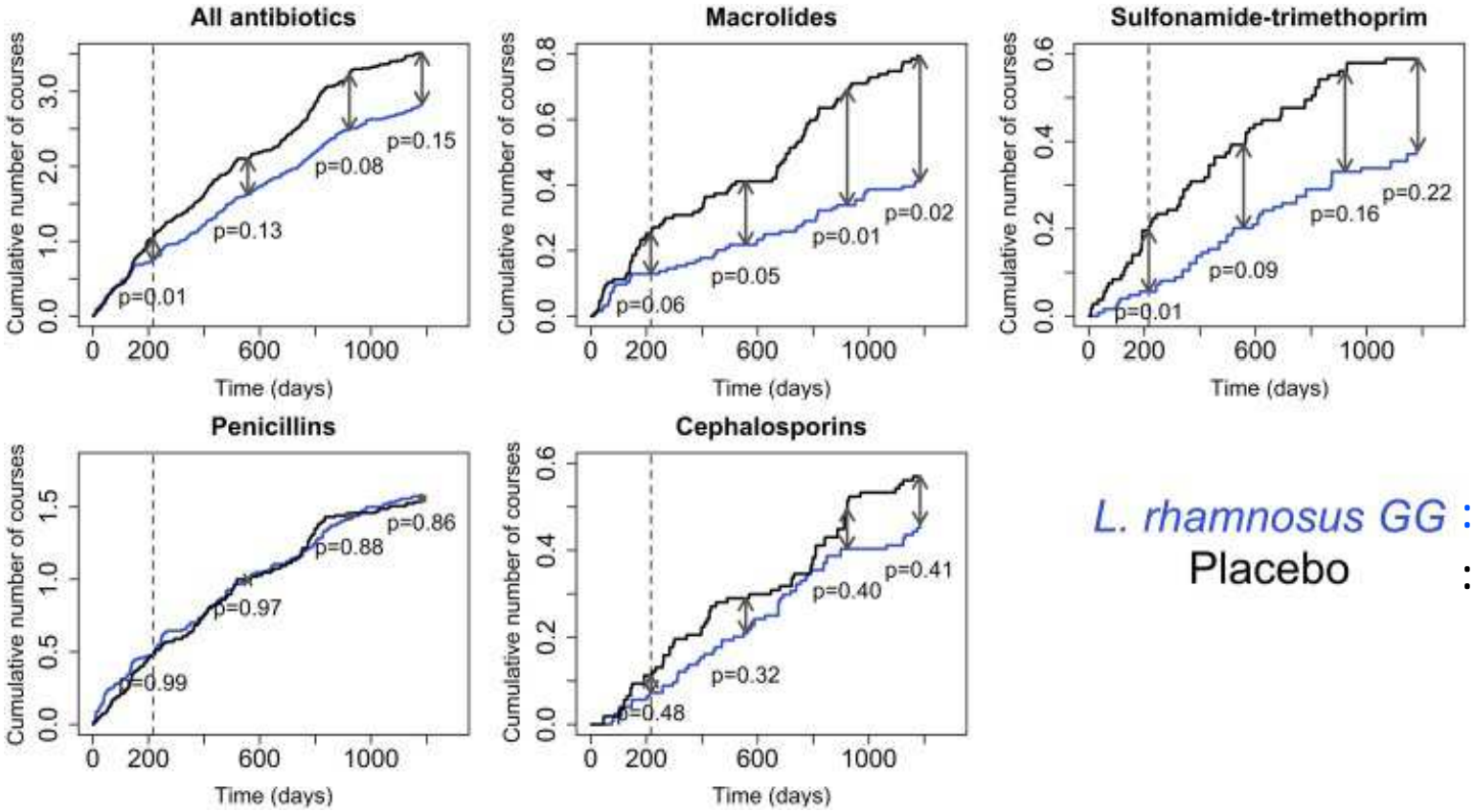


Peptides

Non-mammalian animals' natural defences against infection

Review on Antimicrobial Resistance

ng-term probiotic (LGG) consumption reduces antibiotic u

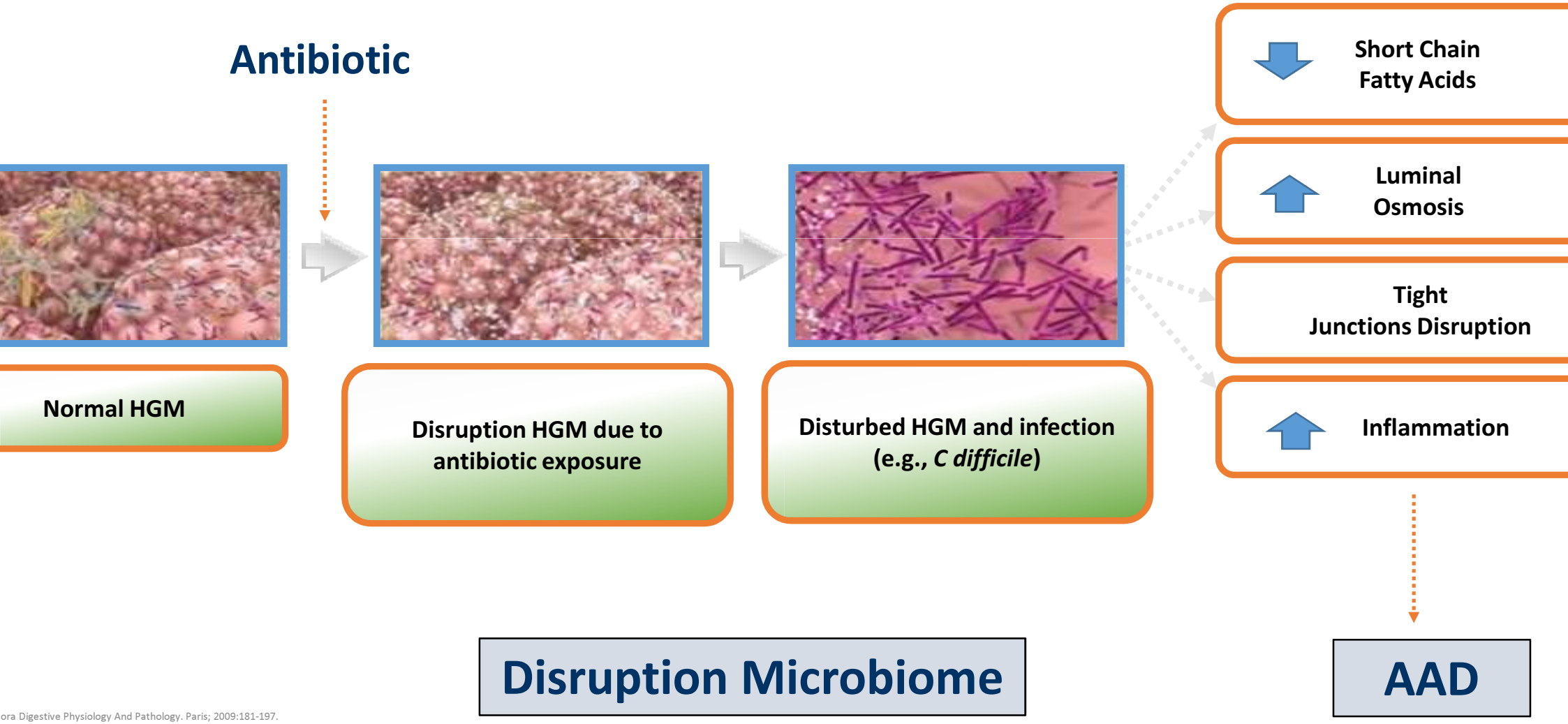


DB PC RCT
(231 children, aged 2-7 yr
Duration: 210 days

L. rhamnosus GG : 400 ml milk with LGG 10^8 cfu/m
Placebo : 400 ml milk

Korpela K, et al. PlosOne: April 25, 201

After antibiotic exposure



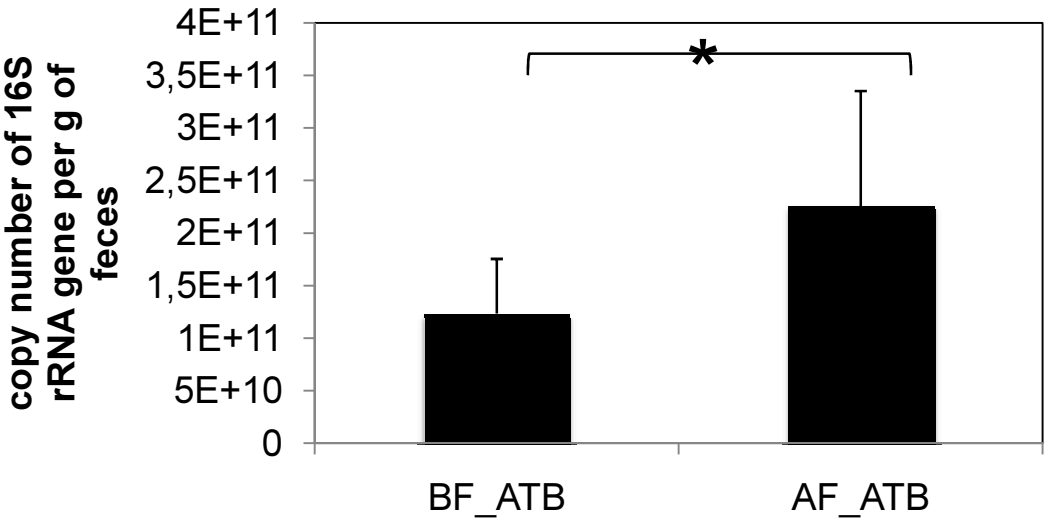
ora Digestive Physiology And Pathology. Paris; 2009:181-197.

Disruption to microbiome (dysbiosis)

- Numbers
- Balance
- Diversity

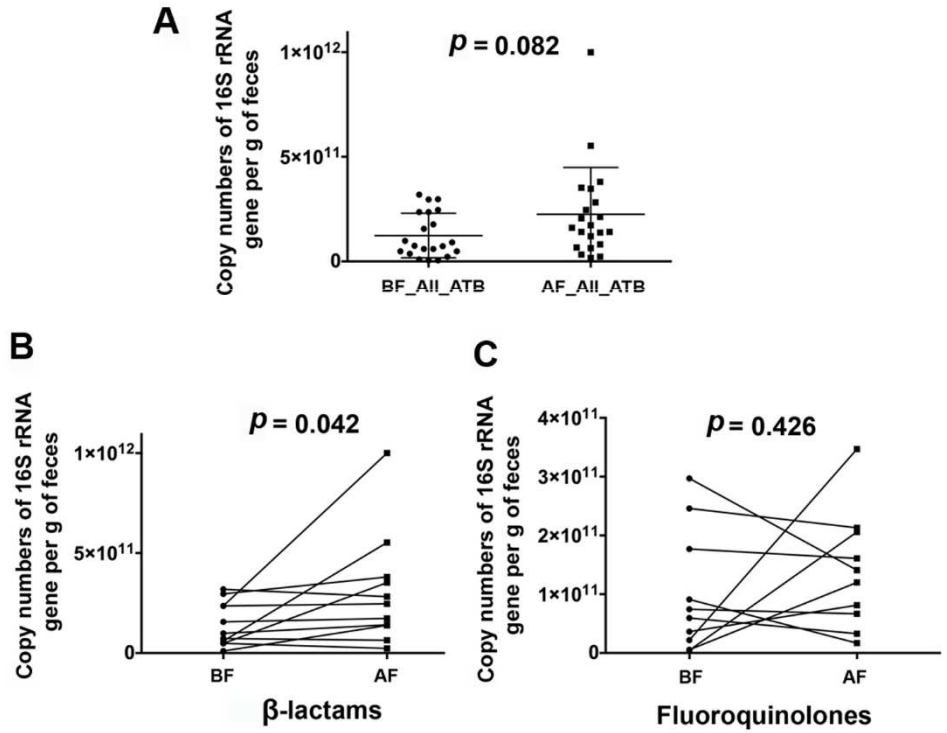
Counterintuitive results

increase of bacterial load after ATB intake in fecal sample



Day 0

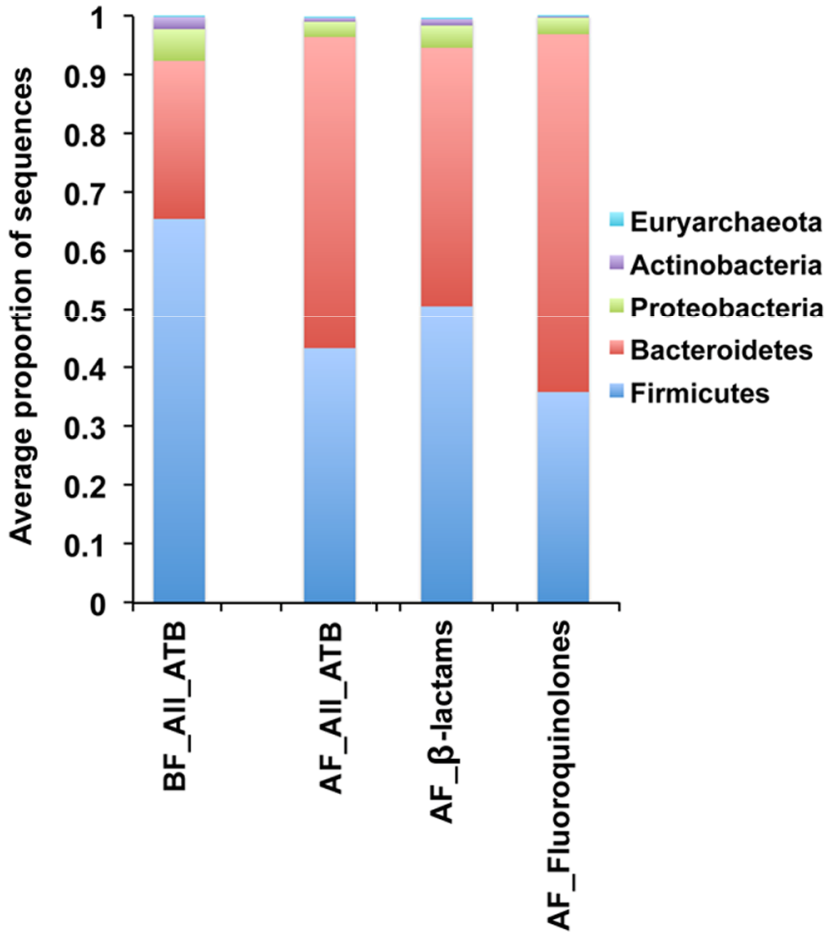
Day 7



P = 0.08 (Wilcoxon matched-pairs signed rank test)

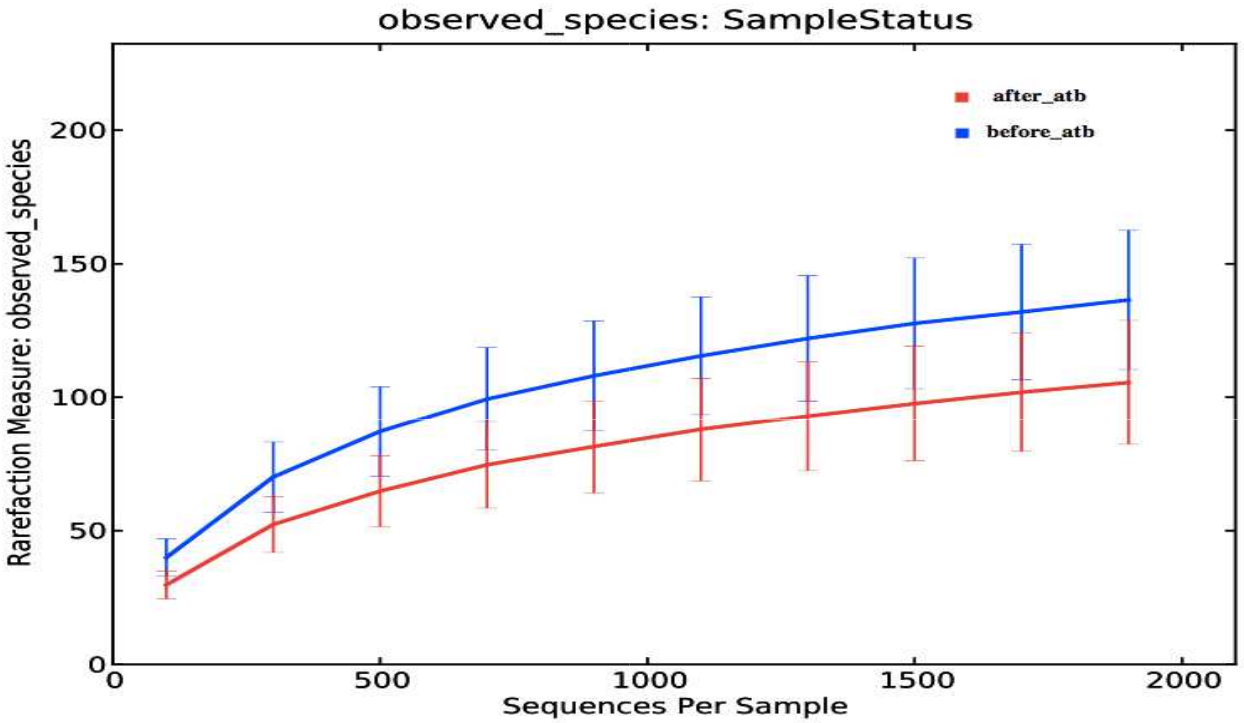
Panda et al. PLoS ONE 20

… and a shift in balance at philum level



Panda et al, PLoS ONE 2

….., but a decrease on bacterial richness (taxa)



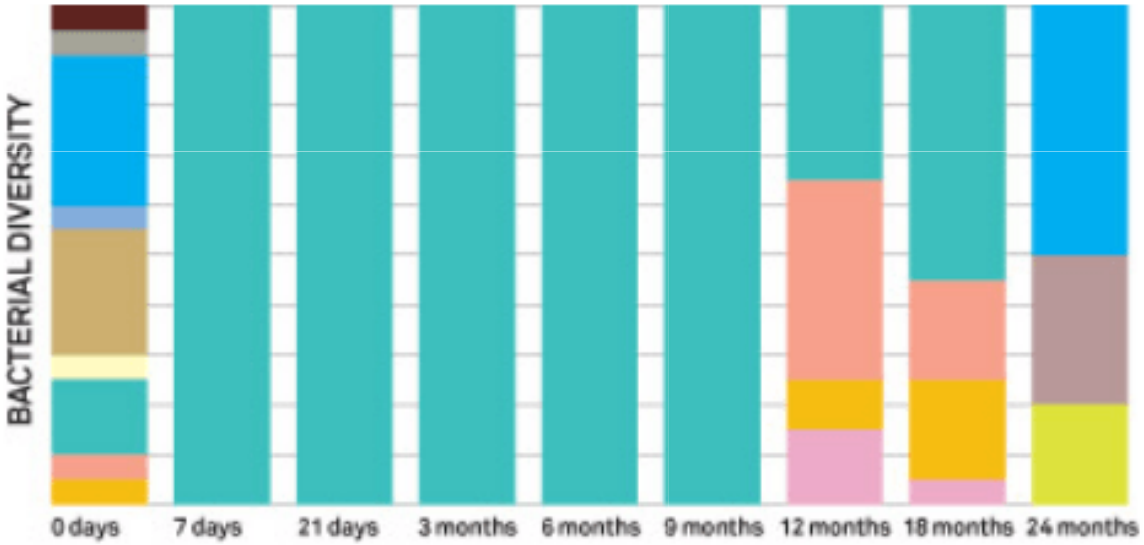
verage number of observed taxa before antibiotic intake: 140 (SD = 22)
verage number of observed taxa after antibiotic intake: 105 (SD = 23)

< 0.0001 (Wilcoxon matched-pairs signed rank test) for observed species and chao1
< 0.0001 (Paired t test)

Panda et al, PLoS ON

Antibiotics = Microbiome Killer

Studies have revealed some alarming costs of taking antibiotics, which don't discriminate between disease-causing bacteria and our natural microbiome. Graphed below is the diversity of gut bacteria from one important genus (*Bacteroides*) in a patient who took a weeklong course of clindamycin; different colors represent the different species. For nine months after exposure, the subject's gut was left with nothing but one type, a clindamycin-resistant strain of *Bacteroides thetaiotaomicron*. Even two years out, the flora had not regained their former diversity.

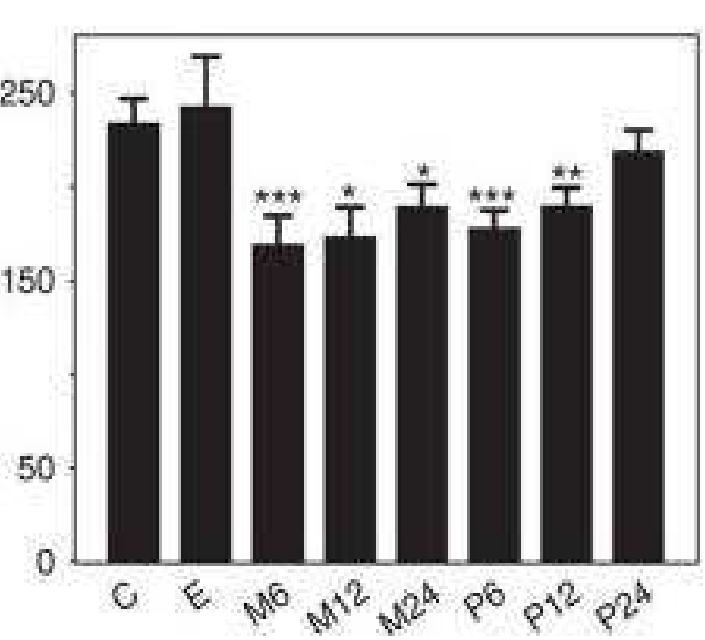


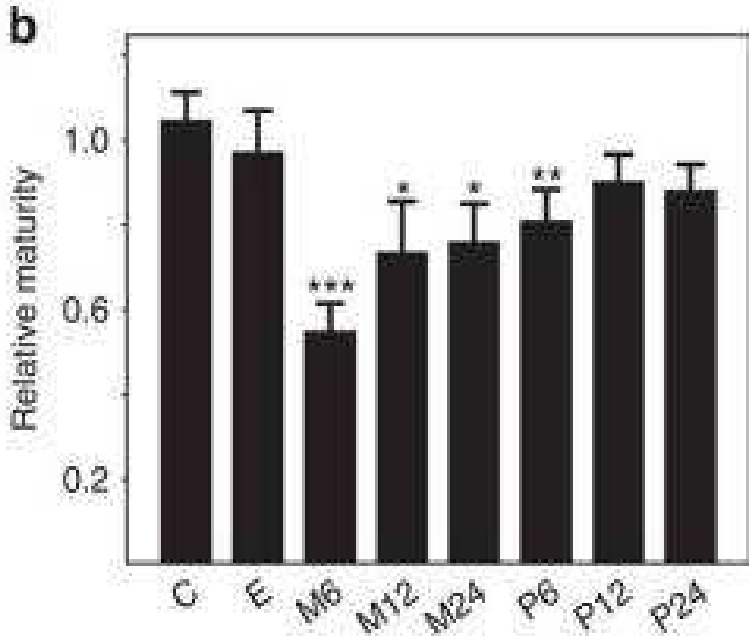
LONG-TERM EFFECTS OF A SEVEN-DAY COURSE OF ANTIBIOTICS

JANSSON 2010. http://www.wired.com/magazine/2011/09/mf_microbiome

Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children

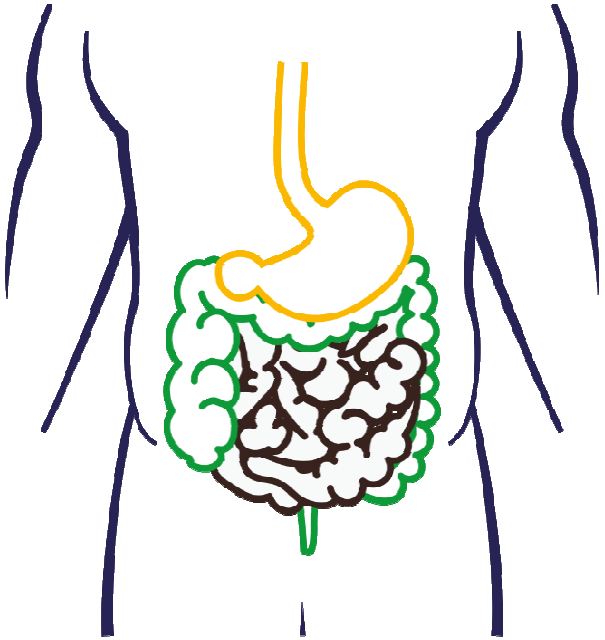
Katri Korpela[1], Anne Salonen[1], Lauri J. Virta[2], Riina A. Kekkonen[3], Kristoffer Forslund[4], Peer Bork[4] & Willem M. de Vos[1,5,6]





C: no AB past 2 yrs and in total <1 cours
E: AB in early life + C
M6: macrolide course within last 6 mo
M12: macrolide course within 6-12 mo
M24: macrolide course within 12-24 m
P6, P12, P24: penicillin courses ….

Disturbances of the gut microbiota & dysbiosis



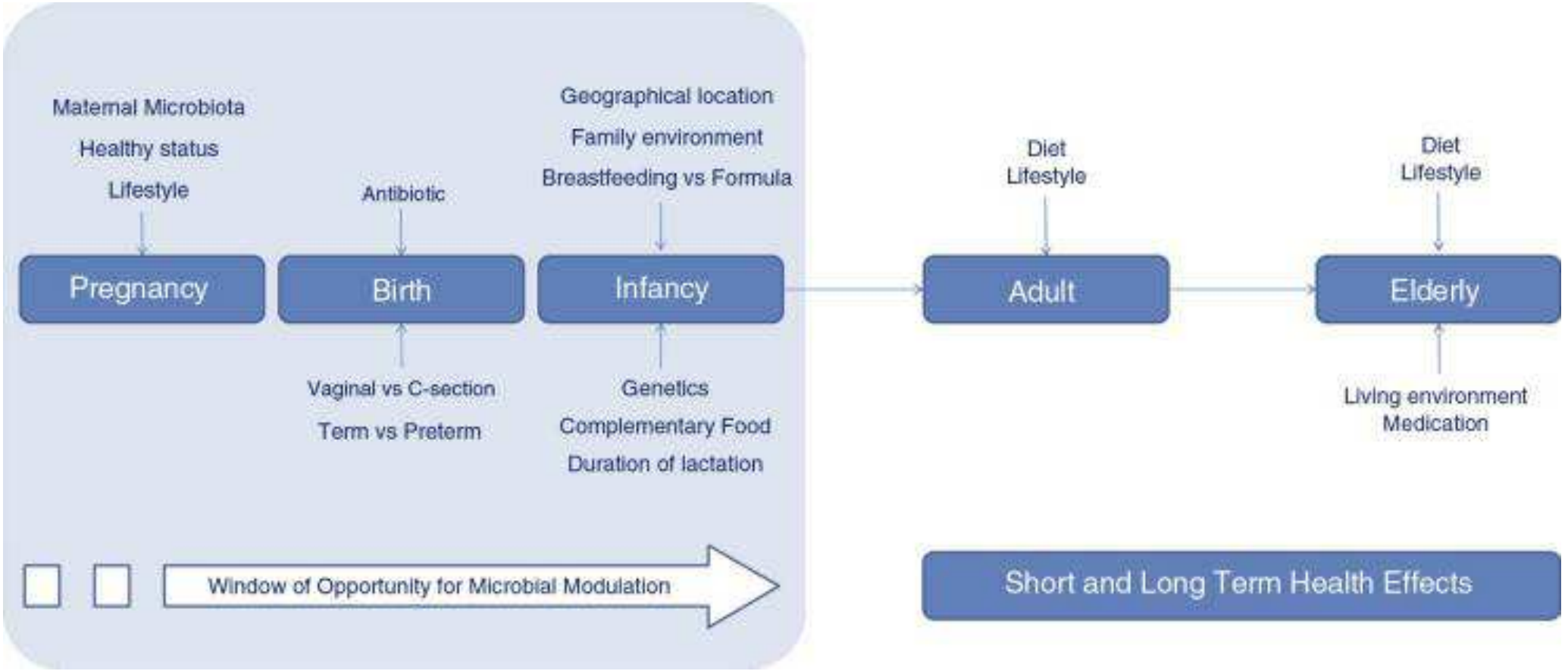
EUBIOSIS => “Normal" and "balanced" intestinal microbiota fulfills all the conditions for us to benefit from its health effects
(metabolism, immunity, trophicity, barrier effect)

VS

DYSBIOSIS => Intestinal dysbiosis can be defined as an **unfavorable dysbalance of the intestinal microbiota**.

Moré, Margret I., Alexander Swidsinski. "Saccharomyces boulardii CNCM I-745 supports regen
the intestinal microbiota after diarrheic dysbiosis–a reviewClinical and Experimental Gastroen
11 (2015): 237

The course of life of a microbiota



Antibiotics and the microbiome throughout development

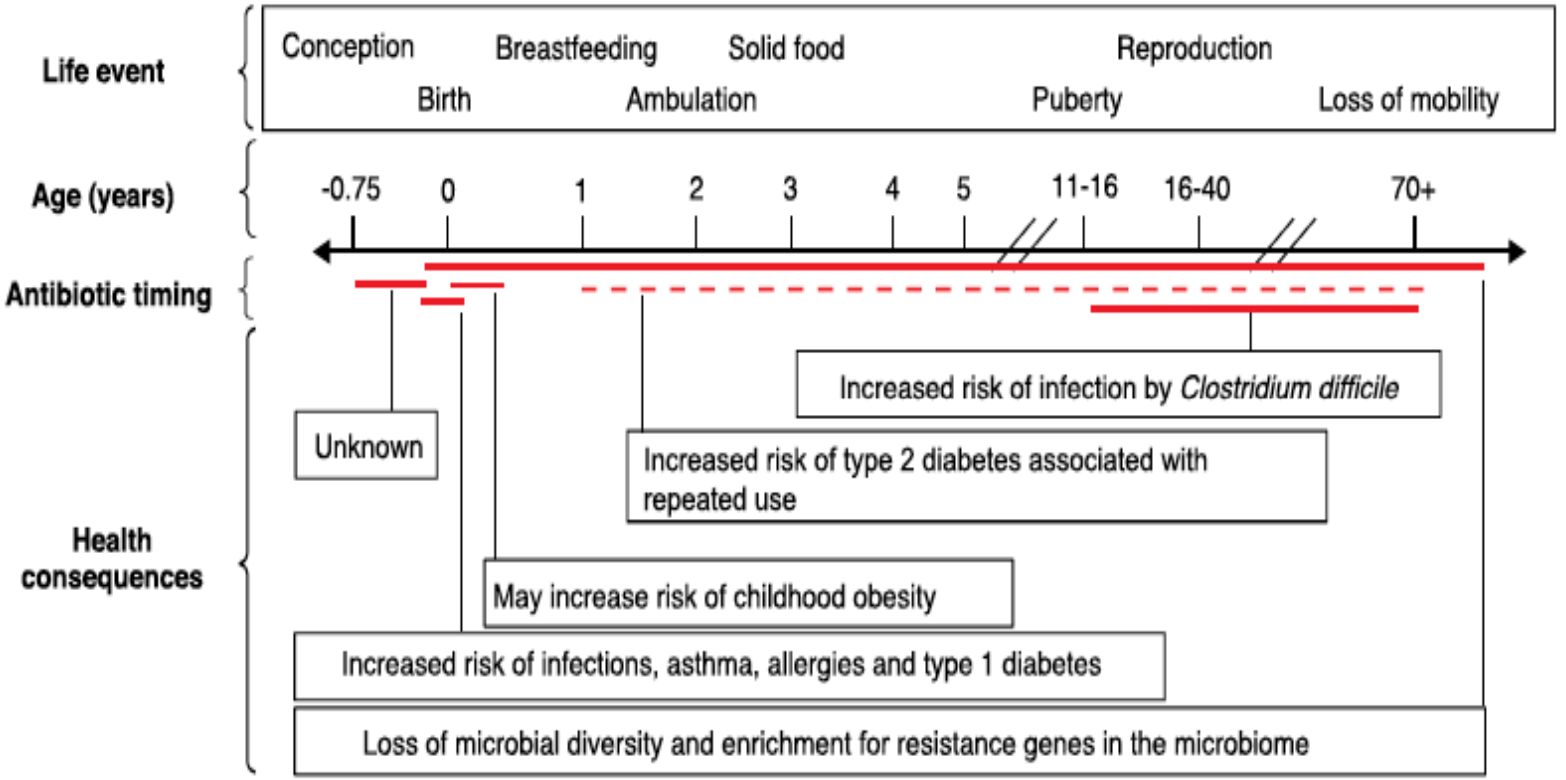


Fig. 1 Health consequences linked to the disruption of human-associated microbiota involving antibiotic use during development and adulthood. *Red lines* indicate that a single dose of antibiotics within the time period has been linked to a health consequence, whereas a *dotted red line* indicates that multiple doses of antibiotics within the time period are required to observe a link

Langdon et al *Genome Med* 2016, 8:39, 2

Gut microbiota dvs

Gut microbiota dysbiosis and disease

orders linked to altered composition of the gut microbiota:

Nutrition-related d lers (obesity, type 2 diabetes and the metabolic syndrome)

Inflammatory bo nd CD)

Celiac disease

Antibiotic-associated diarrhe difficile

Functional bowel disorders

Colo-rectal cancer

Certain allergies

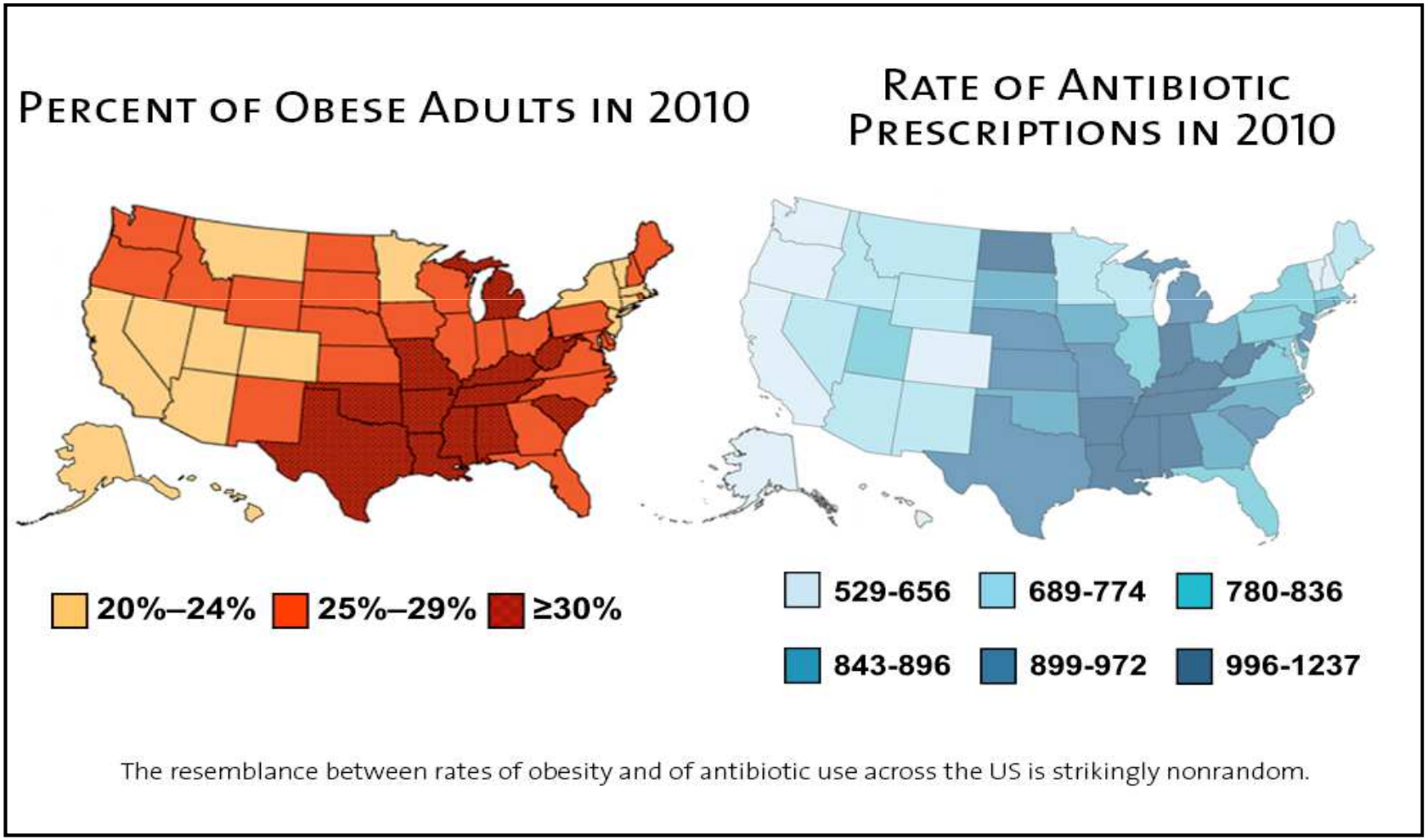
Certain mental and neuro-developmental conditions, such as autism spectrum disorder

Could this be correlation, without causation?

Do these differences matter?

Can anything else explain the results?

Associations, but no proven causuality



Consequences of Antibiotic (Mis)use

- Antibiotic resistance
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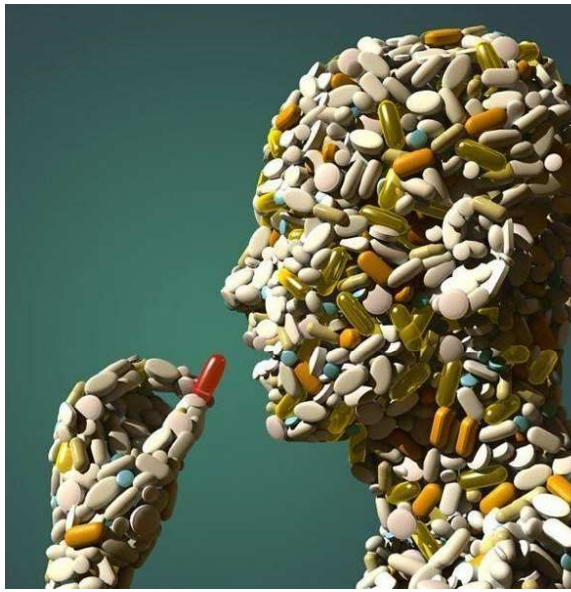


Ohl CA, Luther VP. J. Hosp. Med 2011;6

Definition of antibiotic-associated diarrhea (AAD)

Diarrhea associated with antibiotic exposure either while on antibiotics and up to 8 weeks after the end of therapy

Definition of CDAD: AAD + presence of *Clostridium difficile* in the stools

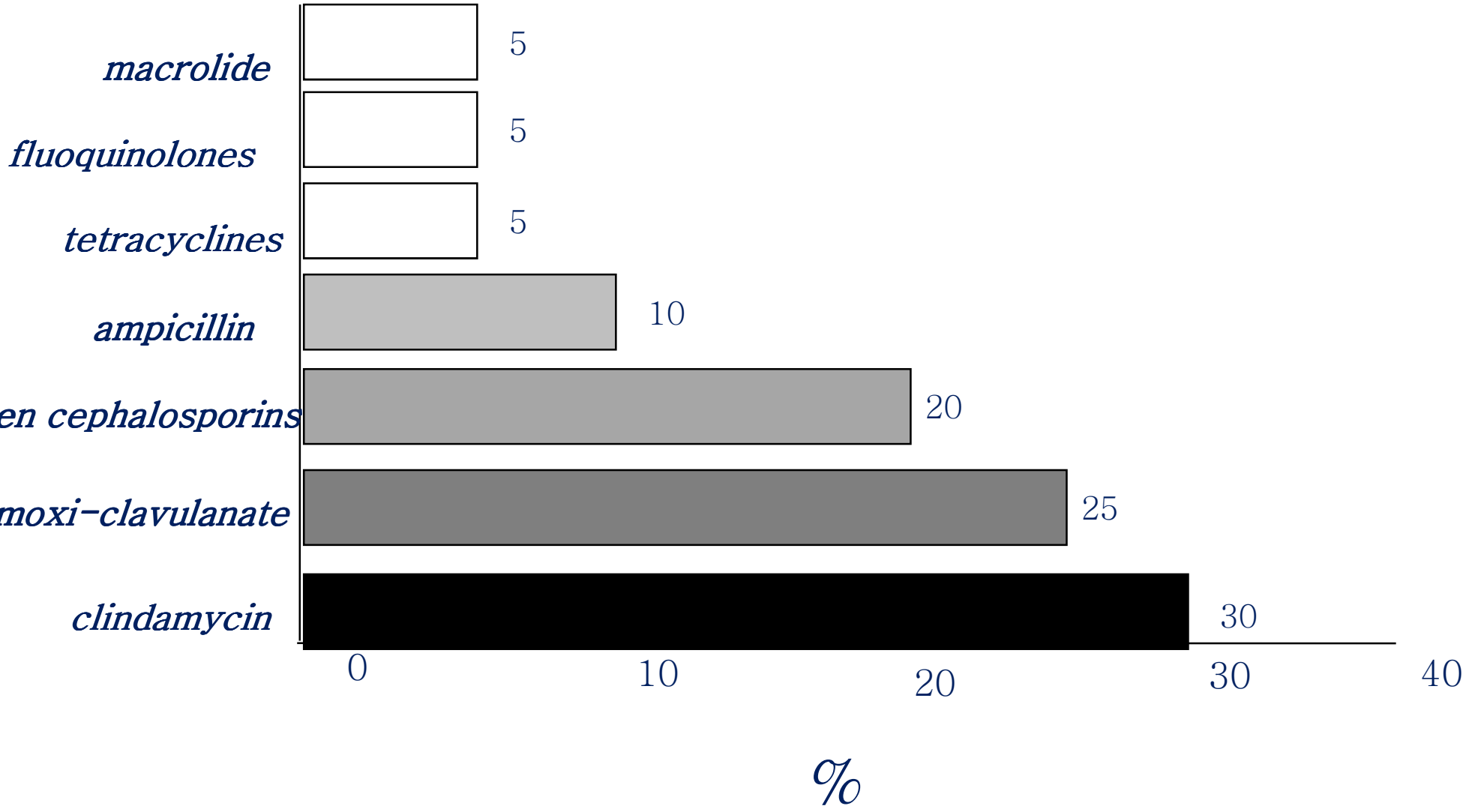
Antibiotic-associated diarrhea in children

- Incidence in children: ~ 20-25% (ranges 6-80%)
- Peak age 18-48 months
- *Clostridium difficile* is the major agent of AAD (25-30% of cases)
- Mostly mild-moderate severity, abdominal pain (35%)
- Is more severe in chronic diseases: GI pathology, immunosuppression and previous episode of AAD
- Prevention: antibiotic stewardship, enhanced infection control, probiotics

Antibiotic therapy with increased risks

- Large spectrum antibiotics
- Antibiotics with high biliary excretion
- Prolonged antibiotic therapy
- Repeated antibiotics cycles
- Antibiotic combination therapies

Classes of antibiotics responsable for diarrhea



Spectrum of *Clostridium difficile* infections

Fulminant colitis
Toxic megacolon

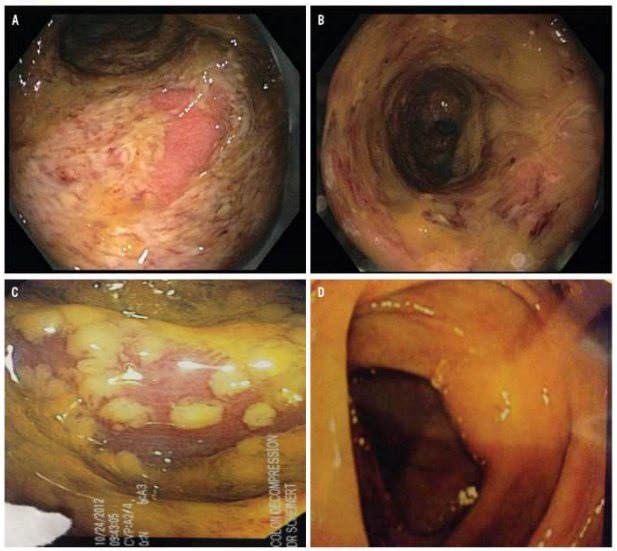
Pseudomembranous colitis

CD colitis

CD -Associated Diarrhea (CDAD/CDI)

Asymptomatic Carrier

Risk factors

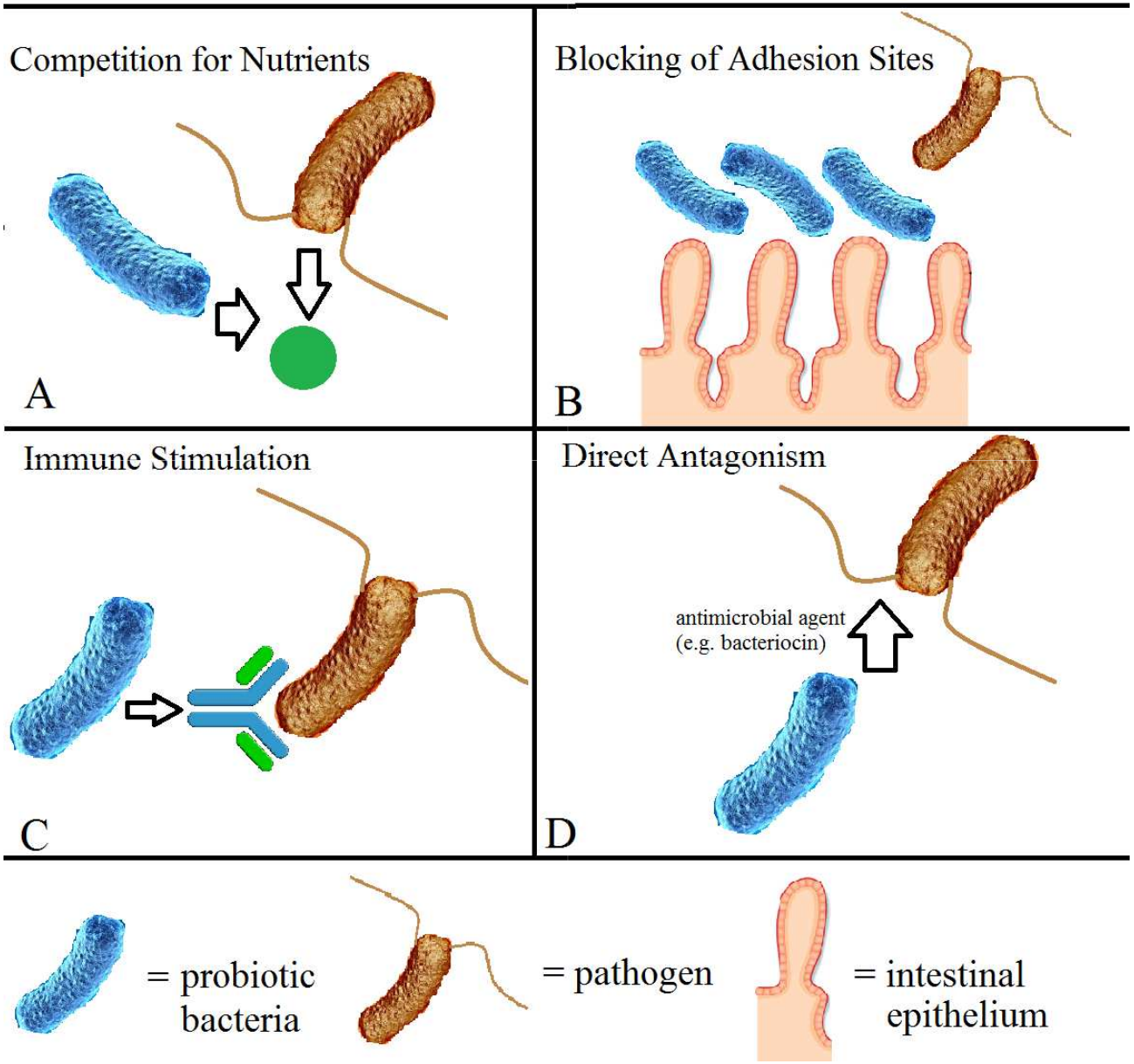


Therapy for AAD and CDAD

- Essential: Discontinuation or changing the type of the inciting antibiotic and giving oral rehydration therapy

- Probiotics?

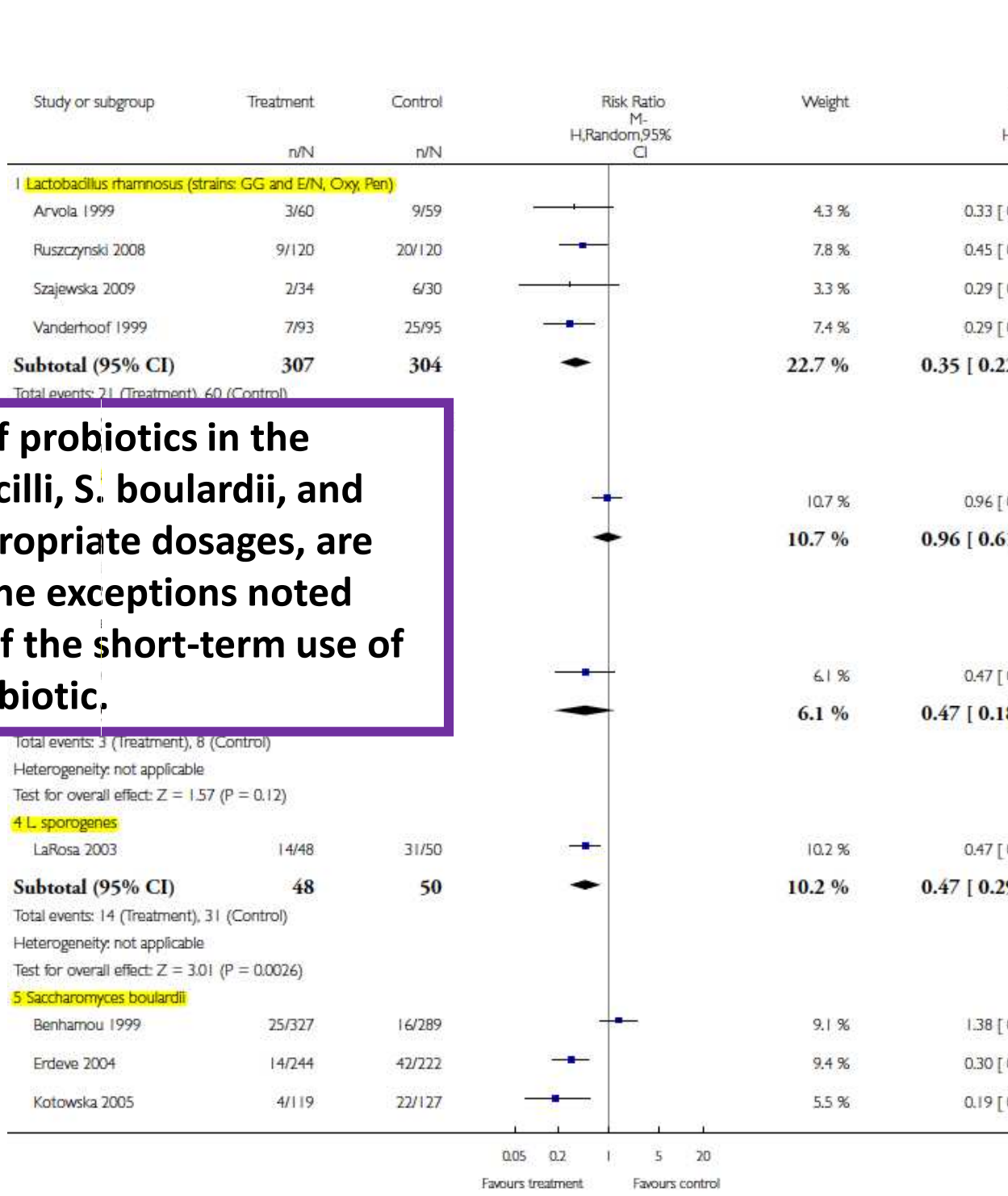
How Probiotics Work



Probiotics for the prevention of pediatric antibiotic-associated diarrhea (Review)

Goldenberg JZ, LytvynL, Steurich J, Parkin P, Mahant S, Johnston BC

LGG



Clearly, current evidence favors the use of probiotics in the prevention of symptoms of AAD. Lactobacilli, S. boulardii, and selected multistrain combinations, in appropriate dosages, are clinically useful. The safety profile, with the exceptions noted earlier, is acceptable particulary in view of the short-term use of an antibiotic when accompanied by a probiotic.

Saccharomyces boulardii

ochrane
brary
hrane Database of Systematic Reviews

Recommendations for Antibiotic-Associated Diarrhea

CLINICAL GUIDELINE

Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children

Hania Szajewska, [†‡]Roberto Berni Canani, [†]Alfredo Guarino, [§]Iva Hojsak, [‖]Flavia Indrio, [§]Sanja Kolacek, [¶]Rok Orel, [#]Raanan Shamir, [**]Yvan Vandenplas, [††]Johannes B. van Goudoever, and [‡‡]Zvi Weizman, on Behalf of the ESPGHAN Working Group for Probiotics/Prebiotics

ESPGHAN

JPGN • Volume 62, Number 3, March 2016

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

uidelines are inconsistent in how they rate the quality of evidence and the strength of commendations. This article explores the advantages of the GRADE system, which is increasing ing adopted by organisations worldwide

ESPGHAN recommendations according to the GRADE system

Strong recommendation (SR): when the desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not

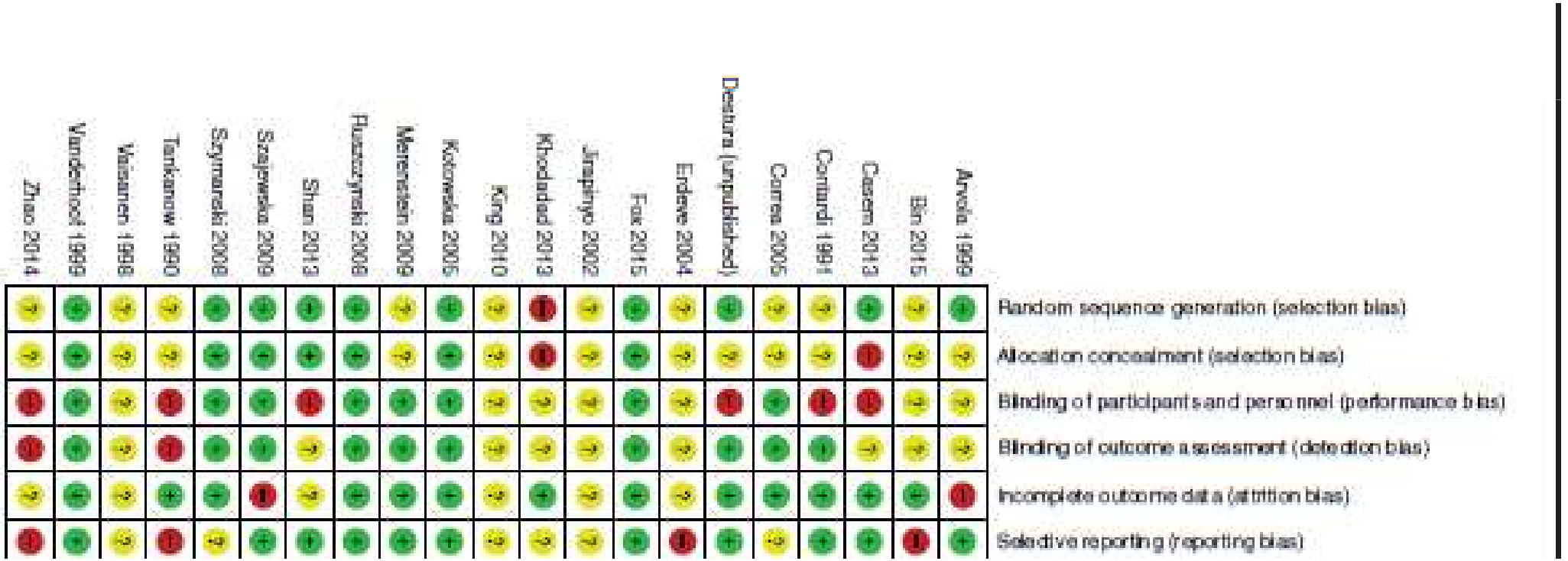
Weak recommendation (WR): when the trade-offs are less certain

Recommendations are formulated if at least 2 RCTs are available

Disclaimer:

- recommendations may be modified in a specific country based on health care organisation, local habits, availability, quality and costs
- recommendations were for Europe (well-nourished children)

Methodological limits in RCTS on prevention of AAD with probiotics



Szajewska et al JPGN March 20

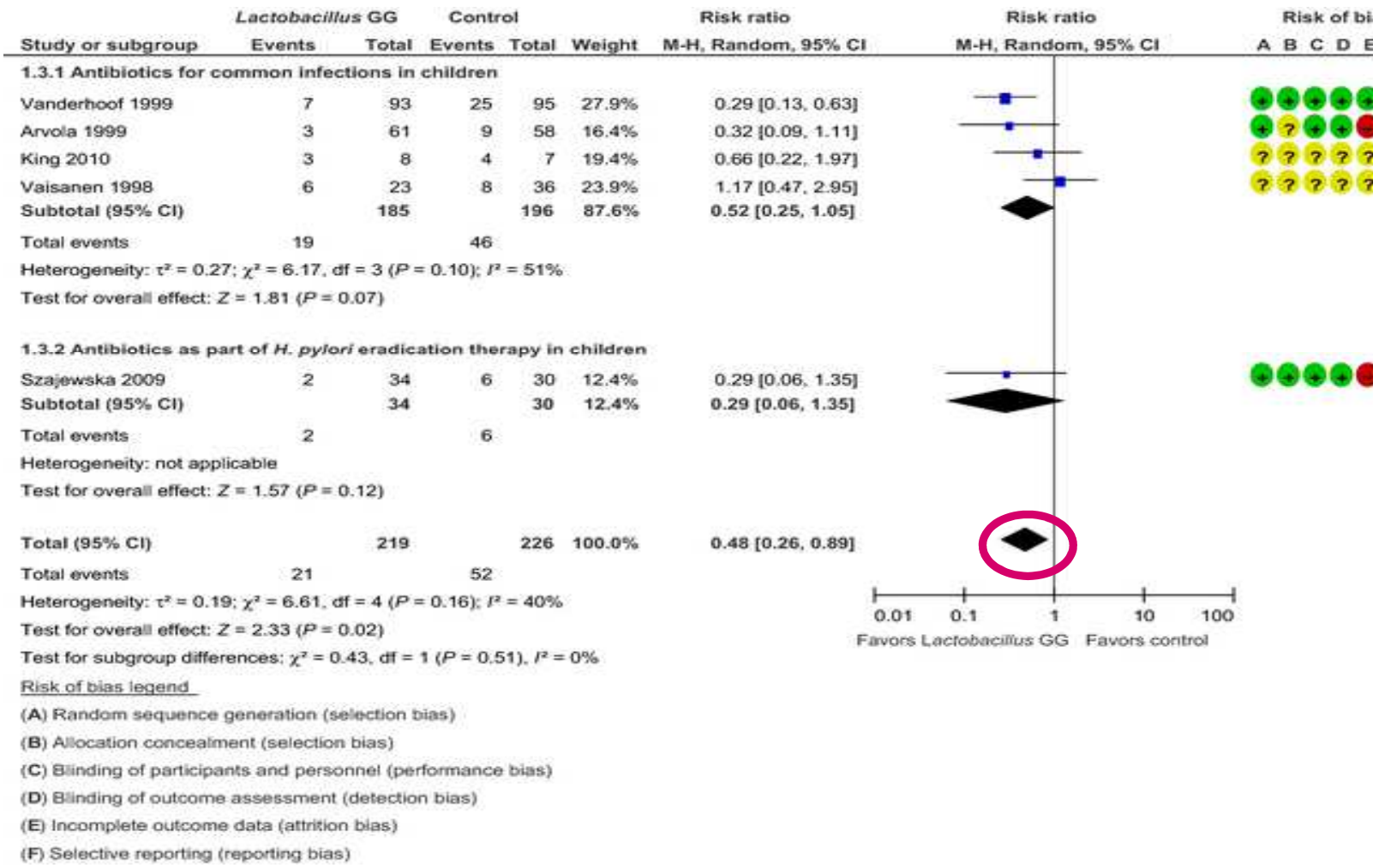
LGG for prevention pediatric AAD

5 RCTs, n=445

Risk Ratio: 0.48

(0.26 to 0.89)

NNT=8



H. Szajewska et al. Aliment Pharmacol Ther 2015; 42:1149-

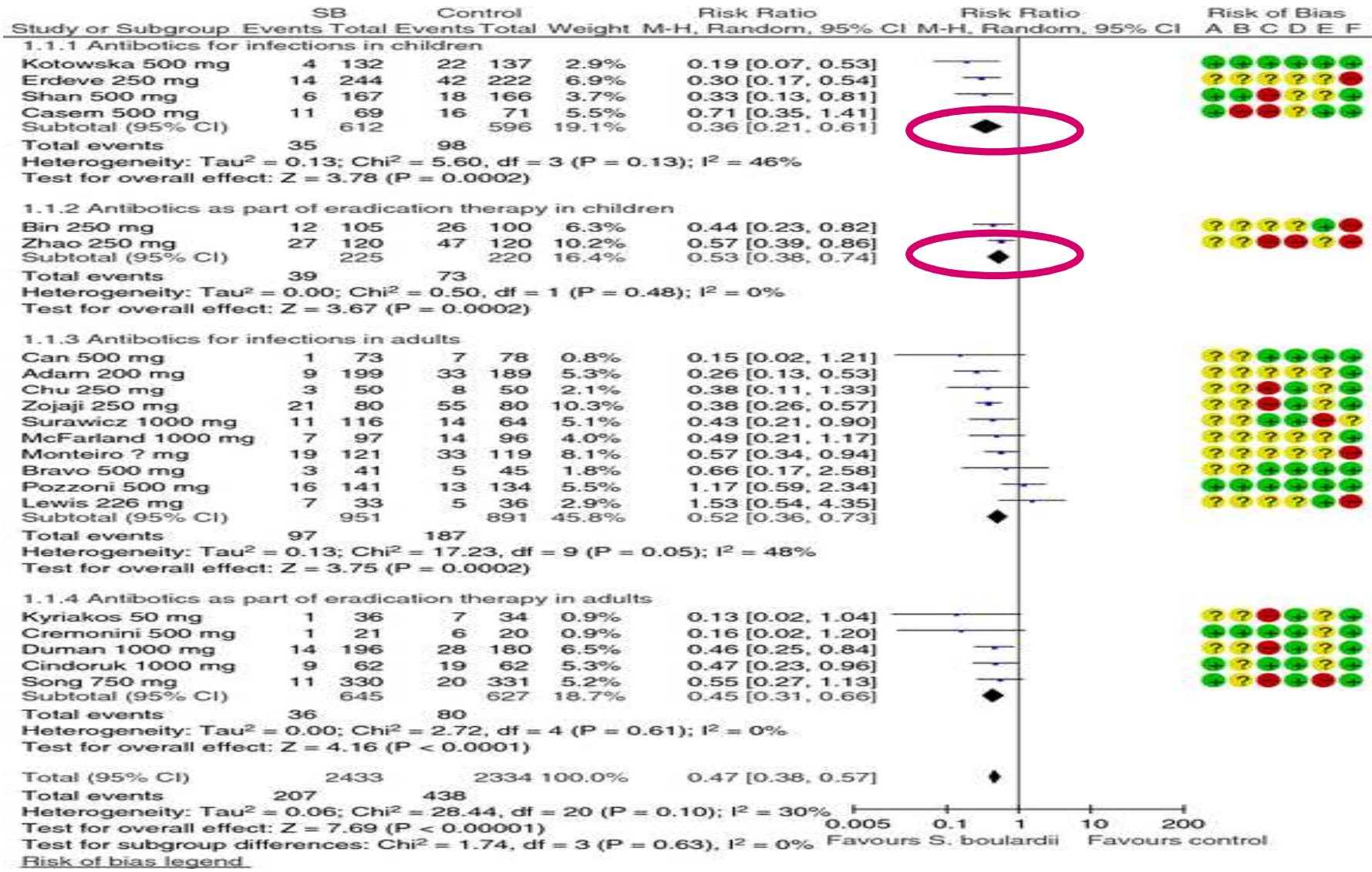
SB for prevention pediatric AAD

RCTs, n=1653

isk Ratio: 0.43

(0.60 to 0.30)

NNT=9



H. Szajewska et al. Aliment Pharmacol Ther 2015; 42: 793-8

Recommended strains by ESPGHAN Working Group for AAD

BIOTIC STRAIN	STUDIES IN SUPPORT	QUALITY OF EVIDENCE	GRADE OF RECOMMENDATION	RECOMMENDATIO
	5 RCTs	Moderate	Strong	May be considere
ulardii CNCM I-	6 RCTs	Moderate	Strong	May be considere

ther strains used in AAD

PROBIOTIC STRAIN	STUDIES IN SUPPORT	RECOMMENDATION
B. clausii	1 RCT	Insufficient data
L. acidophilus L. bulgaricus	1 RCT	Insufficient data
L. acidophilus B. infantis	1 RCT	Insufficient data
L. acidophilus B. breve	1 RCT	Insufficient data
L. Acidophilus, L. rhamnosus L. bulgaricus, L. casei Str. thermophilus B. infantis, B. breve	1 RCT	Insufficient data
L. rhamnosus E/N, Oxy, Pen	1 RCT	Insufficient data
L. Rhamnosus GG Bb-12 L. Acidophilus La-5	1 RCT	Insufficient data
B. longum PL03 L. rhamnosus KL53A L. plantarum PL02	1 RCT	Insufficient data
B. lactis B12 Str. termophilus	1 RCT	Insufficient data
Kefir	1 RCT	Insufficient data

CLINICAL GUIDELINE

Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children

*Hania Szajewska, †‡Roberto Berni Canani, †Alfredo Guarino, §Iva Hojsak, ||Flavia Indrio, §Sanja Kolacek, ¶Rok Orel, #Raanan Shamir, **Yvan Vandenplas, ††Johannes B. van Goudoever, and ‡‡Zvi Weizman, on Behalf of the ESPGHAN Working Group for Probiotics/Prebiotics

JPGN • Volume 62, Number 3, March 2016

ecommendations:

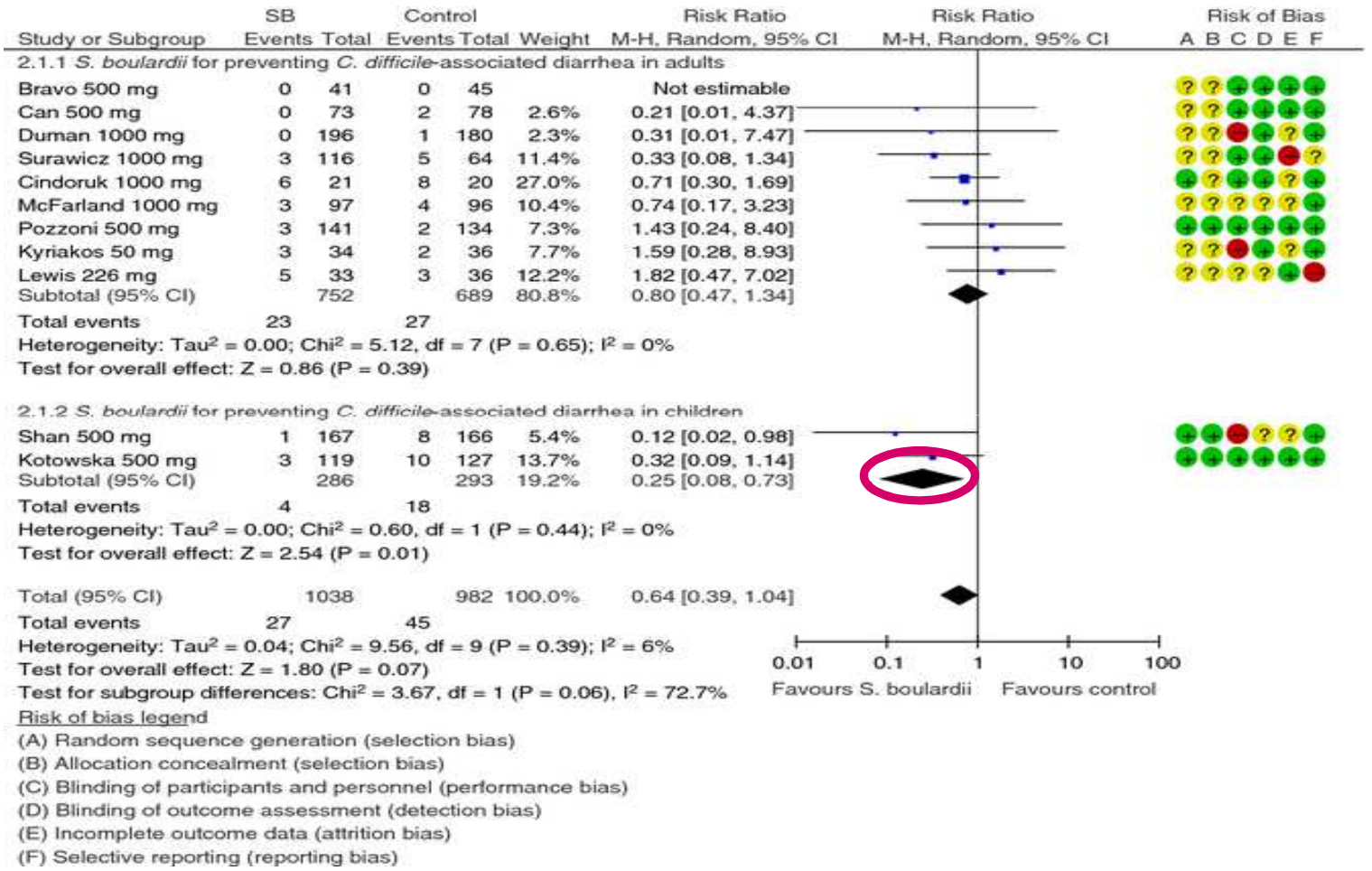
the use of probiotics for preventing AAD is considered because of th
xistence of risk factors such as class of antibiotic(s), duration of
ntibiotic treatment, age, hospitalization, comorbidities, or previous
pisodes of AAD, the WG recommends using *Lactobacillus rhamnosu*
G and *Sacharomyces boulardii* (both: Strong Recommendation)

SB for prevention pediatric CDAD

2 RCTs, n=579

Risk Ratio: 0.25

(0.08 to 0.73)



H. Szajewska et al. Aliment Pharmacol Ther 2015; 42: 793-80

CLINICAL GUIDELINE

Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children

*Hania Szajewska, †‡Roberto Berni Canani, †Alfredo Guarino, §Iva Hojsak, ||Flavia Indrio, §Sanja Kolacek, ¶Rok Orel, #Raanan Shamir, **Yvan Vandenplas, ††Johannes B. van Goudoever, and ‡‡Zvi Weizman, on Behalf of the ESPGHAN Working Group for Probiotics/Prebiotics

JPGN • Volume 62, Number 3, March 2016

ecommendations:

the use of probiotics for preventing CDAD is considered, the WG ecommends using *Sacharomyces boulardii* (Weak Recommendation

What could probiotic use mean in pract

- 50-60% risk reduction of AAD	= ↓ risk of interruption of antibiotic
	= ↓ change of antibiotic treatment
	= ↓ risk of resistance to antibiotics
	= ↓ side effects
	= ↓ cost (e.g., duration of hospitalization}
	= ↑ compliance to antibiotics
	= ↑ recovery

Recommendations in other continents

Recommendations for use of probiotics in childhood intestinal diseases by geographic region

		Europe	USA	Latin America	World	APAC (Cameron et al. 2017)[c]
cute astroenteritis	*T*	*L. rhamnosus GG, S. boulardii, L reuteri*	*L. rhamnosus GG, S. boulardii*	*L. rhamnosus GG, S. boulardii, L. reuteri*	*S. boulardii, L. rhamnosus GG, Indian Dahi*	*S. boulardii, L. rhamnosus GG, L reuteri*
AD	*P*	*L. rhamnosus GG, S. boulardii*	*L. rhamnosus GG, S. boulardii*	*L. rhamnosus GG, S. boulardii*	*S. boulardii; L. rhamnosus GG, B. lactis Bb12 + S. thermophilus, L. rhamnosus strains E/N, Oxy and Pen*	*L rhamnosus GG S.boulardii,*
DAD	*P*	*S. boulardii*				*S. boulardii*

Probiotic products: A call for improved quality control

tudies organized worldwide show:

- Frequent misidentification and misclassification of strains
- Contamination, sometimes with pathogens
- No viable strains, false labelling of number of colonies
- Deminishment of functional properties, shelf live

S. Kolaceck et al. A position paper by the ESPG
Working Group for Probiotics and Prebiotics, JP
2017, in press

Probiotic products: A call for improved quality control

Studies orga rldwide show:

- Frequent n and misclassification of strains
- Contamination, so athogens
- No viable strains, false-lab r of colonies
- Deminishment of functional prope

Quality only guaranteed with registration as a drug, not as food supplement

S. Kolaceck et al. A position paper by the ESPG Working Group for Probiotics and Prebiotics, JP

Probiotic products: A call for improved quality control

tudies organized worldwide show:

- Frequent misidentification and misclassification of strains
- Contamination, sometimes with pathogens
- No viable strains, false labelling of number of colonies
- Deminishment of functional properties, shelf live

→ Health authorities should play their control role, in particular
or the use in vulnerable populations, and for evidence in defined
inical conditions as other pharmaceutical products

S. Kolaceck et al. A position paper by the ESPG
Working Group for Probiotics and Prebiotics, JP
2017, in press

Take home messages

Antibiotic use in children could lead to long term disruption of the microbiome with unknown, and possibly harmful, health effects

Safe medical therapies (probiotics) are available for AAD/CDAD

Positive evidence with probiotic drugs in these conditions mainly comes from *L. rhamnosus* GG and *S. boulardii* CNCM I-745 strains

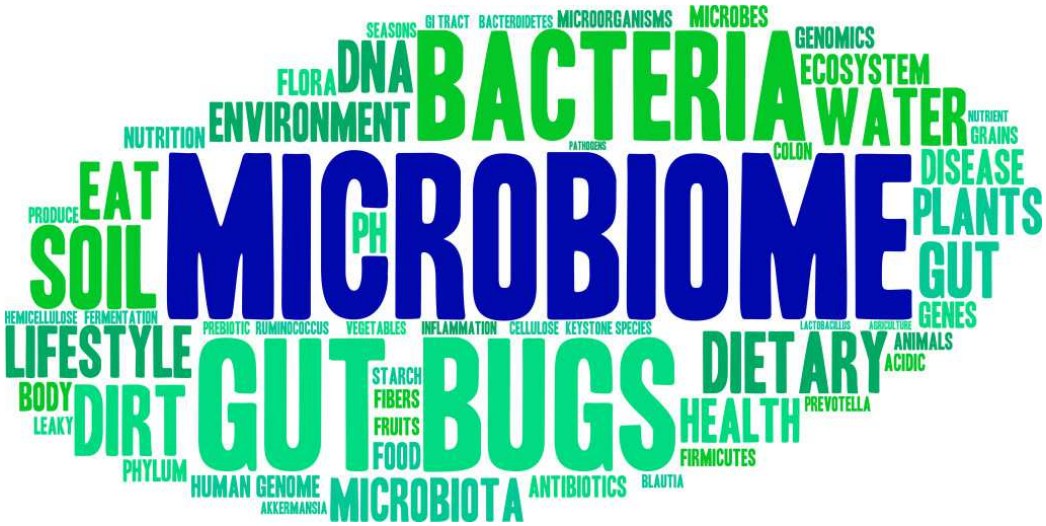
Many other probiotics strains cannot be recommended because of insufficient data or insufficient data on quality

We need more good RCTs

And now all this is open for discussion, …

Thank you!


Antibiotic
Resistance
bacteria
overuse
unnecessarily
abuse
ability
spread
airplane
water
bacteria infection
less effective
contact
cold
genetic
treatment
Different
hands
antibiotics
resist
mutations
coughing
place
wind
resistant
Internet
continue
effective
therapeutic
spontaneous
phenomenon
potent
People
acquire
produce
clinical
others
New resistance
travel
prevention
countries
enzymes
Patients
higher-levels
susceptible
kill
control
current
exchange
viral prescription
antibiotic-resistance
chemicals
move
purchased
Environmentally
without
presence
common
natural
eliminate
spreads
outcomes
inactivate
emerge
threatens
mechanisms
greater
effectively
longer course
without prescription
worse
illnesses
levels
occurs
range
multiply
growth
attributed
bacterial resistance genes
increased
unwashed
first-line
target
yield
words
risk
ever-increasing


MICROBIOME
BACTERIA
GUT
BUGS
DIRT
SOIL
EAT
LIFESTYLE
DIETARY
HEALTH
WATER
ENVIRONMENT
DNA
FLORA
PLANTS
DISEASE
GENES
ANIMALS
ACIDIC
PREVOTELLA
FIRMICUTES
BLAUTIA
ANTIBIOTICS
MICROBIOTA
HUMAN GENOME
PHYLUM
AKKERMANSIA
BODY
LEAKY
STARCH
FIBERS
FRUITS
FOOD
PH
NUTRITION
PRODUCE
HEMICELLULOSE
FERMENTATION
PREBIOTIC
RUMINOCOCCUS
VEGETABLES
INFLAMMATION
CELLULOSE
KEYSTONE SPECIES
LACTOBACILLUS
AGRICULTURE
PATHOGENS
COLON
NUTRIENT
GRAINS
GENOMICS
ECOSYSTEM
MICROBES
MICROORGANISMS
BACTEROIDETES
GI TRACT
SEASONS

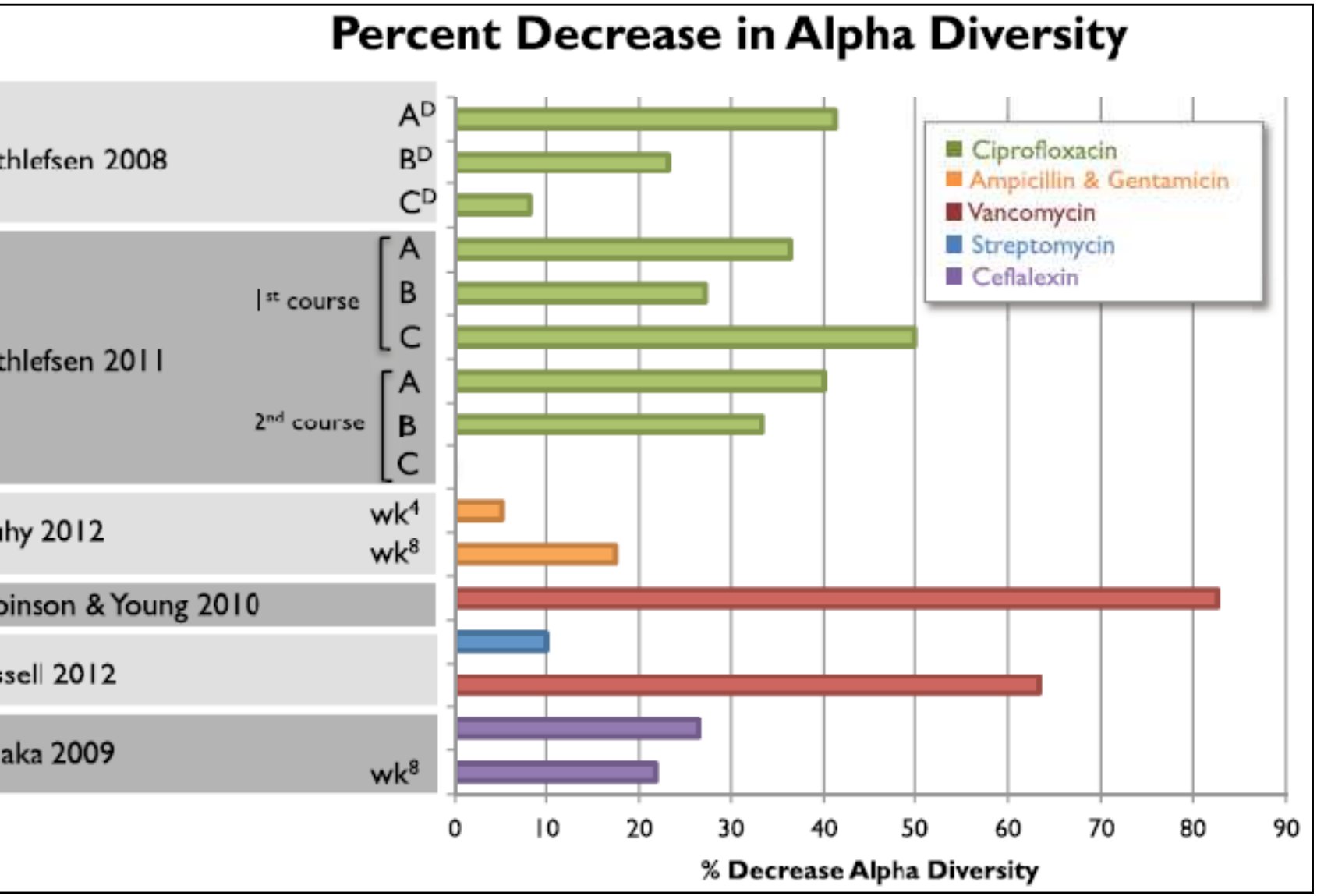
Probiotics and reduced spread of antibiotic resistance

Possible mechanisms:

- Better treatment of bacterial infection
- Concept of eubiosis vs dysbiosis
- Increased bacterial susceptibility to antibiotics?
- Prevention of spread of resistance factors?
- Antimicrobial compounds (e.g. SCFA, bacteriocin?) In vitro only

Ouwehand AC, et al. Ann Med 2016

Decrease % of HGM biodiversity across studies with different antibiotic exposures



Vangay, Pajau, et al. "Antibiotics, pediatric dysbiosis, and disease." Cell host & microb (2015): 553-564.