Thank you Argentina!


Nederland
vs
Argentinië


#NEDARG


Woensdagavond na de wedstrij


BRAZIL

Probiotics: new therapeutic options in acute gastroenteritis and antibiotic associated diarrhea Strategies according to ESPGHAN guidelines

Hans Hoekstra, M.D., Ph.D.
Jheronimus Bosch Teaching Hospit
‘s-Hertogenbosch, The Netherland

European Society for Paediatric Gastroenterology, Hepatology, and Nutrition/European Society for Paediatric Infectious Diseases

Evidence-based Guidelines for Managemer of Acute Gastroenteritis in Children in Europe

Alfredo Guarino (Coordinator), Fabio Albano, Shai Ashkenazi, Dominique Gendrel, J. Hans Hoekst Raanan Shamir, and Hania Szajewska

JPGN 2008; 46: S81-122

ESPGHAN

Disclosures

Biocodex

- Speaker
- Support of the Asia Pacific Probiotics Committee

Abbott

- Speaker

Recommendations for acute Gastroenteritis

Based on System
and Meta-analys

MEDICAL POSITION PAPER

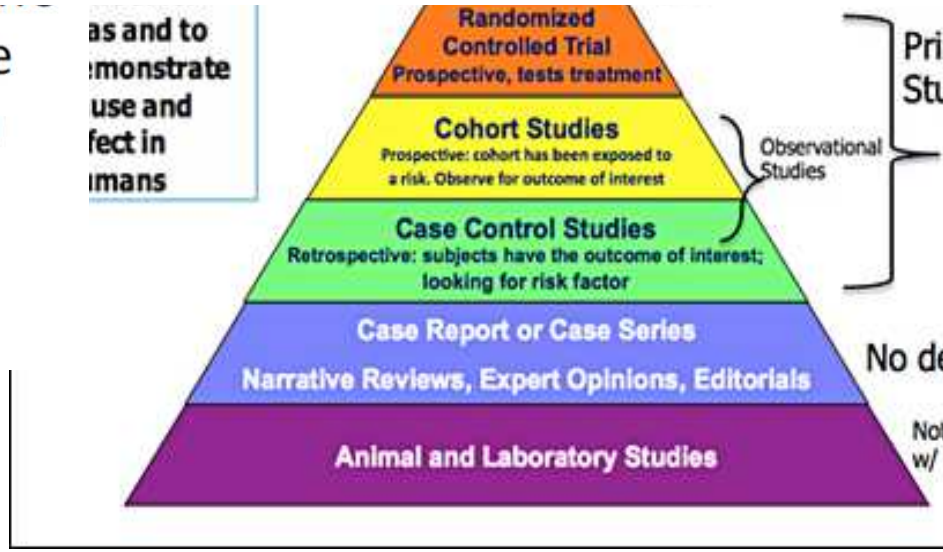
Use of Probiotics for Management of Acute Gastroenteritis: A Position Paper by the ESPGHAN Working Group for Probiotics

*Hania Szajewska, †Alfredo Guarino, ‡Iva Hojsak, §Flavia Indrio, ‡Sanja Kolacek, ||Raanan Shamir, ¶Yvan Vandenplas, and #Zvi Weizman, on behalf of the ESPGHAN Working Group for Probiotics/Prebiotics

CLINICAL C

European Society for Pec
Hepatology, and Nutrition/Eu
Infectious Diseases Evidence-Based Guidelines for the Management of Acute Gastroenteritis in Children in Europe: Update 2014

*Alfredo Guarino (Coordinator), †Shai Ashkenazi, ‡Dominique Gendrel, *Andrea Lo Vecchio, †Raanan Shamir, and §Hania Szajewska

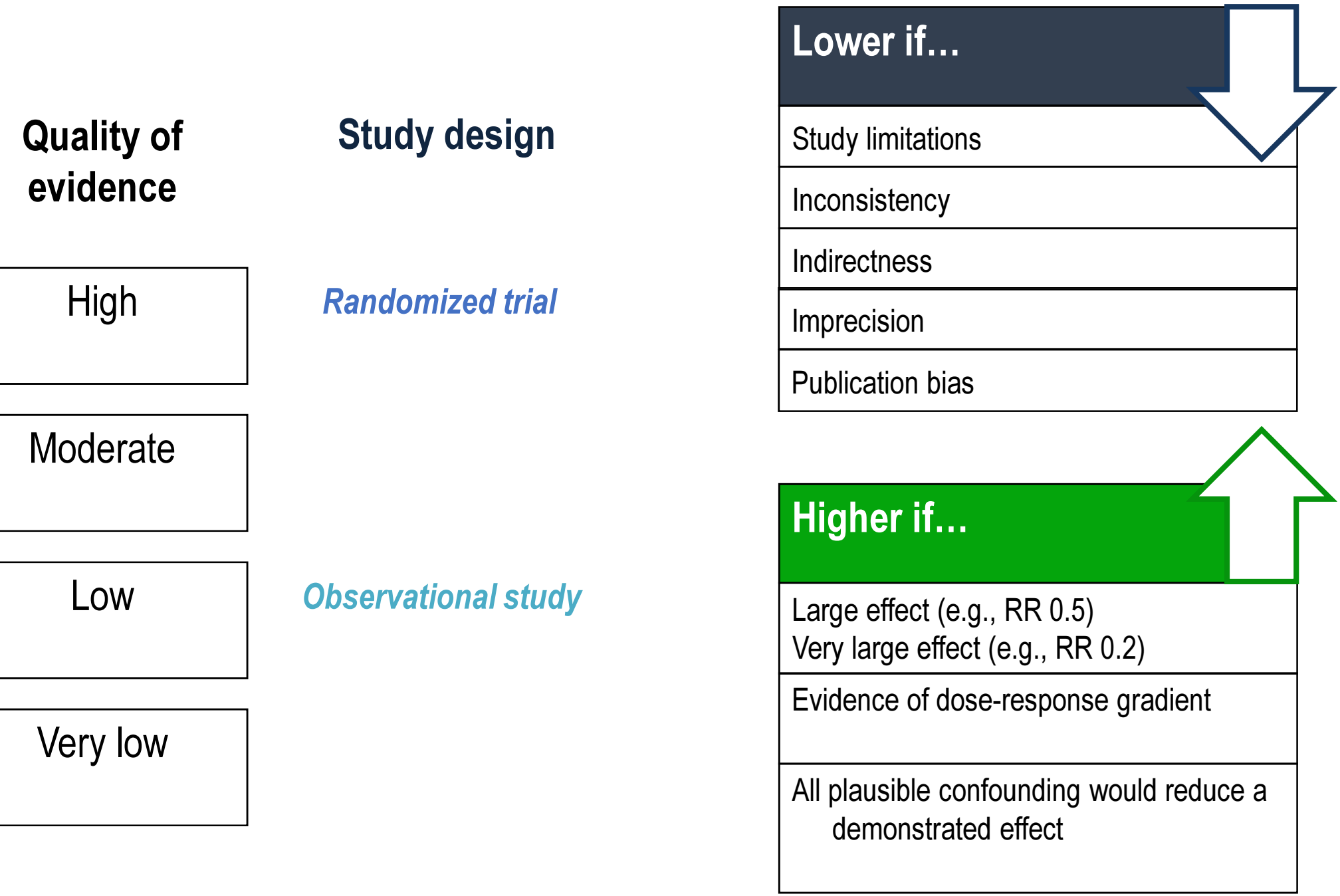


Cochrane Library

ESPGHAN

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


Quality of evidence
Study design
High
Moderate
Low
Very low
Randomized trial
Observational study
Lower if…
Study limitations
Inconsistency
Indirectness
Imprecision
Publication bias
Higher if…
Large effect (e.g., RR 0.5)
Very large effect (e.g., RR 0.2)
Evidence of dose-response gradient
All plausible confounding would reduce a demonstrated effect

ality of evidence

High	Further research is very unlikely to change our confidence in the estimate of effect	⨁⨁⨁⨁
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate	⨁⨁⨁◯
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate	⨁⨁◯◯
Very Low	Any estimate of effect is very uncertain	⨁◯◯◯

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

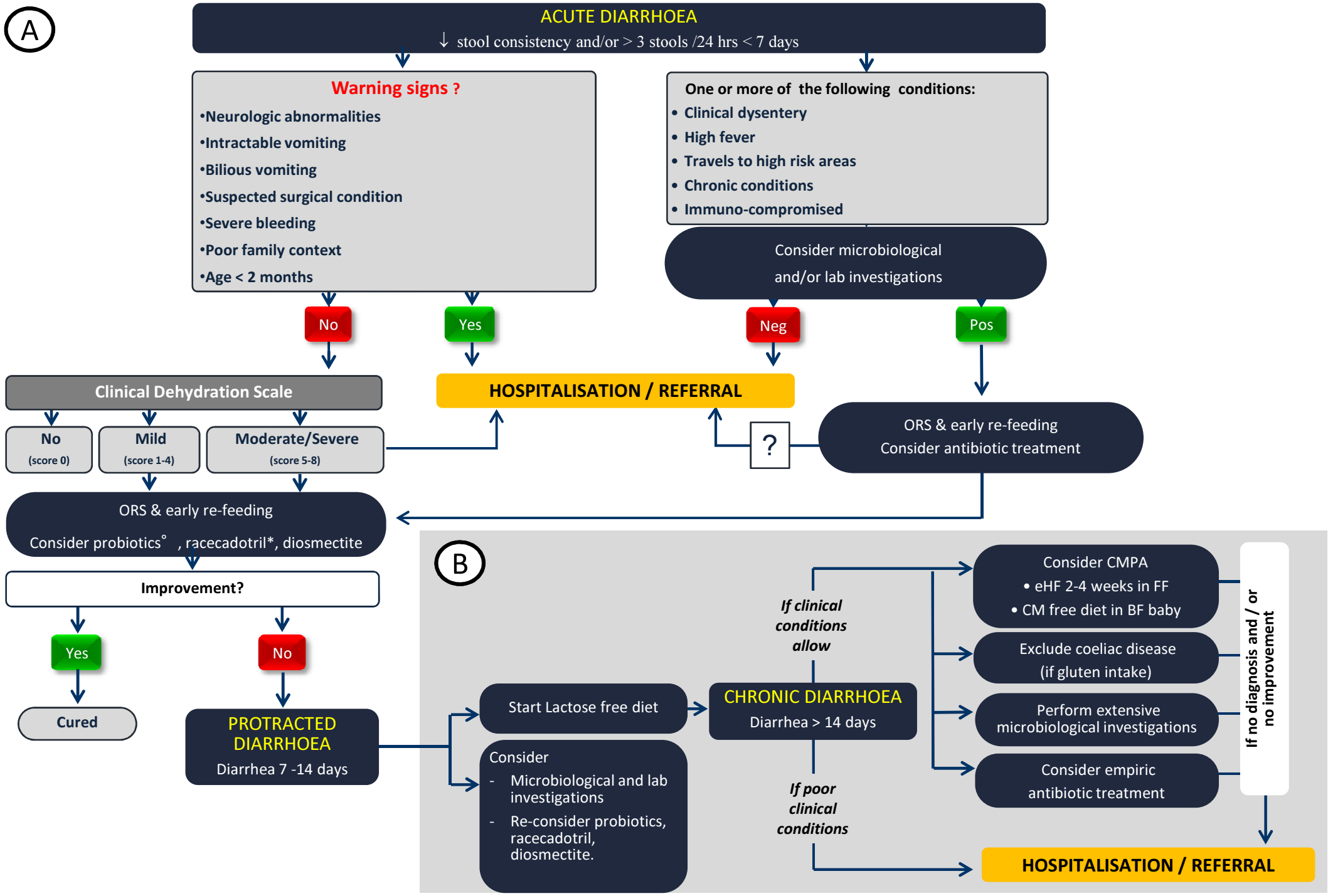
Recommendations are formulated if at least 2 RCTs are available

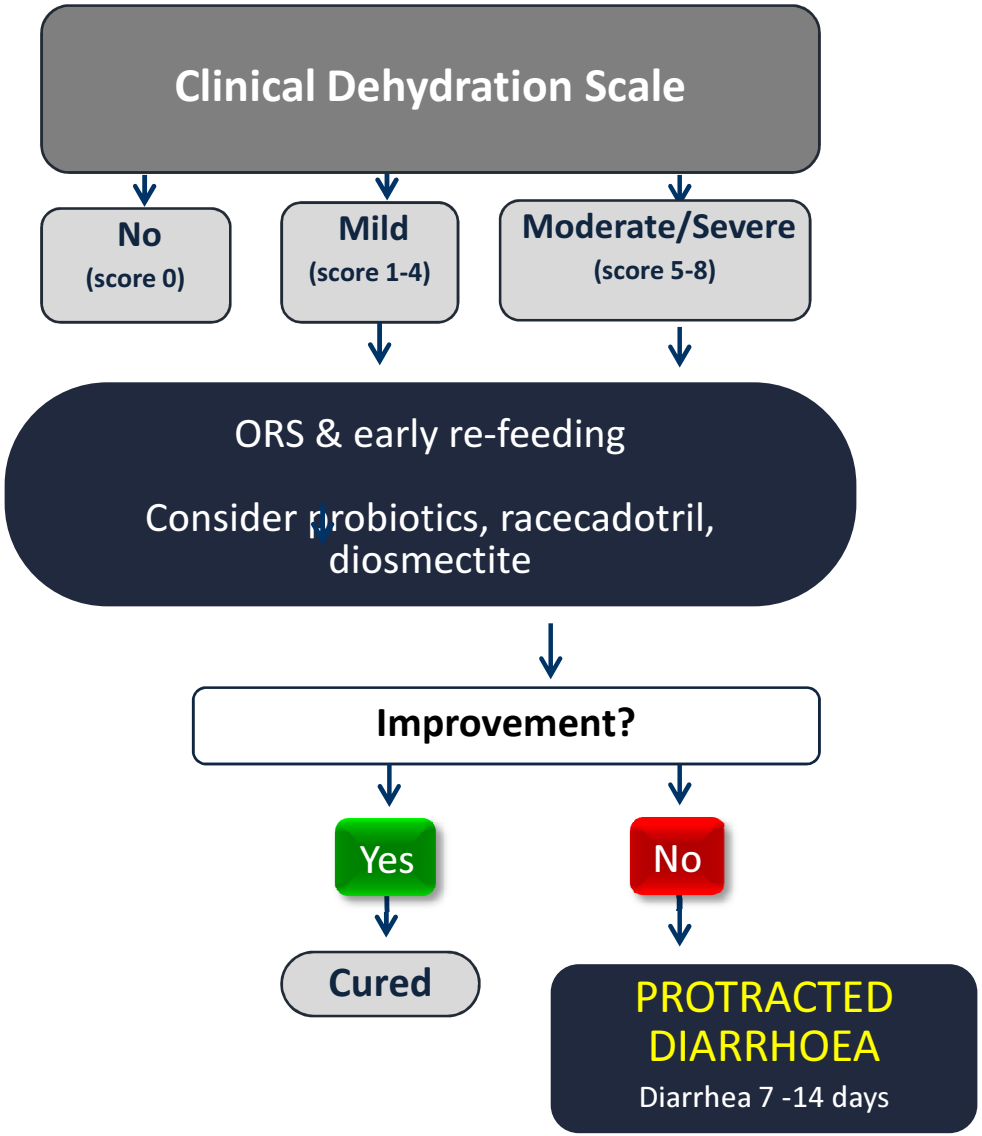
Disclaimer:

- 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)

Evidence based recommendations in an algorithm

ESPGHAN


A
ACUTE DIARRHOEA
↓ stool consistency and/or > 3 stools /24 hrs < 7 days
Warning signs ?
•Neurologic abnormalities
•Intractable vomiting
•Bilious vomiting
•Suspected surgical condition
•Severe bleeding
•Poor family context
•Age < 2 months
One or more of the following conditions:
• Clinical dysentery
• High fever
• Travels to high risk areas
• Chronic conditions
• Immuno-compromised
Consider microbiological and/or lab investigations
No
Yes
Neg
Pos
Clinical Dehydration Scale
No (score 0)
Mild (score 1-4)
Moderate/Severe (score 5-8)
HOSPITALISATION / REFERRAL
?
ORS & early re-feeding
Consider antibiotic treatment
ORS & early re-feeding
Consider probiotics° , racecadotril*, diosmectite
Improvement?
Yes
No
Cured
PROTRACTED DIARRHOEA
Diarrhea 7 -14 days
B
Start Lactose free diet
Consider
- Microbiological and lab investigations
- Re-consider probiotics, racecadotril, diosmectite.
If clinical conditions allow
CHRONIC DIARRHOEA
Diarrhea > 14 days
If poor clinical conditions
Consider CMPA
• eHF 2-4 weeks in FF
• CM free diet in BF baby
Exclude coeliac disease (if gluten intake)
Perform extensive microbiological investigations
Consider empiric antibiotic treatment
If no diagnosis and / or no improvement
HOSPITALISATION / REFERRAL

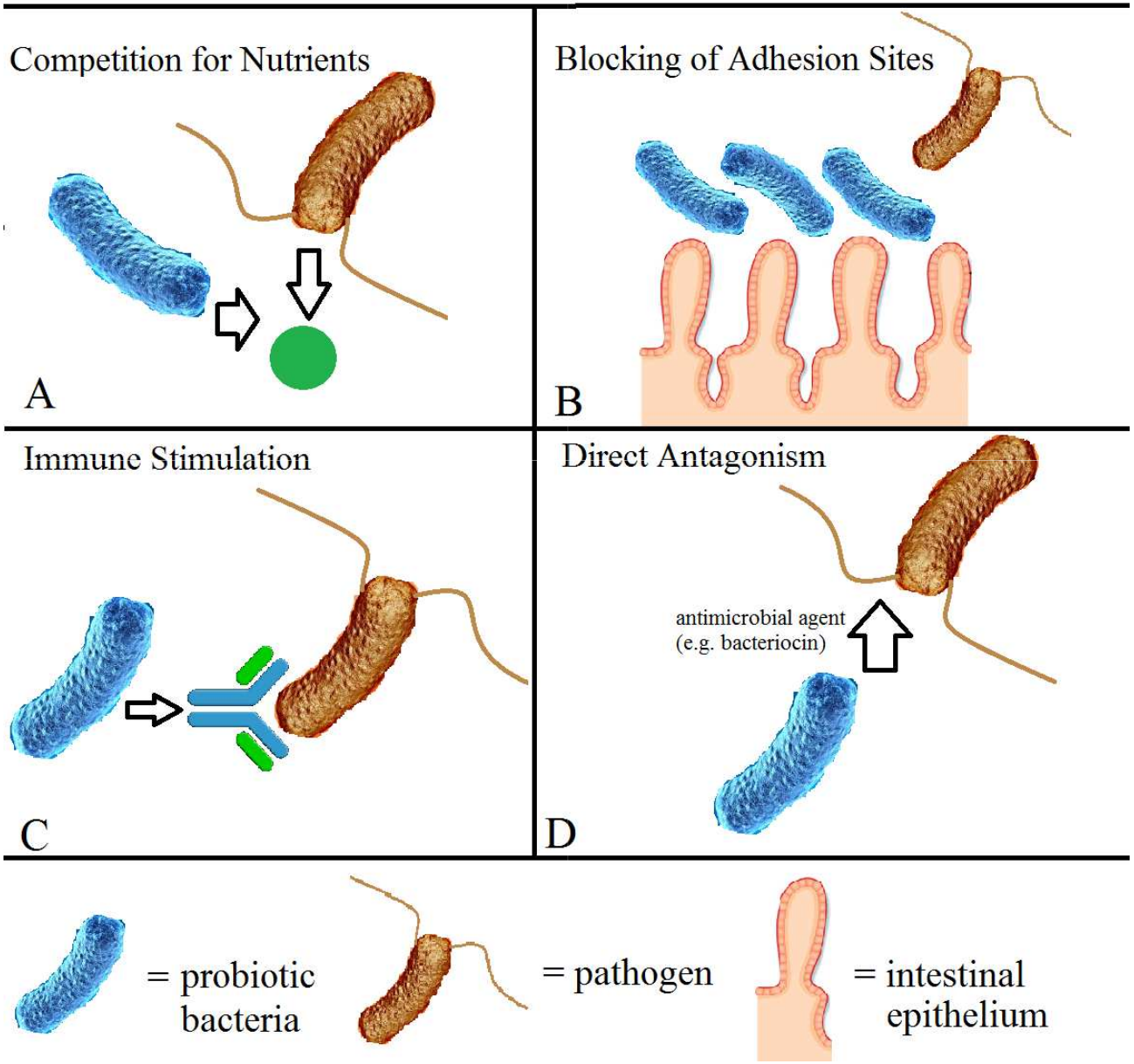

Clinical Dehydration Scale
No
(score 0)
Mild
(score 1-4)
Moderate/Severe
(score 5-8)
ORS & early re-feeding
Consider probiotics, racecadotril, diosmectite
Improvement?
Yes
No
Cured
PROTRACTED DIARRHOEA
Diarrhea 7 -14 days

Therapies for AGE

- Rehydration
- Diets
- Antiemetics
- Antimotility or antiperistaltic drugs
- Adsorbents
- Antisecretory drugs
- Zinc
- Probiotics

What is the evidence?

How Probiotics Work



SPGHAN (2014): more active treatment and effective medica terventions

		Recommendation	
ehydration	(oral – nasogastric – intravenous)	Yes	SR
ormal diet		Yes	SR
ntiemetics	(ondansetron)	Can be considered	SR
robiotics	(LGG, SB, L reuteri DSM 17938)	Can be considered	SR (WR)
acecadotril		Can be considered	WR
mectite		Can be considered	WR
ismuth subsalicylate		No	SR
ntimotility drugs	(loperamide)	No	SR
nc		No (in Europe)	SR
elatine tannate		No	SR
ntimicrobial drugs		Exceptionally	SR

Pharmacological therapy

Always in Addition to Oral Rehydration Therapy

A focus on probiotics

Live microorganisms that, when administered in adequate amounts, confer a health benefit to the host (WHO, 2002)

Identified by genus, species, and strain

Evidence is mostly obtained at strain-specific level as a probiotic drug in a well defined condition and population from a manufacturer with regulated quality control

Evidence for children can only be obtained from trials with only children included

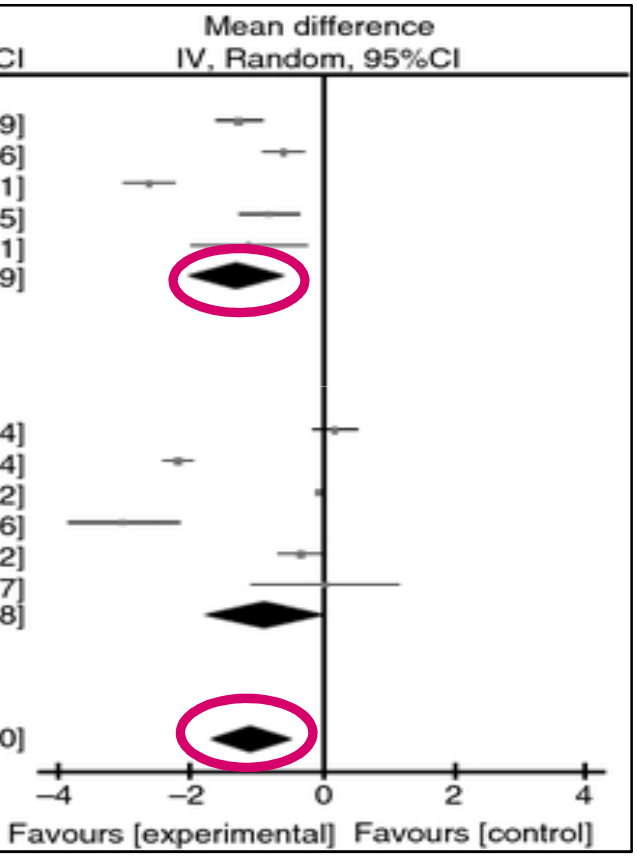
Most investigated probiotics: LGG (*Lactobacillus rhamnosus* GG)

SB (*Saccharomyces boulardii* CNCM 1-745)

LR (*Lactobacillus reuteri* DSM 17938)

LGG in AGE: duration of diarrhea, EU/non-EU

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight (%)	Mean difference IV, Random, 95%CI
1.3.1 Studies in Europe								
Berni Canani 2007	3.46	1.48	100	4.7	0.98	92	9.4	−1.24 [−1.59, −0.89]
Guandalini 2000	2.43	1.15	147	3	1.49	140	9.5	−0.57 [−0.88, −0.26]
Guarino 1997	3.2	1	52	5.8	1	48	9.4	−2.60 [−2.99, −2.21]
Isolauri-Kaila 1994	1.5	0.7	21	2.3	0.8	21	9.3	−0.80 [−1.25, −0.35]
Shornikova 1997	2.7	2.2	59	3.8	2.8	64	8.2	−1.10 [−1.99, −0.21]
Subtotal (95%CI)			379			365	45.8	−1.27 [−2.04, −0.49]
Heterogeneity: $Tau^2 = 0.71$; $Chi^2 = 67.89$, df = 4 ($P < 0.00001$); $I^2 = 94\%$								
Test for overall effect: $Z = 3.21$ ($P = 0.001$)								
1.3.2 Studies in non-Europe								
Basu 2007	6.8	2.1	323	6.6	2.3	323	9.5	0.20 [−0.14, 0.54]
Basu 2009	5.069	1.24	374	7.23	1.27	185	9.6	−2.16 [−2.38, −1.94]
Costa-RIbeiro 2003	1.59	0.16	61	1.63	0.19	63	9.7	−0.04 [−0.10, 0.02]
Jasinski 2002	4	1.9	45	7	2.3	52	8.4	−3.00 [−3.84, −2.16]
Misra 2009	2.94	0.98	105	3.25	1.43	105	9.5	−0.31 [−0.64, 0.02]
Ritchie 2010	2.18	2.44	33	2.13	2.11	31	7.6	0.05 [−1.07, 1.17]
Subtotal (95%CI)			941			759	54.2	−0.87 [−1.81, 0.08]
Heterogeneity: $Tau^2 = 1.31$; $Chi^2 = 374.55$, df = 5 ($P < 0.00001$); $I^2 = 99\%$								
Test for overall effect: $Z = 1.80$ ($P = 0.07$)								
Total (95%CI)			1320			1124	100.0	−1.05 [−1.70, −0.40]
Heterogeneity: $Tau^2 = 1.14$; $Chi^2 = 556.82$, df = 10 ($P < 0.00001$); $I^2 = 98\%$								
Test for overall effect: $Z = 3.16$ ($P = 0.002$)								
Test for subgroup differences: $Chi^2 = 0.41$, df = 1 ($P = 0.52$), $I^2 = 0\%$								



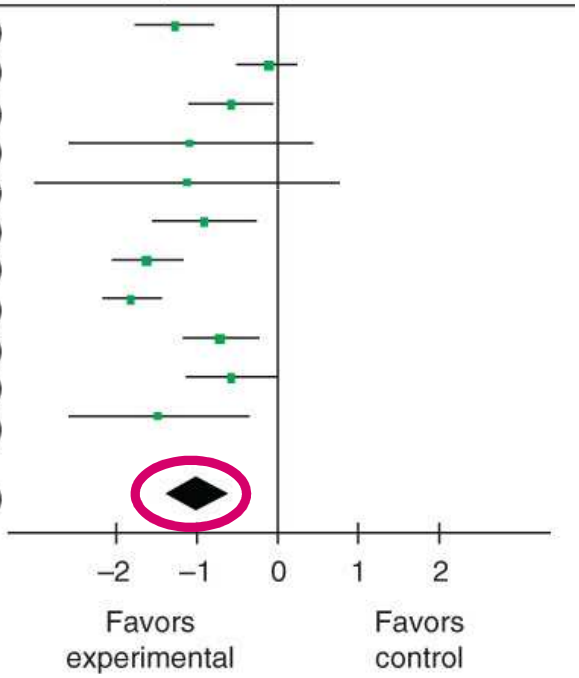
12 RCTs, n=2444
Mean Difference -1.05 day
(-1.7 to -0.4)

Szajewska et al. Aliment Pharmacol Ther 2013; 38:467

Saccharomyces boulardii CNCM I-745 in AGE: duration of diarrhea

Study or subgroup	*Saccharomyces boulardii* Mean	SD	Total	Placebo/control Mean	SD	Total	Weight	Mean difference IV, Random, 95% CI
Billoo *et al.* (2006)	3.56	1.01	50	4.82	1.38	50	10.6%	-1.26 (-1.73, -0.79)
Canani *et al.* (2007)	4.59	1.35	91	4.7	1.17	92	11.3%	-0.11 (-0.48, 0.26)
Dalgic *et al.* (2011)	4.78	1.46	80	5.35	1.8	80	10.4%	-0.57 (-1.08, -0.06)
Eren *et al.* (2010)	4.3	2.46	28	5.38	3.14	27	4.7%	-1.08 (-2.57, 0.41)
Grandy *et al.* (2010)	2.41	1.7	21	3.52	3.91	20	3.5%	-1.11 (-2.97, 0.75)
Hafeez *et al.* (2002)	3.6	16	51	4.5	1.6	50	9.6%	-0.90 (-1.52, -0.28)
Htwe *et al.* (2008)	3.08	0.95	50	4.68	1.23	50	10.9%	-1.60 (-2.03, -1.17)
Kurugol *et al.* (2005)	2	1.1	100	3.8	1.4	100	11.4%	-1.80 (-2.15, -1.45)
Riaz *et al.* (2011)	2.06	0.98	43	2.76	1.21	47	10.8%	-0.70 (-1.15, -0.25)
Vandenplas *et al.* (2007)	2.24	1.6	93	2.8	2.19	95	10.2%	-0.56 (-1.11, -0.01)
Villaruel *et al.*	4.7	1.94	44	6.16	3.2	44	6.5%	-1.46 (-2.57, -0.35)
Total (95% CI)			651			655	100.0%	-0.99 (-1.40, -0.58)

Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 59.19$, df = 10 ($p < 0.00001$); $I^2 = 83\%$
Test for overall effect: $Z = 4.73$ ($p < 0.00001$)



ci, et al. Expert Opin Biol Ther 2012; 12:395-410

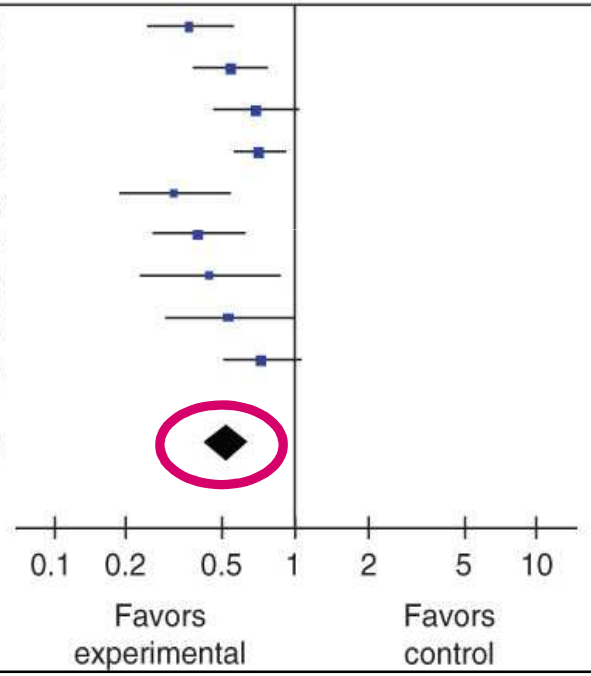
11 RCTs, n=1306

Mean difference 0.99 day (-1.4 to -0.

Saccharomyces boulardii CNCM I-745 in AGE: cure on day 3

Study or subgroup	*Saccharomyces boulardii* Events	Total	Placebo/control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cetina-Sauri *et al.* (1994)	19	65	52	65	11.8%	0.37 (0.25, 0.54)
Correa *et al.* (2011)	29	90	51	86	12.9%	0.54 (0.38, 0.77)
Eren *et al.* (2010)	15	28	21	27	11.7%	0.69 (0.46, 1.03)
Hafeez *et al.* (2002)	32	51	44	50	15.6%	0.71 (0.56, 0.90)
Htwe *et al.* (2008)	12	50	38	50	9.3%	0.32 (0.19, 0.53)
Kurugol *et al.* (2005)	20	100	50	100	10.9%	0.40 (0.26, 0.62)
Riaz *et al.* (2011)	9	43	22	47	7.1%	0.45 (0.23, 0.86)
Vandenplas *et al.* (2007)	13	93	25	95	7.9%	0.53 (0.29, 0.97)
Villaruel *et al.*	22	44	30	44	12.7%	0.73 (0.51, 1.05)
Total (95% CI)		564		564	100.0%	0.52 (0.42, 0.65)
Total events	171		333			

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 21.41$, df = 8 (p = 0.006); $I^2 = 63\%$
Test for overal effect: Z = 5.71 (p < 0.00001)



ci, et al. Expert Opin Biol Ther 2012;12:395-410

9 RCTs; n=1128
Risk Ratio: 0.52 (0.42 to 0.65

Lactobacillus reuteri DSM 17938 in AGE

ion of diarrhea
RCTs, n=196
difference (hr)
(-41.1 to -23.7)

Study or subgroup	Experimental			Control			Weight	Mean difference IV, fixed, 95% CI	Mean difference fixed, 95% CI
	Mean	SD	Total	Mean	SD	Total			
Lactobacillus reuteri DSM 17938									
Dinleyici *et al.*, 2013	70.9	26.1	64	103.8	28.4	63	83.9%	-33.10 [-42.59, -23.61]	
Francavilla *et al.*, 2012	50.4	40.8	35	79.2	50.4	34	16.1%	-28.90 [-50.47, -7.13]	
Subtotal (95% CI)			9			97	100%	-32.41 [-41.10, -23.71]	
Heterogeneity: Chi^2=0.13, df=1 (P=0.72); I^2=0%									
Test for overall effect; Z=7.31 (P<0.00001)									

ure on day 3
RCTs; n=196
sk Ratio: 3.85
.40 to 6.20)

Study or subgroup	Experimental		Control		Weight	Risk ratio M-H, fixed, 95% CI	Risk ratio M-H, fixed, 95% CI
	Events	Total	Events	Total			
Lactobacillus reuteri DSM 17938							
Dinleyici *et al.*, 2013	44	64	7	63	43.6%	6.19 [3.02, 12.68]	
Francavilla *et al.*, 2012	19	35	9	34	56.4%	2.05 [1.08, 3.88]	
Subtotal (95% CI)		99		97	100%	3.85 [2.40, 6.20]	
Total events	63		16				
Heterogeneity: Chi^2=5.43, df=1 (P=0.02); I^2=82%							
Test for overall effect; Z=5.56 (P<0.00001)							

Szajewska, et al. Benef Microbes; 2014;5:28

Recommended strains by ESPGHAN Working Group for AG

BIOTIC STRAIN	STUDIES IN SUPPORT	QUALITY OF EVIDENCE	GRADE OF RECOMMENDATION	RECOMMENDATIO
	15 RCTs	Low	Strong	Should be considered
lardii CNCM I-	13 RCTs	Low	Strong	Should be considered
teri DSM 17938	2 RCTs	Very low	Weak	May be considered +

her strains used in AGE

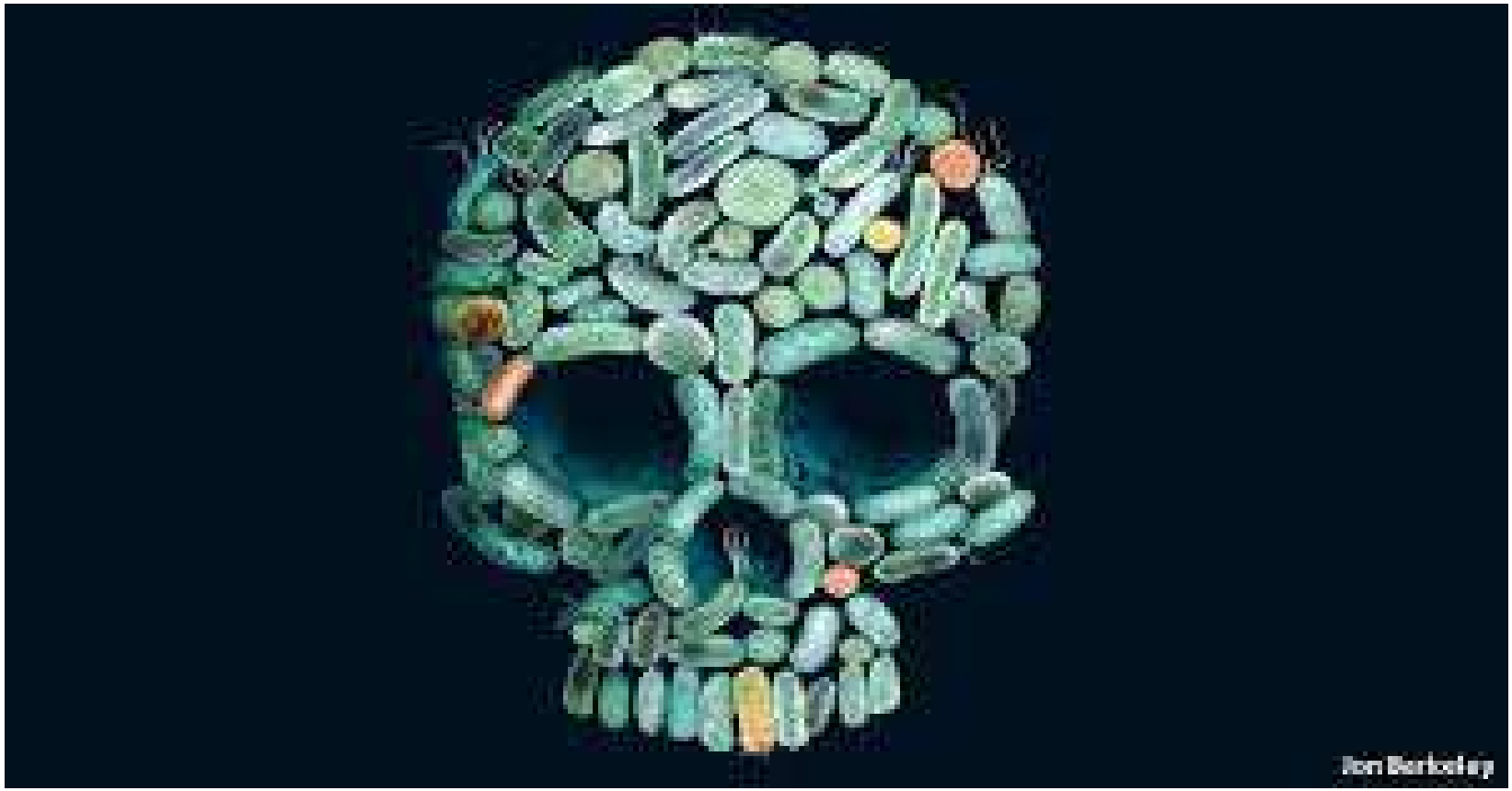
OBIOTIC STRAIN	STUDIES IN SUPPORT	QUALITY OF EVIDENCE	GRADE OF RECOMMENDATION	RECOMMENDATIO
nosus (573/L1-2-3)	1 RCT	Moderate	Weak	Insufficient data
ophilus	1 RCT	Very low	Weak	Insufficient data
casei ST11	1 RCT	Moderate	Weak	Insufficient data
eticus 0052 nosus 0011	None	-	-	Insufficient data
nosus ophilus um ardii	1 RCT	Moderate	Weak	Insufficient data
entericus ycum alis	1 RCT	Very low	Weak	Insufficient data
rueckii ophilus mophilus um	1 RCT	Very low	Weak	Insufficient data
s Bb12	None	-	-	Insufficient data
s B12 mophilus	1 RCT	Very low	Weak	Insufficient data
sii	1 RCT	Very low	Weak	Insufficient data

Considerations with probiotic strains in AGE

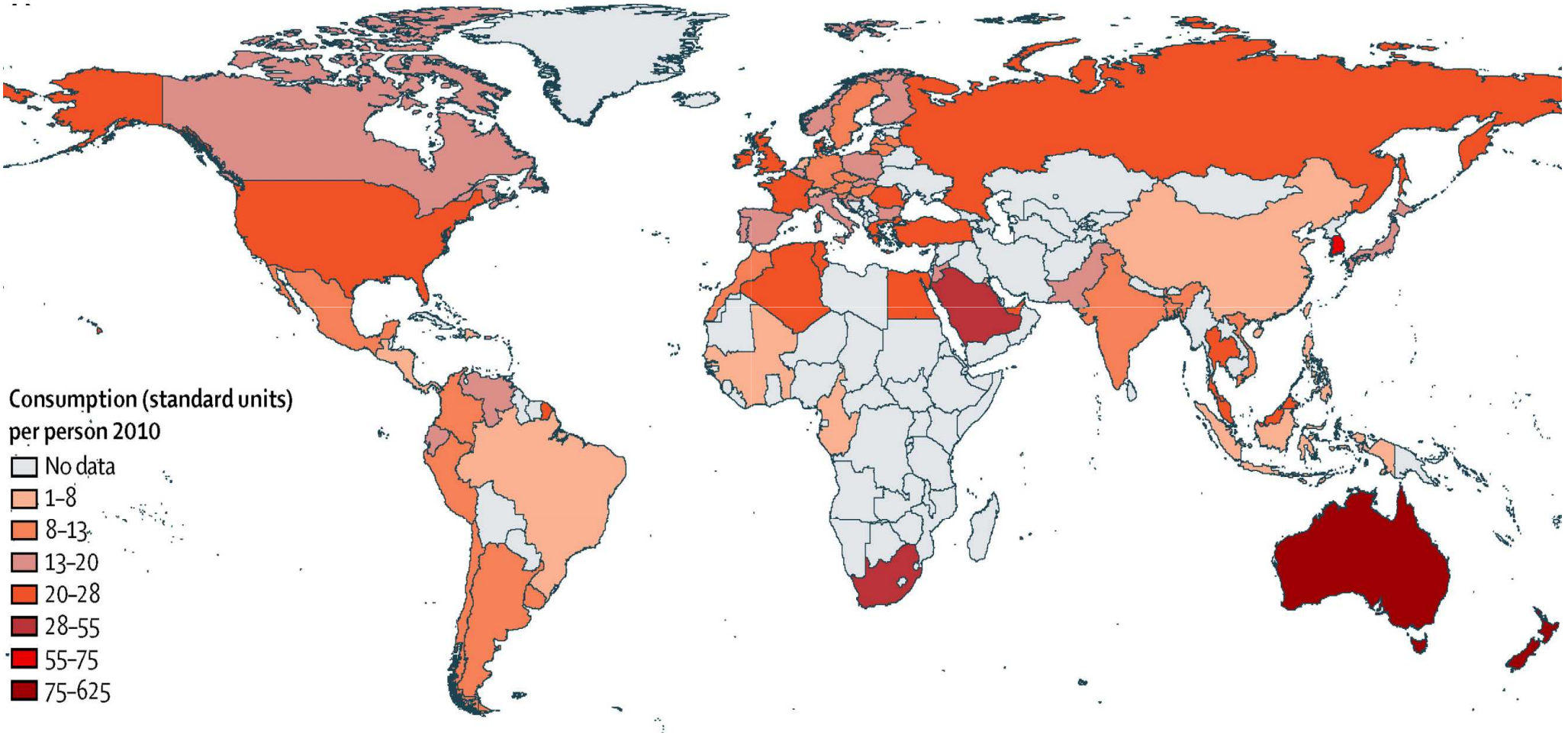
ome issues:

- Quality aspects, dosage
- For all pathogens (norovirus?)
- Outcome measures: positive for duration of diarrhea, weaker for prevention of dehydration, need of hospital admission, duration of hospitalization, quality of life
- Restoration of microbiome: less subsequent new episodes and other advantages
- Costs

Antibiotics are the Most Commonly used Drugs in Western Countries

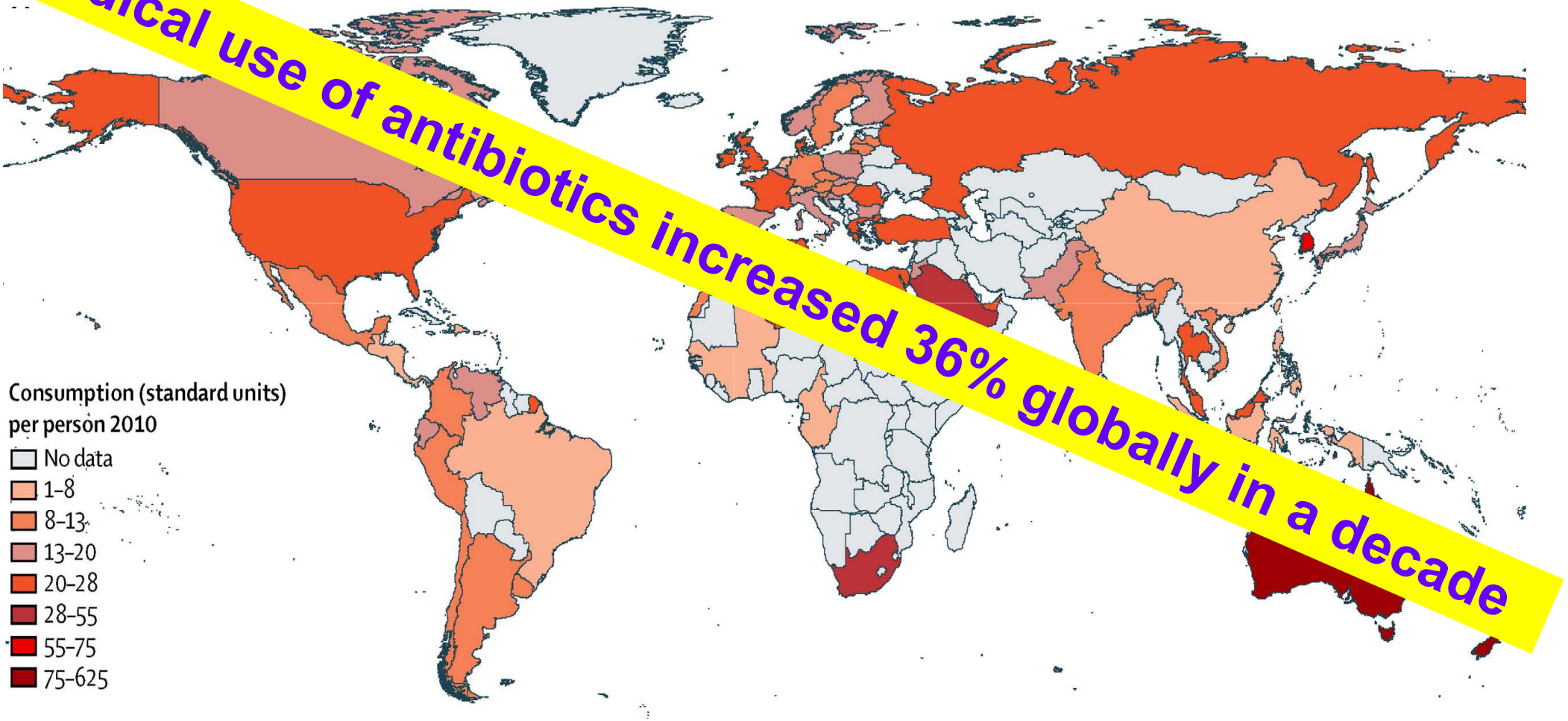


Global Consumption of Antibiotics



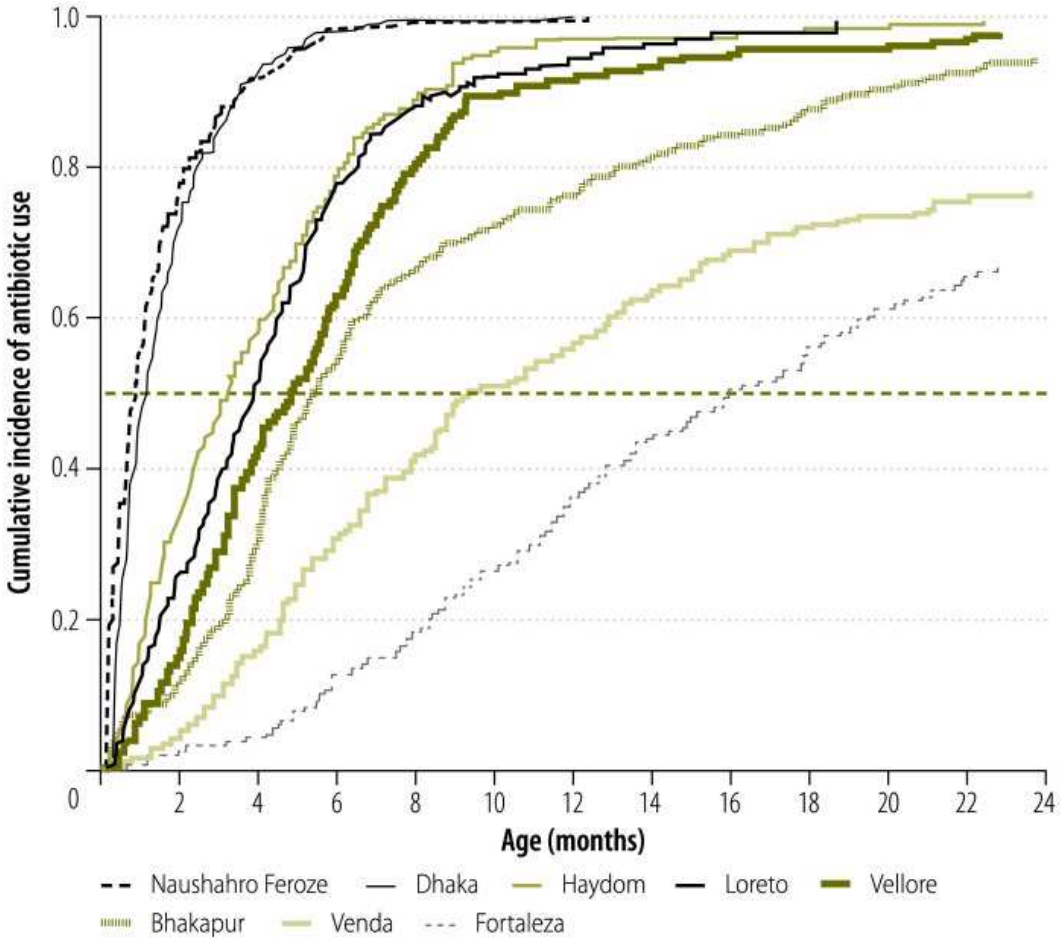
oeckel, Lancet Infect Dis.2014 742–750,

Global Consumption of Antibiotics



oeckel, Lancet Infect Dis.2014 742–750

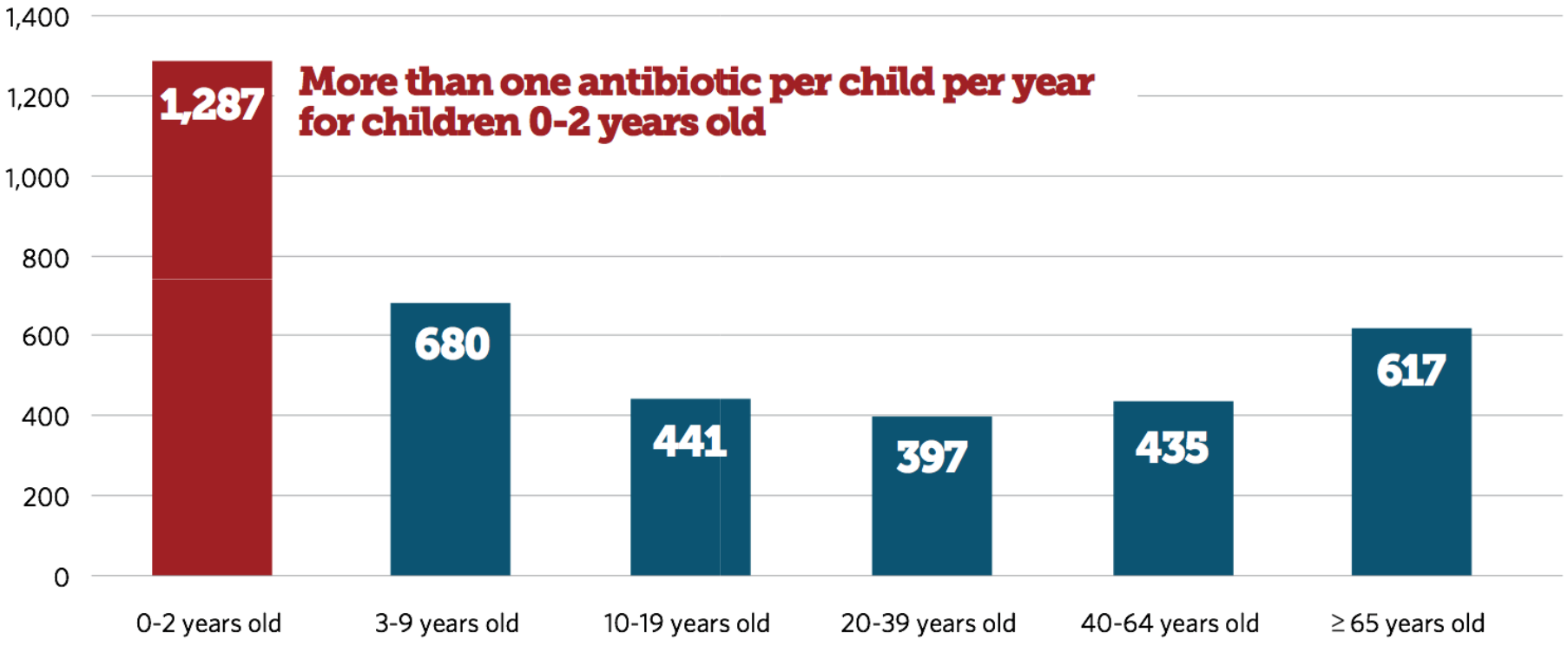
Use of antibiotics age in low resource settings



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

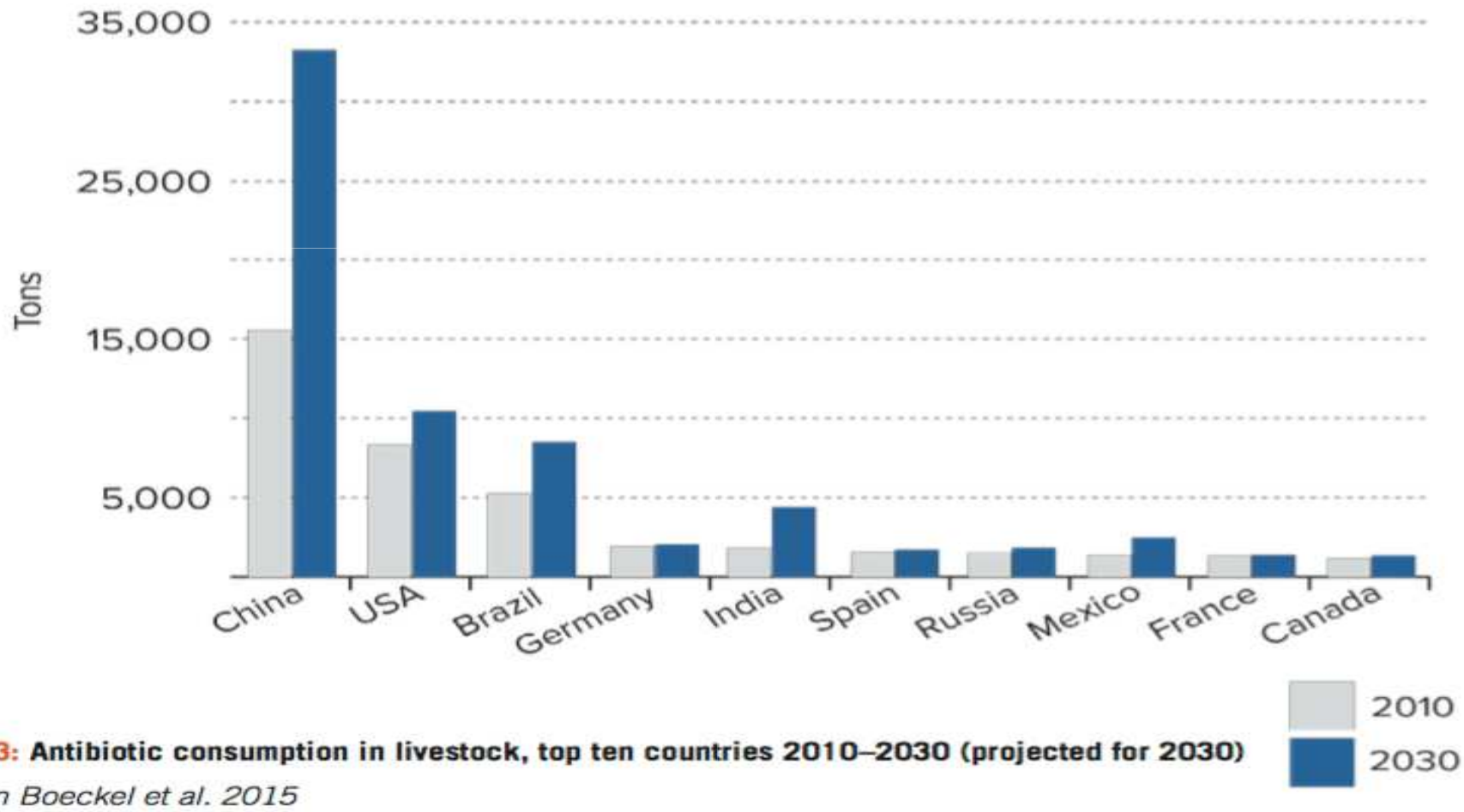


FIGURE ES-3: Antibiotic consumption in livestock, top ten countries 2010–2030 (projected for 2030)

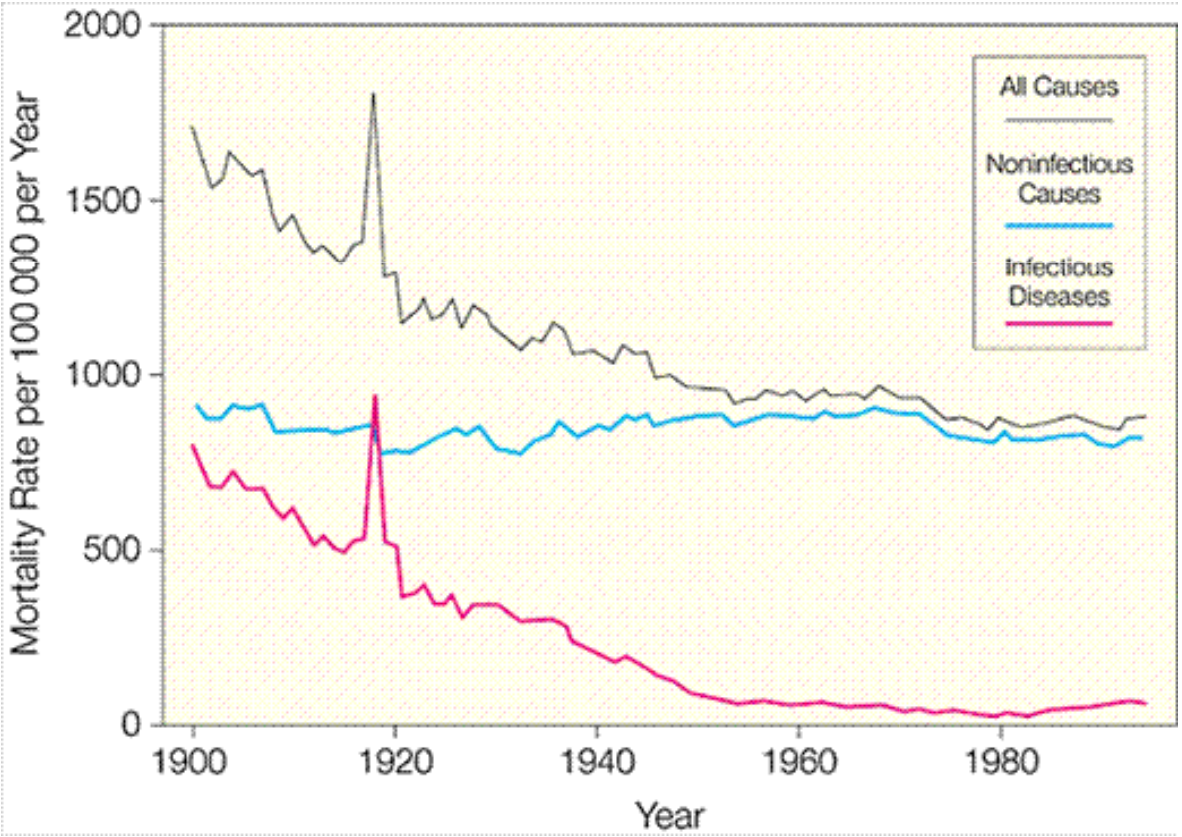
Source: Van Boeckel et al. 2015

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

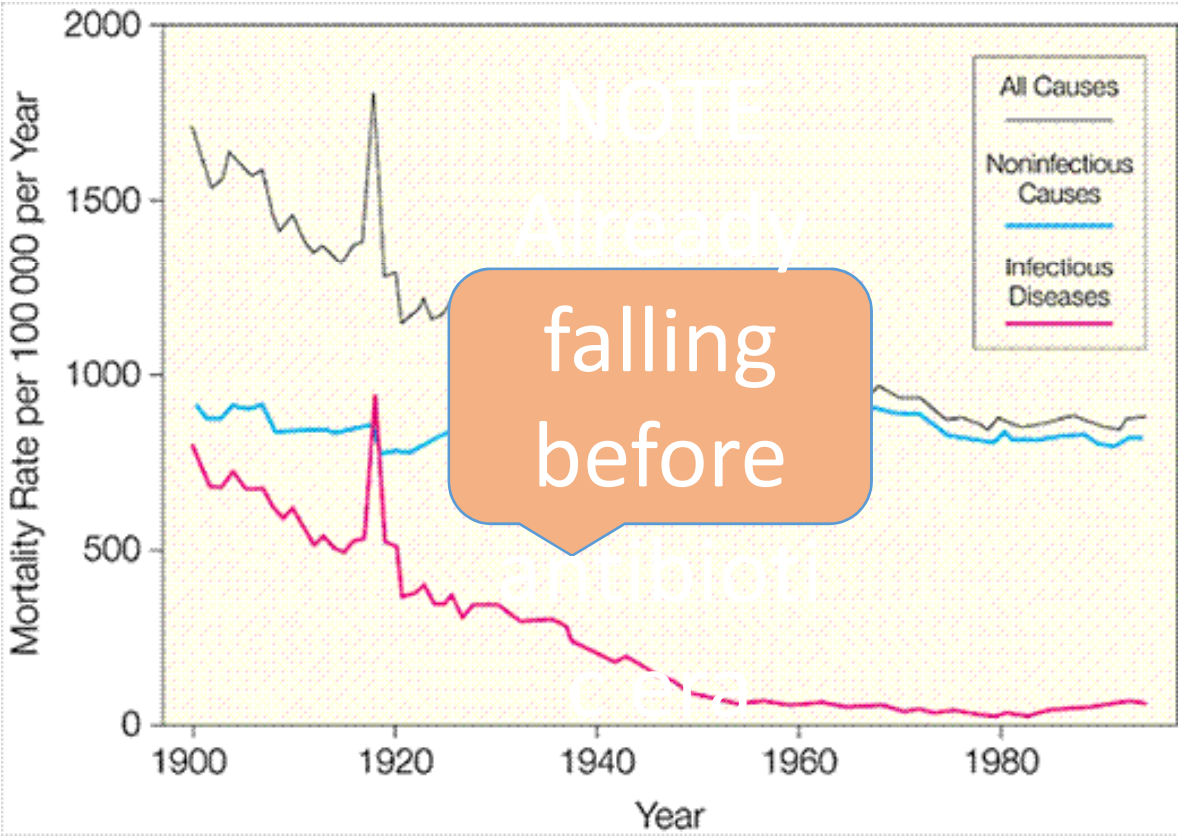
The ‘miracle’ of antibiotics



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

1. Armstrong GL et al, JAMA 1999;281

The ‘miracle’ of antibiotics

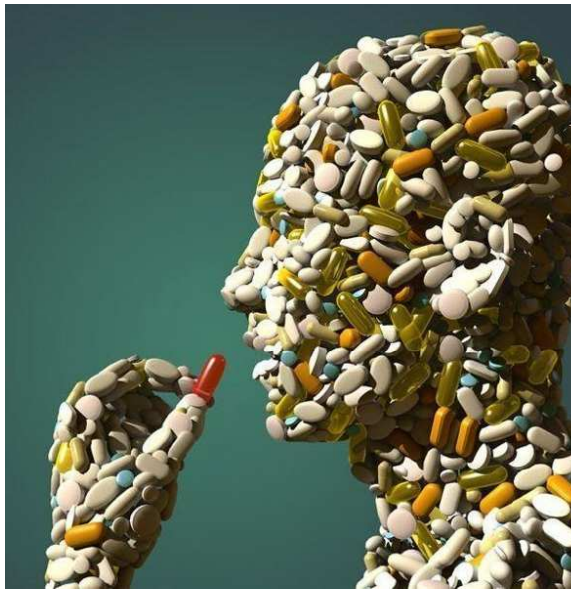


Crude mortality rates for all causes, non infectious causes and infectious diseases over the period 1900-1996.

1. Armstrong GL et al, JAMA 1999;281

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

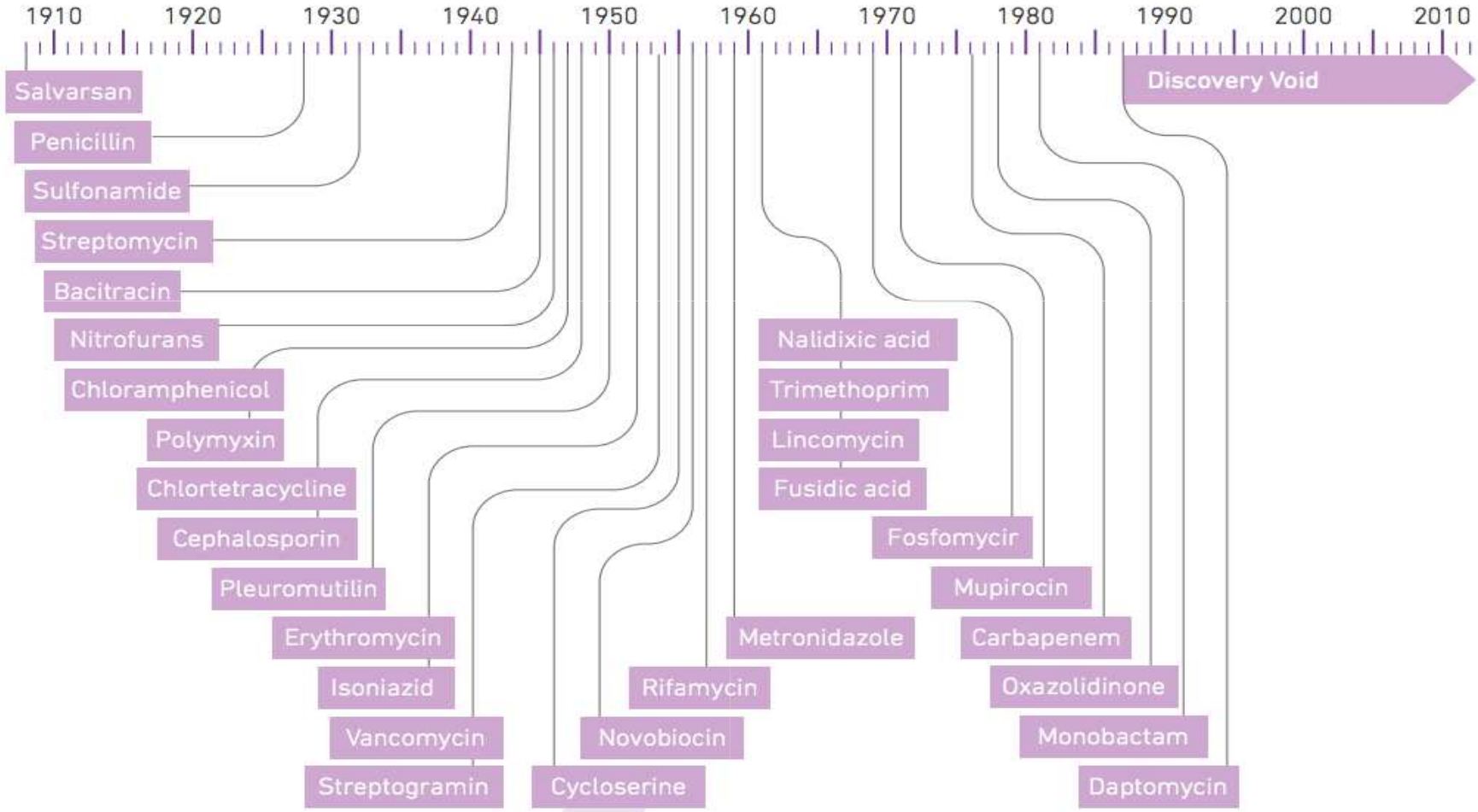


Ohl CA, Luther VP. J. Hosp. Med 2011;6

No significant new antibiotic discoveries for 30 years!

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

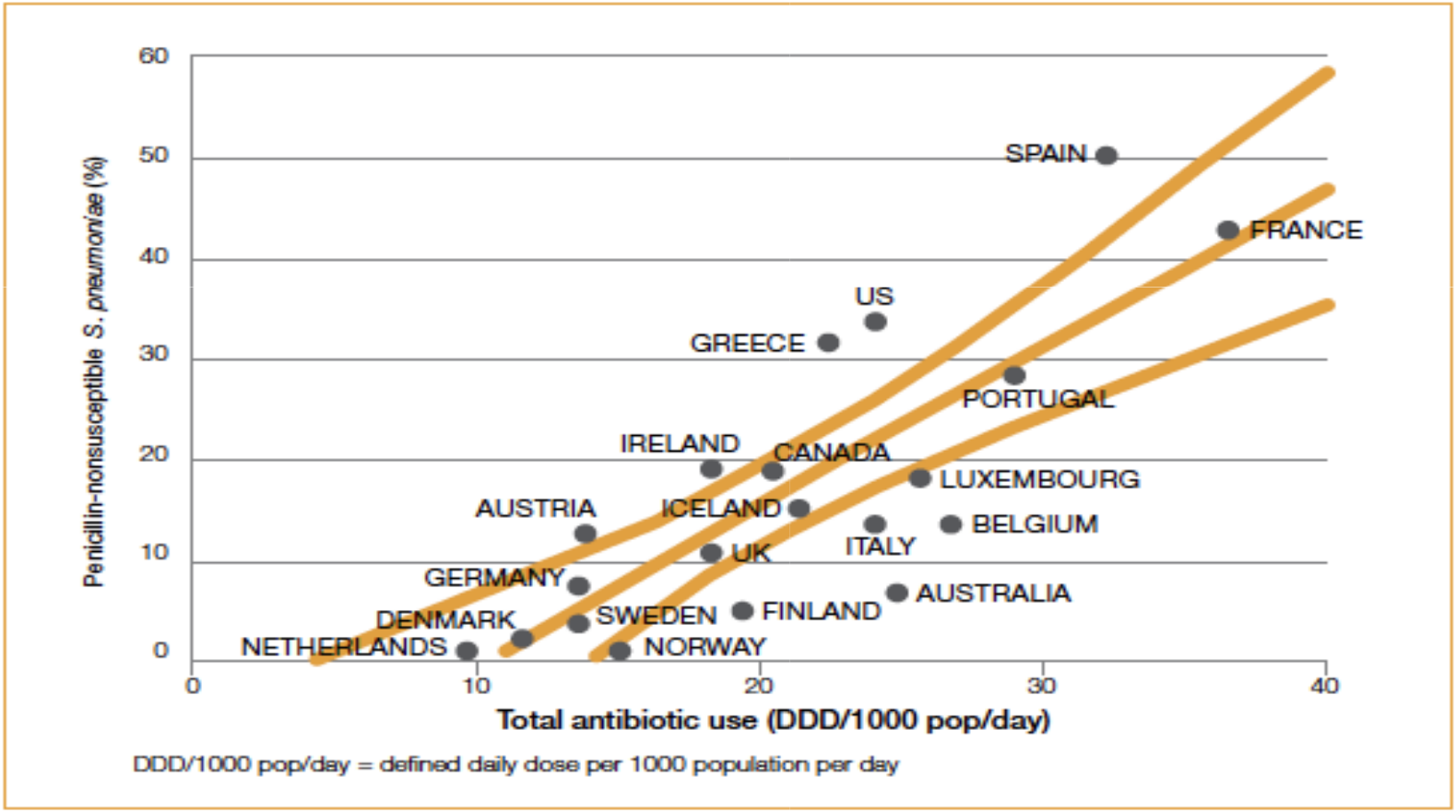
Illustration of the "discovery void." Dates indicated are those of reported initial discovery or patent.



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

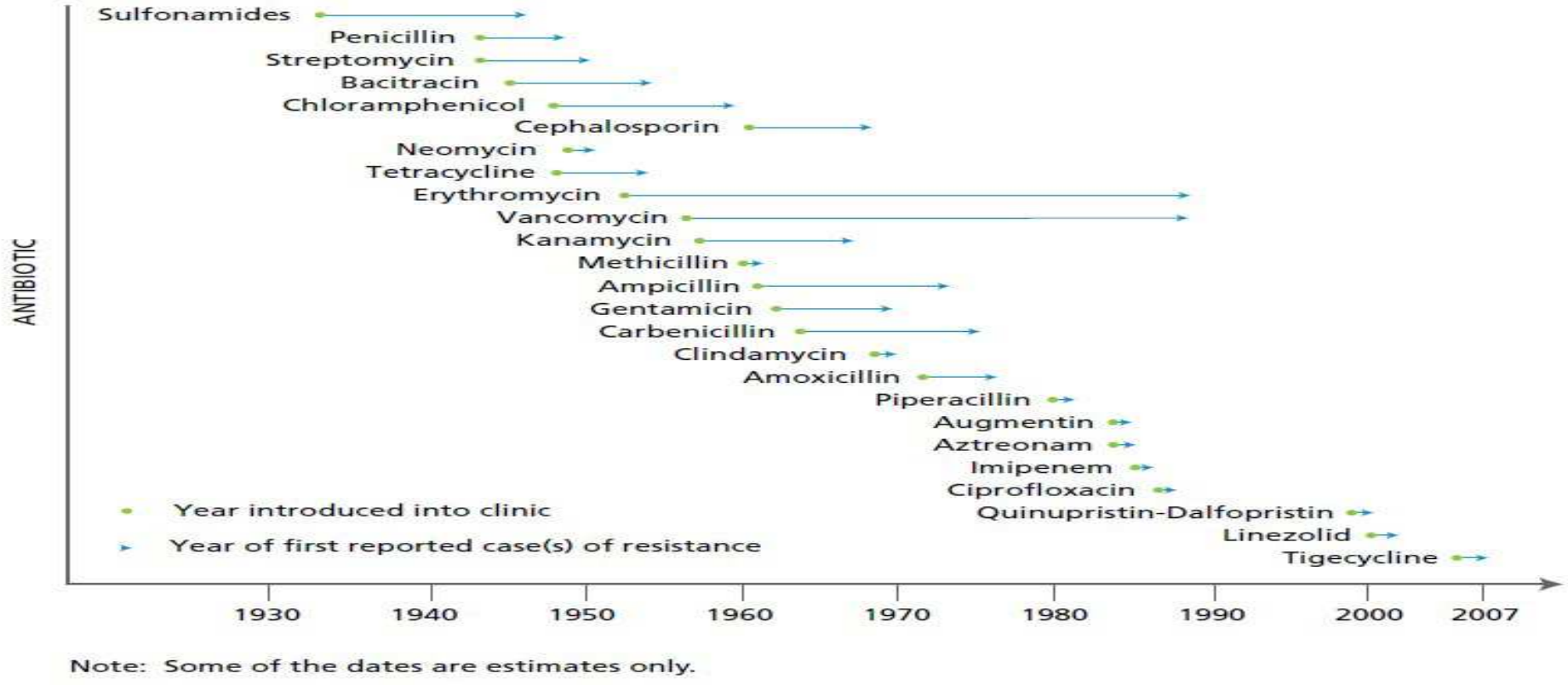
Antibiotic use and antibiotic resistance

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

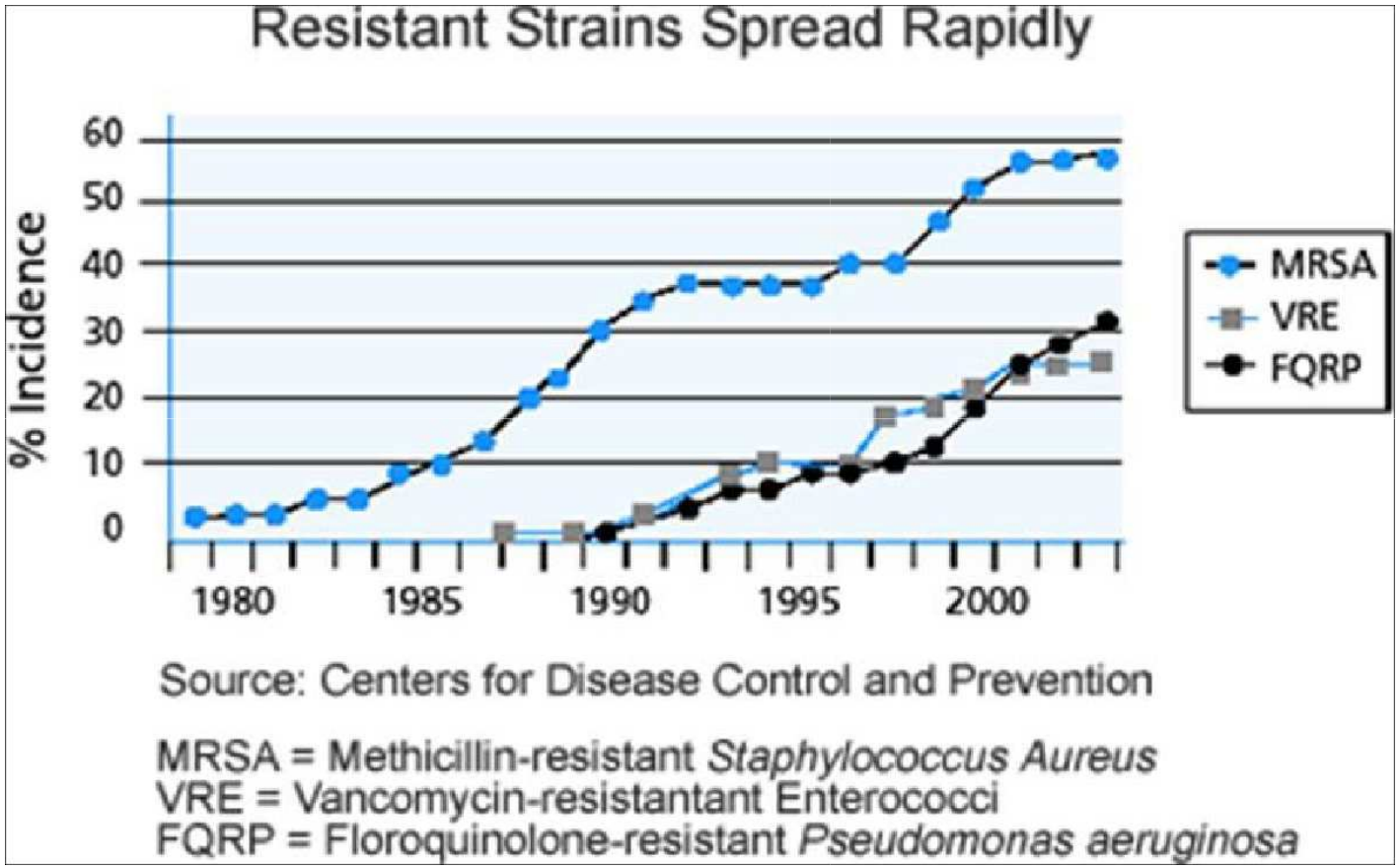


is not difficult to make microbes resistant to penicillin in the laboratory by exposing em to concentrations not sufficient to kill them, and the same thing has occasionally ppened in the body."

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.”

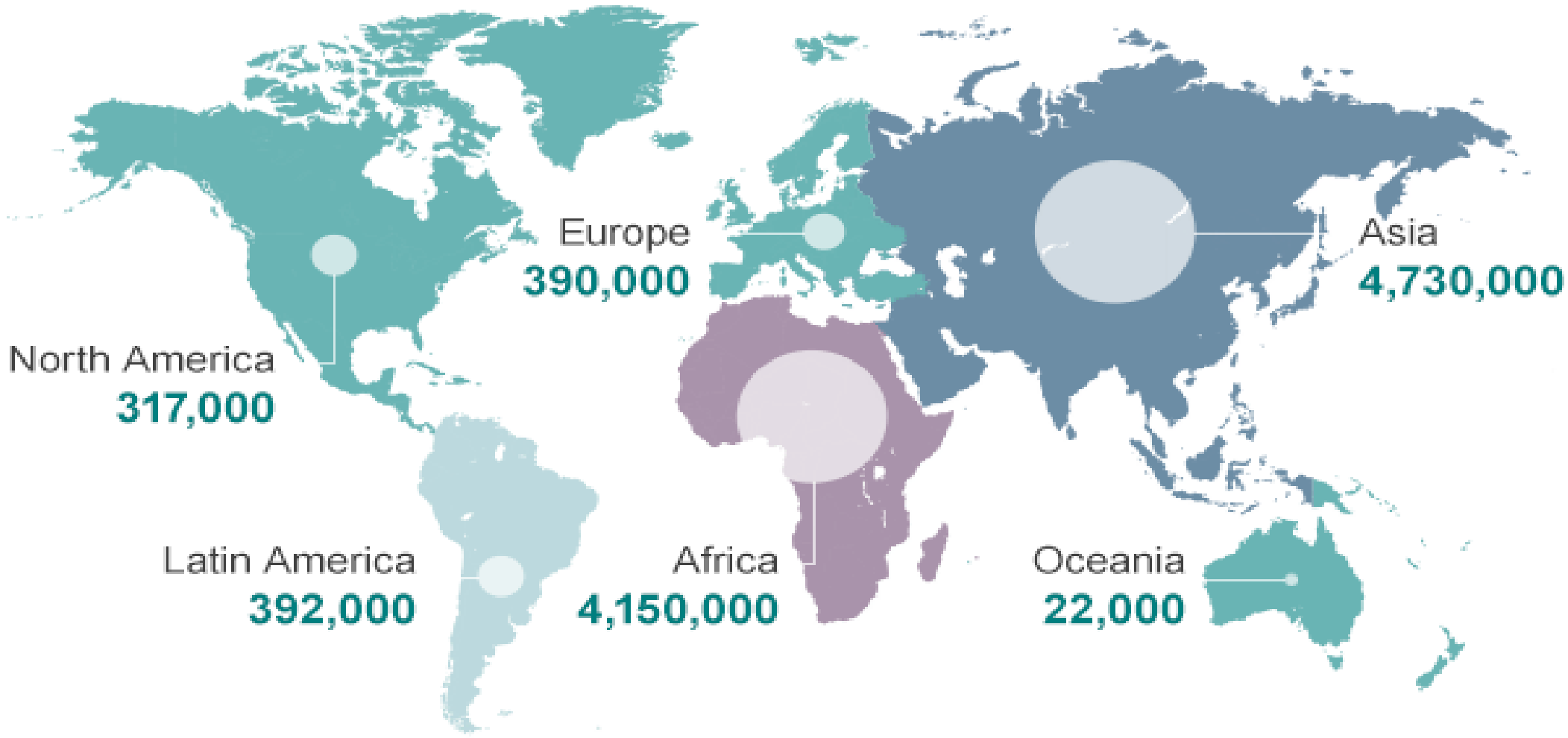
https://amr-review.org/home.html

Closed 2016

Review on Antimicrobial Resistance

Tackling drug-resistant infections globally

Deaths attributable to antimicrobial resistance every year by 2050



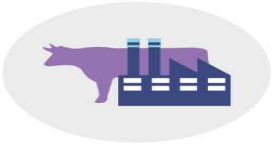
Source: Review on Antimicrobial Resistance 2014

www. weforum.org consulted on February

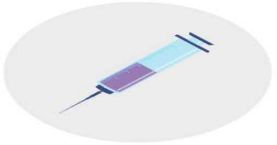
TACKLING ANTIMICROBIAL RESISTANCE ON TEN FRONTS

Public awareness

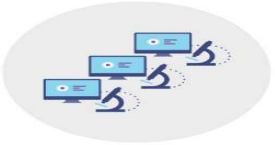
Sanitation and hygiene



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.

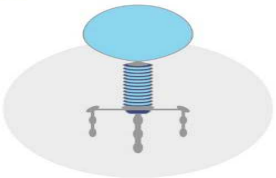
Antimicrobial stewards seek to achieve optimal clinical outcomes related to antimicrobial use, minimize toxicity and other adverse events, reduce the costs of health care for infections, and limit the selection for antimicrobial resistant strains.

ALTERNATIVE PRODUCTS TO TACKLE INFECTIONS

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

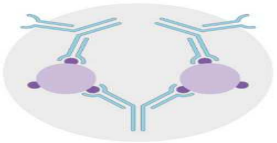
Phage therapy

Natural or engineered viruses that attack and kill bacteria



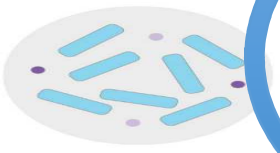
Lysins

Enzymes that directly and quickly act on bacteria



Antibodies

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

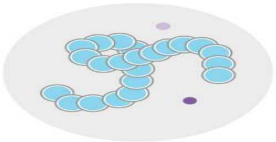


Probiotics

Prevent pathogenic bacteria colonising the gut

Immune stimulation

Boosts the patient's natural immune system

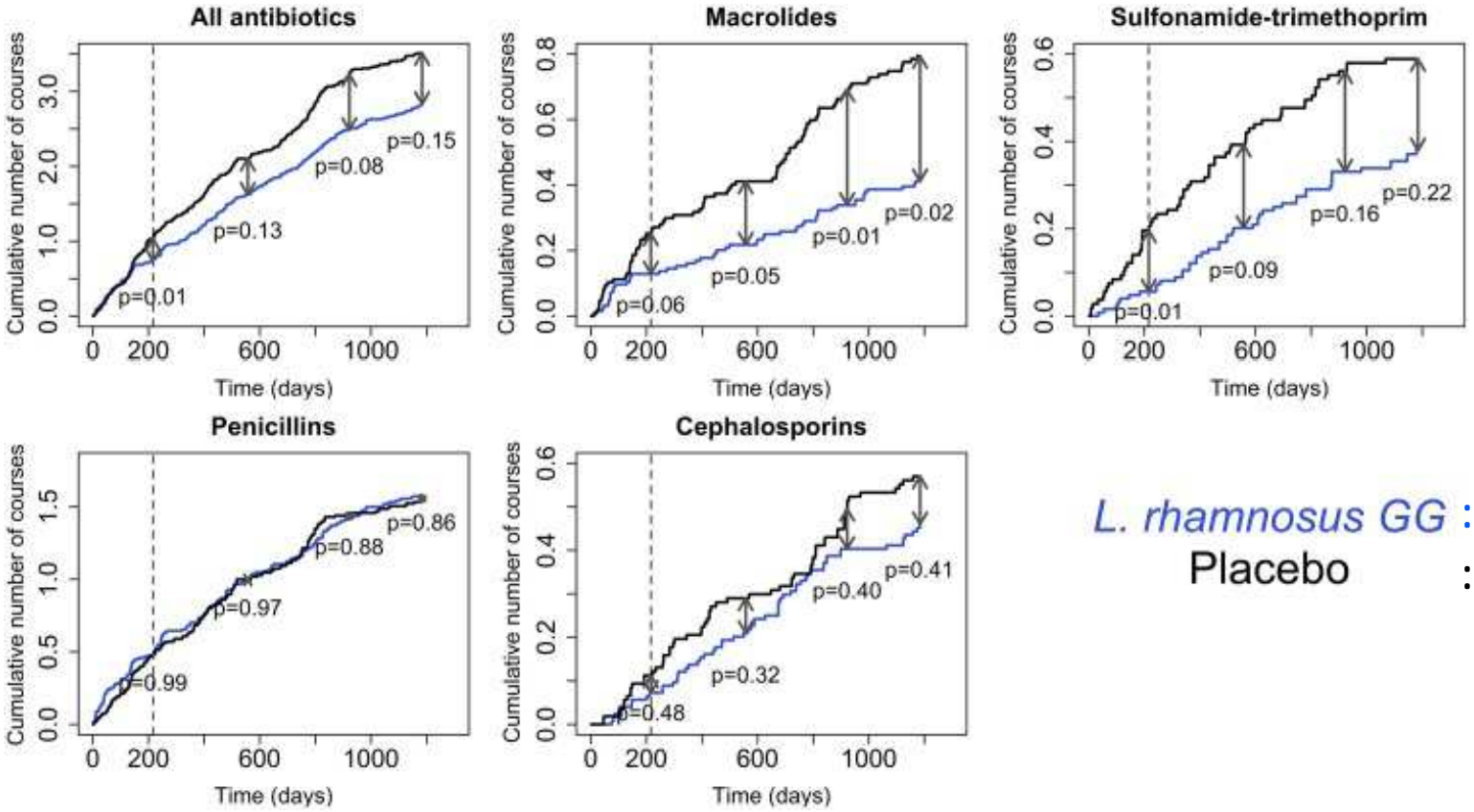


Peptides

Non-mammalian animals' natural defences against infection

Review on Antimicrobial Resistance

ng-term probiotic (LGG) consumption reduces antibiotic u

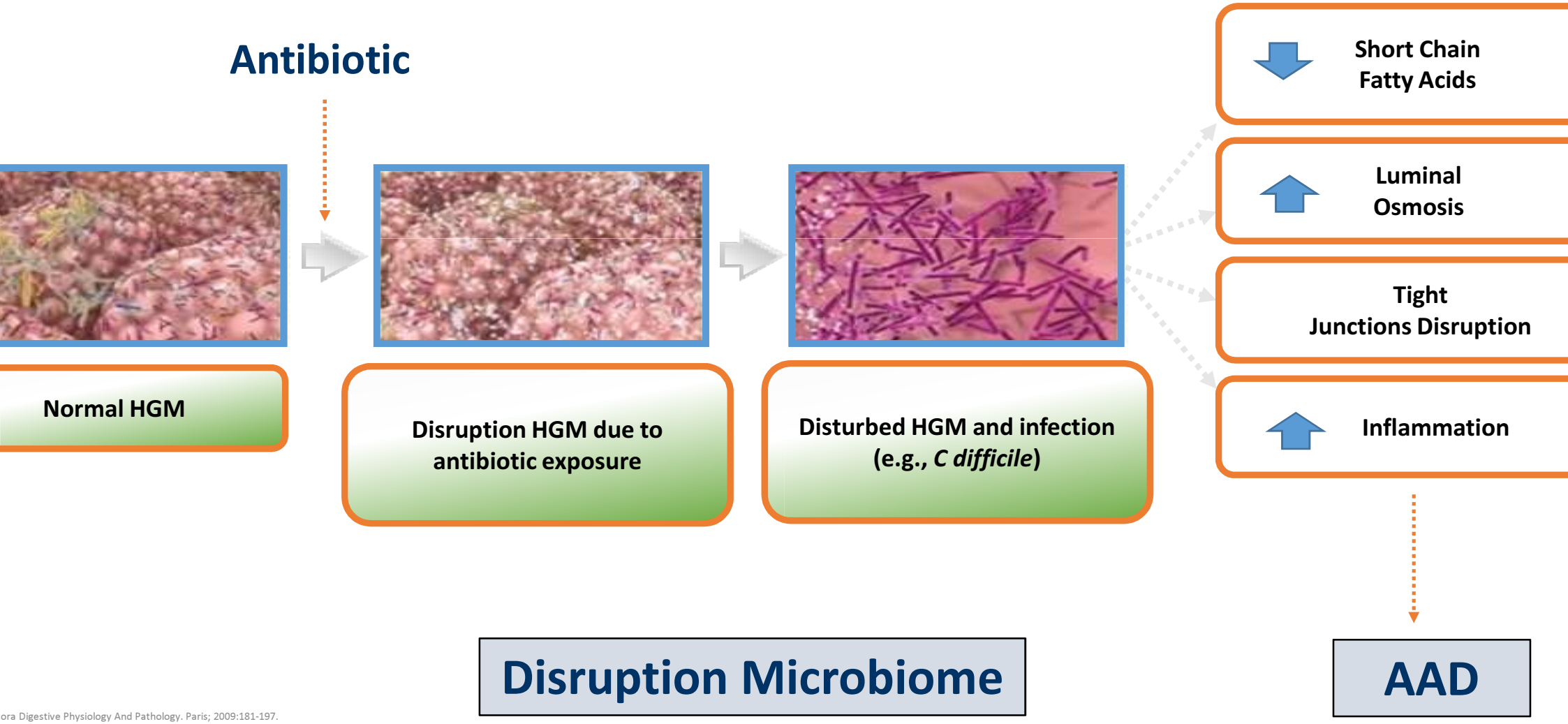


DB PC RCT
(231 children, aged 2-7 yr
Duration: 210 days

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



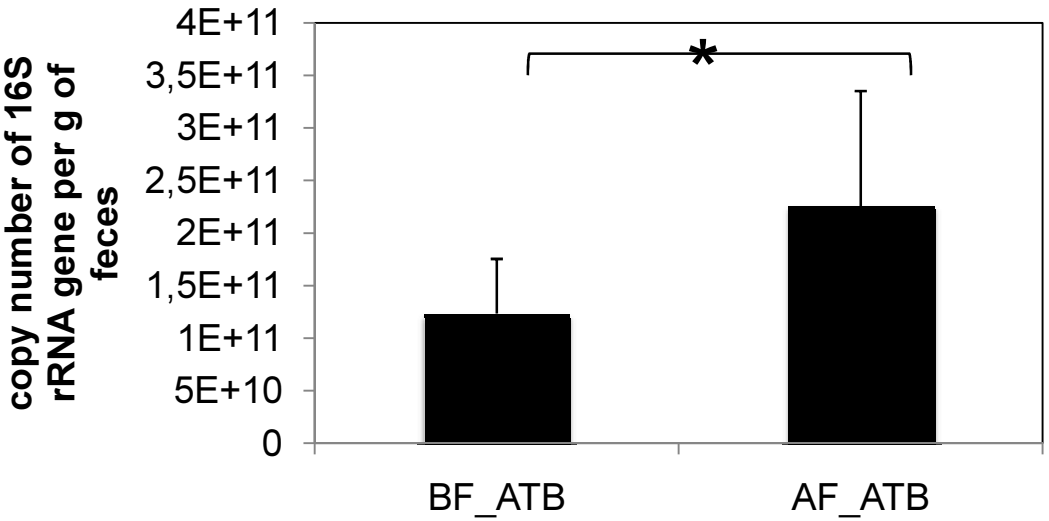
ora Digestive Physiology And Pathology. Paris; 2009:181-197.

Disruption to microbiome (dysbiosis)

- Numbers
- Balance
- Diversity

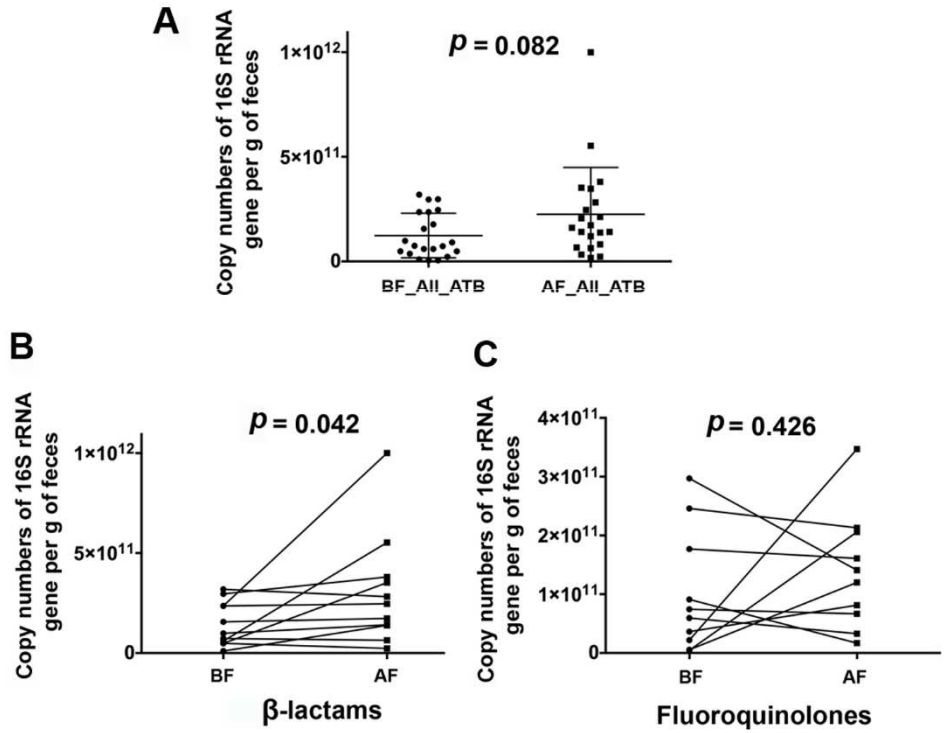
Counterintuitive results

increase of bacterial load after ATB intake in fecal sample



Day 0

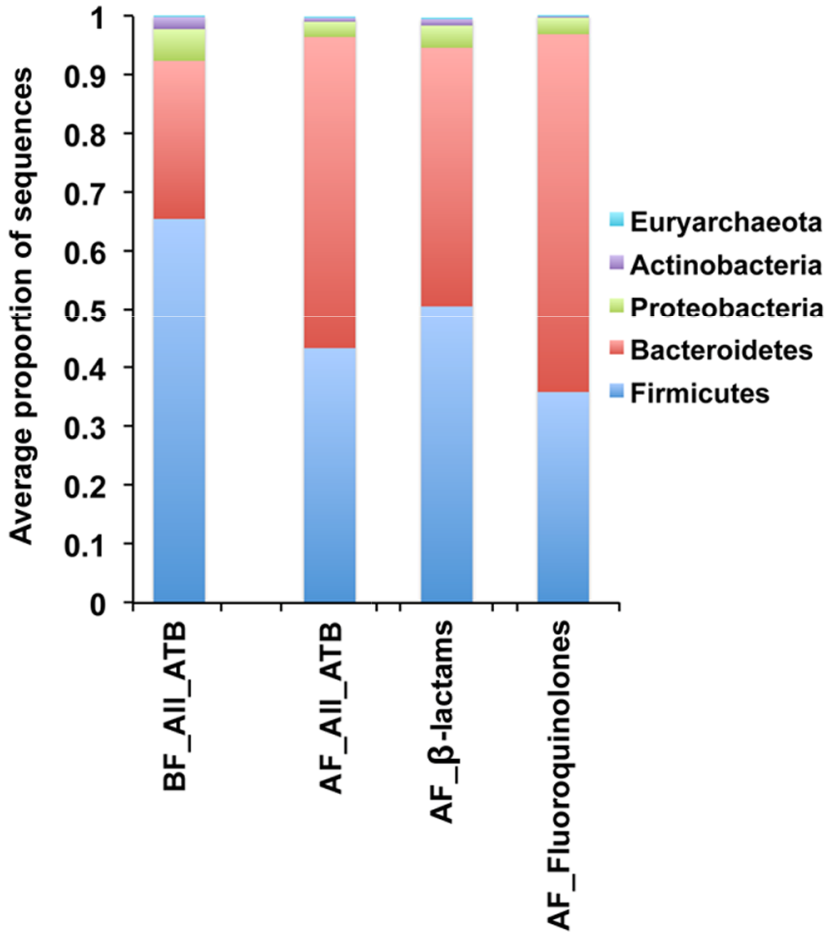
Day 7



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

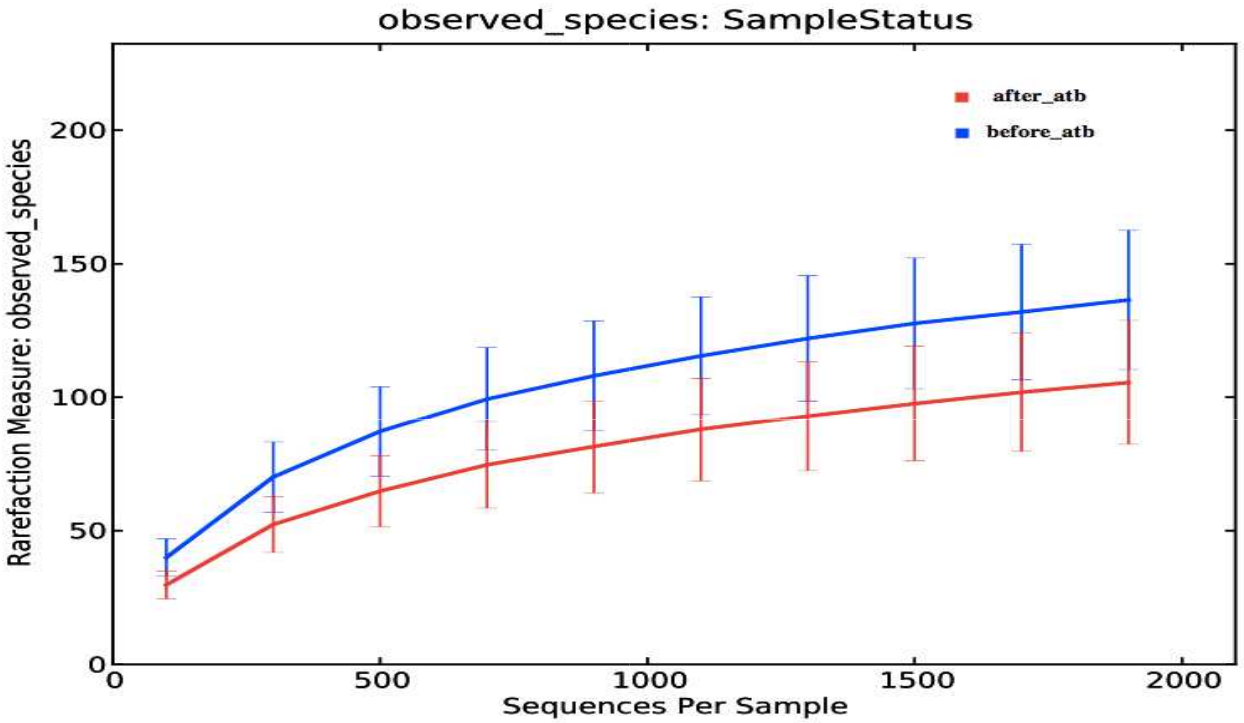
Panda et al. PLoS ONE 20

… and a shift in balance at philum level



Panda et al, PLoS ONE 2

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



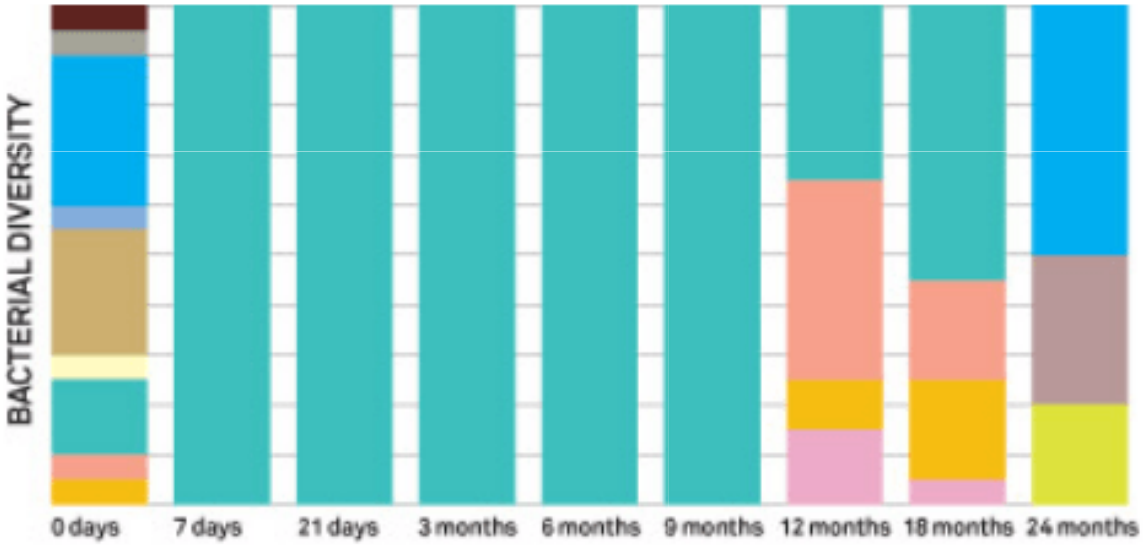
verage number of observed taxa before antibiotic intake: 140 (SD = 22)
verage number of observed taxa after antibiotic intake: 105 (SD = 23)

< 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.

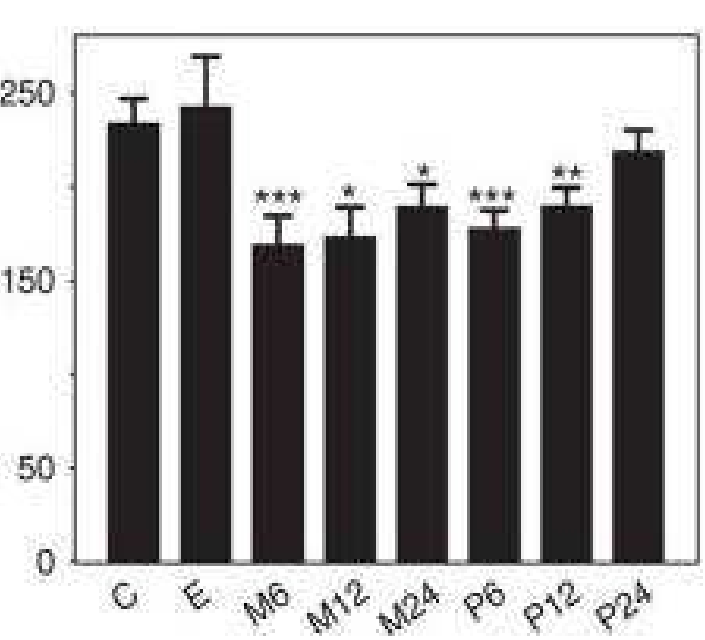


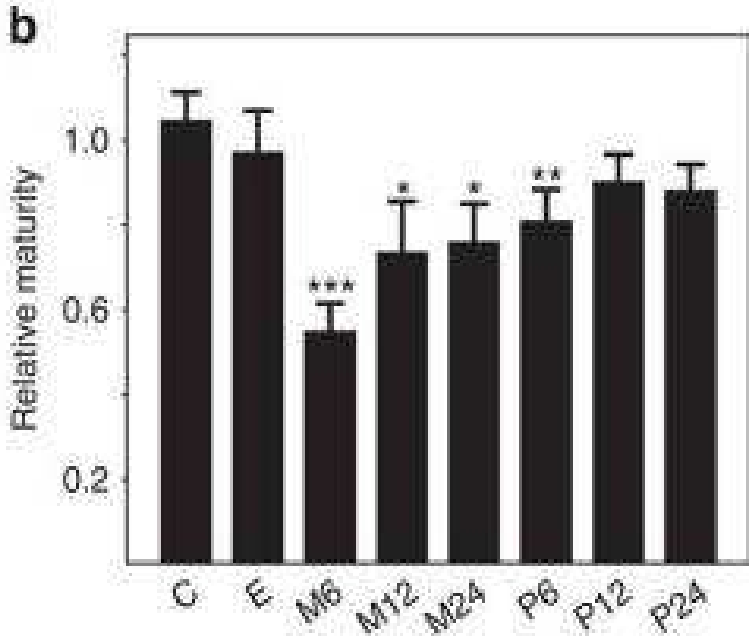
LONG-TERM EFFECTS OF A SEVEN-DAY COURSE OF ANTIBIOTICS

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

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

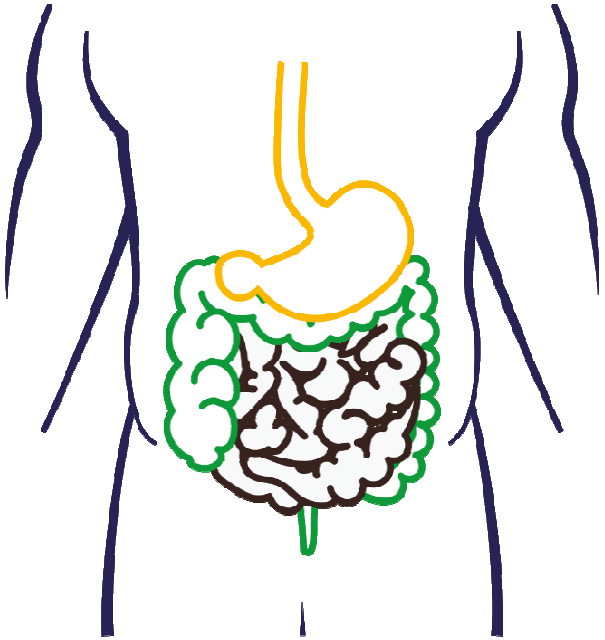
Katri Korpela[1], Anne Salonen[1], Lauri J. Virta[2], Riina A. Kekkonen[3], Kristoffer Forslund[4], Peer Bork[4] & Willem M. de Vos[1,5,6]





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



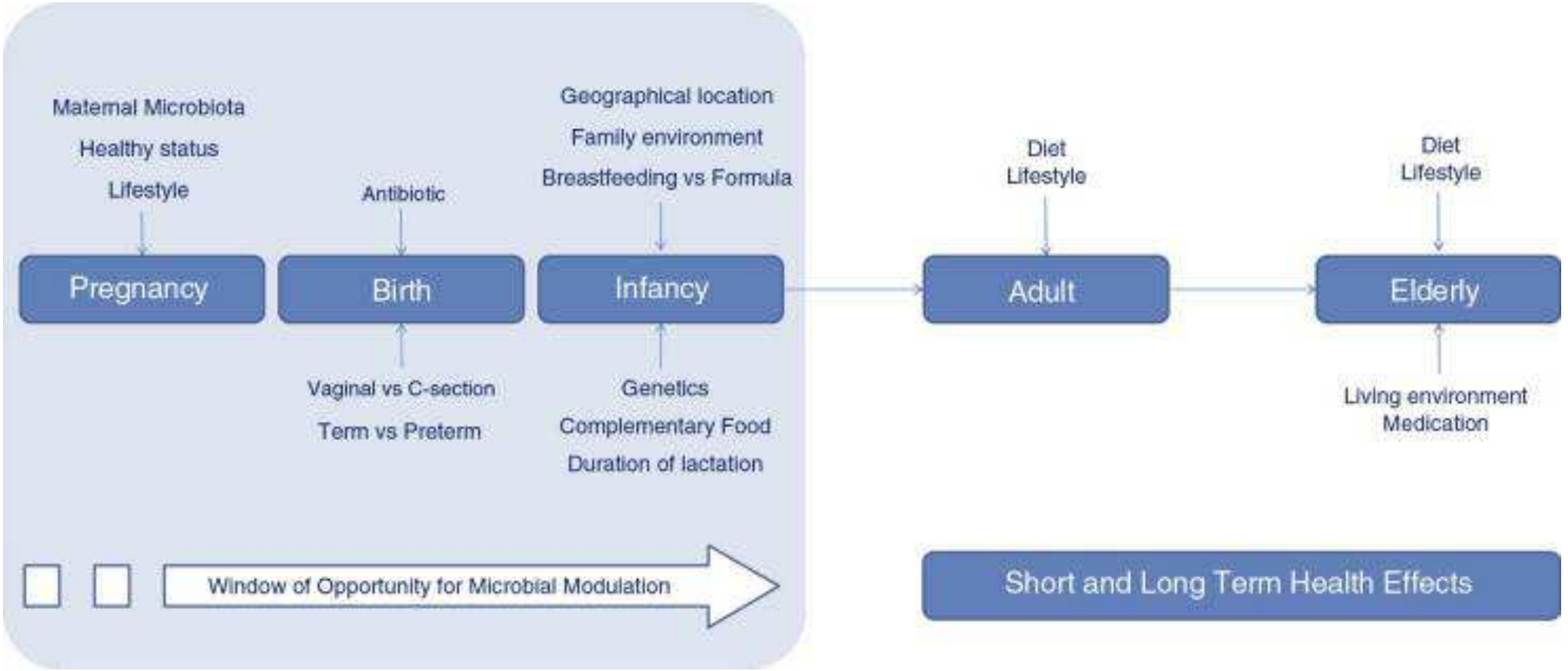
EUBIOSIS => “Normal" and "balanced" intestinal microbiota fulfills all the conditions for us to benefit from its health effects
(metabolism, immunity, trophicity, barrier effect)

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

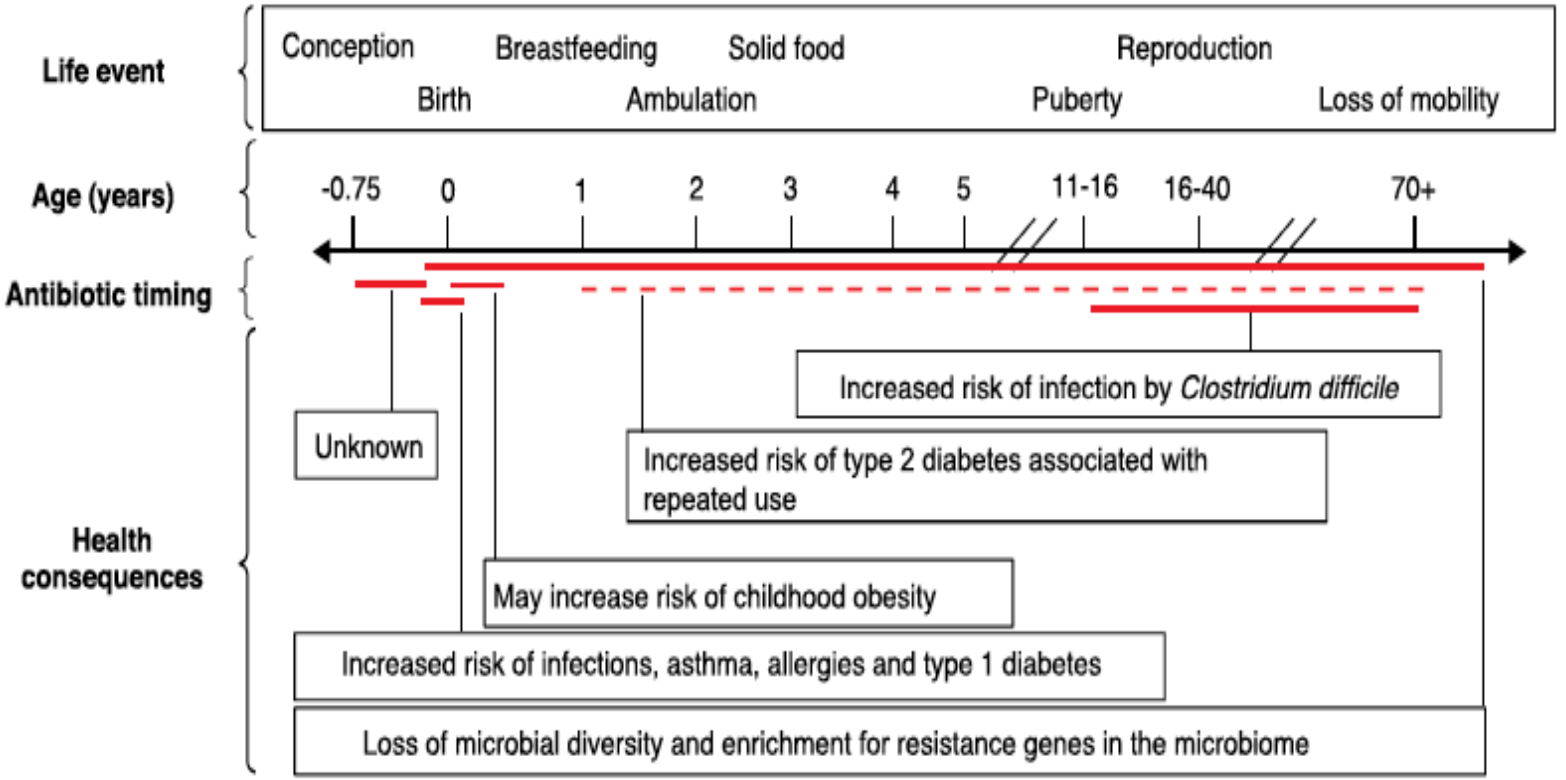


Fig. 1 Health consequences linked to the disruption of human-associated microbiota involving antibiotic use during development and adulthood. *Red lines* indicate that a single dose of antibiotics within the time period has been linked to a health consequence, whereas a *dotted red line* indicates that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

orders linked to altered composition of the gut microbiota:

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

Inflammatory bowel diseases (UC and CD)

Celiac disease

Antibiotic-associated diarrhea, recurrent diarrhea by C. difficile

Functional bowel disorders

Colo-rectal cancer

Certain allergies

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

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

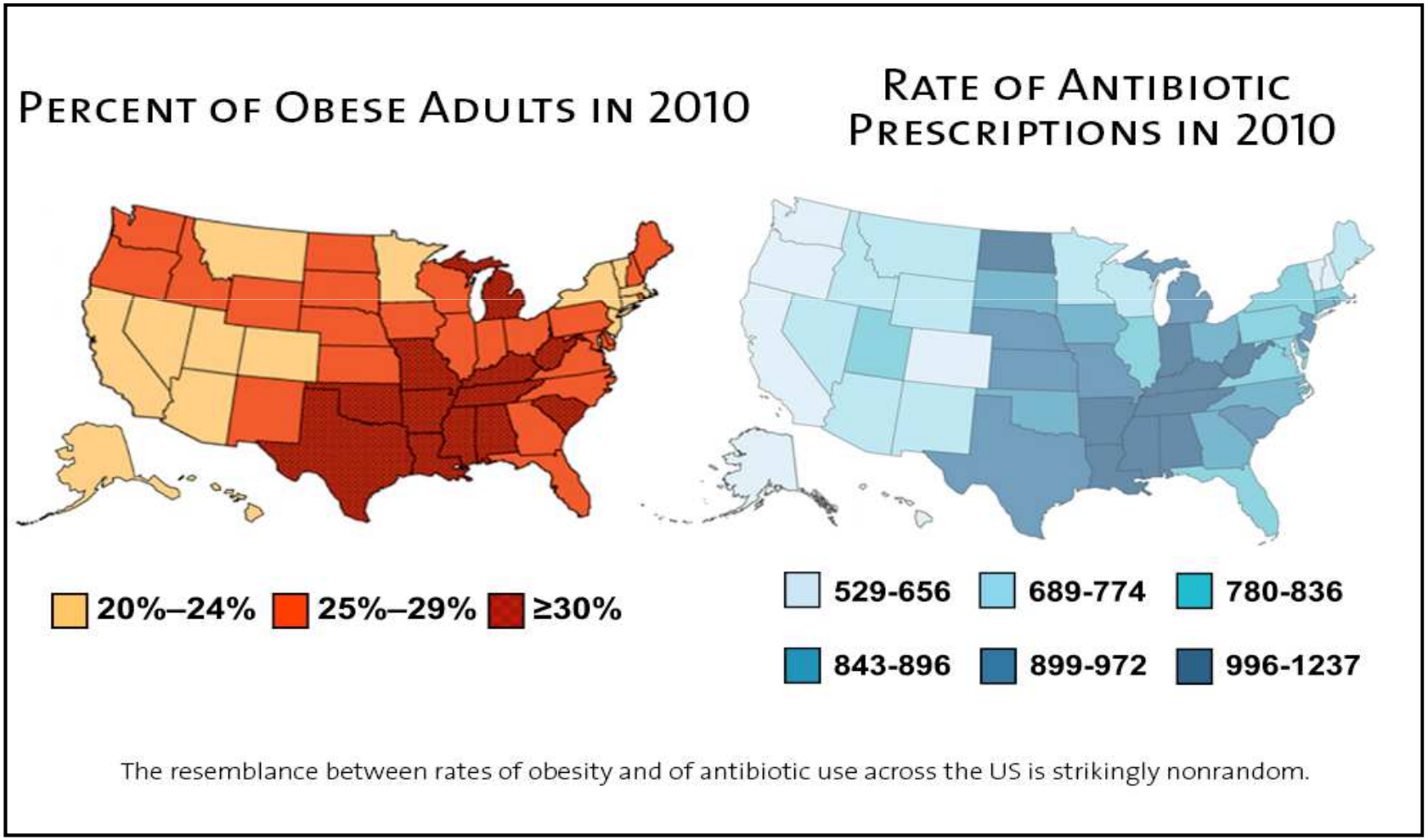
Certain mental and neuro-developmental conditions, such as autism spectrum disorder

Could this be correlation, without causation?

Do these differences matter?

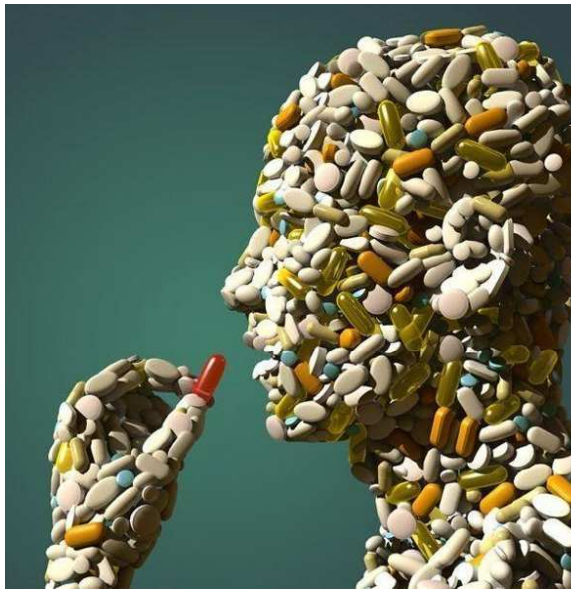
Can anything else explain the results?

Associations, but no proven causuality



Consequences of Antibiotic (Mis)use

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



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

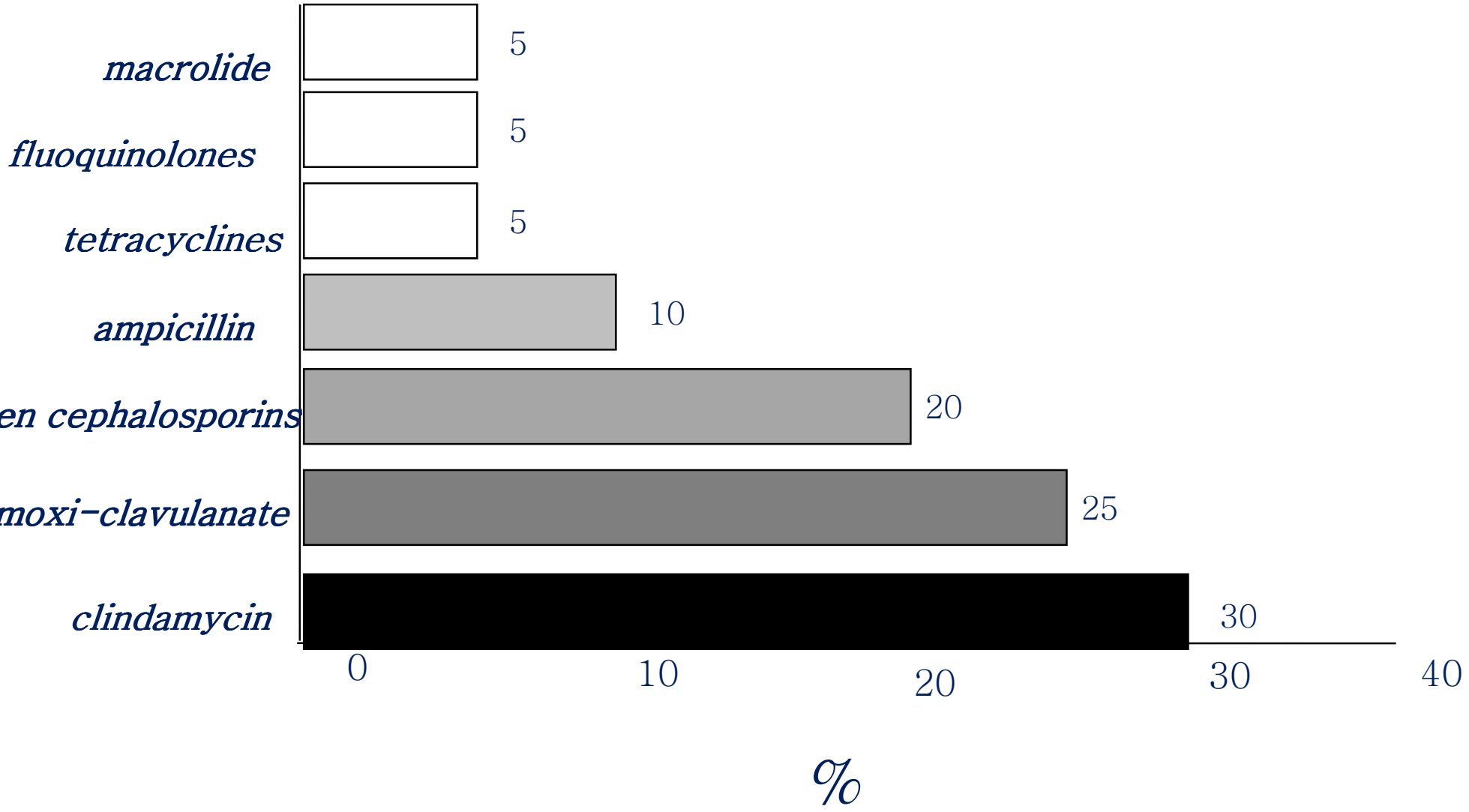
Antibiotic-associated diarrhea in children

- 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

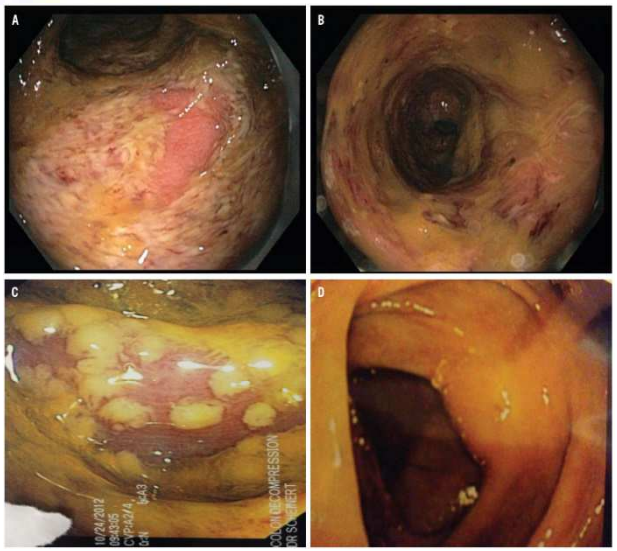
Pseudomembranous colitis

CD colitis

CD -Associated Diarrhea (CDAD/CDI)

Asymptomatic Carrier

Risk factors



Therapy for AAD and CDAD

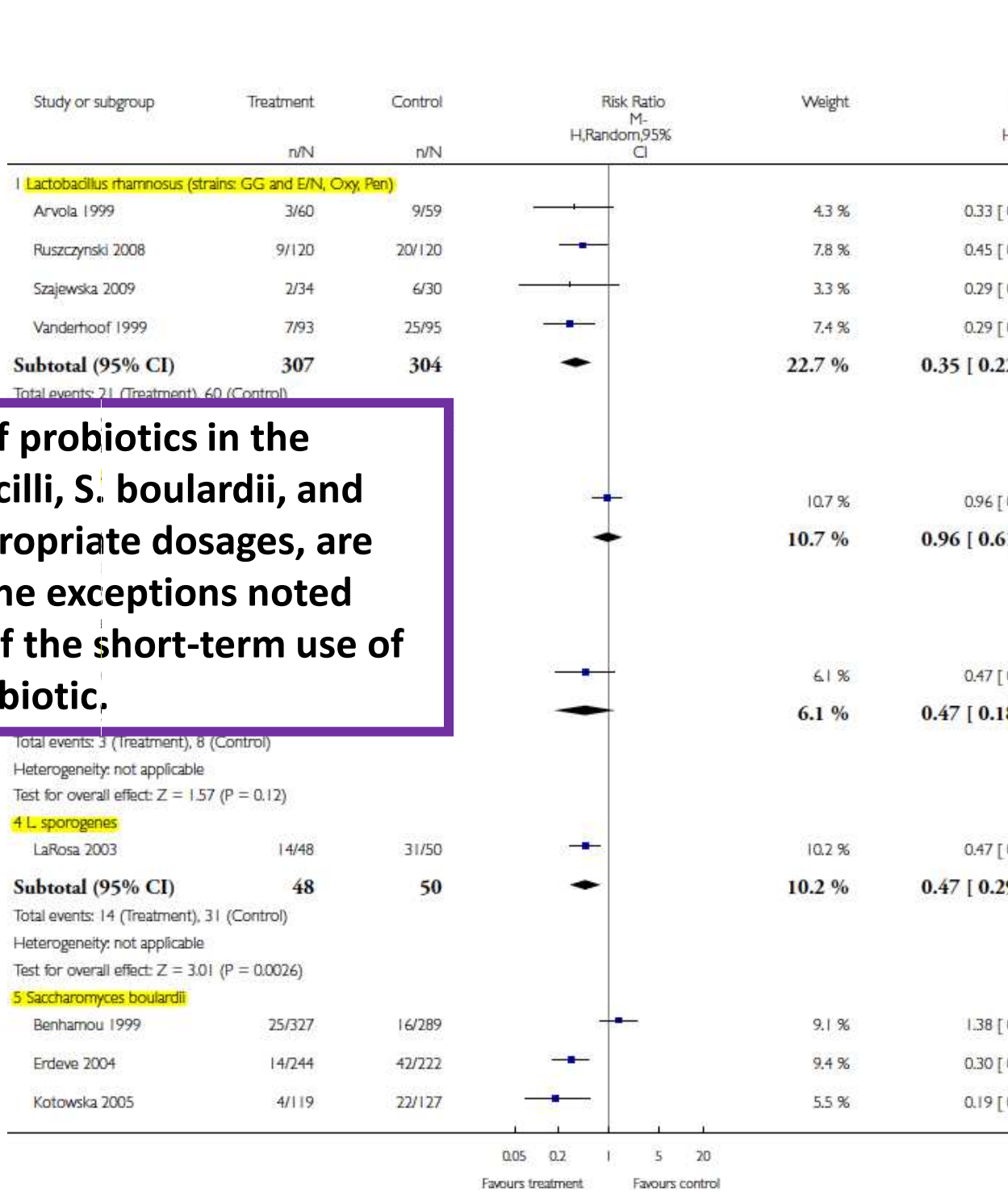
- Essential: Discontinuation or changing the type of the inciting antibiotic and giving oral rehydration therapy

- Probiotics?

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

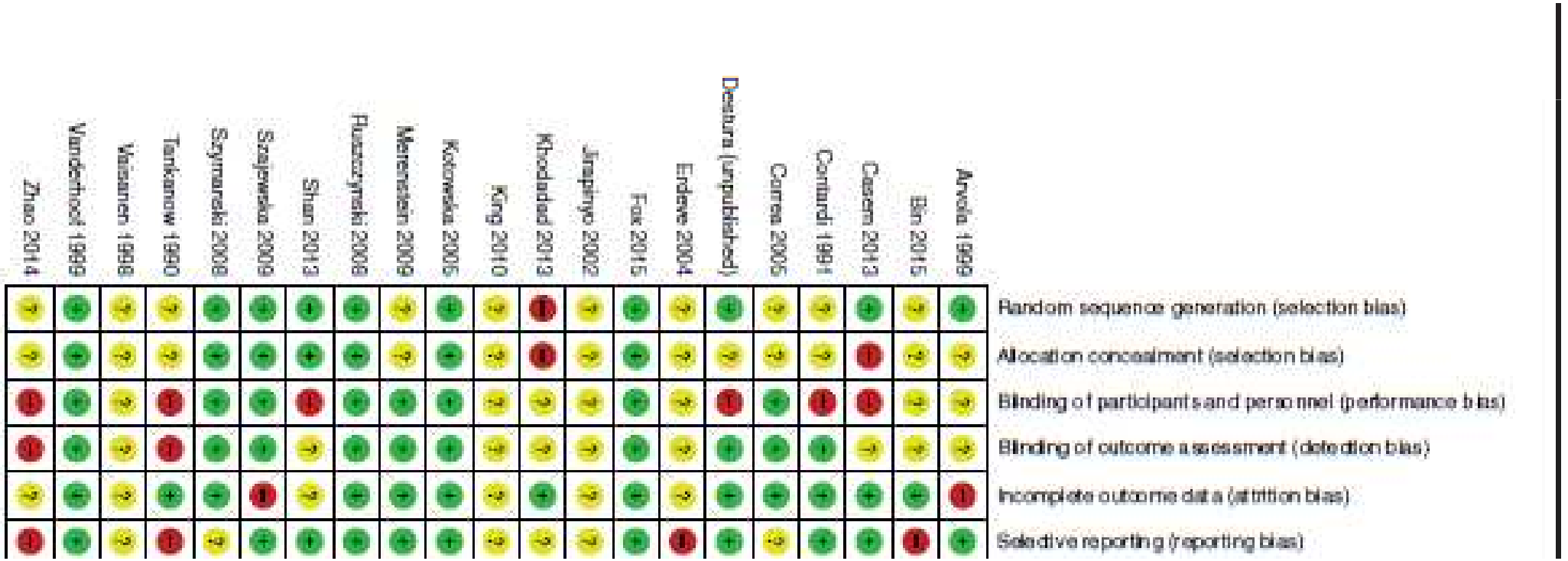
Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children

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

Methodological limits in RCTS on prevention of AAD with probiotics



Szajewska et al JPGN March 20

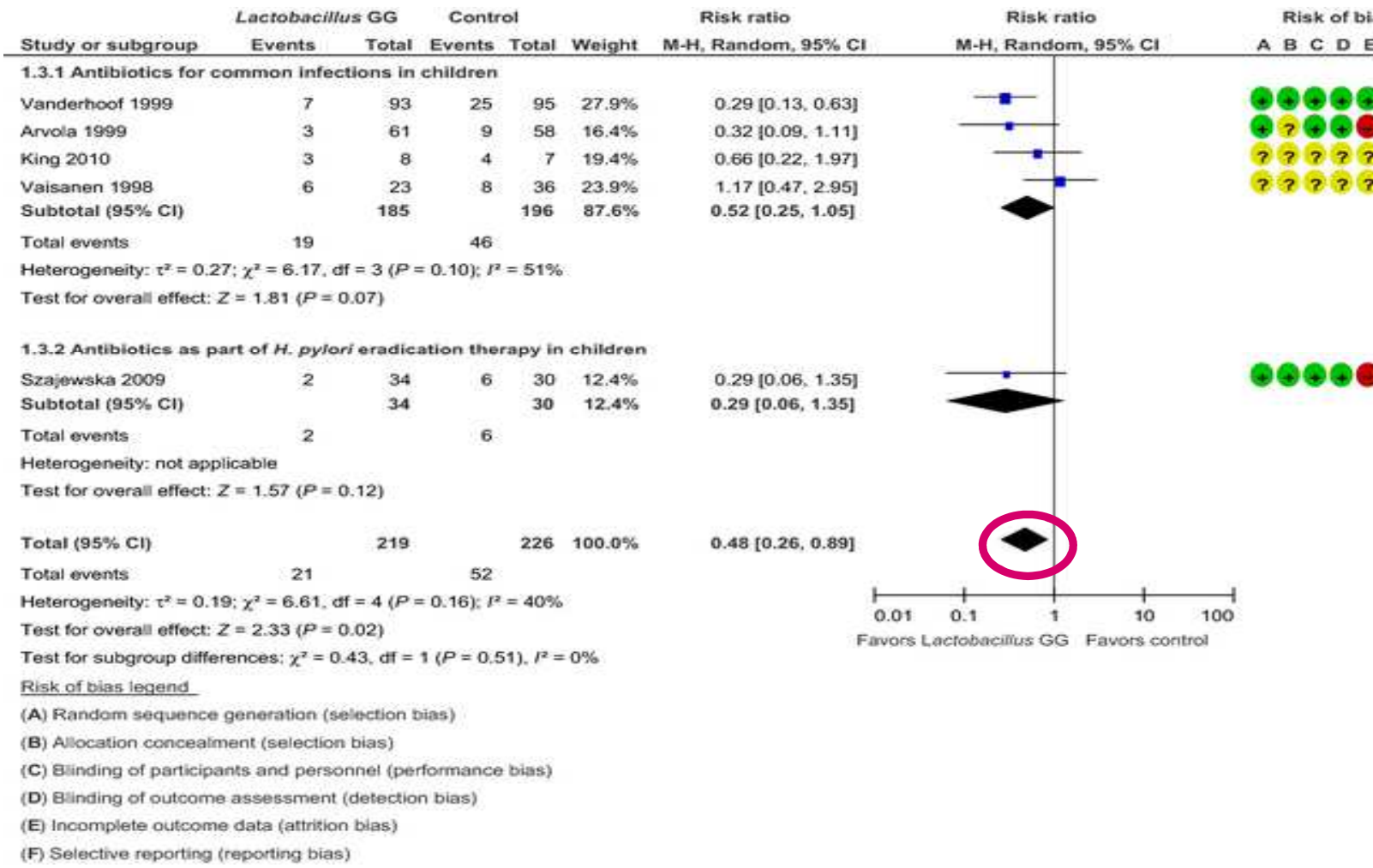
LGG for prevention pediatric AAD

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-

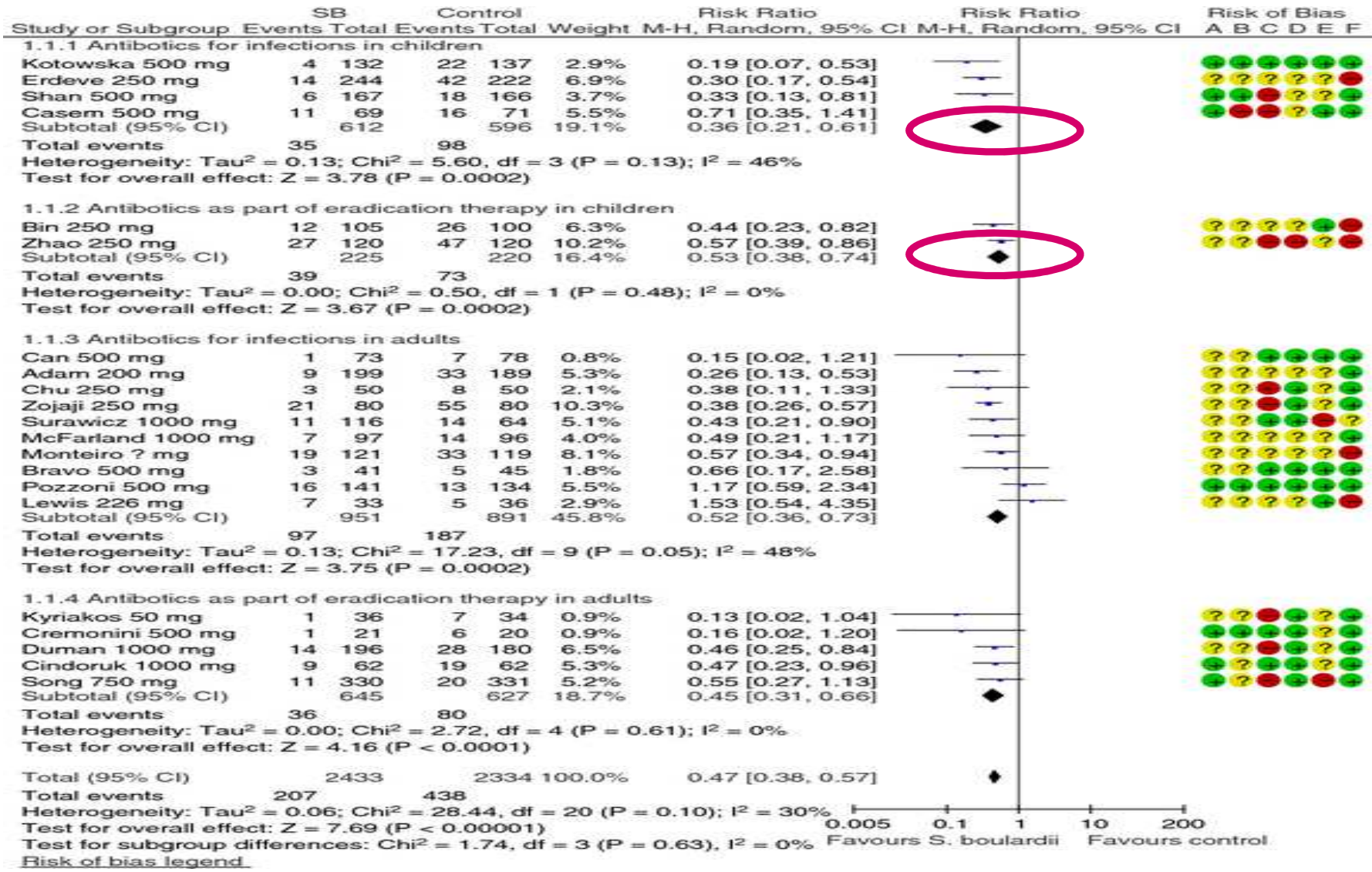
SB for prevention pediatric AAD

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:

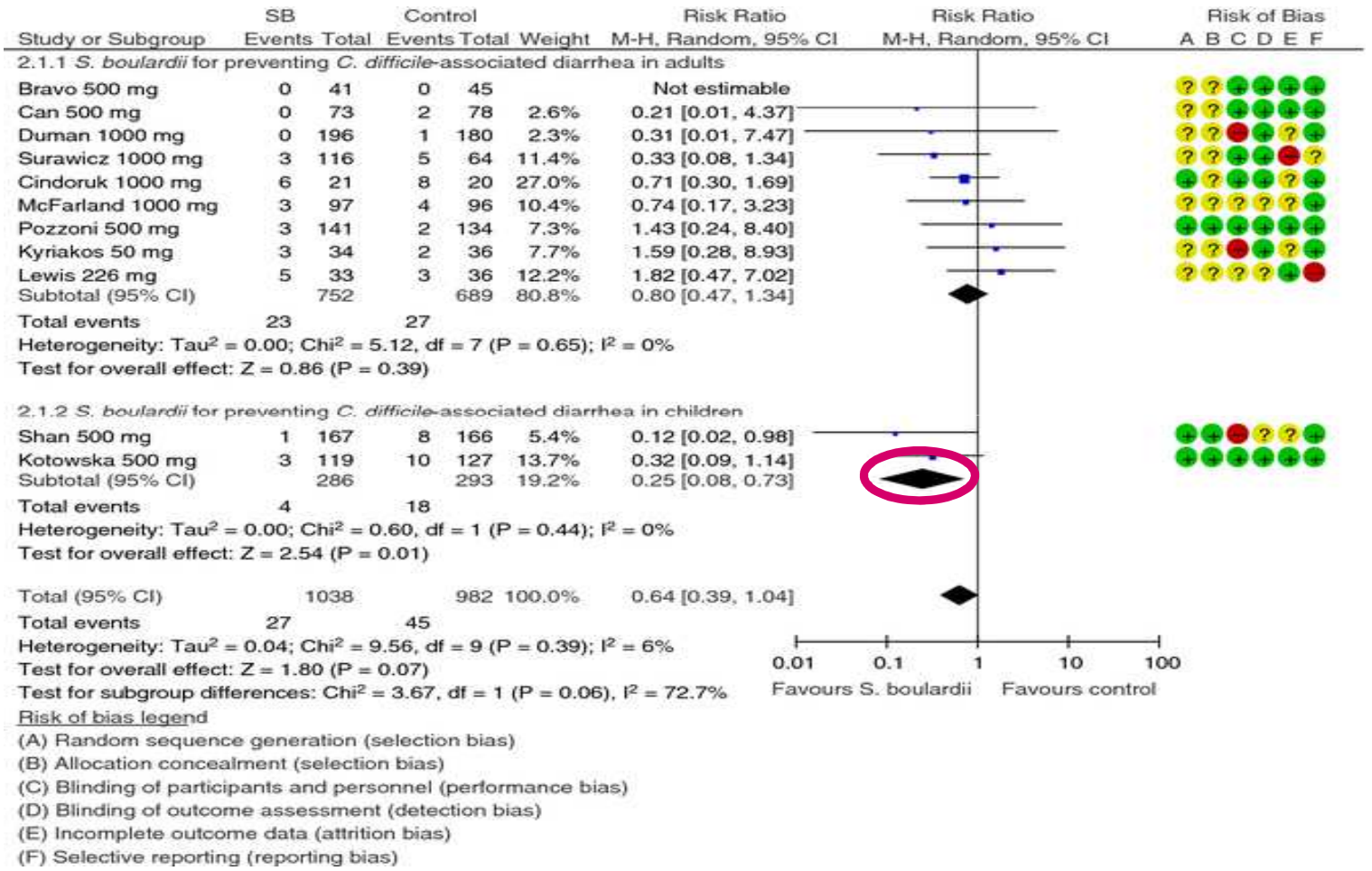
the use of probiotics for preventing AAD is considered because of th
xistence of risk factors such as class of antibiotic(s), duration of
ntibiotic treatment, age, hospitalization, comorbidities, or previous
pisodes of AAD, the WG recommends using *Lactobacillus rhamnosu*
G and *Sacharomyces boulardii*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

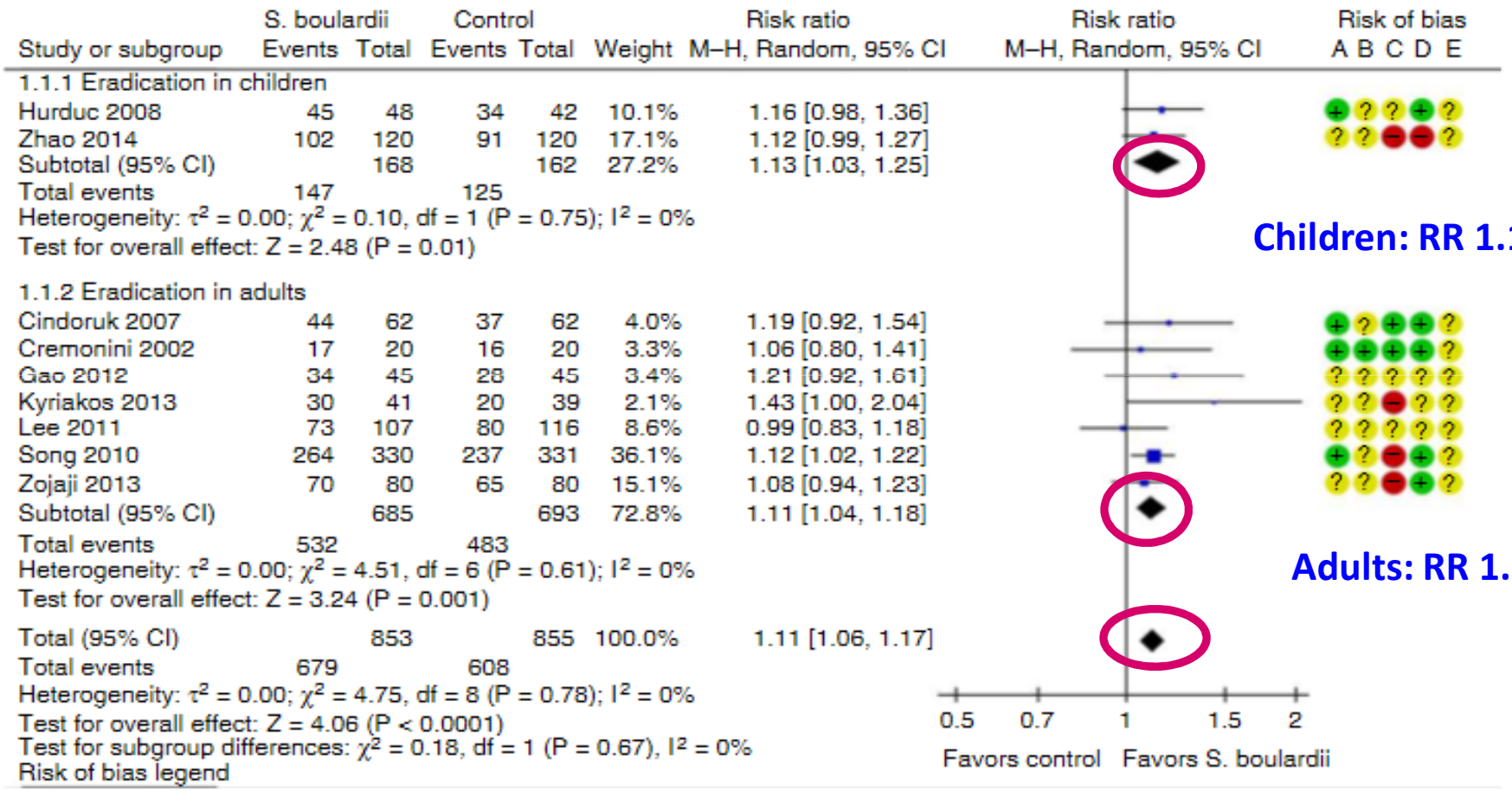
- Frequent misidentification and misclassification of strains
- Contamination, sometimes with pathogens
- No viable strains, false labelling of number of colonies
- Deminishment of functional properties, shelf live

→ 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

Helicobacter pylori eradication

Sb in eradication therapy for *H. pylori* treatment



Study or subgroup	S. boulardii Events	Total	Control Events	Total	Weight	Risk ratio M–H, Random, 95% CI
1.1.1 Eradication in children						
Hurduc 2008	45	48	34	42	10.1%	1.16 [0.98, 1.36]
Zhao 2014	102	120	91	120	17.1%	1.12 [0.99, 1.27]
Subtotal (95% CI)		168		162	27.2%	1.13 [1.03, 1.25]
Total events	147		125			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.10$, df = 1 (P = 0.75); $I^2 = 0\%$						
Test for overall effect: Z = 2.48 (P = 0.01)						
1.1.2 Eradication in adults						
Cindoruk 2007	44	62	37	62	4.0%	1.19 [0.92, 1.54]
Cremonini 2002	17	20	16	20	3.3%	1.06 [0.80, 1.41]
Gao 2012	34	45	28	45	3.4%	1.21 [0.92, 1.61]
Kyriakos 2013	30	41	20	39	2.1%	1.43 [1.00, 2.04]
Lee 2011	73	107	80	116	8.6%	0.99 [0.83, 1.18]
Song 2010	264	330	237	331	36.1%	1.12 [1.02, 1.22]
Zojaji 2013	70	80	65	80	15.1%	1.08 [0.94, 1.23]
Subtotal (95% CI)		685		693	72.8%	1.11 [1.04, 1.18]
Total events	532		483			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.51$, df = 6 (P = 0.61); $I^2 = 0\%$						
Test for overall effect: Z = 3.24 (P = 0.001)						
Total (95% CI)		853		855	100.0%	1.11 [1.06, 1.17]
Total events	679		608			
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 4.75$, df = 8 (P = 0.78); $I^2 = 0\%$						
Test for overall effect: Z = 4.06 (P < 0.0001)						
Test for subgroup differences: $\chi^2 = 0.18$, df = 1 (P = 0.67), $I^2 = 0\%$						

Children: RR 1.13, 95% CI 1.03 to 1.2

Adults: RR 1.11, 95% CI 1.04 to 1.1

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding (performance bias and detection bias)
(D) Incomplete outcome data (attrition bias)
(E) Selective reporting (reporting bias)

H Szajewska et al. Aliment Pharmacol Ther 2015;41:12

Recommendation

Probiotics administration may be considered for the prevention of side effects and improving eradication rates in children undergoing therapy for *H. pylori*.

The recommended strains include *S. boulardii* CNCM I-745 and others for which the quality of evidence is weak.

Strength of recommendation: weak for SB

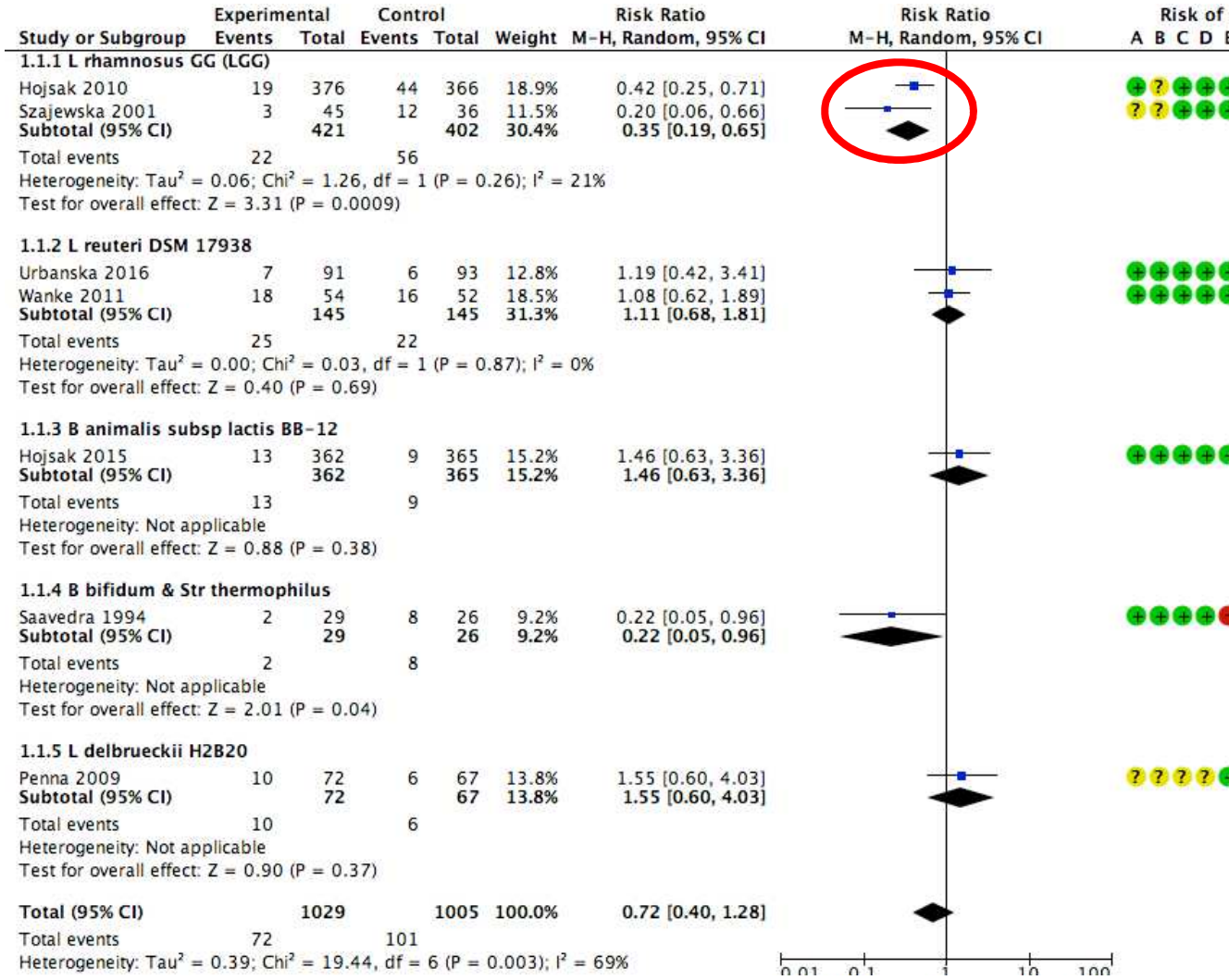
Nosocomial diarrhea

robiotics for the prevention of nosocomial iarrhea

GG administration reduced the risk rom 13.9% to 5.2%; NNT 12

f probiotics are considered the WG ecommends using LGG (at least 10^9 CFU/day, for the duration of hospital tay)

Hojsak I et al. JPGN 2017 (in press)



Other strains used in nosocomial diarrhea prevention

PROBIOTIC STRAIN	STUDIES IN SUPPORT	RECOMMENDATION
L. reuterii DSM 17938	2 RCTs	Not recommended
B. Animalis Subsp Lactis (BB-12)	1 RCT	Insufficient data
L. delbrueckii	1 RCT	Insufficient data
B. bifidum ans Str. Thermophilus	1 RCT	Insufficient data

Recommendation

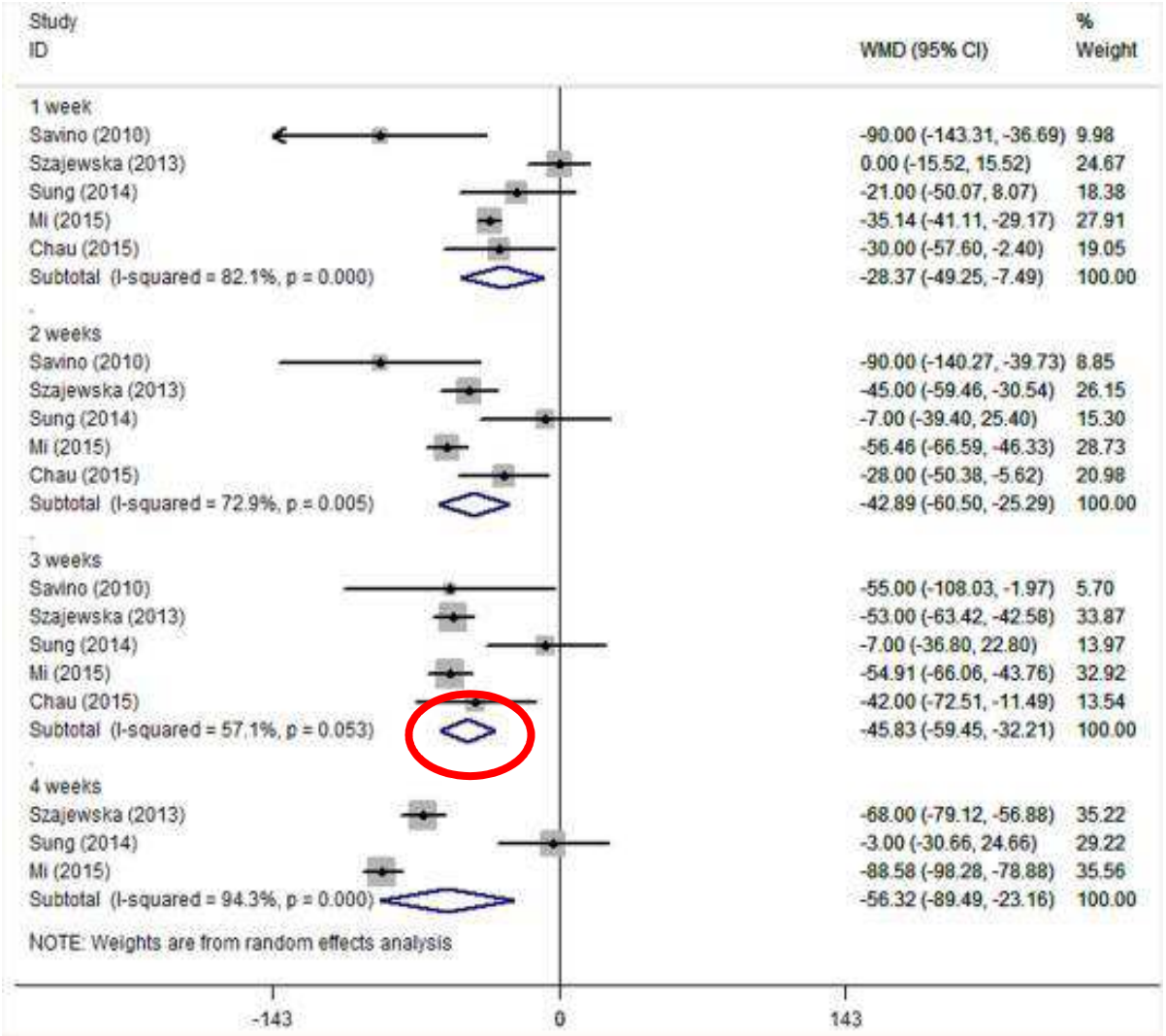
Upon evaluation of local conditions and risk factors, probiotics may be considered to prevent hospital-acquired intestinal infections and diarrhea on a case by case basis in children admitted to hospital.

Although the evidence remains weak, *L. rhamnosus GG* is the strain recommended for this indication.

Strength of recommendation: weak for LGG

Infantile colics

Infant colic: Systematic review of *L. reuteri* DSM 17938 in breast-fed infants



At 3 weeks LR administration (at least $1X10^8$ CFU/day) reduced daily crying time (pooled MD) with -55.1 (-64.4 to -47.2) min/day

Harb T et al. JPGN 2016;62:668-86

Recommendation

Probiotic administration may be considered for the treatment of infantile colic.

At present, the recommended strain is *L. reuteri* DSM 17938, for which the quality of evidence is weak.

Strength of recommendation: weak for LR

Functional intestinal disorders

Recommendation

Based on available data, there is insufficient evidence to recommend probiotics in the treatment of functional intestinal disorders.

Strength of recommendation: weak

Inflammatory bowel diseases (IBD)

Recommendation

There is no strong evidence supporting the treatment of IBD with probiotics.

Only in pouchitis, probiotic therapy may be considered based on evaluation of individual cases. At present, the recommended probiotic preparation is VSL#3 for which the quality of evidence is weak.

Strength of recommendation: weak

Necrotizing enterocolitis (NEC)

Severe NEC: Systematic review and meta-analysis

27 RCTs, n=8535

Risk Ratio: 0.57

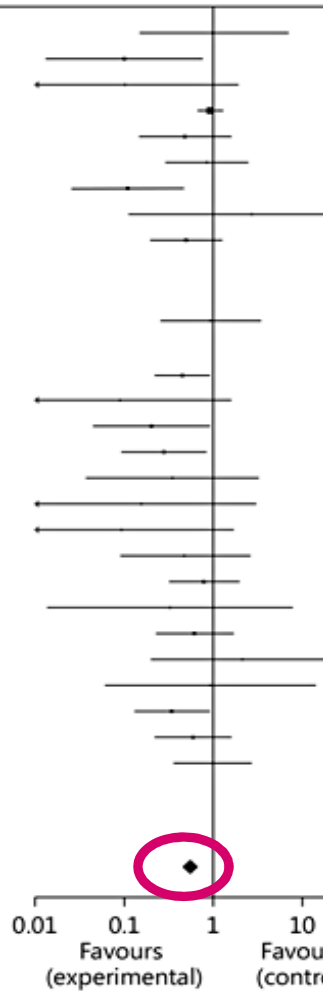
(0.47 to 0.70)

NNT=51

Study or subgroup	Experimental, *n* events	Experimental, *n* total	Control, *n* events	Control, *n* total	Weight, %	Risk ratio M-H, fixed (95% CI)
Al-Hosni [19], 2012 (USA)	2	50	2	51	0.8	1.02 [0.15, 6.96]
Bin-Nun [20], 2005 (Israel)	1	72	10	73	3.9	0.10 [0.01, 0.77]
Braga [21], 2011 (Brazil)	0	119	4	112	1.8	0.10 [0.01, 1.92]
Costeloe [22], 2016 (UK)	61	650	66	660	25.6	0.94 [0.67, 1.31]
Dani [23], 2002 (Italy)	4	295	8	290	3.2	0.49 [0.15, 1.61]
Demirel [24], 2013 (Turkey)	6	135	7	136	2.7	0.86 [0.30, 2.50]
Dilli [25], 2015 (Turkey)	2	100	18	100	7.0	0.11 [0.03, 0.47]
Dutta [26], 2015 (India)	1	38	0	35	0.2	2.77 [0.12, 65.82]
Fernandez-Carrocera [27], 2013 (Mexico)	6	75	12	75	4.7	0.50 [0.20, 1.26]
Fuji [28], 2006 (Japan)	0	11	0	8		not estimable
Hays [29], 2015 (France)	8	145	3	52	1.7	0.96 [0.26, 3.47]
Jacobs [30], 2013 (Australia and New Zealand)	11	548	24	551	9.4	0.46 [0.23, 0.93]
Kanic [31], 2015 (Slovenia)	0	40	5	40	2.1	0.09 [0.01, 1.59]
Lin [32], 2005 (Taiwan)	2	180	10	187	3.8	0.21 [0.05, 0.94]
Lin [33], 2008 (Taiwan)	4	217	14	217	5.5	0.29 [0.10, 0.85]
Manzoni [34], 2006 (Italy)	1	39	3	41	1.1	0.35 [0.04, 3.23]
Manzoni [35], 2009 (Italy)	0	151	3	168	1.3	0.16 [0.01, 3.05]
Manzoni [36], 2014 (Italy)	0	238	5	247	2.1	0.09 [0.01, 1.70]
Mihatsch [37], 2010 (Germany)	2	91	4	89	1.6	0.49 [0.09, 2.60]
Oncel [38], 2014 (Turkey)	8	200	10	200	3.9	0.80 [0.32, 1.99]
Patole [39], 2014 (Australia)	0	77	1	76	0.6	0.33 [0.01, 7.95]
Rojas [40], 2012 (Colombia)	6	176	10	184	3.8	0.63 [0.23, 1.69]
Rougé [41], 2009 (France)	2	45	1	49	0.4	2.18 [0.20, 23.21]
Saengtawesin [42], 2015 (Thailand)	1	31	1	29	0.4	0.94 [0.06, 14.27]
Samanta [43], 2009 (India)	5	91	15	95	5.7	0.35 [0.13, 0.92]
Sari [44], 2011 (Turkey)	6	110	10	111	3.9	0.61 [0.23, 1.61]
Serce [45], 2013 (Turkey)	7	104	7	104	2.7	1.00 [0.36, 2.75]
Tewari [46], 2015 (India)	0	123	0	121		not estimable
Totsu [47], 2014 (Japan)	0	153	0	130		not estimable
Total (95% CI)		**4,304**		**4,231**	**100.0**	**0.57 [0.47, 0.70]**
Total events	146		253			

Heterogeneity: $\chi^2 = 32.27$, df = 25 ($p = 0.15$), $I^2 = 23\%$

Test for overall effect: Z = 5.57 ($p < 0.00001$)



rmyshi E et al.,Neonatology 2016

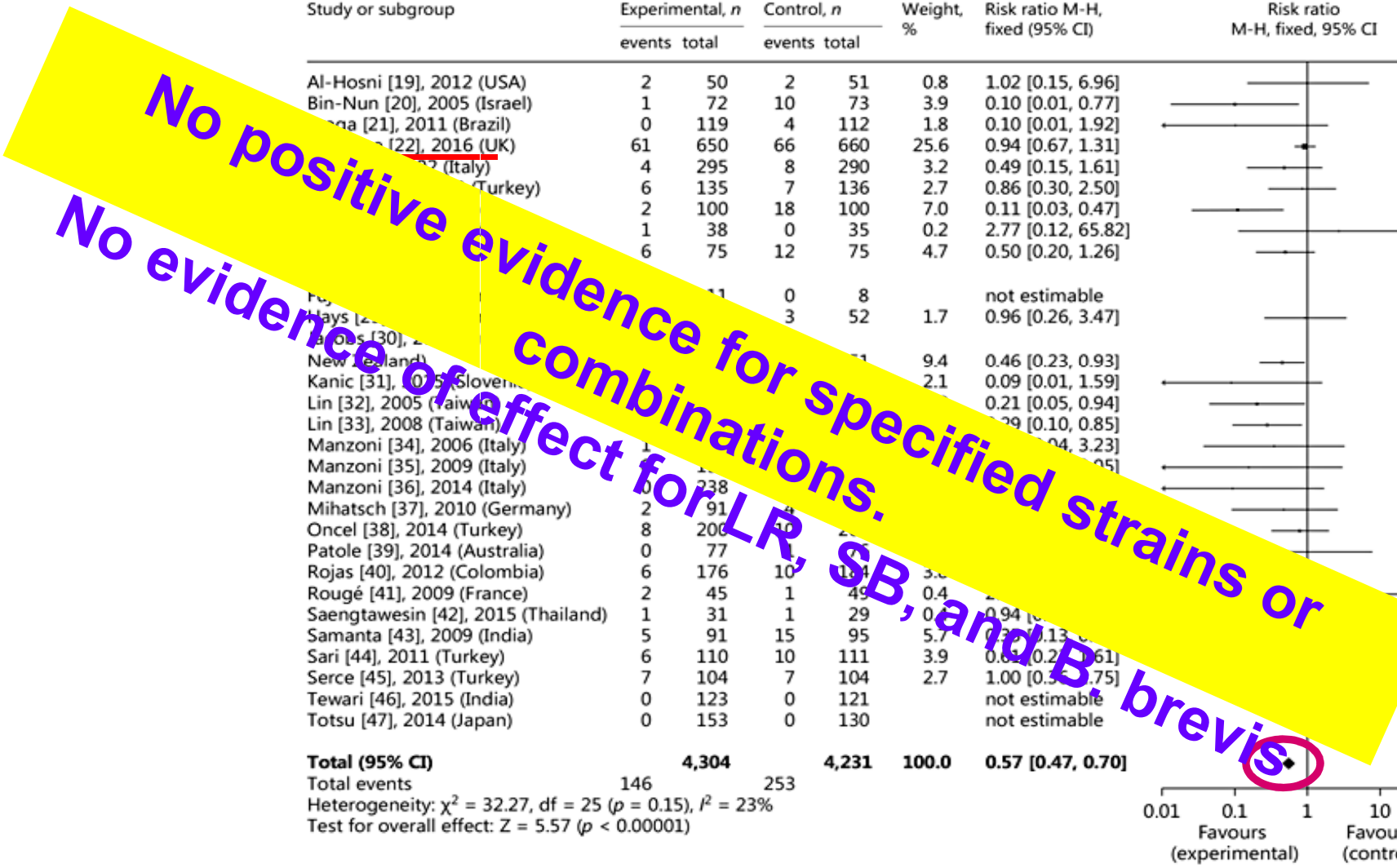
Severe NEC: Systematic review and meta-analysis

27 RCTs, n=1653

Risk Ratio: 0.57

(0.47 to 0.70)

NNT=51



rmyshi E et al.,Neonatology 2016

Recommendation

Probiotics may be considered for prevention of NEC in high-risk populations as there is evidence that the risk of NEC and the associated mortality may be reduced.

However, since there is no agreement on strains, indications and scheme, the decision should be left to the physician and discussed with parents, in the light of current evidence.

Strength of recommendation: weak

One size may not fit all

- Countries, climate, culture, politics
- Conditions, diseases, indications
- Socioeconomic status
- Nutrition, diet
- Microbiomes, pathogens
- Antibiotic exposure
- Vaccination

Take home messages

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

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

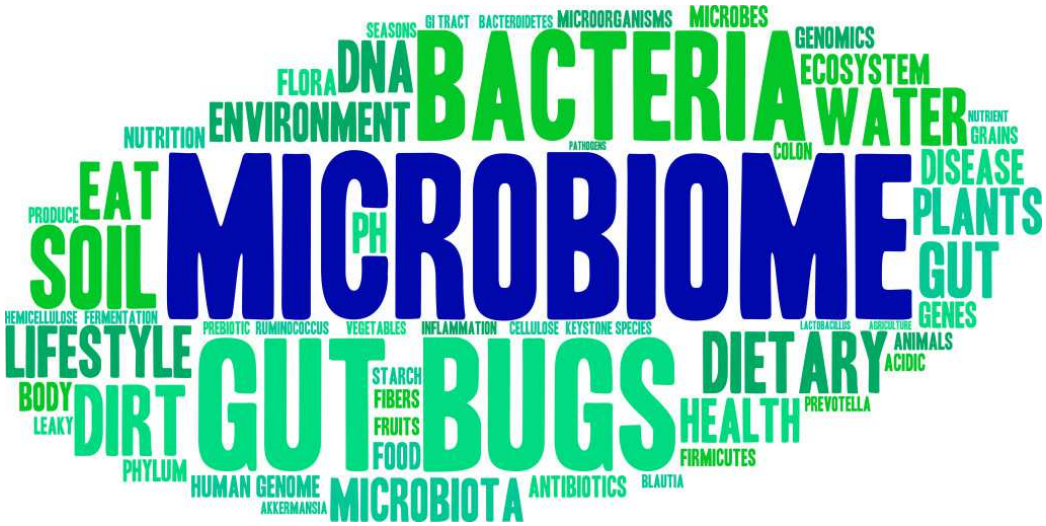
Many other probiotics strains cannot be recommended because of insufficient data or insufficient data on quality

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