"Key Scientific Drivers Behind Probiotic and Prebiotic Applications"
International Symposium of the International Scientific Association of Probiotics and Prebiotics
June 5-6, 2018, Furama Riverfront Hotel, Singapore

Using Probiotics and Prebiotics in Pediatric Medicine

Michael CABANA
USA

Organised by: INTERNATIONAL SCIENTIFIC ASSOCIATION OF PROBIOTICS AND PREBIOTICS
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Using Probiotics and Prebiotics in Pediatric Medicine

June 5, 2018
International Scientific Association for Probiotics and Prebiotics Meeting
Singapore

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Agenda

- Review Common Clinical Examples (& Tradeoffs) with Probiotic Use
- Why Probiotic and Prebiotic Research in Pediatrics is Challenging
- Potential Strategies


SNELLEN (SLOAN) LETTERS
FOR TESTING AT 10 FEET
K H O R Z
C K Z D V O
O Z N R H V C
R K C S Z H V D
S D K H C O R C V N
H O C Z R K D S V N
N Z C O S D K V R H
R H S D O V R N H Z
Z S V D K H N O R C
GOOD-LITE
in USA
UCSF Benioff Children's Hospita
After Hours at Mt Zion is closing
June 30, 2016
Beginning July 1, 2016, we have partnered with the UCSF
Children's Physicians Pediatric Evening Referral Clinic
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Pediatric Primary Care at Mt Zion
2330 Post Street, 3rd floor – Suite 320
Monday to Friday 8:00am – 5:00pm
Pediatric Acute Care at Mt Zion
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Monday to Friday 8:00am – 5:00pm
Pediatric Evening Referral Clinic
3490 California Street, Suite 200
Monday-Friday 6:00pm – 9:30pm
Weekends/Holidays 8:30am – 9:30pm
Please call (415) 885-7478 for an appointment or advice


Nurse
Station A

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A 5 year-old boy with fever, emesis x 1 day (now resolved) and loose (non-bloody) stools x 2 days

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What is the evidence that some probiotic strains are effective for the treatment of acute viral gastroenteritis?

A. Excellent evidence; I don't know why we don't do this all the time
B. Good evidence; but the clinical impact is limited
C. Good evidence; but it only seems to work in Boston
D. No evidence; There are no probiotic strains that have any clinical effect on acute gastroenteritis

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What is the evidence that some probiotic strains are effective for the treatment of acute viral gastroenteritis?

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C. Good evidence; but it only seems to work in Boston

D. No evidence; There are no probiotic strains that have any clinical effect on acute gastroenteritis

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Probiotics for Infectious Diarrhea

- 63 trials; n= 8014 patients (mostly children)
- Probiotics not associated with adverse effects.
- Nearly all studies reported a shortened duration of diarrhea

Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database of Systemic Reviews. DOI: 10.1002/14651858.CD003048.pub3

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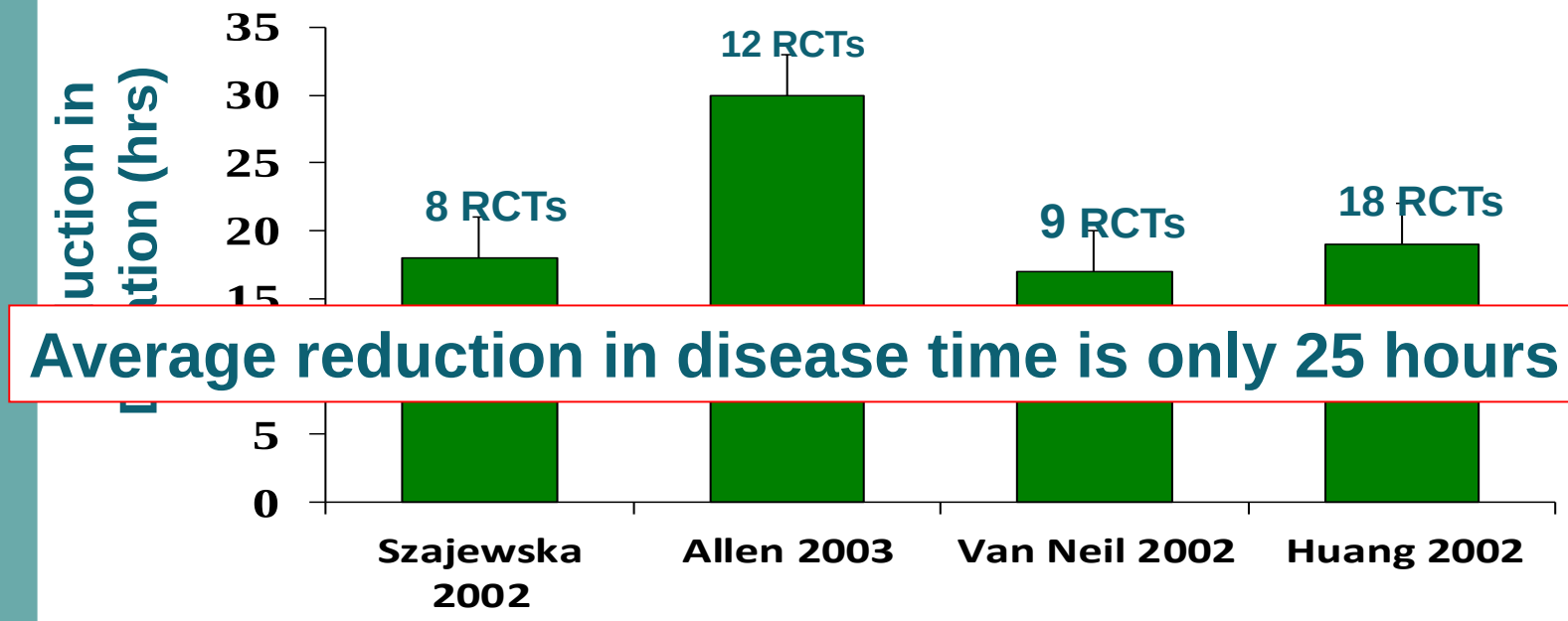
Treatment of Acute Diarrhea:
Meta Analysis Results



Average reduction in disease time is only 25 hours

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Infectious Diarrhea

- Most common scenario was rotavirus
- Strains most frequently cited clinically
  - *Lactobacillus casei* (LGG)
  - *Saccharomyces boulardii*
  - *Enterococcus LAB* SF68
- Published effect is modest—only 25 hours difference

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A 5 year-old girl with otitis media, will start a 10 day course of amoxicillin. Should you start a probiotic supplement to prevent antibiotic associated diarrhea?

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Would you recommend a probiotic supplement to prevent antibiotic associated diarrhea in this case?

A. Yes, Definitely
B. Yes, Probably
C. No, but I would not object to the parent initiating it
D. No and I would object to the parent initiating it

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Would you recommend a probiotic supplement to prevent antibiotic associated diarrhea in this case?

A. Yes, Definitely

B. Yes, Probably

C. No, but I would not object to the parent initiating it

D. No and I would object to the parent initiating it

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CLINICAL REVIEW

CLINICIAN'S CORNER

Probiotics for the Prevention and Treatment of Antibiotic-Associated Diarrhea

A Systematic Review and Meta-analysis

Susanne Hempel, PhD
Sydne J. Newberry, PhD
Alicia R. Maher, MD
Zhen Wang, PhD
Jeremy N. V. Miles, PhD
Roberta Shanman, MS
Breanne Johnsen, BS
Paul G. Shekelle, MD, PhD

Context Probiotics are live microorganisms intended to confer a health benefit when consumed. One condition for which probiotics have been advocated is the diarrhea that is a common adverse effect of antibiotic use.

Objective To evaluate the evidence for probiotic use in the prevention and treatment of antibiotic-associated diarrhea (AAD).

Data Sources Twelve electronic databases were searched (DARE, Cochrane Library of Systematic Reviews, CENTRAL, PubMed, EMBASE, CINAHL, AMED, MANTIS, TOXLINE, ToxFILE, NTIS, and AGRICOLA) and references of included studies and reviews were screened from database inception to February 2012, without language restriction.

Study Selection Two independent reviewers identified parallel randomized controlled trials (RCTs) of probiotics (*Lactobacillus, Bifidobacterium, Saccharomyces, Streptococcus, Enterococcus*, and/or *Bacillus*) for the prevention or treatment of AAD.

Data Extraction Two independent reviewers extracted the data and assessed trial quality.

Results A total of 82 RCTs met inclusion criteria. The majority used *Lactobacillus-*

THE USE OF ANTIBIOTICS THAT DISturb the gastrointestinal flora is associated with clinical symptoms such as diarrhea, which occurs in as many as 30% of patients.[1,2] Symptoms range from mild and

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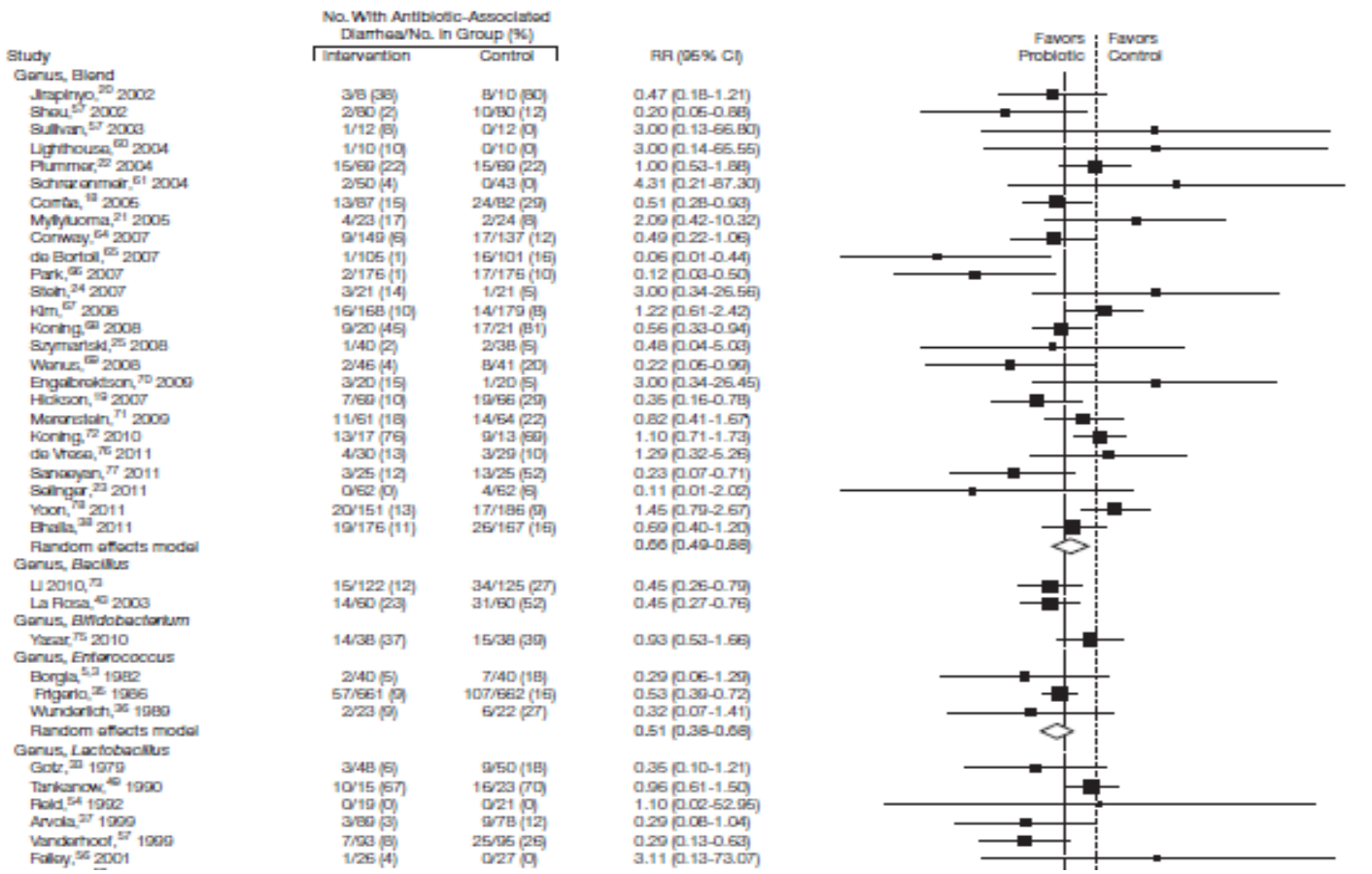
Figure. Efficacy Results of Probiotic Use by Study



Overall RR=0.58 reported in meta-analysis; NNT=13

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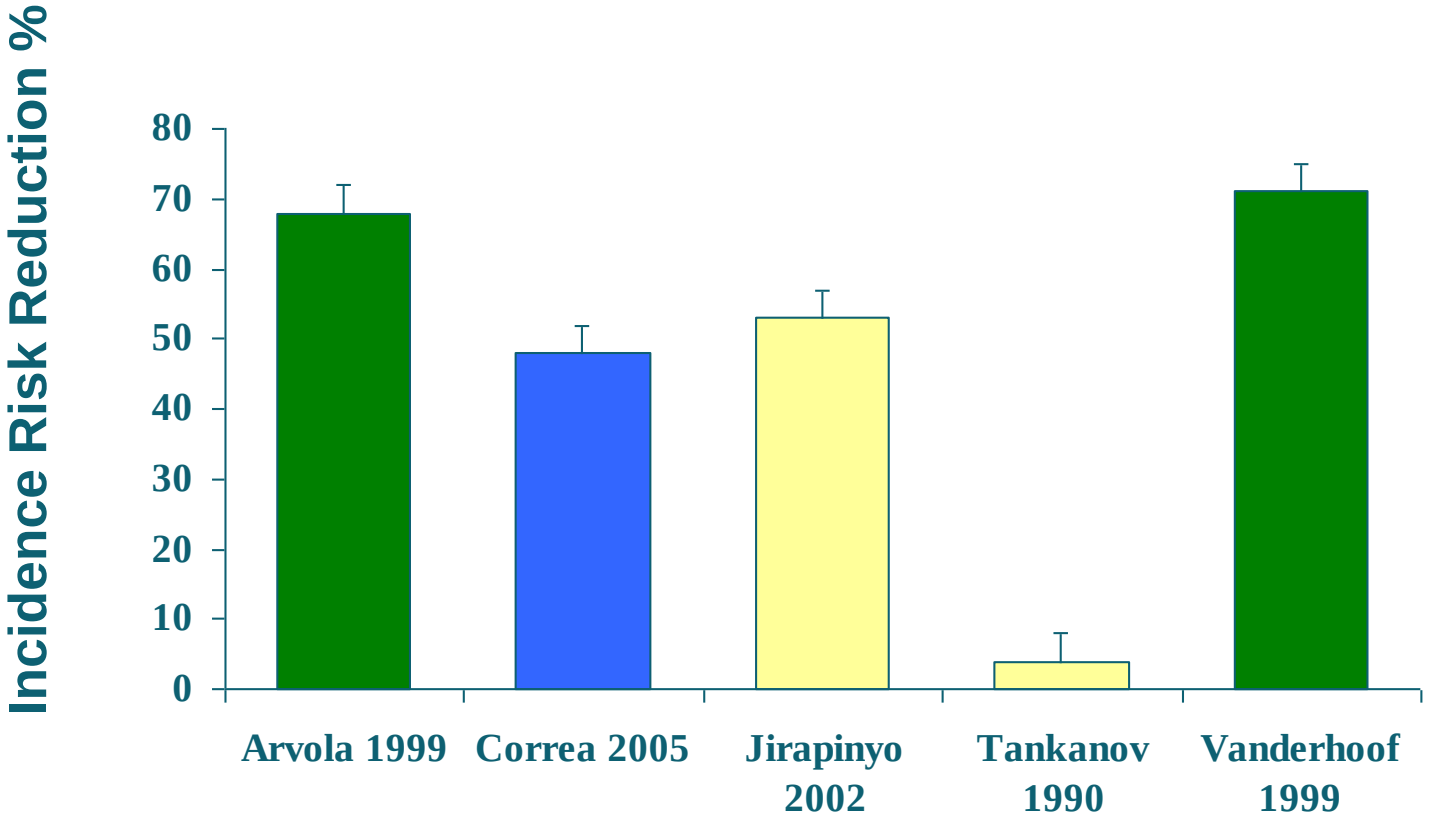
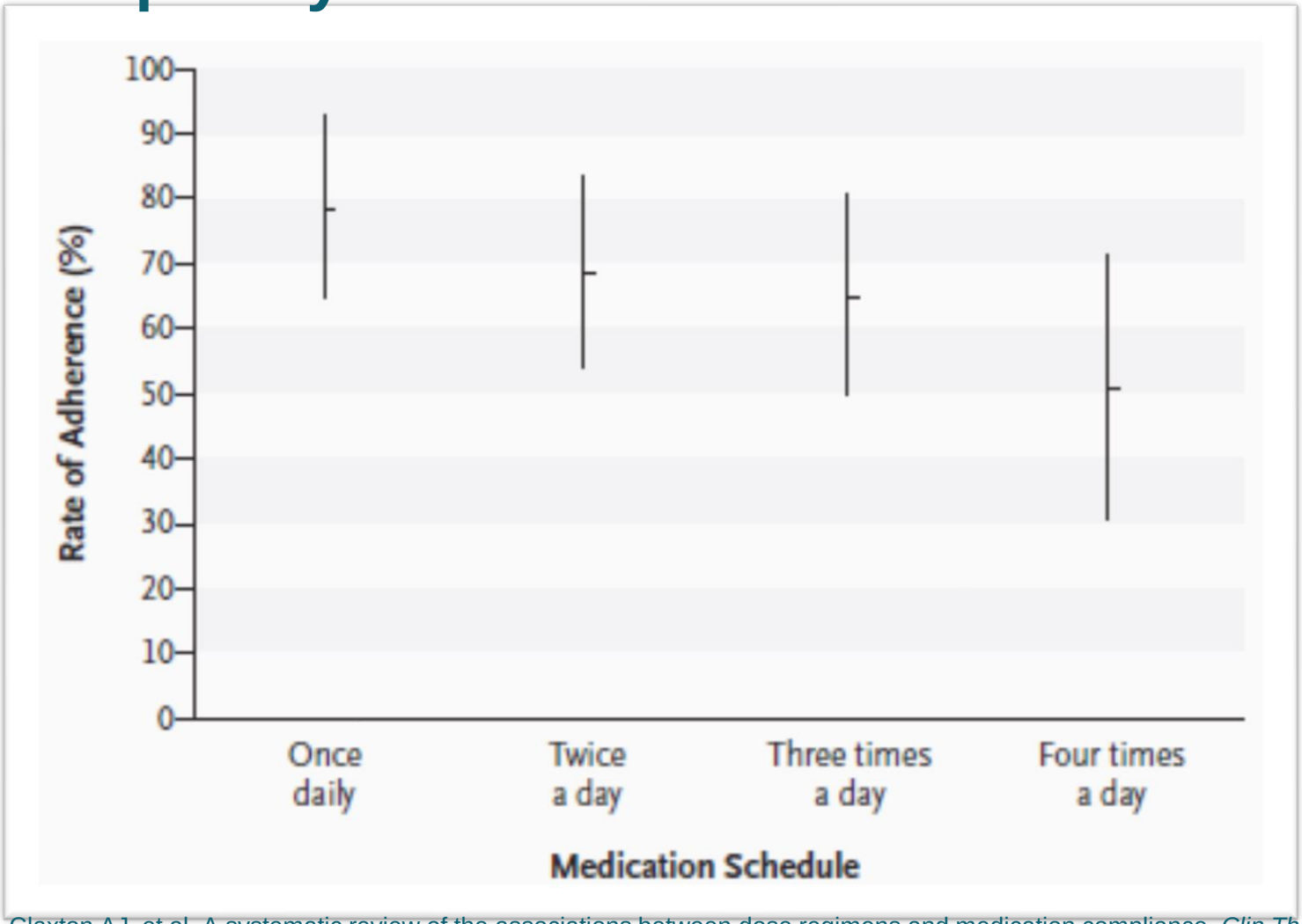
Reduction in Relative Risk of Antibiotic Associated Diarrhea



Adherence decreases as regimen complexity increases



Claxton AJ, et al. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther*. 2001; 23: 1296-1310. Osterberg L, et al. Adherence to medication. *NEJM.* 2005; 353:487-97.

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Antibiotic-Associated Diarrhea Summary

- Prevention of antibiotic-associated diarrhea is well documented; however, it is highly dependent on patient adherence
- Strains frequently cited clinically
  - LGG
  - *Saccharomyces boulardii*

Szajewska H, Dziechciarz P, Mrukowicz J. *Aliment Pharmacol Ther.* 2006 Jan 15;23(2):217-27.

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A 5 month-old, breastfed boy is about to start child care. Parents ask if they should start a probiotic supplement to prevent illness and missed days from child care.

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Would you recommend a probiotic supplement for a 5 month old breastfed boy about to start daycare?

A. Yes
B. Maybe
C. No, but I would not object to the parent initiating it
D. No and I would object to the parent initiating it

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Would you recommend a probiotic supplement for a 5 month old breastfed boy about to start daycare?

A. Yes
B. Maybe
C. No, but I would not object to the parent initiating it
D. No and I would object to the parent initiating it

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Probiotics and Child Care Absence Due to Infections: A Randomized Controlled Trial

Rikke Pilmann Laursen, MSc, Anni Larnkjær, PhD, Christian Ritz, PhD, Hanne Hauger, MSc, Kim Fleischer Michaelsen, DMSc, Christian Mølgaard, PhD

OBJECTIVES: The risk of infections is higher in children attending child care compared with children cared for at home. This study examined the effect of a combination of probiotics on absence from child care because of respiratory and gastrointestinal infections in healthy infants aged 8 to 14 months at the time of enrollment in child care.

METHODS: The ProbiComp study was a randomized, double-blind, placebo-controlled study. A total of 290 infants were randomly allocated to receive a placebo or a combination of *Bifidobacterium animalis* subsp *lactis* and *Lactobacillus rhamnosus* in a dose of 10^9 colony-forming units of each daily for a 6-month intervention period. Absence from child care, occurrence of infant symptoms of illness, and doctor visits were registered by the parents using daily and weekly Web-based questionnaires.

RESULTS: Median absence from child care was 11 days (interquartile range: 6–16). Intention-to-treat analysis showed no difference between the probiotics and placebo groups ($P = .19$). Additionally, there was no difference in any of the secondary outcomes between groups; the number of children with doctor-diagnosed upper or lower respiratory tract infections, the number of doctor visits, antibiotic treatments, occurrence and duration of diarrhea, and

Probiotics in Child Care

- Daily administration of *Bifidobacterium animalis* subsp. *lactis* (BB-12R) and *Lactobacillus rhamnosus* (LGGR) x 6 months
- No difference in
  - Days absent from day care in healthy infants
  - Upper or lower respiratory tract infections
  - Gastroenteritis/diarrhea episodes

Laursen RP, et al. Probiotics and Child Care Absence Due to Infections: A Randomized Controlled Trial. *Pediatrics.* 2017;140(2):e20170735

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Child Care Studies tend to be positive when…

- There is minimal or no breastfeeding
  - In the Laursen et al. study, almost half (47%) the infants enrolled were breastfed
- Children are older (> 3 years of age)
  - In the Laursen et al. study, children were between 8 and 13 months of age
- Thus, would not recommend for a 5 month-old; would encourage continued breastfeeding

Hojsak I, et al. Lactobacillus GG in the prevention of gastrointestinal and respiratory tract infections in children who attend day care centers: A randomized, double-blind, placebo-controlled trial. *Clin Nutr*. 2010;29(3):312-316. Garaiova I, et al. Probiotics and vitamin C for the prevention of respiratory tract infections in children attending preschool: a randomised controlled pilot study. *Eur J Clin Nutr*. 2015;69(3):373-379. Weizman Z, et al. Effect of a Probiotic Infant Formula on Infections in Child Care Centers: Comparison of Two Probiotic Agents. *Pediatrics*. 2005;115(1):5-9. Smerud HK, et al. Effect of a probiotic milk product on gastrointestinal and respiratory infections in children attending day-care. *Microb Ecol Health Dis*. 2008;20(2):80-85.

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Child Care Infection Prevention

- Strains frequently cited
  - *Lactobacillus rhamnosus GG* (LGG)
  - *L. acidophilus* LA-5
  - *Bifidobacterium* Bb-12
  - *Lactobacillus reuteri* (American Type Culture Collection 55730)

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A 5 week-old boy presents with crying for 5 hours/day for the last week. He is well-fed and gaining weight. Physical examination is negative. Based on the negative history and examination you suspect colic.

Should you start a probiotic supplement?

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L reuteri DSM 17938

- At least five randomized controlled trials for *L reuteri*
  - Canada, Poland, Italy, China, Australia, United States
- Overall results, suggest positive benefit
- One negative study (Australia)
- One underpowered study (United States)

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Lactobacillus reuteri to Treat Infant Colic: A Meta-analysis

Valerie Sung, PhD,[a] Frank D'Amico, PhD,[b,c] Michael D. Cabana, MD,[d] Kim Chau, PhD,[e] Gideon Koren, MD,[e] Francesco Savino, PhD,[f] Hania Szajewska, MD,[g] Girish Deshpande, MSc,[h] Christophe Dupont, PhD,[i] Flavia Indrio, MD,[j] Silja Mentula, PhD,[k] Anna Partty, PhD,[l] Daniel Tancredi, PhD[m]

abstract

CONTEXT: *Lactobacillus reuteri* DSM17938 has shown promise in managing colic, but conflicting study results have prevented a consensus on whether it is truly effective.

OBJECTIVE: Through an individual participant data meta-analysis, we sought to definitively determine if *L reuteri* DSM17938 effectively reduces crying and/or fussing time in infants with colic and whether effects vary by feeding type.

DATA SOURCES: We searched online databases (PubMed, Medline, Embase, the Cumulative Index to Nursing and Allied Health Literature, the Database of Abstracts of Reviews of Effects, and Cochrane), e-abstracts, and clinical trial registries.

STUDY SELECTION: These were double-blind randomized controlled trials (published by June 2017) of *L reuteri* DSM17398 versus a placebo, delivered orally to infants with colic, with outcomes of infant crying and/or fussing duration and treatment success at 21 days.

DATA EXTRACTION: We collected individual participant raw data from included studies modeled simultaneously in multilevel generalized linear mixed-effects regression models.

RESULTS: Four double-blind trials involving 345 infants with colic (174 probiotic and 171 placebo) were included. The probiotic group averaged less crying and/or fussing time than the placebo group at all time points (day 21 adjusted mean difference in change from baseline [minutes] −25.4 [95% confidence interval (CI): −47.3 to −3.5]). The probiotic group was almost twice as likely as the placebo group to experience treatment success at all time

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Why was the Australian study different?

- Infants were older
- Use of proton pump inhibitors and H2 blockers
- Use of infant formula

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Patient with colic

- Best evidence is for *L. reuteri* DSM 17938
- Tends to work best in the following situations
  - Breastfed infants
  - Babies not on any GI medications (e.g., randitidine)
  - Babies that start early in the course of symptoms

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During a pre-natal visit, soon-to-be parents ask if they should start a probiotic supplement immediately after birth to prevent colic.

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Would you start a probiotic supplement on a healthy infant for colic prophylaxis?

A. Yes; there is good evidence
B. No; there is not enough evidence
C. No; there are no studies on this topic
D. This is a trick question

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Would you start a probiotic supplement on a healthy infant for colic prophylaxis?

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Research

Original Investigation

Prophylactic Use of a Probiotic in the Prevention of Colic, Regurgitation, and Functional Constipation
A Randomized Clinical Trial

Flavia Indrio, MD; Antonio Di Mauro, MD; Giuseppe Riezzo, MD; Elisa Civardi, MD; Cristina Intini, MD; Luigi Corvaglia, MD; Elisa Ballardini, MD; Massimo Bisceglia, MD; Mauro Cinquetti, MD; Emanuela Brazzoduro, MD; Antonio Del Vecchio, MD; Silvio Tafuri, MD, PhD; Ruggiero Francavilla, MD, PhD

IMPORTANCE Infantile colic, gastroesophageal reflux, and constipation are the most common functional gastrointestinal disorders that lead to referral to a pediatrician during the first 6 months of life and are often responsible for hospitalization, feeding changes, use of drugs, parental anxiety, and loss of parental working days with relevant social consequences.

OBJECTIVE To investigate whether oral supplementation with *Lactobacillus reuteri* DSM 17938 during the first 3 months of life can reduce the onset of colic, gastroesophageal reflux, and constipation in term newborns and thereby reduce the socioeconomic impact of these conditions.

DESIGN A prospective, multicenter, double-masked, placebo-controlled randomized clinical trial was performed on term newborns (age <1 week) born at 9 different neonatal units in Italy between September 1, 2010, and October 30, 2012.

Editorial page 204

Journal Club Slides a
jamapediatrics.com

CME Quiz at
jamanetworkcme.co
CME Questions page

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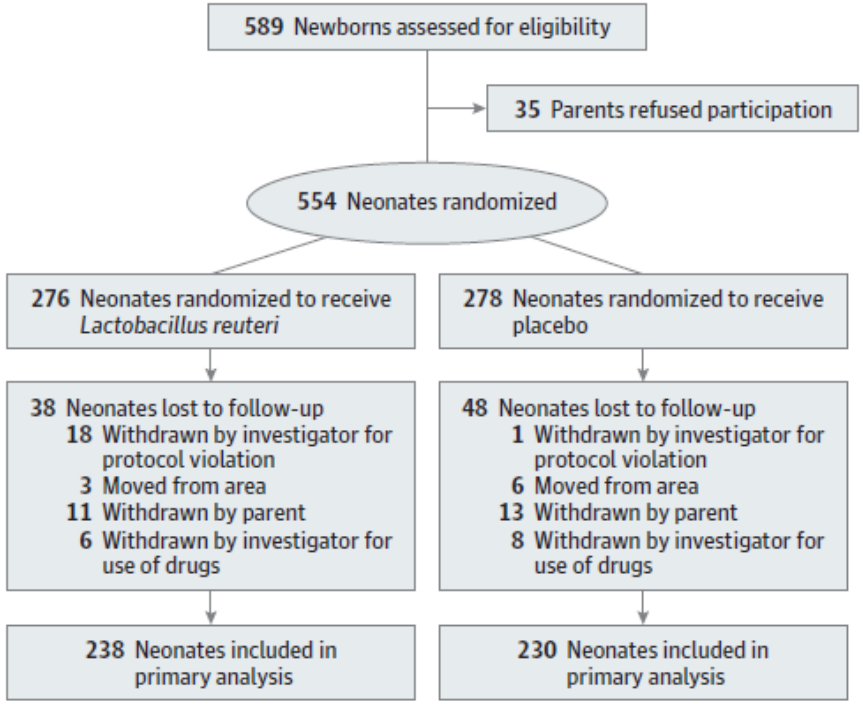
Indrio, at al. 2014



- Design: Double-blind, randomized controlled trial
- Subjects: 554 newborns
- Intervention: 1×10^8 colony-forming units of *L reuteri* DSM 17938 or placebo for 90 days
- Results: Crying time at 3 months of life was lower in the intervention group (38 minutes/day versus 71 minutes/day; $p<0.01$)

Indrio F. *JAMA-Pediatrics*. 2014.

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Colic Summary

- *L. reuteri* DSM 17938 may also be effective in the prevention of colic.
- However, only one randomized controlled trial
- Prevalence of colic was high (25%)
- You may be treating lots of infants who don't necessarily need to be treated

Indrio F. *JAMA-Pediatrics*. 2014.

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Probiotics and Primary Prevention for Atopic Dermatitis

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During a pre-natal visit, soon-to-be parents ask if they should start a probiotic supplement immediately after birth to prevent eczema?

Kalliomaki, at al. 2001

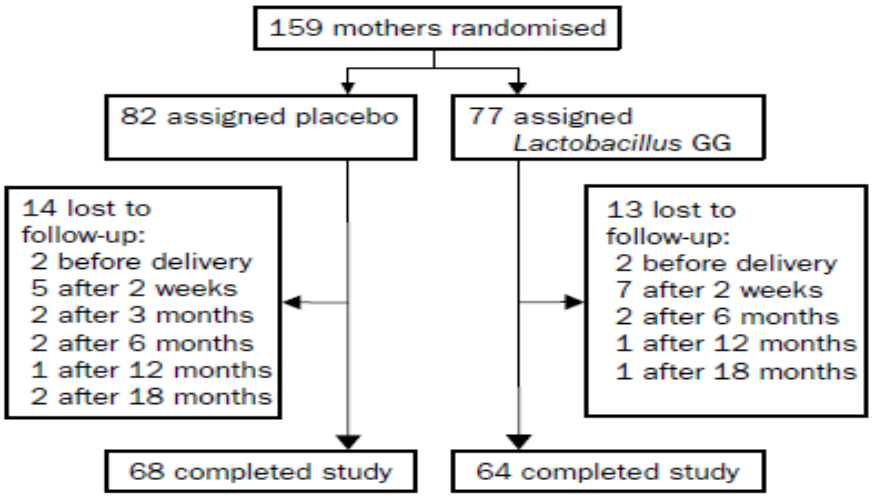

Figure 1: **Trial profile**

- Design: Double-blind, randomized controlled trial
- Subjects: 159 mothers & children
- Intervention: *Lactobacillus GG* supplementation (10^{10} CFU) for 1 month prenatally, and 6 months post-natally for infants
- Results: Decreased likelihood of atopic eczema in the probiotic group (RR=0.51 [95%CI: 0.32,0.84])

Kalliomaki M, et al. Probiotics in primary prevention of atopic disease: a randomized placebo-controlled trial. *Lancet*. 2001;357:1076-1079.

Study (Year)	Treatment	Population	Results
Kalliomaki (2003)	1 x 10^10 CFU of *LGG* daily Started 2 to 4 weeks before delivery and continued 6 months postnatally **Mean breastfeeding duration=6.5 months**	107 Finnish mothers with atopic risk factors	Four-year follow-up of original cohort Decreased risk of atopic dermatitis (AD)
Kopp (2008)	5 x 10^9 CFU *LGG* twice a day Started 4 to 6 weeks before delivery and continued 6 months postnatally. f/u at 2 years of age **Mean breastfeeding duration=9.2 months**	105 German mothers with atopic risk factors	No difference in development of atopic dermatitis and no difference in severity.

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Early Probiotic Supplementation for Eczema and Asthma Prevention: A Randomized Controlled Trial

Michael D. Cabana, MD, MPH,[a,b,c] Michelle McKean, RD, MPH,[a] Aaron B. Caughey, MD, PhD,[d] Lawrence Fong, MD,[e] Susan Lynch, PhD,[e] Angela Wong, MD,[f] Russell Leong, MD,[g] Homer A. Boushey, MD,[e] Joan F. Hilton, ScD, MPH[b]

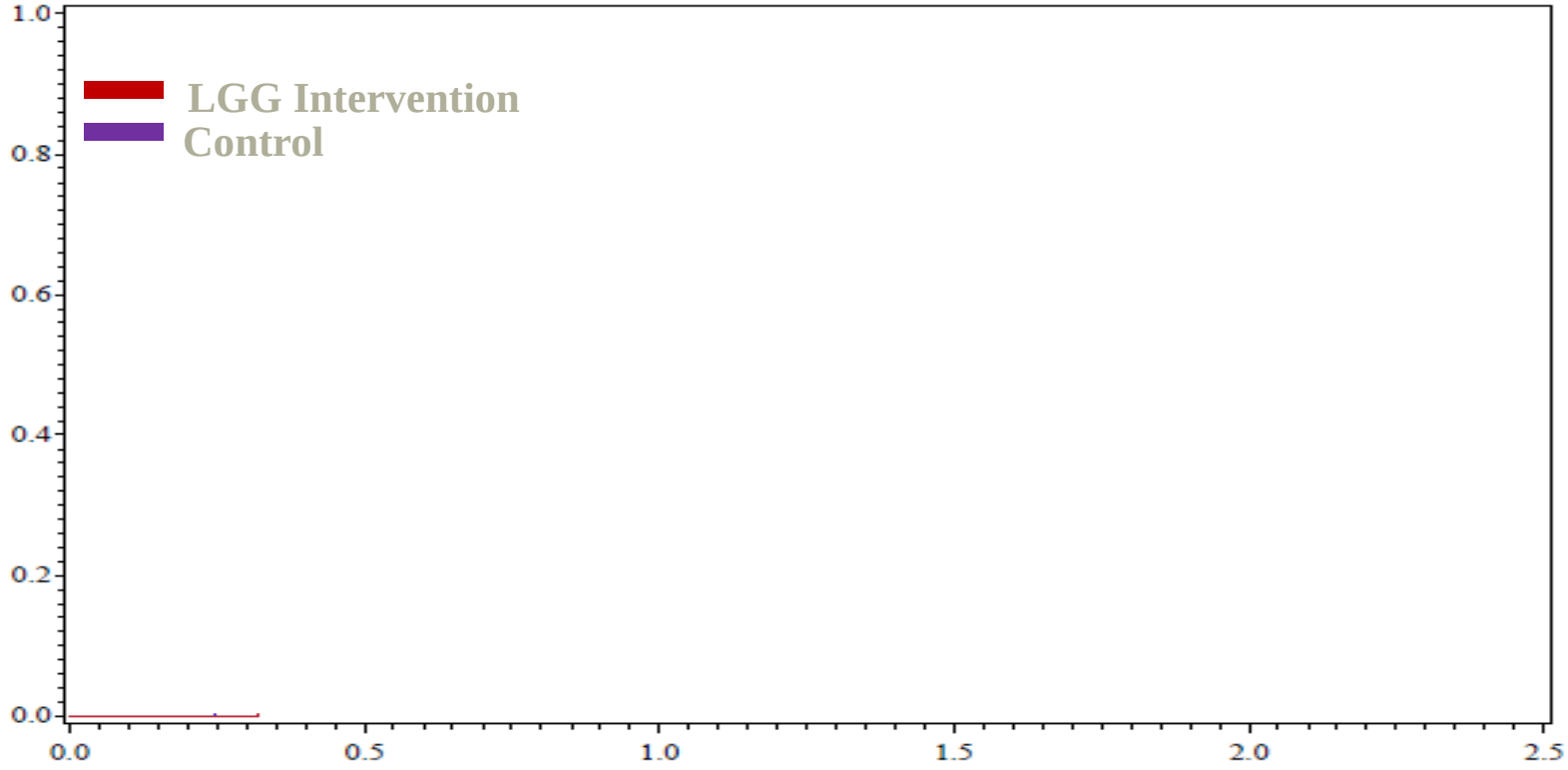
abstract

OBJECTIVES: To determine if probiotic administration during the first 6 months of life decreases childhood asthma and eczema.

METHODS: We conducted a randomized, double-blind controlled trial of *Lactobacillus rhamnosus* GG (LGG) supplementation on the cumulative incidence of eczema (primary end point) and asthma and rhinitis (secondary end points) in high-risk infants. For the first 6 months of life, intervention infants (n = 92) received a daily dose of 10 billion colony-forming units of LGG and 225 mg of inulin (Amerifit Brands, Cromwell, CT), and control infants (n = 92) received 325 mg of inulin alone. We used survival analysis methods to estimate disease incidences in the presence or absence of LGG and to estimate the efficacy of LGG in delaying or preventing these diseases.

RESULTS: Infants were accrued over a 6-year period (median follow-up: 4.6 years; 95% retention rate at 2 years). At 2 years of age, the estimated cumulative incidence of eczema was 30.9% (95% confidence interval [CI], 21.4%–40.4%) in the control arm and 28.7% (95% CI, 19.4%–38.0%) in the LGG arm, for a hazard ratio of 0.95 (95% CI, 0.59–1.53) (log-rank P = .83). At 5 years of age, the cumulative incidence of asthma was 17.4% (95% CI, 7.6%–27.1%) in the control arm and 9.7% (95% CI, 2.7%–16.6%) in the LGG arm, for a hazard ratio of 0.88 (95% CI, 0.41–1.87) (log-rank P = .25).

Cumulative Incidence of Eczema (n=184)

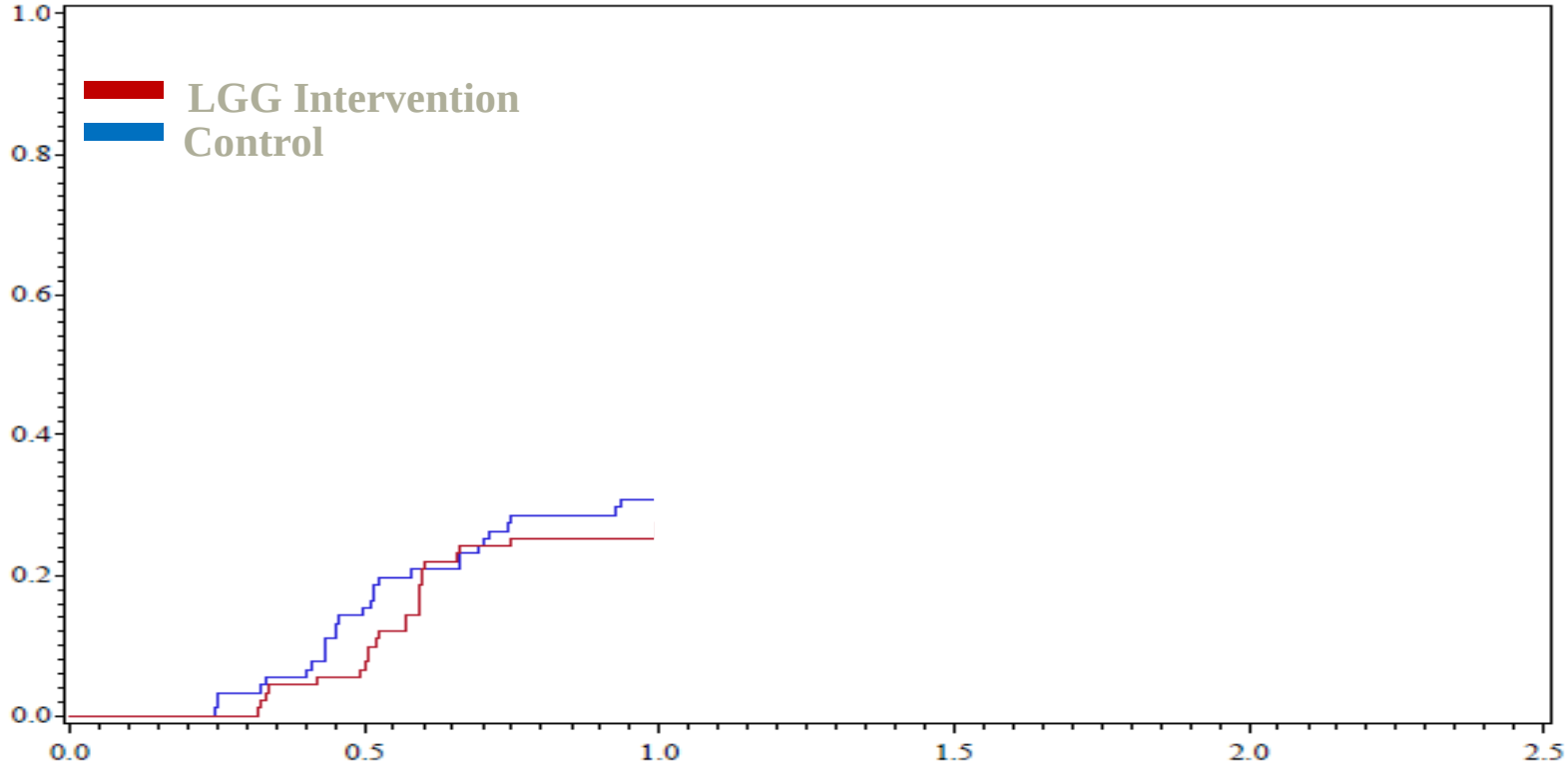


Number at Risk

Control	92
LGG	92

Cabana, et al. *Pediatrics*. 2017.

Cumulative Incidence of Eczema (n=184)

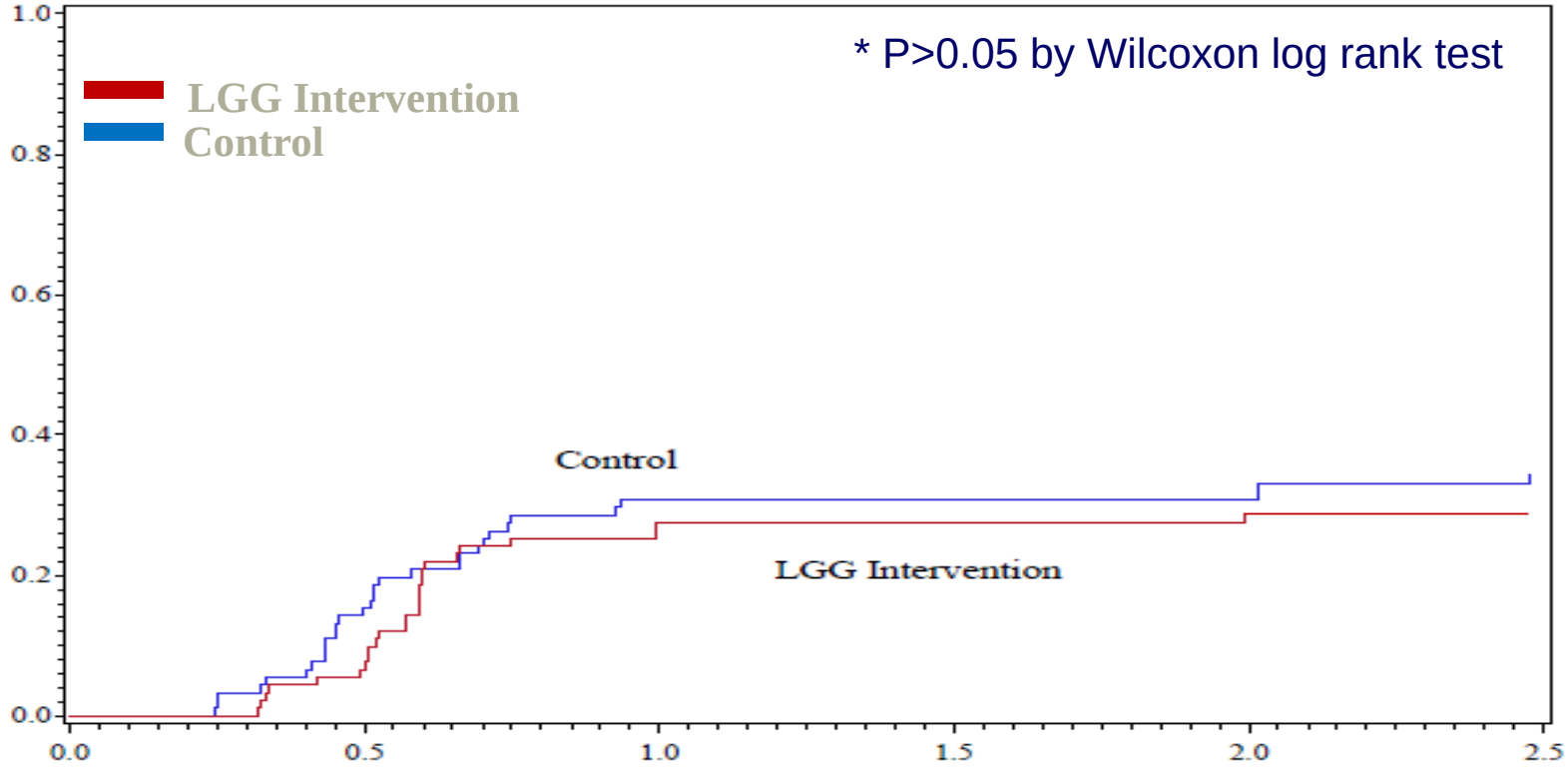


Number at Risk

Control	92	77	61
LGG	92	85	64

Cabana, et al. *Pediatrics*. 2017.

Cumulative Incidence of Eczema (n=184)



Number at Risk

Control	92	77	61	60	59	53
LGG	92	85	64	64	63	61

Cabana, et al. *Pediatrics*. 2017.

Eczema prevention

- Best studied probiotic is LGG
  - Successful in prenatal/postnatal study in Finland, but a negative study in Germany
  - Postnatal San Francisco study was negative
  - Both German and San Francisco studies had high rates of breastfeeding
-

Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergy. Cochrane Database Syst Review. 2018; Mar 28;(3):CD006474. doi: 10.1002/14651858.CD006474.pub3; Cabana, et al. *Pediatrics*. 2017.

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What about prebiotics?

Prebiotics & Eczema prevention

- Cochrane: “There is some evidence that a prebiotic supplement added to infant feeds may prevent eczema.”
  - Cochrane analysis suggests a reduction in eczema in 1218 infants analyzed in the early stages of life when supplemented with GOS/FOS (9:1 ratio; 8 g/L added to cow milk–based formula)
  - “Further research is needed before routine use of prebiotics can be recommended for prevention of allergy in formula fed infants.”
- Cuello-Garcia (2017): Reported a risk of developing eczema of RR: 0.68, 95% CI: 0.40 to 1.15

Cuello Garcia et al. Prebiotics for the prevention of allergies: A systematic review and meta-analysis of randomized controlled trials. Clin Exp Allergy 2017 Nov;47(11):1468-1477. doi: 10.1111/cea.13042. Osborn DA, Sinn JK. Prebiotics in infants for prevention of allergy. Cochrane Database Syst Review. 2018; Mar 28;(3):CD006474. doi: 10.1002/14651858.CD006474.pub3;

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Clinical Summary

- Even with good evidence, there are clinical tradeoffs to consider
  - 25 hours may be statistically significant, but not clinically significant for a family
  - Making a medication regimen more complicated may adversely affect overall adherence
- In many situations, the clinical evidence is mixed (eczema prevention, colic treatment) or limited to one randomized trial (colic prevention)

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Pediatric Care Applications

Diarrhea

Treatment — **Positive**

Antibiotic associated diarrhea

Colic

Treatment

Prevention

Eczema

Prevention

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Pediatric Care Applications

Diarrhea

Treatment	**Positive**
Antibiotic associated diarrhea	

Colic

Treatment	**Positive**
Prevention	

Eczema

Prevention

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Pediatric Care Applications

Diarrhea	
Treatment	**Positive**
Antibiotic associated diarrhea	
Colic	
Treatment	**Positive**
Prevention	**Incomplete**
Eczema	
Prevention	

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Pediatric Care Applications

Diarrhea	
Treatment	**Positive**
Antibiotic associated diarrhea	
Colic	
Treatment	**Positive**
Prevention	**Incomplete**
Eczema	
Prevention	**Mixed**

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Agenda

- Review Common Clinical Examples (& Tradeoffs) with Probiotic Use
- Why Probiotic Research in Pediatrics is Challenging
- Potential Strategies

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The 5 “D”s

- Dependency
- Developmental Issues
- Delayed Payoff
- Differential Epidemiology
- Demographic Patterns

Forrest C, Simpson L, Clancy C. Child Health Services Research. *JAMA.* 1997;277:1787-93.

Category	Issues	Potential Strategies
Dependency		
Development		
Delayed Payoff		
Differential Epidemiology		
Demographic Patterns		

Category	Issues	Potential Strategies
Dependency	Assessments are based on parent perceptions	
Development		
Delayed Payoff		
Differential Epidemiology		
Demographic Patterns		

Category	Issues	Potential Strategies
Dependency	Assessments are based on parent perceptions	Develop better methods to observe & collect data
Development		
Delayed Payoff		
Differential Epidemiology		
Demographic Patterns		

Category	Issues	Potential Strategies
Dependency	Assessments are based on parent perceptions	Develop better methods to observe & collect data
	More complicated consent process	
Development		
Delayed Payoff		
Differential Epidemiology		
Demographic Patterns		

Category	Issues	Potential Strategies
Dependency	Assessments are based on parent perceptions	Develop better methods to observe & collect data
	More complicated consent process	Streamline the consent/assent process
Development		
Delayed Payoff		
Differential Epidemiology		
Demographic Patterns		

Category	Issues	Potential Strategies
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	More complicated consent process	Streamline the consent/assent process
	Greater justification needed for use of placebos	
Development		
Delayed Payoff		
Differential Epidemiology		
Demographic Patterns		

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Differential Epidemiology	Limited numbers of children with specific conditions can limit recruitment	Greater use of network studies, IPDMA
Demographic Patterns	Higher rates of poverty make participation in research studies less of a priority	Outreach to underserved communities with interventions that are appropriate to those communities
	Greater need for study materials that are linguistically and culturally appropriate	

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Agenda

- Review Common Clinical Examples (& Tradeoffs) with Probiotic Use
- Why Probiotic and Prebiotic Research in Pediatrics is Challenging
- Potential Strategies

NHLBI:
http://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php

Michael D. Cabana, MD, MPH
University of California, San Francisco
Twitter: @cabanam
Web: http://chipper.ucsf.edu/

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Prebiotics & Diarrhea Prevention

- Location: Perth, Australia
- Design: Double-blind prospective randomized controlled trial
- Subjects: healthy children 1-3 years of age (n= 496)

Binns CW, Lee AH, Harding H, Gracey M, Barclay DV. The CUPDAY Study: prebiotic-probiotic milk product in 1-3-year-old children attending childcare centres. *Acta Paediatr*. 2007 Nov;96(11):1646-1650.

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Intervention

- Assignment to 2 servings a day for 5 months of ‘CupDay’, a milk product containing *Bifidobacterium lactis* and a prebiotic blend comprising 50% Raftilose P95 (FOS) and Acacia gum
- Control group received a control milk product not containing probiotics or prebiotics.

Binns CW, et al. The CUPDAY Study: prebiotic-probiotic milk product in 1-3-year-old children attending childcare centres. *Acta Paediatr*. 2007 Nov;96(11):1646-1650.

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Outcomes

- **Outcomes:**
  - Risk of diarrhea
- **Results:**
  - The children consuming the ‘Cupday’ drink had an adjusted risk ratio of 0.80 (95% CI: 0.70, 0.91) of diarrhea.
  - Controlling for age, consumption rate and concurrent family illness.

Binns CW, Lee AH, Harding H, Gracey M, Barclay DV. The CUPDAY Study: prebiotic-probiotic milk product in 1-3-year-old children attending childcare centres. *Acta Paediatr.* 2007 Nov;96(11):1646-1650.

FDA Labeling Status of Pediatric Medications

Esther Y. Yoon, MD, MPH[1]
Matthew M. Davis, MD, MAPP[1,2]
Heba El-Essawi, BS[1]
Michael D. Cabana, MD, MPH[1]

Introduction

Prior studies suggest that approximately 75% of prescription medications listed in the Physician's Desk Reference (PDR) lack pediatric labeling.[1-5] Lack of pediatric labeling may be problematic for physicians, who must decide either to treat children based on adult studies or anecdotal experience in children or not to treat with po-

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tic medications.

tion (FDA) listed an indication
for any therapeutic measure for

Many medications do not have a pediatric indication

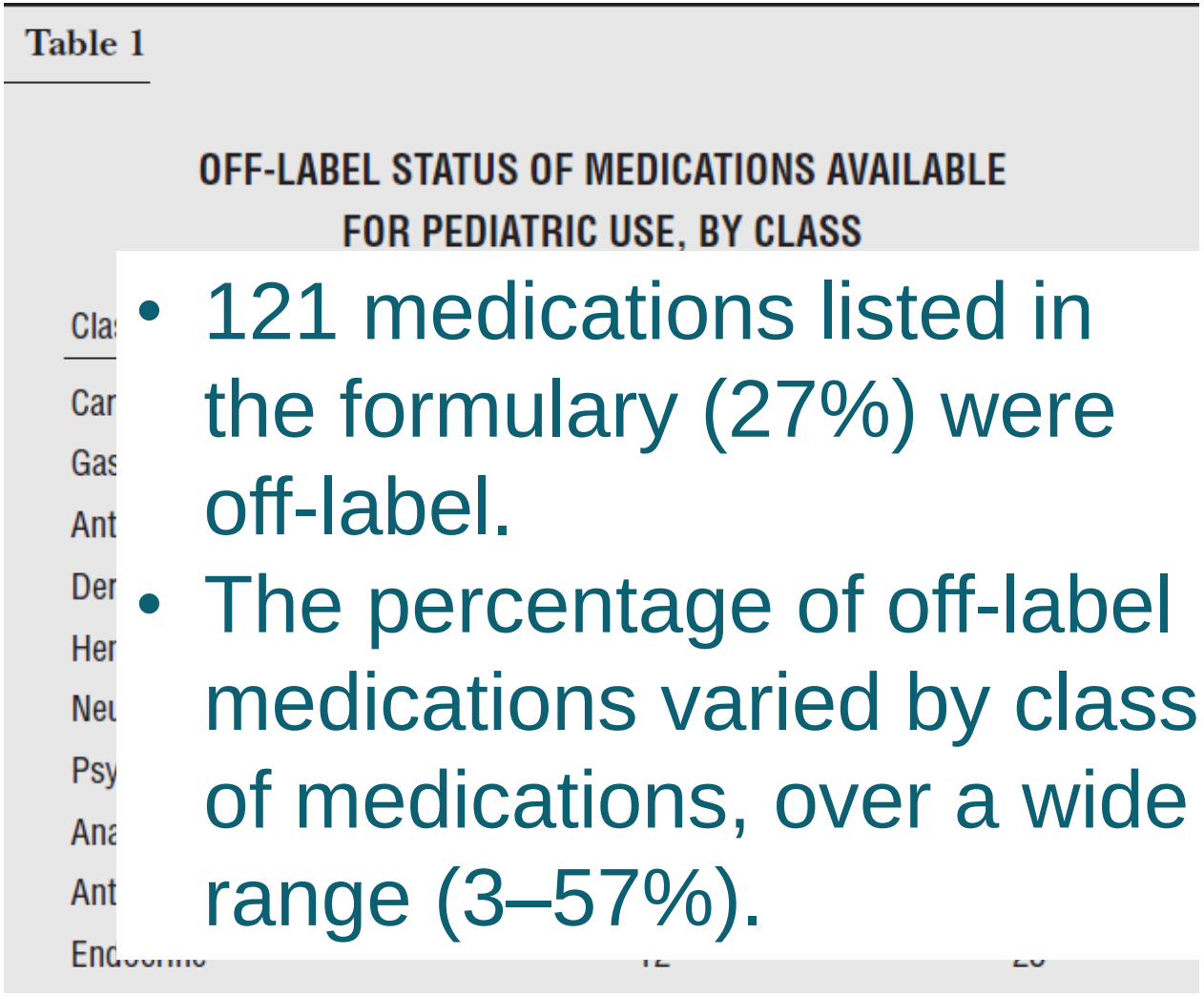

Table 1

OFF-LABEL STATUS OF MEDICATIONS AVAILABLE FOR PEDIATRIC USE, BY CLASS

- 121 medications listed in the formulary (27%) were off-label.
- The percentage of off-label medications varied by class of medications, over a wide range (3–57%).

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Why Pediatric Research is Challenging

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Pediatric Research ≠ Data from Children ≠ Little Adults Adult Research

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The 5 “D”s

- Dependency
- Developmental issues
- Dollars
- Differential epidemiology
- Demographic patterns

Forrest C, Simpson L, Clancy C. Child Health Services Research. *JAMA.* 1997;277:1787-93.

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The 5 “D”s

- **Dependency**
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Forrest C, Simpson L, Clancy C. Child Health Services Research. *JAMA.* 1997;277:1787-93.

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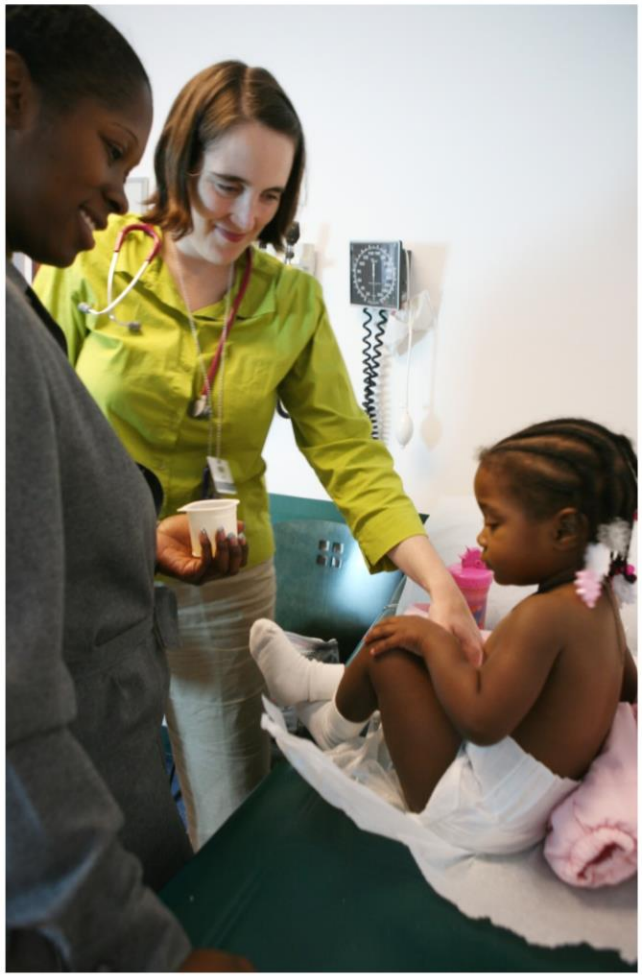
Dependency



- Evaluation of the child involves the parents
- Consent for clinical trials is more complex
- Since children are considered dependent and ‘vulnerable’, there are constraints on study design

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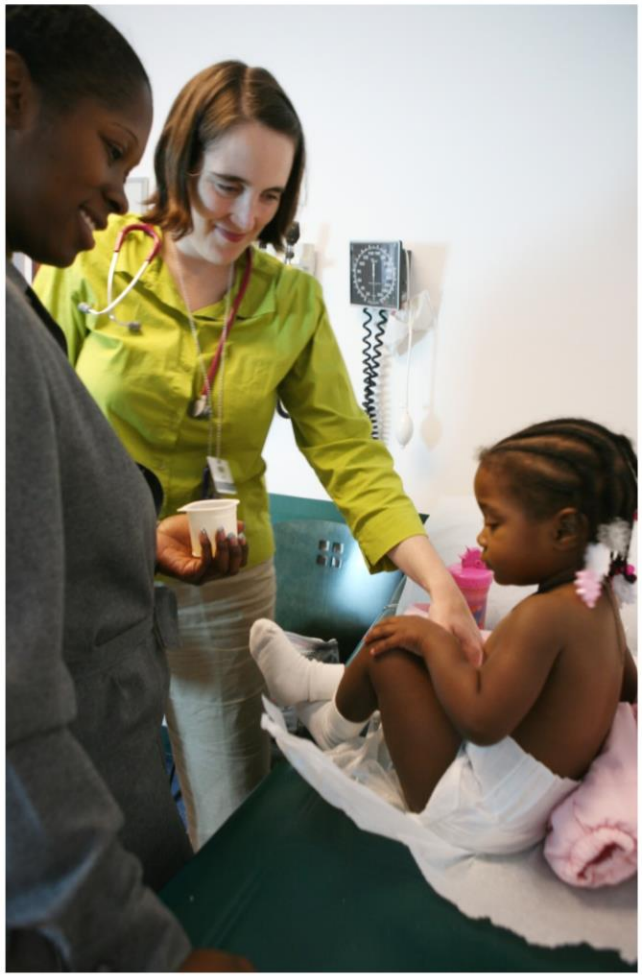
Dependency



- Evaluation of the child involves the parents

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Evaluation of Child via Parent

Evaluation Tool	Acronym	Disease or Condition
Pediatric Quality of Life	PedsQL	N/A
Scoring Atopic Dermatitis	SCORAD	Atopic Dermatitis
Parental Opinions of Pediatric Constipation	POOP-C	Constipation
Pediatric Inventory for Parents	PIP	Stress
Children's Sleep Status Questionnaire	CSSC	Sleep
Childhood Asthma Control Test	C-ACT	Asthma

Childhood Asthma Control Test for children 4 to 11 years

Know your score.

Parent or Guardian: The Childhood Asthma Control Test* is a way to help your child's healthcare provider determine if your child's asthma symptoms are well controlled. Take this test with your child (ages 4 to 11). Share the results with your child's healthcare provider.

Step 1: Have your child answer **the first four questions (1 to 4).** If your child needs help, you may help, but let your child choose the answer.

Step 2: Answer the last **three questions (5 to 7)** on your own. Don't let your child's answers influence yours. There are no right or wrong answers.

Step 3: Write the number of each answer in the score box to the right.

Step 4: Add up each score box for the total.

Step 5: Take the COMPLETED test to your child's healthcare provider to talk about your child's total score.

19 or less

IF YOUR CHILD'S SCORE IS 19 OR LESS, **Your child's asthma symptoms may not be as well controlled as they could be. No matter what the score, bring this test to your child's healthcare provider to talk about your child's results.**

NOTE: If your child's score is 12 or less, his or her asthma may be very poorly controlled. Please contact your child's healthcare provider right away.

Have your child complete these questions.

1. How is your asthma today?

2. How much of a problem is your asthma when you run, exercise or play sports?

3. Do you cough because of your asthma?

4. Do you wake up during the night because of your asthma?

SCORE

Very bad	Bad	Good	Very good

2. How much of a problem is your asthma when you run, exercise or play sports?

 0 It's a big problem, I can't do what I want to do.	 1 It's a problem and I don't like it.	 2 It's a little problem but it's okay.	 3 It's not a problem.

3. Do you cough because of your asthma?

 0 Yes, all of the time.	 1 Yes, most of the time.	 2 Yes, some of the time.	 3 No, none of the time.

4. Do you wake up during the night because of your asthma?

 0 Yes, all of the time.	 1 Yes, most of the time.	 2 Yes, some of the time.	 3 No, none of the time.

Please complete the following questions on your own.

5. During the last 4 weeks, how many days did your child have any daytime asthma symptoms?

5 Not at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday

6. During the last 4 weeks, how many days did your child wheeze during the day because of asthma?

5 Not at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday

7. During the last 4 weeks, how many days did your child wake up during the night because of the asthma?

5 Not at all	4 1-3 days	3 4-10 days	2 11-18 days	1 19-24 days	0 Everyday

TOTAL

*The Childhood Asthma Control Test was developed by GSK.

This material was developed by GSK.

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Infant Colic Clinical Trials

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Infant Colic Clinical Trials

THE JOURNAL OF PEDIATRICS • www.jpeds.com

ORIGINAL ARTICLES

Probiotics for Infantile Colic: A Randomized, Double-Blind, Placebo-Controlled Trial Investigating *Lactobacillus reuteri* DSM 17938

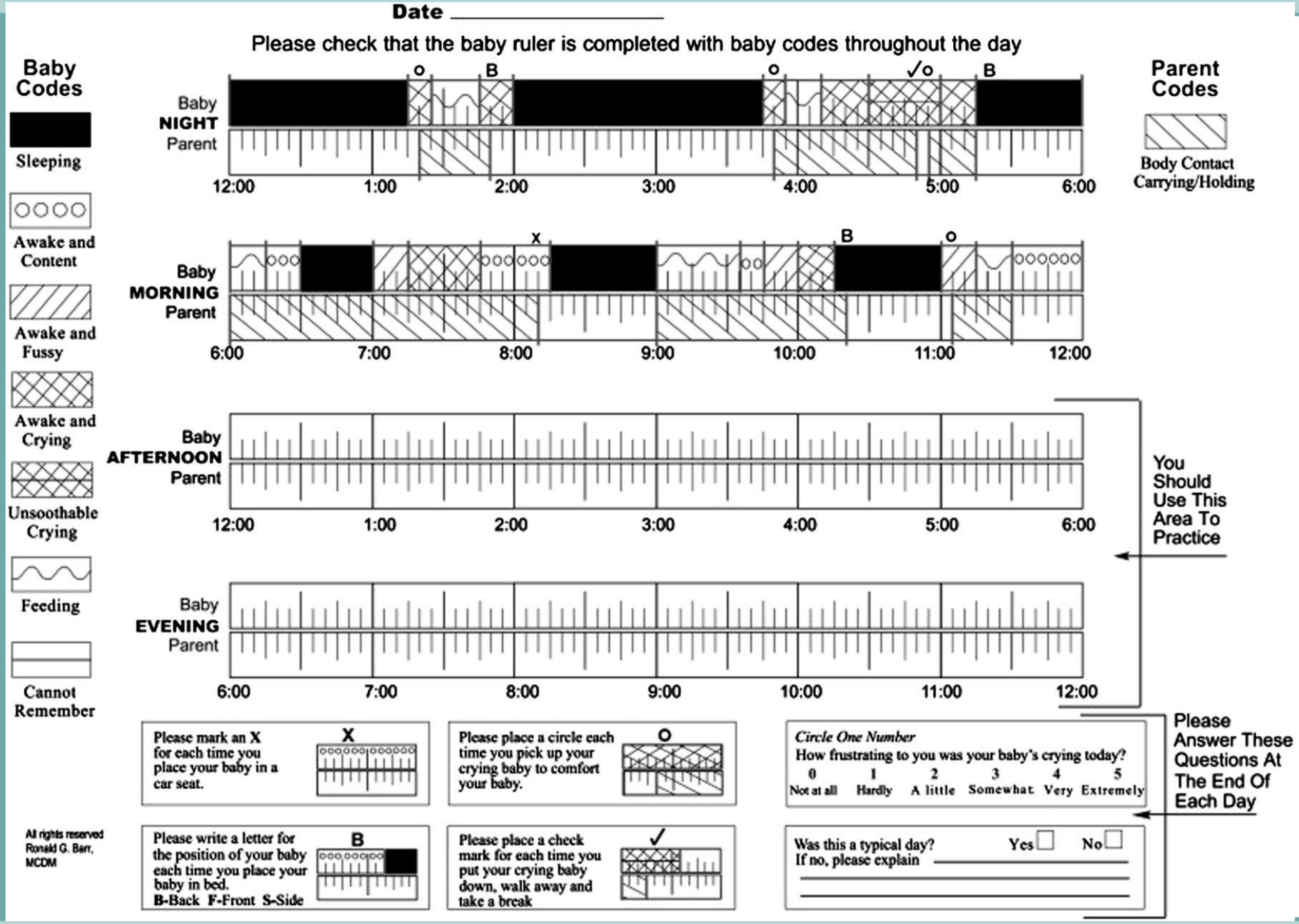
Kim Chau, MSc[1,2], Eddy Lau, MD[3,4,5], Saul Greenberg, MD[6], Sheila Jacobson, MD[2,6], Parvaneh Yazdani-Brojeni, MD[2], Natasha Verma, MD[2], and Gideon Koren, MD[1,2,3,6,7]

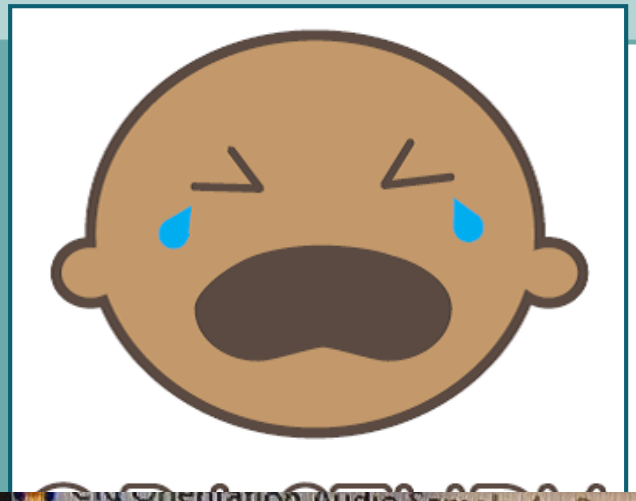
Objective To investigate the effectiveness of *Lactobacillus reuteri* DSM 17938 for the treatment of infantile colic in breastfed Canadian infants, compared with placebo.

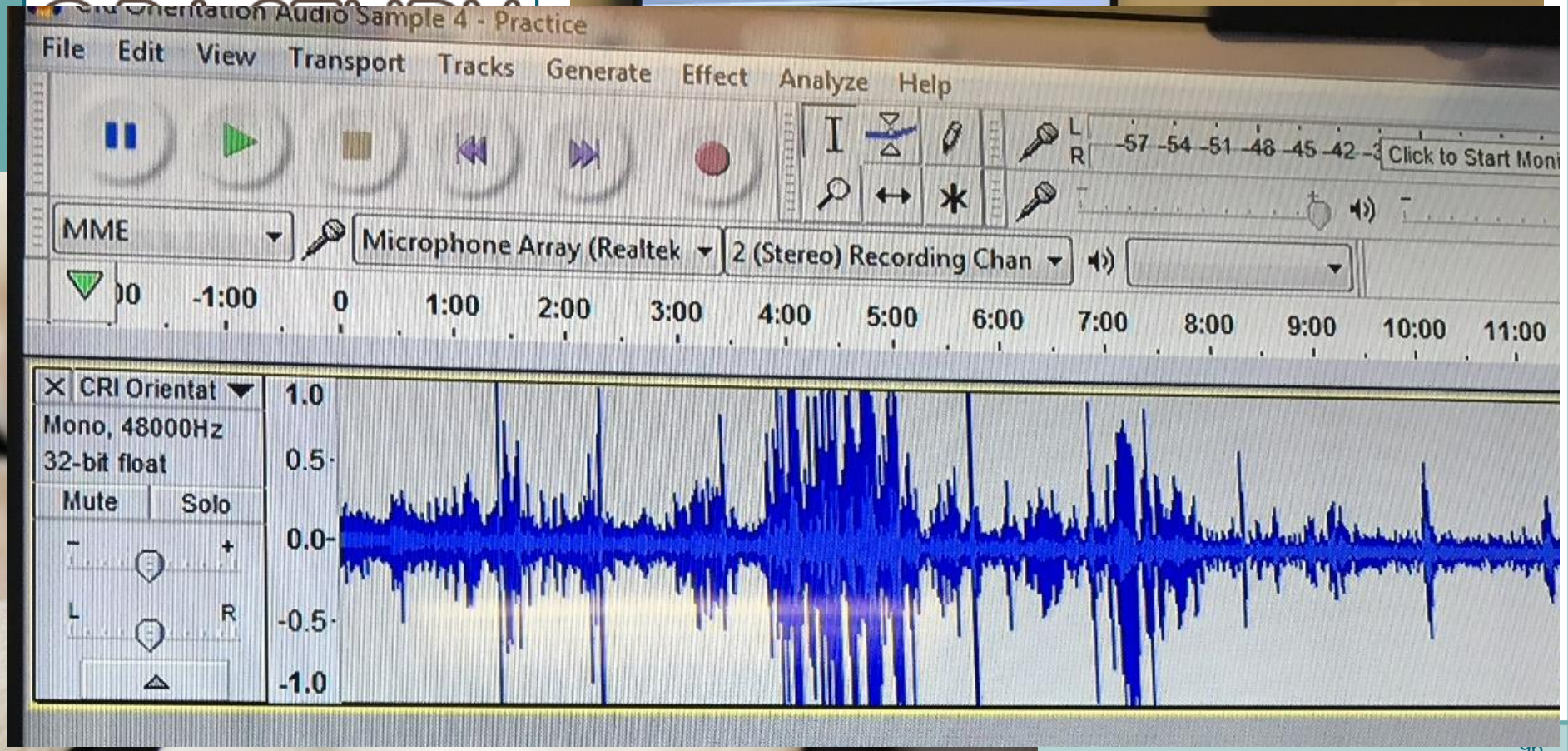
Study design A randomized, double-blind, placebo-controlled trial was conducted involving 52 infants with colic, according to modified Wessel criteria, who were assigned at random to receive *L reuteri* DSM 17938 (10^8 colony-forming units) (n = 24) or placebo (n = 28) for 21 days. Daily crying and fussing times were recorded in a structured diary, and maternal questionnaires were completed to monitor changes in infant colic symptoms and adverse events.

Results Total average crying and fussing times throughout the study (from baseline to day 21) were significantly shorter among infants with colic in the probiotic group compared with infants in the placebo group (1719 ± 750 minutes [29 ± 13 hours] vs 2195 ± 764 minutes [37 ± 13 hours]; *P* = .028) (relative risk, 0.78; 95% CI, 0.58-0.98). Infants given *L reuteri* DSM 17938 showed a significant reduction in daily crying and fussing times at the end of treatment period compared with those receiving placebo (median, 60 minutes/day [IQR, 64 minutes/day] vs 102 minutes/day [IQR, 87 minutes/day]; *P* = .045). On day 21, a significantly higher proportion of infants in the *L reuteri* DSM 17938 group responded to treatment with a ≥50% crying time reduction compared with infants given placebo (17 vs 6, *P* = .035; relative risk, 3.3; 95% CI, 1.55-7.03).

Conclusion Administration of *L reuteri* DSM 17938 significantly improved colic symptoms by reducing crying and fussing times in breastfed Canadian infants with colic. *(J Pediatr 2014; ■:■-■).*


Date _____
Please check that the baby ruler is completed with baby codes throughout the day
Baby Codes
Sleeping
Awake and Content
Awake and Fussy
Awake and Crying
Unsoothable Crying
Feeding
Cannot Remember
Parent Codes
Body Contact Carrying/Holding
Baby NIGHT Parent
12:00 1:00 2:00 3:00 4:00 5:00 6:00
Baby MORNING Parent
6:00 7:00 8:00 9:00 10:00 11:00 12:00
Baby AFTERNOON Parent
12:00 1:00 2:00 3:00 4:00 5:00 6:00
Baby EVENING Parent
6:00 7:00 8:00 9:00 10:00 11:00 12:00
You Should Use This Area To Practice
Please mark an X for each time you place your baby in a car seat.
Please place a circle each time you pick up your crying baby to comfort your baby.
Circle One Number
How frustrating to you was your baby's crying today?
0 Not at all 1 Hardly 2 A little 3 Somewhat 4 Very 5 Extremely
Please write a letter for the position of your baby each time you place your baby in bed.
B-Back F-Front S-Side
Please place a check mark for each time you put your crying baby down, walk away and take a break
Was this a typical day? Yes No
If no, please explain
Please Answer These Questions At The End Of Each Day
All rights reserved Ronald G. Barr, MCDM




Audio Sample 4 - Practice
File Edit View Transport Tracks Generate Effect Analyze Help
MME
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2 (Stereo) Recording Chan
-1:00 0 1:00 2:00 3:00 4:00 5:00 6:00 7:00 8:00 9:00 10:00 11:00
CRI Orientat
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1.0 0.5 0.0 -0.5 -1.0

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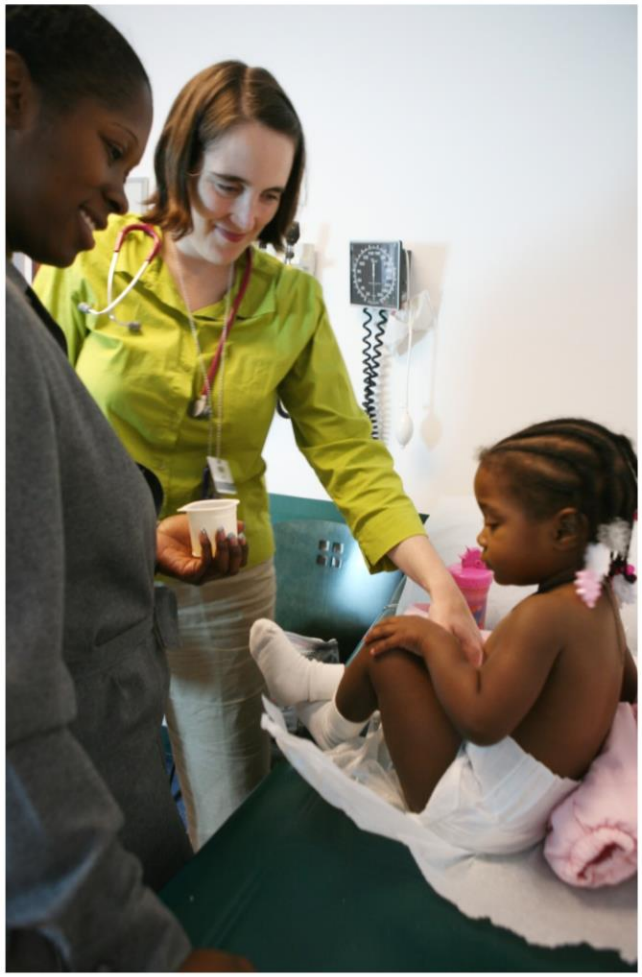
Dependency



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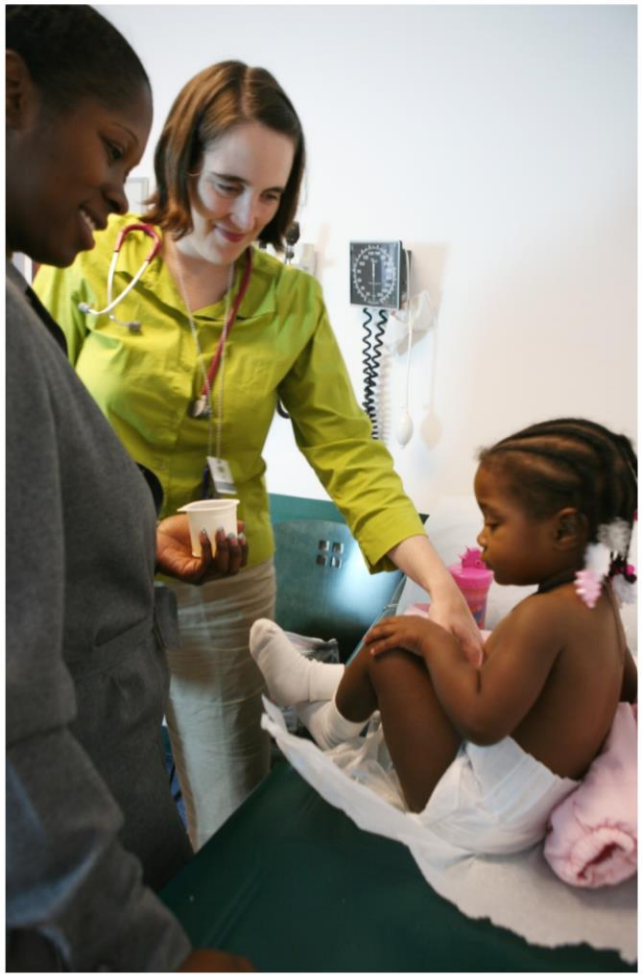

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Research in Children

- **Informed consent** must be obtained from study participants
  - For studies involving prenatal and postnatal interventions, consent is obtained again for the newborn
- **Assent**
  - Older children should not be excluded from decision-making
  - Assent should be obtained whenever appropriate (>7 years old)

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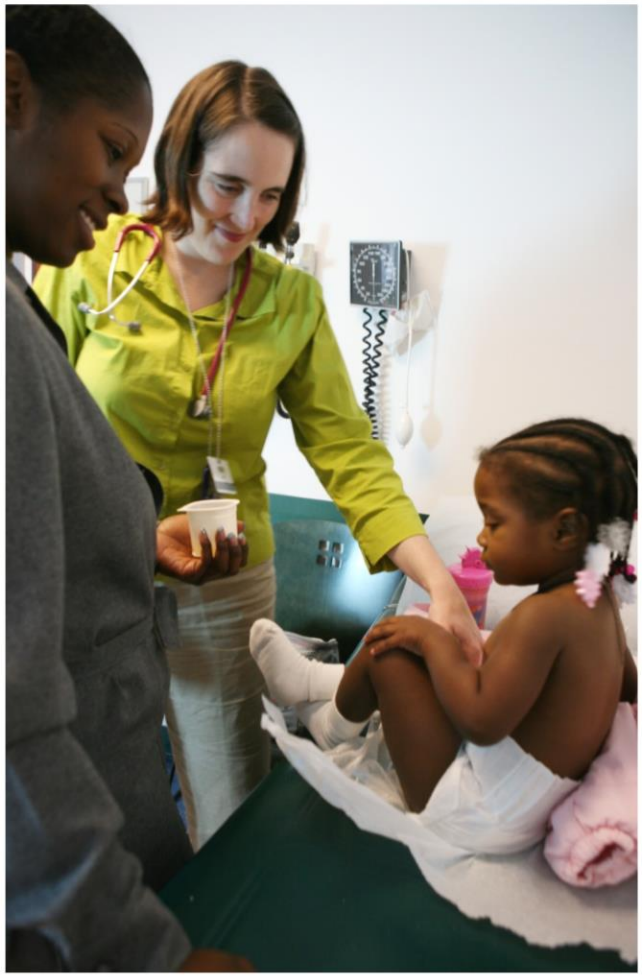
Dependency



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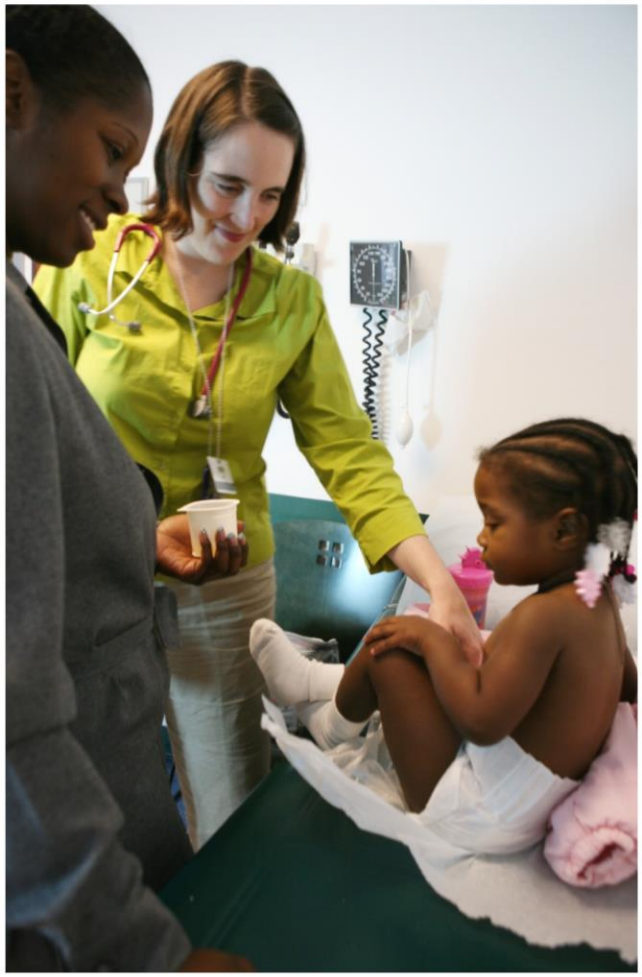

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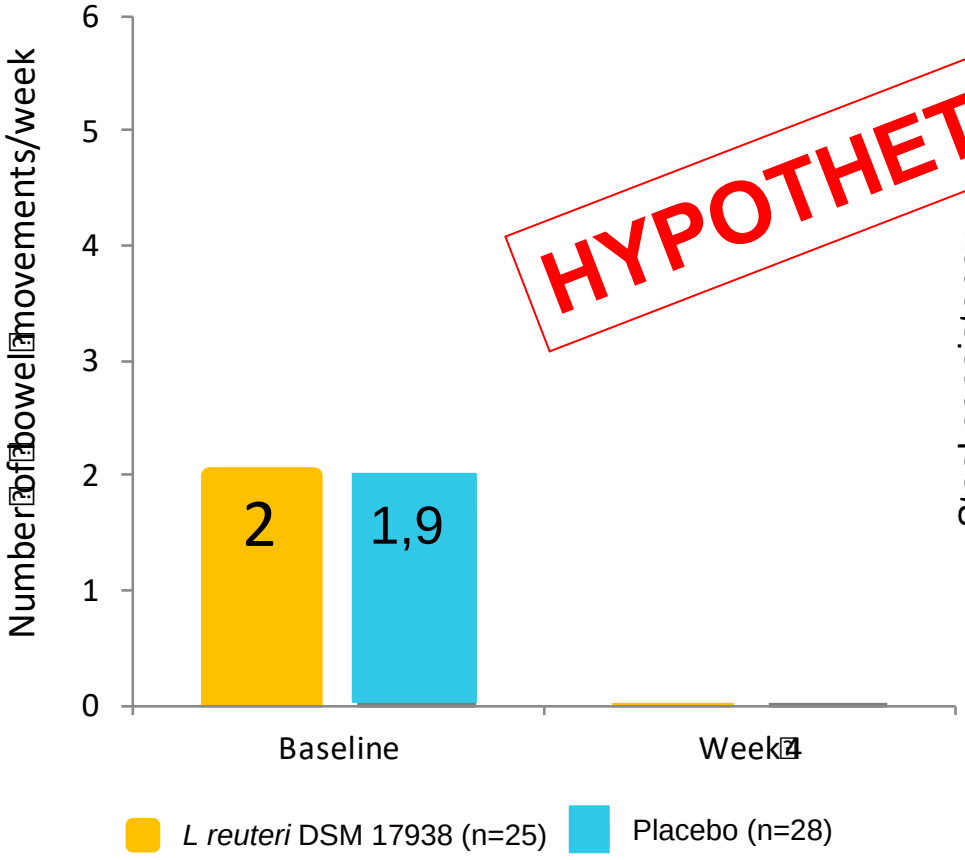
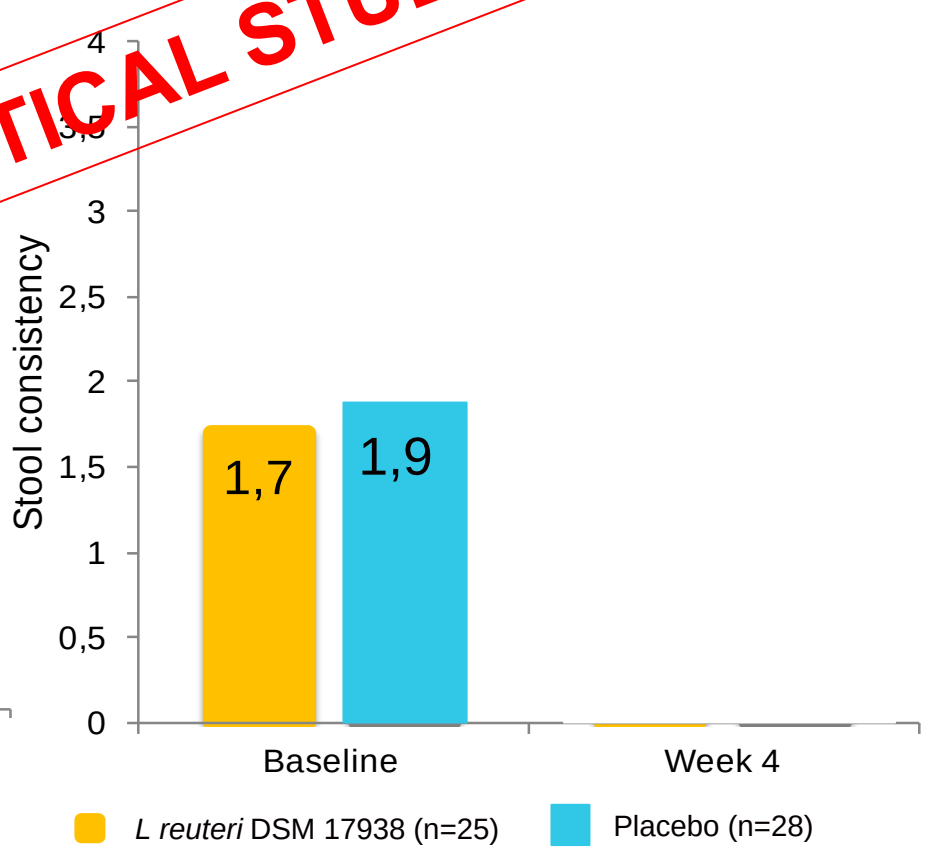
Is 4 weeks of probiotic supplementation effective in treating functional constipation in children?

Comparison of the efficacy of probiotics in children with functional constipation and determination of the effects of constipation treatment on quality of life.

HYPOTHETICAL STUDY

103 children *(4-16 yrs)*

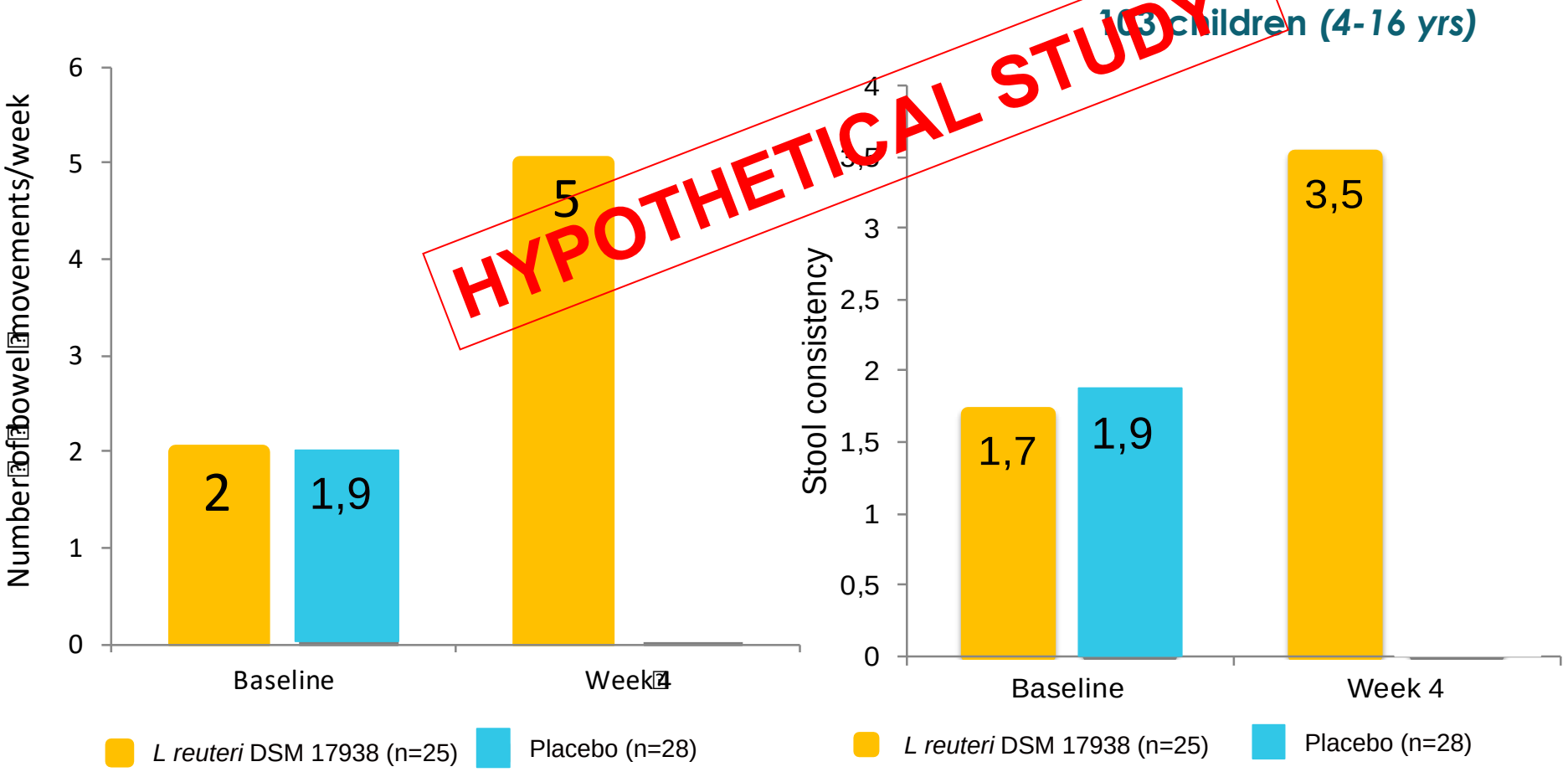




L. reuteri as effective as Lactulose for constipation at 4 weeks

Comparison of the efficacy of probiotics in children with functional constipation and determination of the effects of constipation treatment on quality of life.

HYPOTHETICAL STUDY



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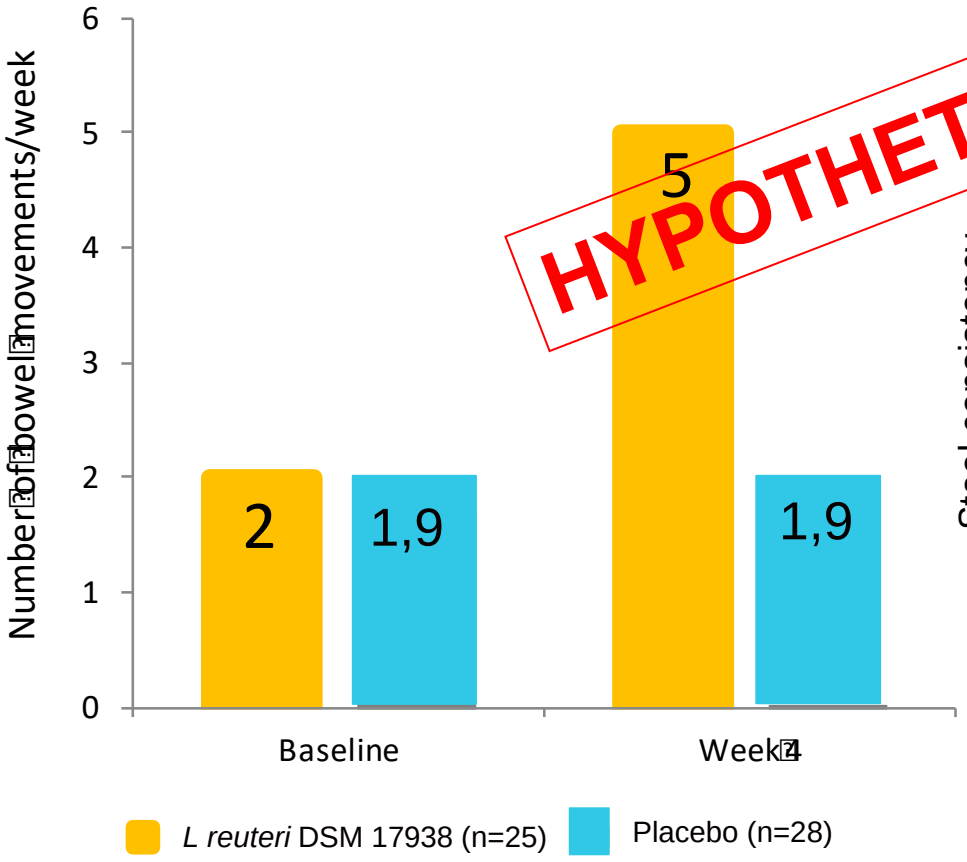

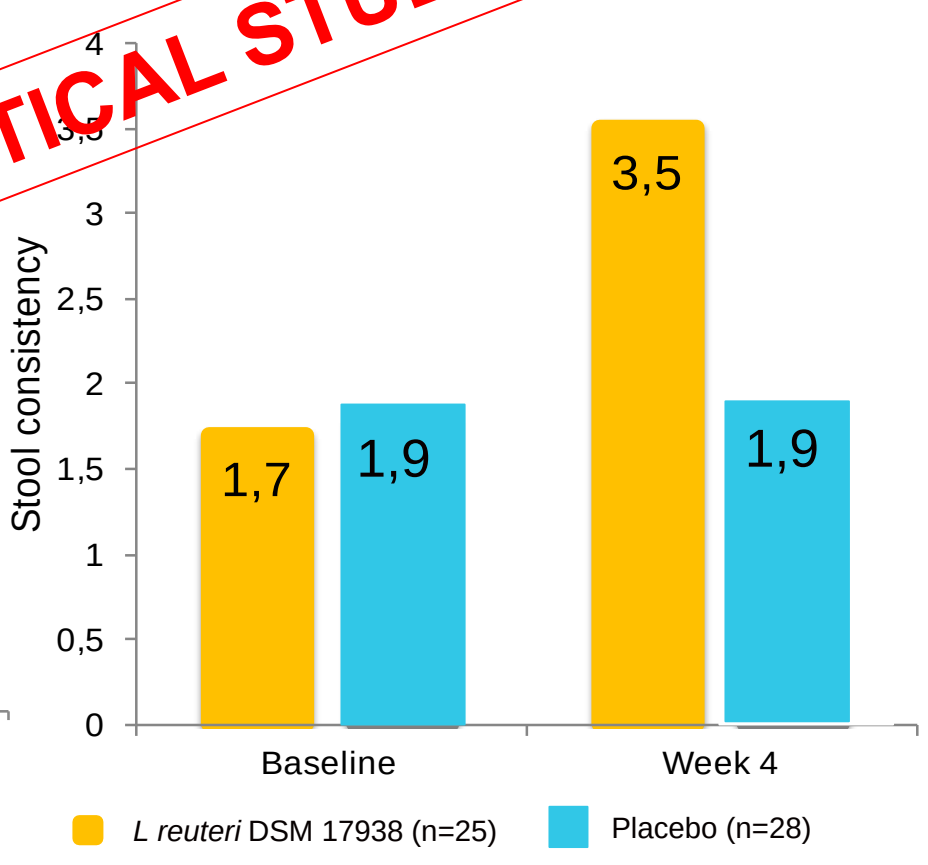

L. reuteri as effective as Lactulose for constipation at 4 weeks

CME

Evaluation and Treatment of Functional Constipation in Infants and Children: Evidence-Based Recommendations From ESPGHAN and NASPGHAN

M.M. Tabbers, C. DiLorenzo, M.Y. Berger, C. Faure, M.W. Langendam, S. Nurko, A. Staiano, Y. Vandenplas, and M.A. Benninga

ABSTRACT

Background: Constipation is a pediatric problem commonly encountered by many health care workers in primary, secondary, and tertiary care. To assist medical care providers in the evaluation and management of children with functional constipation, the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition were charged with the task of developing a uniform document of evidence-based guidelines.

Methods: Nine clinical questions addressing diagnostic, therapeutic, and prognostic topics were formulated. A systematic literature search was performed from inception to October 2011 using Embase, MEDLINE, the Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Clinical Trials, and PsychInfo databases. The approach of the Grading of Recommendations Assessment, Development and Evaluation was applied to evaluate outcomes. For therapeutic questions, quality of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation system. Grading the quality of evidence for the other questions was performed according to the

Results: This evidence-based guideline provides recommendations for the evaluation and treatment of children with functional constipation to standardize and improve their quality of care. In addition, 2 algorithms were developed, one for the infants <6 months of age and the other for older infants and children.

Conclusions: This document is intended to be used in daily practice and as a basis for further clinical research. Large well-designed clinical trials are necessary with regard to diagnostic evaluation and treatment.

Key Words: children, constipation, encopresis, enema, evidence-based, fecal incontinence, fecal soiling, functional constipation, guideline, infants, laxative

(*JPGN* 2014;58: 258–274)

INTRODUCTION

CME

Evaluation and Treatment of Functional Constipation in Infants and Children: Evidence-Based Recommendations From ESPGHAN and NASPGHAN

7.2 Which Pharmacologic Treatment Should Be Given for Maintenance Therapy? (Fig. 1, Boxes 10 and 14; Fig. 2, Box 13)

In conclusion, evidence shows that PEG is more effective compared with lactulose, milk of magnesia, mineral oil, or placebo. More studies have been performed evaluating the effectiveness of lactulose than studies evaluating the effect of milk of magnesia and mineral oil in children with constipation. More important, lactulose is considered to be safe for all ages. For these reasons, lactulose is recommended in case PEG is not available. Furthermore, evidence does not support the addition of enemas to the chronic use of PEG in children with constipation.

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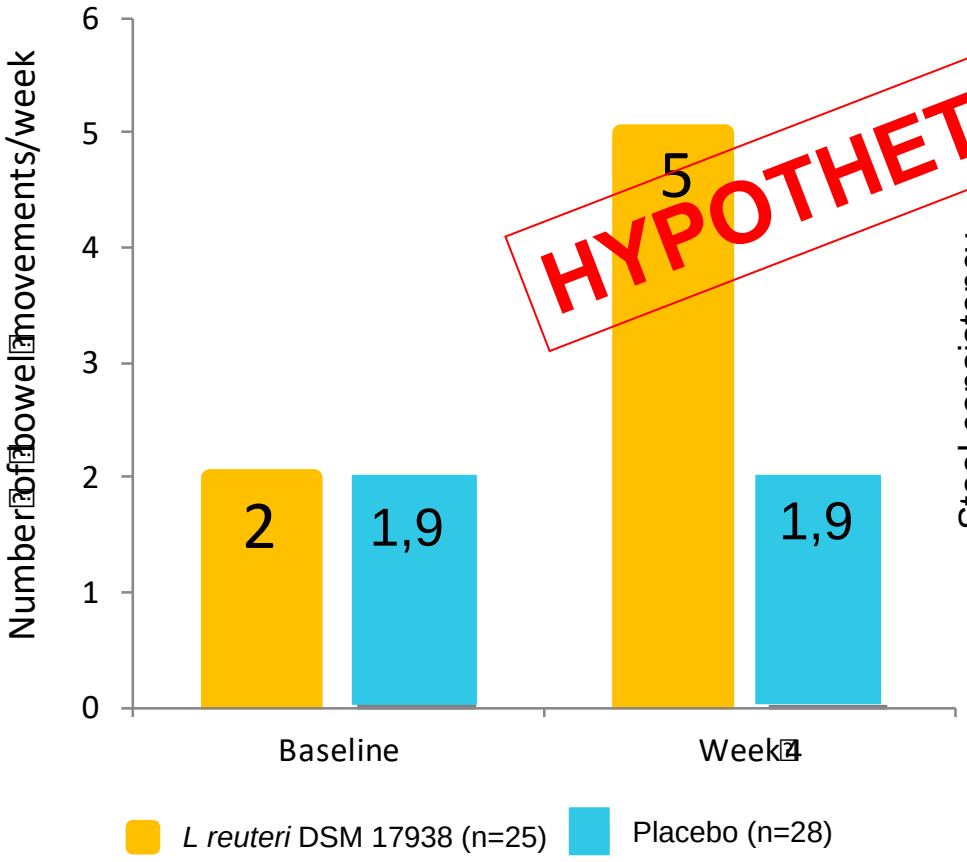
The Use of Placebos for Children

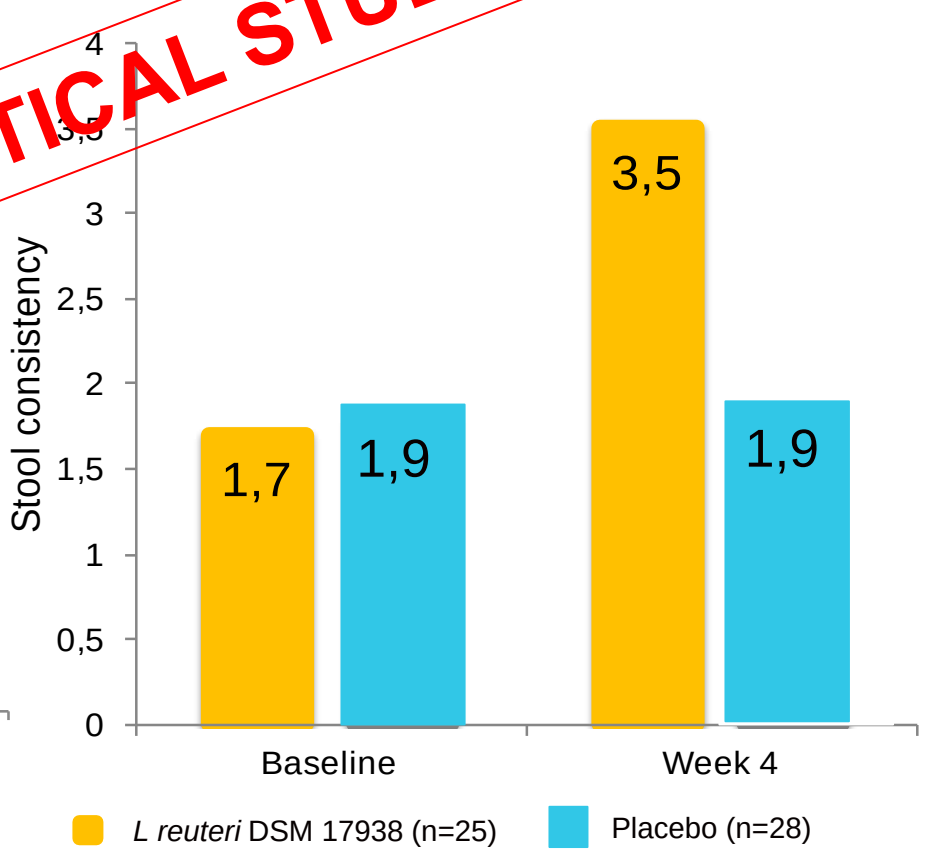
- The Declaration of Helsinki states that every patient in a clinical study, including those in a control group, should be assured of at least the current standard of care
- Children are a ‘vulnerable’ population and the investigator clearly needs to state why a placebo is justified

Comparison of the efficacy of probiotics in children with functional constipation and determination of the effects of constipation treatment on quality of life.

HYPOTHETICAL STUDY

103 children *(4-16 yrs)*



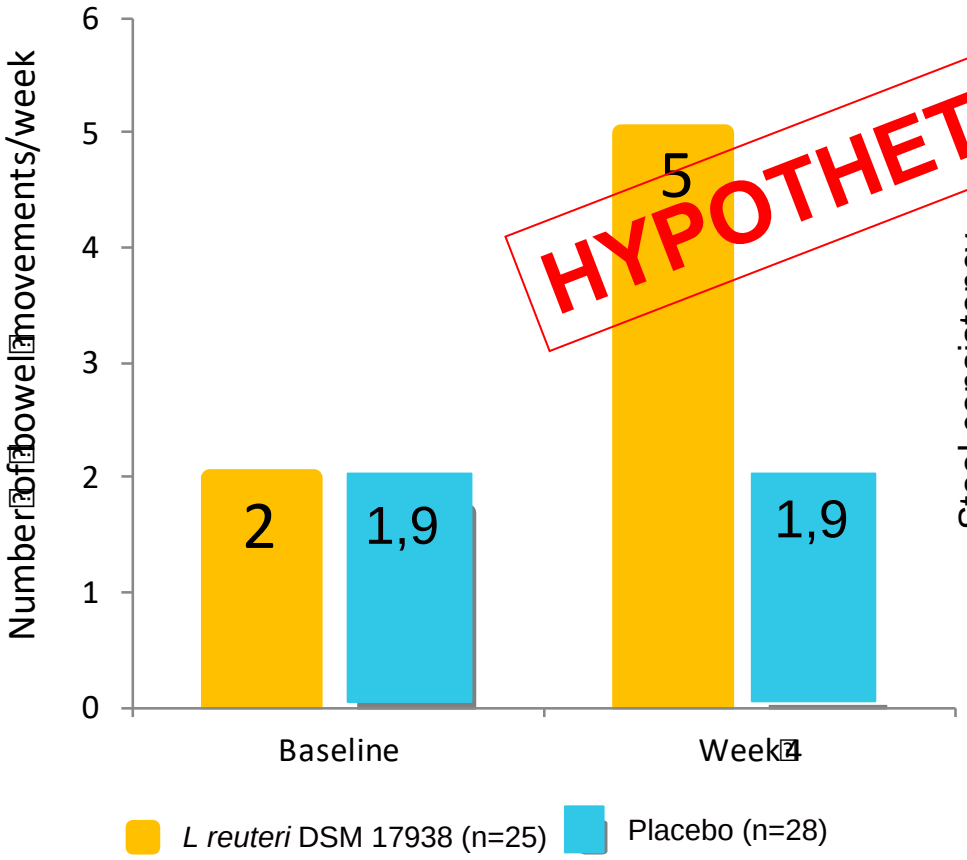


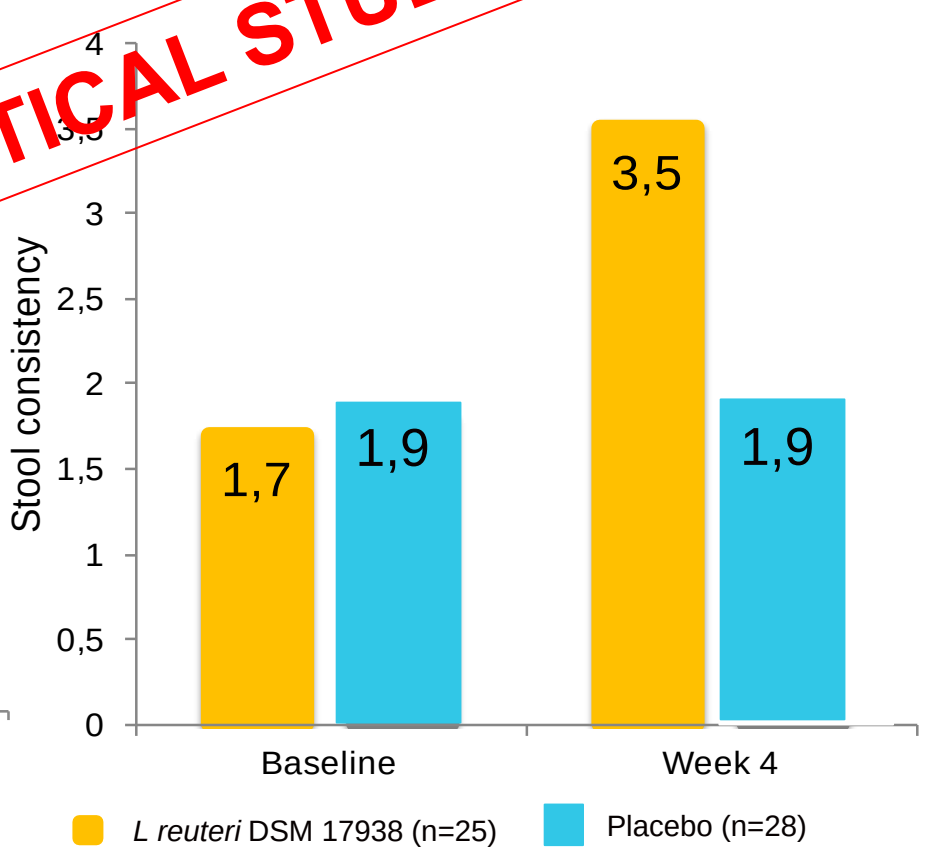
L. reuteri as effective as Lactulose for constipation at 4 weeks

Comparison of the efficacy of probiotics in children with functional constipation and determination of the effects of constipation treatment on quality of life.

HYPOTHETICAL STUDY

103 children *(4-16 yrs)*

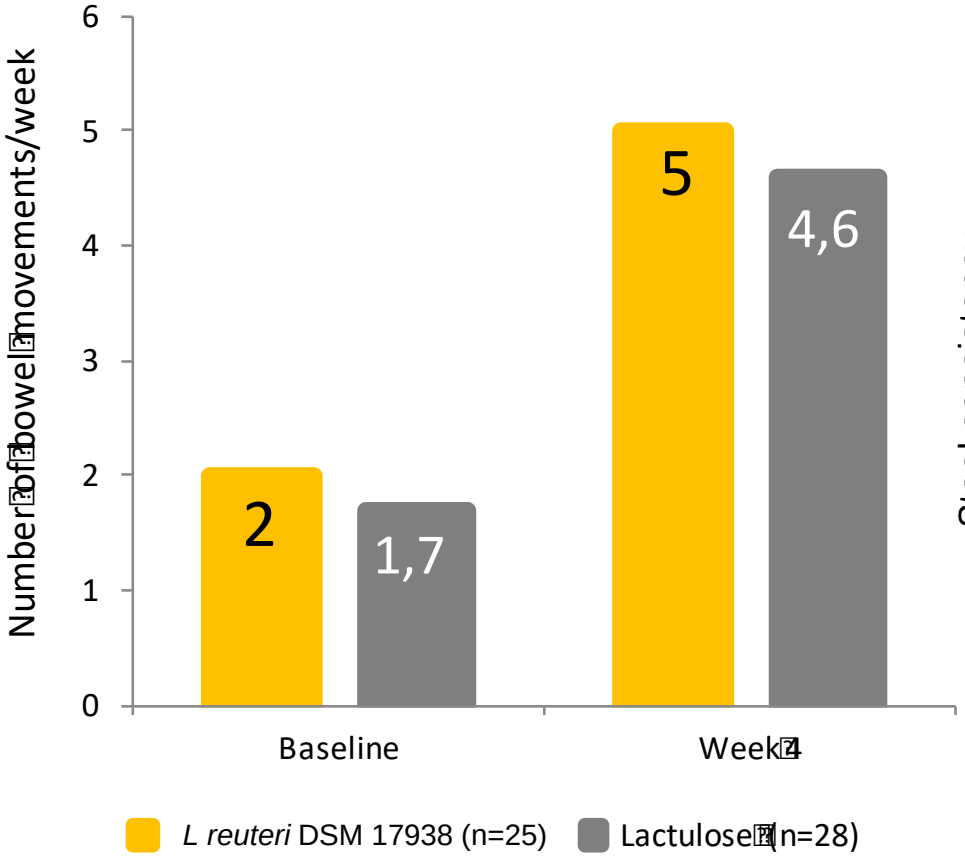


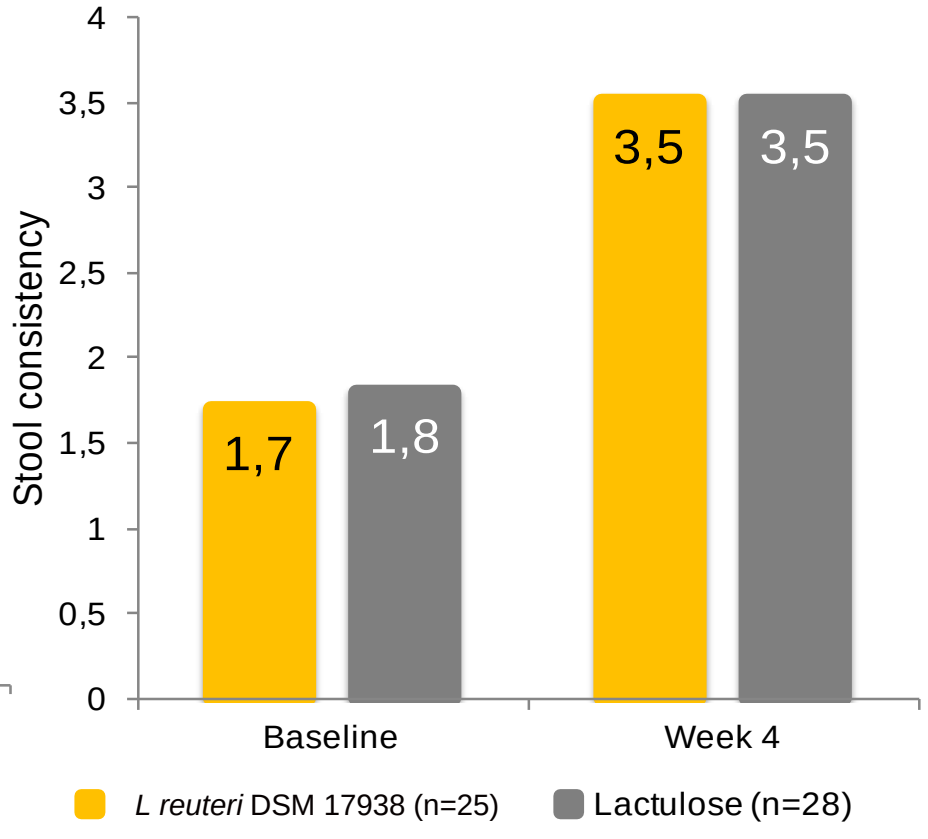


L. reuteri as effective as Lactulose for constipation at 4 weeks

Comparison of the efficacy of probiotics and lactulose treatments in children with functional constipation and determination of the effects of constipation treatment on quality of life.

103 children *(4-16 yrs)*





L. reuteri as effective as Lactulose for constipation at 4 weeks

Dependency

- Children are considered a vulnerable population in research
- Pediatric clinical trials cannot just ‘duplicate’ adult trials
- Use of placebo has to be justified

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The 5 “D”s

- Dependency
- Developmental issues
- Dollars
- Differential epidemiology
- Demographic patterns

Forrest C, Simpson L, Clancy C. Child Health Services Research. *JAMA.* 1997;277:1787-93.

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The 5 “D”s

- Dependency
- **Developmental issues**
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Development

- Childhood is a time of great change and a potential opportunity to affect adult outcomes

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The roots of many 'adult' diseases occur in infancy and childhood

Forrest C, Simpson L, Clancy C. Child Health Services Research. *JAMA.* 1997;277:1787-93.

Early Roots in Childhood

- **Asthma, eczema, allergic rhinitis**
  - Asthma = 10-12% of the population
  - Allergic rhinitis=10-25% of the population
  - Eczema prevalence = 10-20% of pediatric population

1. Leung DY, et al. *Ann Allergy Asthma Immunol.* 2004;93(3 Suppl 2):S1-S21.
2. Breuer K, et al. *Clin Exp Allergy.* 2004;34(5):817-824.

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Hygiene Hypothesis

- The lack of early childhood exposure to infectious agents increases susceptibility to allergic diseases

Objective:
To test the effectiveness of a probiotic supplement in preventing the development of early markers of asthma

Subjects:
184 infants at high risk for developing asthma

Intervention:
Postnatal daily infant probiotic dietary supplementation (first 6 months of life)

Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial

Marko Kalliomäki, Seppo Salminen, Heikki Arvilommi, Pentti Kero, Pertti Koskinen, Erika Isolauri

Summary

Background Reversal of the progressive increase in frequency of atopic disease would be an important breakthrough for health care and wellbeing in Western societies. In the hygiene hypothesis this increase is attributed to reduced microbial exposure in early life. Probiotics are cultures of potentially beneficial bacteria of the healthy gut microflora. We assessed the effect on atopic disease of *Lactobacillus* GG (which is safe at an early age and effective in treatment of allergic inflammation and food allergy).

Methods In a double-blind, randomised placebo-controlled trial we gave *Lactobacillus* GG prenatally to mothers who had at least one first-degree relative (or partner) with atopic eczema, allergic rhinitis, or asthma, and postnatally for 6 months to their infants. Chronic recurring atopic eczema, which is the main sign of atopic disease in the first years of life, was the primary endpoint.

Findings Atopic eczema was diagnosed in 46 of 132 (35%) children aged 2 years. Asthma was diagnosed in six of these children and allergic rhinitis in one. The frequency of atopic

Introduction

Allergy, in the form of atopic diseases such as atopic eczema, allergic rhinitis, and asthma, is a chronic disorder of increasing importance in economically more-developed countries.[1] The International Study of Asthma and Allergies in Childhood[2,3] included 11 607 Finnish children aged 13–14 years; 10–20% of the children had symptoms of asthma, 15–23% allergic rhinitis, and 15–19% atopic eczema. Proof of an inverse association between infections early in life and atopy has led to renewed interest in the hygiene hypothesis devised by Strachan[4] a decade ago. The recent rapid rise in atopy might be a result of improved hygiene and reduced family size. Recent epidemiological studies have yielded results both for,[5–7] and against,[8] such a hypothesis.

We propose that specific microbes in the commensal gut microflora are more important than sporadic infections in atopic disease prevention. Gastrointestinal microflora promote potentially antiallergenic processes: (1) T-helper-1-type immunity;[9] (2) generation of transforming growth factor β,[10,11] which has an essential role in suppression of T-helper-2-induced allergic inflammation[12] and induction of oral tolerance;[13] and (3) IgA production,[14] an essential

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Prevention Studies

First author, year	Patients	Probiotic	Duration of application	Age at follow-up years	Effect of probiotics
Kalliomäki [12–14] 2001, 2003, 2007	132	*Lactobacillus rhamnosus* GG	Prenatal 4 weeks, postnatal 6 months	2 4 7	Significantly reduced rate of AD in the verum group
Abrahamsson [18] 2007	188	*Lactobacillus reuteri*	Prenatal 2 weeks, postnatal 1 year	1	Significantly reduced rate of AD in the verum group (only IgE-associated AD)
Kukkonen [19] 2007	925	Mix of various probiotics + prebiotics	Prenatal 2–4 weeks, postnatal 6 months	2	Significantly reduced rate of AD in the verum group
Taylor [20] 2007	178	*Lactobacillus acidophilus*	Only postnatal (6 months)	1	No difference between verum and placebo
Wickens [21] 2008	474	*Lactobacillus rhamnosus* or *Bifidobacterium animalis* subsp. lactis	Prenatal 4 weeks, postnatal 2 years	2	Significantly reduced rate of AD in the verum group (only for *L. rhamnosus*)
Kopp [22] 2008	94	*Lactobacillus rhamnosus* GG	Prenatal 4–6 weeks, postnatal 6 months	2	No difference between verum and placebo
Kim [23] 2009	112	Mix of probiotics	Prenatal 4–6 weeks, postnatal 6 months	1	Significantly reduced rate of AD in the verum group
Niers [24] 2009	102	Mix of probiotics	Prenatal 4–6 weeks, postnatal 12 months	2	Significantly reduced rate of AD in the verum group
Soh [25] 2009	253	*Lactobacillus rhamnosus* + *Bifidobacterium longum*	Only postnatal (6 months)	1	No difference between verum and placebo

Folster-Holst R, *Ann Nutr Metab*. 2010; 57: 166-19

- Because of issues of fetal development, it can be difficult to have studies approved that allow prenatal intervention early in pregnancy

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Early Roots of Disease in Childhood

- There is great potential in investigating the development (and potential prevention) of diseases early in childhood
- There are limitations with early prenatal interventions

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The 5 “D”s

- Developmental issues
- Dependency
- Dollars
- Demographic patterns
- Differential epidemiology

Forrest C, Simpson L, Clancy C. Child Health Services Research. *JAMA.* 1997;277:1787-93.

The 5 “D”s

- Developmental issues
- Dependency
- **Dollars**
- Demographic patterns
- Differential epidemiology

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Dollars/Return on Investment

- The final ‘product’ of pediatric care is realized over an extended time horizon
- As a result, it is challenging to measure benefits of early intervention
- How can you prove the effectiveness of an early childhood intervention?

Perry Preschool Study

- 123 preschool kids randomly assigned to Head Start pre-school (2.5 hours/day).
  - Start age: 3 years
  - End age: 40 years
- Every $1 invested in Head Start, the return on investment ranged from $7 to $9, based on:
  - Graduation rates and impact on economy
  - Less obesity, decreased smoking rates

http://www.highscope.org/files/BarnettS_Proceedings2012.pdf

Dollars

- The benefits of pediatric interventions may take many years before they can be measured
- Intermediate outcomes are useful, but may not be clinically convincing to change practice

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The 5 “D”s

- Dependency
- Developmental issues
- Dollars
- **Differential epidemiology**
- Demographic patterns

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Differential Epidemiology

- Only a handful of relatively common chronic conditions (e.g., obesity, asthma, etc).
- However, a wide plethora of rare diseases manifest in a very small percentage of children.
- Can make recruitment for clinical studies very difficult

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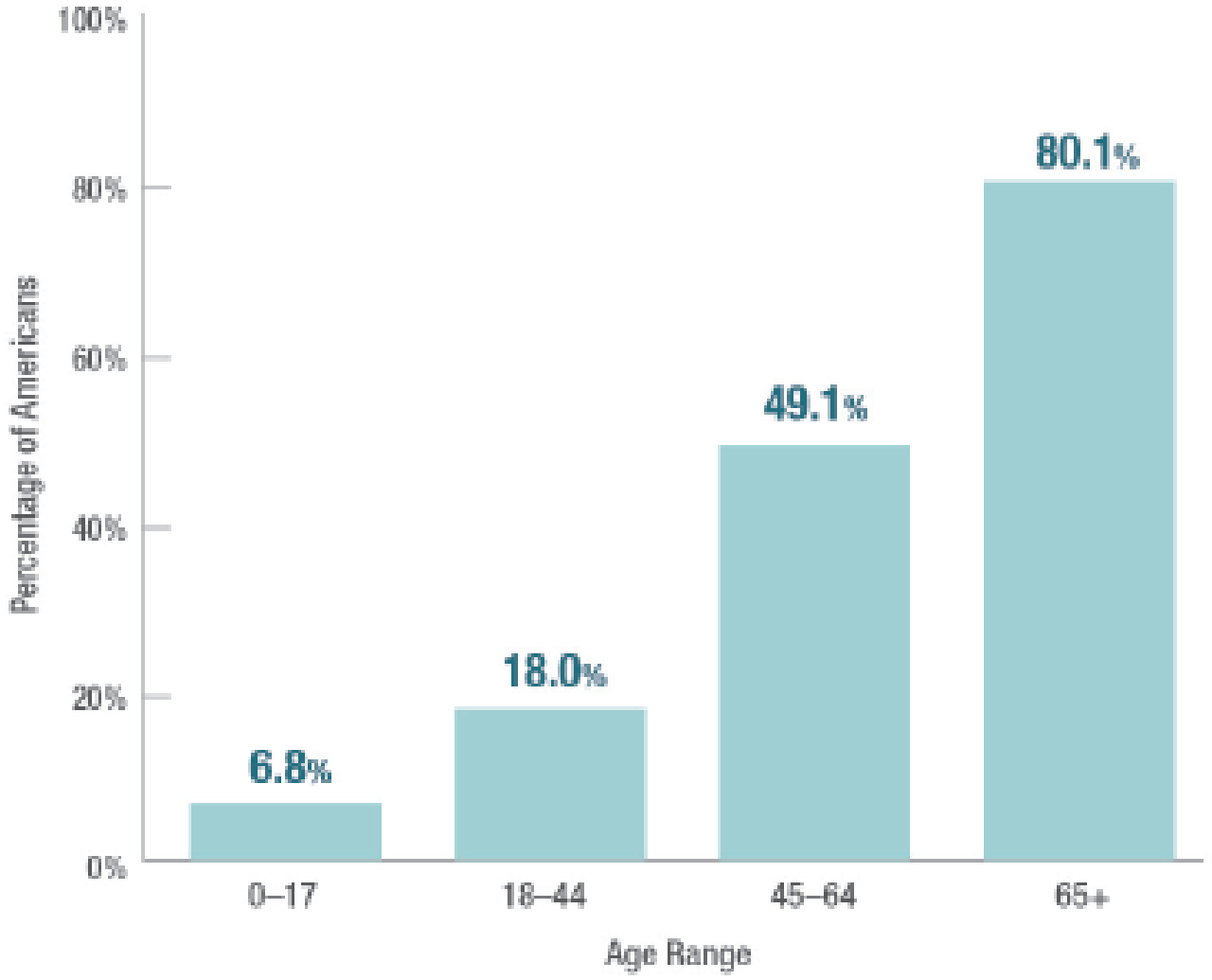
Percent of All Americans with Multiple Chronic Conditions, by Age Group – 2010



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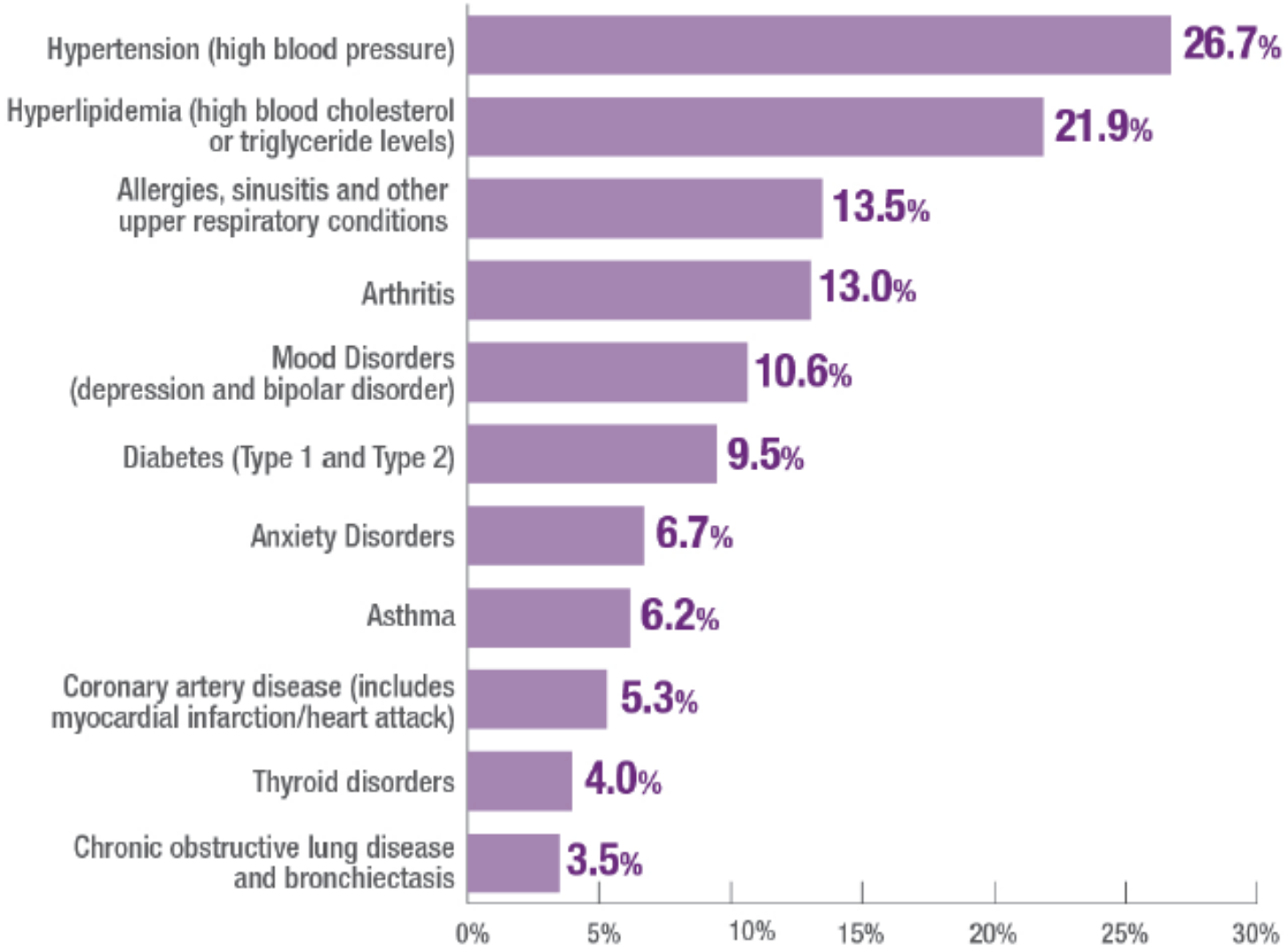
Most common chronic adult conditions



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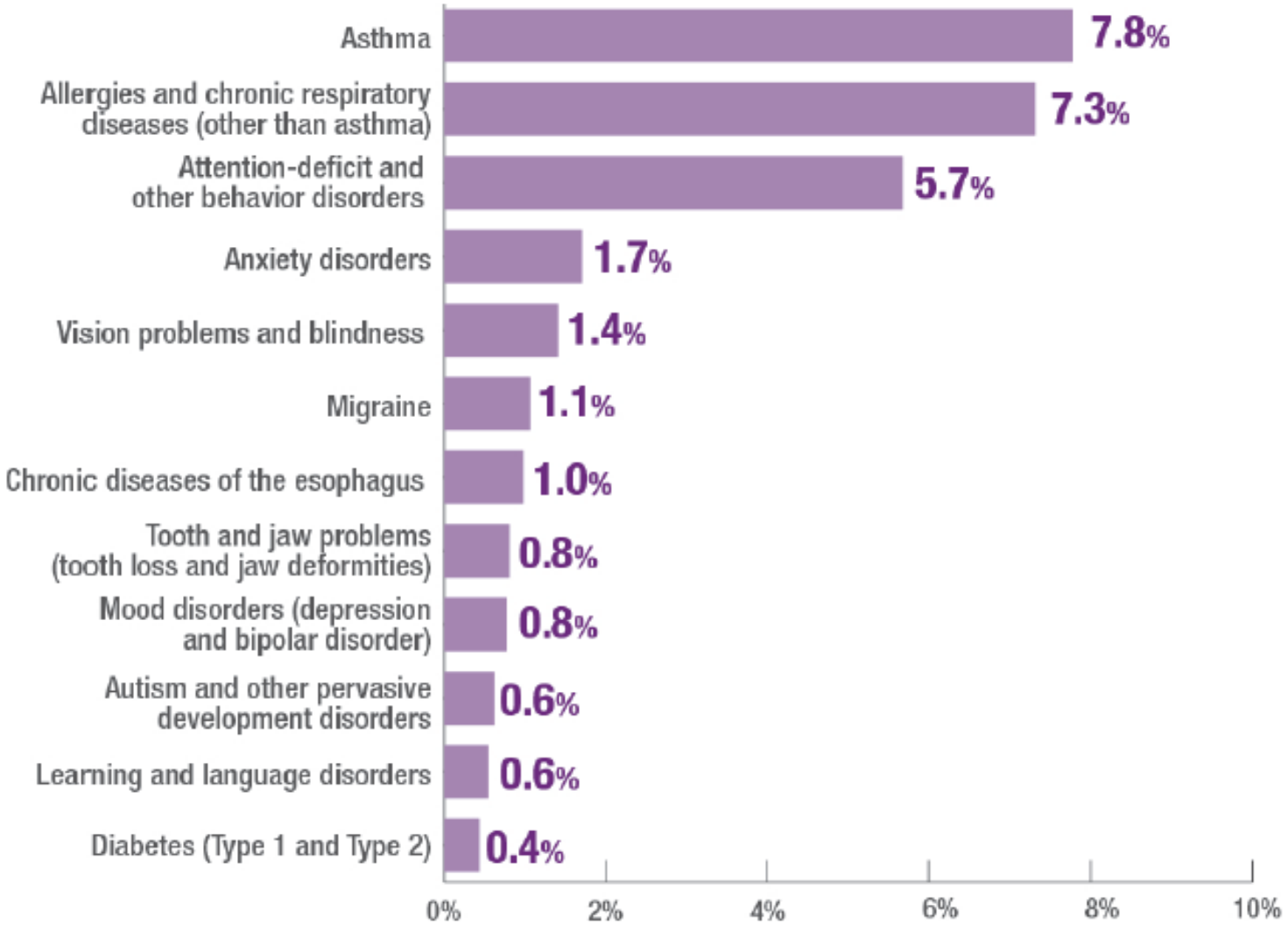
Most common chronic pediatric conditions



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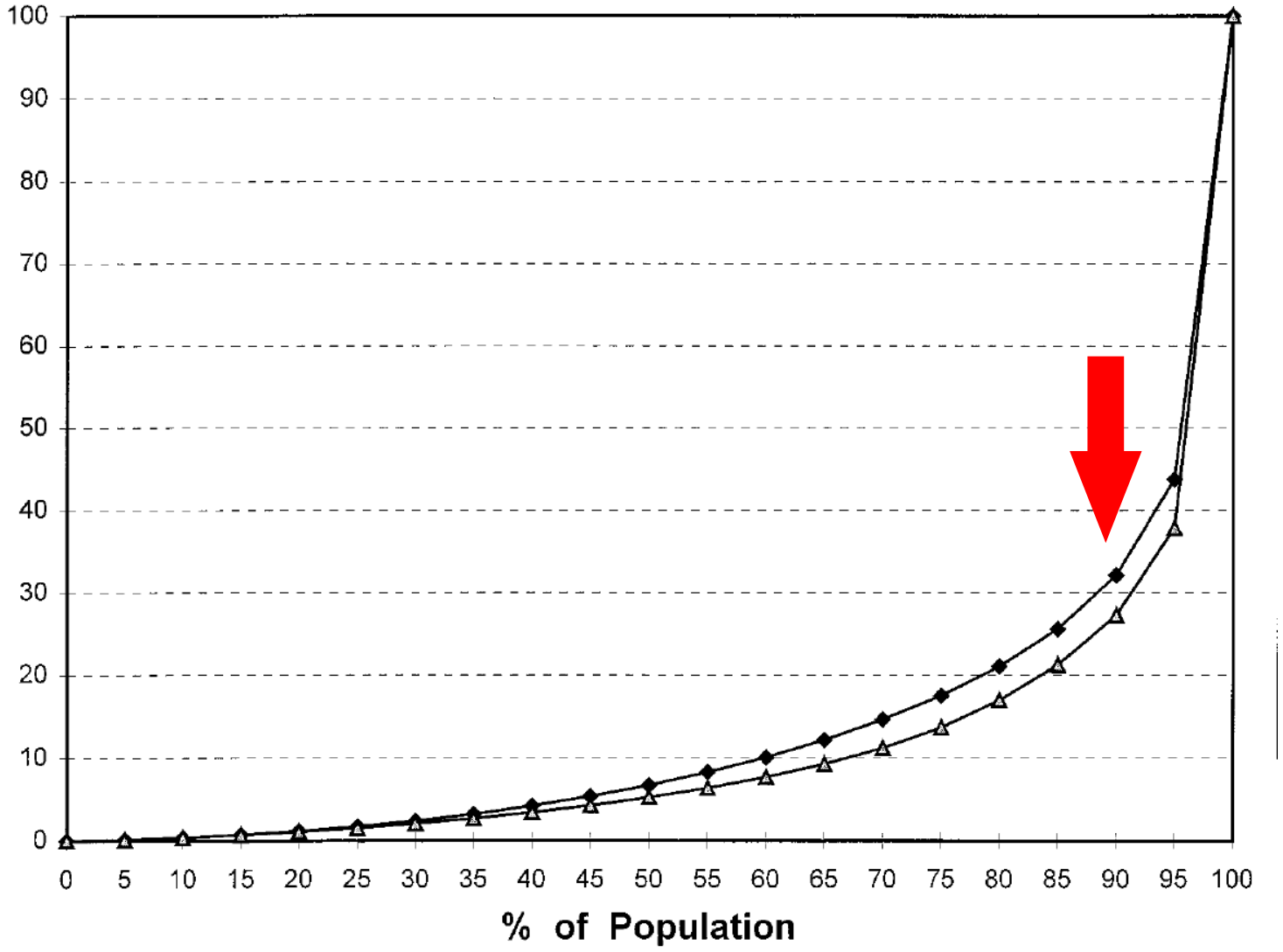
Distribution of Pediatric Health Costs



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Current trials in ClinicalTrials.gov

- Clinical trials for children & ‘probiotics’
- 65 trials currently listed as recruiting, enrolling or active
- The majority of studies focus on common conditions
  - Diarrhea
  - Acne
  - Respiratory tract infections
  - Gastroenteritis
  - Constipation
  - Colic

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Active Trials of Chronic Pediatric Conditions in ClinicalTrials.com

Condition	n	Intervention	Location
Children With Familial Hypercholesterolemia	40	*Lactobacillus paracasei* B21060 + prebiotics	Naples, Italy
Inflammatory bowel disease	80	VSL#3	Czech Republic
Cerebral Palsy (CP) and Chronic Constipation	40	*L. reuteri* DSM 17938	Guadalajara, Mexico
Extremely Low Birthweight Infants	150	LGG	Rockford Memorial Hospital (USA)
Type I Diabetes mellitus	30	VSL#3	Medical College of Wisconsin (USA)
Hirschsprung's associated enterocolitis (HAEC)	40	*Lactobacillus* LB	Cairo University
Juvenile idiopathic arthritis	120	VSL#3	Hôpitaux de Paris

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Active Trials of Chronic Pediatric Conditions in ClinicalTrials.com

Condition	n	Intervention	Location	Frequency
Children With Familial Hypercholesterolemia	40	*Lactobacillus paracasei* B21060 + prebiotics	Naples, Italy	1 in 400
Inflammatory bowel disease	80	VSL#3	Czech Republic	8 in 10,000
Cerebral Palsy (CP) and Chronic Constipation	40	*L. reuteri* DSM 17938	Guadalajara, Mexico	2 in 1000 (for CP)
Extremely Low Birthweight Infants	150	LGG	Rockford Memorial Hospital (USA)	< 1 in 1000
Type I Diabetes mellitus	30	VSL#3	Medical College of Wisconsin (USA)	2 in 1000
Hirschsprung associated enterocolitis (HAEC)	40	*Lactobacillus* LB	Cairo University	1 in 5000 newborns
Juvenile idiopathic arthritis	120	VSL#3	Hôpitaux de Paris	4 in 10,000

International Scientific Association for Probiotics and Prebiotics

Aberdeen 2014

Aberdeen, Scotland Meeting in 2014: Frank D'Amico, Dan Tancredi, Steven Davis, Valerie Sung, Francesco Savino, Flavia Indrio, Anna Partty, Hania Szajewska, Girish Deshpande, Katja Johnson, Silja Mentula, Raish Oozeer, Michael Cabana, Christophe Dupont

Turku 2016

Turku, Finland Meeting in 2016: Michael Cabana, Francesco Savino, Flavia Indrio, Daniel Tancredi, Frank d'Amico, Anna Partty, Valerie Sung, Kim Chau, Hania Szajewska

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Open Access Protocol

BMJ Open

Lactobacillus reuteri DSM 17938 for managing infant colic: protocol for an individual participant data meta-analysis

Valerie Sung,[1] Michael D Cabana,[2] Frank D'Amico,[3] Girish Deshpande,[4,5] Christophe Dupont,[6] Flavia Indrio,[7] Silja Mentula,[8] Anna Partty,[9] Francesco Savino,[10] Hania Szajewska,[11] Daniel Tancredi[12]

Lactobacillus reuteri to Treat Infant Colic: A Meta-analysis

Valerie Sung, PhD,[a] Frank D'Amico, PhD,[b,c] Michael D. Cabana, MD,[d] Kim Chau, PhD,[e] Gideon Koren, MD,[e] Francesco Savino, PhD,[f] Hania Szajewska, MD,[g] Girish Deshpande, MSc,[h] Christophe Dupont, PhD,[i] Flavia Indrio, MD,[j] Silja Mentula, PhD,[k] Anna Partty, PhD,[l] Daniel Tancredi, PhD[m]

abstract

CONTEXT: *Lactobacillus reuteri* DSM17938 has shown promise in managing colic, but conflicting study results have prevented a consensus on whether it is truly effective.

OBJECTIVE: Through an individual participant data meta-analysis, we sought to definitively determine if *L reuteri* DSM17938 effectively reduces crying and/or fussing time in infants with colic and whether effects vary by feeding type.

DATA SOURCES: We searched online databases (PubMed, Medline, Embase, the Cumulative Index

Differential Epidemiology

- Because of the distribution of disease, in many cases, chronic pediatric conditions are difficult to study
- Another reason why pediatric research lags behind adult research

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The 5 “D”s

- Developmental Issues
- Dependency
- Delayed Payoffs/Outcomes
- Differential Epidemiology
- Demographic Patterns

Forrest C, Simpson L, Clancy C. Child Health Services Research. *JAMA.* 1997;277:1787-93.

The 5 “D”s

- Developmental issues
- Dependency
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- **Demographic patterns**

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Demographic Patterns

- Children have disproportionately high rates of poverty and housing insecurity
- This issue can affect the types of health issues most urgent for clinical investigators to address, as well as the ability of children to participate in clinical studies

Figure 2.1 Food insecurity is high in some of the world's richest countries

Percentage share of children below the age of 15 living with a respondent who is food insecure, 2014/15

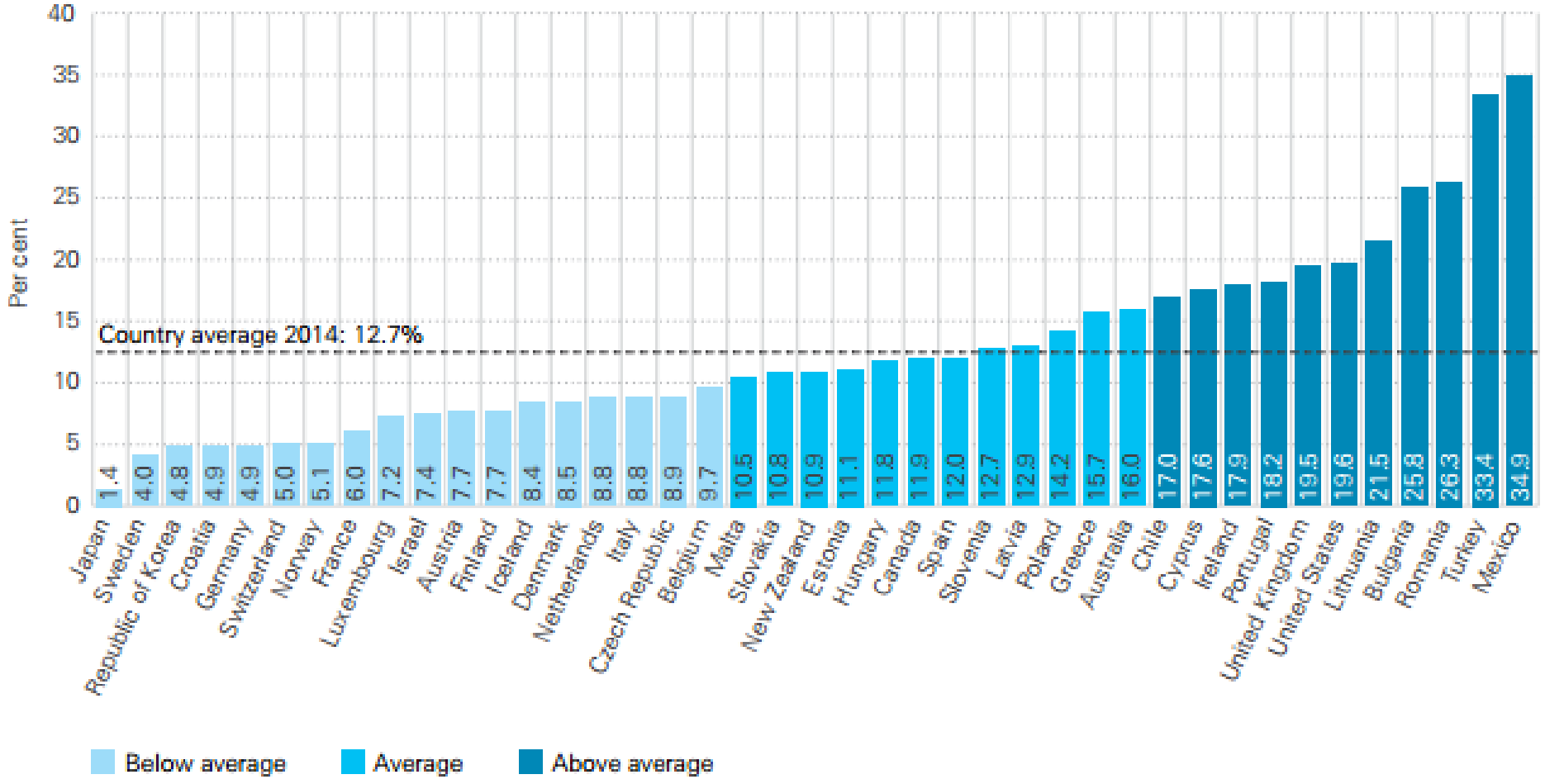
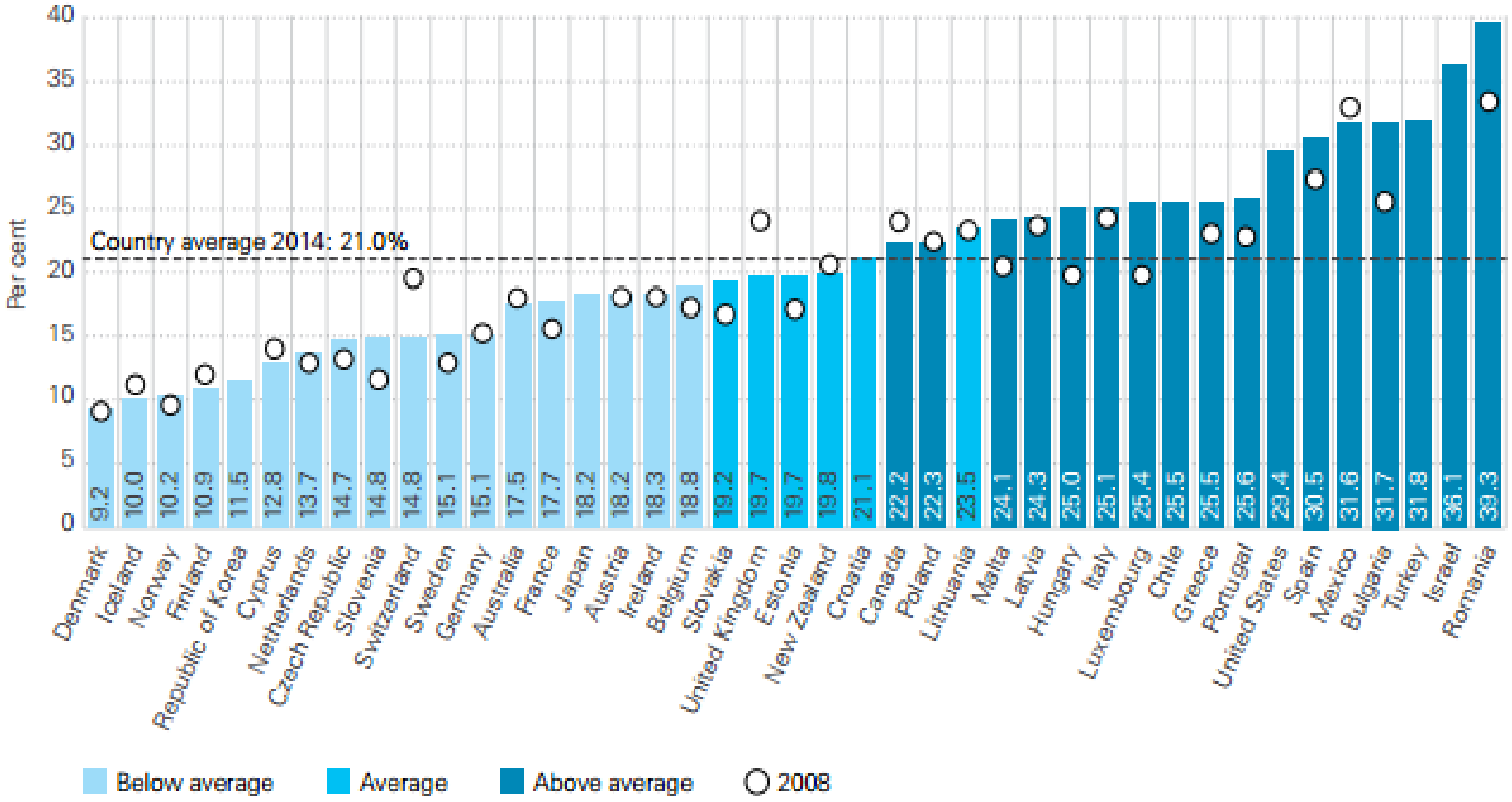


Figure 1.1 An average of one in five children in rich countries lives in relative income poverty

Percentage of children aged 0–17 living in a household with income lower than 60 per cent of the median, 2014 and 2008



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Demographic Patterns

- In the United States, children have the greatest degree of racial and ethnic diversity than any other segment of the population
- As of 2011, the majority of infants born in the United States were to parents of ‘minority’ groups

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UNIVERSITY OF CALIFORNIA, SAN FRANCISCO
CONSENTIMIENTO PARA PARTICIPAR EN UN ESTUDIO DE INVESTIGACIÓN

Título del estudio: Ensayo de suplemento probiótico para lactantes para prevenir el asma.

Éste es un estudio de investigación médica. Un miembro del equipo del estudio, encabezado por Michael Cabana, MD, MPH del Departamento de Pediatría de la UCSF, le explicará este estudio.

PROBIÓTICOS (¿qué son?)

¿Qué son los probióticos?

Los probióticos se definen como "microorganismos vivos que, cuando se toman en las cantidades adecuadas, mejoran la salud del huésped". Estos organismos son idénticos a los que se encuentran normalmente en alimentos fermentados como el yogur, la crema agria, el chucrut y el suero de la leche.

En los últimos años ha crecido el interés en el uso de probióticos para el tratamiento y la prevención de la enfermedad inflamatoria intestinal, la diarrea infecciosa y la asociada con los antibióticos (incluyendo la enterocolitis necrosante) y otras enfermedades como la dermatitis atópica y las infecciones recurrentes del tracto urinario.

¿Los probióticos son seguros para mi bebé?

Por lo general, los suplementos probióticos son seguros debido a que los

que eligen participar en
hijo(a) participe. Puede
de atención médica. Si

estudio debido a que
rte de la fase inicial del
n un mayor riesgo de

ealiza porque es difícil
etivo de este estudio es
de *Lactobacillus GG*
en el yogur) una vez al
go de desarrollar asma

(National Institutes of

Demographics

- Issues associated with poverty & food insecurity are more common in pediatrics and may affect research priorities
- Studies have to be culturally, as well as developmentally appropriate in pediatrics

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The 5 “D”s

- Developmental issues
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Forrest C, Simpson L, Clancy C. Child Health Services Research. *JAMA.* 1997;277:1787-93.

Category	Issues	Potential Solutions
Dependency	Assessment are based on parent perceptions	
	More complicated consent process	
	Greater justification needed for use of placebos	
Development	Higher scrutiny for the safety of early interventions during child development	
“Dollars”	Difficulty in measuring the long-term benefits of early intervention	
Differential Epidemiology	Limited numbers of children with specific conditions can limit recruitment	
Demographic Patterns	Higher rates of poverty make participation in research studies less of a priority	
	Greater need for study materials that are linguistically and culturally appropriate	

Category	Issues	Potential Solutions
Dependency	Assessment are based on parent perceptions	Develop better methods to observe & collect data
	More complicated consent process	Streamline the consent/assent process
	Greater justification needed for use of placebos	Use of equivalence studies, network meta-analysis
Development	Higher scrutiny for the safety of early interventions during child development	
“Dollars”	Difficulty in measuring the long-term benefits of early intervention	
Differential Epidemiology	Limited numbers of children with specific conditions can limit recruitment	
Demographic Patterns	Higher rates of poverty make participation in research studies less of a priority	
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Dependency	Assessment are based on parent perceptions	Develop better methods to observe & collect data
	More complicated consent process	Streamline the consent/assent process
	Greater justification needed for use of placebos	Use of equivalence studies, network meta-analysis
Development	Higher scrutiny for the safety of early interventions during child development	Greater understanding of basic mechanisms of action
“Dollars”	Difficulty in measuring the long-term benefits of early intervention	
Differential Epidemiology	Limited numbers of children with specific conditions can limit recruitment	
Demographic Patterns	Higher rates of poverty make participation in research studies less of a priority	
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Development	Higher scrutiny for the safety of early interventions during child development	Greater understanding of basic mechanisms of action
“Dollars”	Difficulty in measuring the long-term benefits of early intervention	Use of long term pediatric cohorts
Differential Epidemiology	Limited numbers of children with specific conditions can limit recruitment	
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Differential Epidemiology	Limited numbers of children with specific conditions can limit recruitment	Greater use of network studies, IPDMA
Demographic Patterns	Higher rates of poverty make participation in research studies less of a priority	
	Greater need for study materials that are linguistically and culturally appropriate	

Category	Issues	Potential Solutions
Dependency	Assessments are based on parent perceptions	Develop better methods to observe & collect data
	More complicated consent process	Streamline the consent/assent process
	Greater justification needed for use of placebos	Use of equivalence studies, network meta-analysis
Development	Higher scrutiny for the safety of early interventions during child development	Greater understanding of basic mechanisms of action
Delayed Payoff	Difficulty in measuring the long-term benefits of early intervention	Use of long term pediatric cohorts
Differential Epidemiology	Limited numbers of children with specific conditions can limit recruitment	Greater use of network studies, IPDMA
Demographic Patterns	Higher rates of poverty make participation in research studies less of a priority	Support research that reaches out to underserved communities & affects local issues important to communities
	Greater need for study materials that are linguistically and culturally appropriate	

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Agenda

- Review Common Clinical Examples (& Tradeoffs) with Probiotic Use
- Why Probiotic Research in Pediatrics is Challenging
- Potential Strategies

NHLBI:
http://www.nhlbi.nih.gov/childrenandclinicalstudies/index.php

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Beneficial Microbes, 2015; 6(5): 615-630

Wageningen Academic Publishers

Safety of probiotics and synbiotics in children under 18 years of age

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Received: 7 November 2014 / Accepted: 19 January 2015

RESEARCH ARTICLE

Abstract

This study aimed to systematically evaluate safety of probiotics and synbiotics in children ageing 0-18 years. This study is the third and final part in a safety trilogy and an update is provided using the most recent available clinical data (2008-2013) by means of the Common Terminology Clinical Adverse Events (CTCAE version 4.0) classification. Safety aspects are represented and related to number of participants per probiotic strain/culture, study duration, dosage, clinical condition and selected afflictions. Analysis of 74 clinical studies indicated that probiotic and/or synbiotic administration in children is safe with regard to the specific evaluated strains, dosages and duration. The population of children include healthy, immune compromised and obese subjects, as well as subjects with intestinal disorders, infections and inflammatory disorders. This study revealed no major safety concerns, as the adverse events (AEs) were unrelated, or not suspected to be related, to the probiotic or synbiotic product. In general the study products were well tolerated. Overall, AEs occurred more frequent in the control arm compared to children receiving probiotics and/or synbiotics. Furthermore, the results indicate inadequate reporting and classification of

1891

2018

children & CLINICAL STUDIES

Make Text Larger

No More Hand-Me-Down Research

Importance of Research In Kids

Why is research important, how is it different, safety and protections, are there benefits, your right to say no

Find out more

Getting Started In a Study

Information on the research team, what you might need to ask, and what role kids play in participating

Find out more

Once In a Study

Information on how studies affect the family and what kids think, what happens if you leave a study or what happens when it ends

Find out more

Resources

Know what rights you have, where to find information, and terms that you may hear in a study

Find out more

Show Video Transcript

Children have often had to accept medicines and treatments based on what is known to work in adults. As a society, we should not agree to this "hand-me-down" approach. Many efforts are being made to provide proper research for children, to find the best treatments, drugs, and devices for them.

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Summary

- **To stay at the forefront of health advances, continued research is needed**
- **Pediatric research is not 'smaller' adult studies**
- **Unique issues in pediatrics:**
  - Development, dependency, differential epidemiology, demographics and dollars
- **Support pediatric research**
  - Practice-based research networks
  - Stay informed about current research
  - Support families participating in research

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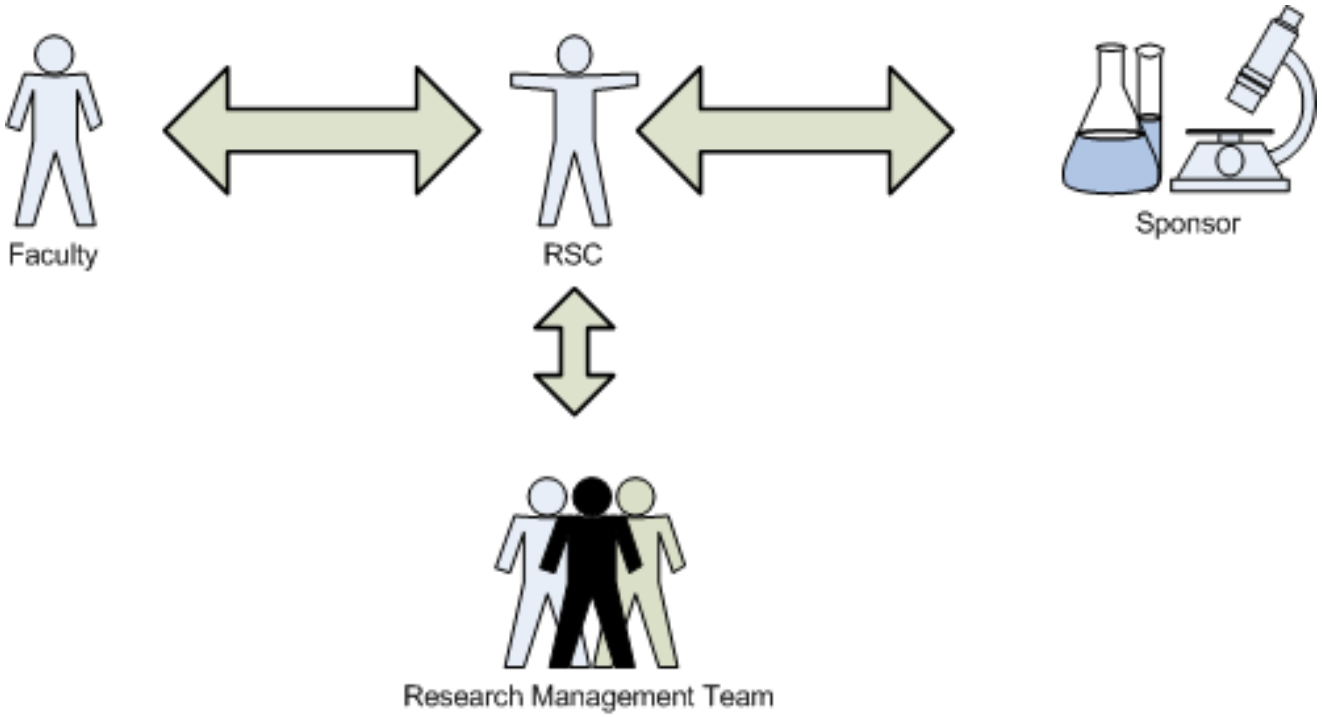
Graphics Slide



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Graphic

Funny joke

Interesting point

Split Slides

- **PI**
  - Point
  - Point

- **Main Point**

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- **How do you develop and implement systems of care to handle the routine conditions as well as the 'uncommon' conditions in child health care?**

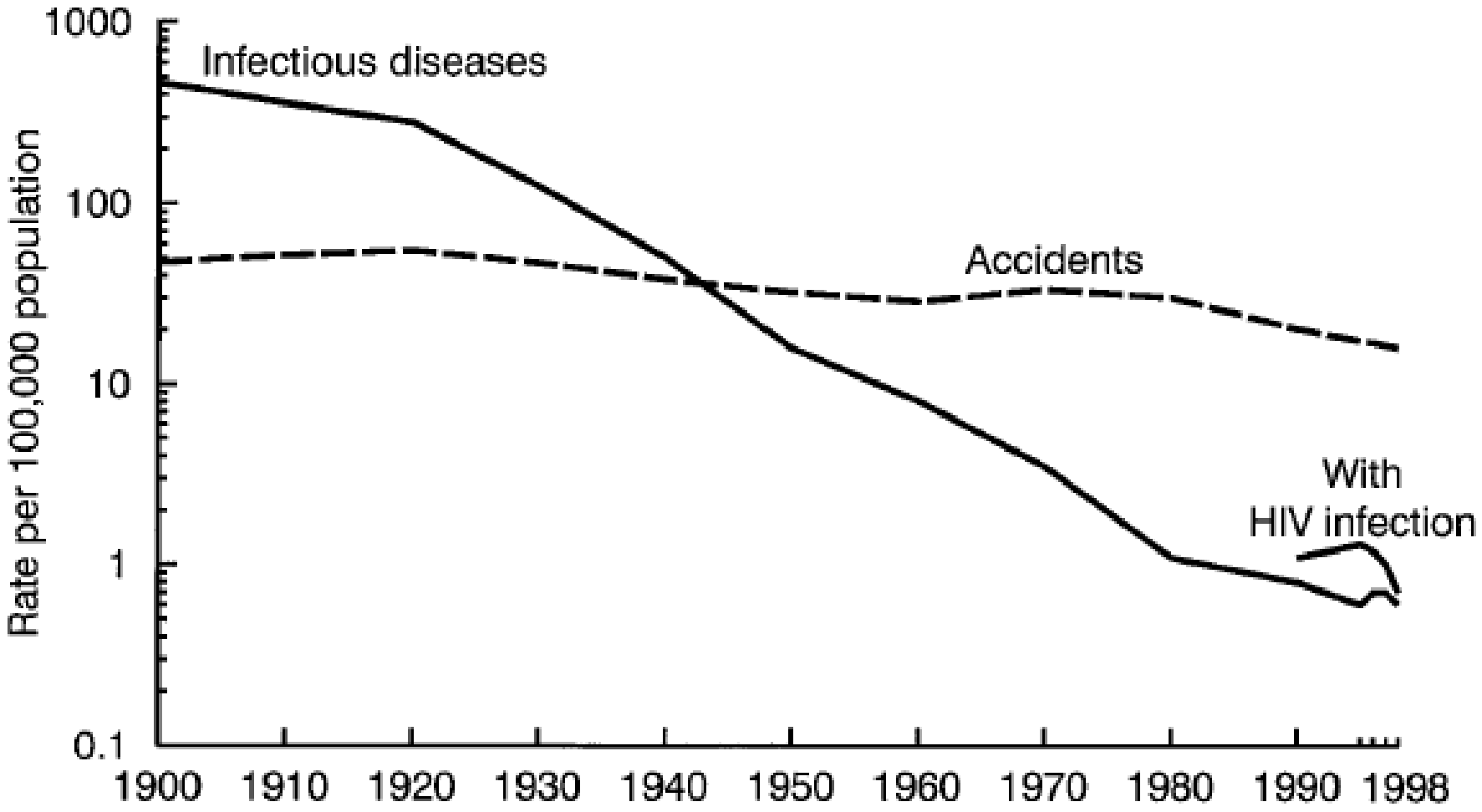

Fig 9. Death rates from infectious diseases and accidents, ages 1–19, selected years: United States, 1990–1998.

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- Acrocephalosyndactylia
- Acrodermatitis
- Addison Disease
- Adie Syndrome
- Alagille Syndrome
- Amylose
- Amyotrophic Lateral Sclerosis
- Angelman Syndrome
- Angiolymphoid Hyperplasia with Eosinophilia
- Arnold-Chiari Malformation
- Arthritis, Juvenile Rheumatoid
- Asperger Syndrome

- Bardet-Biedl Syndrome
- Barrett Esophagus
- Beckwith-Wiedemann Syndrome
- Behcet Syndrome
- Bloom Syndrome
- Bowen's Disease
- Brachial Plexus Neuropathies
- Brown-Sequard Syndrome
- Budd-Chiari Syndrome
- Burkitt Lymphoma

- Carcinoma 256, Walker
- Caroli Disease
- Charcot-Marie-Tooth Disease
- Chediak-Higashi Syndrome
- Chiari-Frommel Syndrome
- Chondrodysplasia Punctata
- Dandy-Walker Syndrome
- De Lange Syndrome
- Dementia, Vascular
- Dermatitis Herpetiformis
- DiGeorge Syndrome
- Diffuse Cerebral Sclerosis of Schilder
- Duane Retraction Syndrome
- Dupuytren Contracture

- Ebstein Anomaly
- Eisenmenger Complex
- Ellis-Van Creveld Syndrome
- Encephalitis

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Polio

- Franklin Roosevelt's contracting polio led to establishment of the National Foundation for Infantile Paralysis (NFIP)
- NFIP is now called the March of Dimes.
- The NFIP funded the 1954 Salk Polio Vaccine Trials.

Courtesy of Gail Pearson, MD

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The Evolution of Pediatric Care

- The field of pediatrics must *continually* add to current knowledge about how to best care for children through pediatric research.
- Research is broadly defined as the "systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge."

AsthmaNet

VIDA - Vitamin D Add-On Therapy Enhances Corticosteroid Responsiveness in Asthma

Mario Castro & Rand Sutherland,
Michael Cabana, Loren Denlinger, Fernando Holguin, Shamsah Kazani, Tonya King, Wendy Moore, James Moy, Chris Sorkness

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Vitamin D Deficiency

- ~1 billion people worldwide have low Vitamin D levels (<30 ng/mL)
- In asthma, Vitamin D deficiency has been associated with:
  - Increased severe exacerbations, hospitalizations, and ED visits
- Vitamin D may increase responsiveness to corticosteroids and also decrease the risk of viral upper respiratory infections

Ginde AA et al. Arch Int Med 2009; 169:384 Brehm JM et al. AJRCCM 2009; 179:765; JACI 2010; 126:52

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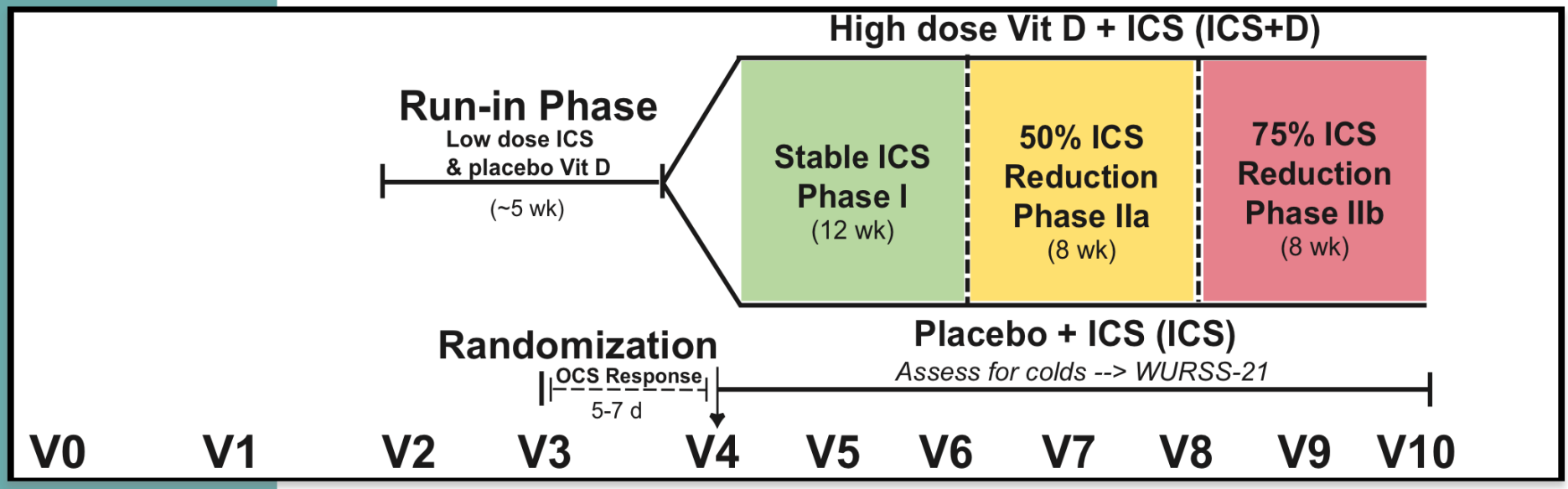
VIDA – Trial Design

- *Population*: Adults with asthma and vitamin D insufficiency (<30 ng/mL)
- *Intervention*: Vitamin D (loading dose then 4,000 U daily) or matching placebo added to low-dose inhaled corticosteroid



American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

CLINICAL REPORT

Prevention of Rickets and Vitamin D Deficiency in Infants, Children, and Adolescents

Guidance for the Clinician in Rendering Pediatric Care

Carol L. Wagner, MD, Frank R. Greer, MD, and the Section on Breastfeeding and Committee on Nutrition

ABSTRACT

Rickets in infants attributable to inadequate vitamin D intake and decreased exposure to sunlight continues to be reported in the United States. There are also concerns for vitamin D deficiency in older children and adolescents. Because there are limited natural dietary sources of vitamin D and adequate sunshine exposure for the cutaneous synthesis of vitamin D is not easily determined for a given individual and may increase the risk of skin cancer, the recommendations to ensure adequate vitamin D status have been revised to include all infants, including those who are exclusively breastfed and older children and adolescents. It is now recommended that all infants and children, including adolescents, have a minimum daily intake of 400 IU of vitamin D beginning soon after birth. The current recommendation replaces the previous recommendation of a minimum daily intake of 200 IU/day of vitamin D supplementation beginning in the first 2 months after birth and continuing through adolescence. These revised guidelines for vitamin D intake for healthy infants, children, and adolescents are based on evidence from new clinical trials and the historical precedence of safely giving 400 IU of vitamin D per day in the pediatric and adolescent population. New evidence supports a potential role for vitamin D in maintaining innate immunity and preventing diseases such as

www.pediatrics.org/cgi/doi/10.1542/peds.2008-1862

doi:10.1542/peds.2008-1862

Key Words
vitamin D, vitamin D deficiency, rickets, vitamin D requirements, infants, children, adolescents, 25-hydroxyvitamin D, vitamin D supplements

Abbreviations
AAP—American Academy of Pediatrics
25-OH-D—25-hydroxyvitamin D

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Agenda

- Background
- Why Pediatric Research is Unique
- Current Threats to Pediatric Research
- How to Support Pediatric Research

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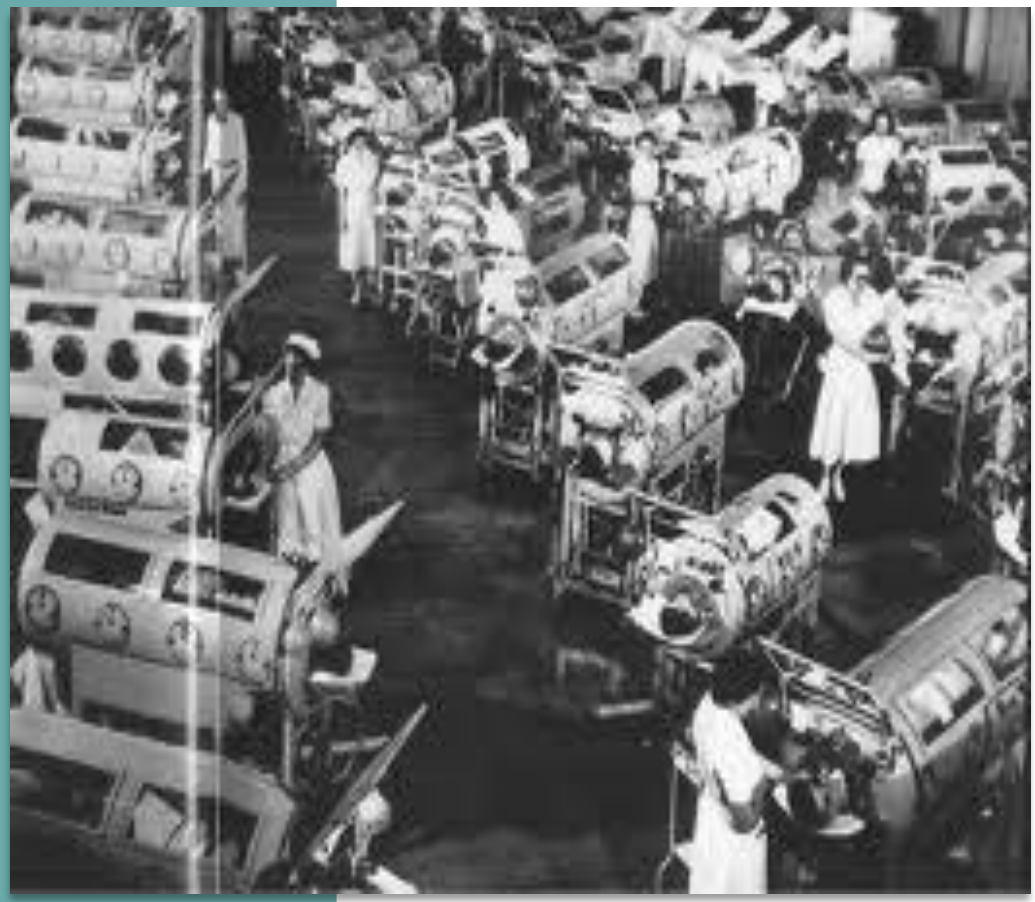
Polio



- Affected adults and children
- However, by the mid-20th century, the group most affected was children 5 to 9 years of age

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Salk Vaccine Trial

- **1952:** 58,000 cases of polio
- **1954:** Salk Vaccine Trial
  - 1,800,000 children
  - 1,000,000 in observational study
  - 750,000 in placebo-controlled trial
  - 220,000 volunteers
  - 64,000 school personnel
  - 20,000 Public Health Officers
- **1955:** Results announced on April 12

Courtesy of Gail Pearson, MD

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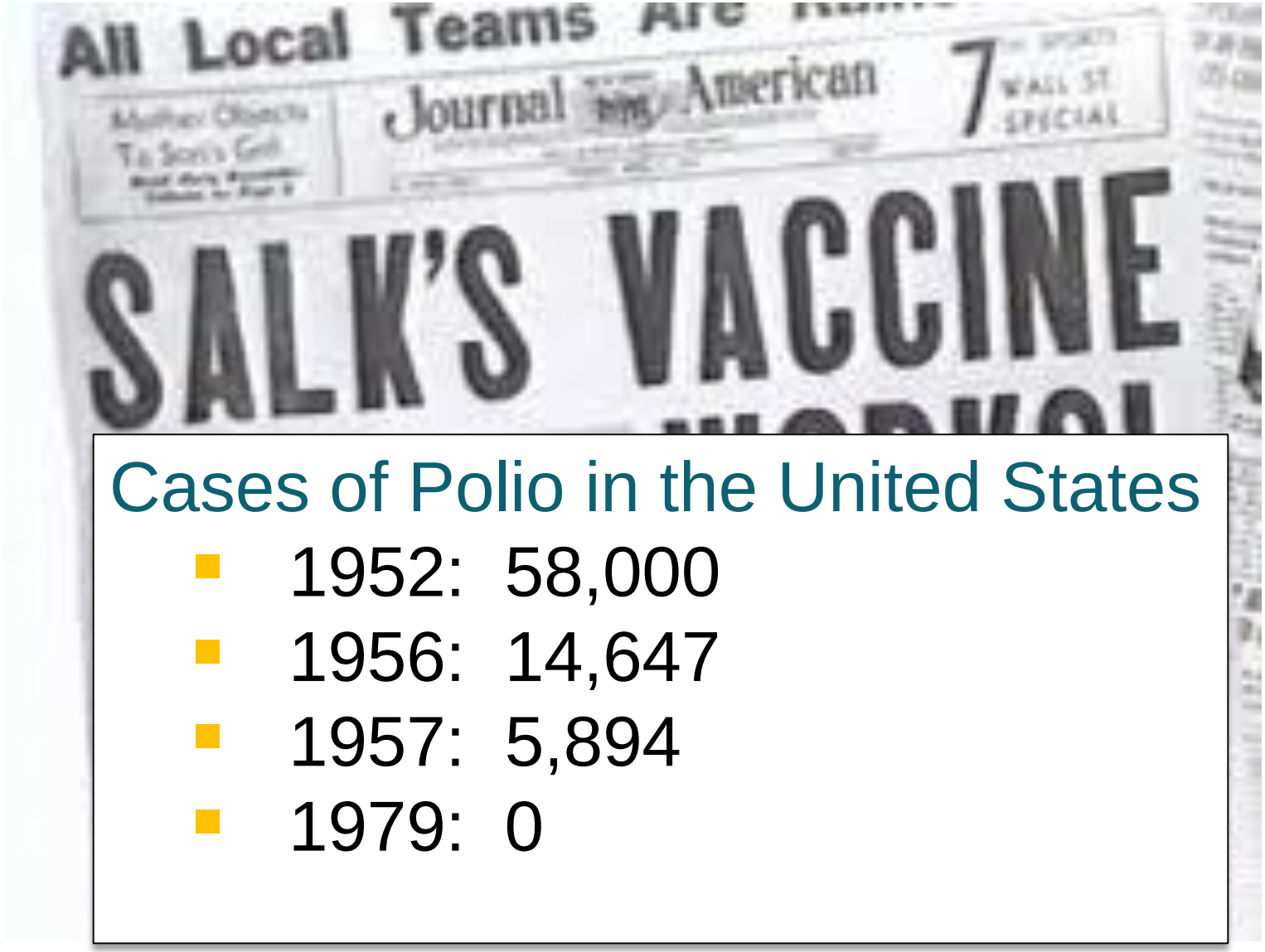
April 12, 1954



Cases of Polio in the United States

- 1952: 58,000
- 1956: 14,647
- 1957: 5,894
- 1979: 0

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So, why isn't more research done in kids?

Children's health on msnbc.com

1 in 4 parents thinks shots cause autism

But most follow doctors' advice and vaccinate kids anyhow

Jump to discuss
268 total comments

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Share 1

Below: Discuss Related

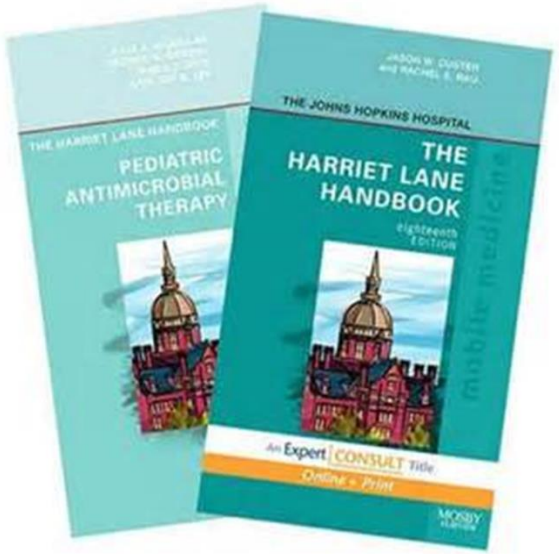
Associated Press

updated 3/1/2010 8:30:21 AM ET

Courtesy of Gail Pearson, MD, PhD

A victim of our own success

- Less concerns about childhood diseases that are vaccine preventable
- Complacency about drug development by providers; we assume that every pediatric medication has a FDA pediatric indication



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Agenda

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Practice Based Research Networks

- A group of clinics that affiliate for the purpose of examining the health care processes through research
- PROS: Primary Care Practices
- PRIS: Pediatric Inpatient Programs
- PECARN: Pediatric Emergency Medicine

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Goal of Pediatrics

- **The attainment of the optimal physical, mental, and social well-being of all infants, children, adolescents, and young adults**

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Developmental Issues

- Data must be placed into context of development and age

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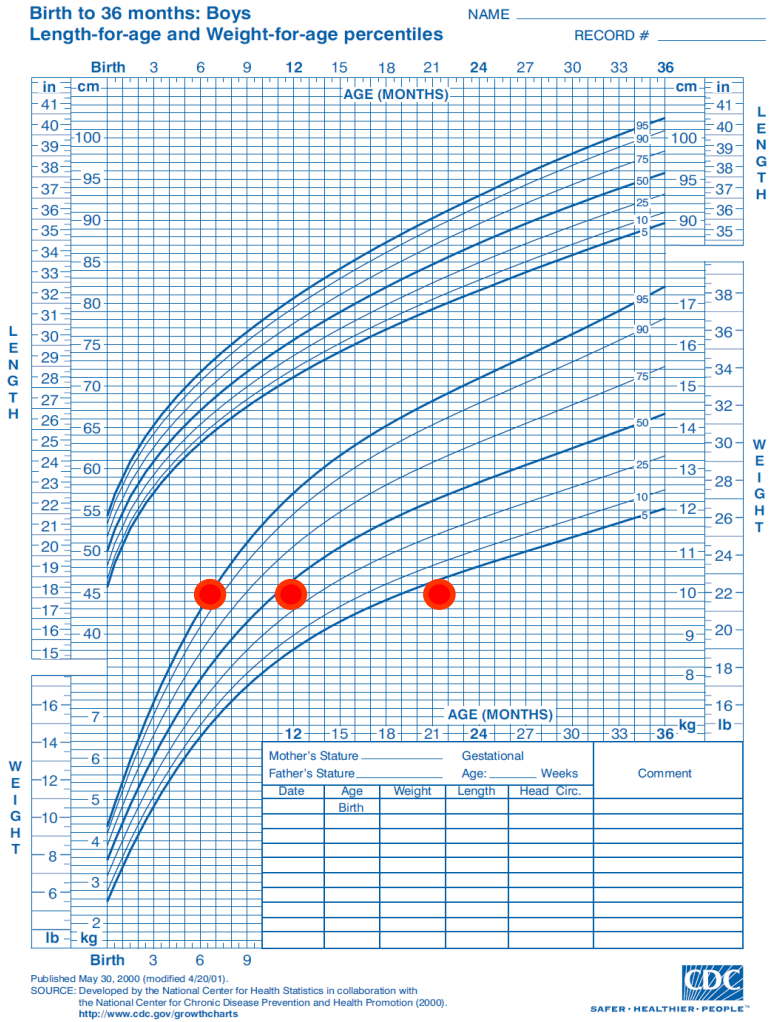
Development

Weight=10 kg

At 12 months?

At 22 months?

At 6 months?



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- Research in the use of probiotics and prebiotics has great potential to create many new therapies to improve the health of children. However, there are unique challenges in studying the effectiveness of probiotics and prebiotics in pediatric populations. Children differ from adults based on the 5 "D"s (Development, Dependency, Differential Epidemiology, Demographics and "Dollars"). This presentation will highlight issues in conducting research on children in the context of probiotic and prebiotic studies. Understanding these issues places the limitations of pediatric research in context and increases awareness of other important questions to answer in terms of pediatric therapies.

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"The Doctor" by Sir Luke Fildes

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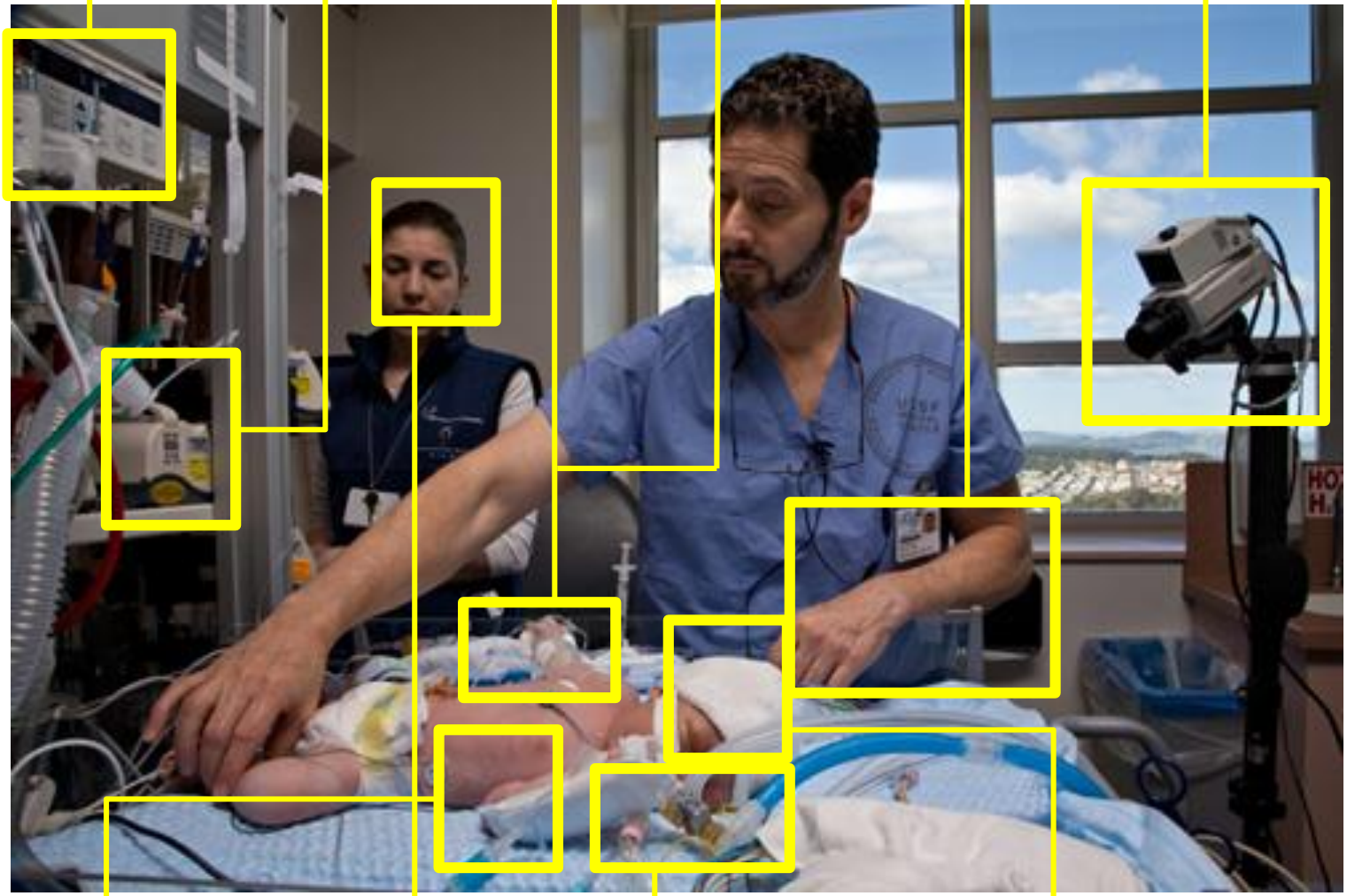

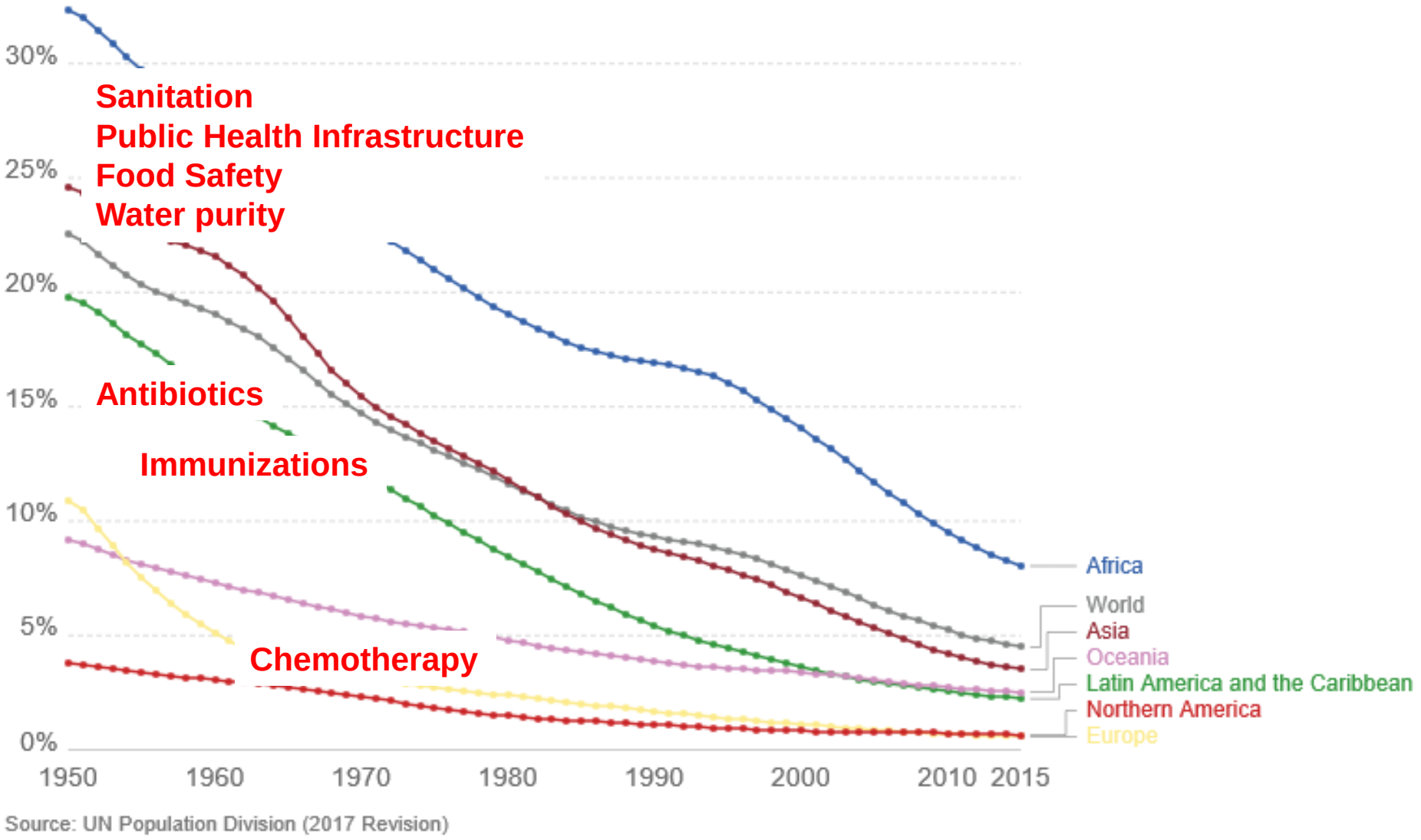
Child mortality
Share of children (born alive) dying before they are five years old.
30%
25%
20%
15%
10%
5%
0%
1950
1960
1970
1980
1990
2000
2010
2015
Sanitation
Public Health Infrastructure
Food Safety
Water purity
Antibiotics
Immunizations
Chemotherapy
Africa
World
Asia
Oceania
Latin America and the Caribbean
Northern America
Europe
Source: UN Population Division (2017 Revision)

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