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Current Trends in Acute Diarrhea

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Disclosure

- No conflict of interest

Outline

- Global Burden of Diarrhea
- Etiology of Acute Diarrhea
- Management Strategies
  - Mainstays
  - Adjuncts
  - Prevention

Global Burden of Diarrhea

- Diarrheal disease in children under 5 years (2015)
  - 688 M cases
  - 499,000 deaths
- Most deaths (90%) occur in South Asia and sub-Saharan Africa
- Progress seen (2000–2016): mortality from diarrhea in < 5 years decreased by 60%

Kotloff KL, et al. Global burden of diarrheal diseases among children in developing countries: Incidence, etiology, and insights from new molecular diagnostic techniques. Vaccine 2017; 35: 6783–9.

https://data.unicef.org/topic/child-health/diarrhoeal-disease.

Etiology of Moderate-to-Severe Diarrhea in Developing Countries

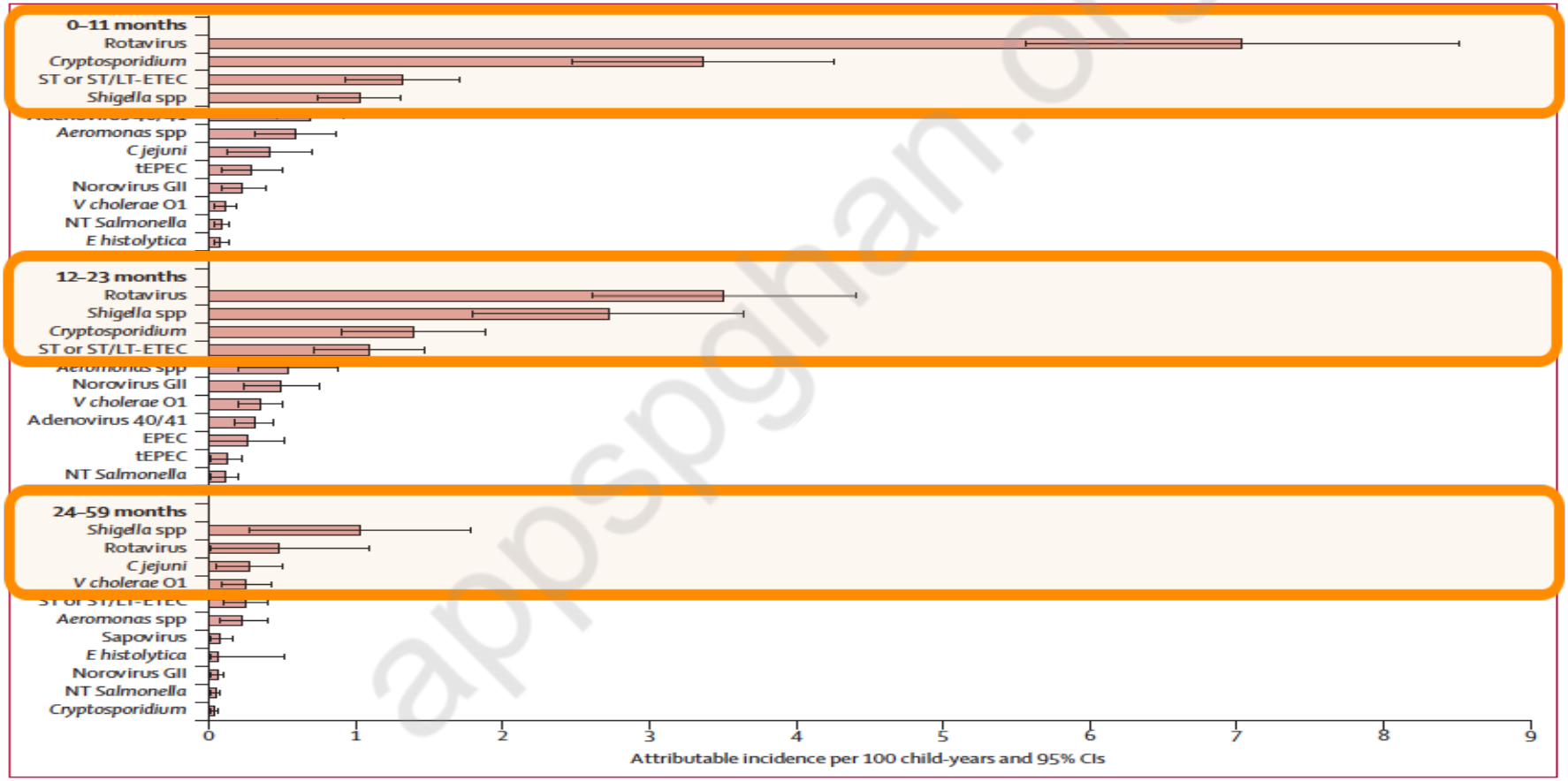
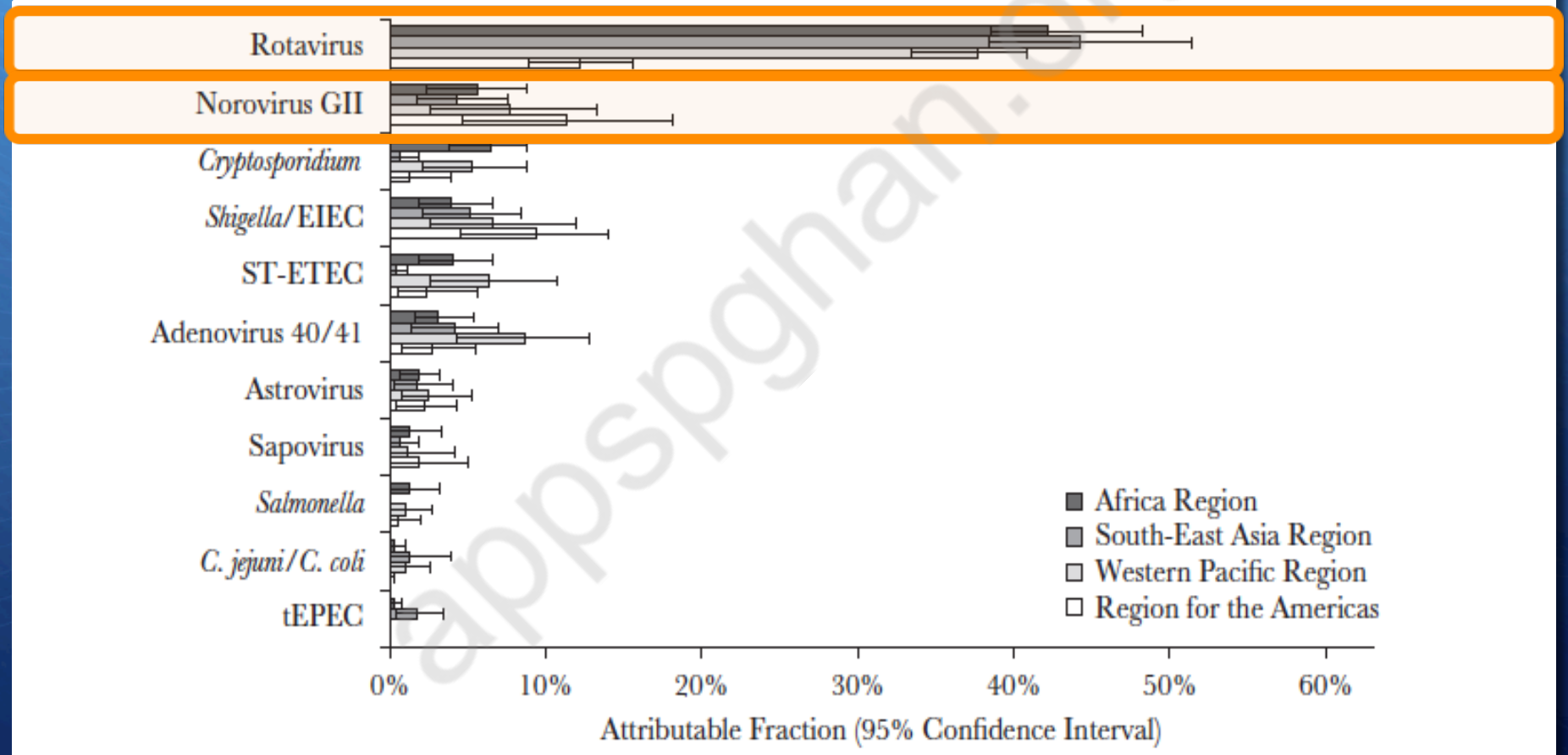


Figure 4: **Attributable incidence of pathogen-specific moderate-to-severe diarrhoea per 100 child-years by age stratum, all sites combined**
The bars show the incidence rates and the error bars show the 95% CIs.

Kotloff KL, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (Global Enteric Multicenter Study, GEMS): a prospective, case-control study. www.thelancet.com. May 14, 2013.

Etiology of Acute Watery Diarrhea in Children in Global Rotavirus Surveillance Network using PCR



Operario DJ, et al. J Infect Dis 2017; 216: 220–7.

Norovirus Prevalence in < 6 yrs old

- 4-country study (Brazil, Chile, Philippines, Thailand) in 8 predominantly urban hospitals (n=1649) by PCR detection

Country	Asymptomatic (%)	OPD (%)	Inpatient (%)	Nosocomial (%)
Brazil	7	31	33	42
Chile	10	30	14	22
Philippines	10	16	15	0
Thailand	10	18	9	0
Overall	10	24	18	21

Bravo LC, et al. Burden of Norovirus Disease in Children. Asia Pacific Congress of Pediatrics. Bali. August 28, 2018

Subclinical Infections

- Highly prevalent among children under 5 years
  - 72% of controls (n=13,129) in the study (Global Enteric Multicenter Study) of children with moderate-to-severe diarrhea had one or more pathogens
- Subclinical infections
  - May lead to alterations in gut structure and function
  - Can result in repeated infections and impaired gut function (environmental enteric dysfunction or tropical enteropathy)

Das JK, Bhutta ZA. Global challenges in acute diarrhea. Curr Opin Gastroenterol 2016; 32: 18–23.
Kotloff KL, et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (Global Enteric Multicenter Study, GEMS): a prospective, case-control study. www.thelancet.com. May 14, 2013.

Subclinical Infections

Prevalence of *Shigella* among episodes of moderate-to-severe diarrhea with and without dysentery in the Global Enteric Multicenter Study (GEMS), all sites combined, as determined by stool culture.

	Total No.	No. of cases (%)	No. of controls (%)	Odds ratio*	95% confidence interval	P value
Watery diarrhea						
0–11 months	7084	65/3264 (2.0)	10/3820 (0.3)	7.5	3.8–14.6	<0.001
12–23 months	5618	144/2420 (6.0)	72/3198 (2.3)	2.0	2.3–4.1	<0.001
24–59 months	3995	103/1492 (6.9)	54/2503 (2.2)	4.3	3.0–6.2	<0.001
Dysentery						
0–11 months	1774	117/747 (15.7)	5/1027 (0.5)	52.0	16.5–163.8	<0.001
12–23 months	1944	339/776 (43.7)	32/1168 (2.7)	33.9	20.2–57.0	<0.001
24–59 months	2060	322/706 (45.6)	40/1354 (3.0)	37.4	22.9–61.0	<0.001

* Estimated from conditional logistic regression.

Kotloff KL, et al. Global burden of diarrheal diseases among children in developing countries: Incidence, etiology, and insights from new molecular diagnostic techniques. Vaccine 2017; 35: 6783–9.

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Environmental Enteric Dysfunction

- Chronic, subclinical inflammatory state considered as probable cause of:
  - Failure of nutritional interventions
  - Susceptibility to infection due to the chronic burden of enteropathogens
  - Chronic malnutrition
  - Poor response to oral vaccines

Syed S, Ali A, Duggan C. JPGN 2016; 63: 6–14.

Mainstays in Diarrhea Treatment

Reduced Osmolarity ORS

+

Continued Feeding

+

Supplementation for > 6 mos in resource-limited countries

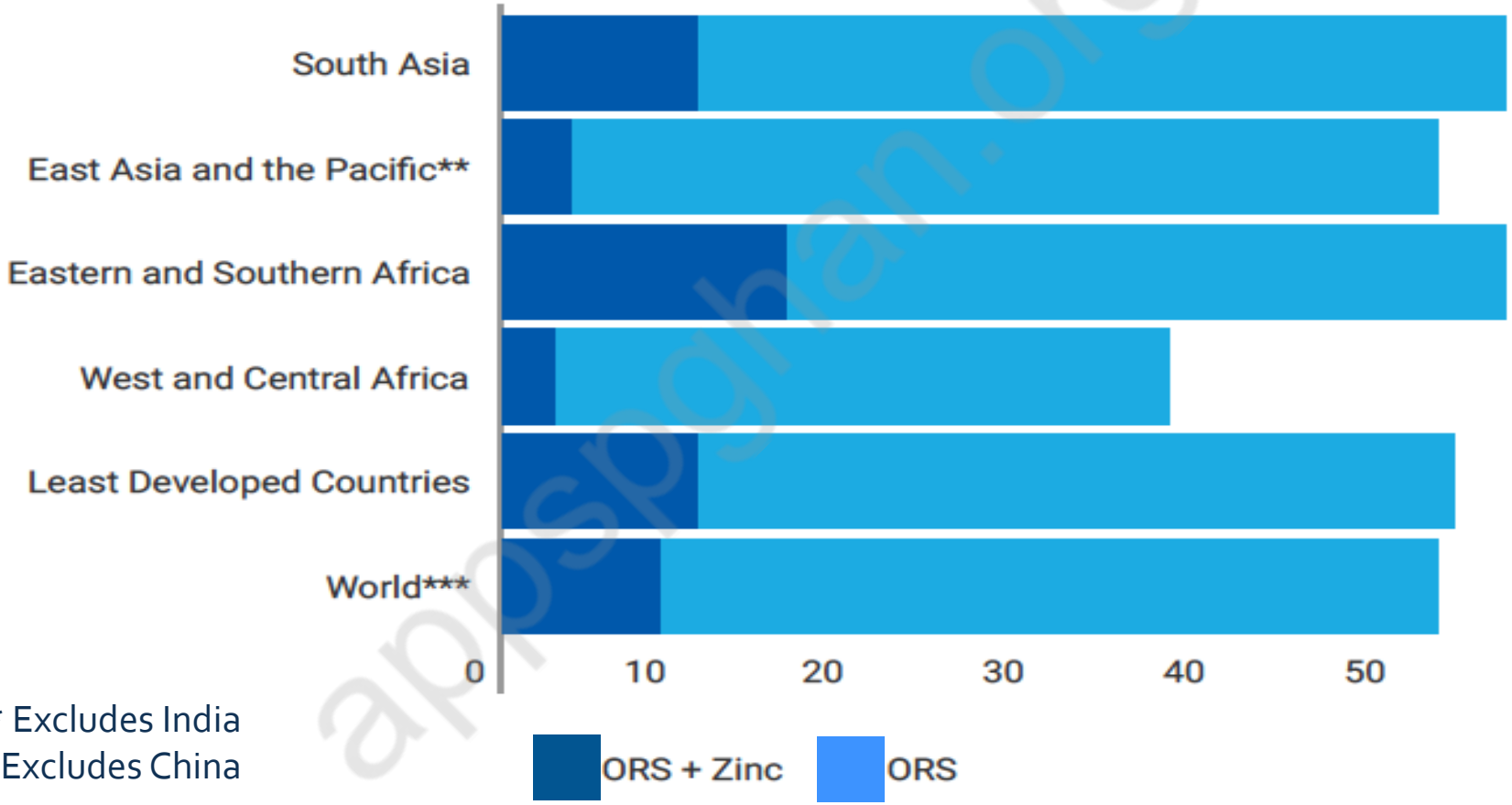
https://data.unicef.org/topic/child-health/diarrhoeal-disease. June 2018.

Interventions and their Impact on Diarrhea Management

Intervention	Effect Estimate [95% CI]
ORS	Reduced diarrhea-specific mortality by **69% [51%, 80%]** and treatment failure to **0.2% [0.1%, 0.2%]**
Zinc supplementation (Therapeutic)	Reduced all-cause mortality by **46% [12%, 68%]** and diarrhea hospitalization by **23% [15%, 31%]**
Zinc supplementation (Preventive)	Reduced diarrhea incidence by **13% [6%, 19%]** but no impact on mortality

Das JK, Salam RA, Bhutta ZA. Global burden of childhood diarrhea and interventions. Curr Opin Infect Dis 2014; 26: 451–8.

Percentage of children with diarrhoea receiving ORS and percentage receiving ORS + zinc supplementation for diarrhoea treatment in Asia and sub-Saharan Africa, by UNICEF region, 2011-2016



* Excludes India
** Excludes China

UNICEF Global databases 2017 based on MICS, DHS, and other nationally representative sources. https://data.unicef.org/topic/child-health/diarrhoeal-disease. June 2018.

Management Strategies

- Intensify compliance with mainstays of treatment
- Community interventions
  - **Increase** in ORS use by **160% [95 CI: 60%, 327%]**
  - **Increase** in zinc use by **80%**
  - **Decline** in inappropriate use of antibiotics by **75% [95% CI: 49%, 88%]**

Das JK, Salam RA, Bhutta ZA. Global burden of childhood diarrhea and interventions. Curr Opin Infect Dis 2014; 26: 451–8.

Feeding in Acute Diarrhea

- Early vs. delayed refeeding (12 hrs from start of rehydration)
  - Early refeeding SAFE: No difference in vomiting episodes, unscheduled IV rehydration, development of persistent diarrhea, and duration of hospital stay
- Lactose Intolerance
  - Transient and only in small group of children
  - Lactose restriction for SAM ± severe dehydration
  - No introduction of CM during or shortly after diarrhea
  - Usual diet with adequate calories

Gregorio GV, et al. Early versus delayed refeeding for children with acute diarrhoea. Cochrane Database Syst Rev 2011; Issue 7. Art. No.: CD007296.
Brandt KG, et al. Acute Diarrhea: evidence-based management. J Pediatr (Rio J) 2015; 91: S36–S43.

Management Strategies: Adjuncts – Probiotics

- Lactobacillus rhamnosus GG (LGG) and Saccharomyces boulardii with strong recommendations
- LGG at a daily dose of $\geq 10^{10}$ CFU significantly reduced duration of diarrhea by −1.05 day [95% CI: −1.7 to −0.4]
- S. boulardii significantly reduced duration of diarrhea by −19.7 hrs [95% CI: −26.05 to −13.34]

Guarino A, et al. Universal recommendations for the management of acute diarrhea in non-malnourished children. JPGN 2018. DOI: 10.1097/MPG.0000000000002053.
Guarino A, et al. J Clin Gastroenterol 2015; 49 (Suppl 1): S37–S45.
Szajewska H, et al. Aliment Pharmacol Ther 2013; 38: 467–76.
Feizizadeh S, et al. Pediatrics 2014; 134: e176–e191.

Management Strategies: Adjuncts – Probiotics

- Lactobacillus reuteri DSM 17938
  - Reduced duration of diarrhea to mean difference of −24.82 hrs [−38.8, −10.8]
  - Heterogeneity high with wide confidence intervals
  - Included in the universal recommendations for management of acute diarrhea (2018)

Guarino A, et al. Universal recommendations for the management of acute diarrhea in non-malnourished children. JPGN 2018. DOI: 10.1097/MPG.0000000000002053.
Urbanska M, et al. Systematic review with meta-analysis: Lactobacillus reuteri DSM 17938 for diarrhoeal diseases in children. Aliment Pharmacol Ther 2016; 43: 1025–34.
Feizizadeh S, et al. Pediatrics 2014; 134: e176–e191.

Management Strategies: Adjuncts – Antisecretory Agents

- Racecadotril
  - Enkephalinase inhibitor
  - Efficacious among hospitalized patients and outpatients
    - Time to cure reduced by **28 hrs** ($p<0.0001$)
    - 48-hr stool output reduced by **53%** [331 ± 39 vs. 157 ± 27 g/kg]
    - Stool output reduced by **40%** (15 vs. 9 g/hr)

Eberlin M, et al. Racecadotril in the treatment of acute diarrhea in children: a systematic, comprehensive review and meta-analysis of randomized controlled trials. BMC Pediatrics 2018; 18: 124–8.

Management Strategies: Adjuncts – Adsorbents

- Diosmectite
  - Ambulatory and in-hospital settings
  - High-income and low- or middle-income countries
  - Reduce duration of diarrhea by **–24.38 hrs [95%CI: –30.91 to –17.85]**
  - Increase clinical resolution by day 3 with **risk ratio = 2.1 [95% CI: 1.3–3.39]**

Pérez-Gaxiola G, et al. Smectite for acute infectious diarrhoea in children. Cochrane Database Syst Rev 2018, Issue 4. Art. No.: CD011526.

Management Strategies: Super ORS

- High-amylose maize starch (HAMS)
  - Mechanism: SCFA stimulate colonic Na and fluid absorption independent of cAMP (Na-hydrogen exchange)
  - Fermentable starch added to ORS: production of SCFA

Binder HJ, et al. Oral rehydration therapy in the second decade of the twenty-first century. Curr Gastroenterol Rep 2014; 16: 376.

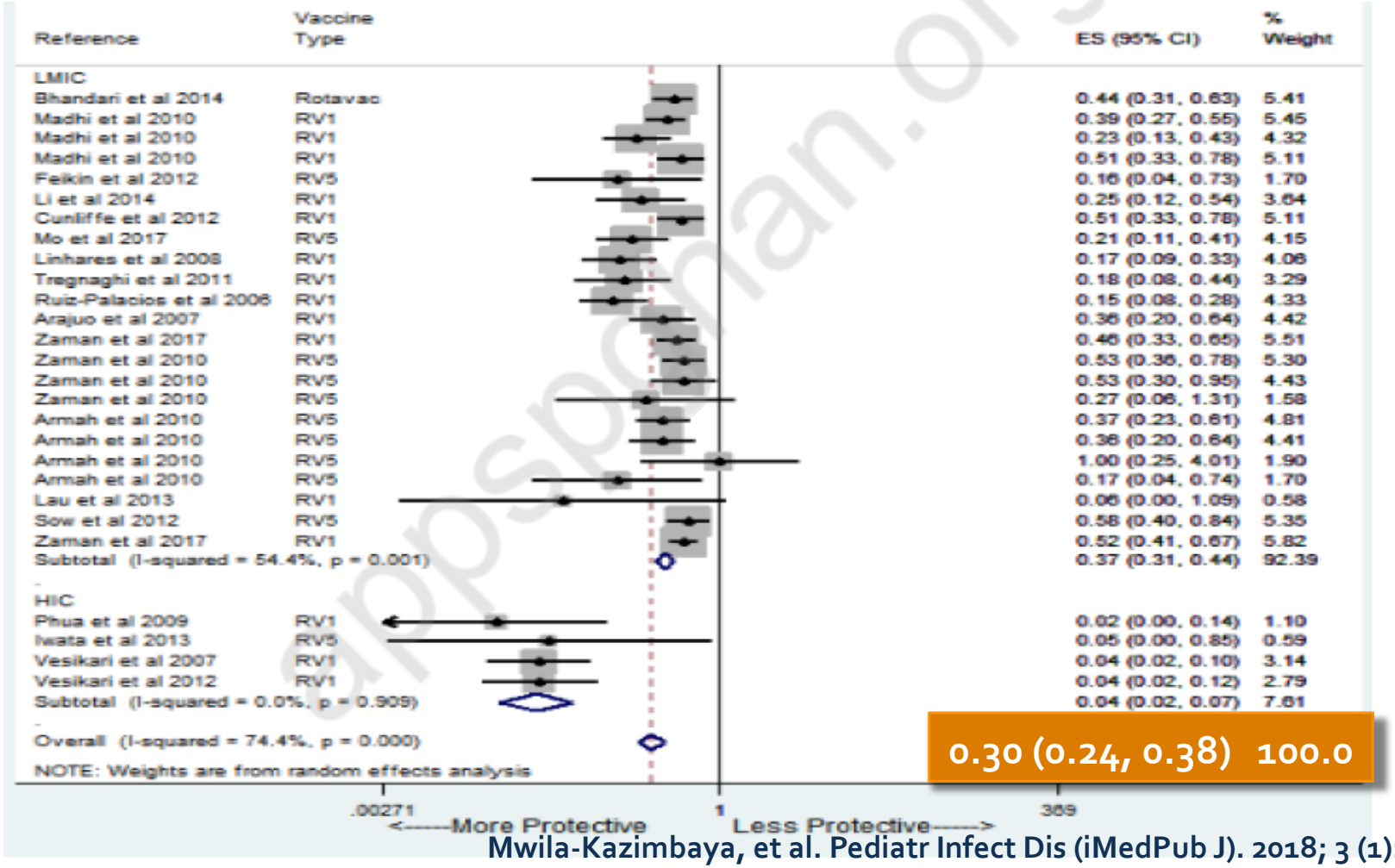
HAMS-ORS in Acute Diarrhea in Children

- Vellore, India; n=178 children; RCT (87 HAMS-ORS vs. 91 WHO-ORS); HAMS-ORS with 50 g starch added
- Results
  - Time from enrolment to last unformed stool decreased [**median 6.75 hrs**; 95% CI: 4.27, 9.22 vs. **median 12.8 hrs**; 95% CI: 8.69. 16.91] p=0.029
  - Time to first formed stool shorter [**median 18.25 hrs** ; 95% CI: 13.09, 23.41 vs. **21.5 hrs**; 95% CI: 17.26, 25.74] p=0.044

Raghupathy P, et al. Amylase-resistant starch as adjunct to oral rehydration therapy in children with diarrhea. JPGN 2006; 42: 362–8.

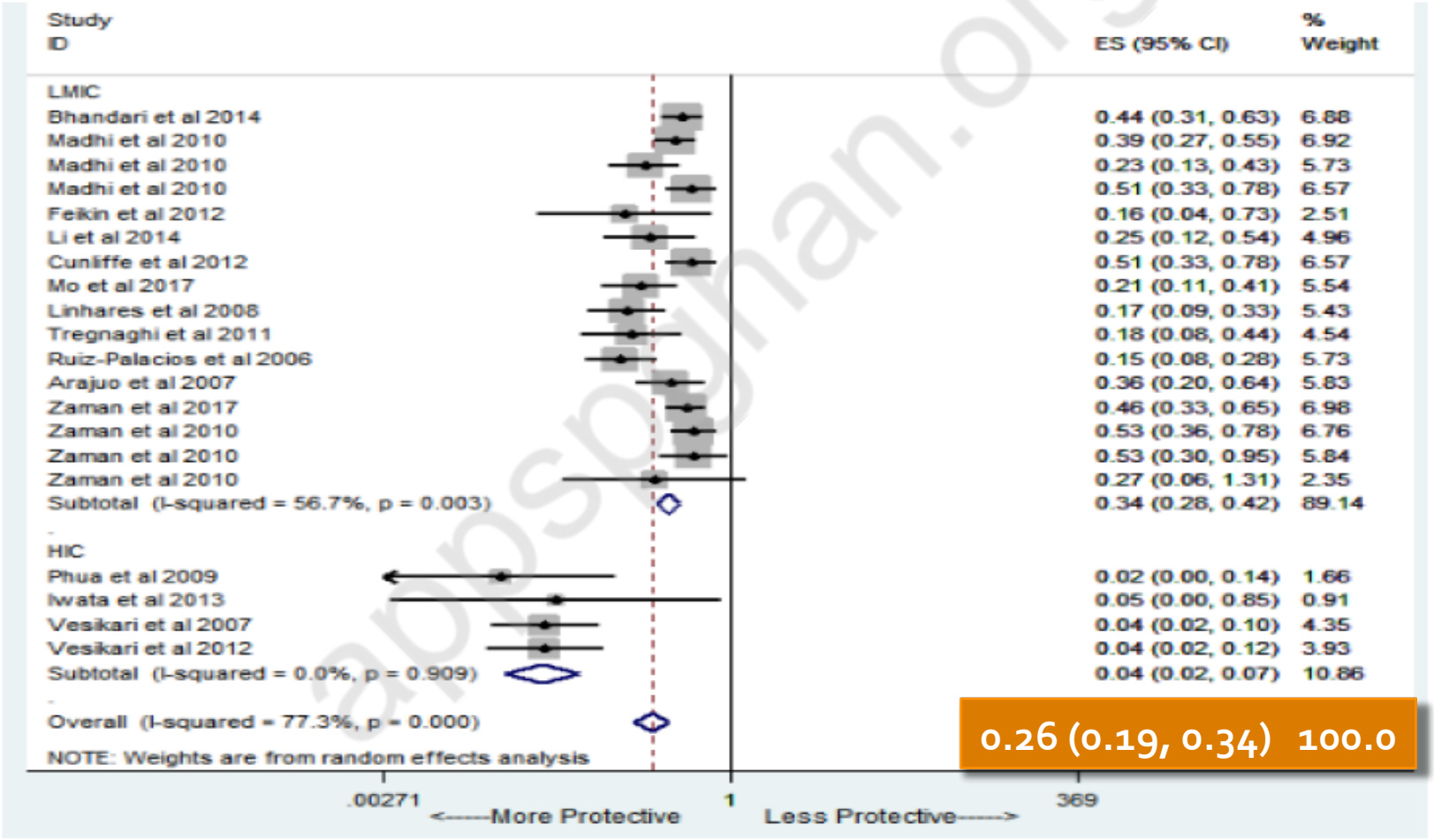
Management Strategies: Prevention through RV Vaccination

Efficacy of RV Vaccine on Incidence of Any & Severe Diarrhea in Children



Mwila-Kazimbaya, et al. Pediatr Infect Dis (iMedPub J). 2018; 3 (1): 4.

Efficacy of RV Vaccine on Incidence of Severe RVGE in Children



Mwila-Kazimbaya, et al. Pediatr Infect Dis (iMedPub J). 2018; 3 (1): 4.

RV Vaccine (RV1 & RV5) Effectiveness on Incidence of Diarrhea in Children by Income Status and Given Doses (expressed as Risk Ratio)

Doses	LMIC	HIC	Overall
One	**0.47** [0.36, 0.62]	**0.17** [0.15, 0.27]	**0.30** [0.22, 0.41]
Two	**0.39** [0.32, 0.47]	**0.14** [0.11, 0.17]	**0.22** [0.18, 0.28]
Three	**0.28** [0.14, 0.56]	**0.15** [0.10,0.22]	**0.18** [0.12, 0.28]

LMIC: Low-middle-income countries
HIC: High-income countries

Mwila-Kazimbaya, et al. Pediatr Infect Dis (iMedPub J). 2018; 3 (1): 4.

Effectiveness of RV1 in the Philippines

- Test-negative case control study on the vaccine effectiveness (VE) in routine public health program
- n=600 aged <5 yrs hospitalized with diarrhea, eligible to have received RV vaccine (3-yr study)

Parameter	Adjusted VE [95% CI]
RV hospitalization	**60%** [24%, 79%]
Severe RV diarrhea	**64%** [11%, 85%]

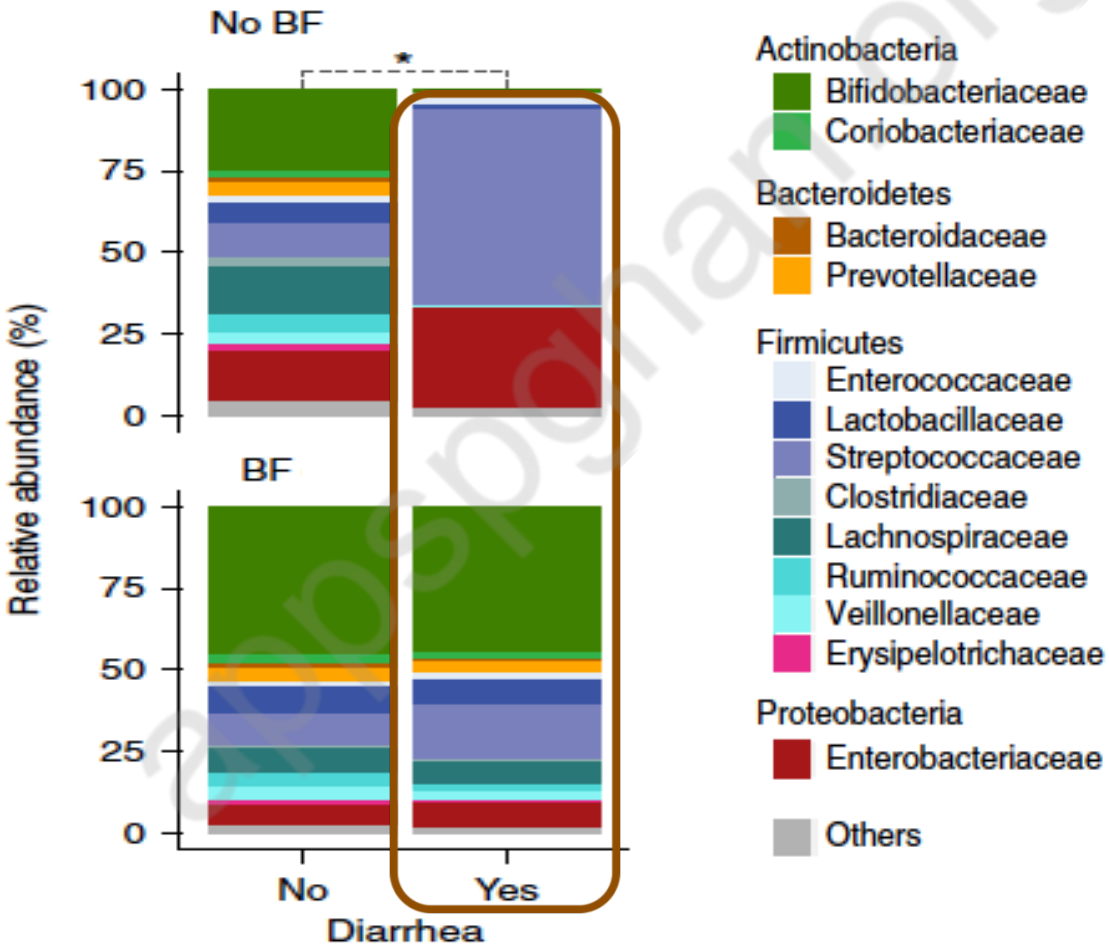
Lopez AL, et al. Sci Report 2018; 8: 14291.

Breastfeeding & Risk of Diarrhea

RELATIVE RISK [95% CI] Compared to exclusive BF (0–5 mos) and BF (6–23 mos)		
Breastfeeding Mode	**Prevalence of Diarrhea**	**Diarrheal Mortality**
0–5 mos old		
Predominant	2.15 [1.81, 2.55]	2.28 [0.85, 6.13] NS
Partial	4.62 [2.37, 9.00]	4.62 [1.81, 11.76]
None	4.90 [2.93, 8.21]	10.52 [2.79, 39.6]
6–23 mos old		
None	2.07 [1.49, 2.88]	2.18 [1.14, 4.16]

Lamberti LM, Fischer Walker CL, Noiman A, Victora C, Black RE. 2011; 11 (Suppl 3): 515.

Breastfeeding & Gut Microbiota during Diarrhea



Ho NT, et al. Meta-analysis of effects of exclusive BF on infant gut microbiota across populations. Nature Comm 2018; 9: 4169.

Summary

ROTAVIRUS is still a leading etiologic agent for severe diarrhea in the young.

MAINSTAYS in diarrhea treatment (fluids, feeding, and zinc) remain but increased compliance needed.

ADJUNCTS to treatment (probiotics, racecadotril, diosmectite) shorten course by ~1 day.

PREVENTION through BF and RV vaccination should be enhanced despite differences in efficacy and effectiveness among LMIC and HIC.