Childhood Diarrhea

Dr Harry Hazelwood MD MPH
World Health Organization/
Geneva Foundation For Medical Education,Geneva,Switzerland

By the end of this session…..

You should be able to:

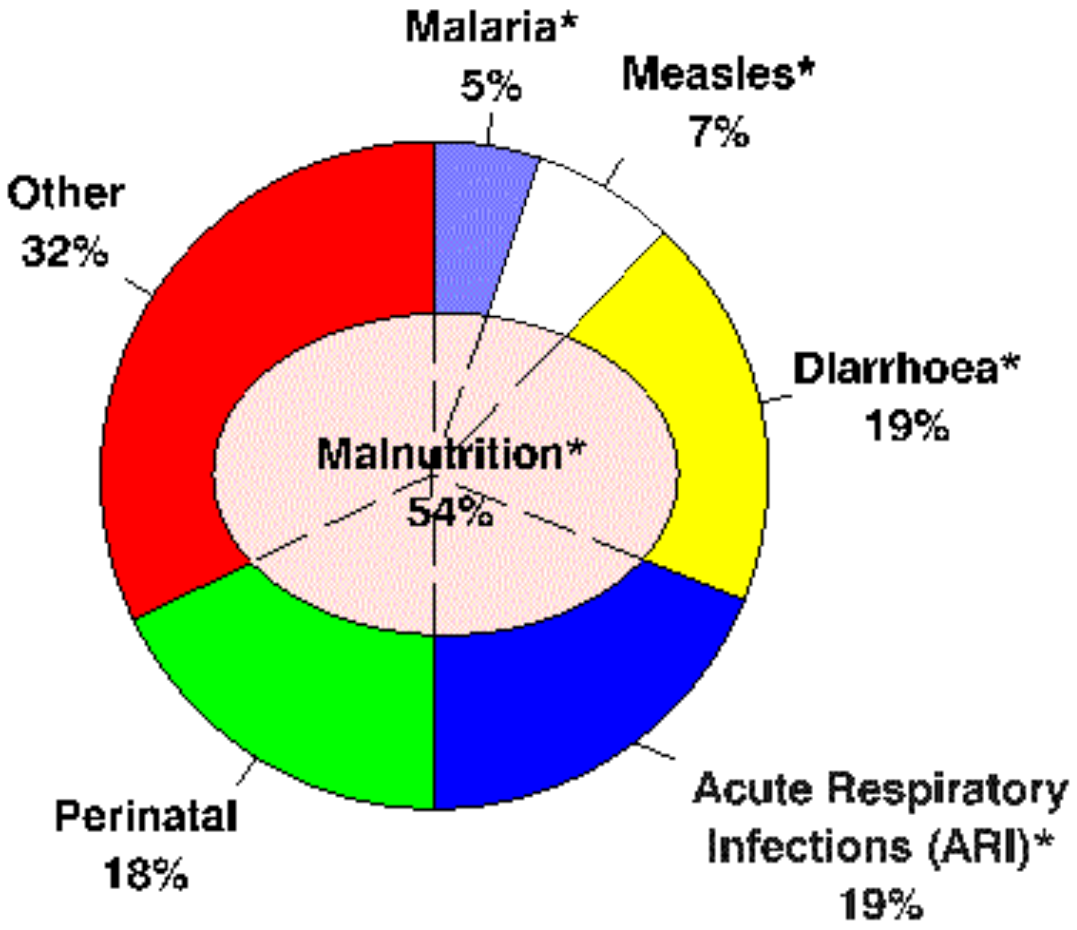
- Describe the global epidemiology of acute gastroenteritis
- Describe the features of gastroenteritis in children
- Discuss the common pathogens and mechanisms of gastroenteritis
- Assess and manage a child with acute or persistent gastroenteritis
- Describe the important preventative measures against diarrhoea

What is Diarrhoea?

A state where fluid, electrolytes and nutrients are lost from the gut

Defined as the passage of 3 or more liquid motions per day

Major causes of death among children under 5 years of age



Diarrhoeal deaths

- 1950s-70s 4.6 million deaths annually
- 1980s 3.3 million deaths annually

STILL causes 1.9 million deaths <5yrs annually (WHO 2003)

80% of deaths occur in children <2yrs

Predisposing factors

- POVERTY
- Poor sanitation
- Unsafe water supply
- Poor access to healthcare
- Malnutrition

Clinical types of diarrhoea

- *Acute watery diarrhoea* - most common, abrupt onset, usually infectious, causes dehydration and weight loss
- *Acute bloody diarrhoea* – may lead to mucosal damage, sepsis and malnutrition and sometimes dehydration
- *Persistent* diarrhoea - >14 days can result in malnutrition sepsis and dehydration
- *Diarrhoea with severe malnutrition* – may result in systemic infection, dehydration, heart failure and vitamin and mineral deficiency

Episodes of diarrhoea

- In developing countries, children <3 years have on average 3 episodes per year
- In the US, children <1 year average 1-2 episodes per year

The Case Fatality Rate

- Even in low income countries, the case fatality rate from a single episode of diarrhoea is low – usually <5%

- However the first attack often heralds the beginning of a slow spiral of recurrent infections and malnutrition

Gut Absorption

- Water is absorbed osmotically from the absorption of solutes
- The villous structure of the intestine greatly increases the effective surface area of absorption
- Solutes are absorbed by 2 main methods:
  - Active absorption through active ionic exchanges e.g. Na/ H pump (and thus requires glucose)
  - Passive absorption

Mechanisms of Diarrhoea

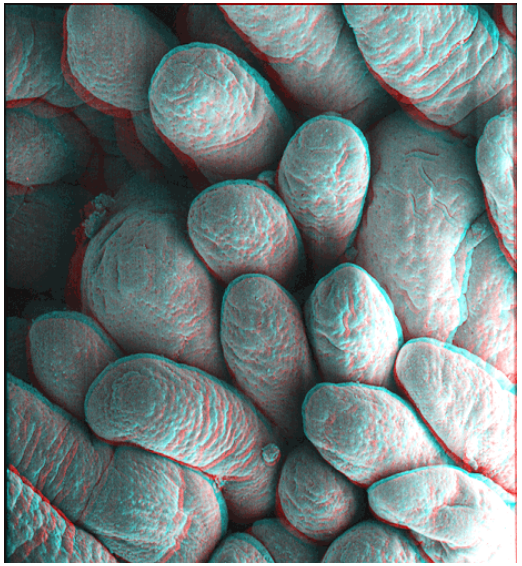
1. Increased Fluid Secretion

- ***Escherichia Coli (ETEC), Vibrio cholerae, Campylobacter*** produce exotoxins that stimulate intestinal fluid secretions without invading or damaging the intestinal mucosa

- Exotoxins stimulate adenyl cyclase which increases the concentration of cAMP. This stimulates chloride and subsequently sodium and water secretion.

- These changes are irreversible, and last as long as the enterocyte lives

Mechanisms of Diarrhoea



- **2. Reduced Absorption**

- Loss of superficial enterocytes (villous tips), following ***rotavirus, Shigella*** infection will result in decreased fluid absorption and increased losses.

- Intraluminal inflammatory mediators produced secondary to the underlying infection are likely to be a further factor

- Invasive bacteria more likely to produce blood in stool and toxaemia, especially in malnourished children

Following an episode of diarrhoea...

- Each cell is ordinarily replaced every 4-5 days
- Regenerated cells are not necessarily functionally mature.
- Following gastroenteritis, there may be significant functional impairment despite minimal histological mucosal changes.
- Adequate regeneration of cells requires nutrients.
- Hence feeding should always continue.

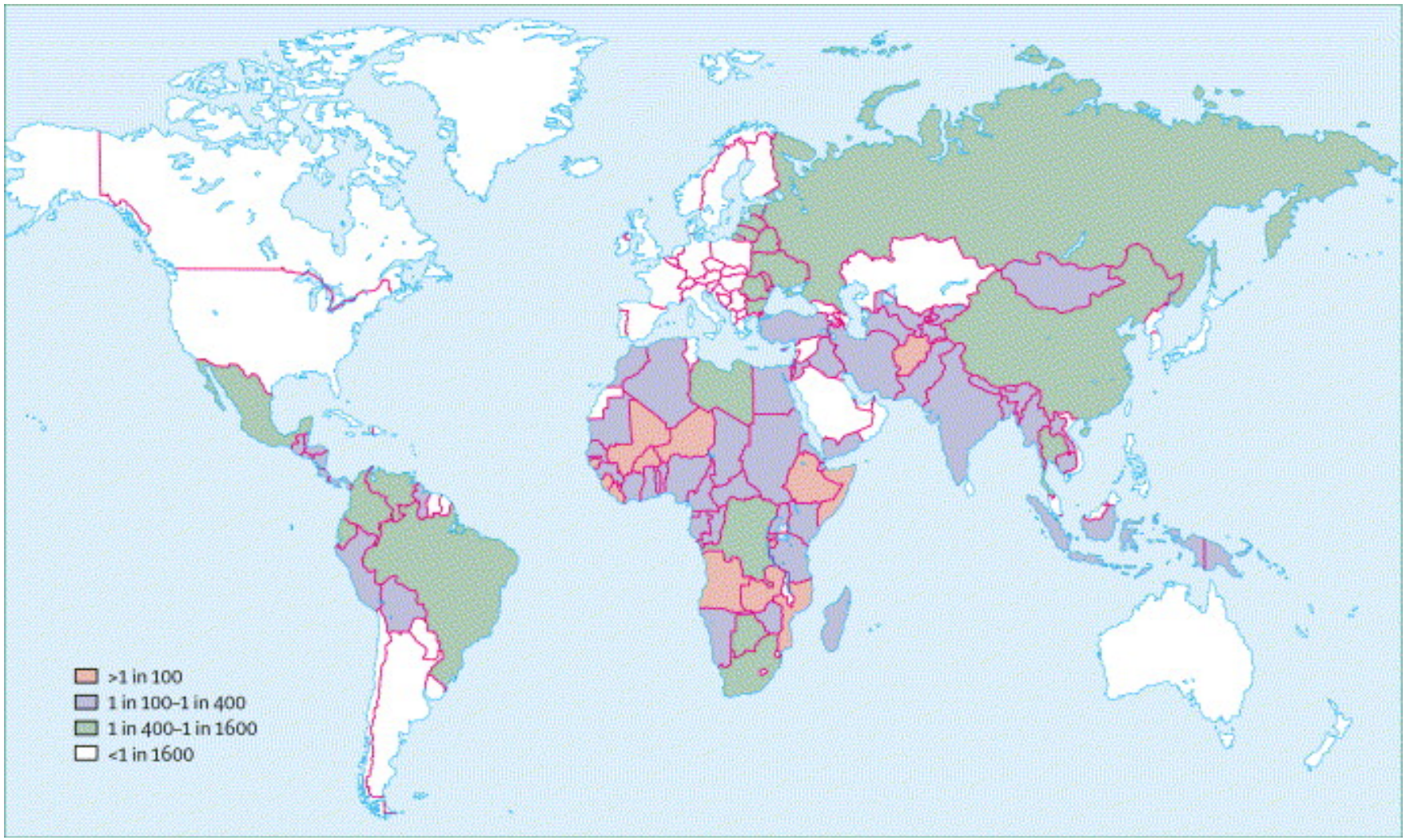
Infectious causes of diarrhoea in children

- Bacterial
  - **E. Coli (ETEC 10-20%)**
  - Shigella (5-15%)
  - V. cholerae (5-10%)
  - Campylobacter (10-15%)
  - Salmonella typhimurium,
  - (Yersinia enterocolitica, Clostridium difficile, and Aeromonas hydrophilia poorly studied in the tropics)
- Viral
  - **Rotavirus (20-50%)**
  - Most others!
- Parasitic
  - Cryptosporidium (5-15%)
  - Giardia lamblia (10%)
  - E. histolytica
  - S. mansoni
  - Malaria
- Most other childhood infections…

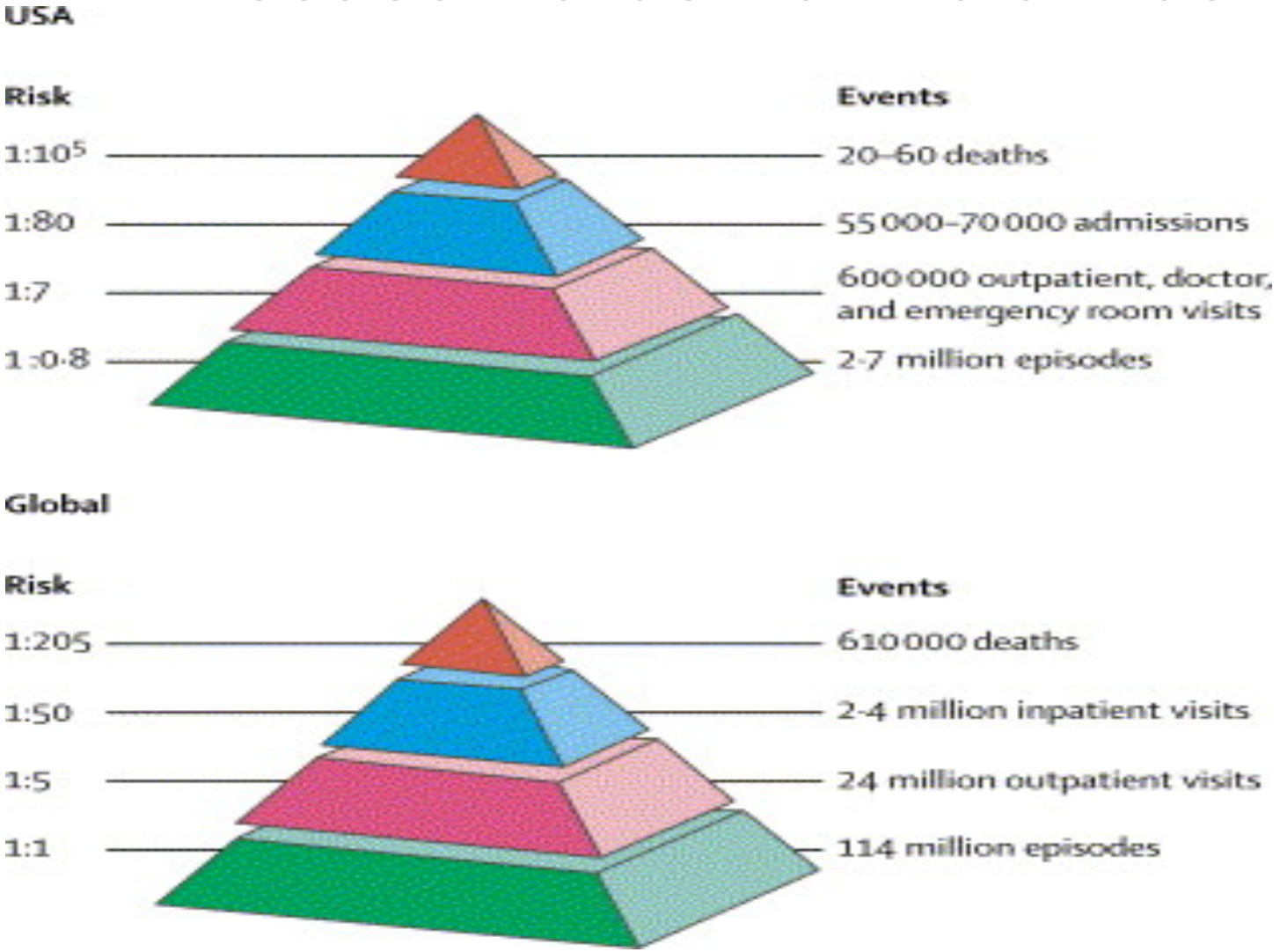
Viral Gastroenteritis

- Rotavirus is COMMON in young children (6m to 2y)
- Most have been infected by 3yrs of age
- Much less common in exclusively breast-fed children
- Ubiquitous and peaks in winter in temperate climates
- Accounts for 60% and 40% of diarrhoeal infections in developing and developed countries respectively
- Estimated 870 000 children die annually (mainly South Asia and sub Saharan Africa)

Rotavirus prevalence

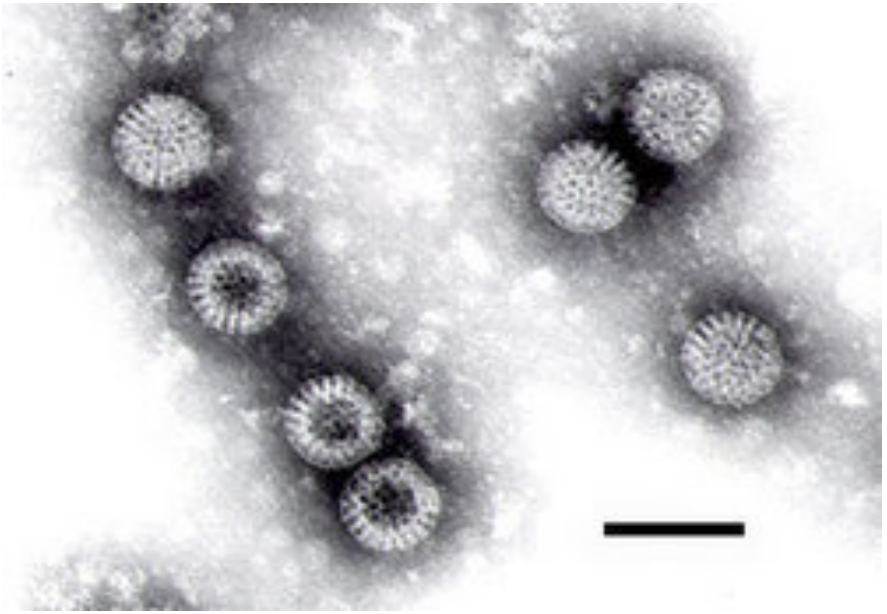


Disease Burden of Rotavirus



Glass R et al, Rotavirus vaccines: current prospects and future challenges, The Lancet 2006 Jul 22, Volume 368, Issue 9532, Pages 323-332

Rotavirus pathophysiology

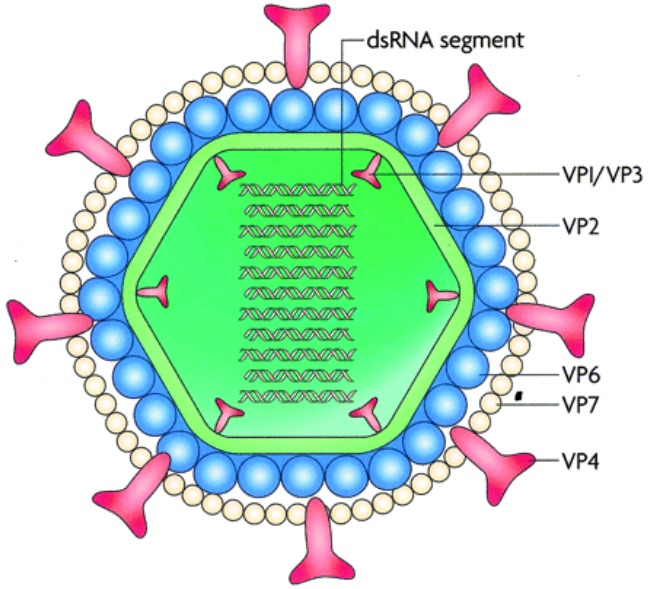


- How does it cause diarrhoea?
  - Invades the proximal portion of the small bowel
  - This invasion is usually patchy, but may involve huge lengths
  - It damages the epithelial absorptive cells which are replaced by undifferentiated secretory cells
- How long does recovery take?
  - Replacement of the damaged absorptive cells takes approximately 4-5 days (the time at which diarrhoea settles)
  - Full absorptive capacity takes 4-5 weeks to recover

Rotavirus features

- Transmission by faecal-oral route
- Profuse, watery, non-foul-smelling diarrhoea, low grade fever, occasionally upper respiratory tract symptoms.
- Clinical features progress usually very quickly
- No effective antiviral treatment for it
- Acquired immune protection (incremental)

Vaccines



- prevalence not affected by improved sanitation so vaccine development necessary
- Aim is to prevent moderate to severe disease
- All licensed vaccines are live oral vaccines. Administered orally in 2 or 3 doses depending on vaccine. (2 and 4 months – Rotarix).
- Vaccine issues:
  - Vaccine selection pressure
  - WHO and Global Alliance for Vaccines and Immunizations (GAVI) supporting introduction of rotavirus vaccines for children in resource poor countries
  - Expensive

E coli

- **Enterotoxigenic:** young children, traveller's diarrhoea
- **Enteropathogenic:** infants, outbreaks
- **Enteroadherent enteropathogenic:** persistent diarrhoea in malnourished children
- **Enterohaemorrhagic:** haemorrhagic colitis, undercooked meat. HUS
- **Enteroinvasive:** dysentery-type illness
- **Enteroaggregative:** dysentery-type. Often causes chronic diarrhoea.

Shigella

- Most common cause in children of bloody diarrhoea
- A gram negative enterobacter, which may cause invasive disease
- Consist of 4 species
  - *S. dysenteriae* (most severe, causes epidemics, usually in tropics)
  - *S. flexneri* (severe, endemic usually in tropics)
  - *S. boydii* (rare except on Indian Subcontinent)
  - *S. sonnei* (mild, usually in industrialised world)

Shigellosis

- Very infectious. Human reservoir.
- Invades and consequently damages the colonic mucosa, causing a interruption to absorption
- Associated symptoms: spectrum from asymptomatic to fulminant
  - abdominal cramps
  - systemic upset
  - fever
  - dysentery
  - tenesmus
  - rectal prolapse.
  - Worse symptoms, risk of gangrenous infection, septicaemia and other complications (toxic megacolon, colitis, strictures, HUS, CNS complications etc) (esp S dysenteriae)
- Antibiotics are indicated (cotrimoxazole or ampicillin; MDR: quinolone or azithromycin)

Campylobacter

- Curved or spiral gram negative rods

- Several species:
  - *C. jejuni. (commonest)*
  - *C.coli*
  - *C.laridis*

- Commensals of wild birds and animals (dogs, chickens)
- Contamination through water/milk, close contact with animals, faecal-oral spread

Campylobacter

- Clinical Presentation
  - Range of disease is large, from asymptomatic carriage to invasive disease
  - Abdominal pain can mimic surgical emergencies.
  - Usually self limiting, but may relapse.
  - Prognosis is good.
- Are antibiotics indicated?
  - Disease is shortened by the use of erythromycin.
  - Usually resistant to cotrimoxazole and cephalosporins.

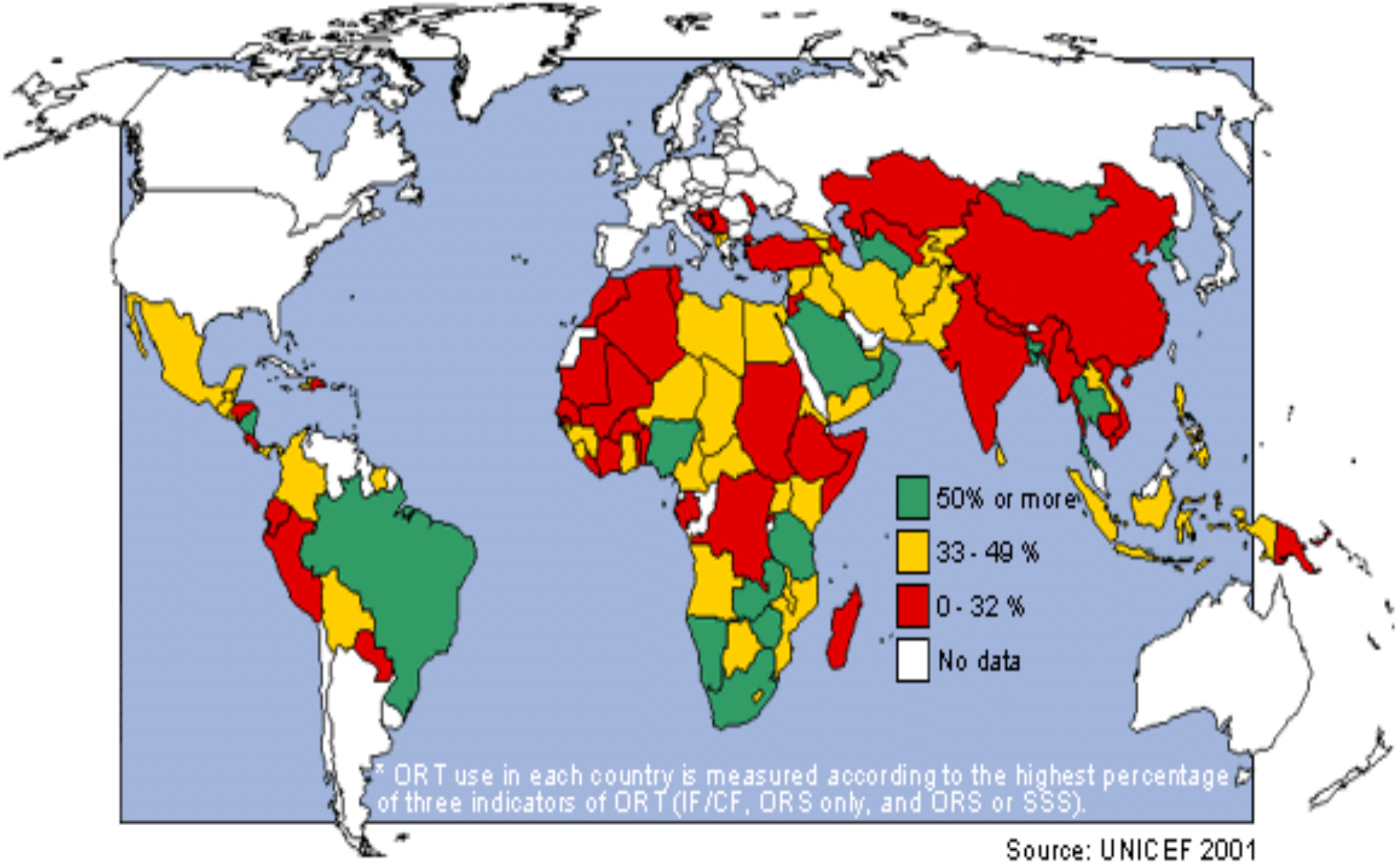
"To save the life of a person with diarrhoea is probably the cheapest health intervention you can think of."

(David Sack, Director of the International Centre for Diarrhoeal Disease Research in Bangladesh)

Oral Rehydration Solution

Widespread Treatment for Diarrhoea

Percentage of children with diarrhoea in the past 2 weeks who received ORT* (1990-2000)



Source: UNICEF 2001

EFFECT OF GLUCOSE ON INTESTINAL ABSORPTION OF SALT AND WATER IN ACUTE WATERY DIARRHOEA

INTAKE:	NOTHING	ISOTONIC SALT	ISOTONIC SALT+ GLUCOSE
			
RESULT:	DIARRHOEA	DIARRHOEA WORSENS	DIARRHOEA
	DEHYDRATION DEVELOPS	DEHYDRATION DEVELOPS	HYDRATION IS MAINTAINED OR CORRECTED

WHO 82743

UNICEF reduced osmolarity ORS

- Reduced osmolarity ORS has been recommended since 2003

- Benefits:
  - Shortens duration of diarrhoea
  - Reduces stool volume
  - Reduces need for unscheduled IV fluid administration

UNICEF reduced osmolarity ORS

- Sodium Chloride 2.6g
- Potassium Chloride 1.5g
- Trisodium citrate dihydrate 2.9g
- Glucose 13.5g

Which equates to

- Sodium 75mmol
- Potassium 20mmol
- Chloride 65mmol
- Citrate 10mmol
- Glucose 75mmol
- Osmolarity 245mmol/l

- Made up with a litre of water. What are the problems with this?

Other types of ORS

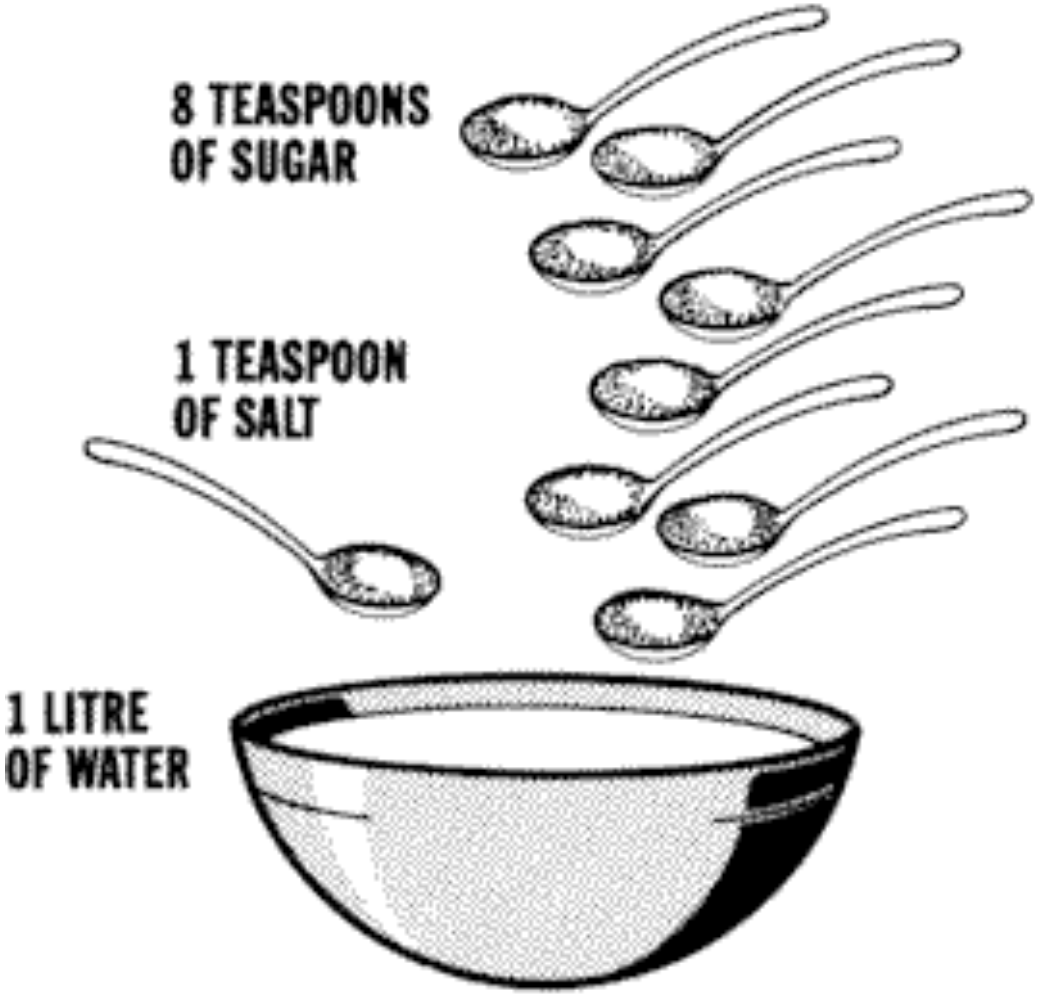
1. ReSoMal: "Rehydration Solution for Malnourished"

   - Less Na, more K, more Glu. Combined mineral and vitamin mix.
   - Better at correcting hypokalaemia

2. Cereal based ORS

   - rice, maize, sorghum, millet, wheat, potato and wheat
   - Cereals contain glucose and amino acid polymers that enhance the absorption of sodium and water
   - Particularly good in secretory diarrhoeas; reduces stool output.
   - Disadvantages
     - time consuming to prepare
     - needs fuel
     - may be confused with weaning
     - may causes confusion with ORS programmes

Salt/Sugar solution

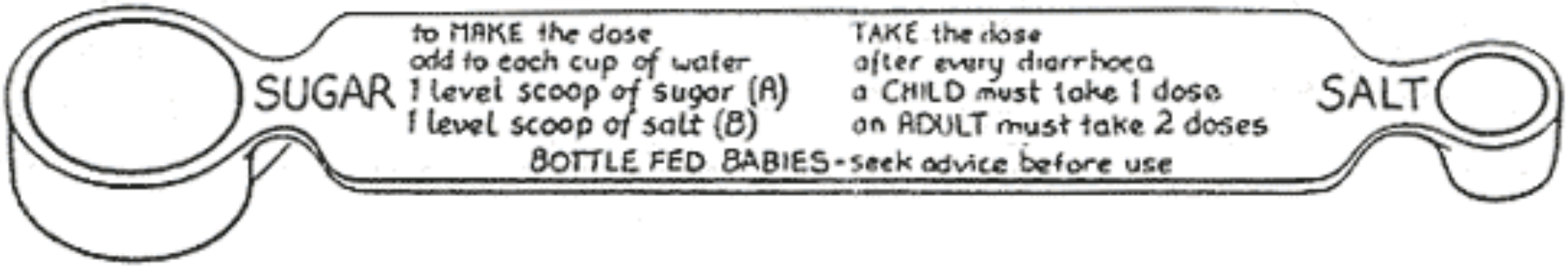


This equates to
- 86mmol of sodium
- 177mmol of glucose

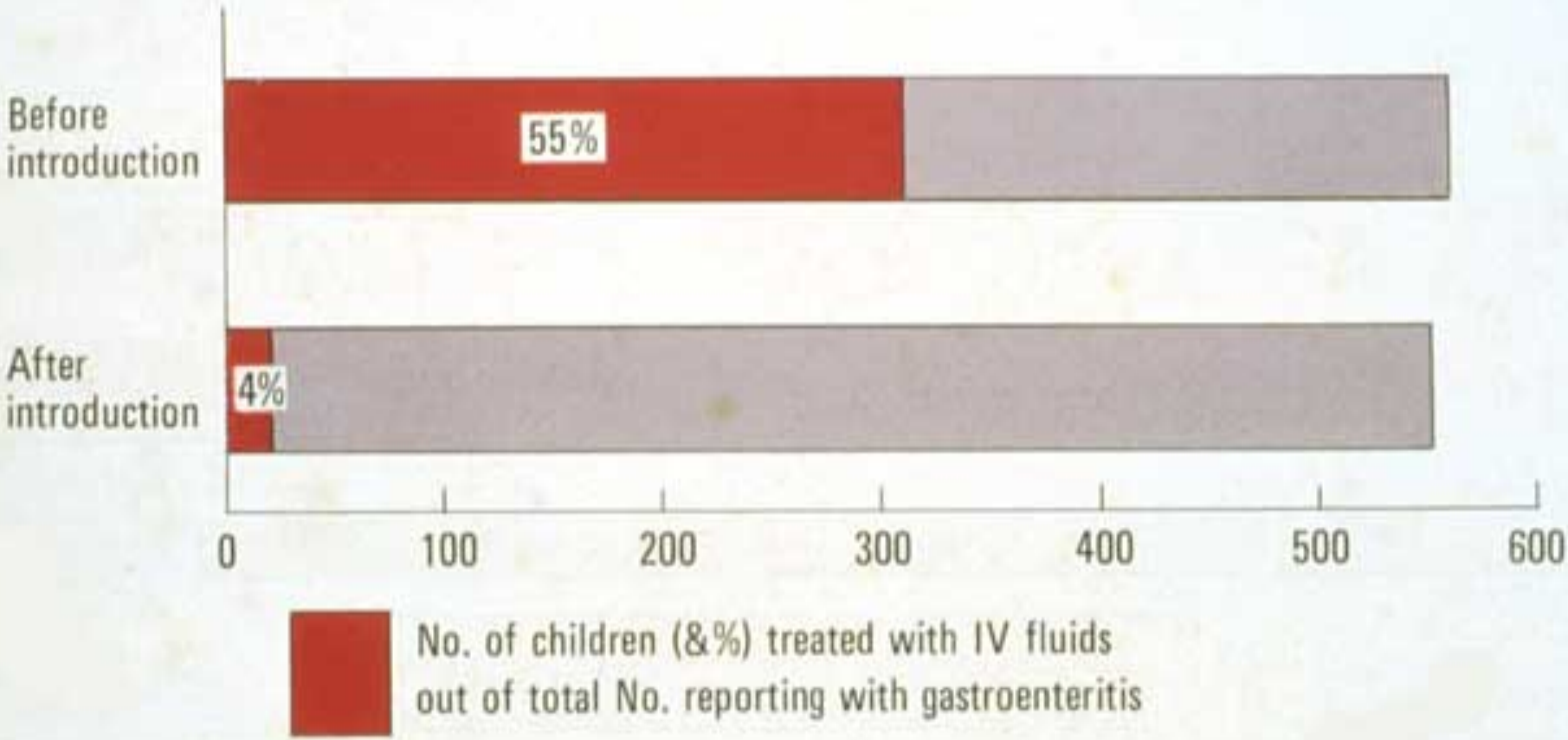
Solution should taste just slightly of salt.

Fruit juice may be added and will supply potassium.

Alternative: Add to 250ml water = 1 coke bottle
2 teaspoons sugar and a pinch of salt


SUGAR
to MAKE the dose
add to each cup of water
1 level scoop of sugar (A)
1 level scoop of salt (B)
TAKE the dose
after every diarrhoea
a CHILD must take 1 dose
an ADULT must take 2 doses
SALT
BOTTLE FED BABIES - seek advice before use

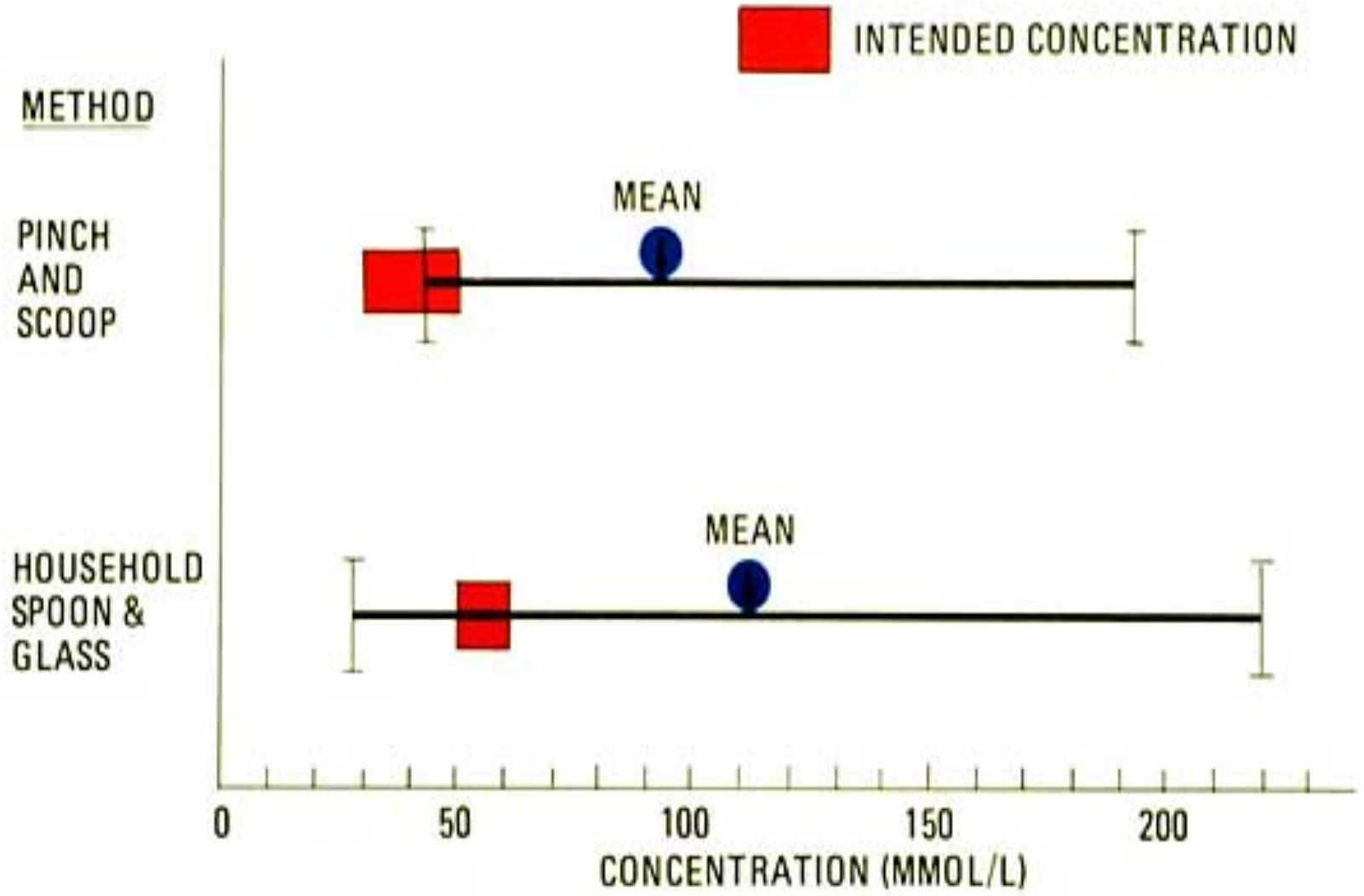
EFFECT OF INTRODUCTION OF ORAL THERAPY ON INTRAVENOUS FLUID USAGE, BUSTAMANTE HOSPITAL, KINGSTON, JAMAICA (1979)*



* Based on: Ashley, D.E.C. et al. In: Acute enteric infections in children - New prospects for treatment and prevention. Amsterdam, Elsevier/North Holland (1981) p. 385

WHO 82136

RANGE OF SODIUM CONCENTRATIONS OF SUGAR/SALT SOLUTIONS PREPARED BY TWO METHODS BY 14 RURAL MOTHERS, HONDURAS*



*BASED ON: LEVINE, M.M. ET AL., J. PED., 97: 324 (1980)

WHO 81953

Indonesian study assessing mothers' ORS preparation and administration practices

- 23.7% of mothers correctly prepared ORS
- None exhibited fully correct administration practices
- Primary sources of instruction were:
  - health workers (62.9%),
  - package instructions (23.7%)
  - family members or friends (12.4%)

MacDonald SE et al, Int Q Community Health Educ. 2005 2006;24 (3):205-14. Correct preparation and administration of ORS

Reported home treatment of diarrhoeal illness among 228 children <5 years of age in rural Mali who were sick during the preceding two weeks

Treatment given in first 24 h	%
No treatment	34.2
Antibiotics/tetracycline	30.7
Traditional medicines	21.1
Chloroquine	9.7
Cereal-based ORT	4.0
ORS sachets	3.1
Paracetamol/aspirin	2.6
Anti-diarrhoeals	2.2
Paracetamol	2.2
Sugar and salt solution	0.9

Ellis AA et al, Soc Sci Med. 2007 Home management of childhood diarrhoea in southern Mali-implications for the introduction of zinc treatment.

Indications for IV therapy

- Severe dehydration
- Coma
- Persistent vomiting
- Abdominal distension
- Diagnosis in doubt, surgery a possibility

Electrolyte disturbances

- Usually not helpful to measure serum electrolytes
- Hypernatraemia - Na >150mmol/l (produces signs of dehydration later, thus appears less severe)
- Hyponatraemia - Na <130mmol/l (produces signs of dehydration sooner, thus appears more severe)
- Hypokalaemia – K+<3mmol/l
- Can be managed by ORS, but if severe with iv.

Antibiotic indications

Cause	Antimicrobial of Choice	Alternative
Cholera	Cotrimoxazole/ Erythromycin	Tetracycline/ Doxycycline
Acute bloody diarrhoea (likely Shigella)	Nalidixic acid 15mg/kg qds x 5 days	Ciprofloxacin 7.5mg/kg bd x 5 days
Campylobacter	Macrolide	Quinolone
Amoebiasis	Metronidazole 10mg/kg tds x 5days	
Giardiasis	Metronidazole 5mg/kg tds x 5days	

What else should she be given?

Zinc

WHO and UNICEF now recommend that children under five years with diarrhoea receive 20 mg zinc for 10–14 days

Zinc deficiency

- Common in developing countries
- dietary deficiency
- inadequate absorption
- mucosal abnormalities and compromised gut integrity

- Pre-existing zinc deficiency is aggravated by intestinal losses
- Severe zinc deficiency is associated with stunting, hypogonadism, impaired immune function, skin disorders, cognitive dysfunction, and anorexia
- Globally 800 000 excess deaths occur that are attributable to zinc deficiency (mainly in the <5yrs)
- 176 000 of these deaths are due to diarrhoea

Zinc and acute diarrhoea

- Children receiving zinc supplementation have shorter episodes of diarrhoea, and passed fewer stools per day
  - 39% fewer episodes lasting beyond 7 days
  - 39% fewer stools per day and pass less liquid stool than do control children (1.5 vs. 2.4 kg; *P* = .0001)
- May have a positive impact on dysentery prevalence for one month after receiving zinc
- Zinc may enhance immunity towards *Shigella*

(Fischer Walker CL, Black RE, Clin Infect Dis. 2007)

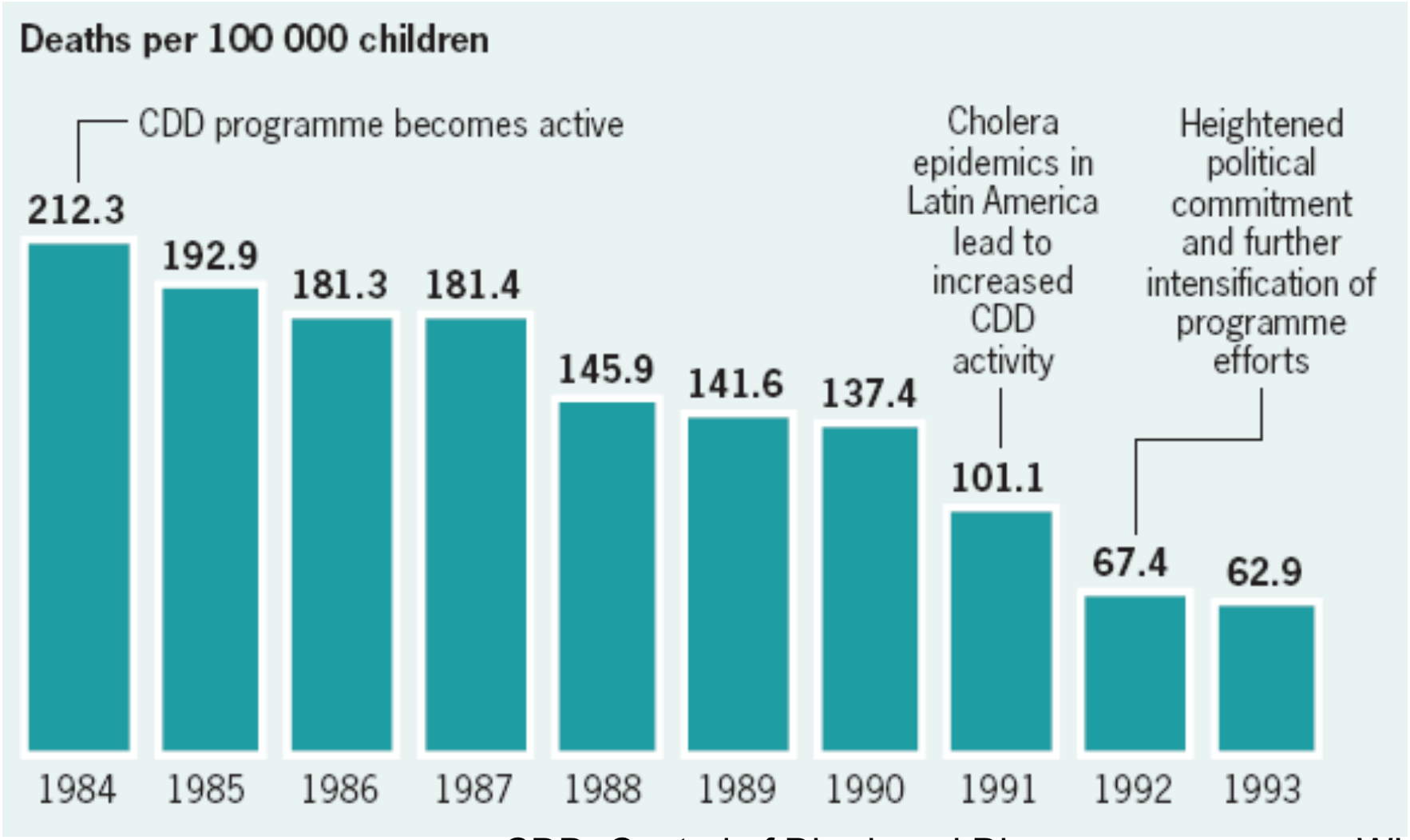
Vitamin A and acute diarrhoea

- Inconsistent evidence of significant effect on the duration or the severity of diarrhoeal episode
- Perhaps Vit A has some benefit as part of treatment of *Shigella* infection:
  - a greater proportion of children receiving vitamin A were "clinically cured" at 5 days, compared with children receiving placebo (45% vs. 20%; *P* = .02)

Specific preventative measures for diarrhoea

- Breastfeeding
- Complementary feeding
- Water, Sanitation and Hygiene (inc food safety and fly control)
- Immunisations (Rotavirus, Measles)
- Zinc (Treatment and Prevention)
- Vitamin A

Under-five mortality due to diarrhoeal diseases, Mexico 1984 -1993



CDD: Control of Diarrhoeal Diseases programme, WHO

<5 deaths from specific causes that could be prevented in 42 countries through child survival interventions

	Number ($\times 10^3$) of under-5 deaths in 2000* (% of total)	Estimated under-5 deaths prevented	
		Number ($\times 10^3$)	Proportion of total for specified disease
Disease or condition			
Diarrhoea	2135 (22%)	1886	88%
Pneumonia	2055 (21%)	1328	65%
Malaria	915 (9%)	829 (812)†	91% (89%)†
HIV/AIDS	312 (3%)	150	48%
Measles	103 (1%)	103	100%
Neonatal disorders‡	3187 (33%)	1743 (1214)†	55% (38%)†
Birth asphyxia	924 (10%)	359 (0)†	39% (0%)†
Sepsis	797 (8%)	750 (745)†	94% (94%)†
Preterm delivery	765 (8%)	453 (288)†	59% (38%)†
Tetanus	223 (2%)	181	81%
Other	478 (5%)	0	0%
Other	919 (10%)	0	0%
Total	9662 (100%)	6040 (5531)†	63% (57%)†

Diarrhoea and Breastfeeding

- Breastfeeding prevents against diarrhoea and its associated mortality
  - OR 6.1 (4.1 - 9.0) in the first 6 months of life

(WHO collaborative study team Lancet 2000; 355: 451-55)

- Breastfeeding counselling in India (intervention) vs no intervention (control) resulted in
  - reduced incidence of diarrhoea at 7 days
  - less infants (3m and 6m olds) taken to a health-care provider

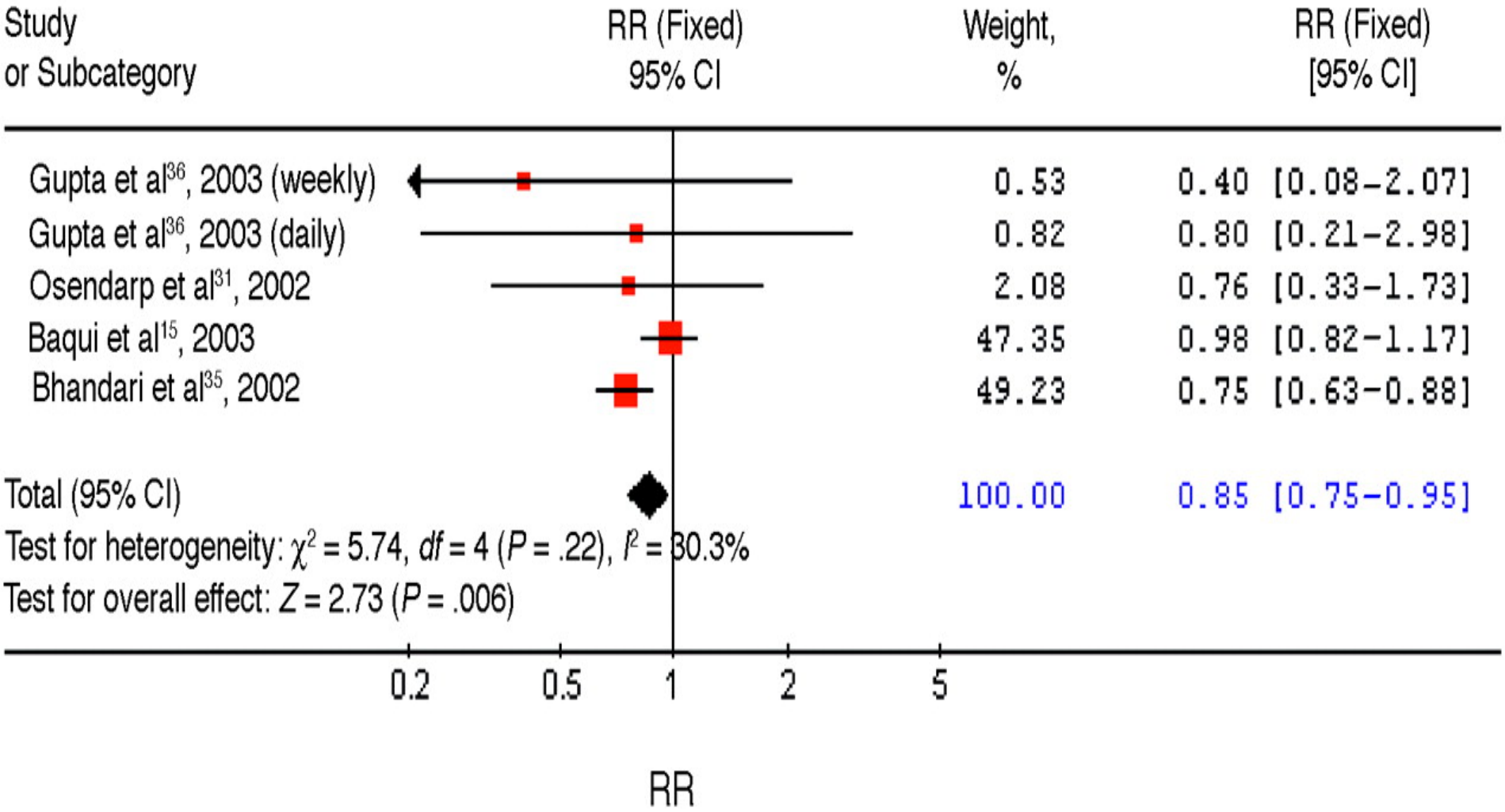
(Bhandari N et al, Effect of community-based promotion of exclusive breastfeeding on diarrhoeal illness and growth. RCT, Lancet. 2003)

Zinc in prevention

- Zinc supplementation for young children (weekly or daily for 4-12months) leads to reductions in the risk of both acute and persistent diarrhoea

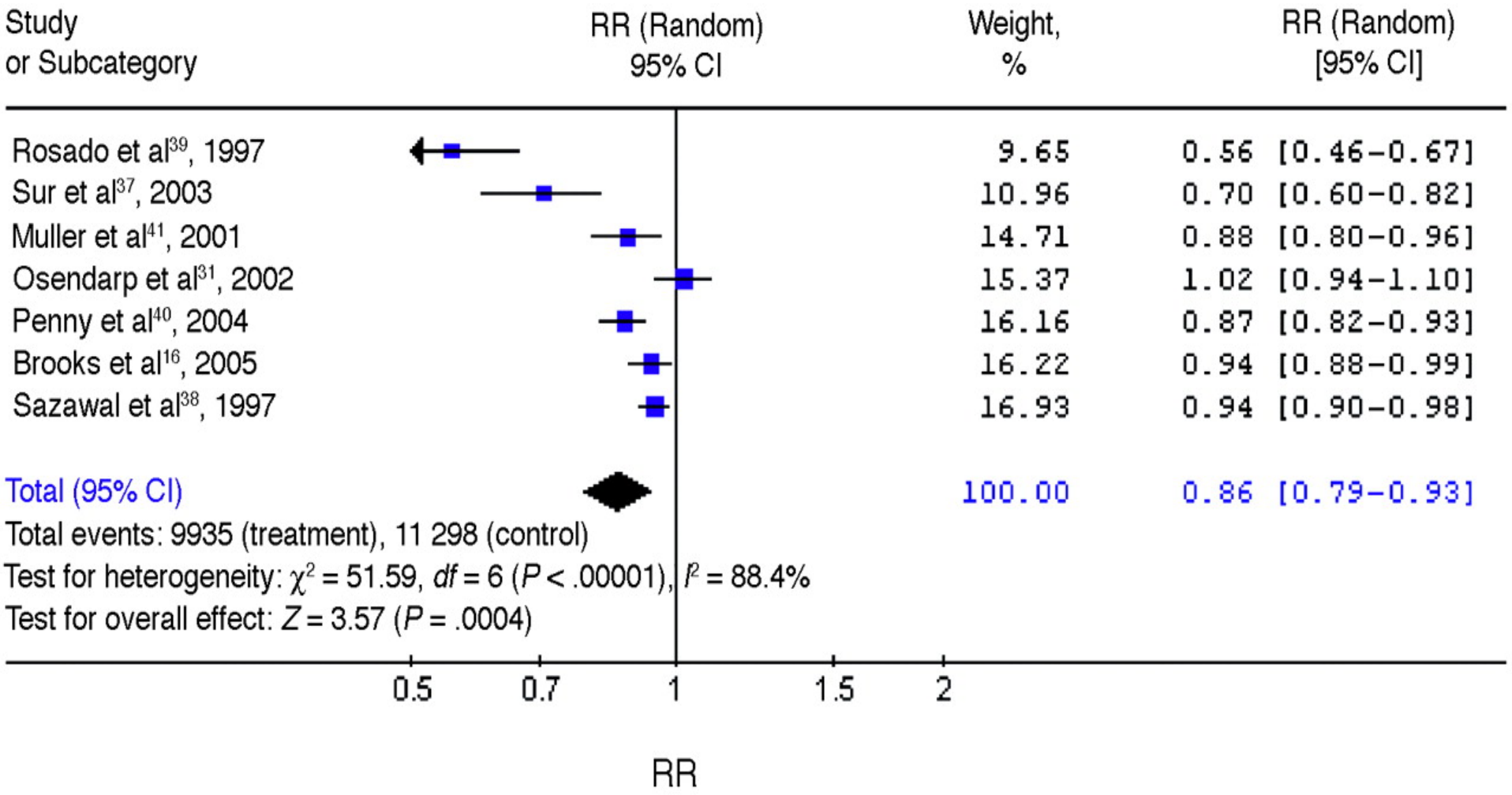
(Fischer Walker Food Nutr Bull. 2008; Zinc Collab Invest Group. J Paediatrics 1999; Aggarwal J Paediatrics 2006)

Meta-analysis of RRs of incidence of episodes of severe diarrhea and/or dysentery in children who received zinc supplementation or a placebo



Aggarwal, R. et al. Pediatrics 2007;119:1120-1130

Meta-analysis of RRs of number of days with diarrhea in children who received zinc supplementation or a placebo



Aggarwal, R. et al. Pediatrics 2007;119:1120-1130

Vitamin A in prevention

- Vitamin A supplementation policies are recommended, but inadequate coverage

- ?Reduces mortality

Vitamin A supplementation data (multi-country study) shows

  - 23% overall reduction in mortality rate for children 6–59 months of age
  - 32% reduction in diarrhoea-specific mortality rate (Beaton et al 1993)

- Decreases the likelihood of developing severe disease, (may decrease mortality via this mechanism)

- Vitamin A has no effect on diarrhoea-associated morbidity (RR 1.00, but small effect on reducing number of episodes (RR 0.97 (0.94–1.00)) (Grotto et al. 2003)

Persistent Diarrhoea is associated with…

- Young infants, especially <1 year
- Malnutrition
- HIV infection
- Reduced cell mediated immunity
- Post infectious enteropathy: Micropathogens e.g. enteroadherent and enteropathogenic *E.Coli;* Cryptosporidium
- Chronic intestinal infections.
- Micronutrient deficiency e.g. zinc, vitamin A, lack of breast feeding, lactose- and milk protein intolerance
- Other causes of chronic diarrhoea are rare in developing countries (cystic fibrosis, hepatitis, prematurity, coeliac disease)

Persistent Diarrhoea

- 3-23% of episodes of diarrhoea persist for >2 weeks
- The basic mechanism is thought to be mucosal injury by pathogens with a prolonged time for regeneration of villi due to reduced crypt cell multiplication
- Associated with 30-50% of deaths
- Most important features of management are nutrition, hydration and zinc (↓ recovery time,↓ probability of continuing diarrhoea/treatment failure/ death)

HIV and diarrhoea

- Diarrhoea morbidity is increased in HIV children
- Acute management is generally the same as for HIV negative children
- Lactose and monosaccharide intolerances are more common

Malnutrition and diarrhoea

- Maybe a ‘chicken and egg’ situation
- First attack of diarrhoea is often the start of recurrent infections and malnutrition
- Enteric infections are possibly emerging as an important cause of malnutrition due to damage or disruption of epithelial cells / intestinal barrier
- Assessment of hydration status may be unreliable
- Rehydration should be done orally and slowly
- ReSoMal
- Antibiotics should be used in severely malnourished children

So to put some of this into context…….

The Goals

Reduce by one half deaths from diarrhoea among children under five by 2010 compared to 2000

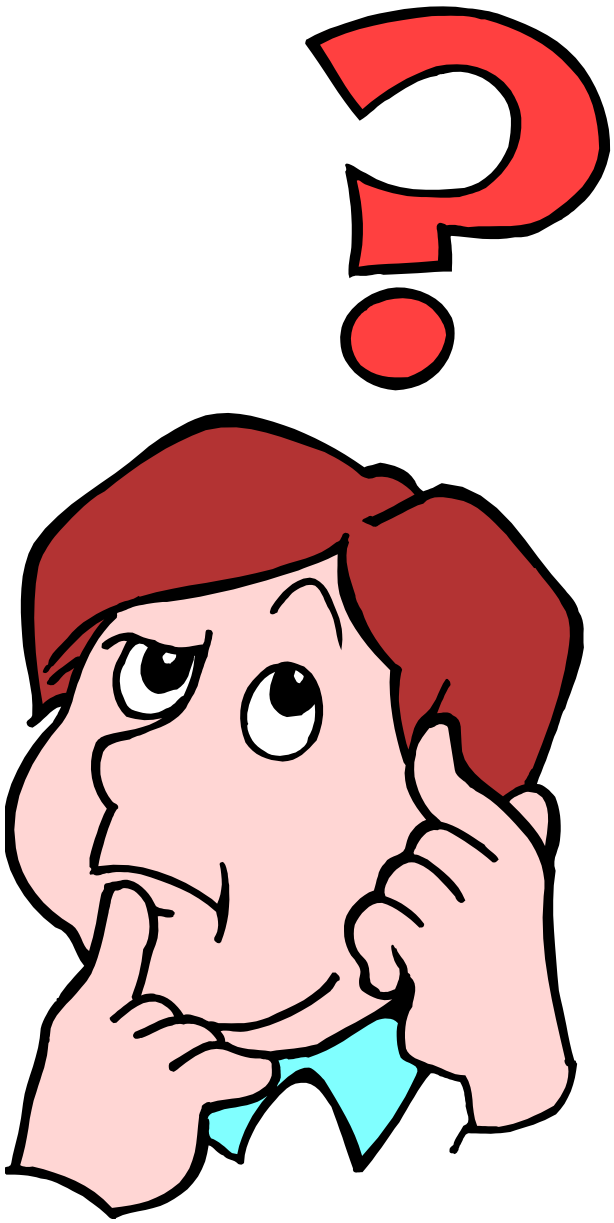
('A World Fit for Children', outcome document on the UN special session for children)

Reduce by two thirds the mortality rate among children under five by 2015 compared to 1990

(United Nations Millennium Development Goals)

	Mean estimated coverage of target population (range among countries*)
Preventive interventions	
Breastfeeding (6–11 months)	90% (42–100)
Measles vaccine	68% (39–99)
Vitamin A	55% (11–99)
Clean delivery (skilled attendant at birth)	54% (6–89)
Tetanus toxoid	49% (13–90)
Water, sanitation, hygiene	47% (8–98)
Exclusive breastfeeding (<6 months)	39% (1–84)
Newborn temperature management	20%
Antibiotics for premature rupture of membranes	10%
Antenatal steroids	5%
Nevirapine and replacement feeding	5%
Insecticide-treated materials	2% (0–16)
Hib vaccine	1%
Antimalarial intermittent preventive treatment in pregnancy	1%
Zinc	0%
Complementary feeding	†
Treatment interventions	
Vitamin A	55% (11–99)
Antibiotics for pneumonia	40%
Antibiotics for dysentery	30%
Antimalarials	29% (3–66)
Oral rehydration therapy	20% (4–50)
Antibiotics for sepsis	10%
Newborn resuscitation	3%
Zinc	0%

Data source: State of the World's Children 2003.[2] *Where available. For interventions with no country-level coverage data a single estimate was used for all countries. †The mean weight for age *z* score was used (see text).



Summary

- Global burden of disease
- Discussion of prevention and risk factors
- Features and causes of diarrhoea in <5yrs
- Acute, bloody and persistent diarrhoea
- Assessment – IMCI guidelines for dehydration
- Management – ORS, IV fluids, antibiotics, nutrition
- Special considerations

References

- IMCI guidelines

http://www.who.int/child-adolescent-health/integr.htm

- The treatment of diarrhoea: A manual and other senior health workers, WHO 2005, Department of Child and Adolescent Health and Development

- Clinical management of acute diarrhoea, WHO/UNICEF Joint Statement

http://www.who.int/child-adolescent-health/publications/CHILD_HEALTH/JS_Diarrhoea.htm

- Implementing the new recommendations on the clinical management of diarrhoea: guidelines for policy makers and programme managers

http://www.who.int/child-adolescent health/publications/CHILD_HEALTH/ISBN_92_4_159421_7.htm

- Forsberg BC et al, Diarrhoea case management in low- and middle-income countries--an unfinished agenda. Bull World Health Organ. 2007 Jan;85(1):42-8.

- Dennehy P, Rotavirus vaccines—An update, Vaccine, Volume 25 , Issue 16, 20 April 2007, Pages 3137-3141