



Taming the Beast: Diarrhea

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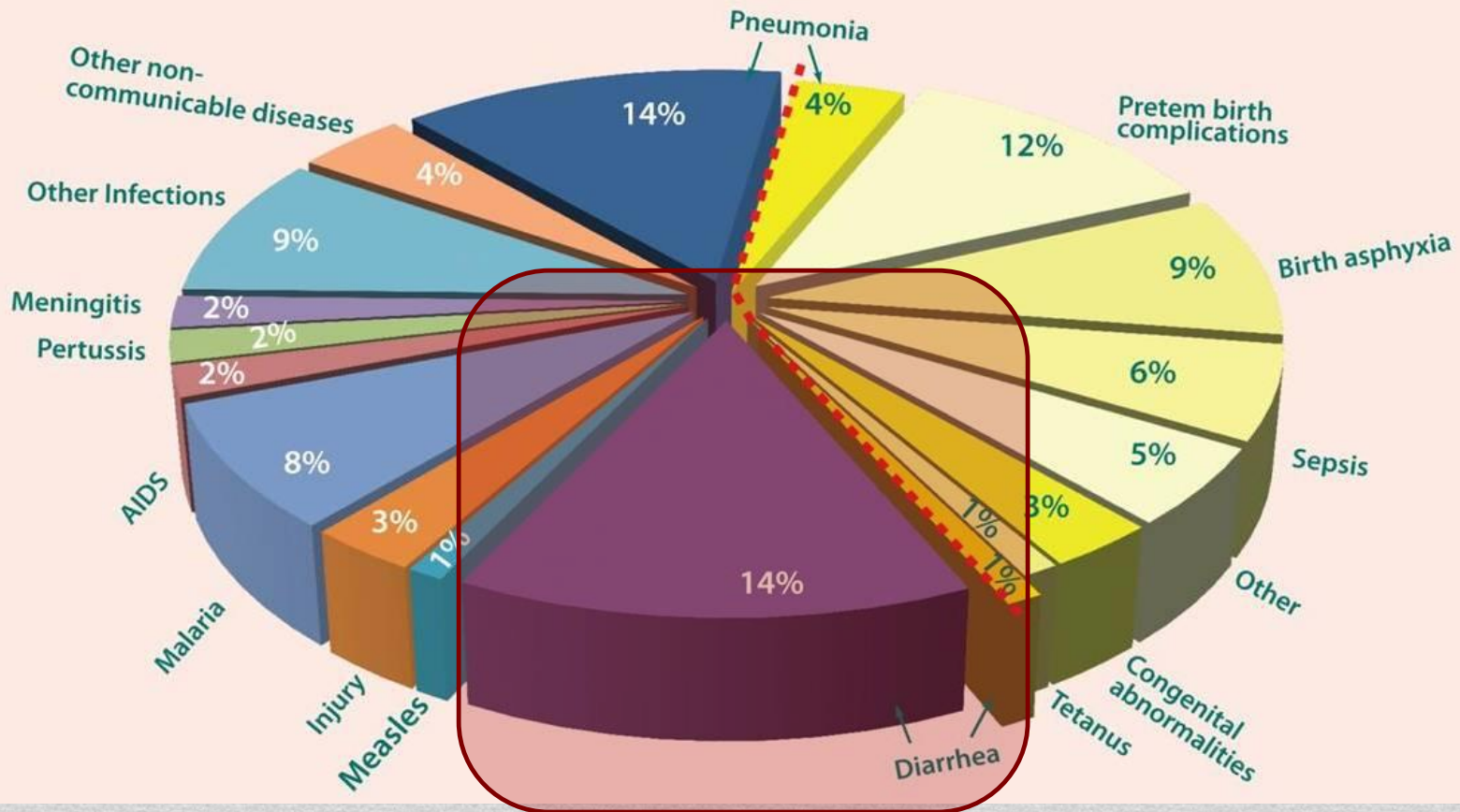
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- “Glocal” Burden
- Local Epidemiology
- Diagnostic Decisions
- Treatment Options
- Preventive Strategies

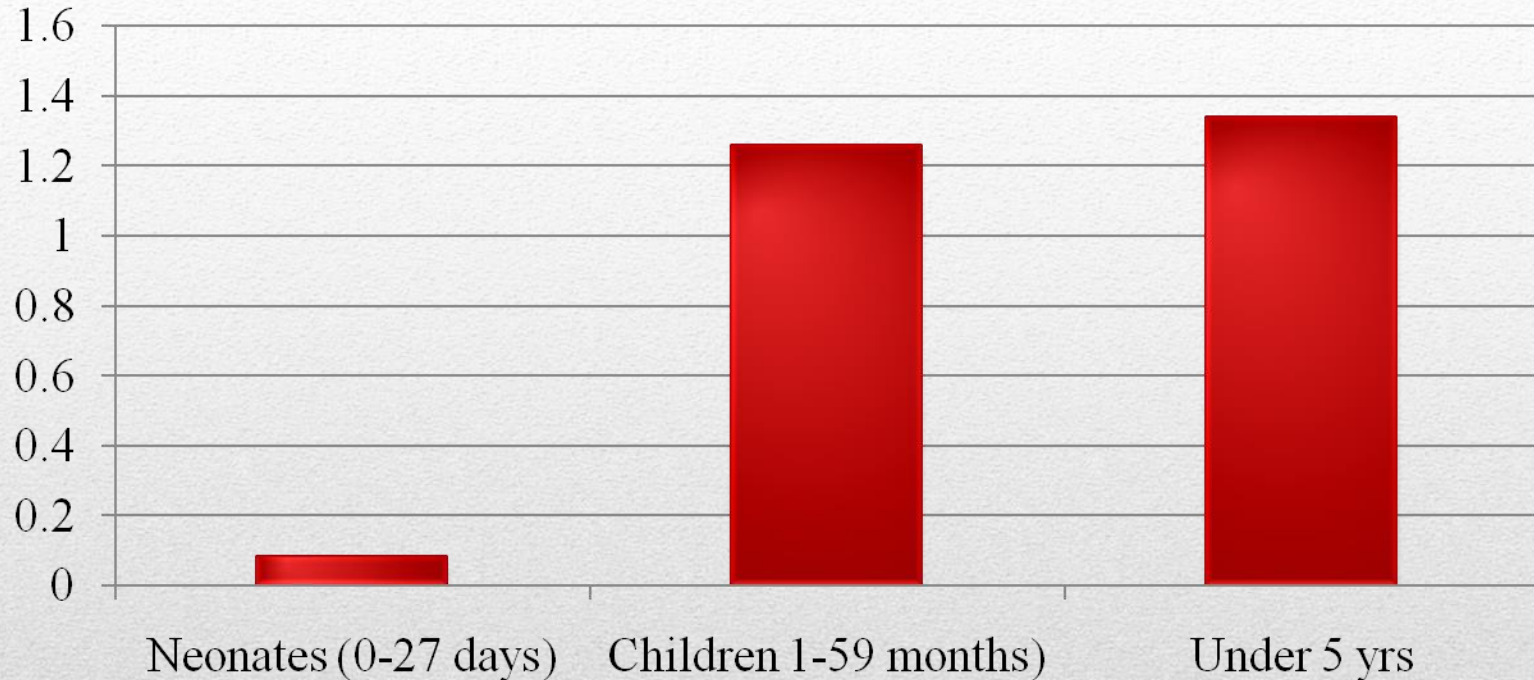
Outline: Taming Killer Diarrhea

GLOBAL CAUSES OF CHILD (0-59 MONTHS) DEATHS IN 2008¹



Global Burden of Diarrhea

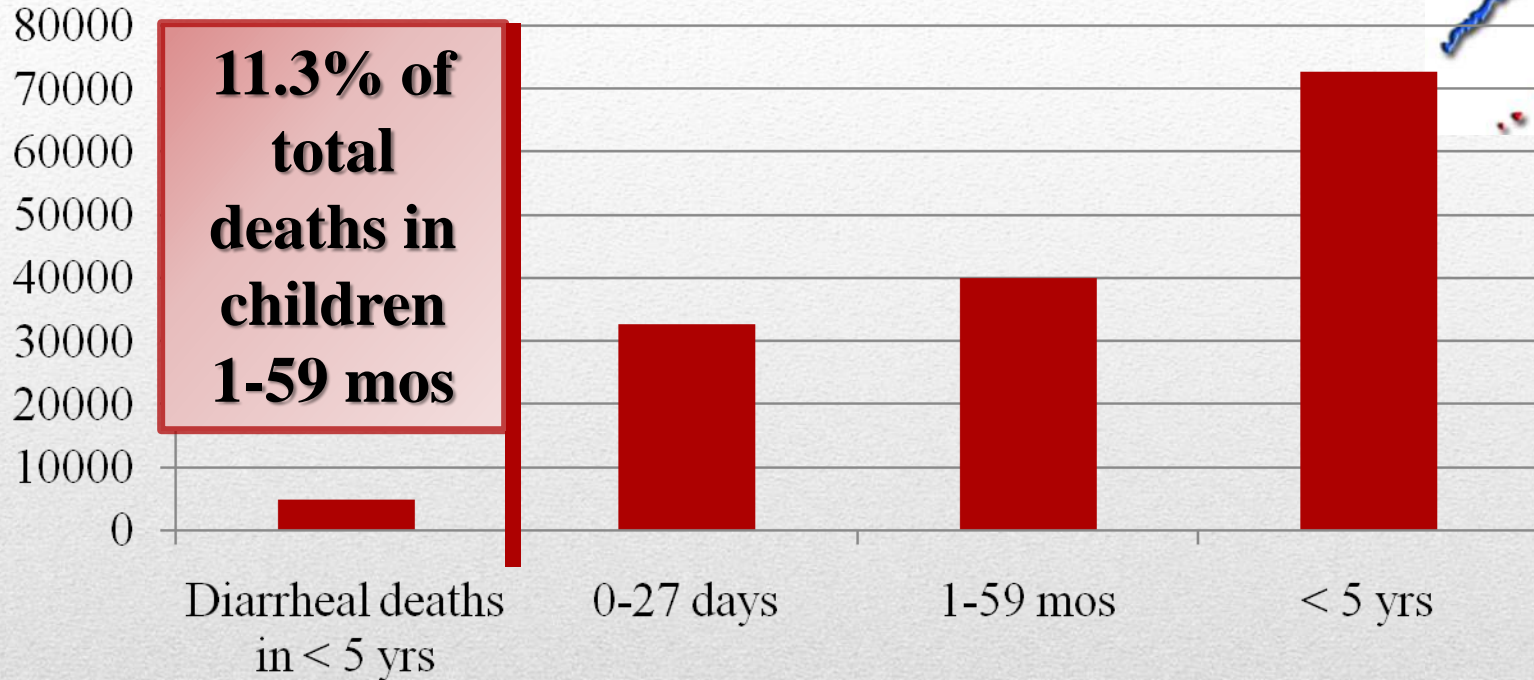
Estimated No. (millions)



Global Deaths from Diarrhea



Estimated no. deaths in Philippines



Every year
~5000 diarrheal deaths

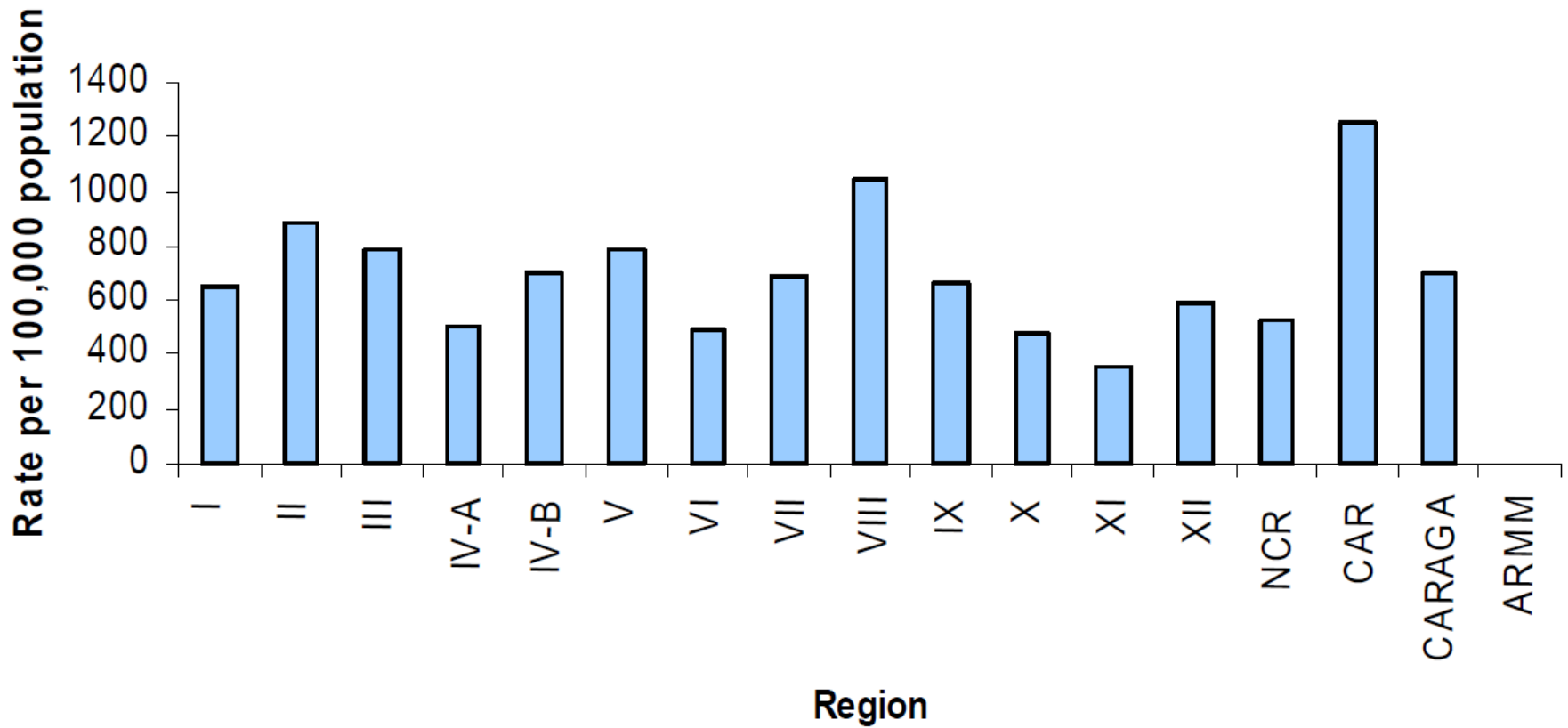
Everyday
~13 young children dying

Local Burden of Diarrhea

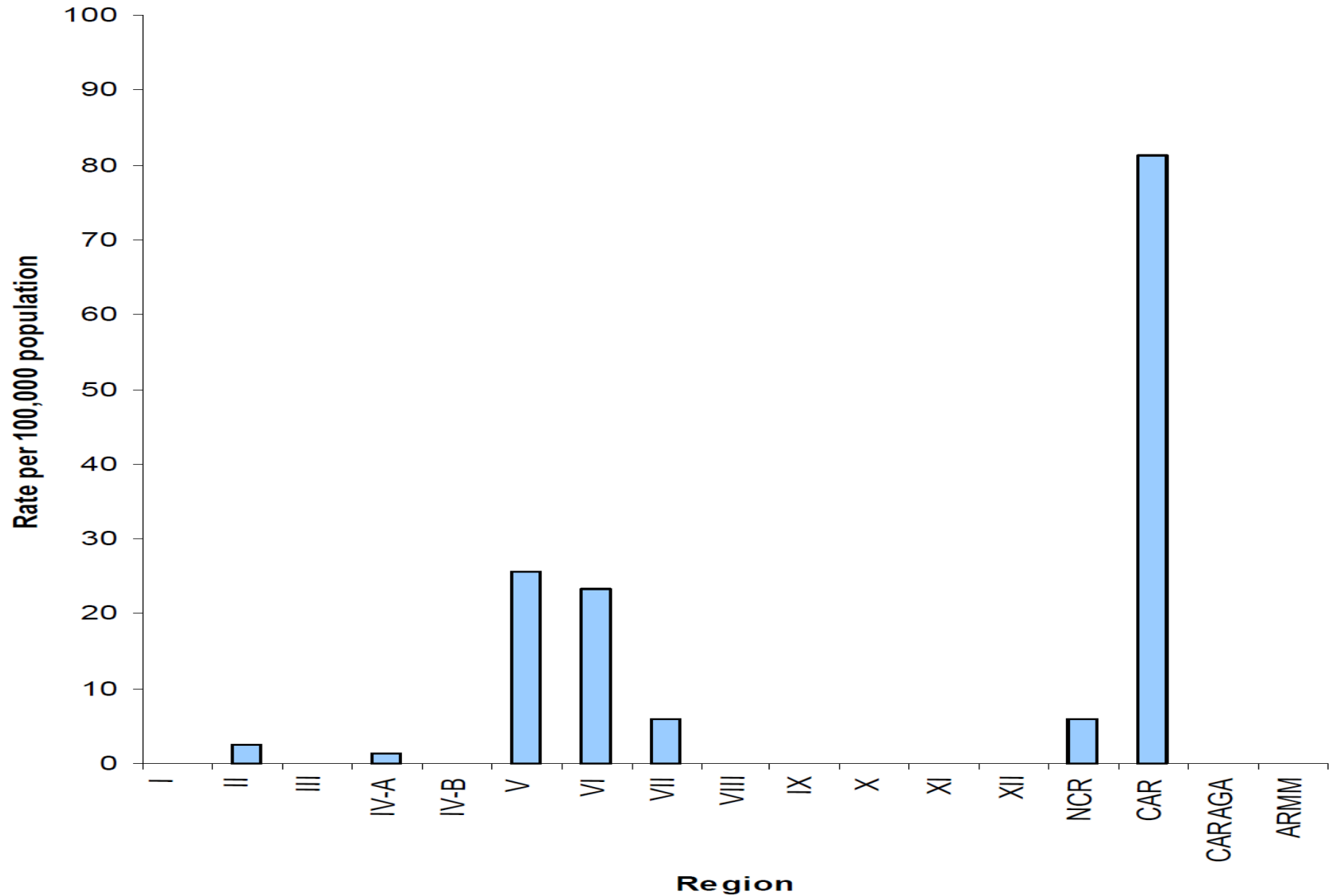
- Underlying cause of under-5 mortality (WHO estimates, 2000-2003)
 - 53% of ALL deaths
 - 61% of deaths due to diarrhea globally
 - 80% of children with diarrhea die during the first 2 years of life

Malnutrition and Diarrheal Diseases

Acute Watery Diarrhea morbidity rate by region Phillipines, 2007



Acute Bloody Diarrhea morbidity rate by region Philippines, 2007



**3-28% of all
diarrheal
episodes**
(de Andrade and
Fagundes-Neto, 2011)

- 10% of acute diarrhea cases in Philippines become persistent (Santos Ocampo et al, 1988)

**Highest
incidence in
the 1st 2 years
of life**
(Black, 1993)

- Highest prevalence in the 1st year of life with 63% of cases (Santos Ocampo et al, 1988)

Persistent Diarrhea

Most Common Microorganisms Reported for Acute Endemic Diarrhea among U5 Children in Developing World

All Episodes	
≤ 2 years	Rotavirus EPEC,ETEC Astrovirus, Caliciviruses, enteric Adenovirus <i>Shigella flexneri</i> , <i>Shigella dysnteriae</i> type 1 <i>Campylobacter jejuni</i> ETEC, EAEC
2-5 years	ETEC <i>S. flexneri</i> , <i>S. dysenteriae</i> type 1 Rotavirus Non-typhi <i>Salmonella</i> <i>Giardia lamblia</i>
Watery Mucous	
≤ 2 years	Rotavirus EPEC,ETEC Astrovirus, Caliciviruses, enteric Adenovirus <i>Shigella flexneri</i> , <i>Shigella dysnteriae</i> type 1 <i>Campylobacter jejuni</i> ETEC,EAEC
2-5 years	ETEC <i>Shigella flexneri</i> , <i>Shigella dysenteriae</i> type Rotavirus

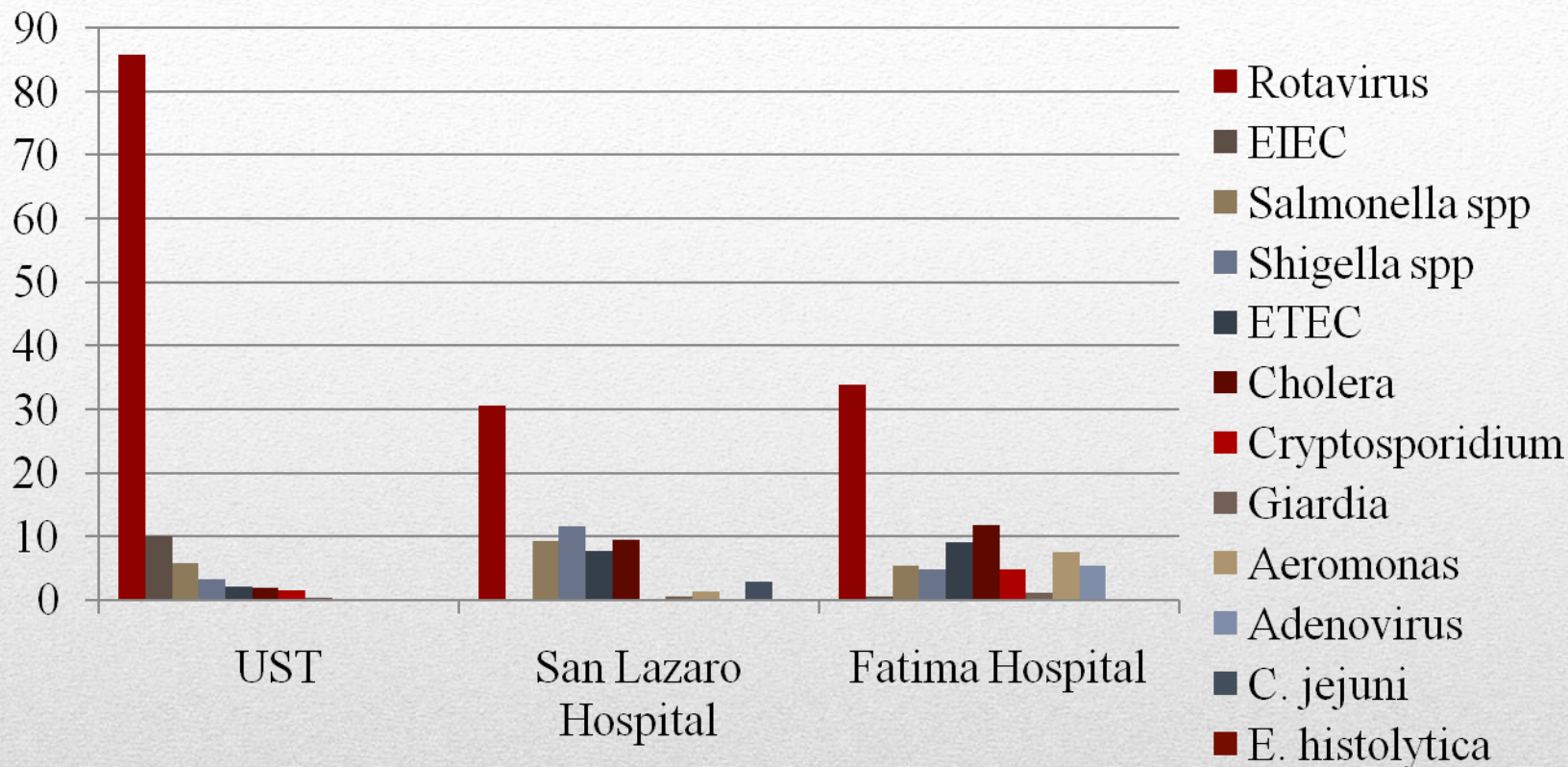
TABLE. Number of children aged <5 years enrolled in the global surveillance network for rotavirus, number of enrolled children with stool specimens tested for rotavirus, and median detection rates of rotavirus for all countries, by World Health Organization (WHO) region — worldwide, 2009

WHO region*	No. of countries	No. of enrolled children [†]		No. of enrolled children with stool specimens tested for rotavirus		Median percentage of test results positive for rotavirus	
		No.	(Range among countries)	No.	(Range among countries)	%	(Range among countries)
African	9	4,377	(153–1,128)	4,191	(151–1,036)	41	(16–57)
Americas	12	16,242	(210–3,698)	13,139	(111–2,327)	25	(19–42)
Eastern Mediterranean	10	14,004	(205–6,227)	10,475	(205–3,442)	38	(14–54)
European	4	4,409	(737–1,485)	4,409	(737–1,485)	36	(12–52)
South-East Asia	2	1,389	(514–875)	1,389	(514–875)	37	(32–42)
Western Pacific	6	5,511	(276–2,026)	4,977	(275–1,874)	47	(24–68)
Total	43	45,932	(153–6,227)	38,580	(111–3,442)	36	(12–68)

* Of 55 countries participating in the global surveillance network for rotavirus, the following 43 countries met the inclusion criteria for analysis (i.e., tested ≥100 stool specimens for rotavirus and reported on the number of stool specimens tested for all 12 months in 2009): (*African Region*) Cameroon, Ethiopia, Ghana, Kenya, Tanzania, Togo, Uganda, Zambia, and Zimbabwe; (*Region of the Americas*) Bolivia, Chile, Colombia, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay, Suriname, and Venezuela; (*Eastern Mediterranean Region*) Afghanistan, Egypt, Iraq, Libya, Morocco, Pakistan, Sudan, Syria, Tunisia, and Yemen; (*European Region*) Azerbaijan, Georgia, Moldova, and Ukraine; (*South-East Asia Region*) Myanmar and Nepal; (*Western Pacific Region*) China, Fiji, Laos, Mongolia, Papua New Guinea, and Vietnam.

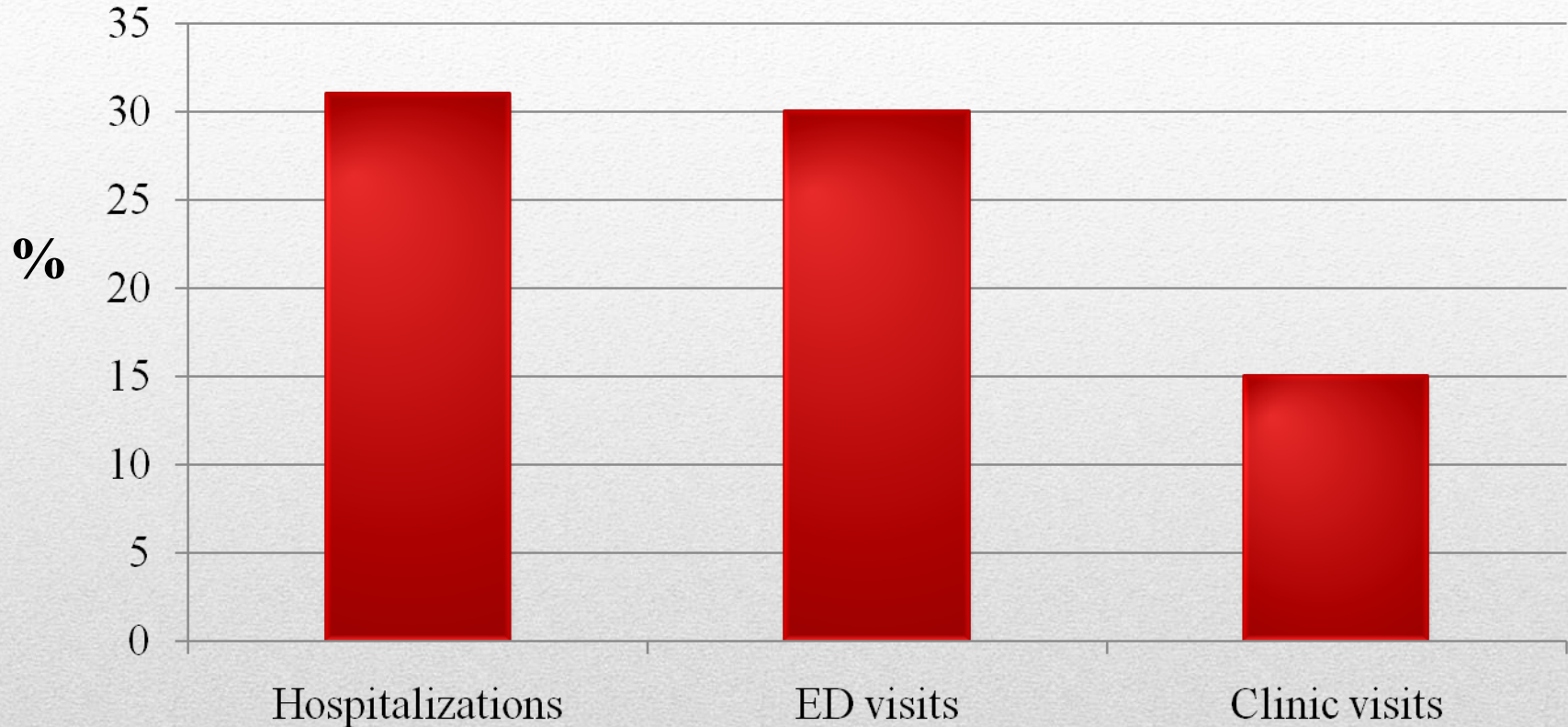
[†] No data available regarding the number of enrolled children in Suriname.

Burden of Rotavirus Disease (Global RV Surveillance Network)



Etiologic Agents of Acute Diarrhea in selected Philippine Hospitals

Philippines



Prevalence of Rotavirus Disease

Bacteria	Protozoa	Viruses
<p><i>E. coli</i> (EAEC; EPEC) <i>Campylobacter</i> spp <i>S. enteritidis</i> <i>Shigella</i> spp <i>C. difficile</i> <i>Klebsiella</i> spp</p>	<p><i>G. lamblia</i> <i>B. hominis</i>* <i>Cryptosporidium</i> spp* <i>E. histolytica</i> <i>Cyclospora</i> <i>cayetanensis</i>* <i>Microsporidium</i> spp*</p> <p>*particularly associated with HIV</p>	<p>Astrovirus Enteroviruses Picornaviruses</p>

Etiologic Agents for Persistent Diarrhea

- Diagnosis for most cases of acute diarrhea: clinical
 - Based on the clinical syndromes
 - Acute watery diarrhea
 - Bloody diarrhea
 - Persistent diarrhea
 - Diarrhea with severe malnutrition
- Routine stool examination not necessary in most cases of acute watery diarrhea
- Stool microscopy and culture indicated only when patients do not respond to fluid replacement, continued feeding, and zinc supplementation

Diagnostic Investigations

- Ascertain if due to an infection
 - 40-60% due to shigellosis
 - Empiric treatment with ciprofloxacin 15 mg/kg/dose BID for 3 days
- Consider differential diagnosis
 - Anal fissure
 - Intussusception
 - Allergic colitis

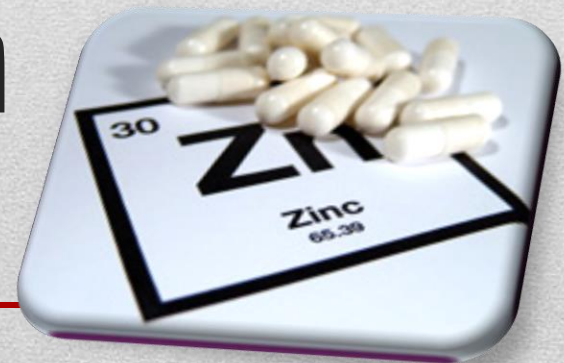
Bloody Diarrhea

- Diagnosis made on clinical grounds (onset and duration of diarrhea)
- Most of the cases (> 60%) due to:
 - Acute intestinal infection
 - Dietary intolerance
 - Protein-sensitive enteropathy (cow's milk)
 - Secondary disaccharide malabsorption (lactose)
- In 30% of cases, no etiologies can be established despite extensive investigations.

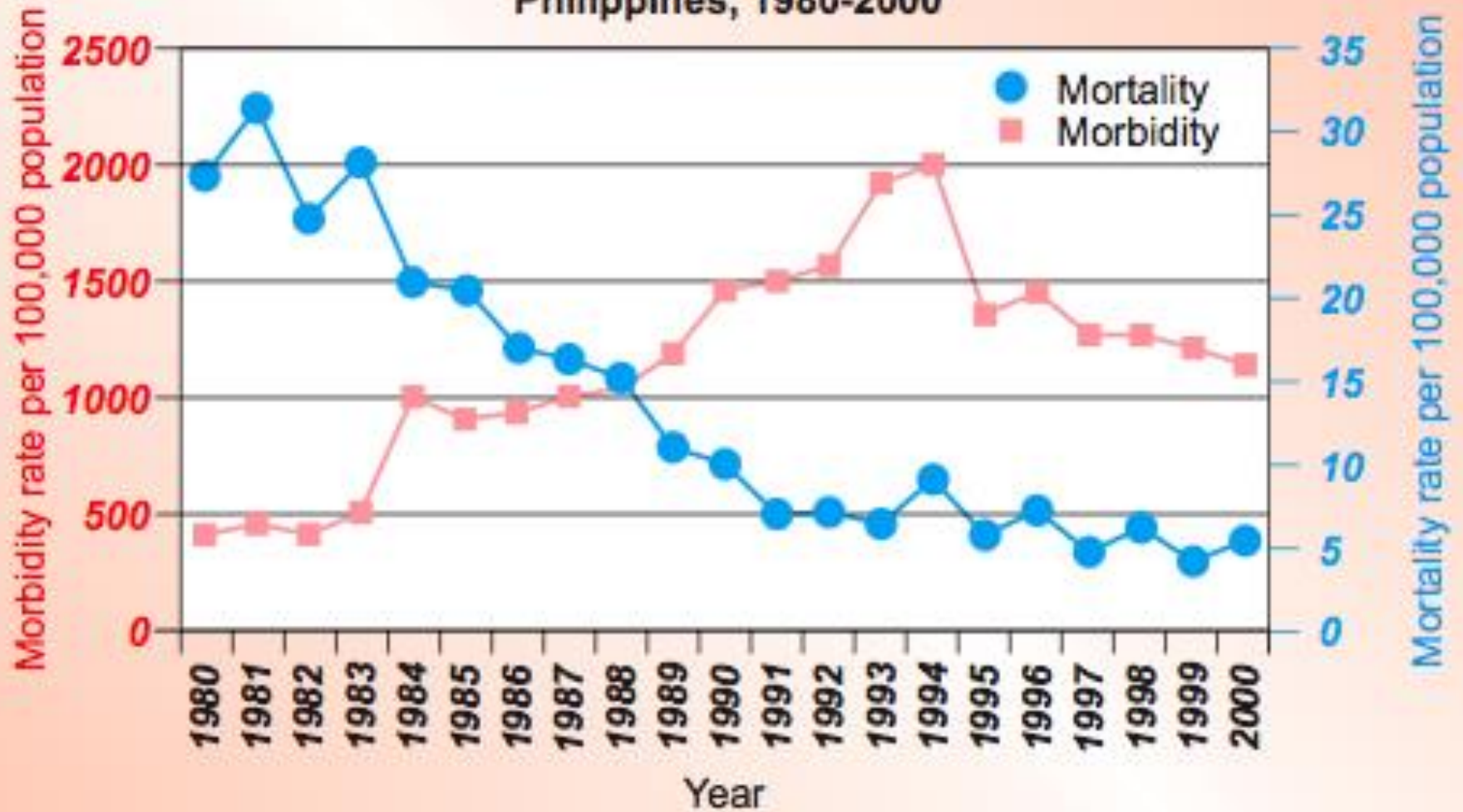
Persistent Diarrhea



Mainstays in Diarrhea Management



**Figure 4.25 Trends in Diarrhea Morbidity and Mortality
Philippines, 1980-2000**



Source: Philippine Health Statistics, 2000

- Malnutrition underlie 61% of diarrheal deaths globally.
- Micronutrient deficiencies
 - Diminish immune function
 - Increase susceptibility to infections
 - Predispose to severe illnesses
 - Prolong duration of illness

Micronutrient Supplementation in Diarrheal Disease

- Early studies: single nutrients
 - To combat diarrhea, respiratory infections, and anemia
 - To improve child growth and development
- Recent studies: multiple nutrients
 - Increasing recognition that micronutrient deficiencies do not occur in isolation
 - Multiple MNS may be more cost-effective

Single vs. Multiple Nutrient Supplementation (MNS)

Therapeutic Strategy

- Zinc
- Vitamin A
- Folic acid

Preventive Strategy

- Zinc
- Vitamin A
- Multiple
micronutrients

Single vs. Multiple Nutrient Supplementation

Acute Diarrhea

- **Reduction in duration of -0.69 day**
[95% CI: -0.97 to -0.40]
- **Reduction in diarrhea risk lasting >7 days**
RR=0.71 [95% CI: 0.53-0.96]
- No reduction in stool output
- Based on 18 RCTs (n=11,180 mainly from developing countries)

Persistent Diarrhea

- Zinc (with MV vs MV alone; singly or with vitamin A) significantly
 - **Reduced stool output**
 - **Prevented weight loss / promoted weight gain**
 - **Promoted earlier clinical recovery**
- Based on 2 RDBCTs in mod malnourished children 6-24 mos (n=190 + 96)

Zinc Supplementation: Treatment

1990s

- Continuous trials (1-2 RDAs 5-7 times/week)
 - **OR= 0.82** [95%CI: 0.72, 0.93] incidence
 - **OR = 0.75** [95%CI: 0.63, 0.88] prevalence
- Short-course trials (2-4 RDAs daily for 2 wks)
 - **OR = 0.89** [95%CI: **0.62**, 1.28] incidence
 - **OR = 0.66** [95%CI: 0.52, 0.83] prevalence

2000s

- 9% reduction in incidence of diarrhea
- 19% reduction in prevalence of diarrhea
- 28% reduction in multiple (≥ 2) diarrheal episodes
- No statistically significant impact on persistent diarrhea, dysentery or mortality

Zinc Supplementation: Prevention

Bhutta A, Black RE, Brown KH et al. J Pediatr 1999; 135: 689-97.

Patel AB, Mamtani M, Badhoniya N, Kulkarni H. BMC Infect Dis 2011; 11: 122.

- Decline in protective efficacy due to variability in:
 - Microbial isolates
 - *Klebsiella sp* most responsive; *E coli* neutral; rotavirus worse outcome
 - Age
 - Less efficacious in infants <12 mos
 - More pathogens in those <12 mos which are refractory to zinc (e.g., rotavirus)
 - Zinc salts used
 - Zinc gluconate with most significant reduction in incidence in comparison to zinc sulfate and zinc acetate

Zinc Supplementation: Prevention

- Inconsistent results as treatment adjunct
 - Beneficial only as prophylactic strategy
- Meta-analysis of 43 trials (215,633 aged 6m-5y)
- Reduction in mortality from diarrhea
RR=0.78 [95% CI: 0.57, 0.91]
 - Reduction in diarrhea incidence
RR=0.85 [95% CI: 0.82, 0.87]
 - No significant effect on hospitalizations due to diarrhea
 - Increased vomiting within 48 hrs of supplementation
RR=2.75 [95% CI: 1.81, 4.19]
- Can ameliorate adverse effect of stunting associated with persistent diarrhea

Vitamin A Supplementation

- RDBPCT on clinical efficacy of combination therapy vs. monotherapy among 6-24 mos with acute diarrhea (n=167) vs. control
 - Supplementation of zinc, zinc + vitamin A, and zinc + micronutrients (vitamin A + Fe, Cu, Se, B₁₂, folate) vs. control
 - Comparable outcomes for supplemented groups with regards to duration, volume of diarrhea, and consumption of oral rehydration solution

Vitamin A or MMN with zinc does not cause further reduction in diarrhea outcomes, confirming the clinical benefit of zinc alone in the treatment of diarrhea.

MMN Supplementation: Treatment

- Most studies in diarrhea prevention
 - No benefit in Peru, Indonesia, South Africa
- South Africa
 - Lower diarrhea incidence only among stunted children when compared with vitamin A alone
 - Vitamin A + zinc
RR=0.52 [95% CI: 0.45, 0.60]
 - MMN (with vit A, zinc)
RR=0.57 [95% CI: 0.49, 0.67]

MMN does not lower incidence of diarrhea except among stunted children when used with supplemental zinc.

MMN Supplementation: Prevention

Acute Diarrhea

- Reduction in duration of diarrhea by 24.76 hrs [95% CI: 15.9-33.6 hrs]
- Decrease risk for diarrhea lasting ≥ 4 days with risk ratio 0.41 [95% CI: 0.32-0.53]

Persistent Diarrhea

- Small review of 464 subjects
- Reduction in duration of diarrhea by 4.02 days [95% CI: 4.61-3.43]
- Decrease in stool frequency

Adjuncts in Treatment: Probiotics

- Individual patient data meta-analysis
- 9 RCTs (n=1384)
- Higher proportion of recovered patients in racecadotril group vs placebo
 - Hazard ratio = 2.04 [95% CI: 1.85-2.32] p<0.001
- Ratio of stool output between racecadotril/placebo
 - = 0.59 [0.51-0.74] p<0.001
- Ratio of mean number of diarrheic stools between racecadotril/placebo
 - = 0.63 [0.51-0.74] p<0.001

Racecadotril in Diarrhea

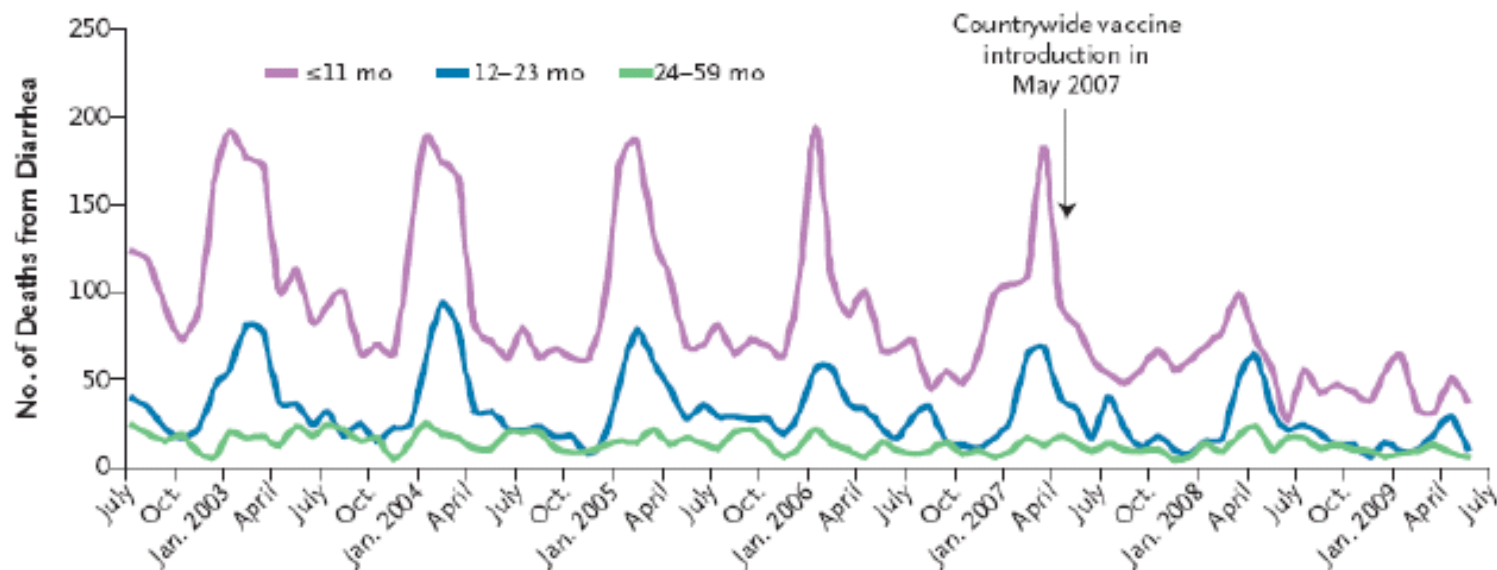
- Breast feeding
- Improved weaning practices
- Immunizations against measles, rotavirus and cholera
- Improved water supply and sanitation facilities
- Promotion of personal and domestic hygiene

Strategies	Cost/DALY US \$
Breast feeding	930
Measles vaccination	981
Rotavirus vaccination	2,478
Cholera vaccination	2,945
Rural water and sanitation improvement	7,876
ORT	10,020
Urban water and sanitation improvement	25,510

Strategies for Diarrheal Disease Control

A significant decline in diarrhoea-related deaths was seen for children aged <5 years after introduction of RV vaccination in Mexico*

Number of diarrhoea-related deaths among children 59 months of age or younger from July 2002 to May 2009 in Mexico, according to age group



A decrease of acute GE deaths in children ≤11 months was observed in 2008 (41%), and a decrease of 66% (cf baseline) in 2009

* Introduction of *Rotarix*[™] in the Mexican immunisation program



Are breastfed babies protected against rotavirus disease?

Case-control study in rural Bangladesh

n=102 cases with clinically severe rotavirus diarrhea;
n=2587 controls

Results

- eBF of infants associated with significant protection against severe rotavirus diarrhea; RR=0.10 [95% CI: 0.03,0.34]
- *Breastfeeding is still important for the control of diarrhea due to non-rotaviral enteropathogens.*

BF and Risk of Rotavirus Diarrhea: Prevention or Postponement?

**Surveillance study in Muntinlupa (2005-2006)
evaluating the burden of RV disease**

**Significantly higher prevalence of RV infection
among non-BF infants <6 mos [24% vs. 15%, p=0.04]**

**No statistically significant difference in prevalence of
RV infection between BF and non-BF infants
(p=0.519) for children <5 yr old**

BF and Risk of Rotavirus Diarrhea

ROTAVIRUS VACCINE FOR ALL FILIPINO CHILDREN

Submitted by pax2011 on January 11, 2012 - 09:57

Health Secretary Enrique T. Ona administering an oral rotavirus vaccine to a six week old baby girl during the 13th Asian Conference on Diarrheal Diseases and Nutrition held at the Taal Vista Hotel. The said oral rotavirus vaccine is expected to benefit children coming from the poorest 5.2million families. The Philippines is the first country in Asia to include rotavirus vaccine in its national immunization program. The inclusion of rotavirus vaccine in national immunization program is also a step towards achieving our Millennium Development Goal. Also in photo are Health Assistant Secretaries Paulyn Ubial and Eric Tayag. (10 January 2012, Taal Vista Hotel, Tagaytay City)

Image:



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Know what you're up against...

Utilize your resources well...

Keep the beast at bay...

Taming the Beast: Diarrhea
