Pneumonia & Diarrhea in Children

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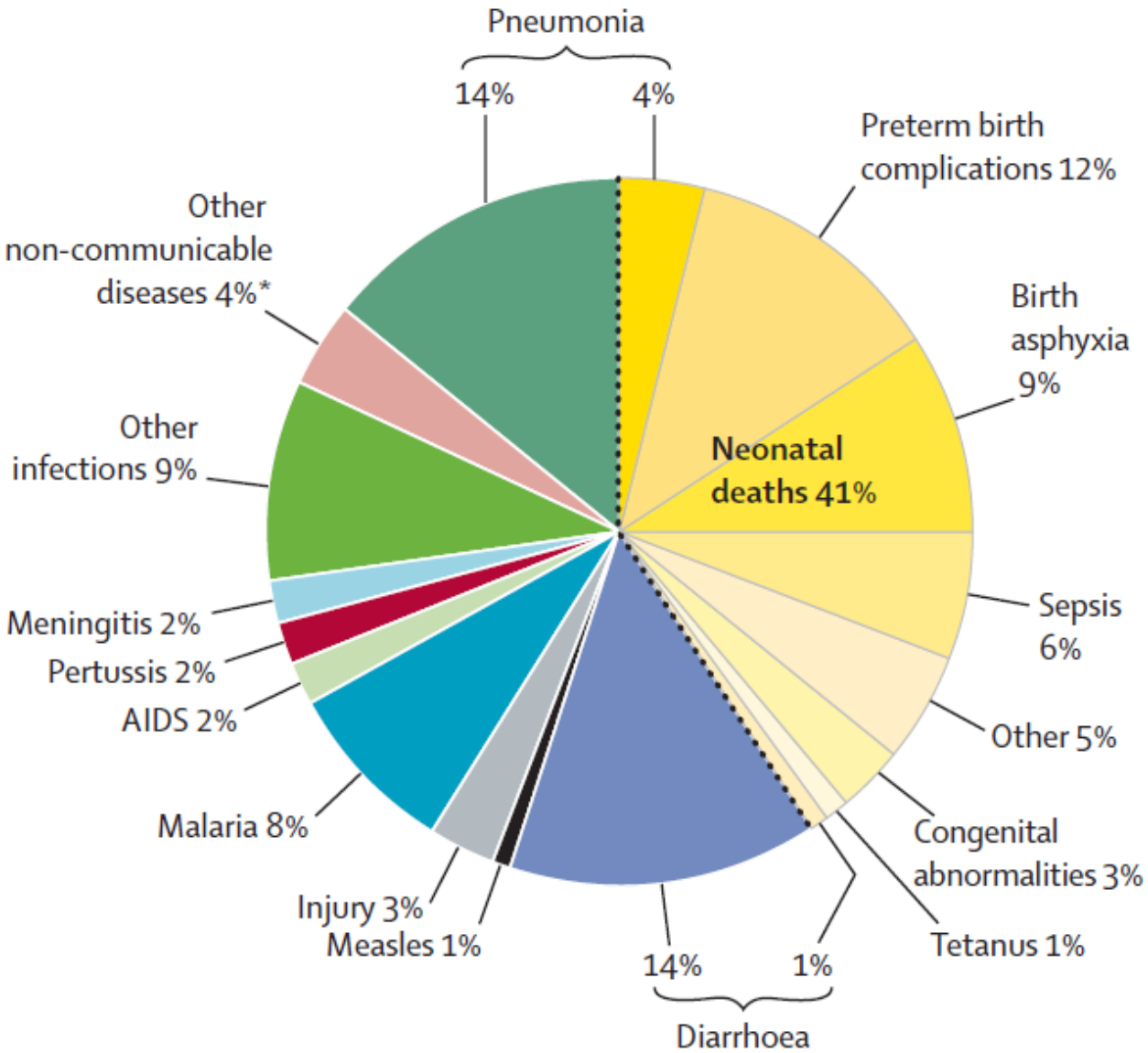
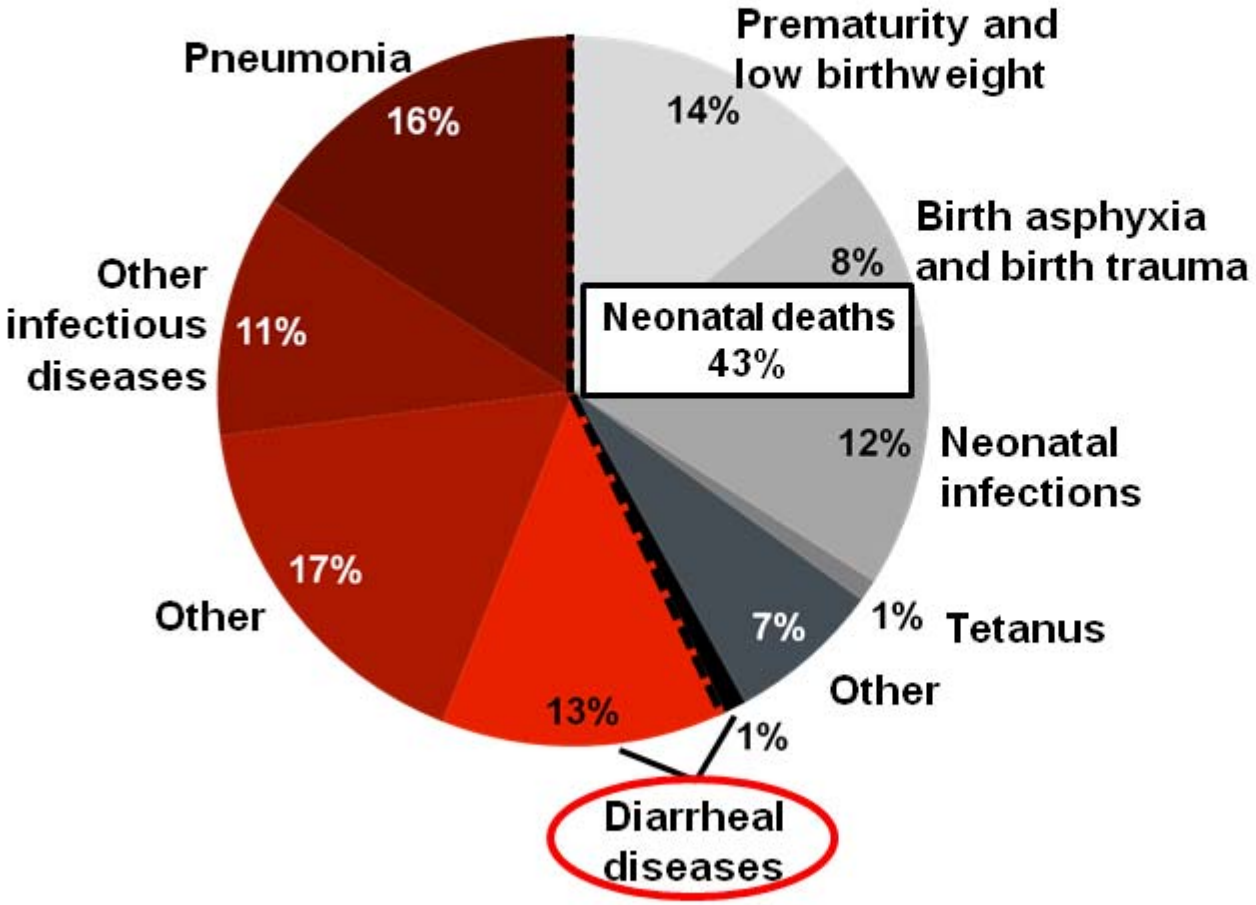
Global Distribution of Causes of Child Deaths: 2008



Diarrhea and Pneumonia

Leading Infectious Disease Causes of Child Mortality in India



Mortality in children < 5 years of age:

- **Total: 2.35 million**
- **Neonatal: 1.01 million**
- **Pneumonia: 530,000**
- **Diarrhea: 334,000**

What is Pneumonia?

- **Pneumonia**: an acute infection of the pulmonary parenchyma

- The term “Lower Respiratory Tract Infection” (LRTI) may include pneumonia, bronchiolitis and/or bronchitis

Pneumonia - Common Pathogens

Age Group	Common Pathogens (in Order of Frequency)
Newborn	Group B *Streptococci* Gram-negative bacilli *Listeria monocytogenes* Herpes Simplex Cytomegalovirus Rubella
1-3 months	*Chlamydia trachomatis* Respiratory Syncytial virus Other respiratory viruses
3-12 months	Respiratory Syncytial virus Other respiratory viruses *Streptococcus pneumoniae* *Haemophilus influenzae* *Chlamydia trachomatis* *Mycoplasma pneumoniae*

From: Tintinalli JE et al. (2004). *Emergency Medicine, A Comprehensive Study Guide, Sixth Edition.* American College of Emergency Physicians. (pp. 784-789). McGraw-Hill. Toronto, ON.

Pneumonia - Common Pathogens

Age Group	Common Pathogens (in Order of Frequency)
2-5 years	Respiratory Viruses *Streptococcus pneumoniae* *Haemophilus influenzae* *Mycoplasma pneumoniae* *Chlamydia pneumoniae*
5-18 years	*Mycoplasma pneumoniae* *Streptococcus pneumoniae* *Chlamydia pneumoniae* *Haemophilus influenzae* Influenza viruses A and B Adenoviruses Other respiratory viruses

From: Tintinalli JE et al. (2004). *Emergency Medicine, A Comprehensive Study Guide, Sixth Edition.* American College of Emergency Physicians. (pp. 784-789). McGraw-Hill. Toronto, ON.

Recognition of Signs of Pneumonia

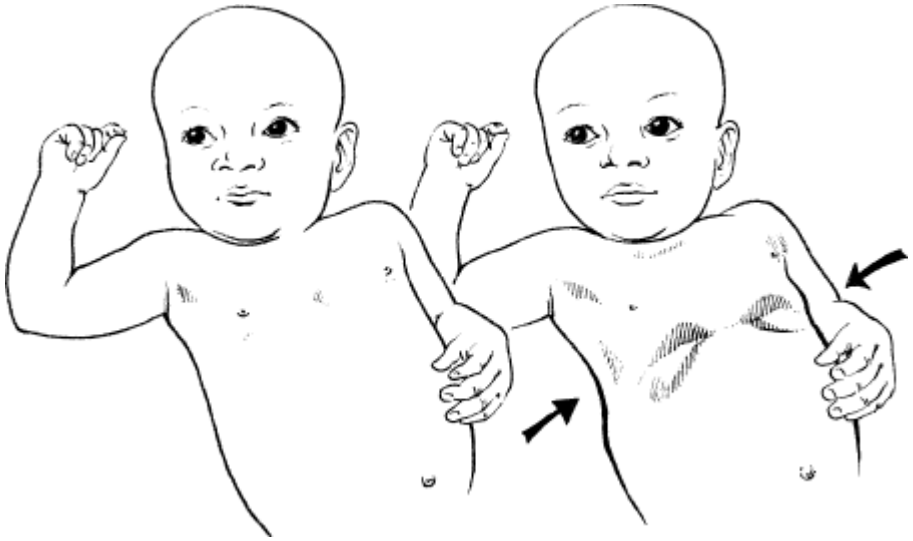
- Tachypnea is the most sensitive and specific sign of pneumonia

- Tachypnea had a Sensitivity of 61% and 79% and Specificity of 79% and 65% for pneumonia in malnourished and well-nourished Gambian children respectively

WHO Definition of Tachypnea

Age	Respiratory Rate (breaths/min)	Indication of severe infection (breaths/min)
< 2 months	> 60	>70
2 to 12 months	> 50	
12 months to 5 years	> 40	>50
Greater than 5 years	> 20	

Other signs of pneumonia - Indrawing

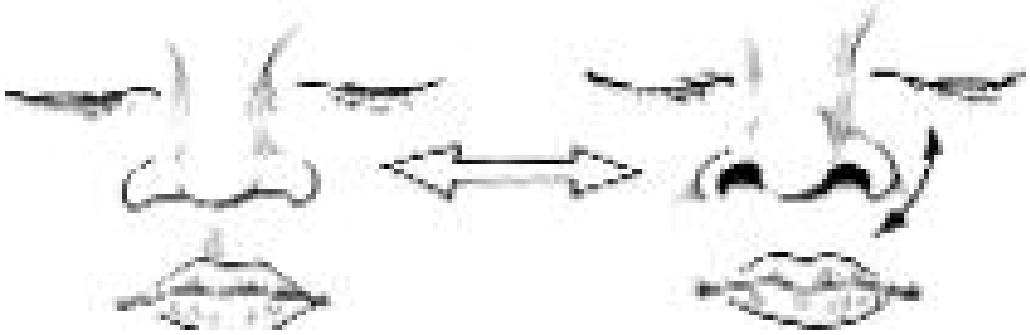


out---breathing---in

Lower chest wall indrawing: with inspiration, the lower chest wall moves in

From: Integrated Management of Childhood Illness. Chapter Three: Cough or difficulty breathing. World Health Organization. 2000 "https://apps.who.int/chd/publications/referral_care/chap3/chap31.htm. Accessed February 2, 2012

Other signs of pneumonia - Nasal Flare



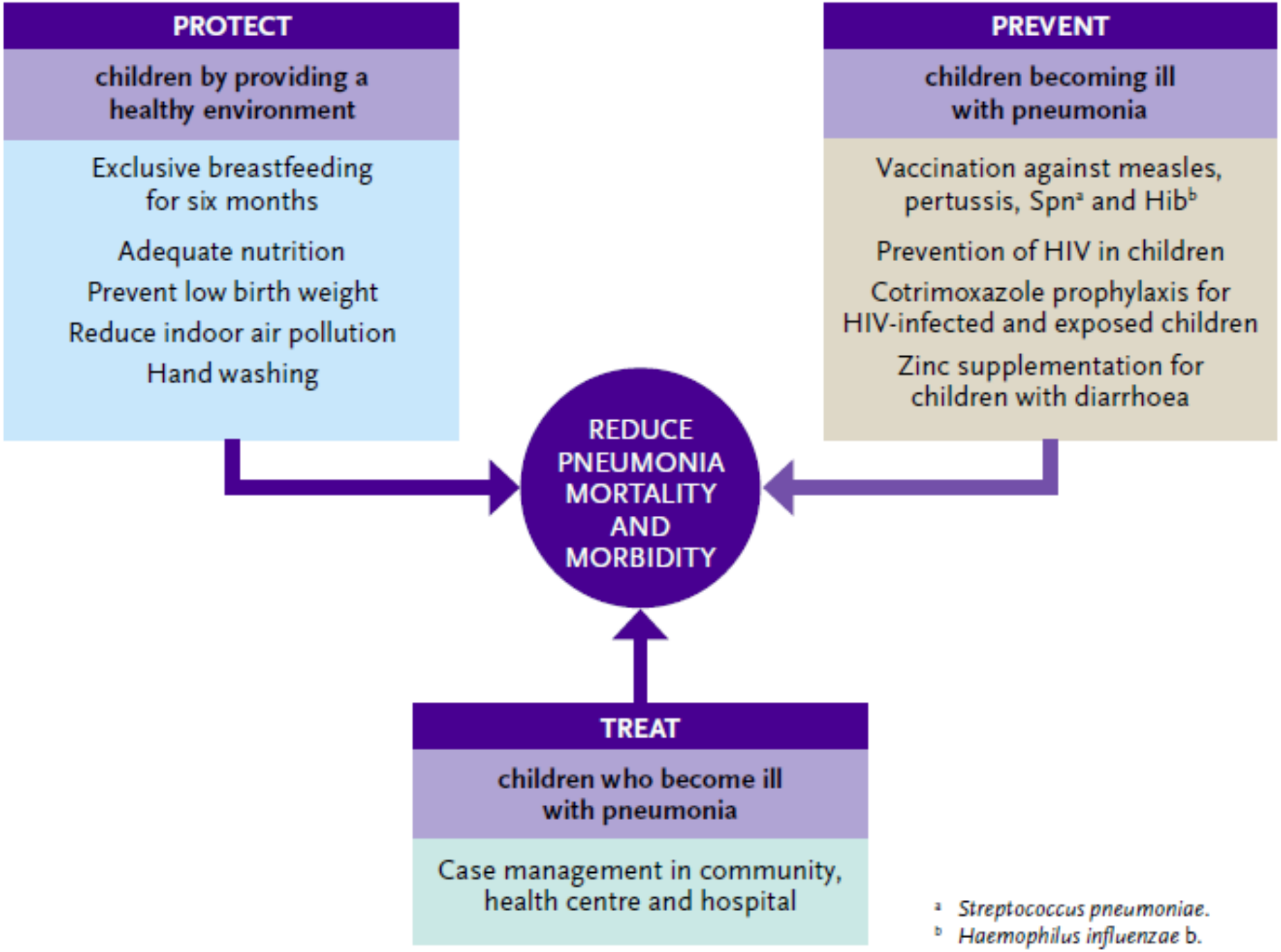
Nasal flaring: with inspiration, the side of the nostrils flares outwards

From: Integrated Management of Childhood Illness. Chapter Three: Cough or difficulty breathing. World Health Organization. 2000 "https://apps.who.int/chd/publications/referral_care/chap3/chap31.htm. Accessed February 2, 2012

Diagnosis in Community Setting

SIGNS	Classify AS	Treatment
•Tachypnea •Lower chest wall indrawing •Stridor in a calm child	Severe Pneumonia	•Refer urgently to hospital for injectable antibiotics and oxygen if needed •Give first dose of appropriate antibiotic
•Tachypnea	Non-Severe Pneumonia	•Prescribe appropriate antibiotic •Advise caregiver of other supportive measure and when to return for a follow-up visit
•Normal respiratory rate	Other respiratory illness	•Advise caregiver on other supportive measures and when to return if symptoms persist or worsen

From: Pneumonia The Forgotten Killer of Children. Geneva: World Health Organization (WHO)/United Nations Children's Fund (UNICEF), 2006.


PROTECT
children by providing a healthy environment
Exclusive breastfeeding for six months
Adequate nutrition
Prevent low birth weight
Reduce indoor air pollution
Hand washing
PREVENT
children becoming ill with pneumonia
Vaccination against measles, pertussis, Spn[a] and Hib[b]
Prevention of HIV in children
Cotrimoxazole prophylaxis for HIV-infected and exposed children
Zinc supplementation for children with diarrhoea
REDUCE PNEUMONIA MORTALITY AND MORBIDITY
TREAT
children who become ill with pneumonia
Case management in community, health centre and hospital
[a] Streptococcus pneumoniae.
[b] Haemophilus influenzae b.

Interventions to Protect Against Pneumonia

Interventions to Protect Against Pneumonia

- It is estimated that **hand washing**, when combined with improved water and sanitation could lead to a 3% reduction in all child deaths.

- Promote **exclusive breast feeding for 6 months**. Impact 15-23% reduction in pneumonia incidence. 13% reduction in all child deaths. Shown to be cost effective.

Interventions to Protect Against Pneumonia

- **Adequate nutrition throughout the first five years of life**, including adequate micronutrient intake. Impact 6% reduction in all child deaths for adequate complementary feeding (age 6-23 months).

- **Reduce incidence of low birth weight**.

Intervention to Protect Against Pneumonia

- **Reducing indoor air pollution**, by changing to cleaner gas or liquid fuels or high-quality, well maintained biomass stoves, may reduce the incidence of pneumonia by 22 to 46% in appropriate settings. This intervention may be cost-effective in low-income settings.

Intervention to Protect Against Pneumonia

- **Reduce Exposure to Second-Hand Tobacco Smoke.**

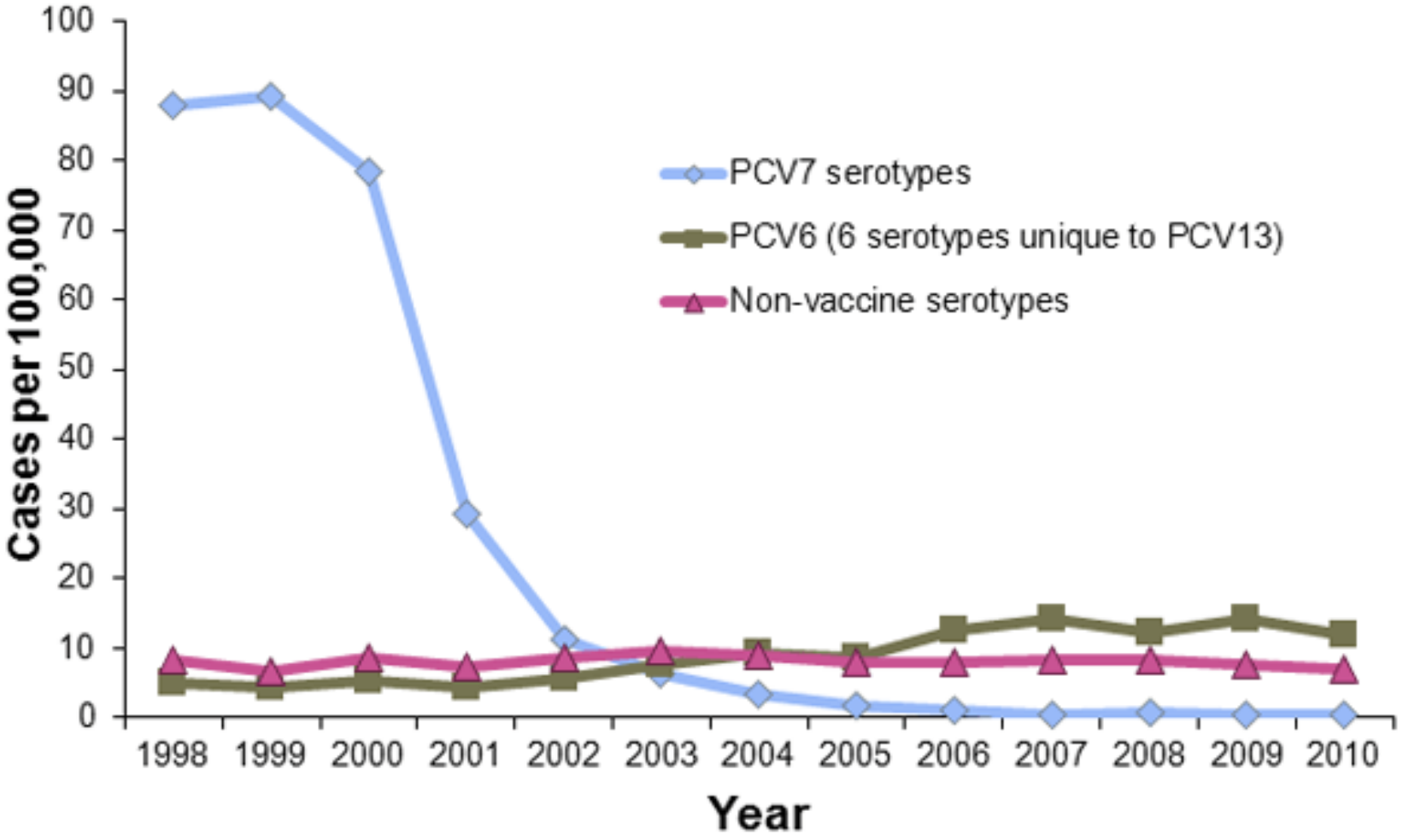
- Both maternal and paternal smoking cause lower respiratory tract illnesses such as pneumonia and bronchitis, particularly during the first year of life.

Interventions to Prevent Pneumonia

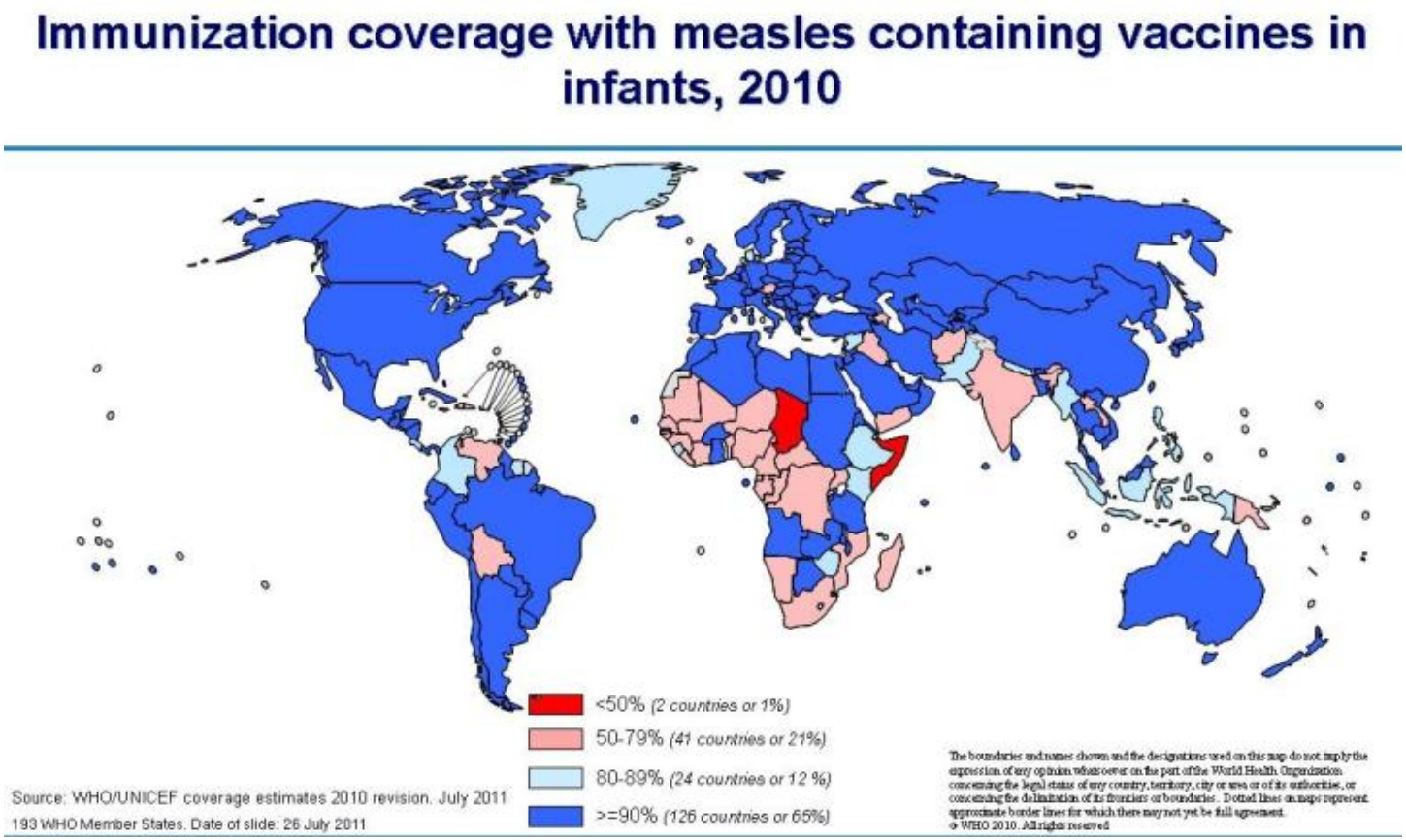
Prevention - Vaccination

- Three vaccinations have the potential to significantly reduce childhood deaths from pneumonia
- Haemophilus Influenzae type B (Hib) vaccine and Pneumococcal conjugate vaccine prevent infections that directly cause pneumonia
- Pneumonia is a possible complication of Measles, thus prevention of measles would decrease the incidence of pneumonia.

Invasive pneumococcal disease among children aged <5 years

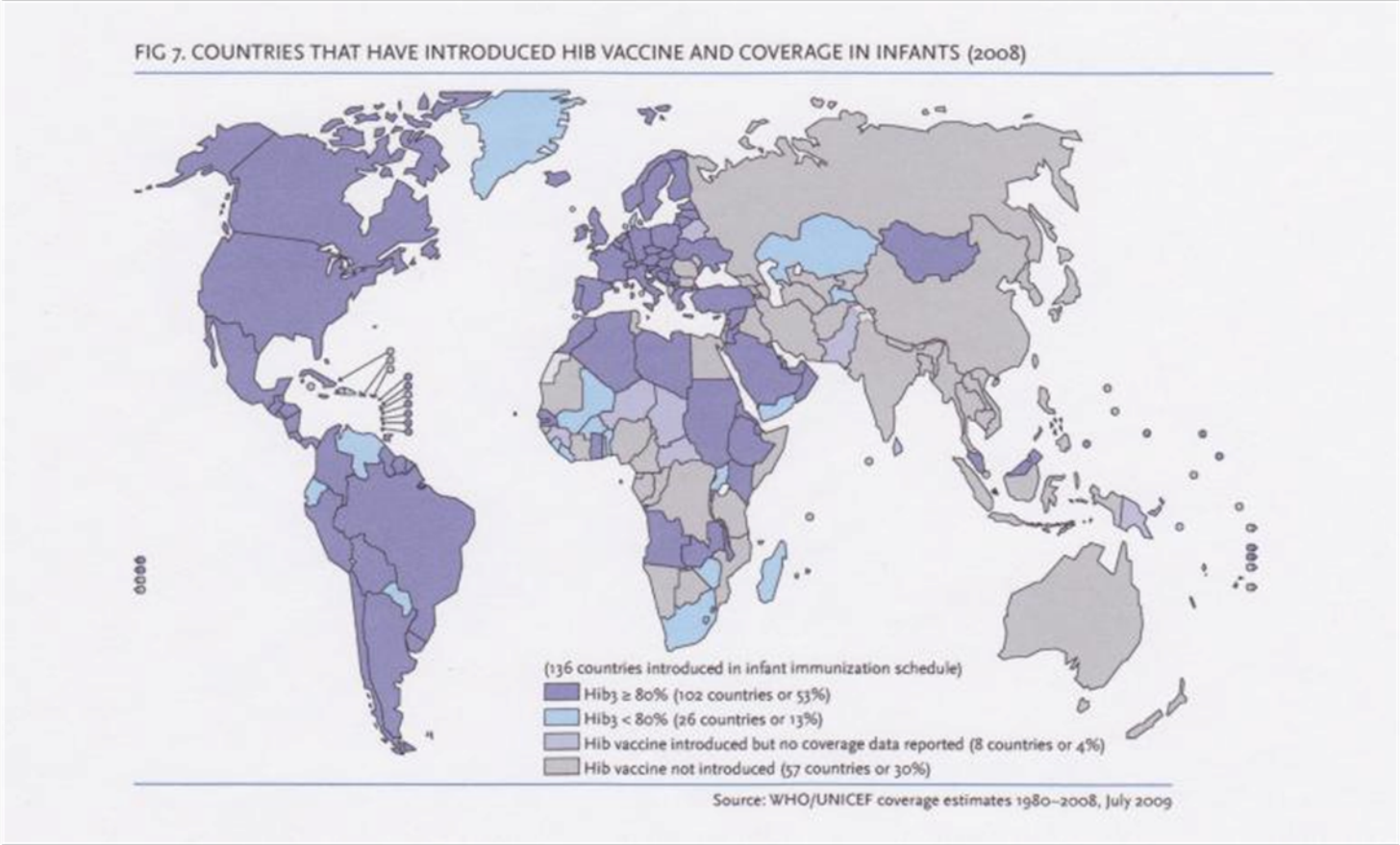


Measles Vaccine 2010



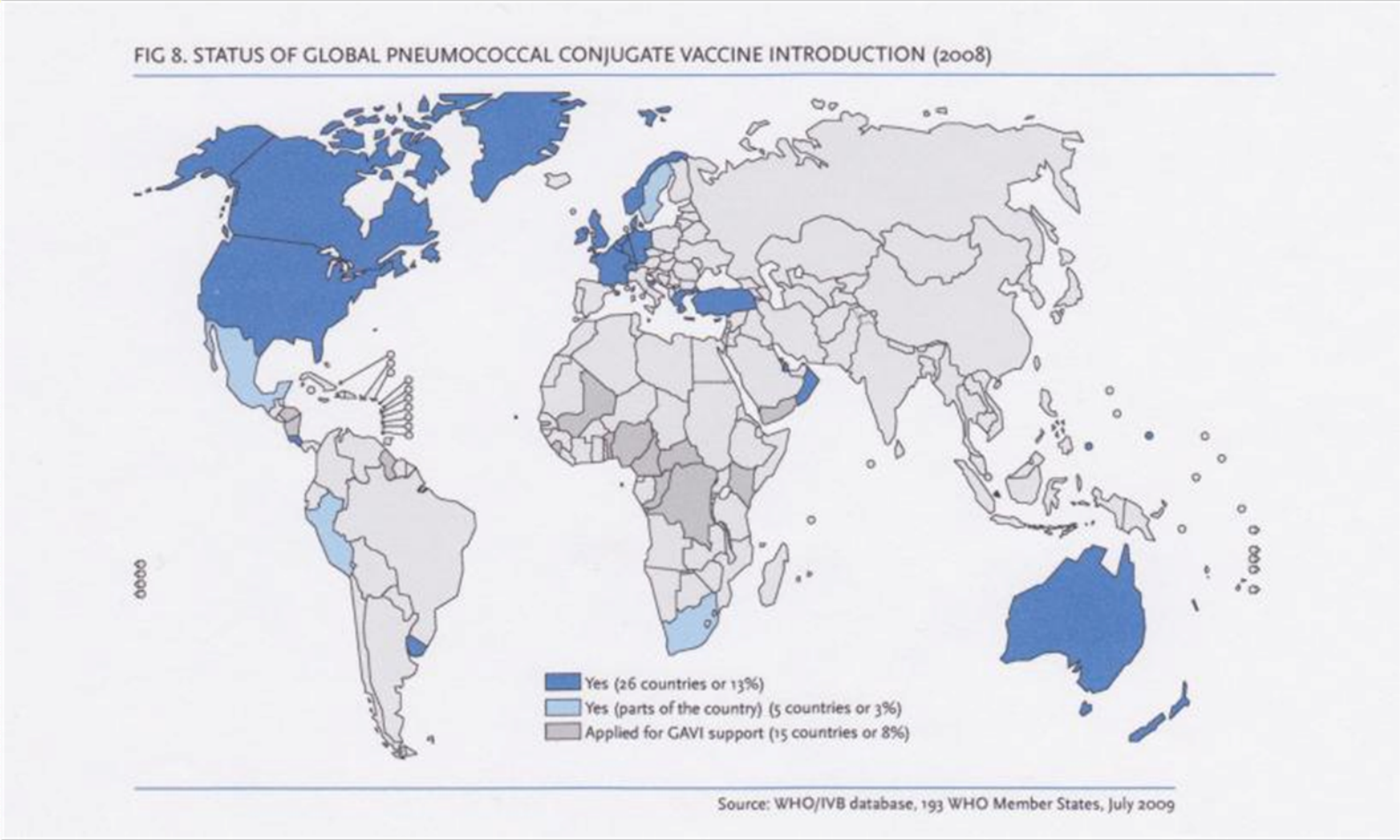
From: WHO. Immunization Surveillance Assessment and Monitoring. [http://www.who.int/immunization_monitoring/diseases/measles/en/index.html]. Accessed on December 9,2011.

HIB Vaccine 2008



From: GAPP. Geneva: WHO/UNICEF, 2009.

Pneumococcal Conjugate Vaccine 2008



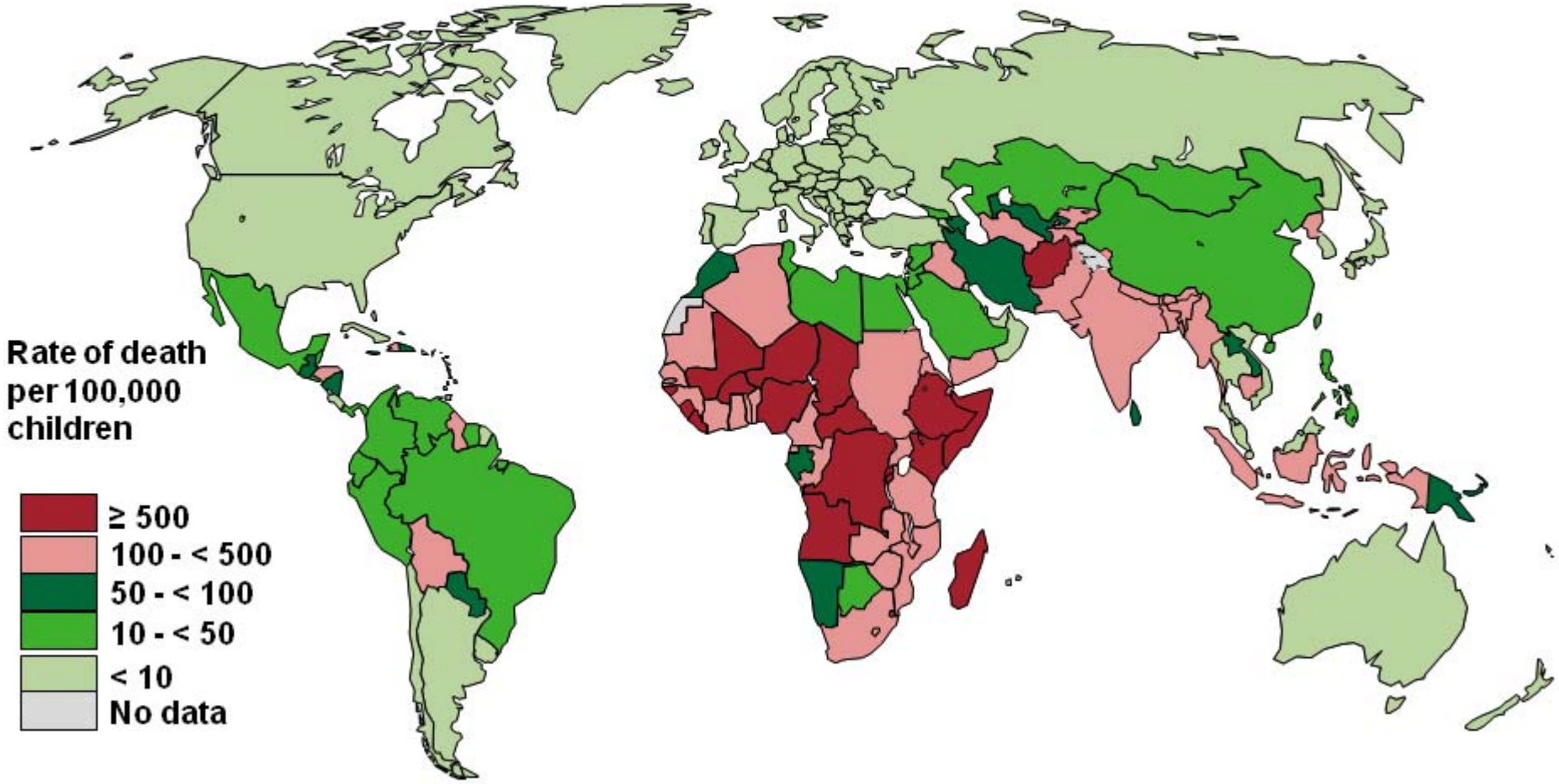
From: GAPP. Geneva: WHO/UNICEF, 2009.

Prevention – Zinc Supplementation

- Zinc supplementation in Bangladesh has been shown to reduce pneumonia mortality in children in children less than 2 years.
- Zinc supplementation was also shown to reduce the incidence of pneumonia, other upper and lower respiratory tract infections and diarrhea.
- Doses of 70 mg per week have been found to be effective.

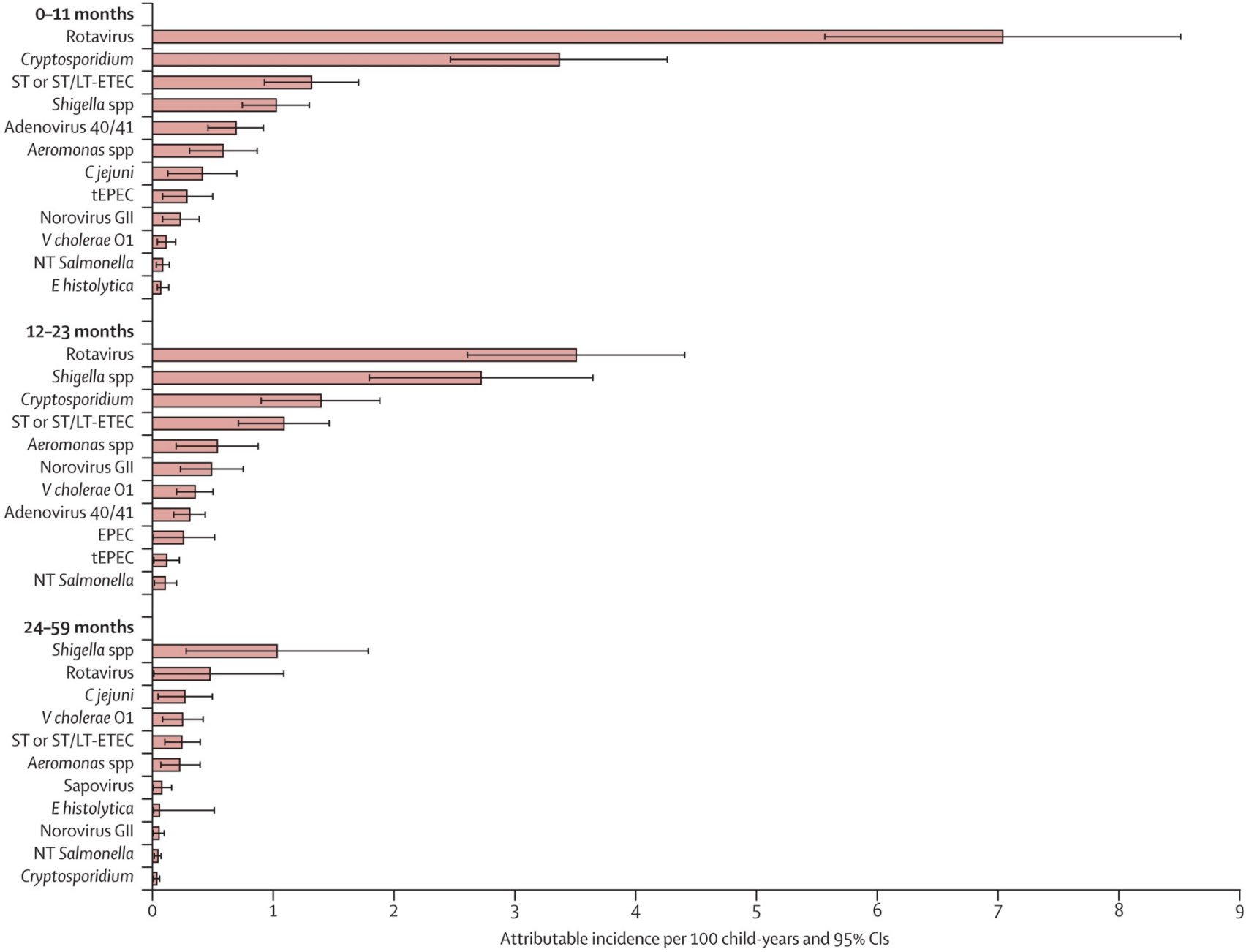
INTERVENTIONS TO PROTECT	EVIDENCE OF IMPACT
Promote exclusive breastfeeding for 6 months	15–23% reduction in pneumonia incidence;[a] 13% reduction in all child deaths[b]
Adequate nutrition throughout the first five years of life, including adequate micronutrient intake	6% reduction in all child deaths for adequate complementary feeding (6–23 months of life)[b]
Reduce incidence of low birth weight	Review in progress
Reduce indoor air pollution	Relative risk reduction with liquid fuel stoves; 75% reduction in incidence in specific settings with improved solid fuel stoves[a]
Hand washing	3% reduction in all child deaths when combined with improved water and sanitation interventions[b]
INTERVENTIONS TO PREVENT	**EVIDENCE OF IMPACT**
Vaccination against measles, pertussis, Spn and Hib	22–34% reduction in incidence for Hib;[a] 23–35% reduction in incidence for Spn;[a] 4% reduction in all child deaths with Hib and 1% with measles[b]
Prevention of HIV in children	2% reduction in all child deaths[b]
Cotrimoxazole prophylaxis for HIV-infected children	Review in progress
Zinc supplementation in children with diarrhoea	14–15% reduction in incidence;[a] 4–5% reduction in all child deaths as preventive measure[b]
INTERVENTIONS TO TREAT	**EVIDENCE OF IMPACT**
Improved care seeking and demand generation within communities	Review in progress
Health facility case management for very severe cases and vulnerable groups such as newborns, HIV-infected and malnourished children	29–45% reduction in case fatality;[a] 6% reduction in all child deaths[b]
Increasing access to appropriate care through community-based case management	34–50% reduction in neonatal case fatality;[a] reduction in total mortality of 27%, 20%, and 24% among neonates, infants, and children, respectively; reduction in pneumonia mortality in the same groups by 42%, 36%, and 36%[c]

Diarrhea-Related Deaths in Children Under 5 Years of Age, 2008

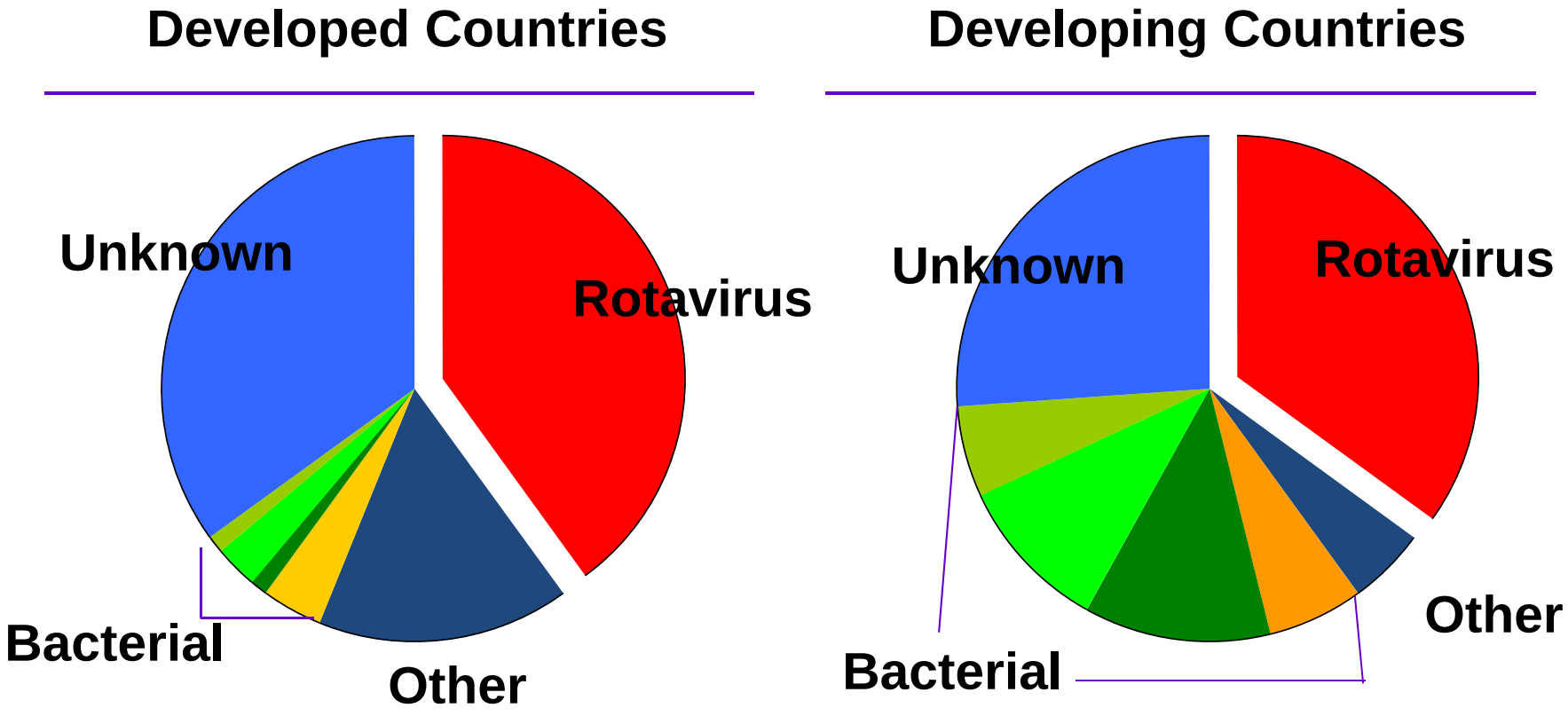


Santosham M, et al. *Lancet*. 2010;376:63-67.

GEM study

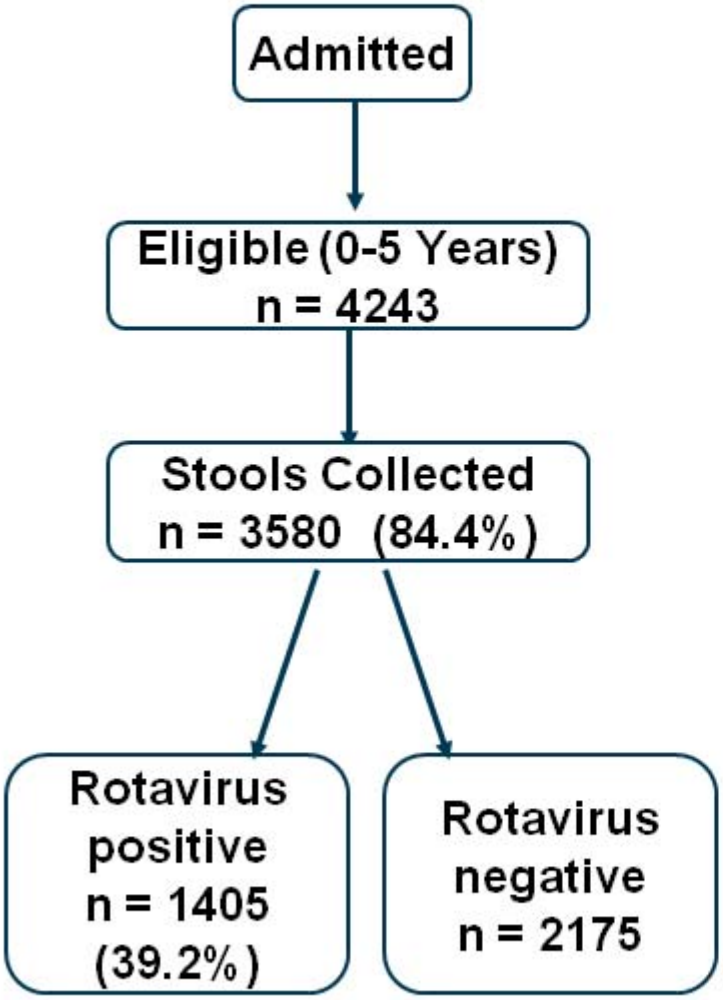

0–11 months
Rotavirus
Cryptosporidium
ST or ST/LT-ETEC
Shigella spp
Adenovirus 40/41
Aeromonas spp
C jejuni
tEPEC
Norovirus GII
V cholerae O1
NT Salmonella
E histolytica
12–23 months
Rotavirus
Shigella spp
Cryptosporidium
ST or ST/LT-ETEC
Aeromonas spp
Norovirus GII
V cholerae O1
Adenovirus 40/41
EPEC
tEPEC
NT Salmonella
24–59 months
Shigella spp
Rotavirus
C jejuni
V cholerae O1
ST or ST/LT-ETEC
Aeromonas spp
Sapovirus
E histolytica
Norovirus GII
NT Salmonella
Cryptosporidium
0
1
2
3
4
5
6
7
8
9
Attributable incidence per 100 child-years and 95% CIs

Rotavirus is the Leading Cause Of Severe Gastroenteritis in Children <5 Years



A. Kapikian, Fields Virology 2003

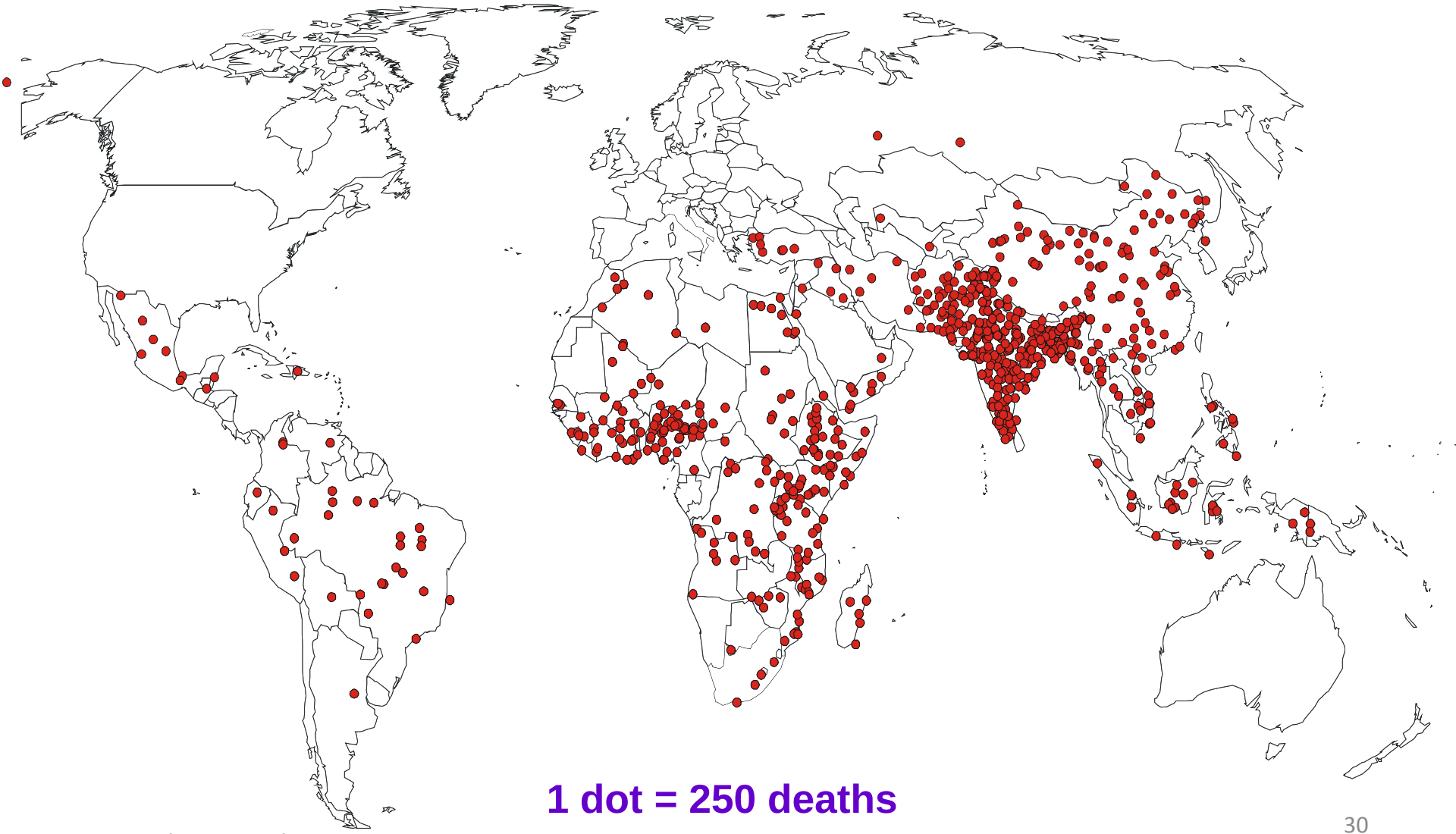
Rotavirus Is Associated With 40% of Hospitalizations for Diarrhea



Site	Stools Collected	Rotavirus Positive
Imphal	394 (73.9%)	179 (45.4%)
Pune	684 (100%)	256 (37.4%)
Mumbai	745 (71.8%)	263 (35.3%)
Vellore	718 (87.1%)	259 (36.1%)
Delhi	633 (85.2%)	232 (36.7%)
Trichy	406 (96.4%)	216 (53.2%)
Total	3580 (84.4%)	1405 (39.2%)

Kang G, et al. *J Infect Dis*. 2009;200:S147-153.

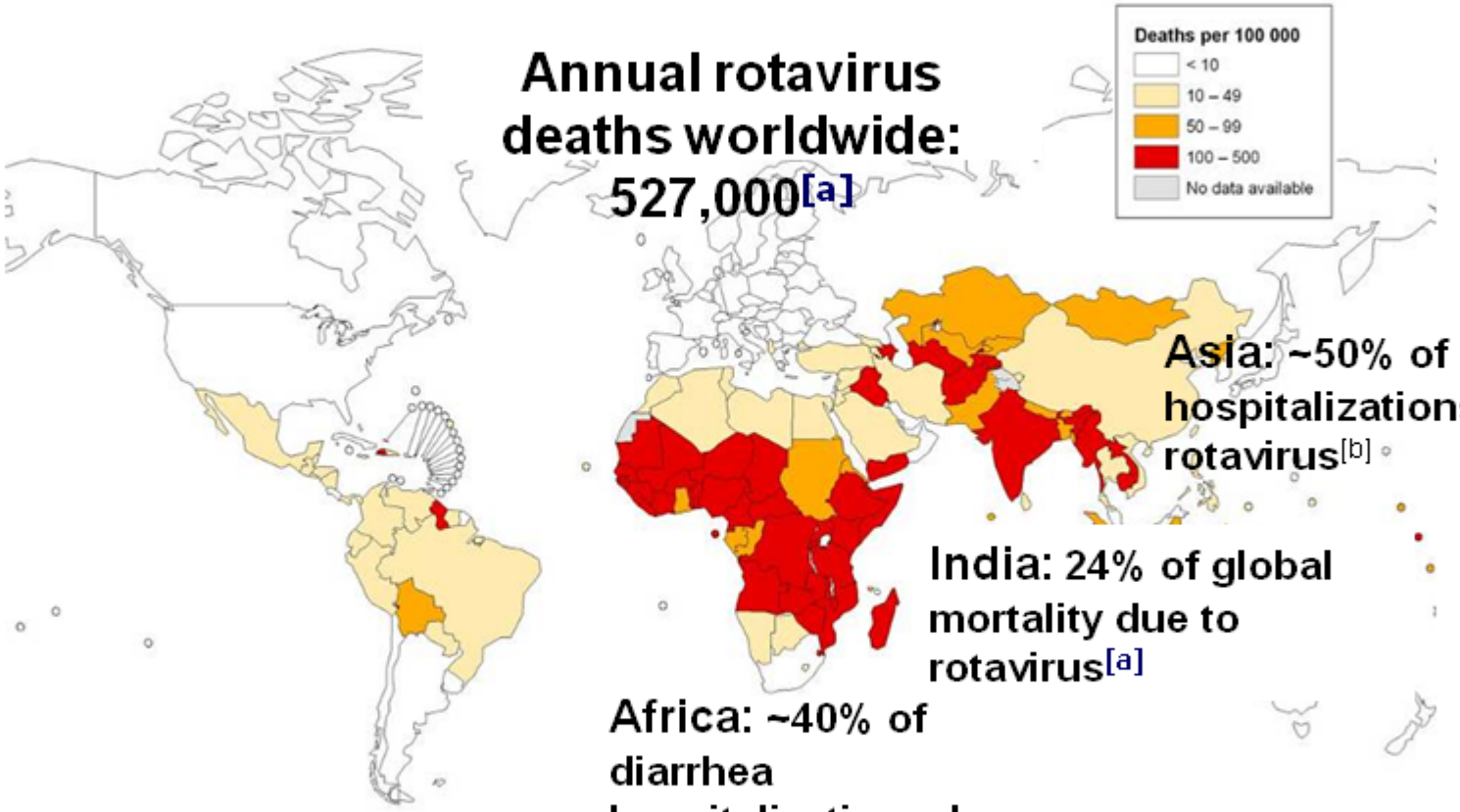
Global Distribution of 527,000 Annual Rotavirus Deaths in Young Children



1 dot = 250 deaths

Parashar et al, JID, 2009

Low Resource Countries in Asia and Africa Carry the Greatest Rotavirus Disease Burden



Annual rotavirus deaths worldwide: 527,000[a]

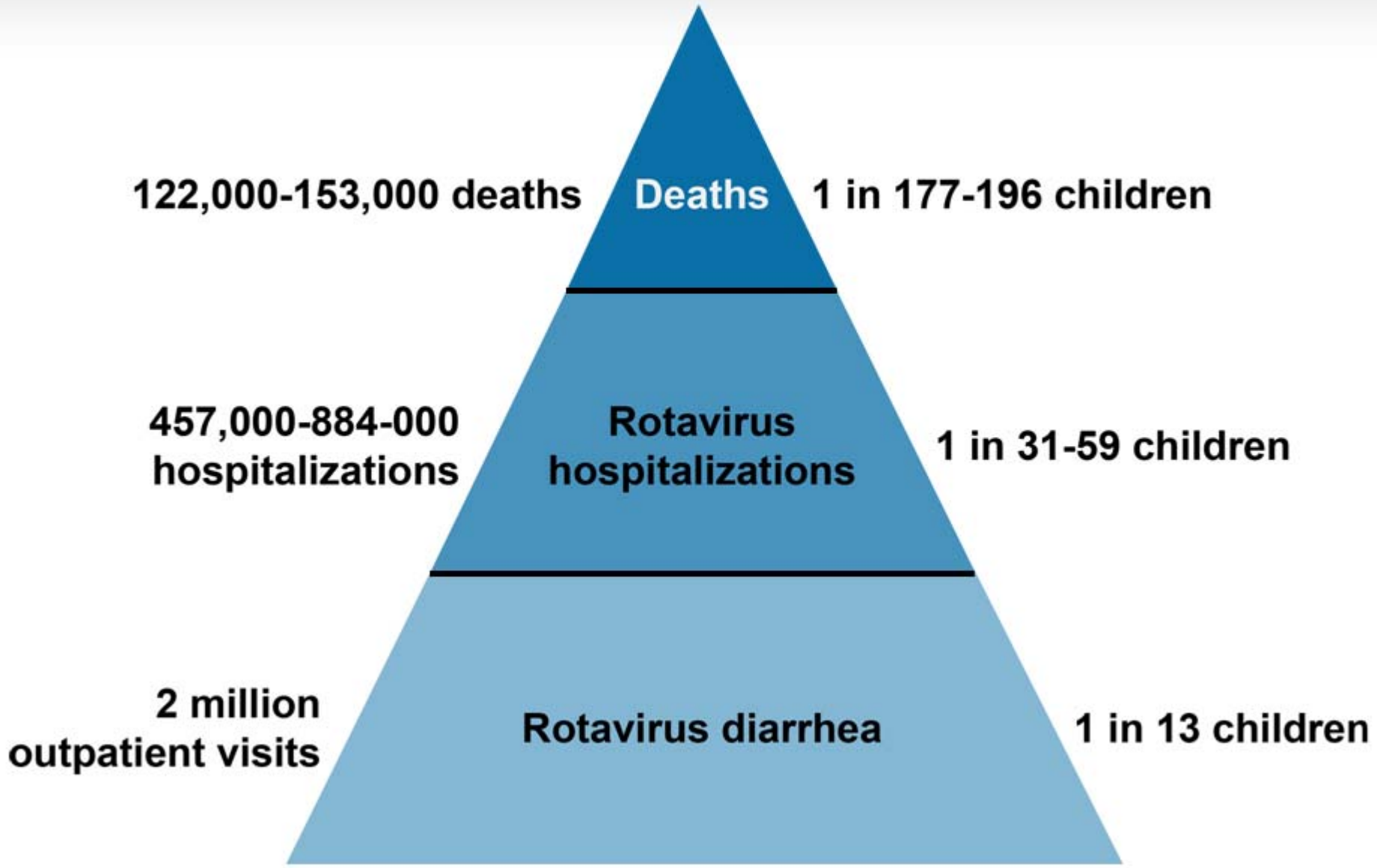
Asia: ~50% of diarrhea hospitalizations due to rotavirus[b]

India: 24% of global mortality due to rotavirus[a]

Africa: ~40% of diarrhea hospitalizations due to rotavirus[b]

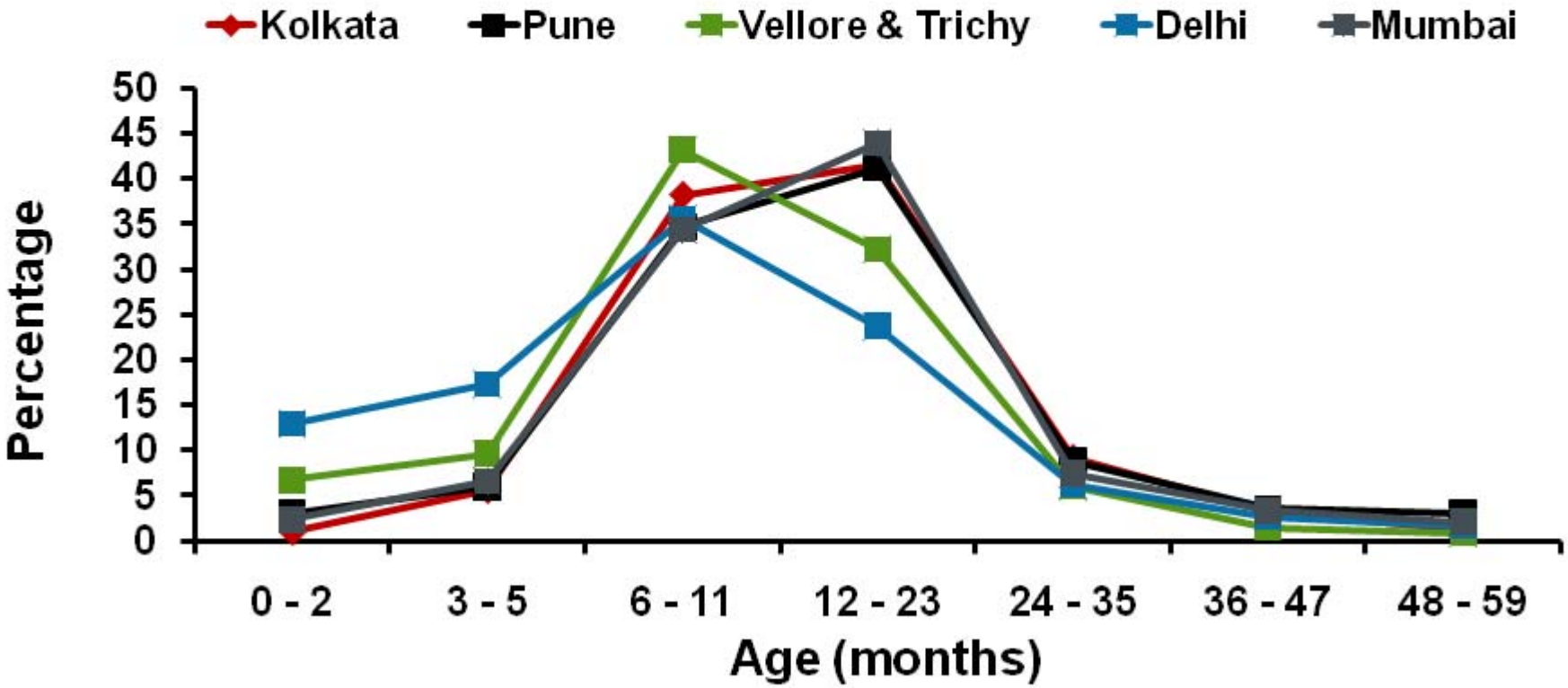
a. WHO. http://www.who.int/immunization_monitoring/burden/rotavirus_estimates/en/
b. Ramani S and Kang G. *Curr Opin Infect Dis*. 2009;22:477-482 .

Rotavirus Disease Burden in India



Tate JE, et al. *Vaccine*. 2009;27 Suppl 5:F18-24..

Proportion of Rotavirus-Positive Cases by Age



Kang G, et al. *J Infect Dis*. 2009;200:S147-S153.

Diarrhoea control

Treatment :

1 - ORT

2 - Zinc treatment

Prevention :

3 - Rotavirus and measles vaccination

4 - Exclusive BF and vit. A supplementation

5 - Handwashing with soap

6 - Safe drinking water

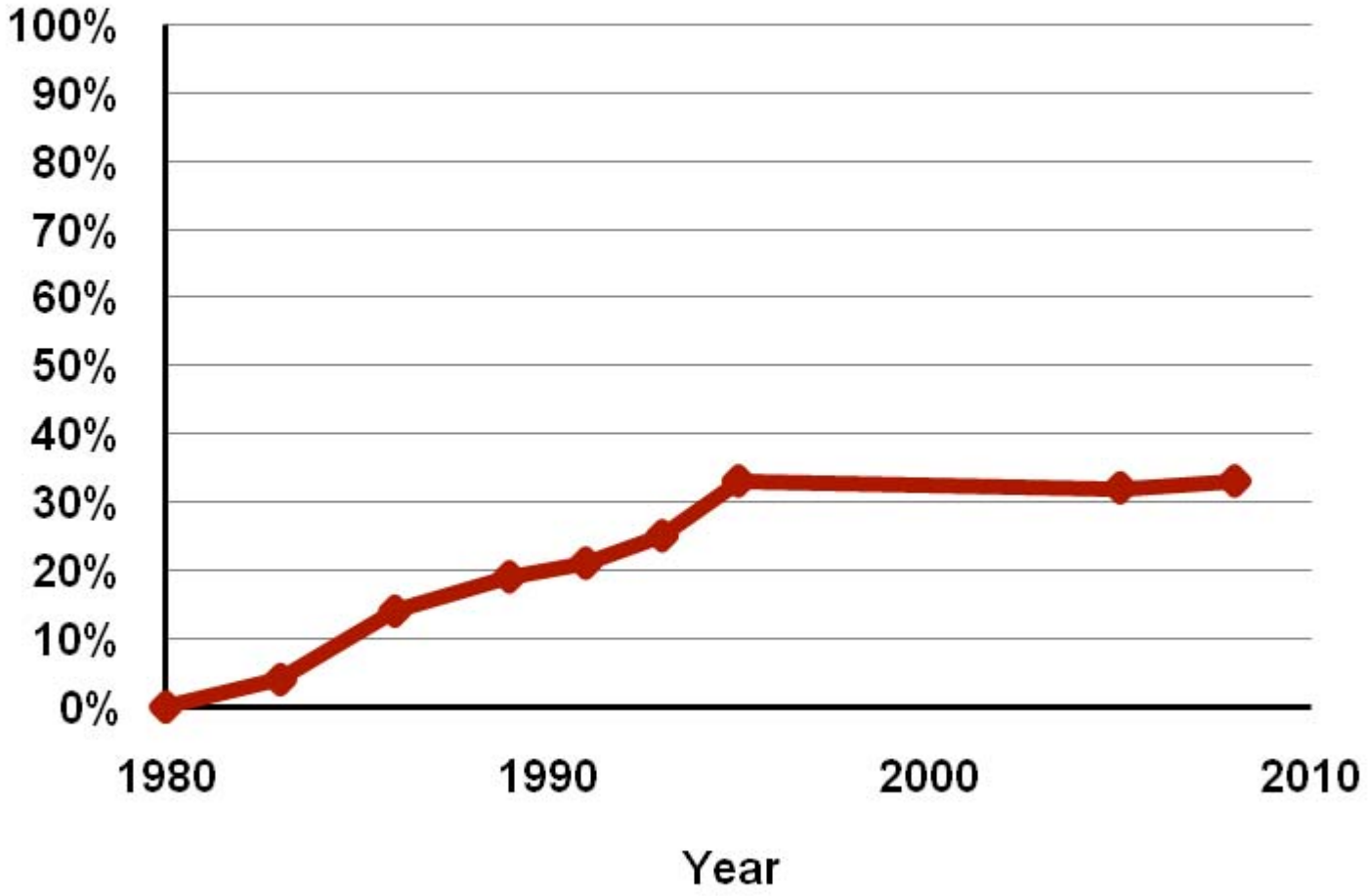
7 - Community-wide sanitation

Global Policy* for Treatment of Diarrhea in Children, May 2004

- Treatment should include:
  - Liberal use of ORS to correct and prevent dehydration
  - Zinc supplementation for 10-14 days to shorten duration and decrease severity of diarrhea
  - Continue feeding

*WHO/UNICEF. Joint statement on the clinical management of acute diarrhea. 2004.

Percentage of Children < 5 Years of Age With Diarrhea Who Received ORS



Santosham M, et al. *Lancet*. 2010;376:63-67.

Use of ORS in India

State	Percentage of Children With Diarrhea Who Received ORS	Performance
Meghalaya	65.1%	Highest performing states
Tripura	58.1%	
Himachal Pradesh	56.3%	
Goa	50.6%	
National Average	26.0%	National Average
Nagaland	16.5%	Lowest performing states
Rajasthan	16.5%	
Assam	14.5%	
Uttar Pradesh	12.5%	

The Mother and Child Health and Education Trust. *National Family Health Survey 2005-2006 (NFHS-3) India Reports*. Chapter 09. Child Health. http://hetv.org/india/nfhs/index.html.

Zinc in acute diarrhea: *meta-analyses*

Reduction in	%
Average duration	25
Stool output	30
Proportion episodes > 5 d	25

WHO/IAP recommendations on use of Zinc in acute diarrhea - 2006

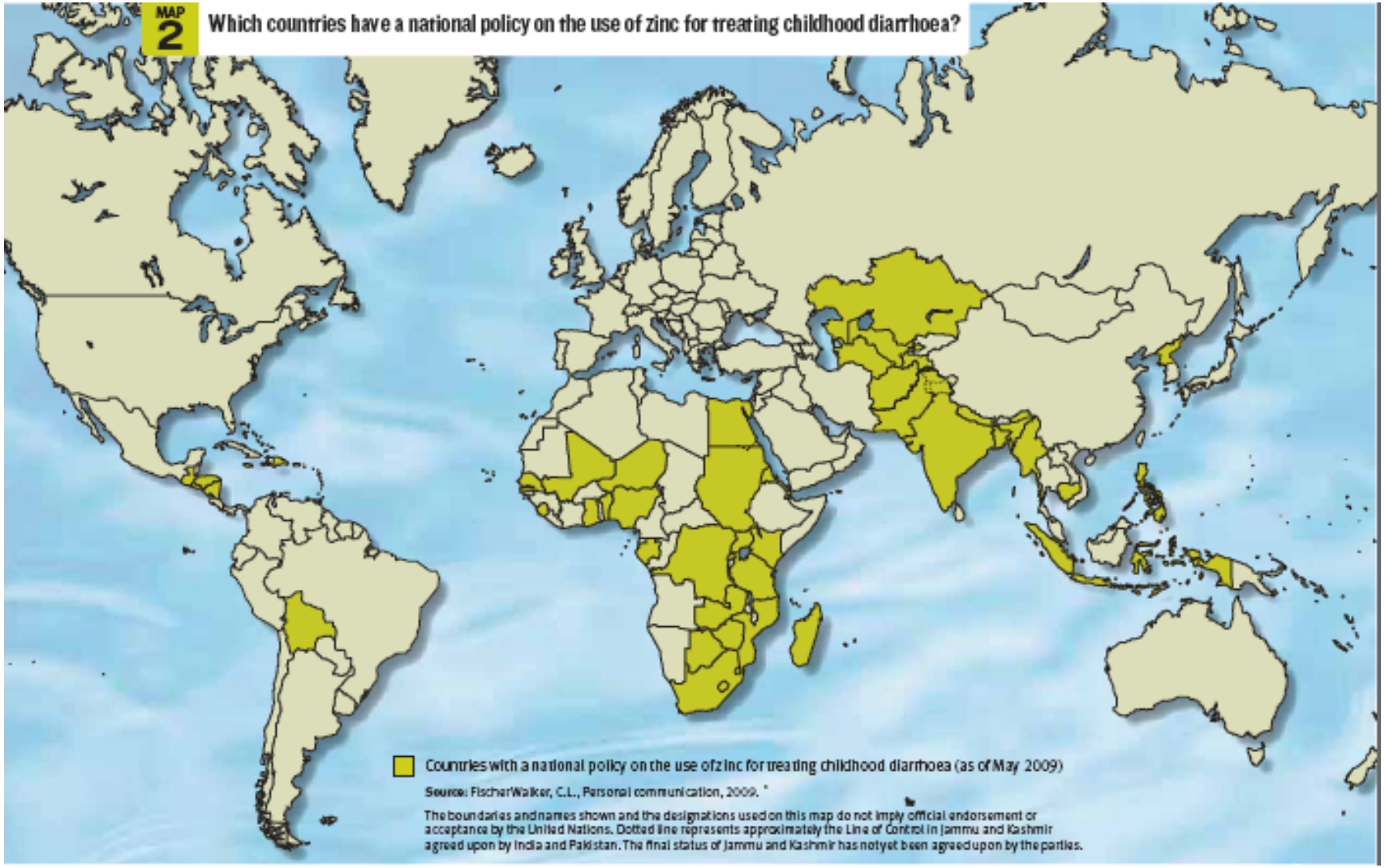
Recommendations

20 mg* per day of zinc supplementation for 14 days starting as early as possible after onset of diarrhoea

**** 10 mg per day for infants 2-6 mo***

Administration: Once or twice daily

Countries with national guidelines including zinc treatment



Probiotics in India ?

- 100+ Single and Combination brands
- Single - bacterial / yeast
- Combination – prebiotic & probiotic
  antibiotic & probiotic
  multivitamin & probiotic
  zinc & probiotics

Some probiotics

- Lactobacillus rhamnosus GG
- L. plantarum 299V
- L. acidophilus
- Bifidobacterium bifidum
- Saccharomyces boulardii
- Bacillus clausii
- Streptococcus thermophilus

Possible benefits

Intestinal disorders

- Diarrhea
  - Antibiotic-induced
  - Traveler's
  - Infantile
- Inflammatory bowel
- Constipation
- Reduce H. pylori infection
- Flatulence
- Colon cancer
- Lactose intolerance

Other disorders

- Vaginitis
- Alcohol liver disease
- Cancer prevention
- Hypercholesterolemia
- Allergy
- Prevention of osteoporosis

Madsen, 2001

Probiotics in management of acute diarrhea

Outcome	Studies (n)	Participants (n)	Effect size
Mean duration of diarrhea	35	4555	-24.76 [-33.61, -15.91]
Diarrhea lasting > 4 days	29	2853	0.41 [0.32, 0.53]
Mean stool frequency on day 2	20	2751	-0.80 [-1.14, -0.45]

Cochrane Syst Reviews 2010

A note of caution !!

- Most studies from developed countries
  - Different breast feeding rates
  - Different gut microflora
  - Rotavirus 50-75%
- Efficacy strain related
  - Lactobacilli *GG* / *S Boulardii*

Diarrhoea control

Treatment :

1 - ORT

2 - Zinc treatment

Prevention :

3 - Rotavirus and measles vaccination

4 - Exclusive BF and vit. A supplementation

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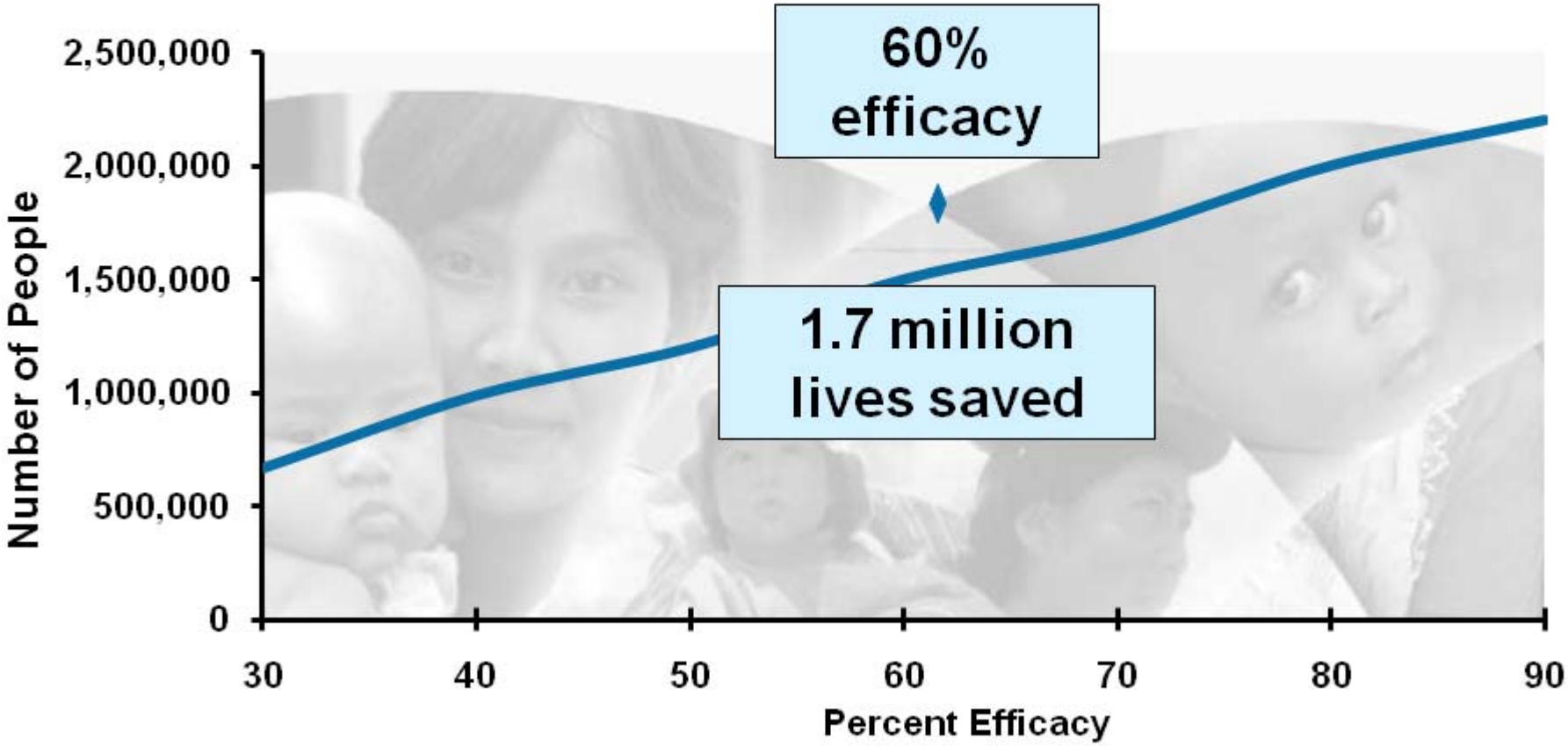
Vaccine Efficacy Against Severe Rotavirus Gastroenteritis in the First Year of Life

Region	Vaccine	Countries	Efficacy (%)	95% CI (%)
Africa[a]	Rotarix®	Malawi, South Africa	61.7	44.0, 73.2
Africa[b]	RotaTeq®	Ghana, Kenya, Mali	64.2	40.2, 79.4
Asia[c]	RotaTeq	Bangladesh, Vietnam	51.0	12.8, 73.3

a. Madhi SA, et al. *N Engl J Med*. 2010;362:346-357.
b. Zaman K, et al. *Lancet*. 2010;376:614-625.
c. Armah GE, et al. *Lancet*. 2010;376:606-613.

How Would Efficacy Translate to Impact at the Population Level?



Atherly DE, et al. *J Infect Dis*. 2009;200:S28-S38.

Cost Effectiveness of Rotavirus Vaccination in India

Variable	Without Vaccine	With Vaccine	Annual Averted Events (%)
Number of Events			
Deaths	147,386	103,423	43,963 (30)
Hospitalizations	884,315	591,229	293,086 (33)
Outpatient visits	1,263,745	935,589	328,156 (26)
DALYs lost	4,564,545	3,203,135	1,361,410 (30)
Medical Treatment Cost in Millions (US$)			
Hospitalizations	61.7	42.0	19.7 (32)
Outpatient visits	3.7	2.8	0.9 (24)
Total	65.4	44.8	20.6 (31)

DALY = disability-adjusted life year

Tate JE, et al. *Vaccine*. 2009;27:F18-24.

Rotavirus Vaccines in Development in India

Bharat Biotech International Ltd

- 116E, a human neonatal, naturally reassorted and "asymptomatic" strain of Indian origin, in phase 3 clinical studies

Serum Institute of India

- Hexavalent human-bovine reassortant rotavirus vaccine containing serotypes G1-G4, G8, and G9, in phase 1 trials

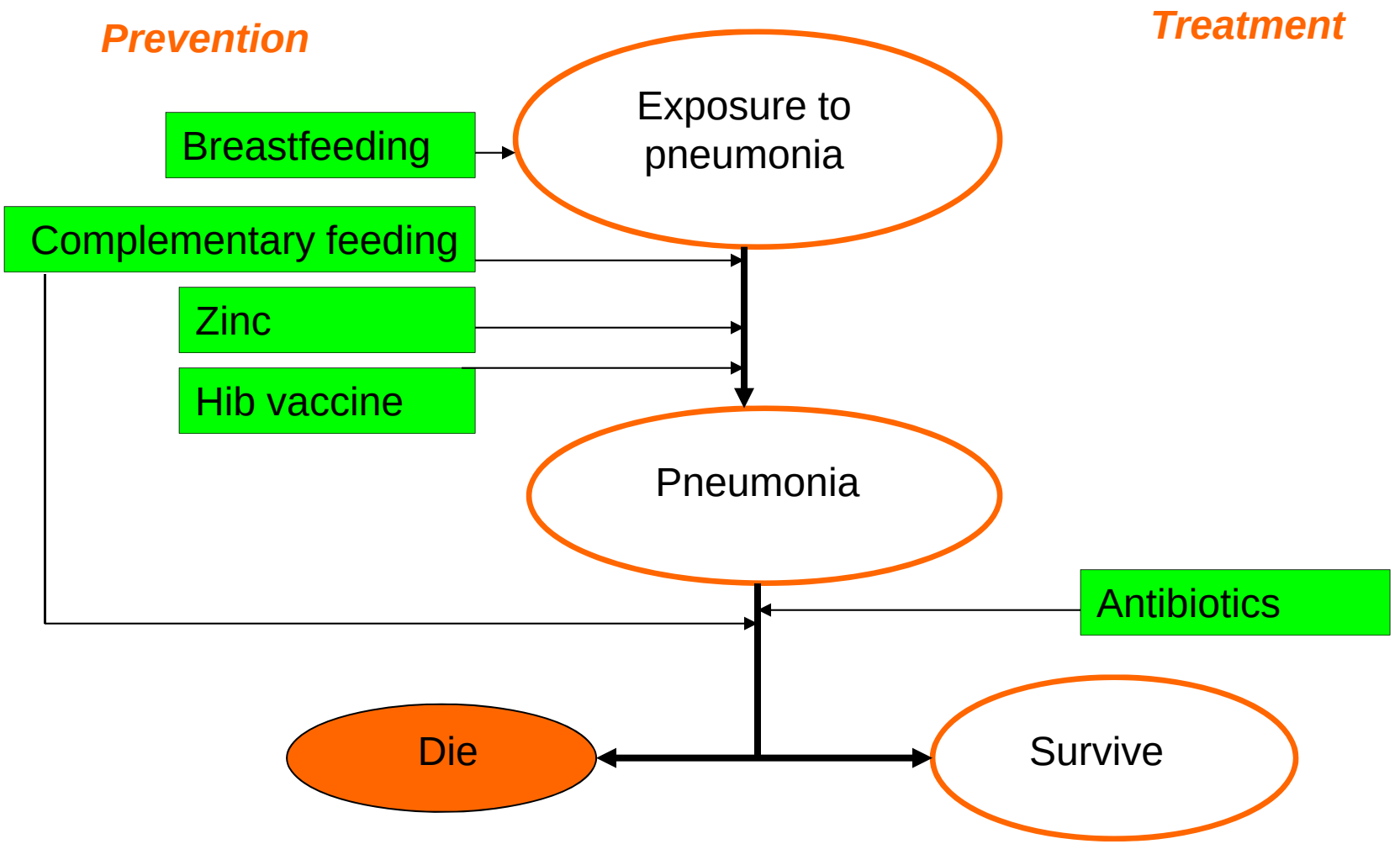
Shantha Biotechnics Ltd

- Oral bovine-human reassortant rotavirus vaccine, in phase 1 trials

Biological E Ltd

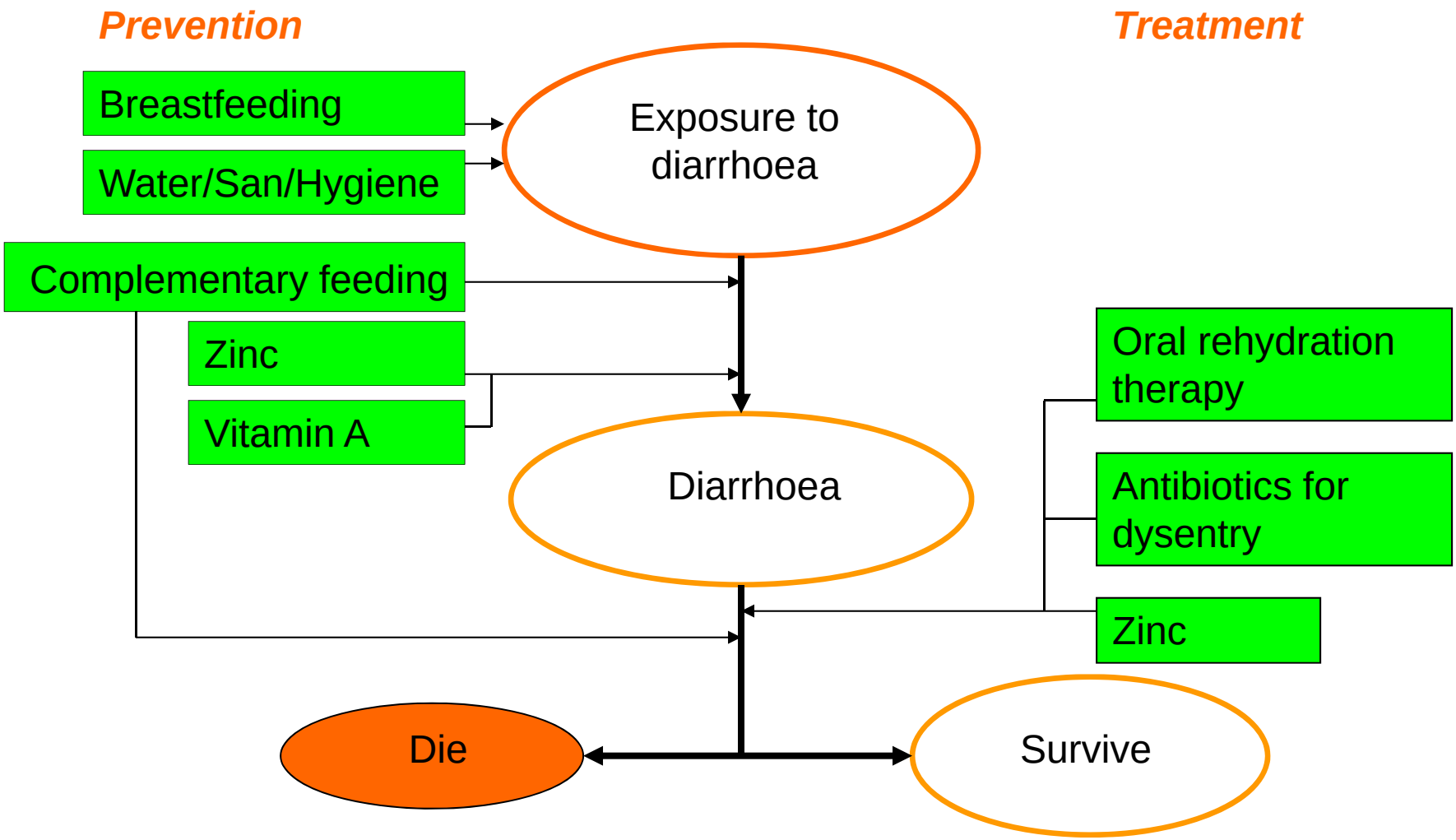
- Hexavalent human-bovine reassortant vaccine containing serotypes G1-4, G9, and G10, expected to enter clinical trials in 2011

Interventions by cause - pneumonia



Future: Pneumococcal vaccine, zinc for therapy, reduction of indoor air pollution

Interventions by cause - diarrhoea

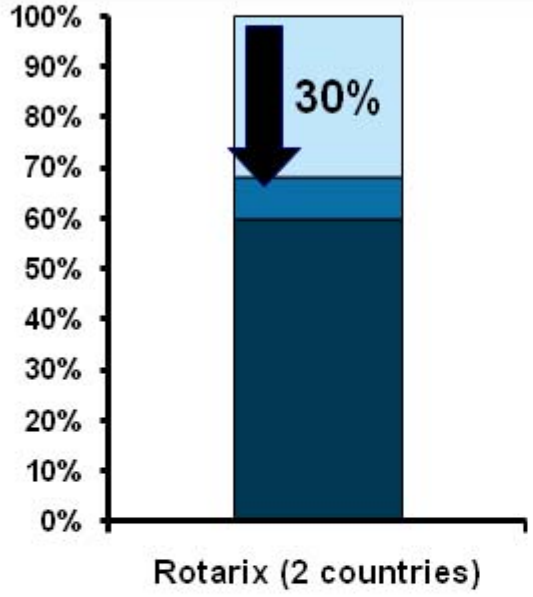


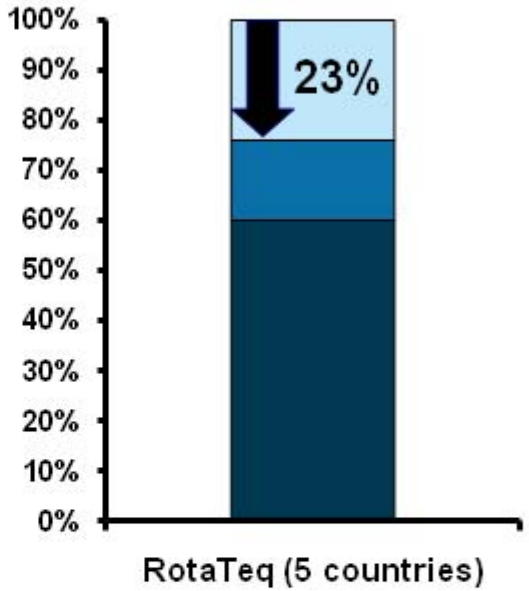
Future: rotavirus vaccine

Potential Impact of Rotavirus Vaccine

More Than 400,000 Lives Could Be Saved in the Next Decade in India Alone!

Reduction in All-Cause Severe Gastroenteritis

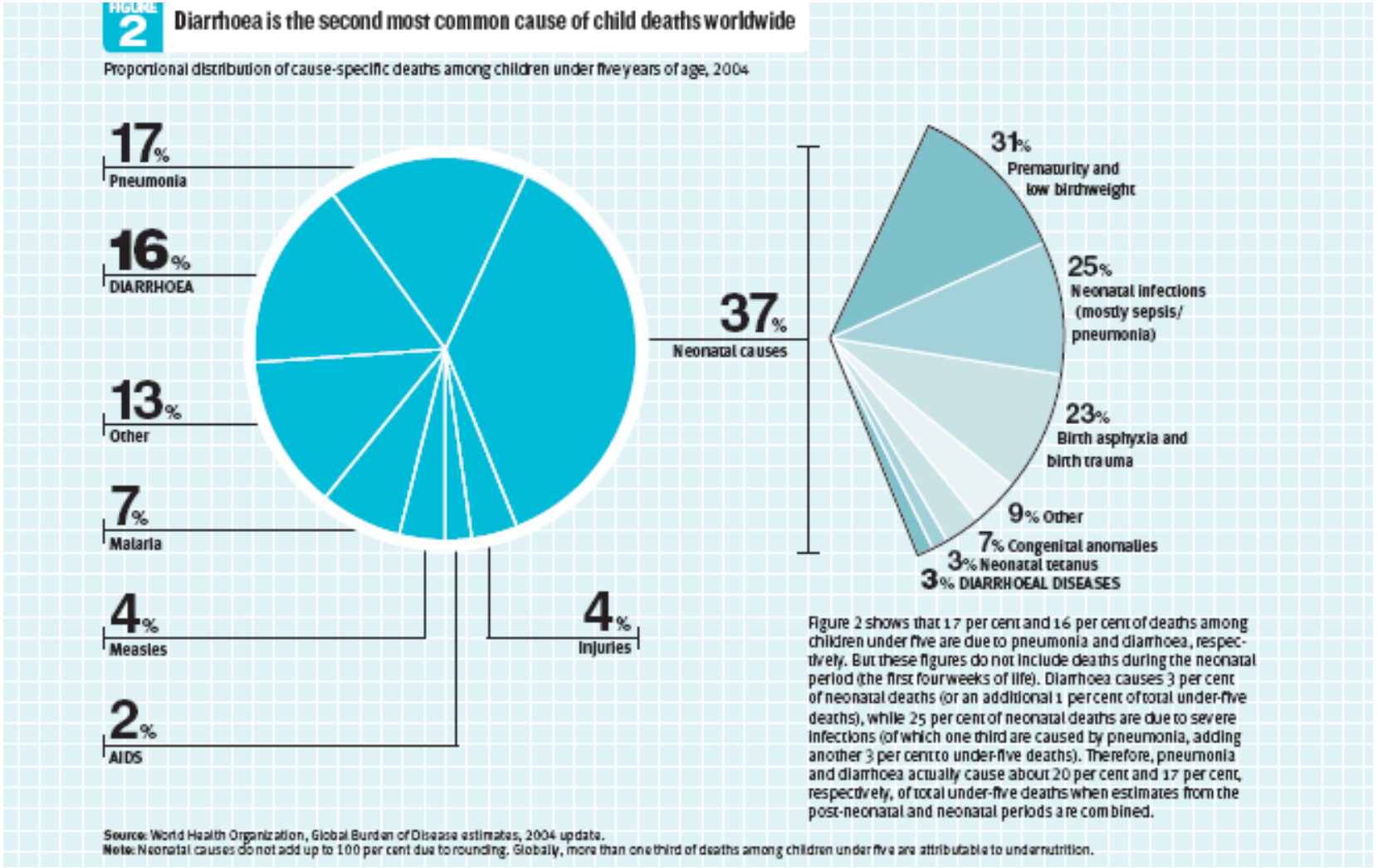




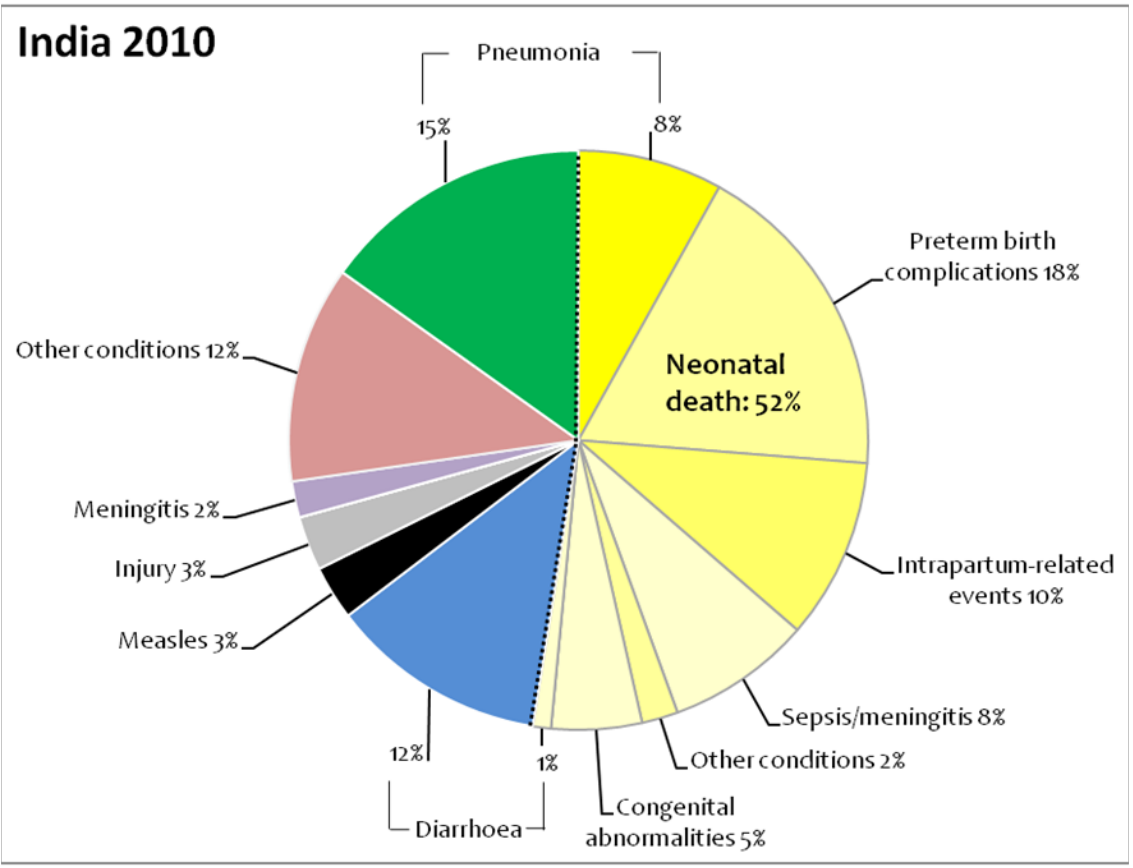
- Globally, rotavirus causes ~ 40% of all severe gastroenteritis
- Vaccine efficacy against severe rotavirus gastroenteritis (GE): 50%-60%
- Vaccine efficacy against all cause severe GE: 30% (Rotarix) and 23% (RotaTeq)

Chandran A, et al. *Biologics*. 2010;4:213-29.

Diarrhoea is the second most common cause of child deaths worldwide

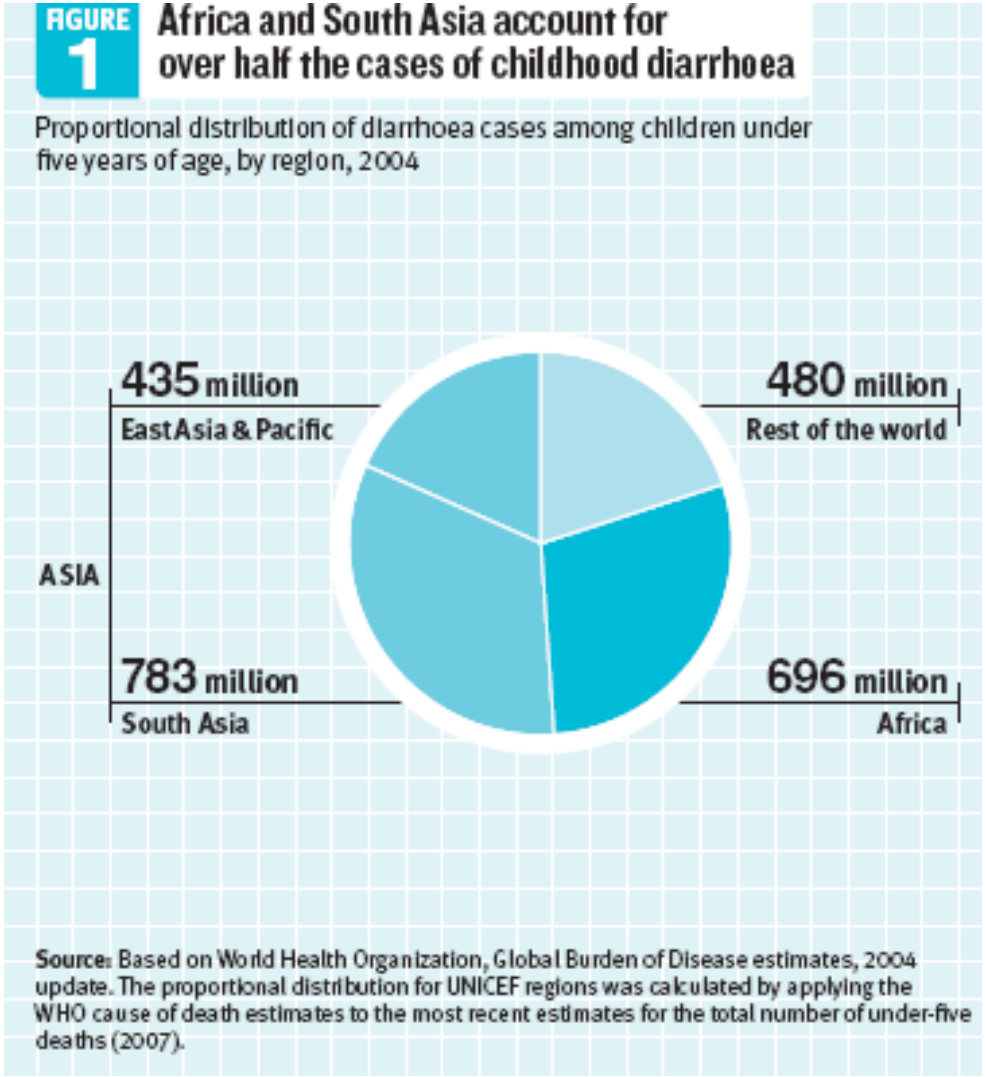


India

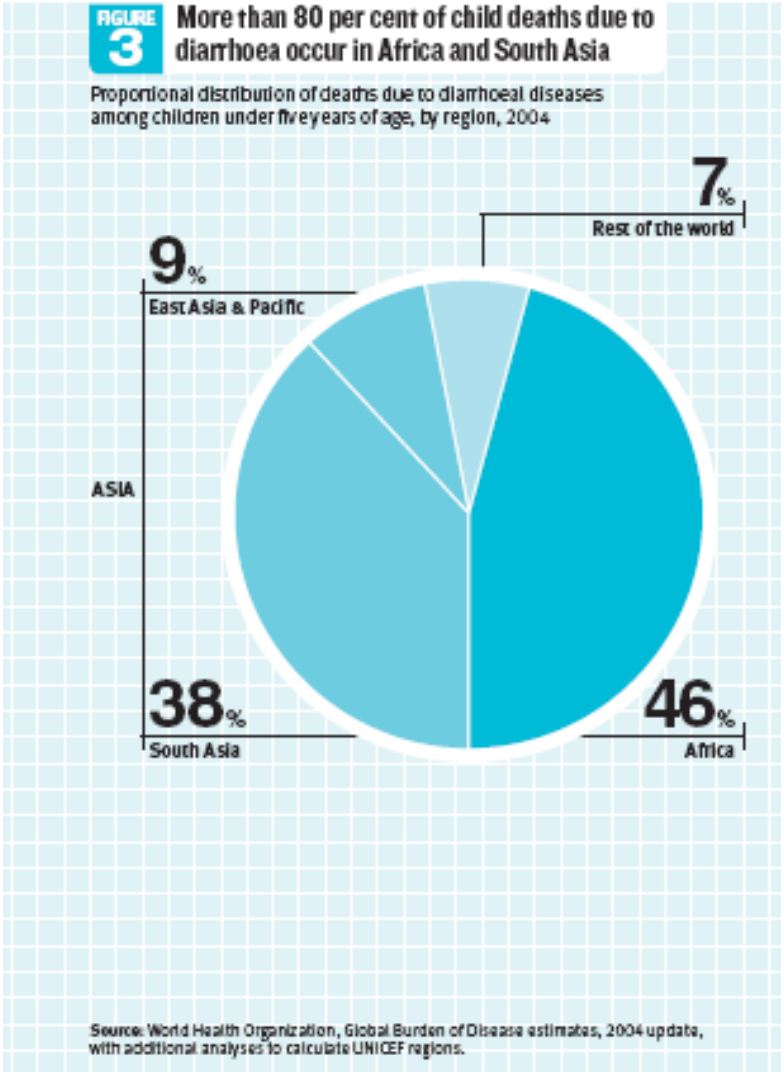


- 1.7m (23% of world total) U5 children died in 2010
- 51% deaths occurred in first month
- Major causes:
  - pneumonia
  - prematurity
  - diarrhea

Asia and Africa account for more than ¾ of childhood diarrhoea



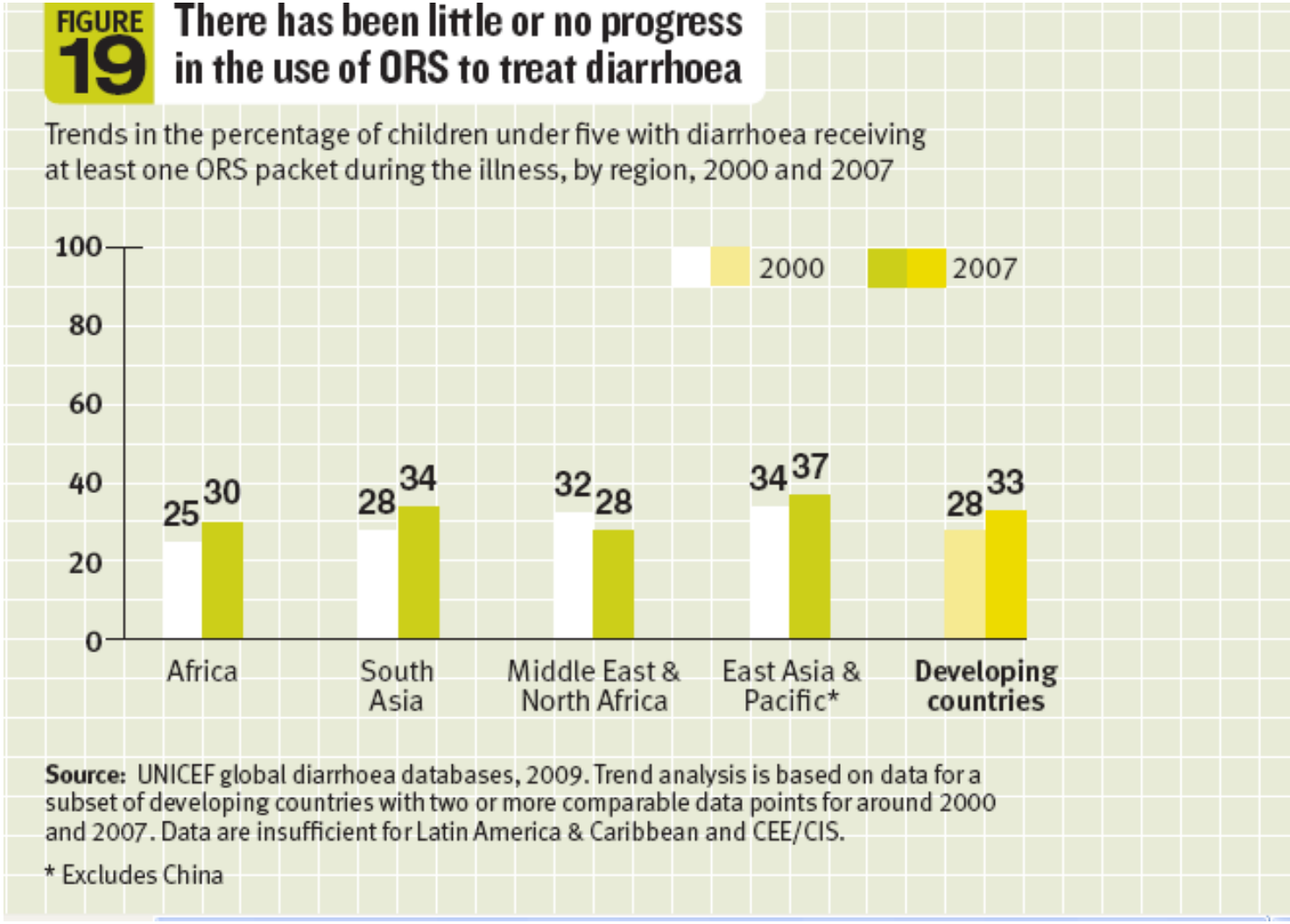
More than 80% of child deaths due to diarrhoea occur in Africa and South Asia



Child deaths from diarrhoea in top five Asian countries

India	386,600
Afghanistan	82,100
Pakistan	53,300
Bangladesh	50,800
China	40,000

Little or no progress in the use of ORS to treat diarrhoea



Present national status

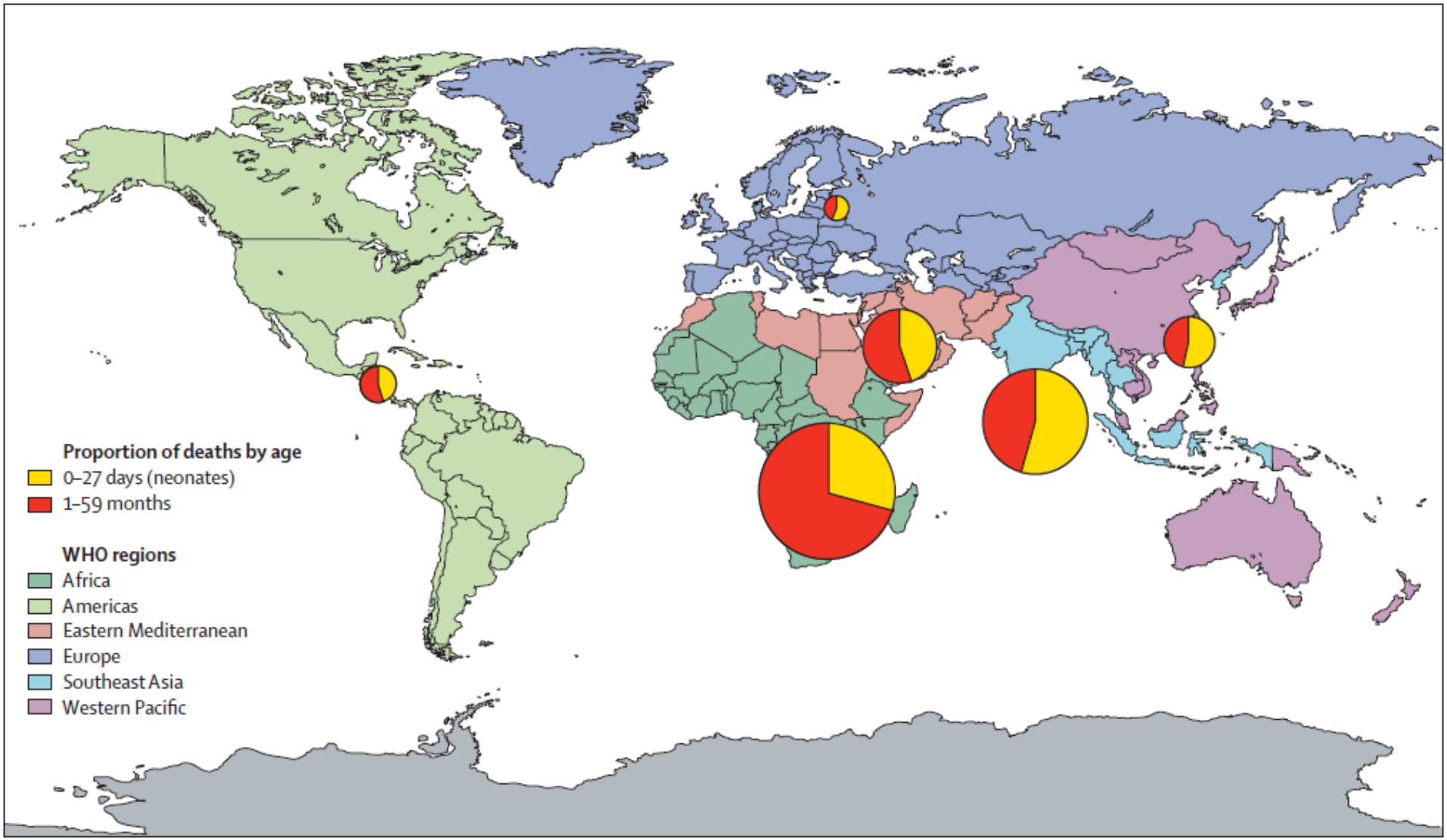
- Introduction in the govt program in 2007
- Industry has prepared Zinc preparations
- Efforts to prepare dispersible tablets by the govt (DBT)

Acute Gastroenteritis - Treatment

- Dose-dependent with > 10^{10} CFU/day effective
- Early use of probiotics = greater benefit
- Mod. to severe dehydration – no effect
- Bacterial diarrheas – ? no effect

  After onset of severe diarrhea - no benefit

Regional Distribution of Causes of Child Deaths: 2008



Public Awareness

- Tachypnea and respiratory distress are considered the most important signs in the diagnosis of pneumonia.

- Only 1 in 5 caregivers know that fast breathing and respiratory distress are a reason to seek care immediately.

Prevention Strategies

- Vaccination against measles, S. pneumoniae, and Haemophilus influenzae type b
- Zinc supplementation
- Prevention of HIV in Children
- Co-trimoxazole prophylaxis for HIV-infected children

Zinc in acute diarrhoea

No evidence of difference in efficacy in sub-groups based on:

- age
- nutritional status
- serum zinc levels
- etiology
- type of salt

New delivery strategies to improve uptake

Possible solutions:

- Products need to be made more attractive to users *(i.e. zinc and ORS taste)*
- Products need to be packaged for more effective use *(i.e. smaller ORS sachets)*
- Products need to be delivered in innovative ways that maximize access *(hygiene and sanitation promotion in schools, marketing of soap, latrines, POU)*

Etiology

- The common pathogens are a **function of the patient's age**.
- The specific agent causing pneumonia can be determined in 1/3 to 2/3 of cases when cultures, antigen detection and serologic techniques are available.
- It is helpful to be aware of local outbreaks as clustering of cases is common.

Care Seeking Behaviour

- In developing countries only half of the children with pneumonia are taken to an appropriate health care provider.
- Rates are similar between boys and girls.
- Children who are rural, poorer, and those with less educated mothers are less likely to be taken to an appropriate health care provider.

Prevention - Vaccination

- The implementation of Haemophilus influenzae type b (Hib) and Streptococcus pneumoniae immunization through an existing immunization program has been shown to be cost effective in reducing pneumonia mortality.
- Measles immunization coverage is high (making cost effectiveness estimates difficult).