

# What's Hot in Pediatric Infectious Diseases?

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# Objectives

- To highlight a selection of the most important and interesting literature in pediatric infectious diseases and vaccination from the last year
- To provide a global perspective on recent developments

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- To provide a global perspective on recent developments
- (To provide a Canadian perspective on recent developments)

# Focus



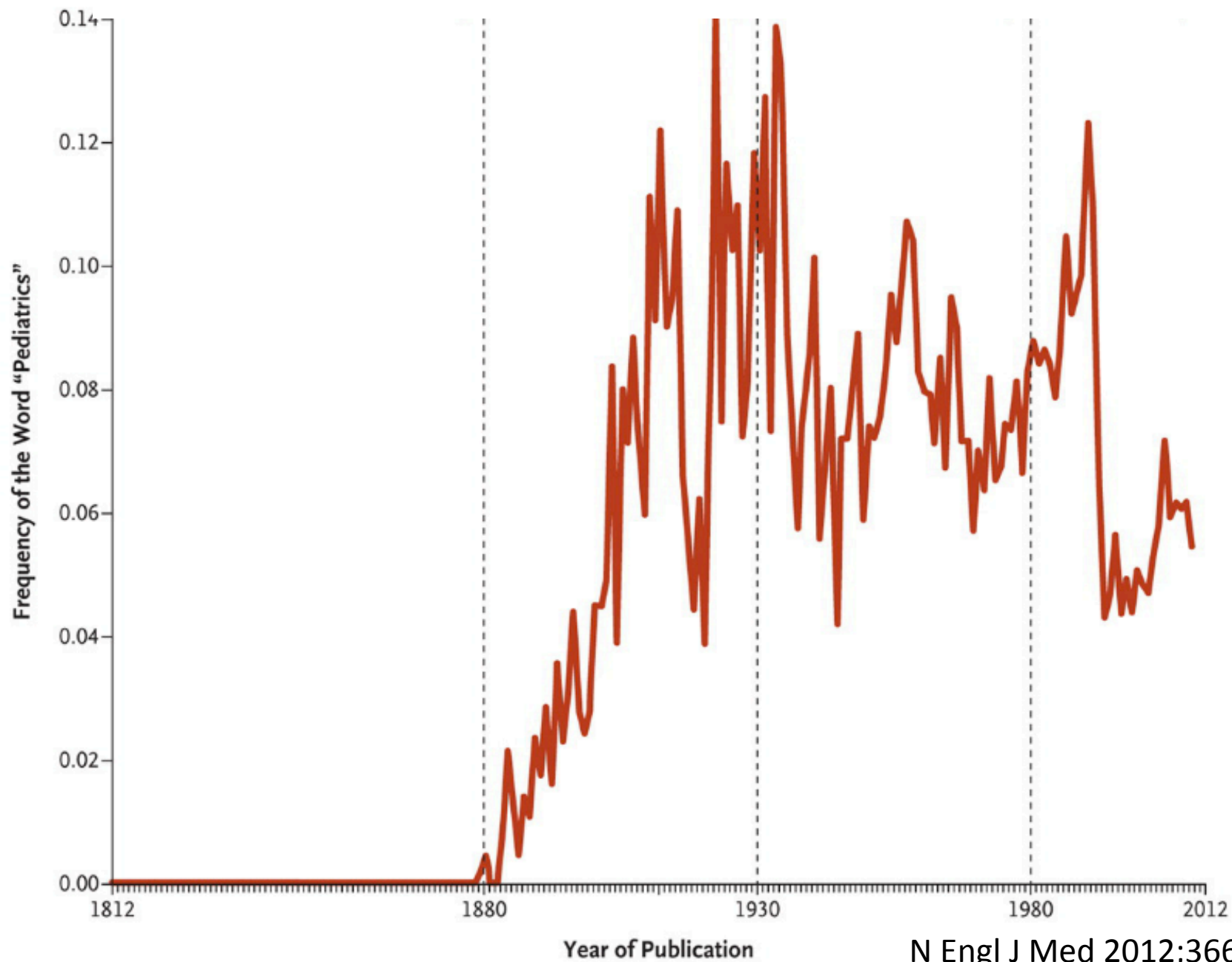
The NEW ENGLAND JOURNAL of MEDICINE

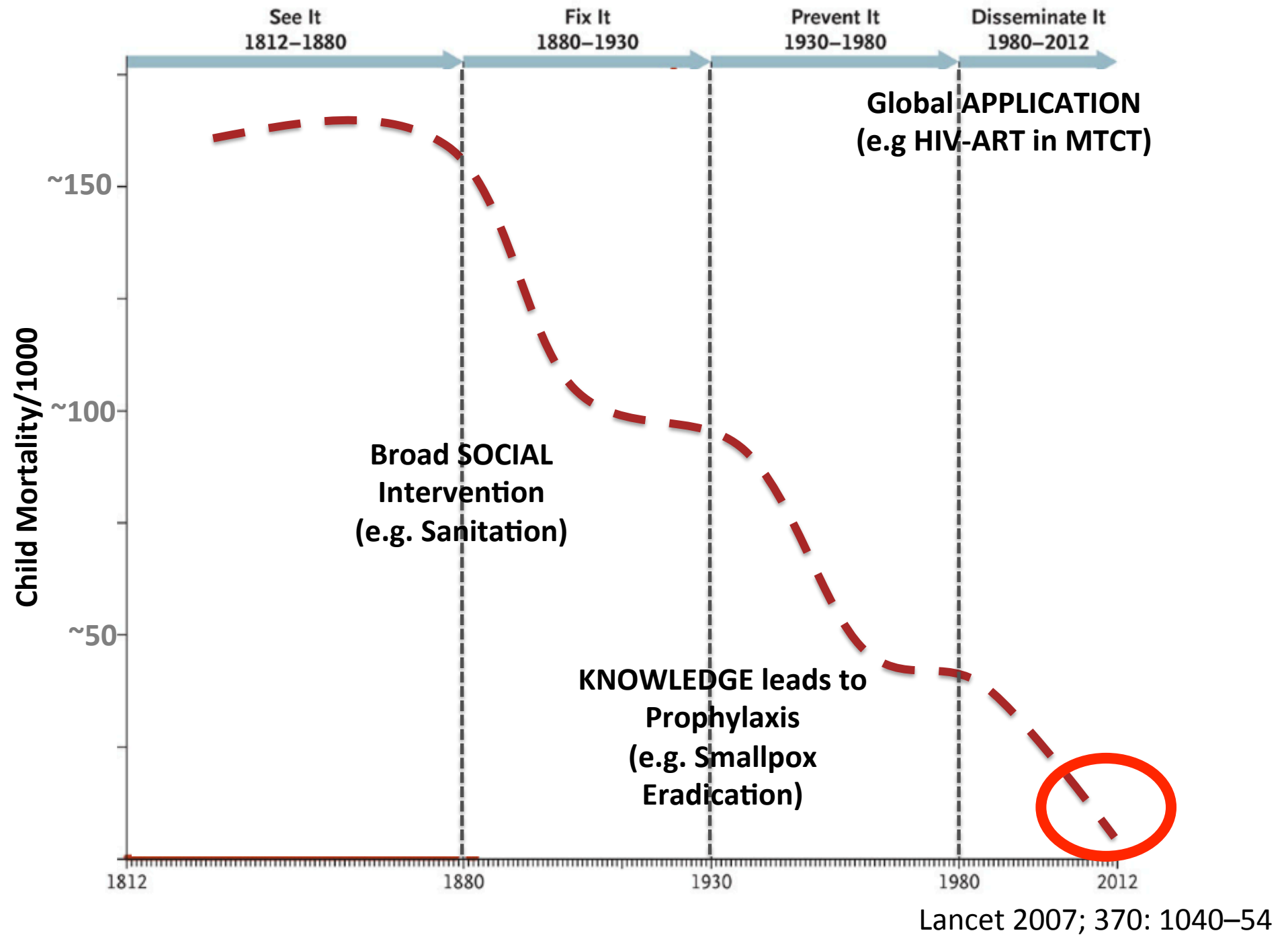
20<sup>th</sup> NEJM ANNIVERSARY ARTICLE

# What We Don't See

Margaret Kendrick Hostetter, M.D.

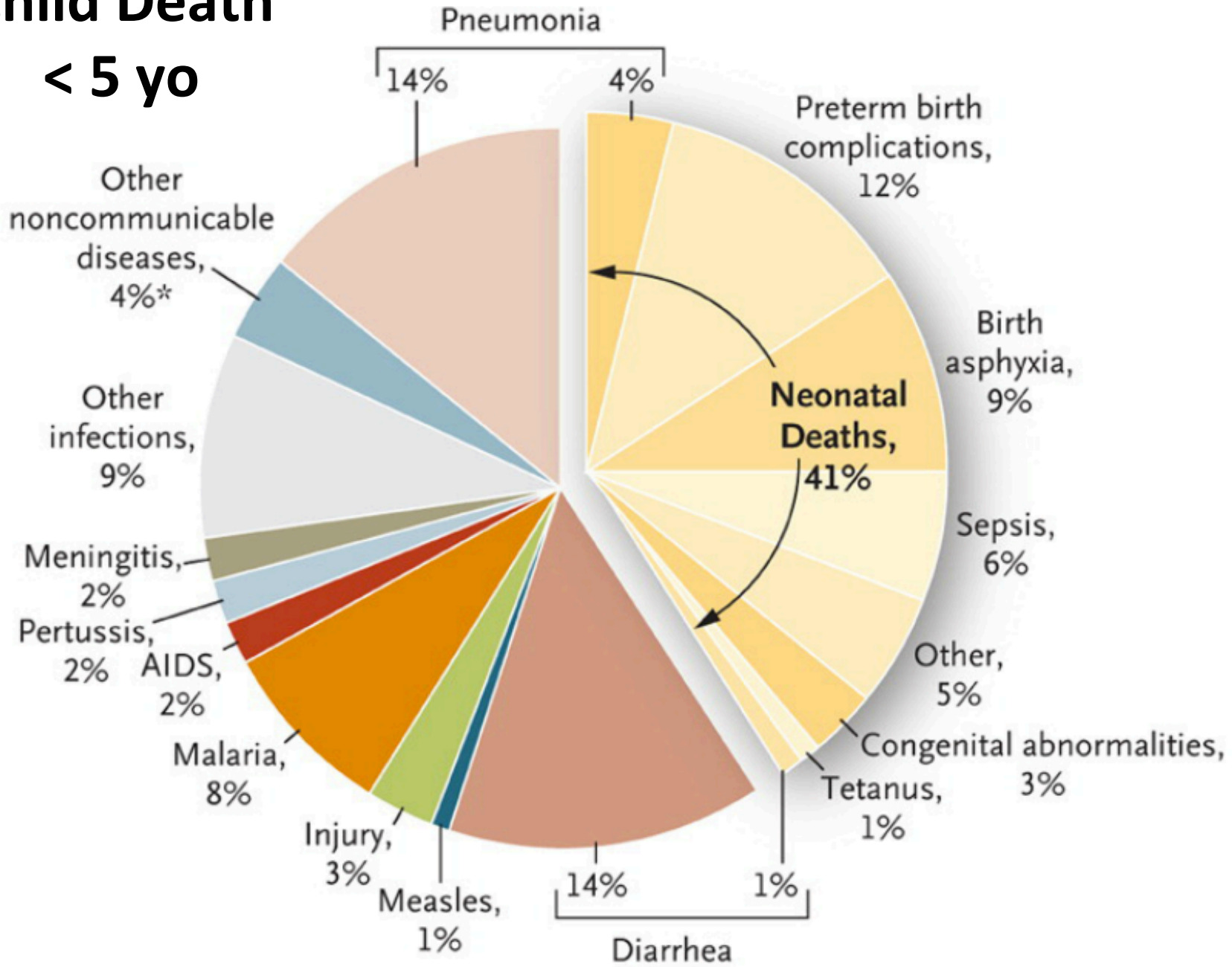
N Engl J Med 2012;366:1328-34.



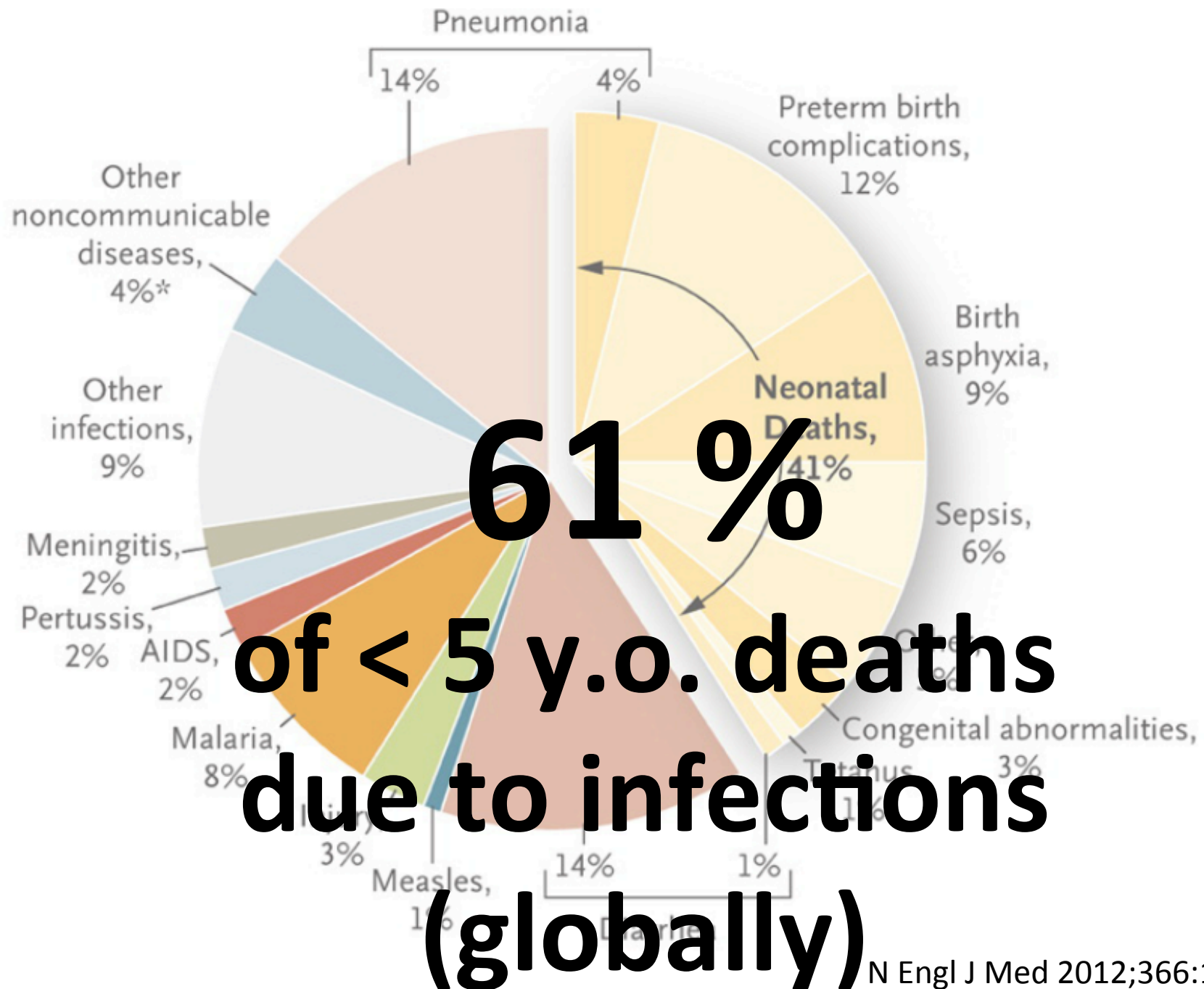


# Child Death

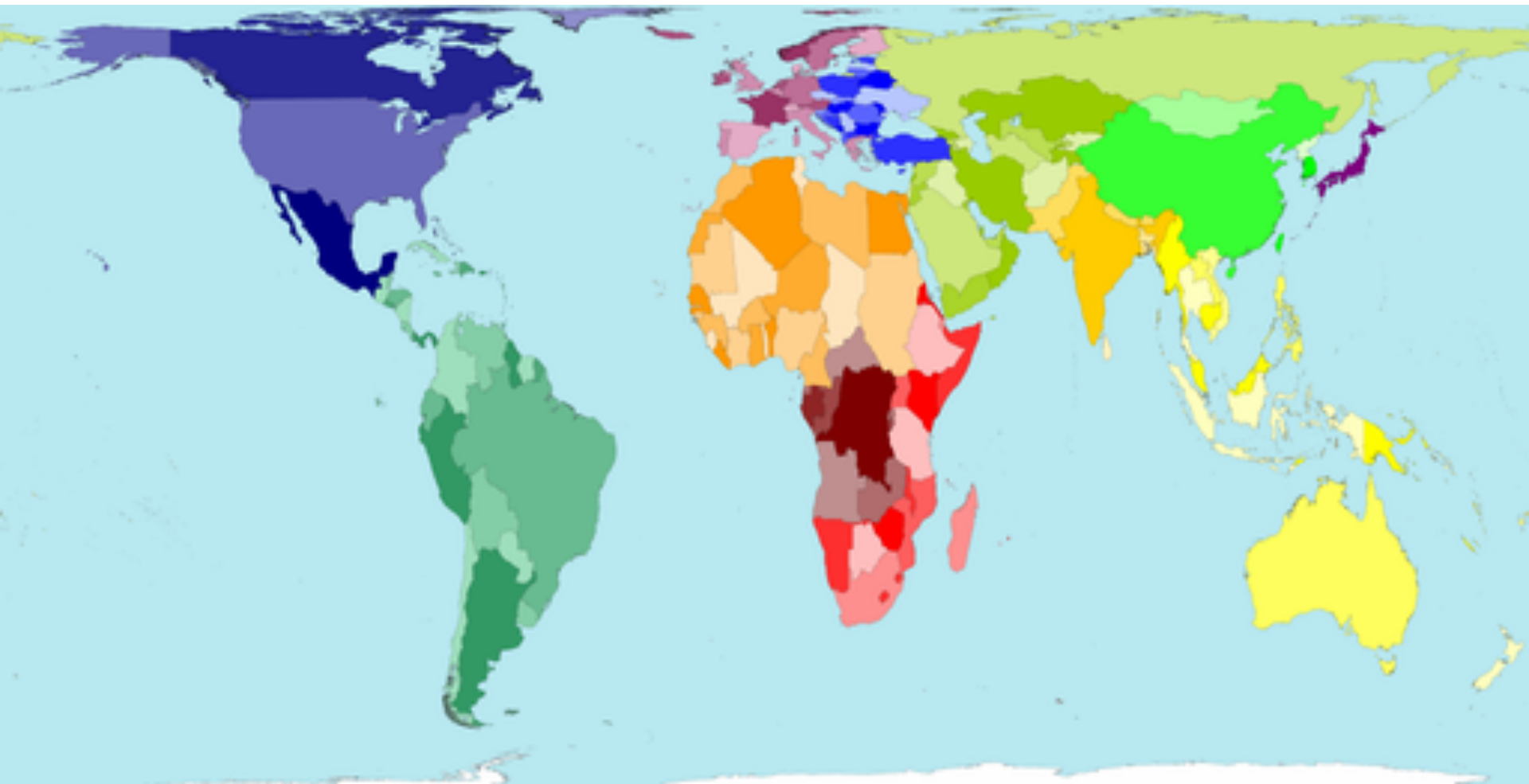
< 5 yo



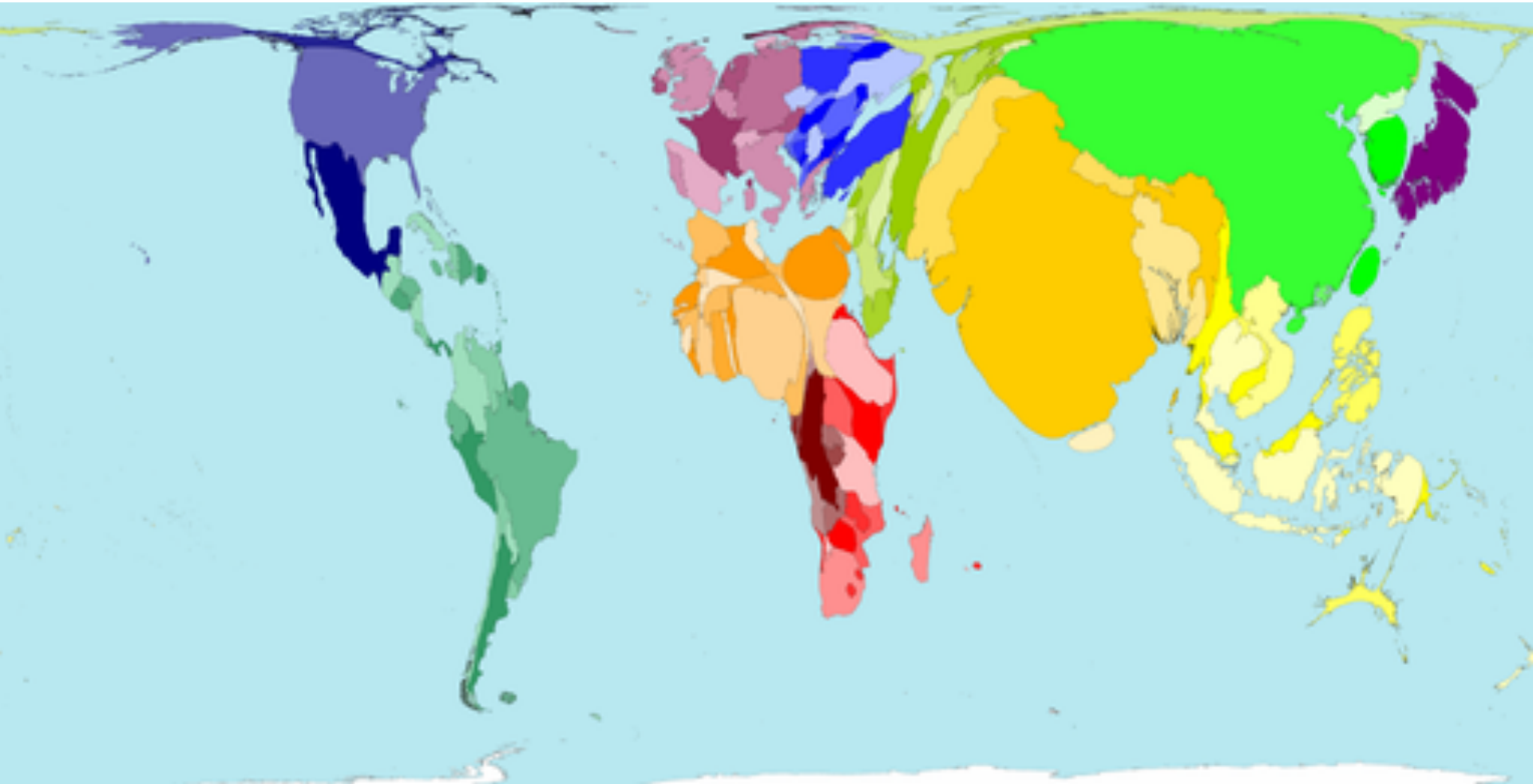




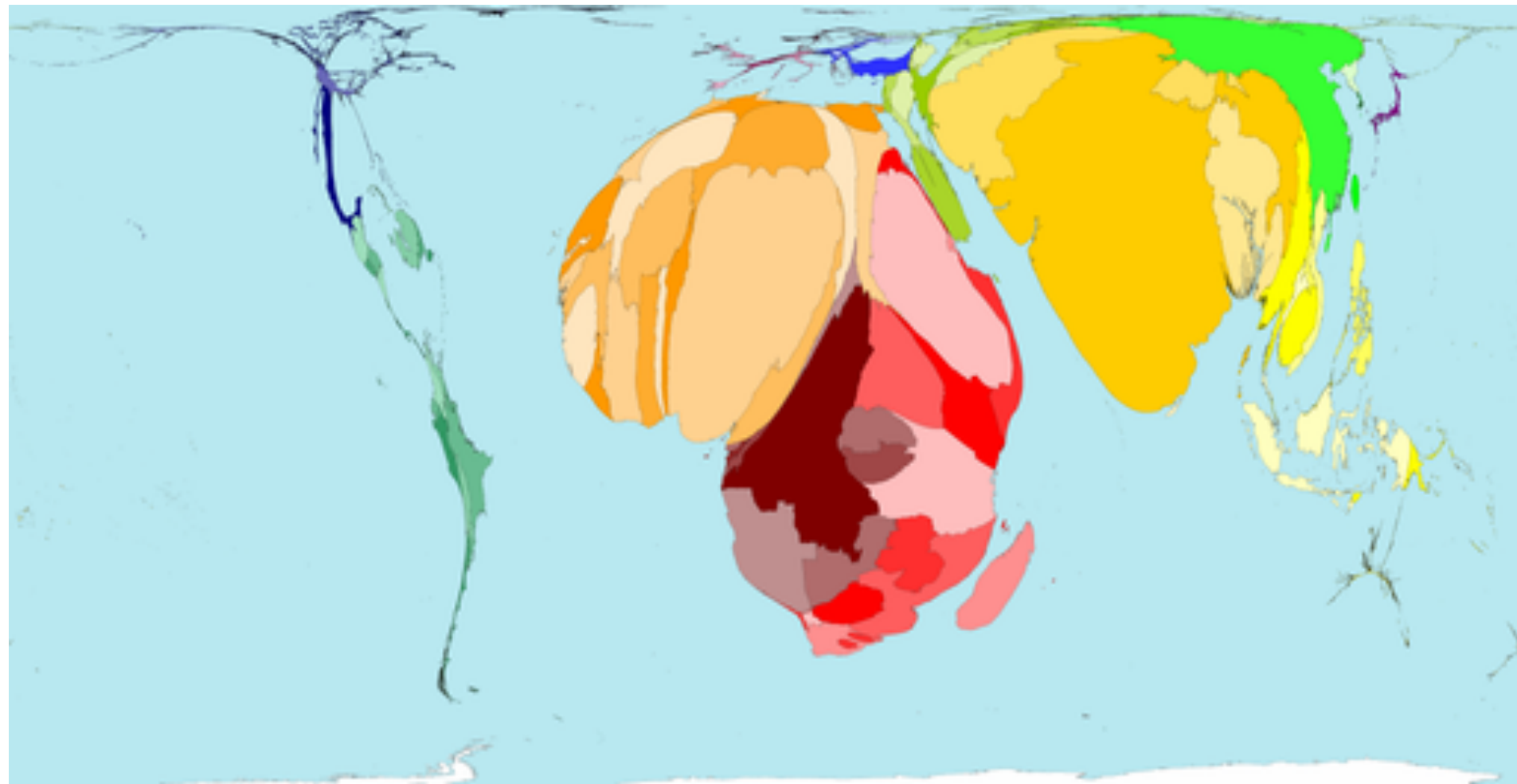
# Land



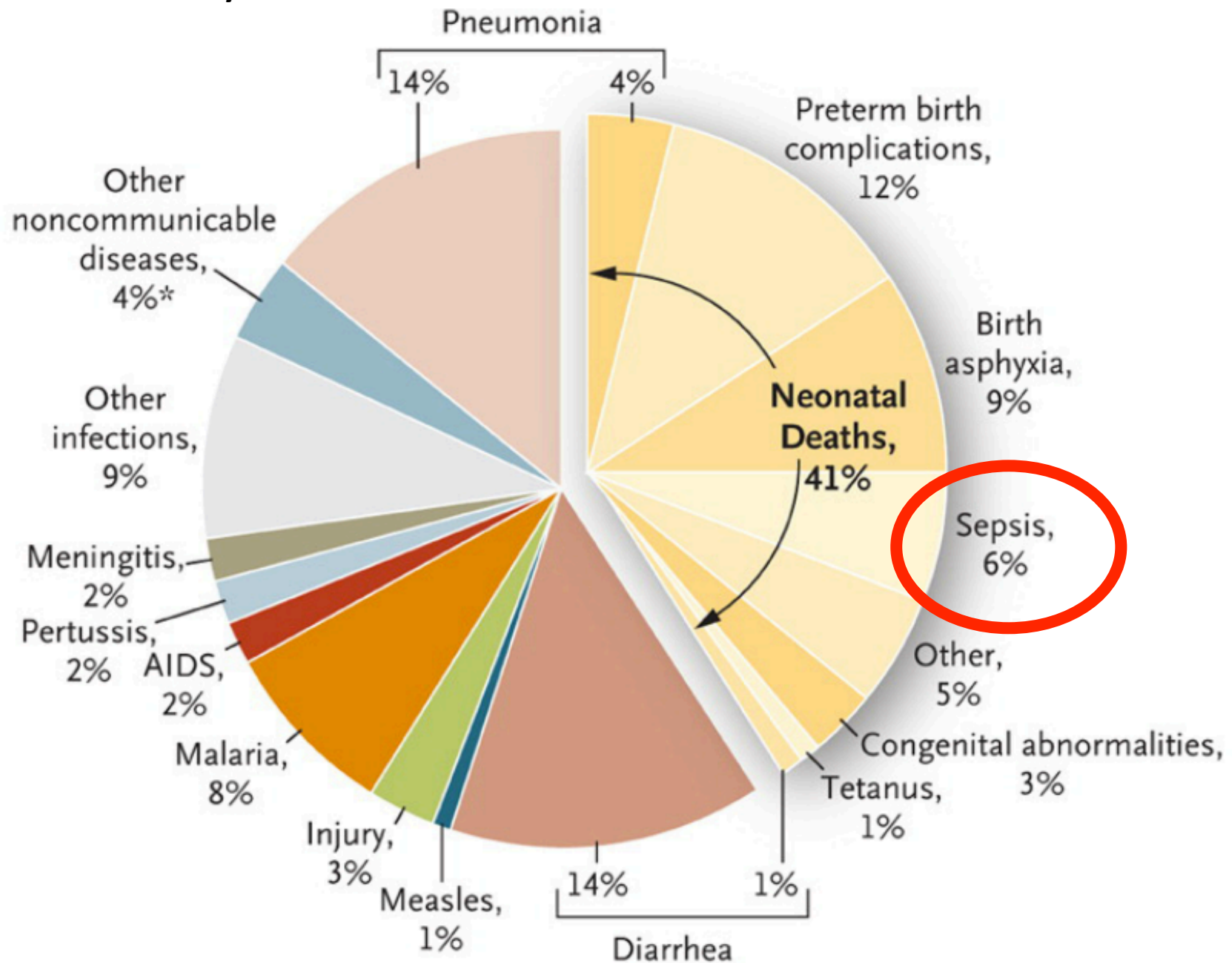
# Population



# Death < 5 yo due to infection



## Child Death < 5 yo



# Neonatal Sepsis 2012

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CPSP HIGHLIGHTS

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## Early-onset neonatal sepsis: It is not only group B streptococcus anymore



Michael Sgro MD FRCPC<sup>1</sup>, Mark H Yudin MD MSc FRCSC<sup>2</sup>, Shoo Lee MD FRCPC PhD<sup>3</sup>,  
Koravangattu Sankaran MD FRCPC<sup>4</sup>, Dat Tran MD FRCPC MSc<sup>5</sup>, Douglas Campbell MSc MD FRCPC<sup>6</sup>

Paediatr Child Health Vol 16 No 5 May 2011





# Changing Face of Neonatal Sepsis



- Predominant pathogen was GAS in 1930-1940 (pre-antibiotic era)
- The “Coliforms” emerged 1940-1960 (*E. coli*; *P. aeruginosa* in up to 20%)
- GBS starts rising in 1960s

# Resurgence of (now Amp<sup>R</sup>) *E. coli*: 1990 onward



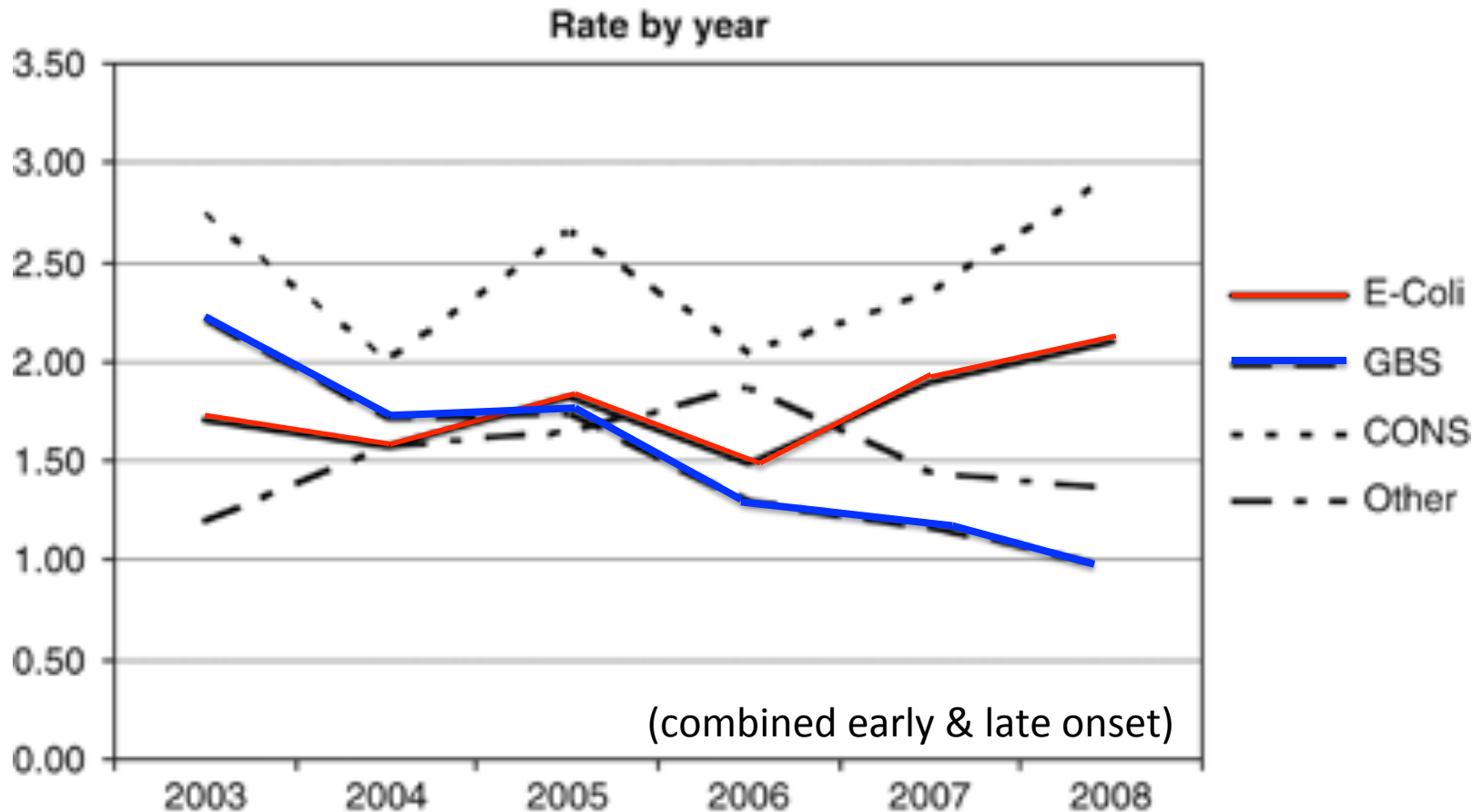
**TABLE 1** Distribution of Organisms Causing EOS in All Infants

Organism	<i>n</i>				Proportion of All Infections, %
	1990–1992	1993–1996	1997–2007	Total	
Gram-positive					68.1
GBS	56	39	44	139	41.5
Enterococci	3	4	6	13	3.9
Other streptococci	13	3	23	39	11.6
<i>Staphylococcus aureus</i>	2	5	6	13	3.8
Coagulase-negative staphylococci	2	2	10	14	4.2
<i>Listeria</i>	0	0	2	2	0.6
Other Gram-positive species	1	0	7	8	2.4
Ampicillin-resistant, Gram-positive species	5	7	26	38	11.6
Gram-negative					31.0
<i>Escherichia coli</i>	15	16	40	71	20.2
<i>Bacteroides</i> spp	1	4	10	15	4.5
<i>Klebsiella</i> spp	0	1	3	4	1.3
<i>Haemophilus influenza</i>	0	2	4	6	1.9
Other Gram-negative species	3	1	4	8	2.6
Ampicillin-resistant, Gram-negative species	12	12	38	62	18.5
Fungi	0	1	2	3	0.9
Total ampicillin-resistant species	17	20	66	103	30.7
Total	96	78	161	335	100

Bizzarro MJ, Raskind C, Baltimore RS, Gallagher PG.  
Seventy-five years of neonatal sepsis at Yale: 1928-2003.  
*Pediatrics*. 2005 Sep;116(3):595-602.



# Neonatal Sepsis in Canada



Early-onset neonatal sepsis: rate and organism pattern  
between 2003 and 2008

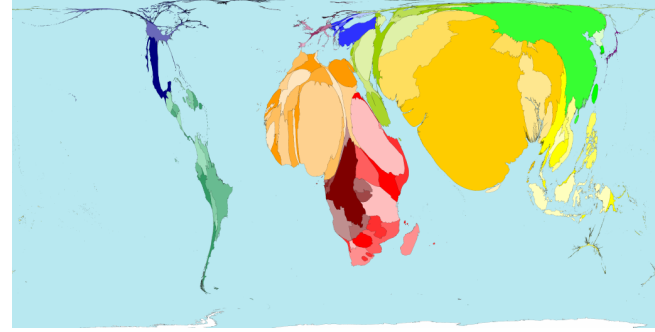
M Sgro<sup>1,2,3</sup>, PS Shah<sup>3,4,5</sup>, D Campbell<sup>2,3</sup>, A Tenuta<sup>2</sup>, S Shivananda<sup>6</sup> and SK Lee<sup>3,4,5</sup>,  
The Canadian Neonatal Network

Journal of Perinatology (2011) 31, 794–798

# What is *not* clear in 2012



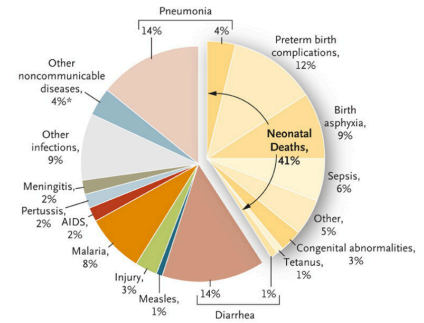
- Whether the increase in Amp-resistance is due to:
  - A. Antepartum or intrapartum antibiotic prophylaxis?
  - B. Community changes in resistance?
- Global Strategy to combat neonatal sepsis
  - Bizzarro MJ, Dembry LM, Baltimore RS, Gallagher PG. Changing patterns in neonatal *Escherichia coli* sepsis and ampicillin resistance in the era of intrapartum antibiotic prophylaxis. *Pediatrics*. 2008 Apr;121(4):689-96.
  - Bliziotis IA, Samonis G, Vardakas KZ, et al: Effect of aminoglycoside and beta-lactam combination therapy versus beta-lactam monotherapy on the emergence of antimicrobial resistance: a meta-analysis of randomized, controlled trials. *Clin Infect Dis* 2005; 41:149-158.
  - Puopolo KM, Eichenwald EC. No change in the incidence of ampicillin-resistant, neonatal, early-onset sepsis over 18 years. *Pediatrics*. 2010 May;125(5):e1031-8.



# Pathogens in neonatal sepsis in the developing world:

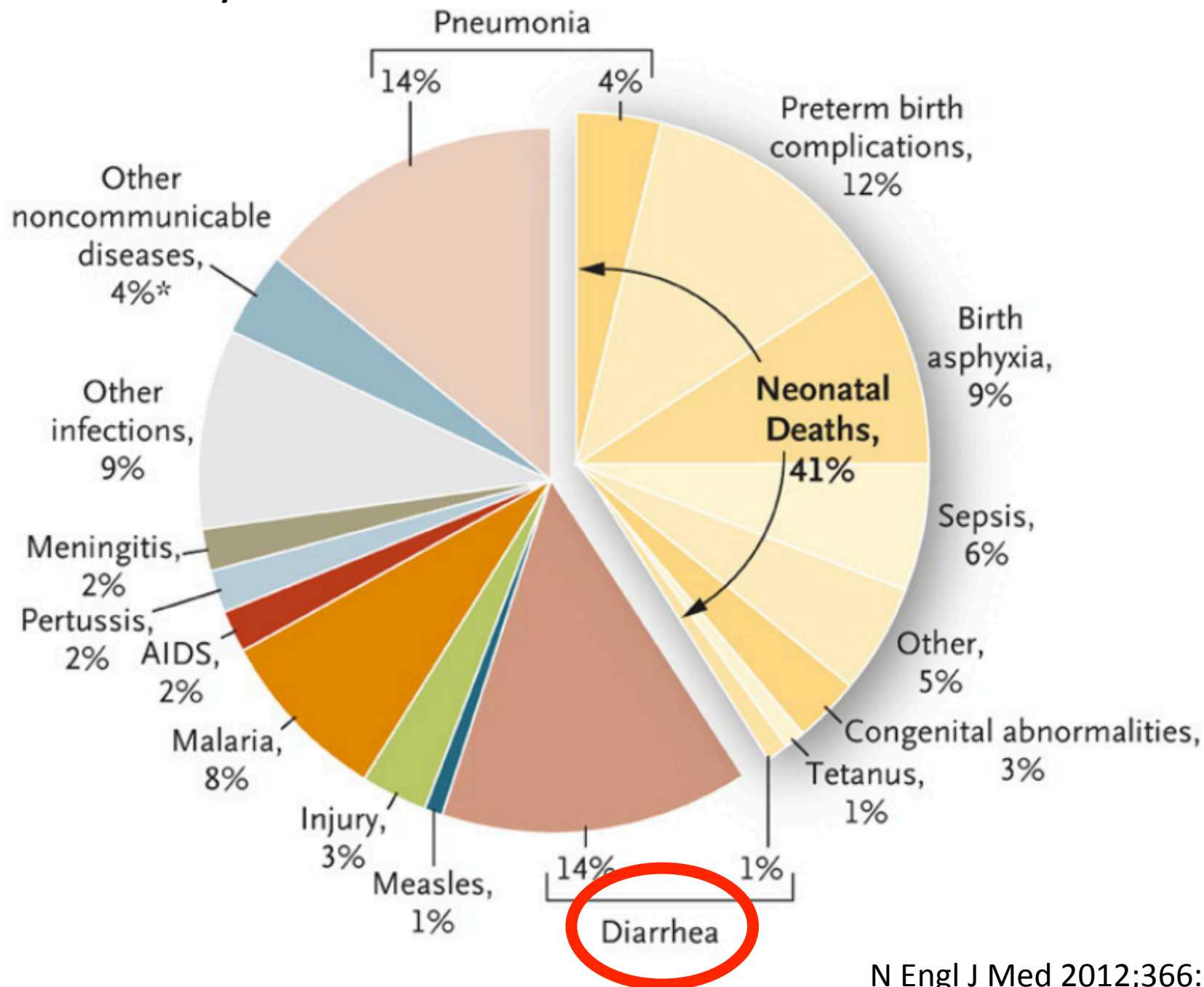
- **Not GBS!**
- **Gram-negatives** predominate

# Summary



1. Microbes causing neonatal sepsis are changing. Consider adapting empiric therapy.

## Child Death < 5 yo



# Diarrhea: Rotavirus rules!

Globally, rotaviruses (RVs)

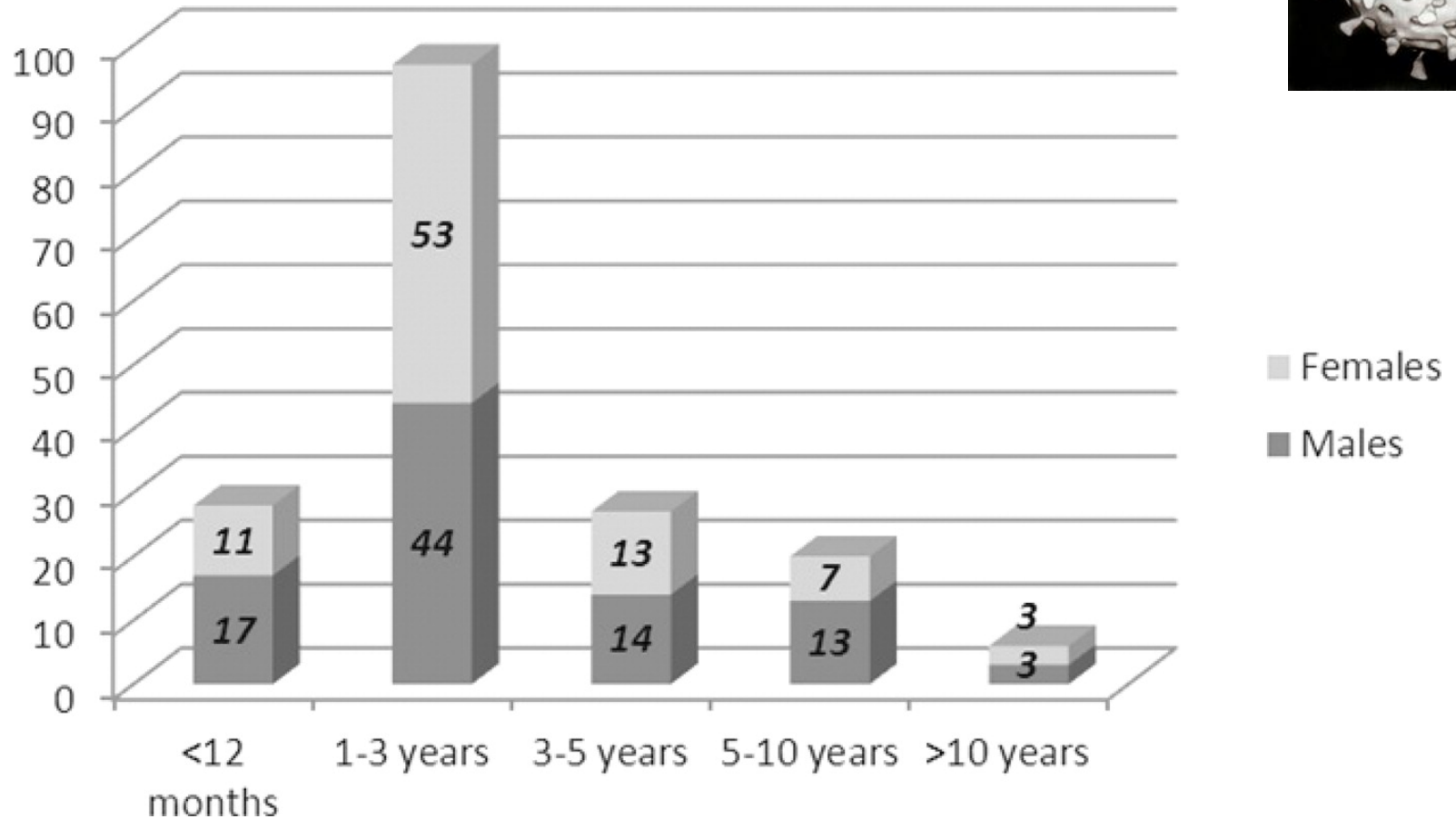
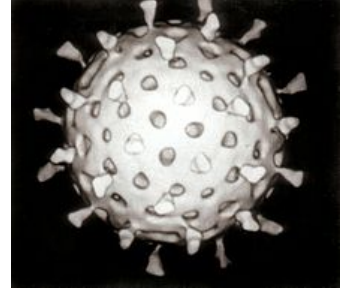
- cause of ~40% of all childhood gastroenteritis
- 125 million cases of acute gastroenteritis/yr
- ~ half a million deaths each year

The incidence of RV gastroenteritis is similar both in industrialized and in developing countries.

The outcome is not!



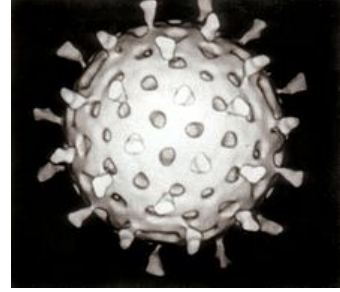
# Diarrhea: Rotavirus rules!



Nearly all children will be infected by RVs before the age of 3-5 years:

- highest incidence rate between 6-24 months of age
- greatest risk for developing severe disease by RV occurs under 12 months of age.

# Diarrhea: Rotavirus rules!

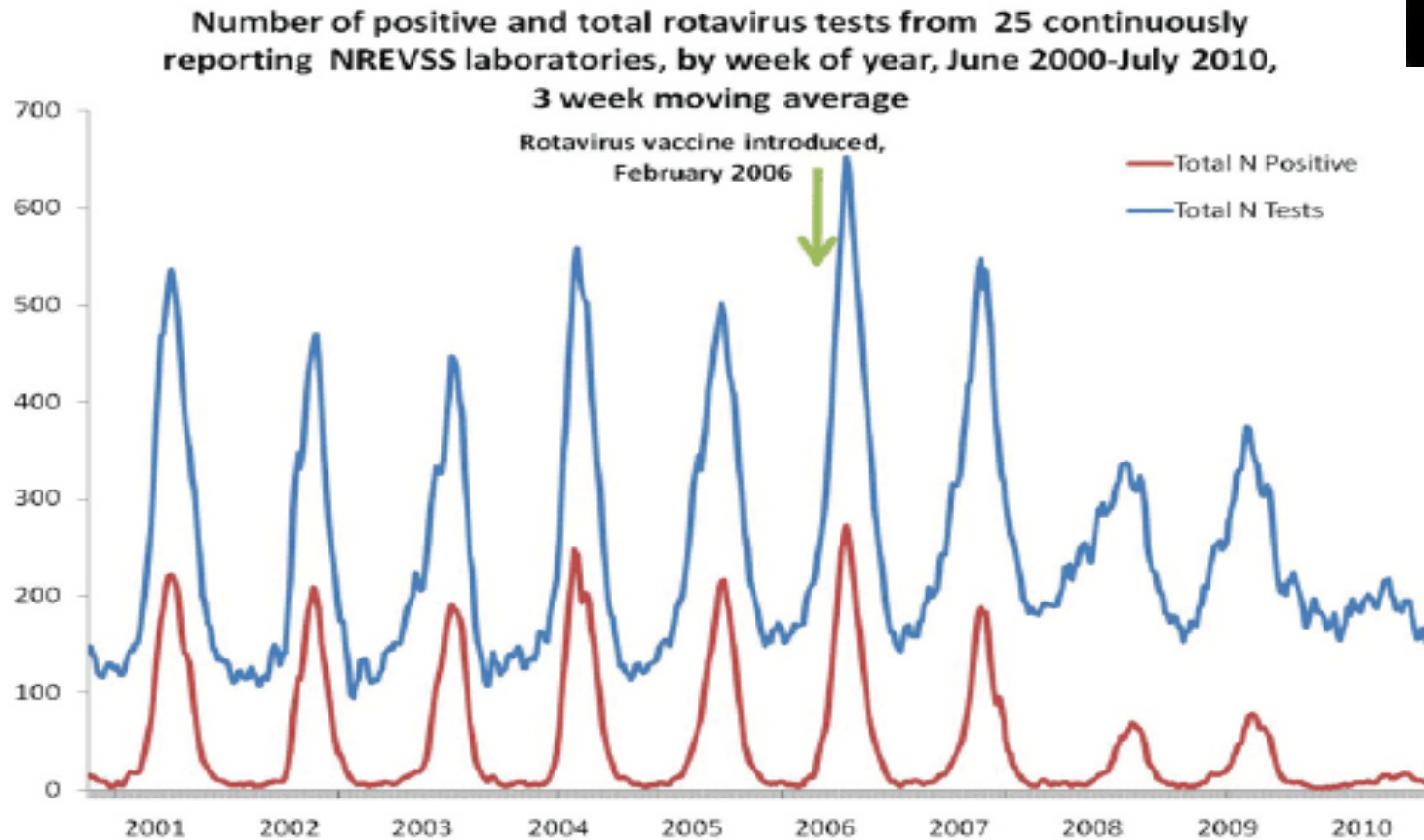
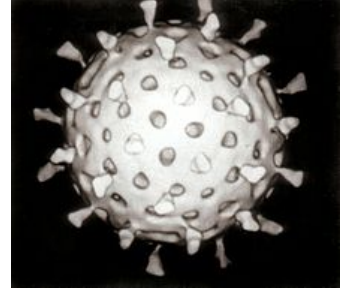


In Canada:

- 36% of children with rotavirus will see a physician
- 15% will be assessed in an emergency room
- 7% will be hospitalized
- societal cost ranges from \$8.9 to \$18.4 million

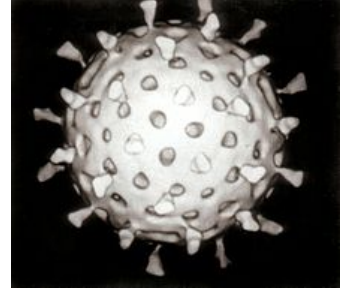


# Diarrhea: Rotavirus vaccine rules!



Vaccine efficacy against severe rotavirus gastroenteritis ranges from 85% to 96% during the first rotavirus season and 79% to 86% during the second season

# Diarrhea: Rotavirus **vaccine** rules!

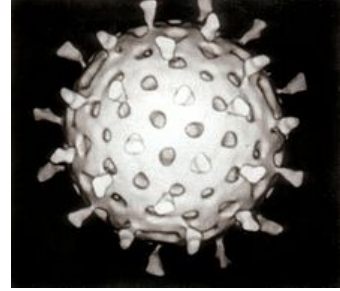


## **Efficacy of pentavalent rotavirus vaccine against severe rotavirus gastroenteritis in infants in developing countries in Asia: a randomised, double-blind, placebo-controlled trial**

*K Zaman, Dang Duc Anh, John C Victor, Sunheang Shin, Md Yunus, Michael J Dallas, Goutam Podder, Vu Dinh Thiem, Le Thi Phuong Mai, Stephen P Luby, Le Huu Tho, Michele L Coia, Kristen Lewis, Stephen B Rivers, David A Sack, Florian Schödel, A Duncan Steele, Kathleen M Neuzil, Max Ciarlet*

Lancet 2010; 376: 615–23

# Diarrhea: Rotavirus **vaccine** rules?



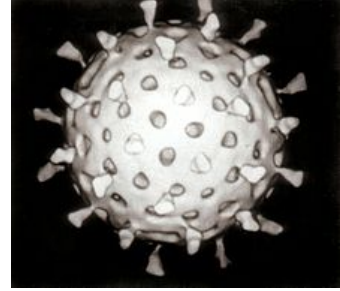
In 1999 the rhesus tetravalent rotavirus vaccine (RRV, Rotashield, Wyeth) was withdrawn from the market due to a significantly increased risk of **intussusception** following vaccination.

The largest increased risk (30-fold) of intussusception was observed during the 3 to 7 days following the first dose of the vaccine.

Since then, 2 vaccines to prevent rotavirus infection have been licensed for use in the United States:

- a pentavalent rotavirus vaccine (RV5, RotaTeq, Merck) in 2006
- a monovalent rotavirus vaccine (RV1, Rotarix, GlaxoSmithKline Biologicals) in 2008.

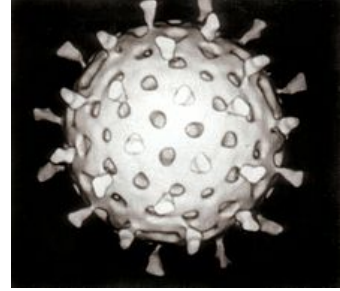
# Diarrhea: Rotavirus **vaccine** rules?



A post-licensure safety study in the United States after 2 years of surveillance (~ 200 000 doses) did **not** find evidence for an increased risk of intussusception

Pediatr Infect Dis J. 2010;29(1):1-5.

# Diarrhea: Rotavirus **vaccine** rules?



However, 2 international post-licensure evaluations have observed an increased risk of intussusception in the first week after administration of the first dose of rotavirus vaccines:

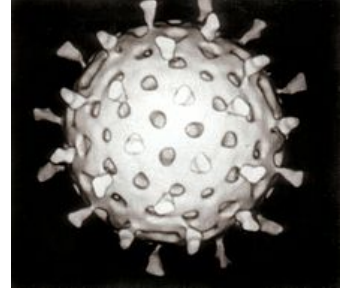
- An Australian study, found a statistically significant increased risk of nearly 5-fold for intussusception in the week following the first dose of RV5.

Vaccine. 2011;29(16):3061-3066.

- A study in Mexico and Brazil, found an approximate 5-fold increased risk of intussusception in the first week following the first dose of RV1 in Mexico but not in Brazil.

N Engl J Med. 2011; 364(24):2283-2292.

# Diarrhea: Rotavirus **vaccine** rules?

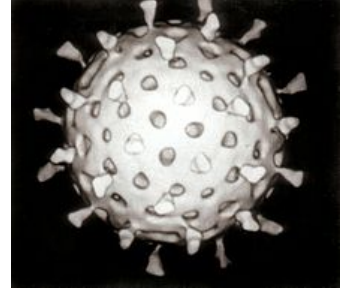


## **Risk of Intussusception Following Administration of a Pentavalent Rotavirus Vaccine in US Infants**

JAMA, February 8, 2012—Vol 307, No. 6

- 786 725 total RV5 doses, which included 309 844 first doses
- **No** statistically significant increased risk of intussusception with in either the 1- to 7-day or 1- to 30-day risk window.

# Diarrhea: Rotavirus **vaccine** rules?

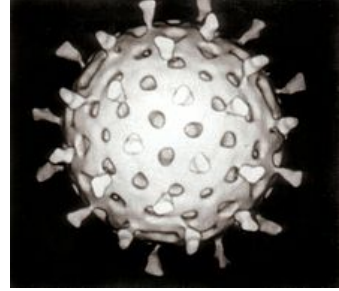


## **Risk of Intussusception Following Administration of a Pentavalent Rotavirus Vaccine in US Infants**

JAMA, February 8, 2012—Vol 307, No. 6

*“The benefits of rotavirus vaccination in US infants outweighs the potential risks, even if a risk similar to that seen in Mexico or Australia would exist in the United States.”*

# Diarrhea: Rotavirus **vaccine** rules!!!

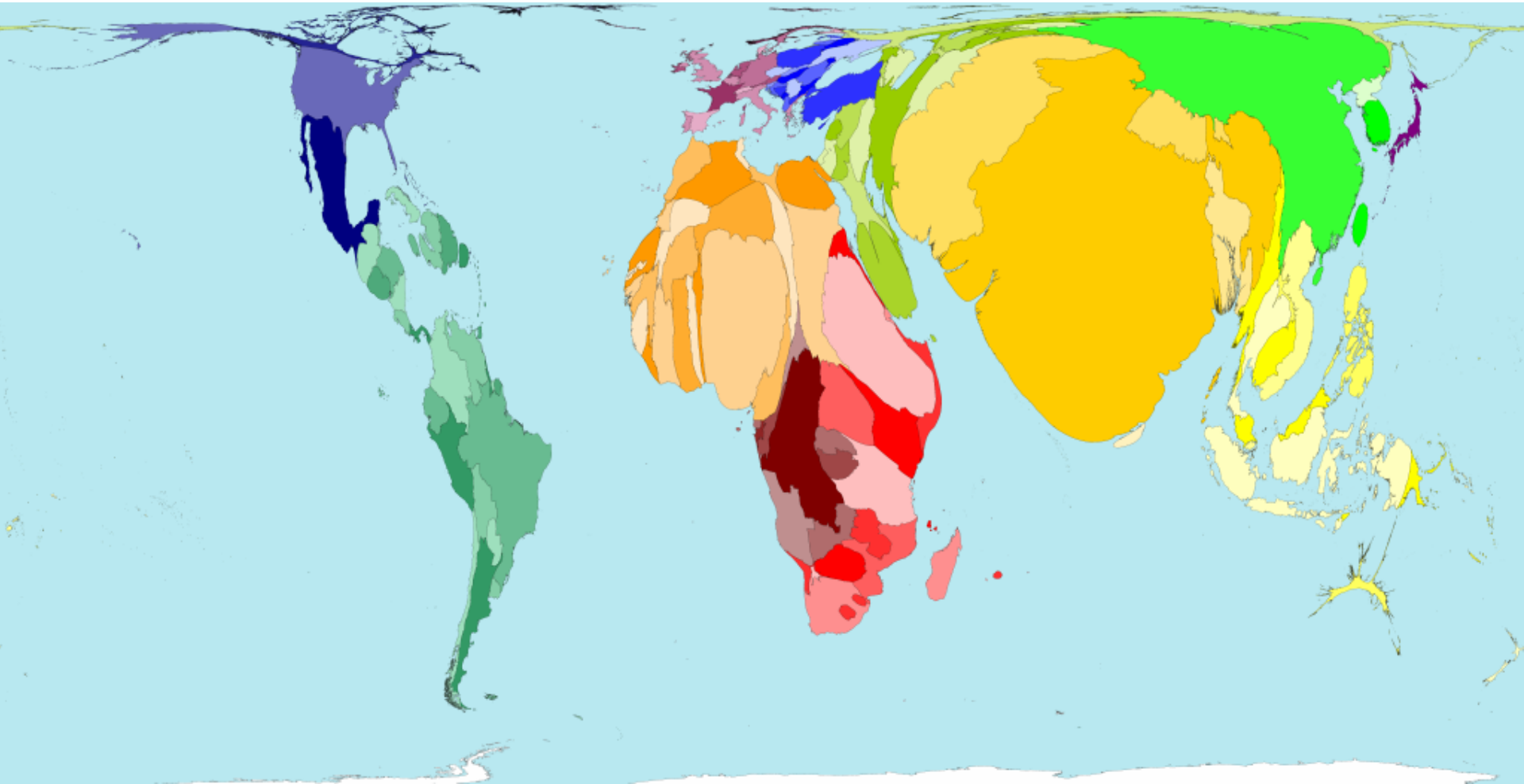


“Rotavirus vaccines are now recommended, and provided free (as of January 1st, 2012), to infants at the routine 2 month and 4 month immunization appointments”.

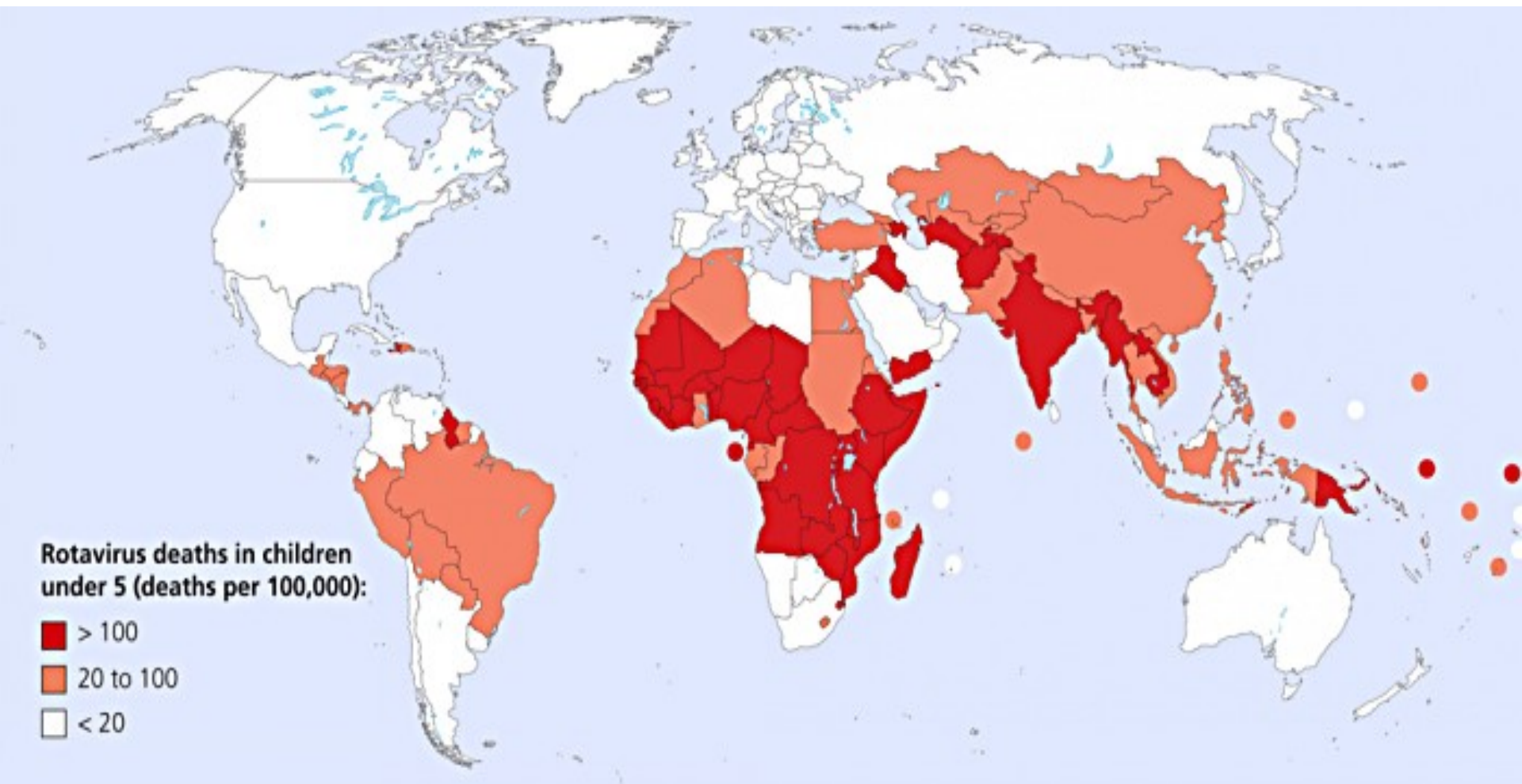
- Ontario implemented RV1 in August 2011
- QC in November 2011



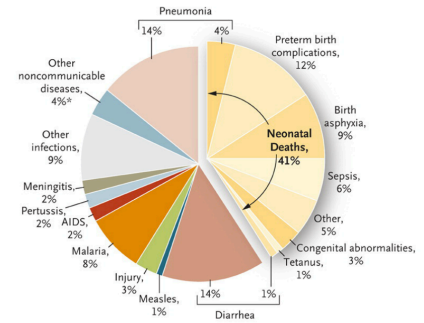
# Diarrhea (all causes)



# Global Rotavirus Deaths vs. Vaccination Coverage

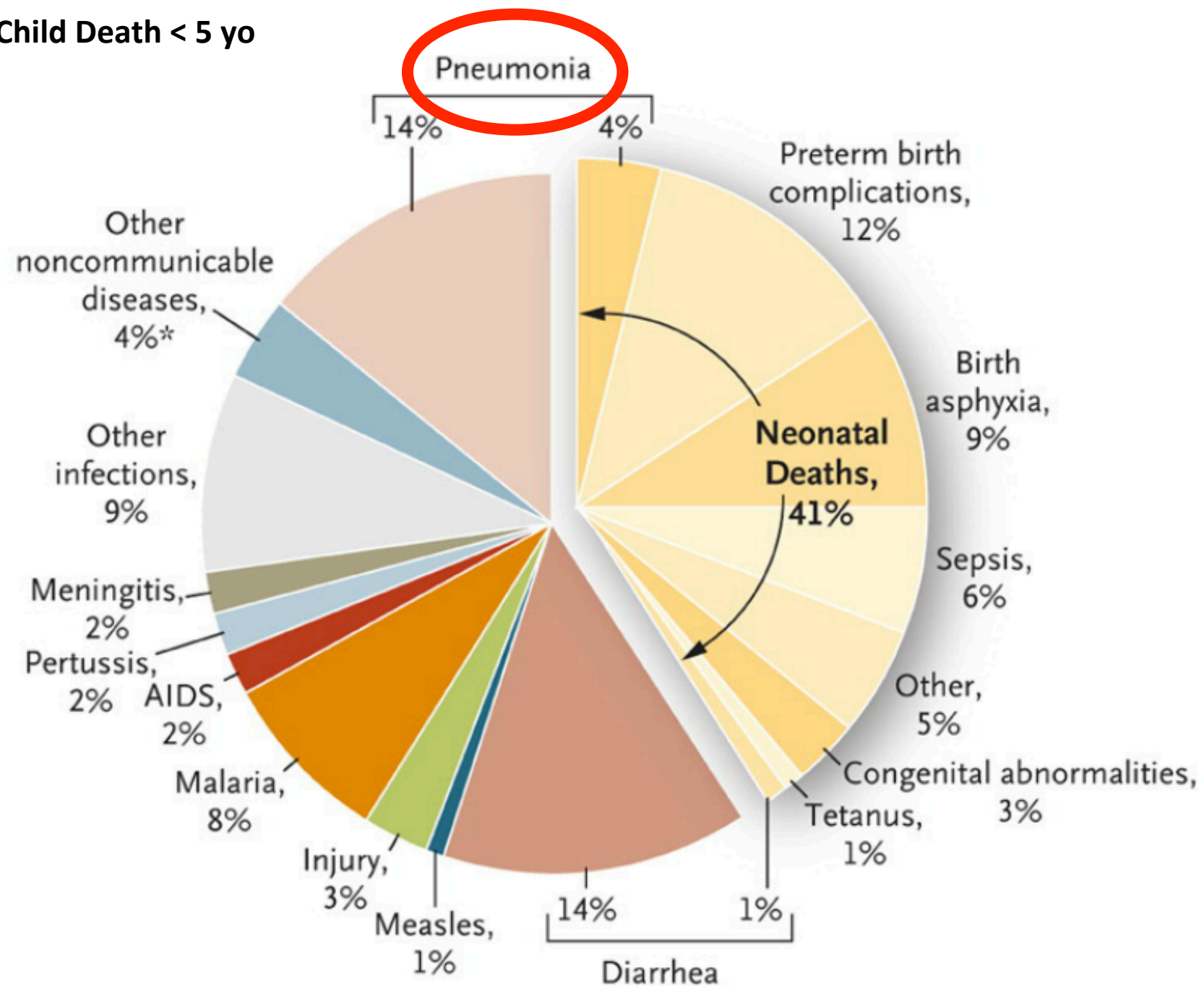


# Summary



1. Microbes causing neonatal sepsis are changing. Consider adapting empiric therapy.
2. Rotavirus infant vaccination is safe and effective. Give 2 doses before 8 months of age.

## Child Death < 5 yo

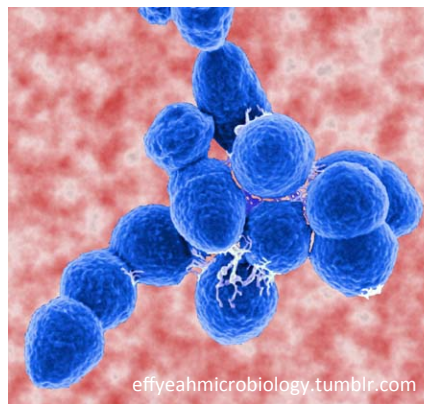




# PNEUMONIA

THE FORGOTTEN  
KILLER OF  
CHILDREN

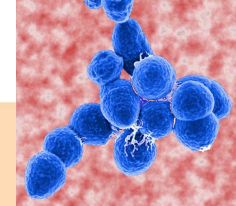




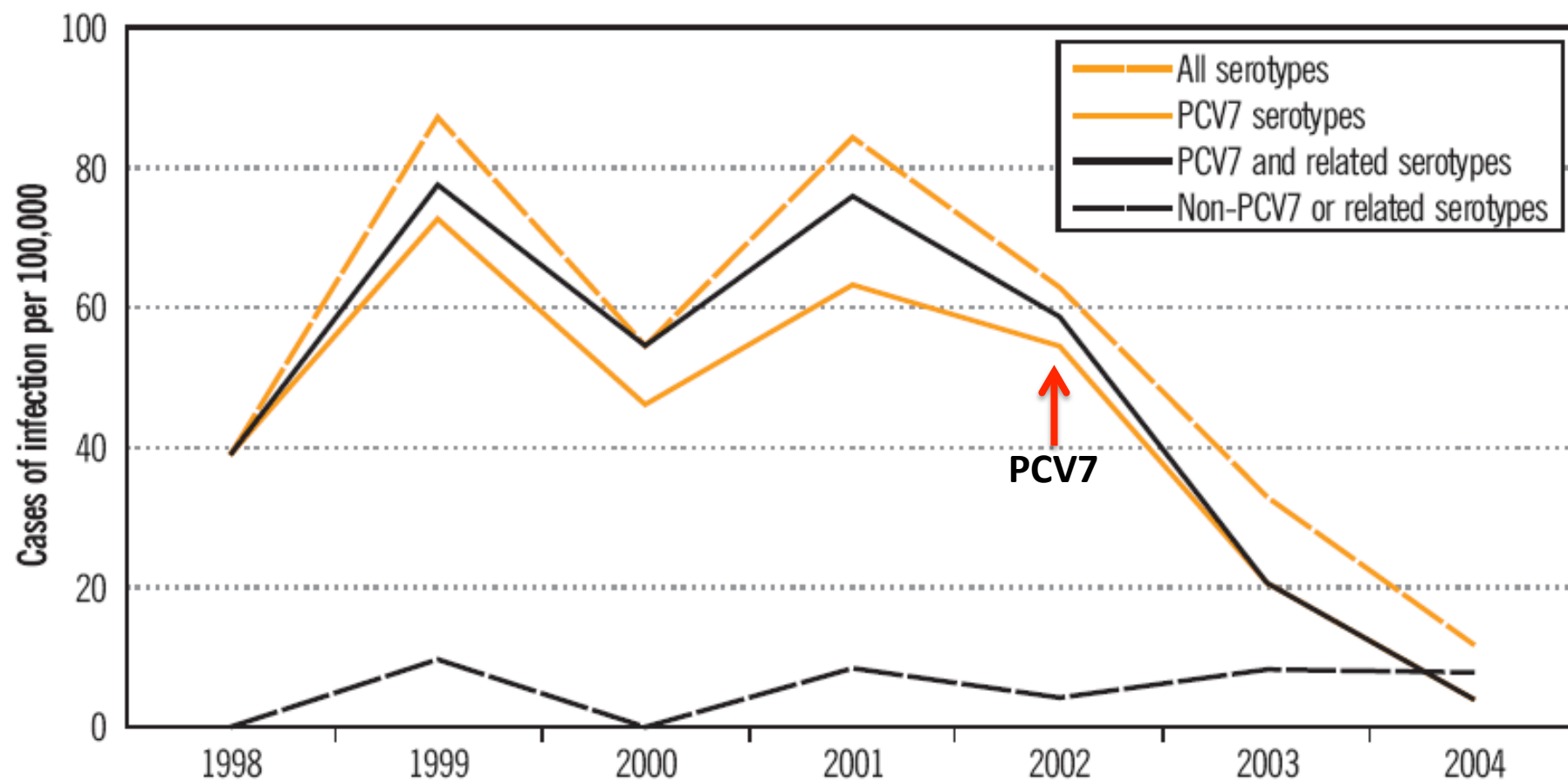
## PATHOGEN-SPECIFIC CAUSES OF SEVERE PNEUMONIA CASES

Pathogen	Distribution of severe pneumonia cases by cause	Discussion
<i>Streptococcus pneumoniae</i> (bacterium)	Leading cause	<i>S. pneumoniae</i> is the leading pathogen in almost all studies from around the world. Recent vaccine trial data indicate that in Africa it <u>may be responsible for over 50%</u> of severe pneumonia cases, and probably a higher proportion of fatal cases. This proportion may vary in different parts of the world.
<i>Haemophilus influenzae</i> (bacterium)	Major cause	Most disease is caused by type b (Hib). Vaccine studies from Bangladesh, Chile and the Gambia suggest that Hib causes around 20% of severe pneumonia cases, although the proportion may vary in different parts of the world.
Other important pathogens	Less common	These pathogens include important viruses such as respiratory syncytial virus (RSV) and influenza; other bacteria, such as <i>Staphylococcus aureus</i> and <i>Klebsiella pneumoniae</i> ; and the fungus <i>Pneumocystis jirovecii</i> (PCP), which is particularly important in young children with AIDS (see Box 3, page 8).

# Canada



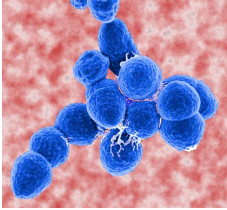
**Figure 11. Rates of Invasive Pneumococcal Infection per 100,000 among Children  $\leq 23$  Months of Age According to Year and Serotype\***



\* Data from CASPER Surveillance 1998–2004. Reprinted from Kellner JD, Church DL, MacDonald J et al. *Progress in the prevention of pneumococcal infection*, Canadian Medical Association Journal 2005;173:1149–1151 by permission of the publisher. © 2005 CMA Media Inc.

# PCV7

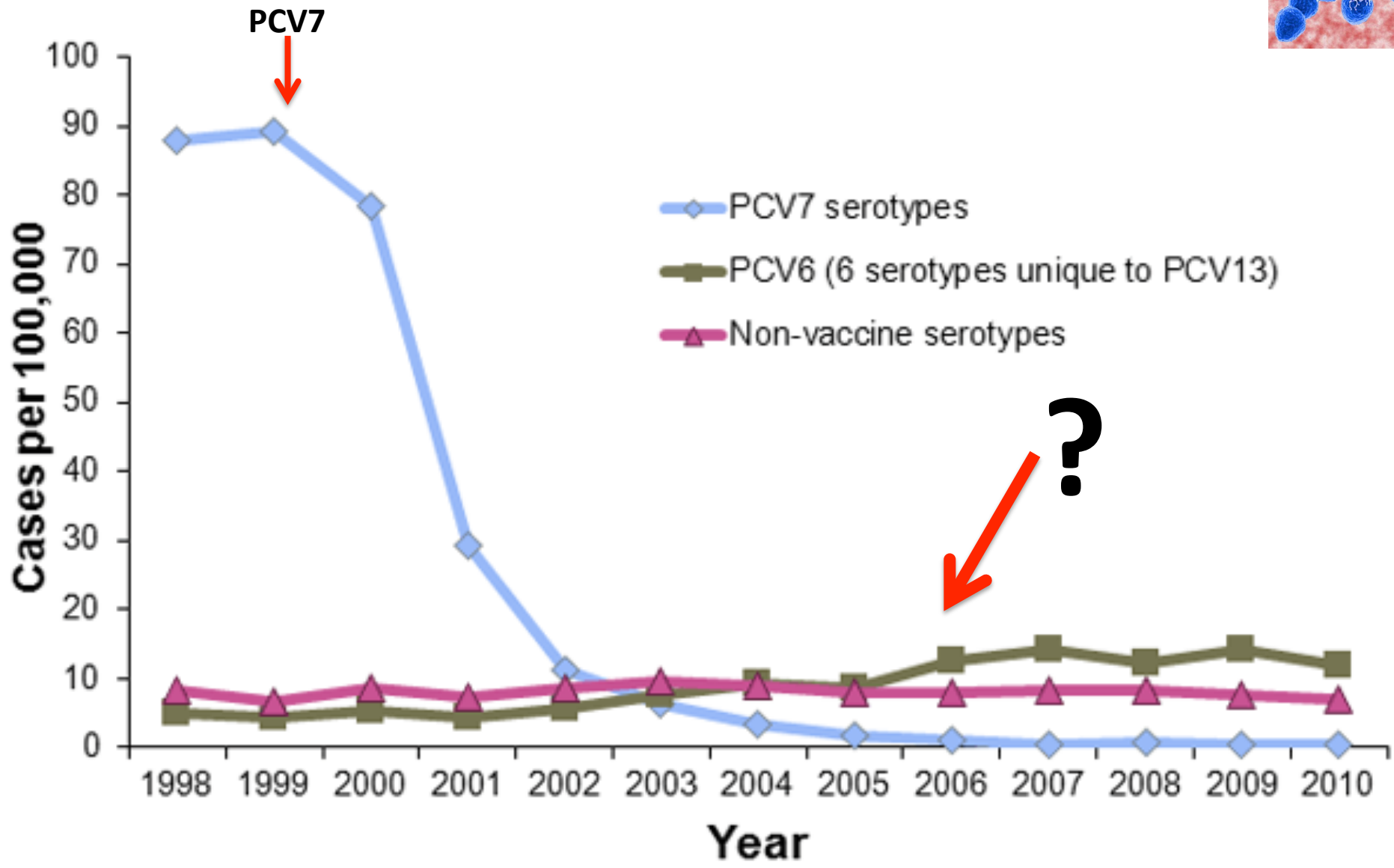
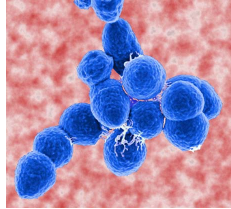
(4, 6B, 9V, 14, 18C, 19F and 23F)



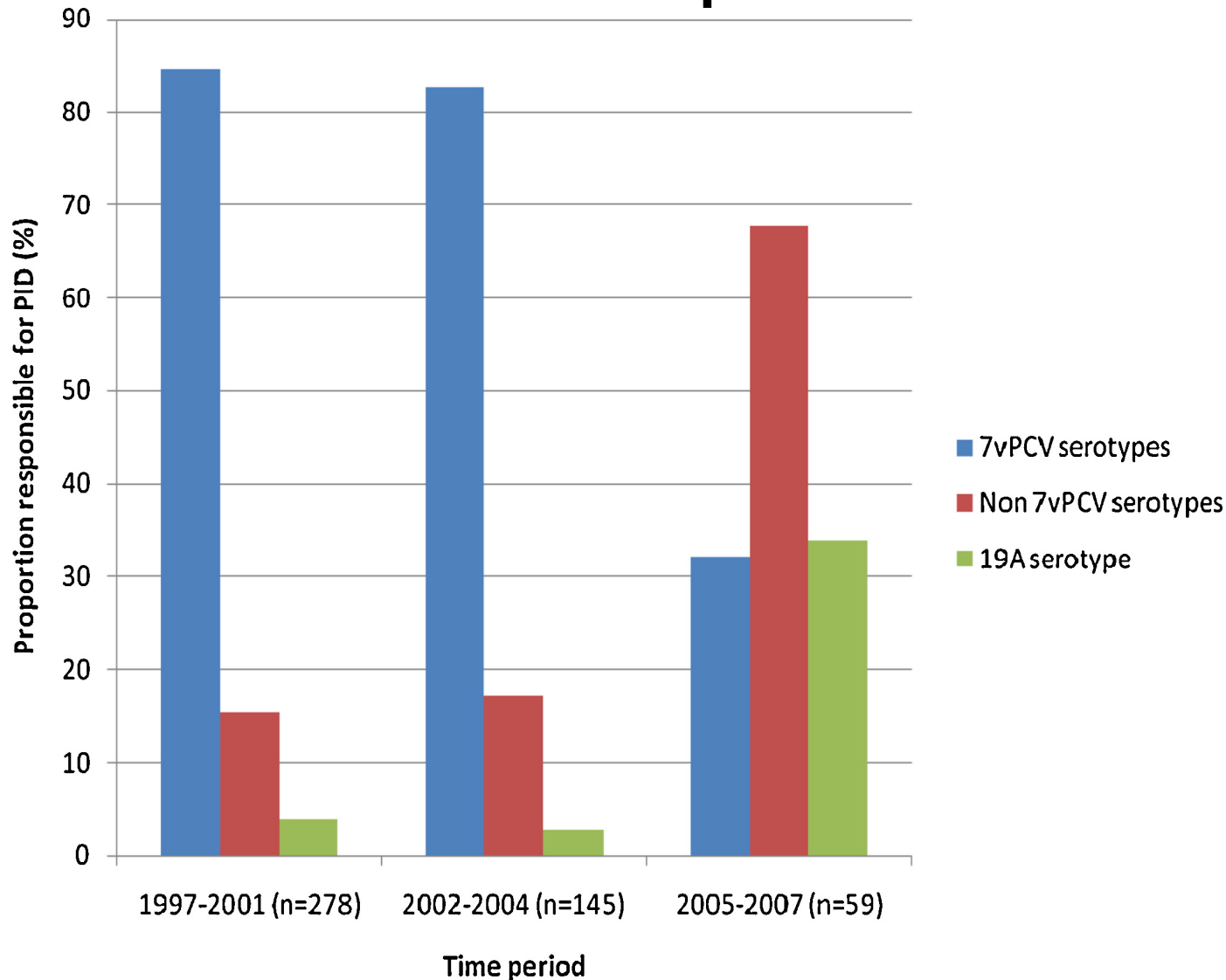
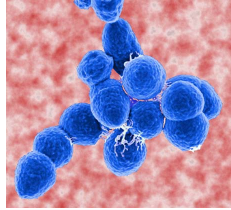
- PCV7 infant immunization has led to near eradication of vaccine- serotype invasive pneumococcal disease (IPD) in vaccinated Canadian children as well as in older children and adults, through herd effect.



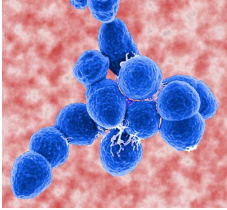
U.S.



# Strain Replacement ?



# Strain Replacement ?



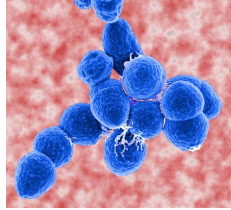
## W Serotype replacement in disease after pneumococcal vaccination

*Lancet 2011; 378: 1962-73*

*Daniel M Weinberger, Richard Malley, Marc Lipsitch*

- Among asymptomatic carriers, the prevalence of non-vaccine types (NVTs) has increased substantially post PCV7
- In many populations, pneumococcal disease caused by NVT has increased
- In most cases this increase has been less than the increase in NVT carriage (except in Alaska)

# Strain Replacement ?



## Niche and Neutral Effects of Acquired Immunity Permit Coexistence of Pneumococcal Serotypes

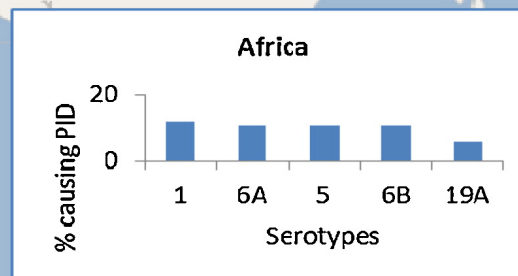
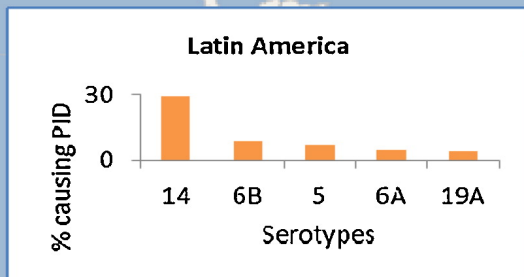
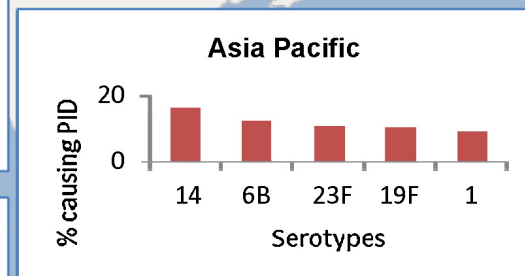
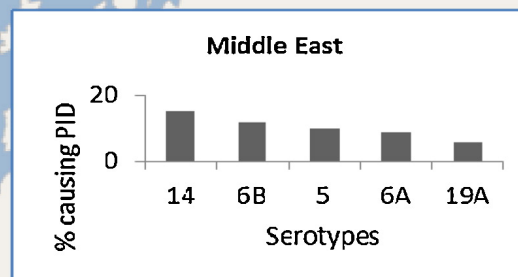
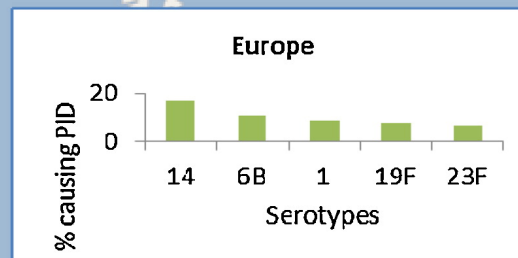
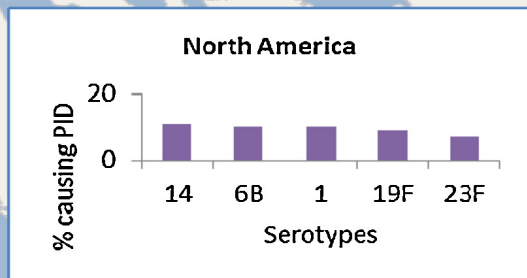
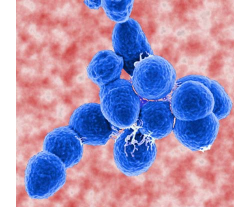
Sarah Cobey<sup>1\*</sup> and Marc Lipsitch<sup>1,2</sup>

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- complex interactions of host and pathogen lead to changes in patterns of colonization
- diversity of a pathogen (*i.e. strain replacement*) can be explained by the interaction of acquired (capsular) specific and nonspecific immunity to pneumococcus

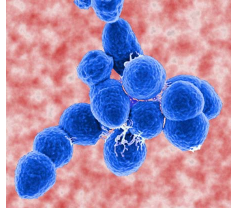
= attention to the details of immune responses needs to be paid to gauge the impact of vaccines

# Strain Diversity

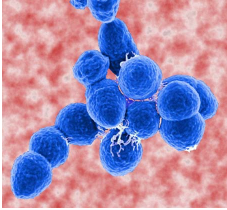


# PCV13

(PCV7 & 1, 3, 5, 6A, 7F and 19A)

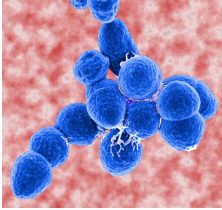


- The serotypes in PCV13 are the most common serotypes causing IPD **globally**, accounting for 75% of IPD in children <5 years of age worldwide.
- PCV13 would prevent 64% of the remaining cases of invasive pneumococcal disease (IPD) in children in, mostly attributed to serotype **19A** (42%), including serotype **5**, which has recently emerged in Western Canada.
- Pneumococcal **empyema** would also be better covered, given that only 48% of isolates in Canada were PCV7 serotypes, whereas the remainder were contained with PCV13.



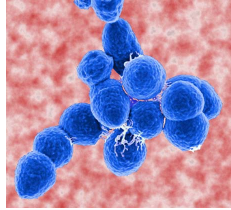
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# Safety and Immunogenicity of a 13-valent Pneumococcal Conjugate Vaccine in Healthy Infants and Toddlers Given With Routine Pediatric Vaccinations in Canada



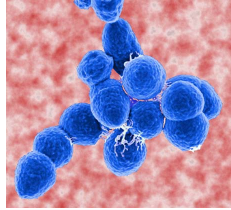
- Double-blind RCT
- Children at 2, 4, 6, and 12 months received PCV13 (n= 300) or PCV7 (n= 303) with routine immunizations
- 1month later responses to Hib, pertussis, menC, and specific pneumococcal serotypes were measured
- Safety and tolerability were assessed daily for 4 days by parents





- No statistically significant differences between the groups in responses to Hib, pertussis, or menC after primary or booster vaccinations.
- >95% of subjects in the PCV13 group had antibody titers correlating with protection ( $>0.35$  mcg/mL) to each pneumococcal serotype 1 month after the third dose, except with serotypes 23F (90%), 3 (80%), and 5 (87%).
- After the fourth dose, 98% to 100% of subjects achieved protective serotype-specific antibody concentrations except for serotype 3 (85%).
- Safety and tolerability did not differ between groups.

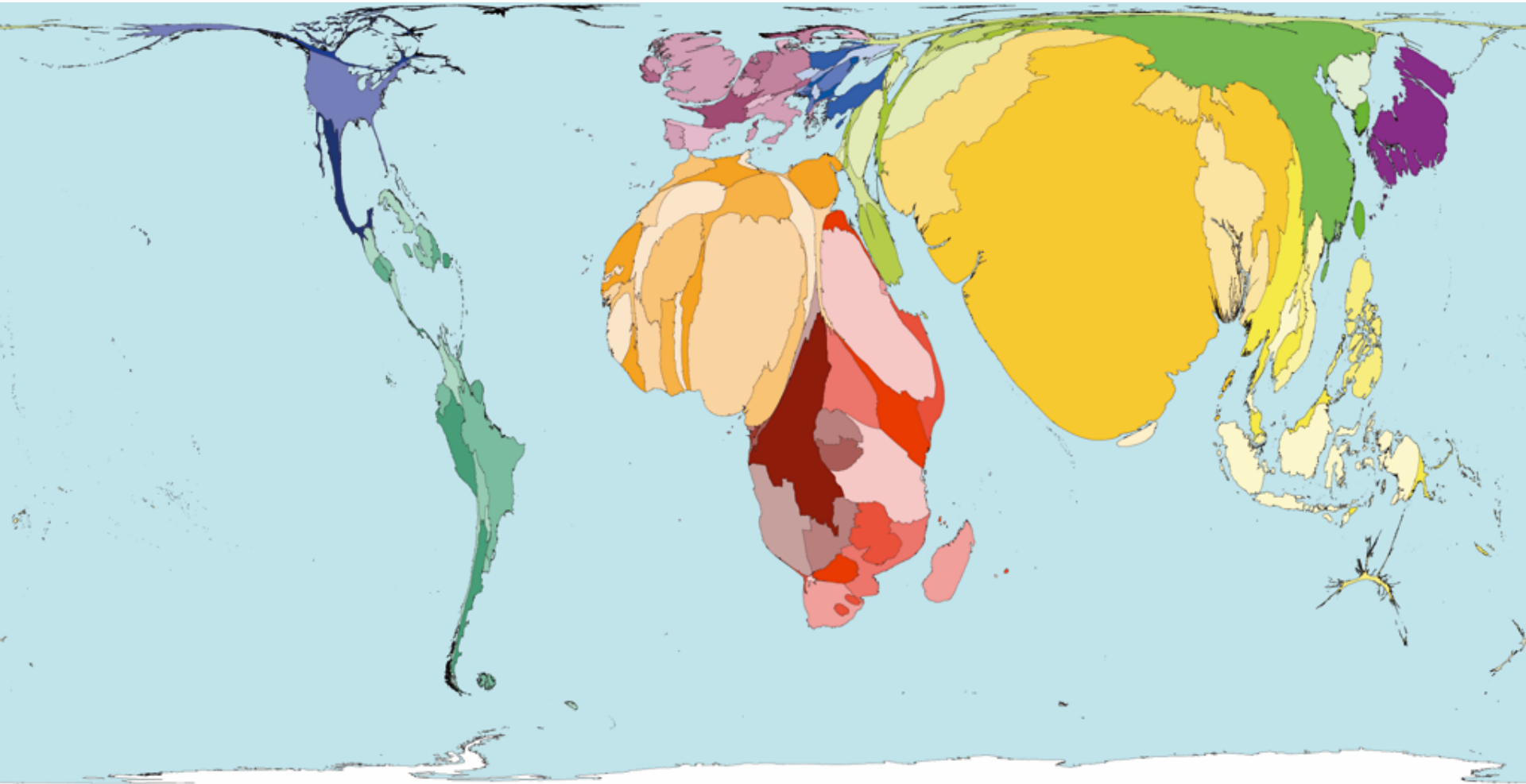
# Pneumococcal Vaccination



“The Pneumococcal Conjugate vaccine (PCV 13) protects against infection from 13 types of pneumococcal bacteria and is free for children as part of their routine immunizations”.

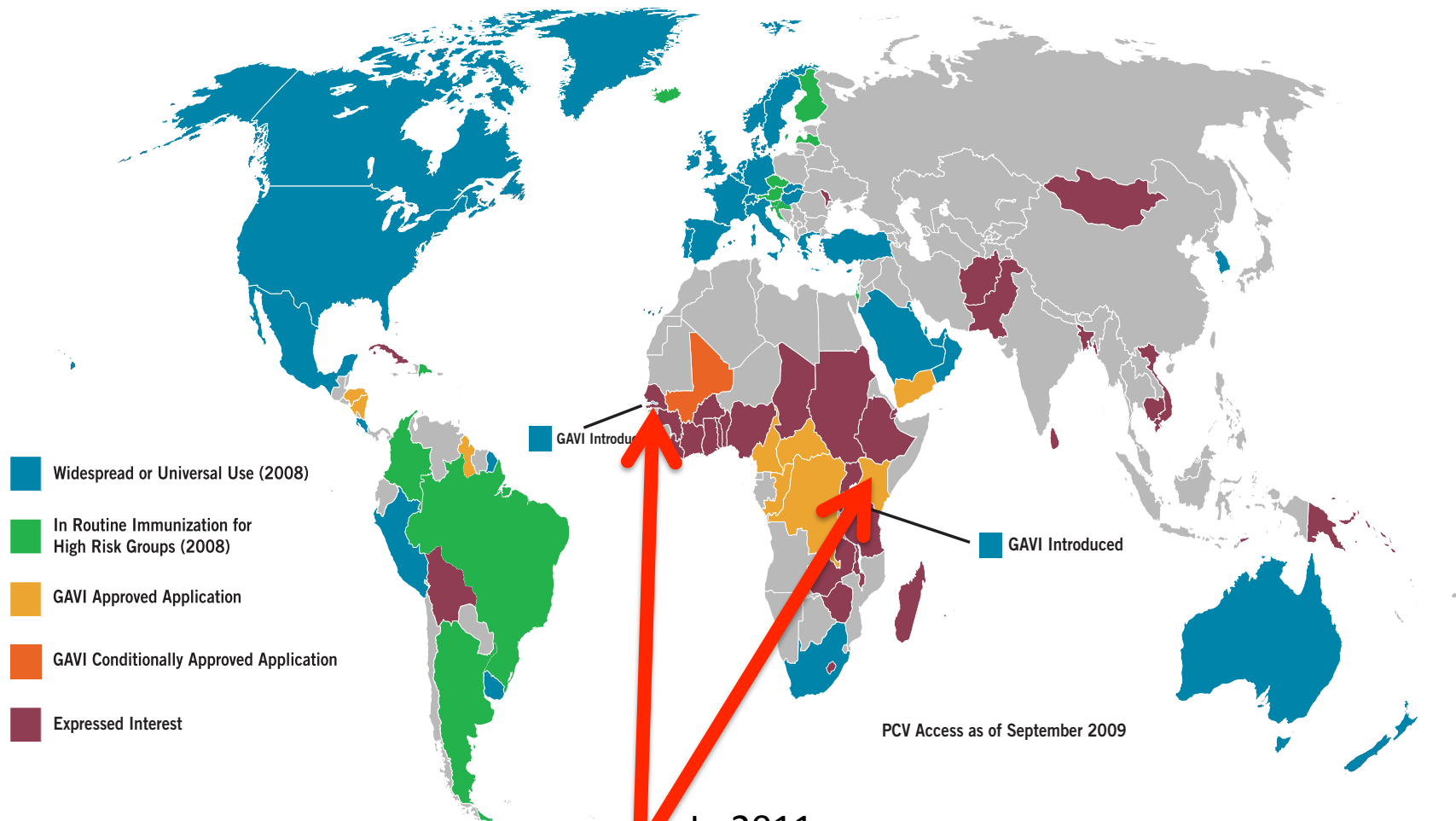
Similar program for PCV13 in all provinces.

# Pneumonia (all causes)



# PCV7

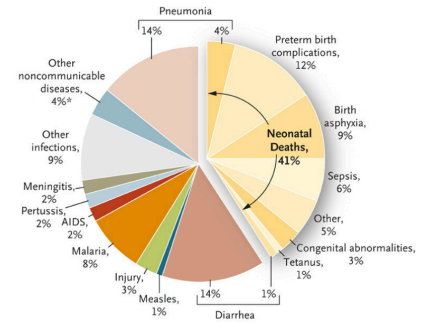
## Status of Global Pneumococcal Conjugate Introduction



In 2011,

- Kenya introduced the PCV10
- Sierra Leone introduced PCV13

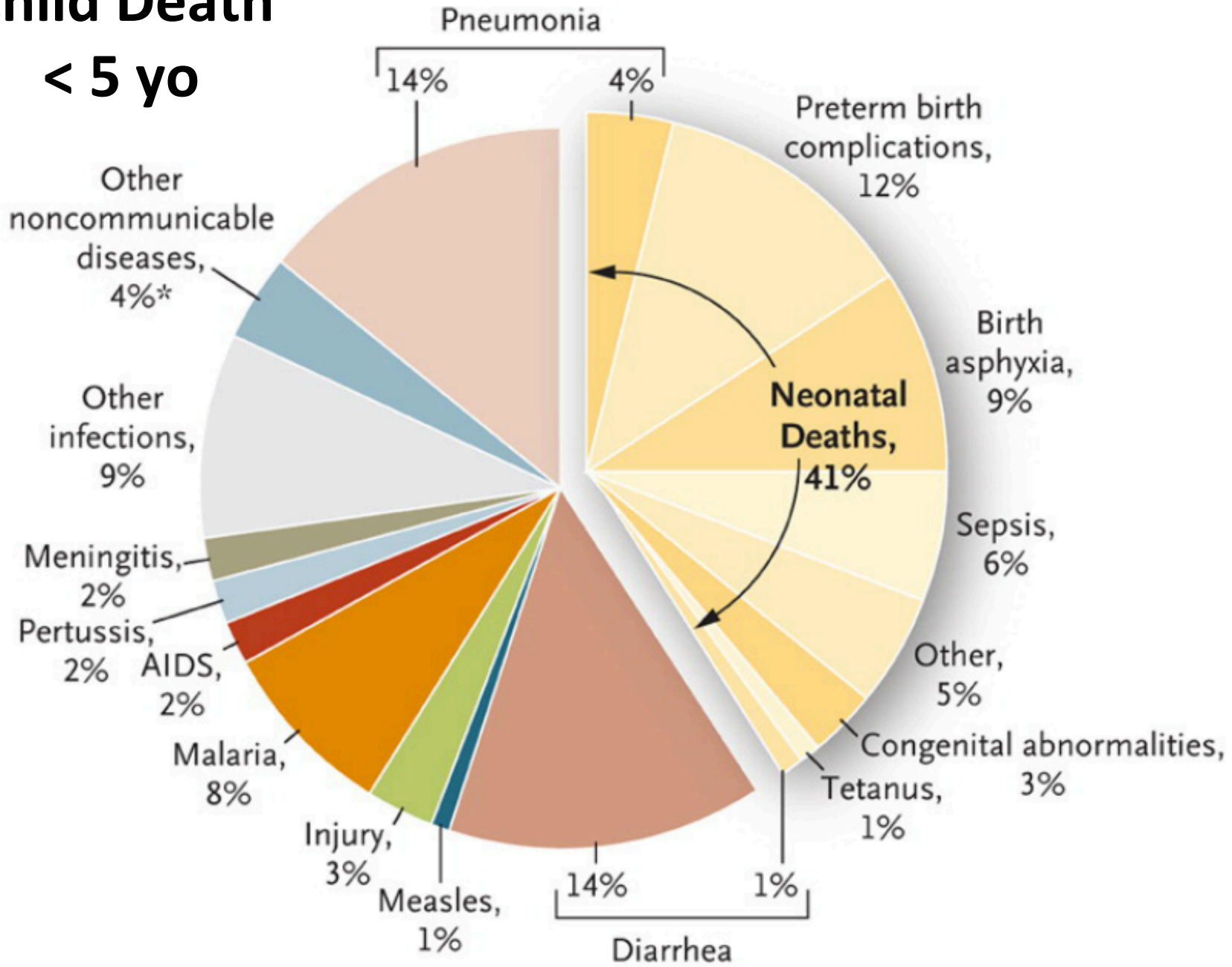
# Summary



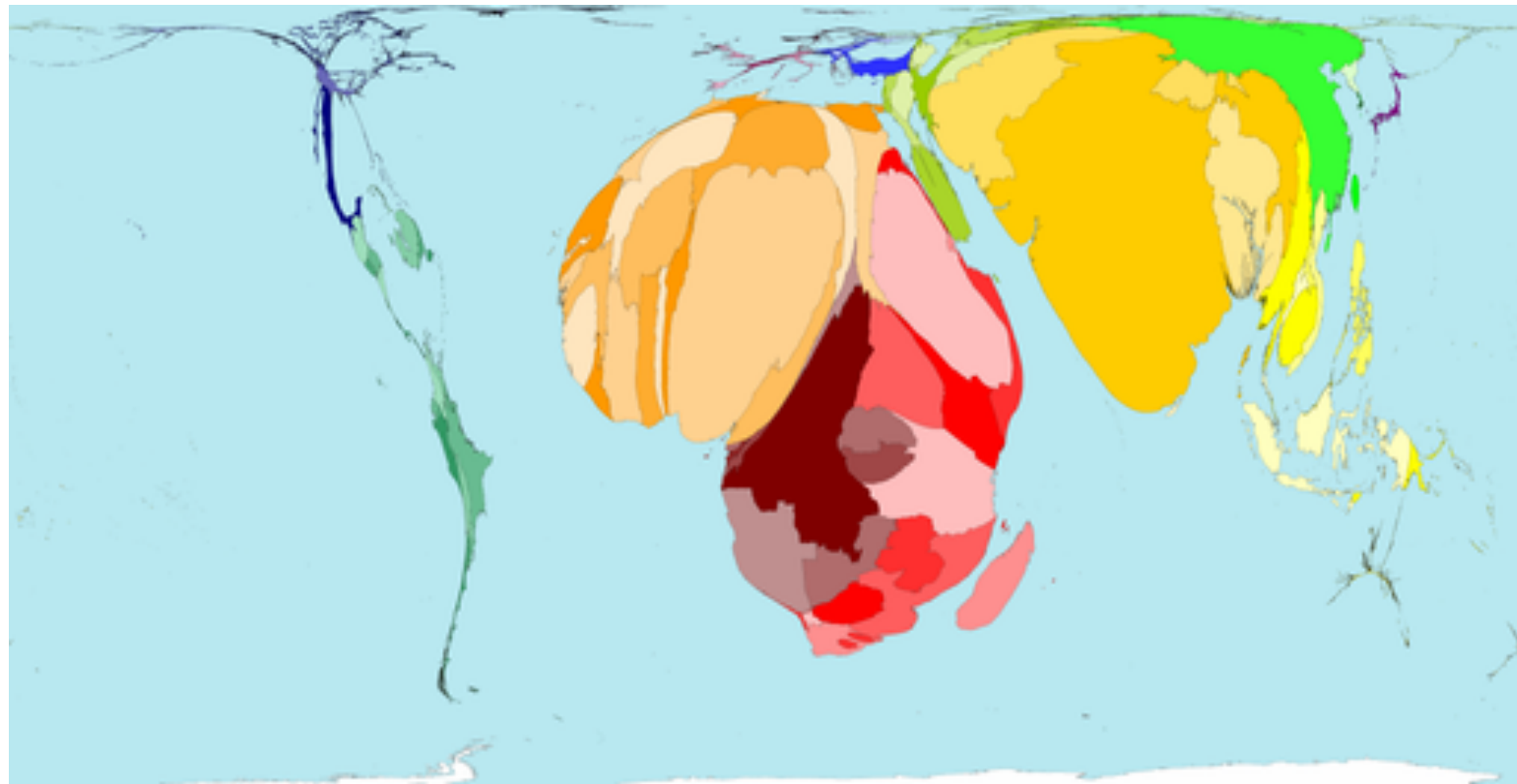
1. Microbes causing neonatal sepsis are changing. Consider adapting empiric therapy.
2. Rotavirus infant vaccination is safe and effective. Give 2 doses before 8 months of age.
3. PCV7 is effective. PCV13 is safe & immunogenic.

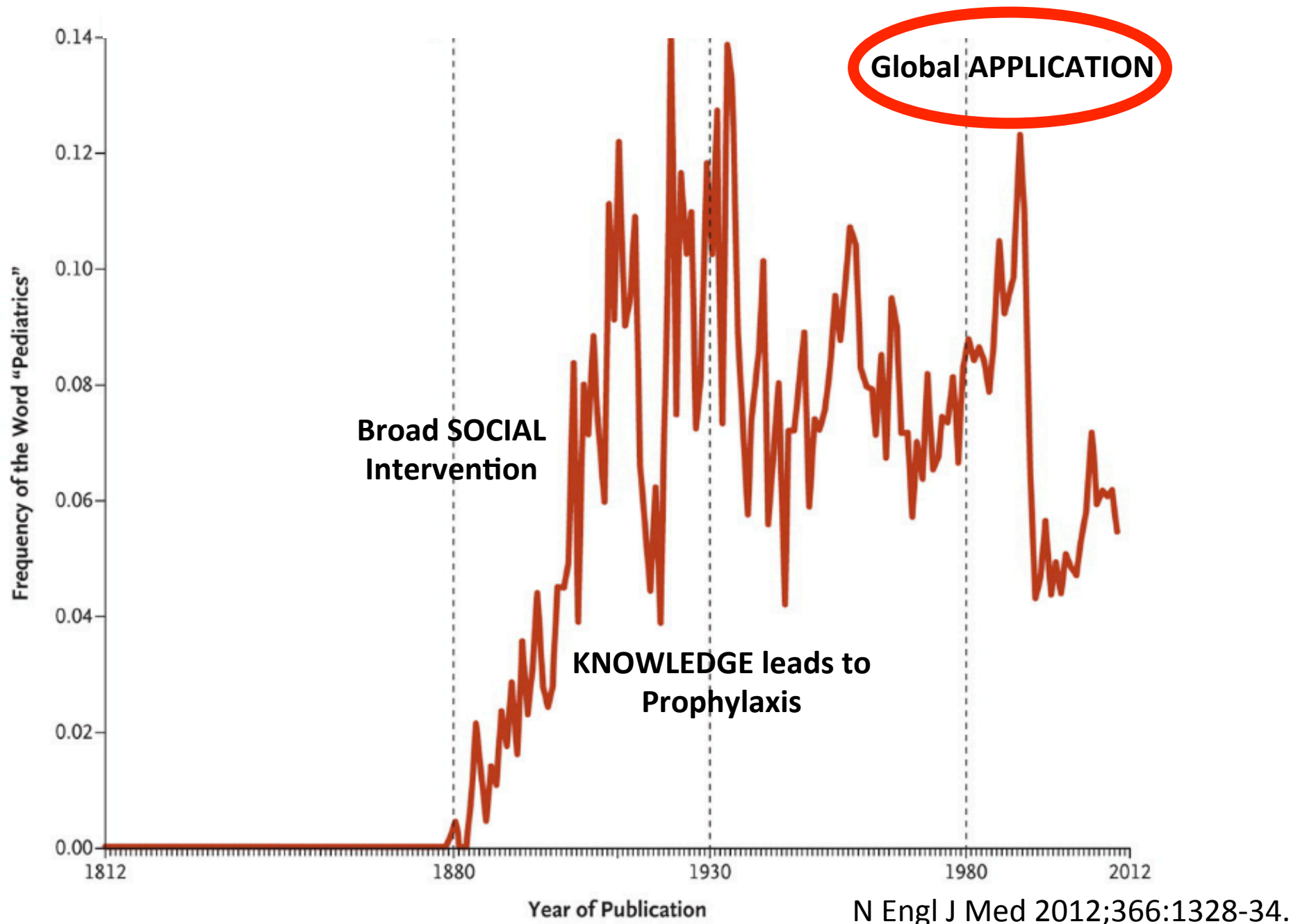
# Child Death

< 5 yo



61% of deaths < 5 yo due to infection



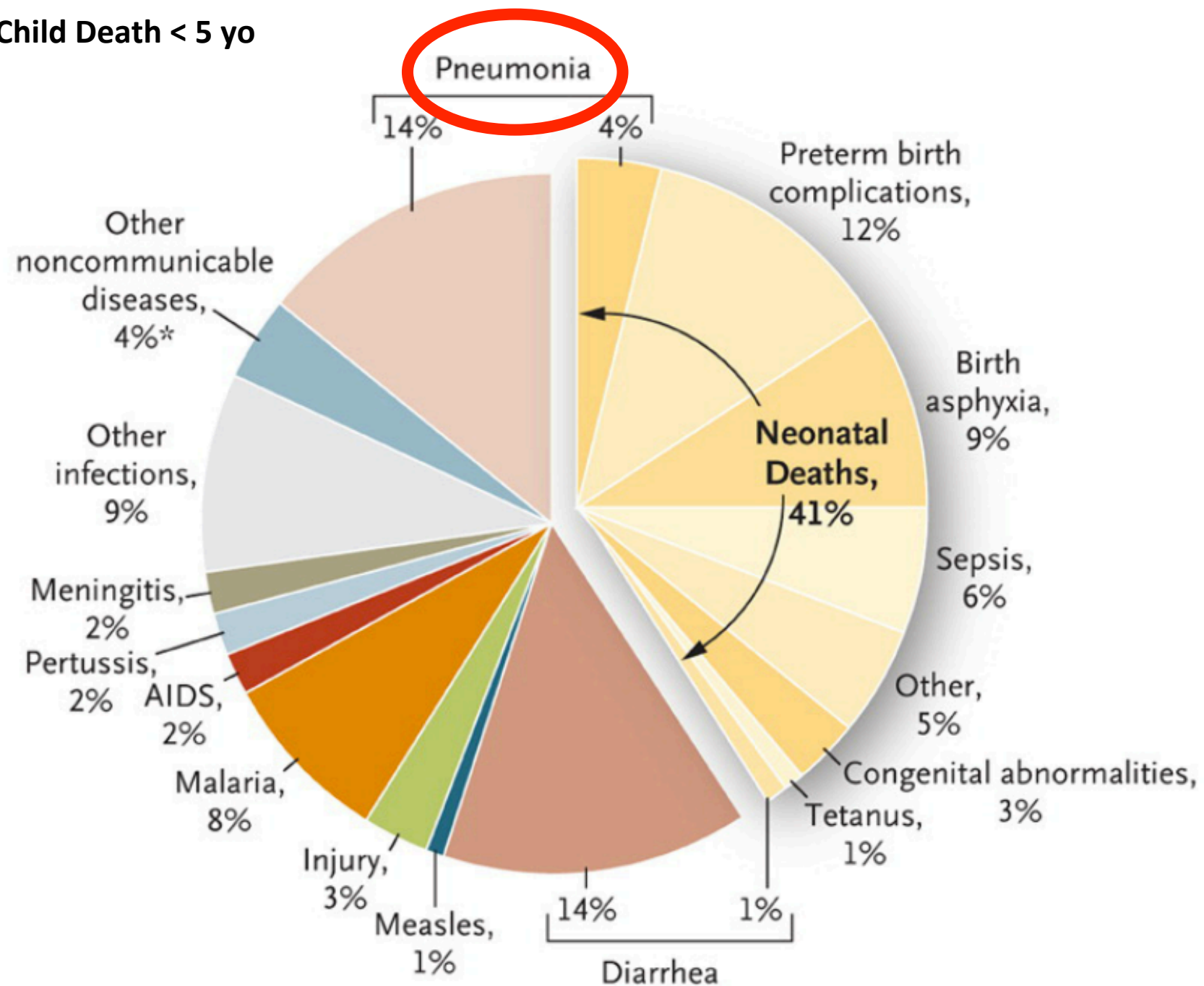




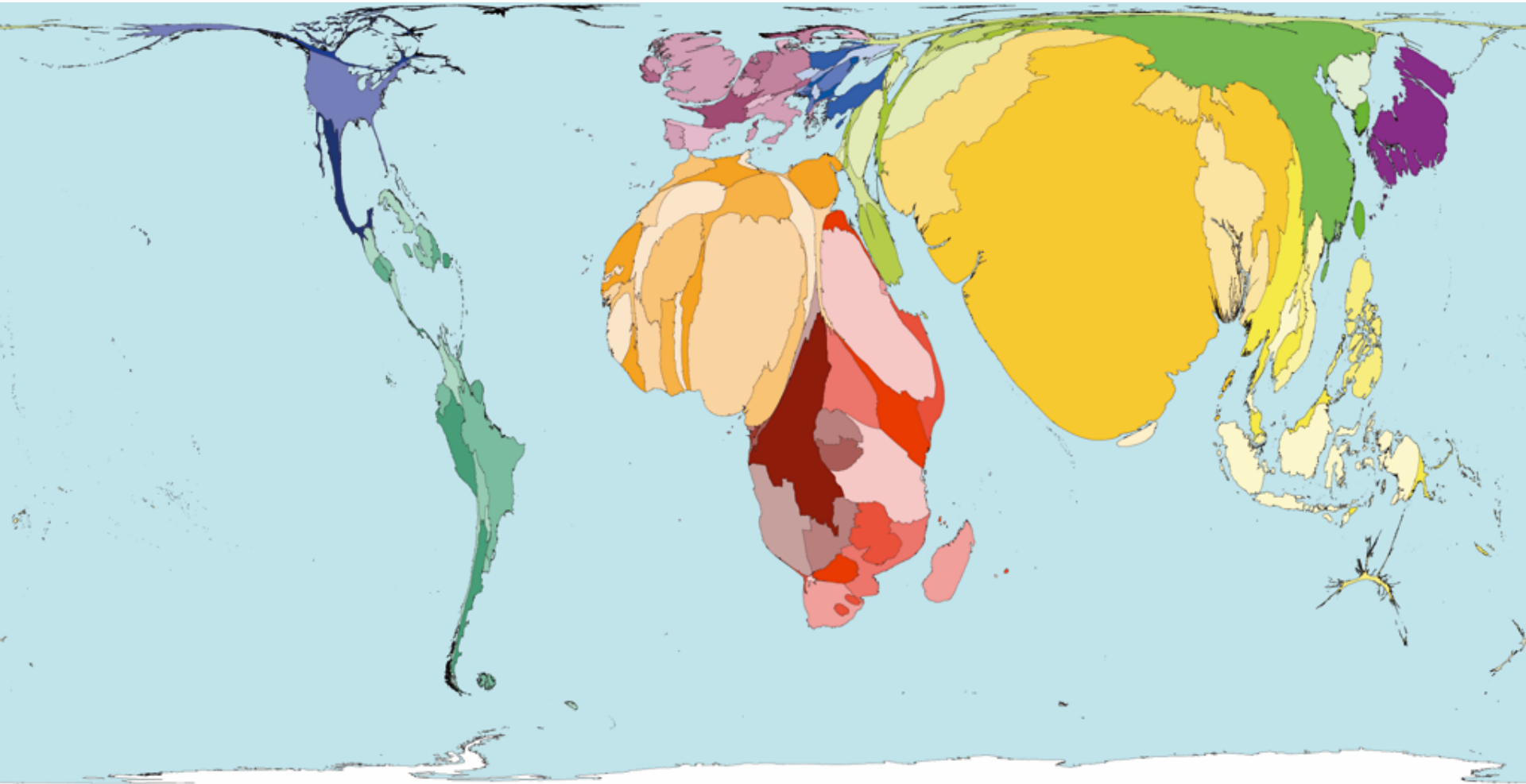
# Objectives



## Child Death < 5 yo

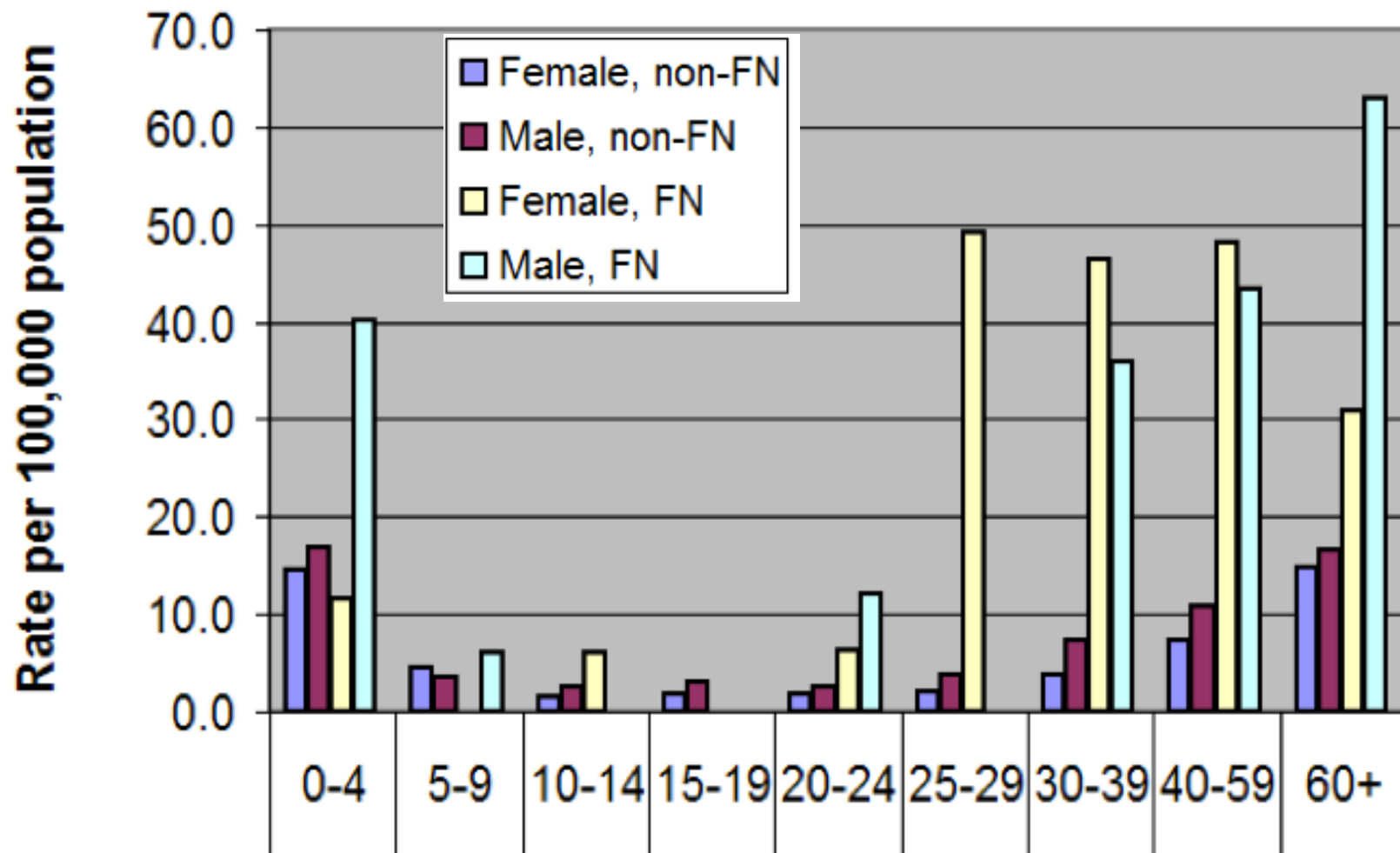


# Pneumonia (all causes)



# 2007-2009 Mean Invasive Pneumococcal Rates by Age

## Gender and Status (FN = First Nations)



Marcus Lem, MD, MHSc, FRCPC

Health Protection Directorate, First Nations and Inuit Health, Health Canada - BC Region

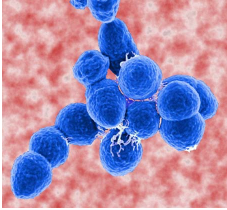
# Indigenous Children's Health Report:

2009 HEALTH ASSESSMENT IN ACTION

[www.crich.ca](http://www.crich.ca)

**Janet Smylie** MD MPH Canada

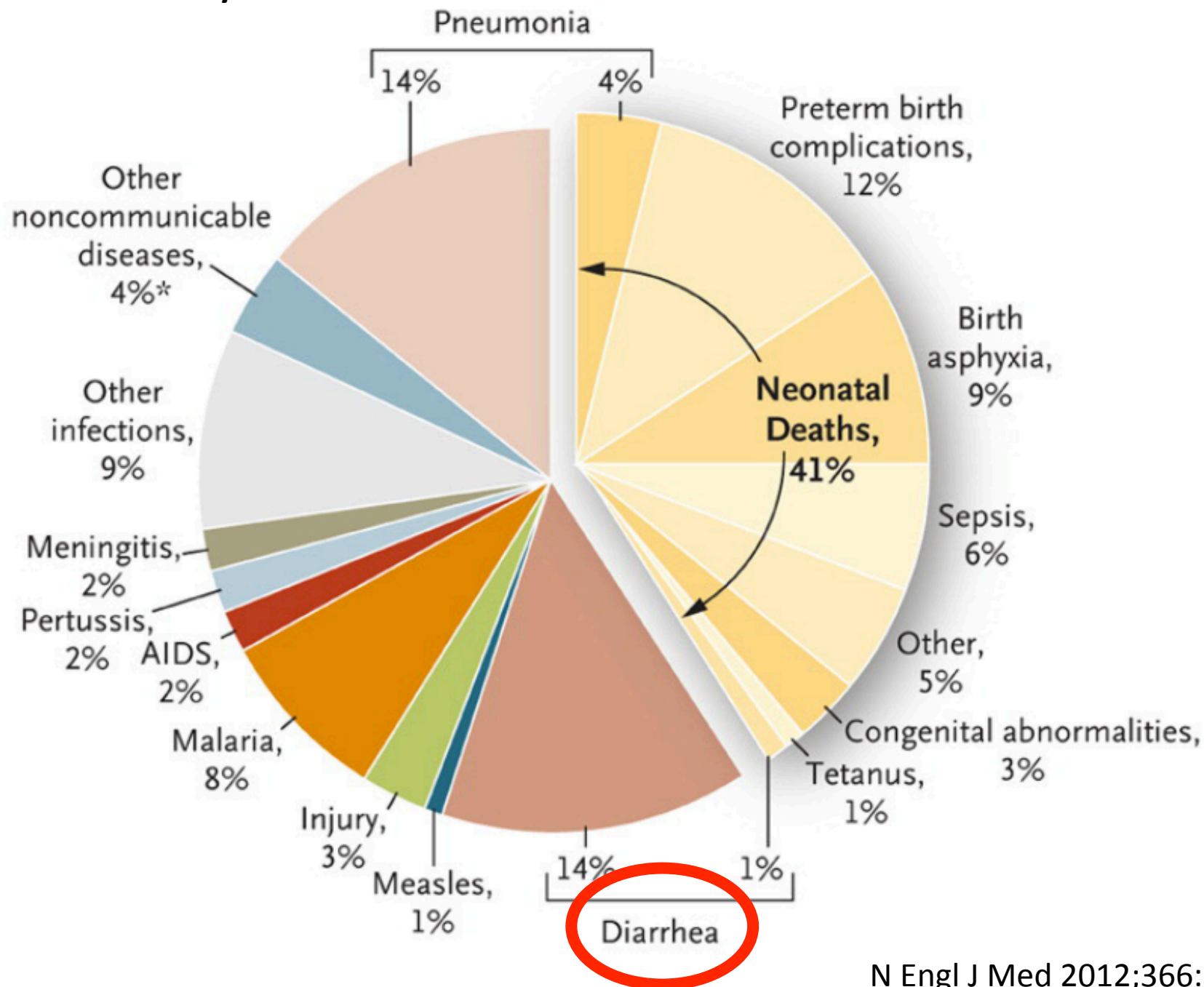
**Paul Adomako** MSc Canada



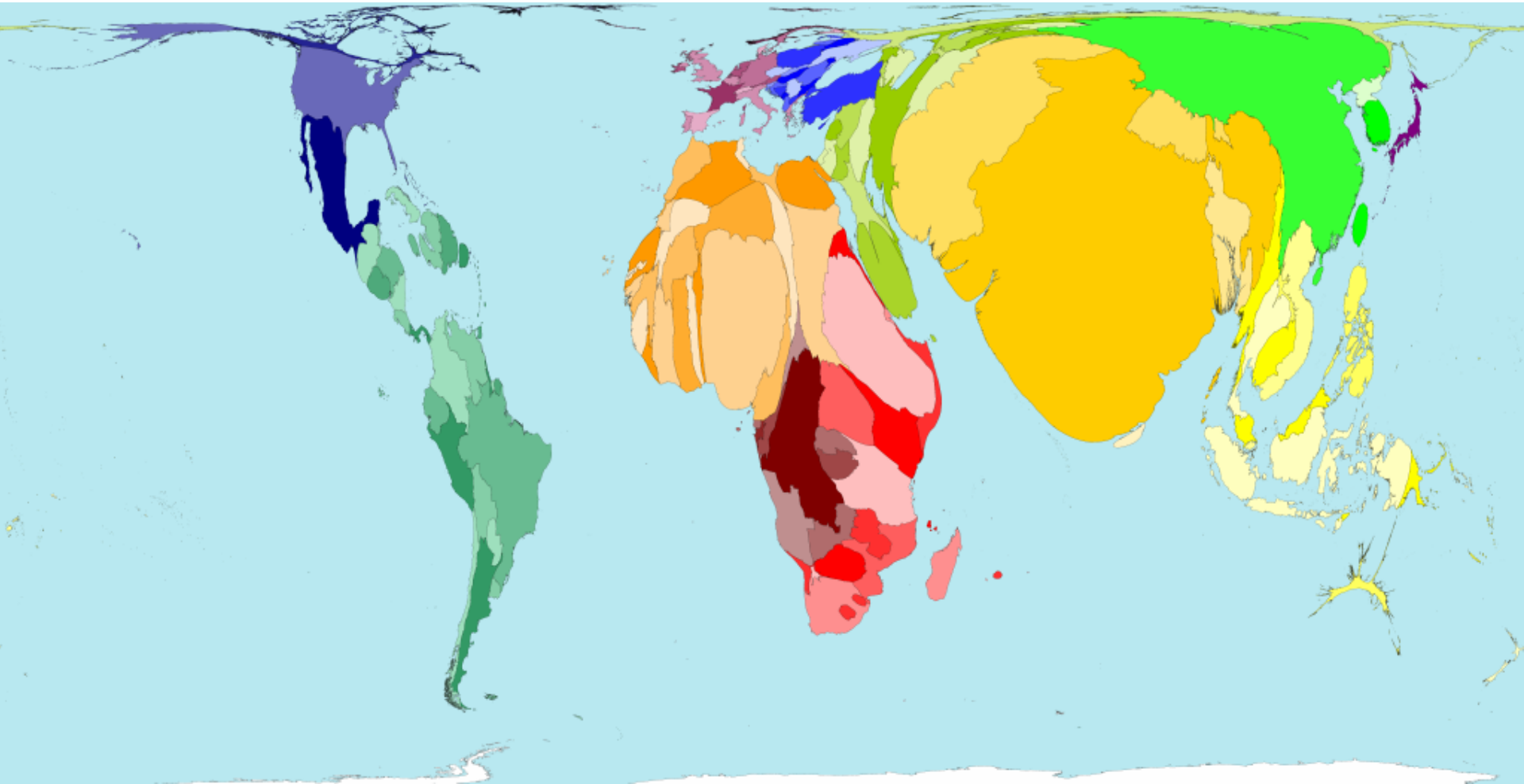
- Disproportionate burden of respiratory tract infection among First Nations living on-reserve and Inuit children.

**(No data** for First Nations without status, Métis and urban Aboriginal children.)

## Child Death < 5 yo

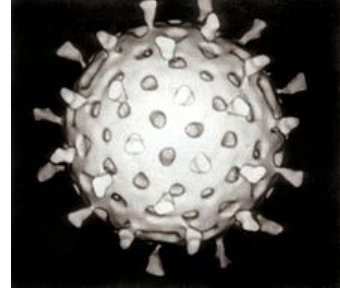


# Diarrhea (all causes)





**Oral rehydration therapy and early  
refeeding in the management of childhood  
gastroenteritis**



“Prolonged diarrhea and malnutrition are  
primary causes of morbidity and mortality in Canadian native populations.”  
(no reference)

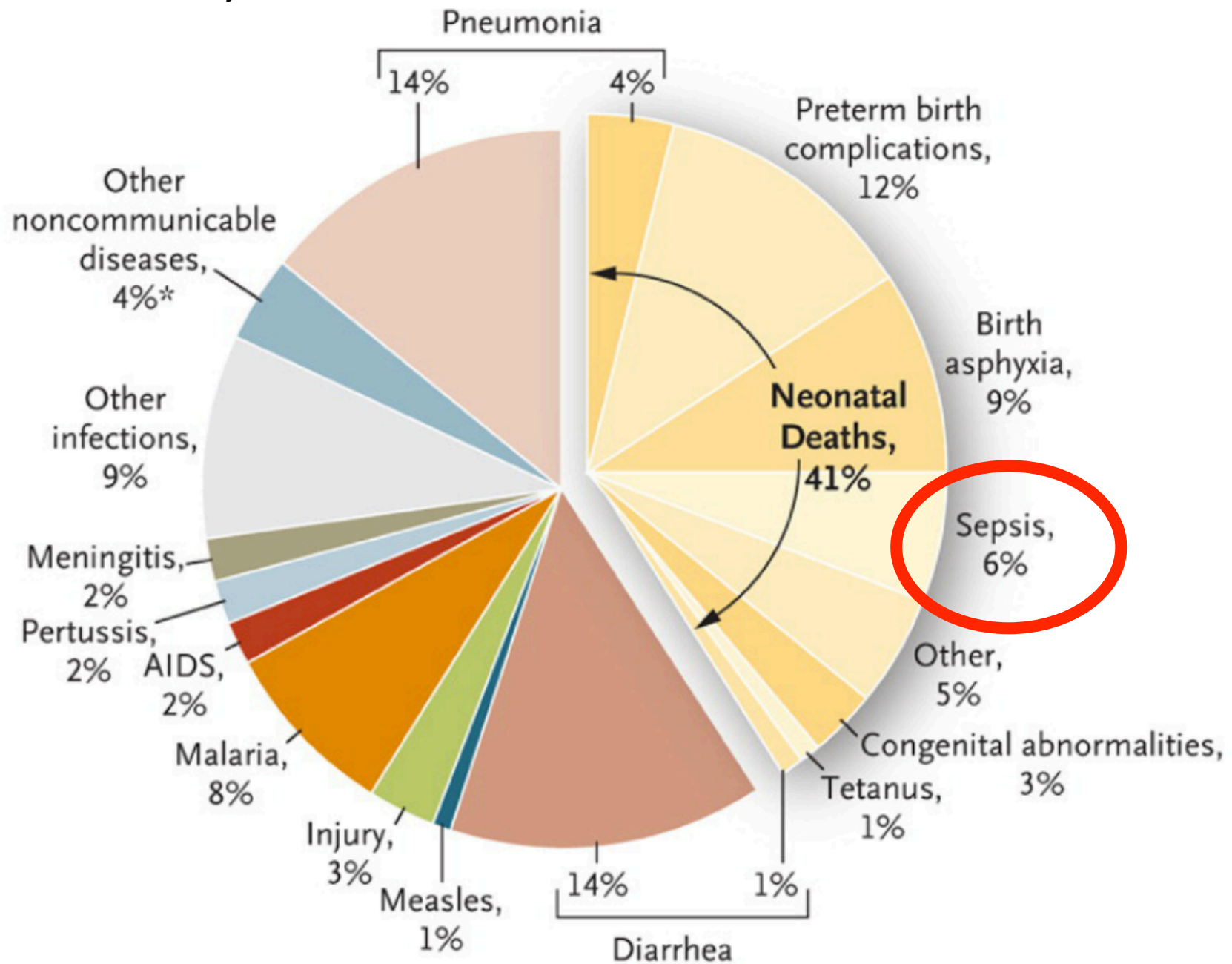
**Indigenous Children's Health Report:**

2009 HEALTH ASSESSMENT IN ACTION

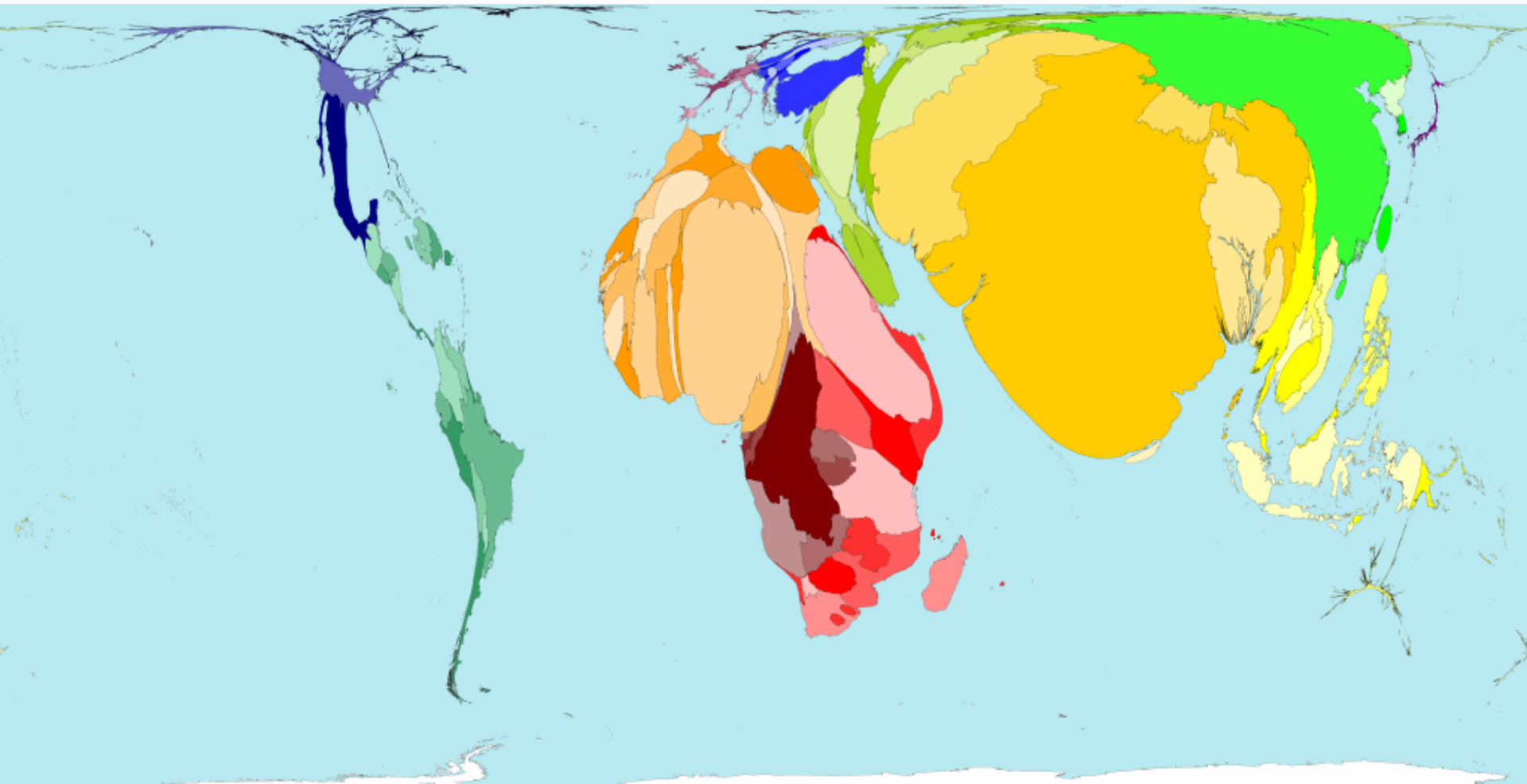
- **No data** on gastroenteritis in the report.



## Child Death < 5 yo



# Newborn death < 1 week of age (all causes)



# Indigenous Children's Health Report:

2009 HEALTH ASSESSMENT IN ACTION



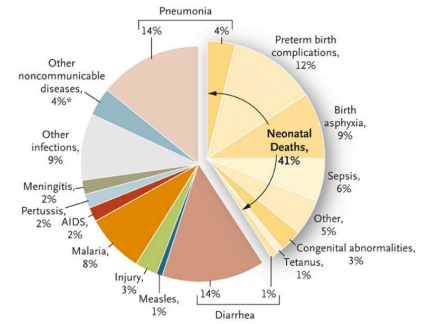
- Neonatal mortality among First Nations is nearly twice the rate in the general Canadian population
- Neonatal mortality among Inuit is four times higher than the general Canadian population
- **No data** (yet) on specific causes of neonatal sepsis in First Nations or Inuit newborns.

20<sup>th</sup> NEJM ANNIVERSARY ARTICLE

## What We Don't See

Margaret Kendrick Hostetter, M.D.

*“But gradually, the attitude of helplessness changed, first to inquiry and then to responsibility.”*



# Thank You!

## Questions?

tkollm@mac.com