TAMING THE BEASTS:
TOP KILLERS OF CHILDREN

Pneumonia, a Global Perspective

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Disclosure of Potential Conflicts of Interest

I have been involved in the development of several pneumococcal conjugate vaccine candidates, including:

- 7-, 9-, and 13*-valent CRM formulations when employed by Wyeth Vaccines

- The pneumococcal *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV) with my current employer GlaxoSmithKline Biologicals.

*patent holder receiving no royalties

Outline

- Global epidemiology of childhood pneumonia
  - A brief summary of recent analyses (thanks to Prof Igor Rudan!)
- Pneumococcal conjugate vaccine candidates and their impact on pneumonia
  - What have we learned?
- Are there other bacterial pathogens to target in addition to pneumococcus?

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- **Global epidemiology of childhood pneumonia**
  - **A brief summary of recent analyses**

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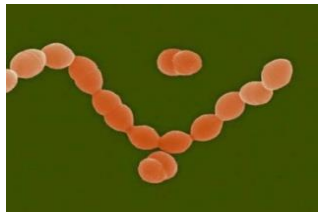
PNEUMONIA: DEFINING AND MEASURING THE BURDEN OF DISEASE

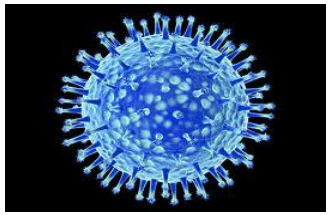
S. pneumoniae

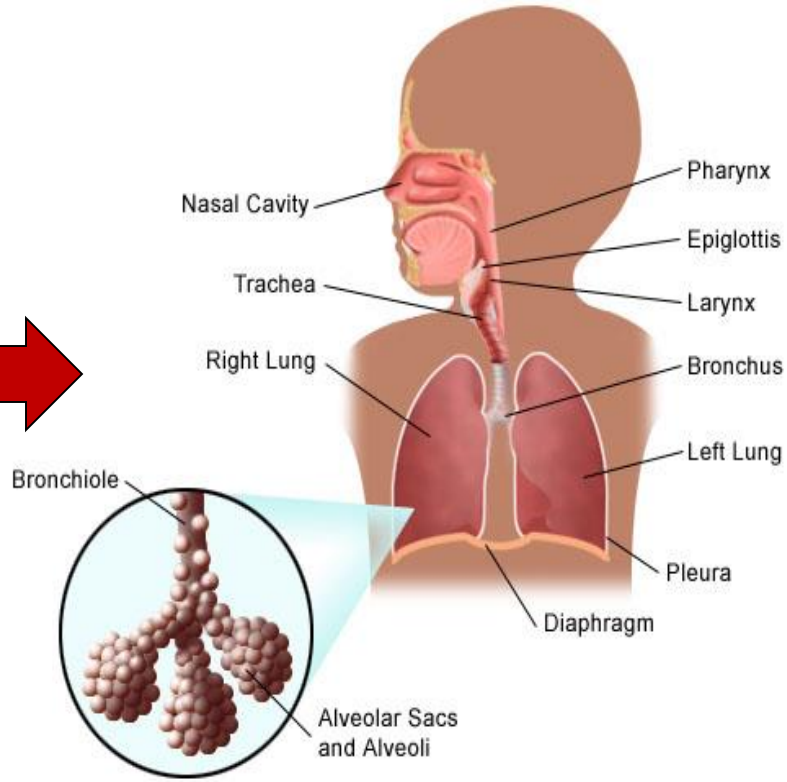


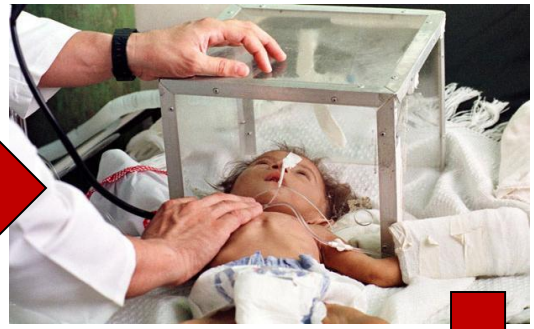
Hib

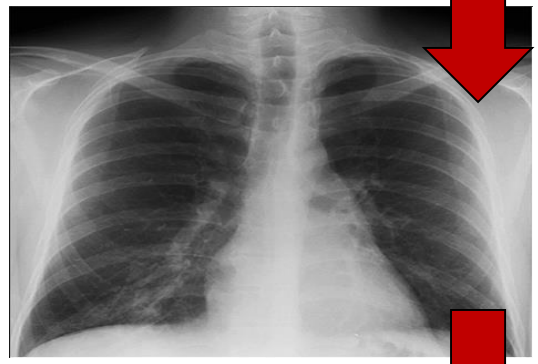
RSV

Influenza









Slide with courtesy from Prof. I. Rudan

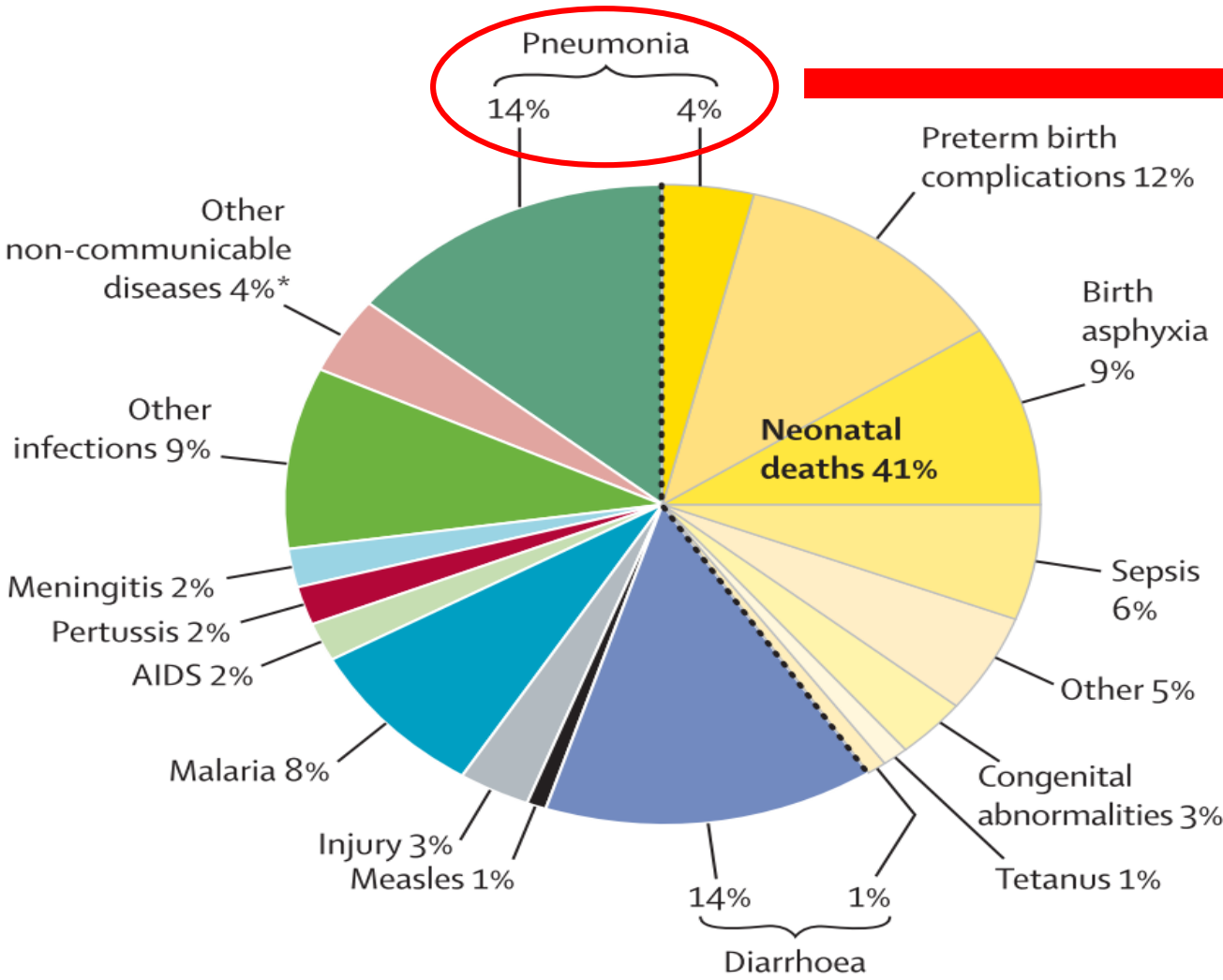
PNEUMONIA: BURDEN

- New episodes each year globally in children 1 mo – 5 y (year 2000):
  - ~156 million according to WHO clinical definition (~50 million X-ray positive)
- 12–15% are severe episodes requiring hospitalisation: (~20 million cases)
- CFR for community-acquired pneumonia ~1%; for severe pneumonia ~7–10%
- Number of deaths globally: 1,575,000
  - 350,000 in neonatal period and 1,225,000 in children 1 mo – 5 y

Slide with courtesy from Prof. I. Rudan

Rudan et al. Bull World Health Org 2008;86:408-41; Theodoratou et al. in press

ALL-CAUSE PNEUMONIA MORTALITY IN CHILDREN



Approximately one in every five deaths is attributed to pneumonia

S. pneumoniae **causes around 11% of all deaths in children aged 1–59 months[2]**

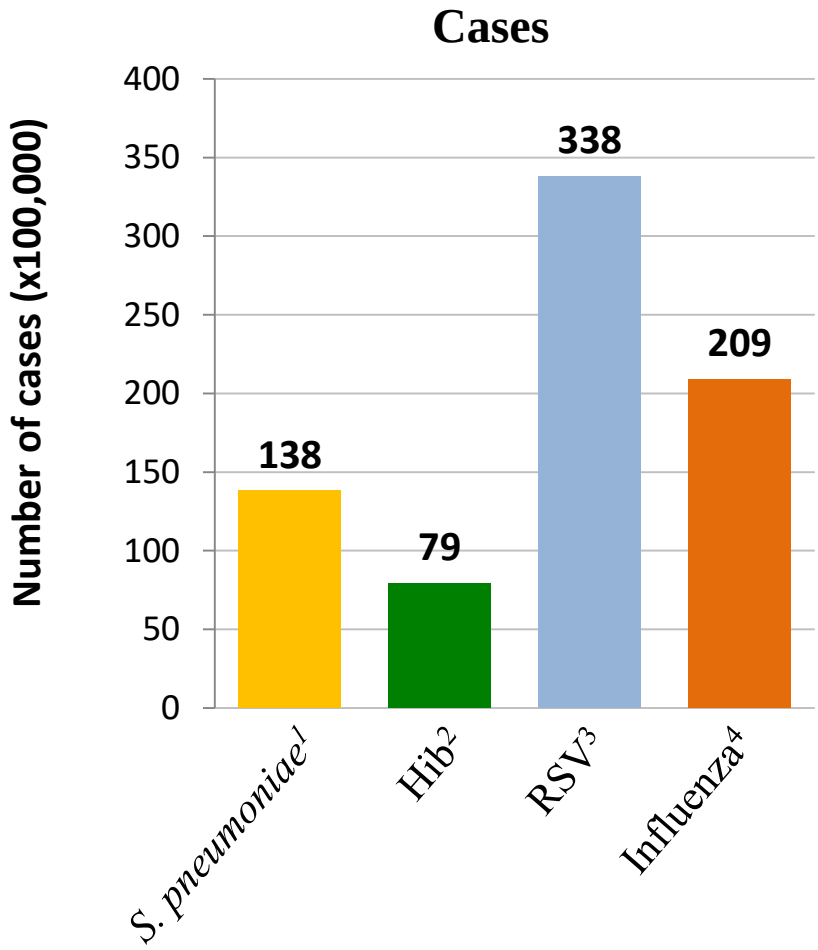
Of all pneumococcal deaths in this period[2]…

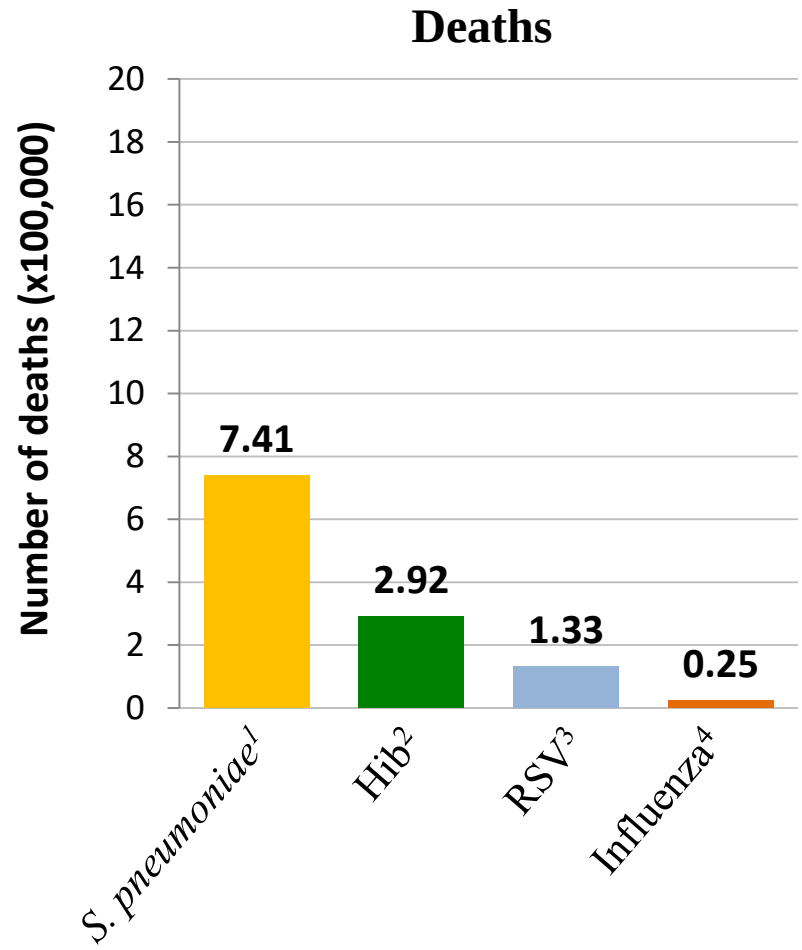
- **90% from pneumonia**
- **7% from meningitis**
- **3% from serious non-pneumonia, non-meningitis clinical syndromes**

Slide with courtesy from Prof. I. Rudan

1. Figure from Black et al. Lancet 2010;375:1969-87; 2. O'Brien et al. Lancet 2009;374:893-902

AETIOLOGY OF CHILDHOOD PNEUMONIA CASES AND DEATHS: GLOBAL ESTIMATES





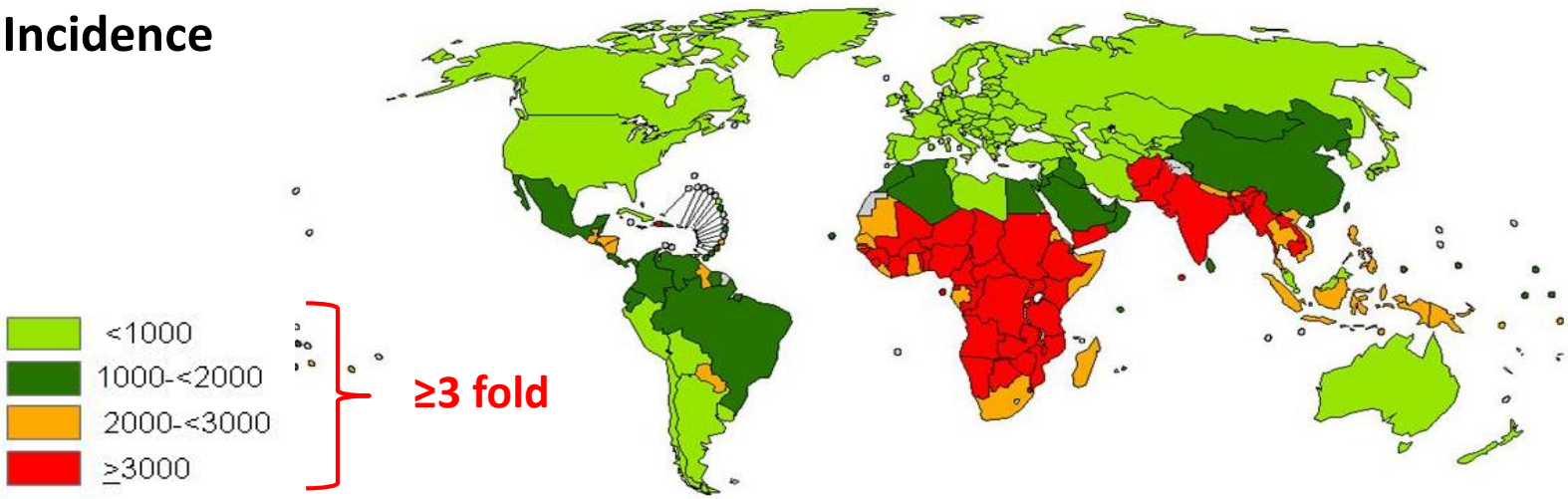
1. O'Brien et al. Lancet 2009;374:893-902; 2. Watt et al. Lancet 2009;374:903-11; 3. Nair et al. Lancet 2010;375:1545-55; 4. Nair et al. in press

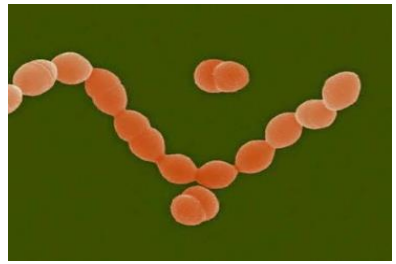
Slide with courtesy from Prof. I. Rudan

PNEUMOCOCCAL INCIDENCE AND MORTALITY RATE

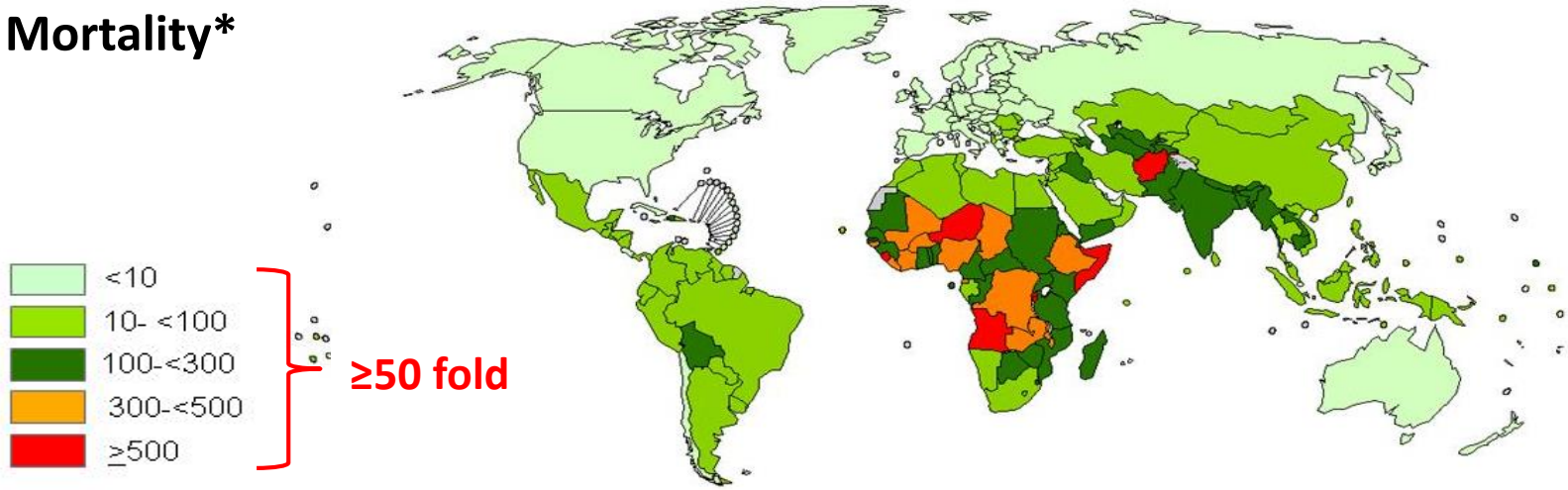
In children aged 1–59 months per 100,000

Incidence





Mortality*



*HIV-negative only

http://www.who.int/immunization_monitoring/burden/Pneumo_hib_estimates/en/index2.html [accessed June 2011] WHO date of slide 3 Aug 2009

Slide with courtesy from Prof. I. Rudan

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- Global epidemiology of childhood pneumonia
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- **Pneumococcal conjugate vaccine candidates and their impact on pneumonia**
  - **What have we learned?**

- Are there other bacterial pathogens to target in addition to pneumococcus?

IDSA GUIDELINES

The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America

- Children should be immunized with vaccines for:
  - ***S. pneumoniae***
  - *H. influenzae* type b
  - Pertussis
  - > 6 mos. : annual influenza vaccine
  - (measles too!)

Bradley et. Al. The Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age: Clinical Practice Guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America CID Aug 2011

Pneumococcal conjugate vaccine (PCV) candidates tested in pneumonia efficacy studies to date

PCV7-CRM

Serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F

CRM_{197} diphtheria variant carrier protein

PCV9-CRM

4, 6B, 9V, 14, 18C, 19F, 23F | 1, 5

CRM_{197} diphtheria variant carrier protein

PCV11-D,T

Serotypes: 4(T),6B(D),9V(T),14(D),18C(D),19F(T),23F(T) | 1(T), 5(T), 7F(T) | 3(D)

Tetatnus and diphtheria toxoid carriers

PHiD-CV

Serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F | 1, 5, 7F | Cross reactivity: 6A, 19A

NTHi protein D — T — D — NTHi protein D

Prevnar™ and Prevenar13™ SPCs; Park IH, et al. J Infect Dis. 2008;198(12):1818-22; http://www.who.int/immunization/sage/target_product_profile.pdf; *Synflorix*™ SPC, 2009; PIDJ supplement volume 28, Number 4, April 2009; Vesikari T, et al. Pediatr Infect Dis J 2009;28(4 Suppl):S66-76; Prymula R, et al. Lancet 2006;367:740-748; Lucero et al PIDJ 2009

Status of PCVs tested in pneumonia efficacy studies to date

PCV7-CRM	Serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F		
	CRM_{197} diphtheria variant carrier protein		
PCV9-CRM	4, 6B, 9V, 14, 18C, 19F, 23F	1, 5	
	CRM_{197} diphtheria variant carrier protein		
PCV11-D,T	Serotypes: 4(T),6B(D),9V(T),14(D),18C(D),19F(T),23F(T)	1(T), 5(T), 7F(T)	3(D)
	Tetatnus and diphtheria toxoid carriers		
PHiD-CV	Serotypes: 4, 6B, 9V, 14, 18C, 19F, 23F	1, 5, 7F	Cross reactivity: 6A, 19A
	NTHi protein D — T — D — NTHi protein D		

NEVER LICENSED

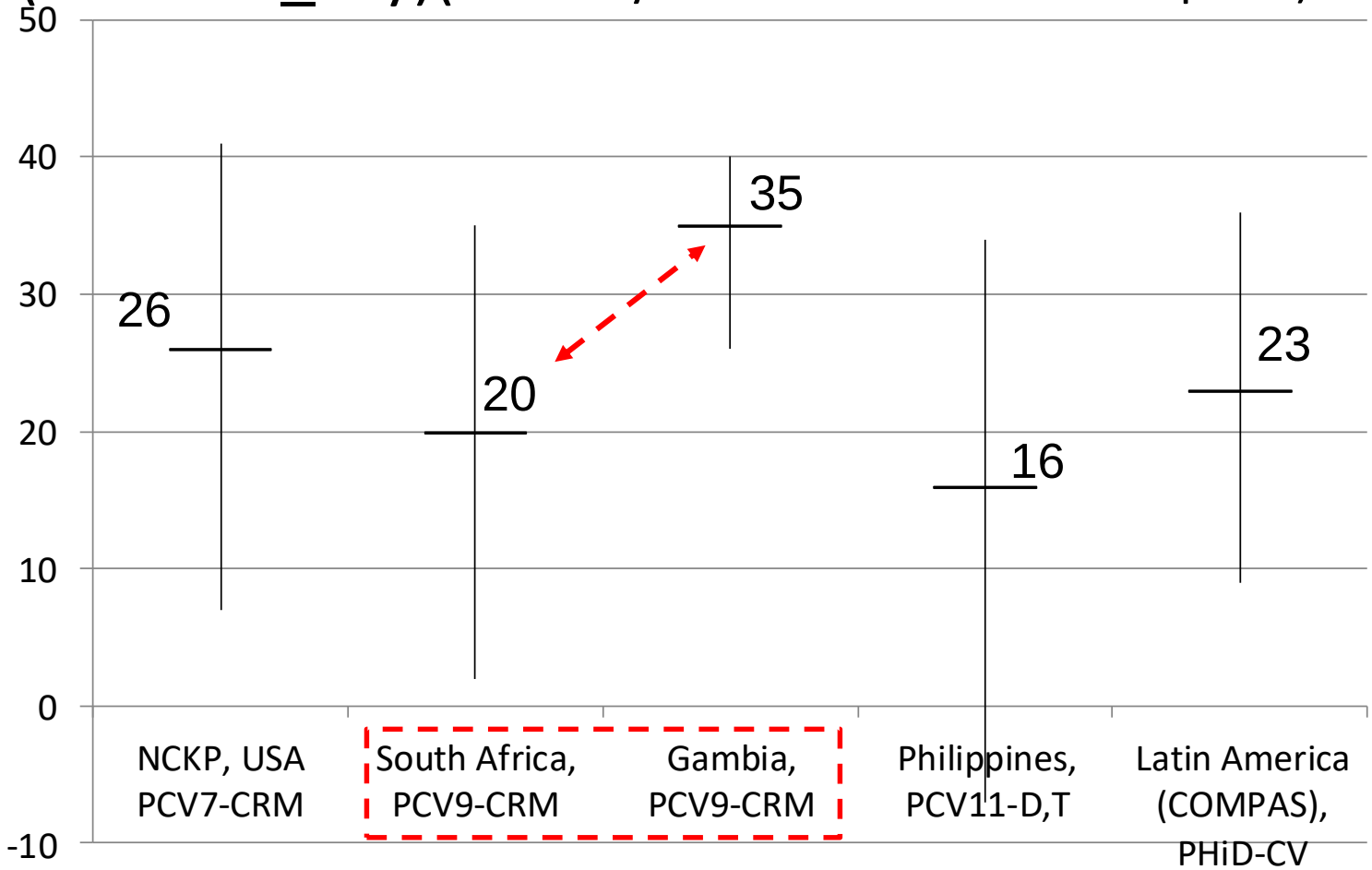
Prevnar™ and Prevenar13™ SPCs; Park IH, et al. J Infect Dis. 2008;198(12):1818-22; http://www.who.int/immunization/sage/target_product_profile.pdf; *Synflorix*™ SPC, 2009; PIDJ supplement volume 28, Number 4, April 2009; Vesikari T, et al. Pediatr Infect Dis J 2009;28(4 Suppl):S66-76; Prymula R, et al. Lancet 2006;367:740-748; Lucero et al PIDJ 2009

Key characteristics of efficacy trials assessing PCV impact on pneumonia

	N.California (NCKP),USA[1]	Soweto, South Africa[2]	The Gambia[3]	Bohol, The Philippines[4]	COMPAS LatinA[5]
Study vaccine	**7vCRM Wyeth/Pfizer, Licensed**	**9vCRM** Wyeth/Pfizer, Not licensed	**9vCRM** Wyeth/Pfizer, Not licensed	**11vDT** Sanofi-Pasteur, Not licensed	**PHiD-CV GSK, Licensed**
Cohort size	~37,800	~39,800	~17,400	~12,200	~24,000
Immunization schedule	2, 4, 6 & 12-15 mos	6, 10, 14 wks	6, 10, 14 wks	6, 10, 14 wks	2, 4, 6 & 15-18 mos
Setting	Urban	Urban	Rural	Rural/Urban	Mainly urban

1.Black S. 2002 PIDJ 2.Klugman KP, 2003, NEJM 3. Cutts F2005 Lancet 4.Lucero MG,2009 PIDJ
5..Tregnaghi et al., XIV SLIPE, Punta Cana, May 2011; Tregnaghi et al., 29th ESPID, The Hague, June 2011

Lesson #1: 4 different PCVs demonstrated similar efficacies against consolidated pneumonia (children ≤ 2 y)(ITT analyses of WHO CXR-AC endpoint)



Similar efficacies despite different immunogenicity, study settings, vaccine formulations, etc

Most striking point-estimate difference is between the two PCV9-CRM studies

1. Black et al., Ped Infect Dis J, 2002; 2. Klugman et al., New Engl J Med, 2003; 3. Cutts et al., Lancet, 2005; 5. Hansen et al., Ped Infect Dis J, 2006; 4. Lucero et al., Ped Infect Dis J 2009; **1**.Tregnaghi et al., XIV SLIPE, Punta Cana, May 2011; **2**.Tregnaghi et al., 29th ESPID, The Hague, June 2011

Why is effect of conjugates on alveolar consolidated pneumonias limited to 23-37%?

Is pneumococcus not as important as we thought?

- Results likely underestimate importance of pneumococcus:
  - Vaccine efficacy undoubtedly <100%
  - There are other pneumococcal serotypes besides those preventable by vaccine formulations
  - Possibly some replacement disease by non-vaccine types or other pathogens

- Involvement of other pathogens?

Lesson #2: PCVs also prevent pneumonias <u>without</u> alveolar consolidation as defined by WHO

		N.California (NCKP,US)[1,2] 7vCRM	Soweto, South Africa (HIV negative)[3,4,5] 9vCRM	The Gambia[6] 9vCRM	Bohol, The Philippines[7] 11vDT	COMPAS Latina[8] PHiD-CV**
Clinical CAP	**ITT**	**6%** (-2,11)	**7%** (-1,14)	**6%** (1, 11)	**1%** (-10,7)	**7%** (2,12)

Relatively small percentages which translate into a large number of cases prevented due to high burden of clinical CAP

ITT: Intent-to-treat analysis

**Final results (from conclusive interim analysis)

1.Black S. 2002 PIDJ; 2.Hansen J, 2006 PIDJ; 3.Klugman KP, 2003, NEJM
4.Madhi SA, Klugman KP, 2007 Vaccine; 5. Madhi 2005 CID; 6. Cutts F2005 Lancet
7. Lucero MG,2009 PIDJ

[8]Tregnaghi et al., 29th ESPID, The Hague, June 2011; 2.10PN-PD-DIT-028; NCT00466947

Lesson #3: PCVs prevent virus-associated pneumonia (presumably due to superinfection with pneumococcus)

Clinical diagnosis	All children[e] Vaccine $n = 18,245$	Placebo $n = 18,268$	Efficacy (95% CI)	*P* value
Total number of pneumonia cases[a]	544	679	20 (10, 28)	0.00009
Pneumonia with alveolar consolidation[b]	251	303	17 (2, 30)	0.03
Pneumonia without identified virus[c]	419	486	14 (2, 24)	0.03
Any identified virus-associated pneumonia[d]	160	231	31 (15, 43)	0.0004
Influenza A	31	56	45 (14, 64)	0.01
RSV	90	115	22 (–3, 41)	0.08
PIV types 1–3	24	43	44 (8, 66)	0.02
Adenovirus	14	15	7 (–94, 55)	0.9

South Africa study with PCV9-CRM

A role for *Streptococcus pneumoniae* in virus-associated pneumonia

Shabir A Madhi[1], Keith P Klugman[1,2] & The Vaccine Trialist Group

VOLUME 10 | NUMBER 8 | AUGUST 2004 NATURE MEDICINE pp.811-813

Lesson #4: In 3 of the 4 trials where data are available, effect on pneumonia seemed to wane rapidly

Age Group (mos)	VE %	95% CI
Northern California (Black PIDJ 2002)		
<12	32.2	(3.3-52.5)
12-24*	~15%	
➢24	9.1	(-30.9-36.8)
Philippines (Lucero PIDJ 2009)		
3-11	34.0	(4.8-54.3)
12-23	2.7	(-43.5-34.0)
South Africa (Klugman NEJM 2003; personal communication S. Madhi)	"Loss of efficacy >24 mo also seen"	
The Gambia (Cutts Lancet 2005)		
3-11	35	(19 -48)
12-23	38	(25-49)
24-29	32	(-10-58)
Latin America (Tregnaghi SLIPE 2011)	Age-stratified data not yet available	

*12-24 mo efficacy estimated from published <24 mo efficacy of 23.4 % (5.2-38.1)

Possible explanations:

1. Waning vaccine efficacy?—but IPD efficacy through 5y in S. Africa trial; NCKP trial included booster dose
2. Other pathogens/serotypes are more important causes of consolidated pneumonia in older ages?

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What other pathogens cause lower respiratory tract infections in children?

At least 1 respiratory pathogen was identified in 79% (122 of 154) of the patients.

US study

TABLE 1. Pathogens Identified in 154 Hospitalized Children with Community-Acquired LRIs

Pathogen	No. of Episodes			Total No. of Episodes, %
	No Coinfection	Coinfection With Bacteria*	Coinfection With Viruses*	
Bacteria				
S pneumoniae	35	12	21	68 (44)
S pyogenes	0	2	2	2 (1)
S aureus	0	2	0	2 (1)
S milleri	0	1	1	1 (<1)
M pneumoniae	11	6	8	21 (14)
C pneumoniae	6	7	7	14 (9)
M tuberculosis	1	1	0	2 (1)
C trachomatis	0	0	0	0
Viruses				
Influenza A or B	9, 1	16, 6	10, 6	26 (17), 7 (5)
RSV	6	11	8	20 (13)
Parainfluenza 1–3	6	12	10	20 (13)
Adenovirus	2	9	5	11 (7)
Rhinovirus	1	2	2	5 (3)
Enteroviruses	0	1	0	1 (<1)

* The categories of coinfection with bacteria and with viruses are not mutually exclusive.

Our inability to attribute all episodes of LRIs in children to known pathogens likely resulted from a combination of clinical and technical limitations such as administration of antibiotic therapy before acquisition of fluid samples, absence of specific tests for *Moraxella catarrhalis*[19] and *Haemophilus influenzae*,[20] absence of convalescent serology in 21% of patients, and inability to identify novel pathogens such as metapneumovirus

Epidemiology and Clinical Characteristics of Community-Acquired Pneumonia in Hospitalized Children

Ian C. Michelow, MBBCh, DTM&H*; Kurt Olsen, BS*; Juanita Lozano, MD*; Nancy K. Rollins, MD‡; Lynn B. Duffy, MT (ASCP)§; Thedi Ziegler, PhD‖; Jaana Kauppila, MD¶; Maija Leinonen, PhD#; and George H. McCracken, Jr, MD*

Pediatrics 2004 113: 701-7

Does non-typable *H. influenzae* play a significant role in pediatric lower respiratory tract infections?

***The role of NTHi in childhood pneumonia remains unclear**, although indirect evidence, including its high prevalence in nasopharyngeal colonization studies [37,38], its demonstrated pathogenic potential in AOM [8,11], another mucosal infection, as well as preliminary evidence of involvement in bronchitis [39] suggests some role in lower respiratory disease in children.* (Hausdorff & Dagan, Vaccine 2008)

Bronchoalveolar lavage isolation of NTHi in non-CF children with LRTIs

Country	Reference	Cases	% NTHi
France	Le Bourgeois, Chest, 2002	Recurrent Wheezing	50%
US	Saito, Ped Pulm, 2006	Recurrent Wheezing	26%
Spain	Romero, ERS, 2009	Persistent bacterial bronchitis	28%
Belgium	De Schutter, CID 2011	Refractory or recurrent bronchopneumonia Persistent radiological abnormalities or wheezing	43%
UK	Marguet, Am J Resp, 1999	Chronic cough	43%
	Davidson, ERS, 2010	Persistent respiratory symptoms	30%
Australia	Hare, J Ped, 2010	Bronchiectasis	47%
Greece	Mammas, ERS, 2010	Prolonged purulent bronchitis	61%

NTHi from Children with Pneumonia: Asian Data

Serotypes of *H influenzae* isolated from children with pneumonia in developing countries

	Children	*H influenzae*			
		Total	Type b	a, c, d, e, f	Non-typable
Lung aspiration*					
Papua New Guinea[2]	83	34†	7 (21%)	9 (26%)	18 (53%)
Gambia[4]	51	9	3 (33%)†	2 (22%)	4 (44%)
Gambia[5]	94	8	5 (63%)†	1 (13%)	2 (25%)
Total (average %)	228	51	39%	20%	41%
Blood culture					
Pakistan[6]	1106	95†	61 (64%)	0	34 (36%)
Philippines[7]	?	40	23 (58%)	3 (8%)	14 (35%)
Papua New Guinea[8]	1024	92	57 (62%)	14 (15%)	21 (23%)
Pakistan[9]	595	81†	6 (7%)	13 (16%)	62 (76%)
Total (average %)		308	48%	10%	43%

*Excluding isolates from blood culture.
†Some *H influenzae* isolates were not serotyped.

"There is an urgent need in developing countries for vaccines against all strains of *H influenzae, serotypeable and non-serotypeable.* »

Shann F. THE LANCET • Vol 354 • October 30, 1999

Conclusions

- Recent global estimates place pneumococcal pneumonia as a top cause of childhood morbidity and mortality

- Pneumococcal conjugate vaccines have proven highly effective in preventing pneumonia, even some thought to be caused by viruses
  - Nonetheless, there is room for improvement

- Other pathogens likely also important causes of pediatric lower respiratory tract infections