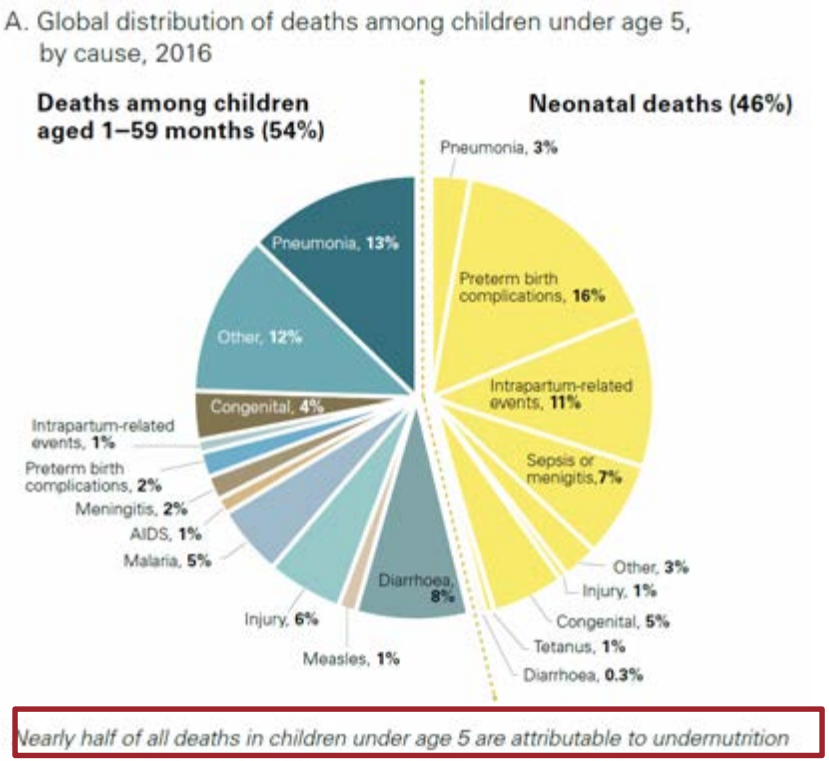
PNEUMOCOCCAL VACCINE UPDATE

Gail L. Rodgers, MD
Bill & Melinda Gates Foundation

PNEUMONIA IS THE LEADING KILLER OF CHILDREN

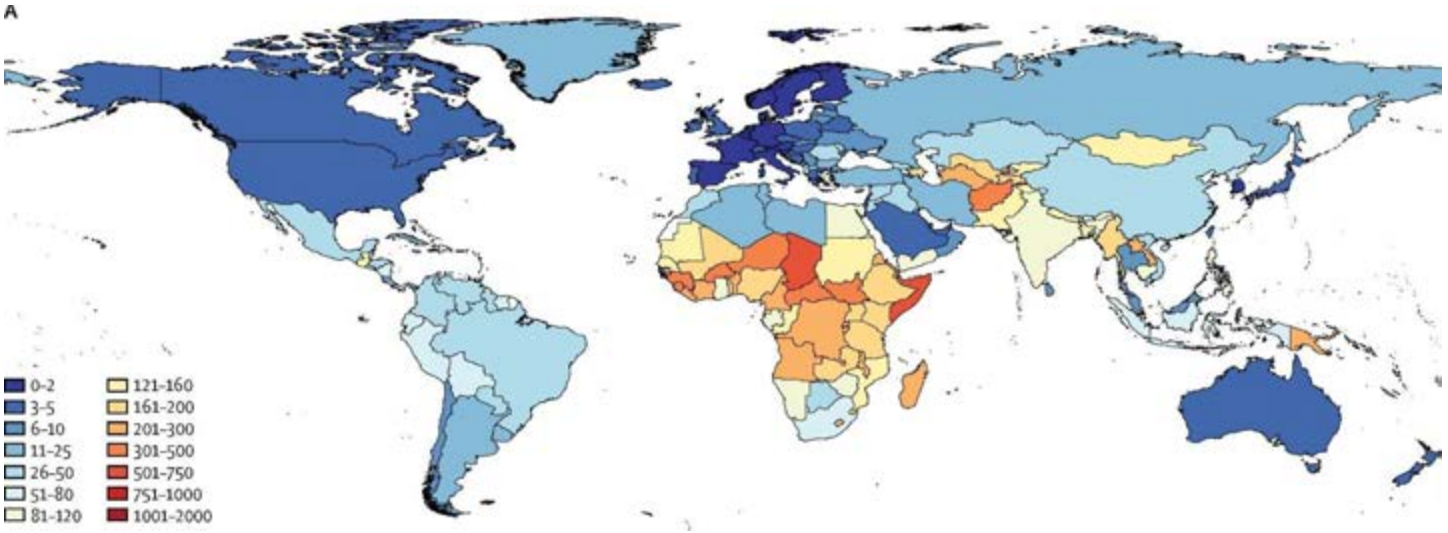
- 5.6 million (5.4-6.0 million) under-5 deaths occurred in 2016; translating to 15,000 per day
- Pneumonia continues to be a leading cause of death in children; causing ~16% of all deaths in under-5 in 2016
- 2.6 million newborns died in 2016 – 7,000 per day, accounting for 46% of all under-5 deaths
- 11% of all <5 deaths are neonatal deaths due to infectious causes: **pneumonia**, tetanus, meningitis, and sepsis



UN Inter-agency Group for Child Mortality Estimation. Levels and Trends in Child Mortality, Report 2017

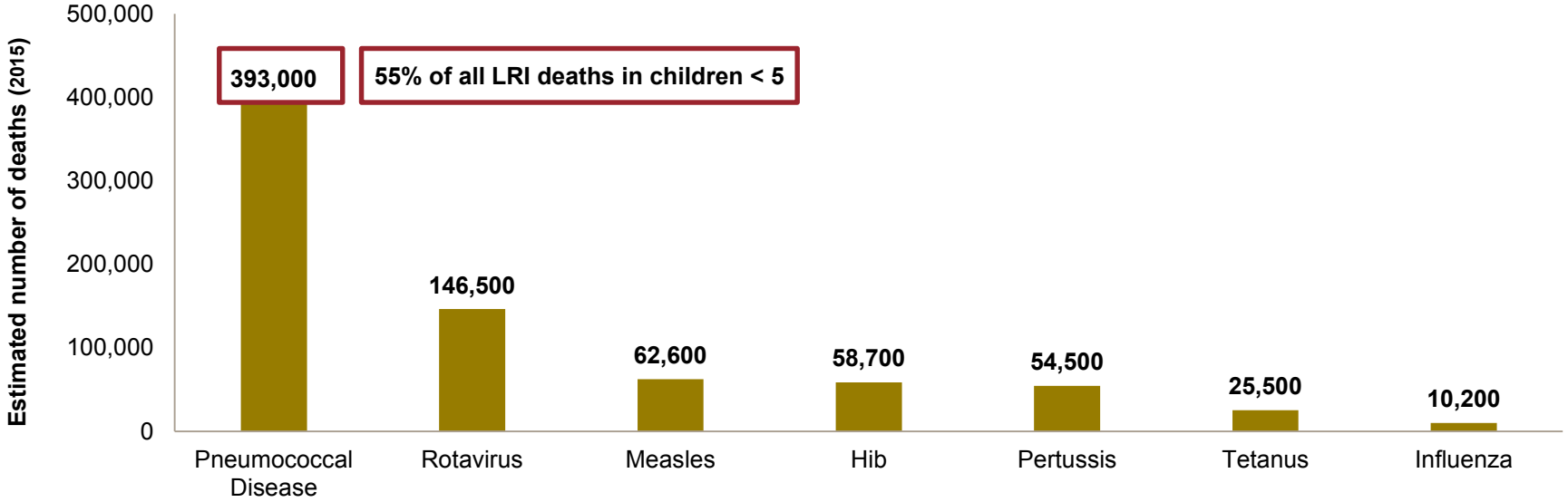
GLOBAL BURDEN OF LRI MORTALITY IN CHILDREN < 5

- LRIs are estimated to cause 2.74 million deaths per year
- Over 700,000 are in children < 5 years of age



GBD 2015 LRI Collaborators. *Lancet Infect Dis* 2017;17:1133-61.

NUMBER OF CHILDREN <5 YEARS OLD WHO DIE ANNUALLY FROM VACCINE-PREVENTABLE DISEASE



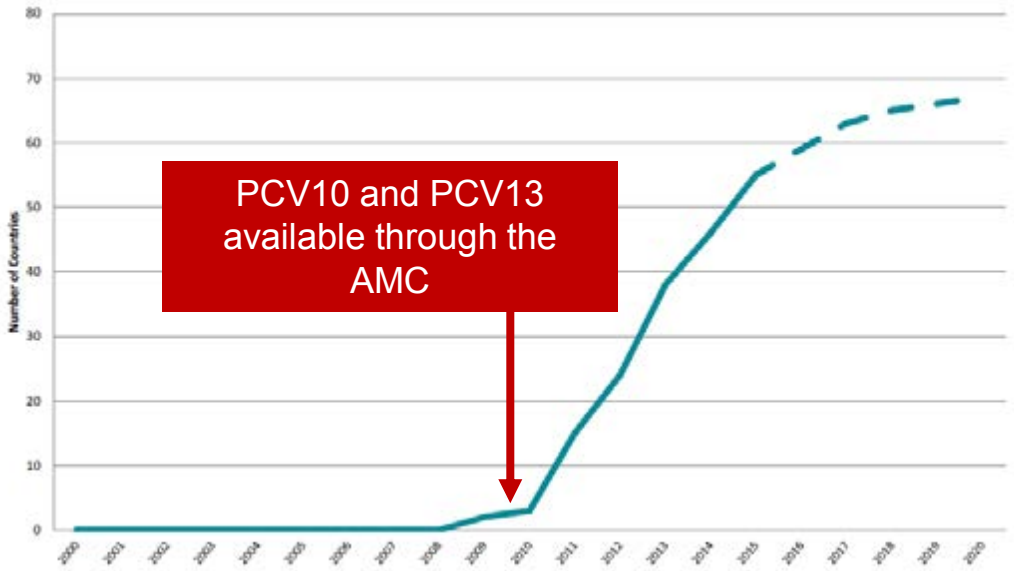
***Streptococcus pneumoniae* is the leading cause of vaccine-preventable deaths globally**

Wang et al. *Lancet* 2016;388:1459 –1544.
GBD 2015 LRI Collaborators. *Lancet Infect Dis* 2017;17:1133-61.

PREVENTION OF PNEUMOCOCCAL DISEASE

- **Vaccine Delivery**
- **Evidence Generation for Sustainable Pneumococcal Immunization Programs**
- **Vaccine Development**

GAVI PCV INTRODUCTION BY YEAR



The pneumococcal Advanced Market Commitment has allowed low income countries to introduce PCVs almost simultaneously to high income countries, thus avoiding the usual 15-20 year lag in new vaccine introductions

http://www.jhsph.edu/research/centers-and-institutes/ivac/vims/ivac-vims-report-2015-jan.pdf

GLOBAL PCV INTRODUCTION STATUS - 2016

http://www.view-hub.org/viz/
http://www.gavi.org/

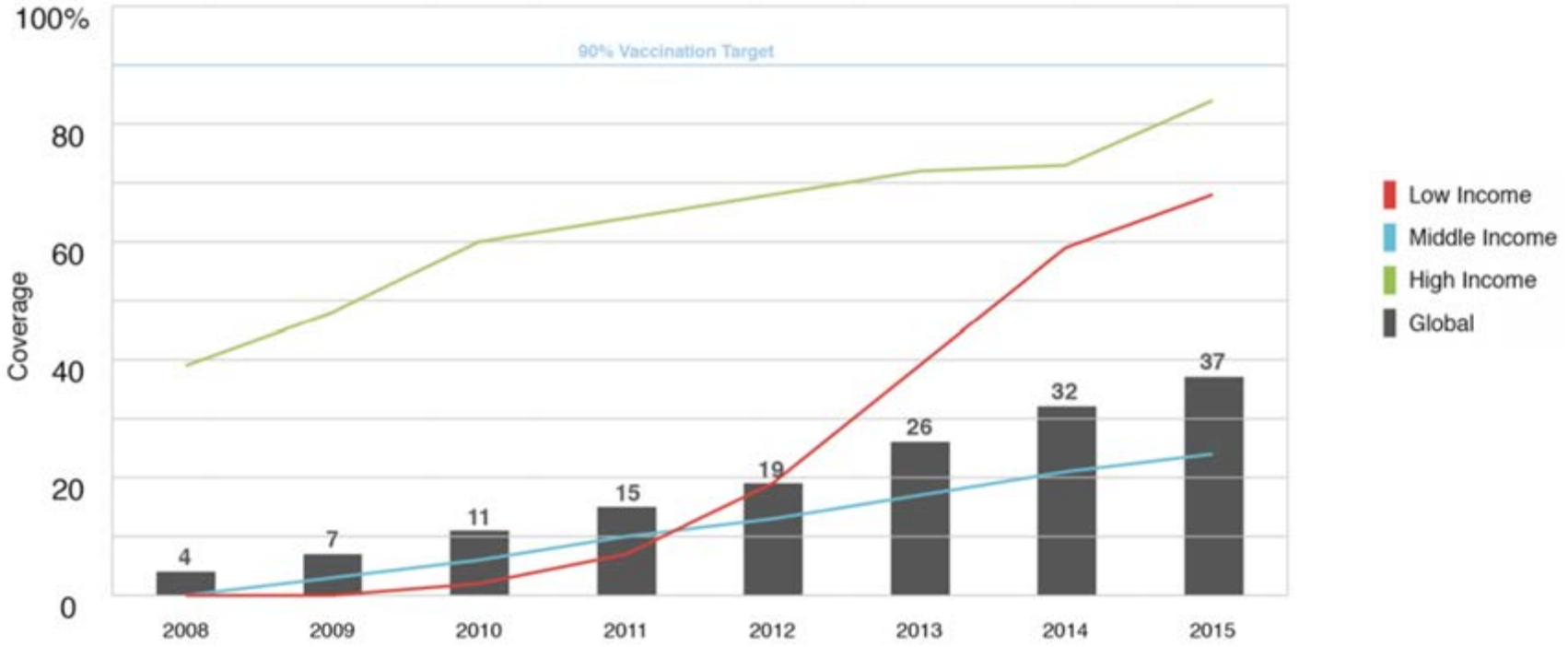
GLOBAL PCV INTRODUCTION STATUS - 2016

	Gavi	Global
National Introductions (as of Dec 2016)	57 (78%)	139 (72%)
Surviving Infants Have Access to PCV	41M (51%)	69M (52%)
Surviving Infants Immunized with PCV	29M (35%)	53M (37%)
Top 10 PCV Countries with Most Unimmunized/underimmunized Infants*	Nigeria, Pakistan, Bangladesh, DRC, Uganda, Ethiopia, Angola, Nepal, Kenya, Afghanistan	Philippines, Venezuela, Poland, South Africa, U.S., Dominican Republic, Brazil, Spain, Mexico, Argentina

*India not included because it introduced PCV in 2017

http://www.view-hub.org/viz/
http://www.gavi.org/

GLOBALLY, GAVI'S RATE OF PCV INTRODUCTIONS IS NEARLY 2X THAT OF THE MIDDLE INCOME COUNTRIES



PREVENTION OF PNEUMOCOCCAL DISEASE

- **Vaccine Delivery – expand coverage of existing vaccines**
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EVIDENCE GENERATION FOR SUSTAINABILITY

Assessment of Global PCV Impact
Ensure that country relevant data is obtained
Evaluate both approved PCVs (PCV10 and PCV13)
Assess endpoints: IPD, Pneumonia, NP Carriage
Evaluate: Direct and Indirect Effects, Serotype Replacement

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Assess endpoints: IPD, Pneumonia, NP Carriage
Evaluate: Direct and Indirect Effects, Serotype Replacement
Assess other potential effects of PCV vaccination

THE BANGLADESH STORY: POTENTIAL UNACCOUNTED FOR BENEFITS OF VACCINATION

Emergency Room at Dhaka Shishu Children's Hospital

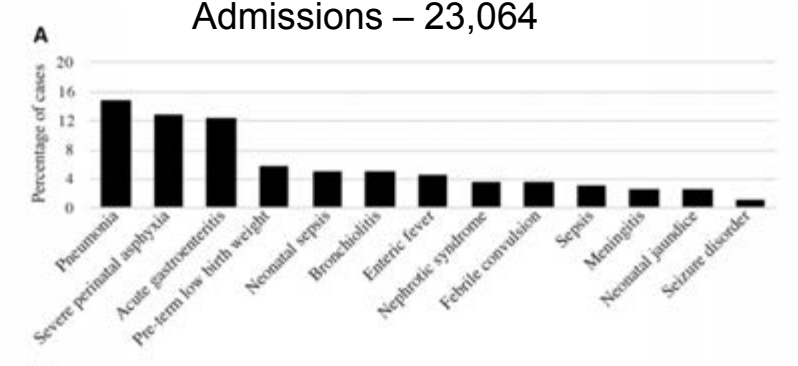
Overcrowding Leads to Bed Sharing

Photographs courtesy of Dr. Samir Saha

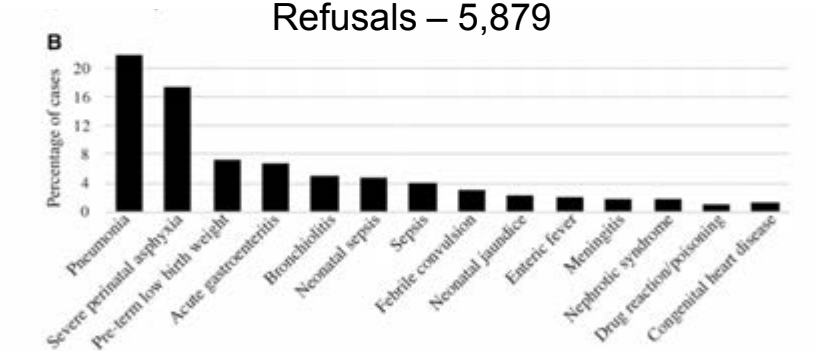
THE BANGLADESH STORY: POTENTIAL UNACCOUNTED FOR BENEFITS OF VACCINATION

Admissions (A) and Refusals (B) at Dhaka Shishu Children's Hospital 2015-2016

Admissions – 23,064



Refusals – 5,879



- Analysis of effect of rotavirus vaccination: in addition to preventing rotavirus associated diarrhea, it would result in release of 629 beds per year (11% of the refusals) with potential to impact mortality for other non-diarrheal diseases
- Analysis of effect of PCV could potentially be additive to rotavirus increasing bed availability and decreasing mortality further.

Saha S et al. *Am J Trop Hyg* 2018;98:360-3..

EVIDENCE GENERATION FOR SUSTAINABILITY

Optimize Dosing Regimens
Move from individual protection to maintenance of herd protection
Evaluate alternate dosing regimens: • **Booster containing regimens vs. primary schedule only** • **Alternate schedules: 1+1, 0+1**
Develop guidelines/policy for changing if studies yield positive results

PCV SCHEDULE – NEED FOR A BOOSTER DOSE

A booster dose provides better reduction in vaccine serotype (VT) carriage and improved impact on serotype 1 disease in children and adults

- Comparison of countries with similar times since introduction (5-6 years) and coverage rates (>90%) show similar reduction in IPD (>90%) but almost 3X greater VT carriage reduction when a booster is given

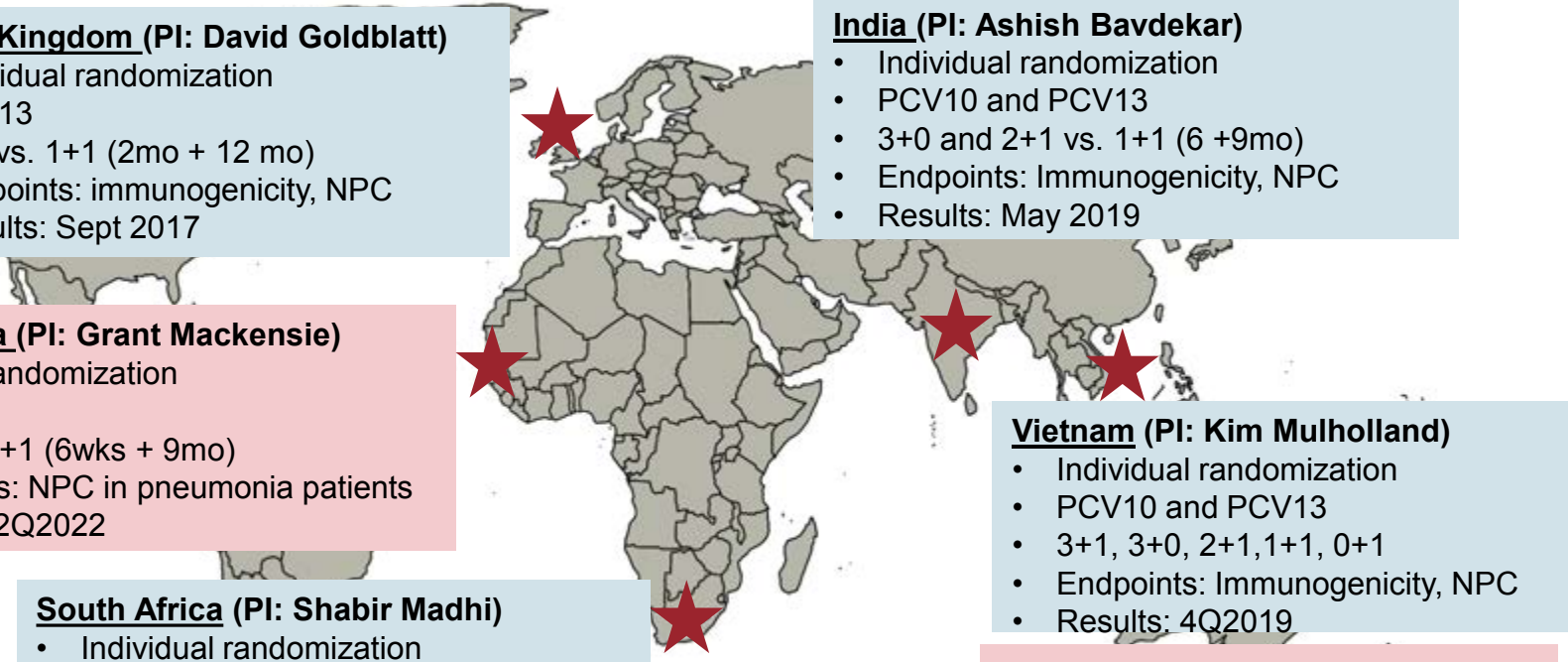
	The Gambia (3+0)[1]		South Africa (2+1)[2]	
IPD	<1 year	No VT disease in last 21 mo	<5 years	94% reduction in VT IPD; 98% reduction in serotype 1
	<5 years	>90% decrease		
	All ages	Effect on serotype 1 variable	>25 years	74% reduction in VT IPD; 93% reduction in serotype 1
VT Carriage	**13%**		**4.2%**	

- Despite PCV coverage of 85%, using a 3+0 schedule, after 3 years of introduction, Ghana experienced a serotype 1 meningitis outbreak (incidence increased from <5 to 300/100,000). Majority of cases were in those >5 and thus unimmunized; median age of 20.

Data suggest that a 2+1 or potentially a 1+1 schedule could provide better herd impact than a 3+0 schedule

[1] Mackensie G. data from OPP1020327
[2] Von Gottberg A et al. Abstract submitted to ISPPD 2018, Melbourne Australia

BMGF SPONSORED ALTERNATE PCV DOSING STUDIES



United Kingdom (PI: David Goldblatt)
- Individual randomization
- PCV13
- 2+1 vs. 1+1 (2mo + 12 mo)
- Endpoints: immunogenicity, NPC
- Results: Sept 2017

India (PI: Ashish Bavdekar)
- Individual randomization
- PCV10 and PCV13
- 3+0 and 2+1 vs. 1+1 (6 +9mo)
- Endpoints: Immunogenicity, NPC
- Results: May 2019

The Gambia (PI: Grant Mackensie)
- Cluster randomization
- PCV13
- 3+0 vs. 1+1 (6wks + 9mo)
- Endpoints: NPC in pneumonia patients
- Results: 2Q2022

Vietnam (PI: Kim Mulholland)
- Individual randomization
- PCV10 and PCV13
- 3+1, 3+0, 2+1,1+1, 0+1
- Endpoints: Immunogenicity, NPC
- Results: 4Q2019

South Africa (PI: Shabir Madhi)
- Individual randomization
- PCV10 and PCV13
- 2+1 vs. 1+1 (6 or 14 wks +9mo)
- Endpoints: immunogenicity, NPC
- Results: 2Q2019

Vietnam (PI: Lay-Myint Yoshida)
- Cluster randomized
- PCV10: 3+0, 2+1,1+1, 0+1
- Endpoints: NPC, pneumonia
- Results: 1Q2021

UK 2+1 VS. 1+1 STUDY

- PCV13 given at **2+1** (2, 4 and 12 mo) or **1+1** (3 and 12 mo)

Post Primary GMCs obtained at 5 mo of age

	Post-primary group 1 (2 m, 4 m; N_{max}=97) *	Post-primary group 2 (3 m; N_{max}=102) *	p value†
1	1·25 (1·07–1·45)	0·57 (0·47–0·69)	<0·0001
3	0·28 (0·23–0·33)	0·27 (0·21–0·34)	0·66
4	1·08 (0·93–1·26)	0·43 (0·36–0·51)	<0·0001
5	0·90 (0·77–1·07)	0·29 (0·24–0·35)	<0·0001
6A	1·25 (1·00–1·56)	0·13 (0·11–0·15)	<0·0001
6B	0·26 (0·20–0·33)	0·09 (0·08–0·09)	<0·0001
7F	2·46 (2·11–2·88)	0·81 (0·69–0·95)	<0·0001
9V	0·73 (0·60–0·89)	0·18 (0·16–0·21)	<0·0001
14	4·19 (3·23–5·43)	1·13 (0·90–1·40)	<0·0001
18C	0·90 (0·73–1·11)	0·22 (0·19–0·27)	<0·0001
19A	1·56 (1·25–1·96)	0·33 (0·27–0·39)	<0·0001
19F	4·54 (3·80–5·42)	0·64 (0·54–0·76)	<0·0001
23F	0·43 (0·34–0·54)	0·09 (0·08–0·10)	<0·0001

Goldblatt D et al. *Lancet Infect Dis* 2018;18:171-9.

UK ALTERNATE PCV DOSE STUDY (1+1 VS. 2+1)

Post Booster GMCs obtained at 13 mo of age

	Post-boost group 1 (2 m, 4 m, 12 m; N_{max}=91)*	Post-boost group 2 (3 m, 12 m; N_{max}=86)*	Group 2 to group 1 ratio‡	Adjusted‡ p value
1	3·07 (2·58–3·64)	8·92 (7·42–10·73)	2·73 (2·13–3·51)	<0·0001
3	0·61 (0·51–0·74)	0·62 (0·52–0·74)	0·93 (0·72–1·19)	0·57
4	2·55 (2·15–3·04)	3·43 (2·86–4·12)	1·29 (1·01–1·64)	0·047
5	1·74 (1·49–2·03)	2·11 (1·81–2·45)	1·15 (0·93–1·42)	0·20
6A	8·62 (7·29–10·21)	6·36 (5·34–7·58)	0·69 (0·54–0·87)	0·002
6B	6·19 (5·10–7·50)	2·39 (1·94–2·94)	0·36 (0·27–0·47)	<0·0001
7F	3·98 (3·42–4·62)	3·36 (2·93–3·86)	0·82 (0·67–1·01)	0·059
9V	2·34 (2·00–2·73)	2·50 (2·16–2·88)	1·02 (0·83–1·26)	0·85
14	10·49 (8·84–12·44)	16·9 (13·54–21·08)	1·57 (1·19–2·08)	0·002
18C	1·98 (1·70–2·30)	1·63 (1·42–1·87)	0·78 (0·64–0·95)	0·017
19A	8·38 (7·17–9·80)	8·83 (7·4–10·52)	1·00 (0·79–1·26)	0·98
19F	11·12 (9·46–13·07)	14·76 (12·54–17·37)	1·28 (1·02–1·61)	0·035
23F	2·87 (2·38–3·46)	1·72 (1·44–2·05)	0·56 (0·44–0·73)	<0·0001

Post-booster dose:

- all GMCs high (>1ug/mL) except serotype 3
- GMCs not significantly different for 5 serotypes: 3, 5, 7F, 9V, 19A
- GMCs lower in the 1+1 group for 4 serotypes: 6A, 6B, 18C, 23F
- GMCs higher in the 1+1 group for 4 serotypes: 1, 4, 14, 19F

Goldblatt D et al. *Lancet Infect Dis* 2018;18:171-9.

PREVENTION OF PNEUMOCOCCAL DISEASE

- **Vaccine Delivery – expand coverage of existing vaccines**
- **Evidence Generation for Sustainable Pneumococcal Immunization Programs**
- **Vaccine Development - develop lower cost vaccines that provide equal or greater protection**

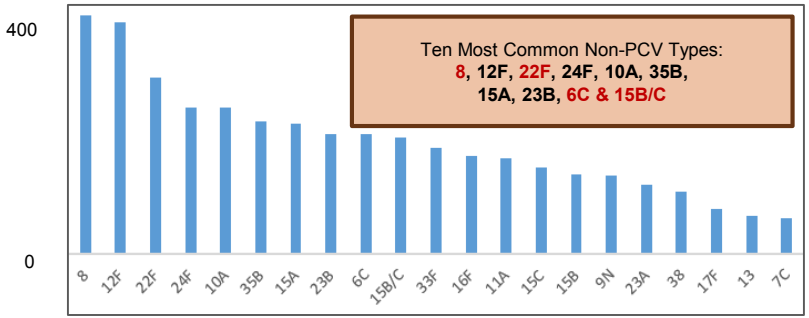
NEXT GENERATION PCV VACCINES

Investigational 10-13 Valent PCVs	
Walvax (China)	• Tetanus conjugated 13 valent PCV • Current status: applied for licensure in China
Serum Institute of India PCV10 (PNEUMOSIL)	• Goal is equal protection to currently available vaccines at affordable prices • Achieved POC in infants • Current status: Phase III
Other manufacturers in earlier stages of development	

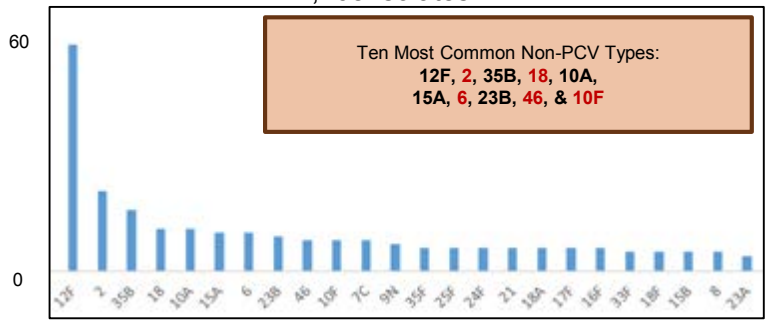
NEXT GENERATION PCV VACCINES

Most Common Non Vaccine Serotypes: 2010- 2017*

Non Gavi Countries
13,126 isolates



Gavi Countries
1,468 Isolates



Higher valency Conjugate Vaccines

- **Several in clinical development extending to 20+ valencies: Pfizer, Affinivax**
- **? Immunogenicity threshold**
- **Large number of serotypes make up the remaining pneumococcal disease, thus increasing valencies adds limited incremental protection**
- **Potential for serotype replacement continues to be present**
- **Additional serotypes most often represent those prevalent in HIC, not LIC, where burden is greatest**

University of Washington START Program, unpublished data – not for citation

FUTURE PNEUMOCOCCAL VACCINES

- **Non-conjugate vaccines (protein vaccines, whole cell vaccine)**
  - Potential to have broad coverage for all serotypes
  - PCV have set a high bar- will these need to affect disease endpoints as well as carriage and transmission?
  - Regulatory pathway potentially requires an efficacy study
  - Currently, no protein vaccine has been successful in advanced clinical development; WCV in Phase I/II
  - Replacement with potentially more pathogenic organisms a concern?

SUMMARY

- Current PCVs have had an enormous impact on disease and mortality.
- Most countries, including LICs, have introduced PCVs, but adequate coverage remains a challenge globally.
- Innovation in vaccine schedules may reduce cost and ensure sustainability of immunization programs.
- Vaccine development with higher valency PCVs and serotype independent vaccines is ongoing and have the potential to expand the reductions in disease and mortality.


THE WORK IS
COMPLICATED.
WHY WE DO IT IS NOT.