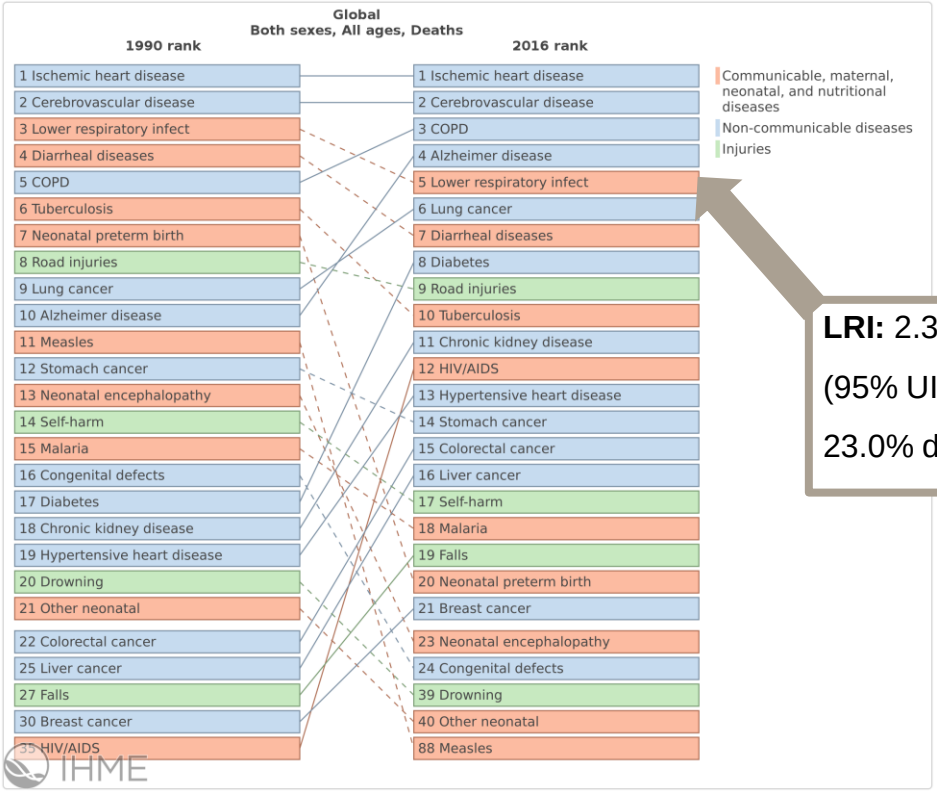
THE FUTURE OF PCV'S

GVIRF, Bangkok, Mar 2018

Keith P. Klugman MD, PhD
Director, Pneumonia Program
Bill & Melinda Gates Foundation, Seattle WA

LOWER RESPIRATORY DISEASES ARE THE LEADING INFECTIOUS CAUSE OF DEATH IN ALL AGES



LRI: 2.38 million deaths in 2016

(95% UI: 2.15-2.51)

23.0% decrease from 1990

IHME. GBD Compare Data Visualization. Univ of Washington, 2016. Available from http:// vizhub.healthdata.org/gbd-compare. (Accessed 9/26/2017)
GBD 2016 Causes of Death Collaborators. *Lancet* 2017; 390: 1151-210.

REGIONAL UNDER 5 LRI MORTALITY AND INCIDENCE PLOTTED AGAINST SDI

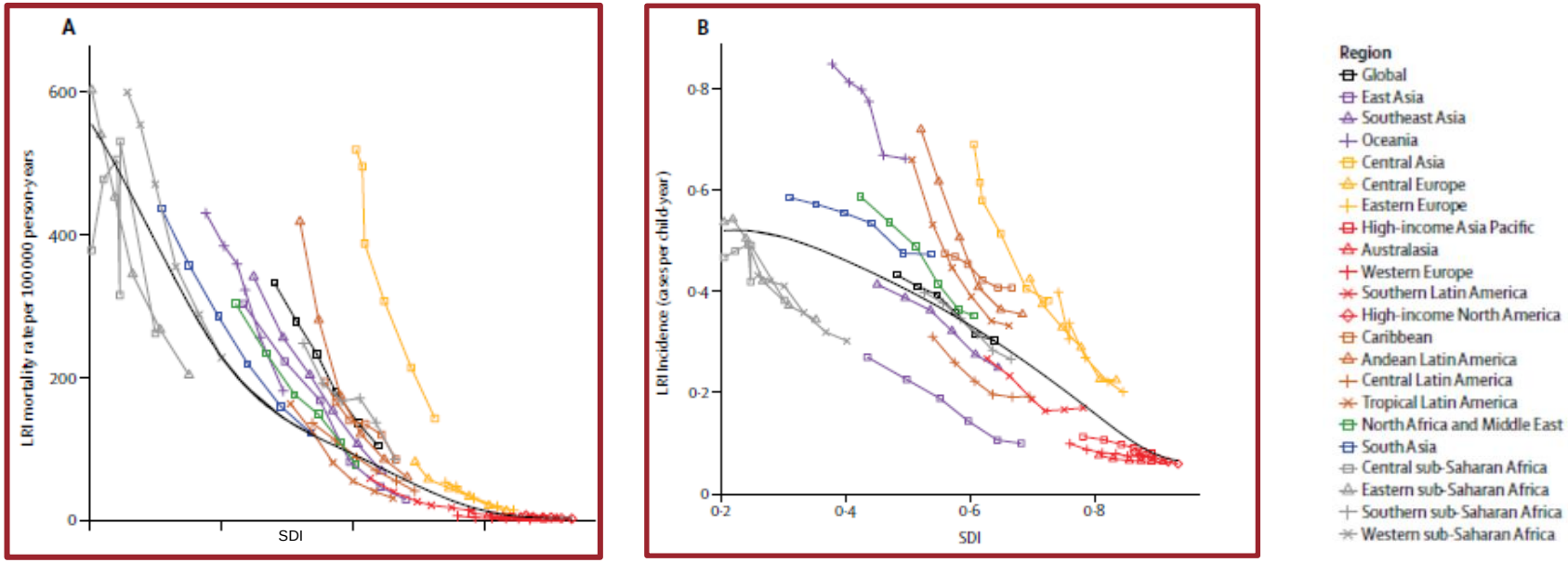


Figure 2: Under-5 LRI mortality rate per 100 000 (A) and incidence per child-year (B) is shown. Data points show 5-year increments from 1990 to 2015. The black line is a least-squares cubic spline regression, with knots at 0·4, 0·6, and 0·8, using the under-5 LRI mortality rate or incidence for each geographic location, and represents the expected rate based on SDI alone (estimates above the black line are higher than expected and those below are lower than expected). More information on the formulation and theory of the SDI can be found in the Cause of Death GBD 2015 capstone paper.5 LRI=lower respiratory tract infection. SDI=Sociodemographic Index.

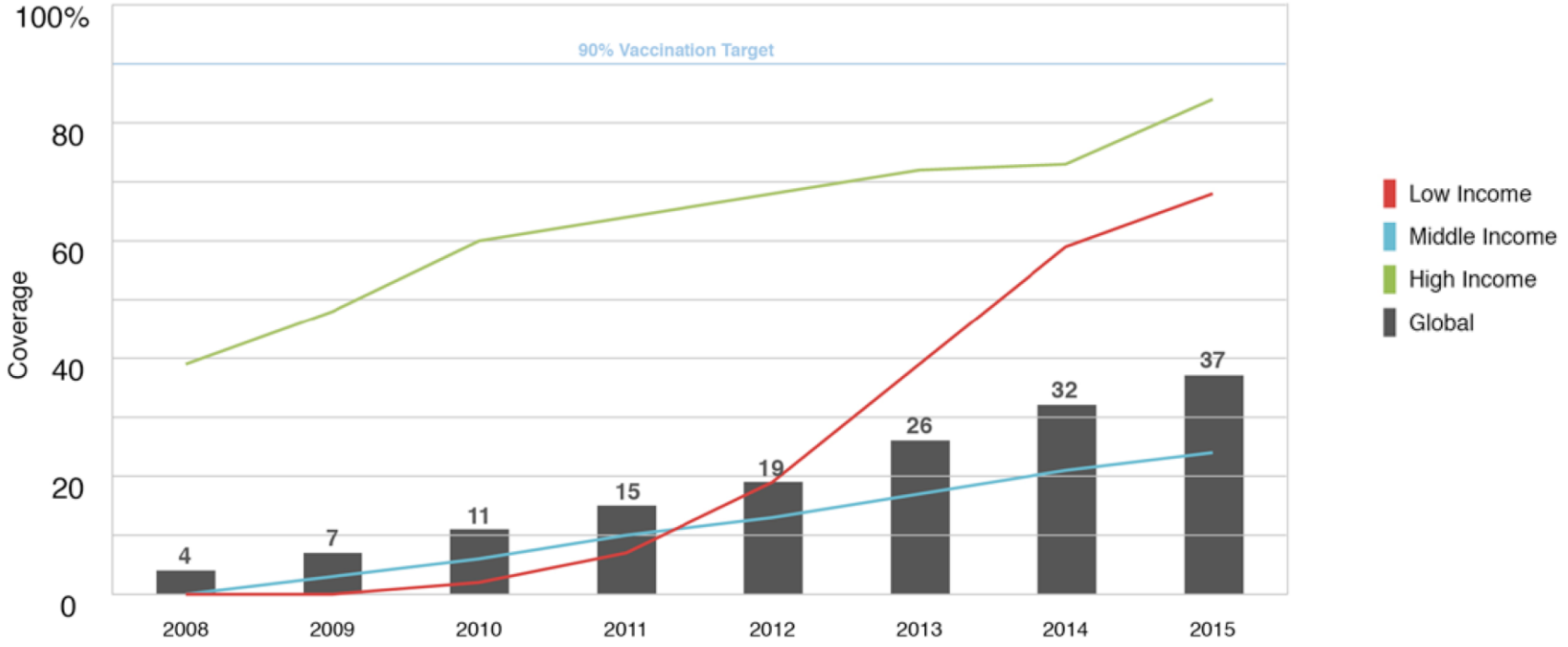
GBD 2015 LRI Collaborators. *Lancet ID* 2017; DOI: 10.1016/S1473-3099(17)30396-1

EFFICACY OF PCV AGAINST PNEUMOCOCCAL DISEASE

Disease	Vaccine	Efficacy, % (95% CI), PP
VT IPD vs VT Pneumonia		
Black S, et al. *Pediatr Infect Dis J.* 2000;19:187-195.	PCV7 3 + 1	97% (83-100)
O'Brien KL, et al. *Lancet*. 2003;362:355-361.	PCV7 3 + 1	77% (-9-95)
Klugman KP, et al. *N Engl J Med*. 2003;349:1341-1348.	PCV9[a] 3 + 0	83% (39-97) (HIV-)
Cutts FT, et al. *Lancet*. 2005;365:1139-1146.	PCV9[a] 3 + 0	71% (76-86)
Palmu AA, et al. *Lancet.* 2013 ;381:214-22	PCV10[c] 3 + 1	100% (83–100)
Palmu AA, et al. *Lancet.* 2013 ;381:214-22	PCV10[c] 2 + 1	92% (58-100)
Tregnaghi MW, et al. *Plos Med*. 2014; 11: e1001657	PCV10[c] 3 + 1	100% (74 – 100)
Bonten MJM, et al. *N Engl J Med*. 2015; 372: 1114-25 (Adults)	PCV13 1	75% (41 – 91)
Bonten MJM, et al. *N Engl J Med*. 2015; 372: 1114-25 (Adults) VT Pneumonia	PCV13 1	45% (14 – 65)
Pneumonia (CXR+) (1st episode)		
Hansen J, et al. *Pediatr Infect Dis J.* 2006;25:779-781.	PCV7	30% (11-46)
Klugman KP, et al. *N Engl J Med*. 2003;349:1341-1348.	PCV9[a]	25% (4-40)
Cutts FT, et al. *Lancet*. 2005;365:1139-1146.	PCV9[a]	37% (27-45)
Lucero MG, et al. *Pediatr Infect Dis J.* 2009;28:455-462.	PCV11[b]	23% (-1-41)
Tregnaghi MW, et al. *PloS Med.* 2014; 11: e1001657	PCV10[c]	23% (9-36)
Bonten MJM et al. *N Engl J Med.* 2015; 372: 1114-25 (Adults)	PCV13	5% (-5–14)

VT = Vaccine type; PP = Per-protocol analysis; CI = confidence interval.
[a]PCV9, investigational CRM_{197}-conjugated pneumococcal conjugate vaccine
[b]PCV11, investigational tetanus-diphtheria toxoid-conjugated pneumococcal conjugate vaccine
[C]11 Pn-PD, investigational and PCV10 licensed nontypeable *Haemophilus influenzae* protein D-conjugated pneumococcal conjugate vaccine
[d]PncOMPC, investigational pneumococcal polysaccharide-meningococcal outer membrane protein complex conjugate vaccine

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



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

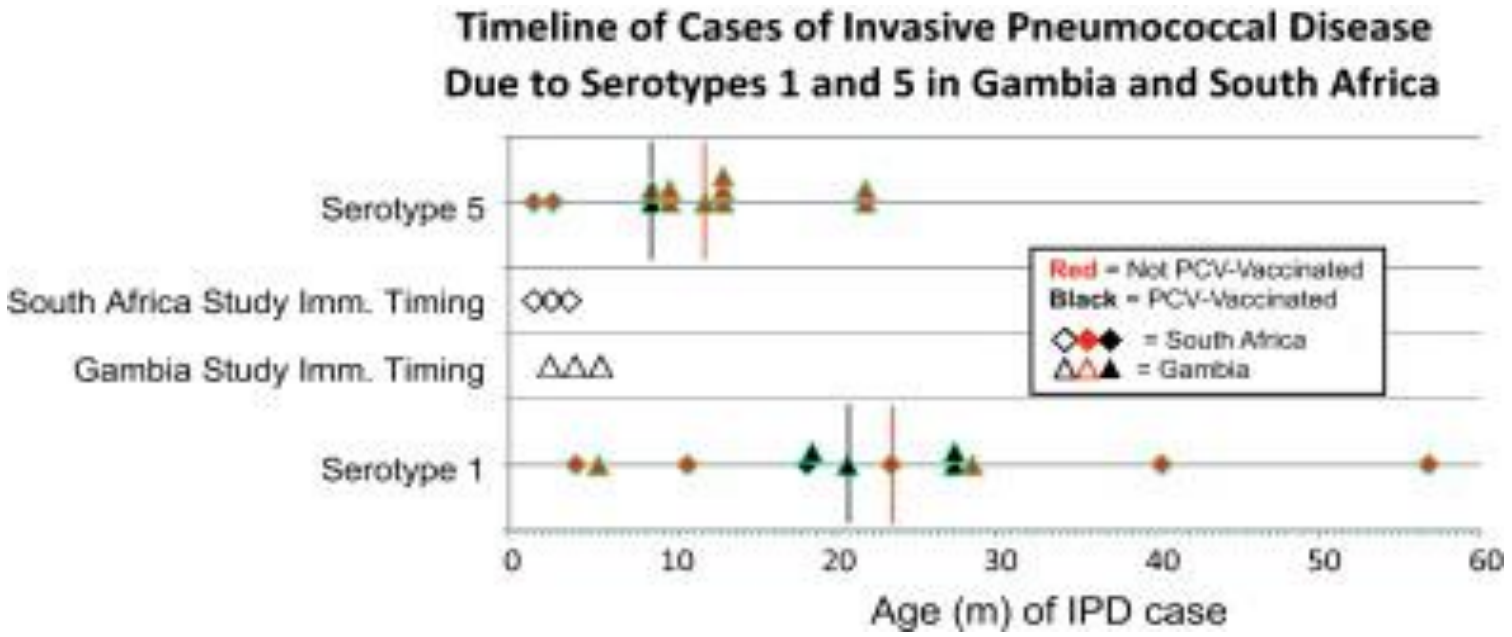
http://www.gavi.org/

EVIDENCE GENERATION FOR SUSTAINABILITY OF IMMUNIZATION PROGRAMS

Optimize PCV 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

A TALE OF SEROTYPE 1 IN TWO COUNTRIES IN AFRICA – THE GAMBIA AND SOUTH AFRICA

PCV9 Trials 3+0 Without A Booster



Klugman et al, Vaccine, 2011, 29, 3372 - 3

PCV 7 AND 13 IMPACT ON IPD IN SOUTH AFRICA: 2 + 1 SCHEDULE

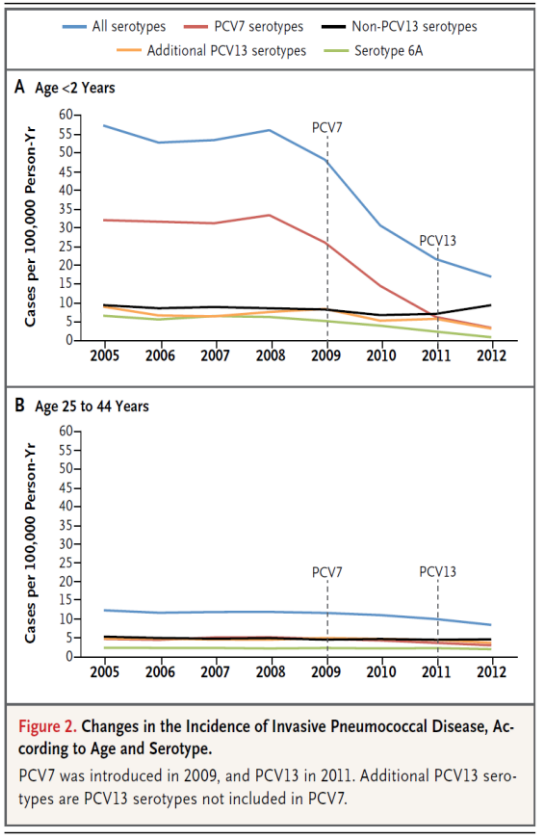
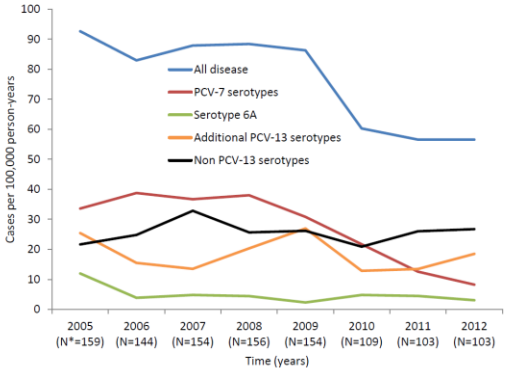


Figure 2. Changes in the Incidence of Invasive Pneumococcal Disease, According to Age and Serotype.

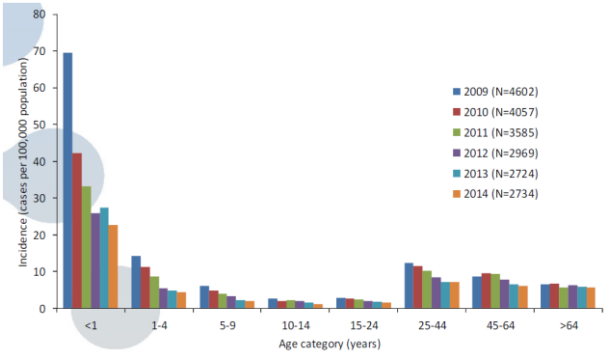
PCV7 was introduced in 2009, and PCV13 in 2011. Additional PCV13 serotypes are PCV13 serotypes not included in PCV7.

PCV Direct and Herd Impact on all Pneumococcal Disease in South Africa

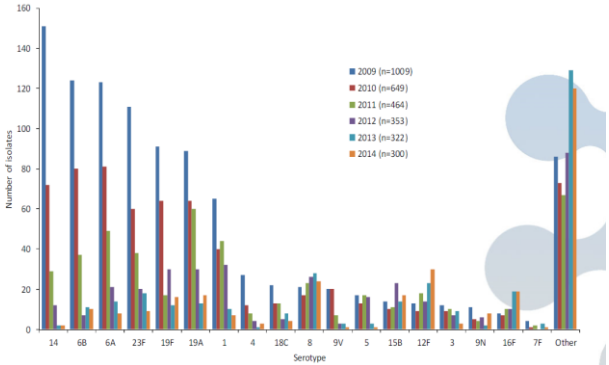


Children too young for direct protection

All ages



<5



Von Gottberg et al, NEJM, 2014, 371, 1889 – 1899; GERMS SA Annual Report 2014.

LACK OF HERD IMPACT ON SEROTYPE 1 USING PCV 13 IN GHANA USING 3 + 0 (NO BOOSTER)

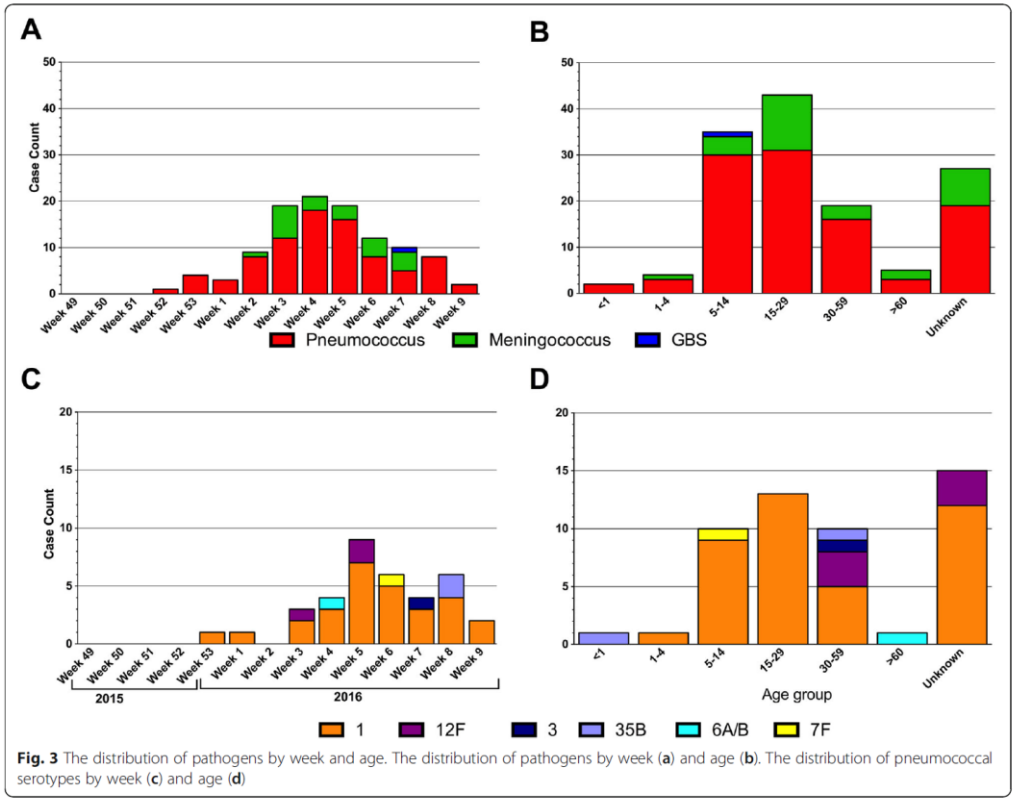


Fig. 3 The distribution of pathogens by week and age. The distribution of pathogens by week (**a**) and age (**b**). The distribution of pneumococcal serotypes by week (**c**) and age (**d**)

Kwambana – Adams et al, BMC Infect Dis, 2016, 16, 575

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] Mackenzie G. unpublished data

[2] Von Gottberg A et al. Abstract submitted to ISPPD 2018, Melbourne Australia

WANING IMMUNITY OF 3 + 0 DIRECT PROTECTION WITH AGE IN AUSTRALIA

Vaccine	Time interval	Cases N (% vaccinated)	Controls N (%vaccinated)	VE (95% CI, p)	Relative odds of VT IPD* (95% CI, p)
PCV7	up to 12 Months post last dose	36 (47.2%)	393 (78.6%)	89.4% (75.8 to 95.3%, <0.001)	Reference
	12-24 Months post last dose	33 (42.4%)	238 (64.7%)	74.0% (23.9 to 91.1%, 0.014)	2.404 (95% CI 0.782-7.392, 0.126)
	24-36 Months post last dose	30 (36.7%)	193 (56.5%)	40.7% (<-100.0 to 84.7%, 0.450)	5.620 (95% CI 1.240-25.421, 0.025)
	≥36 Months post last dose	38 (50.0%)	262 (67.9%)	16.7% (<-100.0 to 77.8%, 0.787)	4.891(95% CI 1.751-35.602, 0.007)
PCV13	up to 12 Months post last dose	48 (54.2%)	460 (78.5%)	87.1% (70.6 to 94.3%, <0.001)	Reference
	12-24 Months post last dose	50 (56.0%)	401 (75.3%)	69.6% (23.1 to 88.0, 0.012)	2.356 (95% CI 0.811-6.848, 0.115)
	24-36 Months post last dose	30 (36.4%)	169 (41.4%)	23.3% (<-100.0 to 86.1%, 0.760)	5.944 (95% CI 1.002-35.220, 0.050)

*Odds ratio for VT IPD calculated with 'up to 12 months post last dose' set as reference (1.0)

Table 3 Effectiveness of PCV7 and PCV13 against IPD due to vaccine serotypes (VT) and relative odds of VT IPD by time since receipt of the 3rd vaccine dose

Table 3: Age groups and serotypes of 13vPCV (3+0 dose) vaccine failures up to 31 December 2015

Serotype	Age group (months)					
	<12	12–<24	24–<36	36–<48	48–<60	Total
1	–	–	1	–	–	1
3	3	15	8	3	–	29
6A	–	–	1	–	–	1
7F	–	1	–	–	–	1
19A	2	38	14	6	2	62
19F	2	9	3	–	–	14
Total	**7 (6%)**	**63 (58%)**	**27 (25%)**	**9 (8%)**	**2 (2%)**	**108 (100%)**

Jayasinghe et el, *Clin Infect Dis*, Mar 8 2018, epub ahead of print
https://consultations.health.gov.au/ohp-immunisation-branch/infant-pneumococcal-vaccination-schedule-recommend/supporting_documents/Public%20Consultation%20Document%20%20Infant%20Pneumococcal%20Vaccination%20Schedule%20Recommendations.pdf

WANING IMMUNITY LEADS AUSTRALIA TO ADD A BOOSTER DOSE

Review of experience in countries with similar longevity of pneumococcal conjugate vaccine use and high quality surveillance but using alternate schedules for 13vPCV (3+1 in the USA and 2+1 in the UK): Published and unpublished data (provided in confidence by Public Health England [UK] and Centers for Disease Control and Prevention [USA]) were reviewed. The comparison across all three schedules showed better protection in children aged 1 year and older following schedules that included a booster dose in the second year of life. This is because immunity wanes following completion of the primary series; administration of a booster dose results in vigorous antibody responses that enhance the degree and duration of protection. This higher level of immunity achieved by second year of life boosting has also been associated with improved herd protection of older age groups.

https://consultations.health.gov.au/ohp-immunisation-branch/infant-pneumococcal-vaccination-schedule-recommend/supporting_documents/Public%20Consultation%20Document%20%20Infant%20Pneumococcal%20Vaccination%20Schedule%20Recommendations.pdf

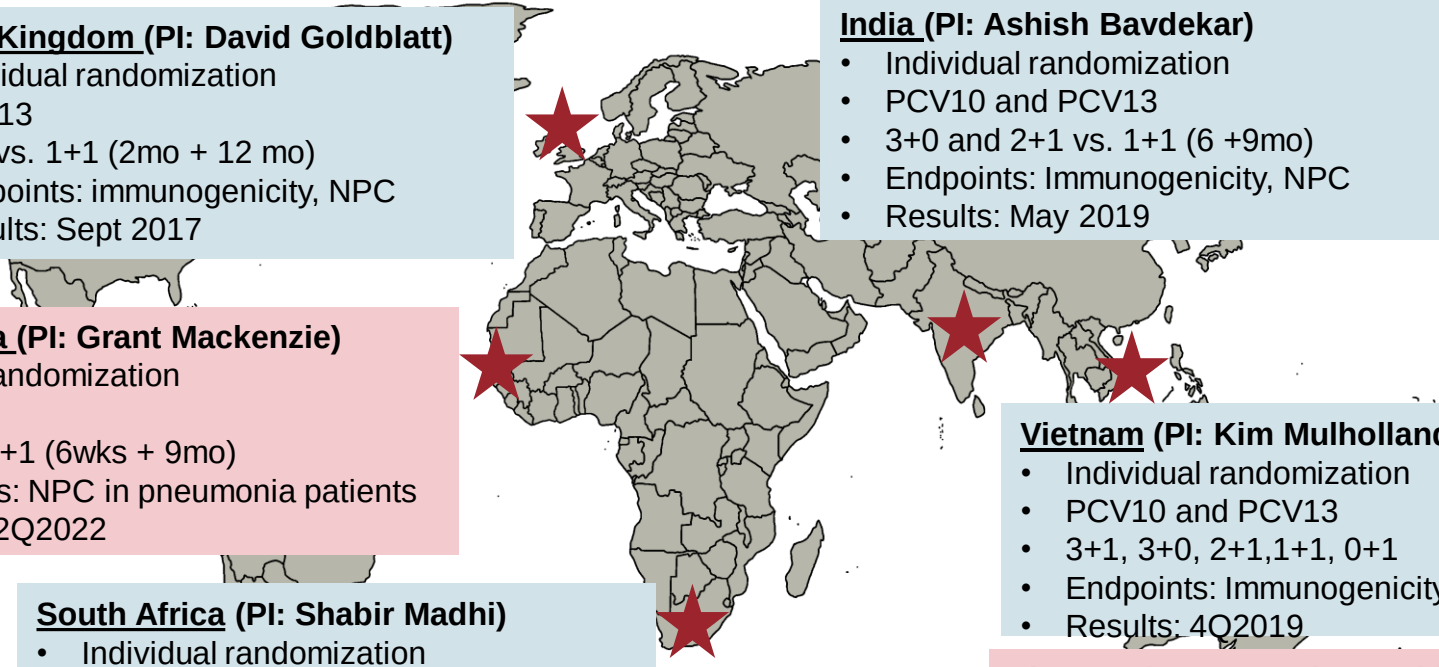
REDUCED HERD PROTECTION IN ADDITION TO WANING IMMUNITY LEADS AUSTRALIA TO ADD A BOOSTER DOSE

In the 2–4 years age group, the reduction in IPD due to 13v-non7v serotypes in Australia was statistically significantly less than that observed in the UK, after 5 years of 13vPCV use. The decline in 13v-non7v serotypes was also less in all adult age groups, especially in the 15–44 years age group. Among individual serotypes, only 19A IPD had significant reductions across all age groups in Australia, while in the UK, significant reductions were also seen in serotypes 7F and 3.

When age-specific reductions in IPD incidence rates in the UK (using a 2+1 schedule) were used to impute incidence rates in Australia, it was estimated that, had the 2+1 schedule been used in Australia over the same time period, a total of approximately 270 fewer cases of 13vPCV serotype IPD would have been observed in the fifth year after 13vPCV introduction.

https://consultations.health.gov.au/ohp-immunisation-branch/infant-pneumococcal-vaccination-schedule-recommend/supporting_documents/Public%20Consultation%20Document%20%20Infant%20Pneumococcal%20Vaccination%20Schedule%20Recommendations.pdf

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 Mackenzie)
- 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

Last updated: February 10, 2022

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.

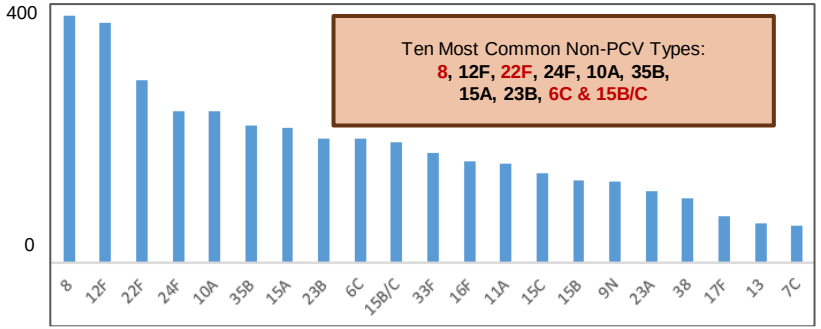
NEXT GENERATION PCV VACCINES

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: SK Chemicals, South Korea; PnuVax, Montreal; BioE, Hyderabad; Finlay Institute, Havana.	

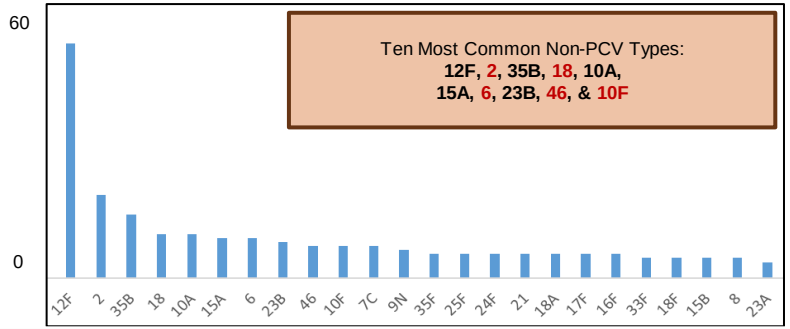
NEXT GENERATION PCV VACCINES

Most Common Non Vaccine Serotypes: 2010- 2017

Non Gavi Countries
13,126 isolates



Gavi Countries
1,468 Isolates



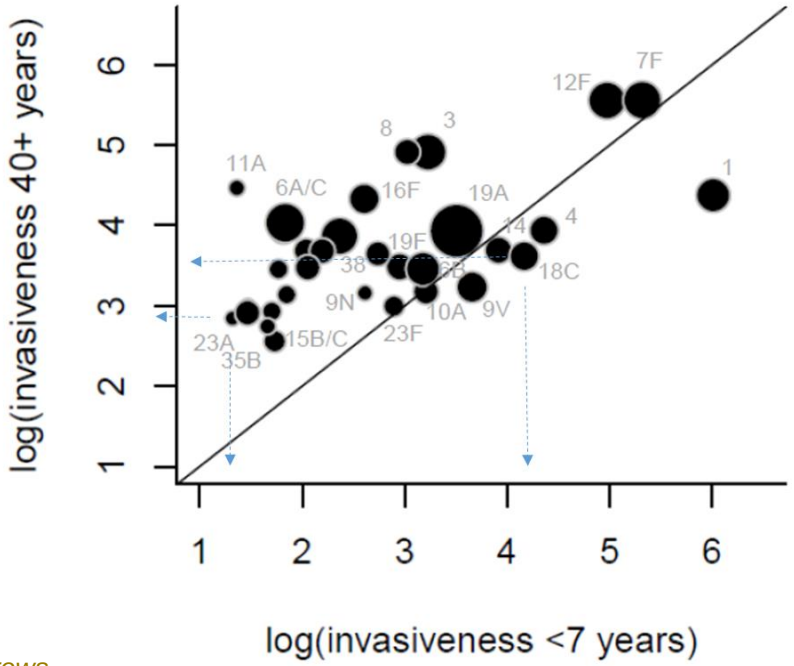
Higher valency Conjugate Vaccines

- **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

DIFFERENCES IN SEROTYPE INVASIVENESS IN CHILDREN VS ADULTS > 40 MAY HELP EXPLAIN LACK OF NET EFFECT

- Serotypes that are poorly invasive in children may still be highly invasive in older adults
- Therefore nasopharyngeal replacement of VT with NVT in adults may NOT necessarily lead to less disease in adults
- E.g., if you replace VT 18C with 23A, in children that would be 1/1000 less invasive. In adults the difference is < 10-fold.



Weinberger et al. Amer J Epidemiol, 2016; 183, Web Appendix – blue arrows contributed by Bill Hausdorff!

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

- Deaths are declining in children, but pneumonia remains a major killer of both children and adults
- Pneumococcal conjugate vaccine has rolled out in many developing countries – optimizing the number of doses and their schedule for herd protection rather than individual protection may make future PCV schedules more sustainable
- Vaccines of 20+ valency may be needed but replacement may further erode future gains
- A whole cell vaccine remains a possibility if it can impact transmission as well as protect against pneumonia


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