PNEUMOCOCCAL FINDINGS IN THE PNEUMONIA ETIOLOGY RESEARCH FOR CHILD HEALTH (PERCH) STUDY

ISPPD-0766

The PERCH Study Group

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INTRODUCTION

- Understanding the causes of pneumonia in diverse settings is critical for designing appropriate prevention and treatment approaches.
- Studies in Kenya, The Gambia, and South Africa, three of the locations where PERCH was conducted, have shown the impact of PCV introduction on pneumococcal (Spn) disease.
- The residual burden of pneumococcal pneumonia in the routine PCV-use era is unknown.
- The Pneumonia Etiology Research for Child Health (PERCH) study estimated pneumonia etiology in young children, using a novel analytic method applied to the observed microbiology results.

METHODS

- **PERCH Study**: case-control study in 7 African and Asian countries enrolling for 2 years at each site (within August 2011 to January 2014)
- **Cases**: hospitalized children aged 1 –59 months admitted with pre-2013 WHO-defined severe or very severe pneumonia
- **Controls**: age- and season-frequency matched, selected randomly from the community
- **Chest x-rays** were interpreted using the WHO method by a trained panel.
- **PCV** was in use in 4 sites: Kenya (PCV10 in 2011 with catch-up), Gambia (PCV13 in 2009), South Africa (PCV7 in 2009, PCV13 in 2011) and Mali (PCV13 in 2011)
- **Testing:** all cases & controls: nasopharyngeal/oropharyngeal (33 pathogens) & whole blood (Spn) by PCR; all cases: blood culture; case subset: lung aspirate & pleural fluid, culture & PCR
- **Analysis:** Observed measurements were integrated using Bayesian, nested partial latent class analysis, accounting for 32 other causes and assay sensitivity and specificity (**Table 2**).

TABLE 1. PERCH site characteristics and pneumococcal descriptive findings, CXR+/HIV- Cases and Controls

Site (Case N)	% PCV < 5 community coverage[1]	Case characteristics				NP Carriage in <5y community[3]		NP/OP PCR (high density)[4] PCV13 type			NP/OP PCR (high density)[4] Non-PCV13 type			Whole Blood PCR (high density)[6]			Blood Culture		Lung Aspirate[8]
		% ≥1 dose PCV	% Age < 1 y	% Very Severe	% Prior Abx[2]	% Any Spn	% PCV13	% Case	% Cont	% AF[5]	% Case	% Cont	% AF[5]	% Case	% Cont	% AF[5]	% Spn+ of all Cases	n/N (%) PCV13-type of all Spn+[7]	n (%) Spn+ of all LA tested
Kenya (282)	72	90	55	40	37	87.5	21.9	1.4	0.5	0.9	3.5	1.6	1.9	5.3	4.1	1.2	1.8	4/5 (80.0)	0/4 (0.0)
Gambia (286)	67	78	62	14	10	93.1	24.7	6.1	2.5	3.7	12.9	5.5	7.7	5.9	4.8	1.0	2.5	2/7 (28.6)	7/21 (33.3)
South Africa (435)	52	75	76	35	59	80.3	18.1	4.6	3.6	1.1	8.5	6.4	2.0	6.3	5.1	1.5	0.0	--	1/5 (20.0)
Mali (N=241)	33	72	65	40	22	82.8	27.0	14.1	6.1	8.9	11.6	8.1	3.9	9.6	3.5	6.3	2.5	3/6 (50.0)	0/10 (0.0)[11]
Zambia (208)	0	2	76	34	92	88.0	43.4	3.4	3.0	0.6	3.5	1.7	1.8	6	2.6	3.5	0.5	1/1 (100)	--
Thailand (98)	0	1	38	20	31	70.5	37.8	2.0	0.9	1.2	1.0	0.6	0.4	0	0.5	--	0.0	--	--
Bangladesh (219)	0	0	46	12	25	87.4	36.6	5.9	5.6	0.5	8.7	5.8	3.3	0.5	0	--	0.0	--	--
All Sites (1769)	34	55	63	29	41	84.0	29.3	5.5	3.2	2.4	7.9	4.3	3.3	5.4	3	--	1.1	10/19 (52.6)	8/40 (20.0)

Abbreviations: PCV, pneumococcal conjugate vaccine; Abx, antibiotics; NP, nasopharyngeal/oropharyngeal; AF, attributable fraction; Spn, pneumococcal.
1. Age-standardized pneumococcal conjugate vaccine coverage in controls. 2. Antibiotics prior to blood collection. 3. Pneumococcal NP/OP PCR carriage among controls, age-standardized to an <5 year old population. 4. Pneumococcal NP/OP PCR high density defined as > 6.9 $\log_{10}$ copies/ml.
5. Attributable fraction defined as case prevalence x (1-1/aOR), where aOR is odds ratio adjusted for age in months and site (for all-site results only).
6. Pneumococcal WB PCR high density defined as > 2.2 $\log_{10}$ copies/ml. 7. One Mali blood culture positive case was missing serotyping data; the NP ST (23F) was used in place of the blood culture serotype given high concordance between NP and blood culture ST at that site. In Kenya, two cases were positive on blood culture for a ST in PCV13 but not PCV10 (ST 19A and ST 6A). 8. Restricted to those specimens obtained within 3 days of admission.

TABLE 2. Sensitivity and specificity of laboratory measures used in integrated analysis, by antibiotic use

Specimen	Sensitivity[1]			Specificity
	No abx	Prior abx	Unknown	
Blood culture	5-20%	1-13%	1-20%	100%
NP/OP PCR	50-90%	15-55%	--	1-Control prevalence
Whole blood PCR	12-65%	--	--	1-Control prevalence

Abx = antibiotics.
[1]Sensitivity priors were adjusted (reduced) if there was prior antibiotic exposure (blood culture and NP/OP PCR) or low blood volume (blood culture only).

FIGURE 1: Etiologic fraction of CXR+ severe/very severe pneumonia caused by pneumococcus in The Gambia

Violin plots estimate the etiologic fraction probability distribution, reflecting both the uncertainty in the observed measurement and uncertainty in the measurement sensitivity.

Abbreviations: NP/OP, nasopharyngeal/ oropharyngeal; WB, whole blood; HD, high density (NP/OP: >6.9 $\log_{10}$ copies/mL, WB: ≥2.2 log10 copies/mL); CI, credible interval.

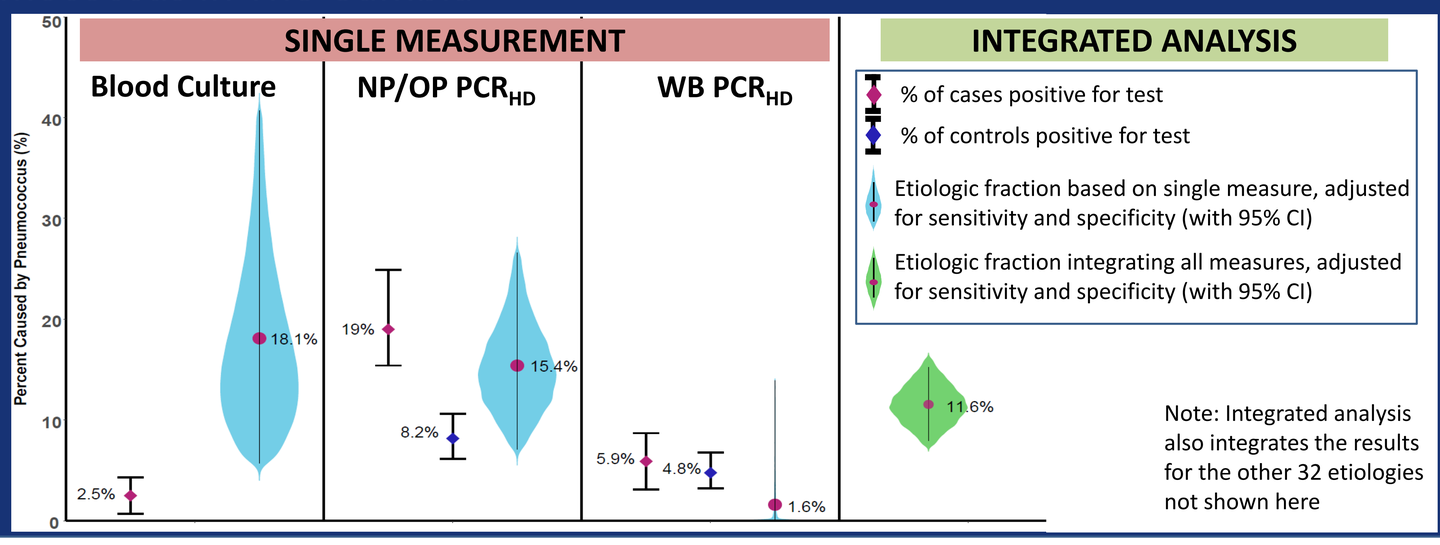
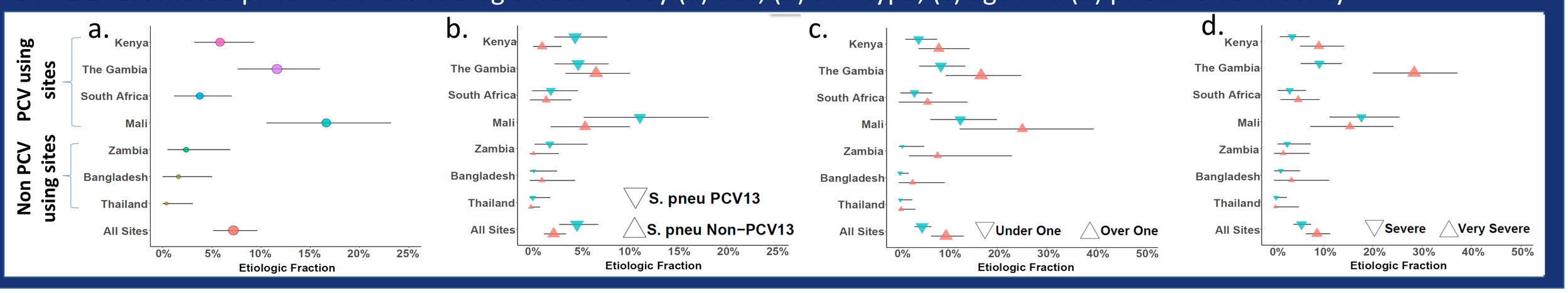


FIGURE 2. Estimated pneumococcal etiologic fractions by (a) site, (b) serotype, (c) age and (d) pneumonia severity



RESULTS

- NP/OP carriage prevalence in the community was high at all sites (range 70-93%); PCV13-type carriage was lower at PCV-using sites (range 18-27% vs. 37-43%) (**Table 1**).
- ST1 and ST5 carriage in cases was low (site range: ST1 0%-0.9%, ST5 0%-0.7%).
- Having high density NP/OP pneumococcal carriage was associated with case status at all sites, though only significant at 3 sites (Kenya, Mali, The Gambia).
- Pneumococcus was the commonest pathogen among positive lung aspirate specimens (73%; 8/11) and positive blood-cultures (34%; 19/56), and also common among positive pleural fluid specimens (42%; 5/12).
- **Figure 1** illustrates the integrated analysis for estimating pneumococcal etiologic fraction (EF) for The Gambia:
  - Using only blood culture and accounting for low sensitivity, EF=18.1%. The wide 95%CI (5.7%-40.7%) reflects uncertainty in both sensitivity (assumed between 5-20%) and small number of positives (n=7).
  - Using only high density NP/OP PCR and accounting for sensitivity and specificity (1-control prevalence), EF=15.4% (7.1%-26.6%).
  - Using only WB PCR and accounting for sensitivity and specificity (1-control prevalence), EF=1.6% (0.0%-13.9%).
  - When all measurements are integrated (also accounting for evidence of etiology due to other pathogens), EF=11.6% (7.6%-15.9%) **(Figure 1 green right panel)**.
- Across all PERCH sites, we estimate the etiologic fraction of pneumonia attributed to pneumococcus to be 7.2% (95% CI: 5.1, 9.6) (**Figure 2a**).
  - Varied by site: <2% (Bangladesh, Thailand) to 12-17% (The Gambia, Mali)
  - More was attributed to PCV13-type (4.8%) then non-PCV13-type (2.5%)
  - Was higher for children ≥1 year (9.5% vs 4.7%) and for very severe pneumonia (8.7% vs 5.6%)
- Lowering the test sensitivities by half increased the pneumococcal EF to 10.8%. (8.1%-13.8%)

CONCLUSION

- Among children hospitalized with severe/very severe pneumonia, pneumococcus was estimated to be an important, but not predominant, etiology, varying greatly by geographic setting and to a lesser extent by age and severity.
- Vaccine-type pneumococcal disease was still present at PCV-using sites 1-3 years after introduction.
- In mature PCV-use settings with optimized vaccination strategies (e.g., schedules, products, coverage), pneumococcus will likely play an even smaller role in severe/very severe pneumonia etiology.

Funding

PERCH was supported by grant 48968 from The Bill & Melinda Gates Foundation to the International Vaccine Access Center, Department of International Health, Johns Hopkins Bloomberg School of Public Health.

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