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Supplementary appendix

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I. Supplementary Tables and Figures, Descriptive

Supplementary Table 1. Pneumonia Etiology Research for Child Health site and country characteristics

Site-level characteristics				Country-level characteristics							
Site	**Country**	**Urban/ Rural**	**PERCH Enrollment Dates**	**2012 Population, Thousands[a]**	**2012 GNI Per Capita, US$[a]**	**2012 U5 Mortality Rate[a]**	**2012 Infant Mortality Rate[a]**	**2012 HIV Infection Prevalence Among Women 15–24 Years Old[a]**	**Malaria Incidence Rate[b]**	**Hib Vaccine Introduction Date[c]**	**PCV Introduction Date[c]**
Dhaka ---------- Matlab	Bangladesh	Urban ---------- Rural	January 2012 - December 2013	154,695	840	41	33	<0.1	…	July 2009	March 2015 (post-PERCH)
Basse	Gambia	Rural	November 2011 - October 2013	1,791	510	73	49	0.5[d]	…	May 1997	August 2009
Kilifi	Kenya	Rural	August 2011 - November 2013	43,178	840	73	49	3.6	0.19	January 2001	February 2011
Bamako	Mali	Urban	January 2012 - January 2014	14,854	660	128	80	0.3 [d]	0.37	January 2007	March 2011
Soweto	South Africa	Urban	August 2011 - August 2013	52,386	7,610[e]	45	33	19.9 [d]	0.00	January 1999	April 2009
Sa Kaeo, Nakhon Phanom	Thailand	Rural/ periurban	January 2012 – January 2014	66,785	5,210	13	11	0.3	…	Not routine	Not routine
Lusaka	Zambia	Urban	October 2011 - October 2013	14,075	1,350	89	56	4.6 [d]	0.33	February 2004	May 2013[f]

Abbreviations: GNI, gross national income; Hib, *Haemophilus influenzae* type b; HIV, human immunodeficiency virus; PCV, pneumococcal conjugate vaccine; U5, under 5.

[a] Applies to country. Source: United Nations Children's Fund, State of the World's Children 2014 (https://www.unicef.org/sowc2014/numbers/).

[b] Applies to country. Source: Roll Back Malaria Partnership (http://www.rollbackmalaria.org/partnership/wg/wg_monitoring/docs/annexes_ARFek4.pdf; accessed 30 November 2011).

[c] Applies to country. Source: International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. Vaccine Information Management System (VIMS) Global Vaccine Introduction Report, [December 2015]. http://www.jhsph.edu/research/centers-and-institutes/ivac/vims/. Accessed [10 March 2017].

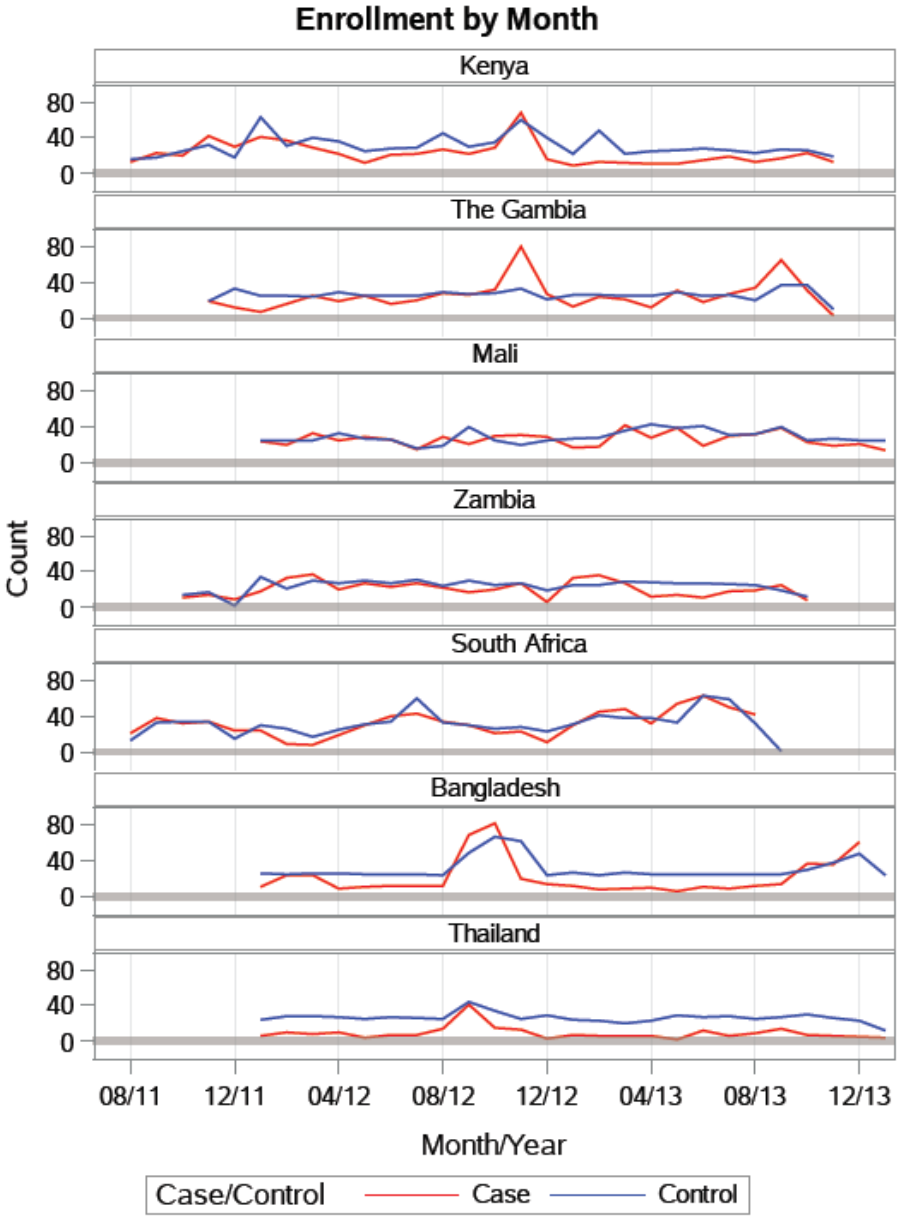
[d] HIV infection prevalence amongst women 15-49 was 29.7% in South Africa (2013), 15.1% in Zambia (2013-2014), 2.1% in The Gambia (2013), and 1.3% in Mali (2012-2013). Source for South Africa data: 2013 National Antenatal Sentinel HIV Prevalence Survey South Africa (https://www.health-e.org.za/wp-content/uploads/2016/03/Dept-Health-HIV-High-Res-7102015.pdf).

[e] This number reflects the country-level GNI per capita. Study setting has high unemployment and low income, with 38% of households in Soweto living on < $2 per day. [STATS SA 2011 Census, Available at: http://www.statssa.gov.za/?page_id=4286&id=11317].

[f] Introduced in Lusaka, Zambia in July 2013 (3 months prior to end of enrollment at the site).

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Figure 1: Case and control enrollment by month and site



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Enrolment at the Kenya site was minimal from December 2012-February 2013 because of a nurses' strike and was therefore extended for three additional months, to complete 24 enrolment months; consequently, a third pneumonia high season period (September/October) was included (S-Figure 1). Enrolment pauses lasting 3-4 weeks occurred at the Zambia, South Africa, and Mali sites due to logistical issues; enrolment was extended at these sites accordingly but did not impact the number of pneumonia high seasons during which enrolment occurred.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Table 2: World Health Organization classifications of pneumonia severity

		PERCH	World Health Organization				
			2000 Management of the Child with a Serious Infection or Severe Malnutrition		2005 Pocket Book of Hospital Care for Children		2013 Pocket Book of Hospital Care for Children
	Cough or Difficulty breathing +		Text	Table	Text	Table	
Non-Severe Pneumonia*	Elevated Respiratory Rate	n/a	✓	✓	✓	✓	✓
	Crackles on auscultation	n/a		✓			
Severe Pneumonia*	LCWI	✓	✓	✓	✓	✓	✓
	Nasal Flaring	-	✓	-	✓	-	
	Grunting	-	✓[1]	-	✓[1]	-	
Very Severe pneumonia**	Central Cyanosis	✓	✓	✓	✓	✓	✓
	Head Nodding	✓	✓	✓	✓[2]	✓	✓[3]
	Inability to Feed/Drink	✓	✓	✓	✓	✓	✓
	Vomiting Everything	✓	✓	-	✓	-	-
	Convulsions	✓[4]	✓[5]	-	✓[5]	-	✓[5]
	Lethargy or Unconsciousness	✓	✓	-	✓	-	✓
	Grunting	-	-	-	-	-	✓
	Nasal Flaring	-	-	-	-	-	✓[3]
	'Severe respiratory distress'	-	✓	✓	✓	✓	✓
	Hypoxemia	-	-	-	-	-	✓
	Very severe LCWI	-	-	-	-	-	✓

*In 2013 Pocket Book of Hospital Care for Children, children with lower chest wall indrawing (LCWI) and no danger signs/signs of respiratory distress (and without HIV, severe malnutrition and other underlying conditions) now considered non-severe pneumonia along with children with elevated respiratory rate and recommended for home care.

**'Very severe' pneumonia now called 'severe' pneumonia in 2013 pocketbook for hospital care.

[1] In young infants.

[2] Head nodding not specifically stated under definition for severe pneumonia in text of 2005 Pocket Book of Hospital Care for Children, but 'severe respiratory distress' is. And, elsewhere in manual, head nodding is included as a sign of 'severe respiratory distress'. Page 17 defines severe respiratory distress as very fast, labored breathing with use of auxiliary muscles for breathing (head nodding). Child appears to tire easily and is not able to feed because of respiratory distress.

[3] Head nodding and nasal flaring not specifically stated under definition for severe pneumonia in 2013 Pocket Book of Hospital Care for Children, but 'severe respiratory distress' is. And, elsewhere in manual (page 4, e.g.), head nodding and nasal flaring are included as signs of 'severe respiratory distress' (when occurring along with labored, fast, gasping breathing). Page 4 defines severe respiratory distress as "The breathing is very laboured, fast or gasping, with chest indrawing, nasal flaring, grunting or the use of auxiliary muscles for breathing (head nodding). Child is unable to feed because of respiratory distress and tires easily."

[4] Multiple or prolonged convulsions.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Table 3: HIV infection and exposure status among PERCH cases and controls

	All Cases	CXR+ Cases	Controls
Total children enrolled			
South Africa and Zambia*	1537	790	1650
All other sites	2695	1145	3675
HIV status			
South Africa and Zambia			
Negative	1316 (85.6)	643 (81.4)	1419 (86.0)
Positive	218 (14.2)	147 (18.6)	221 (13.4)[a]
Unconfirmed	3 (0.2)	0 (0.0)	10 (0.6)
All other sites			
Negative	2280 (84.6)	969 (84.6)	3088 (84.0)
Positive	33 (1.2)	19 (1.7)	2 (0.05)
Unconfirmed	382 (14.2)	157 (13.7)	585 (15.9)
HIV exposure status among the HIV-negative children in South Africa and Zambia			
HIV exposed	432 (32.8)	220 (34.2)	393 (27.7)
HIV unexposed	834 (63.4)	397 (61.7)	1005 (70.8)
HIV Unconfirmed infection/exposure status	53 (4.0)	26 (4.0)	31 (2.2)

Abbreviations: CXR+, chest radiograph positive (consolidation and/or other infiltrate).

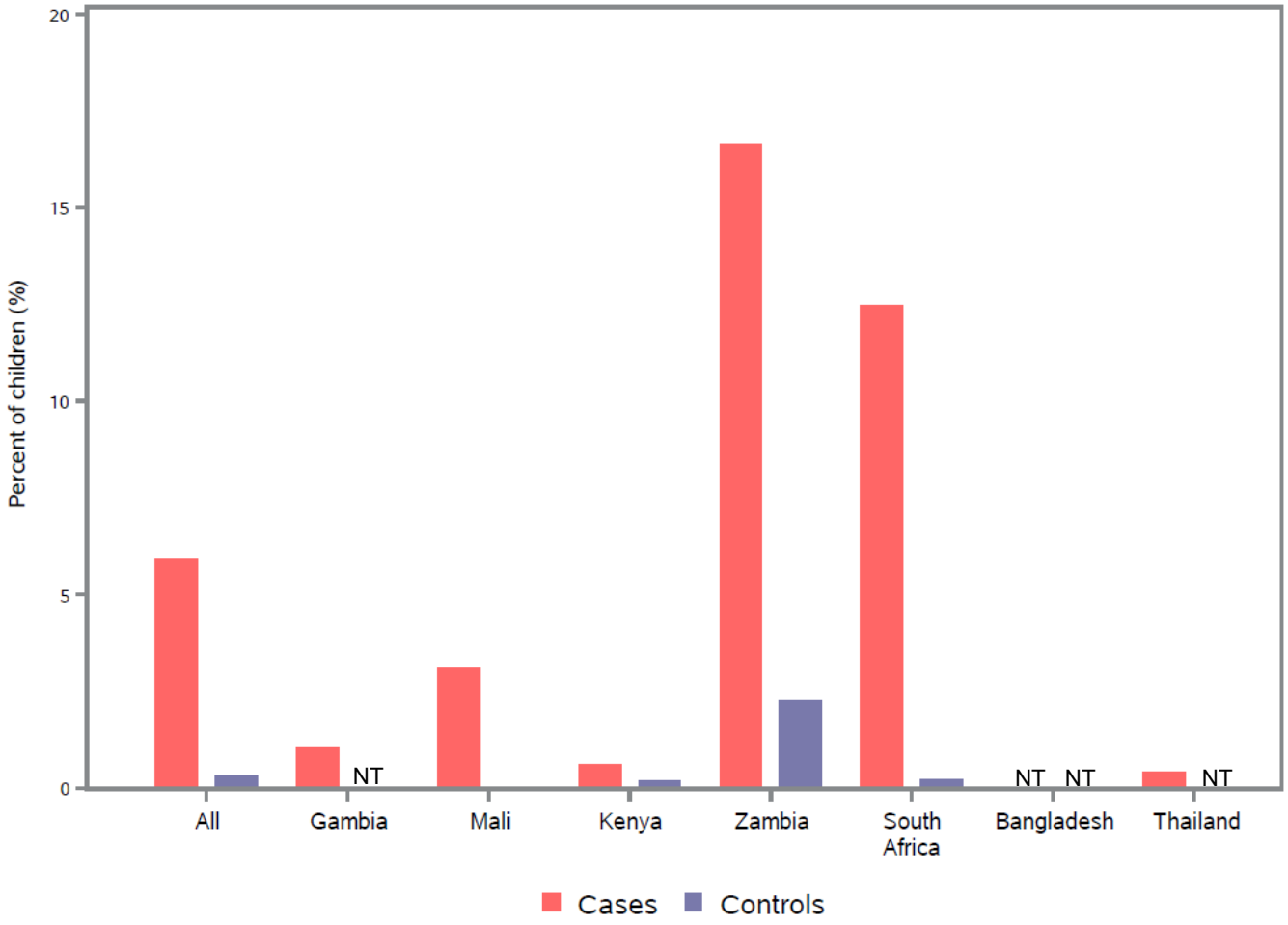
The analyses on HIV exposure status were restricted to South Africa and Zambia, where detailed information on maternal HIV status during and after pregnancy was collected and maternal HIV tests were performed at enrollment; the same level of detail on exposure status was not available from other sites.

*HIV+ controls were oversampled in sites with high HIV prevalence (South Africa and Zambia).

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Figure 2. Descriptive and clinical characteristics of cases and controls, by site

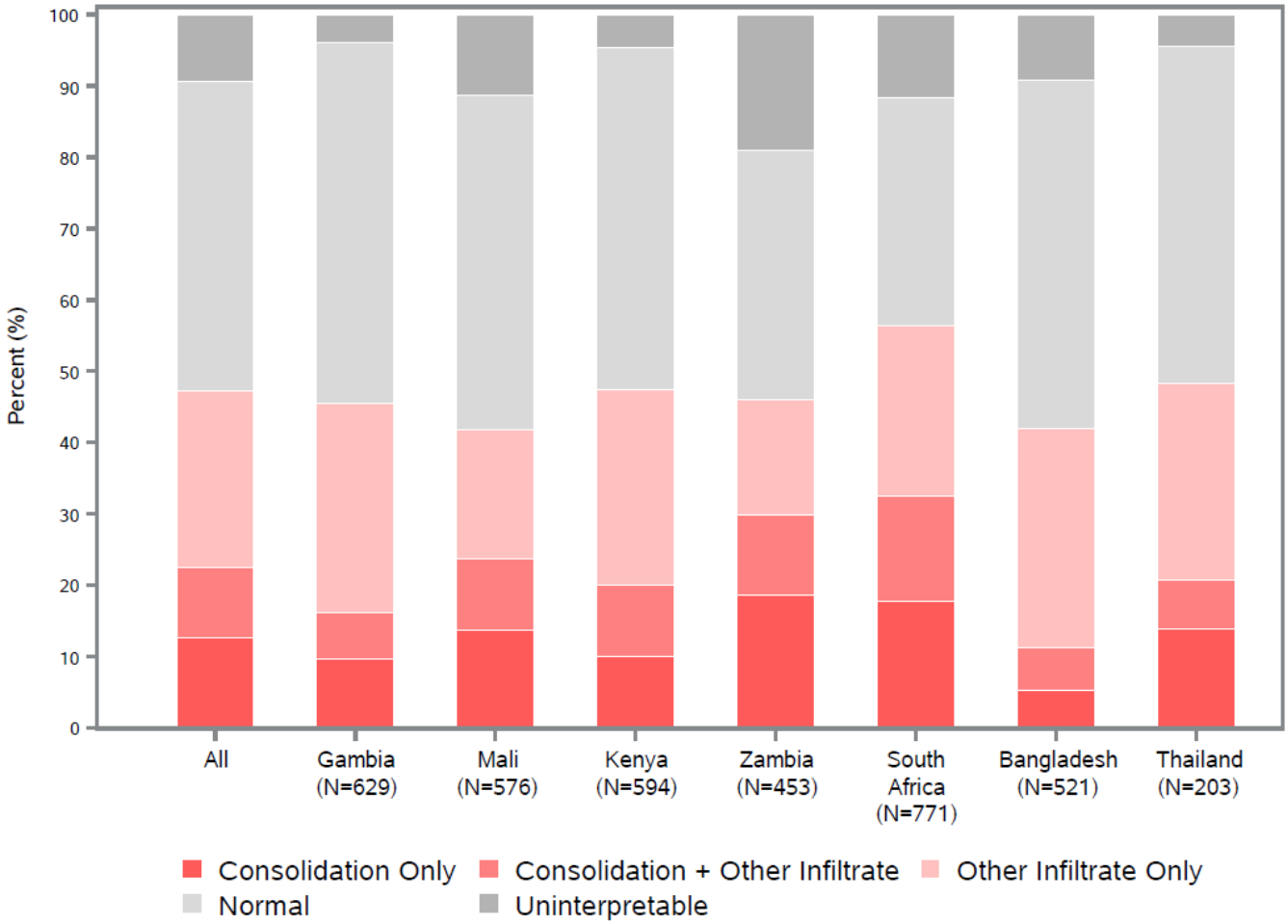
a. Proportion of cases and community controls that are HIV-infected



NT: HIV testing not performed in Bangladesh (cases and controls), and controls in The Gambia and Thailand.

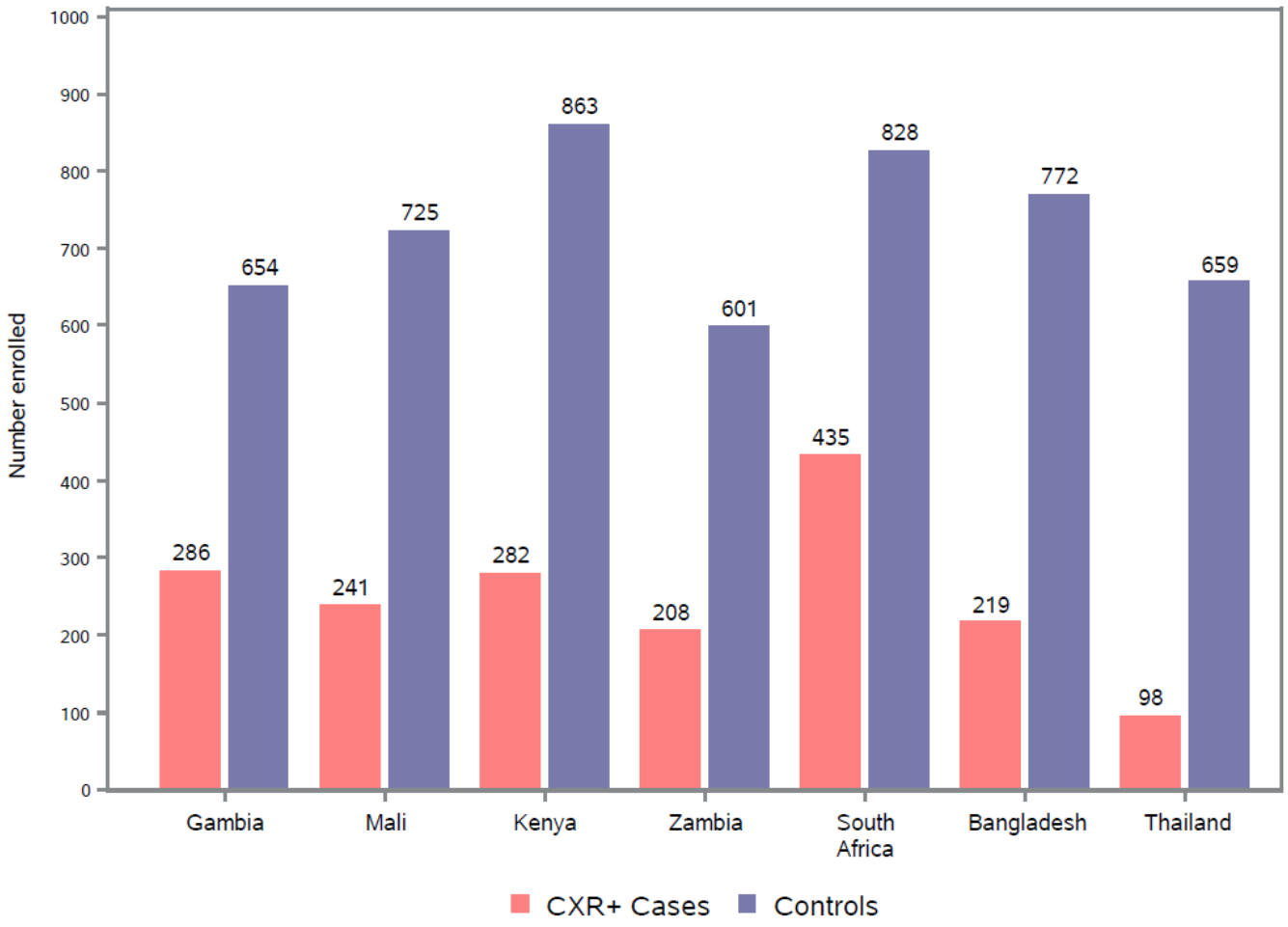
For South Africa and Zambia, only community-enrolled controls are shown here (i.e., controls enrolled at HIV-clinics are excluded).

b. Chest X-ray (CXR) findings among HIV-uninfected cases with an available CXR



5.9% of HIV-uninfected cases were missing a CXR (Kenya, 5.7%; Gambia, 0.3%; Mali, 11.8%; Zambia, 11.9%; South Africa, 4.2%; Thailand, 9.0%; Bangladesh, 0.8%).

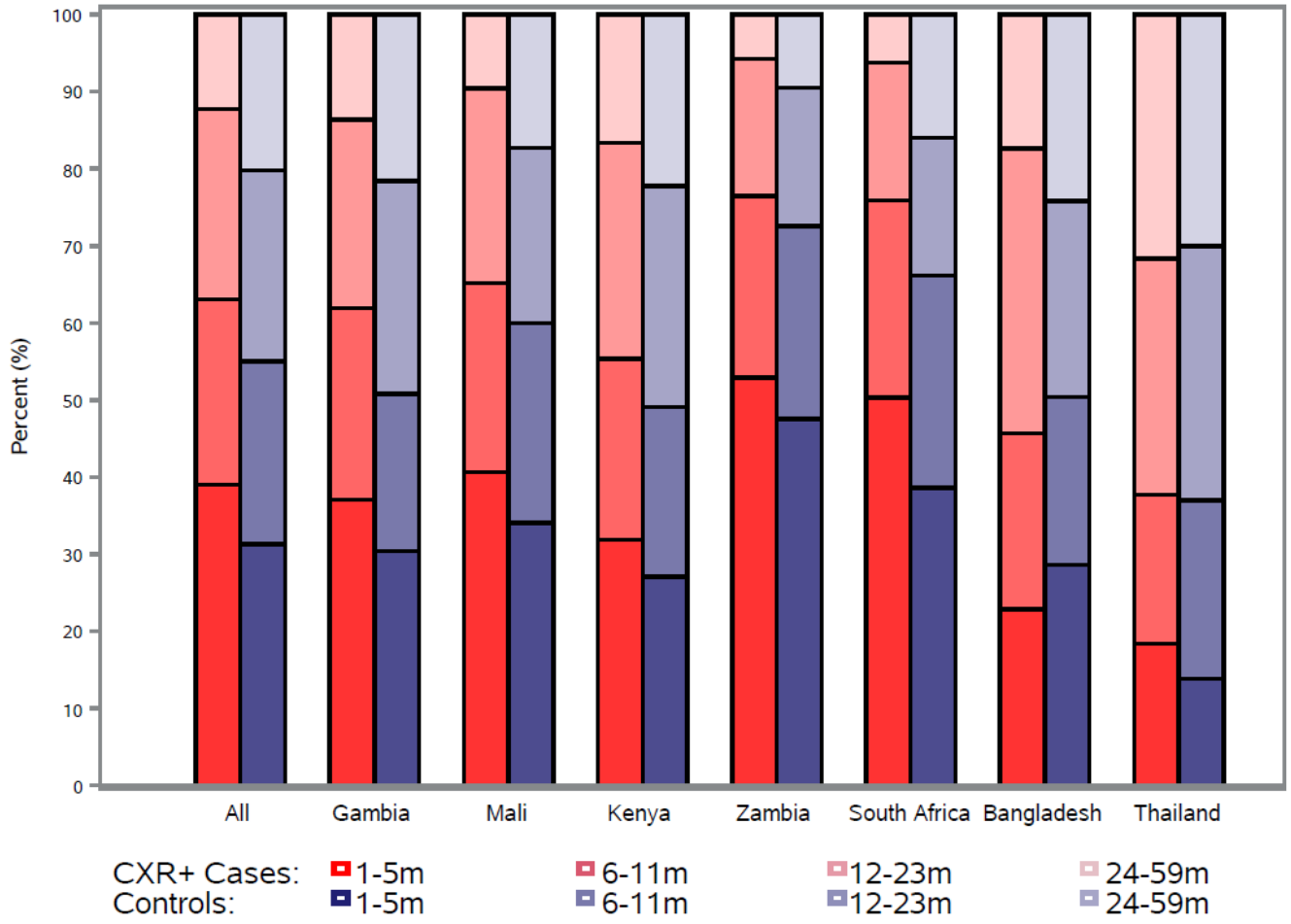
c. Number of enrolled HIV-uninfected/CXR+ cases (total 1,769) and controls (total 5,102)



Abbreviations: CXR, chest radiograph; CXR+, abnormal CXR.

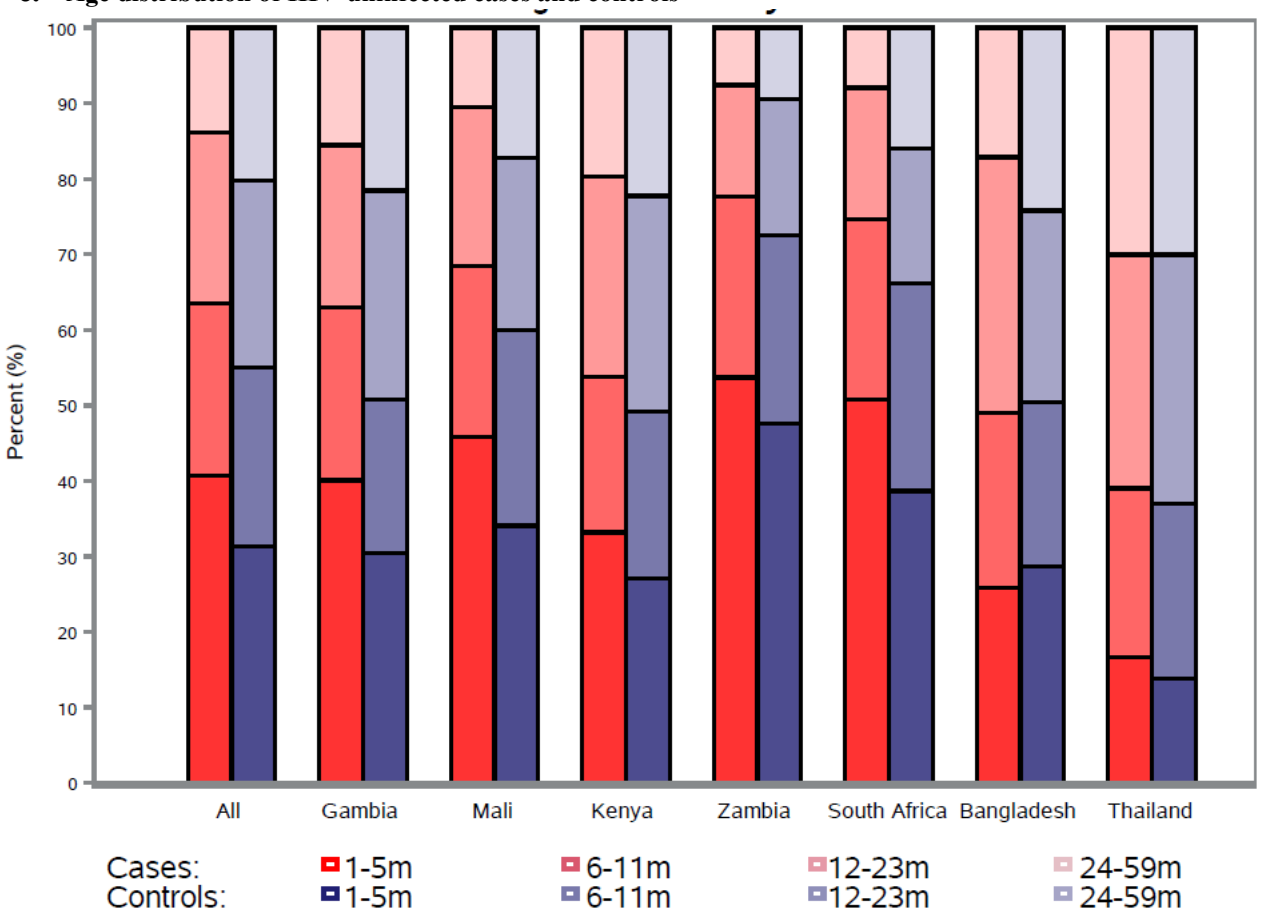
Numbers above bars represent number of CXR+ cases and controls enrolled.

d. Age distribution of HIV-uninfected/CXR+ cases and controls

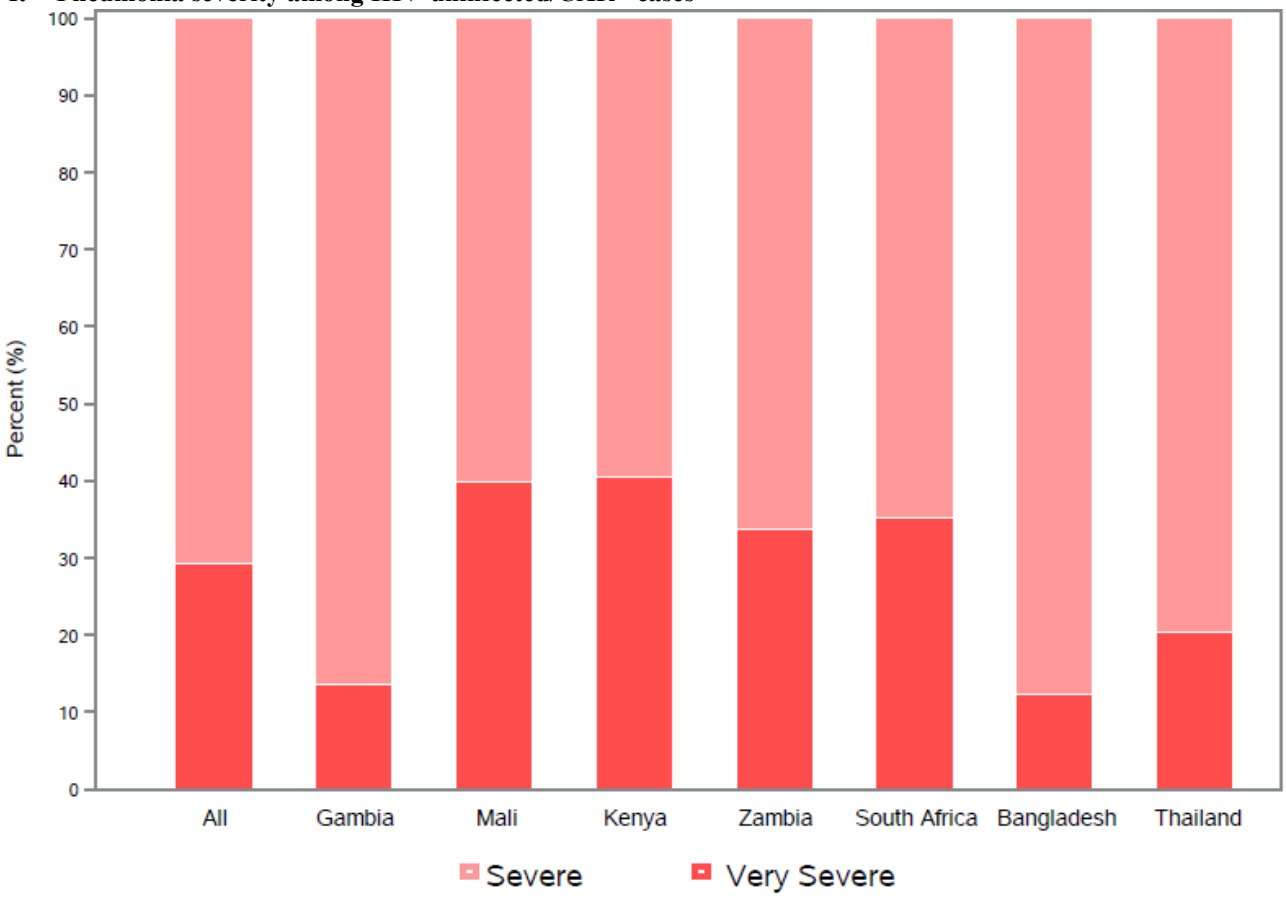


Abbreviations: CXR, chest radiograph; CXR+, abnormal CXR.

e. Age distribution of HIV-uninfected cases and controls

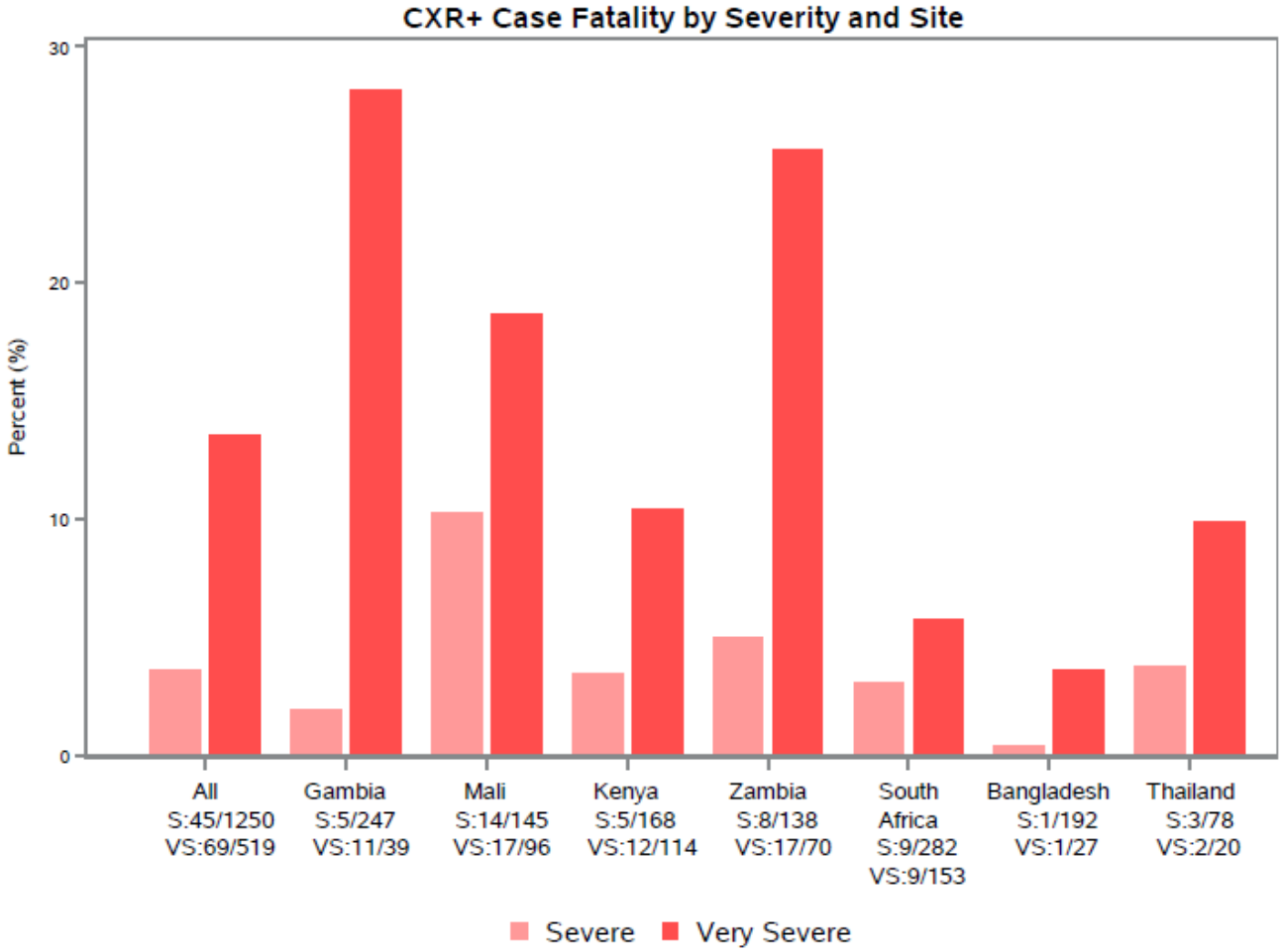


f. Pneumonia severity among HIV-uninfected/CXR+ cases



Abbreviations: CXR, chest radiograph; CXR+, abnormal CXR

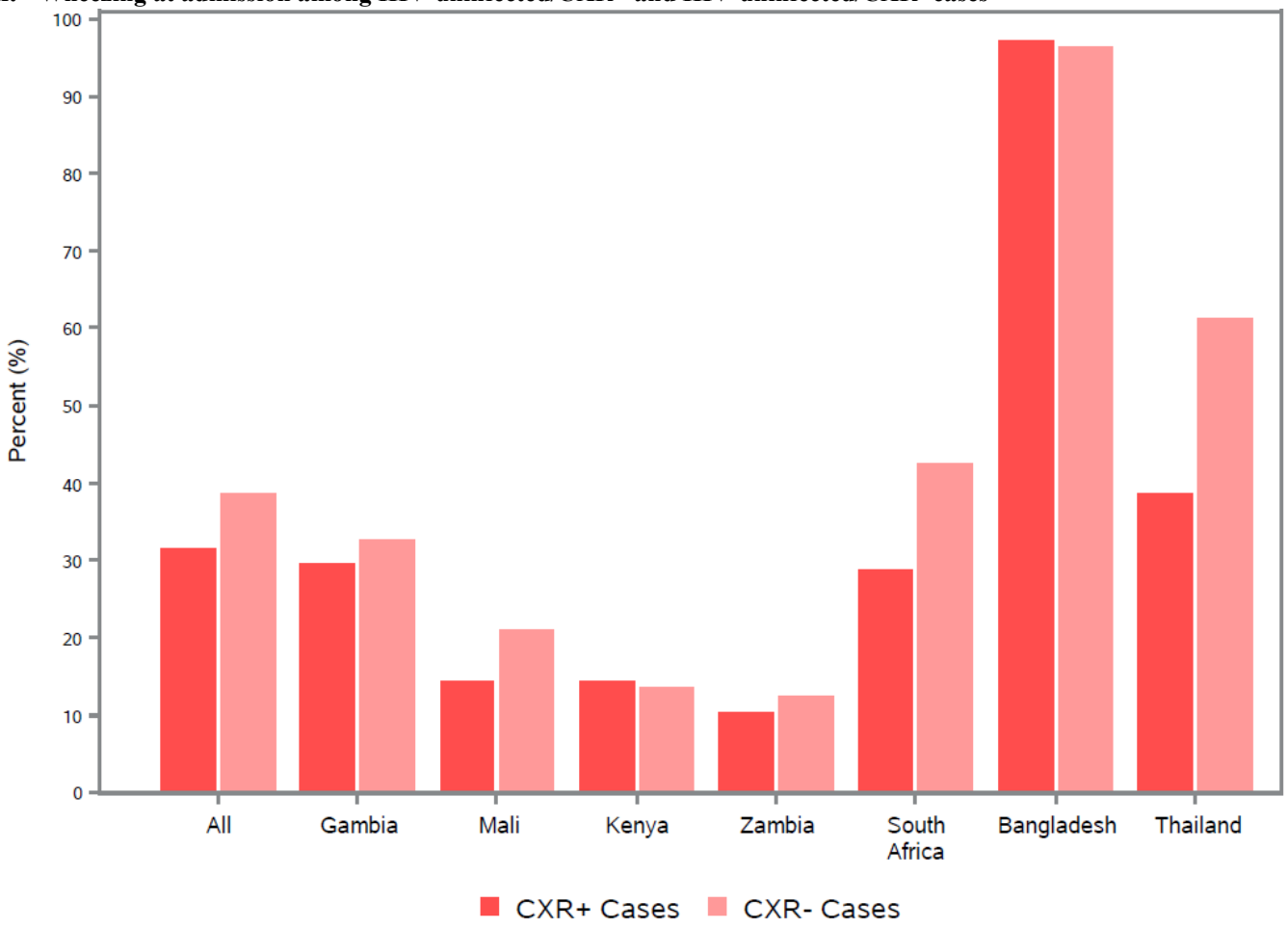
g. Case fatality ratio by site and pneumonia severity among HIV-uninfected/CXR+ cases



Abbreviations: S, severe; VS, very severe. Pneumonia severity attributions were done according to WHO 2005 classification system. Values are the number of severe (S) and very severe (VS) deaths and cases at each site.

Died within 30 days of admission; including in the denominator those without 30-day follow up data.

h. Wheezing at admission among HIV-uninfected/CXR+ and HIV-uninfected/CXR- cases



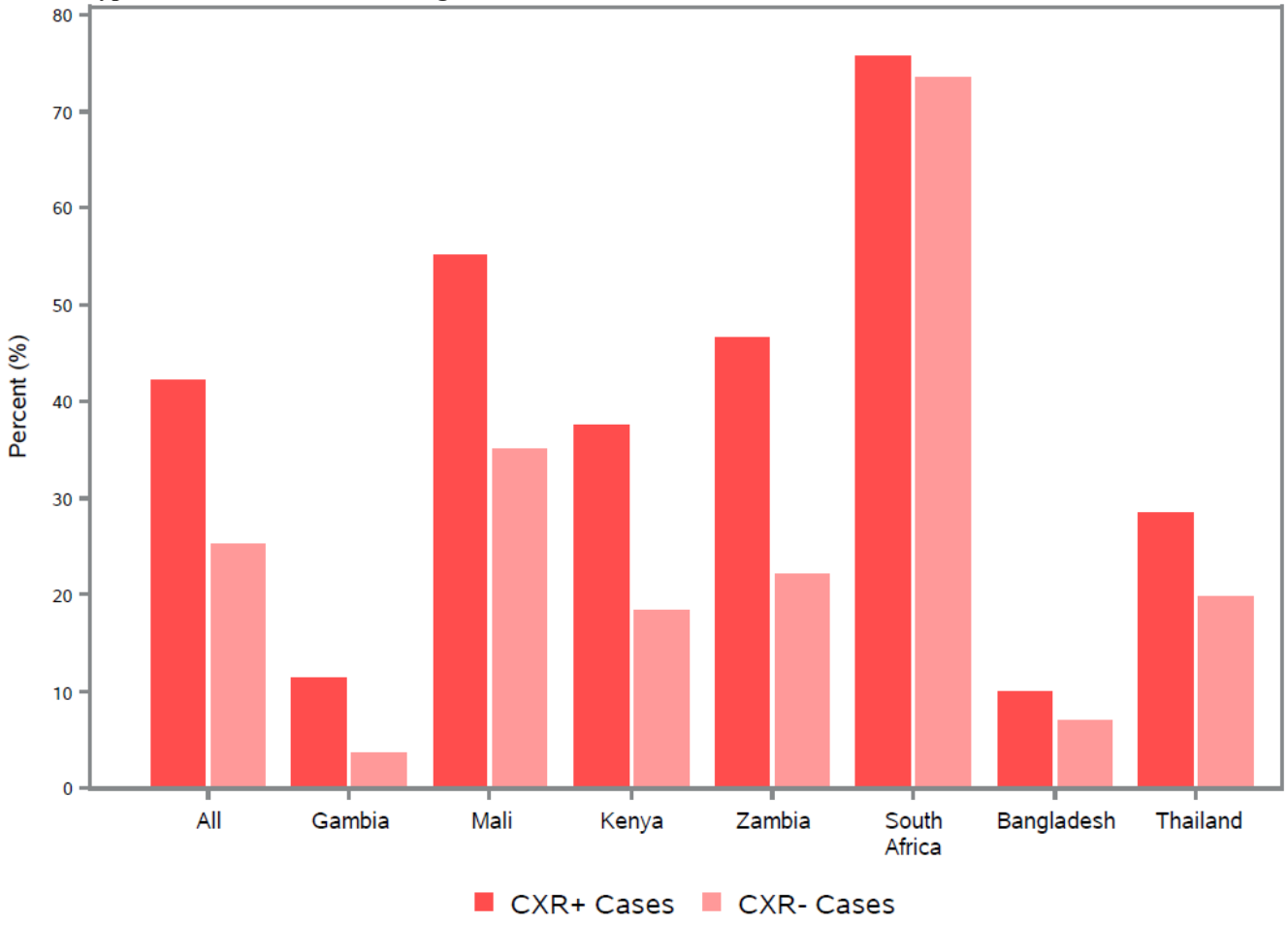
Abbreviations: CXR, chest radiograph; CXR+, abnormal CXR; CXR-, normal CXR.

Missing data: All HIV-uninfected/CXR+ cases (N=17); Gambia (N=2); Mali (N=0); Kenya (N=1); Zambia (N=0); South Africa (N=14); Bangladesh (N=0); Thailand (N=0).

Missing data: All HIV-uninfected/CXR- cases (N=5); Gambia (N=1); Mali (N=0); Kenya (N=2); Zambia (N=0); South Africa (N=2); Bangladesh (N=0); Thailand (N=0).

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

i. Hypoxaemia on admission among HIV-uninfected/CXR+ and HIV-uninfected/CXR- cases



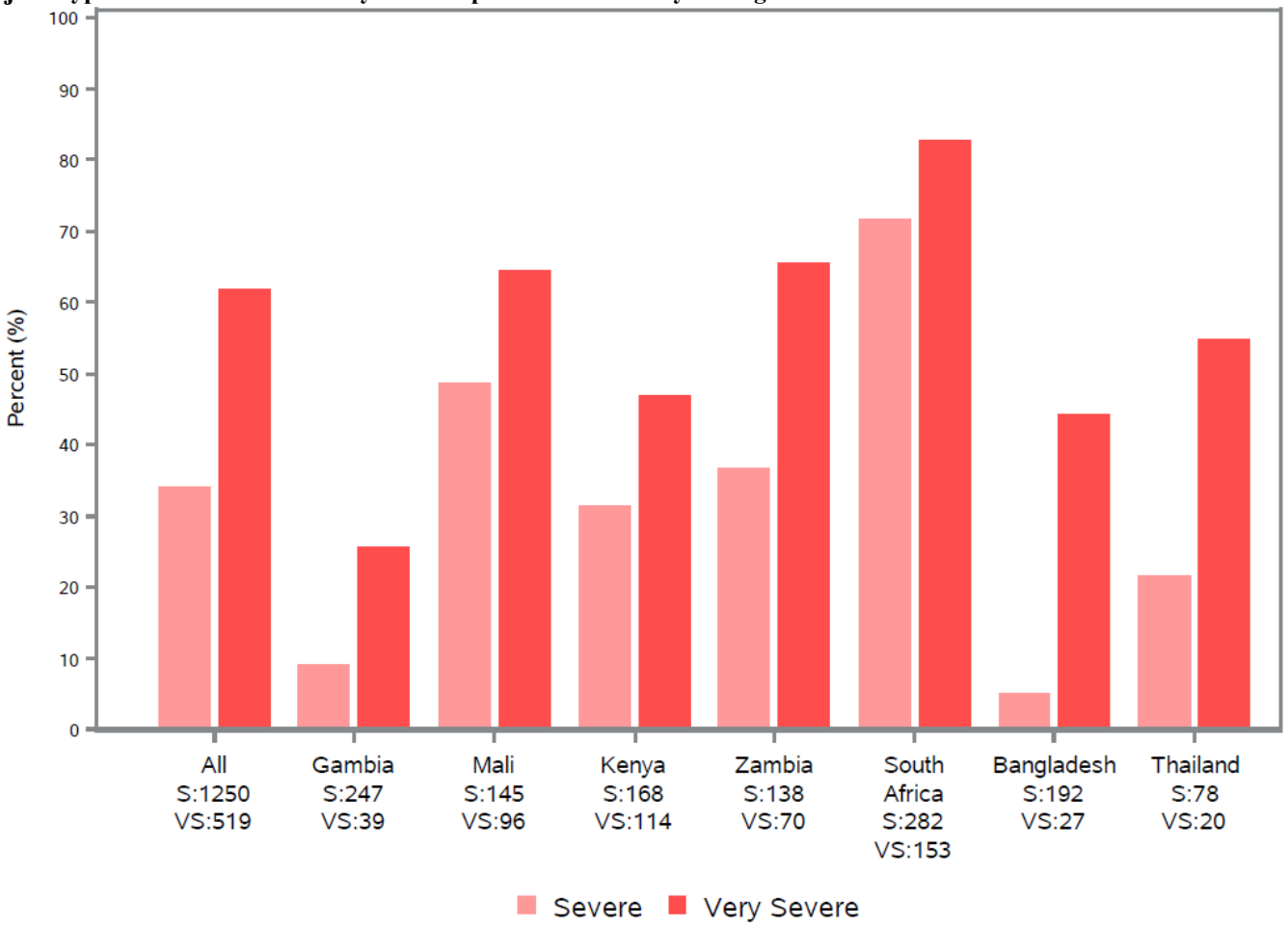
Abbreviations: CXR, chest radiograph; CXR+, abnormal CXR; CXR-, normal CXR.

Hypoxaemia defined as <92% on room air (<90% for sites at elevation: Zambia and South Africa) or a requirement for supplemental oxygen on admission if a room air reading was not available.

Missing data: All HIV-uninfected/CXR+ cases (N=2); Gambia (N=0); Mali (N=0); Kenya (N=1); Zambia (N=0); South Africa (N=1); Bangladesh (N=0); Thailand (N=0).

Missing data: All HIV-uninfected/CXR- cases (N=7); Gambia (N=1); Mali (N=0); Kenya (N=2); Zambia (N=1); South Africa (N=3); Bangladesh (N=0); Thailand (N=0).

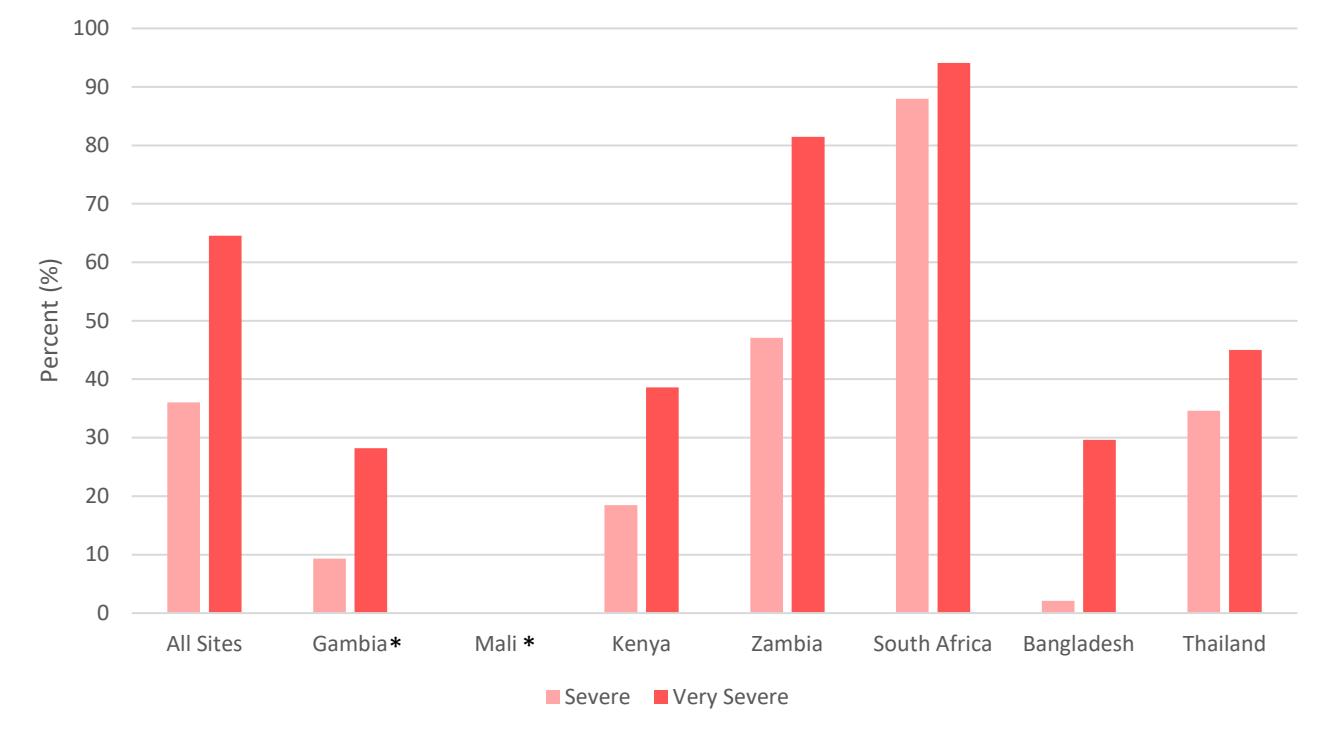
j. Hypoxaemia on admission by site and pneumonia severity among HIV-uninfected/CXR+ cases



Abbreviations: S, severe; VS, very severe. Pneumonia severity attributions were done according to WHO 2005 classification system. Values are the number of severe (S) and very severe (VS) cases at each site.

Hypoxaemia defined as <92% on room air (<90% for sites at elevation: Zambia and South Africa) or a requirement for supplemental oxygen on admission if a room air reading was not available.

k. Oxygen treatment on admission by site and pneumonia severity among HIV-uninfected/CXR+ cases

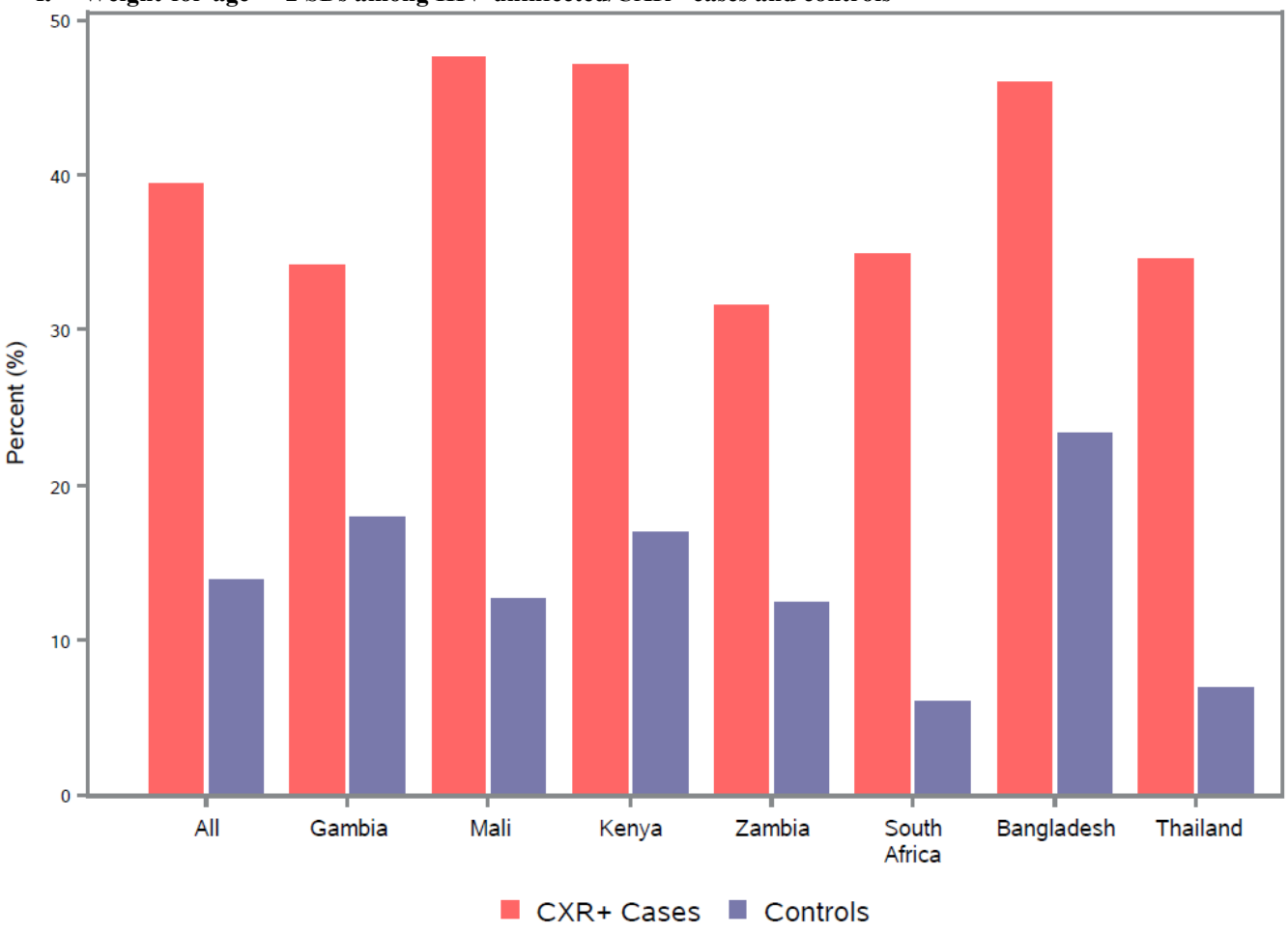


*Data from the Mali was site was excluded from this analysis due to lack of standardization in how the data were recorded for oxygen use. In The Gambia, based on evidence from a concurrent project of clinical care, all children in PERCH were coded as receiving oxygen if they were hypoxemic.

Missing data: All HIV-uninfected/CXR+ cases (N=3); Gambia (N=0); Kenya (N=1); Zambia (N=0); South Africa (N=2); Bangladesh (N=0); Thailand (N=0).

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

l. Weight-for-age < -2 SDs among HIV-uninfected/CXR+ cases and controls

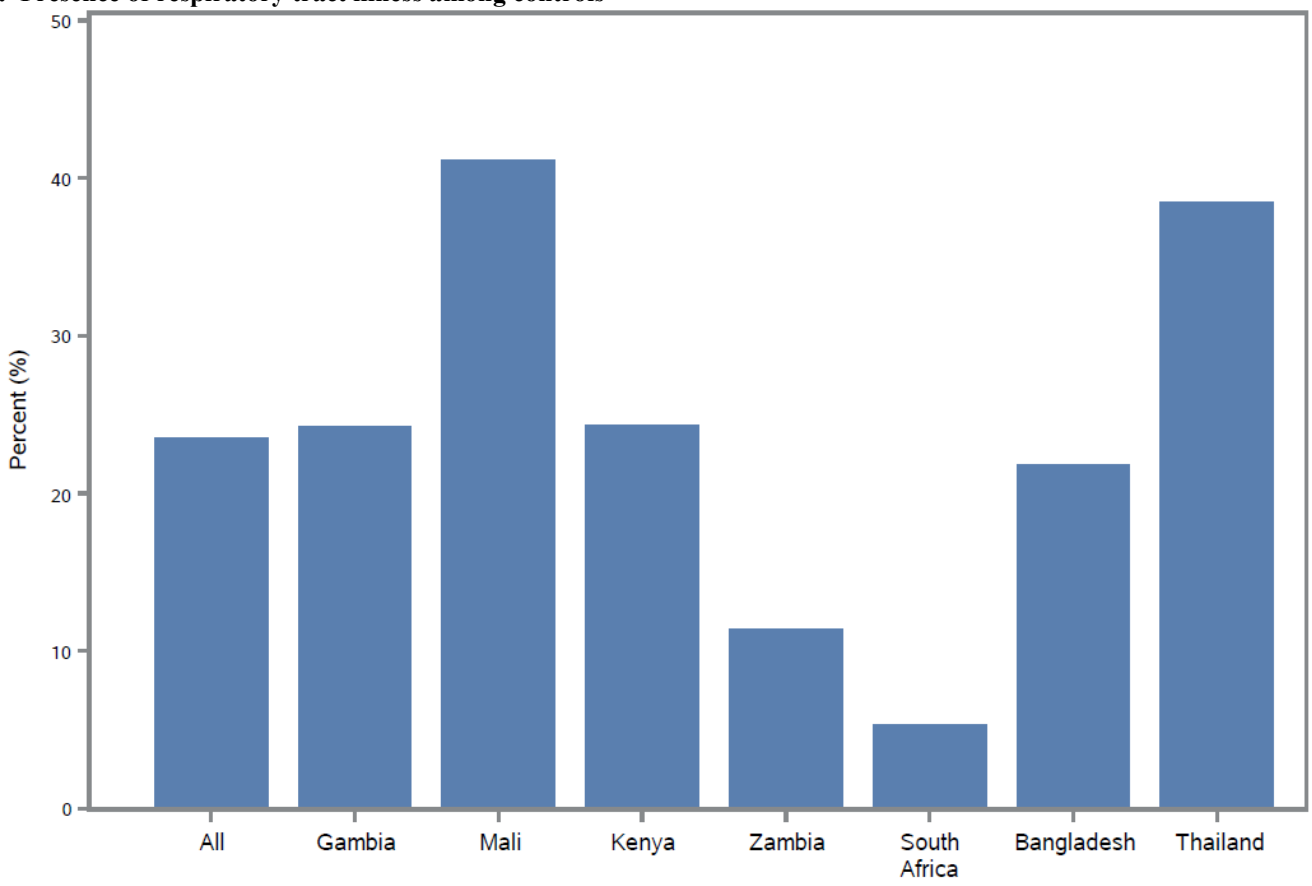


Abbreviations: CXR, chest radiograph; CXR+, abnormal CXR.

Missing data: All HIV-uninfected/CXR+ cases (N=8); Gambia (N=0); Mali (N=0); Kenya (N=3); Zambia (N=0); South Africa (N=5); Bangladesh (N=0); Thailand (N=0).

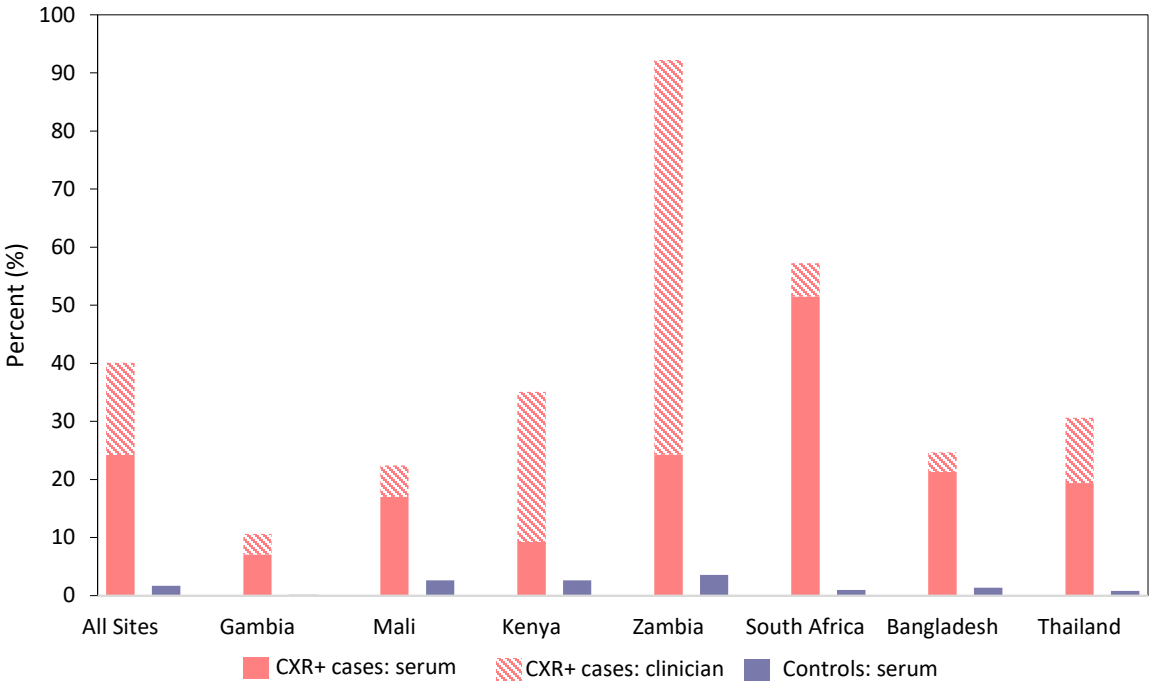
All HIV-uninfected controls (N=23); Gambia (N=5); Mali (N=4); Kenya (N=6); Zambia (N=1); South Africa (N=7); Bangladesh (N=0); Thailand (N=0).

m. Presence of respiratory tract illness among controls



Respiratory tract illness was defined as presence of cough or runny nose, or if a child had (1) at least 1 of ear discharge, wheezing, or difficulty breathing and (2) either a measured temperature of ≥38.0°C within the previous 48 hours or a history of sore throat.

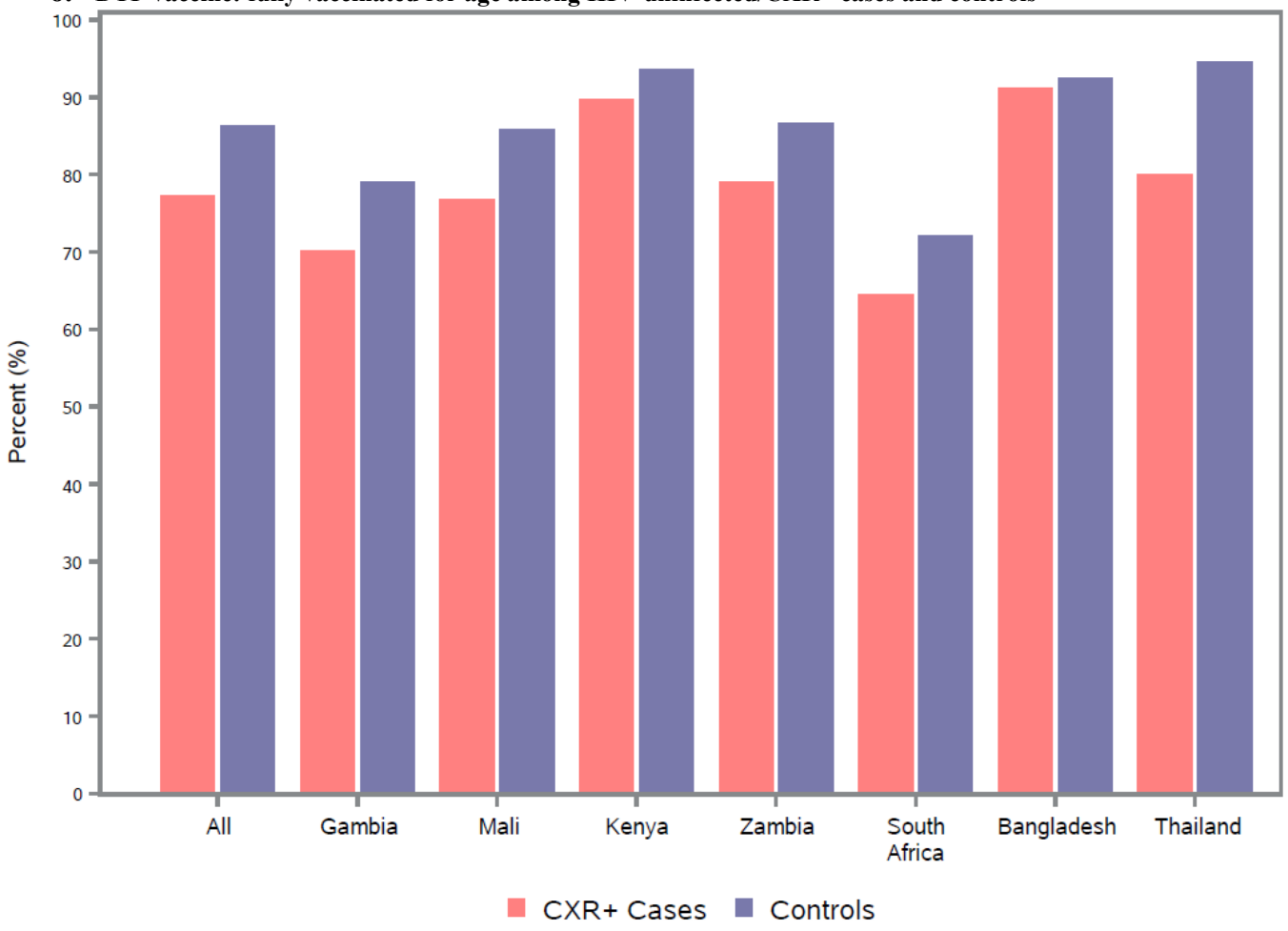
n. Prior exposure to antibiotics of HIV-uninfected/CXR+ cases and controls



Abbreviations: CXR+, abnormal chest radiograph.

Prior exposure to antibiotics was defined as positive serum bioassay for both cases and controls (solid bars) and additional cases (hashed bars) who were serum bioassay negative for antibiotics but identified as having received antibiotics prior to specimen collection based on documentation at study or referral facility. Prior exposure to antibiotics in Zambia is very high due to a health system structure whereby children are hospitalised only after being assessed at a primary care facility where antibiotics are administered prior to transport to hospital.

o. DTP vaccine: fully vaccinated for age among HIV-uninfected/CXR+ cases and controls



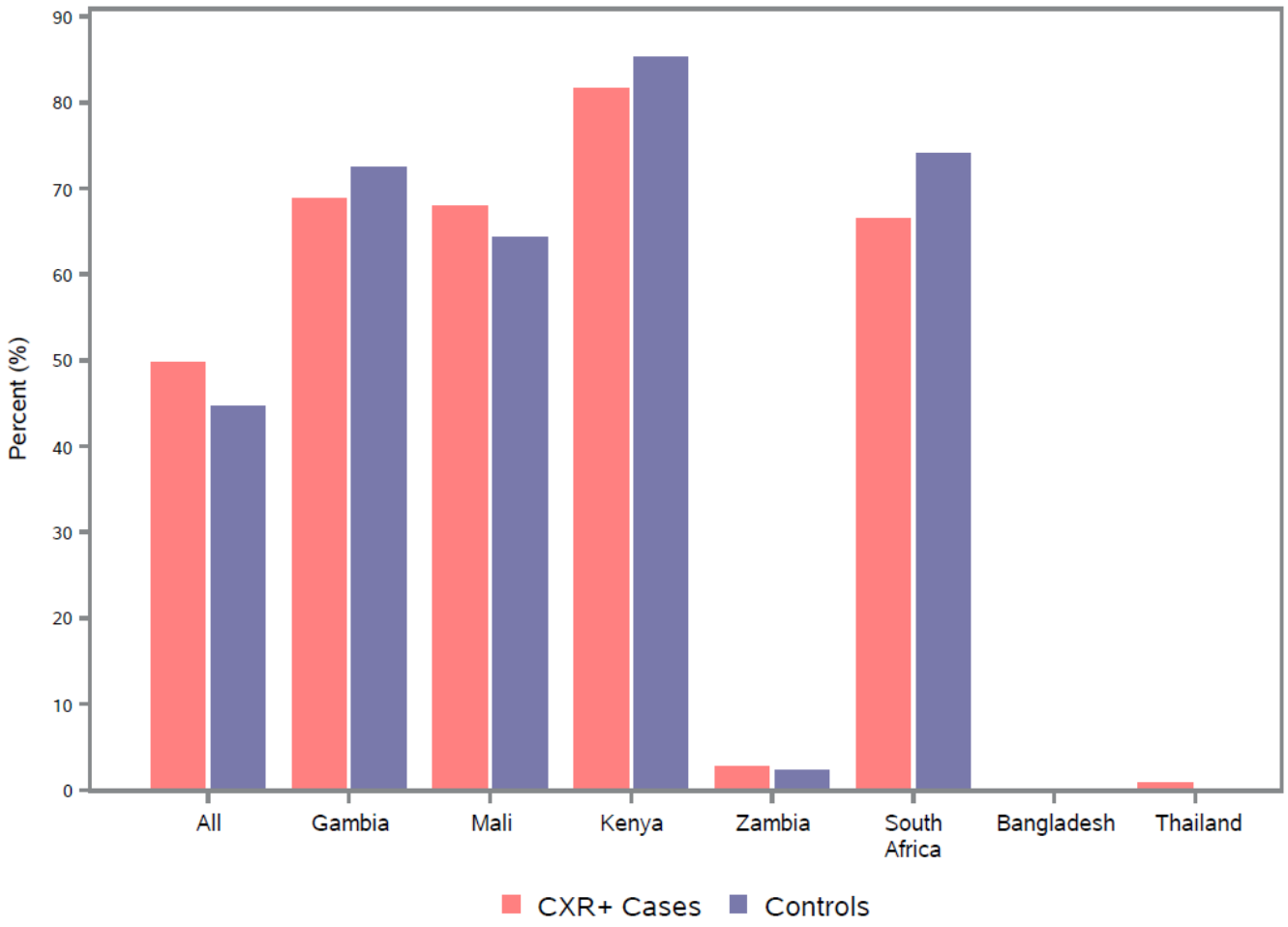
Abbreviations: CXR, chest radiograph; CXR+, abnormal CXR.

Formulation of DTP varied by site. Pentavalent vaccine (DTP-Hib-HepB): Kenya, Gambia, Mali, Zambia, and Bangladesh; DTP-only and DTP-HepB: Thailand; Pentaxim (DTaP-Hib-IPV): South Africa. For children <1 year, fully vaccinated defined as received at least one dose and up-to-date for age based on the child's age at enrollment, doses received, and country schedule (allowing 4-week window each for dose). For children ≥1 year, fully vaccinated defined as 3+ doses.

Missing data: All HIV-uninfected/CXR+ cases (N=67); Gambia (N=12); Mali (N=6); Kenya (N=4); Zambia (N=15); South Africa (N=27); Bangladesh (N=1); Thailand (N=2).

Missing data: All HIV-uninfected controls (N=85); Gambia (N=37); Mali (N=0); Kenya (N=19); Zambia (N=2); South Africa (N=17); Bangladesh (N=6); Thailand (N=4).

p. Pneumococcal conjugate vaccine (PCV): fully vaccinated for age among HIV-uninfected/CXR+ cases and controls



Abbreviations: CXR, chest radiograph; CXR+, abnormal CXR.

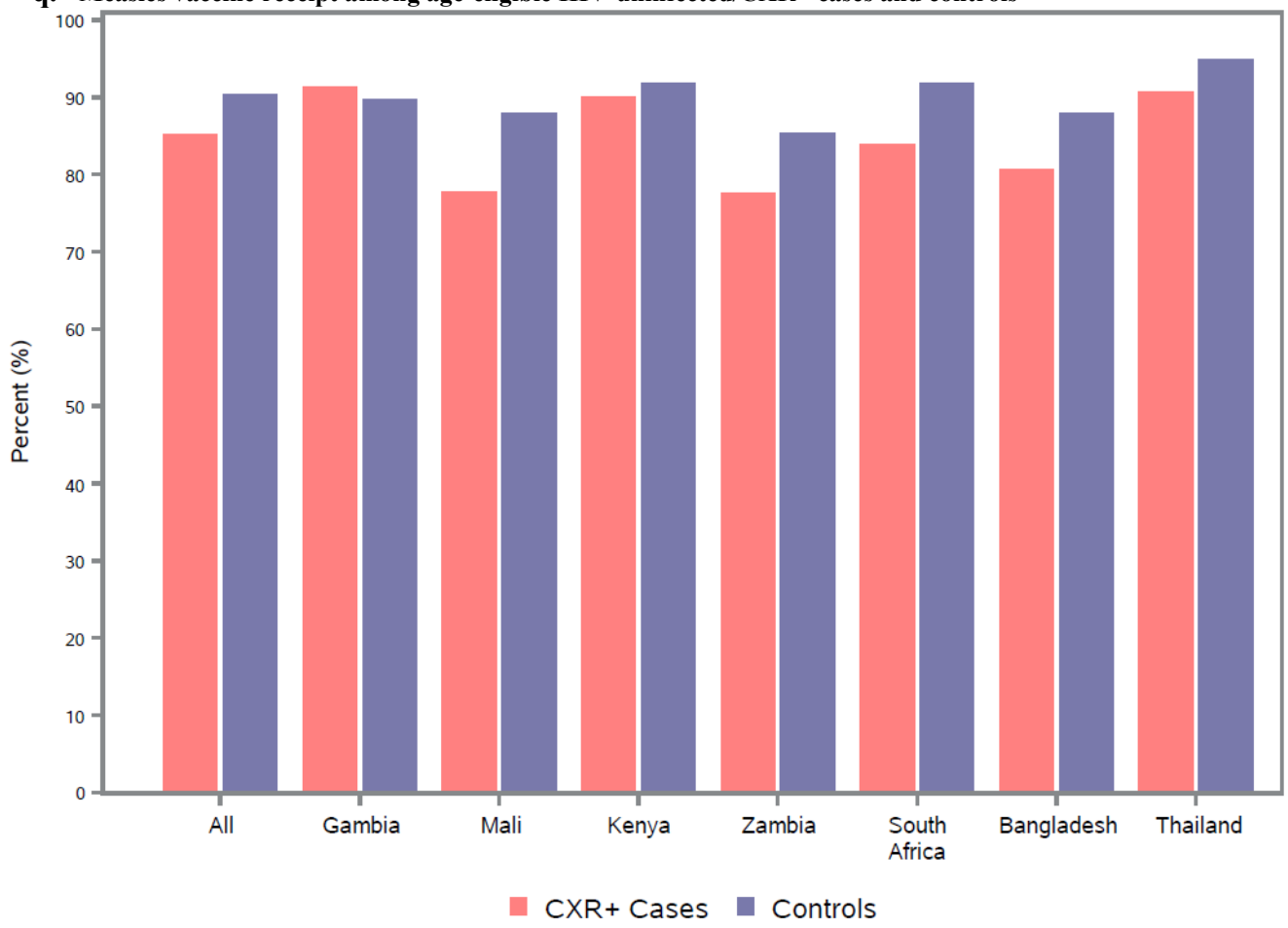
During PERCH, PCV was in routine use in Kenya (introduced February 2011), The Gambia (introduced August 2009), Mali (introduced March 2011), and South Africa (introduced April 2009); PCV was introduced in Zambia in July 2013 (Lusaka), 3 months prior to the end of PERCH enrollment at that site.

For children <1 year, fully vaccinated defined as received at least one dose and up-to-date for age based on the child's age at enrollment, doses received, and country schedule (allowing 4-week window each for dose). For children ≥1 year, in all sites except Kenya, fully vaccinated defined as 3+ doses. For children ≥1 year in Kenya (where PCV was introduced with a catch-up campaign), fully vaccinated defined at 3+ doses, 2 doses if given at least 8 weeks apart and child was ≥1 year of age at first dose, or 1 dose if age at any dose or age at introduction was ≥2 years.

Missing data: All HIV-uninfected/CXR+ cases (N=52); Gambia (N=12); Mali (N=6); Kenya (N=4); Zambia (N=2); South Africa (N=27); Bangladesh (N=1); Thailand (N=2).

Missing data: All HIV-uninfected controls (N=81); Gambia (N=40); Mali (N=2); Kenya (N=18); Zambia (N=0); South Africa (N=17); Bangladesh (N=0); Thailand (N=4).

q. Measles vaccine receipt among age-eligible HIV-uninfected/CXR+ cases and controls



Abbreviations: CXR, chest radiograph; CXR+, abnormal CXR

Fully vaccinated defined as having received at least one dose of measles vaccine, restricted to children >10 months (>10.5 months in Bangladesh).

Missing data: All HIV-uninfected/CXR+ cases (N=41); Gambia (N=6); Mali (N=4); Kenya (N=6); Zambia (N=8); South Africa (N=15); Bangladesh (N=0); Thailand (N=2).

Missing data: All HIV-uninfected controls (N=74); Gambia (N=30); Mali (N=1); Kenya (N=23); Zambia (N=1); South Africa (N=8); Bangladesh (N=7); Thailand (N=4).

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Table 4: Vaccination status of HIV-uninfected cases and controls, by site

	Cases n (%)							
	All Sites	**Kenya**	**Gambia**	**Mali**	**Zambia**	**South Africa**	**Thailand**	**Bangladesh**
DTP[a]								
Number of doses (regardless of age)								
3+	2267 (59.1)	466 (75.0)	334 (55.7)	330 (51.5)	251 (52.4)	311 (41.4)	157 (72.4)	418 (79.9)
Fully vaccinated for age[b]								
< 1 year old	1724 (70.3)	277 (82.0)	213 (55.6)	323 (73.4)	288 (75.6)	350 (61.4)	59 (70.2)	214 (83.9)
≥ 1 year old	1264 (91.5)	273 (96.5)	202 (93.1)	176 (87.6)	91 (92.9)	137 (75.3)	122 (91.7)	263 (98.1)
PCV[c]								
Number of doses (regardless of age)								
3+	1151 (29.8)	382 (61.6)	327 (54.6)	279 (43.5)	0 (0.0)	161 (21.4)	2 (0.9)	0 (0.0)
Fully vaccinated for age[d]								
< 1 year old	1226 (49.7)	287 (84.7)	211 (55.1)	323 (73.4)	11 (2.8)	393 (68.9)	1 (1.2)	0 (0.0)
≥ 1 year old	640 (45.9)	211 (75.1)	192 (88.9)	124 (61.7)	0 (0.0)	112 (61.5)	1 (0.8)	0 (0.0)
PCV[c] (among sites routinely using PCV)								
Number of doses (regardless of age)								
3+	1149 (44.0)	382 (61.6)	327 (54.6)	279 (43.5)	--	161 (21.4)	--	--
Fully vaccinated for age[d]								
< 1 year old	1214 (70.1)	287 (84.7)	211 (55.1)	323 (73.4)	--	393 (68.9)	--	--
≥ 1 year old	639 (72.6)	211 (75.1)	192 (88.9)	124 (61.7)	--	112 (61.5)	--	--
Measles								
Fully vaccinated (restricted to those eligible[e])	1453 (86.8)	306 (92.7)	238 (90.8)	190 (78.5)	105 (78.9)	208 (86.7)	140 (91.5)	266 (84.7)
	Controls n (%)							
	All Sites	**Kenya**	**Gambia**	**Mali**	**Zambia**	**South Africa**	**Thailand**	**Bangladesh**
DTP[a]								
Number of doses (regardless of age)								
3+	3708 (73.9)	712 (84.4)	419 (67.9)	521 (71.9)	389 (64.9)	482 (59.4)	535 (81.7)	650 (84.9)
Fully vaccinated for age[b]								
< 1 year old	2258 (81.0)	387 (91.5)	218 (67.1)	346 (79.5)	368 (84.8)	378 (70.0)	215 (88.5)	346 (88.9)
≥ 1 year old	2083 (93.5)	405 (96.2)	271 (92.8)	278 (95.9)	152 (92.1)	208 (76.8)	405 (98.3)	364 (96.6)
PCV[c]								
Number of doses (regardless of age)								
3+	1561 (31.1)	575 (68.0)	379 (61.7)	365 (50.5)	0 (0.0)	242 (29.8)	0 (0.0)	0 (0.0)

Fully vaccinated for age[d]								
< 1 year old	1384 (49.6)	392 (92.7)	214 (66.0)	332 (76.5)	15 (3.4)	431 (79.8)	0 (0.0)	0 (0.0)
≥ 1 year old	867 (38.8)	330 (78.2)	232 (80.0)	134 (46.4)	0 (0.0)	171 (63.1)	0 (0.0)	0 (0.0)
PCV[c] (among sites routinely using PCV)								
Number of doses (regardless of age)								
3+	1561 (52.2)	575 (68.0)	379 (61.7)	365 (50.5)	--	242 (29.8)	--	--
Fully vaccinated for age[d]								
< 1 year old	1369 (79.6)	392 (92.7)	214 (66.0)	332 (76.5)	--	431 (79.8)	--	--
≥ 1 year old	867 (68.2)	330 (78.2)	232 (80.0)	134 (46.4)	--	171 (63.1)	--	--
Measles								
Fully vaccinated (restricted to those eligible[e])	2459 (90.6)	458 (92.0)	303 (89.9)	326 (88.1)	188 (85.5)	345 (92.0)	455 (95.0)	384 (88.1)

Abbreviations: DTP, diptheria-tetanus-pertussis vaccine; PCV, pneumococcal conjugate vaccine. Data for controls are also reported in Table 1.

a. Formulation varied by site. Pentavalent vaccine (DTP-Hib-HepB): Kenya, Gambia, Mali, Zambia, and Bangladesh; DTP-only and DTP-HepB: Thailand; Pentaxim (DTaP-Hib-IPV): South Africa.

b. For children <1 year, defined as received at least one dose and up-to-date for age based on the child's age at enrollment, doses received, and country schedule (allowing 4-week window each for dose). For children ≥1 year, defined as 3+ doses.

c. During PERCH, PCV was in routine use in Kenya (introduced February 2011), The Gambia (introduced August 2009), Mali (introduced March 2011), and South Africa (introduced April 2009); PCV was introduced in Zambia in July 2013 (Lusaka), 3 months prior to the end of PERCH enrollment at that site.

d. For children <1 year, defined as received at least one dose and up-to-date for age based on the child's age at enrollment, doses received, and country schedule (allowing 4-week window each for dose). For children ≥1 year in all sites except Kenya, defined as 3+ doses. For children ≥1 year in Kenya (where PCV was introduced with catch-up campaign), defined at 3+ doses, 2 doses if given at least 8 weeks apart and child was ≥1 year of age at first dose, 1 dose if age at any dose or age at introduction was ≥2 years.

e. At least one dose, restricted to children >10 months (>10.5 months in Bangladesh).

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Table 5. Organisms detected in case-only specimens from HIV-uninfected/CXR+ cases, by site

	All Sites (1769)	Kenya (282)	Gambia (286)	Mali (241)	Zambia (208)	South Africa (435)	Thailand (98)	Bangladesh (219)
Prior exposure to antibiotics[a]	703 (40.1)	99 (35.1)	30 (10.6)	54 (22.4)	189 (92.2)	249 (57.2)	30 (30.6)	52 (24.6)
Blood Culture								
Results available, n (%)	1749 (98.9)	282 (100)	279 (97.6)	241 (100)	205 (98.6)	433 (99.5)	98 (100)	211 (96.3)
Any organism[b]	56 (3.2)	9 (3.2)	14 (5.0)	12 (5.0)	8 (3.9)	9 (2.1)	2 (2.0)	2 (0.9)
S. pneumoniae	19 (1.1)	5 (1.8)	7 (2.5)	6 (2.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
S. pneumoniae PCV13 type	10 (0.6)	4 (1.4)	2 (0.7)	3 (1.2)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
S. pneumoniae non-PCV13 type	9 (0.5)	1 (0.4)	5 (1.8)	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
H. influenzae	12 (0.7)	2 (0.7)	2 (0.7)	5 (2.1)	1 (0.5)	2 (0.5)	0 (0.0)	0 (0.0)
H. influenzae type b	6 (0.3)	0 (0.0)	0 (0.0)	4 (1.7)	1 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)
H. influenzae non-type b	6 (0.3)	2 (0.7)	2 (0.7)	1 (0.4)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
S. aureus	6 (0.3)	1 (0.4)	1 (0.4)	0 (0.0)	1 (0.5)	3 (0.7)	0 (0.0)	0 (0.0)
Salmonella spp[c]	8 (0.5)	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.5)	1 (0.2)	0 (0.0)	1 (0.5)
Enterobacteriaceae[d]	5 (0.3)	0 (0.0)	1 (0.4)	0 (0.0)	2 (1)	1 (0.2)	0 (0.0)	1 (0.5)
Other streptococci and enterococci[e]	4 (0.2)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	1 (1.0)	0 (0.0)
N. meningitidis	1 (0.1)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
M. catarrhalis	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	0 (0.0)
Candida species	1 (0.1)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Mixed[f]	2 (0.1)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)
Lung Aspirate[g]								
Results available, n (%)	37 (2.1)	--	21 (7.3)	7 (2.9)	--	5 (1.1)	--	4 (1.8)
Any organism	11 (29.7)	--	8 (38.1)	0 (0.0)	--	3 (60.0)	--	0 (0.0)
S. pneumoniae[h]	8 (21.6)	--	7 (33.3)	0 (0.0)	--	1 (20.0)	--	0 (0.0)
H. influenzae non-b[i]	4 (10.8)	--	2 (9.5)	0 (0.0)	--	2 (40.0)	--	0 (0.0)
C. pneumoniae	1 (2.7)	--	0 (0.0)	0 (0.0)	--	1 (20.0)	--	0 (0.0)
M. catarrhalis	4 (10.8)	--	3 (14.3)	0 (0.0)	--	1 (20.0)	--	0 (0.0)
HMPV	1 (2.7)	--	0 (0.0)	0 (0.0)	--	1 (20.0)	--	0 (0.0)

	All Sites (1769)	Kenya (282)	Gambia (286)	Mali (241)	Zambia (208)	South Africa (435)	Thailand (98)	Bangladesh (219)
Adenovirus	1 (2.7)	--	0 (0.0)	0 (0.0)	--	1 (20.0)	--	0 (0.0)
Pleural Fluid[g]								
Results available, n (%)	15 (0.8)	2 (0.7)	1 (0.3)	5 (2.1)	2 (1.0)	5 (1.1)	0 (0.0)	0 (0.0)
Any organism	12 (80.0)	2 (100)	1 (100)	4 (80.0)	2 (100)	3 (60.0)	--	--
***S. pneumoniae*[h]**	5 (33.3)	1 (50.0)	0 (0.0)	1 (20.0)	1 (50.0)	2 (40.0)	--	--
S. aureus	7 (46.7)	1 (50.0)	1 (100)	2 (40.0)	2 (100)	1 (20.0)	--	--
E. coli	1 (6.7)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	--	--
Streptococcus Group F	1 (6.7)	0 (0.0)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	--	--
HBOV	1 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	--	--
Induced sputum and gastric aspirate culture (for *Mycobacterium tuberculosis* only)								
Results available	1571 (88.8)	267 (94.7)	255 (89.2)	223 (92.5)	182 (87.5)	344 (79.1)	82 (83.7)	218 (99.5)
***M. tuberculosis*[j]**	24 (1.5)	1 (0.4)	7 (2.7)	1 (0.4)	5 (2.7)	7 (2.0)	2 (2.4)	1 (0.5)

Abbreviations: HBOV, human bocavirus; HMPV, human metapneumovirus.

Percentages for the 'Results available' rows are out of the total number of cases; percentages for all subsequent rows are out of the total number of cases with results available.

[a] Defined as serum bioassay positive, antibiotics administered at the referral facility, or antibiotic administration prior to whole blood specimen collection at the study facility. Restricted to children with blood culture or whole blood collected.

[b] Excludes contaminants.

[c] Includes *S. typhi*, and Other Salmonella spp.

[d] Includes *Escherichia coli* and *Klebsiella pneumoniae*.

[e] Includes *Enterococcus faecium* and *Streptococcus* Group A.

[f] These two cases had mixed blood culture isolates as follows: *Escherichia coli* & *Klebsiella pneumoniae,* and Salmonella species & *Streptococcus* Group A.

[g] Any lung aspirate positivity by culture or PCR. Results restricted to specimens obtained within 3 days of enrollment and those pathogens determined by the clinical review team to be non-contaminants. Pleural fluid PCR includes multiplex PCR panel and BinaxNOW®.

[h] For *S. pneumoniae* by lung aspirate, three cases were PCV13 type; two cases were non-PCV13 type; three cases did not have serotyping available (PCR positive only). For *S. pneumoniae* by pleural fluid, one case was PCV 13 type, and four cases did not have serotyping available (PCR or BinaxNOW® positive only).

[i] One case positive for *H. influenzae* by lung aspirate was missing serotyping data for the culture isolate but was negative for *H. influenzae* type b by lung aspirate PCR.

[j] *M. tuberculosis* positive on first induced sputum specimen, or first gastric aspirate if induced sputum unavailable. One case who did not have an induced sputum specimen available was positive by gastric aspirate; all other positives were detected by induced sputum. Using any result on induced sputum or gastric aspirate to define positivity, 14 total *M. tuberculosis* positive cases were detected in South Africa.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Table 6. Organisms detected in case-only blood, sputum and gastric aspirate specimens from HIV-uninfected cases, by age and severity

Organisms, specimen and test	All Cases N=3981	CXR+ Cases N=1769	Severe CXR+ Cases N=1250	Very Severe CXR+ Cases N=519	Age <1 CXR+ Cases N=1116	Age ≥1 CXR+ Cases N=653
Blood culture						
Results available	3926 (98.6)	1749 (98.9)	1231 (98.5)	518 (99.8)	1099 (98.5)	650 (99.5)
Any Organism[a]	121 (3.1)	56 (3.2)	31 (2.5)	25 (4.8)	31 (2.8)	25 (3.8)
S. pneumoniae	34 (0.9)	19 (1.1)	9 (0.7)	10 (1.9)	9 (0.8)	10 (1.5)
***S. pneumoniae*, PCV 13**	14 (0.4)	9 (0.5)	4 (0.3)	5 (1.0)	2 (0.2)	7 (1.1)
***S. pneumoniae*, non-PCV 13**	18 (0.5)	9 (0.5)	4 (0.3)	5 (1.0)	7 (0.6)	2 (0.3)
H. influenzae	20 (0.5)	12 (0.7)	7 (0.6)	5 (1.0)	8 (0.7)	4 (0.6)
***H. influenzae* type b**	10 (0.3)	6 (0.3)	3 (0.2)	3 (0.6)	4 (0.4)	2 (0.3)
***H. influenzae* non-type b**	10 (0.3)	6 (0.3)	4 (0.3)	2 (0.4)	4 (0.4)	2 (0.3)
S. aureus	14 (0.4)	6 (0.3)	1 (0.1)	5 (1.0)	6 (0.5)	0 (0.0)
Salmonella species[b]	17 (0.4)	8 (0.5)	5 (0.4)	3 (0.6)	3 (0.3)	5 (0.8)
Other non-fermentative gram-negative rods[C]	8 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Enterobacteriaceae[d]	16 (0.4)	5 (0.3)	3 (0.2)	2 (0.4)	3 (0.3)	2 (0.3)
Other Streptococci and Enterococci[e]	4 (0.1)	4 (0.2)	3 (0.2)	1 (0.2)	3 (0.3)	1 (0.2)
N. meningitidis	4 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)
M. catarrhalis	3 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)
Candida[f]	2 (0.1)	1 (0.1)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)
Mixed[g]	3 (0.1)	2 (0.1)	0 (0.0)	2 (0.4)	1 (0.1)	1 (0.2)
Contaminants	356 (9.1)	175 (10.0)	120 (9.7)	55 (10.6)	110 (10.0)	65 (10.0)
Induced sputum and gastric aspirate culture (for *Mycobacterium tuberculosis* only)						
Results available	3540 (88.9)	1571 (88.8)	1154 (92.3)	417 (80.4)	975 (8704)	596 (91.3)
M. tuberculosis[h]	28 (0.8)	24 (1.5)	15 (1.3)	9 (2.2)	18 (1.8)	6 (1.0)

Abbreviations: PCV, pneumococcal conjugate vaccine; CXR+, abnormal chest radiograph.

Table restricted to those organisms detected on the corresponding case-only specimen.

[a] Excludes contaminants. Isolation rates did not vary substantially by age strata (p=0.21, adjusting for site), but did vary by case severity (p=0.014, adjusting for site and age).

[b] *S. paratyphi* A (N=1); *S. typhi* (N=3); Other Salmonella spp (N=13).

[c] Acinetobacter species (N=1); *Pseudomonas aerugonisa* (N=7).

[d] *Enterobacter cloacae* (N=1); *Escherichia coli* (N=13); *Klebsiella pneumoniae* (N=4).

[e] *Enterococcus faecium* (N=2); *Streptococcus pyogenes* (N=2).

[f] *Candida albicans* (N=1); Candida species (N=1).

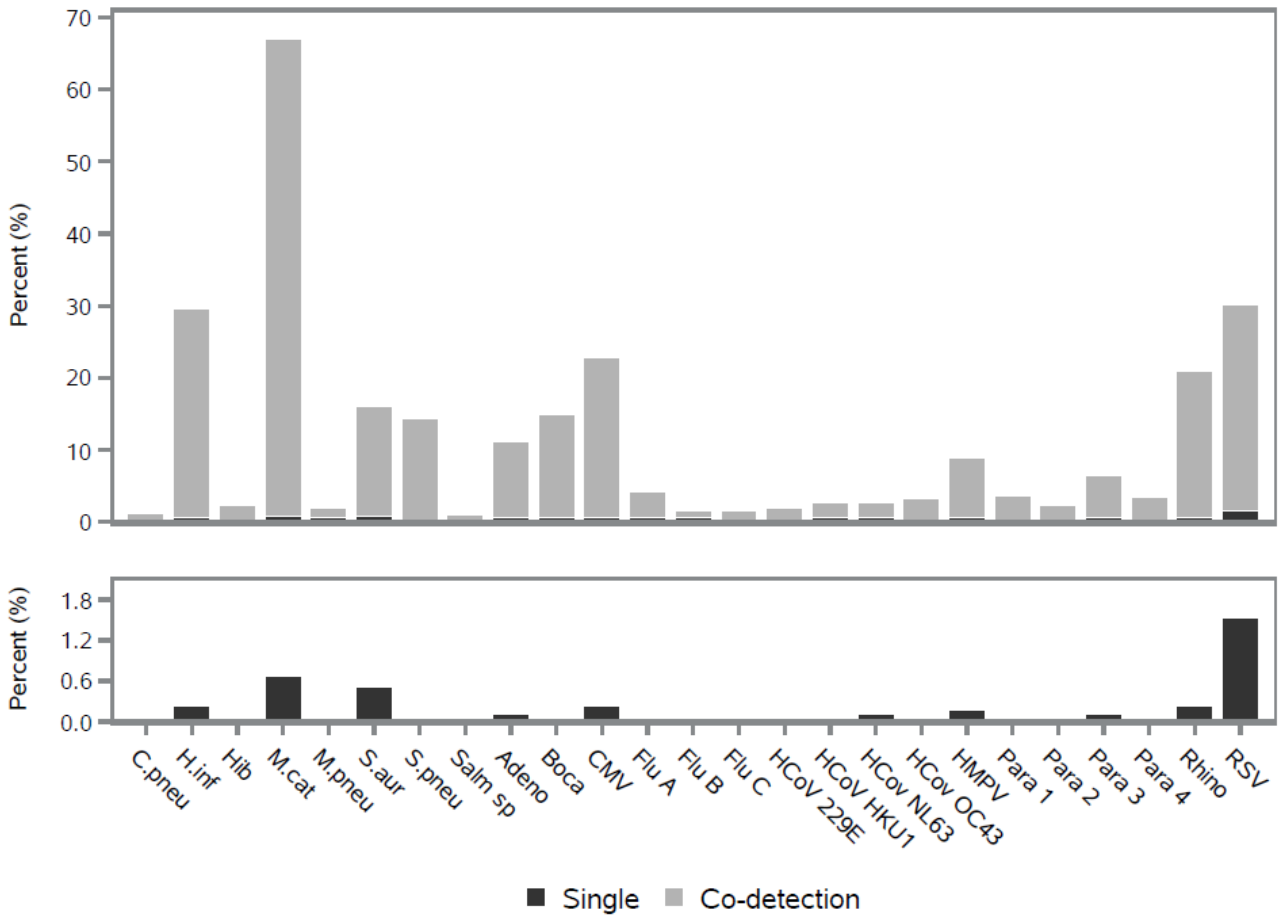
[g] *Escherichia coli* & *Klebsiella pneumoniae* (N=2); Salmonella species & *Streptococcus pyogenes* (N=1).

[h] *M. tuberculosis* positive on first induced sputum specimen, or first gastric aspirate if induced sputum unavailable. One case who did not have an induced sputum specimen available was positive by gastric aspirate; all other positives were detected by induced sputum. Using any result on induced sputum or gastric aspirate to define positivity, 14 total *M. tuberculosis* positive cases were detected in South Africa.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Figure 3: Detection of pathogens by PCR in NP/OP specimens among HIV-uninfected children with density thresholds applied for selected pathogens

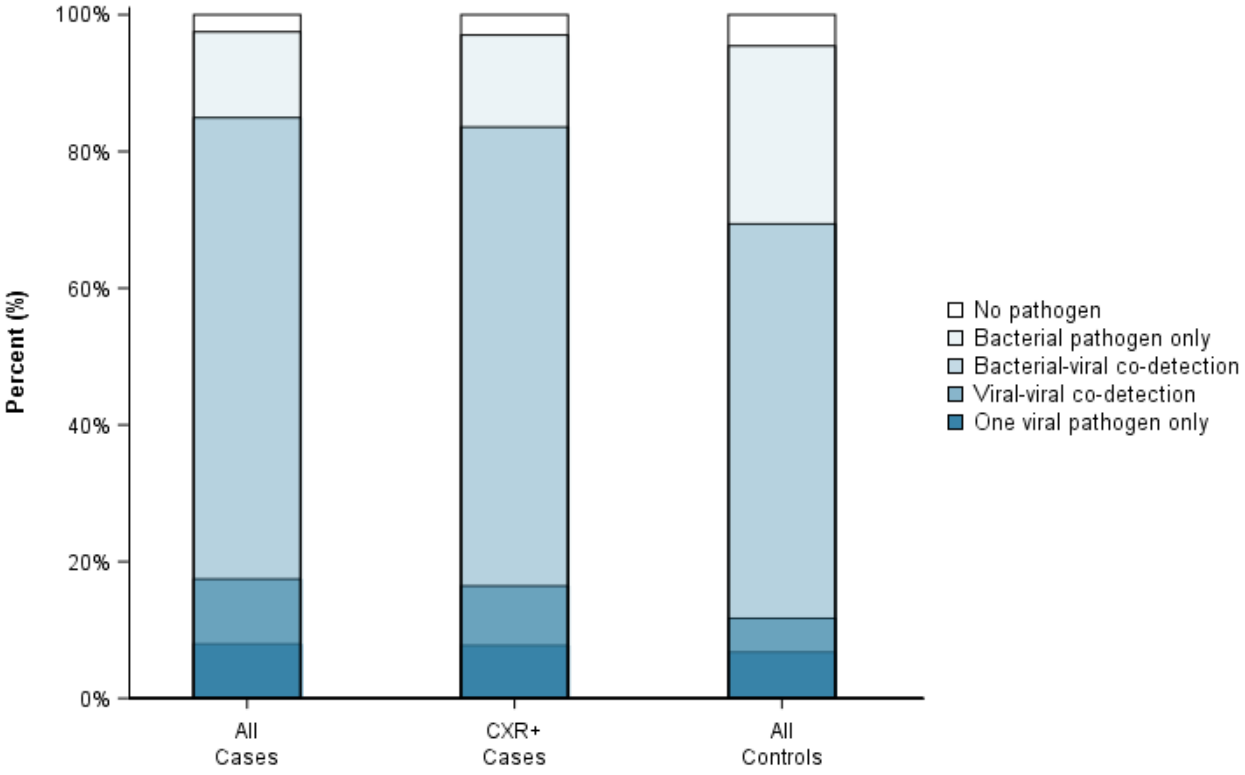
a. CXR+ cases, for individual pathogens by single versus co-detection



Abbreviations: CMV, cytomegalovirus; CXR, chest radiograph; Flu A, influenza A; Flu B, influenza B; Flu C, influenza C; HCoV, human coronavirus; HMPV, human metapneumovirus; NP/OP, nasopharyngeal/oropharyngeal; Para 1, parainfluenza virus 1; Para 2, parainfluenza virus 2; Para 3, parainfluenza virus 3; Para 4, parainfluenza virus 4; PCR, polymerase chain reaction; Rhino, human rhinovirus; RSV, respiratory syncytial virus.

Detection based on NP/OP PCR positivity except for pathogens with specified density thresholds: *H. influenzae*, 5.9 $\log_{10}$ copies/mL; CMV, 4.9 $\log_{10}$ copies/mL; *S. pneumoniae*, 6.9 $\log_{10}$ copies/mL.
Single and co-detection for a given pathogen are mutually exclusive. A case with co-detection for two pathogens will be counted in the co-detection bar for both pathogens.

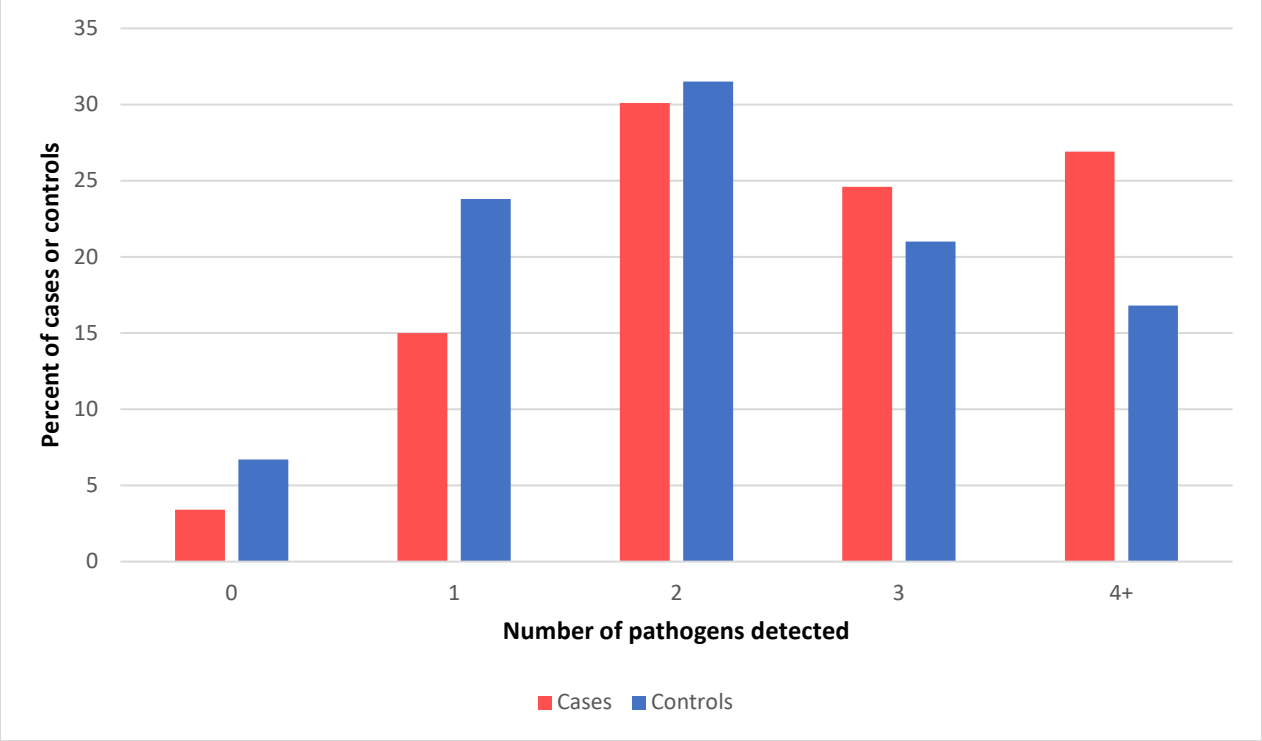
b. Among all cases, CXR+ cases and controls, by bacterial vs. viral combinations



Abbreviations: CXR, chest radiograph; NP/OP, nasopharyngeal/oropharyngeal; PCR, polymerase chain reaction.

Detection based on NP/OP PCR positivity except for the four pathogens with specified density thresholds: *H. influenzae*, 5.9 $\log_{10}$ copies/mL; CMV, 4.9 $\log_{10}$ copies/mL; *S. pneumoniae*, 6.9 $\log_{10}$ copies/mL.

c. Among CXR+ cases and controls, number of pathogens detected



Abbreviation: CXR, chest radiograph; NP/OP, nasopharyngeal/oropharyngeal; PCR, polymerase chain reaction.

Detection based on NP/OP PCR positivity except for pathogens with specified density thresholds: *P. jirovecii*, 4.0 $\log_{10}$ copies/mL; *H. influenzae*, 5.9 $\log_{10}$ copies/mL; CMV, 4.9 $\log_{10}$ copies/mL; *S. pneumoniae*, 6.9 $\log_{10}$ copies/mL.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Table 7. Detection of organisms in NP/OP specimens from HIV-uninfected cases and controls, prevalence and odds ratios.

a. By pathogen detected

				Odds Ratios adjusted for age and site [a]		Odds Ratios adjusted for age, site, and all other NP/OP pathogens[b]	
	All Cases N=3910	CXR+ Cases N=1737	All Controls N=4984	All Cases vs All Controls	CXR+ Cases vs All Controls	All Cases vs All Controls	CXR+ Cases vs All Controls
Any pathogen	3867 (98.9)	1721 (99.1)	4886 (98.0)	1.79 (1.24, 2.59)	2.17 (1.26, 3.71)		
Any pathogen, with thresholds applied	3770 (96.4)	1678 (96.6)	4644 (93.2)	1.74 (1.41, 2.14)	1.84 (1.38, 2.46)		
Any bacteria	3602 (92.1)	1606 (92.5)	4709 (94.5)	0.64 (0.53, 0.77)	0.71 (0.56, 0.90)	--	--
Any bacteria, with thresholds applied for select bacteria[c]	3122 (79.8)	1385 (79.7)	4189 (84.0)	0.68 (0.61, 0.76)	0.70 (0.60, 0.81)	--	--
S. pneumoniae							
Any positivity	2817 (72.0)	1265 (72.8)	3846 (77.2)	0.73 (0.66, 0.80)	0.78 (0.68, 0.89)	0.77 (0.68, 0.86)	0.83 (0.71, 0.97)
>6.9 $\log_{10}$ copies/mL	492 (12.6)	235 (13.5)	380 (7.6)	1.62 (1.40, 1.87)	1.82 (1.52, 2.17)	1.59 (1.35, 1.88)	1.82 (1.48, 2.24)
Among those with high density[d] *S. pneumoniae* on PCR							
PCV13-type	201 (40.9)	97 (41.3)	160 (42.1)	1.57 (1.26, 1.95)	1.80 (1.38, 2.35)	1.52 (1.19, 1.93)	1.83 (1.36, 2.47)
Non PCV13-type	266 (54.1)	138 (58.7)	220 (57.9)	1.43 (1.18, 1.72)	1.71 (1.36, 2.14)	1.36 (1.10, 1.68)	1.60 (1.23, 2.08)
H. influenzae	2099 (53.7)	1004 (57.8)	2566 (51.6)	1.08 (0.99, 1.18)	1.30 (1.16, 1.46)	1.03 (0.93, 1.14)	1.24 (1.08, 1.41)
>5.9 $\log_{10}$ copies/mL	1058 (27.1)	513 (29.5)	1078 (21.7)	1.26 (1.14, 1.40)	1.45 (1.27, 1.65)	1.25 (1.11, 1.41)	1.38 (1.19, 1.61)
H. influenzae non-b	2008 (51.4)	962 (55.4)	2470 (49.6)	1.06 (0.97, 1.15)	1.27 (1.13, 1.42)	1.02 (0.92, 1.12)	1.22 (1.07, 1.40)
H. influenzae non-b >5.9 $\log_{10}$ copies/mL	1020 (26.1)	493 (28.4)	1057 (21.2)	1.23 (1.11, 1.36)	1.40 (1.22, 1.59)	1.22 (1.09, 1.38)	1.35 (1.16, 1.58)
H. influenzae type b	91 (2.3)	42 (2.4)	96 (1.9)	1.26 (0.93, 1.69)	1.33 (0.91, 1.94)	1.33 (0.96, 1.85)	1.74 (1.14, 2.66)
H. influenzae type b >5.9 $\log_{10}$ copies/mL	40 (1.0)	20 (1.2)	24 (0.5)	1.94 (1.16, 3.24)	2.34 (1.28, 4.29)	2.16 (1.23, 3.80)	2.63 (1.33, 5.21)
S. *aureus*	627 (16.0)	268 (15.4)	676 (13.6)	1.16 (1.02, 1.30)	1.09 (0.93, 1.28)	1.13 (0.98, 1.29)	1.05 (0.87, 1.26)
B. pertussis	34 (0.9)	17 (1.0)	14 (0.3)	2.49 (1.32, 4.68)	2.63 (1.27, 5.42)	3.20 (1.65, 6.18)	3.33 (1.55, 7.15)
C. pneumoniae	35 (0.9)	21 (1.2)	66 (1.3)	0.66 (0.43, 1.00)	0.87 (0.53, 1.44)	0.63 (0.40, 1.00)	0.88 (0.50, 1.55)
M. catarrhalis	2600 (66.5)	1153 (66.4)	3705 (74.3)	0.61 (0.55, 0.67)	0.62 (0.54, 0.70)	0.60 (0.54, 0.67)	0.61 (0.52, 0.70)
M. pneumoniae	44 (1.1)	22 (1.3)	52 (1.0)	1.35 (0.89, 2.06)	1.58 (0.94, 2.65)	1.10 (0.69, 1.77)	1.11 (0.60, 2.07)
Salmonella species	28 (0.7)	17 (1.0)	25 (0.5)	1.21 (0.70, 2.09)	1.76 (0.94, 3.31)	0.85 (0.46, 1.57)	1.31 (0.64, 2.68)
Legionella species	1 (0.03)	0 (0.0)	0 (0.0)	--	--	--	--
Fungi							
P. jirovecii	311 (8.0)	154 (8.9)	381 (7.6)	0.81 (0.69, 0.95)	0.89 (0.73, 1.09)	0.86 (0.72, 1.03)	1.00 (0.80, 1.26)
P. jirovecii >4.0 $\log_{10}$ copies/mL	139 (3.6)	74 (4.3)	106 (2.1)	1.30 (1.00, 1.69)	1.54 (1.13, 2.09)	1.42 (1.07, 1.88)	1.85 (1.32, 2.59)
Any Virus	3480 (89.0)	1562 (89.9)	3947 (79.2)	2.13 (1.88, 2.42)	2.40 (2.02, 2.85)	--	--

Any virus, with thresholds applied for CMV[C]	3275 (83.8)	1483 (85.4)	3337 (67.0)	2.47 (2.22, 2.74)	2.77 (2.38, 3.21)	--	--
Adenovirus	405 (10.4)	169 (9.7)	616 (12.4)	0.94 (0.82, 1.08)	0.89 (0.74, 1.07)	1.16 (1.00, 1.34)	1.08 (0.88, 1.33)
CMV	1961 (50.2)	890 (51.2)	2739 (55.0)	0.82 (0.75, 0.90)	0.88 (0.79, 0.99)	0.93 (0.84, 1.03)	1.00 (0.88, 1.14)
CMV >4.9 $\log_{10}$ copies/mL	873 (22.3)	394 (22.7)	1124 (22.6)	0.82 (0.74, 0.91)	0.84 (0.73, 0.96)	0.83 (0.73, 0.93)	0.83 (0.71, 0.97)
Coronavirus 43	108 (2.8)	39 (2.2)	191 (3.8)	0.67 (0.53, 0.85)	0.53 (0.37, 0.76)	0.84 (0.65, 1.09)	0.71 (0.48, 1.03)
Coronavirus 63	85 (2.2)	36 (2.1)	159 (3.2)	0.63 (0.48, 0.83)	0.61 (0.42, 0.89)	0.77 (0.58, 1.03)	0.81 (0.55, 1.21)
Coronavirus HKU	61 (1.6)	37 (2.1)	111 (2.2)	0.65 (0.47, 0.89)	0.92 (0.63, 1.34)	0.84 (0.60, 1.18)	1.12 (0.74, 1.70)
Coronavirus 229	44 (1.1)	18 (1.0)	54 (1.1)	0.98 (0.66, 1.48)	0.95 (0.55, 1.63)	0.76 (0.48, 1.22)	0.65 (0.34, 1.22)
HBOV	513 (13.1)	235 (13.5)	657 (13.2)	1.09 (0.96, 1.24)	1.15 (0.98, 1.36)	1.21 (1.05, 1.39)	1.25 (1.03, 1.50)
HMPV A/B	267 (6.8)	147 (8.5)	115 (2.3)	3.00 (2.40, 3.76)	3.92 (3.03, 5.06)	4.58 (3.62, 5.80)	6.26 (4.78, 8.20)
Influenza virus (all subtypes)	180 (4.6)	90 (5.2)	114 (2.3)	2.05 (1.61, 2.61)	2.28 (1.71, 3.04)	2.53 (1.95, 3.28)	2.66 (1.94, 3.66)
Influenza A	118 (3.0)	62 (3.6)	57 (1.1)	2.68 (1.94, 3.71)	3.16 (2.18, 4.57)	3.30 (2.34, 4.64)	3.55 (2.37, 5.33)
Influenza B	43 (1.1)	18 (1.0)	29 (0.6)	2.05 (1.27, 3.33)	1.87 (1.02, 3.42)	2.76 (1.65, 4.61)	2.66 (1.40, 5.03)
Influenza C	19 (0.5)	10 (0.6)	29 (0.6)	0.75 (0.42, 1.34)	0.87 (0.42, 1.80)	0.69 (0.36, 1.32)	0.73 (0.32, 1.70)
Measles[e] (n=33)	4 (0.1)	0 (0.0)	N/A	--	--	--	--
Parainfluenza virus	440 (11.3)	208 (12.0)	296 (5.9)	1.94 (1.66, 2.27)	2.15 (1.78, 2.60)	2.62 (2.22, 3.10)	2.91 (2.37, 3.58)
Parainfluenza 1	99 (2.5)	45 (2.6)	27 (0.5)	4.63 (3.00, 7.14)	4.98 (3.05, 8.14)	7.52 (4.79, 11.80)	7.74 (4.62, 12.97)
Parainfluenza 2	51 (1.3)	23 (1.3)	54 (1.1)	1.13 (0.77, 1.68)	1.21 (0.73, 2.00)	0.98 (0.63, 1.51)	1.01 (0.57, 1.78)
Parainfluenza 3	224 (5.7)	104 (6.0)	143 (2.9)	1.91 (1.54, 2.37)	2.06 (1.59, 2.68)	2.62 (2.08, 3.29)	2.87 (2.17, 3.80)
Parainfluenza 4	90 (2.3)	44 (2.5)	86 (1.7)	1.37 (1.01, 1.85)	1.55 (1.07, 2.26)	1.74 (1.25, 2.41)	1.92 (1.27, 2.90)
PV/EV	349 (8.9)	131 (7.5)	436 (8.7)	1.04 (0.89, 1.21)	0.86 (0.70, 1.05)	1.44 (1.22, 1.70)	0.98 (0.77, 1.24)
Rhinovirus	901 (23.0)	360 (20.7)	1036 (20.8)	1.12 (1.01, 1.24)	0.94 (0.82, 1.08)	1.61 (1.43, 1.81)	1.32 (1.12, 1.54)
RSV	1036 (26.5)	506 (29.1)	161 (3.2)	10.03 (8.42, 11.94)	11.79 (9.72, 14.30)	12.59 (10.49, 15.12)	13.97 (11.39, 17.13)

[a] Odds ratios adjusted for age (months) and site.

[b] Odds ratios adjusted for age (months), site, and all other pathogens, which quantifies the degree of association between pneumonia case status and pathogen detection for persons who are otherwise similar with respect to age, site and the other measured pathogens.

[c] NP/OP PCR thresholds: *P. jirovecii*, 4.0 $\log_{10}$ copies/mL; *H. influenzae*, 5.9 $\log_{10}$ copies/mL; CMV, 4.9 $\log_{10}$ copies/mL; *S. pneumoniae*, 6.9 $\log_{10}$ copies/mL.

[d] High density *S. pneumoniae* defined as > 6.9 log10 copies/mL (NP/OP PCR). Pneumococcal serotypes were determined from culture isolates by Quellung method or PCR; for NP/OP-culture negative but PCR-positive specimens, microarray was used to determine serotype.

[e] Measles PCR testing was done using a single-plex PCR method on the NP/OP viral transport medium specimen from cases meeting one or more of the following criteria: history of measles, measles admission diagnosis, measles discharge diagnosis, or measles rash at enrollment.

Organism abbreviations: CMV, cytomegalovirus; HBOV, human bocavirus; HMPV, human metapneumovirus; PV/EV, parechovirus/enterovirus; RSV, respiratory syncytial virus.

Note: no adjustments were made to the odds ratio for prior antibiotic use, which is known to influence bacterial positivity.

b. By number of organisms detected

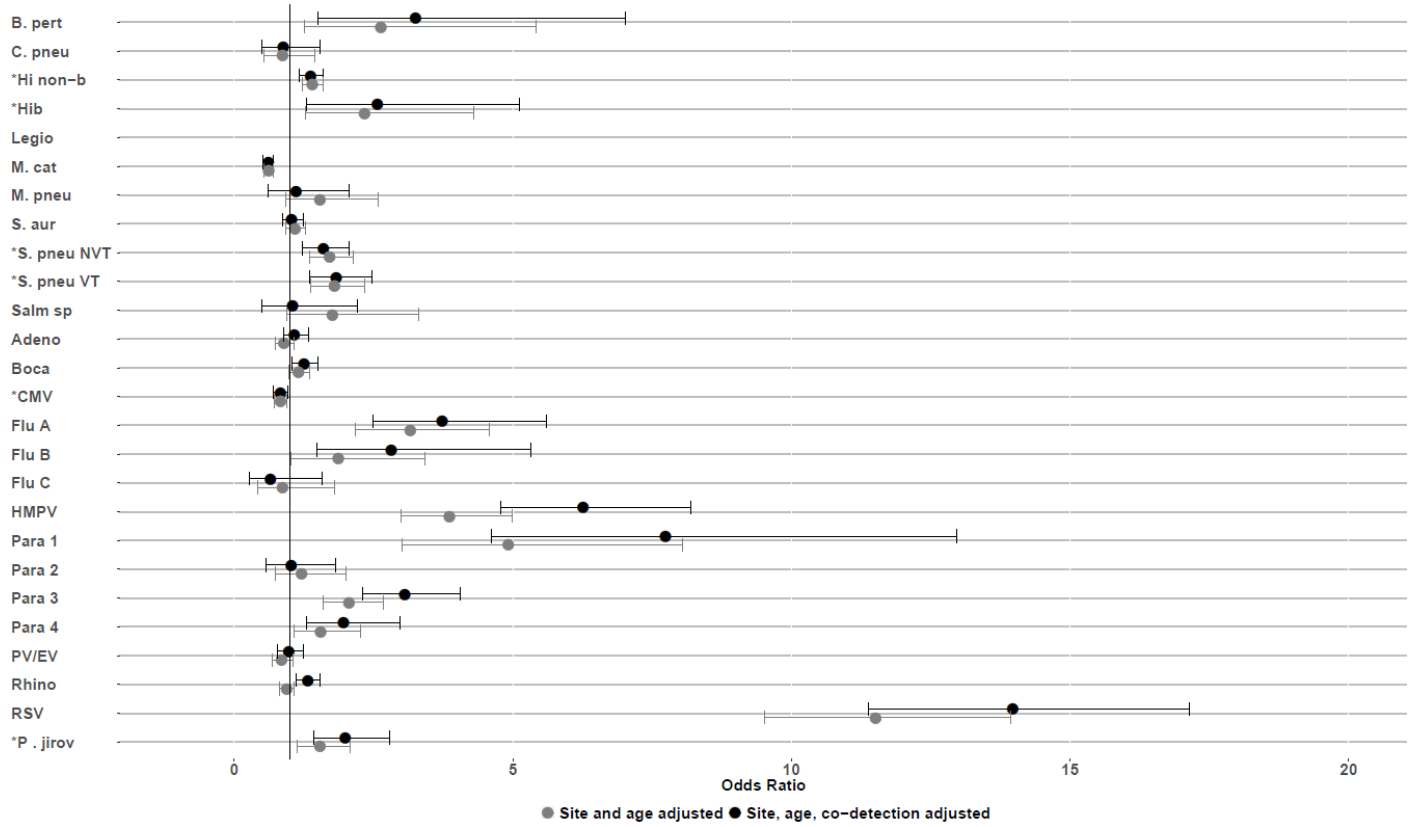
	All Cases N=3910	CXR+ Cases N=1737	All Controls N=4984	All Cases vs All Controls	CXR+ Cases vs All Controls
Number of organisms, any positivity					
Mean number of organisms, any positivity (SD)	3.83 (1.52)	3.91 (1.52)	3.62 (1.49)	.	.
0	41 (1.0)	16 (0.9)	94 (1.9)	0.0001	<0.0001
1	225 (5.8)	91 (5.2)	277 (5.6)		
2	485 (12.4)	202 (11.6)	742 (14.9)		
3	844 (21.6)	363 (20.9)	1197 (24.0)		
4+	2313 (59.2)	1065 (61.3)	2667 (53.5)		
Number of organisms, with thresholds applied for select pathogens*					
Mean number of organisms, with thresholds applied (SD)	2.65 (1.37)	2.70 (1.38)	2.25 (1.32)		
0	138 (3.5)	59 (3.4)	336 (6.7)	<0.0001	<0.0001
1	653 (16.7)	261 (15.0)	1187 (23.8)		
2	1150 (29.4)	523 (30.1)	1568 (31.5)		
3	971 (24.8)	427 (24.6)	1049 (21.0)		
4+	996 (25.5)	467 (26.9)	837 (16.8)		
Pathogen Patterns, any positivity					
Bacteria only				<0.0001	<0.0001
Single bacteria	96 (2.5)	42 (2.4)	195 (3.9)		
2 or more bacteria	287 (7.3)	113 (6.5)	736 (14.8)		
Virus only					
Single virus	139 (3.6)	53 (3.1)	102 (2.0)		
2 or more viruses	122 (3.1)	58 (3.3)	67 (1.3)		
Bacterial-Viral	3219 (82.3)	1451 (83.5)	3778 (75.8)		
Pathogen Patterns, with thresholds applied for select pathogens *					
Bacteria only				<0.0001	<0.0001
Single bacteria	301 (7.7)	108 (6.2)	899 (18.0)		
2 or more bacteria	189 (4.8)	82 (4.7)	407 (8.2)		
Virus only					
Single virus	365 (9.3)	159 (9.2)	308 (6.2)		
2 or more viruses	278 (7.1)	129 (7.4)	146 (2.9)		
Bacterial-Viral	2632 (67.3)	1195 (68.8)	2883 (57.8)		

*NP/OP PCR thresholds: *P. jirovecii*, 4.0 $\log_{10}$ copies/mL; *H. influenzae*, 5.9 $\log_{10}$ copies/mL; CMV, 4.9 $\log_{10}$ copies/mL; *S. pneumoniae*, 6.9 $\log_{10}$ copies/mL.

P-values are from logistic regression adjusted for site and age (in months).

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Figure 4: Pathogen-specific case-control odds ratios, by analytic method



Abbreviations: Adeno, Adenovirus; B. pert, *Bordetella pertussis*; Boca, Human bocavirus; C. pneu, *Chlamydophila pneumoniae*; CMV, cytomegalovirus; Flu, influenza virus; HCoV, Human coronavirus; Hib, *Haemophilus influenzae* type b; Hi non-b, *Haemophilus influenzae* non-type b; HMPV, Human metapneumovirus A/B; Legio, Legionella; M. cat, *Moraxella catarrhalis*; M. pneu, *Mycoplasma pneumoniae*; Para, Parainfluenza virus; P. jirov, *Pneumocystis jirovecii*; PV/EV, Parechovirus/Enterovirus; Rhino, Human rhinovirus; RSV, Respiratory syncytial virus A/B; S. aur, *Staphylococcus aureus*; S. pneu, *Streptococcus pneumoniae*; Salm sp, Salmonella species.

*Analysis includes the use of NP/OP PCR thresholds: *P. jirovecii*, 4.0 $\log_{10}$ copies/mL; *H. influenzae*, 5.9 $\log_{10}$ copies/mL; CMV, 4.9 $\log_{10}$ copies/mL; *S. pneumoniae*, 6.9 $\log_{10}$ copies/mL.
Gray: Odds ratios adjusted for age (months) and site.
Black: Odds ratios adjusted for age (months), site, and presence of other pathogens from NP/OP PCR, which quantifies the degree of association between pneumonia case status and pathogen detection for persons who are otherwise similar with respect to age, site and the other measured pathogens.
Note: no adjustments were made to the odds ratio for prior antibiotic use, which is known to influence bacterial positivity.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Table 8. Detection of organisms in specimens collected from HIV-uninfected/CXR+ cases and controls, by age and WHO-pneumonia severity

a. By pathogen detected

	Age <1		Age ≥1		Pneumonia severity	
	CXR+ Cases N=1095	All Controls N=2735	CXR+ Cases N=638	All Controls N=2242	Severe CXR+ Cases N=1227	Very Severe CXR+ Cases N=506
Any pathogen	1084 (99.0)	2678 (97.8)	637 (99.2)	2208 (98.4)	1224 (99.4)	497 (98.2)
Any pathogen, with thresholds applied	1067 (97.4)	2572 (93.9)	611 (95.2)	2072 (92.3)	1188 (96.5)	490 (96.8)
Any Bacteria	1003 (91.6)	2562 (93.5)	603 (93.9)	2147 (95.6)	1138 (92.4)	468 (92.5)
Any bacteria, with thresholds applied for select bacteria*	878 (80.2)	2304 (84.1)	507 (79.0)	1886 (84.0)	968 (78.6)	417 (82.4)
S. pneumoniae						
Any positivity	780 (71.2)	2080 (75.9)	485 (75.5)	1766 (78.7)	888 (72.1)	377 (74.5)
>6.9 $\log_{10}$ copies/mL	138 (12.6)	219 (8.0)	97 (15.1)	161 (7.2)	154 (12.5)	81 (16.0)
Among those with high density[a] *S. pneumoniae* on PCR						
PCV13-type	45 (32.6)	87 (39.7)	52 (53.6)	73 (45.3)	66 (42.9)	31 (38.3)
Non PCV13-type	90 (65.2)	130 (59.4)	48 (49.5)	90 (55.9)	86 (55.8)	52 (64.2)
H. influenzae						
H. influenzae non-b	600 (54.8)	1259 (46.0)	362 (56.4)	1211 (53.9)	685 (55.6)	277 (54.7)
H. influenzae non-b >5.9 $\log_{10}$ copies/mL	313 (28.6)	550 (20.1)	180 (28.0)	507 (22.6)	357 (29.1)	136 (26.9)
H. influenzae type b	24 (2.2)	44 (1.6)	18 (2.8)	52 (2.3)	30 (2.4)	12 (2.4)
H. influenzae type b >5.9 $\log_{10}$ copies/mL	10 (0.9)	12 (0.4)	10 (1.6)	12 (0.5)	13 (1.1)	7 (1.4)
S. *aureus*	201 (18.4)	454 (16.6)	67 (10.4)	222 (9.9)	168 (13.6)	100 (19.8)
B. pertussis	17 (1.6)	12 (0.4)	0 (0.0)	2 (0.1)	10 (0.8)	7 (1.4)
C. pneumoniae	13 (1.2)	24 (0.9)	8 (1.2)	42 (1.9)	14 (1.1)	7 (1.4)
M. catarrhalis	704 (64.3)	1986 (72.5)	449 (69.9)	1719 (76.6)	808 (65.6)	345 (68.2)
M. pneumoniae	10 (0.9)	24 (0.9)	12 (1.9)	28 (1.3)	18 (1.5)	4 (0.8)
PCP	146 (13.3)	360 (13.1)	8 (1.2)	21 (0.9)	100 (8.1)	54 (10.7)
PCP >4.0 $\log_{10}$ copies/mL	69 (6.3)	104 (3.8)	5 (0.8)	2 (0.1)	46 (3.7)	28 (5.5)
Salmonella species	11 (1.0)	16 (0.6)	6 (0.9)	9 (0.4)	11 (0.9)	6 (1.2)
Legionella species	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any Virus	987 (90.1)	2177 (79.5)	575 (89.6)	1766 (78.7)	1111 (90.3)	451 (89.1)
Any virus, with thresholds applied for CMV*	953 (87.0)	1952 (71.3)	531 (82.7)	1388 (61.8)	1055 (85.7)	429 (84.8)
Adenovirus	87 (8.0)	218 (8.0)	82 (12.8)	398 (17.7)	117 (9.6)	52 (10.3)
CMV	537 (49.4)	1556 (56.9)	353 (55.2)	1183 (52.7)	651 (53.3)	239 (47.4)
CMV >4.9 $\log_{10}$ copies/mL	332 (30.5)	964 (35.2)	62 (9.7)	160 (7.1)	285 (23.3)	109 (21.6)
Coronavirus 43	26 (2.4)	108 (3.9)	13 (2.0)	83 (3.7)	24 (1.9)	15 (3.0)
Coronavirus 63	23 (2.1)	93 (3.4)	13 (2.0)	66 (2.9)	28 (2.3)	8 (1.6)

Coronavirus HKU	28 (2.6)	59 (2.2)	9 (1.4)	52 (2.3)	24 (1.9)	13 (2.6)
Coronavirus 229	8 (0.7)	34 (1.2)	10 (1.6)	20 (0.9)	15 (1.2)	3 (0.6)
HBOV	117 (10.8)	285 (10.4)	118 (18.5)	372 (16.6)	172 (14.1)	63 (12.5)
HMPV A/B	97 (8.9)	59 (2.2)	50 (7.8)	56 (2.5)	103 (8.4)	44 (8.7)
Influenza A	34 (3.1)	28 (1.0)	28 (4.4)	29 (1.3)	42 (3.4)	20 (4.0)
Influenza B	11 (1.0)	10 (0.4)	7 (1.1)	19 (0.8)	13 (1.1)	5 (1.0)
Influenza C	8 (0.7)	15 (0.5)	2 (0.3)	14 (0.6)	7 (0.6)	3 (0.6)
Measles[b] (n=10)	0 (0.0)	--	0 (0.0)	--	0 (0.0)	0 (0.0)
Parainfluenza 1	21 (1.9)	15 (0.6)	24 (3.8)	12 (0.5)	34 (2.8)	11 (2.2)
Parainfluenza 2	15 (1.4)	24 (0.9)	8 (1.2)	30 (1.3)	21 (1.7)	2 (0.4)
Parainfluenza 3	76 (6.9)	89 (3.2)	28 (4.4)	54 (2.4)	79 (6.4)	25 (4.9)
Parainfluenza 4	24 (2.2)	38 (1.4)	20 (3.1)	48 (2.1)	33 (2.7)	11 (2.2)
PV/EV	71 (6.5)	254 (9.3)	60 (9.4)	182 (8.1)	97 (7.9)	34 (6.8)
Rhinovirus	207 (19.0)	632 (23.1)	153 (23.9)	404 (18.0)	237 (19.4)	123 (24.4)
RSV	396 (36.4)	91 (3.3)	110 (17.2)	70 (3.1)	380 (31.1)	126 (25.0)

Abbreviations: CMV, cytomegalovirus; HBOV, human bocavirus; HMPV, human metapneumovirus; PV/EV, parechovirus/enterovirus; RSV, respiratory syncytial virus.

[a] High density *S. pneumoniae* defined as > 6.9 log10 copies/mL (NP/OP PCR). Pneumococcal serotypes were determined from culture isolates by Quellung method or PCR; for NP/OP-culture negative but PCR-positive specimens, microarray was used to determine serotype.

[b] Measles PCR testing was done using a single-plex PCR method on the NP/OP viral transport medium specimen from cases meeting one or more of the following criteria: history of measles, measles admission diagnosis, measles discharge diagnosis, or measles rash at enrollment.

b. By number of organisms detected

	Age <1		Age ≥1		Pneumonia severity	
	CXR+ Cases N=1095	All Controls N=2739	CXR+ Cases N=638	All Controls N=2245	Severe CXR+ Cases N=1231	Very Severe CXR+ Cases N=506
Number of organisms, any positivity						
Mean number of organisms, any positivity (SD)	3.92 (1.55)	3.61 (1.54)	3.90 (1.48)	3.64 (1.45)	3.91 (1.52)	3.92 (1.54)
0	11 (1.0)	59 (2.2)	5 (0.8)	35 (1.6)	7 (0.6)	9 (1.8)
1	59 (5.4)	181 (6.6)	32 (5.0)	97 (4.3)	69 (5.6)	22 (4.3)
2	129 (11.8)	394 (14.4)	73 (11.4)	349 (15.5)	151 (12.3)	51 (10.1)
3	225 (20.5)	635 (23.2)	138 (21.5)	563 (25.1)	248 (20.1)	115 (22.7)
4+	671 (61.3)	1468 (53.6)	394 (61.4)	1199 (53.4)	756 (61.4)	309 (61.1)
Number of organisms, with thresholds applied for select pathogens*						
Mean number of organisms, with thresholds applied (SD)	2.82 (1.39)	2.35 (1.35)	2.56 (1.38)	2.14 (1.30)	2.71 (1.40)	2.75 (1.38)
0	28 (2.6)	165 (6.0)	31 (4.8)	171 (7.6)	43 (3.5)	16 (3.2)
1	155 (14.2)	595 (21.7)	105 (16.4)	589 (26.2)	190 (15.4)	70 (13.8)
2	306 (27.9)	852 (31.1)	214 (33.3)	709 (31.6)	366 (29.7)	154 (30.4)
3	285 (26.0)	610 (22.3)	135 (21.0)	437 (19.5)	293 (23.8)	127 (25.1)
4+	321 (29.3)	515 (18.8)	157 (24.5)	337 (15.0)	339 (27.5)	139 (27.5)
Pathogen Patterns, any positivity						
Bacteria only						
Single bacteria	24 (2.2)	125 (4.6)	18 (2.8)	70 (3.1)	31 (2.5)	11 (2.2)
2 or more bacteria	69 (6.3)	369 (13.5)	44 (6.9)	371 (16.5)	79 (6.4)	34 (6.7)
Virus only						
Single virus	39 (3.6)	74 (2.7)	14 (2.2)	28 (1.2)	43 (3.5)	10 (2.0)
2 or more viruses	38 (3.5)	35 (1.3)	20 (3.1)	32 (1.4)	40 (3.2)	18 (3.6)
Bacterial-Viral	910 (83.1)	2068 (75.5)	541 (84.3)	1706 (76.0)	1028 (83.5)	423 (83.6)
Pathogen Patterns, with thresholds applied for select pathogens*						
Bacteria only						
Single bacteria	62 (5.7)	427 (15.6)	45 (7.0)	468 (20.8)	75 (6.1)	32 (6.3)
2 or more bacteria	48 (4.4)	193 (7.0)	34 (5.3)	215 (9.6)	55 (4.5)	27 (5.3)
Virus only						
Single virus	99 (9.0)	188 (6.9)	59 (9.2)	120 (5.3)	121 (9.8)	37 (7.3)
2 or more viruses	86 (7.9)	80 (2.9)	44 (6.9)	65 (2.9)	96 (7.8)	34 (6.7)
Bacterial-Viral	768 (70.1)	1684 (61.5)	428 (66.7)	1203 (53.6)	838 (68.1)	358 (70.8)

*NP/OP PCR thresholds: *P. jirovecii*, 4.0 $\log_{10}$ copies/mL; *H. influenzae*, 5.9 $\log_{10}$ copies/mL; CMV, 4.9 $\log_{10}$ copies/mL; *S. pneumoniae*, 6.9 $\log_{10}$ copies/mL.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Table 9. Whole-blood pneumococcal PCR results from HIV-uninfected cases and controls, by age and severity status of cases

					Age <1			Age ≥1			Pneumonia severity (cases only)			
	All Cases N=3757	CXR+ Cases N=1676	All Controls N=4779	OR (95% CI) CXR+ Cases vs All Controls	CXR+ Cases N=1053	All Controls N=2606	OR (95% CI)	CXR+ Cases N=623	All Controls N=2173	OR (95% CI)	Severe CXR+ Cases N=1184	OR (95% CI)	Very Severe CXR+ Cases N=492	OR (95% CI)
WB PCR positivity	254 (6.8)	128 (7.6)	255 (5.3)	1.2 (1.0, 1.6)	80 (7.6)	154 (5.9)	1.1 (0.8, 1.5)	48 (7.7)	101 (4.7)	1.5 (1.0, 2.1)	78 (6.6)	1.1 (0.8, 1.4)	50 (10.2)	1.6 (1.1, 2.2)
WB PCR density ≥ 2.2 $\log_{10}$ copies/mL	177 (4.7)	91 (5.4)	144 (3.0)	1.6 (1.2, 2.1)	57 (5.4)	86 (3.3)	1.5 (1.0, 2.1)	34 (5.5)	58 (2.7)	1.9 (1.2, 2.9)	52 (4.4)	1.3 (1.0, 1.9)	39 (7.9)	2.2 (1.5, 3.2)

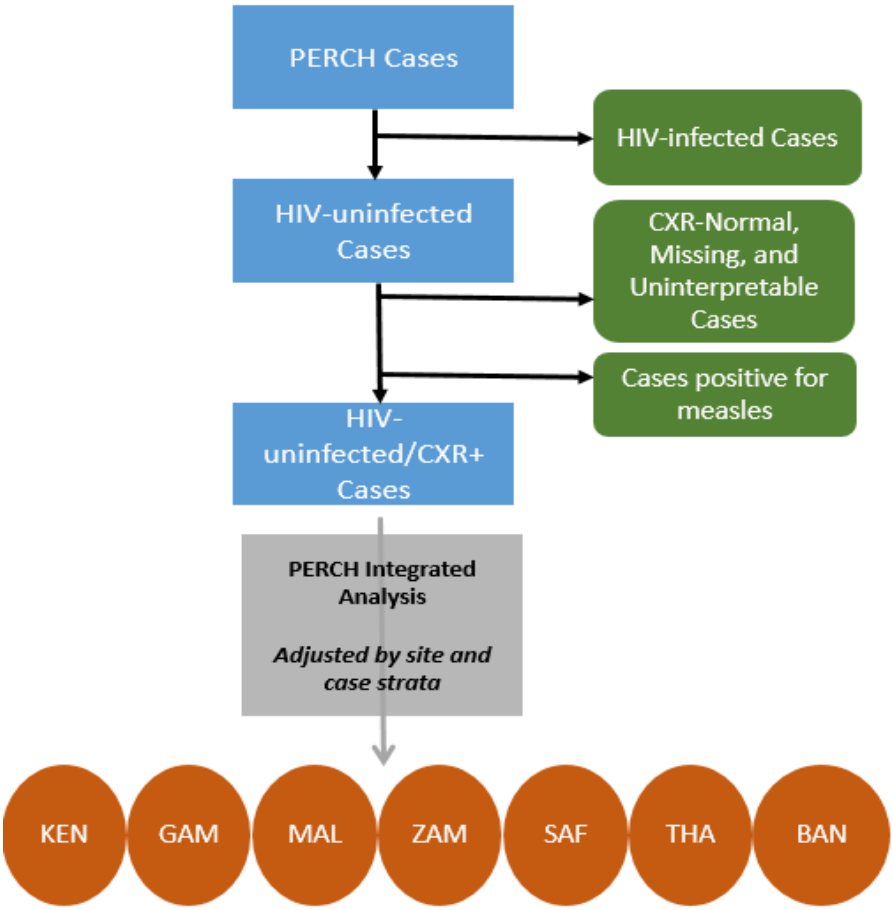
Abbreviations: OR, odds ratio, CI, confidence interval, WB, whole blood; CXR+, chest X-ray positive (consolidation and/or other infiltrate).

Odds ratios adjusted for site and age in months.

II. Supplementary Tables and Figures, Aetiologic

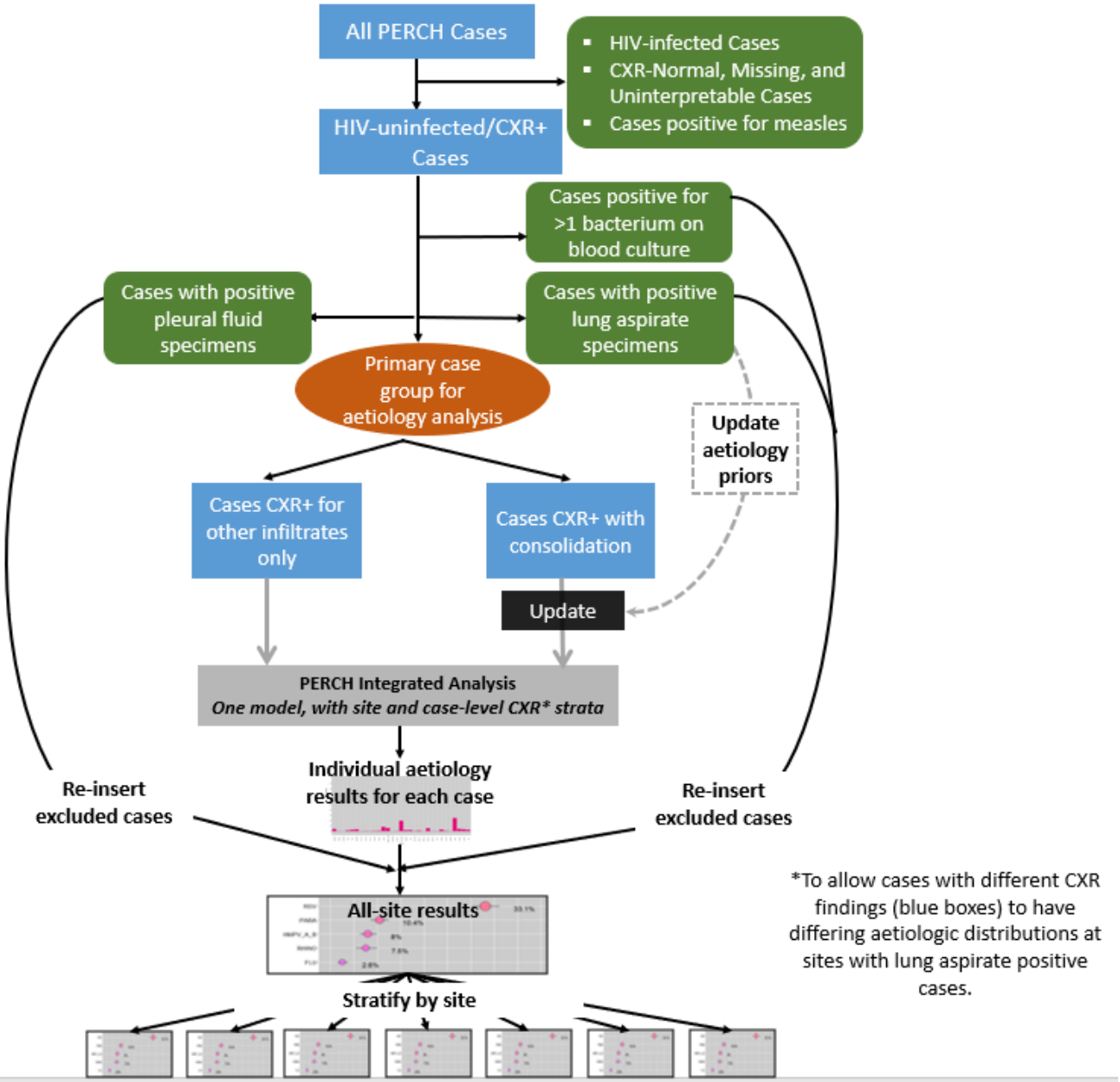
Supplementary Figure 5. Aetiology analysis methods

a. Flow diagram of analytic case group used in aetiology analysis



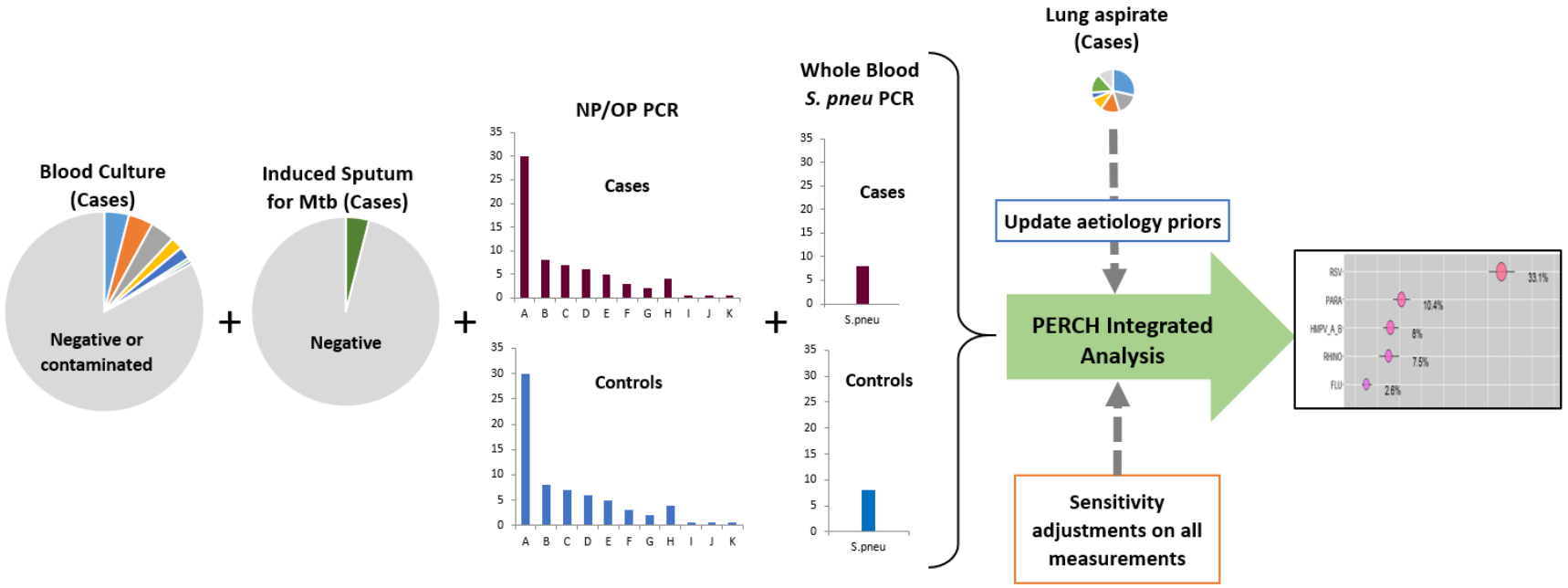
Abbreviations: BAN, Bangladesh; GAM, The Gambia; KEN, Kenya; MAL, Mali; SAF, South Africa; THA, Thailand; ZAM, Zambia.

b. Flow diagram of aetiology analysis within a site



For sites with lung aspirate positive cases (The Gambia and South Africa), cases positive on lung aspirate ('known cause') were accounted for in the final population aetiology estimate by using their results to update the prior distributions for the remaining consolidated cases. These remaining cases were then used in the PIA model to update the aetiology prior a second time to complete the analysis of all cases. Cases positive on pleural fluid similarly had a 'known cause' but due to the small numbers of remaining cases with a confirmed pleural effusion on CXR without pleural fluid findings, these positive results were not used to update their aetiology prior distributions but were used to determine the aetiology of those positive cases after the model was run. For sites with lung aspirate positives, cases are identified as being in one of two groups; one group representative of those with lung aspirates collected (cases with consolidation on CXR), and a second group of cases with other infiltrate. The aetiology analysis has been run on all sites and case groups combined, allowing the aetiologic distribution and false positive rates to vary across sites, and the aetiologic priors to vary by case sub-group within a site (e.g., based on lung aspirate or pleural fluid data), while the data informing sensitivity are from all the sites. The analysis allows for the estimation at the all-site level as well as the site-specific level.

c. PERCH Integrated Analysis (PIA) schematic



Abbreviations: NP/OP, nasopharyngeal/oropharyngeal swab; PCR, polymerase chain reaction; S. *pneu*, *Streptococcus pneumoniae*; Mtb = *Mycobacterium tuberculosis*.

For induced sputum *M. tuberculosis* analyses, positivity was assigned by first induced sputum, or by first gastric aspirate if induced sputum unavailable.

Lung aspirate results are restricted to specimens obtained within 3 days of enrollment and those pathogens determined by the clinical review team to be non-contaminants. Cases positive on lung aspirate ('known cause') were accounted for in the final population aetiology estimate by using their results to update the prior distributions for the remaining consolidated cases.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Table 10: Integrated aetiology results for HIV-uninfected/CXR+ cases from all PERCH sites combined by age and severity

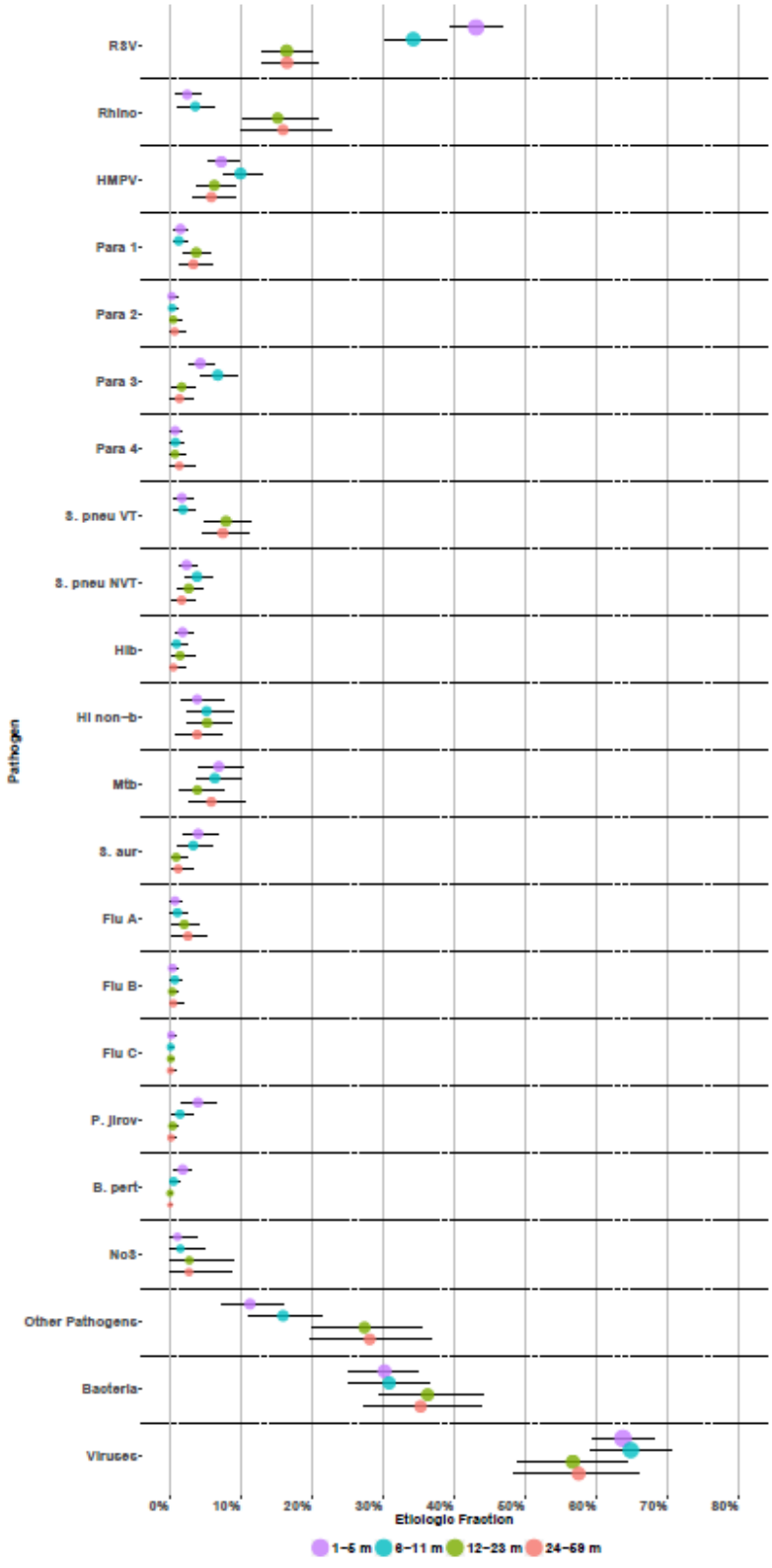
	All CXR+ Cases	Stratified by Age		Stratified by Severity*	
		<1 Year	≥1 year	Severe	Very Severe
Aetiology	**Aetiologic Fraction (95% CI)**	**Aetiologic Fraction (95% CI)**	**Aetiologic Fraction (95% CI)**	**Aetiologic Fraction (95% CI)**	**Aetiologic Fraction (95% CI)**
Bacteria					
B. pertussis	0.9 (0.4, 1.4)	1.4 (0.5, 2.2)	0.1 (0.0, 0.5)	0.5 (0.0, 1.1)	1.0 (0.2, 2.1)
C. pneumoniae	0.3 (0.0, 0.7)	0.3 (0.0, 0.8)	0.2 (0.0, 0.9)	0.4 (0.0, 0.9)	0.3 (0.0, 1.0)
Enterobacteriaceae	2.3 (0.8, 4.6)	2.2 (0.5, 5.0)	2.5 (0.6, 6.1)	2.1 (0.6, 4.6)	2.1 (0.6, 4.8)
H. influenzae	5.9 (3.8, 8.5)	5.9 (3.3, 9.3)	6.0 (3.2, 9.5)	4.9 (2.8, 7.5)	7.9 (4.0, 12.7)
Type b	1.4 (0.7, 2.4)	1.5 (0.7, 2.8)	1.2 (0.3, 2.9)	1.3 (0.6, 2.6)	1.8 (0.8, 3.9)
Non-b	4.5 (2.7, 7.0)	4.4 (2.1, 7.8)	4.8 (2.3, 8.0)	3.6 (1.7, 6.1)	6.1 (2.5, 10.8)
Legionella species	0.8 (0.0, 2.8)	0.5 (0.0, 2.5)	1.2 (0.0, 5.5)	0.6 (0.0, 2.7)	0.9 (0.0, 4.6)
M. catarrhalis	2.0 (0.7, 4.0)	1.2 (0.1, 3.4)	3.4 (0.9, 7.5)	2.2 (0.6, 4.7)	1.6 (0.2, 5.0)
M. pneumoniae	0.3 (0.0, 0.7)	0.1 (0.0, 0.4)	0.6 (0.0, 1.7)	0.3 (0.0, 0.9)	0.2 (0.0, 1.0)
M. tuberculosis	5.9 (3.9, 8.3)	6.7 (4.2, 9.9)	4.6 (2.1, 8.1)	5.4 (3.3, 8.2)	6.3 (3.3, 10.2)
N. meningitides	0.6 (0.1, 1.8)	0.4 (0.0, 1.6)	1.1 (0.2, 3.5)	0.6 (0.1, 1.8)	0.6 (0.0, 2.7)
Non-fermenting gram-negative rods	0.9 (0.1, 2.6)	0.7 (0.0, 2.8)	1.3 (0.0, 4.7)	0.8 (0.0, 3.0)	1.1 (0.0, 4.2)
Other streptococci and enterococci	2.2 (0.8, 4.2)	2.1 (0.5, 4.7)	2.4 (0.5, 6.0)	2.9 (1.0, 5.8)	1.2 (0.0, 4.6)
S. aureus	2.7 (1.5, 4.3)	3.7 (1.8, 6.1)	1.0 (0.3, 2.6)	1.1 (0.4, 2.4)	5.8 (2.9, 9.6)
S. pneumoniae	6.7 (5.1, 8.5)	4.7 (3.2, 6.6)	10.1 (7.4, 13.6)	4.6 (3.2, 6.2)	9.7 (6.9, 13.1)
VT	4.0 (2.8, 5.5)	1.8 (0.7, 3.1)	7.8 (5.2, 11.0)	2.9 (1.8, 4.2)	4.4 (2.5, 6.9)
NVT	2.7 (1.8, 3.9)	2.9 (1.8, 4.5)	2.4 (1.1, 4.1)	1.7 (0.9, 2.7)	5.3 (2.9, 8.1)
Salmonella species	1.6 (0.7, 3.4)	1.0 (0.3, 2.8)	2.7 (0.9, 5.8)	1.7 (0.6, 3.8)	1.3 (0.2, 3.7)
Fungi					
Candida species	1.5 (0.3, 3.4)	0.7 (0.0, 2.6)	2.9 (0.5, 7.0)	1.2 (0.2, 3.4)	1.2 (0.0, 4.8)
P. jirovecii	2.0 (0.9, 3.3)	3.0 (1.3, 5.1)	0.4 (0.0, 1.1)	1.2 (0.2, 2.4)	2.3 (0.4, 4.6)
Viruses					
Adenovirus	1.4 (0.6, 2.6)	1.5 (0.4, 2.8)	1.3 (0.0, 3.5)	1.3 (0.2, 2.9)	2.5 (0.4, 5.6)
Bocavirus	1.6 (0.4, 3.2)	1.0 (0.1, 2.5)	2.7 (0.2, 6.3)	1.6 (0.2, 3.7)	1.0 (0.0, 3.1)
CMV	0.7 (0.1, 1.9)	0.6 (0.0, 2.2)	1.0 (0.0, 3.2)	0.4 (0.0, 1.7)	1.1 (0.0, 4.0)
Coronavirus	0.4 (0.0, 1.1)	0.4 (0.0, 1.2)	0.5 (0.0, 1.8)	0.4 (0.0, 1.2)	0.5 (0, 1.9)
HMPV A/B	7.5 (5.9, 9.5)	8.3 (6.5, 10.7)	6.1 (4.0, 8.7)	8.2 (6.5, 10.6)	7.8 (5.2, 11.0)
Influenza	2.0 (1.1, 3.2)	1.6 (0.6, 2.9)	2.8 (1.1, 4.9)	2.0 (1.0, 3.3)	2.8 (1.0, 5.2)
A	1.4 (0.6, 2.3)	0.9 (0.2, 1.9)	2.2 (0.8, 4.1)	1.4 (0.6, 2.5)	2.0 (0.4, 4.0)
B	0.5 (0.1, 1.0)	0.5 (0.0, 1.3)	0.4 (0.0, 1.2)	0.5 (0.0, 1.0)	0.6 (0.0, 1.5)
C	0.2 (0.0, 0.5)	0.2 (0.0, 0.7)	0.1 (0.0, 0.6)	0.2 (0.0, 0.6)	0.2 (0.0, 1.0)
Parainfluenza	7.4 (5.8, 9.3)	7.8 (5.7, 10.1)	6.7 (4.1, 9.6)	9.0 (6.7, 11.6)	5.0 (2.7, 7.7)
1	2.2 (1.5, 3.2)	1.4 (0.7, 2.3)	3.6 (2.1, 5.4)	2.8 (1.8, 4.0)	1.8 (1.0, 3.1)
2	0.4 (0.0, 1.0)	0.3 (0.0, 1.0)	0.6 (0.0, 1.5)	0.5 (0.0, 1.1)	0.2 (0.0, 0.8)

	3	3.9 (2.7, 5.4)	5.2 (3.6, 7.3)	1.6 (0.3, 3.4)	4.8 (3.2, 6.8)	2.3 (0.6, 4.2)
	4	0.9 (0.3, 1.6)	0.8 (0.2, 1.7)	1.0 (0.0, 2.5)	0.9 (0.2, 2.0)	0.8 (0.0, 1.9)
PV/EV		1.6 (0.6, 2.8)	0.4 (0.0, 1.2)	3.8 (1.2, 6.6)	1.8 (0.4, 3.4)	0.9 (0.0, 3.1)
Rhinovirus		7.5 (5.3, 10.1)	2.9 (1.1, 5.0)	15.4 (10.6, 21.0)	8.1 (5.4, 11.1)	7.7 (3.3, 12.5)
RSV A/B		31.1 (28.4, 34.2)	39.7 (36.3, 43.5)	16.5 (13.5, 19.8)	35.2 (31.7, 39.6)	25.2 (22.0, 29.1)
Not otherwise specified		1.8 (0.2, 4.5)	1.3 (0.0, 4.0)	2.8 (0.0, 8.6)	1.5 (0.0, 5.0)	2.0 (0.0, 6.9)
Summary Estimates						
Bacteria**		27.3 (23.3, 31.6)	24.3 (19.7, 29.0)	32.6 (25.9, 40.1)	22.8 (18.3, 27.6)	33.7 (27.2, 40.8)
Viruses		61.4 (57.3, 65.6)	64.1 (59.7, 68.7)	56.9 (49.3, 64.3)	68.0 (62.7, 72.7)	54.5 (47.4, 61.5)

Abbreviation: CI, credible interval, VT, vaccine-type, PV/EV, parechovirus/enterovirus; CMV, cytomegalovirus; RSV, respiratory syncytial virus.
* Severity assigned according to the pre-2013 World Health Organization case definition.
**The bacteria summary estimate excludes *M. tuberculosis*.
Integrated etiology results are presented in Figure 4A-4C.
CXR+ defined as consolidation and/or other infiltrate on chest radiograph.
For pathogens presented grouped in Figure 4 (e.g., Parainfluenza virus types 1, 2, 3 and 4), both grouped and subspecies level results are presented here, with subspecies level results in gray.
Not otherwise specified represents pathogens not tested for.
Other Strep includes *Streptococcus pyogenes* and *Enterococcus faecium*.
Nonfermentative gram-negative rods includes Acinetobacter species and Pseudomonas species.
Enterobacteriaceae includes *E. coli*, Enterobacter species, and Klebsiella species, excluding mixed gram-negative rods.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Figure 6: All site integrated aetiology results, HIV-uninfected/CXR+ cases, stratified by age



Abbreviations: B. pert, *Bordetella pertussis*; Flu, influenza virus A, B and C; Hib, *Haemophilus influenzae* type b; Hi non-b, *Haemophilus influenzae* non-type b; HMPV, Human metapneumovirus A/B; Mtb, *Mycobacterium*

tuberculosis; NoS, Not Otherwise Specified (i.e., pathogens not tested for); P. jirov, *Pneumocystis jirovecii*; Para, Parainfluenza virus type 1, 2, 3 and 4; Rhino, Human rhinovirus; RSV, Respiratory syncytial virus A/B; S. aur, *Staphylococcus aureus*; S. pneu, *Streptococcus pneumoniae*; VT, PCV13 type pneumococci; NVT, non PCV 13 type pneumococci.
CXR+ defined as consolidation and/or other infiltrate on chest radiograph. Figure is restricted to the 10 focus pathogens from the All-Site analysis, plus *B. pertussis* (given its relevenace in the youngest children). The bacteria summary estimate excludes *M. tuberculosis*. 'Other Pathogens' represents sum of aetiology fraction for all remaining pathogens.
Exact figures are given in Supplementary Table 11.

Description of symbols: The size of the symbol is scaled based on the ratio of the estimated aetiologic fraction to its standard error. Of two identical aetiologic fraction estimates, the estimate associated with a larger symbol is more informed by the data.

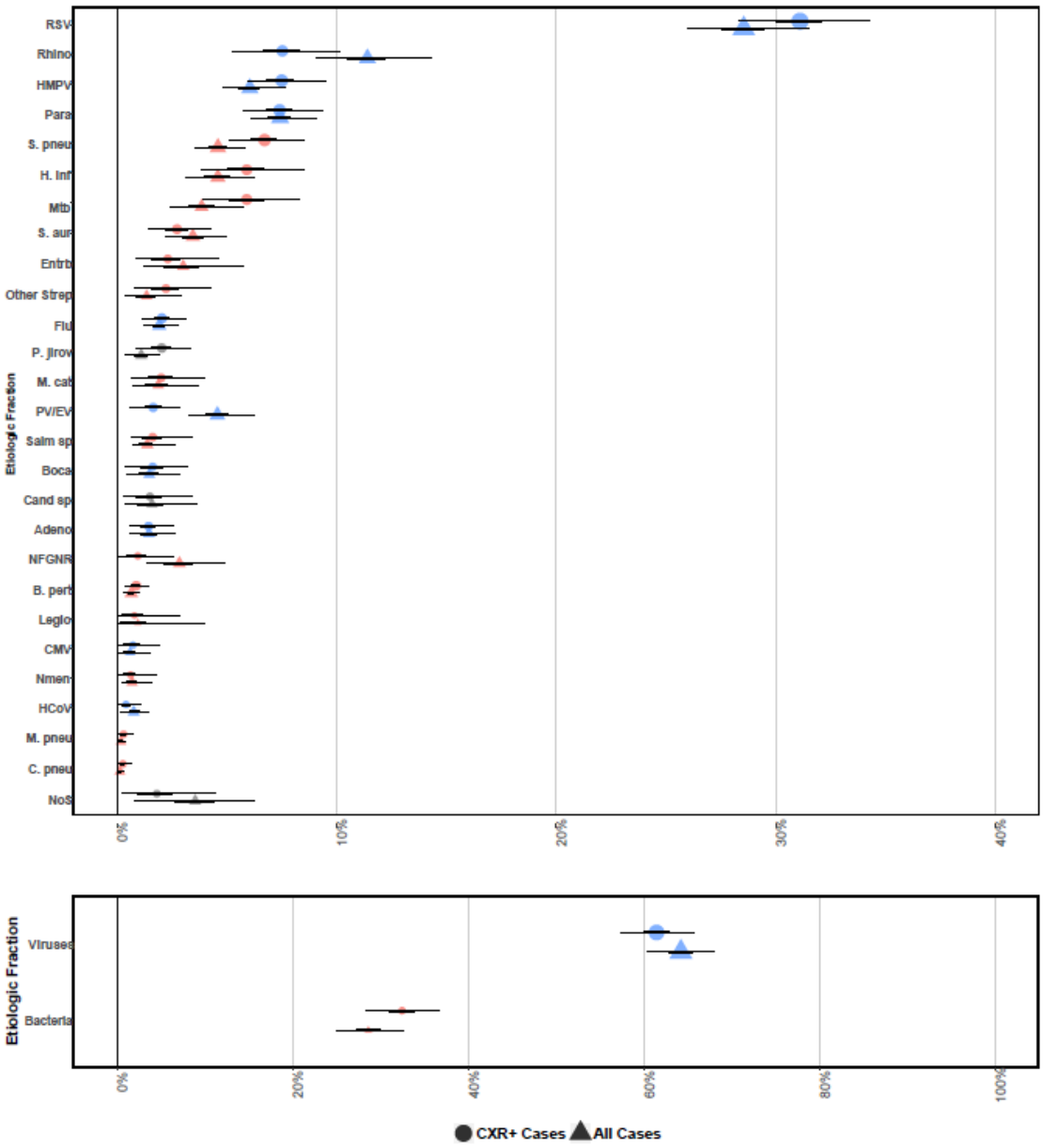
Supplementary Table 11: All site integrated aetiology results, 10 focus pathogens, HIV-uninfected/CXR+ stratified by age

	Stratified by Age			
	1-5 months	**6-11 months**	**12-23 months**	**24-59 months**
Aetiology	**Aetiologic Fraction (95% CI)**	**Aetiologic Fraction (95% CI)**	**Aetiologic Fraction (95% CI)**	**Aetiologic Fraction (95% CI)**
RSV A/B	43.0 (39.6, 46.8)	34.2 (30.2, 38.9)	16.4 (13.1, 20.0)	16.5 (12.9, 20.7)
Rhinovirus	2.5 (0.9, 4.3)	3.6 (1.2, 6.4)	15.2 (10.3, 20.9)	15.9 (10.1, 22.6)
HMPV A/B	7.3 (5.5, 9.7)	10.0 (7.5, 13)	6.3 (3.9, 9.2)	5.9 (3.2, 9.2)
Parainfluenza	6.9 (4.9, 9.3)	9.2 (6.4, 12.3)	6.7 (4.1, 9.9)	6.8 (3.2, 11.1)
S. pneumoniae	4.1 (2.5, 6.1)	5.7 (3.8, 8.0)	10.6 (7.3, 14.4)	9.2 (6.0, 12.9)
H. influenzae	5.7 (3.0, 9.4)	6.2 (3.1, 10.1)	6.7 (3.7, 10.6)	4.4 (1.4, 8.3)
M. tuberculosis	6.9 (4.1, 10.4)	6.4 (3.8, 9.9)	3.9 (1.4, 7.6)	5.9 (2.8, 10.6)
S. aureus	4.0 (2.0, 6.7)	3.3 (1.2, 5.9)	0.9 (0.2, 2.5)	1.2 (0.5, 3.2)
Influenza	1.4 (0.4, 2.6)	2.0 (0.5, 3.8)	2.6 (0.9, 4.8)	3.2 (0.9, 6.0)
P. jirovecii	4.0 (1.7, 6.5)	1.5 (0.2, 3.3)	0.4 (0.0, 1.1)	0.2 (0.0, 0.9)
B. pertussis	1.8 (0.7, 2.9)	0.6 (0.0, 1.4)	0.1 (0.0, 0.5)	0.1 (0.0, 0.5)
NoS	1.1 (0.0, 3.8)	1.5 (0.0, 5.0)	2.8 (0.0, 8.9)	2.7 (0.0, 8.8)
10 Focus Pathogens	85.8 (81.0, 90.0)	82 (76.4, 87.0)	69.8 (61.9, 77.3)	69.1 (60.4, 77.9)
Other Pathogens	13.1 (9.0, 17.8)	16.5 (11.6, 21.9)	27.4 (20.0, 35.3)	28.2 (19.8, 36.9)
Bacteria	23.8 (19.1, 28.6)	25.1 (19.6, 30.7)	33.5 (26.6, 41.5)	30.6 (22.6, 39.2)
Viruses	63.6 (59.3, 68.1)	64.8 (59.2, 70.5)	56.6 (48.9, 64.2)	57.4 (48.4, 65.9)

Abbreviations: CI, credible interval; HMPV, human metapneumovirus; NoS, Not Otherwise Specified (i.e., pathogens not tested for); RSV, respiratory syncytial virus.
Data presented in Supplemental Figure 6. CXR+ defined as consolidation and/or other infiltrate. Table is restricted to the 10 focus pathogens from the All-Site analysis, plus *B. pertussis* (given its relevenace in the youngest children). The bacteria summary estimate excludes *M. tuberculosis*. 'Other Pathogens' represents sum of all pathogens excluding the 10 focus pathogens. *B. pertussis* is included in the 'Other Pathogens' summary measure. Pathogens estimated at the subspecies level but grouped to the species level for display (Parainfluenza types 1, 2, 3 and 4; *S. pneumoniae* PCV 13 and *S. pneumoniae* non PCV 13 types; *H. influenzae* type b and *H. influenzae* non-type b; influenza A, B, C).

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Figure 7: all site aetiology results among HIV-uninfected cases. CXR+ Cases vs All Cases



Abbreviations: Adeno, Adenovirus; B. pert, *Bordetella pertussis*; Boca, Human bocavirus; C. pneu, *Chlamydophila pneumoniae*; Cand sp, Candida species; CMV, cytomegalovirus; Entrb, Enterobacteriaceae; Flu, influenza virus; H. inf, *Haemophilus influenzae*; HCoV, Coronavirus; HMPV, Human metapneumovirus A/B; Legio, Legionella species; Mtb, *Mycobacterium tuberculosis*; M. cat, *Moraxella catarrhalis*; M. pneu, *Mycoplasma pneumoniae*; NFGNR, nonfermentative gram-negative rods; N. men, *Neisseria meningitidis*; NoS, Not Otherwise Specified (i.e., pathogens not tested for); Para, Parainfluenza virus types 1, 2, 3 and 4; PV/EV, Parechovirus/Enterovirus; Rhino, Human rhinovirus; RSV, Respiratory syncytial virus A/B; S. aur, *Staphylococcus aureus*; S. pneu, *Streptococcus pneumoniae*; Salm sp, Salmonella species.
CXR+ defined as consolidation and/or other infiltrate on chest radiograph. The bacteria summary estimate excludes *M. tuberculosis*.
Other Strep includes *Streptococcus pyogenes* and *Enterococcus faecium*. NFGNR includes Acinetobacter species and Pseudomonas species. Enterobacteriaceae includes *E. coli*, Enterobacter species, and Klebsiella species, excluding mixed gram-negative rods.

Pathogens estimated at the subspecies level but grouped to the species level for display (Parainfluenza virus 1, 2, 3 and 4; *S. pneumoniae* PCV 13 and *S. pneumoniae* non PCV 13 types; *H. influenzae* type b and *H. influenzae* non-type b; influenza A, B, and C).

Description of symbols: Line represents the 95% credible interval; darker region of line represents the interquartile range. The size of the symbol is scaled based on the ratio of the estimated aetiologic fraction to its standard error. Of two identical aetiologic fraction estimates, the estimate associated with a larger symbol is more informed by the data.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Table 12: Site-specific aetiology results for 10 focus pathogens, HIV-uninfected/CXR+ cases

	Aetiologic Fraction (95% CI)						
	Gambia	**Mali**	**Kenya**	**Zambia**	**South Africa**	**Bangladesh**	**Thailand**
RSV	33.9 (28.5, 39.9)	21.8 (16.6, 27.2)	36.1 (32.1, 41.0)	21.2 (16.4, 26.8)	30.1 (25.5, 34.6)	32.2 (26.8, 38.8)	30.7 (24.1, 39.2)
Rhinovirus	1.6 (0.0, 6.7)	0.7 (0.0, 4.1)	12.9 (7.4, 20.4)	1.4 (0.0, 7.2)	3.6 (0.0, 8.8)	29.7 (16.9, 41.4)	4.7 (0.0, 16.4)
HMPV	4.0 (1.1, 7.0)	11.6 (8.1, 16.0)	10.9 (7.6, 14.9)	14.3 (8.5, 22.0)	3.5 (0.8, 6.7)	8.9 (5.1, 13.9)	2.6 (0.0, 8.5)
Parainfluenza	9.6 (5.1, 14.4)	11.2 (7.3, 16.3)	8.0 (3.7, 12.8)	2.6 (0.0, 7.6)	7.3 (4.2, 10.7)	4.7 (1.0, 10.0)	2.3 (0.0, 7.7)
S. pneumoniae	15.1 (11.0, 19.6)	17.4 (11.0, 25.2)	5.1 (2.8, 8.5)	4.3 (1.0, 10.6)	4.8 (2.2, 8.3)	1.5 (0.0, 4.6)	0.3 (0.0, 2.7)
VT	6.8 (4.0, 10.4)	12.2 (6.4, 19.5)	3.9 (1.9, 6.7)	3.7 (1.0, 9.8)	2.8 (0.6, 5.9)	0.3 (0.0, 2.4)	0.2 (0.0, 1.8)
NVT	8.3 (5.1, 12.0)	5.3 (2.2, 9.3)	1.2 (0.3, 3.1)	0.6 (0.0, 3.1)	2.0 (0.4, 4.7)	1.2 (0.0, 4.2)	0.1 (0.0, 1.5)
H. influenzae	5.6 (2.2, 10.5)	7.1 (3.3, 12.6)	5.7 (1.9, 10.9)	6.0 (0.4, 18.4)	11.2 (5.2, 18.2)	0.7 (0.0, 4.7)	5.0 (0.0, 17.7)
Type b	0.2 (0.0, 1.1)	4.2 (2.0, 7.7)	0.1 (0.0, 0.9)	3.4 (0.4, 12.1)	1.2 (0.2, 3.4)	0.1 (0.0, 0.9)	0.3 (0.0, 3.1)
Non-type b	5.4 (2.1, 10.3)	2.8 (0.3, 7.7)	5.6 (1.9, 10.8)	2.6 (0.0, 13.3)	10.0 (4.2, 16.7)	0.6 (0.0, 4.6)	4.7 (0.0, 17)
M. tuberculosis	8.4 (4.5, 14.1)	2.8 (0.5, 8.5)	1.9 (0.3, 6.0)	10.2 (4.1, 19.1)	6.4 (3.1, 11.3)	2.3 (0.8, 6.7)	7.0 (1.2, 20.5)
S. aureus	1.7 (1.1, 3.3)	4.8 (0.9, 11.0)	1.3 (0.3, 3.5)	4.1 (0.8, 9.8)	3.7 (1.3, 8.0)	0.2 (0.0, 2.3)	1.3 (0.0, 10.0)
Influenza	1.7 (0.0, 4.3)	1.2 (0.0, 3.6)	2.4 (0.0, 5.5)	6.2 (0.5, 12.6)	2.6 (0.4, 6.0)	0.5 (0.0, 2.3)	1.1 (0.0, 4.0)
P. jirovecii	0.2 (0.0, 1.4)	2.4 (0.0, 5.6)	2.3 (0.0, 5.0)	4.1 (0.0, 8.0)	2.1 (0.0, 5.0)	0.4 (0.0, 2.2)	0.1 (0.0, 1.5)
Not Otherwise Specified	1.0 (0.0, 6.4)	2.3 (0.0, 13.3)	1.8 (0.0, 10.1)	1.6 (0.0, 10.3)	1.7 (0.0, 8.7)	1.9 (0.0, 11.5)	7.4 (0.0, 34.7)
% of Etiology attributed to 10 Focus Pathogens	81.8 (74.0, 89.5)	80.9 (70.7, 90.0)	86.6 (77.4, 93.7)	74.2 (60.6, 86.5)	75.4 (66.3, 83.9)	81.3 (67.8, 91.6)	55.1 (37.0, 77.2)
Other Pathogens tested for	37.9 (29.9, 45.7)	41.4 (30.0, 51.6)	22.4 (14.4, 31.2)	34.4 (21.6, 48.2)	38.9 (29.6, 48.4)	19.1 (9.2, 31.9)	42.8 (18.0, 62.3)
Bacteria	32.7 (25.9, 40.8)	37.6 (27.0, 48.7)	17.5 (10.5, 26.3)	34.2 (21.2, 48.0)	33.2 (24.2, 43.2)	10.4 (3.4, 21.3)	34.5 (11.4, 57.3)
Viruses	53.7 (45.7, 61.8)	54.2 (44.4, 64.4)	75.4 (66.1, 83.8)	48.8 (37.7, 60.5)	55.4 (45.4, 65.0)	83.9 (70.5, 93.0)	47.4 (32.4, 65.7)

Data presented in Figure 5.

Abbreviations: CI, credible interval; HMPV, Human metapneumovirus A/B; RSV, Respiratory syncytial virus A/B.

CXR+ defined as consolidation and/or other infiltrate on chest radiograph. Restricted to the 10 focus pathogens from the all-site analysis. The bacteria summary estimate excludes *M. tuberculosis*. 'Other Pathogens' represents sum of all remaining pathogens (excluding NoS).

Site-specific results were standardized to the following case mix: 40% <1 year old (yo) with severe pneumonia; 20% <1yo with very severe pneumonia; 30% ≥1yo with severe pneumonia; 10% age ≥1yo with very severe pneumonia.

Pathogens estimated at the subspecies level but grouped to the species level for display (Parainfluenza virus types 1, 2, 3 and 4; *S. pneumoniae* PCV 13 and *S. pneumoniae* non PCV 13 types; *H. influenzae* type b and *H. influenzae* non-type b; influenza A, B, and C). Not Otherwise Specified represents pathogens not tested for.

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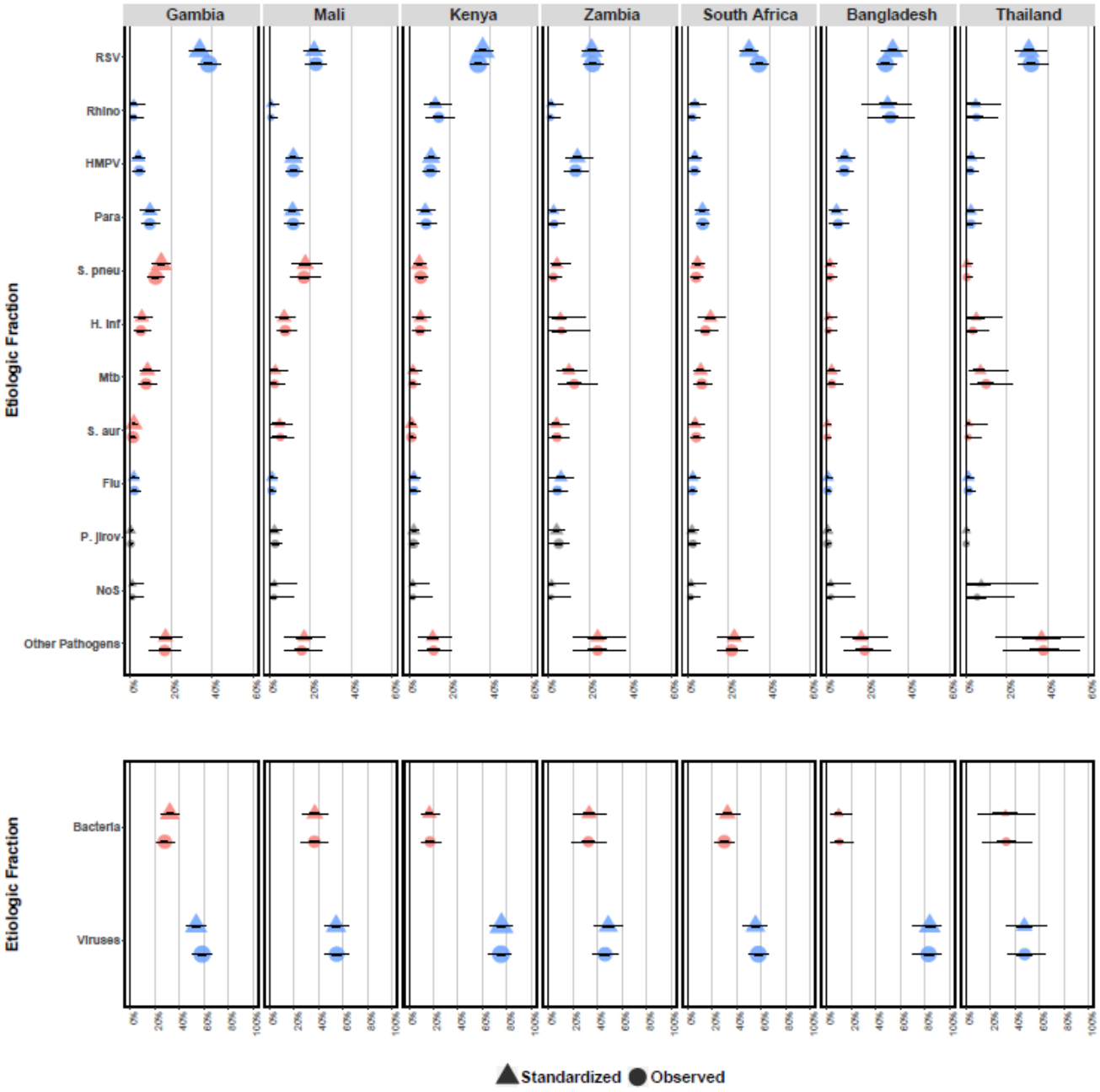
Supplementary Figure 8: Site-stratified aetiology results for 10 focus pathogens among HIV-uninfected/CXR+ cases, stratified by standardized and observed case distributions



Abbreviations: Flu, influenza A, B and C; H. inf, *Haemophilus influenzae*; HMPV, Human metapneumovirus A/B; Mtb, *Mycobacterium tuberculosis*; NoS, Not Otherwise Specified (i.e., pathogens not tested for); Para, Parainfluenza virus types 1, 2, 3 and 4; Rhino, Human rhinovirus; RSV, Respiratory syncytial virus A/B; S. aur, *Staphylococcus aureus*; S. pneu, *Streptococcus pneumoniae*.
CXR+ defined as consolidation and/or other infiltrate on chest radiograph. Restricted to the 10 focus pathogens from the All-Site analysis. The bacteria summary estimate excludes *M. tuberculosis*. 'Other Pathogens' represents sum of aetiology fraction for all remaining pathogens tested for not presented in this figure.
Site-specific results were standardized to the following case mix: 40% <1 year old (yo) with severe pneumonia; 20% <1yo with very severe pneumonia; 30% ≥1yo with severe pneumonia; 10% age ≥1yo with very severe pneumonia.

Pathogens estimated at the subspecies level but grouped to the species level for display (Parainfluenza virus types 1, 2, 3 and 4; *S. pneumoniae* PCV 13 and *S. pneumoniae* non PCV 13 types; *H. influenzae* type b and *H. influenzae* non-type b; influenza A, B, and C).
Description of symbols: Line represents the 95% credible interval; darker region of line represents the interquartile range. The size of the symbol is scaled based on the ratio of the estimated aetiologic fraction to its standard error. Of two identical aetiologic fraction estimates, the estimate associated with a larger symbol is more informed by the data than the priors.

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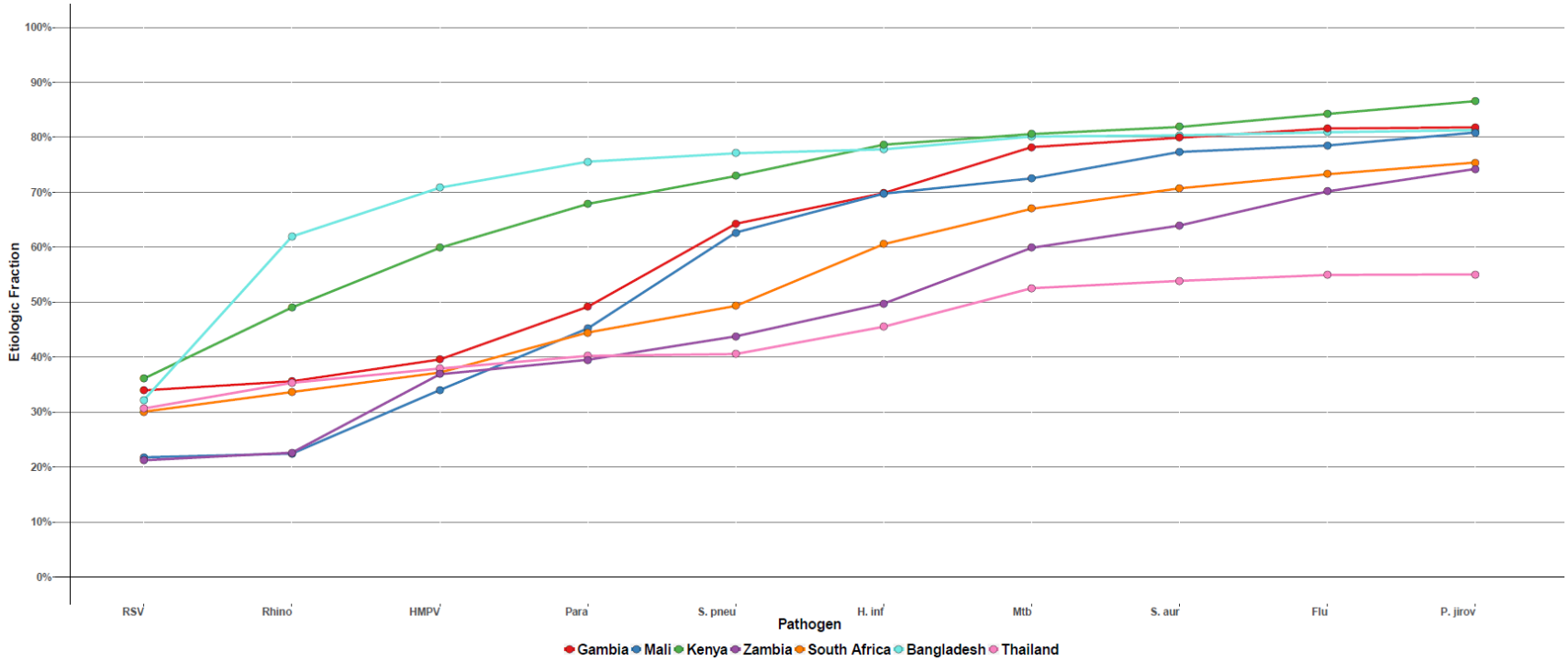
Supplementary Figure 9: All site 10 Focus pathogens, cumulative contribution of selected pathogens in HIV-uninfected/CXR+ cases, by site



Restricted to the 10 focus pathogens from the all-site analysis.
Abbreviations: Flu, influenza A, B, and C; H. inf, *Haemophilus influenzae*; HMPV, Human metapneumovirus A/B; Mtb, *Mycobacterium tuberculosis*; Para, Parainfluenza virus type 1, 2, 3 and 4; Rhino, Human rhinovirus; RSV, Respiratory syncytial virus A/B; S. aur, *Staphylococcus aureus*; S. pneu, *Streptococcus pneumoniae*.
CXR+ defined as consolidation and/or other infiltrate on chest radiograph. Pathogens estimated at the subspecies level but grouped to the species level for display (Parainfluenza virus type 1, 2, 3 and 4; *S. pneumoniae* PCV 13 and *S. pneumoniae* non PCV 13 types; *H. influenzae* type b and *H. influenzae* non-type b; influenza A, B, and C).
Site-specific results were standardized to the following case mix: 40% <1 year old (yo) with severe pneumonia; 20% <1yo with very severe pneumonia; 30% ≥1yo with severe pneumonia; 10% age ≥1yo with very severe pneumonia.

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Supplemental Table 13: Rank order of the 10 focus pathogens, by site among HIV-uninfected/CXR+ cases

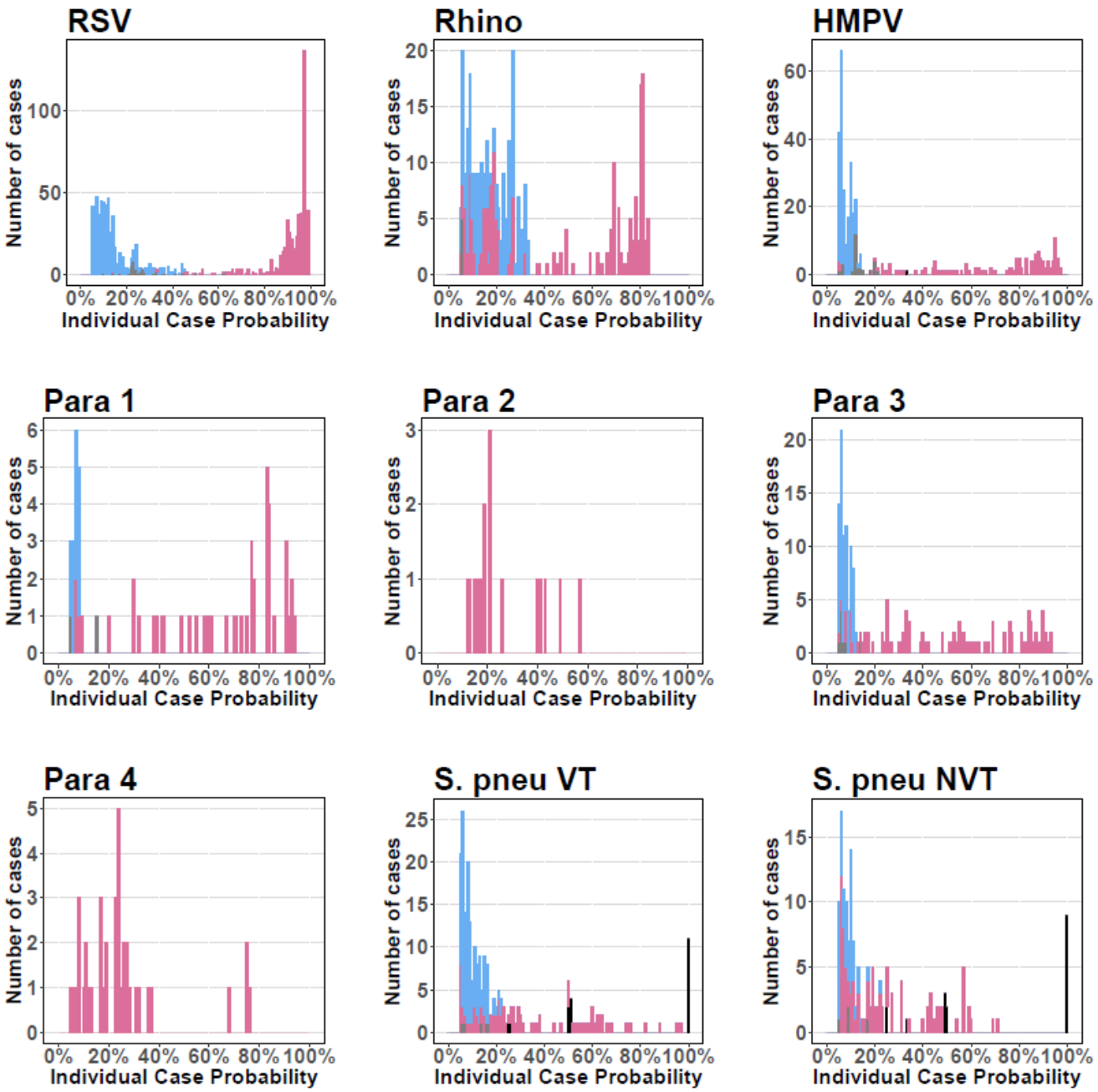
	The Gambia	Mali	Kenya	Zambia	South Africa	Bangladesh	Thailand
RSV	1	1	1	1	1	1	1
Parainfluenza	3	4	4	>10	3	4	>10
Rhinovirus	>10	>10	2	>10	9	2	7
HMPV	7	3	3	2	10	3	10
S. pneumoniae	2	2	6	8	5	>10	>10
M. tuberculosis	4	8	10	3	4	7	5
H. influenzae	5	5	5	7	2	>10	6
S. aureus	10	6	>10	10	8	>10	>10
Influenza	>10	>10	8	6	>10	>10	>10
P. jirovecii	>10	10	9	9	>10	>10	>10
Not otherwise specified	>10	>10	>10	>10	>10	9	4

Etiologic Fraction: < 2% | 2 - < 5% | 5 - <10% | 10 - <20% | ≥ 20%

Pathogen abbreviations: HMPV, Human metapneumovirus A/B; RSV, Respiratory syncytial virus A/B.
Number in cells indicate the site-specific rank order of the given pathogen. Shading of cells corresponds to the site-specific aetiologic fraction of the given pathogen.
CXR+ defined as consolidation and/or other infiltrate on chest radiograph. Restricted to the 10 focus pathogens from the all-site analysis. Not otherwise specified represents pathogens not tested for.
Pathogens estimated at the subspecies level but grouped to the species level for display (Parainfluenza virus types 1, 2, 3 and 4; *S. pneumoniae* PCV 13 and *S. pneumoniae* non PCV 13 types; *H. influenzae* type b and *H. influenzae* non-type b; influenza A, B, and C).
Site-specific results were standardized to the following case mix: 40% <1 year old (yo) with severe pneumonia; 20% <1yo with very severe pneumonia; 30% ≥1yo with severe pneumonia; 10% age ≥1yo with very severe pneumonia.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

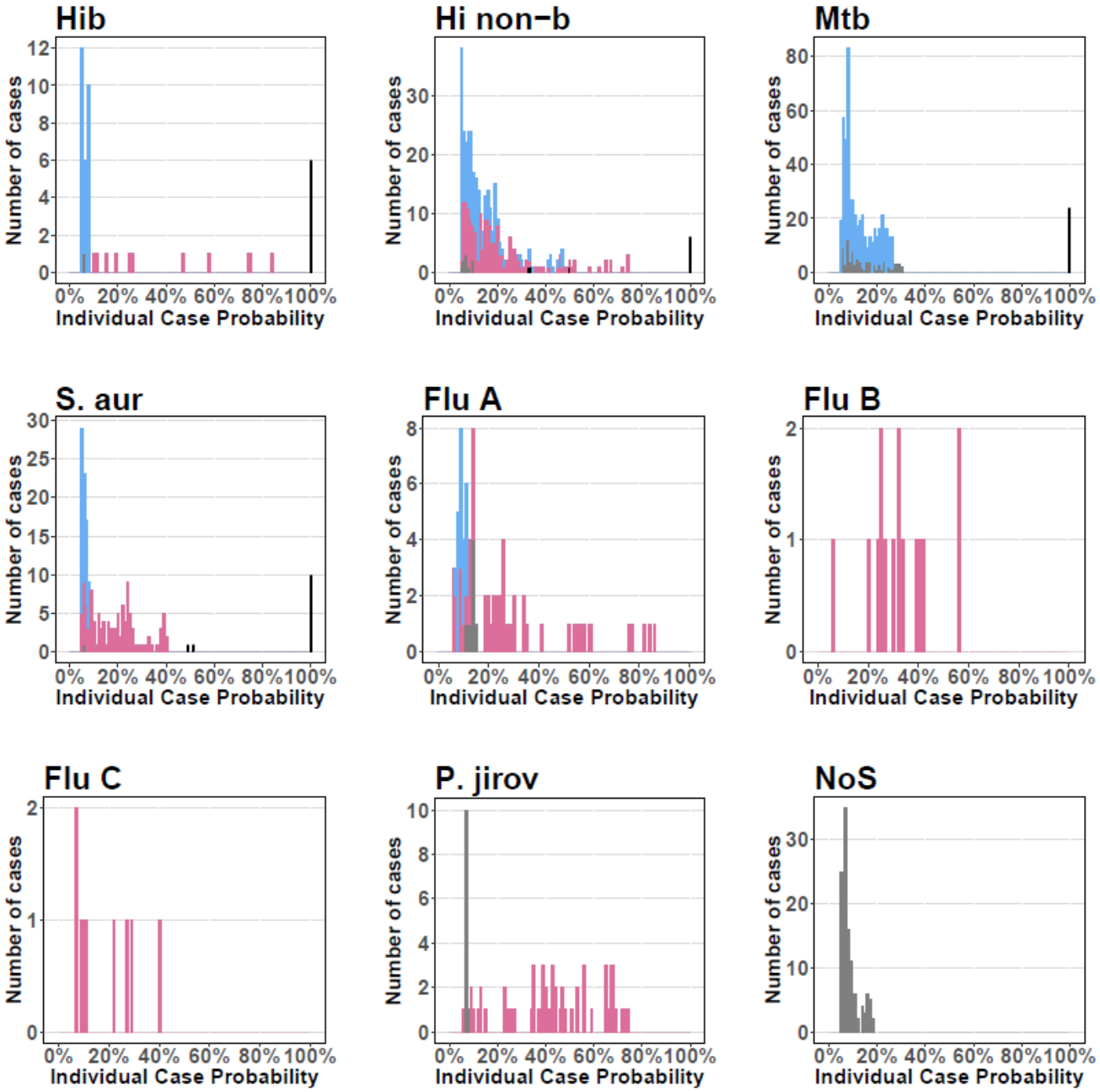
Supplemental Figure 10: Distribution of case-level aetiologic probability, by pathogen among HIV-uninfected/CXR+ cases



Abbreviations: HMPV, human metapneumovirus; NVT, non-vaccine type; Para 1-4, parainfluenza virus types 1-4; RSV, respiratory syncytial virus; S. pneu, *Streptococcus pneumoniae*; Rhino, human rhinovirus; VT, vaccine type.
For each pathogen, the figures display the distribution of the individual case probability for that pathogen, excluding cases with an aetiologic probability < 5% for the pathogens so as to scale the y-axis and display the children with higher probability. Red: cases testing positive for the pathogen by NP/OP PCR (or WB PCR for *S. pneumoniae* only); blue: cases testing negative; gray: cases missing data; black: cases with a positive silver standard specimen (i.e., positive on lung aspirate, pleural fluid, or blood culture). Cases with more than one pathogen detected in silver standard specimen(s) had

their probability distributed equally among the pathogens detected (e.g., a lung aspirate specimen positive for *M. catarrhalis* and *S. pneumoniae* attributed 50% of the aetiology to *M. catarrhalis* and 50% to *S. pneumoniae*).

Supplemental Figure 10: Distribution of case-level aetiologic probability, by pathogen among HIV-uninfected/CXR+ cases (continued)



Abbreviations: Hib, *Haemophilus influenzae* type b; Hi non-b, *Haemophilus influenzae* non-type b; Flu, influenza virus A, B and C; Mtb, *Mycobacterium tuberculosis*; NoS, Not Otherwise Specified (i.e., pathogens not tested for); P. jirov, *Pneumocystis jirovecii*; S. aur, *Staphylococcus aureus*. For each pathogen, the figures display the distribution of the individual case probability for that pathogen, excluding cases with an aetiologic probability < 5% for the pathogens so as to

scale the y-axis and display the children with higher probability. Cases testing positive for the pathogen by NP/OP PCR (or WB PCR for *S. pneumoniae* only) are displayed in red. Cases who tested negative by PCR for that pathogen are displayed in blue. Cases with missing data for the measurement are shown in gray. Cases with a positive silver standard specimen are displayed in black (a child positive on lung aspirate, pleural fluid, or blood culture for multiple pathogens had their probability distributed equally among the pathogens detected, e.g., a lung aspirate specimen positive for *M. catarrhalis* and *S. pneumoniae* attributed 50% of the aetiology to each pathogen).

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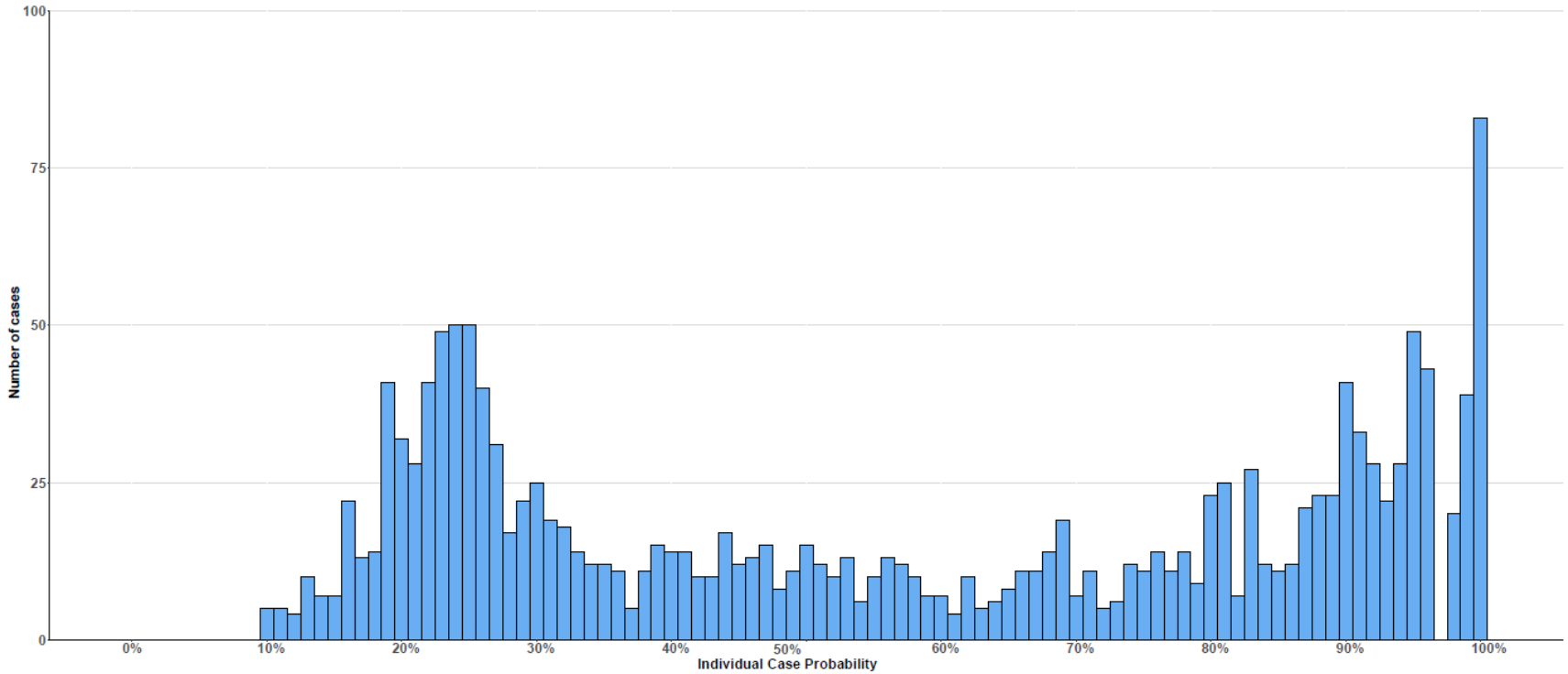
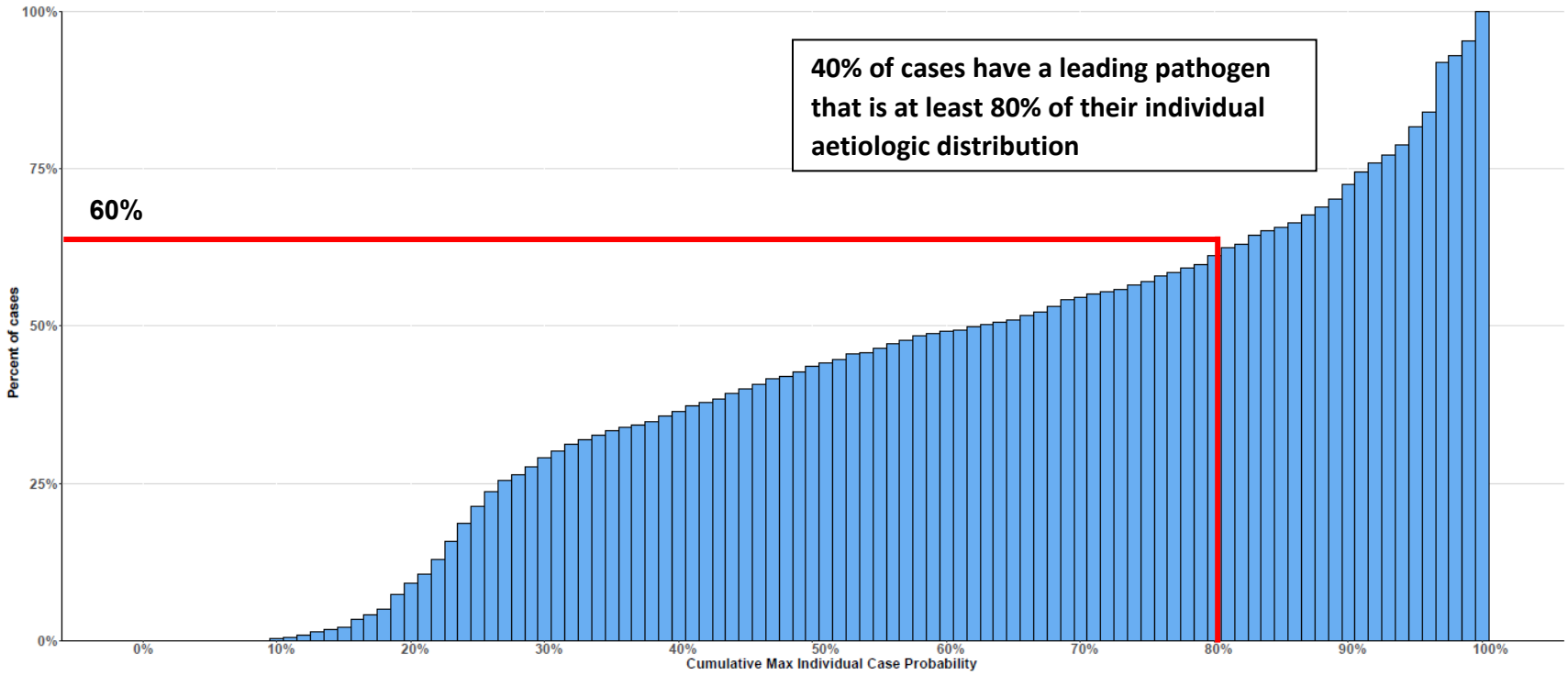
Supplemental Figure 11: Individual Case Probability of the Leading Pathogen

a. Distribution of the individual case-level probability of the leading pathogen, HIV-uninfected/CXR+ cases



Graph depicts the distribution of the individual case-level probability (i.e. individual level probability) for each case's leading pathogen, regardless of what that leading pathogen is for each case. For example, the 2nd bar from the right indicates there are 41 cases whose leading pathogen has an aetiologic probability of 99%. The bar at 50% probability indicates there are only 7 cases whose leading pathogen has an aetiologic probability of 50%. The cases plotted are CXR+ cases only, defined as consolidation and/or other infiltrate on chest radiograph.

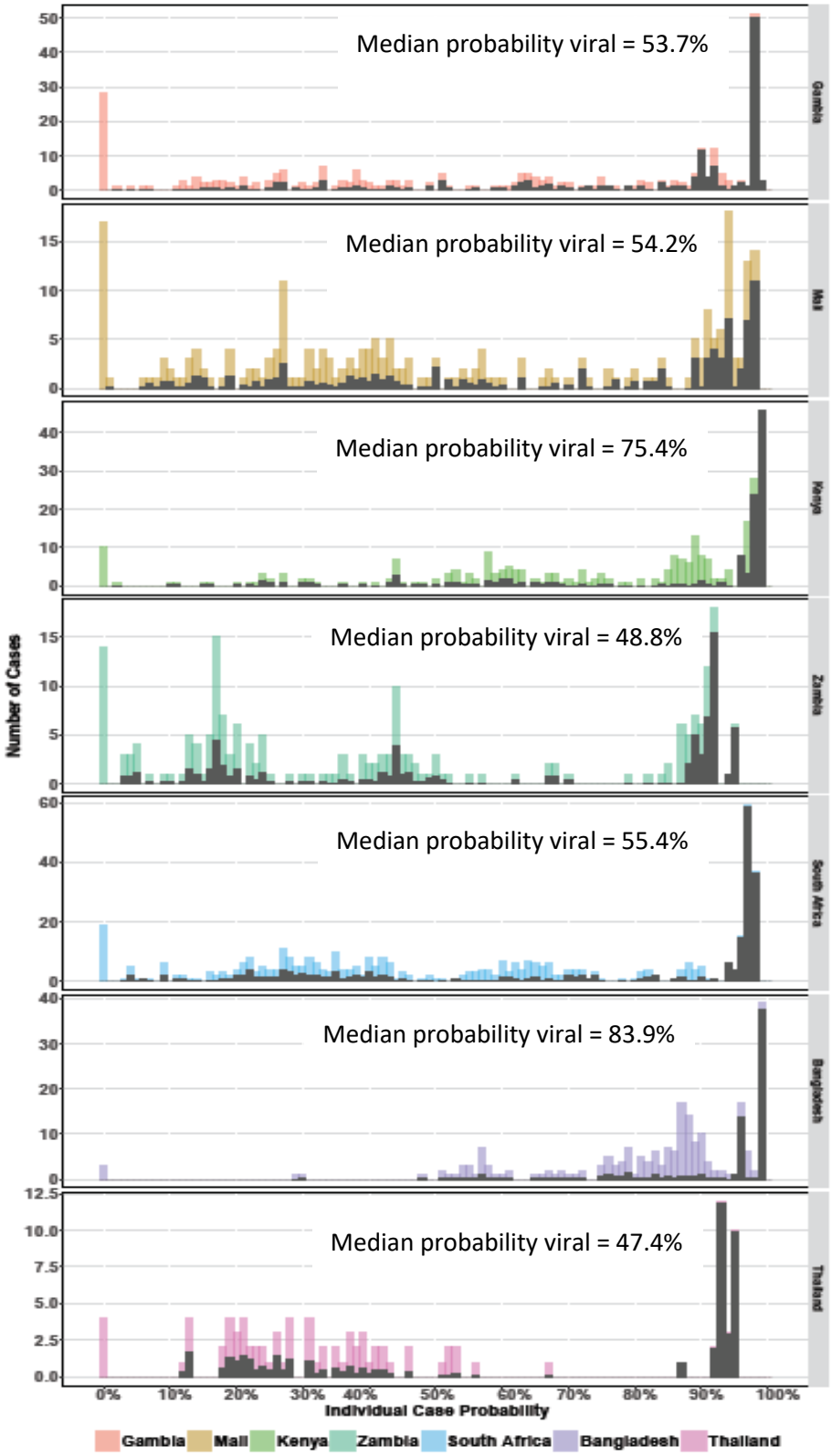
b. Cumulative distribution of the case-level leading pathogen aetiologic probability, HIV-uninfected/CXR+ cases



Graph depicts the cumulative distribution of the individual case probability for each case's top pathogen, regardless of what the top pathogen is for each case. 40% of CXR+/HIV- cases have a top pathogen with an aetiologic fraction of ≥80%, suggesting increased confidence in our estimation of that child's aetiology. The subset of cases with top aetiologic probabilities ≥80% is driven mostly (25.7%) by cases with high probability for RSV. CXR+ defined as consolidation and/or other infiltrate on chest radiograph.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplementary Figure 12: Distribution of the probability for each child that their pneumonia was due to a virus, by site



Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Coloured bars: Distribution of the individual case probability that the child's pneumonia was viral.
Black bars: Distribution of the individual case probability for RSV.
The probability that a case's pneumonia was caused by a virus varied by site from a median of 47% in Thailand and Zambia, to ≥75% in Kenya and Bangladesh (Supplementary Figure 8). For cases with the highest probability virus-associated pneumonia, RSV was estimated to be the predominant cause of their pneumonia (black bars).

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Supplemental Figure 13: Aetiology Results from Sensitivity Analyses on Aetiology and Sensitivity Priors for HIV-uninfected/CXR+ Cases

a. Narrowing and lowering the blood culture sensitivity priors for pneumococcus

Evidence for pneumonia etiology due to *S. pneumoniae* is based on three independent pieces of information: high load nasopharyngeal/oropharyngeal (NP/OP) PCR, high density whole blood (WB) PCR, and blood culture.

This sensitivity analysis evaluated the impact of lowering the blood culture sensitivity priors for *S. pneumoniae* only, while also specifying increased certainty. The midpoint value of the sensitivity prior ranges decreased from approximately 11% to 2%; no changes were made to the other sensitivity or aetiology priors.

	Base-Case sensitivity priors	Lower and narrower sensitivity priors	Ratio Base:Lower
No prior antibiotic exposure and adequate blood volume	• 5-20% (midpoint 11.4%)	• 0.5-5% (midpoint 2.2%)	• 5.2
Prior antibiotic exposure or low blood volume	• 1-13% (midpoint 5.4%)	• 0.25-2.5% (midpoint 1.1%)	• 4.9
Unknown antibiotic exposure or unknown blood volume[a]	• 1-20% for cases with unknown antibiotic exposure or unknown blood volume (midpoint 7.6%)	• 0.25-5% (midpoint 1.9%)	• 4

[a]After applying assumptions for select sites based on data for cases with known antibiotic exposure and blood volume, see Appendix.

Characteristics of selected sites:

	Gambia	South Africa	Zambia
PCV status	Introduced (Aug 2009)	Introduced (April 2009)	Not available[a]
S. pneumoniae blood culture positivity[b]	7 (2.5%)	0 (0%)	1 (0.5%)
Antibiotic pre-treatment[b,c]	10.4%	58.9%	92.2%

Abbreviation: PCV, pneumococcal conjugate vaccine.
[a]PCV was introduced in Lusaka July 2013 (3 months prior to end of enrollment at site).
[b]Among CXR+/HIV- cases.
[c]Prior exposure to antibiotics defined as clinician documented antibiotics administered at the study facility prior to blood collection (cases only), antibiotics at a referral facility (cases only), or positive serum bioassay (cases and controls).

Resulting *S. pneumoniae* etiologic fraction by sensitivity priors:

	Base *S. pneumoniae* Aetiologic Fraction (%)*	**Lowered and narrowed *S. pneumoniae* sensitivity priors Aetiologic Fraction (%)***	**Ratio Lowered: Base**
Gambia	12.3 (8.8, 16.5)	13.7 (9.9, 18.3)	1.11
South Africa	4.2 (1.6, 7.1)	5.0 (2.1, 8.5)	1.19
Zambia	2.5 (0.5, 6.7)	3.1 (0.5, 8.7)	1.24

*Site-specific observed results.

Interpretation: Decreasing the blood culture sensitivity priors for *S. pneumoniae* had little impact on the aetiology results. Evidence for pneumonia aetiology due to *S. pneumoniae* is based on three independent pieces of information: high load nasopharyngeal/oropharyngeal (NP/OP) PCR, high density whole blood (WB) PCR, and blood culture. At sites with weak blood culture evidence (i.e., low number of pneumococcal positive isolates), the model relies more on the evidence from NP/OP and WB PCR data. Therefore, changes in the blood culture sensitivity prior will have minimal impact when there are few blood culture positives. In sites with more blood culture positive cases there is still limited influence of the blood culture sensitivity prior due to the additional contributing data for *S. pneumoniae* provided by NP/OP PCR and WB PCR.

b. Narrowing and lowering the blood culture sensitivity priors for all pneumococcal measurements

This sensitivity analysis evaluated the impact of lowering the sensitivity priors for all pneumococcal measurements (which should result in higher etiological estimates for pneumococcus), while also specifying increased certainty. The midpoint value of the sensitivity prior ranges decreased as described below; no changes were made to the other sensitivity or aetiology priors.

Blood Culture (sensitivity analysis presented in Supplementary Figure 13A)

	Base-Case sensitivity priors	Lower and narrower sensitivity priors	Ratio Base:Lower
No prior antibiotic exposure and adequate blood volume	• 5-20% (midpoint 11.4%)	• 0.5-5% (midpoint 2.2%)	• 5.2
Prior antibiotic exposure or low blood volume	• 1-13% (midpoint 5.4%)	• 0.25-2.5% (midpoint 1.1%)	• 4.9
Unknown antibiotic exposure or unknown blood volume[a]	• 1-20% for cases with unknown antibiotic exposure or unknown blood volume (midpoint 7.6%)	• 0.25-5% (midpoint 1.9%)	• 4

NP/OP PCR

	Base-Case sensitivity priors	Lower and narrower sensitivity priors	Ratio
No prior antibiotic exposure and adequate blood volume	• 50-90% (midpoint 72%)	• 5-35% (midpoint 17%)	• 4.2
Prior antibiotic exposure	• 15-55% (midpoint 33.4%)	• 2-20% (midpoint 8.8%)	• 3.8

WB PCR

	Base-Case sensitivity priors	Lower and narrower sensitivity priors	Ratio
No prior antibiotic exposure and adequate blood volume	• 12-65% (midpoint 36.1%)	• 5-40% (midpoint 19%)	• 1.9

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Resulting *S. pneumoniae* aetiologic fraction by sensitivity priors:

	Base *S. pneumoniae* Aetiologic Fraction (%)*	**Lowered and narrowed *S. pneumoniae* sensitivity priors Aetiologic Fraction (%)***	**Ratio of Lowered: Base**
Bangladesh	1.6 (0.0, 5.0)	2.2 (0.0, 8.7)	1.38
Gambia	12.3 (8.8, 16.5)	16.8 (11.6, 22.9)	1.37
Kenya	5.7 (3.2, 9.2)	11.1 (5.7, 18.4)	1.95
Mali	16.8 (10.4, 24.5)	28.6 (18.7, 39.0)	1.70
South Africa	4.2 (1.6, 7.1)	5.8 (1.8, 11.0)	1.38
Thailand	0.4 (0.0, 3.1)	1.0 (0.0, 6.1)	2.5
Zambia	2.5 (0.5, 6.7)	5.0 (1.0, 13.9)	2.0

*Site-specific observed results.

Interpretation: Decreasing the sensitivity priors for *S. pneumoniae* for all three pneumococcal measurements (high load nasopharyngeal/oropharyngeal PCR, high density whole blood PCR, and blood culture) while also increasing the certainty with which the priors are specified, the absolute magnitude of the aetiologic fraction remained small at most sites. Decreasing the sensitivity priors for blood culture and NP/OP PCR by 4- to 5-fold only resulted in a $\leq$2-fold increase in the *S. pneumoniae* aetiology fraction at all sites except Thailand, where the base estimate was very small (0.4%).

c. Increasing the aetiology prior for *S. pneumoniae*

An analysis was performed increasing the aetiology prior for *S. pneumoniae* from 3% to a site-specific estimate based on the pre-Hib vaccine, pre-PCV *S. pneumoniae* estimate (28%) from Scott JAG et al. 2008 (J. Clin. Invest. 118:1291–1300) and adjusting based on use of Hib and PCV vaccines in each setting.

Site	Base aetiology prior for *S. pneumoniae*	Increased aetiology prior for *S. pneumoniae*
Kenya	Pneu PCV13 VT 3% (0-29%)	Pneu PCV13 VT 8.5%
	Pneu PCV13 NVT 3% (0-29%)	Pneu PCV13 NVT 12.1%
Gambia	Pneu PCV13 VT 3% (0-29%)[a]	Pneu PCV13 VT 10.2%[a]
	Pneu PCV13 NVT 3% (0-29%)[a]	Pneu PCV13 NVT 11.8%[a]
Mali	Pneu PCV13 VT 3% (0-29%)	Pneu PCV13 VT 16.9%
	Pneu PCV13 NVT 3% (0-29%)	Pneu PCV13 NVT 10.9%
Zambia	Pneu PCV13 VT 3% (0-29%)	Pneu PCV13 VT 24.8%
	Pneu PCV13 NVT 3% (0-29%)	Pneu PCV13 NVT 9.9%
South Africa	Pneu PCV13 VT 3% (0-29%)[a]	Pneu PCV13 VT 8.5%[a]
	Pneu PCV13 NVT 3% (0-29%)[a]	Pneu PCV13 NVT 12.1%[a]
Thailand	Pneu PCV13 VT 3% (0-29%)	Pneu PCV13 VT 20%
	Pneu PCV13 NVT 3% (0-29%)	Pneu PCV13 NVT 8%
Bangladesh	Pneu PCV13 VT 3% (0-29%)	Pneu PCV13 VT 24.8%
	Pneu PCV13 NVT 3% (0-29%)	Pneu PCV13 NVT 9.9%

Abbreviation: PCV, pneumococcal conjugate vaccine; VT, PCV13 vaccine type; NVT, non PCV13 vaccine type; Pneu, *S. pneumoniae*.
[a.]Updated based on lung aspirate findings; only relevant to Gambia and South Africa. Refer to Appendix for more details.

Resulting *S. pneumoniae* etiologic fraction by aetiology priors:

	S. pneumoniae		***S. pneumoniae* VT**		***S. pneumoniae* NVT**	
	Base	**Increased prior**	**Base**	**Increased prior**	**Base**	**Increased prior**
Gambia	12.3 (8.8, 16.5)	13.8 (9.9, 18.7)	5.5 (3.2, 8.8)	6.2 (3.5, 9.9)	6.8 (3.9, 10.2)	7.5 (4.6, 11.3)
Mali	16.8 (10.4, 24.5)	20.0 (13.3, 28.2)	11.1 (5.8, 17.8)	13.2 (7.1, 21.2)	5.7 (2.5, 10.0)	6.8 (2.9, 11.6)
Kenya	5.7 (3.2, 9.2)	7.0 (3.9, 11.3)	4.5 (2.5, 7.4)	5.2 (2.5, 8.9)	1.2 (0.4, 3.2)	1.9 (0.4, 4.3)
Zambia	2.5 (0.5, 6.7)	7.3 (1.9, 15.4)	2.0 (0.5, 5.8)	5.5 (1.4, 12.5)	0.5 (0.0, 3.4)	1.7 (0.0, 6.7)
South Africa	4.2 (1.6, 7.1)	5.3 (2.3, 9.2)	2.3 (0.5, 5.1)	2.8 (0.5, 6.0)	1.9 (0.2, 4.4)	2.5 (0.5, 5.3)
Bangladesh	1.6 (0.0, 5.0)	5.1 (1.4, 10.5)	0.4 (0.0, 2.7)	2.8 (0.0, 6.9)	1.2 (0.0, 4.6)	2.3 (0.0, 6.4)
Thailand	0.4 (0.0, 3.1)	2.6 (0.0, 8.2)	0.3 (0.0, 2.0)	2.2 (0.0, 7.1)	0.1 (0.0, 1.0)	0.4 (0.0, 2.0)

*Site-specific observed results.

Interpretation: Use of a higher aetiology prior modestly increased *S. pneumoniae* aetiology by 1.1-4.7% compared to the base model, resulting in posterior *S. pneumoniae* aetiology estimates ranging from 2.6-20.0% across the sites. The posterior aetiology estimate for *S. pneumoniae* was consistently lower than the aetiology prior that was specified for that site. Even when the combined aetiology prior for VT and NVT *S. pneumoniae* was 34.7% for sites

which had not introduced PCV (Zambia, Thailand, and Bangladesh), the resulting posterior aetiology estimate ranged from 2.6-7.3%.

d. Increasing the aetiology prior for the 'Not Otherwise Specified' aetiology category

Base-Case aetiology prior for NoS	Increased aetiology prior for NoS
3% (0-29%)	25% (0.5-75%)

Not Otherwise Specified (NoS) aetiology results by aetiology prior:

	NoS	
	Base (3%)	**Increased aetiology prior (25%)**
Gambia	1 (0, 6.3)	7.8 (1.4, 15.8)
Mali	2.2 (0, 12)	11.9 (2.1, 24.5)
Kenya	1.9 (0, 11)	12.4 (2.1, 24.8)
Zambia	1.5 (0, 10.6)	12 (1.4, 27.9)
South Africa	1.4 (0, 6.2)	9.3 (2.5, 17.5)
Bangladesh	2 (0, 13.2)	15.5 (2.7, 32.9)
Thailand	5.4 (0, 23.5)	23.9 (5.1, 44.9)

*Site-specific observed results.

Interpretation: Increasing the aetiology prior of NoS from 3% (the base case) to 25% increased the aetiology attributed to NoS by 6.8-13.5% at all sites except Thailand (where evidence for causality was weakest), resulting in a posterior NoS estimate of 7.8-15.5%. At the Thailand site which had the fewest number of cases and fewest number of blood culture positives, NoS aetiology increased from 5.4% (base) to 23.9%. This finding demonstrates that the amount of pneumonia due to pathogens that are not measured (NoS), which is determined by lack of evidence for the measured pathogens, is hard to quantify. However, this also demonstrates there is evidence in the data for measured pathogens to suggest that NoS is likely less than the prior of 25% because the NoS estimate was $\geq$10% lower than the prior for all sites except Thailand, where there was weak data for aetiologic evidence. While a precise estimate for NoS is not possible, the relative magnitude of the aetiology for the measured pathogens remains constant regardless of this assumption (i.e., the distribution of the pathogens tested for is similar).

III. Methods to Estimate Pneumonia Aetiology Using the PERCH Integrated Analysis

Supplement to Aetiology of severe hospitalised pneumonia in HIV-uninfected children from Africa and Asia: Integrated Analysis of the PERCH Case-Control Study

Prepared by Christine Prosperi[1], Maria Deloria Knoll[1], Zhenke Wu[2,3], Qiyuan Shi[1], Scott L. Zeger[2], Katherine O'Brien[1]

Affiliations:

1. Department of International Health, International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

2. Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland;

3. Department of Biostatistics, University of Michigan, Ann Arbor, Michigan

Correspondence:

Christine Prosperi, Department of International Health, International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, cprospe1@jhu.edu.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

A. Clinical and Laboratory Methods

1. Study Population and Clinical Procedures

1.1. Case and control enrollment

Screening was performed 24/7 at four sites (Kilifi, Sa Kaeo, Nakhon Phanom and Matlab) during which all eligible consenting cases were enrolled. At the remaining sites, screening was performed during established hours; all eligible consenting cases presenting during pre-defined screening hours were enrolled, with the exception of Mali which used a systematic sampling process. See below table with site-specific screening hours.

Table 1: Screening hours by site

Site	Hours + Days of Case Enrollment
Kamalapur, Bangladesh	8 a.m.- 5 p.m., 7 days a week
Matlab, Bangladesh	24 hours a day, 7 days a week
Gambia	08:00-18:00, M-Sun (except holidays)
Kenya	24 hours a day, 7 days a week
Mali	Approximately 21 8-hour shifts per month. Shifts were different every week and month to minimize selection bias. But, site did never enrolled overnight. Enrollment always between hours of 8 am and midnight.
South Africa	0700-2000 M – F; 0800-1400 Sa-Su
Thailand	24 hours a day, 7 days a week
Zambia	07:30-00:00 M-F & Sun (Two screening shifts: 07:30-16:00 & 15:30-00:00)

Hospitalisation was an inclusion criterion at all sites except Bangladesh where PERCH study enrollment included children recommended for hospitalisation but not admitted (n=33);[1] for hospitalised children, case assessment occurred within 24 hours of admission. The majority of these children were not admitted because the parent refused admission (32/33).

Controls were randomly selected from residents of the study catchment areas and frequency matched to cases by age group (1 to <6 months, 6 to <12 months, 12 to <24 months, and 24-59 months of age).[1] All sites aimed to enroll approximately 1 control per case. To achieve this, all the African sites and Nakhon Phanom, Thailand aimed to recruit a minimum of 25 controls each month, Matlab and Dhaka Bangladesh each aimed to enroll 10-15 controls per month, and Sa Kaeo, Thailand aimed to enroll 13 controls per month. In months where the number of cases exceeded the target control enrollment, sites enrolled additional controls to achieve a 1:1 ratio case:control ratio for that month.

1.2. Clinical procedures

Cases underwent a comprehensive standardised clinical examination at admission, 24 and 48 hours (if still hospitalised), and vital status was assessed at 30 days.[2] Respiratory signs, anthropometry, level of consciousness, and oxygen saturation (on room air whenever possible) were recorded, among other signs. Cases still hospitalised at 24 and 48 hours after admission underwent follow-up clinical assessments. Vital status of cases was assessed during a follow-up visit or phone interview conducted 30 days after admission (window 21-90 days). Controls were similarly assessed for clinical findings at enrolment but had no follow-up assessments.

Chest radiographs (CXRs), obtained from cases at enrolment, were interpreted blinded to site and clinical factors by two (of 14) radiologists and paediatricians trained in the WHO standardised interpretation of paediatric CXRs.[3–5]

CXRs were classified as consolidation, other infiltrate, both, normal, or uninterpretable. CXRs obtained more than 3 days following enrolment were excluded from analyses because these films were not routinely collected, would reflect clinical progression (improvement/deterioration), and may represent nosocomial disease.

1.3. Eligibility criteria for lung aspirate and pleural fluid collection

Lung aspirate collection was performed at four sites (The Gambia, Bangladesh, Mali, and South Africa). Eligible cases were those with large, dense peripheral consolidation on CXR. Contraindications for lung aspirate collection included:

1. Presence of pneumatocoeles on CXR.
2. Post measles pneumonia.
3. If the patient was clinically unstable as determined by a clinician, the procedure would be deferred until stabilisation.
4. Cardiorespiratory resuscitation (CPR) performed within the last 24 hours.
5. Parental refusal to have their child subjected to lung aspiration.

Pleural fluid was collected from a minority of cases as indicated by attending clinicians. The methodology for obtaining pleural fluid followed local clinical practice guidelines, including standard safety precautions. Contraindications for pleural fluid collection included:

1. Coagulopathy or thrombocytopenia.
2. Haemodynamic or respiratory instability (unless therapeutic thoracentesis was required for management of clinical instability).

Further details on lung aspirate and pleural fluid collection and results will be published separately.

1.4. Clinical analytic definitions

Antibiotic pre-exposure was defined as having either a positive serum bioassay at enrolment (cases and controls), or clinician-documented antibiotic administration at the referral or study hospital prior to specimen collection (cases only).[6]

Children were defined as being HIV-infected if they had direct viral detection at any age or were HIV seropositive at >12 months of age. At the South African site, where routine clinical practice is to confirm all HIV-seropositive cases under-18 months of age using molecular tests (including HIV PCR and HIV viral load testing), all children under-18 months of age with positive HIV serology had their status confirmed using molecular tests. Others were defined as being HIV-uninfected, including children with unknown HIV status (n=385 cases, n=595 controls, mostly from Kenya, The Gambia and Mali) because HIV testing was not performed.

Tachypnoea was defined as ≥60 breaths per minute (bpm) for children <2 months of age, ≥50 bpm for children 2-11 months, and ≥40 bpm for children 12-59 months. Hypoxaemia was defined as either 1) room air pulse-oximetry oxygen saturation <90% at the two sites with elevation above 1,200 metres (Zambia and South Africa) or <92% at all other sites, or 2) a child being treated with oxygen in the absence of a room air oxygen saturation reading. Fever was defined as $\geq$ 38°C.

Controls were considered to have respiratory tract illness (RTI) if they had 1) cough (observed or reported) or runny nose (reported), or 2) one of the following: ear discharge (reported), wheeze (reported), or difficulty breathing (reported), in the presence of either sore throat (reported) or fever (observed temperature ≥38°C or reported fever in the past 48 hours).

2. Laboratory procedures

The specimens collected, microbiology tests conducted, and density thresholds used in analyses have been described elsewhere.[6–15] In brief, we used quantitative multiplex polymerase chain reaction (PCR) (FTD Resp-33 kit; Fast-

track Diagnostics, Sliema, Malta) and routine culture to test nasopharyngeal/oropharyngeal (NP/OP) swabs (cases and controls; culture for *S. pneumoniae* only), induced sputa (cases only), gastric aspirates (cases only, for mycobacteria), lung aspirates (cases only; at The Gambia, Bangladesh, Mali, and South Africa sites), pleural fluid (cases only), and blood (cases and controls for *Streptococcus pneumoniae* PCR*;* cases only for blood culture). Cases and controls were also tested for antibiotic activity in serum and C-reactive protein (all cases and subset of controls).[6,16]

Refer to the below sections and Section 4 for more details on the laboratory results and how they were used in the aetiology analysis.

2.1. Nasopharyngeal/oropharyngeal (NP/OP) PCR results

The Fast Track Diagnostics Respiratory Pathogens 33 (FTD Resp-33) multiplex PCR kit which was used in the PERCH study includes the following 33 viral, bacterial and fungal targets:

- influenza A, B and C
- parainfluenza viruses types 1, 2, 3 and 4
- coronaviruses NL63, 229E OC43 and HKU1
- human metapneumovirus A/B
- human rhinovirus
- respiratory syncytial virus A/B
- adenovirus
- enterovirus
- parechovirus
- bocavirus
- cytomegalovirus
- *Pneumocystis jirovecii*
- *Mycoplasma pneumoniae*
- *Chlamydophila pneumoniae*
- *Streptococcus pneumoniae*
- *Haemophilus influenzae* type b
- *Haemophilus influenzae* species
- *Staphylococcus aureus*
- *Moraxella catarrhalis*
- *Bordetella pertussis*
- *Klebsiella pneumoniae*
- Legionella species
- Salmonella species

Data from all nasopharyngeal/oropharyngeal swabs (NP/OP) PCR targets were used in the analysis except *Klebsiella pneumoniae* and *Moraxella catarrhalis*. Some targets underwent additional confirmatory testing, as described below.[10]

- ***Klebsiella pneumoniae***: Positive results were considered invalid because of poor assay specificity.[17]
- ***Moraxella catarrhalis*:** This target was summarized in the descriptive NP/OP PCR analyses but excluded from aetiology analyses due to poor specificity (odds ratio significantly less than 1.0) and inability to determine a density threshold that improved specificity such that is was positively associated with case status.[12] *M. catarrhalis* is a commensal bacterium that can cause pneumonia but was observed more commonly among controls than among cases. There is some evidence in the literature that presence in the NP/OP may be protective against developing pneumonia. The hypothesized biological rationale is that if the child's microbiome is slanted more toward colonization of *M. catarrhalis*, it may out compete other more pathogenic organisms.[18] Because the underlying assumption of the analytic model is that what is measured in the NP is a signal of what is in the lung, the statistically significantly higher rate in controls

who do not have pneumonia is in direct conflict with this assumption. Therefore, these NP/OP data do not provide useful diagnostic evidence of pneumonia etiology and so are not used.

- ***Legionella* species**: Samples positive for Legionella species underwent confirmatory PCR testing using a different extraction method due to contamination of the original extraction reagents. Only one positive remained following confirmatory testing. Although there was only one positive, since we systematically tested for Legionella species and it is thought to be a potential cause of paediatric pneumonia, it was included as a possible cause in the aetiology analysis; this was handled consistently across all sites, including those where no Legionella species positives were detected.
- ***Bordetella pertussis*:** All samples positive for *Bordetella pertussis* underwent uniplex *B. pertussis* IS481 and *Bordetella holmesii* recA PCR assays. Only those children that tested positive for *B. pertussis* IS481 and negative for *B. holmesii* recA were considered positive for *B. pertussis*.
- ***H. influenzae* type b:** A higher proportion of samples were positive for *H. influenzae* type b in the Fast Track PCR assay than expected, especially from countries with Hib vaccine, which called into question the specificity of that pathogen target. We retested the Hib positive samples with an established Hib assay and used the results from this second assay in our analyses.[19]

Handling *H. influenzae* type b and *H. influenzae* targets: The FTD Resp-33 panel (FTD Resp-33 kit; Fast-track Diagnostics, Sliema, Malta) included targets for both *H. influenzae* and *H. influenzae* type b. All children who were positive for *H. influenzae* type b were, by design, also positive for *H. influenzae*. For the analysis, a measurement (*H. influenzae* non-type b) was derived based on the *H. influenzae* and *H. influenzae* type b as follows: if above the density threshold for *H. influenzae* but negative or below the threshold for *H. influenzae* type b (based on the confirmatory assay), then the child was considered *H. influenzae* non-type b.

Quantitative PCR density thresholds were applied to NP/OP for pathogens with poor specificity (i.e., odds ratio <1) where a threshold that improved distinction between cases and controls could be identified: pneumococcus, *H. influenzae*, cytomegalovirus, and *Pneumocystis jirovecii* by NP/OP.[11–13]

Measles was not systematically tested for in the PERCH study. Of all PERCH study enrolled cases, 33 cases were identified who met the PERCH study clinical criteria for measles testing (history of measles in past month, measles rash, measles admission diagnosis, measles discharge diagnosis); the NP/OP swabs from these 33 cases were tested for measles. Of the 33 suspected measles cases, 4 (12.1%) tested positive (Kenya n=2; Mali n=2; all had either an admission or discharge diagnosis of measles), none of whom had a positive CXR. Since measles was not systematically tested for, we elected to remove this as a potential cause in the aetiology analysis and simply describe the number of positives identified in the PERCH study. These four cases were excluded from the aetiology analyses and population aetiology distributions.

2.2. Whole blood pneumococcal PCR results

Quantitative PCR density thresholds were applied to whole blood results to improve distinction between prevalence in cases and controls.[14,15]

2.3. Pneumococcal serotyping

Pneumococcal serotypes were determined from culture isolates by Quellung and/or PCR, or by microarray (NP/OP only) for specimens that were NP-culture negative and PCR-positive.[10] Pneumococcal serotypes were stratified into vaccine-type (VT) or non-vaccine type (NVT), based on their inclusion in the 13-valent pneumococcal conjugate vaccine (the VT serotypes being 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F).

Handling mixed or ambiguous serotypes: Pneumococcal serotype results that were mixed or ambiguous following Quellung and/or PCR and unable to be resolved at the study sites were serotyped by Quellung reaction at a reference laboratory (National Institute for Communicable Diseases, Johannesburg, South Africa or the Institute of Environmental Science and Research (ESR), Porirua, New Zealand). Serotyping for all pneumococcal isolates from

sterile sites as well as a sample of pneumococcal isolates from the NP swab culture (50-70 per site) were verified by Quellung at the ESR laboratory.[10]

Serotyping by microarray: Pneumococcal serotypes for specimens that were positive by NP/OP PCR but negative by nasopharyngeal (NP) skim milk, tryptone, glucose and glycerin medium (STGG) culture were determined through microarray testing.[20] Samples with pneumococcal NP/OP PCR results above the density threshold (>6·9 $\log_{10}$ copies/mL) were prioritised for testing. Of the 87 samples meeting this criterion, 58 had serotyping results available by microarray. Multiple pneumococcal serotypes were detected in 13/58 (22%) of all samples tested by microarray. The output from the microarray provides the relative abundance of each serotype detected in the specimen (e.g., 15B [69%] + 10F [31%]). Microarray results were adjudicated by PERCH study investigators, including the PERCH study laboratory director, to determine the final serotype based on the relative abundance of each. For mixed serotype specimens, the dominant serotype was selected as the final serotype result, with pneumococcal serotype data from other specimens used to assist in the serotype confirmation process when available.

In addition, a limited number of culture-positive/PCR-positive STGG samples (n=45) were tested by both methods (culture and microarray) as part of an initial validation step for the microarray; for these children, the serotype result from the culture test was used as the final serotype. Of these tested by both methods, 34 (76%) had identical results by the two methods.

2.4. Blood culture results

Blood culture was performed at each site's laboratory for each case enrolled. Positive specimens underwent confirmatory testing at the central laboratory.[10] Below is a summary of the review process:

- Out of 4,176 cases with blood culture data, 526 (12·6%) had an organism isolated from blood
    - 328/526 (63·4%) cases were classified as having only a contaminant organism isolated (based on *a priori* list of contaminants; see below Table 2)
- The remaining 198 blood culture positive cases underwent individual case reviews by a panel of PERCH study senior investigators to determine whether the organism detected was the likely cause of the child's hospitalisation or a contaminant. The review included clinical, laboratory and risk factor data.
    - This review resulted in an additional 51 cases being classified as having only a contaminant organism isolated.
    - A total of 147 cases had one or more pathogen identified that were considered to be plausible causes of the hospitalisation.

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Table 2: Results of the blood culture review (pathogen determination)

1) Contaminant	2) Pathogen	3) Pathogen unless evidence to suggest otherwise
▪ Coagulase-negative staphylococci ▪ Micrococcus species ▪ Propionibacterium species ▪ Alpha-haemolytic streptococci (except pneumococcus) ▪ Corynebacterium species (diphtheroids) ▪ Bacillus species (except *Bacillus anthracis*) ▪ Pseudomonas species (except *P. aeruginosa*) ▪ Other environmental non-fermenting Gram-negative rods	▪ *S. pneumoniae* ▪ *H. influenzae* ▪ *S. aureus* ▪ Group A *Streptococcus* ▪ *N. meningitidis* ▪ Enterobacteriaceae ▪ Enterococcus species ▪ *M. catarrhalis* ▪ *P. aeruginosa*	▪ Acinetobacter (unless no objective signs of active infection, or other contaminant isolated, or improvement without antibiotics) ▪ Candida (unless improved without antifungal treatment)

A similar review was conducted for PCR and culture results from lung aspirate and pleural fluid specimens.

Pneumococcal BinaxNOW® testing of blood cultures
We planned to test all blood cultures that were alarm positive, culture negative with the BinaxNOW® assay for pneumococcal antigen, however this was not implemented consistently at all sites. Of the 13 cases who met the criteria for testing, only seven were tested, and all were negative. An additional 20 samples that did not meet the criteria were tested; of those, two were positive (both in South Africa) and are described below:

Table 3. Listing of pneumococcal BinaxNOW® positive children

Case	Age (m)	HIV	CXR finding	Pneumococcal WB result	Gram stain results
1	58	Positive	Consolidation	Positive (4.8 $\log_{10}$ copies/ml)	Gram-positive cocci in chains
2	5	Negative	Other infiltrate	Negative	Gram-positive cocci in chains

Pneumococcal BinaxNOW® testing of pleural fluid specimens
Only some sites implemented pleural fluid specimen testing with the BinaxNOW® assay for pneumococcal antigen. Of the 22 cases with pleural fluid samples, only eight were tested and three were positive. Of those eight cases tested, three were positive for *S. pneumoniae* by culture or PCR of the pleural fluid; two of those three were also positive by BinaxNow®. Among those tested who were *S. pneumoniae* negative by both culture and PCR of pleural fluid (data available for both culture and PCR), none were BinaxNow® positive.

There is no specimen identified among those without BinaxNow® performed where an additional test by BinaxNow® would have provided diagnostic information that was not already provided by blood culture, pleural fluid culture or pleural fluid PCR, given that among the tested cases who were *S. pneumoniae* negative by both culture and PCR none were BinaxNOW® positive. Furthermore, among those 14 children who were not tested by BinaxNOW®, *S. aureus* and other pathogens were detected in the pleural fluid culture, providing diagnostic information for a pathogen other than *S. pneumoniae*.

In the aetiology analysis all three cases positive for pneumococcal antigen by BinaxNow® were considered ‘confirmed pneumococcal cases’; for the case positive for two specimens on pleural fluid (Table 4) the aetiology was divided evenly between the pathogens (see Section 7).

Table 4. Listing of children with pleural fluid pneumococcal BinaxNOW® testing result

Case	CXR finding	Pleural fluid culture	Pleural fluid PCR	Blood Culture	Pleural Fluid Pneumococcal BinaxNOW®
1	Consolidation	*S. pneumoniae*	*S. pneumoniae*	*S. pneumoniae*	**Positive**
2	Consolidation with Other Infiltrate	Negative	*S. pneumoniae*	Negative	**Positive**
3	Consolidation	*S. aureus*	Missing	Negative	**Positive**
4	Consolidation	Negative	Negative	Negative	Negative
5	Consolidation	Negative	*S. pneumoniae*	Negative	Negative
6	Consolidation with Other Infiltrate	Negative	Negative	Negative	Negative
7	Consolidation	*S. aureus*	*S. aureus*	Negative	Negative
8	Uninterpretable	Negative	Human bocavirus *S. aureus*	Negative	Negative

2.5. Induced sputum

We attempted to obtain a single sputum specimen from each case; in South Africa multiple sputum specimens were obtained from cases for *M. tuberculosis* testing as part of routine clinical practice.[21] In situations when more than one sputum or gastric aspirate specimen was collected, only the first specimen result for *Mycobacterium tuberculosis* was used; hence, if for example a child had two induced sputum specimens and three gastric aspirates submitted and only the second induced sputum specimen was positive for *M. tuberculosis* culture, such a case was not deemed to be a case of tuberculosis.

Induced sputum specimens were tested by culture and using the FTD Resp-33 multiplex PCR. For the majority of pathogens the IS PCR data was strongly correlated with the NP/OP PCR data.[22] Because IS specimens were not collected from controls, we could not estimate and account for specificity which we assumed was not 100% (i.e., not a 'silver standard' measure like blood culture). Given lack of information on specificity and the strong correlation with NP/OP PCR data, we concluded that IS data would not meaningfully contribute to and improve the analysis, so, except for induced sputum culture for *M. tuberculosis*, they were not used in the determination of aetiology.

B. Analytic methods for estimating aetiology

3. Overview

To estimate the aetiology of pneumonia, we needed an analytic method that could integrate the multiple specimens and tests results from the cases and the controls.[23] We developed a novel analytic method called the Bayesian Analysis Kit for Etiology Research (BAKER), which is a nested, partially latent class analysis.[24–26] This method was used to integrate the PERCH study data to estimate the aetiology distribution for each individual case and for the population of cases.

The purpose of this appendix is to provide additional details related to the analytic inputs and methods specific to the PERCH Integrated Analysis (PIA) beyond that presented in the main paper.

4. Measurements and pathogens in the aetiology analysis

In this section we describe nuances related to the specimen and laboratory measurements and pathogens included in the integrated aetiology analysis.

4.1. Summary of pathogens and measurements in the PERCH Integrated Analysis (PIA)

PIA component		Description for Final Analysis
Specimens/ Tests	Gold	None
	Silver	Blood culture (following clinical review to remove contaminants). Pleural fluid and lung aspirate (culture or PCR; following clinical review to remove contaminants) by 1) updating the aetiology priors for cases with consolidation (lung aspirate results only), and 2) manually updating individual probabilities for pleural fluid and lung aspirate positive cases.
		Induced sputum culture for Mtb (positive by first IS specimen, or first gastric aspirate if IS unavailable).
	Bronze	NP/OP PCR, with density thresholds for the following targets: • *S. pneumoniae*: 6.9 $\log_{10}$ copies/mL • *H. influenzae* and *H. influenzae* type b: 5.9 $\log_{10}$ copies/mL • CMV: 4.9 $\log_{10}$ copies/mL • PCP: 4 $\log_{10}$ copies/mL
		Ignore NP/OP PCR data for *Moraxella catarrhalis* and *Klebsiella pneumoniae* (see Section 2.1 – Laboratory Procedures).
		WB PCR (*S. pneumoniae* only) with density threshold (2.2 $\log_{10}$ copies/mL).
Pathogens		All bacterial and viral NP/OP PCR targets except *Moraxella catarrhalis* and *Klebsiella pneumoniae* Coronavirus OC43, NL63, HKU1, and 229E were measured as separate targets but grouped as 'Coronaviruses' for the aetiology analysis.
		Additional bacteria detected in blood culture (no corresponding NP/OP PCR measurement used in the aetiology analysis): • Enterobacteriaceae (grouped) • Nonfermentative gram-negative rods (grouped) • Candida species • Other streptococci/enterococci (grouped) • *Moraxella catarrhalis*

	• *Neisseria meningitidis*
	S. pneumoniae and *H. influenzae* split by serotype based on blood culture (both pathogens), nasopharyngeal swab culture (*S. pneumoniae* only), NP/OP PCR (both; microarray for *S. pneumoniae* and FastTrack panel for *H. influenzae*): • *S. pneumoniae* PCV13-type • *S. pneumoniae* Non PCV13-type • *H. influenzae* type b • *H. influenzae* non-type b
	M. tuberculosis
	'Not otherwise specified'
	Measles –not included in PIA and not assigned a slice in the aetiology fraction. Descriptive text for measles positive cases only.

4.2. Pathogens with sub-species

As described in Section 2.1, the FTD Resp-33 panel includes some organisms grouped at the target level (e.g., HMPV A/B, RSV A/B), and some organisms split across multiple targets (e.g., Parainfluenza types 1, 2, 3 and 4 and, Influenza A, B and C). Analyses were performed using the results of each target wherever possible as opposed to grouping across targets for a given organism, except for Coronavirus which we grouped across targets (coronaviruses NL63, 229E, OC43 and HKU1) due to the low numbers of positives. Another exception is *S. pneumoniae*, for which we applied the serotyping data to subsequently split pneumococcus into relevant sub-groupings (e.g., PCV13-type vs not) rather than analysing each pneumococcal serotype separately which would have spread those data too thinly.

The aetiology results for pathogens estimated at the sub-species level were subsequently aggregated at the species level for presentation in the most figures (Table 5). Note that because the analysis had an equal aetiology prior for each pathogen, pathogens that are post-hoc grouped (e.g., Influenza) have in aggregate a larger cumulative aetiology prior than other pathogens without sub-species or do not have a FastTrack target at the subspecies level (e.g., Influenza virus has 3 times the aetiology prior as Rhinovirus because each Influenza type [A/B/C] is given the same aetiologic prior as Rhinovirus when the output is combined as 'Influenza virus').

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Table 5. Handling of pathogens with sub-species in the aetiology analysis and presentation of results

Pathogen estimated in aetiology analysis	How summarized for the figures
S. pneumoniae PCV13-type	*S. pneumoniae*
S. pneumoniae Non PCV13-type	
H. influenzae type b	*H. influenzae*
H. influenzae non-type b	
Parainfluenza 1	Parainfluenza
Parainfluenza 2	
Parainfluenza 3	
Parainfluenza 4	
Influenza A	Influenza
Influenza B	
Influenza C	

5. Aetiology priors

As the PIA is a Bayesian analysis, we needed to specify starting values for the distribution of the aetiology fractions (aetiology prior distributions). To reduce *a priori* bias, we used uninformed aetiology priors wherein each pathogen tested for has an equal starting probability to be the cause; in this study the aetiology prior for all pathogens was 1/34 (i.e., 33 pathogens plus a 'Not Otherwise Specified' (NoS) category), a 34-dimension symmetric Dirichlet distribution with hyperparameter $\alpha = 0.1$. The exchangeable nature of the symmetric Dirichlet prior treats all pathogens equally likely to be the most important cause prior to being updated by PERCH study data. The distribution and uncertainty around the aetiology priors were also specified (i.e., not a fixed point estimate) and assumed that the majority of pneumonia cases were caused by a subset of the pathogens, without specifically indicating which pathogens; this was implemented by using a small hyperparameter ($\alpha = 0.1$) to make the prior distribution more flexible and the prior uncertainty larger in contrast to under larger α values. Even with this assumption, all organisms are included in the analysis (Table 6) and have a non-zero aetiologic fraction estimated by the analysis, in contrast to other analytic approaches that exclude pathogens not associated with case status.

Table 6. Pathogens included in the final PIA output (alphabetical listing)

1	Adenovirus
2	*Bordetella pertussis*
3	Candida species
4	*Chlamydophila pneumoniae*
5	Cytomegalovirus
6	Enterobacteriaceae
7	*Haemophilus influenzae* type b
8	Human bocavirus
9	Human coronavirus (includes types 229E, OC43, NL63 and HKU1)
10	Human metapneumovirus
11	Human rhinovirus
12	Influenza virus A
13	Influenza virus B
14	Influenza virus C
15	Legionella species
16	*Moraxella catarrhalis*

17	*Mycobacterium tuberculosis*
18	*Mycoplasma pneumoniae*
19	*Neisseria meningitidis*
20	Non-fermenting gram-negative rods
21	Non-pneumococcal streptococci, including enterococci
22	Non-type b *H. influenzae*
23	Parainfluenza virus type 1
24	Parainfluenza virus type 2
25	Parainfluenza virus type 3
26	Parainfluenza virus type 4
27	Parechovirus/ Enterovirus
28	*Pneumocystis jirovecii*
39	Respiratory syncytial virus
30	Salmonella species
31	*Staphylococcus aureus*
32	*Streptococcus pneumoniae* non-PCV13 type (NVT)
33	*Streptococcus pneumoniae* vaccine-type (VT)
34	Not otherwise specified

Abbreviation: PCV13, 13-valent pneumococcal conjugate vaccine.

5.1. Updating aetiology priors based on lung aspirate and pleural fluid data

The lung aspirate and pleural fluid specimens provide valuable information about a child's pneumonia cause, but few children had this information and extrapolating their results to other children would have been challenging because of small numbers and because they represented only a fraction of the cases (e.g., results from pleural fluid are only representative of children with pleural effusion, not all pneumonia cases). In this section we describe methods used to incorporate this valuable information into the integrated aetiology analysis, which was done by updating the aetiology priors for the subset of representative cases.

5.1.1. Challenges with using lung aspirate and pleural fluid data

There were three primary challenges with incorporating the lung aspirate and pleural fluid data into the analysis:

1. Very few cases had available specimens and only a subset were positive.
2. Of the children who were positive, many were positive for multiple organisms. This creates conflict between the PIA assumption of a single-pathogen cause and that test results from these specimens have 100% specificity.
3. Obtaining a lung aspirate or pleural fluid specimen from a child was determined based on strict clinical characteristics, therefore these children were unlikely to be clinically or aetiologically representative of all PERCH study cases.

5.1.2. Methods for incorporating lung aspirate and pleural fluid in the analysis

We made four key decisions in determining how the lung aspirate and pleural fluid data were to be used in the analysis of determining the cause for the latent (unknown) cases:

1. Instead of using these silver standard measurements as direct inputs in the PIA model (where 97% of cases would have missing data), the positive results were used to 'update' the uniform aetiology prior values such that those pathogens detected on the silver standard measurement had a higher probability of being the cause.
    - This process was done on a site-specific basis, i.e., the distribution of pathogens found was only applied to other cases at the same site.
2. The updated aetiology priors were only applied to the subset of cases who were deemed representative of those with the corresponding specimen obtained (see next section).
3. Given the small number of cases with pleural effusion confirmed on chest x-ray (n=22, ranging from n=3 to n=7 across sites) who would be representative of those with pleural fluid specimens, we decided against using the pleural fluid data to update the aetiology priors, as done for the lung aspirate positive cases, because the analytical group to which these would be applied was too small for a robust analysis (i.e., requires stratified analysis). For these confirmed cases the pleural fluid results were used to inform their individual aetiology but not extrapolated to other cases.
4. For the cases with positive lung aspirate or pleural fluid results, those with more than one pathogen detected had aetiology apportioned equally across the pathogens.

5.1.3. Defining representative case groups for the lung aspirate data

Decision 2 above required us to define the subgroups of cases representative of those with specimens obtained.

For lung aspirates, we identified cases with consolidation on chest radiograph (CXR), an eligibility criterion for obtaining the specimen, and analyzed them separately, updating their aetiology prior using the lung aspirate results.

5.1.4. Specimen eligibility for using the positive results

The lung aspirate results used to update the aetiology priors were restricted by the following criteria:

1. The specimen was obtained within 3 days of enrollment to exclude any nosocomial infections.
2. The positive result was confirmed to be a cause of the child's pneumonia by the Silver Standard Working Group (see Section 2.4) based on their clinical presentation, course of treatment, and the laboratory data (e.g., weakly positive PCR results were excluded).
3. The child was not HIV+ (as the primary analysis excludes HIV+ children).

5.1.5. Process for updating the aetiology priors using the positive results

To inform the aetiology priors the following rules were applied to the eligible specimens to determine the updated aetiology priors used in the PIA (Table 7):

1. Culture and PCR results were given the same diagnostic weight.
2. A child positive for one pathogen attributed aetiology to that pathogen.
3. A child positive for multiple pathogens distributed the probability equally among them (e.g., a lung aspirate specimen positive for *M. catarrhalis* and *S. pneumoniae* attributed 50% of the aetiology to each pathogen).
4. A child positive for *S. pneumoniae* or *H. influenzae* but missing serotyping data attributed 50% of the aetiology to each serotype grouping: serotype groups for *S. pneumoniae* were PCV13-type and non PCV13-type, and for *H. influenzae* were type b and non-type b.

Table 7. Updated aetiology priors based on lung aspirate and pleural fluid specimen results used as input parameters to the aetiology analyses

Site	Model	Pathogen	Beginning Dirichlet	Final Dirichlet (updated from LA/PF data)
Gambia	Consolidation	*S. pneumoniae* PCV13-type	0.1	3.1
Gambia	Consolidation	*S. pneumoniae* non PCV13-type	0.1	2.43
Gambia	Consolidation	*H. influenzae* non-type b	0.1	1.43
Gambia	Consolidation	*M. catarrhalis*	0.1	1.43
South Africa	Consolidation	*S. pneumoniae* PCV13-type	0.1	0.35
South Africa	Consolidation	*S. pneumoniae* non PCV13-type	0.1	0.35
South Africa	Consolidation	*H. influenzae* non-type b	0.1	0.933
South Africa	Consolidation	*M. catarrhalis*	0.1	0.4333
South Africa	Consolidation	HMPV A/B	0.1	0.4333
South Africa	Consolidation	Adenovirus	0.1	0.6
South Africa	Consolidation	*C. pneumoniae*	0.1	0.6

Abbreviations: LA, lung aspirate; PCV13, 13-valent pneumococcal conjugate vaccine.

6. Sensitivity priors

6.1. Background

Use of non-informative values of sensitivity (i.e. uniform likelihood from 0-100%) contradicts our belief that (a) NP/OP PCR is highly sensitive (i.e., likely greater than 50%) for detecting pathogens given they are in the lung and (b) blood culture (BCx) is poorly sensitive (i.e. likely less than 20%). The sensitivity priors for each pathogen/test were selected *a priori* to analysing the PERCH study data by an internal working group. Available information external to the PERCH study was evaluated to determine the sensitivity of the measurements.

When developing the sensitivity priors, we are referring to ***diagnostic sensitivity*** for a given organism**,** which is the probability the test correctly identifies those children with pneumonia caused by the organism.

In the below sections, we detail the final sensitivity priors for each pathogen/test combination as well as the processes for developing those priors. The PIA integrates these sensitivity prior distributions with the observed data, changing ('updating') the priors with contributions of the study data which results in posterior sensitivity estimates for each pathogen/test combination.

6.2. Blood cultures

6.2.1. Overview of blood culture sensitivity priors

The final sensitivity priors for pathogens measured by blood culture are summarized below. The sections that follow describe the information used to inform the sensitivity priors.

Table 8. Blood culture sensitivity priors

Bacteria[a]	Bacterial Grouping	Sensitivity Prior: No prior antibiotic exposure and adequate blood volume	Sensitivity Prior: Prior antibiotic exposure and/or low blood volume	Sensitivity Prior: Unknown antibiotic exposure status and/or blood volume	Source of information
Streptococcus pneumoniae PCV13 type		5-20%	1-13%	1-20%	Re-analysis of data from the pneumococcal conjugate vaccine (PCV) trials conducted in South Africa and The Gambia, restricted to PERCH-like conditions (i.e., severe and very severe cases only). Assessed number blood culture positive cases prevented relative to number of pneumonia cases prevented to estimate the proportion bacteraemic (i.e., sensitivity of BCx to detect pneumococcal pneumonia) [see Section 6.2.2]. Given similarities between pneumococcal and Hib disease and inability to re-analyze the Gambian Hib trial, we assumed the same sensitivity (i.e., proportion bacteraemic) for *H. influenzae* as for *S. pneumoniae.*
*Streptococcus pneumoniae non-*PCV13 type		5-20%	1-13%	1-20%	
Haemophilus influenzae type b		5-20%	1-13%	1-20%	
Haemophilus influenzae non-type b		5-20%	1-13%	1-20%	
Moraxella catarrhalis		5-15%	1-10%	1-15%	5-15% was set as the base sensitivity prior.
Staphylococcus aureus		5-15%	1-10%	1-15%	
Salmonella paratyphi A	Salmonella species	10-50%	1-34%	1-50%	Limited evidence in literature; selected wide prior to reflect uncertainty, but likely to be ≤50% given the specimen (blood culture).
Salmonella typhi		10-50%	1-34%	1-50%	
Enterobacter cloacae	Entero-bacteriaceae	10-50%	1-34%	1-50%	
Escherichia coli		10-50%	1-34%	1-50%	
Klebsiella pneumoniae		10-50%	1-34%	1-50%	
Neisseria meningitidis		10-50%	1-34%	1-50%	
Acinetobacter baumannii	Non-fermenting gram negative rods	5-15%	1-10%	1-15%	5-15% was set as the base sensitivity prior.

Acinetobacter radioresistens		5-15%	1-10%	1-15%	
Acinetobacter species		5-15%	1-10%	1-15%	
Pseudomonas aeruginosa		5-15%	1-10%	1-15%	
Candida albicans	Candida species	5-15%	1-10%	1-15%	
Candida species		5-15%	1-10%	1-15%	
Enterococcus faecium	Other streptococci/ enterococci	5-15%	1-10%	1-15%	
Streptococcus group A		5-15%	1-10%	1-15%	

Abbreviations: PCV13, 13-valent pneumococcal conjugate vaccine.

[a]This list of bacteria represents the complete list of non-contaminant bacteria detected on blood culture amongst the PERCH study cases.

Diagnostic sensitivity of blood cultures

The common pneumonia pathogens associated with bacteraemia are typically in concentrations of at least 10-100 CFU/mL. Therefore, 1 mL of blood inoculated into a blood culture bottle should have high sensitivity (estimate 90%) to detect the pathogen given that it entered the blood, as only one bacterium in the bottle is needed to eventually alarm the blood culture instrument. Antibiotic pretreatment and contamination will lower this estimate. If there are no skin contaminants, culture sensitivity is about 100% for detecting pathogens in blood assuming microbial identifications are accurate.

Therefore, sensitivity of blood culture to detect pathogens in the lung is driven primarily by the prevalence of bacteraemia. There is direct evidence of the diagnostic sensitivity for *Streptococcus pneumoniae* and *Haemophilus influenzae* from vaccine probe studies (see section 6.2.2), which was estimated to be between 5-20%. For all other pathogens we set the base blood culture sensitivity prior to 5-15%, except for Salmonella species, Enterobacteriaceae and *Neisseria meningitidis*, for which we selected wider priors (10-50%) to reflect their greater uncertainty.

6.2.2. Estimating blood culture sensitivity from vaccine probe studies

S. pneumoniae

The results of the pneumococcal conjugate vaccine (PCV) trials in South Africa and The Gambia were reanalysed, restricting to PERCH-like conditions (i.e., severe and very severe pneumonia cases only), to estimate the number of pneumococcal blood culture confirmed cases relative to all pneumococcal pneumonia cases (i.e., to estimate the percent of pneumococcal pneumonia cases that were bacteraemic). The number of pneumococcal blood culture confirmed cases (numerator) was estimated by the number BCx+ for pneumococcus in the control group who met the PERCH study case definition. The denominator was estimated by the number of PERCH-like pneumonias in the control group that had a BCx taken multiplied by the vaccine efficacy against PERCH-defined pneumonia, adjusted for the vaccine efficacy against vaccine-type BCx+ and the percent of BCx+ that was vaccine-type: results were 6.1% in South Africa and 17.7% in The Gambia (both with wide confidence intervals due to small number of vaccine-type BCx+ in controls (n=6 in SA and n=14 in The Gambia). We also conducted a sensitivity analysis assuming the vaccine efficacy against vaccine-type pneumonia was lower for non-bacteraemic cases (50%) than for BCx+ cases (4/6=67% in South Africa and 11/14 =79% in The Gambia): results were 4.6% in South Africa and 11.3% in The Gambia. Restricting analyses to CXR+ cases only reduced the sample size of vaccine-type BCx+ in controls to only 2 in South Africa (too small to analyse) and 10 in The Gambia, which produced similar results as for all cases (18.5% and 13.2% for the sensitivity analysis). Taking the lowest and highest values from these four results (4.6% to 18.5%) and rounding up (because impact of prior antibiotics was not accounted for in these analyses but is adjusted for the in the PIA – see section 6.2.3) **produced the range 5-20%**.

H. influenzae

A similar re-analysis exercise was intended for *H. influenzae* using results of The Gambian Hib probe trial; however, the data from that 20+ year old trial could not be located. Given the similarities to pneumococcus, we elected to apply the *S. pneumoniae* blood culture priors to *H. influenzae*.

6.2.3. Adjusting blood culture sensitivity priors to account for prior antibiotic exposure and low blood volume

Both antibiotic exposure prior to specimen collection and low blood volume reduce pathogen detection in blood cultures for all bacteria by approximately 50%.[6] Therefore, we halved the sensitivity priors of blood culture for children with evidence of either factor. For the analysis, prior antibiotic exposure was defined as having either a positive serum antibiotic bioassay or clinician report of antibiotics administered prior to specimen collection, and low blood volume was defined as <1.5 mL.

To adjust the sensitivity prior, the midpoint of the originally specified sensitivity prior range was calculated (e.g., 11.4% is the midpoint of the sensitivity prior range of 5-20% for *S. pneumoniae*) then halved (5.7%). The beta distribution was applied to this halved midpoint to construct the adjusted range. We specify the two parameters of a beta probability density with mode at the midpoint sensitivity (Table 9).

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Table 9. Blood culture sensitivity priors, adjusted for prior antibiotic exposure and blood culture volume

Pathogen	No prior antibiotic exposure and adequate blood volume			Prior antibiotic exposure or low blood volume		Unknown
	Range (%)	Midpoint[a]	Target Midpoint, 50% reduction	Range (%)	Resulting Midpoint	Range (%)
Streptococcus pneumoniae	5-20	11.4	5.7	1-13	5.4	1-20
Haemophilus influenzae	5-20	11.4	5.7	1-13	5.4	1-20
Moraxella catarrhalis	5-15	9.4	4.7	1-10	4.3	1-15
Staphylococcus aureus	5-15	9.4	4.7	1-10	4.3	1-15
Salmonella species	10-50	27.6	13.8	1-34	12.1	1-50
Enterobacteriaceae	10-50	27.6	13.8	1-34	12.1	1-50
Non-fermenting gram negative rods	5-15	9.4	4.7	1-10	4.3	1-15
Candida species	5-15	9.4	4.7	1-10	4.3	1-15
Other streptococci	5-15	9.4	4.7	1-10	4.3	1-15
Neisseria meningitidis	10-50	27.6	13.8	1-34	12.1	1-50

[a.] The lower and upper values of sensitivity prior range correspond to 2.5% and 97.5% quantiles of a beta distribution, not necessarily symmetric around the midpoint. 'Other streptococci' includes *Streptococcus pyogenes* and *Enterococcus faecium*.

For children who were missing data for prior antibiotic exposure and/or blood volume, we developed rules for how to handle the missing data based on the results for children with data at the same site (Tables 10 and 11). When the proportion of cases with adequate blood volume (or no prior antibiotic use) was >70%, children with missing data were assumed to have adequate blood volume (or no prior antibiotic use) and no changes were made to sensitivity priors. If <30%, then children with missing data were assumed to have low blood volume (or prior antibiotic use) and their sensitivity priors were halved. When the proportion was between 30-70%, no assumptions could be made on the status for children with missing data (i.e., "unknown" status), and the sensitivity prior range was widened to the minimum of the adjusted range and maximum of the base range to reflect this uncertainty.

Table 10. Proportion of cases with adequate blood volume and no prior antibiotic use by site among those with available data (CXR+/HIV- cases)

Site	Blood volume >1.5mL	No prior antibiotic use
Gambia	87%	88%
Mali	81%	77%
Bangladesh	96%	75%
Zambia	76%	6%
Thailand	79%	68%
Kenya	61%	61%
South Africa	33%	36%

Red = between 30-70%; set to "unknown" for cases missing data.

Table 11. Site-specific rules for handling children missing data on blood volume or prior antibiotic use

Site	How handled
Gambia	Assume adequate blood volume and no prior antibiotic use
Mali	Assume adequate blood volume and no prior antibiotic use
Bangladesh	Assume adequate blood volume and no prior antibiotic use
Zambia	Assume adequate blood volume and prior antibiotic use
Thailand	Unknown prior antibiotic use [a]
	Assume adequate blood volume
Kenya	Unknown prior antibiotic use and unknown blood volume [a]
South Africa	Unknown prior antibiotic use and unknown blood volume [a]

[a]Use wider sensitivity prior range that spans the minimum of the adjusted range and maximum of the base range to reflect this uncertainty.

6.3. Nasopharyngeal/oropharyngeal PCR

The final sensitivity priors for pathogens measured by NP/OP PCR are summarized below.

Table 12. Nasopharyngeal/oropharyngeal PCR sensitivity priors

Pathogen	Grouping	No evidence of prior antibiotic exposure		Prior antibiotic exposure
		Sensitivity Prior (%)	Source of information	Sensitivity Prior (%)
RSV	Virus	50-90	Based on prior literature and laboratory sensitivity. Unlikely that 100% of true cases are test positive; upper bound reduced to 90%. Unlikely that <50% of true cases are test negative; lower bound set to 50%. Given the absence of evidence to develop pathogen-specific estimates, we applied this range to all PCR targets.	50-90
Rhinovirus	Virus	50-90		50-90
HMPV A/B	Virus	50-90		50-90
Adenovirus	Virus	50-90		50-90
CMV	Virus	50-90		50-90
Parainfluenza 3	Virus	50-90		50-90
PV/EV	Virus	50-90		50-90
Influenza A	Virus	50-90		50-90
Parainfluenza 1	Virus	50-90		50-90
Parainfluenza 4	Virus	50-90		50-90
Influenza B	Virus	50-90		50-90
HBOV	Virus	50-90		50-90
Coronavirus (OC43, NL63, HKU1, 229E)	Virus	50-90		50-90
Parainfluenza 2	Virus	50-90		50-90
Influenza C	Virus	50-90		50-90
Staphylococcus aureus	Bacteria	50-90		50-90
Pneumocystis jirovecii	Fungi	50-90		50-90
Mycoplasma pneumoniae	Bacteria	50-90		50-90
Bordetella pertussis	Bacteria	50-90		50-90
Chlamydophila pneumoniae	Bacteria	50-90		50-90
Streptococcus pneumoniae PCV13-type	Bacteria	50-90		15-55*
Streptococcus pneumoniae non-PCV13-type	Bacteria	50-90		15-55*
Haemophilus influenzae type b	Bacteria	50-90		15-55*

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Pathogen	Grouping	No evidence of prior antibiotic exposure		Prior antibiotic exposure
		Sensitivity Prior (%)	Source of information	Sensitivity Prior (%)
Haemophilus influenzae non-type b	Bacteria	50-90		15-55*
Salmonella species	Bacteria	0.5-90	Little/no evidence to inform sensitivity, therefore wide prior was selected.	0.5-90
Legionella species	Bacteria	0.5-90		0.5-90

* See section 6.3.1 on antibiotic adjustment.

Diagnostic sensitivity: All the PCR assays have lower limits of detection of around 10-100 copies/mL, therefore, the assays should have high sensitivity to detect target pathogens in the quantities expected during an infection. However, specimen collection and quality issues may reduce the sensitivity so 90% sensitivity was selected as a reasonable estimate. Diagnostic sensitivities are likely to be high for the viruses, which normally replicate in the nasopharynx. For bacteria that colonise the upper airways (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. aureus*) and non-colonising bacteria that are known to replicate in the upper airways (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *B. pertussis*), the sensitivities are also likely to be high. Based on this evidence, we set the lower bound of the sensitivity prior to 50% for these pathogens. For Salmonella species and Legionella species, there was no evidence regarding frequency of colonisation so a wide sensitivity prior range was selected (0.5-90%). For relevant pathogens, applying PCR density thresholds is likely to decrease the percentage of confirmed cases positive on NP/OP PCR.[11–13]

Evidence in PERCH study data: We evaluated PERCH study data that were not directly being used in the PIA to provide additional evidence on which to base the NP/OP PCR sensitivity priors.

> ***S. pneumoniae:*** There were eight cases positive on lung aspirate (culture and/or PCR) for *S. pneumoniae*. Of the seven with NP/OP PCR data, all were positive for *S. pneumoniae*, but only five were above the density threshold (6.9 $\log_{10}$ copies/mL). The two cases below the density threshold (6.2 $\log_{10}$ and 6.8 $\log_{10}$ copies/mL, respectively) did not have evidence of prior antibiotic use.
>
> There were five cases positive on pleural fluid for *S. pneumoniae* (culture and/or PCR [including BinaxNOW® pneumococcal antigen testing]); all five were positive for *S. pneumoniae* by NP/OP PCR but none were above the density threshold (density range: 4.4 $\log_{10}$ copies/mL to 5.9 $\log_{10}$ copies/mL). Of these five cases, 4 had prior antibiotic exposure.
>
> ***H. influenzae*:** There were four cases positive on lung aspirate (culture and/or PCR) for *H. influenzae*. Of the three with NP/OP PCR data, all three were positive for *H. influenzae*, but only two were above the density threshold (5.9 $\log_{10}$ copies/mL) (2/3). The one case below the density threshold (4.1 $\log_{10}$ copies/mL) had evidence of prior antibiotic use.
>
> ***S. aureus:*** There were seven cases positive on pleural fluid (culture and/or PCR) for *S. aureus*; four were also positive for *S. aureus* by NP/OP PCR (4/7).
>
> **HBOV:** There was one case positive on pleural fluid PCR for HBOV; this child was negative for HBOV by NP/OP PCR (0/1).
>
> **HMPV A/B:** There was one case positive for HMPV A/B by lung aspirate, and also positive on NP/OP PCR for HMPV A/B (1/1).
>
> **Adenovirus:** There was one case positive on lung aspirate PCR for adenovirus; this child was also positive for adenovirus by NP/OP PCR (1/1).
>
> ***C. pneumoniae*:** There was one case positive on lung aspirate PCR for *C. pneumoniae*; this child was also positive for *C. pneumoniae* by NP/OP PCR (1/1).

We also evaluated the sensitivity of NP/OP PCR by comparing results to induced sputum PCR data among cases with results from both specimens. The percent of induced sputum PCR positive cases who were also NP/OP positive differed by PCR target from 12.2% (*Salmonella* species) to 94.5% (*P. jirovecii*) (Table 13).

Table 13. Sensitivity of NP/OP PCR as assessed by induced sputum (IS) PCR positivity among cases with available data[a]

Pathogens	Positive by NP/OP and IS		Positive by NP/OP only		Positive by IS only		NP/OP-neg and IS-neg		Percent of IS+ cases who were also NP/OP+
	n	%	n	%	n	%	n	%	%
Adenovirus	265	7.3	106	2.9	228	6.2	3050	83.6	53.8
B. pertussis	29	0.8	2	0.1	14	0.4	3615	98.8	67.4
CMV	1630	44.7	270	7.4	328	9	1421	38.9	83.2
Coronavirus 229E	25	0.7	14	0.4	20	0.5	3583	98.4	55.6
Coronavirus OC43	72	2	17	0.5	42	1.2	3510	96.4	63.2
Coronavirus NL63	58	1.6	16	0.4	26	0.7	3541	97.3	69
Coronavirus HKU1	39	1.1	15	0.4	24	0.7	3563	97.9	61.9
C. pneumoniae	18	0.5	14	0.4	25	0.7	3603	98.4	41.9
Influenza C	13	0.4	6	0.2	6	0.2	3635	99.3	68.4
HBOV	281	7.7	213	5.9	277	7.6	2869	78.8	50.4
H. influenzae type b	53	1.4	26	0.7	26	0.7	3558	97.1	67.1
H. influenzae	1626	44.4	354	9.7	277	7.6	1403	38.3	85.4
HMPV A/B	204	5.6	50	1.4	50	1.4	3336	91.6	80.3
Influenza A	92	2.5	17	0.5	18	0.5	3514	96.5	83.6
Influenza B	38	1	5	0.1	10	0.3	3588	98.5	79.2
M. catarrhalis	2077	56.7	368	10.1	126	3.4	1089	29.8	94.3
M. pneumoniae	27	0.7	14	0.4	19	0.5	3580	98.4	58.7
Parainfluenza 1	91	2.5	5	0.1	17	0.5	3526	96.9	84.3
Parainfluenza 2	17	0.5	27	0.7	26	0.7	3578	98.1	39.5
Parainfluenza 3	162	4.4	39	1.1	56	1.5	3391	93	74.3
Parainfluenza 4	61	1.7	26	0.7	26	0.7	3535	96.9	70.1
S. pneumoniae	2388	65.2	260	7.1	140	3.8	872	23.8	94.5
P. jirovecii	214	5.8	96	2.6	117	3.2	3238	88.3	64.7
PV/EV	222	6.1	94	2.6	186	5.1	3147	86.2	54.4
Human rhinovirus	601	16.5	259	7.1	252	6.9	2529	69.5	70.5
RSV	907	24.9	84	2.3	80	2.2	2578	70.6	91.9
Salmonella species	5	0.1	17	0.5	36	1.0	3606	98.4	12.2
S. aureus	378	10.3	230	6.3	201	5.5	2851	77.9	65.3

[a]All cases with results for both specimens, regardless of CXR findings or IS quality.

6.3.1. Adjusting NP/OP PCR sensitivity priors to account for prior antibiotic exposure

Prior antibiotic exposure has been shown to reduce test positivity of NP/OP PCR specimens for *S. pneumoniae* and *H. influenzae* by approximately half.[6,13] The sensitivity prior range was changed from 50-90% (midpoint 72%) to 15-55% (midpoint 33%). For the analysis, prior antibiotic exposure was defined by having either positive serum bioassay (cases and controls) or clinician report of antibiotics administered prior to specimen collection (cases only).

6.4. *Mycobacterium tuberculosis* (Mtb) Culture

Two induced sputum specimens were routinely obtained from cases at the PERCH study South Africa site in order to estimate the sensitivity of Mtb culture using capture-recapture methods comparing the first and second induced sputum

results. Using this method, the sensitivity of a single IS specimen was estimated to be between 15-50%. However, this is a setting with high HIV prevalence which may have higher sensitivity. The standard thinking is that the sensitivity of sputum or gastric aspirate has an upper bound of ~30% and a lower bound of about 10%.[27] Based on discussions with the Executive Committee it was decided that the South Africa PERCH study estimate in a high Mtb prevalence setting might be too high to apply to the other sites so the group decided to use the standard **(10-30%) as the sensitivity prior** for Mtb for all sites (i.e., those with high rates of TB as well as those with low rates).

6.5. Lung aspirates and pleural fluid data

The lung aspirate and pleural fluid data were used to estimate aetiology for the cases with positive results. For extrapolation of the lung aspirate data to cases with unknown aetiology, these results were used to update the aetiology priors for other cases who were (1) at the same site and (2) clinically representative of those with a specimen obtained (see Section 5.1). As such, sensitivity priors were not a relevant parameter for these data in the analysis.

6.6. Pneumococcal whole blood (WB) PCR

Sensitivity of pneumococcal WB PCR was estimated by comparing the fraction of blood culture positive specimens that were also PCR positive. In the PERCH study, among cases with pneumococcus detected in blood by culture, 68% had pneumococcus detected by PCR in whole blood; this reduced slightly to 62.5% after applying the optimal quantitative PCR load threshold.[14,15] We observed a similar proportion in pneumonia cases enrolled in a pilot study at the Kilifi site.[14]

Because the integrated aetiology analysis estimates the sensitivity of WB given blood culture positivity, it cannot be also used to set the priors because these data then would be incorporated twice. Therefore, to determine the sensitivity prior of WB PCR we considered the evidence from the lung aspirate and pleural fluid specimens. Children who are positive on a pleural fluid specimen are likely different from those positive on lung aspirate since they have advanced to the state where the pathogen is able to travel outside the lung and into the pleural space; as such, they are likely to have a higher sensitivity for detection of pneumococcus on whole blood (i.e., more likely that the pathogen also moved into the blood) than for most pneumonia cases. Indeed, the evidence in the data supports this hypothesis, since high density WB PCR among cases positive for pneumococcus on pleural fluid was 80%, while for lung aspirate it was 33%.

Starting from the non-informative sensitivity range of 2.8-97% (a distribution of beta(1,1)), we updated the range using the lung aspirate and pleural fluid data. For cases with consolidation (representative of those with lung aspirate specimens obtained), the 3/9 positive lung aspirate cases resulted in an updated sensitivity prior range of 12-65%. Given the small number of cases with pleural effusion to whom the pleural fluid results would apply, and in the absence of data to inform the sensitivity priors for cases with other infiltrate or normal CXR findings, we applied the lung aspirate range (12-65%) to all cases.

Whole blood PCR	Sensitivity prior
Streptococcus pneumoniae	12-65%

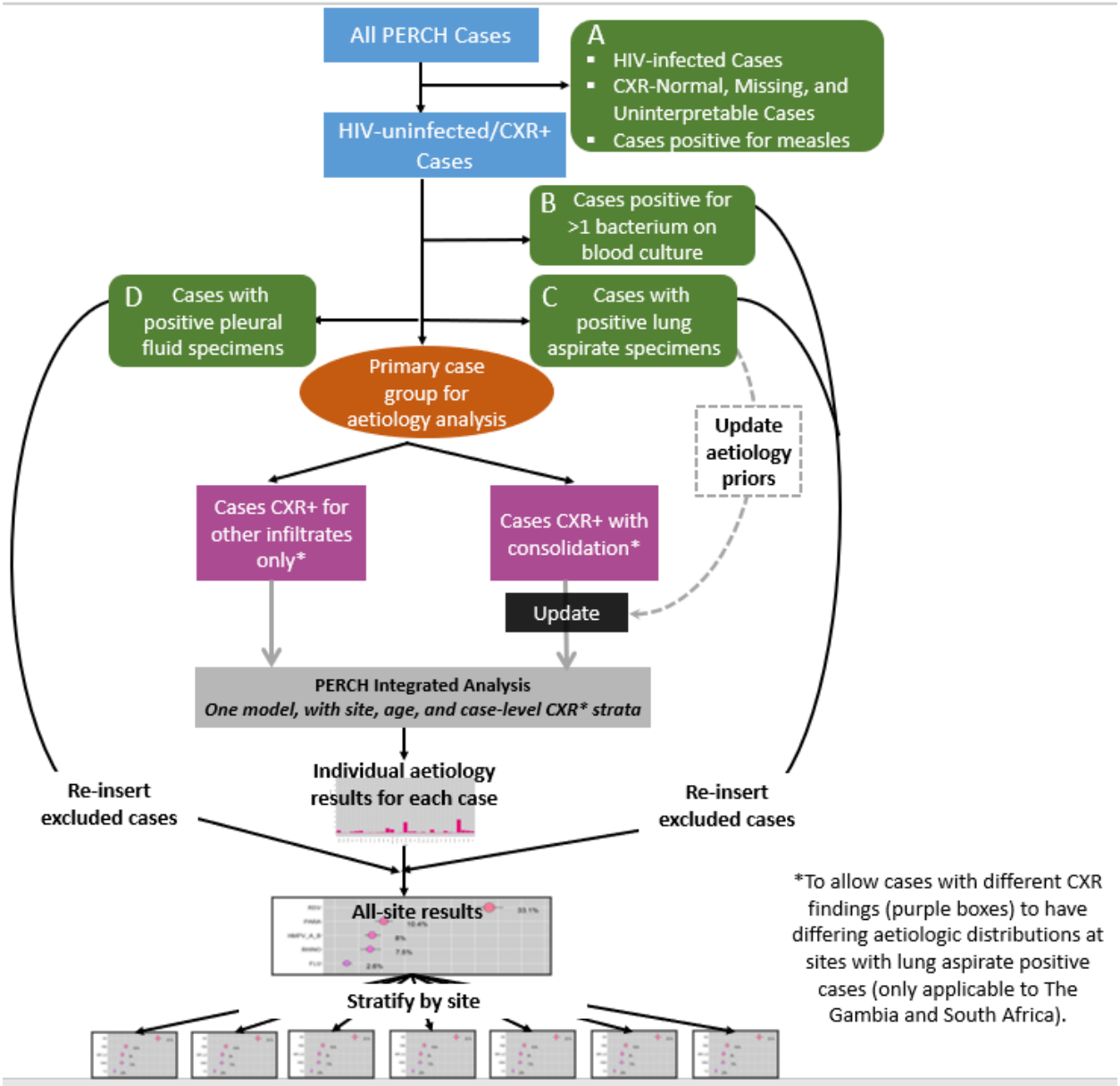
7. PERCH Integrated Analysis (PIA): methods

Overview of analytic methods

A partially latent class model (PERCH Integrated Analysis [PIA]), the BAKER method, was used to integrate the blood culture and induced sputum (TB only) results from the cases, and the NP/OP PCR and WB pneumococcal PCR results from both cases and controls to estimate the aetiology distribution for each individual case and for the population of cases, with the probability for each organism ranging from 0% to 100%.[24–26]

Appendix: Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study

Figure 1. Case flowchart for primary aetiology analysis



The PIA model was run to determine aetiology of the latent cases, i.e., those without known aetiology. Those children with a known aetiology were handled differently, as described in Figure 1 and Table 14.

Table 14. Handling of cases with known aetiology in the PERCH Integrated Analysis

Category of cases with known aetiology	How handled in the analysis	Informs on individual's aetiology	Informs on aetiology of the latent cases
Blood culture positive for a single pathogen	Used within the model to inform on the aetiology of the latent cases.	Yes	Yes
Blood culture positive for more than one pathogen (green box, B)	Single case (positive for two bacteria on blood culture, Salmonella species and *Streptococcus pyogenes*). Handled separate from the model because blood culture is assumed to be 100% specific in the model. Only used to inform the individual child's aetiology.	Yes	No
Lung aspirate positive (green box, C)	Excluded from the model run and appended to the output dataset to inform on the individual child's aetiology. Lung aspirate results were used to update the aetiology prior distributions for the remaining cases with x-ray consolidation using a multinomial likelihood to inform on the population aetiology.	Yes	Yes (through updated aetiology priors)
Pleural fluid positive (green box, D)	Excluded from the model run and appended to the output dataset to inform on the individual child's aetiology. [a] Due to the small numbers of latent cases with a confirmed pleural effusion on CXR (i.e., those to whom the pleural fluid results would be applicable, see section 5.1), these positive results were not used to update their aetiology prior distribution.	Yes	No
Measles (green box, A)	Excluded from the analysis and described separately (i.e., not appended to final aetiology distribution), see Section 2.1.	Yes	No

[a]Two cases whose pleural fluid was positive also had blood cultures positive for the same pathogen as detected on pleural fluid remained in the PIA model so that their blood culture data could inform the aetiology for other cases, but their pleural fluid results were not used as input measurements for the reasons described above.

To estimate the all-site aetiology attribution (main paper Figure 4), a single model was run that included the cases and controls from all the sites, adjusting for site and age (age < 1 year and age $\geq$ 1 year). The adjustment consisted of stratifying the cases and controls within the model by age and site to allow the aetiology to vary by strata. Including all sites and age strata in a single model (i.e., instead of running separate site-age stratified models) enabled estimation of an all-sites-combined aetiology estimate across the strata. The algorithm does this by using the stratum-specific blood culture data, prevalence and odds ratios for NP/OP PCR and pneumococcal WB PCR to inform on aetiology. At the same time the algorithm updates the sensitivity priors of each measurement by combining evidence across the site-age strata to obtain the posterior sensitivity values for the measurements. For example, the model updates the *S. pneumoniae* NP/OP PCR sensitivity for sites with no *S. pneumoniae* positive blood cultures based on the fraction of *S. pneumoniae* positive blood culture cases at other sites who were also *S. pneumoniae* positive on NP/OP PCR.

At sites with positive lung aspirate data (The Gambia and South Africa), cases were categorized as representative of those with the lung aspirate specimens collected versus those not; the aetiology priors were updated using those results, but only for the subset of cases representative of those with lung aspirates, and only for the respective site (The Gambia or South Africa), informed by the distribution of pathogens detected on lung aspirates (purple boxes in Figure 1; see Section 5.1). Aetiology priors were not updated at the other sites without lung aspirate data (Table 15).

Table 15. Updates to model priors based on availability of lung aspirate positive results

Availability of Lung Aspirate Positives	Site	Case groupings	Group-specific updates to priors
Yes	The Gambia South Africa	Cases with x-ray consolidation	Aetiology prior updated using lung aspirate results (Section 5.1)
		Cases without consolidation[a]	No updates
No	Thailand Bangladesh Kenya Mali Zambia	All cases	No updates

a. In the CXR(+) analysis this is restricted to children with 'other infiltrate'. In the all-case analysis (regardless of CXR finding), this includes children with either other infiltrate, normal, uninterpretable or missing CXRs.

Analyses were run for 25,000 iterations; the first 5,000 were excluded as a 'burn-in' stage and the remaining were sampled every 5th iteration and were averaged to obtain the aetiology probability distribution of each case, ranging from 0% to 100% for each pathogen. At each iteration of the analysis, PIA assigns each case to a specific pathogen based on their measurements, the measurements of the 'population' of the other cases, the control measurements and the sensitivity and aetiology priors. In this Bayesian model, the unknown parameters to be estimated are the true cause of the infection for each child (aetiology) and the sensitivities for each measurement. The set of unknowns is assumed to follow a joint prior distribution representing prior uncertainty about their values. The Markov Chain Monte Carlo (MCMC) estimation method simulates a large number of values for all of the unknowns from their posterior distribution given the observed data. In this simulation, the estimate of the aetiology for each pathogen is approximately the average of the individual case probabilities and is provided with a 95% credible interval (CrI), the Bayesian analogue of the confidence interval. Convergence was checked by repeating the analysis multiple times using different starting seed values and comparing the posterior distributions between the runs.

Cases with known aetiology who were excluded from the models (see Figure 1 and Table 14) were appended to the output dataset from the model at each iteration with aetiology probability assigned as follows:

1. Cases with 1 pathogen detected: assigned 100% to the aetiology detected for all iterations.
2. Cases with more than 1 pathogen detected: assigned 100% to the aetiology detected, where the 100% aetiology assignment for a given pathogen is distributed equally across the iterations relative to the number of pathogens detected. For example, a case with two pathogens detected (pathogens A and B) would have 50% of their iterations indicated as 100% aetiology for Pathogen A and the remaining 50% of the iterations indicated as 100% aetiology for Pathogen B.

7.1. Stratifying by age and severity

To estimate the aetiology results stratified by age or severity, a single analysis was run with all sites combined, including site, the case-level CXR strata (described above), and the stratifying variable of interest (i.e., age or severity) as regression components. This allows the aetiologies to vary by strata. Stratum-specific estimates (e.g., age < 1 year and age $\geq$ 1 year, or individual sites, or severe and very severe) were calculated, in addition to calculating the estimate combined across the strata, as described above.

7.2. Standardizing sites by age and severity distribution

To evaluate how the pathogen aetiologic distribution of pneumonia cases varies by site, we standardised the site-specific aetiology distributions by age and pneumonia severity strata (according to World Health Organization definitions used pre-2013), using the average of the age and severity distribution across the sites as the standard. The

age by severity breakdown amongst CXR+/HIV- cases (Table 17a) and all HIV- Cases (Table 17b) by site and averaged across sites are shown below. Given the similarity in the case mix between the CXR+/HIV- and the all HIV- cases, we elected to use the same case mix for standardisation in each of these analyses. For the standardised results, at each iteration of the MCMC posterior sampling, we assigned for each case a weight between 0 and 1 according to the standardising distribution that defines the weight based on the individual's covariate profile. The population level aetiology results were estimated for each site using the weighted datasets. Results are presented in the paper both as observed and standardised.

Table 17a. Age and severity distribution among CXR+ cases, excluding HIV+ cases

					Standardisation weights used when stratifying by severity		Standardisation weights used when stratifying by age		
	Age <1 Severe	Age <1 Very Severe	Age ≥1 Severe	Age ≥1 Very Severe	Age <1	Age ≥1	Severe	Very Severe	Total
Kenya, n (%)	98 (34.8)	58 (20.6)	70 (24.8)	56 (19.9)	55.3	44.7	59.6	40.4	282
Gambia, n (%)	154 (53.9)	23 (8)	93 (32.5)	16 (5.6)	61.9	38.1	86.4	13.6	286
Mali, n (%)	86 (35.7)	71 (29.5)	59 (24.5)	25 (10.4)	65.2	34.9	60.2	39.8	241
Zambia, n (%)	109 (52.4)	50 (24)	29 (13.9)	20 (9.6)	76.4	23.6	66.4	33.7	208
South Africa, n (%)	210 (48.3)	120 (27.6)	72 (16.6)	33 (7.6)	75.9	24.1	64.8	35.2	435
Thailand, n (%)	26 (26.5)	11 (11.2)	52 (53.1)	9 (9.2)	37.8	62.2	79.6	20.4	98
Bangladesh, n (%)	85 (38.8)	15 (6.8)	107 (48.9)	12 (5.5)	45.7	54.3	87.7	12.3	219
Average[1] %	41.5	18.2	30.6	10.3	59.7	40.3	72.1	27.9	1769
Case mix for standardization	40	20	30	10	60	40	70	30	

[1] Average distribution of age*severity strata across all sites.

Table 17b. Age and severity distribution among all cases, excluding HIV+ cases

	Age <1 Severe	Age <1 Very Severe	Age ≥1 Severe	Age ≥1 Very Severe	Total
Kenya n (%)	187 (29.7)	152 (24.1)	120 (19.1)	171 (27.1)	630
Gambia n (%)	351 (55.6)	46 (7.3)	186 (29.5)	48 (7.6)	631
Mali n (%)	211 (32.3)	236 (36.1)	103 (15.8)	103 (15.8)	653
Zambia n (%)	281 (54.7)	118 (23)	73 (14.2)	42 (8.2)	514
S Africa n (%)	407 (50.6)	194 (24.1)	139 (17.3)	65 (8.1)	805
Thailand n (%)	61 (27.4)	26 (11.7)	111 (49.8)	25 (11.2)	223
Bangladesh n (%)	225 (42.9)	32 (6.1)	247 (47.1)	21 (4)	525
Average[1] %	41.9	18.9	27.5	11.7	3981
Case mix for standardization	40	20	30	10	

[1] Average distribution of age*severity strata across all sites.

7.3. Presenting all-site aetiology results

The PERCH study sites were selected to represent a diverse range of urban and rural settings, demographic settings, geographies, economic conditions, and HIV and malaria prevalence. Despite the variability across the sites in these and other factors, we felt it was valuable to present a single aetiology distribution reflecting all sites combined (the 'all-site' results), in addition to the site-specific results, for communication and policy making purposes. This all-site 'aetiologic attribution' is not intended to reflect the distribution of pneumonia aetiology globally or in any given setting, but simply reflects what was observed at the nine PERCH study sites during the years in which the study was conducted. Each case contributed equal weight (i.e., the all-site aetiology will be weighted more toward the aetiology of the site(s) with the largest sample size).

7.4. Presenting site-specific aetiology results for focus pathogens

One goal of the PERCH study was to evaluate homogeneity and heterogeneity across the sites with regards to pneumonia aetiology. To simplify the presentation of the site-specific results to facilitate comparison across sites, we display and report 10 focus pathogens, defined as those with an all-site aetiology estimate above 5% (N=7) and an additional three pathogens with an aetiology estimate $\geq$ 2% and of epidemiologic interest. Credible intervals of those three pathogens overlap with some non-focus pathogens hence our use of the term focus pathogen rather than commonest pathogens. The focus pathogens include:

- RSV
- Rhinovirus
- HMPV A/B
- Parainfluenza (1, 2, 3, and 4)
- *S. pneumoniae* (all types)
- *H. influenzae* (all types)
- *M. tuberculosis*
- *S. aureus*
- Influenza (A, B, C)
- *P. jirovecii*

All other pathogens estimated in the aetiology analysis were summarized as 'All Other Pathogens' for presentation of the site-specific results. Aetiologic fraction estimates for all pathogens are presented at the all-site level; forthcoming site-specific papers will include aetiologic fraction results for the full list of pathogens.

8. Presentation of aetiology results

The output from a single PIA analysis is displayed in the form of a 'bubble plot'. The bubble plot improves upon the box plot, the usual method to visualize estimates and their uncertainty, by drawing attention to pathogens with the most relative precision instead of those with the most uncertainty. The bubble plot does this by plotting a larger bubble for pathogens with less uncertainty (i.e., the area of the bubble is proportional to the estimated aetiologic fraction divided by its standard error), whereas the box plot presents the largest boxes for pathogens with the most uncertainty. This format was selected over a standard pie chart to display the uncertainty around each estimate.

9. Individual aetiology probability results

Since the population level aetiologic contribution of a given pathogen is approximately the average of the aetiologic probabilities of individual study cases, we display the distribution of the individual case aetiologic fractions for the 10 focus pathogens (Supplemental Figure 10). Examining the aetiologic probabilities among individual children shows that 26% had a high probability (>80%) that RSV was the cause of their pneumonia. This contrasts with *S. pneumoniae* for which only 2% of children had a high probability for this as the aetiologic agent; most of the cumulative population probability for *S. pneumoniae* is made of up many children with a small probability that this pathogen was the cause of their pneumonia. The distribution of the case-level probabilities for each cases' highest probability pathogen is presented in Supplementary Figures 11a and 11b; the individual case-level aetiologic probability for the top pathogen is >80% for 40% of these HIV- /CXR+ cases, driven mostly by cases with high

probability for RSV. The probability that a case's pneumonia was caused by a virus varied by site from a median of 47% in Thailand and Zambia to ≥75% in Kenya and Bangladesh (Supplementary Figure 12). For cases with the highest viral probability, RSV was estimated to be the predominant cause of their pneumonia (black bars). At certain sites, cases with high viral probability (>80%) were estimated to be caused by other viruses (coloured bars; for example, HMPV and parainfluenza virus in Mali).

IV. PERCH Study Contributors

We acknowledge the work of all PERCH Study Contributors who were involved in data collection at the local sites and central laboratories, and members of the PERCH Study Chest Radiograph Reading Panel:

PERCH Study Chest Radiograph Reading Panel

Readers: Dr. Kamrun Nahar, Dr. Fariha Bushra Matin, Dr. Claire Oluwalana, Dr. Bernard E. Ebruke, Dr. Joyce Sande, Dr. Micah Silaba Ominde, Dr. Mahamadou Diallo, Dr. Breanna Barger-Kamate, Dr. Nasreen Mahomed, Dr. David P. Moore, Dr. Anchalee Kruatrachue, Dr. Piyarat Suntarattiwong, Dr. Musaku Mwenechanya, Dr. Rasa Izadnegahdar, **Arbitrators:** Dr. Vera Manduku, Dr. John DeCampo, Dr. Marg DeCampo, Dr. Fergus Gleeson.

PERCH Study Contributors:

Bangladesh: Kamrun Nahar, Arif Uddin Shikder, Sharifa Yeasmin, Dilruba Ahmed, Mohammed Ziaur Rahman, Mohammed Yunus, Md. Alfazal Khan, Abu Sadat Mohammad Sayeem Bin Shahid, Md Shahriar Bin Elahi, Mustafizur Rahman, Sayera Banu, Fariha Bushra Matin, Razib Mazumder, Md. Saifullah, Muntasir Alam, Fahim Haque, Sabiha Sultana; **The Gambia:** Michel Dione, Emmanuel Olutunde, Peter Githua, Ogochukwu Ofordile, Rasheed Salaudeen, David Parker; **Kenya:** Shebe Mohamed, Siti Ndaa, Micah Silaba, Neema Muturi, Angela Karani, Sammy Nyongesa, Anne Bett, Daisy Mugo, Salim Mwarumba, Robert Musyimi, Andrew Brent, James Nokes, David Mulewa, Joyce Sande, John Odhiambo, Joshua Wambua, Nuru Kibirige, Caroline Mulunda, Hellen Mjalla, Norbert Katira, Karen Dama, Loice Masha, Christine Mutunga, Mwanajuma Ngama, Stephen Mangi, Riziki Anthony, Mwarua Yubu, Elijah Wakili, Benson Katana, Shoboi Mgunya, Emmanuel Mumba, Benedict Mver, George Kuria, Felix Githinji, Norbert Kihuha, Boniface Jibendi, Tahreni Bwanaali, Agustus Kea; **Mali:** Nana Kourouma, Aliou Toure, Mahamadou Diallo, Breana Barger-Kamate, Mariam Samake, Seydou Sissoko, Abdoul Aziz Maiga, Mariam Samake, Toumani Sidibe, Mariam Sylla, Aziz Diakite, Bassirou Diarra; **South Africa:** Azwidihwi Takalani, Andrea Hugo, Susan Nzenze, Ndulela Titi, Mmabatho Selela, Malebo Motiane, Minah Nkuna, Nonhlanhla Tsholetsane, Sibonsile Moya, Debra Katisi, Tondani Netshishivhe, Lerato Mapetla, Gudani Singo, Simphiwe Gasa, Cece Mgenge, Nozipho Mthunzi, Nombulelo Monedi, Tanja Adams, Shafeeka Mangera, Jeannette Wadula, Peter Tsaagane, Jenifer L. Vaughan, Sakina Loonat, Martin Hale, Sugeshnee Pather, Mariëtte Middel, Siobhan Trenor, Palesa Morailane, Ntombi Maya, Rene Sterley, Charné Combrinck, Given Malete, Lerato Qoza, Grizelda Liebenberg, Hendrik van Jaarsveld, Zunaid Kraft, Lisa-Marie Mollentze, Lourens Combrinck, Tsholofelo Mosome; **Thailand:** Sununta Henchaichon, Dr. Tussanee Amornintapichet, Dr. Somchai Chuananont, Toni Whistler, Juraiporn Ratanodom, Patranuch Sapchookul, Ornuma Sangwichian, Sirirat Makprasert, Manoon Hirunsalee, Possawat Jorakate, Anek Kaewpan, Duangkamol Siludjai, Apiwat Lapamnouysup, Dr. Wantana Paveenkittiporn, Waraporn Ubonphen, Dr. Peera Areerat, Ms.Yupapan Wannachaiwong, Ms Tewa Faipet, Ms Punnat Natnarakorn, Ms Ahchanan Sacharone, Mr.Winai Makmool, Ms. Kanlaya Sornwong, Ms. Promporn Sansuriwong, Ms. Ratchanida Potiya, Ms. Wasana Hongsawong, Ms.Wipa Matchaikhen, Ms. Thatsanawan Chaiyabil, Ms.Piyapai Wannarach, Ms Chamaiporn Wadeesirisak, Mr. Yuttapong Norapet, Mattana Bangkung, Mr. Barameht Piralam, Sathapana Naorat, Anchalee Jatapai, Prasong Srisaengchai, Dr. Leonard Peruski, Ms.Dawan Phaensoongnoen, Ms.Tussaaorn Klangprapan, Ms.Narawadee Dumrongdee, Ms.Atchara Srithongkham, Mr. Piyawut Noinont, Ms. Pornthip Kamlee, Ms.Siyapa Mongkornsuk; **Zambia:** Justin Mulindwa, Musaku Mwenechanya, John Mwaba, Magdalene Mwale, Julie Duncan, Kazungu Siazele, Muntanga Mapani, Emily Hammond; **Microbiology Unit Canterbury Health Laboratories, Christchurch, New Zealand:** Rose Watt, Shalika Jayawardena; **Streptococcal Reference Laboratory at the Institute of Environmental Science and Research (ESR), Porirua, New Zealand:** Julie Morgan; **National Institute for Communicable Diseases in Johannesburg, South Africa:** Linda De Gouveia, Anne Von Gottberg; **The Emmes Corporation, Rockville, Maryland:** Mark Wolff, Megan Sanza, Omid Neyzari.

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