ASSOCIATION OF MALARIA INFECTION WITH PNEUMOCOCCUS AMONG CHILDREN WITH PNEUMONIA IN THE PNEUMONIA ETIOLOGY RESEARCH FOR CHILD HEALTH (PERCH) STUDY

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INTRODUCTION

- One of the major causes of childhood illness and death in sub-Saharan Africa is invasive bacterial disease (IBD) and the high prevalence is sustained by contributory risk factors.
- Previous studies have reported IBD among children with malaria[1,2], suggesting that malaria infection predisposes individuals to bacteraemia and might also be a risk factor for invasive pneumococcal disease (IPD).
- There have been many suggested mechanisms to explain how malaria causes susceptibility to bacteraemia and these are: macrophage dysfunction, increased gut permeability and the most consistent evidence is malarial haemolysis which creates conditions favorable for bacterial growth by impairing neutrophil function and increasing iron availability[3].
- We therefore assessed the association between pneumococcal pneumonia and malaria infection and the overlap in clinical signs and symptoms in the PERCH study.

METHODS

- PERCH was a case-control study in seven countries in Africa and Asia. This analysis was restricted to countries with >10 malaria smear-positive cases (Kenya, The Gambia and Mali).
- **Cases** were children aged 1-59 months hospitalized with WHO defined-severe or very severe pneumonia and age frequency-matched **controls** were recruited from the community.
- Microbiologically confirmed pneumococcal pneumonia (**MCPP**) was defined as detection of pneumococcus by blood culture or by culture/PCR of lung aspirate or pleural fluid.
- **High-density pneumococcal infection** was defined as PCR >6.9 $\log_{10}$copies/ml in nasopharyngeal/oropharyngeal swabs or >2.2 $\log_{10}$copies/ml in whole blood.
- Chest X-ray positive **(CXR+)** was defined as radiographic finding of consolidation and/or other infiltrate.
- Odds ratios (aOR) adjusted for age and site were calculated comparing malaria smear-positivity (at any density) and case-control status, MCPP, high-density pneumococcal infection and other etiologies.

RESULTS

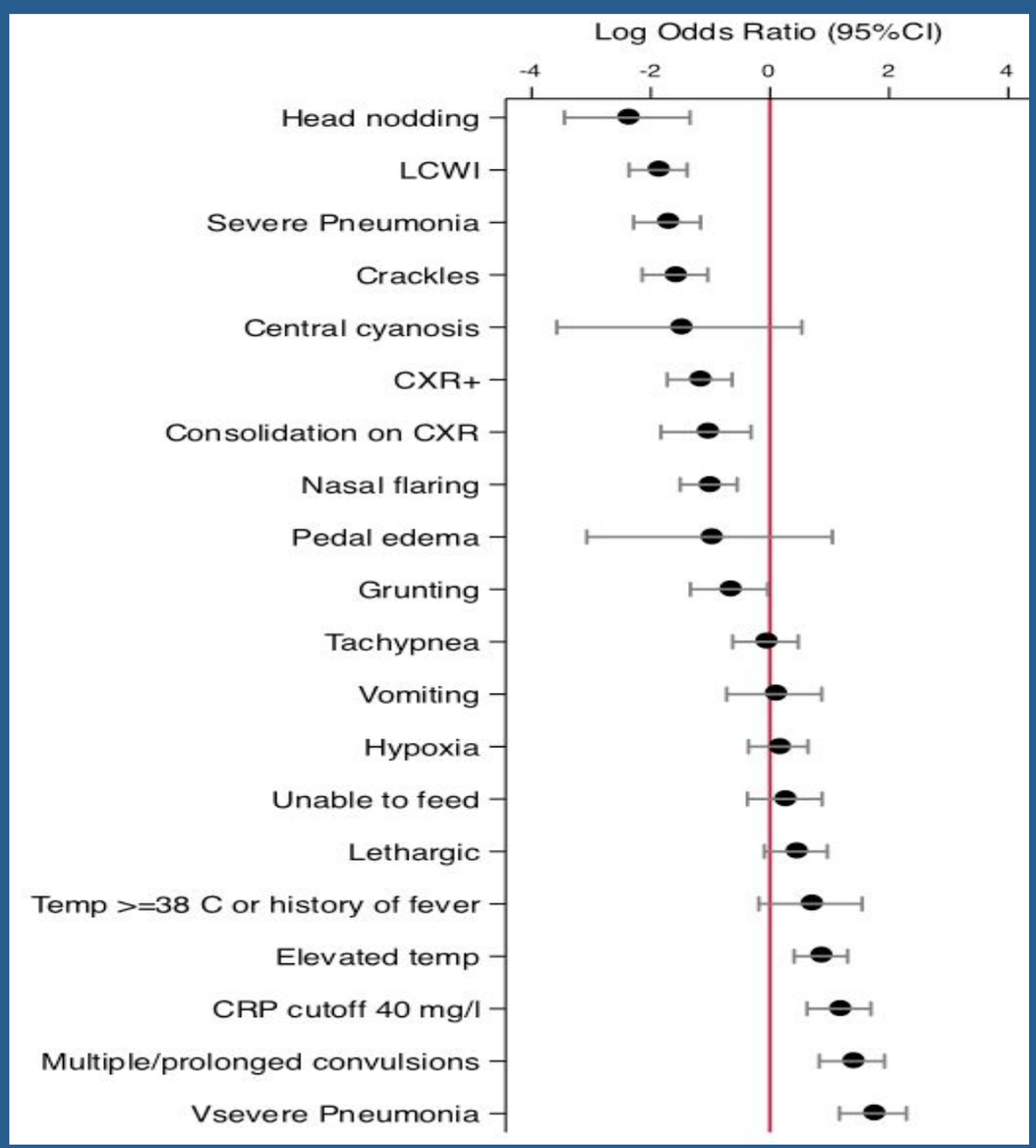
- The prevalence of malaria among the pneumonia cases in the 3 study-sites was low: 44/630 (7.0%) in Kenya, 11/584 (1.9%) in The Gambia and 36/672 (5.4%) in Mali.
- Multiple/prolonged convulsions, elevated temperature (>38°C) and high (>40mg/l) C-reactive Protein (**CRP**) had strong evidence of positive association with malaria infection, **Figure 1**.
- Malaria infection was strongly negatively associated with typical pneumonia signs (head nodding, LCWI, crackles, CXR+, nasal flaring), **Figure 1**.
- Malaria positivity was higher in cases [91/1886 (4.8%)] than in controls [30/2153 (1.4%); aOR=4.2, p<0.001]; 18/798 (2.3%) CXR+ cases vs. controls (OR=1.7, p=0.10).
- Malaria positivity was neither associated with MCPP [1/45 (2.2%) vs. 89/1834 (4.9%) non-MCPP cases; p=0.28] nor high-density pneumococcal infection [16/382 (4.2%) vs. 75/1503 (5.0%) not high/negative; p=0.94]; results were similar for CXR+ and other etiologies, **Table 1**

TABLE 1: Association between malaria positivity and pneumococcal or other etiologies, cases with severe or very severe pneumonia

	Factors	Malaria Smear Positive, n (%)	aOR† (95% CI)	p-value
All Cases	MCPP Cases (n=45)	1 (2.22)	0.33 (0.04-2.51)	0.28
	Non-MCPP Cases (n=1834)	89 (4.85)		
	High density pneumococcal infection (n=382)	16 (4.2)	0.98 (0.54-1.77)	0.94
	Negative/low density pneumococcal infection (n=1503)	75 (5.0)		
	RSV NP/OP or IS positive (N=441) †	**8 (1.8)**	**0.44 (0.21-0.95)**	**0.036**
	RSV NP/OP and IS negative (N=1436) †	**83 (5.8)**		
	Confirmed bacterial infection on an invasive specimen (n=100)	4 (4.00)	0.66 (0.22-1.93)	0.44
	No confirmed bacterial infection (n=1779)	86 (4.83)		
	Hinf NP/OP+ above 6.5log10 copies/ml (n=364)†	15 (4.1)	1.03 (0.56-1.90)	0.93
	Hinf negative or below NP/OP Threshold (n=1498) †	76 (5.1)		
CXR+ Cases	High density pneumococcal infection (n=170)	1 (0.59)	0.23 (0.03-1.79)	0.16
	Negative/low density pneumococcal infection (n=628)	17 (2.71)		

†Abbreviations: NP/OP, nasopharyngeal/oropharyngeal swab; IS, induced sputum; RSV, respiratory syncytial virus; Hinf, *Haemophilus influenzae;* aOR, odd ratios adjusted for site and age. **Bold** = p<0.05.

Figure 1: Association between clinical features and malaria smear positivity, cases with severe or very severe pneumonia



LCWI: lower chest wall indrawing; CRP: C-reactive protein; Vsevere: very severe

CONCLUSIONS

- The study has relatively poor power to examine the interaction of malaria with pneumonia because it was conducted in areas with low malaria endemicity (parasitaemia prevalence in community controls 1.4%). Nonetheless, malaria was associated with admission to hospital with WHO-defined severe or very severe pneumonia [OR= 4.2 (95% CI; 2.72-6.34)].
- Among cases of pneumonia, the clinical features associated malaria co-infection were pyrexia, raised CRP and IMCI "danger signs" and those associated with malaria smear negativity were lower chest wall indrawing, crackles and head nodding.
- Children with pneumonia-malaria co-infection were no more common among those with good evidence of pneumococcal etiology than among all other cases. Malaria co-infection was found much less frequently in children who had evidence of RSV infection.
- Malaria case definition did not use any clinical features or parasite density, therefore since we see malaria positivity in controls not all malaria smear positive children are definite malaria cases.
- Case-control studies are observational in nature and thus may be confounded by other factors.

References

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