

C-REACTIVE PROTEIN (CRP) IN BACTERIAL VERSUS NON-BACTERIAL PNEUMONIA IN THE PNEUMONIA ETIOLOGY RESEARCH FOR CHILD HEALTH (PERCH) STUDY

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INTRODUCTION

Elevated C-reactive protein (CRP) is known to be associated with pneumococcal pneumonia and, more generally, with bacterial pneumonia [1]. We describe the distribution of CRP level among severe and very severe pneumonia cases with suspected bacterial and viral etiology factors with the aim of determining if CRP may be a useful tool to inform or validate the PERCH etiology results.

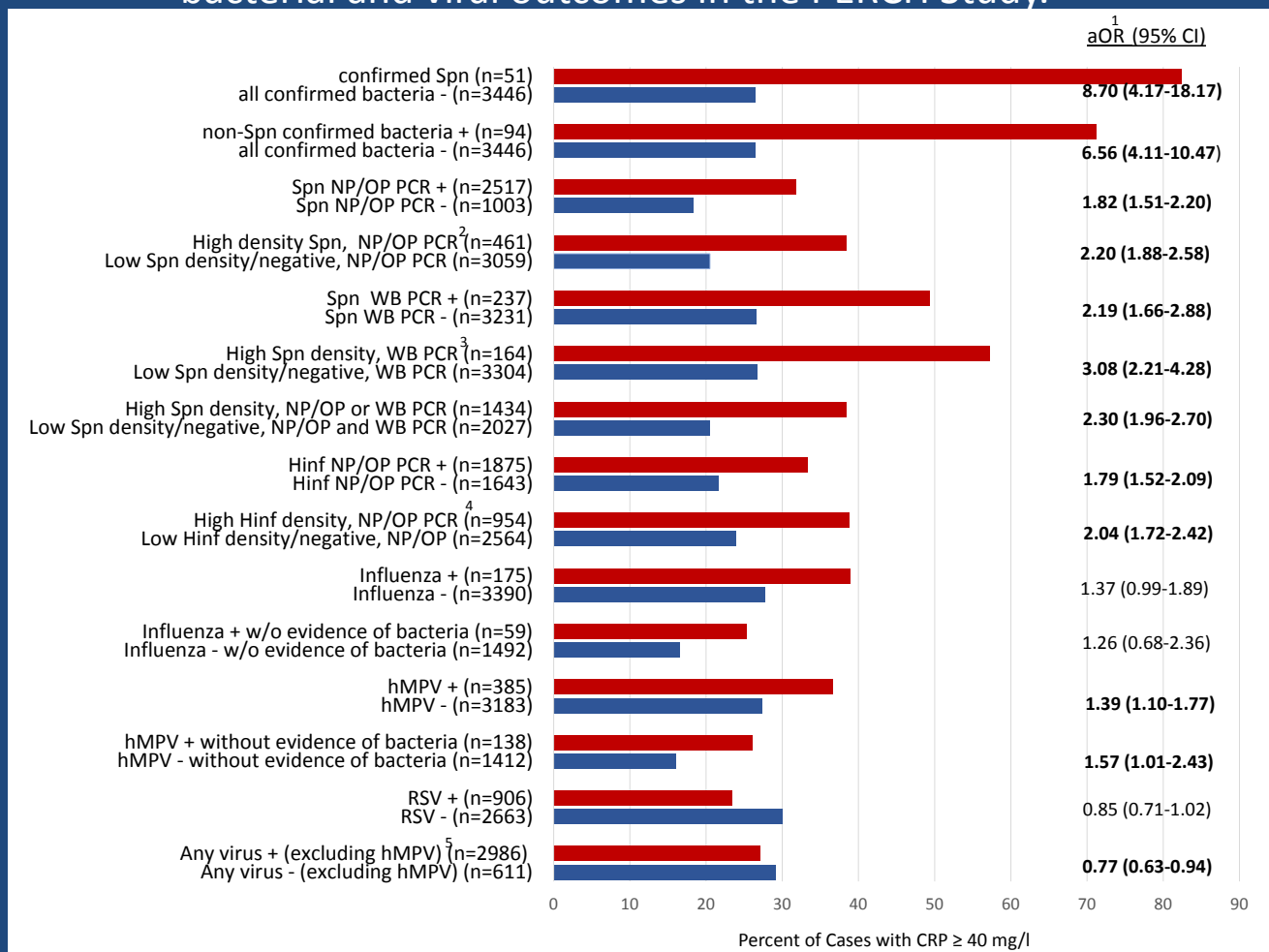
METHODS

- PERCH is a 7 country case-control study; **cases:** aged 1-59 months hospitalized with WHO-defined severe and very severe pneumonia; **controls:** age-frequency-matched to cases, randomly selected from the community without pneumonia.
- Enrollment blood CRP levels were measured for all PERCH cases.
- Case groups representing likely bacterial or viral pneumonia were defined as:
 - Confirmed bacterial pneumonia:** bacteria detected by blood culture or by lung aspirate or pleural fluid culture or PCR, including **confirmed pneumococcal (Spn)** and **confirmed *H. influenzae* (Hinf)** pneumonia
 - Viral pathogen positivity:** detected by PCR from naso/oropharyngeal (NP/OP) swab or induced sputum specimens (assessed 17 viruses)
 - Cases with respiratory syncytial virus (RSV) were considered likely viral pneumonia cases since odds ratio compared to controls was 10.6 (8.8-12.7)
 - High-density Spn:** Spn PCR density in NP/OP (>6.6 log₁₀ copies/mL, >4.4 log₁₀ copies/mL for children with prior antibiotics) or whole blood (WB) >2.2 log₁₀ copies/mL (thresholds derived comparing confirmed Spn cases to controls)
 - High-density Hinf:** Hinf PCR density in NP/OP > 5.9 log log₁₀ copies/mL
 - Evidence of bacterial infection:** high-density Spn or high-density Hinf or confirmed bacterial pneumonia
- Odds ratios and 95% confidence intervals (95%CI) for elevated CRP adjusted for site and age (aORs) were calculated for the defined bacterial/viral case groups.
- The proportion of cases with CRP ≥ 40 mg/L and ≥ 100 mg/L and 95%CI were calculated for the defined bacterial/viral case groups, overall and by site.
- An optimal CRP cut-off was obtained using ROC analysis comparing RSV+ without evidence of bacterial infection to confirmed bacterial cases.

RESULTS

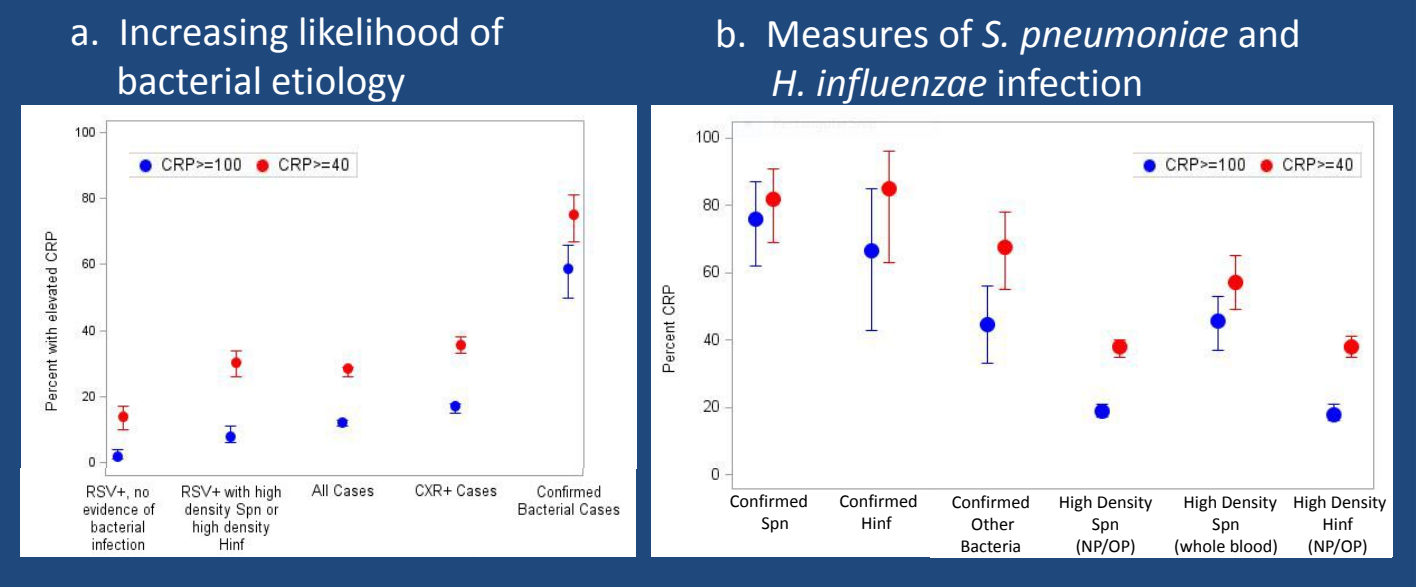
- CRP ≥40 mg/L was consistently associated with bacterial case groups (all p<0.05)
 - Strongly assoc. with Confirmed Spn and Non-Spn bacterial pneumonia (**FIGURE 1**)
 - High density Spn, in NP/OP and/or whole blood, and any Spn positivity
 - High density Hinf in NP/OP and any Hinf positivity
- CRP ≥40 mg/L was inconsistently associated with viral case groups (**FIGURE 1**)
 - No association found for cases positive for any virus vs. negative for all viruses (aOR=0.92; 95%CI: 0.73,1.15) (not shown)
 - Elevated CRP was less common in RSV+ compared to RSV- cases (p=0.08)
 - Elevated CRP was more common in human metapneumovirus (hMPV)+ cases (p<0.05) and also for influenza+ but did not reach statistical significance

FIGURE 1. Association of elevated CRP (≥ 40 mg/L) with various bacterial and viral outcomes in the PERCH Study.



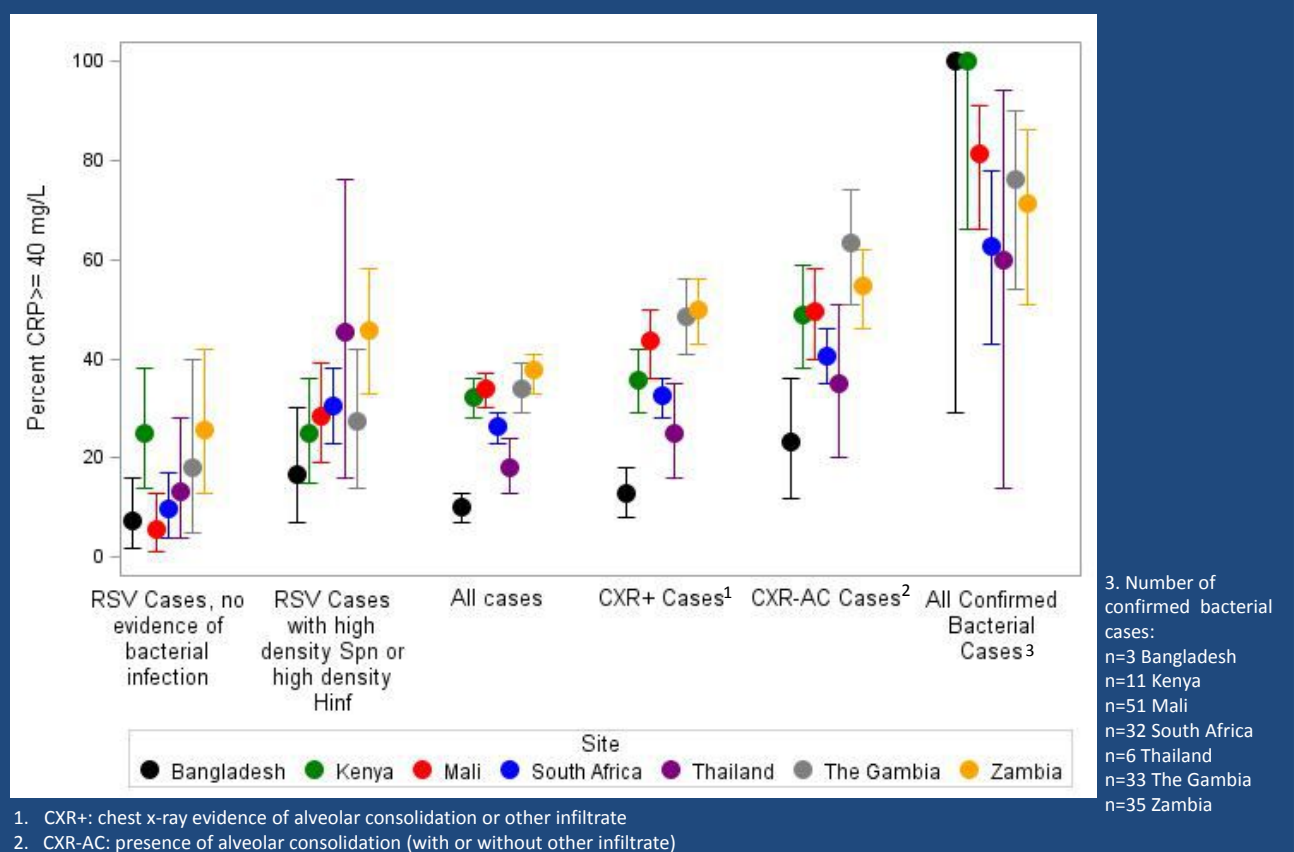
1. adjusted for site and age 2. NP/OP Spn PCR >6.6/4.4 log copies/mL for children without/with prior antibiotics 3. Whole blood (WB) Spn PCR density >2.2 log copies/mL 4. NP/OP Hinf PCR >5.9 log copies/mL 5. Of 17 viruses tested by NP PCR or induced sputum PCR (excluding CMV)

FIGURE 2. Percent of Cases with CRP ≥ 40 mg/L and ≥ 100 mg/L by:



- The proportion of cases with elevated CRP increased with increasing likelihood of bacterial infection (**Figure 2a**); this trend was consistent across sites (**Figure 3**).
- 82% (42/51) of confirmed Spn cases had CRP ≥40 mg/L; 76% (39/51) had CRP ≥100 mg/L.
- 13% of RSV+ cases without evidence of bacterial infection had CRP ≥40 mg/L (2.1% had CRP ≥100 mg/L) compared to 30% of RSV+ cases with high density Spn or high density Hinf (8.6% had CRP ≥100 mg/L; **Figure 2a**); this was true across all sites except Kenya where CRP ≥40 mg/L was equally prevalent (25%) in both groups (**Figure 3**).
- Elevated CRP was less frequent at the two Asian sites, particularly in Bangladesh, for all cases, CXR+ cases and CXR+ cases with alveolar consolidation (p<0.05 controlling for age and prior antibiotic use; **Figure 3**).
- ROC analyses estimated the optimal CRP cut-off to be 28.5 mg/L comparing RSV+ without evidence of bacterial infection to confirmed bacterial cases.

FIGURE 3. Percent of PERCH cases with CRP ≥ 40 mg/L by increasing likelihood of bacterial etiology by site



1. CXR+: chest x-ray evidence of alveolar consolidation or other infiltrate 2. CXR-AC: presence of alveolar consolidation (with or without other infiltrate)

3. Number of confirmed bacterial cases: n=3 Bangladesh n=11 Kenya n=51 Mali n=32 South Africa n=6 Thailand n=33 The Gambia n=35 Zambia

CONCLUSIONS

- Elevated CRP was positively associated with confirmed pneumococcal and non-pneumococcal bacterial pneumonia in PERCH and negatively associated with RSV positivity; its usefulness to inform or validate etiology in PERCH cases is being further evaluated.
- Variation by site suggests that bacterial etiologies may be more common in the African than Asian sites; this may in part be due to early treatment with antibiotics in the Asian sites with high access to care (e.g., the Bangladesh site was nested in active respiratory disease case-finding surveillance).
- While elevated CRP was uncommon in RSV+ cases, especially CRP ≥100 mg/L (only 2.1%), elevated CRP was positively associated with influenza and hMPV. Although this may indicate synergistic bacterial co-infection in these cases, the association remained after excluding cases with evidence of bacterial infection.
- The increased frequency of elevated CRP in RSV+ cases with high density Spn and Hinf compared to RSV+ cases without evidence of bacterial infection may provide a clue as to the proportion of RSV+ cases with a concurrent bacterial infection.

References: 1. Albrich WC, Madhi SA, Adrian PV, et al. Use of a rapid test of pneumococcal colonization density to diagnose pneumococcal pneumonia. Clin Infect Dis. 2012; 54:601-9

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

