Author’s response to reviews

Title: Respiratory virus surveillance in hospitalised pneumonia patients on the Thailand-Myanmar border

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Author’s response to reviews: see over
Dear Sir/Madam,

Re: MS1748864178902748, “Respiratory virus surveillance in hospitalised pneumonia patients on the Thailand-Myanmar border”

We would like to thank the reviewers for their constructive comments on the above manuscript: we have addressed these in order to strengthen the manuscript, as outlined below.

Reviewer 1
We agree that the inclusion of additional viral PCRs to detect, amongst other possible viruses of interest, rhinoviruses and human bocaviruses would have been interesting. As commented, this would have undoubtedly increased the proportion of cases in which one or more viruses were detected. However, the association between nasopharyngeal detection of several respiratory viruses, including human bocavirus and rhinoviruses, and the aetiology of a pneumonia episode is still somewhat unclear. We have updated the discussion (p14) to reflect this limitation of our surveillance:

• “The panel of viruses tested for included the key pathogens for which evidence of an association with pneumonia is proven, but inclusion of PCR assays to detect additional respiratory viruses would have added value and may have identified a higher prevalence of multiple infections. Studies using multiplexed virus PCR assays have detected both an increased proportion of children with single and multiple viral lower respiratory infections. Both human bocavirus and rhinoviruses may be detected in a large proportion of pneumonia cases, although data regarding causality from case-control studies are still limited. Despite this, it was demonstrated that influenza virus and/or RSV were associated with a third of hospitalised pneumonia episodes in Maela.”

We also agree that collection of additional severity and outcome data would have been ideal. Unfortunately this was not possible with the surveillance resources available to our team. We have commented specifically on this in the updated discussion (p14):
• Additional severity data (e.g. need for supplemental oxygen and length of stay) and outcome data were not collected, which further limit the conclusions that can be drawn from the surveillance and the comparisons that can be made with other studies.

Reviewer 2
1. 

Patients vs. episodes. A total of 698 individuals were sampled (689 patients with single episodes, eight patients with two episodes, and one with three episodes). Aside from deduplicating repeat episodes within 14 days of the first specimen, these repeat episodes were not further adjusted for in the analyses. The number of patients included in the analyses has now been included in the abstract (p2) and results section (p8, “Patient characteristics”).

2. 

Virus detection vs. prior antimicrobials. Interestingly, individuals with RSV infection were more likely to have received an antimicrobial within the 14 days prior to admission. This association remained after adjusting for age, but was not seen for the other viruses. This result has been included in the results section (p10, “Virus detection”).

3. 

PCR details. The following statements have been added to the methods section (p6/7, “Laboratory methods”):

a. “NPA specimens, in 1ml viral transport medium (VTM, prepared in-house), were transported daily to the SMRU microbiology laboratory, which is located in the town of Mae Sot, approximately 50km from Maela. Specimens were placed into an insulated cool box immediately after collection and were transported back to the Mae Sot laboratory within eight hours of collection, where they were stored at -80°C until analysis.”

b. “To ensure the reproducibility of results approaching the assay limits of detection (approximately 100 copies per reaction for each target; SMRU internal QC data), specimens with low positive PCR results (cT values of 35 - 39) were repeated and only if the cT was < 40 in both runs was the virus PCR considered positive.”

4. 

Association between NPA virus detection and pneumonia. See Reviewer 1 comments.

Editorial team

As requested, the ethics section has been expanded with the following statement (p7/8): “Local ethical review in Maela was not possible at the commencement of surveillance. However, the surveillance activity was discussed with PU-AMI staff, and all concerns were addressed, prior to the beginning of the project.”

We hope that these changes render the manuscript acceptable for publication.

Yours sincerely,

Dr Paul Turner, on behalf of the authors