Reviewer's report

Title: Acute Lower Respiratory Infections in [greater than or equal to]5 year -old Hospitalized Patients in Cambodia, a Low-Income Tropical Country: Clinical, Viral and Bacterial Characteristics

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Reviewer: Henry Baggett

Reviewer's report:

General comments
This manuscript describes the clinical characteristics, CXR findings, and prevalence of various pathogens among older children and adults hospitalized with ALRI in Cambodia. The investigators have important and unique data that should be shared. Their findings are highlighted by a very high prevalence of TB disease and a high proportion of other bacterial infections, albeit most of the non-TB bacterial infections are confirmed only by sputum culture. The prevalence of viral pathogens was lower than what has been published from other studies, which may partially be related to differences in case definitions.

While the manuscript has some very relevant data, there are some issues that should be considered. The authors place disproportionate emphasis on detailed clinical comparisons and associations with a ‘severe disease’ category that is somewhat arbitrarily defined. The strengths of the paper lie in the detailed clinical descriptions with CXR findings and, very importantly, the pathogen testing results. This reviewer would encourage the authors to focus more on these aspects of the data and less on the multiple comparisons of clinical characteristics. The clinical characteristics are relevant but primarily as general descriptions of patients meeting the case definition and by outcome and pathogen results.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Abstract

• Methods. Give specific parameters for ‘severe’. What is low oxygen sat? increased respiratory rate?. Reader should know values used for cut off. Severe clinical symptoms is very non-specific. Can you fit some description into the abstract?

• Results. “1,904 patients presented with… “Please clarify if this is admission diagnosis or based on some clinical case criteria.

• Results. Bacterial etiologies. Need to say AFB-positive. For other bacteria, it is important to know how many H. influenzae and pneumococcus were diagnosed by positive blood culture (vs. sputum only)

• Results. <15 year old children should be 5-14 years, correct?
• Results. It would be important to give the overall case fatality proportion

Background
• The authors cite a 2004 study from the US to support the point that few recent studies have looked at ALRI and etiologies [sentence actually does not say ALRI but we assume that is the point]. In the 8 years since the 2004 paper by Michelow et al, there has been a fair amount of work in this area, including in Southeast Asia (e.g., REF 12: Olsen et al. Incidence of respiratory pathogens in persons hospitalized with pneumonia in two provinces in Thailand. Epidemiol Infect. 2010 Dec;138(12):1811-22. Epub 2010 Mar 31.) . The authors should revise their literature search and update this section of the paper.

Methods
• Study site. Infant mortality is not the same as under 5 mortality. Be clear on what you are showing.
• Study design. Case definition in first sentence would benefit from editing. It is such an important part of the methods that the reader should be very clear on how it was applied. Be clear that the patients needed to have cough PLUS another respiratory symptom. Is the full list of ‘other’ respiratory symptoms provided? Note that crackles is not a symptom but a clinical sign.
• Please make it clear that patients with known HIV were excluded. It currently states that those with ‘acquired immunodeficiency’ were excluded.
• The wording of this sentence is unclear: “This policy integrates routine HIV testing of sexually transmitted diseases and TB patients, pregnant women and hospitalized patients with suspicion of HIV infection (national HIV/AIDS program; http://www.nchads.org). For example, what is ‘HIV testing of sexually transmitted diseases’? Please make clear what this means for the patients in the study.
• Sputum is very difficult to obtain from younger children. The authors should mention success rates by age in the results.
• What kind of swabs were used for NP/throat?
• Microbiology. Authors cite a 2004 study for the PCR methods. Did they really use the same assays as the 2004 study?
• Case definitions. Specify that first sentence refers to sputum
• Case definitions. To define necrotizing, authors refer to ‘radiologic images’. Is it not just CXR? If not, please specify what other images were used.
• Case definitions. From a methodological standpoint, it is not clear why the authors would create a category of patients whose illness was ‘probably caused by a virus’. Is that not the point of doing the study with all of the testing for viruses and bacteria? The wording of the sentence also makes it difficult to determine how this group is defined.

Results
• Table one is not labeled
• Table one formatting needs work
• Table 1. Methods state that NP and throat swabs were collected but table refers only to NP.

• Table 1. Needs to be more specific about what was positive from each specimen. What does positive blood culture mean? Does it exclude contaminants and what was contamination rate? When giving viral results, it should be clear that this represents positive PCR on NP/throat specimens. For ‘bacterial etiologies’, it needs to be clear how this is defined. Avoid the term ‘etiology’, especially for viruses. The positive results represent detection of a virus, but whether it represents the etiology of ALRI is not clear, especially for rhino, boca, and corona.

• Table 1. It should be clear in the table or the text the frequency of key bacteria from blood cultures vs. sputum only

• Table 1. What is the test for comparing age group distribution? Is there a referent group?

• Table 1. Leukocytosis, neutrocytosis, and lymphocytosis should be defined. It is not clear why lymphocytosis would be considered a marker of severe disease as is the title for this section of the table

• Microbiological etiology. Avoid the term etiology for situations when pathogen detection is not equivalent to etiology. This is especially true for many of the viral detections and sometimes sputum culture.

• Etiology. The text is a little confusing because percentages don’t match the table. It seems that the text presents the percent of each pathogen among those with a pathogen identified. Either make the data match the table or make very clear the way the percentages are calculated in the text

• Mortality. Make clear if the pathogen categories among fatal cases are mutually exclusive. Did 5 fatal cases have rhinovirus only?

• Do the authors have data on HIV prevalence among cases?

• It would help to interpret blood culture results to know frequency of prior antibiotics by positive vs. negative culture.

• Authors should consider removing tachypnea and tachycardia from case definition for severe. These could confound relationships because of differences by age in these characteristics. Suggest focusing on more objective measures of severity: intubation, death, low oxygen saturation, possibly hypotension. It seems much more relevant to focus on predictors of outcome.

• A disproportionate amount of text is spent describing comparisons of symptoms and signs among age groups and pneumonia categories. This detracts from the information on microbiology and outcomes.

• Because TB is such a major contributor to pneumonia in this patient population, I encourage the authors to explore these cases in more detail, especially with regard to co-infections. Present more details about which pathogens were also detected to help sort out whether TB is responsible for the acute disease or whether TB-infected patients came to hospital primarily due to a superimposed acute infection with another pathogen. There has been a fair amount of recent
work on acute presentations of TB disease as well as the role of co-infections such as pneumococcus and influenza. The authors have an opportunity to make an important contribution to this discussion.

• Last paragraph of results. This section seems to belong in the section with the other microbiology results. The percentages do not match those in table 1, which creates some confusion. The section seems to focus on the patients assigned to the group ‘with little evidence of bacterial infection’. As mentioned in comments on the methods, this category seems arbitrary and associations self-fulfilling. The group is defined by lack of bacterial identification so not surprising that there is a higher proportion with viruses detected.

• Figure 1 and throughout paper. Authors refer to TB cases as ‘AFB’. They define TB disease in the methods as a positive AFB sputum smear. After defining, it would be more clear to simply refer these cases as having TB disease. Authors can mention the minor limitation of not having culture confirmation in the discussion.

Discussion

• First paragraph. The authors state that “our knowledge, it is the first report of a comprehensive picture of radiographically confirmed ALRI that resulted in hospitalization in a low-income tropical country of Southeast Asia.” This may be true, but it should be noted that reference 12 does give data on CXR confirmed pneumonia in Thailand, a country in the region, albeit a middle (not low) income country. The low income distinction may be lost on readers not clear on income levels by country in the region.

• The main findings of public health importance should be clearly highlighted in the first paragraph. In this reviewer’s opinion, the study’s strengths lie in the laboratory data and outcomes among patients with well characterized clinical characteristics and CXR findings. The TB prevalence is remarkable and seems worth highlighting in the beginning. The discussion should center around how these data can influence policy and case management strategies.

• The authors mention a few patients with urine tested by urine antigen. They should mention which assay was used. What was the age of the patients because the assay is probably only valid in age >17 years? What were the blood culture and sputum results of those with a positive urine test? The added information is only relevant in the context of the larger study. The authors might just put these data in the results.

• The authors also insert data on Mycoplasma and Chlamydia in the discussion. Were these patients a subset of the study population? If so, these data would go better in the results even though not all patients were tested. 304 is not a small number.

• “This relatively low yield contrasted with a much higher proportion of pneumonia-related patients (~40%) who had high blood neutrophils count,…” Do the authors mean ELEVATED neutrophil count?

• In discussing the low bacterial yield, discussion points should be specific to blood culture and sputum culture. Blood culture yields were especially low, which
is similar to other studies from the region but still worth exploration. The authors mention prior antibiotic use but don’t give specifics. There are data on antibiotic use; did it differ by culture positivity? Are cultures routinely collected before antibiotics are administered in hospital? Can you comment on blood volume?

• It might be a stretch to say that rhinovirus and influenza were ‘extremely’ common in children. The prevalence of flu and other individual viruses by age group was not apparent in the results

• The proportion positive for several of the viruses is lower than what I would have expected especially for influenza. Data from other studies in the region and elsewhere suggest 8-12%. Please comment on the potential reasons for differences

• It is certainly fair to question rhinoviruses contribution to disease, but RSV is clearly pathogenic and, although occasionally found in patients without ALRI, it is much more common in ill patients. The authors might note the lack of a control population as a limitation in assessing the pathogenic role of viruses like rhino, boca, and corona

• The last paragraph of the discussion is disappointing and focuses on the study findings with the least direct implications for public health. The authors should again highlight the key findings and their implications for case management and health policy. What are the recommendations for clinicians and policy makers in Cambodia and the region?

• The authors should note study limitations somewhere in the discussion

Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

• The background should make the case for why this study includes only age 5 years and older. They state that ALRI is the leading cause of death in <5s. so why is this critical group left out of the paper?

• Methods. Pneumonia is a major category for results presentation and is divided into 2 mutually exclusive categories: with and without cavitation. In the case definition section, a definition of ‘pneumonia’ is needed. It would also help to know what cavitation was chosen as the only categorization of those with pneumonia. There is no mention of proportion of those with pneumonia who also had pleural effusion.

Results

• Of 959 patients with pneumonia, 289 had necrotizing imaging and the remainder did not have ‘cavities’. Are necrotizing imaging and cavities equivalent? Please use consistent language and specify what is meant by ‘necrotizing imaging’. Was CXR not the only imaging?

• Table 2 is very messy and difficult to follow. Definitions are unclear. How is tachycardia defined? Tachypnea? What is meant by ‘cyanosis - dyspnea’? this information could be worked into the text fairly easily. Table 2 may not be needed. In the current form, it is difficult to even interpret.

• Tables 3 and 4. These tables essentially treat severe and non-severe diseases
as outcomes in the analytic sense. Severe is defined by a constellation of clinical parameters, some of which by confounded by age and therefore hard to interpret (heart rate, blood pressure, respiratory rate). It seems more relevant to describe the frequency of these characteristics individually among cases and possibly subgroups of patients (e.g., virus vs. bacteria). Rather than look for predictors of severe disease by these categories, consider looking at predictors of very objective and relevant outcomes like death or other indicators of truly severe disease.

Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

• Title. Make clear that the work refers to patients with community-acquired infections. Current wording could include hospital-acquired. Last part of title has awkward wording: “viral and bacterial characteristics”. Suggest something like ‘clinical characteristics and etiology’, or …and viral and bacterial pathogens

• Abstract. I encourage authors to consider whether the association between viruses and wheezing is really one of the paper’s major findings to warrant highlighting in the conclusion

Methods

• Are there more recent population estimates than 2008?

• Site. GDP might be nice as another indicator

• Site. Would be nice to know a little more about the capacity in these hospitals. Is supplemental oxygen available for example? IV antibiotics? Capacity for mechanical ventilation

• Design. It would be nice to know why patients with known TB were excluded. It is certainly possible that those patients had ALRI due to a pathogen other than TB

• Design. What is an expert pulmonologist? Board certified?

• Microbiology. Did the hospital use automated blood culture machines?

• Case definitions. Some of the clinical case definitions are non-specific. For example, it is not clear how predictive of diabetes is a blood glucose of 140 in a non-fasting person who is acutely ill. Similarly, enlarged heart for cardiovascular disease. This not necessarily a problem unless the authors rely heavily on these categories to make inference about the population.

• Case definitions. What is ‘radiological images with retraction’?

• Was pleural fluid ever cultured? Can you include the results?

Results

• Patient characteristics. The categorization of patients is a bit confusing. If the journal will allow another figure, please consider a table or flow diagram to show how the patients break out into different groups and how the groups are defined.

• Patient characteristics. Consider moving demographic descriptions to beginning of section
• Table 1. Shows 5 different comparisons for each category. Authors should note what is considered statistically significant. With multiple comparisons, several with p<0.05 would be expected. Consider whether a correction is appropriate.

• Table 1. How is dry cough defined? This was not in methods.

• Please consider mentioning outcome in the text and providing any information on what happens with transferred patients. Does this mean transferred to a higher level facility usually? How often are patients discharged to die at home? This could be mentioned in discussion.

• Table 1. Are there data on other markers of severity such as intubation?

• Was supplemental oxygen available?

• Not familiar with the term ‘sibilant wheeze’

**Level of interest:** An article of importance in its field

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.