Author's response to reviews

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

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Version: 3 Date: 24 November 2012

Author's response to reviews: see over
Dear Editor,

We thank you and the reviewers for the attention you have paid to our manuscript entitled "Acute Lower Respiratory Infections in ≥5 year-old Hospitalized Patients in Cambodia, a Low-Income Tropical Country: Clinical Characteristics and Pathogenic Etiology" (#BMCID_MS 8553218397309289). We found the reviewers' comments very useful and helpful.

We would like to submit a revised version of the manuscript that takes into account each reviewer’s comment. Please also find below the detailed responses to each of the comments. All co-authors agree with these modifications.

We hope that the revised manuscript will be suitable for publication in BMC Infectious Diseases.

Yours sincerely,
Sirenda Vong

Reviewer's report
Title: Acute Lower Respiratory Infections in ≥5 year-old Hospitalized Patients in Cambodia, a Low-Income Tropical Country: Clinical, Viral and Bacterial Characteristics
Version: 2 Date: 11 June 2012
Reviewer: Sonja J Olsen

Reviewer's report:
This is a very comprehensive paper describing the clinical and radiologic characteristics and etiologies of respiratory diseases in persons 5 and older in Cambodia. The data are from a study lasting 1.5 years from two hospitals. TB was the most common diagnosis (based on AFB), but viral pathogens (rhinoviruses and RSV) were also important. Vaccine-preventable pneumococcus and Hib were also relatively common.

Abstract
First sentence. What do the authors mean by “unclear.” Do you mean there are no data, the data are not good or what? I suggest you be more specific. There are some good data now coming out of the tropics on respiratory disease. Consider using the word “independent” instead of “regardless.” Conclusions. It also appears that some viral infections were very common and worthy of mention. Maybe instead of saying further research is needed it would be better to talk about using the data to inform prevention strategies, such as the reduction of vaccine preventable disease.

Response: we made substantial changes to reflect the reviewer's concern

Background
Again, I think there is more than one good study (Ref 4) on the etiologies of respiratory disease in the tropics. I would acknowledge the advances in the last decade.

Response: we added more references to reflect the reviewer's comment
Why did you exclude children <5 years?

Response: Children aged <5 years are known to have different epidemiological and clinical features compared with older children or adults. In addition, bacterial infection is difficult to diagnose as bacteremia is rarely found and sputum specimens are difficult to obtain. As such we performed a separate analysis, which made into a manuscript that was recently published in The Pediatric Inf Dis Journal (Guerrier G et al, 2012).

Methods
Change “Cambodia is dominated by..” to “Cambodia has…”

Response: done, thanks

Why were known TB, AIDS or cancer patients excluded? These people can have an acute respiratory disease.

Response: studies on bacterial etiologies in these HIV/AIDS patients were conducted prior to the present study in Cambodia. References for these studies are provided in our manuscript. In addition as Cambodia is known with having one of the highest prevalence of TB and HIV infection in the region, we estimated that our funding and laboratory capacity would not have been sufficient to absorb known TB and HIV cases. We therefore chose to focus on non-TB and non-immunosuppressed patients. Besides, we did not expect to have had so many TB cases in acute pneumonia. In hindsight, we agree this study would have been valuable should we have included known TB cases as well.

Please clarify if the swabs were one throat and one NP on each person or was it either or.

Response: we collected for each patient one throat swab AND one nasopharyngeal swab. We clarified in the text

Was whole blood immediately put into a blood culture bottle? How was it stored?

Response: yes, blood was collected directly in blood culture bottle. The blood bottle was labeled with time and date of collection and patient's ID code, immediately brought from the ward to the hospital laboratory. It was then stored in an incubator that is provided by the present project. Finally, all blood bottles were transported by taxi to IPC in a box at transportation temperature (room temperature without air-condition) within 12 hours.

The information was provided but misplaced in the text, we made changes accordingly

Multiplex often decreased sensitivity over singleplex PCR. Do you have any data on your assay?

Response: The sensitivity of the five multiplex PCR/RT-PCR was actually evaluated and published by our group: BUECHER C et al. Use of multiplex PCR/RT-PCR approach to assess the viral causes of influenza-like illnesses in Cambodia during three consecutive dry seasons. J. Med. Virol 2010; 82:1762-72. Table 4 of Buecher et al showed the sensitivity of detection of each virus by monoplex and multiplex. It is true that one can miss some viral strains if the design of primers is not well done. However, these multiplex were an optimization of the techniques described by Bellau-Pujol et al and others (also cited in Buecher et al.). Clinical specimens were validated using IF, which is not affected by the genetic variability of virus. In addition, we designed the primers using stable genomic regions to avoid this problem.
Finally we participated in two external quality controls (1 QC using commercial panels and one whose panel was provided by the Virology lab of the University Hospital of Caen, Prof. Freymuth). Results in both QCs were excellent. We added a sentence in the methods section to reflect this.

How did you define an uncontaminated specimen?


Severity definition – did the authors consider any of the existing pneumonia severity indices for adults or how was this definition established? I assume your definition is based on data collected at presentation and that your findings could be used to assist in clinical management? If yes, it would be helpful to explicitly state that.

Response: Unfortunately, like a typical secondary hospital in rural Cambodia, ICU (e.g. mechanic ventilation) or urea testing was not available in our hospital sites. In addition, we realized that diagnosis of neurological symptoms (e.g. confusion) was not reliable or missing on the medical chart. As some of these symptoms and signs are among the existing severity indices (e.g. CURB65, PSI) we could not apply them accurately. So the 3 expert pulmonologists (French Professors of Pulmonology from University Hospitals in Paris, France) agreed upon available parameters to define severity. The definition was not validated but for the epidemiological purposes, we believe the definition was plausible and likely acceptable. We added a sentence in the case-definition paragraph to clarify

ALRI probably caused by a virus – I assume this is used only among patients without a PCR positive viral results? Please specify. Also, there is no definition for a viral diagnosis except for this one. It would be helpful to add that.

Response: Actually we meant a different idea. 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 viruses. So we created an additional clinical diagnostic group defining criteria for causality link between virus and ALRI. We made changes to clarify.

Data analysis – I don’t understand what the authors mean when they say “We restricted our analysis…” What exactly is excluded?

Response: we realized in hindsight that clinical signs that were collected and recorded by the hospital clinicians were incoherent and therefore not reliable (e.g. neurological symptoms and signs, detailed respiratory auscultation's results). We chose to only consider signs and symptoms that were less subjective or clinical skills or person-dependent. We made changes to clarify.

Results
Reference to Table 2 implies it is about mixed infections but it is not.

Response: apologies, we corrected the error

The authors state that 61 patients died. Is this in hospital?
Response: yes they did die during hospitalization. We had limited mean to follow up on the patients' outcomes after they were discharged from hospital.

The authors say “high hear frequency.” Do they mean high hear rate or high pulse?

Response: sorry we meant heart rate or tachycardia. We made the correction.

Since the lower limit of the age range is 5, I suggest changing “… aged 15 year or younger” to say “5-15 years old.”

Response: correct, thanks.

Can the authors look at the relationship between wheezing and RSV (instead of just any virus)?

Response: we actually did perform the comparison between wheezing and all viruses separately adjusting by age. Only rhinovirus came out independently associated with wheezing. We added this information in the results.

Discussion

TB findings – This suggests hospitalized pneumonia patients should all be tested for MTB. Is this currently the recommended clinical management guidelines? This is an opportunity to highlight the importance of testing or perhaps suggest a change in the guidelines if that recommendation is not currently there.

Response: According to the national guideline, in non-high risk groups who are pulmonary TB suspects, all health facilities use cough of more than two weeks to screen for TB. However, like in our hospitals, physicians may not follow official guidelines. We made changes in the discussion to suggest further investigation to confirm high prevalence of TB among patients with acute lower respiratory infection and explore potential multi-symptoms screening (diabetes, elderly, contacts, ..etc).

Also, suggest changing the wording of “…was abbreviated by the patient” to “poor recall. I think what you are trying to say is that patients may not recall how long their symptoms have been occurring.

Response: done, thank you for the suggestion.

The discussion about testing for S. pneumoniae is important and the urine testing results are a good addition. Can the authors add one more sentence on the implication of this finding? In other words, if you take this into account, what would be the revised frequency of detection?

Response: we added several sentences in the discussion to address the reviewer's comment.

I suspect there is a reference for the sentence that culture is more sensitive than AFB for TB. This would be better than (data not shown).

Response: we added a reference as suggested by the reviewer.

I would add a sentence in the discussion about the possible decrease in viral pathogens due to the use of a multiplex PCR.

Response: please see our reply above with regard to the validation we conducted on our multiplex techniques.
I think the discussion about severity could be strengthened if you bring in the idea of admission triage. In other words, if you can identify severe cases right away based on your criteria or associated symptoms, if there something you can do to improve outcome (e.g., send to ICU)?

Response: we agree with the reviewer's comment with respect to the relevance for an admission triage, however, we believe that expanding the discussion on this subject is a bit too theoretical as capacity for severe/life-threatening case management is still limited in rural Cambodia. Indeed, our study hospitals are typical of a secondary hospital in rural Cambodia where there is no ICU i.e. no intubation and no mechanical ventilation. We clarified this in the text.

I would like to see some comment on vaccine-preventable diseases. Are vaccines for pneumococcus and Hib being used in Cambodia or is this an opportunity to use these data to advocate for their introduction?

Response: we made changes to address the reviewer's comment

Reference # 14 is missing

Response: apologies. Thank you for identifying this

Table 2. This table has some formatting issues so was difficult to read. Also, the numbers of the last 3 columns are really too small to interpret within any stability. I suggest cutting this table and just summarizing in the text.

Response: We removed this table and summarized the content in the text.

Figure 1. This is interesting but in my view suggests that the CXR classifications are somewhat artificial or perhaps just not very useful as correlates of etiology. Yes, there are some differences. However, it is you do find all pathogens in every category.

Response: To some extent we agree with the reviewer's comment; however, we reckon it is also interesting to show the overwhelming predominance of viral detection or "etiology" in ALRI with normal radiological image of the pulmonary parenchyma. We added a sentence in the results section to emphasize this.

Level of interest: An article of outstanding merit and interest 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.
Reviewer's report

Title: Acute Lower Respiratory Infections in \( \geq 5 \) year-old Hospitalized Patients in Cambodia, a Low-Income Tropical Country: Clinical, Viral and Bacterial Characteristics

Version: 2 Date: 14 September 2012

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.

Response: we agree with the reviewer that the definition of severity was not validated. Like a typical secondary hospital in rural Cambodia, ICU (e.g. no mechanic ventilation) or urea testing was not available in our hospital sites. In addition, we realized that diagnosis of neurological symptoms (e.g. confusion) was not reliable or frequently missing on the medical chart. As some of these symptoms and signs are among the existing severity indices (e.g. CURB65, PSI) we could not apply them accurately. So the 3 expert pulmonologists and 1 ID specialist agreed upon available parameters to define severity. For the epidemiological purposes, we believe the definition was plausible and likely acceptable. We added a sentence in the case-definition paragraph to clarify

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?

Response: we chose not to present severity data in the abstract to reflect the reviewer's comment regarding the lack of validity of severity criteria we used

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

Response: we made changes to address the reviewer's comments
• 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)

Response: we made changes to address the reviewer's comments

• Results. <15 year old children should be 5-14 years, correct?

Response: ok, thanks

• Results. It would be important to give the overall case fatality proportion

Response: we added this information

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.

Response: we added more references as suggested

Methods
• Study site. Infant mortality is not the same as under 5 mortality. Be clear on what you are showing.

Response: corrected, thanks

• 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.

Response: we made changes to address the reviewer's concern

• Please make it clear that patients with known HIV were excluded. It currently states that those with ‘acquired immunodeficiency’ were excluded.

Response: done, thanks

• 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.

Response: apologies, we meant HIV testing of patients with STD or TB

• Sputum is very difficult to obtain from younger children. The authors should mention success rates by age in the results.
Response: we added this information in the results section as suggested by the reviewer

• What kind of swabs were used for NP/throat?

Response: we used cotton swabs with plastic stem. This is what is recommended for viruses. We added the brand name of the swabs

• Microbiology. Authors cite a 2004 study for the PCR methods. Did they really use the same assays as the 2004 study?

Response: We described our methods in Buecher et al. These multiplex are an optimization of the techniques described by Belleau-Pujol et al and others (also cited in Buecher et al.). Clinical specimens were validated using IF, which is not affected by the genetic variability of virus. In addition, we designed the primers using stable genomic regions to avoid this problem. Finally we participated in two external quality controls (1 QC using commercial panels and one whose panel was provided by the Virology lab of the University Hospital of Caen, Prof. Freymuth). Results in both QCs were excellent. We added 2 references in the methods section to reflect this.

• Case definitions. Specify that first sentence refers to sputum

Response: blood and sputum cultures were actually performed to define bacterial etiology. We edited the sentence to clarify

• Case definitions. To define necrotizing, authors refer to ‘radiologic images’. Is it not just CXR? If not, please specify what other images were used.

Response: only CXR was available. We made the correction

• 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.

Response: we made changes to address the reviewer's concern

Results

• Table one is not labeled

Response: sorry for this omission

• Table one formatting needs work

Response: done, thanks

• Table 1. Methods state that NP and throat swabs were collected but table refers only to NP.

Response: thanks for identifying this

• 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?
Response: the numbers we provided excluded contaminants. We added the overall contamination rate of blood culture in the footnote and have provided the overall contamination rate from sputum samples in the text.

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.

Response: ok, thanks

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

Response: we made substantial changes to address the reviewer’s comment

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

Response: this information was provided as requested by the reviewer. Thanks

• 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

Response: Data on WBC is not a subgroup of severe disease section. We provided the definition of leukocytosis, neutrocytosis in the footnote of table 1 as suggested by the reviewer. We also deleted lymphocytosis as we reckon this does not bring added value into the description of the study.

• 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.

Response: agreed, thanks

• 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

Response: we made changes in table in hope to clarify

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

Response: done, thanks

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

Response: unfortunately we do not have this information.

• It would help to interpret blood culture results to know frequency of prior antibiotics by positive vs. negative culture.
Response: we added one sentence in the results section to report this information

• 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.

Response: Unfortunately, like a typical secondary hospital in rural Cambodia, ICU (e.g. mechanic ventilation) or urea testing was not available in our hospital sites. In addition, we realized that diagnosis of neurological symptoms (e.g. confusion) was not reliable or missing on the medical chart. As some of these symptoms and signs are among the existing severity indices (e.g. CURB65, PSI) we could not apply them accurately. So the 3 expert pulmonologists and 1 ID specialist agreed upon available parameters to define severity. The definition was not validated but for the epidemiological purposes, we believe the definition was plausible and likely acceptable. We added a sentence in the case-definition paragraph to clarify

• 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.

Response: we summarized the information on clinical characteristics, age groups and pneumonia in a new figure

• 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.

Response: We agree this point is interesting and made substantial changes in the discussion to address the reviewer's comment

• 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.

Response: we wanted to point out at the potential cause of death due to viruses exclusively by identifying cases whose etiologies were unlikely to be caused by bacteria. We acknowledge this last paragraph is not clear and have made changes to address the reviewer's concern.

• 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.

Response: done, thanks
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.

Response: we made changes and hope it has addressed the reviewer's comment

• 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.

Response: we made substantial changes to reflect the reviewer's concern

• 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.

Response: as the reviewer rightfully pointed out, we did not mention the results of urinary antigen assay because of the small scale of the testing and for the sake of space. We added more information as suggested by the reviewer.

• 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.

Response: we do agree with the reviewer's suggestion; however, again for the sake of space we thought to indicate this one information in the discussion, otherwise, we would have to write up a special paragraph detailing the PCR methods we used for detecting these pathogens.

• “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?

Response: we corrected this. Thanks

• 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?

Response: it is true that medical and paramedical personnel were not used to collecting blood or sputum for culture prior to this surveillance project. We did address this major issue by continuously training the staff using standard operating procedures, monitoring contamination.
rates monthly and carrying out continuous refreshment courses. We made changes in the
discussion to address the reviewer's concern

• 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

Response: we deleted the word in the text

• 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

Response: actually the percentage we gave for influenza was ~12%. We recognize the
percentages we presented in the text and table 1 were confusing and have made the correction.
We hope this clarifies.

• 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

Response: we added a sentence to reflect the reviewer's comment

• 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?

Response: we made changes to reflect the reviewer's concern

• The authors should note study limitations somewhere in the discussion

Response: we edited to have a separate paragraph for study limitations

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?

Response: Children aged <5 years are known to have different epidemiological and clinical
features compared with older children or adults. In addition, bacterial infection is difficult to
diagnose as bacteremia is rarely found and sputum specimens are difficult to obtain. As such
we performed a separate analysis, which made into a manuscript that was recently published

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.
Response: we added a definition for pneumonia

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?

Response: CXR was indeed the only imaging. We made changes to be more consistent as suggested by the reviewer

• 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.

Response: We deleted this table and summarized our point in the text

• 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 sub groups of patients (eg, 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.

Response: we fully agree with the reviewer. As the reviewer has already raised it, our definition of severity is not validated and relied on limited criteria i.e. what we had available. In addition, we did not have the capacity to follow up on the patients after they were discharged or referred to confirm severe outcomes and death. We recognize this major limitation which is inherent to a surveillance project rather than a clinical research one and clarified this in the methods section

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

Response: thanks for the good suggestion

• 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

Response: we agree and have changed the conclusion to highlight other findings

Methods
• Are there more recent population estimates than 2008?

Response: unfortunately no. We used what was available

• Site. GDP might be nice as another indictor
• 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

Response: we added more information in the methods

• 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

Response: When designing this surveillance project we did not want to interfere with the TB control program which has been running and considered successful for many years. This is a vertical program for which laboratory technician have been well trained for screening TB using sputum smear. In addition as Cambodia is known with having one of the highest prevalence of TB and HIV infection in the region, we estimated that our funding and laboratory capacity would not have been sufficient to also include known TB and HIV cases. We therefore chose to focus on non-TB and non-immunosuppressed patients. Besides, we did not expect to have had so many TB cases in acute lower respiratory infection. In hindsight, we agree this study would have been valuable should we have included known TB cases.

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

Response: yes, in our case, experts meant board certified

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

Response: no they did not have this capacity. We added more information on hospitals' capacity in the methods to clarify

• 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.

Response: the reviewer is correct to point out that information about diabetes may not be relevant for our analysis. We deleted references to it in the methods section.

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

Response: we consulted an American internist of a proper medical English word for this. She suggested partial collapse; we hope this clarifies

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

Response: unfortunately the project was not able to provide this service to the hospitals

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.

Response: we made another figure and took off table 2

• Patient characteristics. Consider moving demographic descriptions to beginning
Response: We have thought to refer the readers to table 1 regarding demographic characteristics instead and save space in the text

• 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

Response: we agree with the reviewer; as such we did not try further analysis or make further inferences and left the p values as an indication for readers

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

Response: Cough without expectoration; for the sake of space in the paper we did not add it believing that readers with minimum medical background could make a sense of the definition

• 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.

Response: we agree this is an important piece of information; however, the project did not have the mean for the follow up of patients out of the study hospitals

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

Response: no as ICU with mechanical ventilation is not available and transfers to a better equipped hospital is not common.

• Was supplemental oxygen available?

Response: yes there was. For information, Standard Operating Procedures manual for this surveillance study included measuring oxygen saturation before providing supplemental oxygen

• Not familiar with the term ‘sibilant wheeze’

Response: sorry we corrected it to wheezing

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