Author's response to reviews

Title: Clinical outcomes of children with acute asthma and pneumonia in Mulago hospital, Uganda: a prospective study

Authors:

Rebecca Nantanda Dr (rnantanda@gmail.com)
James K Tumwine Prof (kabaleimc@gmail.com)
Marianne S Ostergaard Prof (moster@sund.ku.dk)
Grace Ndeezi Prof (gndeezi@gmail.com)

Version: 3
Date: 9 August 2014

Author's response to reviews: see over
RESPONSE TO REVIEWER I: MARIA FRANCESCA PATRIA

**Major revisions**

**Comment:** Row 60: the concept is not correct and has to be specified: there are gold standards for asthma and pneumonia diagnosis, although it is appreciated that they may be difficult to apply in a low income country, as you define Uganda.

**Response:** Thank you so much for this comment. It is true that the gold standard for diagnosis of children with pneumonia is available but may be difficult to implement in low-income settings. The World Health Organization (WHO) guidelines use the chest x-ray as the Gold standard for diagnosis of pneumonia in children. However, chest x-ray services are not readily available in many low-income countries like Uganda. On the other-hand, diagnosis of pneumonia in primary care settings in low-income countries is based on presence of cough and/or difficult breathing plus fast breathing with/without chest in-drawing (1-2). This approach has high sensitivity but very low specificity and hence leads to over-diagnosis of pneumonia.

This sentence has been revised accordingly.

**Comment:** Row 87: In the BTS guidelines bacterial pneumonia should be considered in children aged up to 3 years when there is fever of >38.5°C. Viral pneumonia can occur in the absence of fever.

**Response:** Thank you so much for this comment. We have revised this section to indicate the fact that some children without fever may have pneumonia, but also considering the fact that recurrent respiratory symptoms especially in the absence of fever may indicate a diagnosis of asthma rather than pneumonia (3-5).
Comment: Row 125: Mortality should be included among the primary outcome measures.

Response: This sentence has been revised accordingly.

Comment: Row 128: I am afraid the reference n° 24 is not acceptable, as it is by all evidence, an internal document. Moreover the definition of oxygen saturation normalization is reported below. It is better to remove the entire sentence from “(92%) “ to the full stop. Remove the reference (24).

Response: Thank you so much for this observation. Reference 24 has been deleted.

Comment: Row 133: it is better to report the definitions used in the previous study, because the authors claim to have no gold standard for the diagnosis.

Response: Thank you for this very important comment. In this study of children aged 2-59 months, we modified the GINA (Global Initiative for Asthma) guidelines for diagnosis of asthma in young children (5). The following modifications were made:

1) We excluded “chest tightness” as a symptom because it is not easily expressed by children less than five years (6).
2) We excluded peak expiratory flow measurements/spirometry because children less than five years are not able to perform these test effectively (7).
3) We also included chest x-rays to distinguish asthma from pneumonia. Pneumonia is common in Uganda and its presentation is similar to that of asthma (8-9).

Bronchiolitis was defined based on South African guidelines for diagnosis, management and prevention of acute viral bronchiolitis (10). It is defined as an acute illness in children less 2 years of age characterized by mild upper respiratory tract signs, low-grade fever, hyper-inflation of the chest and wheezing. Severe cases present with tachypnoea and lower chest wall retractions.

Pneumonia: We defined pneumonia as presence of cough and/or difficult breathing, and fast breathing with/without chest retractions (11). However, studies among children with WHO-
defined pneumonia have indicated that using this approach, leads to over-diagnosis of pneumonia, particularly bacterial pneumonia. (12-13). Therefore the following modifications were made to improve on the specificity of this definition.

a) We included results of chest x-ray to help distinguish viral and bacterial pneumonia in some children. We acknowledge that chest x-ray findings alone cannot be used to differentiate viral from bacterial pneumonia (14-15). However, in some cases, the chest x-ray findings imply a particular aetiology. For example, consolidation is associated with *Streptococcus pneumoniae* infection whereas pneumatoceles are characteristic of Staphylococcal infection(14, 16).

b) We also included test results for white cell count (total and differential), blood culture and serum C-reactive protein, to help differentiate viral from bacterial pneumonia. Again, we acknowledge that these tests do not expressly identify the aetiology of pneumonia (17). However, when used in combination with findings in the history and physical examination, they can be helpful in identifying the cause of the pneumonia.

c) We included fever to help us distinguish pneumonia and asthma syndrome. Fever was defined as caretaker’s report of the child being hot and/or axillary temperature of $\geq 38^\circ$ C. Fever is more likely to be present in children with pneumonia compared to those with asthma syndrome (18).

**Comment:** Row 166: the reference n° 28 is not acceptable, as it is by all evidence, an internal document.

**Response:** This reference has been deleted and replaced with reference number 37.

**Comment:** Row 166: did all wheezing patient received sistemic steroids? All asthma guidelines modulate the therapy on the basis of clinical symptoms. Specify this point.

**Response:** Thank you so much for this comment.
Systemic steroids were given to those children who had chest indrawing. In this study, 198 of the 203 (97.5%) of the children with asthma syndrome alone had severe acute asthma as evidenced by chest in-drawing and were therefore given systemic steroids (3).

We have clarified this point in the text.

**Comment:** Row 168: see above for the pneumonia definition. Remove reference 28.

**Response:** This reference has been deleted

**Comment:** Rows: 228-233: this consideration should be inserted in the discussion

**Response:** Thank you so much for this observation. This section has been deleted from the results section. This information has been discussed under the section on mortality.

**Comment:** Row 257-258: in the text the authors describe the following variables: “combined asthma and bacterial pneumonia” and “asthma syndrome”. However in the figure 3 the variable are “asthma syndrome” and “pneumonia”

**Response:** Thank you so much for this observation. We have revised this part as follows

- Figure 2-refers to comparisons for all diagnostic categories, that is, asthma, bronchiolitis, bacterial pneumonia, viral pneumonia and combined asthma and bacterial pneumonia. In this figure, children with asthma had the shortest duration of hospitalization whereas those with bacterial pneumonia were hospitalized for the longest duration.

- Figure 3 compares duration of hospitalization among children with combined asthma and bacterial pneumonia versus asthma syndrome. This is in line with our study hypothesis that children with combined asthma and pneumonia have a worse outcome (longer duration of hospitalization) compared to those with asthma syndrome alone.
The children who had a combination of features from the category of asthma syndrome and bacterial pneumonia according to the study definition were referred to as ‘combined asthma and bacterial pneumonia’. This categorization was aimed at showing the children who would benefit from both asthma medicines and antibiotics. The rest of the comparisons between the different diagnoses are provided only in text.

**Minor revisions**

**Comment:** As a whole the text is clear, but the text of the article would have benefited from a more careful review.

Examples and recommended amendments are reported below. I would change the order of the sentences in the abstract’s background: Little attention has been paid to asthma in ‘under-fives’ in Sub-Saharan Africa. In ‘under-fives’, acute asthma and pneumonia have similar clinical presentation and most children with acute respiratory symptoms are diagnosed with pneumonia according to the WHO criteria. The mortality associated with acute respiratory diseases in Uganda is high but is improving, dropping from 24% in 2004 to 11.9% in 2012. We describe the immediate clinical outcomes of children with acute asthma and pneumonia and document factors associated with prolonged hospitalization and mortality. Thank you for your advice and suggestions on this paragraph. We have revised it accordingly to improve on the logical flow of the sentences/issues presented.

**Comment:** Row 54: the authors have forgotten “asthma” after “acute”

**Response:** The correction has been effected.

**Comment:** Row 65: double space between “only” and “19.8%”
Response: The space has been removed.

Comment: Row 66: missing space between “pneumonia” and “(4)”
Response: This has been corrected.

Comment: Row 73: missing space between “therapy” and “(8-10)”
Response: This has been corrected.

Comment: Row 87: remove “and” before “fast”
Response: The word “and” before “fast” has been deleted.

Comment: Row 90: missing space between “mortality” and “(22)”
Response: The correction has been done.

Comment: Row 94: it is more effective to write: “clinical outcome of children with asthma, pneumonia or combined asthma and pneumonia”
Response: Thank you very much for this suggestion. This sentence has been revised accordingly.

Comment: Row 126: remove the comma before “mortality”
Response: The comma has been deleted.

Comment: Row 128: the full stop has to be put after “(24)”
Response: The full stop has been inserted.
Comment: Row 142: missing space between “days” and “(16)”
Response: This has been corrected.

Comment: Row 166: missing verb after “intravenous hydrocortisone”
Response: This sentence was revised to make it clearer. It now reads “Children with wheezing and chest indrawing were given oral predinisolone and for those who were unable to take the oral predinisolone, intravenous hydrocortisone was given.”

Comment: Row 181: it is better to write: Statistical analysis
Response: This sub-heading has been changed accordingly.

Comment: Row 184: missing space between “pneumonia” and “(29)”
Response: This has been corrected

Comment: Row 193: multicollinearity instead of multi-colinearlity
Response: We have corrected this spelling error

Comment: Row 207: add the number of patients and remove “the majority”
Response: This sentence has been revised. It reads “Five hundred and ninety three (96.6%) of children had chest in-drawing and hence fulfilled the WHO definition of severe pneumonia.

Comment: Row 218: add the number (22/614)
Response: This has been inserted
The highest case fatality was among children with *Pneumocystis jirovecii pneumonia* (50%), and pulmonary tuberculosis (28.6%) while that for bacterial pneumonia was 9.0% and viral pneumonia was 1.2%. None of the children with asthma syndrome (asthma+bronchiolitis) or combined asthma and bacterial pneumonia died (figure 1).”

Comment: Row 225: double space between “(16.3%)” and “and”
Response: This has been corrected

Comment: Row 249: remove the comma after “and”
Response: The comma has been removed

Comment: Row 263: remove “and” before fever.
Response: This has been corrected

Comment: Row 263: it is better to write: severe acute malnutrition, hypoxemia (SaO2 < 92%), fever on admission and age < 12 months old were variables significantly associated to prolonged hospitalization
Response: Thank you so much for this comment. This sentence has been revised accordingly.
Comment: Row 297: write: diagnosing and treating or diagnosis and treatment
Response: This sentence has been revised accordingly

Comment: Row 298: add “recent” before “study”
Response: The word “recent” has been added. The sentence now reads “According to the findings in a recent study by our team, on the same population, many children with asthma syndrome were misdiagnosed as pneumonia by the ward doctors (19).”

Comment: Row 303: missing space between “mortality” and “(9)”
Response: This has been corrected

Comment: Row 327: missing space between “effectively” and “(29)”
Response: This has been corrected.

Comment: Row 328: missing space between “immunity” and “(32)”
Response: This has been corrected.

Comment: Row 329: double space between “8” and “30”
Response: This has been corrected.

Comment: Row 355: missing space between “ingestion” and “(16)”
Response: This has been corrected.

Comment: Row 457: missing space between “Geneva” and “2004”
Response: This reference has been edited.
Comment: Row 475: BTS instead of Society BT
Response: This reference has been deleted after revising the introduction.

Comment: Row 477: WHO instead of Organization WH
Response: This reference has been edited.

Comment: Row 485: it is not an acceptable reference
Response: This reference has been deleted.

Comment: Row 490: missing space between “Geneva” and “2005”
Response: This reference has been edited.

Comment: Row 494: the reference is not acceptable. There are hospital internal guidelines explained in the methods.
Response: This reference has been deleted.

Comment: Rows 512, 534, 557: there is a layout problem: the figures do not follow the titles
Response: This part has been revised to correctly indicate the data being presented.

REFERENCES

5. GINA. Pocket Guide for Asthma Management and Prevention in Children 2005
9. UBOS. Uganda Demographic and Health Survey 2011.