Author's response to reviews

Title: Systemic bacteraemia in children presenting with clinical pneumonia and the impact of non-typhoid salmonella (NTS)

Authors:

Norbert G Schwarz (schwarznorbert@bni-hamburg.de)
Nimako Sarpong (nimakosarpong@yahoo.com)
Frank Hünger (huenger@kccr.de)
Florian Marks (fmarks@ivi.int)
Samuel EK Acquah (ekubanus2000@yahoo.co.uk)
Alex Agyekum (agyekum@kccr.de)
Bernard Nkrumah (skraky@yahoo.com)
Wibke Loag (loag@bni-hamburg.de)
Ralf M Hagen (hagen@bni-hamburg.de)
Jennifer Evans (jevans9@doctors.org.uk)
Denise Dekker (dekkerdenise@hotmail.com)
Julius Fobil (fobil@bni-hamburg.de)
Christian G Meyer (c.g.meyer@bni.uni-hamburg.de)
Jürgen May (may@bni-hamburg.de)
Yaw Adu-Sarkodie (sax@ghanatel.com.gh)

Version: 2 Date: 9 August 2010

Author's response to reviews: see over
Concerning: MS 1435635659390782 Replies to Reviewers

Dear Editors,

thanks for choosing two very competent reviewers resulting in very useful and constructive remarks. We revised the manuscript according to the Reviewer’s suggestions.

The remarks and how we addressed them:

Reviewer 1 (Stephen Graham)

The data presented in this paper refer to an important and often under-recognised problem that in tropical Africa, NTS are a common blood isolate from children with WHO-defined clinical pneumonia.
The authors generally present the data clearly and do not try to over-interpret or analyse recognising limitations.

Title: suggest “clinical pneumonia” rather than “pneumonia symptoms” as classified by signs as well as symptoms.
We changed the title accordingly.

Abstract:
Represents a cut and paste of results from text. Present important data more clearly and succinctly. For example, it is not clear from abstract whether the numbers of isolated pathogens are from all blood cultures or only from the subset that presented with pneumonia.
The abstract has been revised paying special attention to the Results focussing on the proportion of NTS (and S. pneumonia) among pathogen isolates in different analytical strata.

Text: important points that need to be addressed:
Methods and results: Is Hib vaccine implemented in Ghana – in this population? Important to state. What is background HIV prevalence in study population.
The HIV/AIDS prevalence according to the National AIDS Control Programme in 2009 lies at around 1.9%; vaccination against Haemophilus influenza was introduced in 2001. These informations have been embedded in to the Methods part of the manuscript.

What were the indications for blood culture? Was there a prospectively defined criteria for blood culture or is this a retrospective report of blood culture results from those that the attending physician decided that blood culture was indicated?
Blood cultures were taken from all children who were hospitalized (so hospitalisation was the inclusion criterion).

The definition as described for clinical pneumonia is NOT exactly as per WHO. It appear that those with “pneumonia” in this study would refer to WHO both non-severe and severe, whereas those with “severe” (danger signs) in this study fit the criteria for “very severe”. This needs to be better defined. Any child with chest indrawing has severe – and needs different antibiotics and hospitalisation – while no chest indrawing and just fast breathing would be “non-severe” managed at home with oral antibiotics. This needs clarification as also relates
to later discussion about antibiotic susceptibilities.

Data were reanalysed using the criteria found in the “WHO-Pocket Book of Hospital Care for Children, Guidelines for the Management of common illnesses with Limited resources” using Table 7 on page 72 of this book. Following these criteria cases were categorised into “very severe pneumonia”, “severe pneumonia”, & “pneumonia”. As the category “severe pneumonia was very small compared to the category “very severe pneumonia”, these two categories were merged together for the presented analysis.

The predominance of very severe cases is probably due to the fact that we are dealing with a population of hospitalized children. Most of the time during which our study took place it was not possible to make chest x-rays at the Agogo Presbyterian Hospital (malfunction of the x-ray facilities). Therefore chest x-ray examinations can not be taken into account, when analysing our data.

Are there any data about prior antibiotic usage? This affects blood culture yields of more fastidious organisms such as Hib and pneumococcus so can skew “in favour” of more NTS. NTS can also refer to Salmonellae (plural).

The following passage was added to the Results: “Of all 1032 children included into the study, antibiotic premedication before coming to the hospital was reported for 77 children; among the 128 NTS isolates for 9 (7%). Prior use of antibiotics was reported in 7.4% of children with negative or contaminated cultures and in 7.7% of children with a pathogen isolate. The proportion of children with prior antibiotic use by pathogen isolate was not significantly different for the four most important pathogens with 7% for NTS, 10% for S.pneumonia, 9.1% for S. aureus and 6.7% for S.typhi (p=0.9, chi2-test).”

What were the common serovars – s.typhimurium and S.enteritidis are the usual reported. No extensive NTS serotyping was done, only S.typhi and NTS were differentiated.

Are there any outcome data?

We added the following information: “There was no fatality among the 96 pneumonia cases. The one death among the 13 severe pneumonia cases had a systemic NTS infection. In the very severe pneumonia group 9 children died, 3 with S. pneumonia, 1 with NTS, 1 with S.typhi and 4 with a negative blood culture or a contaminant.”

Discussion is too long for data presented here. We shortened the discussion substantially.

What do authors think of penicillin alone for severe pneumonia as still recommended by WHO in non-HIV endemic setting? This is the main challenge highlighted by NTS. We added the following sentence to the discussion: “One of the two isolates from the 13 severe pneumonia cases was an NTS, which was resistant to amino-penicillins. However, from the 19 pneumonia cases 63% of the isolated were NTS challenging the WHO first line antibiotic.”

Note that in vitro penicillin resistance in some pathogens (ie pneumococcus) does not necessarily mean that penicillin will not be effective in vivo. This is a precious remark, however as our S. pneumonia isolate did not show strikingly low sensitivities towards penicillins. We added the following statement to
Reference to data from India is using S typhi information – this should be clear. There are important regional differences in NTS: typhi prevalence and differences of resistance/virulence issues between Africa and elsewhere are referred to in work from Gordon MA et al Clin Infect Dis 2008, and Kingsley R et al Genome Research 2009.

We deleted the reference to Indian data.

There are studies that have also found that NTS are the other common isolate from blood in child pneumonia studies in the region even before implementation of Hib vaccine and these should be more carefully considered and referred to as they relate more directly to this work – rather than the long list of references. (refs 6-16). These include ref 11 (O'Demsey et al PIDJ 1994 – The Gambia) plus Graham SM et al Lancet 2000 - Malawi; Berkley JA et al BMJ 2006 - Kenya; Siguaque B et al J Trop Pediatr 2009 - Mozambique.

We added the sentence “Already in some studies that were carried out before the vaccination against against H. influenzae (Hib-vaccination) was introduced, NTS were among the most important isolates in Sub Saharan African children with clinical pneumonia” with the references recommended by the Reviewer. However we preserved the mentioned long list of references as it will facilitate the literature review for readers who are interested in the topic. If from an editor’s point of view this is seen as “excessive referencing” we are predisposed to take out these references.

Level of interest: An article of importance in its field Quality of written English: Needs some language corrections before being published Statistical review: Yes, and I have assessed the statistics in my report. Declaration of competing interests: I declare that I have no competing interests.

Reviewer 2 (James Berkley)

The manuscript describes a blood culture study of about a thousand children admitted to hospital with the findings interpreted in relation to clinical syndromes of pneumonia. The subject is of significant public health importance.

Major compulsory revisions

i) Methods: the authors have used the syndromes defined in the original IMCI guidelines, which are aimed at identifying children requiring referral to hospital. There was a technical update in 2005, coinciding with the publication of the WHO pocketbook of guidelines for inpatient treatment. The findings would be more easily compared with other studies if the standardised clinical database were reanalysed using the current definitions for the syndromes of ‘pneumonia’, ‘severe pneumonia’ and ‘very severe pneumonia. If this is not possible from the database, this should be discussed as a significant weakness.

We reanalysed our data. We assume that the Reviewer is referring to the “Pocket Book of Hospital Care for Children, Guidelines for the Management of common illnesses with Limited resources” by the World Health Organisation. We analysed our data using these criteria thus categorising cases into “very severe pneumonia”, “severe pneumonia”, & “pneumonia”. When using this categorisation the category “severe pneumonia” was rather small as most children already fulfilled the “very severe pneumonia” criteria regarding registered clinical signs. We therefore merged the category “severe pneumonia” with the category “very severe pneumonia”.

ii) Laboratory methods: Please include details of any external quality control procedures in place, which are helpful for readers to interpret the microbiological findings.
The microbiological laboratory of the KCCR-Agogo Presbyterian Hospital cooperation is enrolled in a quarterly external quality assurance program in bacteriology from the National Institute for Communicable Diseases (NICD) of South Africa. This information was added to the Methods part.

Which scheme of antimicrobial susceptibility breakpoints was used? How were pneumococci classified (by an oxacillin disk)? How were contaminants defined?

Antibiotic susceptibility testing was carried out using the disc diffusion method and with the susceptibility breakpoints of the Clinical and Laboratory Standards Institute (CLSI) for susceptibility testing. Identification of pneumococci was based on colony morphology and the optochin test. (pneumococci are optochin sensitive, other streptococci would be resistant to this agent). Oxacillin discs were used to determine sensitivities to penicillin. Diphteroids and propionibacteriae were classified as contaminants. Depending on the clinical picture (HIV etc.) coagulase negative staphylococci, Bacillus species and non-fermenters were usually also classified as contaminants.

iii) Analysis: what was the rationale for splitting the data at 1 year of age? It seems more logical to stratify groups of ‘pneumonia’ and ‘severe pneumonia’ since their antibiotic management differs (antibiotic treatment does not differ with this age cut off)

The initial reason for the split was that 1 year is the age until which a child is usually classified as an infant and 1 year is the age for the respiratory rate classifying cut-off change from 50/min in infants to 40/min in children between 1 and 5 years of age. We rediscussed the usefulness of this stratification and decided to drop it. In the revised version we show now data for all children between 2 month and 5 years of age, as we assume that this simplifies the presentation making it easier for the reader to extract the essential information.

iv) Findings: Please give some details of those who did not have a blood culture so that bias may be assessed.

The following sentence was added: When comparing the 1032 for whom blood culture results were available with the 137 without, the proportion of cases without bacteriology result did not significantly differ between the 3 case categories “non-case” (12.3%), “pneumonia” (8.6%) and “severe & very severe pneumonia” (9.8%); (p=0.4, chi2).

For all groups: How many patients died in each group? What was their length of hospital stay?

We added the following information: “There was no fatality among the 96 pneumonia cases. The one death among the 13 severe pneumonia cases had a systemic NTS infection. In the very severe pneumonia group 9 children died, 3 with S. pneumonia, 1 with NTS, 1 with S.typhi and 4 with a negative blood culture or a contaminant.” We did not collect data on the length of hospital stay

How many had concomitant malaria parasitaemia and/or anaemia (given a likely association between NTS and malaria)? Again, these allow comparison with other studies.

We added the following sentence to the Results section: Among all children with pathogen isolates, 24% had malaria parasites compared to 34 % among those whose blood culture was negative or contaminated. Among children with NTS and children
with *S. pneumonia* the proportion with malaria parasites was 24% and 18% respectively. Stratified by case classification, 35% of non-cases, 28% of pneumonia cases and 22% of severe & very severe pneumonia cases had malaria parasites.

v) Discussion: The sentence 'The results of the presented studies show that blood cultures of most of the children admitted to a rural hospital in central Ghana with pneumonia were positive for NTS.' is not correct, in fact only 19 (11%) had NTS.

This sentence was deleted.

There are two important implications of the study findings that are not adequately discussed:

a) The pattern of organisms were not different between cases and non cases. The purpose of WHO syndromic classification is to allocate different treatments, rather than to give patients a diagnostic label. However, these data suggest that the syndromes might not be helpful in this setting. Either the WHO syndrome classification really doesn't work (here it is important to use the current guidelines) or there may be unreliability in eliciting clinical signs or in microbiology, or the study is too small. This should be discussed, along with potential weaknesses of the study.

The following passage addresses these points: “The pattern of organisms was not different between cases and non-cases. The association between clinical pneumonia and *Streptococcus pneumoniae* was stronger than that with NTS. However, due to the fact that NTS are much more common in the study area than *Streptococcus pneumoniae*, it is important to consider NTS in children presenting with pneumonia symptoms.”

The weaknesses of the study were addressed at the end of the discussion: “Our study certainly has some limitations. Blood culture results are from a population of hospitalized children. Even the children that were classified as pneumonia (non-severe) may be sicker than children that are treated as pneumonia outpatients in peripheral health facilities. Although we included more than 1000 children into the study the distribution of pathogens relies on the much smaller number of 162 pathogen isolates. Small volumes of inoculated blood in paediatric patients and the use of antibiotics prior to blood sampling may compromise the sensitivity of blood cultures [32]. If the sensitivity is better for one pathogen compared to another the observed pathogen spectrum may be distorted.”

b) The antimicrobial sensitivities suggest use of ceftriaxone. Please discuss more detailed positive and negative consequences of changing to ceftriaxone e.g. dosing schedule, cost, promotion of resistance including extended spectrum beta lactamase in Enterobacteriaceae.

The following passage was added to the discussion: “The antimicrobial sensitivity pattern suggests use of ceftriaxone, however one also has to consider some disadvantages of this drug. First the uncritical use of ceftriaxone may promote the development of resistance against this antibiotic. Second the application needs a well equipped health facility as it can only be administered intravenously or intramuscularly, and well trained staff because of some technical pitfalls, for example ceftriaxone may not be given together with calcium containing infusions such as Ringer’s or Hartmann’s solution. Third ceftriaxone is more expensive than amoxicillin. A treatment course with ceftriaxone for a child at the APH costs 10 Ghanaian Cedis (GHC, around 5 Euros) compared to 3 GHC for amoxicillin (around 1.5 Euros).”

Level of interest: An article of importance in its field Quality of written English: Acceptable
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

Please do not hesitate to contact me for further inquiries.

Best wishes

Norbert Schwarz