Antibiotic and systemic therapies for pneumonia in human immunodeficiency virus (HIV)-infected and HIV-exposed children

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Abstract

Introduction: Pneumonia is the leading cause of mortality in both human immunodeficiency virus (HIV)-infected and HIV-exposed children. Administration of appropriate empirical antimicrobial and/or adjunctive systemic therapies may improve clinical outcomes.

Methodology: To identify effective antimicrobial and/or adjunctive systemic therapy for pneumonia in HIV-infected and HIV-exposed, uninfected children, we searched for published and unpublished studies from 11 databases including MedLine, Global Health Database, Biological Abstracts (BIOSIS), the Cochrane Central Register of Controlled Trials, the World Health Organization Library Information System, AIDSLine, and the System for Information on Grey Literature in Europe, along with additional four regional databases including African Index Medicus, Latin America and Caribbean, Eastern Mediterranean, and South-East Asian databases. Data from full articles of selected studies were independently extracted by two reviewers.

Results: No a priori planned randomized controlled trials (RCT) were identified, only subgroup analyses of an RCT comparing oral amoxicillin versus parenteral penicillin for severe pneumonia in children. HIV-infected children had significantly higher treatment failure rates compared to their uninfected counterparts. An RCT study investigating adjunctive corticosteroid therapy for Pneumocystis jiroveci pneumonia (PCP) failed to identify a statistically significant reduction in mortality in the treatment group with a relative risk of 0.57 (95% CI 0.30–1.07). A before-after observational study showed substantial beneficial effect of corticosteroid treatment in reducing mortality among HIV-infected children with PCP.

Conclusions: Insufficient evidence exists to identify effective antimicrobial treatment regimens for HIV-associated pneumonia in paediatric populations or confirm the beneficial effect of corticosteroid treatment for HIV-infected children with PCP.

Key words: HIV; pneumonia; children; opportunistic infection; meta-analysis; antimicrobial therapy; adjunctive therapy


(Received 30 March 2011 – Accepted 04 July 2011)

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Introduction

Acute respiratory infections (ARIs), predominantly two million deaths in children under five years of age annually [1], predominantly in industrialising countries [2]. The human immunodeficiency virus (HIV) epidemic has worsened the situation, especially in sub-Saharan African countries, where HIV contributes to significant childhood mortality including 40% of all childhood deaths in South Africa, with pneumonia being a leading cause of death in these children [3]. Ninety percent of HIV-infected children live in low-income African countries with limited access to antiretroviral therapy [4].

In most developing countries, Hemophilus influenzae type b and Streptococcus pneumoniae remain important pathogens in children under five years as protection through conjugate vaccines targeting these pathogens have only recently been scaled up for H. influenzae type b and are yet to be rolled out in developing countries for pneumococcal conjugate vaccine [5,6]. Other bacteria identified in the aetiology of community-acquired pneumonia (CAP) include Staphylococcus aureus, non-typhoidal Salmonella, and other gram-negative organisms [7,8]. Differences in the aetiology and antibiotic susceptibility patterns of pathogens causing CAP in HIV-affected children may affect the effectiveness of the current World Health...
Organization (WHO) recommendations for the empirical treatment of CAP in HIV-infected children.

Pneumocystis jirovecii is a significant cause of pneumonia (PCP) in HIV-infected children, especially in the absence of antiretroviral (ARV) therapy or prophylactic treatment (CPT), with high (28-63%) mortality rates [9-15]. The estimated risk of PCP among perinatally HIV-infected children during the first year of life ranges from 7% to 20% [16-19]. Younger age (< 1 year) is associated with increased risk of PCP, especially during the first six months of life [10,15-18,20-24]. Studies from Africa reported PCP prevalence rates from 10% to 48.5% among HIV-infected children hospitalized with severe pneumonia [10,12,14,15]. Post-mortem studies have shown that the prevalence of PCP among HIV-related deaths in children ranged from 11.5% to 52% [18,25-29].

The HIV epidemic has changed the epidemiology of pneumonia. The current WHO standard case management antibiotic guidelines for pneumonia treatment may not be as effective in countries with a high burden of HIV infection as it is primarily designed on the premise that S. pneumoniae and H. influenzae are the leading causes of CAP [30]. Evidence-based guidelines are needed to decrease CAP-related morbidity and mortality in children exposed to and infected with HIV. Currently, there is no standardized approach to antibiotic and/or adjunctive therapy for the management of CAP in countries with a high prevalence of paediatric HIV infection. The objective of this systematic review of various antimicrobial and/or adjunctive systemic treatment strategies is specifically targeted toward determining the most appropriate empirical management of CAP in HIV-infected and HIV-exposed, uninfected children.

**Methodology**

**Search strategies**

The literature search included articles (both published and unpublished) that contained information on HIV-affected children and management of CAP without language restriction. The search was limited to children (0-15 years) and articles published between 1990 to February 2009. We conducted key word searches of eleven databases: MedLine, Global Health Database, Biological Abstracts (BIOSIS), Cochrane Central Register of Controlled Trials (CENTRAL), World Health Organization Library Information System (WHOLIS), AIDSLine, and the System for Information on Grey Literature in Europe (SIGLE), along with four regional databases including African Index Medicus (AFI), Latin America and Caribbean (LILACS), Eastern Mediterranean, and South-East Asian Databases. The search terms were based on the following key words: pneumonia, HIV infection, HIV-exposed, AIDS, treatment, and children. Key words and search strategies were modified and tailored to capture the most sensitive results for each database. For example, three different search strategies were used for the MEDLINE database including MeSH terms, Clinical Query (with sensitive search option), and simple search options using the key words pneumonia, HIV, and child. In contrast, for certain databases where MeSH search option and Clinical Query were not available, advanced or simple search option using Boolean operators were applied. The results were then imported into a bibliographic database from which duplicates were discarded. One reviewer also searched the bibliographic references of review articles for published and unpublished data on pneumonia, treatment and/or management in HIV-infected and HIV-exposed children. We also searched for any ongoing trials conducted in the United States (ClinicalTrials.gov). The date of the most recent searches conducted is February 2009.

**Selection criteria**

Types of studies: Initially, we aimed to include only randomized controlled trials (RCTs) comparing different antibiotic regimens, duration of treatment and/or adjunctive systemic therapy for CAP on mortality rates and treatment failure rates in HIV-infected and HIV-exposed children, irrespective of publication status and language. However, observational studies with a control or comparison group were also included because of the limited availability of the RCT studies. Exclusion criteria included ecological studies; studies with less than 20 pneumonia cases; studies investigating prophylaxis against pneumonia (such as vaccines, CPT, micronutrients, and antiretroviral therapy); studies assessing adverse drug reaction; pharmacokinetics studies of antimicrobial agents; and policy papers or review articles.

Study populations were HIV-infected or HIV-exposed uninfected children 0 to 15 years of age with CAP. Primary outcome included pneumonia-related mortality (48 hours, 14 days). Secondary outcomes included treatment failure at 48 hours and 14 days post-initiation of treatment.
Table 1. Characteristics of a study examining the effectiveness of antimicrobial treatment: Jeena PM 2006 [30]

<table>
<thead>
<tr>
<th>Methodology</th>
<th>A sub-analysis of an RCT of 3- to 59-month-old children with severe pneumonia (WHO criteria) focusing on the effectiveness of oral amoxicillin versus parenteral penicillin among HIV-infected children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>106 HIV-infected children with severe pneumonia receiving the assigned treatment regimen were compared with those who were HIV-uninfected.</td>
</tr>
<tr>
<td>Interventions</td>
<td>Oral amoxicillin and injectable penicillin</td>
</tr>
<tr>
<td>Outcomes</td>
<td>The primary study endpoint: treatment failure rate by day 2 and day 14 of treatment.</td>
</tr>
<tr>
<td>Notes</td>
<td>All HIV-infected children included were either asymptomatic or mildly symptomatic and did not receive antiretroviral therapy. Both treatment options appeared to be equally inadequate and their response rates were comparable regardless of HIV status [35]. However, effect of HIV infection was only apparent among young infants (&lt; 1 year) whose treatment failure rate was approximately three times higher than that of uninfected infants.</td>
</tr>
</tbody>
</table>

Table 2. Characteristics of a study’s risk of bias: Jeena PM 2006 [30]

<table>
<thead>
<tr>
<th>Item</th>
<th>Judgment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Unclear</td>
<td>Yes, in the original study population but unclear whether this is adequate for the HIV-infected subgroup of children</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>No</td>
<td>Open label design</td>
</tr>
<tr>
<td>Blinding?</td>
<td>No</td>
<td>Open label design</td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td>8.2% with unknown HIV status and 3% of participants whose samples were lost were excluded from the analysis</td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td>All important outcomes were reported</td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Subgroup analysis* GRADE = low</td>
</tr>
</tbody>
</table>

* Although subgroup analysis can provide valuable information from well-conducted RCT, increased risk of type 1 error remains an important concern when interpreting its results [45,46]. Further, the finding should be viewed primarily as exploratory [46]. A simulation study shows that the chance of obtaining false positive and thus spurious results is high and the extent is generally underestimated when subgroup analysis is utilized [47].

Data extraction and management

The abstracts of all articles identified by the searches detailed earlier were independently reviewed by two reviewers using the selection criteria above. Translation of abstracts and articles were obtained for those published in languages other than English. Studies identified as eligible by both reviewers were included in the review. Discordance between reviewers regarding the relevance of a particular study was referred to a third reviewer for final arbitration.

Each reviewer independently extracted the data from included studies. A data extraction form was designed to capture all relevant data from selected studies. This included data on the study design, demographics, diagnostic criteria, interventions, outcomes measured, potential biases per study design, control for confounding, magnitude of effect, consistency with other studies, directness of evidence, precision of estimates, and possible publication bias.

For randomized controlled trials, we focused on methods used for randomization sequence generation; the allocation concealment; the level of blinding (clinician, subject, and outcome evaluator) [31]; participant flow [32]; whether an intention-to-treat analysis was used; and whether the number of cases lost to follow-up was accounted for in the trial. For allocation concealment, the following was used to grade the trials: A (appropriate i.e., central randomisation, using random number table, opaque sealed envelopes, or other described method indicating the adequacy of concealment process); B (unclear i.e., insufficient information to determine adequacy of the concealment process); C (inappropriate i.e., no allocation concealment was applied or if one was applied, it was deemed to be inadequate). Assessment of the quality of evidence was made independently by two authors using the GRADE profiler software (Version 3.2 for Windows) based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system [33]. Quality of evidence was assessed as high, moderate, low or very low. Due to the limited number of RCTs available, data from a before-and-after study is presented for completeness and to enable comparison with the concurrent, controlled studies.

Results

A total of 1,103 unique citations were identified using key words HIV or AIDS, pneumonia, and children through the initial,
Figure 1. Search results

Database searches and hand searching
1103 citations reviewed

301 titles reviewed

41 abstracts reviewed

16 articles reviewed

802 citations excluded:
- not relevant

260 citations excluded:
- not management aspect

25 articles excluded:
- guidelines/consensus statements: 6
- non medications (bronchoscope, positive pressure ventilation): 3
- nonHIV-infected children: 9
- LIP only: 1
- prevention/prophylaxis: 5
- sample size <20: 1

14 articles excluded:
- comments: 2
- pneumococcal pneumonia in adults only: 1
- case report/no control group: 11

3 articles included

1 antimicrobial treatment strategy (Post hoc analysis)

2 adjunctive corticosteroid for PCP

1 RCT

1 observational study
broad bibliographical searches. Of these, 301 were deemed to be relevant by title. After manually checking the titles and abstracts, we identified 41 potentially eligible articles. However, only three articles fulfilled the criteria for inclusion: one for antimicrobial treatment and two for adjunctive corticosteroid therapy for PCP (Figure 1). Notwithstanding, no *a priori* planned RCT or observational studies examining either the efficacy/effectiveness of different antibiotic regimens including class of antibiotics, antibiotic dosing or duration of therapy and/or other case management strategy of pneumonia among HIV-infected or HIV-exposed uninfected children were identified.

Only one subgroup analysis [30] of an RCT comparing oral amoxicillin versus parenteral penicillin for severe pneumonia in children [34] was included in our review. This selection of HIV-infected children in this substudy was also biased toward children who were either asymptomatic or only mildly symptomatic for AIDS. The results of this RCT indicated that HIV-infected children had significantly higher treatment failure rates compared to HIV-uninfected children with the risk ratios of 2.07; (95% CI 1.07–4.00) at 48 hours and 1.88; (95% CI 1.11–1.37) at day 14 following randomization to study-drug [30]. The response rates were comparable between the two antibiotic regimens among both HIV-infected and uninfected children [35]. HIV-infected infants (younger than 12 months of age), however, had a significantly higher treatment failure rate at day 14 (40.7% vs. 24.3%; OR 2.8; 95% CI 1.35 to 3.5).

<table>
<thead>
<tr>
<th>Methodology A random number generator was used to determine the allocation sequence. No information regarding the method of allocation concealment used. Intention to treat analysis was employed. No exclusion of subjects from the final analysis.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants HIV-exposed infants with clinical diagnosis of PCP. HIV status and PCP infection were not confirmed for all participants.</td>
<td></td>
</tr>
<tr>
<td>Interventions Prednisone 2 mg/kg/day or placebo for 7 days.</td>
<td></td>
</tr>
<tr>
<td>Outcomes The primary study endpoint: in-hospital survival. Secondary outcome: time to recovery or oxygen independency.</td>
<td></td>
</tr>
<tr>
<td>Notes The study was conducted during the period when antiretroviral therapy was unavailable. The survival among the treatment group appeared to be higher but it did not reach a statistically significant level. There is no information to determine whether the study was adequately powered.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Judgment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation?</td>
<td>Yes</td>
<td>A random number generator was used to determine the allocation to steroid or placebo treatments, which were provided in a double-blind fashion by the hospital pharmacists according to study number.</td>
</tr>
<tr>
<td>Allocation concealment?</td>
<td>Unclear</td>
<td>Insufficient information to determine a judgment</td>
</tr>
<tr>
<td>Blinding?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data addressed?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Free of selective reporting?</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Free of other bias?</td>
<td>No</td>
<td>Biases were likely given the use of clinical diagnosis of PCP rather than microbiologically proven method and the lack of PCR confirmation for HIV-exposed infants. Given the relatively small sample size, randomization may not successfully result in the comparable distribution of outcome predictors, e.g., proportion of those truly HIV and PCP infected among the two groups. Neither were the data sufficient to estimate the magnitude and the overall direction of bias these potential misclassifications could introduce, nor did the study design permit us to adjust for potential confounders statistically. GRADE = low</td>
</tr>
</tbody>
</table>

Table 3. Characteristics of a randomized control trial examining the effectiveness of adjunctive corticosteroid therapy for *P. jirovecii* pneumonia by Terblanche AJ 2008 [48]

Table 4. Characteristics of a randomized control trial risk of bias: Terblanche AJ 2008 [48]
compared to HIV-uninfected infants [36]. On the other hand, response rates to the studied antibiotic regimens were similar in children older than 12 months of age, irrespective of HIV infection status. Additionally, HIV-infected children with “other type” of infiltration on chest radiograph, i.e., infiltrate not consistent with that of “alveolar consolidation” (which has been developed as a benchmark to allow for comparison of results of studies evaluating pneumococcal conjugate vaccines rather than a tool for diagnosing any form of pneumonia) [37], had higher rate of treatment failure (OR 5.45; 95% CI 1.58 to 21.38). Details of the study characteristics and risk of bias based on the GRADE guideline are shown in Tables 1 and 2, respectively.

Apart from the subgroup analysis detailed earlier, the majority of clinical trials addressing antimicrobial therapy identified by our search mainly focused on the efficacy of the alternative treatment regimen for PCP, e.g., atovaquone suspension [38], the combination of clindamycin/primaquine [39], trimetrexate/leucovorin [40], and co-trimoxazole/folinic acid [41]. These studies were conducted in adolescent and adult populations. As the focus of this review is to develop guidelines for the empirical antimicrobial management of CAP in resource poor settings, the efficacy and effectiveness of alternate agents to co-trimoxazole for the management of CAP in HIV-infected children was not further analysed. Further, we were not able to identify any ongoing trials from a clinical trial registry (ClinicalTrials.gov).

Two studies examining the efficacy of corticosteroid treatment as an adjunctive therapy for clinical PCP in HIV-infected children satisfied the selection criteria. One was an RCT; the other was an observational study with a before-and-after comparison. Study characteristics and risk of bias of these two studies are shown in Tables 3-6.

Meta-analysis was performed for neither the antimicrobial treatment nor the adjunctive corticosteroid therapy as either only one RCT or one RCT and one observational study were identified for these interventions, respectively. In addition, pooled analysis for the adjunctive corticosteroid therapy was not deemed to be appropriate given substantial clinical and statistical heterogeneity of the studies identified. A summary of the findings for the use of adjunctive corticosteroid for Pneumocystis jirovecii pneumonia in HIV-infected children is shown in Table 7. Table 8 illustrates the quality of evidence and comparative risk of adjunctive corticosteroid treatment for Pneumocystis jirovecii pneumonia in HIV-infected children by type of outcomes using GRADEprofiller software.
Table 7. Summary of findings table for the use of adjunctive corticosteroid for *Pneumocystis jirovecii* pneumonia in HIV-infected children

**Question:** Should adjunctive corticosteroid be used for *Pneumocystis jirovecii* pneumonia in HIV-infected children?

**Settings:** inpatients

**Bibliography:** Terblanche AJ, 2008

<table>
<thead>
<tr>
<th>Quality assessment</th>
<th>Summary of findings</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No of patients</td>
<td>Effect (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.52</td>
</tr>
</tbody>
</table>

### Mortality rate (follow-up 0-70 days)

<table>
<thead>
<tr>
<th>No of studies</th>
<th>Design</th>
<th>Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Adjunctive corticosteroid</th>
<th>Control</th>
<th>Relative</th>
<th>Absolute</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>randomised trial</td>
<td>serious¹</td>
<td>no serious inconsistency</td>
<td>no serious indirectness</td>
<td>Serious²</td>
<td>none</td>
<td>18/47 (38.3%)</td>
<td>27.5%</td>
<td>RR</td>
<td>0.812</td>
<td>(0.512 to 1.288)</td>
</tr>
</tbody>
</table>

¹The use of only unvalidated clinical diagnosis of HIV and PCP infection (no microbiologically-confirmed diagnosis of both HIV and *Pneumocystis jirovecii* pneumonia)

²Sample size was less than 300 without precalculation for optimal sample size and thus no information regarding adequacy of study power.

Table 8. Quality of evidence, comparative risk of adjunctive corticosteroid treatment for *Pneumocystis jirovecii* pneumonia in HIV-infected children by type of outcomes based on GRADE guideline

<table>
<thead>
<tr>
<th>Adjunctive corticosteroid for <em>Pneumocystis jirovecii</em> pneumonia in HIV-infected children</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of Participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient or population: patients with <em>Pneumocystis jirovecii</em> pneumonia in HIV-infected children</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Settings: inpatients</td>
<td>Intervention: adjunctive corticosteroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td>RR 0.812</td>
<td>100 (1)</td>
<td>low 1,2</td>
</tr>
<tr>
<td></td>
<td>Mortality rate</td>
<td>Low risk population 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(follow-up: 0-70 days)</td>
<td>Control</td>
<td>275 per 1,000</td>
<td>223 per 1,000</td>
<td>(0.512 to 1.288)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>adjunctive corticosteroid</td>
<td>(141 to 354)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Medium risk population</td>
<td>440 per 1,000</td>
<td>357 per 1,000</td>
<td>(225 to 567)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High risk population 3</td>
<td>520 per 1,000</td>
<td>422 per 1,000</td>
<td>(260 to 670)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Treatment failure at 48 hours</td>
<td>Not estimable</td>
<td>Not estimable</td>
<td>Not estimable</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Treatment failure at day 14</td>
<td>Not estimable</td>
<td>Not estimable</td>
<td>Not estimable</td>
<td>-</td>
</tr>
</tbody>
</table>

*The basis for the assumed risk (e.g., the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; RR: Risk ratio;

GRADE Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

1 The use of only unvalidated clinical diagnosis of HIV and PCP infection (no microbiologically-confirmed diagnosis of both HIV and *Pneumocystis jirovecii* pneumonia)
2 Sample size was less than 300 without precalculation for optimal sample size and thus no information regarding adequacy of study power.

* GRADE: Grading of Recommendations Assessment, Development and Evaluation
Discussion

Our findings are limited by the paucity of RCTs available. A single RCT illustrated a non-significant advantage against mortality in HIV-exposed children with clinical suspicion of PCP, while the observation study in the United States indicated a significant reduction in PCP case fatality rates. This finding is consistent with existing literature which indicates that observational studies using historical controls may overestimate interventions [42]. The observational study on adjunctive steroid therapy was also unclear on whether all cases in the control group underwent invasive diagnostic procedure and attained microbiologically proven diagnosis as was done in the intervention group. Additionally, no information was provided on CPT among the children who developed PCP, which was first recommended in early 1991 [43], i.e., prior to when the historical control group were identified and during the period when the intervention group were recruited. This would be important as a history of CPT was found to be associated with substantial reduction in mortality risk among HIV-infected children with CAP in whom P. jirovecii was identified [15]. Despite the strong association (RR > 5), the lack of control for potential confounding factors and possibility of publication bias due to favourable results render this study low quality as scientific evidence.

Additionally, neither study was specifically designed to systematically evaluate the potential for steroid therapy to be associated with adverse events, particularly the effect of possible re-activation of latent CMV infection. Although adjunctive steroid therapy has been shown to be beneficial in the management of PCP in HIV-infected adults in industrialized country settings [44], its extrapolation to HIV-infected infants has limitations. Reasons include the likely differences in the pathogenesis of PCP in young infants; i.e., it is most likely related to progression of primary Pneumocystis jirovecii infection in a naive host, instead of re-infection or re-activation as would occur in severely immunocompromised HIV-infected adults. Additionally, the potential for high-dose steroid therapy to interfere with the control of co-existing CMV infection may be greater in HIV-infected infants in Africa compared to HIV-infected adults in industrialized settings. Coupled with the absence of safety data in populations most affected by HIV/AIDS the results in this review do not support the empirical use of adjunctive steroid treatment in HIV-infected children with suspected or proven PCP.

No a priori planned clinical trials against CAP in HIV-affected children which examined different antibiotic regimens including antibiotic drug class, antibiotic doses, or antibiotic duration of therapy were identified through the systematic review. This is despite the fact that HIV-infected children account for as much as 45% of all CAP hospitalizations [7] in some sub-Saharan African countries which contributes to a disproportionately high burden of the global childhood pneumonia mortality. The high failure rate of the WHO-recommended antibiotic regimens for management of severe pneumonia in HIV-infected children [30], coupled with the greater diversity of pathogens and differences in antibiotic susceptibility patterns of bacteria causing CAP, as well as the greater frequency of polymicrobial pathogens in HIV-infected compared to HIV-uninfected children with CAP, dictates that there is an urgent need to reconsider the recommended empiric management of CAP in countries with a high prevalence of HIV infection. This appears to be particularly pertinent in infants, among whom the burden of CAP is greatest [2] and in whom there is a high incidence of PCP, polymicrobial infection, and infection caused by resistant pathogens [7,35]. There is an urgent need to conduct RCT comparative studies on different anti-bacterial and/or anti-viral agents in HIV-infected children.

Conclusion

This systematic review has identified the need for well-designed, adequately powered randomized controlled trials to assess different antibiotic regimens which are better tailored toward adequately targeting pathogens commonly implicated in the aetiology of pneumonia in HIV-infected as well as possibly HIV-exposed uninfected children. The variable availability of antiretroviral treatment, CPT as well as conjugate bacterial vaccines targeting H. influenzae type b and selected pneumococcal serotypes, however, is likely to be a major factor in the design of studies evaluating optimal antibiotic regimen in HIV-infected children. Studies are also required to specifically address issues related to the management of CAP in HIV-exposed uninfected children, among whom there have been case series reports of heightened susceptibility to pathogens not commonly identified in immunocompetent HIV-unexposed uninfected children [14,35].
Acknowledgements
The authors thank members of the WHO Guideline Development Group on Management of Pneumonia and Diarrhoea in HIV-infected infants and children for their participation in the review of the meta-analysis and efforts at revising the guidelines for the management of pneumonia in HIV-infected children.

References


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**Conflict of interests:** No conflict of interests is declared.