

Management of children with pneumonia and HIV in low-resource settings

Report of a consultative meeting
Harare, Zimbabwe, 30-31 January 2003

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Report of a consultative meeting of children with pneumonia and HIV infection

30-31 January 2003

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ACRONYMS

AFRO	Regional Office for Africa
AIDS	Acquired Immunodeficiency Syndrome
ALRI	Acute lower respiratory infection (ALRI)
ARCH Project	Applied Research on Child Health Project, Boston University
ARI	Acute respiratory infection
ARV	Antiretroviral
CAH	Department of Child and Adolescent Health and Development
CFR	Case fatality rate
CMV	Cytomegalovirus
HAART	Highly active anti-retroviral therapy
Hib	<i>Haemophilus influenzae</i> type b
HIV	Human Immunodeficiency Virus
HQ	Headquarters
IM	Intramuscular
IMCI	Integrated Management of Childhood Illness
IMR	Infant mortality rate
IUATLD	International Union against Tuberculosis and Lung Disease
IV	Intravenous
MTCT	Maternal to Child Transmission
PCP	<i>Pneumocystis jiroveci</i> (previously <i>Pneumocystis carinii</i>) pneumonia
RSV	Respiratory syncytial Virus
SA	South Africa
TMP-SMX	Trimethoprim sulfamethoxazole
TB	Tuberculosis
USA	United States of America
WHO	World Health Organization

EXECUTIVE SUMMARY

Pneumonia is among the commonest causes of morbidity and mortality in children under the age of 5 years. With increasing prevalence of Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) the management of pneumonia has become more challenging and its contribution to morbidity and mortality has grown significantly particularly in developing countries. Although the common presentation of the HIV-infected child with pneumonia may be similar to those of all children addressed by the Integrated Management of Childhood Illnesses (IMCI), the prevalence of opportunistic infections and associated high mortality has made the task of managing these children increasingly difficult in resource poor areas. This meeting was organized by the Department of Child and Adolescent Health and Development (CAH), World Health Organisation (WHO), IMCI unit, Regional Office for Africa (AFRO) and the Applied Research in Child Health (ARCH) Project to review data and experiences related to aetiology and outcomes of pneumonia in HIV-infected children with existing therapeutic regimens, in order to develop recommendations for case management guidelines.

The participants of the meeting were composed of representatives from six countries in East and Southern Africa (Botswana, Malawi, South Africa, Uganda, Zambia and Zimbabwe) and collaborators and researchers from the United States of America (USA) and France.

The presentations from all the countries revealed that pneumonia in HIV-infected children under the age of 5 years was the leading cause of admission and the commonest cause of death. The frequent bacterial aetiologies were *Streptococcus pneumoniae* and *Haemophilus influenzae* while *Pneumocystis jiroveci* (previously *Pneumocystis carinii*) pneumonia (PCP) was identified as the most important cause of severe and very severe pneumonia. The case fatality rate for PCP ranged from 40% in Uganda to 62% in Malawi. The infection was observed to be more serious in young children less than 12 months with a significant mortality rate in those less than 6 months. Most countries reported the median age at presentation to be between 3 - 4.5 months. The major challenges identified were the lack of clear clinical predictors for diagnosis of PCP and the lack of resources to ascertain HIV infection for initiating prophylaxis. Other organisms identified as causes of pneumonia in HIV-infected children included Cytomegalovirus (CMV) and Tuberculosis (TB). It was recognized that the difficulty to differentiate between the different aetiologies was an obstacle to appropriate therapy and this area needs further research.

Emergence of resistance and the possible implication on pneumonia and malaria treatment was identified as a major concern regarding the implementation of wide use of cotrimoxazole as prophylaxis.

Following the presentations and discussions, recommendations were made for management of pneumonia in children with HIV infection. In addition, areas of research issues and priorities were identified.

I. INTRODUCTION

Respiratory tract infection particularly pneumonia has long been recognized as the major cause of morbidity and mortality in children under the age of 5 years, particularly in developing countries. With increasing prevalence of HIV/AIDS, the contribution of pneumonia to morbidity and mortality in children has become a major area of concern. The common presenting complaints of HIV-infected children with pneumonia may be similar to those of all children addressed by IMCI; however the associated infection with opportunistic organisms and high mortality in these children prompted the need to evaluate closely the data and experience on the management of pneumonia in these children. Previously, WHO had conducted consultative meetings and developed guidance for the management of children with HIV/AIDS in the context of IMCI for the outpatient setting. This meeting was organized by WHO CAH/HQ and IMCI/AFRO to share the experiences from countries and formulate recommendations for guidelines for the management of children with pneumonia and HIV infection.

II. OBJECTIVES OF THE MEETING

1. Review data/evidence about pneumonia aetiology and outcomes with existing therapeutic regimens in children with HIV infection.
2. Recommend case management guidelines for pneumonia in children with HIV infection.

III. EXPECTED OUTCOMES

1. Potentially effective therapeutic regimens for empiric treatment of pneumonia in children living in areas of high HIV prevalence to be identified.
2. Plans for testing clinical efficacy and effectiveness of the above-mentioned regimens for the management of pneumonia in children infected with HIV.
3. Priority research questions in this area to be identified.

IV. PARTICIPANTS

The participants included representatives from six countries in East and Southern Africa (Botswana, Malawi, South Africa, Uganda, Zambia and Zimbabwe) and collaborators and researchers from the USA, France, CAH, WHO HQ and AFRO. (Participants List -Annex 1).

V. AGENDA AND PROCEEDINGS

The two meeting objectives were used as the focus for the sessions.
(Agenda – Annex 2)

VI. SUMMARY OF PRESENTATIONS

Malawi

The data from Malawi were presented by Dr Stephen Graham from the Department of Paediatrics, College of Medicine, University of Malawi, Blantyre. His presentation provided information on the burden of HIV and pneumonia in children, the results from post-mortem pneumonia studies from the region and hospital-based study of *Pneumocystis jiroveci* (previously *Pneumocystis carinii*) pneumonia (PCP) in Malawi. The experience in Malawi showed that there has been a steady increase in the rate of HIV infection in women presenting for antenatal visit and in infants since 1989.

The following summarizes the main points of the hospital-based studies in Blantyre.

- Ten percent of children born in hospitals were HIV-infected.
- Pneumonia with HIV/AIDS was among the most common causes of death.
- Comparison of survival showed that only 25% of HIV-infected children survived up to 5 years of age in Malawi in contrast to 80% of survival in Europe.
- Acute severe pneumonia was the leading cause of admission and is associated with increased (three-fold) mortality in HIV-infected children.
- HIV prevalence among acute severe pneumonia and chronic respiratory disease was 60% and 65% respectively.
- It was noted that an increased number of severe pneumonia cases are becoming unresponsive to standard treatments.

In a study of hospitalized children (2-60 months) with acute severe pneumonia¹:

- Nasopharyngeal aspirate (with squirting of saline) isolated *P. jiroveci* as the commonest organism among HIV-infected children.
- PCP was common in the first year of life with median age at presentation of 2-3 months of age.
- Outcome was poor despite management.
- The case fatality rate was 62%. This figure was higher than a similar study done in South Africa where the case fatality was reported as 49%².

¹ Graham SM et al. Lancet 2000; 355:369-373

² Zar HJ et al. Pediatr Infect Dis J. 2000;19:603-7

The conclusion of the study was that:

- Persistent hypoxia following admission, lack of treatment response and lack of improvement of oxygen saturation to nasopharyngeal administration of oxygen was characteristic of PCP.
- PCP was the commonest cause of death in HIV-infected children accounting for 30-50% of mortality.
- PCP was frequently associated with poor outcome and placed huge demands on limited resources.
- Prevention was possible but required effective guidelines and timely identification of at-risk children.

Zimbabwe

The presentation from Zimbabwe was made by Professor Kusum Nathoo from the Department of Paediatrics, University of Zimbabwe, Harare. Data from a number of studies that looked at pneumonia mortality, aetiology, antimicrobial resistance and impact of HIV were presented.

- In Harare Hospital, it was observed that case fatality among children admitted with pneumonia had been increasing from 15% in 1989-1990 to 16.4% in 1995 and 21 % in 1999.
- A study on comparison of clinical features of HIV-infected and uninfected children with pneumonia showed that the relative risk of pneumonia mortality was higher in children less than 6 months of age, duration of cough for more than 14 days, and in those who had a previous history of acute lower respiratory infection (ALRI) and concurrent diarrhoea. The risk of dying was also noted to be three times higher in HIV-infected children.
- In a maternal to child transmission (MTCT) study, of the 101 HIV-infected children between 1991-1995, 45 had died by the end of 24 months (case fatality rate 44.6%). Pneumonia accounted for 75% of the total deaths. The median age at death was 4.3 months with 75% of the deaths occurred before the age of 6 months.
- The aetiology of pneumonia was studied in 704 children of whom 443 had blood cultures done on admission. Bacterial growth was found in 22% and the most commonly isolated organism was *S. pneumoniae*. There was no significant difference in the pattern of organisms between children below and above 3 months of age.
- In a post-mortem study where pulmonary manifestations in HIV and malnutrition were examined, histological evidence of pneumonia was seen in 89% of HIV positive and 53% of HIV negative subjects. PCP was isolated in 16% of the HIV positive children. Lung aspiration revealed bacteria in 92% of malnourished and 69% of well-nourished children.

-
- A study was done to determine trends (1994-2000) in resistance of invasive *S. pneumoniae* among hospitalized patients at two major referral hospitals in Harare. In 2000, reduced susceptibility for penicillin was documented in over 50% of the *S. pneumoniae* isolates. High-level resistance was 16% in HIV positive individuals (adults and children) while it was 6% in HIV negative patients.
 - Over the years there was an increasing trend towards resistance to cotrimoxazole. In 2000, reduced susceptibility of *S. pneumoniae* to cotrimoxazole was recorded in 54% of HIV positive and 62% of HIV negative patients.

Uganda

Dr Sabrina Bakeera-Kitaka presented the study on the prevalence and outcome of PCP in children admitted with severe pneumonia at Mulago Hospital, Kampala. One hundred and twenty one children (2months-5years) who fulfilled the WHO criteria for severe pneumonia were enrolled. Samples were collected using sputum induction with saline and nasopharyngeal aspiration.

The findings of the study were as follows:

- 16.5% of children with severe pneumonia had PCP.
- 41.5% of HIV positive children had PCP compared to 2.6% of HIV negative children.
- 60% of the infants less than 6 months of age had PCP.
- The case fatality for PCP was 40%.

The study concluded that:

- PCP should be considered in children less than 6 months of age with pneumonia in the presence of AIDS (as defined by the WHO case definition).
- HIV positivity and a clear chest on clinical examination in severe pneumonia strongly predict PCP.

South Africa

- A. Dr Shabir Madhi presented results of several studies from South Africa. Like other countries in the region, the studies showed that there was an exponential increase in cases of pneumonia. In a study done in Soweto, where 548 HIV positive and 617 HIV negative children with severe pneumonia were enrolled, the median age of HIV-infected children with pneumonia was 9 months. It was noted that in comparison to the HIV negative children the HIV positive children presented with pneumonia at an older median age with high rates of malnutrition, longer duration of illness and high case fatality.

The study on aetiology of severe ALRI among hospitalized children at Chris Hani-Baragwanath Hospital, Johannesburg showed that:

- 45% of cases of severe pneumonia in HIV-infected children were due to PCP.
- Respiratory Syncytial Virus (RSV) was the dominant cause in the non-HIV-infected children.
- 8% of HIV-infected children with acute pneumonia had TB.
- However the study on bacteraemia in children with severe community acquired pneumonia showed that *S. pneumoniae* and *H. influenzae* were the commonest pathogens.

The study suggested that the contribution of bacteria to the burden of pneumonia was higher in HIV-infected children. Dr Madhi highlighted that this had implications for the development and use of vaccine.

A study on *H. influenzae* type b (Hib) vaccine in South Africa in children less than two years of age showed:

- There was a six-fold increase of Hib pneumonia in HIV-infected children compared to those who were not HIV-infected.
- The Hib conjugate vaccine showed 54% reduction of pneumonia in HIV-infected compared to 90% in HIV-uninfected children. Overall pneumonia reduction in all children was 78%.

A study on invasive *S. pneumoniae* among HIV-infected children showed that:

- 65% of children with invasive pneumococcal disease were HIV-infected in Soweto
- Impact of cotrimoxazole prophylaxis on trimethoprim sulfamethoxazole (TMP-SMX) susceptibility of invasive pneumococcal isolates in HIV-infected children showed reduced susceptibility in 80% of those who were on TMP-SMX compared to 45% in those who were not on TMP-SMX prophylaxis.

An efficacy study of pneumococcal conjugate vaccine showed:

- A 53% reduction in pneumococcal disease in HIV-infected children. Vaccine attributable reduction of pneumococcal pneumonia was much greater in HIV-infected versus uninfected children.
- Irrespective of aetiology the vaccine prevented about 12% of pneumonia.

The investigators concluded that the pneumococcal conjugate vaccine was efficacious (65%) in preventing invasive pneumococcal disease due to vaccine serotypes in HIV-infected children not receiving highly active anti-retroviral therapy (HAART). They also believe that there is a potential impact for reducing morbidity and mortality in developing countries. Though the

durability of efficacy without booster was questioned, the vaccine is recognized to have greater benefit in reducing burden of invasive pneumococcal disease amongst HIV-infected than HIV-uninfected children.

A study of PCP in HIV-infected children showed that:

- Median age for PCP pneumonia was 4.5 months.
- Isolation of the organism and mortality was higher in those not receiving prophylaxis.
- The mean age at death in children with PCP pneumonia was 3 months.

The investigators concluded that prophylaxis improved survival and should begin early, possibly coinciding with EPI vaccines.

- B.** Dr Prakash Jeena presented data from Durban, South Africa. First he presented data from the Durban Paediatric Pneumonia Pathogen Study (unpublished data: LM McNally and P Jeena). The aims of the study are to determine response rates and aetiology of severe pneumonia in children admitted to King Edward Hospital, Durban. Recruitment finished in December 2002 and interim results from the first year of the study were presented at the meeting.

The study included children aged 1-59 months old admitted with WHO-defined severe or very severe pneumonia. Children who did not respond within 48 hours had further investigations including a repeat blood culture and chest radiograph. The non-responders were further investigated with either a non-bronchoscopic broncho-alveolar lavage or lung aspirate dependent on the chest radiograph findings and clinical condition. The results of the study were as follows:

- 80% of the 179 children in the study were HIV positive by PCR.
- *S. pneumoniae* was isolated from 10% of admission blood cultures.
- There was a significant difference between HIV-infected and uninfected children (84%) in their response to the antimicrobials used to treat severe pneumonia (54%).
- The commonly identified organisms in the non-responders were CMV (47%) and PCP (30%).
- The overall case fatality rate was 16%.

The investigators concluded that this study had the highest recorded HIV rate in any paediatric pneumonia cohort in the world. They also concluded that non-bronchoscopic broncho-alveolar lavage demonstrated conclusively that PCP was the most important organism and that the majority of severe pneumonias in a high HIV prevalence region could still be treated by the conventional WHO antimicrobial regimens.

In his subsequent presentation Professor Jeena summarized a meta-analysis of six intervention trials in settings with high infant mortality, which showed that the WHO standard case management has resulted in a reduction of infant mortality rate (IMR) by 15.9 per 1000 live births and under 5 mortality by 36 per 1000 live births with an overall 20% reduction in IMR and a 25% reduction in under 5 mortality. He also summarized some of the findings on prevalence and outcome of HIV on childhood ALRI in the region as follows:

- Etiological studies on pneumonia in HIV endemic regions demonstrate that the most common pathogens are *S. pneumoniae* and *H. influenzae*.
- HIV associated pneumonia was the commonest cause of hospitalization.
- ALRI occurred in 45-65% of children with AIDS often as an initial sign of HIV disease.
- In one study from Zimbabwe, the prevalence of HIV in childhood acute lower respiratory tract infection admissions was 34% and case fatality rate (CFR) of HIV-infected versus uninfected was 34% versus 9%.

Finally, Dr Jeena shared data from a study comparing the efficacy of oral amoxicillin versus injectable penicillin in children aged 3 to 59 months with severe pneumonia.

The study enrolled 1702 children with WHO-defined severe pneumonia who were randomized to receive oral amoxicillin or injectable penicillin. Baseline nasopharyngeal sampling was done for RSV in addition to routine microbiology. The study showed that treatment failure rates were higher than expected; however oral amoxicillin and injectable penicillin were equally effective in terms of treatment failures and clinical relapse rates. In addition, clinical efficacy of amoxicillin and penicillin was found to be equivalent to other more expensive antibiotics.

In a sub-group of children from South Africa and Zambia, the prevalence of HIV among children with severe pneumonia was 22.4%. The analysis of this sub-group also found that:

- Nasopharyngeal carriage/infection was similar between the HIV-infected and uninfected group.
- HIV-infected children with severe pneumonia had worse treatment response rates to standardized therapy.
- Infants had worse outcomes than children 12-59 months. This was exaggerated in those children who were HIV-infected.
- HIV exposure without infection carries a poorer treatment response rate than HIV uninfected.
- Parental penicillin and oral amoxicillin had similar rates of treatment failure.

Dr Jeena concluded that the findings might suggest that the WHO guidelines may be better for older children than for young children.

Zambia

Professor Chifumbe Chintu presented a descriptive post-mortem aetiology study of Zambian children dying of respiratory disease at the university teaching hospital, Lusaka.

The post-mortem study was done on 264 children who died of respiratory diseases between 1997-2000. Autopsy was restricted to the chest and serum samples from cardiac chambers were stored for later analysis. The HIV prevalence was 68% and pyogenic pneumonia was the leading cause of death despite HIV status. *P. jiroveci* was the most common organism isolated in HIV-infected young children 0-5 months of age and isolation was significantly higher (22%) in the HIV-infected than the non- HIV-infected (7%) at all ages. CMV and TB were also among the important organisms responsible for pneumonia in the HIV-infected children.

The investigators concluded that:

- Most children died of preventable infectious disease.
- Necropsy is an important method to obtain accurate etiologic information in children who died of pneumonia.
- Acute pyogenic pneumonia was the commonest cause irrespective of HIV status.
- PCP is an important cause of death in young infants.

They also recommended that inexpensive, rapid and practical tests should be developed for diagnosis of *P. jiroveci* and TB.

Botswana

Professor Gabriel Anabwani presented the experience from Botswana as being similar to other countries in the region. He alluded that before 1995 mortality from pneumonia was 5% with a declining trend, however since 1995 the pattern has been that of increase in hospital admissions, longer hospital stay and steady rise in hospital mortality. He summarized the current situation in hospital setup in Botswana as follows:

- Over 95% of hospital deaths in children were HIV related.
- Hospital mortality from pneumonia was 7-10% with HIV prevalence of 15-30% in 1996-1999. Between 1999-2002 the mortality figure had risen to 10-15% with HIV prevalence to more than 60%.
- PCP accounted for 5-10% of all pneumonia.
- Clinical malnutrition had become more frequent. Data from a study with 145 children on Antiretroviral (ARV) (2002) showed that 60% were underweight while 75% were stunted.

Professor Anabwani also informed that since April 2002, antiretroviral therapy was being offered to all HIV-infected children admitted to hospital. He added that diagnosis of pneumonia was mainly based on clinical findings and children were offered intravenous (IV) cotrimoxazole with steroids whenever PCP was considered. He also highlighted the importance of TB in HIV-infected children and the challenges of early diagnosis for treatment in children. He concluded his presentation with the remark that although pneumonia remains the dominant cause of hospital admission for children, HIV has had a major impact on the spectrum of acute and chronic respiratory disease in Botswana in the last decade. He also emphasized that specific treatment of pneumonia in HIV-infected children must be guided by the most likely causative pathogens. He stressed that efforts to prevent and treat HIV in the African region are likely to have a major favourable impact on pneumonia in children.

VII. SUMMARY OF DISCUSSIONS

Each presentation was followed by thorough discussion. The main issues raised and highlights of the discussion are as follows.

Aetiology of pneumonia

The data presented from the six countries indicate that the most common cause of pneumonia in HIV-infected children was bacterial, thus justifying the use of antibiotics in these children. The studies also show that viral pneumonia was relatively less common. The importance of PCP in HIV infection was recognized as a serious disease associated with higher mortality, particularly in children under the age of one year. Other important pathogens reported in HIV-infected children were CMV and TB.

Pneumocystis jiroveci isolation and clinical signs

It was noted that there was variability in the methods of isolation of *P. jiroveci* as well as differences in the number of trophozoites used as a cut off limit to determine diagnosis and treatment. It was suggested that squirting of saline and aspirating would give a better yield than dry aspirate. The meeting agreed that efforts should be made to develop cheap and rapid methods of isolation for *P. jiroveci*.

The clinical manifestation of PCP pneumonia in most of the studies included cyanosis and hypoxia with clear chest. There was little variation among the countries in the criteria used to consider clinical PCP. In most cases, the decision to treat PCP in the hospital was guided by the child's response to pneumonia treatment within 48 to 72 hours after which cotrimoxazole was added. The effectiveness of secondary prophylaxis was identified as an area for further investigation.

Prophylaxis for PCP

The use of effective prophylaxis early in life was a major concern as most countries in the region lacked the resources to determine the presence of HIV infection and risk of PCP. In places where the resources were available, rapid HIV testing would assist in making the decision. However, treating all cases of very severe pneumonia for PCP or initiating empiric therapy based on clinical finding and later referring patients for intensive investigation was pointed out as an alternative. The meeting suggested that there was a need to develop guidelines for clinical predictors of PCP.

Among HIV-infected children, the incidence of PCP falls rapidly from late infancy through the second year of life. There was concern among participants that PCP infection after one year of life was rare, therefore the relatively small added benefit of extending primary prophylaxis from 12 to 15 months of age needs to be supported by empirical data.

Tuberculosis

Tuberculosis was found to be among the common causes of pneumonia and its importance in HIV-infected children was emphasized. However, it was recognized that there was a lack of simple and specific tests for TB in children. It was agreed that there was a need for more research on an early and conclusive method of diagnosis of TB in children. The meeting was also informed that International Union against Tuberculosis and Lung Diseases (IUATLD) was in the process of establishing a working group for TB in children.

Blood culture

The use of blood culture in the etiologic determination of pneumonia required further refinement with regard to methods of blood culture system and timing of post-mortem blood culture.

Antibiotic regimen

Most countries use the standard WHO regimens to treat severe pneumonia. On the issue of use of penicillin or ampicillin with gentamicin versus cefotaxime/ceftriaxone, it was suggested that due to the high cost of the latter, the drug should be reserved as a second-line antibiotic for treatment failures with first-line antibiotics.

It was also noted that more studies were documenting increasing pneumococcal resistance to cotrimoxazole. However, the issue of clinical efficacy and *in vitro* resistance is still on the agenda as previous studies showed that oral amoxicillin and cotrimoxazole have equal efficacy against non-severe pneumonia despite high *in vitro* resistance. Furthermore, the impact of the wide use of cotrimoxazole is also an area of concern in countries where sulphadoxine-pyrimethamine (Fansidar) is recommended as the first-line treatment for malaria.

Steroids

Experience in the use of steroids in the treatment of PCP in HIV-infected children varied among the countries. Lack of a clear guideline for use of steroids in the management of PCP or HIV-infected children in general is acknowledged. It was therefore agreed that more information was required for the development of a guideline on the use of steroids in the management of children with HIV infection.

Vaccine

It was highlighted that in developed countries the 7-9 valent pneumococcal conjugate vaccines will probably protect close to 80% of children. However, it was noted that the vaccine might not be available in developing countries in the immediate future. It was agreed that efforts should continue to make these vaccines available for children in these countries. In young infants between 0-2 months of age, conjugate vaccine use will produce herd immunity.

The issue of a booster for Hib vaccination was also discussed and it was noted that there is a need for more data to establish how often and when to administer booster doses.

VIII. CONCLUSION

The objectives of the meeting were met and recommendations developed for the management of pneumonia in HIV-infected children. The meeting also identified important research issues that will be useful to develop further and to adapt guidelines to meet the special needs of this group of children.

IX. RECOMMENDATIONS

After thorough discussion, the following recommendations were made for the management of pneumonia in HIV-infected children³.

Non-severe pneumonia (all age groups up to the age of 5 years)

- WHO recommends oral cotrimoxazole and oral amoxicillin as first-line antibiotics for the treatment of non-severe pneumonia. Oral amoxicillin wherever recommended should continue to be used. However, in light of the increasing use of cotrimoxazole for PCP prophylaxis, the impact on antimicrobial resistance of common organisms to antibiotics and antimalarials like sulphadoxine-pyramethamine, the countries with high HIV burden that recommend cotrimoxazole may want to review these guidelines. Oral amoxicillin should be used if it is affordable, if the child is HIV exposed/infected or if the child has been on cotrimoxazole prophylaxis
- Regular follow-up is essential to monitor progress

³ Doses given in Annex 3.

Severe pneumonia

- Advocate for antenatal HIV testing to identify HIV exposed children

0-2 months

- Efforts should be made to make Hib and pneumococcal conjugate vaccines available
- Use existing WHO standard case management guidelines.

2-11 months

HIV-infected

- Hospitalize.
- Administer injectable antibiotic (ampicillin / penicillin +gentamicin or oral amoxicillin + gentamicin) and if not improving in 48 to 72 hrs change to second-line antibiotic (ceftriaxone)
- PCP therapy with cotrimoxazole IV or suspension⁴
- Start PCP prophylaxis on recovery

HIV unknown

- Determine HIV status of child
- If positive, treat as mentioned above for HIV-infected child

HIV negative

- Use existing WHO standard case management guidelines

Where HIV test is not available

HIV suspected

- Follow the recommendations for HIV-infected child

HIV not suspected

- Injectable antibiotic (ampicillin /penicillin +gentamicin)
- If not responding within 48-72 hours change to second-line antibiotic (ceftriaxone) and evaluate for PCP, TB and complications
- If the child returns with another episode of pneumonia within 12 months add cotrimoxazole
- Secondary prophylaxis

⁴ Tablets could be used, if intravenous or suspension form is not available.

12-59 months

HIV Positive

- Hospitalize
- Administer injectable antibiotic (ampicillin / penicillin +gentamicin or oral amoxicillin + gentamicin)
- If not improving in 48 - 72 hours change to second-line antibiotic- (ceftriaxone)
- PCP treatment if clinically indicated
- Start PCP prophylaxis on recovery, if treated for PCP

HIV negative

- Use existing WHO standard case management guidelines

HIV Unknown

- Test for HIV
- PCP treatment if clinically indicated

Where HIV test is not done or not available

HIV suspected/symptomatic HIV

- Administer injectable antibiotic (ampicillin / penicillin +gentamicin or oral amoxicillin + gentamicin)
- Add oral cotrimoxazole suspension or IV for PCP
- If not improving in 48 - 72 hours change to second-line antibiotic (ceftriaxone)
- Evaluate for complications and TB
- Start PCP prophylaxis on recovery, if treated for PCP

Very severe pneumonia

0-2 months

- Use existing WHO standard case management guidelines

Above 2 months

HIV Positive

- Administer injectable antibiotic (ampicillin / penicillin +gentamicin or oral amoxicillin + gentamicin)
- PCP therapy (parenteral or oral suspension cotrimoxazole)
- PCP prophylaxis
- If not improving in 48 - 72 hrs change to second-line antibiotic (ceftriaxone)

HIV suspected or symptomatic

- Same as above

HIV unknown

- Test for HIV
- PCP prophylaxis if test not available

HIV negative

- Use existing WHO standard case management guidelines

PCP Prophylaxis

- The current provisional WHO/UNAIDS guidelines (Annex 4) recommend that PCP prophylaxis should be given to children born to HIV-infected mothers for a duration of 15 months. Among HIV-infected children, the incidence of PCP falls rapidly from late infancy through the second year of life and the relatively small added benefit of extending primary prophylaxis from 12 to 15 months of age needs to be supported by empirical data. It is therefore recommended to re-evaluate the current recommendation in light of PMTCT activities that might have altered the risk of peri-natal HIV infection
- All HIV exposed children should receive cotrimoxazole beginning at 6 weeks of age
- Periodic review of a child on prophylaxis is needed
- PCR should be done as early as possible (wherever available) to avoid overuse of prophylaxis for children who don't require the drug and to curtail the emergence of resistance
- Studies should be done to determine the optimal time for PCR testing in order to identify the risk of HIV infection and PCP in breastfeeding children

X. RESEARCH ISSUES

The major areas identified for research were related to development of management guidelines, aetiology of pneumonia, PCP management and steroid administration.

Management guidelines

- Evaluation of first-line and second-line antibiotics (new guidelines) for treatment of non-severe, severe and very severe pneumonia.
- Assess the effectiveness of use of steroids in HIV-infected children with pneumonia.
- Effect of steroids in the management of PCP (timing of administration, versus placebo, racial/social differences, co-infection with CMV and/or TB).
- Effectiveness and availability of Hib and *S. pneumoniae* conjugate vaccines to reduce morbidity and mortality from pneumonia in HIV-infected children.
- Development of nutritional interventions for management of HIV-infected children with pneumonia.

Aetiology and Diagnosis

- Development of inexpensive and rapid tests for diagnosis of *P. jiroveci* and tuberculosis in children.
- Assessment of optimal time for PCR testing in breastfeeding children to identify HIV infection and risk for PCP.
- Evaluation of affordable and appropriate blood culture methods to identify respiratory pathogens.
- Aetiology of pneumonia in the African region.
- Documentation of pattern of serotypes of *S. pneumoniae* in HIV-infected and uninfected children with pneumonia.
- Quantitative analysis of *P. jiroveci* carriage in children, mothers and breast milk.
- Role of TB and CMV in HIV-infected children with acute pneumonia.
- Importance of pathogens identified at necropsy in children with HIV infection.

PCP prophylaxis and treatment

- Evaluation of current WHO PCP prophylaxis recommendation beginning at the age of 6 weeks till 15 months of age.
- Clinical predictors of PCP.
- Assessment of alternative prophylaxis (Pentamidine and Dapsone) in countries where HAART is available and cotrimoxazole is not tolerated.

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- Assessment of compliance to primary and secondary PCP prophylaxis.
 - Evaluation of effectiveness of secondary PCP prophylaxis.
 - Evaluation of feasibility of directly observed therapy (DOT) for PCP prophylaxis.
 - Evaluation of the pattern of *P. jiroveci* resistance to cotrimoxazole.
 - Emergence of resistance to common bacteria like *S. pneumoniae* and *H. influenzae* in light of wide use of cotrimoxazole and sulphadoxine-pyramethamine.
 - Evaluation of different types of nasopharyngeal aspiration methods for diagnosis of *P. jiroveci*.

Though the discussions suggest that all the above listed issues were important, the following were considered as the priority areas.

Priority areas for research:

1. Evaluation of first-line and second-line antibiotics (new guidelines) for treatment of non-severe/ severe and very severe pneumonia
2. Emergence of resistance to common bacteria like *S. pneumoniae* and *H. influenzae* in light of wide use of cotrimoxazole and sulphadoxine-pyramethamine (Fansidar).
3. Evaluation of the pattern of *P. jiroveci* resistance to cotrimoxazole.
4. Evaluation of current WHO PCP prophylaxis recommendation beginning at the age of 6 weeks till 15 months of age.
5. Assessment of compliance to primary and secondary PCP prophylaxis.
6. Evaluation of effectiveness of secondary PCP prophylaxis.
7. Assessment of optimal time for PCR testing in breast feeding children to identify HIV infection and risk for PCP.
8. Assessment of the effectiveness of use of steroids in HIV-infected children with pneumonia.
9. Documentation of pattern of serotypes of *S. pneumoniae* in HIV-infected and uninfected children with pneumonia.
10. Evaluation of different types of nasopharyngeal aspiration methods for diagnosis of *P. jiroveci*.
11. Development of inexpensive and rapid tests for diagnosis of *P. jiroveci* and tuberculosis in children.
12. Effectiveness and availability of Hib and *S. pneumoniae* conjugate vaccines to reduce morbidity and mortality from pneumonia in HIV-infected children.
13. Evaluation of affordable and appropriate blood culture methods to identify respiratory pathogens.

ANNEX I:

LIST OF PARTICIPANTS

Professor Gabriel Anabwabi, Clinical Professor of Paediatrics, Baylor College of Medicine, Texas, USA and Director, Botswana-Baylor Children's Clinical Centre of Excellence, Gaborone, Botswana (Formerly: Senior Consultant and Head Department Paediatrics, Princess Marina Hospital, Gaborone, Botswana)

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Ms. Penny Enarson, Chief, Child Lung Health Division, International Union Against Tuberculosis and Lung Disease, Paris, France

Dr Stephen M Graham, Wellcome Trust Research Laboratories, Blantyre, Malawi

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Dr Ntakibirora Marcelline, WHO Consultant, Harare, Zimbabwe

Dr Mary Kaluma-Nyathi, Mpilo Central Hospital, Bulawayo, Zimbabwe

Dr Senait Kebede (*Rapporteur*), WHO Consultant, Harare, Zimbabwe

Professor Keith P. Klugman (*Chairman*), Professor of International Health, Department of International Health, Rollins School of Public Health, Professor of Medicine, Division of Infectious Diseases, School of Medicine, Emory University, Atlanta, Georgia, United States of America and Director, Medical Research Council / National Health Laboratory Service / University of the Witwatersrand Respiratory and Meningeal Pathogens Research Unit, Johannesburg, South Africa

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WHO participants

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Dr Elizabeth Mason, Regional Advisor, IMCI, AFRO
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Dr Francis Onyango, Regional Advisor, HIV, AFRO
Dr Shamim Qazi, CAH/FCH, HQ

ANNEX 2: AGENDA

Day 1

8.30-8.45	Welcome and Introductions	DDC & IMCI
8.45-9.00	Objectives of the meeting; Overview of the agenda	S. Qazi – HQ
<i>Objective 1: Review data/evidence about pneumonia aetiology and outcomes with existing therapeutic regimens in children with HIV infection.</i>		
9.00-9.45	Malawi: PCP pneumonia in children with HIV	S. Graham
09.45-10.30	Zimbabwe: Pneumonia aetiology and outcomes	K. Nathoo
10.30-10.45	<i>Coffee/Tea break</i>	
10.45-11.30	Uganda: PCP pneumonia in children with HIV	S. Bakeera
11.30-12.15	South Africa: Johannesburg; Pneumococcal vaccine trial data	S. Mahdi
12.15-13.30	<i>Lunch break</i>	
13.30-14.15	Durban: APPIS trial data/therapy failure	P. Jeena
14.15-15.0	Durban: Therapy failure/antimicrobial resistance/aetiology	P. Jeena
15.00-15.15	<i>Coffee/Tea break</i>	
15.15-16.0	Zambia : Necropsy data in children with pneumonia	C. Chintu
16.00-16.45	Experiences from Botswana	G. Anabwani
16.45-17.30	Discussion	

Day 2

<i>Objective 2: Recommend case management guidelines for pneumonia in children</i>		
08.30-09.15	Synthesis of aetiology and resistance data	K. Klugman
09.15-10.30	Identification of potential antibiotic regimens for treatment of pneumonia therapy in children with probable HIV – PCP Prophylaxis – Recurrent pneumonia	

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- 10.30-10.45 *Coffee/Tea break*
- 10.45-12.30 Identification of potential antibiotic regimens for treatment of pneumonia therapy in children with probable HIV (cont'd)
- 12.30-13.30 *Lunch break*
- 13.30-15.0 Discussion of other management issues for treatment of
– Pneumonia therapy in children with HIV
– Chronic lung disease
– LIP
- 15.00-15.15 *Coffee/Tea break*
- 15.15-16.30 Identify research needs and ways to address them
- 16.30-17.00 Summary, conclusions and recommendations

ANNEX 3: DRUG DOSAGES /REGIMENS

Antibiotics	Dosage	Form	3-6kg	6-<10kg	10-<15kg	15-20kg
Cotrimoxazole (trimethoprim-sulfamethoxazole)	4mg TMP/kg and 20 mg SMX/kg two times/day	Oral: adult tablet (80mg TMP+ 400mg SMX)	¼	½	1	1
		Oral: pediatric tablet (20mg TMP+ 100mg SMX)	1	2	3	3
		Oral: syrup (40mg TMP + 200mg SMX per 5ml)	2ml	3.5ml	6ml	8.5ml
Avoid cotrimoxazole in neonates who are premature or jaundiced. For PCP pneumonia: Oral or IV cotrimoxazole (trimethoprim 5mg/kg/day, sulfamethoxazole 25mg/kg/day) 4 times a day for 3 weeks. If the child has a severe drug reaction to cotrimoxazole, change to pentamidine (4mg/kg once per day) by IV infusion for 3 weeks.						
Amoxicillin	15mg/kg 3 times per day	250mg tab Syrup (125mg/5ml)	¼ 2.5 ml	½ 5ml	¾ 7.5ml	1 10ml
Ampicillin	Oral: 25mg/kg 4 times per day Intramuscular (IM)/Intravenous	250mg tab Vial of 500mg mixed with 2.1 ml sterile water to give 500mg/2.5ml (IV): 50mg/kg every 6 hrs	½ 1ml	1 2ml	1 3ml	1½ 5ml
These oral doses are for mild disease. If oral ampicillin is required after a course of injectable ampicillin for severe diseases, the oral dose must be 2-4 times higher than that given here						
Ceftriaxone	80mg/kg once daily	IV Vial of 1gm mixed with 9.6ml sterile water to give 1g/10ml or vial of 2gm mixed with 19ml sterile water to give 2gm/20ml	3 ml	6ml	10ml	14ml
Gentamicin	7.5mg/kg once daily	IM/IV: vial containing 20mg (2ml at 10mg/ml) undiluted	2.25-3.75ml	4.5-6.75ml	7.5-10.5ml	-
		IM/IV: vial containing 80mg (2ml at 40mg/ml) mixed with 6ml sterile water	2.25-3.75ml	4.5-6.75ml	7.5-10.5ml	-
		IM/IV: vial containing 80mg (2ml at 40mg/ml) undiluted	0.5-0.9ml	1.1-1.7ml	1.9-2.6ml	2.8-3.5ml
Benzyl penicillin (Penicillin G)	50,000 units/kg every 6 hrs	IV: vial of 600mg mixed with 9.6ml sterile water to give 1,000,000 units/10ml	2ml	3.75ml	6ml	8.5ml
		IM: vial of 600mg (1,000,000 units) mixed with 1.6 ml sterile water to give 1,000,000 units/2ml	0.4ml	0.75ml	1.2ml	1.7ml
Doseage for meningitis	100,000 units/kg every 6 hrs	IV	4ml	7.5ml	12ml	17ml
		IM	0.8ml	1.5ml	2.5ml	3.5ml
Procaine benzyl penicillin	50,000 units/kg once a day	IM: vial of 3gm (3,000,000 units) mixed with 4 ml sterile water	0.25ml	0.5ml	0.8ml	1.2ml

ANNEX 4:

PROVISIONAL WHO/UNAIDS SECRETARIAT RECOMMENDATIONS ON THE USE OF COTRIMOXAZOLE PROPHYLAXIS IN ADULTS AND CHILDREN LIVING WITH HIV/AIDS IN AFRICA⁵

Selection criteria:

Cotrimoxazole prophylaxis should be offered to all HIV-exposed infants from six weeks of age, using the following criteria:

- Any child born to an HIV-infected woman irrespective of whether the woman received antiretroviral therapy in pregnancy
- Any child who is identified as being HIV infected within the first year of life by PCR, HIV serology or by a clinical diagnosis of HIV infection (according to WHO/national guidelines).
- Children older than 15 months who have had a PCP event, have symptomatic HIV disease, an AIDS defining illness, or have CD4 percentage less than 15.

Drug regimens

Children:

- Cotrimoxazole syrup should be administered once a day on a daily basis,
- If syrup is unavailable, crushed tablets may be used.
- The health professional may switch from syrup to tablet to ensure ongoing access to medication
- The recommended dose is 150mg TMP/m² SMX 750 mg/m²

Duration:

- Prophylaxis should be lifelong in both adults and children over the age of 15 months.
- For infants up to 15 months of age, prophylaxis should continue until HIV infection has been reasonably ruled out and the risk of exposure has ceased.
- For children older than 15 months of age, prophylaxis should be continued if they have had PCP, have symptomatic HIV disease or an AIDS defining illness, or a CD4 percentage less than 15.

⁵ The provisional WHO/UNAIDS secretariat recommendations on the use of cotrimoxazole prophylaxis in adults and children living with HIV/AIDS in Africa can be accessed at <http://www.unaids.org/publications/documents/care/general/recommendation-eng.pdf>

Criteria for stopping:

In children prophylaxis should be stopped:

- In the event of occurrence of severe cutaneous reactions such as fixed drug reaction or Stevens Johnson syndrome, renal and/or hepatic insufficiency or severe hematologic toxicity
- If antiretroviral agents become available.

Note

- In some places doses by TMP/m²/day may be difficult to follow. Proposed regimen using weight and age of the child is as follows:
 - 240 mg (1/2 adult size tablet) daily for 6 months to 5 years
 - 480 mg (1 adult size tablet) daily for older than 5 years
