

CONSULTATIVE MEETING TO REVIEW EVIDENCE AND RESEARCH PRIORITIES IN THE MANAGEMENT OF ACUTE RESPIRATORY INFECTIONS (ARI)

Geneva, 29 September - 1 October 2003

MEETING REPORT



Department of Child and Adolescent Health and Development
World Health Organization

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Background and objectives of the meeting

Acute respiratory infections (ARI) were estimated to be responsible for around two million childhood deaths in year the 2000. The World Health Organization (WHO) developed standard ARI case management guidelines in the 1980s to reduce mortality. Standard ARI case management guidelines have been shown to reduce mortality in community-acquired pneumonia. Many developing countries instituted ARI control programmes and adapted those guidelines. These ARI guidelines have now been incorporated into the Integrated Management of Childhood Illness (IMCI) guidelines. However, these ARI programmes started facing problems due to increasing treatment failure rates. One of the major reasons for these rising treatment failure rates was considered to be antimicrobial resistance of *Streptococcus pneumoniae* and *Haemophilus influenzae* to the recommended first-line drugs. There were some other factors besides antimicrobial resistance like differentiation between viral and bacterial, role of wheezing, sensitive therapy failure criteria, clinical overlap with malaria, especially in high endemic malaria regions and high prevalence of HIV in many countries.

During the past 8-10 years some of the above-mentioned issues have been addressed through targeted research in order to improve the ARI case management guidelines. The results from these studies were presented and discussed in an informal consultative meeting arranged in Geneva by the Department of Child and Adolescent Health and Development (CAH), WHO Geneva, the Applied Research on Child Health (ARCH) project, Center for International Health, Boston University, and other partners.

The meeting objectives were to:

- review data and evidence from recent ARI case management studies;
- identify gaps in knowledge and suggest research for the future.

The expected outcomes were:

- suggested revisions in WHO ARI/IMCI case management guidelines;
- research priorities to be addressed in future.

Participants included researchers, public health specialists, policy makers, planners and programme managers. The list of the participants and the agenda of meeting are attached as annexes I and II.

Setting the stage

Epidemiology of pneumonia and issues with defining pneumonia

Dr Campbell presented an overview of the ARI mortality estimates for the last decade. The estimate for ARI mortality for the year 2002 is 2.1 million/year. Most of these ARI mortality estimates were dependent on verbal autopsy studies which had certain limitations, such as varying definitions of ARI and different methods used to study causes of death. A need for aetiology-specific estimates of ARI mortality was expressed/recommended. It was estimated that 154 million new Acute Lower Respiratory Infection (ALRI) cases occur every year and 11-17 million were severe enough for hospital admission. However, it was cautioned that these estimates were based on reports from 28 selected studies and were unlikely to be representative of wider regions.

The major focus of this session was on ALRI case definition. The specificity and sensitivity of various clinical signs used in the diagnosis of pneumonia in young children in developing countries were given. It was stated that WHO ARI criteria detect about 80% of the children that require antibiotic treatment and probably detect more than 80% of those with more severe pneumonia. This approach to detect pneumonia has been shown to reduce ARI mortality. However, 20%-30% of childhood ARI episodes which do not need antibiotics will receive them. There is a need to identify other signs, which can improve the specificity of the diagnosis of pneumonia, for the purposes of research, especially in studies looking at the disease burden and various management interventions. The need to find signs for detection of severe ALRI, which can serve as predictors of hospitalization in pneumonia and ARI related mortality, was also highlighted.

Among the topics for further consideration it was pointed out that there was a need to resolve the issues relating to wheeze associated ARI. The prevalence of wheezing is increasing with urbanization. Though wheeze-related mortality is low it complicates the use of the WHO ARI case management algorithm. It can lead to unnecessary referral to hospital. It was recommended that an evidence base is required for developing guidelines for the management of neonates/young infants with ARI, sore throat, acute/chronic ear infections, usefulness of oxygen therapy and ARI in endemic HIV regions. Finally, the potential impact of vaccination on ARI outcome was discussed.

Standardized diagnosis of radiological pneumonia for epidemiological studies

Dr Thomas Cherian presented the data from the WHO pneumonia vaccine trialists radiology working group “Standardized diagnosis of radiological pneumonia for epidemiological studies”. He emphasized the need to develop an objective and standardized method for defining pneumonia. This could be suitable for epidemiological studies carried out to measure the burden and cost of the disease and also to estimate the burden of the disease that may be prevented by vaccination or other intervention. The method must have optimal sensitivity and specificity in diagnosing bacterial pneumonia, low interobserver variability and should be simple, so that it can be used in field conditions in developing countries. He then gave details of the recently developed standardized radiological diagnosis of pneumonia. It was felt that there is a need to have more specific radiological definition. It is important to review the data from completed studies to understand better the factors that influence the use of the radiological definition of pneumonia.

The case management of non-severe pneumonia

WHO recommends oral cotrimoxazole and oral amoxicillin as the first-line drugs for the treatment of non-severe pneumonia. There have been reports of high *in vitro* resistance of *H. influenzae* and *S. pneumoniae* to cotrimoxazole. In countries where cotrimoxazole is being used as a first-line drug, the national ARI control programmes are under pressure to switch over to oral amoxicillin.

Short course antibiotic therapy for the treatment of non-severe pneumonia

a) Three days versus 5 days amoxicillin therapy for non-severe pneumonia

The duration of five-day therapy for non-severe pneumonia is not based on hard data. If shorter courses of antibiotics were found to be equally effective they could cut down the overall cost of treatment in addition to improving the compliance and reducing the antimicrobial resistance in the

community. Two double-blind randomized controlled trials by the MASCOT Study Group¹ in Pakistan and the ISCAP Study Group² in India compared the treatment outcome with three-day oral amoxicillin with that of currently recommended five-day therapy for non-severe pneumonia in children 2-59 months of age.

In the MASCOT study, 2000 children aged 2-59 months with non-severe pneumonia (WHO criteria) diagnosed in the outpatient department of seven hospitals in Pakistan were enrolled. Patients were randomly assigned to three days or five days of treatment with oral amoxicillin. The primary outcome was treatment failure. Analyses were by intention to treat. One thousand children were allocated to 3 days of treatment and 1000 to 5 days. Treatment failed in 209 (21%) patients in the 3-day group, and 202 (20%) in the 5-day group (difference 0.7%; 95% CI - 1.8 to 3.2). In 12 (1%) children in the 3-day group and in 13 (1%) in the 5-day group the disease relapsed (difference 0.1%; - 0.6 to 0.8). Treatment was more likely to fail in children who did not adhere to treatment ($p < 0.0001$), in those younger than 12 months ($p < 0.0001$), in those whose illness lasted for three days or longer ($p = 0.004$), in those whose respiratory rate was more than 10 breaths/min above the age-specific cut-off ($p = 0.004$), and in those with vomiting ($p = 0.009$). Non-adherence was also associated with failure of treatment in the 5-day group ($p < 0.0001$).

The ISCAP Study conducted in ambulatory care settings in seven referral hospitals in India included children aged 2-59 months with WHO- defined non-severe pneumonia. They received oral amoxicillin, 30-45 mg/Kg/day, in three divided doses for the first three days and then either continued on an active drug or placebo for the next two days. The primary outcome was clinical cure. 2188 cases were randomized, 1095 to 3-day and 1093 to 5-day treatment with amoxicillin. Clinical cure was achieved in 980 (89.5%) and 983 (89.9%) patients on 3-day and 5-day treatment respectively (difference 0.4, 95% CI: - 2.1 to 3.0). Adherence assessed on day 3 and day 5 follow-up was 94% and 85.2%, respectively. Loss to follow-up was 5.4% by day 5. There were no deaths, 41 hospitalizations and 36 minor adverse reactions. Overall, there were 225 (10.28%) clinical failures and 106 relapses (5.3%) and these rates were similar in both groups. At enrollment, RSV was identified from nasopharyngeal samples in 513 (23.4%), *Streptococcus pneumoniae* in 878 (40.4%) and *Haemophilus influenzae* in 496 (22.8%) patients. While there was no change in resistance of *H. influenzae* over time, proportion of *S. pneumoniae* resistant to co-trimoxazole rose significantly from 66.1% to 78.2% in 5-day amoxicillin treatment over 15 days ($p = 0.02$). Clinical failure was associated with non-adherence (adjusted OR 11.57, 95% CI: 7.4 to 18.0) and excess respiratory rate of > 10 breaths per minute (adjusted OR 2.89, 95% CI: 1.83 to 4.55).

b) Three days versus five days oral cotrimoxazole for non-severe pneumonia

Cissy Kartasasmita presented the data on behalf of the investigators. This double-blind, randomized, placebo-controlled multicentre equivalence trial was carried out at two sites in Indonesia and Bangladesh in which three days versus five days oral cotrimoxazole for the treatment of non-severe pneumonia, and their effect on antimicrobial resistance in nasopharyngeal *S. pneumoniae* and *H. influenzae* isolates was compared. All children were followed up for 15 days. Of 2022 enrolled children, 1014 were randomized to 5-day cotrimoxazole group and 1008 to 3-day group. On Day 5 follow-up, 224 (22.1%) children failed therapy in the 5-day therapy group, and 209 (20.7%) in the 3-day group (Difference

¹ Pakistan Multicentre Amoxicillin Short Course Therapy (MASCOT) authors and Shamim Qazi. Oral amoxicillin for childhood pneumonia. *Lancet* 2003;361:76-77.

² INDIACLEN Short Course Amoxicillin Pneumonia (ISCAP) Study Group. Three- versus five-day treatment with amoxicillin for non-severe pneumonia in young children: a multicentre randomized trial. *BMJ* 2004 (in press).

1.36, 95% CI - 2.22 to 4.94). Between days 6 to 15, 5.4% (55/1014) relapsed in the 5-day group and 6.2% (62/1008) in the 3-day group (Difference - 0.73, 95% CI - 2.77 to 1.31). By per protocol analysis after excluding loss to follow-up and protocol violations, at Day 5 follow-up, 9.4% (82/872) children failed therapy in the 5-day group and 9.1% (80/879) in the 3-day group (Difference 0.3, 95% CI - 2.41 to 3.01). Between days 6 to 15, 6.3% (55/872) relapsed in the 5-day group and 7.0% (62/879) in the 3-day group (Difference - 0.74, 95% CI - 3.078 to 1.598). Overall, 84.3% (735/872) children in the 5-day group and 83.8% (737/879) in the 3-day group were cured 15 days after enrollment. At enrollment cotrimoxazole non-susceptible *S. pneumoniae* were 54.7% (359/656) and 51.3% (329/641) in the 5-day and 3-day groups, which became 64.1% (409/262) and 61.5% (266/432) on day 15, in that order (P=0.50). In the case of *H. influenzae* prevalence of non-susceptible strains on 0 and 15 day were 44.6% vs. 61.9% and 41.7% vs. 53.7% in the 5-day and 3-day groups respectively (P= 0.06).

Non-severe pneumonia: ARI Case Management: Is Antimicrobial Therapy Necessary?¹

Donald Thea presented data from this study, which was undertaken because of a concern that with increasing antimicrobial resistance, there is a need to review the antibiotic therapy of non-severe pneumonia in children. Furthermore, some health professionals believe that much of the non-severe pneumonia may be non-bacterial, and thus does not pose a high risk of ARI mortality. Inappropriately treated children may be exposed to the known risks of antibiotic use and the community is at risk of the potential selection of drug resistant strains. This small study was conducted as phase I of a placebo control trial, for the management of non-severe pneumonia to be conducted as Phase II. The goal of this study was to determine the failure rate of standard therapy for non-severe pneumonia (amoxicillin), its association with respiratory syncytial virus (RSV) and level of prior antibiotic use in children 2 -59 months old with non-severe pneumonia. A prospective single-arm observational study based at two sites in Durban, South Africa and Ho Chi Minh City, Vietnam enrolled children 2-59 months of age presenting with cough and tachypnoea without signs of severe or very severe pneumonia. Those with malnutrition, hypoxemia (<90%), or conditions requiring antibiotic treatment, or measles within the last month were excluded. A chest radiograph and nasal aspirate were obtained at enrolment and the subjects were given oral amoxicillin for five days. Subjects were evaluated at 48 hours, and five (primary outcome) and 10 days for signs of pneumonia. RSV antigen was determined from nasal washings using a standard clinical kit (Abbot). 194 subjects were enrolled at the two study sites; 95 in Viet Nam and 99 in Durban. Subjects enrolled at the Durban site were more likely at presentation to be febrile (96% vs. 72%), stunted (-1.0 vs. - 0.2 HFA Z-score), have a higher RR (57 vs. 50bpm), positive chest radiograph (75% vs. 48%), and significantly less likely to have used antibiotics for the current episode (11% vs. 44%). Cumulative failure was 2.6%, 5.7% and 11% at 48 hrs, five days and 10-12 days, respectively. RSV was detected in 23% of children and was associated with failure at 48 hours and wheezing at presentation (40% vs. 21%, p <. 05). Conclusions included that prior antibiotic use occurred in a high proportion of children presenting to these facilities with non-severe pneumonia; and that failure was associated with the presence of RSV in nasal aspirates. As a large proportion of these children had radiological evidence of pneumonia, it would be unethical to embark upon a placebo control trial for non-severe pneumonia.

¹ Thea DM, Vy N, Tran AT, Thula S, Qazi S, Fontaine O, and the NARIMA Study Group A multicentre observational study of clinical outcome following amoxicillin treatment of non-severe acute respiratory tract infection (NARIMA). Global Congress on Lung Health, 32nd World Conference of International Union against Tuberculosis and Lung Disease (IUATLD), Paris, France, 14 November 2001. Int J Tub and Lung Dis 2001;5 (Suppl 1):S11.

Use of a monitoring tool in the management of non-severe pneumonia in Pakistan¹

Qayyum Noorani presented their experience to develop and use a tool at the primary health-care level to monitor the response of non-severe pneumonia to cotrimoxazole and to revise the tool after use. At 14 centres in Chitral, 949 children aged 2-59 months with non-severe pneumonia were recruited. The primary outcome was treatment failure, which included change of cotrimoxazole therapy, loss to follow-up and death. 110/949 (11.6 %) children failed therapy, including five children who were lost to follow-up. 944 children who were followed up were analyzed further. 527 (55.8%) were male and 334 (35.4%) were 2-11 months of age. On examination, 421(45.0%) children were febrile, 146 (15.5%) had very fast respiratory rate and 290 (30.7%) had wheezing. Clinical failure was significantly higher in children with very fast respiratory rate (OR 2.3, 95% CI 1.3-4.2 p=0.003), those who had past history of wheezing (OR 1.5, 95% CI 1.0-2.2 p=0.029), wheezing on examination (OR 1.8, 95%CI 1.2-2.8, p=0.004) and fever (OR 1.3, 95% CI 0.9-2.08 p=0.070). Clinical failure had no significant relationship with health site, type of health personnel, duration of illness, age, sex or history of cough. They concluded that cotrimoxazole was effective for treatment of non-severe pneumonia.

Shamim Qazi presented data from the following three studies:

Efficacy of standard versus double dose cotrimoxazole twice daily for pneumonia in children²

This study compared the clinical efficacy of twice daily cotrimoxazole in standard versus double dosage for treatment of non-severe pneumonia. This randomized controlled multicentre trial was conducted in seven hospital outpatient departments and two community health services in Pakistan. A total of 1143 children aged 2-59 months with non-severe pneumonia were randomly assigned to 4 mg trimethoprim/kg or 8 mg trimethoprim/kg given orally twice daily for five days. Of 1134 children analyzed, 578 were assigned to standard strength and 556 to double strength cotrimoxazole. Treatment failed in 112 (19.4%) in the standard and 118 (21.2%) in the double strength group (RR 1.10, 95% CI 0.87-1.37). By multivariate analysis, treatment was more likely to fail in children who did not adhere to treatment (p=0.001), those younger than 12 months (p=0.004), those with history of previous antibiotic use (p=0.002), those whose respiratory rate was >20 breaths/min above the age-specific cut-off (p=0.006), and those from urban areas (p=0.042). Both standard and double strength cotrimoxazole were found to be equally effective for treatment of non-severe pneumonia. They recommended that the definition of clinical failure be made more specific. Surveillance in both rural and urban areas is essential in the development of treatment policies that are based on clinical outcomes.

Comparing pharmacokinetics of amoxicillin given twice or three times per day to children older than three months with pneumonia³

For children with ambulatory pneumonia, the World Health Organization (WHO) recommends oral amoxicillin (15 mg/kg of body weight/dose) thrice daily or oral cotrimoxazole (4 mg of trimethoprim/kg/dose) twice daily. The more frequent amoxicillin dosing may lead to compliance problems. This

¹ Experience with a monitoring tool and cotrimoxazole in the management of non-severe pneumonia in Pakistan. Noorani QA, Qazi SA, Rasmussen ZA, Rehman ZA, Salahuddin SK, Muhamadullah I, Muhammad Y (Submitted for publication).

² Randomised controlled trial of standard and double dose cotrimoxazole for treatment of childhood pneumonia in Pakistan: implications for antibiotic policy. Rasmussen Z, Bari A, Qazi S, Rehman GN, Azam I, Khan S, Aziz F, Rafi S, Roghani MT, Iqbal I, Nagi AG, Hussain W, Bano N, (late) van Latum JC, Khan M and Pakistan COMET (Cotrimoxazole Multicentre Efficacy Trial) Study Group (Submitted for Publication).

³ Fonseca W, Hoppu K, Rey LC, Amaral J, Qazi S. Comparing pharmacokinetics of amoxicillin given twice or three times per day to children older than 3 months with pneumonia. *Antimicrob Agents Chemother* 2003;47:997-1001.

study compared the pharmacokinetics and levels of oral amoxicillin (15 mg/kg of body weight/dose) thrice daily with the 25-mg/kg/dose twice-daily regimen in 66 children ages 3 to 59 months with pneumonia. Amoxicillin concentrations were determined by high-performance liquid chromatography after the first dose on days 1 and 3. After the first dose on day 1, the mean area under the concentration-time curve (AUC) for amoxicillin after the 25-mg/kg dose was 54.7 versus 24.9 $\mu\text{g/ml} \times \text{h}$ after the 15-mg/kg dose. After the first dose on day 3, the mean AUC was 44.1 versus $\mu\text{g/ml} \times \text{h/ml}$. All but two children had plasma amoxicillin concentrations above 0.5 $\mu\text{g/ml}$ for >50% of the dose interval on both days. Six children on day 1 and five children on day 3 had concentrations above 1.0 $\mu\text{g/ml}$ for <50% of the dose interval. On day 1, 16 of 27 children in the twice-daily group and 11 of 26 children in the thrice-daily group had concentrations that were above 2.0 $\mu\text{g/ml}$ for <50% of the dose interval, and on day 3, 18 of 31 children in the twice-daily group and 8 of 31 children in the thrice-daily group had concentrations that were above 2.0 $\mu\text{g/ml}$ for <50% of the dose interval. Amoxicillin twice-daily is a feasible alternative for thrice-daily dosing. To lengthen the time above the MIC at higher concentration levels, a 30- to 40-mg/kg/dose twice-daily should be considered instead of the 25 mg/kg/dose used in this study.

Efficacy of cotrimoxazole versus amoxicillin twice daily for pneumonia in children¹

This randomized, controlled, double blind trial compared the clinical efficacy of twice daily oral cotrimoxazole with twice daily oral amoxicillin for treatment of childhood pneumonia in outpatient departments of seven hospitals and in one community health service in Pakistan. Children, aged 2-59 months, with non-severe pneumonia were randomly assigned on a 1:1 basis to 25 mg/kg/dose of amoxicillin (n=730) or 4 mg/kg/ trimethoprim and 20 mg/kg sulphamethoxazole (cotrimoxazole) per dose (n=741). Both medicines were given orally twice daily for five days.

Data from 1459 children were analyzed, 725 were randomized to amoxicillin and 734 to cotrimoxazole. The treatment failure in the amoxicillin group was 16.1% as compared to 18.9% in the cotrimoxazole group (OR 0.83, 95%CI 0.63-1.08, p = 0.160). In the multivariate analysis the treatment failure rate was more likely in infants (OR 1.5, 95%CI 1.12-1.91, p= 0.005), who had history of difficult breathing (OR 1.61, 95%CI 1.13-2.15, p= 0.006) or those who had been ill for more than three days before presentation (OR 1.4, 95%CI 1.03-1.8, p= 0.028). They concluded that both amoxicillin and cotrimoxazole provided equally effective therapy for non-severe pneumonia.

Issues with the classification of therapy failure in pneumonia

S. Qazi discussed this issue in light of the high therapy failure results reported from some of the above-mentioned studies. Most of the above-mentioned studies on children with non-severe pneumonia in general used the following criteria for assessment, defining therapy success and failures. At the follow-up visit, “improved” was defined as slower respiratory rate (either back to normal range for age, or lower by more than 5 compared to previous evaluation), eating better and less fever. “Same” was defined as still breathing fast (respiratory rate was ± 5 breaths/minute compared to previous evaluation or higher than that) and no chest indrawing or danger sign. “Worse” was defined as development of severe pneumonia or very severe disease. “Clinical cure” was defined as return of respiratory rate to age specific normal range at day 5 if compliant or at day 7 if non-compliant. “Treatment failure” included any case where antibiotic therapy was changed, was lost to follow-up or

¹ Cotrimoxazole Amoxicillin Trial In Children Under 5 Years For Pneumonia (CATCHUP Study Group). Clinical efficacy of cotrimoxazole versus amoxicillin twice daily for treatment of pneumonia: A randomized controlled clinical trial in Pakistan. Arch Dis Child 2002;86:113-118.

died after enrollment. The treatment was changed if the child was either “same” or “worse.” It was noted that in all of the above trials very few children were “worse”, most of the children who needed treatment change were “same.” Secondly a large number of failures were associated with the presence of wheezing. It is felt that a fair number of children who are being classified as non-severe pneumonia may either have a viral infection, which does not require treatment with an antibiotic. Some of the children who have a viral infection will continue to have fast breathing and lower chest indrawing without being sicker. The same issue would be true for children with wheezing. According to the current WHO ARI guidelines these children are being classified as treatment failures whereas in reality their disease has a self limiting course and does not require a change in therapy to second-line drugs. It was discussed that the current therapy failure criteria need to be made more specific.

Summary of discussion points

The summary also included the issues related to classification of therapy failure in non-severe pneumonia. The following issues were highlighted:

- There is a need to improve the specificity of diagnostic criteria for WHO ARI classification of pneumonia. It would be useful to have higher specificity for the health facilities where better trained staff, such as physicians, was available.
- Some participants raised the issue that the validity of the WHO case definition of pneumonia and treatment failures cannot be addressed unless there are data comparing the efficacy of the currently “Best” available antibiotic with that of a placebo, because this would be the way to determine the maximum expected benefit, if any, of antibiotic therapy in WHO-defined non-severe pneumonia. There was a need to conduct a trial, which compared placebo with currently recommended first-line antibiotics for the treatment of non-severe pneumonia. The high prevalence of radiological pneumonia in the NARIMA study would not justify the use of a placebo. There was a suggestion instead to compare cotrimoxazole with third generation cephalosporin.
- WHO case definition of treatment failure in non-severe pneumonia was not stringent enough and needed to be revised.
- If the children with wheeze are excluded from the cases of pneumonia the rates of treatment failure could decrease.
- There was a need to look at children less than one year of age, as they constitute a special group having a high risk of treatment failure.
- Perhaps lack of knowledge about pneumonia is the reason for some of the problems of case management. There is a need to look into the aetiology of non-severe pneumonia with more sophisticated and meticulous methods, which can help resolve some of the current issues related to ARI case management guidelines.
- There was ample evidence now to suggest that twice a day amoxicillin is as good as three times a day regimen for the treatment of most ARI.
- The potential benefits of a switch-over to a shorter course include reduced costs, better patient compliance and a decrease in antimicrobial resistance in the community. Oral amoxicillin has also been shown to be effective in children having severe pneumonia. One additional advantage of a switch-over to oral amoxicillin could be its usefulness in the treatment of severe pneumonia, especially in situations where referral is difficult. The duration of treatment of non-severe pneumonia should be changed to three days instead of the currently recommended five days.

However, the following points were also made during the discussion for the possibility of a switch-over to a 3-day therapy with first-line antibiotics for non-severe pneumonia:

- Some concern was expressed about 3-day antibiotic therapy being effective in children with non-severe pneumonia in HIV endemic areas, where similar data are not yet available.
- Another concern was using 3-day regimen in children less than 6 months of age, due to the safety issue. It was clarified that data showed that 2-6 months old children had an equal chance of responding to either 3-day therapy or 5-day therapy and that this would not be recommended for children less than 2 months of age.
- A criticism for the switch-over from cotrimoxazole to amoxicillin in malaria-endemic regions was that amoxicillin would not be effective against malaria. It was pointed out that, cotrimoxazole was not recommended as a first-line anti-malarial in any country. Therefore, the switch-over would not effect the treatment of malaria.

Recommendations

- The duration of treatment of non-severe pneumonia should be changed to three days instead of the currently recommended five days, but this recommendation should be evaluated carefully in high HIV endemic areas.
- Oral amoxicillin given twice daily should be used instead of thrice daily for the treatment of non-severe pneumonia.
- More data is needed to evaluate which patients really require a change of antibiotic therapy and what is the right time for such a change.

Wheeze and the specificity of WHO/ARI diagnostic criteria for pneumonia

There is concern that children with wheeze are not being managed properly using current WHO ARI case management guidelines. Most of the children with non-recurrent wheeze probably have a viral infection and hence will not benefit from the use of an antibiotic. Some of these children will benefit from the use of bronchodilators. These children are being classified as pneumonia according to the current WHO ARI case management guidelines. It has long been felt that more information is needed for children who present with wheeze. It was decided in a consultative meeting in 1999 in Geneva to carry out a descriptive study at four sites to collect some baseline information on children with wheeze.

Dr Tabish Hazir from Pakistan and Dr Sorasak Lochindarat from Thailand presented data from “The assessment and management of wheeze in children 1-59 months of age presenting with cough and/or difficult breathing”. They highlighted the fact that the majority of children with wheeze are not being identified using the current WHO ARI guidelines for the management of wheeze. In this multicentre prospective study, children 1-59 months of age with auscultatory/audible wheeze with fast breathing and/or lower chest indrawing were screened. Response to up to three cycles of inhaled salbutamol was recorded. The responders were enrolled and sent home on inhaled bronchodilators and followed up on days 3 and 5. Data on their clinical course was collected. In Pakistan, 1622 children with wheeze were screened, of which 1004 (61.8%) had WHO defined non-severe and 618 (38.2%) severe pneumonia. Wheeze was audible in only 595 (36.7%) of children. Of 1004 non-severe pneumonia children, 621 (61.8%) responded to up to three cycles of bronchodilator. Of 618 severe pneumonia children only 166 (26.8%) responded. Among responders, 93 (14.9%) children in non-severe and 63

(37.9%) in the severe pneumonia group showed subsequent deterioration on follow-ups. Logistic regression identified no family history of wheeze, temperature more than 100°F and severe pneumonia at the time of screening as predictors of subsequent deterioration.

In Thailand, 521 children with wheeze were screened, of which 256 (49.1%) had WHO defined non-severe and 265 (50.9%) severe pneumonia. Wheeze was audible in only 48 (9.2%) children. Of 256 non-severe pneumonia children, 217 (84.8%) responded to up to three cycles of bronchodilator. Of 265 severe pneumonia children 189 (71.3%) responded. Among responders, 14 (6.4%) children in non-severe and 24 (12.7%) in the severe pneumonia group showed subsequent deterioration on follow-ups. Logistic regression identified temperature more than 100°F and severe pneumonia at the time of screening as predictors of subsequent deterioration.

These results verified the previously reported findings that two thirds of children do not have audible wheeze and can only be picked up by the help of a stethoscope. As a result a great majority of children with wheeze are being classified as pneumonia and are being prescribed antibiotics unnecessarily. Bronchodilators are being underutilized in children with wheeze. The results showed that a great majority of children with wheeze who respond to a trial of inhaled bronchodilators continue to do well when sent home without an antibiotic. And those children who have fever and lower chest indrawing along with wheeze have a greater risk of deteriorating on subsequent follow-ups.

Management of recurrent wheeze

The incidence of asthma is rising all over the world and current WHO ARI case management guidelines do not have an effective algorithm for the management of children with recurrent wheeze. Work has been going on for the development of such guidelines. A draft algorithm for wheeze has been developed and was presented in the meeting for information. These algorithms are given as Figures I, II and III. There is a need to evaluate this algorithm in the field.

Summary of discussion on wheezing issues

- Issues of specificity of the clinical criteria used for the diagnosis of non-severe pneumonia were discussed. In this context the first issue discussed was a child with ARI and wheeze. Response to the cycles of inhaled bronchodilators as a tool to distinguish between pneumonia and no pneumonia was criticized. It was argued that children with viral infections will not respond to bronchodilators but that does not provide the justification for the use of an antibiotic in these children. It was suggested that ideally all children with wheeze should not be treated with an antibiotic irrespective of their response to inhaled bronchodilators since most of them are more likely to have a viral infection. It was pointed out that there are ample data to suggest that giving two cycles of inhaled bronchodilators significantly cuts down the rate of unnecessary antibiotic prescription and hospitalization in children with fast breathing and lower chest indrawing.
- Many participants felt that children with wheeze probably have a viral infection. It was suggested that a randomized controlled trial must be done where children with wheeze are given either a placebo or an antibiotic to answer this question, that whether or not to include children with wheezing in the WHO classification of non-severe pneumonia will depend on the outcome of these trials. Considering the reservations some people have about the safety of this trial it was suggested that high-risk children should be excluded from the study. On the other hand it was argued that by excluding such children it will not be possible to identify clinical predictors which can help in identifying high risk children who are more likely to deteriorate subsequently and who probably may need an antibiotic later. Concerns were also raised about the feasibility of such a trial, as it would require a

large sample size, which may be challenging as only a proportion of children presenting as non-severe pneumonia with have wheeze. Furthermore, such a trial would also require children without prior antibiotic use in the illness episode being studied, which may be difficult to establish only with history and would need urine examination to rule out prior antibiotic use.

Figure 1

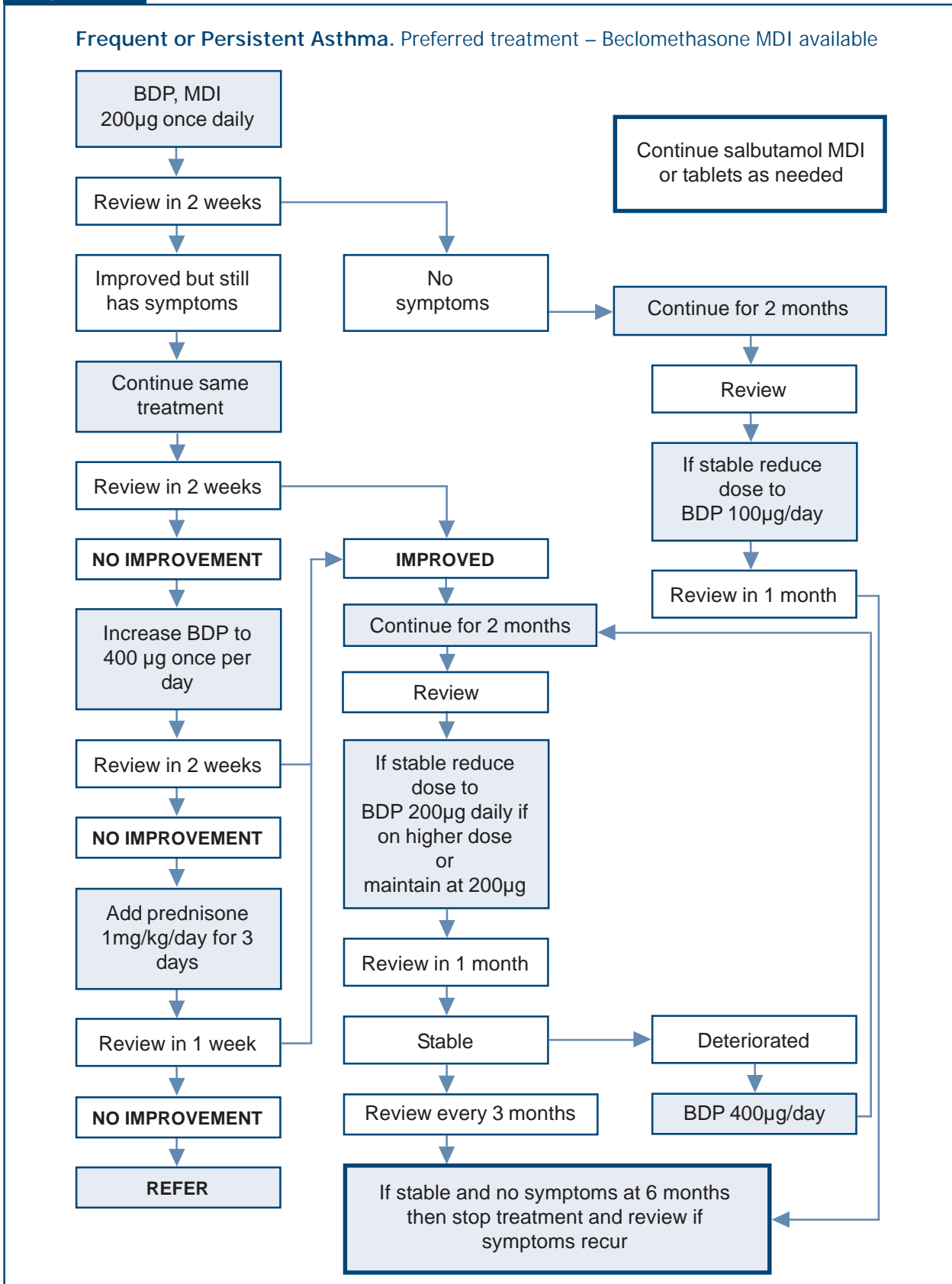
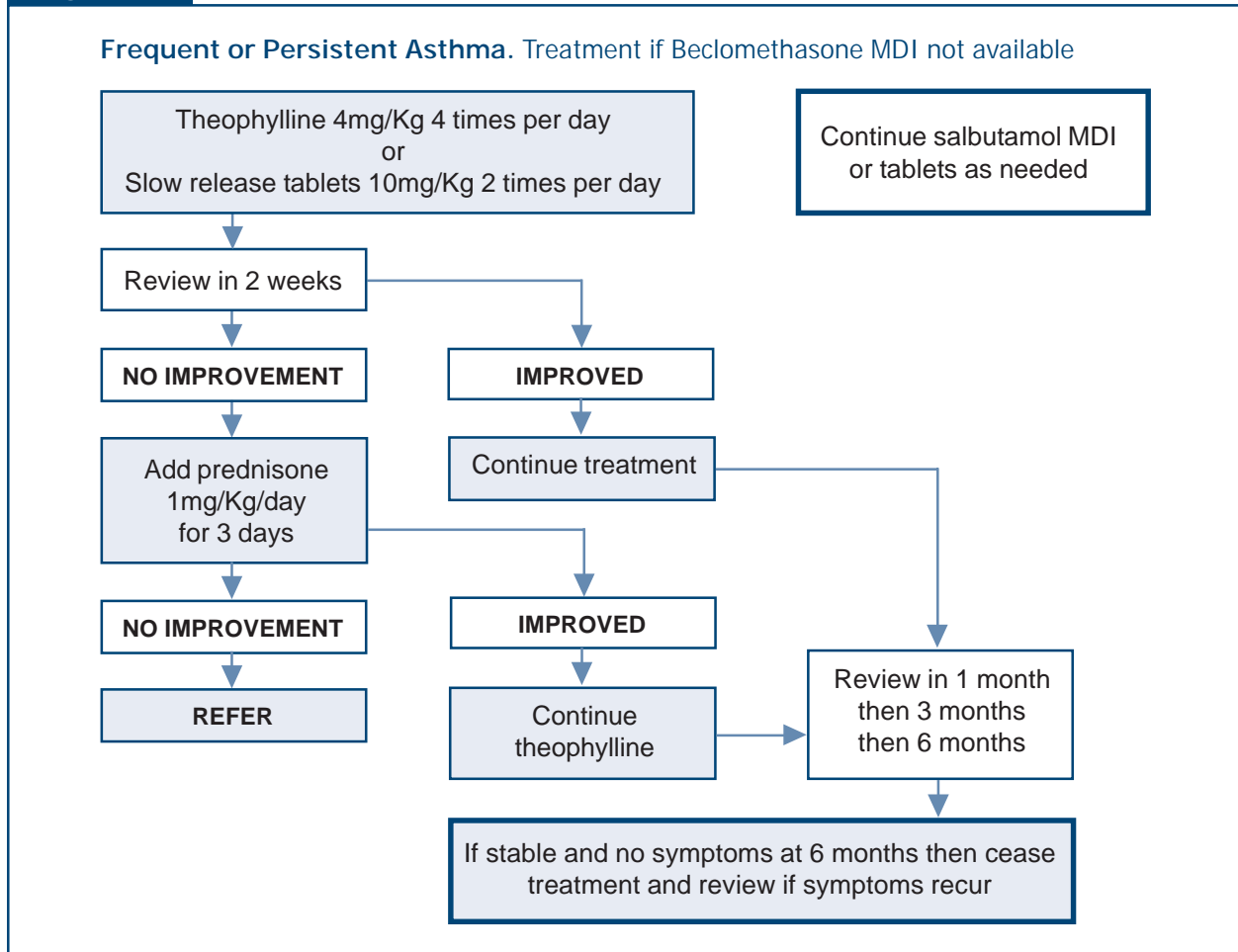


Figure 11



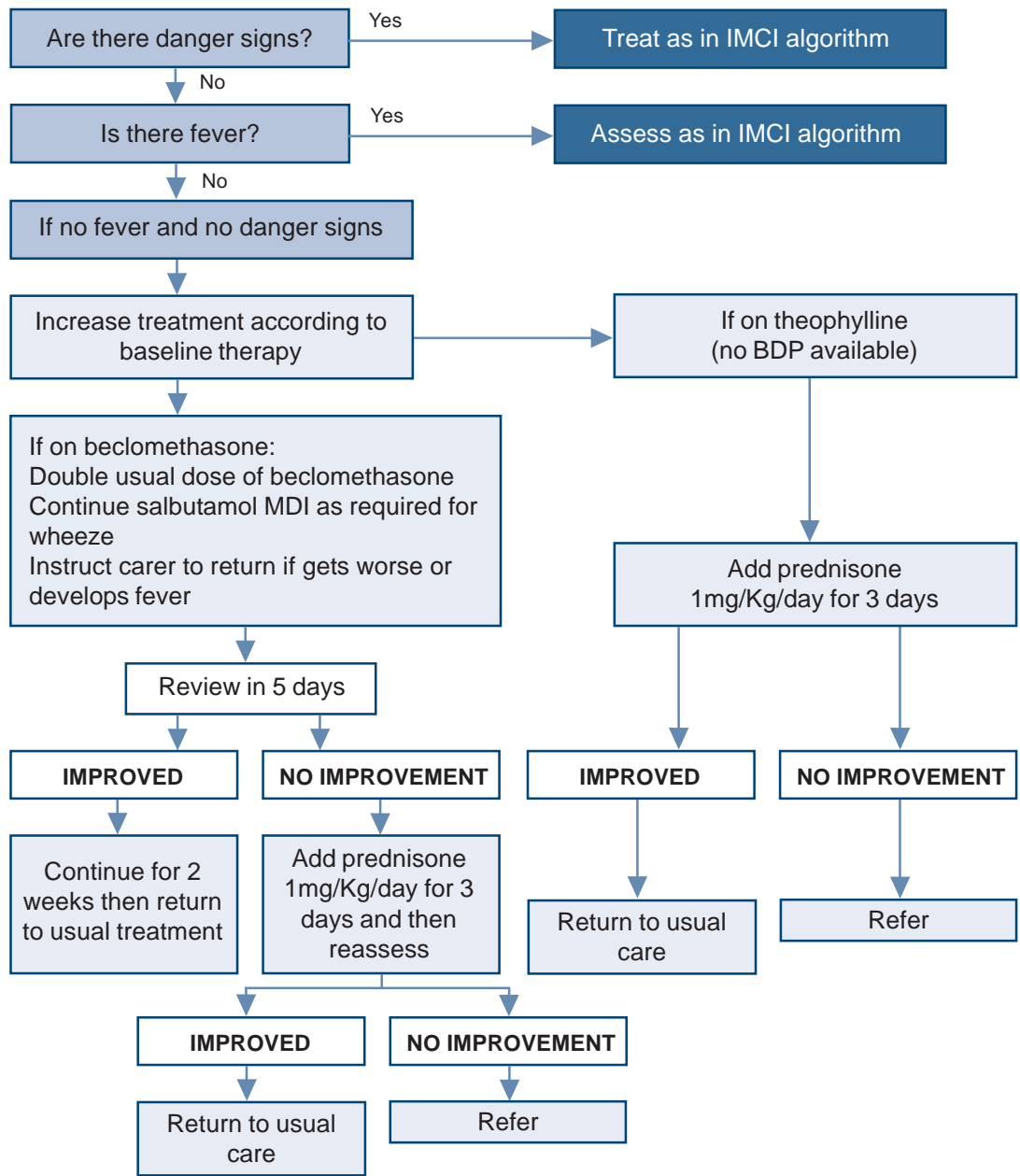
Acute suppurative otitis media

The overview on the treatment of AOM, presented by Ron Dagan, identified some management issues. There is a wide-ranging controversy about the most appropriate management of acute otitis media (AOM). It was pointed out that there is a great deal of variation in the use of antibiotics for treating AOM, from settings where antibiotics are not used to places where they are given routinely for up to 10 days, because of different perceptions of this disease in different regions. In the USA, AOM is considered to be a disease that needs to be treated promptly and adequately. In the Netherlands AOM is considered to be a disease that needs to be treated only if not improving. In the developing world AOM is not generally perceived to be a major health problem. Most of the health facilities in developing countries do not have otoscopes to make diagnosis of AOM. Health workers identify most children only when they have suppurative complications. It was recommended that the diagnosis of AOM be improved and antibiotics withheld if possible. High dose short course antibiotics are preferable and it was emphasized that the otoscopic findings may persist in a child who otherwise is well and these otoscopic findings alone do not justify treatment with an antibiotic. There is a need to develop a consensus on the treatment of AOM. In the meantime the proposed IMCI guidelines should only include the management of acute and chronic suppurative otitis media.

Figure III

Management of acute worsening of symptoms in a child between 2 and 6 years of age with asthma (exacerbation)

Classify as exacerbation if:
 New onset or increased frequency of waking from sleep with wheeze (and cough)
 or
 Increased wheezing and chest tightness needing salbutamol



Group A beta hemolytic streptococcal (GABHS) throat infection

Proper management of two common upper respiratory tract infections (URTIs), i.e. sore throat and middle ear infection, continues to pose problems. Timely diagnosis and treatment of streptococcal sore throat in settings where rapid diagnostic tests are not available is important for reducing the burden of rheumatic heart disease. The current WHO guidelines for the management of sore throat

use certain clinical criteria such as presence of high fever, enlarged cervical lymph nodes and pharyngeal exudates for making the diagnosis of streptococcal sore throat. The sensitivity of these current WHO guidelines is 11.2% to 13.1% and the specificity is 90.4% to 95%. There is a concern that these guidelines miss 90% of the children who actually have GABHS pharyngitis.

Anne Rimoin presented data from a study (GRASP) that evaluated the performance of the WHO prediction rule for the diagnosis of streptococcal sore throat. The main study was carried out in Cairo, Egypt and Zagreb, Croatia. Children between 2-12 years of age seeking care for symptoms of acute respiratory infections in the outpatient clinics were enrolled. It was found that though the WHO criteria were quite specific, its sensitivity was quite low in all the settings evaluated. The data showed that the sensitivity of WHO criteria ranged from .00 to .25. It was concluded that in countries where post-group A streptococcal (GAS) sequelae are important causes of morbidity, physicians might sacrifice specificity for increased sensitivity to avoid missing a true case. It was suggested that physicians may choose different rules depending upon the prevalence of GAS, rheumatic fever and rheumatic heart disease in that particular population. The other component of the study was the “Treatment of Pharyngitis Study” (TOPS), which compared the efficacy of a single dose of intramuscular benzathine penicillin-G with oral amoxicillin for 10 days for the treatment of GABHS pharyngitis in children in low and middle income countries. Children were classified as GABHS positive by rapid antigen test. A total of 248 patients were randomized either to receive 600,000 – 1,200,000 IU of intramuscular benzathine penicillin G (IM BPG) (n=125) or oral amoxicillin (n=123) in a single daily dose. The results of the study showed no difference in treatment success rates between the two antibiotic regimens used. 62/88 (70.5%) in IM BPG group and 63/97 (64.9%) in the oral amoxicillin group had treatment success. One dose treatment with injectable penicillin for sore throat will ensure compliance, reduce the cost of treatment and reduce antimicrobial resistance in the community. It was recommended that larger studies should be undertaken to confirm that IM BPG and oral amoxicillin treatments are comparable in low and middle income country settings and if this dosage of amoxicillin should be included in WHO recommendations for the treatment of GABHS pharyngitis for compliant populations.

The management of severe/very severe pneumonia

According to the current WHO ARI guidelines all children who have lower chest indrawing and/or any of the WHO defined danger signs require referral for hospitalization and treatment with injectable antibiotics. In most developing countries taking the child to a referral facility, especially from a community setting, poses several problems which may lead either to a delay in treatment or no treatment at all. In addition, admission to the hospital means greater costs and the potential side-effects associated with injections.

Oral amoxicillin versus injectable penicillin in children with severe pneumonia¹

Some data exists that oral amoxicillin may be effective against WHO defined severe pneumonia. If oral antibiotic treatment is shown to be as effective as currently recommended injectable therapy for the treatment of severe pneumonia it would become relatively easy to manage on an outpatient basis. Juan Lozano presented data from a multinational, multicentre trial conducted in eight countries. A

¹ Addo-Yobo E, Chisaka N, Hassan M, Hibberd H, Lozano JM, Jeena P, MacLeod WB, Maulen I, Patel A, Qazi S, Thea DM, Vy NNT and APPIS Study group. A randomized multicentre equivalency study of oral amoxicillin versus injectable penicillin in children aged 3 to 59 months with severe pneumonia. (Submitted for publication).

total of 1702 children aged 3-59 months with WHO defined severe pneumonia were enrolled. Patients were randomly assigned to injectable penicillin (n=857) or oral amoxicillin (n=845). The primary outcome was treatment failure. Treatment failed in 187 (21.8%) patients in the injectable penicillin group, and 185 (21.8%) in the oral amoxicillin group. In 26 (3.0%) children in the injectable penicillin group and in 39 (4.6%) in the oral amoxicillin group the disease relapsed. The results showed that the clinical outcome with oral amoxicillin was comparable to injectable penicillin in hospitalized children with severe pneumonia.

Antibiotic resistance of *S. pneumoniae* from children with severe pneumonia

Regina Cardoso presented data from the “Latin American multicentre study on antibiotic resistance of *S. pneumoniae* isolated from children with severe pneumonia”, which looked at the association of antimicrobial susceptibility *S. pneumoniae* with the risk of clinical treatment failure. A total of 289 pneumococcal isolates were identified from children aged 3-59 months presenting with history of cough and/or difficult breathing with lower chest indrawing (i.e., severe pneumonia). Antimicrobial susceptibility of *S. pneumoniae* was found to be susceptible in 47.1%, intermediate susceptibility in 23.9% and resistant in 20.4%. There was no relationship of clinical treatment failure with *in vitro* penicillin resistance. However, additional analyses are in progress to look at some other aspects of this study.

Chloramphenicol versus penicillin and gentamicin in very severe pneumonia¹

WHO currently recommends chloramphenicol for the treatment of very severe pneumonia. Up to 20% of children receiving chloramphenicol for severe pneumonia fail treatment. An alternative to chloramphenicol at similar costs could be injectable penicillin plus an amino-glycoside. Both treatment options will have a good cover in the blood or the lungs against sensitive strains of *S. pneumoniae* and *H. influenzae*. Some patients with severe pneumonia may have meningitis, which may not be clinically evident at presentation. Chloramphenicol penetrates the blood brain barrier effectively whereas gentamicin does not. *Staphylococcus aureus* may be a common pathogen causing treatment-unresponsive severe pneumonia, and may be more susceptible to chloramphenicol than to gentamicin. On the other hand a major advantage of a penicillin-amino glycoside combination is that it is likely to provide superior treatment of enteric gram negative bacilli. Trevor Duke presented data from a trial in Papua New Guinea. These aimed to establish whether the combination of benzylpenicillin and gentamicin or chloramphenicol would be better as first-line treatment in children with severe pneumonia in an open randomized trial in which 1116 children aged 1 month to 5 years of age were enrolled who fulfilled the WHO criteria for very severe pneumonia. Children were randomly assigned to receive chloramphenicol (25 mg/kg 6 hourly) or benzylpenicillin (50 mg/kg 6 hourly) plus gentamicin (7.5 mg/kg daily) by intramuscular injection. The primary outcome measure was a good or an adverse outcome. 559 children were treated with chloramphenicol and 557 with benzylpenicillin and gentamicin. At presentation the median haemoglobin oxygen saturation was 71% (IQR 57-77) for those allocated chloramphenicol and 69% (55-77) for those allocated penicillin and gentamicin. 147 (26%) children treated with chloramphenicol and 123 (22%) treated with penicillin and gentamicin had adverse outcomes (p=0.11). 36 children treated with chloramphenicol and 29 treated with penicillin and gentamicin died. More children treated with chloramphenicol than penicillin and gentamicin represented with severe pneumonia within 1 month of hospital discharge (p=0.03). They concluded that for children with severe pneumonia in less-developed countries the probability of a good outcome is similar if treated with chloramphenicol or with the combination of benzylpenicillin and gentamicin.

¹ Duke T, Poka H, Dale F, Michael A, Mgone J, Wal T. Chloramphenicol versus benzylpenicillin and gentamicin for the treatment of severe pneumonia in children in Papua New Guinea: a randomised trial. *Lancet*. 2002;359:474-80.

Neonatal pneumonia in developing countries

T. Duke presented an overview of neonatal pneumonia in developing countries. It highlighted the problems in understanding the burden and aetiology of this condition. There were difficulties in distinguishing pneumonia from other non-infective respiratory conditions of the newborn, specially, where laboratory and radiological investigations are limited. The literature on the aetiology of neonatal pneumonia is influenced by the predominance of studies that include nosocomial pneumonia in neonatal intensive care units in western countries. Several reasons were given as to why interventions that only function in the hospitals will make little impact on deaths from neonatal pneumonia. It was also felt that there is a lack of sufficient information and more local data is needed before developing intervention strategies for sick neonates. It was concluded that efficient interventions must be targeted at all levels of the health service and community. Interventions that will reduce mortality from neonatal pneumonia will have a large range of general positive effects: improve maternal health, better management of other common neonatal conditions and reduced long-term childhood and adult morbidity.

Efficacy of zinc supplements in severe pneumonia

Zinc has been reported to prevent ALRI since it is part of an acute phase response to stress, inflammation and infections. Zinc supplement, therefore, might help in reducing the acute phase of respiratory illness resulting in decreased duration of the severity, hospitalization and a decreased treatment failure rate in severe pneumonia. Abdullah Brooks presented data from 'Efficacy of zinc as an adjuvant in the management of severe pneumonia in children < 2 years old'. Out of 270 children enrolled, 135 (50.0%) were randomized to zinc and 135 (50.0%) to placebo groups. It showed that 20 mg/day of zinc supplementation during the acute phase of severe pneumonia can decrease the duration of severity of pneumonia, reduce treatment failure rates and duration of hospitalization when compared with a placebo. It was shown to be especially beneficial in non-wheezers.

Summary of discussion on severe pneumonia

- Previously published data also shows convincingly that *in vitro* resistance does not have a consistent relationship with clinical treatment failures for pneumonia.
- The switchover from injectable antibiotics to oral amoxicillin for the treatment of severe pneumonia will be beneficial from a practical point of view. Oral therapy gives an option to the health worker at the first level health facility to start the treatment for severe pneumonia at the health facility rather than to refer to a district hospital. This would certainly have many advantages especially in situations where parents are reluctant to take the child to the referral facility.
- It was argued that the trial of oral amoxicillin for severe pneumonia was conducted in a controlled environment, where these children were monitored very closely by the study staff. Therefore, it might not be safe to treat severe pneumonia in the community on an outpatient basis, so some safety issues need to be addressed before a switchover to oral therapy is recommended. The question of sending children home with hypoxemia could not be addressed by the APPIS trial. Furthermore, the mild hypoxemia could only be picked up by using pulse oximetry and in settings where pulse oximetry is not available, sending these children home might not be safe. Moreover, there were reasons for hospitalization other than the administration of injectable antibiotics, like oxygen therapy or need for additional observation or to ensure adherence to therapy.

- Some further analysis is needed from the APPIS trial data about clinical features of hypoxemic children to identify predictors of severe hypoxemia and thus hospitalization. Relationship of hypoxemia and therapy failure should be looked at in more detail. It is also necessary to have a further look at the children who were excluded from APPIS study.
- There is a need to collect information from the hospitals in the developing countries regarding the availability of oxygen, and the prevailing practices for oxygen administration.
- One suggestion was to carry out a trial in which half the patients are hospitalized and the other half are sent home on oral amoxicillin and then comparing the outcome at 48 hours.
- In high malaria endemic areas, in children who have overlapping clinical signs of severe malaria and severe pneumonia may need to be observed at a health facility and it may not be safe to send them home.
- There is a need to have more data from the zinc efficacy trials before making any definitive recommendations.
- It was recommend that there is was a need to conduct two studies in the community setting, one with and one without pulse oximetry, before any recommendations to change to oral amoxicillin for the treatment of severe pneumonia could be made. It was recommended that pulse oximetry readings should not influence the decision about the use of antibiotics.

Hypoxemia and pneumonia mortality

Mark Steinhoff presented the overview on “Role of hypoxemia on pneumonia mortality”. It very convincingly demonstrated that the risk of mortality is 2-4 times higher in children having hypoxemia. It was also demonstrated that the severity of hypoxemia is directly proportional to the risk of death due to ARI. It was argued that hypoxemia can serve as a reliable predictor of mortality. Various clinical signs have been evaluated for their predictive value for hypoxemia. Current WHO clinical guidelines for oxygen therapy predicts $\text{SaO}_2 < 90\%$ with 62% sensitivity and 76-82% specificity. The clinical criteria for the new proposed guidelines for oxygen therapy include central cyanosis, inability to feed or vomiting, convulsions, lethargy/unconsciousness and head-nodding.

Summary of discussion

- Feasibility of oxygen therapy in settings with limited resources was discussed. The expense, difficulty, and relative complexity of oxygen therapy in low-resource settings suggest that the use of oxygen requires careful study before it is widely recommended for use in these settings. It was recommended that a pragmatic assessment of best strategies for oxygen therapy in a variety of settings is needed. Information about the availability and delivery of oxygen and its use in low-income country hospital settings needs to be collected.
- The utility of pulse oximetry for optimizing oxygen therapy in the clinical setting should be studied.
- Good evidence needs to be generated to show the impact of oxygen therapy on pneumonia related mortality, for which studies need to be designed. A potential design could be applied before and after provision of appropriate and adequate oxygen therapy
- Co-existing hypercapnia needs to be looked at in addition to the hypoxemia.
- Altitude should be taken into account when recommendations on the use of oxygen in hypoxemia are developed.

Pneumonia and HIV

Failure of standard WHO antimicrobial therapy among children with mild or asymptomatic HIV and severe pneumonia¹

Prakash Jeena presented some data from this study which determined if children 3-59 months of age with WHO-defined severe pneumonia and mild or asymptomatic HIV-infection have a higher failure rate when treated with the standard WHO treatment of parenteral penicillin or oral amoxicillin compared with HIV uninfected children. This was a subgroup analysis of data from two sites in Durban, South Africa and Ndola, Zambia. Clinical treatment failure at 48 hours and 14 days were assessed in 523 children enrolled at the two sites, of which 464 were tested for HIV infection and only 106 were HIV-infected. Fifty-seven (12.3%) children were treatment failures at 48 hours and 110 (23.7%) failed (cumulative) at 14 days. Twenty (18.9%) HIV-infected children failed at 48 hours compared with 37 (10.3%) uninfected children (RR 1.83 95% CI 1.11 – 3.01). HIV-infected children were 1.7 (95% CI 0.52 – 5.26) times more likely to relapse at day 14 and 2.3 (RR 95% CI 0.65 – 7.83) times more likely to die as uninfected children. The detection rates from the nasopharynx of *S. pneumoniae*, *H. influenzae* and RSV detection rates were 54.1%, 27.5% and 13.9%, respectively. They concluded that HIV-infected children with severe pneumonia fail WHO-standard treatment (or equivalent) at 48 hours more often than do HIV-uninfected children and that the addition of cotrimoxazole early in the course of treatment for these cases should be considered.

Management of children with pneumonia and HIV infection²

Keith Klugman who chaired the “Consultative meeting on management of children with pneumonia and HIV infection” held in Harare, presented a brief summary of the guidelines for the management of pneumonia in HIV endemic areas and other recommendations made during that meeting. Priority research areas identified during that meeting included the evaluation of first- and second-line antibiotics, emergence of cotrimoxazole resistance, evaluation of pattern of pneumocystis resistance, evaluation of current WHO/UNAIDS cotrimoxazole prophylaxis guidelines and compliance, assessing the effectiveness of steroids, developing inexpensive and rapid tests for the diagnosis of pneumocystis and tuberculosis and evaluating the impact of the vaccination. Some other recommendations included provision of HIV testing for children, evaluation for the diagnosis of tuberculosis, PCP prophylaxis, nutritional interventions provision of Hib and pneumococcal vaccinations etc.

Overlap of clinical signs and management of pneumonia and malaria

Mike English highlighted difficulties associated in diagnosing pneumonia in highly endemic areas for malaria due to an overlap in clinical signs. He showed that due to the high sensitivity required for the diagnosis, clinical discrimination of malaria and mild pneumonia at the outpatient level is impractical. It is also not possible to definitively discriminate clinically between the respiratory distress due to

¹ Jeena P, Chisaka N, Thea DM, MacLeod WM, Coovadia HM, Qazi S and the Amoxicillin Penicillin Pneumonia International Study (A.P.P.I.S. Group). Failure of standard antimicrobial therapy among children 3 to 59 months of age with mild or asymptomatic HIV infection and severe pneumonia (submitted for publication)

² World Health Organization. Report of a consultative meeting on management of children with pneumonia and HIV Infection 30-31 Jan 2003 Harare, Zimbabwe.

malaria and severe pneumonia. It was recognized that malaria is being over-treated and there was a need to streamline malaria management. Trustworthy diagnostics for malaria might prevent use of an anti-malarial but the issue of “hidden malaria” would need to be addressed. The value of reliable malaria diagnostics was identified as a priority research area.

Community management of ARI

Lulu Muhe informed the meeting participants about the deliberations from a consultative meeting held in June 2002 in Stockholm on the issue of community management of ARI¹. He also informed about the ongoing review on “Community health-worker programmes and the management of sick children” and the preparation of a “WHO-UNICEF Joint Statement on Management of Pneumonia in Community Settings”, that would help the country programmes in management of ARI.

Summary of discussion on malaria/ARI and community management of ARI

- It was mentioned that there is a perception among Ministry of Health (MOH) policy makers that there is no evidence to support case management of pneumonia, as opposed to malaria.
- There is a need to update existing guidelines for ALRI as well as clinical overlap with malaria.
- There is a need to develop an intervention for home/community management of malaria/pneumonia that achieves high coverage and is sustainable.

Impact of vaccinations on ARI

Kim Mulholland presented an overview of Hib and pneumococcal vaccines trials. The Hib vaccine trial from The Gambia included 42,000 children. It showed a 100% vaccine efficacy (VE) for Hib-proven pneumonia and 20% VE for radiological pneumonia. The Chile Hib trial showed a VE of 20% for radiological pneumonia. Finally, the Lombok Hib field trial had 55000 children and showed no impact on the incidence of radiological pneumonia or pneumonia related deaths. However, there was an impact on the clinical meningitis. Pneumococcal 23 valent polysaccharide vaccine has shown significant impact on clinical pneumonia and mortality in children in Papua New Guinea. Pneumococcal 7 valent conjugate vaccine has been shown to be effective against invasive disease but is quite expensive. In South Africa pneumococcal 9 valent conjugate vaccine has shown 25% reduction in pneumonia. The trial in The Gambia is ongoing. All pneumococcal vaccines have shown an impact on the carriage rate of vaccine serotypes and also a decrease in the circulation of antibiotic resistant strains.

Summary of discussion

- The impact of vaccines on clinical, radiological pneumonia and death is not completely known but probably will not be very large.

¹ World Health Organization. Meeting report from “Evidence base for community management of Pneumonia” consultation. June 11-12, 2002, Stockholm, Sweden. Department of Child and Adolescent Health and Development. World Health Organization. WHO/FCH/CAH/02.23. http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/WHO_FCH_CAH_02.23.pdf

- It was also stressed that the effect of vaccines will be temporary unless accompanied by global reduction in antibiotic use.
- Research is needed for a better understanding of aetiology and pathophysiology of pneumonia.
- There is a need to look into pneumonia deaths in depth. Mortality patterns for pneumonia need to be studied, as relatively little is known about these deaths.
- WHO should adopt a more holistic approach, drawing together vaccine, nutritional and case management approaches.

The ecology of antibiotic resistance: the case of *S.pneumoniae*

R. Dagan stressed that improper use of an ineffective antibiotic can have a significant effect on antimicrobial resistance in the community. The issues of dual and multiple drug resistance and the use of long-acting antibiotics such as macrolides were elaborated upon. It was stressed that in order to reduce antibiotic resistance it is important to reduce not only antibiotic use but also use antibiotics that are safer to the environment.

Recommendations for changes in the current IMCI/ARI guidelines

Non-severe pneumonia

- Three days of antibiotic therapy with WHO recommended first-line oral antibiotics (amoxicillin and cotrimoxazole) could be implemented in countries where HIV is not a major public health problem.
- Oral amoxicillin is the better choice in countries where antimicrobial resistance to cotrimoxazole is high, in high HIV prevalence countries where cotrimoxazole is recommended for PCP prophylaxis and in countries where sulphadoxine-pyramethamine (Fansidar) is recommended for malaria.
- Oral amoxicillin should be recommended twice daily instead of thrice daily.
- Children presenting with wheeze and pneumonia should be given a trial of rapid acting bronchodilator (where feasible) before an antibiotic is prescribed.

Severe pneumonia

- If HIV infection is clinically suspected or the child is HIV-positive, routine WHO ARI case management for severe pneumonia should not be used. WHO draft treatment guidelines for management of children with pneumonia and HIV infection should be followed instead.

Otitis media

- It was recommended that only treatment of acute and chronic suppurative¹ otitis media should be included in the generic IMCI guidelines.
- Oral amoxicillin is a better choice for management of suppurative otitis media in countries where antimicrobial resistance to cotrimoxazole is high.

¹ Only pain in the ear should not be used to treat with antibiotics

Recommendations for further research

Non-severe pneumonia

- Improve the specificity of clinical diagnostic criteria.
- In light of the overall high therapy failure rates, reassess the current WHO recommended treatment failure criteria for non-severe pneumonia.
- Re-analyze data from short course therapy studies to better identify the determinants of treatment failures.
- In some special settings with high prevalence of wheezing, a placebo controlled trial in children presenting with wheeze and pneumonia is recommended to see whether children with wheezing need an antibiotic.

Severe pneumonia

A randomized clinical trial (APPIS group) in a controlled environment showed oral amoxicillin to be equivalent in efficacy to injectable penicillin/ampicillin for therapy. However, before it can be recommended on a general basis the following actions need to be taken.

- Analyze the data on exclusions from the APPIS trial. Identify predictors, which can help identify children who require hospitalization and who subsequently deteriorate.
- In light of the overall high therapy failure rates, reassess the current WHO recommended treatment failure criteria for severe pneumonia.
- Descriptive studies in several centres around the world should be conducted in a public health setting to evaluate clinical outcome to oral amoxicillin in children 2-59 months old presenting with lower chest indrawing.
- Effectiveness of WHO drafted treatment guidelines for management of children with pneumonia and HIV infection should be documented.

Pneumonia deaths

- The epidemiology of pneumonia deaths in various geographical regions should be studied in detail, including social and verbal autopsies and making use of routine and advanced laboratory techniques. This will help develop more effective interventions to reduce pneumonia mortality.

Oxygen therapy

- In order to show the effectiveness of oxygen for the management of severe respiratory infections, studies should be carried out and a potential design could be application of before and after provision of appropriate and adequate oxygen therapy.
- Baseline information about the availability and delivery of oxygen and its use in low-income country hospital settings needs to be collected.
- Explore the utility of pulse oximetry for optimizing oxygen therapy in clinical settings.

Clinical overlap of pneumonia and malaria

- Studies to improve the specificity of clinical overlap for malaria and pneumonia diagnosis should be undertaken. Rapid diagnostic tests for malaria should be studied to differentiate malaria from pneumonia.
- The impact of the widespread use of cotrimoxazole on sulphadoxine-pyramethamine resistance to *Plasmodium falciparum* should be studied.

Aetiology

- The data about aetiology of pneumonia in children is old. New aetiology studies are needed, using more modern technology.

Recurrent wheeze

- The draft algorithm for management of recurrent wheeze should be evaluated.

List of participants

Annex 1

Participants

Richard Adegbola	Medical Research Council, The Gambia
Shams-el -Arifeen	International Centre for Diarrhoeal Diseases Research, Bangladesh
Shally Awasthi	King Edward Medical College, India
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Kim Mulholland	Royal Children's Hospital, Australia
Kusum Nathoo	University of Zimbabwe, Zimbabwe
Qayyum Noorani	Aga Khan Foundation, Pakistan
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* Unable to attend

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Hans Troedsson	Director, Department of Child and Adolescent Health and Development (CAH)
Martin Weber	Department of Child and Adolescent Health and Development (CAH)

* Unable to attend

Agenda

Annex 2

DAY 1

8.45-9.00	Registration	
9.00-9.15	Welcome and Introductions	Director, CAH
9.15-9.30	Objectives of the meeting/Overview of the agenda	S. Qazi

Setting the stage

9.30-9.45	Epidemiology of pneumonia and issues with defining pneumonia Discussion (10 minutes)	H. Campbell
9.55-10.10	Issues with diagnosis of pneumonia: radiology and other diagnostic techniques Discussion (10 minutes)	T. Cherian
10.20-10.40	Coffee/Tea break	

OBJECTIVE 1: Review data/evidence recent ARI studies

Non severe pneumonia

10.40-11.10	Three vs. five days oral amoxicillin for non-severe pneumonia (Multicentre studies from India and Pakistan)	S. Awasthi/T. Hazir
11.10-11.40	Three versus five days oral cotrimoxazole for non-severe pneumonia (Bangladesh and Indonesia)	C. Kartasmita/S. Saha
11.40-12.05	Clinical outcome following amoxicillin treatment of non-severe pneumonia	D. Thea
12.05-12.20	Monitoring tool to determine the outcome for non-severe pneumonia	Q. Noorani
12.30-14.00	Lunch break	
14.00-14.20	Summary results from <ul style="list-style-type: none"> ■ Twice a day amoxicillin vs. cotrimoxazole for non-severe pneumonia ■ Standard vs. double dose cotrimoxazole for non-severe pneumonia ■ Standard versus double dose of oral amoxicillin pharmacokinetic study for pneumonia 	
	Issues with the classification of therapy failure in pneumonia	S. Qazi
14.20-15.20	Discussion and summary (possible revisions in case management and research recommendations)	
15.20-15.40	Coffee/Tea break	

Wheezing/pneumonia and upper respiratory infections

15.40-16.10	Assessment/management of wheeze with fast breathing and/or lower chest indrawing (Thailand and Pakistan)	T. Hazir/S. Lochindrat
16.10-16.30	Management of recurrent Wheezing	M. Weber
16.30-17.00	Clinical prediction instrument and randomized trial of intramuscular vs. oral antibiotics for GABHS pharyngitis	A. Rimoin
17.00-17.15	Antibiotic therapy for acute otitis media	R. Dagan
17.15-18.00	Discussion and summary (possible revisions in case management and research recommendations)	

DAY 2

OBJECTIVE 1: Review data/evidence recent ARI studies (continued)

Severe/very severe pneumonia

9.00-9.25	Efficacy of oral amoxicillin vs injectable penicillin in severe pneumonia	J. Lozano
9.25-9.50	Pneumococcal resistance vs. clinical outcome in severe pneumonia A multicentre study from five Latin American countries	R. Cardoso
9.50-10.25	Efficacy of chloramphenicol vs. penicillin + gentamicin in the severe pneumonia in Papua New Guinea	T. Duke
10.25-10.45	Coffee/Tea break	
10.45-11.05	WHO case management guidelines for severe pneumonia in high prevalence HIV settings	P. Jeena
11.05-11.30	Role of hypoxemia on pneumonia mortality	M. Steinhoff
11.30-11.55	Neonatal pneumonia: aetiology, antimicrobial susceptibility, prevention and treatment	T. Duke
11.55-12.10	Role of zinc in severe pneumonia	A. Brook
12.10-13.00	Discussion and summary (possible revisions in case management and research recommendations)	
13.00-14.00	Lunch break	

Setting the context

14.00-14.25	Overview of Hib and pneumococcal vaccines and cost effectiveness of interventions	K. Mulholland
14.25-14.50	Ecology of antimicrobial resistance (Effects of antibiotics vs. conjugate vaccines on antibiotic resistance)	R. Dagan
14.50-15.15	Community management of ARI (Stockholm meeting, CHW review, TDR malaria/pneumonia treatment)	L. Muhe
15.15-15.40	Guidelines for therapy of pneumonia in children exposed to HIV (Briefing on Harare meeting report)	K. Klugman
15.40-16.00	Coffee/Tea break	
16.00-16.20	Overlap of clinical signs and management of pneumonia and malaria	M. English
16.20-17.30	Discussion and summary of this session	

DAY 3

Possible revisions in the ARI/IMCI case management guidelines

9.00-9.30	Summaries from previous sessions including possible revisions in guidelines and future research issues	Rapporteurs
	<ul style="list-style-type: none"> ■ Non-severe pneumonia session ■ Wheezing/pneumonia and upper respiratory infections session ■ Severe pneumonia session ■ Setting the context session 	
9.30-10.30	Discussion	
10.30-11.00	Coffee/Tea break	
11.00-12.30	Discussion continued	
12.30-12.45	Summary of possible modifications in case management guidelines and recommendations	L. Muhe
12.45-14.00	Lunch break	

OBJECTIVE 2: Identify gaps in knowledge and suggest research areas for the future

14.00-15.30	Identify research needs and ways to address them
15.30-15.50	Coffee/Tea break
15.50-17.00	Summary, conclusions and recommendations