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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 orking 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 Group[1] in Pakistan and the ISCAP Study Group[2] 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