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PROGRAMME FOR THE CONTROL OF
ACUTE RESPIRATORY INFECTIONS

SURVEILLANCE OF ANTIMICROBIAL RESISTANCE
OF STREPTOCOCCUS PNEUMONIAE AND HAEMOPHILUS INFLUENZAE

Report of a Meeting
(Geneva, 10-13 December 1990)

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1. INTRODUCTION

Acute respiratory infections (ARI) are a major cause of mortality in children in developing countries, accounting for 25-30% of childhood deaths. Over half of all pneumonia deaths occur in infants, mortality being especially high during the first 2 months of life. Morbidity is also substantial, the annual incidence of pneumonia in children under 5 years being between 10% and 20%. Factors that may contribute to the high incidence of pneumonia in children in developing countries include malnutrition, low birth weight, and high levels of nasopharyngeal colonization with pathogenic organisms.

Most episodes of pneumonia in developing countries have a bacterial etiology. Lung punctures are positive for bacterial pathogens in about 60% of children who present to hospitals with community-acquired pneumonia that has not received prior antibiotic treatment. In addition, many children with a viral isolate have evidence of bacterial co-infection. The major bacterial pathogens isolated from children with pneumonia are Streptococcus pneumoniae and Haemophilus influenzae, which together account for approximately 80% of isolates.

Strategies to reduce morbidity due to pneumonia in children in developing countries include: improving nutrition, increasing child spacing, increasing birth weight, and immunization against measles and pertussis. The primary intervention to prevent mortality from pneumonia in children is early diagnosis and appropriate antimicrobial treatment. Protocols for the case management of children with cough or difficult breathing have been developed by the WHO Programme for the Control of Acute Respiratory Infections (ARI). These include the use of easily recognized signs of pneumonia for diagnosis (fast breathing, lower chest wall indrawing) and empirical antibiotic therapy aimed at the most likely pathogens. The primary goal of the WHO ARI Programme is to have national programmes established in all countries with an infant mortality rate greater than 40 per 1000 live births by 1995.

Antimicrobial resistance in S. pneumoniae and H. influenzae may reduce the effectiveness of the case management strategy by rendering antimicrobial therapy useless. Organisms resistant to penicillin, ampicillin, cotrimoxazole, and chloramphenicol have been reported from countries throughout the world. To address this problem, the WHO ARI Programme decided to develop a system of surveillance for antimicrobial resistance that could be incorporated into national ARI control efforts.

Accordingly, a working group was convened in Geneva, Switzerland, in December 1990 to address the following questions:

- (1) What would be the best system for conducting surveillance of antimicrobial resistance?
- (2) Can nasopharyngeal isolates be used in surveillance as an alternative to isolates from normally sterile fluids?
- (3) What are the optimal microbiological tests for determining resistance to S. pneumoniae and H. influenzae?
- (4) What relationship is there between laboratory measures of resistance and the clinical efficacy of therapy?
- (5) What research is needed to guide further efforts to establish surveillance of antimicrobial resistance?

2. USE OF NASOPHARYNGEAL ISOLATES FOR SURVEILLANCE

The most accurate way of measuring resistance patterns in the organisms that cause pneumonia is to obtain lung puncture isolates from children with infection. However, the degree of technical expertise required and the potential complications limit the use of this procedure in clinical settings. Cultures of blood or other normally sterile fluids (pleural or cerebrospinal fluid) provide the best approximation for the strains that cause pneumonia. Unfortunately, only 10-35% of children with pneumonia will be bacteraemic and culturing blood specimens is difficult and costly. It would be desirable to use upper respiratory tract cultures for surveillance since these specimens are easier to obtain, the yield is substantially greater, and the cost is less. The advantages and disadvantages of the two sources of isolates are summarized in Table 1. In deciding on technical recommendations for national surveillance activities, issues of feasibility have a strong influence. The surveillance system must generate useful information of reasonable validity that will enable countries with national ARI control programmes to establish guidelines for antimicrobial treatment.

Table 1

Advantages and disadvantages of nasopharyngeal and invasive strains for surveillance of the antimicrobial resistance of respiratory bacteria

	NASOPHARYNGEAL STRAINS	INVASIVE STRAINS
Obtaining samples	<ul style="list-style-type: none"> ■ Easy procedure ■ Feasible for the collection of large numbers of samples ■ Transport in Amies within 48 hours ■ More acceptable to mothers 	<ul style="list-style-type: none"> ○ Skilled procedure to lower risk of contamination; venipuncture may lead to complications ○ Difficult outside large hospitals ○ Transport for sub-culturing must take place within 18 hours ○ Mothers may refuse ○ Health risk to blood drawer and to laboratory worker
Laboratory	<ul style="list-style-type: none"> ○ Isolation technically more demanding than for invasive strains ■ Microbiological expertise needed only at central laboratory 	<ul style="list-style-type: none"> ○ Microbiological expertise on site or nearby required (within 18 hours)

- Advantages
- Disadvantages

A decision regarding the suitability of upper respiratory tract isolates for the surveillance of bacterial drug resistance must be based on data showing that these isolates are similar in type and resistance pattern to invasive isolates. Few good studies that have examined this correlation in respect of S. pneumoniae have been published.¹ Most of the comparisons made were based only on capsular type because susceptibility testing of invasive and nasopharyngeal strains was not available. Gray et al.² found no substantial differences between carried and invasive isolates other than for type 14, which was isolated more frequently from invasive sites. Other studies had methodological problems which made comparisons difficult; however, in general the types were found to be comparable for invasive and carried strains, only type 14 being consistently more invasive. While these data suggest that upper airway isolates may be appropriate for surveillance, further studies are needed.

There is more published evidence to suggest a similarity between invasive and upper airway isolates of H. influenzae.³ Six studies reported ampicillin susceptibility in upper airway isolates of H. influenzae type b and non-type b (including noncapsulated strains and other capsular types). In four of these studies a comparison was made with invasive isolates. In general, resistance to ampicillin differed significantly between type b and non-type b isolates from either invasive or non-invasive sites. However, in no instance did the rate of resistance differ significantly between type b isolates at carried or invasive sites and non-type b isolates at carried or invasive sites. These data suggest that if surveillance results are stratified for type b and non-type b, the resistance patterns of upper airway isolates adequately reflect those of invasive isolates.

In an unpublished study conducted in Islamabad-Rawalpindi, Pakistan, in 1989-1990⁴ (the only one designed specifically to address this question), specimens were obtained from 612 children between the ages of 2 and 59 months who presented to hospital with cough or difficult breathing. They were divided into three groups: children with fast breathing but no chest indrawing (classified as "pneumonia" according to the WHO guidelines); children with chest indrawing or danger signs ("severe pneumonia" or "very severe disease"); and children without any of these signs and a rectal temperature of 39°C or greater. In addition, 133 healthy children from urban areas and 300 healthy children from rural areas were enrolled in the study.

The overall bacteraemia rate was 37% in the three groups of sick children (18% for S. pneumoniae, 17% for H. influenzae, and 2% for other bacteria). The carriage rate in all groups averaged 60% for S. pneumoniae and nearly 40% for H. influenzae.

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- 1 Mastro, T. The comparability of upper airway tract and invasive isolates of Streptococcus pneumoniae. To be published.
 - 2 Gray G.M. et al. Serotypes of Streptococcus pneumoniae causing disease, Journal of Infectious Diseases, 1979, 140: 979-983.
 - 3 Schwartz, B. Surveillance for antimicrobial-resistant Haemophilus influenzae using pharyngeal isolates: A review of the literature and a surveillance strategy. To be published.
 - 4 Children with acute respiratory infection: Antimicrobial resistance and serotypes of invasive and carried isolates of Streptococcus pneumoniae and Haemophilus influenzae, Pakistan, 1989-1990. Principal investigators: A. Chafoor and T. Mastro.

The distribution of pneumococcal types was similar for carried and invasive isolates from sick children in the three groups; only type 19F was found significantly more frequently among invasive isolates. Antimicrobial resistance also was similar for invasive strains and strains carried by these children. Cotrimoxazole resistance in the pneumococcal isolates exceeded 75% for both invasive and nasopharyngeal isolates; almost 15% had partial resistance to penicillin; and 30-35% were resistant to chloramphenicol. The resistance rates among healthy children and in the rural cohort differed from those of sick children in the three groups.

The data for H. influenzae showed a similar pattern. Approximately 40% of invasive and nasopharyngeal isolates from children with pneumonia were resistant to cotrimoxazole. Ampicillin resistance was uncommon. The data suggest that the antimicrobial resistance of invasive isolates is similar to that of strains carried by children with pneumonia or ARI and high fever, but differs from that of strains carried by healthy children.

The resistance patterns of invasive and nasopharyngeal isolates have also been examined in Papua New Guinea, Philippines, and Gambia. The data from Papua New Guinea suggested that carried and invasive pneumococcal isolates are mostly similar in type. This relationship was not found during one pneumonia season and may not exist during outbreaks of infection caused by certain types. Antimicrobial resistance rates were also similar, though the rates for nasopharyngeal isolates tended to exceed those for invasive isolates by about 10%. Data from the Philippines for S. pneumoniae suggested that the types isolated from the blood were similar to those from the upper airways; and data from the Gambia showed similar rates of antimicrobial resistance for invasive and nasopharyngeal pneumococcal isolates. The results from these three countries are preliminary and require further analysis.

Nasopharyngeal samples are preferable to oropharyngeal samples for several reasons. They allow more uniform sampling of the upper airway by less skilled workers. In the above studies in Papua New Guinea and Pakistan, the pneumococcal isolation rate was higher when the swab included the nose; this was also true for H. influenzae in Pakistan. In some settings with a high rate of mucopurulent nasal discharge, such as in Papua New Guinea, nasal samples produce comparable results to nasopharyngeal samples, but this may not be the case in all countries.

Despite the limited data these studies suggest that surveillance of the antimicrobial resistance of organisms that cause invasive pulmonary infection can be conducted using nasopharyngeal isolates. However, the existing data need to be analysed further to examine the strength of this relationship. In order to monitor the results obtained in national surveillance programmes using nasopharyngeal isolates, a sample of specimens from blood and other sterile sites should be collected and analysed when possible.

3. RELATIONSHIP BETWEEN DISC DIFFUSION TESTS AND MIC RESULTS

For S. pneumoniae, oxacillin discs are a sensitive test for determining whether an organism is resistant to penicillin. However, the test is not specific in that some isolates identified as resistant will be sensitive. Furthermore, the test does not distinguish between partial and high levels of resistance. For both S. pneumoniae and H. influenzae, the disc results for cotrimoxazole only indicate whether the organism is sensitive or has some level of resistance; MIC testing is needed to differentiate intermediate from high-level resistance, which may be important for interpreting results. A simpler method of differentiating organisms with partial and complete resistance is to use a "break point" MIC system. Plates are prepared with a known concentration of

the drug, then inoculated with the organism; no growth indicates a high level of resistance. The "break point" for cotrimoxazole and the correlation of MIC values with clinical efficacy are poorly understood.

Disc diffusion results are adequate, without MIC confirmation, for determining the penicillin, ampicillin, and gentamicin susceptibility of H. influenzae, the erythromycin susceptibility of S. pneumoniae, and the chloramphenicol susceptibility of both H. influenzae and S. pneumoniae.

4. RELATIONSHIP BETWEEN ANTIMICROBIAL RESISTANCE AND CLINICAL EFFICACY

The relationship between in vitro measures of antimicrobial resistance and the clinical efficacy of therapy is not well established for children with pneumonia. More data are available for acute otitis media, where samples are more easily obtained to document the bacteriological response to antimicrobial therapy. In the USA, 30% of H. influenzae isolates from cases of acute otitis media are beta-lactamase producing, but these represent only 10% of all cases of otitis media. Thus, amoxicillin remains the drug of choice for otitis media. In children with H. influenzae infections, beta-lactamase-mediated resistance to amoxicillin is frequently but not always associated with clinical failure. No data are available that correlate clinical outcome with various levels of resistance to cotrimoxazole, though there are data that suggest a failure of cotrimoxazole to sterilize the middle ear fluid infected by strains with borderline MICs. Intermediate penicillin resistance may not diminish the effectiveness of therapy for respiratory tract infections but could have a major impact on the success of therapy for meningitis. Failure to sterilize the cerebrospinal fluid is associated with therapeutic failure in this infection.

5. INTERPRETATION OF SURVEILLANCE DATA

Once antimicrobial resistance has been documented (and, if possible, correlated with clinical response) a decision needs to be made concerning standard antimicrobial therapy. Factors to be considered in making this decision include the cost of the alternative antimicrobials and their clinical spectrum, adverse effects, and pharmacokinetics. In some cases, rather than changing the antimicrobial agent, it may be possible to increase the dose. Agents that are not at present recommended by the WHO ARI Programme for the standard treatment of pneumonia may have a role at some future date if resistance to the currently recommended antimicrobials increases. Possible agents include the combinations erythromycin/sulfa and amoxicillin/clavulinate, and intramuscular ceftriaxone. Cost currently precludes the use of these options. It may be possible to add probenecid to raise the serum levels of penicillins and thus improve clinical efficacy. In the future, macrolide antimicrobials that are more active against H. influenzae than erythromycin and new formulations of quinolones with greater activity against S. pneumoniae may become available.

6. EPIDEMIOLOGICAL AND MICROBIOLOGICAL METHODS OF SURVEILLANCE

Working groups were established to evaluate and revise the draft manual for the surveillance of bacterial antimicrobial resistance. The recommended changes will be incorporated in a revised version. In brief, the epidemiology working group discussed the administrative structure (including the formation of an advisory committee), selection criteria for children to be sampled, ways of simplifying the estimation of sample size, and the need for better guidance in interpreting surveillance data and reaching decisions concerning the standard treatment of pneumonia. The microbiology working group discussed the transport of specimens, optimal media for bacterial isolation, standardization of methods, and quality control.

7. RESEARCH ISSUES

The comparability of nasopharyngeal and invasive isolates needs further study to validate the usefulness of nasopharyngeal isolates from children with clinical pneumonia for predicting antimicrobial resistance in invasive isolates of S. pneumoniae and H. influenzae. Given the unusually high rate of bacteraemia found in sick children in the study in Pakistan (section 2), the investigation needs to be repeated elsewhere and should examine children presenting both at a large hospital and at a peripheral clinical facility. Such a study, together with experience gained in initial field tests of the manual, should help to determine the most suitable population of sick children for nasopharyngeal sampling, i.e., whether it should be composed only of children with clinical pneumonia or also include children with cough or difficult breathing and high fever.

The existing data from the Gambia, Papua New Guinea, and the Philippines need further analysis, with a statistician's advice on how to compare nasopharyngeal and invasive isolates.

Studies are needed to correlate in vitro bacterial resistance with clinical outcome in children with pneumonia. This is especially important for cotrimoxazole. A study has been planned in Pakistan and further opportunities will be sought to investigate the clinical efficacy of an antimicrobial in treating pneumonia caused by an organism with documented in vitro resistance. The possibility of correlating an antimicrobial's ability to sterilize a middle ear infection caused by S. pneumoniae or H. influenzae with the clinical response of pneumonia will be explored in cases in which both conditions, pneumonia and acute otitis media, co-exist.

Several laboratory studies are required to define the optimal laboratory methods and media to be used in surveillance systems in developing countries:

- What are the time and temperature limitations for the transport of inoculated blood culture media before incubation?
- Can horse blood be substituted for sheep blood in Mueller-Hinton blood agar for antimicrobial susceptibility testing of S. pneumoniae?
- Can goat blood be used for blood agar plates and for susceptibility testing of S. pneumoniae and H. influenzae?
- Can trans-isolate media be used for the storage of isolates for 2-3 weeks at room temperature?
- At peripheral hospitals or health centres that have limited laboratory facilities and no personnel with expertise in microbiology, what is the survival time of the organisms and would the following approach be feasible? The Roche Septicheck is attached to incubated blood culture media (BCB), and the incubated media are inverted and observed daily; if growth is observed on the paddles, the attachment is recapped using sterile technique and mailed to the central or reference laboratory for susceptibility testing.
- What other simple, appropriate technologies are available to facilitate the transport and laboratory processing of specimens during surveillance?

8. ISSUES TO BE ADDRESSED DURING FIELD TESTING OF THE MANUAL

What is the actual cost of staff (in local and foreign currency) and what are the logistic requirements and cost of implementing the procedures recommended in the manual?

How do the disc zone sizes determined by national laboratories, using the procedures outlined in the manual, correlate with the disc zone sizes and MIC values determined at the reference laboratories?

Would intensive surveillance, carried out over several months with outside assistance as needed, be a satisfactory means of estimating antimicrobial susceptibility in countries or regions where it would be difficult to maintain laboratory capacity?

9. CONCLUSIONS AND RECOMMENDATIONS

- 9.1 Case management for children with ARI depends on effective empirical antimicrobial therapy. Antimicrobial resistance may reduce the effectiveness of such therapy. Therefore, a programme of surveillance of resistance is important to ensure the use of effective antimicrobials.
- 9.2 Conducting surveillance of the antimicrobial resistance of H. influenzae and S. pneumoniae using only isolates from sterile sites would be difficult in many countries. The most valid isolates are obtained by lung puncture; the next best are blood cultures. Lung puncture cannot be justified clinically for surveillance purposes and, in most developing country settings, blood culturing is usually not feasible in facilities other than large hospitals.
- 9.3 Data reported in the literature, and from unpublished studies in the Gambia, Pakistan, Papua New Guinea, and the Philippines, suggest that nasopharyngeal isolates from children with pneumonia may reflect the resistance patterns of invasive organisms with reasonable accuracy. Although it is uncertain whether the resistance patterns of nasopharyngeal and invasive strains will always be similar, the surveillance system should be based primarily on nasopharyngeal isolates, and a smaller sample of invasive isolates should be collected where feasible to monitor the nasopharyngeal results. Nasopharyngeal swabs should be used in preference to oropharyngeal swabs.
- 9.4 Nasopharyngeal isolates should be obtained from children 2 months to 5 years of age with clinical evidence of pneumonia. Such samples can also be obtained from children with cough or difficult breathing and a temperature equal to or exceeding 39°C (rectal) or 38.5°C (axillary); however, these data should be analysed separately since they may not as closely reflect the pattern of antimicrobial susceptibility of invasive organisms. The usefulness of sampling in this additional group should be examined both during the field testing of the manual and in a further research study.
- 9.5 Countries wishing to conduct surveillance should design a system based on the principles described in the epidemiology section of the surveillance manual. A limited system may be used when resistance is low or when a more extended system is impractical. A more extensive system will give more complete data concerning resistance patterns throughout the country and should be employed where the level of resistance is high. Surveillance can be carried out during the entire pneumonia season or during a part of this season. In areas where malaria is seasonal and the seasonality differs from that of pneumonia, an attempt should be made to avoid the malaria season. Data on the overlap in clinical presentation of malaria and pneumonia should be reviewed as they become available.

- 9.6 Simplified but valid laboratory methods of surveillance are described in the manual. For most organisms, disc diffusion tests accurately reflect the results of MIC testing and are acceptable for surveillance purposes. However, it will be necessary to perform MIC testing in a reference laboratory for S. pneumoniae with reduced penicillin susceptibility and for S. pneumoniae and H. influenzae with reduced cotrimoxazole susceptibility, since in these cases disc diffusion tests cannot distinguish partial from complete resistance.
- 9.7 When a national surveillance programme (collecting nasopharyngeal specimens) finds that bacterial drug resistance is at a very low level or inexistant, it may be appropriate to plan to monitor the levels again after a period of 1-3 years. If, however, a programme finds significant levels of resistance, increased efforts should be made to obtain data from blood culture isolates and monitoring should be carried out every year.
- 9.8 Data on the relationship between in vitro antimicrobial resistance and the efficacy of therapy are limited, especially for cotrimoxazole (see below). The lack of such data makes it difficult to make firm recommendations regarding the advisability of changing antimicrobial therapy on the basis of surveillance results. Further factors to be considered in making decisions on whether to change or retain therapy include cost, compliance, adverse effects, and clinical efficacy. When resistance to the current therapy is in the range of 10-20% the surveillance system should be extended to obtain additional information. When the level of resistance is higher than 20% the national programme should strongly consider changing the recommended therapy.
- 9.9 Several issues require further investigation in order to make surveillance as effective as possible and to improve the ability of programme managers to interpret resistance data. The comparability of nasopharyngeal and invasive isolates should be further studied to validate the usefulness of the former for the prediction of levels of antimicrobial resistance in invasive isolates of S. pneumoniae and H. influenzae. It is also necessary to determine the best population for nasopharyngeal sampling, i.e., whether it should be made up only of children with pneumonia or also of children with cough or difficult breathing and fever. Studies are needed to establish a clinical correlation between in vitro bacterial resistance and clinical outcome; this is especially the case for cotrimoxazole. Finally, studies are required to better define the laboratory methods and media that are most suitable for use in surveillance systems in developing countries.
- 9.10 As a first step towards determining the feasibility of the approach and methods contained in the surveillance manual, prior to its widespread application, a surveillance system as described therein should be instituted (as a field test) in one or more countries while the studies discussed under item 7 are being conducted.