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Technical bases for the WHO recommendations on the management of pneumonia in children at first-level health facilities

Programme for the Control of Acute Respiratory Infections

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TECHNICAL BASES FOR THE WHO RECOMMENDATIONS ON THE MANAGEMENT OF PNEUMONIA IN CHILDREN AT FIRST-LEVEL HEALTH FACILITIES

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1. INTRODUCTION

About 13 million children under 5 years of age die every year in the world, 95% of them in developing countries. Pneumonia is one of the leading causes, accounting for about 4 million of these deaths.

Despite this fact, for a combination of technical and operational reasons, pneumonia has been a neglected problem until very recently. Clinicians and epidemiologists thought that the control of respiratory infections did not deserve high priority because of the difficulties involved in preventing and managing these infections; it was said that antibiotics might not be an effective treatment against pneumonia because patients are often weakened by conditions such as chronic malnutrition and parasitic infections, and that a wide variety of viruses and bacteria are associated with pulmonary infections making it impossible to identify the specific etiological agent in each patient (1). On the other hand, some public health experts felt that a programme aimed at preventing mortality from pneumonia could not succeed because it would be difficult to deliver the available technology (antibiotics) through peripheral health units and community-based health workers.

At most, one quarter of the pneumonia cases in children can be prevented by the measles and pertussis vaccines included in the immunization schedule of the Expanded Programme on Immunization. There is a clear need for research to develop and test vaccines against the most frequent agents of pneumonia in children. Such research has been pursued by WHO, notably within the Programe for the Control of Acute Respiratory Infections (ARI) and the Vaccine Development Programme; however, WHO has simultaneously been utilizing current clinical knowledge to formulate a case management strategy to reduce the high mortality from pneumonia in children.

The present document is not intended to provide detailed case management guidelines. These are to be found in the manual "Acute respiratory infections in children: Case management in small hospitals in developing countries. A manual for doctors and other senior health workers", document WHO/ARI/90.5 (1990).

2. TECHNICAL BASES FOR STANDARDIZED CASE MANAGEMENT OF ACUTE RESPIRATORY INFECTIONS

2.1 Importance of bacterial pneumonia

Present evidence indicates that in the developing countries bacteria play a far greater role as causes of pneumonia in children than they do in developed countries. Two kinds of data lend support to this evidence: etiological studies of pneumonia and information on the prevalence of nasopharyngeal carriers of pathogenic bacteria.

Etiological studies of pneumonia. The etiological diagnosis of pneumonia in infants and young children is very difficult to establish because sputum is usually not available (2). Rapid immunological techniques such as counter immunoelectrophoresis,

ELISA, latex agglutination, or coagglutination are not yet entirely satisfactory for determining the role of bacteria in the etiology of pneumonia in children (3). Only cultures of lung aspirates and blood cultures can produce a reliable bacteriological diagnosis (4).

Lung puncture is the most sensitive method for recovery and identification of the bacterial agents of pneumonia in children. Cultures of lung aspirates yield a very low false-positive rate (a positive result is strong evidence of bacterial infection if common contaminating skin organisms, like *Staphylococcus epidermidis,* are excluded). In the 1970s and early 1980s they were used in 13 studies in developing countries in children with pneumonia who had not received previous antimicrobial treatment (5-8). When the results of these studies were pooled, bacteria were isolated in 456 (55%) of the 835 aspirates examined (Table 1); they were found in at least 50% of the children in all but three studies. In fact, a high proportion of the negative results were probably false-negatives because of the many factors that mask the presence of bacteria: for example, the appropriate lung lesion may not be reached with the needle, the material collected may be scanty, or the laboratory methods may be inadequate to isolate all the possible bacterial

TABLE 1

POSITIVITY OF BACTERIOLOGICAL CULTURES OF LUNG ASPIRATES FROM CHILDREN WITH PNEUMONIA WHO HAD NO PREVIOUS ANTIBIOTIC TREATMENT

Place	Year of publication	N° of children	Age in years	Bacterial cultures (+) Number	%
Brazil: Recife	1978	60	0- 4	34	60.0
São Paulo	1974	37	0- 7	20	54.1
Chile: Santiago (Mimica)	1971	160	0- 2	91	56.8
Santiago (Schuster)	1966	125	0-10	67	53.6
Colombia: Cali	1976	71	0-14	15	21.1
Gambia: Fajara*	1986	51	0- 9	33	64.6
India: Pune	1981	50	0-11	30	60.0
Nigeria: Benin	1981	46	0-12	34	73.9
Zaira	1977	88	0- 8	54	61.3
Papua New Guinea: Goroka	1984	71	0- 5	48	67.6
Tari	1983	18	0- 9	8	44.0
Philippines: Manila	1979	18	0-14	9	50.0
Zimbabwe: Bulawayo	1988	40	0-11	13	32.5
TOTAL		835		456	54.6

* including the results of blood cultures.

NOTE: Gambia study, reference (6); Zimbabwe study, reference (7); the other studies, reference (5).

pathogens. Cases that have received previous antibiotic therapy may also have been included in these series since it is not always possible to determine with accuracy the treatment background of young children. Thus, the actual proportion of positive bacterial cultures was probably higher than that reported.

Published evidence from lung aspirate studies performed in the pre-antibiotic era indicates that the bacteriology of pneumonia in developed countries used to be similar to that observed in many developing countries today (5). Nowadays, however, it is accepted that most episodes of pneumonia in children in developed countries are of viral origin, the most important organisms being respiratory syncytial virus, parainfluenza, influenza, and adenoviruses. In a lung aspirate study conducted in Newark, USA, a bacterial etiology was demonstrated in only 11% of untreated cases of community-acquired pneumonia (9). Nevertheless, recent studies using antigen detection techniques have concluded that bacterial infections may be more common in developed countries than has generally been recognized (2,10,11).

Since lung puncture is an invasive method that exposes the child to serious risks, there have been strong ethical objections to its use in clinical research. In recent years, the best information on the bacterial etiology of pneumonia in young children has been obtained through blood cultures, despite the fact that the sensitivity of this method is somewhat lower. In studies in three countries supported by BOSTID (Board on Science and Technology for International Development, US National Research Council), cultures were made on blood samples taken from children with acute lower respiratory infections, mostly pneumonia, diagnosed by hospital services (Table 2). The positivity of the bacterial cultures was 26.1% in Pakistan (12), 26.8% in Papua New Guinea (13), and 13.4% in the Philippines (14). These results represent a fraction of the real rates of bacterial lung infection, because it is generally admitted that blood cultures yield positive results in one quarter to one third of bacterial pneumonia cases.

TABLE 2

POSITIVITY OF BLOOD CULTURES FROM CHILDREN 0-4 YEARS OLD WITH PNEUMONIA WHO HAD NO PREVIOUS ANTIBIOTIC TREATMENT

Place	Reference	N° of children	Bacterial cultures (+)	
			Number	%
Pakistan: Islamabad (BOSTID Study*)	10	1331	347	26.1
Papua New Guinea: Goroka	11	253	68	26.8
Philippines: Manila	12	537	72	13.4

* includes children with any of the following signs: fast breathing, chest retractions, cyanosis, wheezing or rales upon auscultation.

Although the evidence from lung aspirate and blood culture studies relates to hospitalized children with pneumonia, these are the children who die if they are left untreated.

These studies also have consistently demonstrated that *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most frequently isolated bacteria. Table 3 summarizes the findings from the studies that provided this information. These two bacteria accounted for more than two thirds of all bacterial isolates, 73.9% of lung aspirate isolates, and 69.1% of blood isolates.

TABLE 3

DISTRIBUTION OF BACTERIA ISOLATED FROM LUNG ASPIRATES AND BLOOD CULTURES

Place	*Strepto-coccus pneumoniae*	*Haemophilus influenzae*	*Staphy-lococcus aureus*	Other bacteria	Total isolates
I. LUNG ASPIRATES					
Brazil: Recife	25	13	0	0	38
São Paulo	15	3	1	1	20
Chile: Santiago (Schuster)	26	19	15	13	73
Colombia: Cali	4	4	5	2	15
Gambia: Fajara	26	12	1	2	41
Nigeria: Zaira	31	9	8	20	68
Papua New Guinea: Goroka	27	41	1	23	92
Tari	7	1	0	0	8
Zimbabwe: Bulawayo	7	3	4	1	15
Subtotal	168	105	35	62	370
Percent	45.5	28.4	9.4	16.7	100.0
II. BLOOD CULTURES					
Pakistan: Islamabad	132	144	25	87	388
Papua New Guinea: Goroka	29	30	0	9	68
Philippines: Manila	11	19	11	31	72
Subtotal	172	193	36	127	528
Percent	32.6	36.5	6.8	24.1	100.0
TOTAL	340	298	71	189	898
PERCENT	37.9	33.2	7.9	21.0	100.0

Pneumonia is often caused by multiple microbial agents. Concurrent bacterial infection is quite frequent in children who have an acute viral infection. Viral infections may alter the host defense factors and reduce the efficiency of the antibacterial activities of the lungs, creating suitable conditions for invasion by the pathogenic bacteria that are commonly present in the upper respiratory tract (15). In about 20% of confirmed cases of viral acute lower respiratory infection (pneumonia or wheeze) a bacterial superinfection was also demonstrated by culture of blood or lung aspirates (Table 4). In view of the number of false-negative results that are expected with these isolation techniques, the true positivity should be higher. Mixed bacterial and viral infections in children are also being recognized more frequently in developed countries (2,16). Therefore, the presence of a viral infection does not exclude concomitant bacterial infection.

TABLE 4

CONCOMITANT BACTERIAL INFECTION IN CHILDREN WITH VIRAL ACUTE LOWER RESPIRATORY INFECTIONS

Place	Reference	(+) Viral cases		(+) Bacterial cases		
		Type	Number	Diagn. method*	Number	%
Colombia: Cali	16	Pneumonia	27	LA	5	18.5
Pakistan: Islamabad	10	Pneumonia/ Wheeze	553	BC	135	24.4
Papua New Guinea: Goroka	5	Pneumonia	62	LA/BC	12	19.4
Philippines: Manila	12	Pneumonia/ Wheeze	180	BC	17	9.4
TOTAL			822		169	20.6

* BC - Blood culture
LA - Lung aspirate culture

Similarly, multiple bacterial isolates were often found in lung aspirates. Table 5 presents the information on multiple bacterial isolates from the nine studies listed in the upper part of Table 3. Multiple isolates were reported by six studies. Pooling all the results, two bacteria were identified in 14.5% of cases, and more than two in 4.4% of cases.

Nasopharyngeal carriage of bacteria. Pneumonia in children is probably often caused by inhalation of infected nasopharyngeal secretions into the lungs. The pneumococcus and *H. influenzae* are components of the normal flora of the upper respiratory tract. Aspiration of secretions is a common event in normal individuals, particularly during sleep. Because upper respiratory secretions may contain large numbers of potential pathogens that have colonized the nasopharynx, the aspiration of a very small amount

could deliver a large enough inoculum to cause bacterial pneumonia, especially if the local defenses of the lower respiratory tract are impaired because of malnutrition, a viral infection, or other factors. The close association between the nasopharyngeal acquisition of pneumococcus strains and the incidence of invasive disease has been documented in epidemiological studies (17). A recent study conducted in Islamabad, Pakistan, showed that 98% of children with clinical pneumonia and bacteraemia carried the same pneumococcus serotypes with the same drug sensitivity in the blood and in the nasopharynx (18). This finding was confirmed in a subsequent study in Islamabad, Pakistan, in which the prevalence of antimicrobial resistance was similar for invasive isolates of pneumococcus and *H. influenzae* and isolates carried by children with clinical pneumonia for all the antimicrobials tested.

TABLE 5

SINGLE AND MULTIPLE BACTERIAL ISOLATES FROM LUNG ASPIRATE CULTURES

Place	N° of patients with (+) culture	Bacterial isolates			Total bacterial isolates
		1	2	>2	
Brazil: Recife	34	30	4	0	38
São Paulo	20	20	0	0	20
Chile: Santiago (Schuster)	67	61	6	0	73
Colombia: Cali	15	15	0	0	15
Gambia: Fajara	33	29	2	2	41
Nigeria: Zaira	54	36	14	4	76
Papua New Guinea: Goroka	48	27	14	7	76
Tari	8	8	0	0	8
Zimbabwe: Bulawayo	13	11	2	0	15
TOTAL	292	237	42	13	362
PERCENT	100.0	81.1	14.5	4.4	

It has been found that the acquisition of *S. pneumoniae* and *H. influenzae* in the upper respiratory tract occurs earlier in life and is more common in infants and young children in developing countries than in developed countries (Table 6) (11, 19-27). In cross-sectional studies undertaken in Kenya, Papua New Guinea, Senegal, and among Australian Aborigines, the nasopharyngeal carrier rate of *S. pneumoniae* in children aged 0-4 years has ranged from 72 to 97%, compared with 28 to 44% in studies in developed countries. In Papua New Guinea, 25 infants followed from birth all became colonized with *S. pneumoniae* within the first three months of life (28). *H. influenzae* type b, the most virulent type, was shown to be carried in the nasopharynx of 6-

13% of children in the Gambia, Kenya, and Papua New Guinea; in contrast, it has been found in 2% or less of children in community-based studies in developed countries (the rates are higher in closed populations such as orphanages, or in settings such as day-care centres where children are in close contact).

TABLE 6

NASOPHARYNGEAL CARRIAGE OF *S. PNEUMONIAE* AND *H. INFLUENZAE* TYPE B IN CHILDREN

Place	Reference	No. of children	Age	*S. pneumoniae* %	*H. influenzae* type b %
Gambia: Basse	19	401	0- 4	98.0	12.9
Kenya: Maragua	20	331	0- 4	89.0	9.0
Papua New Guinea: Goroka	11	165	0- 5	97.6	6.1
Senegal: Dakar	21	205	0- 4	72.2	-
Australia: (Aborigines)	22	174	0-14	89.1	-
Sweden: Göteborg	23	67	1- 9	28.3	-
UK: N. Wales	24	996	0- 5	-	1.1
USA: Nebraska	25	1084	4- 7	-	2.0
N. Carolina	26	81	0- 9	44.0	-
Virginia	27	18	0- 5	37.8	-

NOTE: Cross-sectional studies in the Gambia, Kenya, Papua New Guinea, Sweden, UK and USA (Nebraska); longitudinal studies in USA (N. Carolina and Virginia).

2.2 Efficacy of antimicrobial treatment

The introduction of antibacterial chemotherapy in the industrialized countries was associated with a dramatic reduction in the pneumonia death rate in children. Although this rate had been declining since the beginning of the century, a relatively sharp acceleration occurred in 1938, when the first sulfonamide became widely available. For example, in the USA, comparing the periods of 15 years before and after 1 January 1938, the annual rate of decline in the pneumonia death rate jumped from 1.8 to 7.8% in infants and from 3.7 to 5.9% in children aged 1 to 4 years (29,30). Although historical data of this kind do not prove a cause-and-effect association, there can be no doubt that the decline was attributable to the use of antimicrobials. Several controlled clinical trials conducted in the first years of antibacterial chemotherapy showed that sulfonamides significantly reduced the case fatality from pneumonia in children in developed countries (31-33). This impact was later diminished due to the emergence of bacterial resistance to sulfonamides, but the widespread use of penicillin after 1945 sustained the reduction in mortality. The effect of antimicrobials on the trend of mortality from pneumonia was evident in most European countries after the introduction of penicillin (34,35); any previous benefit resulting from the use of sulfonamides may have been nullified by the effects on general health conditions of the

Second World War. Even a critic of modern medicine, Ivan Illich, has stated that "....chemotherapy has played a significant role in the control of pneumonia .... deaths from pneumonia, once the old man's friend, declined yearly by 5 to 8% after sulfonamides and antibiotics came on the market" (36).

There has been a tendency in the last two decades to stress the negative side of the use of antimicrobials and to focus on their harmful side-effects and the emergence of drug resistance. It should, however, be emphasized that there are no alternatives to antimicrobials for the treatment of bacterial pneumonia, and that, prior to the advent of antimicrobials, case-fatality rates for pneumococcal pneumonia in children ranged from 12 to 41%, being highest in infants (37).

2.3 Effectiveness of the standard case management intervention

On the assumption that early treatment with antimicrobials that are effective against *S. pneumoniae* and *H. influenzae* can prevent deaths from pneumonia in children, WHO has sponsored seven studies in recent years to determine the impact of a standard case management strategy implemented through the primary health care system, including community health workers. The studies were conducted in: Haryana, India (38); Kediri, Indonesia (39); Jumla (40) and Kathmandu Valley, Nepal (41); Abbottabad, Pakistan (42); Bohol Island, Philippines (43); and Bagamoyo, United Republic of Tanzania (44); two other similar studies were carried out in Matlab, Bangladesh (45), and Gadchiroli, India (46). Taken together, the results provided epidemiological and clinical evidence that the case management strategy was effective. A substantial impact on pneumonia-specific mortality rates in children was found, which was also reflected in a reduction in overall childhood mortality (Table 7) (47). This effect was also detectable in high-risk groups such as low-birth-weight infants (in Haryana, India), in cases with high prevalence of malnutrition (in Gadchiroli, India), in areas with high infant mortality (most studies), and in settings in which case management relied almost entirely on community health workers and home treatment because referral was very difficult (most studies).

Very probably, the pneumonia episodes detected and treated in the intervention areas represented a fraction of the total incidence, in all studies, since many children might have had pneumonia which passed unnoticed by the parents. In fact, many deaths attributed to pneumonia occurred in untreated children. It is difficult to estimate the actual proportion of pneumonia episodes that were detected and treated because of the uncertainties in establishing the incidence of pneumonia on the basis of mothers' reports and recollection, and no study included the systematic radiological and medical examination of children with respiratory symptoms. It is, however, important to note that, even if coverage was incomplete, a substantial reduction in mortality from pneumonia was achieved in most studies. The studies further showed that it is feasible to transmit to community health workers the knowledge and skills required to assess and manage cases of acute respiratory infection, particularly pneumonia in children, even in underprivileged and poorly served areas.

TABLE 7

REDUCTIONS IN MORTALITY SPECIFIC FOR ACUTE LOWER RESPIRATORY INFECTIONS (ALRI) AND IN OVERALL MORTALITY IN CHILDREN UNDER 5 YEARS OF AGE IN INTERVENTION STUDIES

Place	Reduction in ALRI-specific mortality %	Reduction in overall mortality %
Bangladesh: Matlab	51	30
India: Gadchiroli	54	30
Haryana*	42	24
Indonesia: Kediri	67	41
Nepal: Jumla	-	28
Kathmandu Valley	62	40
Pakistan: Abbottabad	56	55
Philippines: Bohol	25	13
United Republic of Tanzania: Bagamoyo	30	27

* in low-birth-weight infants.

Lack of antibiotic treatment is an important reason for the high mortality rates from pneumonia in developing countries. In the intervention study in the United Republic of Tanzania, 68% of children who died from pneumonia in the control area and 46% in the intervention area had not received any antibiotic treatment before death; 50% of the deaths occurred within three days of the onset of symptoms. The average duration of illness, from the appearance of signs of pneumonia to death, was found to be 3.5 days in the Jumla, Nepal, project. Therefore, rapid access to correct case management is essential to prevent mortality from pneumonia in children (48).

3. RATIONALE FOR EMPIRICAL TREATMENT OF PNEUMONIA

Since pneumonia can be caused by a variety of organisms, the ideal approach to its management would be to identify rapidly the causative agent(s) in each individual case so that an appropriate antimicrobial (if the cause is a bacterium or a chlamydia) can be prescribed. However, the spectrum of etiological agents is wider in paediatric than in adult pneumonia, and only in a minority of cases do distinctive clinical features suggest a particular pathogen.

As discussed above (section 2.1), the only available methods of establishing the bacterial etiology of pneumonia in young children are lung aspiration or blood culture, the latter being much less sensitive. Clinical and radiological criteria do not accurately reflect the etiology of childhood pneumonias. Clinical data, such as auscultatory findings and the level or evolution of fever, are

imprecise in defining the bacterial or viral etiology of pneumonia in children (12). Segmental or lobar consolidation on chest X-ray, which are considered typical of bacterial pneumonia, may frequently be caused by viruses (49-51). Conversely, diffuse or disseminated infiltrates which suggest a viral infection are often caused by bacteria, or both viruses and bacteria may be present. Laboratory data indicating the white-cell count and differential, erythrocyte sedimentation rate, and the C-reactive protein estimation do not discriminate sufficiently between bacterial and viral etiologies to be a useful guide for antimicrobial treatment (52,53). As a result, an etiological agent can be established in less than one-quarter of children hospitalized with pneumonia in developed countries with full diagnostic facilities, and in an even smaller proportion of ambulatory cases (54).

Because of these diagnostic problems, empirical antimicrobial therapy for pneumonia is the commonly accepted practice worldwide. Even in developed countries, where only 5-15% of radiologically diagnosed pneumonia is likely to be caused by bacteria, many paediatricians treat all children with pneumonia with antimicrobials because it is impossible to exclude the presence of bacterial infection (55,56).

In developing countries, and especially in those with high infant mortality rates, as many as half of the pneumonia cases in children attending the health services are of bacterial origin (see section 2.1). Almost all of these cases can be detected by simple clinical signs, without radiography or laboratory data (see section 5). Because of the higher probability of bacterial pneumonia, there is an even stronger justification for the empirical use of antimicrobials than in developed countries.

However, when recommending standard antimicrobials it is necessary to take into account the probable etiological agents involved and their drug sensitivity. The effect of age on likely pathogens is so pronounced that it is probably the single most important variable to be considered (57). Young infants may have acquired infection perinatally or become infected with organisms such as gram-negative bacteria or Group B streptococci which are rarely found in community-acquired pneumonia in older children. The etiological agents of pneumonia and sepsis in young infants in developing countries are not well known, and are currently being investigated (58).

There have been few studies of the clinical efficacy of antibiotics in the treatment of childhood pneumonia in developing countries. Controlled clinical trials of the efficacy of cotrimoxazole in the treatment of pneumonia in children have been conducted in the Gambia and Zimbabwe. In the Gambia, children with severe pneumonia were admitted into the study. After two weeks of follow-up, there was no significant difference in outcome (about 90% completely recovered) between the groups treated with cotrimoxazole for 5 days and the group treated with a single intramuscular dose of fortified procaine penicillin and 5 days of oral ampicillin (59). In Zimbabwe, the comparison was made between cotrimoxazole and procaine penicillin for the outpatient

treatment of pneumonia in children. There were no significant differences in outcome between the two treatment groups. Both drugs were highly and equally effective (60).

It is important that all recommended antibiotics have good activity against *S. pneumoniae* and *H. influenzae* in children older than 2 months, and against a wide range of gram-positive and gram-negative bacteria in infants less than 2 months old (see section 5.3). National recommendations should not be based only on the local drug sensitivity patterns of the most common bacterial agents. Other factors to be considered in issuing recommendations are the cost of the different antimicrobials, and their clinical spectrum, adverse effects, and pharmacokinetics.

4. CLASSIFICATION OF ACUTE RESPIRATORY INFECTIONS

The procedures for case management and the use of antimicrobials now recommended by the WHO Programme for the Control of Acute Respiratory Infections (ARI) are in general appropriate for developing countries having limited resources and an infant mortality rate of over 40 per 1000 live births. The guidelines are based on the assumption that there is a substantial prevalence of bacterial pneumonia among children visiting first-level health facilities, and that risk factors for pneumonia, such as malnutrition and low birth weight, are relatively common, resulting in high rates of pneumonia-specific mortality.

There are different ways of classifying ARI, which is a complex group of clinical conditions of different etiology and severity. From the point of view of a public health programme, it is pertinent to adopt a classification related to management categories (rather than etiological, anatomical, or diagnostic groups), based on clearly defined signs that are relevant to the two management decisions: whether or not to prescribe antimicrobials, and whether to treat at home or to refer to a higher-level health facility. Thus, among children with ARI, there are three main groups to be identified: those with severe pneumonia or other very severe disease who require antimicrobial treatment and immediate referral for inpatient care; those who have pneumonia (non-severe) and require antimicrobial treatment at home; and those who do not have pneumonia. In the non-pneumonia group four categories can be distinguished: wheezing disorders, bacterial upper respiratory infection (acute otitis media, suspected streptococcal pharyngitis), chronic cough, and simple coughs and colds.

5. STANDARD PLAN FOR CASE MANAGEMENT

The core of the WHO protocol for case management of ARI for use in first-level health facilities (61) is distinguishing cases of pneumonia from other cases of acute respiratory infection and providing appropriate treatment. For simplicity and ease of training, the smallest number of criteria that is adequate to diagnose and classify cases is used.

The current recommendations for case management were based on a review of studies in different parts of the world; a primary concern in preparing the guidelines was that they should be highly sensitive for each age group in order to ensure that antibiotic treatment is given to most children in the initial stages of pneumonia.

The guidelines aim to teach health workers to focus their attention on the breathing of a child rather than on the severity of cough or the presence of fever. Available evidence suggests that this approach will more often identify children with pneumonia and will result in fewer prescriptions for antibiotics being given to children with simple coughs and colds.

The WHO protocol comprises three essential steps:

- identify the children who should be examined for possible pneumonia (case-finding or assessment on the basis of "entry criteria"),
- identify the cases of pneumonia (case classification),
- institute the appropriate treatment (home treatment or referral).

5.1 Entry criteria

The WHO protocol puts forward two signs as the "entry criteria" or basis for examining a child below 5 years of age for possible pneumonia: **cough** or **difficult breathing**. Fever is not an efficient criterion. Although many children with pneumonia have fever, so do those with other very common diseases (malaria, upper respiratory infection, diarrhoea), most of whom will not benefit from antimicrobial therapy directed at bacterial pathogens of pneumonia. Also, a number of children with pneumonia do not present with fever, especially those with very severe disease or malnutrition. Studies relating clinical or radiological pneumonia to presenting signs in developed (62) and developing (63) countries have *not* shown the presence of fever to be a useful sign in the identification of children with pneumonia.

5.2 Identification of pneumonia cases

Among the many children with cough or difficult breathing, those with pneumonia have to be identified in order to ensure that they receive antimicrobial therapy. At this stage it is necessary to distinguish between infants under 2 months of age and older children because the etiology and clinical manifestations of pneumonia are different in these age groups.

Children 2 months - 4 years old. The traditional method of making a clinical diagnosis of pneumonia has been by the recognition of auscultatory signs, in particular crepitations, in a child with a cough. However, auscultatory signs are not very reliable in children, even when they are examined by a paediatrician. In a study in Philadelphia in which 29 different presenting signs in children were compared with subsequent radiological findings, **fast breathing** was found to be a better predictor of pneumonia than auscultatory findings (62).

The validity of this approach was confirmed by studies which determined the pathognomonic value of clinical signs for the diagnosis of pneumonia in children in the Gambia (64), Lesotho (65), India (66), Papua New Guinea (63), and the Philippines and Swaziland (67). The results confirmed that fast breathing is a sensitive and specific indicator of the presence of pneumonia, and that observation of this sign can help to categorize children with cough into two groups with high and low probability of pneumonia. They have also provided detailed information on the sensitivities and specificities of different respiratory rate criteria in different age groups.

Table 8 shows data from five studies on the sensitivity and specificity of two differential respiratory rate thresholds: 50 breaths per minute or greater, and 40 breaths per minute or greater. In all the studies the sensitivity of fast breathing increases if the cut-off criterion is lowered from 50 to 40: the increases observed were from 59-89% to 84-100% in infants 2-11 months old, and from 19-64% to 38-87% in children 1-4 years old. The same change in the cut-off criterion produces a decrease in the specificity for both age groups. The analysis of these data led to the conclusion that the best combination of sensitivity and specificity is achieved by the following definitions of fast breathing:

TABLE 8

EFFECTS OF AGE ON THE SENSITIVITY AND SPECIFICITY OF THE RESPIRATORY RATE AS A SIGN OF PNEUMONIA IN CHILDREN (FROM FIVE STUDIES)

Study	2-11 months		1-4 years	
	RR≥50 %	RR≥40 %	RR≥50 %	RR≥40 %
A. SENSITIVITY				
Gambia	85	100	64	87
India	89	96	57	71
Lesotho: Paediatricians	79	100	19	54
Nurses	59	84	35	38
Papua New Guinea	80	-	57	74
Philippines	77	90	52	78
B. SPECIFICITY				
Gambia	98	55	98	82
India	93	62	96	87
Lesotho: Paediatricians	59	25	91	69
Nurses	72	44	94	77
Paupa New Guinea	81	59	90	72
Philippines	90	51	85	75

RR: Respiratory rate

(1) in infants aged 2-11 months:
a respiratory rate of 50 per minute or above

This cut-off has both high sensitivity and high specificity; a cut-off of 40 has very low specificity, less than 30% in some places, with the result that many infants without pneumonia would be treated for pneumonia (more than 70% of cases classified as pneumonia would be false-positives in some places).

(2) in children aged 1-4 years:
a respiratory rate of 40 per minute or above

This cut-off has almost the same sensitivity (with the exception of Lesotho) and specificity as a cut-off of 50 for infants 2-11 months old; a cut-off of 50 has rather low sensitivity for children 1-4 years old, leading to a significant proportion (36-81%) of pneumonia cases being classified as no pneumonia, and hence receiving no antimicrobial treatment.

A comparison of the sensitivity, specificity, and positive predictive value of the three criteria to define fast breathing is presented in Table 9. The data were obtained from the studies in the Philippines and Swaziland (67). The combined cut-off of 50 in infants 2-11 months old and of 40 in children 1-4 years old produces the best compromise in the trade-off between sensitivity and specificity (around 80% for both values in both studies) in the whole group of children aged 2 months to 4 years. The positive predictive value, however, is different between the two places because the prevalence of pneumonia (and consequently the positive predictive value) in the study population of Swaziland was lower than in the study population of Manila.

TABLE 9

SENSITIVITY AND SPECIFICITY OF THE RESPIRATORY RATE AS A SIGN OF PNEUMONIA IN CHILDREN 2 MONTHS - 4 YEARS OLD (MANILA, PHILIPPINES, AND MBABANE, SWAZILAND)

Respiratory rate cut-off	Study	Sensitivity %	Specificity %	Positive predictive value %
≥50	Manila	60	93	80
	Mbabane	65	92	17
≥40	Manila	82	69	57
	Mbabane	77	69	35
Combination ≥50 for age 2-11 months and ≥40 for age 1-4 years	Manila	78	79	64
	Mbabane	77	83	25

It is essential that respiratory rates are recorded when the child is calm and not crying. Variability in respiratory rate is particularly marked in the first two months of life. Raised respiratory rates found in these young infants should be confirmed by taking a second measurement after a period of at least 10 minutes.

As pneumonia progresses and becomes more severe lung elasticity is gradually reduced and **chest indrawing** develops (the lower chest wall draws in when the child breathes in). The presence of lower chest indrawing means that the child has severe pneumonia (63,66). A child with chest indrawing may not have fast breathing because the respiratory rate can fall when pneumonia becomes severe or the child is exhausted. A child with chest indrawing is at higher risk of death from pneumonia than a child with fast breathing without chest indrawing. It is important to point out that the definition of chest indrawing does not include intercostal or supraclavicular retractions. If these were included in the definition, too many children for whom hospitalization is not warranted would be referred; therefore, when the soft tissue between the ribs or above the clavicle goes in when the child breathes in, this is not considered to be chest indrawing nor a sign of severe pneumonia (63).

Chest indrawing may also be caused by **wheezing**, which is usually due to asthma, bronchiolitis, or other respiratory infections. There are, however, marked geographical differences in the prevalence of wheeze. In places where wheeze is very common, the case management protocol should include instructions on how to manage these cases. An element of these instructions is to give antimicrobials to wheezing children when there is fast breathing (a respiratory rate of 50 per minute or above in infants 2-11 months of age, or 40 per minute or above in children 1-4 years of age) because of the possibility that they may have bronchiolitis complicated with bacterial pneumonia, or even wheeze due to bacterial pneumonia. In the absence of radiography, it is very difficult to exclude clinically these two possibilities from uncomplicated bronchiolitis. In a clinical and etiological study of acute lower respiratory infections in children in Islamabad and Rawalpindi, Pakistan, wheezing was noted in 36% of the children with bacteraemia due to *S. pneumoniae* and in 44% of those with bacteraemia due to *H. influenzae* (12).

For children with recurrent wheeze, the WHO guidelines recommend treatment with a rapid-acting bronchodilator before further assessment of the need for antimicrobial therapy. Children who continue to show respiratory distress 30 minutes after adequate bronchodilator treatment should be admitted to hospital for further treatment including antimicrobial therapy. However, in many areas wheezing is not common and peripheral health workers can be taught to interpret fast breathing and chest indrawing only as signs of pneumonia.

Conditions causing **stridor** are also a cause of chest indrawing, but they are rare in many developing countries. Frequent causes of stridor used to be diphtheria and measles, both of which can be prevented by immunization. Stridor in a calm child may be a sign of severe croup (e.g., epiglottitis or laryngotracheitis) and is an indication for inpatient treatment.

Cough with **fever** is not a sufficient criterion for the diagnosis of pneumonia; its specificity and predictive value are very low. Many children would be unnecessarily treated with antimicrobials if fever was used as an indication for therapy; this is particularly true for malaria-endemic areas. The presence or degree of fever and the response to antipyretics cannot distinguish bacterial from viral respiratory infections.

If no signs of pneumonia are detected, the protocol suggests examining the patient for chronic cough (possibility of asthma or persistent pertussis, tuberculosis) or upper respiratory infection that requires antimicrobial treatment (otitis media, streptococcal pharyngitis). Otitis media is the leading cause of preventable deafness and a major contributor to learning problems in children in developing countries. It can be effectively treated with the same antimicrobials as for pneumonia. Without treatment, streptococcal pharyngitis is a precursor of rheumatic heart disease, which accounts for about half of all cardiovascular disease and the majority of cardiovascular deaths in the first four decades of life in many developing countries (68). If these conditions are not present, the case is considered to be a simple cough or cold.

Infants less than 2 months of age. For young infants (under 2 months of age), fast breathing and chest indrawing are defined differently than for older children. Since neonates normally breathe about 50 times per minute and may have slight chest indrawing (because of the softness of the thoracic bones), pneumonia is identified when the respiratory rate is 60 per minute or above (confirmed by a second reading), or when there is marked chest indrawing. Young infants can become sick and die very quickly from pneumonia. Therefore, any young infant who has a sign of pneumonia is classified as having severe pneumonia. Fast breathing and marked chest indrawing are not sensitive enough, however, to detect most pneumonias in young infants, and it is necessary to look for certain non-specific signs that indicate that the young infant may have pneumonia, sepsis, or meningitis (which often cannot be distinguished clinically). The signs are: the infant stops feeding well, is abnormally sleepy or difficult to wake, has fever or hypothermia (body temperature $< 35.5^{\circ}C$), or has convulsions.

It is of key importance that special guidelines be observed for the detection of pneumonia in young infants, because it is a frequent cause of death during this period. In fact, from 20 to 30% of all deaths from ARI in children under 5 years in many developing countries occur during the first two months of life (69).

5.3 Treatment

Although antimicrobial therapy is recommended for children with signs of pneumonia, the type of antimicrobial and the place of treatment vary with the age of the child and the severity of the disease.

The protocol takes into account the fact that in many places access to referral facilities is limited or even impossible due to high cost, adverse weather, lack of transportation, very long distances, or conflicting cultural beliefs. In such situations, children will depend more for their survival on the abilities of peripheral health workers, which will usually be limited to the provision of oral antimicrobial treatment and home care.

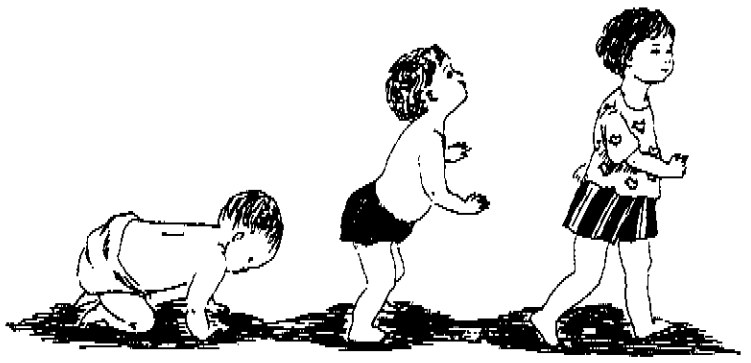
In **children older than 2 months**, chest indrawing indicates severe pneumonia and a need for referral to hospital (Table 10). The standard antimicrobial for the treatment of severe pneumonia is intramuscular benzyl-penicillin; but if the child has very severe pneumonia (shows central cyanosis or is unable to drink) injectable chloramphenicol and oxygen should be given. Chloramphenicol is indicated for these cases because it is effective against a wide spectrum of organisms, including *Staphylococcus aureus* and gram-negative bacteria. It may cause some serious side-effects (aplastic anaemia or haemopoietic toxicity) but these are rare toxic events and are an acceptable risk if the drug is used only in these very severe cases (70). Oxygen is indicated because in children with very severe pneumonia the lungs are unable to transfer enough oxygen from the air into the bloodstream and, as a result, the level of oxygen in the blood falls to dangerously low levels. Infants are particularly sensitive to hypoxaemia, and are likely to develop irregular breathing and apnoea (71). Hypoxaemia may also impair the flow of blood through the lungs, particularly in the first three months of life. All these effects further reduce the amount of oxygen that reaches the blood. In other words, when an infant is already ill, the effects of lack of oxygen make the situation worse, and may lead to death.

Children older than 2 months who present with fast breathing without chest indrawing are classified as pneumonia (non-severe) and treated at home (Table 10). The standard antimicrobial for outpatient treatment should be effective against the two most common agents of pneumonia: *S. pneumoniae* and *H. influenzae* (70). The choice includes injectable procaine penicillin and two oral antimicrobials: cotrimoxazole and amoxycillin. Amoxycillin is preferred to ampicillin because it is better absorbed, is given three times a day instead of four, and has fewer gastrointestinal side-effects. Because of its broad-spectrum efficacy, low cost, ease of administration, and relatively low rate of adverse side-effects, cotrimoxazole is the preferred drug in most settings. Oral phenoxymethyl-penicillin and benzathine penicillin should *not* be used to treat pneumonia in children because they do not reach high enough levels in the serum to be effective against *H. influenzae* or strains of *S. pneumoniae* with reduced sensitivity to penicillin, which are becoming increasingly common in some countries (e.g., Papua New Guinea, the Philippines). Erythromycin is not recommended because it is insufficiently active against *H. influenzae*.

TABLE 10

MANAGEMENT OF THE CHILD AGED 2 MONTHS - 4 YEARS WITH COUGH OR DIFFICULT BREATHING

SIGNS:	• Not able to drink, • Convulsions, • Abnormally sleepy or difficult to wake, • Stridor in calm child, or • Severe malnutrition.
CLASSIFY AS:	VERY SEVERE DISEASE
TREATMENT:	▸ Refer URGENTLY to hospital. ▸ Give first dose of an antibiotic. ▸ Treat fever, if present. ▸ Treat wheezing, if present. ▸ If cerebral malaria is possible, give an antimalarial.



SIGNS:	• Chest indrawing. [If also recurrent wheezing, go directly to ▸ ***Treat Wheezing***]	• **No** chest indrawing, and • Fast breathing (**50** per minute or more if child 2 months up to 12 months; **40** per minute or more if child 12 months up to 5 years).	• **No** chest indrawing, and • **No** fast breathing (Less than **50** per minute if child 2 months up to 12 months; Less than **40** per minute if child 12 months up to 5 years).
CLASSIFY AS:	SEVERE PNEUMONIA	PNEUMONIA	NO PNEUMONIA: COUGH OR COLD
TREATMENT:	▸ Refer URGENTLY to hospital. ▸ Give first dose of an antibiotic. ▸ Treat fever, if present. ▸ Treat wheezing, if present. (If referral is not feasible, treat with an antibiotic and follow closely.)	▸ Advise mother to give home care. ▸ Give an antibiotic. ▸ Treat fever, if present. ▸ Treat wheezing, if present. ▸ Advise mother to return with child in 2 days for reassessment, or earlier if the child is getting worse.	▸ If coughing more than 30 days, refer for assessment. ▸ Assess and treat ear problem or sore throat, if present (see chart). ▸ Assess and treat other problems. ▸ Advise mother to give home care. ▸ Treat fever, if present. ▸ Treat wheezing, if present.

	Reassess in 2 days a child who is taking an antibiotic for pneumonia:		
	WORSE		IMPROVING
SIGNS:	• Not able to drink. • Has chest indrawing. • Has other danger signs.	THE SAME	• Breathing slower. • Less fever. • Eating better.
TREATMENT:	▸ Refer URGENTLY to hospital.	▸ Change antibiotic or Refer.	▸ Finish 5 days of antibiotic.

All children with pneumonia should be reassessed by the health worker after two days of antimicrobial treatment at home. The procedures, as described in the protocol, are important to reduce mortality due to inadequate treatment or antimicrobial resistance.

It is evident that the WHO protocol does not propose an indiscriminate and widespread use of antimicrobials for the treatment of ARI. In fact, the indications for their use are very selective. In many locations, the quantity of antimicrobials required to treat suspected pneumonia is small compared with the current, usually inappropriate use of antimicrobials (often in inadequate doses) for most respiratory infections. The guidelines emphasize the fact that most children with a cough do not need an antimicrobial. Nevertheless, it is important that mothers are taught to provide special home care for children with simple coughs and colds and to watch for the appearance of signs of pneumonia or other life-threatening complications. The key elements of home care are fluid and nutritional support: appropriate fluid intake, continued breast-feeding, and small frequent meals. The child can also be helped by reducing high fever, clearing the nose, and avoiding overheating or chilling.

Most cough medicines are expensive and of little or no value for the management of the child with cough. Some can be harmful because they contain ingredients such as alcohol and codeine which are toxic for infants and young children. Others have an irrational composition, combining in the same product ingredients with opposing actions, e.g., expectorants (which stimulate cough) and cough suppressants. In general, a productive cough should not be suppressed because it is a useful physiological reflex. Supportive measures should be directed to stimulating secretions. Good hydration is the most beneficial approach. Safe, inexpensive, remedies may help to moisten and soothe the throat and reduce the coughing reflex (72). These can be commercially prepared or mixed at the health facility. Home-made cough remedies and warm herbal teas which have a soothing effect on the throat can also be recommended if they are acceptable to mothers; they are as effective at soothing as commercial remedies.

All **young infants under 2 months of age** with any sign of pneumonia or other sepsis should be referred to a hospital for treatment with benzyl-penicillin plus gentamicin (Table 11), in order to cover both gram-positive and gram-negative organisms. Chloramphenicol, which is recommended for older children, may be used in young infants in a dosage of 25 mg per kg every 12 hours (instead of every 6 hours), but it should not be used in premature or low-birth-weight neonates. High doses of chloramphenicol (greater than 100mg/kg/day) have been associated in young infants with acute circulatory collapse, often fatal (grey syndrome). Antimicrobials are only part of the management of pneumonia in the newborn infant. Supportive measures are also of the utmost importance: oxygen if the child has central cyanosis, is not able to drink, has severe chest indrawing, is grunting, or is restless (if oxygen improves this condition); frequent breast-feeding; and control of temperature, especially protection from chilling.

TABLE 11

MANAGEMENT OF THE INFANT LESS THAN 2 MONTHS OLD WITH COUGH OR DIFFICULT BREATHING

THE YOUNG INFANT (AGE LESS THAN 2 MONTHS)

SIGNS:	• Stopped feeding well, • Convulsions, • Abnormally sleepy or difficult to wake, • Stridor in calm child, • Wheezing, or • Fever or low body temperature.
CLASSIFY AS:	VERY SEVERE DISEASE
TREATMENT:	► Refer URGENTLY to hospital. ► Keep young infant warm. ► Give first dose of an antibiotic.

SIGNS:	• Severe chest indrawing, or • Fast breathing (60 per minute or MORE).	• No severe chest indrawing, and • No fast breathing (LESS than 60 per minute).
CLASSIFY AS:	SEVERE PNEUMONIA	NO PNEUMONIA: COUGH OR COLD
TREATMENT:	► Refer URGENTLY to hospital. ► Keep young infant warm. ► Give first dose of an antibiotic. (If referral is not feasible, treat with an antibiotic and follow closely.)	► Advise mother to give the following home care: ► Keep young infant warm. ► Breast-feed frequently. ► Clear nose if it interferes with feeding. ► Return quickly if: ► Breathing becomes difficult. ► Breathing becomes fast. ► Feeding becomes a problem. ► The young infant becomes sicker.

Even in tropical climates, hypothermia (less than 35.5°C) is a major cause of sickness and death in young infants (73). It is a common reason for failure to gain enough weight. Even when hypothermia is not severe, there is evidence that it can increase the risk of acquiring a bacterial infection, in particular pneumonia. Mothers and health workers need to be taught the importance of keeping young infants warm at all times. Young infants admitted to a health centre or hospital with hypothermia are in great danger unless their body temperature can be raised to a normal level.

6. ACTION AT HOUSEHOLD LEVEL

Because many episodes of pneumonia lead to death within 3-5 days, easy and quick access to antimicrobial therapy is a crucial factor in the reduction of mortality from pneumonia. Unlike diarrhoeal disease control programmes, which promote health care practices in the home that can by themselves reduce diarrhoea mortality, ARI control programmes require that caretakers know when to seek care outside the home. Many deaths from pneumonia occur because sick children are brought to a health worker for care too late, or not at all. For an effective case management programme, mothers should know how to recognize the signs of pneumonia, be motivated to seek appropriate health care outside the home, and comply with a full course of antimicrobials. The mother must not expect an immediate cure from the antimicrobial and should know that she must return to the health service if the child does not improve or worsens.

Experience has shown that it is possible to teach family members to observe the breathing of young children, and the qualitative impression of fast breathing has been found to be predictive of the presence of pneumonia (62-64). Some languages contain words for fast and difficult breathing, showing an existing cultural recognition of these signs.

To be effective, health education must be based on an accurate understanding of the prevailing knowledge, beliefs, and practices of the community. Messages that encourage mothers to recognize the signs of pneumonia should be the result of good ethnographic research that provides information on how mothers perceive pneumonia and identifies obstacles to care-seeking from an appropriate health care provider.

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