IJE vol.33 no.6 © International Epidemiological Association 2004; all rights reserved.
Advance Access publication 27 May 2004

International Journal of Epidemiology 2004;**33**:1362–1372
doi:10.1093/ije/dyh229

THEORY AND METHODS

Methodological and quality issues in epidemiological studies of acute lower respiratory infections in children in developing countries

Claudio F Lanata,[1] Igor Rudan,[2,3] Cynthia Boschi-Pinto,[4] Lana Tomaskovic,[4] Thomas Cherian,[5] Martin Weber[4] and Harry Campbell[2]

Accepted 14 April 2004

Acute respiratory infections are the most important single cause of global burden of disease in young children globally and a major cause of child mortality. A recent review of studies reporting the incidence of acute lower respiratory infections (ALRI) in young children in the developing world was carried out by the WHO Child Health Epidemiology Reference Group in order to inform global burden of disease estimates. The review highlighted the low number of community-based longitudinal studies of ALRI incidence in young children which met minimum quality criteria. It underscored the need to give attention to issues of study design and the reporting of a basic minimum dataset which describes circumstances under which the studies were being conducted and the key design features of the study which may influence the ALRI estimate. This paper aims to provide methodological guidelines for the design, conduct, and reporting of epidemiological studies of ALRI in under-5s in developing countries. It discusses determinants of study quality related to both study design and statistical analysis and also issues requiring further research. It is hoped that these guidelines will stimulate further work in this field and encourage the publication of reports which contain sufficient data to permit a meaningful meta-analysis of the data, thus forming the basis of more reliable future estimates of global burden of ALRI.

Acute respiratory infections (ARI) are the most important single cause of global burden of disease in young children globally and the largest single cause of mortality.[1,2] Prospective community-based surveillance for new episodes of acute lower respiratory infections (ALRI) is necessary for reliable estimates of ALRI incidence to be obtained.[3] In addition, community-based surveillance of ALRI episodes is important in the evaluation of the impact of interventions, such as reduction of exposure to indoor air pollution or micronutrient supplementation, seeking to prevent ALRI in young children. Surveillance studies usually employ a combination of interviews asking for recall of the occurrence of respiratory symptoms and signs recognized by the mother and simple assessments by trained field workers to identify ALRI episodes. However, there are numerous important issues relating to the collection and analysis of such data which can compromise the validity or complicate the interpretation of the incidence estimates that are reported. Examples of such issues include the combination of symptoms and signs upon which an ALRI case definition is based, the conditions under which the study was performed, and the degree to which the study population can be considered to be representative of a wider region.[3–6]

In the 1980s the WHO programme for the control of acute respiratory infections supported a number of methodological

[1] Instituto de Investigacion Nutricional, AP 18-0191, Lima 18, Peru.

[2] Public Health Sciences, University of Edinburgh Medical School, Teviot Place, EH8 9AG, Edinburgh, Scotland, UK.

[3] Department of Epidemiology, School of Public Health 'Andrija Stampar', Rockefellerova 4, 10000 Zagreb, Croatia.

[4] Child and Adolescent Health and Development, World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland.

[5] Vaccines and Biologicals, World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland.

Correspondence: Dr Harry Campbell, Public Health Sciences, University of Edinburgh Medical School, Teviot Place, EH8 9AG, Edinburgh, Scotland, UK. E-mail: Harry.Campbell@ed.ac.uk

studies aimed at clarifying some of these issues. An expert meeting was convened in January 1990, which reviewed the methods and experiences of these studies and attempted to formulate recommendations on the design and data analysis of prospective studies.[6] In 2000–2003 a Child Health Epidemiology Reference Group (CHERG) was constituted by WHO to provide data to improve the evidence base of burden of disease estimates in children. As part of this effort we completed a review of more than 2000 studies on childhood ALRI published between 1961 and 2001. A database containing selected data from each of 300 studies which reported on ALRI incidence, risk factors, or case fatality ratio was created and has been made available by the WHO Child and Adolescent Health and Development programme at: http://www.who.int/child-adolescent-health/New_Publications/Overview/ari_db.htm in order to support further research on this topic. In this paper, we attempt to define and discuss important issues to consider in designing or conducting an ALRI incidence study or in assessing the quality of published studies and interpreting data and comparing estimates from various studies. The CHERG review identified only 28 studies which were well-designed prospective studies that provided valid ALRI incidence estimates.[3] This underscores the need for greater priority to be given to such studies to inform global burden of disease estimates and for guidelines for the proper conduct of these studies.

Acute lower respiratory infections (ALRI) are defined in the International Classification of Diseases as those infections that affect airways below the epiglottis and include acute manifestations of laryngitis, tracheitis, bronchitis, bronchiolitis, lung infections or any combination among them, or with upper respiratory infections, including influenza. The focus of the global burden of disease programme has been on conditions accounting for substantial loss of disability-adjusted life years. Within the WHO CHERG a decision was made to concentrate on pneumonia and bronchiolitis which are considered to be the major components of ALRI accounting for global burden of disease from ARI in young children. This approach is consistent with the WHO approach to case management of ARI and now incorporated in the global Integrated Management of Childhood Illness programmes. These programmes train health workers to identify children with fast breathing, lower chest wall indrawing or selected danger signs (such as cyanosis or inability to drink) in children with respiratory symptoms. For programmatic purposes these are labelled as 'pneumonia' although it is recognized that the children identified in this way include those with pneumonia, bronchiolitis, and a proportion of those with reactive airways disease associated with a respiratory infection. Some authors have used the term 'clinical pneumonia' to describe these conditions but in this review we have used the term ALRI. It is important to recognize that the term ALRI in this context does *not* include the conditions acute laryngitis, bronchitis, or tracheitis.

Determinants of study quality

Determinants related to study setting (Table 1)

ALRI risk factor prevalence[7] varies markedly among different study populations in different countries. The variation can be due to cultural and socioeconomic reasons, geographical or climate differences, or variations in the health care system.

Table 1 Determinants of study quality: study setting

Study population
• geographical location within the country**
• reason why study population selected
• representativeness of wider region**
Geographical context
• altitude**
• annual rainfall**
• number and nature of the seasons
• average monthly temperatures
• outdoor air pollution levels
Socio-cultural context
• classification of population as rural, suburban, or urban**
• socio-economic status and/or average income of typical households
• crowding level
• maternal age and child care experience
• breastfeeding practices**
• exposure to indoor air pollution
• exposure to parental smoking
• birth order
Concomitant public health problems
• prevalence of malnutrition**
• prevalence of AIDS**
• prevalence of other concomitant diseases (e.g. diarrhoea and malaria)
• prevalence of micronutrient deficiency (especially vitamin A or zinc)
Local health care system
• description of local health care system (including maternal and paediatric care)
• access to health care (e.g. http://www.childinfo.org/eddb/ARI.datbase.htm)**
• immunization coverage against measles, pertussis, and Hib**
• proportion of low birthweight infants**
• morbidity from other childhood diseases

** Denotes minimum data set: items which should be reported in all studies.

Study setting

In addition to noting the study site and country it is important to give details that will permit an assessment of the representativeness of the study population to the wider region or national setting. This should include details of the geographical location within the country, the study population, the reasons why the specific population was chosen for study, and a discussion of the extent to which it may represent wider region within that country.

Geographical context

Geographical parameters can substantially affect ALRI incidence estimates.[3] Thus, altitude, annual rainfall, number and nature of the seasons (wet/dry), average monthly temperatures, and any indicators of outdoor air pollution should be reported.

Socio-cultural context

The population under study should be classified as rural, suburban, or urban. Details of socioeconomic status and/or

details of average household income,[8,9] and the prevalence of known risk factors for ALRI should be reported. This should include data on crowding,[10] maternal age and child care experience,[11] breastfeeding practices,[12,13] exposure to indoor air pollution,[14–16] parental smoking,[17] and birth order.[18,19]

Concomitant public health problems

The prevalence of public health problems that are recognized ALRI risk factors should be reported: malnutrition,[18,20,21] other concomitant diseases (primarily diarrhoea, AIDS, and malaria),[18] low birthweight, and micronutrient deficiency (especially vitamin A and zinc deficiency).[22–24]

Local health care system

Details of the local health care system and the level of access to it should be reported. This should focus particularly on factors which may influence ALRI incidence: immunization coverage against measles,[9] pertussis,[25] and Hib[26] and details of maternal and paediatric care.[27] Data on access to health care are available from demographic surveys for regions in over 80 countries from UNICEF at http://www.childinfo.org/eddb/ARI.datbase.htm.

Determinants related to study design (Table 2)

Study duration

The study period should cover all the major periods of annual climate changes (such as wet and dry seasons) and should cover a period of one year or multiples of one year since seasonal factors typically have a major effect on ALRI incidence. Longer study durations may be expected to lead to more robust estimates since any temporary fluctuations in ALRI occurrence will be 'smoothed' to some extent over the longer period of observation.[1] Against this, however, it has been shown that conduct of a surveillance study in a community can affect the results of the study, usually by decreasing the estimates over time (the 'Hawthorne effect'). Thus, it is appropriate in longer-term studies to evaluate this effect by reporting the time trends of estimates.

In theory, active treatment of ALRI cases early in the course of the disease might reduce the level of infectivity of the case and therefore the extent of disease transmission to other children. It is possible, therefore, that this could be one reason for any observed 'Hawthorne effect'. In practice, however, spread of respiratory infection is considered to occur early in the infection and before treatment is likely to have commenced. There was no clear evidence for such an effect among the 28 studies reported in the recent review[3] of global incidence (I Rudan, personal communication).

Site of surveillance

The site of surveillance usually refers to home, field clinic, or hospital, depending on the study design. We have recently shown this to be an important independent determinant of variability in published ALRI incidence estimates, even when correcting for the assessor's experience, case definition, and population type.[3] This effect may be due to other factors related to site of surveillance which were not reported.

Surveillance strategy

Recognition of ALRI episodes by the trained field worker during home visits

Field workers should be trained with standard operating procedures to observe and/or measure clinical symptoms and signs to establish a diagnosis of ALRI. It is important to give precise details of how these measurements were made (Table 2). Standardization exercises using an expert as a standard and ideally having field workers and the expert performing observations on the same children are important aspects of training. The methods used to standardize diagnoses and check inter-rater reliability, if more than one field worker participated in the study, should be given and any results described in full.

Diagnosis of ALRI episode by the physician at a field clinic or hospital

Some ALRI studies employ regular home surveillance of a cohort of children by field workers but require confirmation of any ALRI episode by a hospital-based medical doctor. This has the potential to result in a considerably more reliable procedure for ALRI identification. However, the criteria used and the methods for standardization of the diagnosis if more than one physician participated in the study should be described. If a single physician established all diagnoses then details of what provisions were made to validate these diagnoses should be reported.

Since the referral process is a major potential sources of bias it must be described in detail (Table 2). This should include the average length of time between first identification of the episode and the physician examination, and the proportion of suspected cases not seen by the physician. It is important to specify how the repeat visits to the clinic within the same ALRI episode were dealt with: whether data were collected on all attendances or only for new episodes, and if the latter, the criteria for defining a new episode (i.e. how many days without the symptoms or between visits were used to separate two episodes). A description of how many clinical diagnoses were allowed in the same visit and, if more than one, the provisions for ranking the diagnoses and for selecting the ones to be coded should be reported. The procedure for dealing with a case that came initially with one clinical condition or diagnosis but later, in a separate visit within the same clinical episode, had a second diagnosis of ALRI should be made clear.

Low perceived quality of health care or cultural factors can prevent care takers from presenting children at health facilities. It is therefore important that studies adopt active surveillance in which each cohort child is examined regularly. ALRI incidence estimates from passive surveillance (in which children with ALRI are identified when they present to a health facility) may be strongly influenced by the level of care seeking and access to health facilities and have been shown to decline with distance from and cost of reaching the health facility.[28]

Cohort structure and size

Large age-related and sex-related differences in ALRI incidence (and mortality) exist throughout childhood. In our recent review we found that when the incidence in the first year of life is set to 1.0, the mean ratios of age-specific incidence were 1.00–0.58–0.35–0.22–0.15 over the first 5 years of life.[3] In addition, it has been shown consistently that incidence in male children is greater than in female children. It is important, therefore, to give details of the age and sex structure of the cohort or to report age-specific ALRI incidence rates for each year of age over the 0–4 year range. We identified only five published studies which had reported these age-specific rates.[3]

Study size should be guided by the required precision of the ALRI estimate in observational studies or size of difference in ALRI incidence considered to be important in intervention

Table 2 Determinants of study quality: study design

Definition of the study aims and research questions

- clear statement of a *priori* hypotheses
- definition of study outcomes e.g. acute lower respiratory infections (ALRI) prevalence, incidence, case-fatality ratio

Study duration (multiples of one year)

- month and year at start and end of surveillance
- time trends of estimates (to identify 'Hawthorne effect').

Surveillance procedures

- surveillance location—home, field clinic, health centre, or hospital**
- frequency of surveillance visits**
- level of experience of assessors**

Cohort structure and size

- age and sex structure of the cohort**
- cohort size**
- type of cohort—continuous enrolment or fixed cohort (if latter describe method of any replacement of losses to follow up)**

Maternally reported signs or symptoms

- definition of each sign or symptom (including details of how it was asked)**
- spontaneously elicited or with prompting (or both)
- details of any direct observations of the child
- identity of the interviewer and the informant at each individual check-up
- day on which the recalled information was obtained

Case definition—clinical

- respiratory rate thresholds adopted**
- lower chest wall indrawing definition**
- auscultatory findings and their definitions)**
- presence of other clinical signs e.g. temperature (oral, axillary or rectal), observed cough, sub-costal retraction, intercostal retraction, nasal flaring, grunting, audible wheezing and stridor**
- exact definitions of wheeze (audible and/or auscultatory)
- criteria used to diagnose wheezing disorders or specific diagnoses such as bronchiolitis, asthma, or other wheezing disorders
- details of how children with both ALRI and wheeze were recorded**
- clinical diagnosis (note who made the diagnosis)**
- radiological findings/diagnosis**
- laboratory investigations (e.g. ELISA, immunofluorescence or PCR testing for viral infection)

Case definition—other

- criteria for defining a new episode (criteria to define two separate episodes)**
- number of clinical diagnoses recorded at same visit (if more than one, details of how diagnoses were ranked and selected for recording)

Methods of respiratory rate measurement

- activity level of the child (e.g. sleeping, calm but awake, breastfeeding, crying)**
- type of chronometer used
- observation time**
- counting method employed
- whether second, confirmatory respiratory rate obtained and how final rate decided**

Identification of severe ALRI episodes

1. Presence of clinical signs of severity**
   - nasal flaring
   - noisy breathing
   - lower chest wall indrawing
   - vomiting
   - refusal to (breast)feed
   - breathing rate >70/min
   - episodes of illness prompting the mother to attend a health facility
   - cyanosis
   - data on hypoxaemia from pulse oximeters
2. Need for referral to 2nd or 3rd level health facility**
   - referral routes used by the population under study
   - detailed description of system of referral
   - quality of the referral system (e.g. proportion of suspected cases seen within 24 hours; proportion not seen by physician; proportion who should have been referred and were not)

Radiological recognition of pneumonia

- procedure for taking and reading the chest X-rays
- physicians' access to radiological findings before the clinical diagnosis made**
- method of selection of cases for chest X-ray examination**
- proportion of ALRI episodes in which chest X-ray was taken
- time elapsed between clinical assessment and X-ray examination
- X-ray views taken (e.g. postero-anterior or antero-posterior; lateral)
- X-ray interpretation—with or without access to clinical information**
- system of validating radiological diagnoses (e.g. double or independent reading of all or a subsample of films)**
- level of agreement between readers**
- details of standard features: definite consolidation; other infiltrates; pleural effusion (see text)**
- details of standard categories: definite pneumonia; other consolidation/infiltrate; or no consolidation/infiltrate/effusion (see text)**

Other laboratory investigations

- details of any laboratory tests used to identify aetiological agents
- percentage of cases in which the isolate was positive

Quality control procedures

- methods employed to reduce measurement error
- quality assurance/monitoring methods employed**
- measures of (intra and/or inter) observer reliability**

** Denotes minimum data set: items which should be reported in all studies.

studies. Cohort sizes meeting quality criteria in our recent review varied from <300 (6 studies), 300–1000 (12 studies) to >1000 (10 studies).[3] The total number of enrolled children over the entire study period and mean number of children under surveillance each month should be reported. It should be clear whether enrolment was continuous or a fixed cohort design was employed. If the cohort was fixed, the replacement of losses of follow-up should be described.

Case definition

We have recently reported the effect of case definition on ALRI incidence estimates.[3] Almost all published studies can be classified into one of the two broad groups. The first group used some modification of the original WHO/ARI classification of acute respiratory infections into mild, moderate, and severe based on simple clinical signs (with ALRI episodes falling into the moderate and severe categories) (see below). In the second group of studies, ALRI cases were diagnosed based on physician's own assessment and experience including use of auscultatory findings. We have shown that requiring auscultatory findings, such as crepitations or rales, to be present in the case definition tends to decrease the reported ALRI incidence estimate.[3] Thus, it is important to give a clear description of the exact case definition employed (Table 2). Since most studies have reported estimates based on the presence of fast breathing (see below) or lower chest wall indrawing then separate reporting of these findings would facilitate comparisons of estimates across published studies. Ideally, the data should be reported in a way that ALRI incidence based on a number of differing case definitions can be obtained.

ALRI case definitions based on clinical signs

Shann, on the basis of a study in Papua New Guinea, proposed a simple clinical method for the assessment of ARI in children.[29] A WHO *Working Group on Case Management of Acute Respiratory Infections* reached a consensus that three signs related well to acute respiratory infection severity: rapid breathing, chest indrawing, and 'too sick to feed'.[30,31] The increased respiratory rate associated with pneumonia or bronchiolitis is a patho-physiological response by the body to compensate for the reduction in gas exchange capacity in the lung due to the lung pathology caused by the infection and the resultant ventilation—perfusion imbalance. This results in a respiratory rate which is *continuously* raised over a period of time. This is quite different to the *transient* rise in respiratory rate that can occur in infants and young children in response to a stressful event (as when being examined). The mean respiratory rate is influenced by body temperature rising by about 2.5 breaths per minute for every 1°C rise.[31]

A simple classification of ARI into three categories according to severity was proposed.

(1) '*mild*': cough with no fast breathing (⩾50 breaths per minute) and no chest indrawing, sore throat, ear discharge for >2 weeks, and blocked or runny nose (requires home treatment with supportive measures only);
(2) '*moderate*': cough and fast breathing but no chest indrawing (requires home treatment with antimicrobials and supportive measures);
(3) '*severe*': cough and chest indrawing, cough and not being able to drink, or stridor at rest (requires hospital referral)

This classification system has since been revised to improve the sensitivity of respiratory rate thresholds for identifying pneumonia episodes (sensitivity increasing from approximately 65% to 80%, although specificity decreasing from around 90% to 80%)[32–34] and to improve the definition of chest indrawing.[35]. The WHO classification was thus amended: children <5 years with cough or difficulty breathing were considered to have 'clinical pneumonia' (termed ALRI in this review) if they had fast breathing (⩾60 breaths/min in children ⩽2 months; ⩾50 breaths/min in children 2–11 months; ⩾40 breaths/min in children 1–4 years) or lower chest wall indrawing.[31] Details of the sensitivity and specificity of different respiratory rate thresholds are given in Table 3.

Table 3 Validity of respiratory rate criteria for identification of acute lower respiratory infection (ALRI) episode by age group of child

Study	Age						
	2–11 months		1–4 years		2 months–4 years		
	RR50	RR40	RR50	RR40	RR50	RR40	50/40[a]
PNG—Goroka	80/81		67/90	74/72	72/81		78/73
Gambia—Basse	85/98	100/55	64/98	87/82			
India—Vellore	89/93	96/62	57/96	71/87	75/96	86/78	82/89
Lesotho							
Paediatrician	79/59	100/25	19/91	54/69			
Nurse	59/72	84/44	35/94	69/77			
Philippines	77/90	90/51	52/85	78/75	62/92	83/68	79/78
Swaziland					65/92	77/69	77/83
Gambia—Banjul							81/89[b]
Ethiopia—Gondar							88/87[b]
Kenya—Siaya							97/49[b]
Uganda							76/60[b]

[a] Respiratory rate ⩾50 in age 2–11 months; ⩾40 in age 1–4 years.
[b] Fast breathing or chest indrawing.

We recommend that studies seeking to measure ALRI incidence adopt respiratory rate criteria with high test specificity. The much greater incidence of ARI (around 4–6 episodes per child per year) than of ALRI (around 0.3 episodes per child per year) means that if test specificity is not very high then estimates of ALRI may be greatly inflated. Thus we consider it good practice to obtain a second, confirmatory respiratory rate if the first is elevated and to require both counts to be raised to define ALRI as a means of increasing test specificity. We also recommend that the WHO definition of lower chest wall indrawing be adopted. This requires it to be consistently present in a calm child, since agitation or a blocked nose or breastfeeding can all cause temporary indrawing, especially in infants.

Classification of children with wheeze

Wheezing in young children is now considered to be a broad category of bronchospastic airways disease including bronchiolitis, other associated viral infections, and asthma. Most published ALRI studies from developing countries have either commented that wheeze was not a common finding or excluded children with wheeze from their case definition of ALRI. We have recently shown that inclusion of wheeze in diagnostic criteria for ALRI will tend to inflate the ALRI incidence, as expected.[3] It is important, therefore, to give details of how children with both ALRI and wheeze were recorded.

We recommend that exact definitions of wheeze be given since the nomenclature is this area is confusing. For example, British textbooks tend to refer to (sibilant) rhonchi whereas those from the US refer to wheezes. It should be noted whether the wheeze was audible and/or heard by auscultation. It is difficult to clearly distinguish between wheezing disorders such as bronchiolitis and pneumonia, as crepitations on auscultation and segmental or lobar changes on chest X-ray can be found in both conditions[36] so the criteria used to diagnose bronchiolitis, asthma or other wheezing disorders should be recorded. Where attempts were made to identify infection with respiratory syncytial virus (RSV) the proportion of children with wheeze who were positive for RSV (by ELISA, immunofluorescence, PCR testing, or culture) should be given.

Indicators of severity of the ALRI episode

A severe episode is usually defined as one that results in higher mortality or one that requires hospital treatment or has the presence of a sign used to define a severe episode. The need to receive hospital care is a severity indicator associated with a variety of clinical indications including need for parenteral antibiotics, oxygen therapy, help with feeding difficulties, or when the care giver cannot be relied upon to give oral antibiotic treatment at home. Need for hospital treatment is the most useful definition of severe ALRI for burden of disease studies. This outcome has a meaning that is readily understood and one that can be used directly for planning of health services and when performing cost-benefit analyses of potential interventions to reduce ALRI incidence. However, the study surveillance system usually affects the management of ALRI cases, aborting the need for hospitalization and so this important severity indicator is seldom available from these studies or is underestimated.

The WHO case management algorithm utilizes the presence of lower chest wall indrawing as the main sign indicating severity. However, this is also problematic as it is one of the most difficult clinical signs to teach and standardize and studies have employed different definitions. This has resulted in a very wide range of reported prevalence of chest indrawing. This indicator is also influenced by the prevalence of wheezing disorders in the study population since bronchospastic airways diseases are commonly associated with indrawing.

The signs most often considered in the assessment of severity are given in Table 2.[37] Other indicators such as data on hypoxaemia from pulse oximeters are used where the data are available. In the four published community-based studies that separately reported the incidence of severe ALRI and the incidence of all ALRI, the proportion of severe cases (defined as requiring hospital inpatient treatment) was consistently between 6% and 12%.[3] A more objective way of defining severity of ALRI may be by pulse oximetry. Oximetry measurements of oxygen saturation need to be adjusted for altitude, but at sea level, a cut-off of 90% has been used to denote severe ALRI requiring oxygen.[38]

Radiological recognition of pneumonia

Chest X-rays can often be performed even in community-based studies in developing countries. They can permit a permanent record to be made of the illness episode that allows future review of the study. If a standard procedure for taking and reading the chest X-rays is employed then ALRI estimates between studies can be compared. In addition, if these same procedures are adopted in vaccine intervention trials then an estimate of the vaccine preventable burden of ALRI disease can be obtained by extrapolating impact estimates from intervention trials to local ALRI incidence (burden of disease) data.

The relationship between clinical and radiological assessment depends on the criteria and definitions used. In several Hib and pneumococcal vaccine trials where the radiological criteria have been used for the diagnosis of pneumonia, between 10–20% of cases who meet the WHO clinical criteria for severe episodes of ALRI have evidence of alveolar consolidation or pleural effusion and, therefore, are categorized as primary end point pneumonia for these trials by the standardized WHO radiological criteria (WHO Pneumonia Vaccine Trialists Group—unpublished data). It is important give details of the procedures and definitions adopted in any study (Table 2).

Since the clinical criteria for the recognition of ALRI may vary among studies, the use of radiological criteria have been proposed for defining ALRI episodes that are likely to be due to bacterial agents since chest X-rays are considered more specific than clinical criteria. In addition, data from a number of studies can be later evaluated together using a common protocol thus allowing direct comparison of ALRI case definitions. In order to maintain a reasonably high level of inter-observer agreement, the interpretation of radiographs needs be simplified. The WHO Pneumonia Vaccine Trialists Group[39] classify cases of suspected ALRI into one of three categories (rather than attempting aetiological or pathological diagnosis based on the detailed description of the radiological findings). A computer-based training program has been developed by the WHO Vaccines and Biologicals Programme (VAB) to ensure optimal interpretation. The categories are:

End point consolidation: A dense opacity that may be a fluffy consolidation of a portion or whole of a lobe or of the entire

lung, often containing air-bronchograms and sometimes associated with pleural effusion.

Other (non-endpoint) infiltrate: linear and patchy densities (interstitial infiltrate) in a lacy pattern involving both lungs, featuring peribronchial thickening and multiple areas of atelectasis. Lung inflation is normal to increased. It also includes minor patchy infiltrates that are not of sufficient magnitude to constitute primary endpoint consolidation, and small areas of atelectasis which in children may be difficult to distinguish from consolidation.

Pleural effusion: The presence of fluid in the lateral pleural space between the lung and chest wall. In most cases this will be seen at the costo-phrenic angle or as a layer of fluid adjacent to the lateral chest wall. This does not include fluid seen in the horizontal or oblique fissures. Pleural effusion was considered as primary end point if it was in the lateral pleural space (and not just in the minor or oblique fissure) and was spatially associated with a pulmonary parenchymal infiltrate (including other infiltrate) OR if the effusion obliterated enough of the hemithorax to obscure an opacity.

Based on the above findings a case is categorized into one of three groups:

Primary endpoint pneumonia: The presence of end point consolidation (as defined above) or pleural effusion that meets criteria for primary end point (as defined above).

Other consolidation/infiltrate: The presence of other (non-end point) infiltrate as defined above in the absence of a pleural effusion.

No consolidation/infiltrate/effusion: Absence of end point consolidation, other infiltrate, or pleural effusion.

These criteria are designed for epidemiological studies and may not be suitable for patient care decisions. They are currently being used and evaluated in *Haemophilus influenzae* type b and *Streptococcus pneumoniae* conjugate vaccine trials, pneumonia burden studies, and antibiotic intervention trials. The use of common standardized radiological criteria should facilitate comparability of results and easy application of the data from intervention studies to disease burden studies.

Use of other laboratory investigations

Other laboratory investigations are not generally helpful in establishing a diagnosis of ALRI. Certain laboratory tests are known to be associated more often with bacterial infection and if used in conjunction with radiological criteria may increase the specificity of the diagnosis of bacterial pneumonia. These include total leucocyte and granulocyte counts, erythrocyte sedimentation rate, C-reactive protein, and serum procalcitonin. However, in practice their usefulness is limited by their weak predictive power and the requirement for testing early in the course of the infection. Details of any investigations made should be given together with a report of any biological specimen (such as blood, pharyngeal smear, or lung aspirate) analysed. A note should be made of which laboratory tests were used to identify bacterial and viral aetiological agents, and in what percentage the isolate was successful.

While the specificity of high leucocyte and granulocyte counts in diagnosing bacterial pneumonia is reasonably high depending on the breakpoint chosen, the sensitivity is low.[40] The erythrocyte sedimentation rate is higher in children who have pneumonia with alveolar consolidation compared with those with interstitial pneumonia.[41,42] C-reactive protein has been shown to be significantly higher in patients with bacterial pneumonia, compared with those with non-bacterial pneumonia.[41] Circulating levels of calcitonin precursors are known to increase several thousand-fold with microbial infections and various forms of severe systemic inflammation.[43] Serum procalcitonin has been shown to be helpful in predicting the presence of serious bacterial infections in patients with fever without localizing signs. In pneumonia there is a significant difference between the levels of procalcitonin in those with bacterial and viral pneumonia. Using a cut-off value of 1 ng/l serum procalcitonin demonstrated a sensitivity and specificity of 0.86 and 0.88 respectively in one study.[44] However, malaria may substantially increase serum procalcitonin levels and this may limit the use of this test in malaria endemic populations given the overlap of clinical manifestations of pneumonia and malaria.

Recording of maternally reported signs or symptoms

Local concepts and words used for describing ALRI signs and symptoms and illness categories should be identified prior to surveillance. The most important signs and symptoms relate to the terms used for cough, difficulty breathing, fast breathing, chest indrawing, noisy breathing, phlegm, nasal discharge, not looking well (maternal perception that child is ill), changes in appetite, and reported fever. For each of these signs and symptoms a record should be kept of the study definition used, whether the reported symptom was prompted or not, whether there were any attempts made to classify these symptoms according to severity (e.g. mild, moderate, or severe) and how this was done. When reporting breathing difficulties, blocked nose as a single symptom should not be included in the ALRI definition.[6] The day on which the recalled information was obtained should be recorded since prevalence estimates are strongly influenced by recall period. This effect tends to be greater for milder/commoner signs and symptoms of illness. Because of this effect, home surveillance studies should ideally be done with visits that are no less frequent than weekly.

Frequency of monitoring

There is a general concern that the ALRI incidence estimates will increase with a greater frequency of monitoring in community-based studies. However, our recent review[3] did not find any strong correlation between frequency of monitoring and reported ALRI incidence when the interval between monitoring was not longer than 2 weeks. We recommend that frequency of monitoring should ideally be once a week and not greater than every 2 weeks.

Level of experience of assessors

Assessors can range from lay reporters, trained field workers, medical students, nurses, physicians, to paediatricians or combinations of the above. It has been shown that assessors with higher qualifications are generally associated with lower reported ALRI incidence estimates.[3] This is, at least in part, because they are likely to apply case definitions which have higher specificity for the recognition of ALRI. The exact qualification of the assessor and details of any training for the study should therefore be described.

Definition of an episode

There is no clear consensus on the definition of the start and end of a discrete ALRI episode. This will influence estimates of

ALRI duration but also of ALRI incidence. We recommend that an episode begins with the first day of cough and rapid breathing (reported or measured), and ends with the last day of the same combination. However, a minimum of 14 days free of these combined symptoms should be required between the end of one episode and the beginning of the next. If symptoms recur within a period of less than 14 days, these days of symptoms, as well as the intervening symptom-free days, should be considered part of the immediately preceding episode. Some episodes may start with days of cough before rapid breathing/raised respiratory rate develops. Children with bronchospastic airways disease may be particularly prone to cough for prolonged periods of time and pneumonia may occur with this clinical background in these children. These 'cough-only' days should not be included in the episode of ALRI. Similarly, cough alone after rapid breathing ceases to be reported or respiratory rates return to normal levels should not be considered part of the ALRI episode.[6] Clearly, this definition will be affected by the frequency of home or clinic visits at which the respiratory rate was counted.

Duration of ALRI signs and symptoms during an episode

If duration of ALRI episodes is an important study endpoint then the mean, median, and range of duration of episodes and of symptoms and signs associated with the episode should be calculated. If there are interruptions within the episode, two periods of symptoms should not be counted, but instead the mean and duration calculated for the whole period.[6]

Determinants related to statistical analysis

The specific method of dealing with the occurrence of multiple episodes of illness within the same child and the methods of calculating prevalence and incidence estimates are important to consider.

Prevalence of ALRI symptoms

Reporting the prevalence of ALRI signs and symptoms in all studies might help understand differences in reported ALRI incidence rates. Prevalence estimates may be based on data on the presence or absence of symptoms for each day under surveillance, or only on observations made on the day of the home visit. Days with missing data, such as due to temporary study absences, should be excluded from the denominator in these estimates. It would be useful to report prevalence rates by age, sex, season, and study year.

In addition, it would be useful to examine the mean respiratory rate and the prevalence of elevated respiratory rates in children without reported or observed cough, or any symptoms and signs of ALRI. This would not be possible in all studies, as some are designed to measure breathing rates only for children with respiratory symptoms or signs.

Where data are available, the prevalence of fast breathing should be available, using the cut-off points described above. The prevalence of an elevated respiratory rate could further be investigated separately for first and second count (to explore the benefit of two consecutive counts).

Incidence of ALRI

Most studies use child-weeks of follow-up (number of weeks each child was under surveillance) as the denominator to calculate the incidence rate of ALRI. These should include all weeks when the child was seen by the field-worker, as well as the weeks when the child was temporarily absent from the home, but should not include periods of time when the child had moved away from the study area. We recommend weeks of illness should not be subtracted from the total weeks of follow-up. Some studies may use child-days of follow up instead, but for ALRI surveillance, child-weeks may be more appropriate.

Some issues requiring further research

Sensitivity and specificity of ALRI symptoms and signs

The WHO criteria were developed to serve as a diagnostic test in health facilities with poor access to properly trained physicians or other health workers rather than for use in epidemiological studies. In this context high sensitivity is the dominant test attribute. However, there is a need to consider further the most appropriate respiratory rate thresholds for research purposes where high specificity is relatively more important. For example, misclassification of cough and cold episodes as ALRI (due to low test specificity) will act to reduce the true power of an intervention study to detect a difference in ALRI incidence among intervention groups. The criterion reference or 'gold standard' for the assessment of sensitivity and specificity of any clinical sign or symptom could be the assessment of a trained paediatrician on the same child or the assessment of the WHO panel of radiologists (or other panel using the WHO criteria). One area of particular importance for future research is to identify clinical, radiological, or laboratory criteria that can reliably distinguish between ALRI and bronchospastic airways diseases in children who present have audible and/or auscultatory signs of wheeze.

Aetiology-specific ALRI incidence and prevalence

It has recently been estimated that approximately 165 million episodes of ALRI occur globally each year in children aged 0–4 years, resulting in 2.1 million deaths.[3] Current published data suggest that after excluding measles and pertussis-related deaths, the remaining deaths, attributed collectively to ALRI, are in large part due to *Streptococcus pneumoniae, Haemophilus influenzae,* and respiratory syncytial virus.[26] A future goal will be to improve the estimates of the proportion of ALRI morbidity which can be assigned to specific aetiologic agents. This would be important for health planning and the assessment of the likely impact of aetiology-specific interventions such as immunization against *Haemophilus influenzae type b, Streptococcus pneumoniae* and respiratory syncytial virus. However, the other agents, such as *Staphylococcus aureus*, might have a greater role than generally thought, especially in particular locations of the world.

It has been proposed that the preferred approach to investigate the proportion of new cases/deaths attributable to each agent is to study the decrease in incidence or mortality associated with the introduction of a new vaccine—the so-called 'probe' study design. This has already been successfully performed with *Hib* vaccine in the Gambia,[26] and several other intervention trials using conjugate pneumococcal vaccines are underway.

However, until the completion of these studies, a review of hospital-based studies which investigate the aetiology of ALRI using reasonably sensitive methods (lung aspirate and naso-pharyngeal aspirate studies employing recommended bacterial and viral isolation and identification methods in centres with proven ability to study these microbiological agents) can be performed. The validity of this approach, however, is restricted by

concerns about bias in the referral of cases to hospital, selection bias in the hospital cases which are studied and the generally low and differential sensitivity (across different aetiological agents—e.g. 80–90% for RSV by immunofluorescence or polymerase chain reaction but only 10–20% for bacterial agents by blood culture) of currently available methods.[36]

Other medical conditions that may affect the diagnosis of ALRI

The influence of (co-existing) medical conditions on the diagnosis of ALRI require further study. Malaria, which can present with fast breathing due to high fever, severe anaemia, acidosis or pulmonary sequestration of parasites, may thus be classified as an ALRI episode. A recent study[3] investigated this problem and concluded that, generally, the risk of malaria at the study site was not correlated with ALRI incidence estimates in published studies. Severe anaemia may also result in fast breathing which may be classified incorrectly as ALRI but this has not been studied formally. The effect of (severe) malnutrition on the performance of fast breathing and lower chest wall indrawing as a predictor of ALRI and on ALRI incidence estimates[45] also merits further study.

Clustering of ALRI

Some published studies suggest that the majority of episodes of ALRI may be clustered among a small (20%) group of children. The degree of clustering will be an important consideration to take into account when discussing the optimal approach to the analysis of these data. Further thought is required about how to handle data from children with multiple episodes since these are clearly not independent of each other. Incidence studies should report ALRI incidence with and without controlling for repeat episodes.[6] A substantial proportion of children with recurrent ALRI in some settings may have wheeze and may be classified as asthma.[46]

Recall of ALRI signs and symptoms by informant type

There are few studies reporting data on the ability of informants to recall individual ARI signs or symptoms (which could help inform the definition of the optimal recall period for surveillance and thus the best frequency of home visits). Examination of this issue would require recording of the day on which the information was obtained and ideally the type of informant that provided the information about the child on each visit, as mentioned above.[6] The reliability of future recall by the care-taker of ALRI symptoms and signs in the child could then be assessed in comparison with direct observations and reports on the day of examination.

Effects of the environment and climate

The effects of climate on ALRI incidence, such as altitude, average temperature, annual rainfall, and number and duration of wet and dry seasons have not been investigated in detail. Our recent review has identified annual rainfall as a significant independent determinant of ALRI variation across 28 published studies, possibly reflecting an effect on RSV or other respiratory virus activity.[3]

Conclusion

Although ALRI represents the leading single cause of death and burden of disease in young children globally, estimates of ALRI incidence are based on only a small number of studies meeting minimum quality criteria. Demographic and health surveys (DHS) collect information on maternal and child health and child survival from many developing countries. However, their only data which are relevant to estimating childhood ALRI incidence are the:

percentage of children under 3 (5) years who were ill with a cough accompanied with rapid breathing,
percentage who were ill with fever during the two weeks preceding the survey, and
percentage of ill children who were treated with specific remedies.'

These point prevalence estimates will be strongly influenced by the season during which the survey took place and are only based on mothers' self reports. This results in highly variable and in many instances implausible (with respect to other published incidence data) estimates. It is conceivable that these prevalence estimates could be improved by training assessors in the methods described in this review and then deriving an incidence estimate by assuming an average episode duration of 2–4 weeks. The point prevalence estimate would then be roughly equivalent to 1-month incidence estimate. However the strong seasonal influence on ALRI would mean that these data would only be meaningful to monitor time trends in a specific setting if the surveys were carried out in the same season each year. Comparisons of DHS estimates across countries and settings would remain very problematic, as at present.

There is therefore a need for further ALRI surveillance studies to be conducted to improve the global estimates and to explore the extent to which true national and regional variations exist. Since a large number of factors can affect ALRI incidence estimates in longitudinal community-based studies it is essential that study design measure these factors. Furthermore, in order to permit valid comparisons of ALRI incidence across studies it is important that a minimum dataset related to study setting, study methods, and statistical analysis is reported in all publications. In this paper, we attempt to identify and describe many of these factors and propose how these data should be reported. It would be helpful if international agencies who fund such studies make available on the Internet any essential data that were not accepted for inclusion in the publication but which might be of interest to the wider research and public health policy community. Finally, we highlight several issues that warrant further research to provide better understanding of determinants of ALRI incidence in developing country settings. Giving priority to this research agenda would result in improved understanding of published data and improved estimates of the global burden of disease from ALRI in young children in developing countries.

Acknowledgements

The authors CL and HC participated in the WHO meeting on methodological issues related to the measurements of ALRI in 1990 which formed a starting point for this paper. We would like to acknowledge the contribution of the other participants of this meeting (including Betty Kirkwood, Sandy Gove, Steven Rogers, Julian Lob-Levyt, and Paul Arthur—see ref. 6). We also acknowledge the support of the William and Melinda Gates

Foundation and the WHO Child and Adolescent Health and Development programme in supporting the work of the WHO Child Health Epidemiology Reference Group which helped direct and review this paper.

References

[1] Mathers CD, Murray CJL, Lopez AD, Stein C. *The Global Burden of Disease 2000 Project: Objectives, Methods, Data Sources and Preliminary Results*. Evidence and Information for Policy (EIP), World Health Organization, October 2001. http://www3.who.int/whosis/discussion_papers/pdf/paper36.pdf.

[2] Morris S, Black RE. Where and why are 10 million children dying every year? *Lancet* 2003;**361:**2226–34.

[3] Rudan I, Tomaskovic L, Boschi-Pinto C, Campbell H. Estimating the incidence of acute lower respiratory infections (ALRI) in children under five years in developing countries: 1 Global estimate. *Bull WHO* 2003 (submitted for publication).

[4] Lanata CF, Quintanilla N, Verastegui HA. Validity of a respiratory questionnaire to identify pneumonia in children in Lima, Peru. *Int J Epidemiol* 1994;**23:**827–34.

[5] Kirkwood BR, Cousens SN, Victora CG, De Zoysa I. Issues in the design of studies to evaluate the impact of community-based interventions. *Trop Med Int Health* 1997;**2:**1022–29.

[6] Lanata C, Black B, Kirkwood B *et al*. *Programme for the Control of Acute Respiratory Infections. Report of a Meeting on Methodological Issues Related to the Measurement of Episodes of Childhood Pneumonia in Prospective Home Surveillance Studies*. WHO/ARI/90.15. Geneva: World Health Organization, 1990.

[7] Kirkwood BR, Gove S, Rogers S, Lob-Levyt J, Arthur P, Campbell H. Potential interventions for the prevention of childhood pneumonia in developing countries: a systematic review. *Bull World Health Organ* 1995;**73:**793–98.

[8] Tupasi TE, Leon LE, Lupisan S *et al*. Patterns of acute respiratory tract infection in children: A longitudinal study in a depressed community in Metro Manila. *Rev Infect Dis* 1990;**12:**S940–49.

[9] Oyejide CO, Osinusi K. Acute respiratory tract infection in children in Idikan Community, Ibadan, Nigeria: severity, risk factors and severity of occurrence. *Rev Infect Dis* 1990;**12(Suppl.8):**S1042–46.

[10] Ruutu P, Halonen P, Meurman O *et al*. Viral lower respiratory tract infections in Filipino children. *J Infect Dis* 1990;**161:**175–79.

[11] Selwyn BJ. The epidemiology of acute respiratory tract infection in young children: Comparison of findings from several developing countries. *Rev Infect Dis* 1990;**12(Suppl.8):**S870–88.

[12] Victora CG, Kirkwood BR, Ashworth A *et al*. Potential interventions for the prevention of childhood pneumonia in developing countries: improving nutrition. *Am J Clin Nutr* 1999;**70:**309–20.

[13] Lopez de Romana G, Brown KH, Black RE, Kanashiro HC. Longitudinal studies of infectious diseases and physical growth of infants in Huascar, an underprivileged peri-urban community in Lima, Peru. *Am J Epidemiol* 1989;**129:**769–84.

[14] Romieu I, Samet JM, Smith KR, Bruce N. Outdoor air pollution and acute respiratory infections among children in developing countries. *J Occup Environ Med* 2002;**44:**640–49.

[15] Armstrong J, Campbell H. Indoor air pollution exposure and lower respiratory infections in young Gambian children. *Int J Epidemiol* 1991;**20:**424–29.

[16] Smith KR, Samet JM, Romieu I, Bruce N. Indoor air pollution in developing countries and acute lower respiratory infections in children. *Thorax* 2000;**55:**518–32.

[17] Pedreira FA, Guandolo VL, Feroli EJ, Mella GW, Weiss IP. Involuntary smoking and incidence of respiratory illness during the first year of life. *Pediatrics* 1985;**75:**594–97.

[18] Black RE, Brown K, Becker S. Longitudinal studies of infectious diseases and physical growth of children in rural Bangladesh. *Am J Epidemiol* 1982;**115:**305–14.

[19] De Romana GL, Brown KH, Black RE, Kanashiro HC. Longitudinal studies of infectious diseases and physical growth of infants in Huascar, an underprivileged peri-urban community in Lima, Peru. *Int J Epidemiol* 1989;**129:**769–835.

[20] James JW. Longitudinal study of the morbidity of diarrheal and respiratory infections in malnourished children. *Am J Clin Nutr* 1972;**25:**690–94.

[21] Tupasi TE, Velmonte MA, Sanvictores MEG *et al*. Determinants of morbidity and mortality due to acute respiratory infections: implications for intervention. *J Infect Dis* 1988;**157:**615–23.

[22] Barreto ML, Santos LM, Assis AM *et al*. Effect of vitamin A supplementation on diarrhoea and acute lower respiratory tract infections in young children in Brasil. *Lancet* 1994;**343:**228–331.

[23] Black RE. Zinc deficiency, infectious disease and mortality in the developing world. *J Nutr* 2003;**133(Suppl.1):**1485S–89S.

[24] Sazawal S, Black RE, Jalla S, Mazumdar S, Sinha A, Bhan MK. Zinc supplementation reduces the incidence of acute lower respiratory infections in infants and preschool children: a double-blind, controlled trial. *Pediatrics* 1998;**102:**1–5.

[25] Mulholland K. Measles and pertussis in developing countries with good vaccine coverage. *Lancet* 1995;**345:**305–07.

[26] Mulholland K, Hilton S, Agdebola R *et al*. Randomised trial of Hib tetanus protein conjugate for prevention of pneumonia and meningitis in Gambian infants. *Lancet* 1997;**349:**1191–97.

[27] Bang AT, Bang RA, Tale O *et al*. Reduction in pneumonia mortality and total childhood mortality by means of community-based intervention trial in Gadchiroli, India. *Lancet* 1990;**336:**201–06.

[28] Weber MW, Milligan P, Sanneh M *et al*. An epidemiological study of RSV infection in The Gambia. *Bull World Health Organ* 2002;**80:**562–68.

[29] Shann F, Hart K, Thomas D. Acute lower respiratory tract infections in children: possible criteria for selection of patients for antibiotic therapy and hospital admission. *Bull World Health Organ* 1984;**62:**749–51.

[30] World Health Organization. Clinical management of acute respiratory infections in children: a WHO memorandum. *Bull World Health Organ* 1981;**59:**707–16.

[31] Pio A. Standard case management of pneumonia in children in developing countries: the cornerstone of the ARI programme. *Bull World Health Organ* 2003;**81:**298–99.

[32] Cherian T, John TJ, Simoes E, Steinhoff MC, John M. Evaluation of simple clinical signs for the diagnosis of acute lower respiratory tract infection. *Lancet* 1988;**ii:**125–28.

[33] Campbell H, Byass P, Greenwood BM. Simple clinical signs for diagnosis of acute lower respiratory infections. *Lancet* 1988;**ii:**742–43.

[34] Mulholland EK, Simoes EA, Costales MO, McGrath EJ, Manalac EM, Gove S. Standardized diagnosis of pneumonia in developing countries. *Pediatr Infect Dis J* 1992;**11:**77–81.

[35] Campbell H, Lamont AC, O'Neill KP *et al*. Assessment of clinical criteria for identification of severe acute lower respiratory tract infections in children. *Lancet* 1989;**i:**297–99.

[36] Weber MW, Dackour R, Usen S *et al*. The clinical spectrum of RSV disease in The Gambia. *Pediatr Infect Dis J* 1998;**17:**224–30.

[37] Shann F, Barker J, Poore P. Clinical signs that predict death in children with severe pneumonia. *Pediatr Infect Dis J* 1989;**12:**852–55.

[38] Usen S, Weber M, Mulholland K, Jaffar S, Oparaugo A, Omosigho C. Clinical predictors of hypoxaemia in Gambian children with acute lower respiratory tract infection: prospective cohort study. *BMJ* 1999;**318:**86–91.

[39] World Health Organization Pneumonia Vaccine Trialists Group. *Standardisation of Interpretation of Chest Radiographs for the Diagnosis of*

Pneumonia in Children. WHO Department of Vaccines and Biologicals. WHO/V&B/01.35, 2001.

[40] Korrpi M, Kroger L, Laitenen M. White blood cell differential counts in acute viral and bacterial infections in childhood. *Scand J Infect Dis* 1993;**25:**435–40.

[41] Korrpi M, Heiskanen-Kosma T, Leinonen M. White blood cells, C-reactive protein and erythrocyte sedimentation rate in pneumococcal pneumonia in children. *Eur Respir J* 1997;**10:**1125–29.

[42] Triga MG, Syrogiannopoulos GA, Thoma KD, Fezoulidis IB, Pastromas VG, Beratis NG. Correlation of leucocyte count and erythrocyte sedimentation rate with day of illness in presumed bacterial pneumonia of childhood. *J Infect* 1998;**36:**63–66.

[43] Muller B, Becker KL. Procalcitonin: how a hormone became a marker and mediator of sepsis. *Swiss Med Wkly* 2001;**131:**595–602.

[44] Moulin F, Raymond J, Lorrot M, Marc E, Coste J, Iniguez JL. Procalcitonin in children admitted to hospital with community acquired pneumonia. *Arch Dis Child* 2001;**84:**332–36.

[45] Falade E, Tschappeler H, Greenwood BM, Mulholland EK. Use of simple clinical signs to predict pneumonia in young Gambian children: the influence of malnutrition. *Bull World Health Organ* 1995;**73:**299–304.

[46] Heffelfinger JD, Davis TE, Gebrian B, Bordeau R, Schwartz B, Dowell SF. Evaluation of children with recurrent pneumonia diagnosed by World Health Organisation criteria. *Pediatr Infect Dis J* 2002;**21:**108–12.