Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children

World Health Organization Pneumonia Vaccine Trial Investigators’ Group

DEPARTMENT OF VACCINES AND BIOLOGICALS

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Abbreviations

CDC Centers for Disease Control and Prevention (USA)
Hib H. influenzae type B
HIV human immunodeficiency virus
WHO World Health Organization
This document describes the process developed by an international working group to standardize the radiological diagnosis of pneumonia in children. The purpose of this tool is to enable the collection of comparable data when measuring pneumonia disease burden or estimating the impact of various interventions in reducing the pneumonia burden. Thus, the definitions and methods described in this document are more for epidemiological purposes rather than for use in direct patient care. The definitions are aimed at achieving a high specificity, which is important for the purpose for which the tool was developed. The criteria for diagnosis of pneumonia described in this document may not always be appropriate for making decisions regarding patient care. In the latter situation one would opt for criteria that are more sensitive, especially if the consequences of a missed diagnosis are serious.

The document also describes an elaborate process for digitizing chest radiographs. This process is designed for large field trials where chest radiographs are taken at one of several participating hospitals and the original films are often not available to investigators for interpretation and storage. This process is seldom required when interpreting films for direct patient care.

The standardized process for interpreting chest radiographs described in this document is considered an important tool in generating comparable data on the burden of pneumonia disease and the impact of interventions. We would recommend that readers view it in this context and exercise caution in using the criteria therein for patient management.
Background

Acute lower respiratory infection, primarily pneumonia, is the leading cause of childhood death in developing countries, resulting in an estimated four million deaths annually. (1) The two leading causes of pneumonia in developing countries are Streptococcus pneumoniae and H. influenzae. (2) The current strategy to reduce pneumonia deaths is by appropriate case management, which focuses on early detection and treatment of pneumonia. (3) The case management strategy has been a moderate success as demonstrated in several intervention trials (4) but such a programme may be difficult to sustain outside a trial setting, especially in areas with poor access to basic health care. The increasing incidence of antimicrobial resistance in the pathogens causing pneumonia may further limit its use in the future. Cotrimoxazole resistance in pneumococci is being increasingly recognized in some developing countries. (5) In an area of high prevalence of cotrimoxazole resistance in Pakistan, high rates of treatment failure with cotrimoxazole in patients with severe pneumonia and bacteraemic pneumonia were observed in comparison to amoxycillin; in patients where pneumococci were isolated no treatment failures were seen with amoxycillin whereas there was a 28% failure rate with cotrimoxazole. (6)

An alternate approach to reducing pneumonia mortality and morbidity is through vaccination. The burden of pneumonia preventable by the introduction of the H. influenzae type b (Hib) vaccine was demonstrated in trials in The Gambia and Chile (7,8) and other trials are under way to determine the efficacy of this vaccine in reducing the pneumonia burden in other parts of the world, particularly Asia. Since S. pneumoniae is a more frequent cause of pneumonia than Hib, it is anticipated that an effective pneumococcal vaccine will have a far greater impact on pneumonia mortality and morbidity than Hib vaccine. Till recently, large-scale use of pneumococcal vaccine was not considered because the available 23-valent polysaccharide vaccine was not immunogenic for important serotypes in infants below two years, the age at which most of the disease and mortality occur. A 7-valent protein conjugated pneumococcal vaccine has recently been licensed for use in the United States. A trial in California showed that the vaccine efficacy for preventing invasive disease caused by the pneumococcus vaccine serotypes was 97.4% (95% CL 82.7 – 99.9) (9,10). Trials with 9 or 11-valent protein-conjugated pneumococcal vaccines are currently underway or are being planned in several developing countries. In the California study, like in most other similar studies, the primary endpoint was reduction in invasive disease, defined as cases with bacteria isolated from sterile body sites. This approach to the definition of vaccine efficacy, when used in the context of Hib and pneumococcal vaccine efficacy in developing countries has several limitations. The currently available techniques are not sufficiently sensitive in identifying cases of Hib and pneumococcal pneumonia, the primary outcome of interest in developing countries; the use of blood culture will only enable
the identification of a small proportion of such cases and lung aspirates will not be feasible in all cases. It is conceivable that the vaccine may reduce the frequency of bacteraemic pneumonia without reducing the incidence of non-bacteraemic pneumonia or that antibody produced in response to vaccination may suppress or obscure bacteraemia while not affecting the rate or severity of pneumonia. It is also possible that the reduction in pneumonia by vaccine serotypes may be offset by an increase in disease by other serotypes. These limitations favour the use of an approach that measures reduction in clinical pneumonia rather than bacteriologically proven disease. Such an approach would also give a more accurate estimate of the public health impact of a vaccination programme and make it easier for policy-makers to understand the cost benefits of a vaccination programme.

**Vaccine probe method for estimating disease burden**

Currently, establishing the etiological diagnosis of pneumonia in children is limited by the lack of a suitable specimen for bacterial culture. Studies using other tests such as antigen detection and serology lack specificity. Blood culture is most often used to determine etiology of bacterial pneumonia but lacks sensitivity and is positive in only about 19 to 39% of culture-proven Pneumococcal pneumonia (13, 16–19). Lung aspirates are considered the gold standard for bacteriological diagnosis but are not practical in field studies and are limited to those children with a significant area of consolidation in an accessible area. Thus most studies on the etiology of pneumonia have a significant proportion of cases where the etiology is not established. It is also likely that the proportion of cases with a mixed bacterial-viral infection is underestimated.

Vaccine trials with clinical and radiological end points have the potential to provide information about the etiology of pneumonia, such information may be useful for case management, and help to restrict antibiotics use to cases that are most likely to benefit from them.

Field trials with the Hib conjugate vaccine in the Gambia and in Chile (7,8) showed remarkably consistent results in that there was an approximately 20% decline in the incidence of cases of radiological pneumonia at each site. It would not be unreasonable to conclude, therefore, that Hib was responsible for approximately 20% of cases of severe pneumonia in these areas. Similar data from the pneumococcal vaccine trials could provide an estimate the contribution of this organism to pneumonia burden. On the other hand, if the vaccine is not effective in reducing all pneumonia while reducing bacteraemic disease, there is a real danger of underestimating the significance of this pathogen, although a pure focus on bacteriologic end-points would overestimate the value of the vaccine in this setting.

The concept of disease burden studies focused on childhood pneumonia, regardless of cause, is a WHO initiative in which personnel from the Centers for Disease Control and Prevention (CDC) have been invited to facilitate the development of a generic protocol to be used to generate disease burden data for developing countries. These data would be referable to data from the efficacy studies in countries in the same regions and such data would facilitate the introduction of pneumococcal vaccines into those countries. Starting such studies now should minimize the delay in pneumococcal vaccine introduction and avoid the problems with the introduction of Hib vaccines.
In selecting the basic parameters to be used for this project, the focus, WHO’s current focus, would be on hospitalizations in 0 to 23-month-old children. Since there may be considerable variation in the threshold for hospitalization in different countries and since in some countries death may occur before arrival at hospital, this parameter by itself would not be adequate and would have to be supplemented with adequate definitions of pneumonia for use in evaluation of hospital databases. The use of a standardized set of definitions for pneumonia related to those used in efficacy trials would be very valuable in that they would provide a reliable estimate of the reduction of disease burden with the use of vaccine.

Radiological diagnosis of pneumonia

Currently, the best available method for diagnosing pneumonia is radiography. It is universally agreed that there exists at present no strict radiological definition of pneumonia in children. Instead, there is a spectrum of appearances that are consistent with the clinical and pathological diagnosis of pneumonia. At one end is the typical appearance of severe lobar consolidation, which is known to be strongly associated with bacterial pneumonia. At the other end are the mild interstitial and perihilar changes that are often associated with viral infections or asthma, and that may be part of the spectrum of normal appearances for children in developing countries. While the contribution of pneumococcus in those with lobar consolidation is known (see Table 1), its contribution to cases with these milder X-ray appearances is not as well recognized and will be an important finding in the current generation of vaccine trials.
Data from some of the etiological studies using lung aspirates along with the radiological findings in the children studied and the proportion in whom any bacteria or pneumococcus was detected are summarized in Table 1.

Table 1. Summary of radiological findings and bacterial isolation rates from lung aspirates in children with pneumonia.

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Site</th>
<th>N</th>
<th>Radiological criteria</th>
<th>% bacterial*</th>
<th>% pneumococcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mimica (12)</td>
<td>Chile</td>
<td>505</td>
<td>Bronchopneumonia (pleural effusion and lobar consolidation excluded)</td>
<td>45.1 (56.8)</td>
<td>1</td>
</tr>
<tr>
<td>Mimica (12)</td>
<td>Chile</td>
<td>25</td>
<td>Lobar consolidation</td>
<td>28</td>
<td>24</td>
</tr>
<tr>
<td>Shann (13)</td>
<td>PNG</td>
<td>83</td>
<td>Consolidation away from hilum</td>
<td>61.4</td>
<td>34</td>
</tr>
<tr>
<td>Kalra (14)</td>
<td>India</td>
<td>70</td>
<td>Consolidation</td>
<td>51.3 (60)</td>
<td>25.7</td>
</tr>
<tr>
<td>Cunanan (15)</td>
<td>Philippines</td>
<td>185</td>
<td>Confluent densities, consolidation, fluid or air in pleural space, pneumatocele, abscess (bronchopneumonia 43%, effusion 37%, lobar pneumonia 16%)</td>
<td>53 (50)</td>
<td>9</td>
</tr>
<tr>
<td>Falade (16)</td>
<td>Gambia</td>
<td>100</td>
<td>Lobar consolidation (6 with empyema)</td>
<td>52</td>
<td>36</td>
</tr>
<tr>
<td>Wall (17)</td>
<td>Gambia</td>
<td>64</td>
<td>Lobar consolidation</td>
<td>64</td>
<td>53</td>
</tr>
<tr>
<td>Adegbola (18)</td>
<td>Gambia</td>
<td>35</td>
<td>Consolidation adjacent to chest wall (malnourished)</td>
<td>37.1</td>
<td>20</td>
</tr>
<tr>
<td>Adegbola (18)</td>
<td>Gambia</td>
<td>59</td>
<td>Consolidation adjacent to chest wall (well nourished)</td>
<td>49.1</td>
<td>40.6</td>
</tr>
<tr>
<td>Silverman (19)</td>
<td>Nigeria</td>
<td>56</td>
<td>Lobar consolidation or effusion</td>
<td>82.1</td>
<td>53.6</td>
</tr>
<tr>
<td>Silverman (19)</td>
<td>Nigeria</td>
<td>44</td>
<td>Bronchopneumonia (ill-defined infiltrates)</td>
<td>84</td>
<td>15.9</td>
</tr>
<tr>
<td>Diakparomre (20)</td>
<td>Nigeria</td>
<td>73</td>
<td>Consolidation</td>
<td>54.2 (73.9)</td>
<td>8.2</td>
</tr>
</tbody>
</table>

* Figure in parentheses indicates the percentage of patients without prior antimicrobial treatment who had positive culture.

Though some degree of alveolar consolidation is necessary for lung aspirates, there were a few studies where aspirates were obtained even in children without lobar consolidation. In two studies, one from Chile (12) and the other from Nigeria (19) the authors clearly differentiated between lobar consolidation and other infiltrates (termed as bronchopneumonia). In these studies, bacteria were isolated from 45% and 84%, respectively, of children with bronchopneumonia though pneumococci formed only a small proportion of the isolates. In another study from the Philippines a majority of patients had bronchopneumonia (which was defined as diffuse alveolar infiltrates) but the bacteriological results from these patients were not presented separately from those with lobar pneumonia. In this study also, while overall isolation rates of bacteria were high, pneumococcus was isolated in only a small proportion. In contrast, in most of the studies where patients had lobar
consolidation, the predominant bacterial pathogen was S. pneumoniae, especially in well-nourished children; in malnourished children mycobacteria were often detected (18). These data suggest that the radiological manifestation most likely to be associated with pneumococcal infection is lobar consolidation; the presence of other types of infiltrates may also suggest bacterial etiology in a sizeable proportion of cases but is usually due to bacteria other than pneumococcus. However, a proportion of these, albeit small, are also caused by pneumococcus. Since the number of children who have infiltrates other than lobar consolidation is likely to be substantially higher than those with lobar consolidation, this small proportion may add up to a sizeable number of cases prevented by vaccination. Therefore, though pneumonia with lobar consolidation may remain as the primary end-point of interest inasmuch as it represents pneumonia most likely to be due to pneumococcus, it would be important to count cases with other pulmonary infiltrates.

In most of the studies cited above, there was no clear description of the radiological findings and there does not appear to have been a standardized interpretation of the radiographs. Therefore, no definite conclusions can be drawn from these studies. This makes it difficult to apply the results of these studies to define clear end-points for vaccine trials and has been one of the difficulties in comparing the results from many of the reported studies. It is a problem that must be addressed in future studies.

An additional problem in certain sites would be the increasing prevalence of HIV infection in the study population. Pneumococcal pneumonia in HIV-infected individuals may have an atypical presentation, with multilobar distribution of pathology being more common (21). On the other hand, opportunistic infections, such as P. carinii pneumonia, which are common in this population may produce radiological changes that are similar to those associated with pneumococcal pneumonia (19). In areas with high prevalence of HIV this may lead to errors in estimation of vaccine efficacy when the definitions that are based on radiological end-points do not take into consideration the HIV status of the patient.

In the context of a vaccine trial, an end-point comprising only cases with severe changes offers the best prospect of showing an impact of the vaccine. However, numbers will be small in some settings, limiting power, and such an analysis may seriously underestimate the vaccine-preventable burden of disease by excluding many cases of pneumococcal pneumonia. At the other end of the spectrum noise due to the many mild, mostly viral infections means that the differences between vaccine and control groups might be small and not statistically significant. However, between these two ends of the spectrum are other categories that may represent bacterial pneumonia preventable by vaccines. Therefore, it will be necessary to identify and count other categories of changes seen on X-ray that may potentially be affected by vaccination.
Observer variation in interpretation of chest radiographs in pneumonia

Previous experience suggests that there may be considerable variation in interpretation of chest radiographs by clinicians as well as radiologists. However, there are relatively few studies that have critically looked at this issue. It is heartening to note that in these studies agreement for the presence or absence of consolidation or the presence of or absence of infiltrates was high. However, there was significant disagreement about minor changes and in the description of the infiltrates. Since the level of training and the understanding of the terminology used for describing radiological changes may vary considerably between study sites in different countries, it is absolutely essential to agree on the descriptive terminology to be used and to standardize the interpretation of radiographs across study sites.

The focus of this exercise will be to define criteria for the interpretation of chest radiographs from study subjects for the purposes of vaccine trial endpoint definition and for disease burden studies and to determine inter and intraobserver variation in interpretation while using these standardized criteria. This aspect of the studies is important, as the diagnosis of pneumonia is either a primary or co-primary endpoint in most pneumococcal vaccine trials to date and in some of the Hib vaccine trials being conducted in Asia. The criteria will be developed, standardized and validated using material obtained from these sites and then offered for use in these and other trials as well as in the generic protocol developed to determine pneumonia disease burden once again. It should be emphasized that the standards and definitions described in this document are meant as an epidemiological tool and may not always apply for patient care.
Objectives

1) To establish standard definitions for the interpretation of chest radiographs in children with suspected pneumonia for use as an epidemiological tool.

2) To establish a mechanism for ensuring the quality of radiographic images stored in digital format.

3) To determine inter and intra-observer variation in interpretation of a standard reference panel of chest radiographs compiled and coded by a WHO radiologist reference panel, using standard definitions.

4) To establish a mechanism for central reference reading to maintain uniformity in interpretation of chest radiographs at the study sites and to resolve discordant readings and maintain ongoing quality control.

5) To establish a standardized training software for interpretation of chest radiographs for the diagnosis of pneumonia for use at newer vaccine trial sites and by those carrying out disease burden studies of pneumonia or evaluating the efficacy of various intervention in reducing the pneumonia disease burden.
Image quality and interpretation of the images

Optimal interpretation of a chest radiograph will depend on the quality of the image and the methods used to interpret the image. Since interpretation will mainly be performed on digitized images, the quality of the image being interpreted will depend on the quality of the original image (the radiograph) as well as the quality of the digitization process. In addition the monitor and the setting of the monitor used to view the digitized images are crucial for optimal interpretation.

Quality of the original radiograph

A readable X-ray is crucial for the diagnosis of radiological pneumonia. There is a risk that in the sickest patients, films that are taken with poor positioning and with portable machines are more likely to be unreadable, leading to a systematic bias. X-ray procedures and processing of films must be optimized to ensure that the best possible quality films are produced. In particular, proper attention needs to be paid to positioning and collimation, which appear to be the primary reason for unreadable films. In addition X-ray safety must be optimized to minimize radiation exposure.

It is recommended that radiologists at the study sites closely interact with radiographers and technicians, stressing the importance of film quality as well as adequate radiation protection measures. This is to ensure that the proportion of uninterpretable and suboptimal films are kept to a minimum, and that radiation exposure for patients as well as staff members and/or other people is kept as low as possible, and according to national and international laws and regulations. Initial training workshops for all radiographers involved in the trial, with periodic reinforcement would be one way of achieving this. When the initial radiograph is unsatisfactory for the purposes of treating the patient, the treating physician may authorize a repeat radiograph.

A few suggested guidelines for checking film quality are as follows:

1) Exposure – are you able to discern the bones, soft tissue and lungs as different densities?
2) Development – is there complete blackening of the film outside the body on the edge of the film (where the X-rays have passed through air) and maintaining whiteness in the very dense areas such as the lower thoracic spine behind the heart? If the film outside the body were hazy or mottled, shadows within the lung would be difficult to interpret.
3) Positioning – are the medial ends of the clavicles approximately equidistant from the midline?
A copy of the checklist used in Lombok, Indonesia for determining film quality is given in Annex 1.

The American College of Radiology standard for obtaining paediatric chest radiographs is available at www.acr.org.

Are lateral films necessary?

Though certain sites may take lateral films routinely for all cases of suspected pneumonia other sites do not. Only frontal films (AP or PA views) will be mandatory at all sites. Sites where lateral films are taken routinely may continue to do so. Studies have shown that lateral films added to the information available in frontal films in only a few instances and that limiting lateral films to those patients where a there was a specific indication is a reasonable option. (26,27)

Digitization of radiographic images

Where conventional (analogue) X-ray machines are used for obtaining images, these will need to be converted to digital images. Members of this group have experimented with a number of systems. Based on their experience, the following methods will be used at the various sites:

- **Purpose-built X-ray scanning machines** - the CCD film digitizers provide results that are equivalent to laser scanners but are they less expensive. Most of the current study sites are proposing to use CCD scanners. This method is recommended (budget permitting) for sites that have not yet decided on which method to use. The listed price for the cheapest CCD scanner is approximately US $10 000. Cheaper prices may be negotiated with the company if several study groups place a joint order. Details for the Vidar scanner being used by several sites is available on the Internet at: http://www.filmdigitiser.com.

- **Simple flat bed scanner** - this method was evaluated at a few sites. The image quality is not as good as the one obtained with a CCD scanner. This requires the use of a transparency adapter along with a flat bed scanner. The procedure that was used in Lombok is given in Annex 2.

- **Hand held digital camera** - this method has been evaluated in Chile. Careful attention has to be paid to the type of camera used, the illumination source and the camera settings for getting a suitable image. Practical tips on getting the best images while using digital cameras have been published (28) and those planning to use this method should read this paper to optimize the images. The details of the procedure used in Chile are given in Annex 3. Even with all the modifications, there is some loss of image quality and definition of shadows that constitute “other infiltrates” may not be optimal.

The American College of Radiology standards for digital image management are available at their web site: www.acr.org.
Maintaining quality of digitized images

During the calibration workshop where original films and the corresponding digitized images were viewed, it was clear that the method of digitization and the settings of the digitizer could affect the quality of the image produced and a mechanism to assure quality of the digitized images are required. The following methods will be used to maintain quality of the digitized images:

1) Use of a standard test pattern which could be used along with every batch of films scanned to assure quality. A special software distributed by Vidar called the “Assure” Quality Control Software would be suitable for this purpose. Details of this software are available at the company’s web site: www.filmdigitiser.com. This program may be particularly useful in sites using the CCD scanners to assure themselves that their scanner settings and techniques were optimal. The quality assurance package could even be run with every batch of films scanned.

2) Since the image quality as decided by the above software may not be necessary for interpreting radiographs for study purposes, it may be useful to use a standard set of chest radiographs with delineation of what findings should be clearly visible in the digitized version of the radiograph. A standard set of paediatric chest radiographs and the features that require to be delineated in the digitized image will be distributed to the study sites. These films could be scanned periodically to check the quality of the digitization process.

Viewing images on a computer

For optimal viewing of images it is very important that the computer monitor should be of good quality and have the right brightness and contrast adjustment. The following computer specifications will allow optimal viewing of digital images:

- Pentium III microprocessor or equivalent with clock speed 600 MHz, on board RAM of 64 Mb or higher, and display card of 4 Mb or more and able to support at least 1024 X 768 resolution. The display unit (monitor) should be able to display at least 1028 X 768 pixels and preferably 0.26 dot pitch size.

The monitor performance should be checked with the SMPTE and GREY SCALE test patterns that have been distributed. It is important that the 5% and 95% contrast boxes and the 1 pixel stripes on the SMPTE test pattern are clearly visible and at least 14 of the 16 rectangles (i.e. the 8 to 247) are clearly visible on the GREY SCALE test pattern. If they are not, try adjusting the contrast and brightness of the monitor to get optimal results. If the test patterns are still not visible as described despite adjustments on the monitor, a better quality monitor is necessary.

Film interpretation

At earlier meetings of the group, agreement was reached on a radiological appearance that is most likely to be associated with bacterial pneumonia but still occurs with reasonable frequency and is therefore felt to be the best discriminator to demonstrate the impact of a vaccine on pneumonia rates. The following descriptive definition was agreed upon:
Description of primary end-point consolidation (likely bacterial pneumonia as judged by the study group): dense fluffy consolidation (alveolar infiltrate) of a portion of a lobe or entire lung. This often contains air bronchograms, and may be associated with a pleural effusion.

There has been considerable discussion around this definition and in general it is easier to reach agreement on the actual images than on the description of those images. Nevertheless, the group was comfortable with this as a definition of the agreed primary end-point. Most felt that the terms “alveolar infiltrate” or “alveolar consolidation” adequately described the appearance, although some found the term “confluent infiltrate” a better description. The concept of specifying a specific size, such as 2.5 cm across, as used in the initial reading of the California study X-rays, was rejected on the grounds that size on an X-ray does not correspond to actual size of the pathology and it can be significantly affected by the conditions under which the film is taken, which may themselves vary systematically from site to site. In previous meetings the term “obvious consolidation” was felt useful to describe the end-point appearance and, in particular, the intention of the group not to include subtle changes that may be difficult for non-radiologists to see. However, significant and major consolidation behind the heart may not be obvious to the paediatrician’s eye, particularly in the absence of a lateral film, as will usually be the case.

This and other definitions are attached in Annex 4. The eventual goal is to develop a global standard for the diagnosis of pneumonia for the purposes of vaccine trials and disease burden studies. Of necessity this standard will be more specific and less sensitive than that used for clinical purposes. It was agreed that a second level is needed that describes consolidation or infiltrates that are abnormal but are not of sufficient magnitude to be included as part of the agreed “primary radiological end-point”. It would be of interest to evaluate the impact of pneumococcal vaccination in reducing such cases.
Standardization of radiological interpretation of pneumonia

The process of standardization of radiological interpretation of pneumonia will consist of the following phases:

1) Calibration
2) Standardization
3) Ongoing quality control

The initial calibration phase will consist of identifying systematic variation in interpretation of radiological findings using a standard panel of X-ray images and then between study sites taking measures to resolve these differences. After this initial phase mainly aimed at ensuring that all those interpreting X-rays in different countries have in common understanding of the selected definitions, a second panel of films will be constructed to determine the inter and intraobserver variation in interpretation of X-rays using the standard definitions between readers at each study site and between readers across all the participating study sites.

Once the initial training and standardization in interpretation of X-rays is completed, a system for interpreting X-rays at study sites will be developed. This will consist of two independent readings of each film at the study sites and transmission of X-rays with discordant readings for arbitration by a WHO expert panel of radiologists.

In addition, an ongoing quality control system will be established wherein a sample of concordant films read at each site will be reviewed by the expert panel to check for quality of the film and the interpretation of the X-ray, with discussions with investigators from individual study sites if there are problems identified with these aspects.

A. Stage 1. Determination of systematic intersite variation in interpretation (calibration)

- A set of reference films (100 from South Africa and 120 from 3 sites, i.e. Chile, Lombok and Israel) will be put together. In compiling this panel care would be taken to include sufficient numbers of films showing the entire spectrum of changes likely to be encountered in children with clinical pneumonia. These will include films from South Africa, where the high prevalence if HIV infection in the study subjects seems to lead to increased pathology and atypical findings, and from Israel and Chile, where lesser degrees of pathology are likely to be encountered.
- A WHO radiology reference panel will be formed. The consensus reading of the WHO panel will constitute the reference coding for a standard set of radiographs.

- The entire reference panel of X-rays (100+120) will be sent to each study site. Site readings will comprise an open consensus view to be reached between the readers at each site. Readings will be recorded using data entry software prepared at WHO or in an Excel spreadsheet (See Annex 5). The site readers will together fill one form per film. The data will be analysed to determine systematic disagreements in interpretation between sites as well as between sites and the reference panel.

- The results of the calibration exercise will be distributed and discussed. Areas where there is systematic disagreement in interpretation will be identified and remedial measures will be discussed and instituted. The intention of this phase is to determine whether major differences exist between the sites in the interpretations of the planned positive end-point and to resolve major differences in interpretation.

B. Stage 2. Standardization analysis

- The WHO radiology reference panel will compile a set of approximately 200 films (see sample size calculation in the data management and analysis section).

Scoring will be done independently by each of the readers at individual study sites, including the two readers of the WHO central panel. These will be performed in a blinded manner with no comparisons between readers at individual sites. Unlike stage 1, these will not be consensus readings at individual sites. The data will be analysed as overall score agreement, and component (subscore) agreement, looking at inter-observer agreement between the two panel readers, the panel and the individual site readers, and inter-observer agreement measurement between individual site readers.

- A random sample of 100 films from this panel will be re-read by the site readers to check for intra-observer variation.

- The results of this exercise will be analysed and written up for publication. It is anticipated that the exercise will result in a standardized method for interpretation of X-rays that can be used for disease burden studies and for defining end-points for trials using pneumococcal and other vaccines to reduce the pneumonia disease burden.

C. Scheme for interpretation of chest X-rays from study sites

- The site readers will read all X-rays from each study site independently in a blinded manner and enter their findings using the format supplied by WHO. The digitized X-rays will be maintained as electronic files (with back up file, as required).

- The data will be analysed at each site by the site data manager on at least a quarterly basis.
The data manager will identify ALL films where there is discordance in the primary end-point diagnosis (i.e. primary end-point consolidation vs. other infiltrate or no infiltrate/effusion) among the site readers and copy them on to a CD. This will then be forwarded to the WHO reference panel for arbitration. The WHO reference radiologists will read the X-rays in a blinded manner with any discordance resolved by consensus. Their reading will be taken as final.

A 10% sample of positive and an equal number of negative ones (an estimated 12–30 positive and an equal number of negative films per quarter per site), selected at random (method to be decided by site data manager), will also be copied on to the same CD and sent quarterly to the reference panel for a check on the quality of the film and as an ongoing quality check on interpretation.

The study sites will provide information to the WHO study co-ordinator as to which of the films have discordant readings and which have concordant readings but are for quality assurance only. This information will not be available to the WHO reference panel who will read all films in a blinded fashion (without knowing whether they have concordant or discordant reading by the site readers).

The report of the WHO reference radiology panel on discordant films will be sent back to the study site. This will be taken to be the final reading. Agreement between the findings of the site readers and the expert panel on films with concordant reading will be determined by the WHO study coordinator, with help from the statisticians at the Clinical Epidemiology and Biostatistics Unit, Royal Children’s Hospital, Parkville, Victoria, Australia. The data on agreement for each site will be sent back to the site for their records. A significant degree of discordance (to be decided by consensus after review of the results of the standardization exercise) will necessitate discussion with the site readers to resolve the areas of discordance and possible review of all the films read at that site.

The central expert panel will also review the quality of films at each site and suggest remedial measures, when necessary. If more than 5% of the films from any one site are interpreted as unreadable, discussions will be initiated with the site investigators and retraining of radiographers undertaken, if necessary.

Data management and analysis

For the first two standardization exercises, all the data will be entered (and re-entered) at the study sites on a computerized data entry program (See Annex 1). This will then be forwarded to the central reference centre at WHO, where the data will be checked for inconsistencies and then be forwarded to the Clinical Epidemiology and Biostatistics Unit, Royal Children’s Hospital, Parkville, Victoria, Australia for analysis.

For the ongoing quality control check, data will be entered and managed by the study sites. Each reader will enter their X-ray readings separately (either as hard copies or electronically). The study data manager will analyse the data at least once in 3 months to identify the X-rays with discrepant readings and also generate a list of 10% of positive and an equal number of negative X-rays (where reading is concordant) for quality check. These films will then be copied on to a CD and sent to the central reference centre for arbitration or
quality check, as the case may be. A list of the concordant and discordant X-rays will also be forwarded along with the CD to the WHO study coordinator. The WHO reference radiologists will read the X-rays in a blinded manner with any discordance resolved by consensus. The interpretation of discordant readings will be conveyed back to the study site and will be entered into the study database. This reading will be taken as the final reading. The data from the X-rays with concordant reading by the site readers will be analysed for inter-observer variability. The results will be discussed with the site readers if significant discordance is found in agreement on primary end-point.

Stage 1. Calibration studies

For the calibration studies, frequency tables and simple cross tabulations between data from the sites compared to the reference panel and between data from various sites will be generated. These will be examined for systematic variation in interpretation of radiological findings or diagnosis. Individual films on which there is disagreement will be reviewed again by the reference panel. A report will be generated from these analyses, and circulated. A decision on whether to have a review meeting to resolve major differences will be made after reviewing this report.

Stage 2 Agreement studies: analysis and sample size

Introduction

The study of Stage 2 inter-observer and intra-observer variability aims to compare agreement in readings of a test panel of films:

1) between a reference panel (Geneva) and individual readers at each site - this inter-observer agreement is considered to be of primary importance, and

2) between and within readings at individual sites - this agreement is of secondary importance, and evaluates reading and repeat readings for inter-observer and intra-observer variability.

Proposed method of analysis for agreement studies

1. Panel/site inter-observer variability.

The analytic approach of using proportions of agreement/disagreement, expressed as sensitivity and specificity, with reference panel readings as the gold standard, is appropriate for the primary aim of assessing the performance of site readers in relation to that of the reference panel, since the latter is assumed to be the gold standard. These analyses will show explicitly whether site readers are able to classify truly positive films and truly negative films reliably.

2. Individual site inter-observer and intra-observer variability.

The kappa coefficient (k) is an appropriate index of agreement between two (or more) readers who are regarded as more or less interchangeable, and between repeat readings by the same rate.
The intraclass k on which nQuery’s (nQuery Advisor Version 4.0, 2000) sample size calculations are based, is essentially a “bias-corrected k” that ignores marginal imbalances between raters (Bloch & Kraemer, Biometrics 1989). If marginal rates of positivity (prevalence) are similar between raters, this version of k will be very similar to the more standard definition, with similar precision. (If there were substantial bias between readers, we would report this separately since k becomes less interpretable in such cases.)

Sample size issues

Proposed sample size has been obtained by considering the precision of estimation that can be expected for both the sensitivity and specificity, and kappa.

1. Sensitivity and specificity

A reasonable minimum value of both sensitivity and specificity in this study is 0.8 (e.g. Lamme et al, CMAJ, 1986). At this value, a sample size of 200 will produce a two-sided 95% confidence interval (using the usual normal approximation) of width ±5.5%. With higher sensitivity or specificity, the confidence interval will be narrower.

2. Inter-observer agreement

Sample size estimates are based on \( k = 0.8 \) and (95% confidence interval) precision of ±0.1, and are dependent on pneumonia prevalence, which is expected to vary between sites.

Larger numbers are required for the same precision as prevalence (p) moves away from 0.5. Numbers needed for \( p = 0.75 \) are the same as those needed for \( p = 0.25 \).

Using nQuery, if \( k = 0.8 \), precision of ±0.1 can be expected with \( n = 200 \) if \( p = 0.75 \) or 0.25. With \( p = 0.50 \), similar precision would be obtained using \( n = 140 \).

In summary, a sample size of 200 films should provide adequate precision for most estimands of interest.

3. Intra-observer agreement

It is proposed that lower precision would be acceptable for estimating intra-observer agreement than for inter-observer agreement, and that an acceptable practical value would be to repeat the readings on half the films, i.e. \( n=100 \). See the Table for resulting precision values.

Mechanics of readings for intra-observer agreement

It is proposed that the 200 test panel films be sent (Day1), read, and results returned, and that these be followed in a week (Day 8) by a random selection, randomly re-ordered, of 100 of these films, to be read independently without any reference back to the readings for the original set.
Concurrently with the calibration and standardization exercises, training software for the interpretation of films will be created. This software will serve in training new sites or groups undertaking studies on childhood pneumonia in interpretation of chest radiographs. The software may also be used for ongoing quality assessment of readers at the study sites.

The software will consist of a repository of films which describe the spectrum of radiological changes seen in children with suspected pneumonia, including sets of normal films and unreadable films. This will be combined with appropriate software to view the films, to read text describing the abnormalities seen in each of the films, to manage the film repository and for self-assessment. This software will be prepared in collaboration with a commercial company specialized in the preparation of training software in radiology.

Ideally, this software should be distributed at the beginning of each study. However, since many of the studies are already under way or are nearing completion, preparation of this software will run concurrently with the calibration and standardization exercise. It is anticipated that this software will be useful in training those interpreting X-rays in future intervention studies or disease burden studies of bacterial pneumonia.
Bibliography


## Annex 1:

Radiology quality criteria for Lombok radiographs  
(Benson, Steinhoff, 1999)

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>ID</strong></td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Study ID number and 2.5 cm marker are visible and legible.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td><strong>Position</strong></td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>The clavicles and ribs are symmetric to each side of the spine.</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td><strong>Image boundaries</strong></td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Image area is confined to the rib cage and includes both costophrenic angles.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><strong>Inspiration</strong></td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Dome of the diaphragm is below the 8th rib.</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><strong>Movement</strong></td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>The heart, diaphragm, large pulmonary vessels and ribs are sharply defined without blurring.</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><strong>Exposure I</strong></td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Vascular shadows can be seen in the lung periphery.</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><strong>Exposure II</strong></td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Large lower lobe vessels and the thoracic vertebrae are visible through the cardiac silhouette.</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><strong>Contrast</strong></td>
<td>Y</td>
</tr>
<tr>
<td></td>
<td>Background outside of patient’s silhouette is black, not grey. Bones and airways should be easily distinguished from soft tissue.</td>
<td></td>
</tr>
</tbody>
</table>
Annex 2:
Procedure for scanning with UMAX Astra 2400S scanner, with transparency adapter (Steinoff 1999)

1) Before scanning
   Orient film so heart shadow is mostly on the left side of film (viewer's right), and “R” marker is on the right side of the film (viewer's left).
   Apply 2.5 cm. marker to film, outside of ribcage, below diaphragm.
   Use black marker to write study form number on film, near 2.5 cm marker.
   Place film face down on scanner bed and close cover.

2) Use the VISTA scan software:

3) Go to advanced menu

4) Then select the following from the menu:
   · UTA transmissive
   · B/W photo
   · 300 dpi
   · no descreen
   · no filter
   · 50% size
   · auto adjustment

5) Do preview scan of film

6) Adjust image margins to include rib cage only

7) Do another preview scan (to allow auto exposure for new size image)

8) Do full scan

9) Save file as GIF format, or as JPEG at 80% compression, using Hib form number as file name
Annex 3: Procedure for converting X-rays into digital images using a digital camera (Lagos R, Chile)

Equipment:
1) Camera: Agfa 1680 or Mavica FD 90.
2) White-light screen with two switches and four 10-Watts tubes. Two tubes on are enough for most films, but 4 might be necessary for dark films.
3) Monitor: SVGA, 17". Resolution must be similar to the resolution of the image.

Capturing the image:
1) Set the camera at a resolution of 1024 x 768 or higher.
2) Place the film on the screen and cover the empty edges with cardboard strips.
3) Adjust the distance manually (digital zoom off), so that the image is properly centred on the LCD.
4) Shoot.

JPEG file: download the image from the camera to the computer using lowest possible compression. Convert to greyscale.
Annex 4:
Chest radiograph interpretation document, for WHO trialists group

Goal: to offer instruction sufficient for radiologists and non-radiologists to consistently interpret frontal chest radiographs in terms of the presence or absence of findings likely to be associated with bacterial pneumonia.

Caveats: some of the radiographs will be normal. Many of the radiographs will be abnormal, because the patient has viral pathology. There is a great deal of overlap in the radiographic appearance of viral and bacterial disease. The challenge will be to maximize the number of true positives, without including too many false positives.

Film artefacts: films that are very light or that are blurry will appear more abnormal than they actually are. Normal markings will be accentuated by light X-ray technique and by outdated developer, and blurry normal markings will look like infiltrates.

Definitions of terms: for the purposes of this study. (See also accompanying diagrams)

1) **Infiltrate**: any pathologic density in the lung.
2) **Alveoli**: tiny air-filled spaces where oxygen and CO₂ are exchanged (see diagram B)
3) **Bronchi**: tubes leading from the trachea to the alveoli
4) **Interstitial (adj: interstitial)**: lung tissue outside the air-containing spaces: includes support tissues, blood vessels, bronchial walls, lymphatics
5) **Alveolar infiltrate**: alveoli filled with fluid (pus, oedema, etc.)
6) **Heart and diaphragm borders**: see accompanying diagram A.
7) **Air bronchogram**: branching linear lucent structure representing air still present in bronchi after the alveoli around them have consolidated; not to be confused with peribronchial thickening (an interstitial infiltrate)
8) **Consolidation**: especially dense, often homogeneous, confluent alveolar infiltrate sometimes may encompass an entire lobe or large segment, fluffy, mass-like, cloud-like density, erases heart and diaphragm borders (silhouette sign); often contains air bronchograms
9) **Atelectasis**: volume loss as air is absorbed from lung tissue, usually distal to an airway obstruction (e.g. a mucous plug). The lung tissue collapses like a Japanese fan, leaving a dense streak on the film that radiates outward from the hilum. (see diagram D)
10) **Interstitial infiltrate**: includes peribronchial thickening and tiny areas of atelectasis (thought to be typical of viral infection).
11) **Pleural effusion:** fluid collecting in the pleural space around the lung, seen as a dense rim (the same density as the chest-wall muscles) interposed between the lung and the ribs (diagram C)

12) **Peribronchial thickening or cuffing:** increased density of the walls of the smaller bronchi (away from the immediate hilar area) so that they become visible as circles or parallel lines (diagram E)

**Definitions of study end-points:**

**Quality**

1) **Uninterpretable:** an image is classified as “uninterpretable” if the features of the image are not interpretable in terms of presence or absence of “primary end-point” without additional images. No further reading should be made for such images.

2) **Suboptimal:** an image is classified as “suboptimal” if the features allow interpretation of primary end-point but not of other infiltrates or findings. No entries should be made for other infiltrates for such images.

3) **Adequate:** an image is classified as “adequate” if the features allow confident interpretation of end-point as well as other infiltrates.

**Classification of findings**

1) **Significant pathology:** this refers specifically to the presence of consolidation, infiltrates or effusion. If none of these are present then no further reading or recording is required for that film.

2) **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.

3) **Other (non-end-point) 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 end-point consolidation, and small areas of atelectasis which in children can be difficult to distinguish from consolidation.

4) **Pleural effusion:** this refers to the presence of fluid in the 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 is considered as primary end-point if it is in the lateral pleural space (and not just in the minor or oblique fissure) and is spatially associated with a pulmonary parenchymal infiltrate (including other infiltrate) OR if the effusion obliterates enough of the hemithorax to obscure an opacity.

---

1 Atelectasis of an entire lobe that produces a dense opacity and a positive silhouette sign with the mediastinal border will be considered to be an end-point consolidation.
Conclusions

1) **Primary end-point consolidation or pleural effusion**: the presence of end-point consolidation (as defined above) or pleural effusion that meets criteria for primary end-point (as defined above).

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

3) **No consolidation/infiltrate/effusion**: absence of end point consolidation, other infiltrate or pleural effusion.

**Diagrams**

1. Right diaphragm – erased by a right lower lobe infiltrate. 2. Right heart (right atrium) – erased by a right middle lobe infiltrate. 3. Minor fissure – divides the right upper lobe from the right middle lobe; seen as a line when there is fluid in it; seen as a border when there is infiltrate in the lobe adjacent to it. 4. Left heart (left ventricle) – erased by an infiltrate in the lingula (homolog of the right middle lobe; actually a part of the left upper lobe). 5. Left diaphragm – erased by an infiltrate in the left lower lobe, often behind the heart shadow. 6 and 7. Right hilum and left hilum – contain large blood vessels, lymph nodes, and main bronchi; bronchial walls may be normally visible here, but should disappear quickly just outside the immediate hilar area. 8. Thymus – bi-lobed semi-lucent structure in the upper mid chest with defined borders, may resemble an upper lobe infiltrate but often shrinks when the child is sick. 9. Heart – from the spine to the left heart border should be the same density.
A spreadsheet in Microsoft Excel has been developed for data entry for the purposes of calibration and standardisation of films. It consists of the following fields:

- **Study site:**
- **Reader ID:**
- **Date of reading:**
- **X-ray ID:**
- **Is the film quality adequate?**
  - a. Adequate
  - s. Suboptimal
  - u. Unreadable
- **Does the film contain significant pathology?** Yes/no
- **Primary end-point consolidation?** Right Yes/No Left Yes/No
- **Other consolidation/infiltrate?** Right Yes/No Left Yes/No
- **Pleural fluid?** Right Yes/No Left Yes/No

**Conclusion**

1) Primary end-point consolidation or pleural effusion
2) Other consolidation/infiltrate
3) No consolidation/infiltrate/effusion

**Notes:**

The findings may be entered using the definitions given in Annex 4 and the notes for entering data into the spreadsheet (given below).

The entry for “conclusion” will be logically constrained by the answers to the other questions. For example, if “Does the film contain significant pathology?” is “no”, then the conclusion will be obliged to be “no consolidation/infiltrate/effusion”. Also if “Primary end-point consolidation?” is “yes”, then the conclusion must to be “Primary end-point pneumonia”. If “Other infiltrate/abnormality?” and “Pleural effusion?” are “yes”, the conclusion will have to be “Primary end-point pneumonia”. If the answers to “Pleural effusion?” alone are “yes” and “Primary end-point consolidation?” and “Other infiltrate/abnormality?” are “no”, the conclusion will
be “Other infiltrate/abnormality”. If answers to “Other infiltrate/abnormality?” are “yes” and all others are “no”, the conclusion will be “Other infiltrate/abnormality”. If the answers to all, “Primary end-point consolidation?” “Other infiltrate/abnormality?” and “Pleural effusion?”, are “no”, then the conclusion must be “No consolidation/infiltrate/effusion”. These answers will be automatically entered, based on responses to earlier questions.

Notes for using the Excel spreadsheet “X-ray.xls”:

1) The original file “X-ray.xls” itself should not be used for data entry. Data should be entered into a copy of this file, which can be named appropriately for your site (e.g. “X-ray_aus1.xls”). A new copy of a file can be made very simply using the Windows Explorer, or you can open the original file in Excel and make a new copy immediately by using the “Save As” dialog on the File menu. (Please seek help if you are not familiar with these Windows operations.) The worksheet has been programmed to take 500 rows of data. To enter data for more than 500 films, you will need to make a new copy of the spreadsheet file and start afresh.

2) Some of the columns have dropdown boxes containing valid options. The valid options for Quality (column E) are “a”, “s” and “u” while the valid options for Significant Pathology to Pleural fluid_R (columns F to L) are “yes” and “no”. Note that once a value has been entered in a column, there is no need to type in the entire word again. For instance, if “yes” has previously been entered in column F, entering only “y” in that column (followed by Tab or Enter) is sufficient.

3) If you enter “u” for quality, no further entries are required for that image.

4) If you enter “s” for quality, do not record any findings for “other infiltrates” since by definition a suboptimal film does not allow interpretation of other infiltrates.

5) When “no” is entered in Significant Pathology (column F), Primary cons_L to Pleural fluid_R (columns G to L) are automatically filled in with “no”.

6) Conclusion and Flag (columns M and N) are locked so that nothing can be entered in either of these columns. The entire worksheet is also “protected” so that formatting changes cannot be made.

7) Conclusion (column M) is updated automatically as per the definition above.

8) Flag (column N) will show the word ERROR in red under the following circumstances:

- If Significant Pathology is “yes” and Primary cons_L to Pleural fluid_R are all “no”.
- If Significant Pathology is “no” and at least one of Primary cons_L to Pleural fluid_R is “yes”.
- If a value for Conclusion is displayed and at least one of the columns from Date to Pleural fluid_R (columns C to L) is blank. Note that ERROR will appear in the Flag column as soon as the value for Conclusion is displayed if at least one of the columns from C to L of that record are blank. Once all of these cells have been filled, the word ERROR will vanish, assuming there are no other inconsistencies.
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