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Evaluation of the Diagnostic Performance of Lung Ultrasound Compared to Chest X-rays for Diagnosis of Pneumonia in Children.

By Jacob A M Stadler

A mini-dissertation submitted to the University of Cape Town in partial fulfillment of the requirements of the Masters of Public Health (Epidemiology) degree.

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Abstract

Pneumonia remains a global health priority in children. It is the leading cause of death in children outside the neonatal period, over 90% of which occur in low-resource settings, and a major cause of morbidity, accounting for over 100 million episodes globally each year. Early, correct diagnosis is a modifiable factor which can potentially improve pneumonia outcomes. Current guidelines recommend the use of clinical signs and symptoms alone to make a diagnosis of pneumonia in low risk, ambulatory cases with clinically mild disease. However, clinical diagnosis lacks specificity and may lead to antibiotic overuse and drive antibiotic resistance. Addition of chest X-ray (CXR) to diagnostic algorithms improves specificity, but CXR use is limited by radiation exposure and relatively high costs, limiting access in low-resource settings. Current guidelines therefore reserve CXR for moderate to severe disease and hospitalised cases, even in well-resourced settings. Lung ultrasound (LUS) is a promising imaging modality which uses no radiation, is less costly than CXR and can improve the time to results when used as a point-of-care tool by clinicians outside the radiology department. These characteristics make LUS, at least theoretically, a potential option either as add-on screening test aimed at decreasing unnecessary antibiotic prescription or as a lower risk, lower cost definitive diagnostic test capable of replacing CXR, or both. The objective of this study was to understand the role of LUS as a diagnostic test for pneumonia in children by performing a structured literature review and meta-analysis summarizing the current evidence comparing diagnostic performance of LUS and CXR, and by reporting previously unpublished data from the Drakenstein Child Health Study comparing diagnostic performance of LUS and CXR for pneumonia in children in a resource-constrained, African setting.

Acknowledgements

I would like to thank the participants of the Drakenstein Child Health Study and their families, as well as the Western Cape Provincial Department of Health for their ongoing support of the study. Thanks to Eckart von Delft and Dave le Roux who assisted with reporting of CXR images despite their busy clinical schedules. I am sincerely grateful to my supervisors Prof Heather Zar and Prof Savvas Andronikou who afforded me the opportunity to be part of the project and invested a lot of time and resource in me, as well as Assoc Prof Maia Lesosky for provided guidance and encouragement during the writing process and statistical support.

List of abbreviations

AP	anterior-posterior
BTS	British Thoracic Society
CAP	community acquired pneumonia
CI	confidence interval
cm	centimeter
CT	computed tomography
CXR	Chest X-ray
DCHS	Drakenstein Child Health Study
ED	Emergency Department
F	female
FN	false negative
FP	false positive
HIV	Human Immunodeficiency Virus
ICS	intercostal space
IQR	interquartile range
LAT	lateral
LRTI	lower respiratory tract infection
LUS	lung ultrasound
M	male
MHz	Megahertz
MRI	Magnetic Resonance Imaging
NICU	Neonatal Intensive Care Unit
NR	not reported
OOA	observed overall agreement
PA	posterior-anterior
PNA	proportion negative agreement
PPA	proportion positive agreement
Se	sensitivity
Sp	specificity
TB	tuberculosis
TN	true negative
TP	true positive
UCT-HREC	University of Cape Town Human Resource Ethics committee
WHO	World Health Organization

List of tables and figures

PART 1: Research Protocol

Protocol Title:	**Evaluation of the diagnostic performance of lung ultrasound compared to chest X-rays for the diagnosis of pneumonia in children.**
Author:	**Dr Jacob A M Stadler**
Version & Date:	**Version 1.0 (Dated: 20 Jun 2018)**

Background and significance

Pneumonia and other forms of lower respiratory tract infections (LRTI) remain the leading causes of death and a major causes of morbidity in children under 5 years of age, accounting for 13-20% of childhood deaths globally, despite advances in prevention and treatment strategies such as expansion of routine childhood vaccinations and strong prevention of mother to child HIV transmission programs[1]. The incidence of pneumonia remains high[2] but early, correct diagnosis and treatment can improve pneumonia outcomes in young children.

Prominent evidence-based guidelines for management of pneumonia in children consider the condition to be primarily a clinical diagnosis based on a typical symptom history and presence of clinical signs. These guidelines therefore recommend against routine use of chest X-ray (CXR) imaging when uncomplicated community-acquired pneumonia is suspected[3–5]. This recommendation is based mainly on evidence suggesting that CXR does not significantly impact pneumonia outcomes in these cases[6]. However, clinical signs and symptoms have also been shown to have limited diagnostic accuracy[7]. Clinicians therefore still prefer the use of imaging tests to confirm their clinical diagnosis despite these guidelines[8]. There are also many scenarios where CXR imaging is recommended to aid in the diagnosis and management of more complicated pneumonia cases[3–5]. CXR therefore is currently the most frequently performed imaging test for diagnosing LRTI in children.

Despite its wide use, several well recognised factors limit the usefulness of CXR as a diagnostic tool for LRTI, most importantly the relatively poor accuracy and reliability when interpreting imaging results[9–14]. CXR can therefore by no means be considered a gold standard for pneumonia diagnosis. Access to CXR imaging is also limited in many settings due to the regulatory requirements, expertise

and cost necessary to run a radiology service. This is particularly import as the vast majority of pneumonia deaths occur in low and middle-income countries[2]. The perception of increased risk of malignancy associated with ionising radiation exposure, especially in young children, is also often used to discourage routine use of CXRs, despite limited evidence for this argument[15,16].

Ultrasound has historically been viewed as unsuitable for visualisation of the lungs for two reasons: the air in healthy lung tissue scatters the ultrasound waves which makes direct visualisation of air-filled lung parenchyma and deep lung structures with ultrasound impossible; secondly, much of the lung surface is covered by calcified bone of the thoracic cage which is impenetrable to ultrasound. However, many disease processes in the lung tend to increase the extravascular fluid component of lung tissue and when severe, affected areas of the lung become consolidated, with alveolar air being displaced by fluid. In other cases, lung disease gives rise to pleural pathology such as pleural effusion or pneumothorax. It has long been recognised that these areas of diseased lung give rise to distinct ultrasound patterns not present in normal lungs[17,18]. This means that ultrasound can be used to discriminate healthy from unhealthy lungs and describe different types of lung pathology. Early studies of lung ultrasound (LUS) evaluated its usefulness in dyspnoeic adults in intensive care settings and showed good accuracy of certain sonographic patterns for detecting certain types of lung pathology when compared against a gold standard of computed tomography (CT) scans[19].

Since then a growing body of evidence has surfaced suggesting that the diagnostic performance of LUS may be similar if not better than CXR for detecting evidence of LRTI[20,21]. LUS has also gained popularity for several reasons other than its diagnostic accuracy, most importantly the fact that it is radiation free, which makes it ideal for use in the paediatric population, which also represent the highest pneumonia risk group. This absence of radiation, combined with the development of newer, portable ultrasound devices means it can be used outside of the radiology department by non-radiologists, a feature which holds significant promise in resource constrained settings where access to radiology services are limited or as a screening tool in a variety of primary care settings which could potentially lead to decreased use of CXR, especially in children.

Despite its growing popularity, implementation in clinical practice has been slow and LUS has not yet been included as alternative to CXR in major evidence-based pneumonia management guidelines. This may be due to certain limitations of LUS and some significant questions regarding its role in the management of childhood LRTI which have not yet been fully clarified. Much like CXR, LUS has been shown to be an imperfect diagnostic tool which will miss lung consolidations not extending to the pleura or in areas obstructed by bony structures such as the scapulae[22–25]. There is

also recognition in current literature that image quality and interpretation of scans are user-dependent and questions regarding adequate training, equipment specifications and standardized terminology remain[26–29].

The number of studies assessing the diagnostic accuracy of lung ultrasound in children are limited and even fewer such studies have been done outside of a developed world context and academic environments. Further, these studies most frequently include children treated in hospital rather than in a primary care setting and LUS are frequently performed by expert sonographers rather than primary care clinicians[20,21]. These factors limit the external validity of findings on the diagnostic performance of LUS to diverse real-world situations. Methodology used in these studies is also fairly heterogenous and often do not adhere to good reporting guidelines which makes comparison of results across studies difficult[30].

We propose a study to better understand the role of LUS as a diagnostic tool for childhood LRTI, both in a primary care and in-hospital setting. To do this we plan to analyse data from a series of LRTI cases from the Drakenstein Child Health Study, a multi-year birth cohort study conducted in Paarl, South Africa, which investigates the early life determinants of lung health. We will describe findings and compare the diagnostic performance of LUS, performed by a general practitioner with basic training, to CXR images, the current standard of care, in a cohort of African children presenting with both ambulatory and hospitalised episodes of suspected LRTI.

Objectives & Aims

The primary objective of this study is to compare the diagnostic performance (validity and reliability) of LUS with that of CXR for diagnosing pneumonia in children who present with clinical symptoms and signs of LRTI.

Specific aims:

1. To describe the type and frequency of CXR and LUS findings in a series of clinically defined pneumonia cases from the Drakenstein Child Health Study.
2. To compare the diagnostic performance of LUS and CXR for diagnosis of pneumonia by means of:
    - Sensitivity and specificity, using CXR as reference standard
    - Concordance (inter-test agreement) between LUS and CXR
    - Comparing inter-observer agreement (reliability) between LUS and CXR

Methods

We plan to perform secondary analysis of previously collected data. Data collection was performed under protocol of the primary study which has received ethics approval (Drakenstein Child Health Study, UCT-HREC #: 401/2009). Described below is the methodology and data analysis plan for our proposed analysis. We also outline relevant methodology used by the primary study during collection of the data.

- **Study Design, Setting & Population**

The primary study is a multi-year birth cohort which enrolled 1225 pregnant women (leading to 1143 live births) between 2012 - 2015 from two public sector primary health clinics in Paarl, a town with a population of approximately 200000 people, in the Drakenstein district of the Western Cape province, approximately 50km from Cape Town. The cohort of mother-infant dyads is currently in its sixth year of follow-up.

The study population can broadly be divided into two distinct peri-urban communities based on the drainage area for the two enrolment clinics: Mbekweni clinic serving a predominantly Black African township population (680 mothers) and TC Newman clinic serving a predominantly mixed-race population (545 mothers). Both communities are characterised by high prevalence of unemployment, poverty and related social determinants of health as well as a high burden of infectious diseases including TB and HIV.

We propose to conduct a secondary analysis of data collected by the Drakenstein Child Health Study between Aug 2014 - Dec 2015. The analysis will be a cross-sectional (at the time of LRTI diagnosis) diagnostic accuracy study of a prospectively observed series of clinically defined cases of suspected LRTI occurring in infant participants.

- **Sampling, Participant Selection & Recruitment**

The primary study enrolled participants attending antenatal care at the two facilities described above using convenience sampling. Inclusion criteria for pregnant women in the primary study were as follows: 18 years or older; between 20-28 weeks gestation at enrolment; at the time of enrolment not planning to relocate out of the area for a least a year following enrolment; willing and able to consent to study participation. There were no specific exclusion criteria.

Inclusion into the proposed secondary analysis will be based on occurrence of LRTI episodes and the availability of CXR and LUS data collected around the time of diagnosis. Cases where imaging were performed >72 hours from the date of diagnosis or where the CXR and LUS were performed >72 hours apart, will excluded from the analysis, as delayed imaging by either modality may affect accuracy measures.

- **Study Procedures & Outcome Measures**

As part of the primary study the mother-infant dyads where followed up during several scheduled antenatal and post-natal study visits to record baseline health and risk factor data. Following delivery, active surveillance by study staff through regular surveillance rounds at public health facilities in the district and passive surveillance in the form of a 24-hour study hotline was used to identify any symptomatic infants suspected of having a LRTI. Symptomatic infants where then assessed within 24 hours by clinically trained study staff to determine if diagnostic criteria for LRTI were present.

A clinical diagnosis of LRTI was made based on World Health Organisation (WHO) clinical pneumonia case definition. Infants with clinically confirmed LRTI then received a full clinical evaluation and a lung ultrasound performed by a trained study clinician within 72hrs from diagnosis. A CXR was performed at diagnosis for most infants who were hospitalised with LRTI as part of routine care as well as for some infants receiving outpatient care, as deemed necessary by the treating clinicians. Additional data relating to risk factors, clinical presentation, severity, management and outcomes were also recorded at the time of diagnosis, as well as at a 2-3 day and again at 4-6 weeks follow-up visits, when ultrasound was also repeated.

LUS and CXR images performed at pneumonia diagnosis were reported by two separate reporters for each imaging modality. CXR were reported by two specialist paediatricians and findings were classified using the WHO Pneumonia Working Group standardised interpretation method for pneumonia in children. Lung ultrasound images where reported by a trained general practitioner (unblinded study clinician performing the scan) as well as a blinded expert paediatric radiologist using a classification system based on current literature with diagnostic categories compatible (representing similar disease processes) to those used for CXR. Findings from CXR and LUS performed on the same infant during the same pneumonia episode are then compared.

The proposed secondary analysis only involves statistical analysis of previously collected data only and therefore no new study procedures will be conducted.

- **Sample Size & Statistical Analysis Plan**

Descriptive analysis will be done using medians and inter-quartile ranges (IQR) for continuous variables, while categorical variables will be summarized using frequencies and percentages. Comparison of inter-observer agreement (reliability) as well as agreement between LUS and CXR (inter-test agreement) will be performed using appropriate measures of agreement (direct agreement indexes and Kappa-coefficients). Traditional accuracy measures such as sensitivity, specificity and positive and negative predictive values are not considered meaningful in the absence of a definitive gold standard. For the diagnosis of pneumonia, CT scan demonstration of air-space consolidation is probably the one imaging method which can be considered a diagnostic gold standard, but its use is not ethically feasible in mild to moderate paediatric pneumonia. We will therefore consider appropriate 'absent gold standard' methods to assess and compare diagnostic accuracy (validity).

The size of the available sample for this analysis is dependent on availability of data from the primary study, and as such prior sample size calculation was not performed. However, we performed sample size calculations for inter-rater agreement (Cohen's Kappa) which determined that a sample of 61 cases would be required at a significance level of 0.05 and 80% statistical power, with expected agreement for CXR set at Kappa=0.55 and for LUS at Kappa=0.80 and expected true prevalence of lung consolidation, interstitial disease picture and normal imaging findings to be 35%, 40% and 25% respectively (expected values based on prior literature). We therefore conclude that the available study sample of approximately 100 cases provides adequate power for detecting the expected difference in agreement (Kappa-coefficients) for the two imaging modalities when reported by two independent readers using the described three outcome categories.

Statistical analysis will be performed using STATA version 14 statistical software package. Sample size calculations was performed using R statistical software (kappaSize package).

Ethical Considerations

- **Informed consent**

For the primary study all participants signed informed consent at enrolment and again annually in a language of their choice. This included consent for primary data collection, sharing and storage and publication of results, therefore no additional consent will be sought for this secondary data analysis. Infants in the primary study are currently still under 6 years of age, therefore assent was

not sought. A copy of the primary study informed consent form is included in this application (Appendix B).

- **Participant safety**

The proposed research only involves secondary analysis of previously collected data which holds no direct safety risk to participants.

The primary study is purely observational and does not aim to influence the outcomes of participants, however any clinically significant findings identified during study visits or procedures are referred for appropriate care by study staff according to standard referral pathways within the local public health care system. This included any LUS, CXR or clinical examination findings to be used in the proposed analysis, deemed clinically relevant at the time by the study clinician. Where required, these findings were immediately made available to treating clinicians to potentially assist with diagnosis and management of LRTI cases.

Ionising radiation (X-rays) theoretically carries a dose-related increase in risk of later-life malignancy, although the risk from standard radiographs is generally considered extremely low and acceptable for diagnostic use in the context of children hospitalised with suspected LRTI. In view of this theoretical risk, the primary study protocol did not require CXR imaging to be done for suspected LRTI cases, but only required collection and reporting of CXR images performed if requested by treating clinicians, based on their clinical judgement.

Ultrasound is not known to carry any risks to humans, which forms part of the rationale for conducting this study, as it may potentially offer a better risk-benefit ratio than X-ray imaging. During the ultrasound procedure cold jelly is applied to the skin of the infant which may cause mild discomfort and anxiety in the infant, but typically do not persist beyond the duration of the procedure.

- **Privacy, Confidentiality & Database Protection**

Only anonymized data will be made available by the primary study for this analysis and the data will be stored on a password protected computer. Risks related to the use of personal data are therefor considered no more than minimal.

- **Benefits of study participation**

There are no direct benefits for participants to be included in the proposed research. There may be future, indirect benefit for participants and the general paediatric population from the knowledge generated by this research.

- **Compensation for study participation**

Secondary data is used, therefore reimbursement for participants are not applicable.

- **Insurance**

The planned secondary data analysis poses no direct risk of bodily harm and no more than minimal data-related risk, therefore insurance or indemnity cover of any kind for the investigators or the University are not considered necessary.

- **Inclusion of vulnerable populations**

This protocol only involves secondary data analysis of previously collected data. The primary study has ethics approval for research involving minors.

- **Post-trial treatment**

Although data collection by the primary study involved a clinical intervention (LUS), the study design was observational in nature, and as such secondary analysis of this data will not be able to conclusively and exhaustively determine whether LUS is superior to the standard of care (CXR). It would therefore not be appropriate to recommend post-study intervention based on the findings of the proposed research alone.

Authorship

Dr Stadler will be credited as first author in any publications originating from the proposed research and Prof. Zar, being principal investigator (PI) and owner of the primary study data, will be credited as PI. All other investigators shall be credited as co-authors.

Funding

Bursary funding was received from the National Research Foundation for the proposed secondary analysis.

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Conflict of Interest

None of the investigators have any conflicts of interest to declare.

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PART 2: Literature Review

OBJECTIVES AND AIMS

The objective of this literature review was to understand the role of lung ultrasound (LUS) as a diagnostic imaging tool for pneumonia in children, and to summarise current literature comparing the diagnostic accuracy of LUS to chest X-ray (CXR).

Specific aims:

1. To review lung ultrasound methodology and applications in children with suspected pneumonia by identifying and summarising aspects, including:
   - Equipment used, imaging techniques, training requirements, and clinical settings where LUS in children is used.
   - The type and frequency of sonographic findings associated with pneumonia, diagnostic definitions used and classification of results.
   - Considerations (strengths and limitations) other than accuracy, including safety profile, cost and time-efficiency relative to other imaging modalities.
2. To summarise current evidence of the diagnostic accuracy of LUS compared to CXR for detecting pneumonia in children and explore methodological factors influencing accuracy.
3. To critically appraise the quality of evidence current literature and identify areas requiring further study.

SEARCH STRATEGY AND STUDY SELECTION

An electronic Pubmed Medline database search was done for English language publications from inception to 31 December 2018. Search terms used, and search results are summarised in the table below:

Search Nr	Search Terms	Nr of results
#1	paediatric OR paediatrics OR childhood OR children OR child	2606173
#2	pneumonia OR (lung infection) OR (lower respiratory tract infection) OR LRTI OR (chest infection) OR (respiratory infection) OR bronchiolitis	487779
#3	lung OR pulmonary OR chest OR thorax OR thoracic	1571106
#4	ultrasound OR ultrasonography OR sonography OR sonographic OR sonar	1483116
#5	#1 AND #2 AND #3 AND #4	4805

Full search terms used in PubMed (MEDLINE):

((((paediatric OR paediatrics OR childhood OR children OR child)) AND (pneumonia OR (lung infection) OR (lower respiratory tract infection) OR LRTI OR (chest infection) OR (respiratory infection) OR bronchiolitis)) AND (lung OR pulmonary OR chest OR thorax OR thoracic)) AND (ultrasound OR ultrasonography OR sonography OR sonographic OR sonar)

Titles and abstracts were screened to identify observational or interventional studies evaluating the diagnostic accuracy of LUS. Of these, all studies comparing, directly or indirectly, the diagnostic performance of LUS to CXR in children presenting with suspected lower respiratory tract infection of any form (including bronchiolitis), were included. A further manual search of the reference lists of included studies were performed to identify any additional studies not identified during the database search. Final selection criteria were as follows:

Inclusion criteria:

1. The study population was children (<21 years) presenting for care with clinical signs and symptoms of lower respiratory tract infection, i.e. it could be considered reasonable to perform imaging studies for suspected pneumonia.
2. Participants received both LUS and CXR around the time of symptomatic presentation to care, thus allowing for comparison of paired LUS and CXR results, either directly by using CXR as reference standard or indirectly by using a reference standard other than CXR, with LUS as index test and CXR as comparator test.
3. LUS and CXR results were reported as positive or negative for the presence of pneumonia, or sufficient details of radiographic and sonographic findings were reported to allow re-classification of results as positive or negative for pneumonia based on the presence or absence of either consolidation or interstitial disease picture or both.

Exclusion criteria:

1. Insufficient information reported to construct a 2x2 table indicating the number of true positive (TP), false positive (FP), true negative (TN) and false negative (FN) cases required to calculate diagnostic accuracy (sensitivity and specificity)
2. Studies focussed on diagnosis of conditions other than acute lower respiratory tract infection (pneumonia or bronchiolitis).
3. Studies focussed primarily on mediastinal ultrasound.

INTRODUCTION

Childhood pneumonia: pathology, aetiology and epidemiology

Lower respiratory tract infection (LRTI) is a spectrum of disease affecting the lungs that ranges from bronchiolitis to pneumonia. In the pre-vaccination era, bacterial pathogens such as *Streptococcus pneumoniae* and *Heamophilus influenzae* were the most frequently implicated pathogens in severe pneumonia[1], but more recent aetiology studies equally implicate both viruses and bacteria[2,3]. In severe cases, air-space in the lungs become fluid-filled (consolidated) due to the inflammatory process. When large enough, these areas of consolidation are visible on chest radiographs and can be used to confirm the diagnosis of pneumonia. Despite a steady decline in mortality in recent decades, pneumonia remains the leading cause of death and a major cause of morbidity in children under 5 years old, neonatal period excluded, accounting for an estimated 102 million episodes and 704000 deaths globally in 2015[4,5]. Pneumonia outcomes are strongly associated with poverty-related determinants of health such as malnutrition and access to and quality of healthcare, with an estimated burden of 72 deaths / 100000 population in low-income settings compared to only 1.7 / 100000 in high-income settings[5]. In South Africa the incidence of pneumonia (ambulatory and hospitalised) in children less than 1 year was recently reported as between 0.20-0.27 episodes per child year[6].

Diagnostic imaging in pneumonia

Though the incidence of pneumonia remains high, effective treatment is available once the diagnosis is made. Clinical signs and symptoms are a sensitive way to diagnosis pneumonia, but has limited specificity for distinguishing bacterial from other forms of pneumonia[7,8]. Nonetheless, international guidelines rely on clinical features alone to diagnose and treat cases where mild, uncomplicated community-acquired pneumonia (CAP) or viral aetiology is clinically suspected[9–11]. Such empiric treatment is not ideal, as it can lead to antibiotic overuse and drive antibiotic resistance. Additional diagnostic tools are required to detect those with a high probability of bacterial pneumonia who are likely to benefit from further intervention such as antibiotics. Adding CXR imaging is widely available may improve specificity. CXR can also be valuable to establish alternative diagnoses, identify complications and monitor response to therapy. A major drawback of CXR, however, is ionizing radiation exposure and the associated theoretical risk of carcinogenesis which, despite limited supporting evidence[12], remains of particular concern in children. Other limitations of CXR include high inter-observer variation[13–16] and the cost, specialized expertise and regulatory requirements of a radiology service, which limits access, especially in low resource settings. Even with all these factors aside, studies have failed to demonstrate a significant clinical benefit from routine CXR use in uncomplicated CAP[17], hence the recommendations by guidelines. The regulatory requirements, expertise and cost of operating a radiology service further limits its availability in low-resource settings. Other modalities used less frequently

for childhood pneumonia include computed tomography (CT) and magnetic resonance imaging (MRI)[18]. CT can be considered the 'gold standard' for pneumonia imaging, but is not commonly used in uncomplicated CAP in children, primarily due to the much higher radiation doses used[19]. MRI, on the other hand, is radiation free, but may require sedation in young children, which also reserves its use for selected scenarios.[20] The prohibitively high cost of both CT and MRI and need for specialised operators and paediatric radiologists further limits its availability to well-resourced, in-hospital settings.

Ultrasound can also discriminate healthy from unhealthy lungs and detect different types of lung and chest pathology, including signs of pneumonia[21]. Ultrasound has the advantage of being completely radiation free which makes it attractive from a safety perspective for use in paediatrics, especially in situations where repeated imaging is required. Increasingly mobile ultrasound machines have also sparked growing interest in its use outside the radiology department by non-radiologists clinicians[22,23] referred to as point-of-care, clinician-performed or bedside ultrasound and telemedicine has enabled images to be sent remotely for interpretation of images by skilled radiologists[24]. Point-of-care ultrasound is already a regular part of everyday practice in specialities such as emergency medicine and critical care, with some reports even suggesting it will eventually become as common a diagnostic aid as the stethoscope[22]. These factors, combined with relatively lower cost compared to CXR makes ultrasound a potentially safer and more accessible diagnostic tool for pneumonia in children. However, the starting point to understanding the role of LUS relative to other imaging modalities is to know its relative accuracy. The objective of this paper was to perform a structured literature review and meta-analysis to assess the diagnostic accuracy of LUS compared to CXR.

LUNG ULTRASOUND

Equipment and technique

A variety of commercially available ultrasound systems have been used in diagnostic accuracy studies. Comparative studies to determine an optimal combination of machine specifications, settings and scanning protocols have not been done and are probably unnecessary. Rather, users should understand how to optimise equipment settings and probe selection to the size and individual characteristics of each patients. High frequency (5-15MHz), small linear or micro-convex probes are usually appropriate for visualisation of the pleura and sub-pleural anatomy through the narrow intercostal spaces of young children. A standardized, systematic scanning protocol, similar to that described by Copetti et al should be used to ensure scanning of the entire chest[25]. One study found that addition of a trans-abdominal approach was able to detect pneumonia in the lung bases which would otherwise have been missed and should be a standard part of any scanning protocols[8]. Patients can by scanned in laying or sitting position[26]. Pleural effusions tend to collect in

dependent areas and need to be specifically looked for to avoid missing small collections. Efforts should be made to keep the child comfortable and calm, as excessive movement from an uncooperative child can affect scans quality.

Sonographic findings

Several sonographic findings have been described which can be used to distinguished those with and without pneumonia. The most prevalent pneumonia-related abnormal findings are sub-pleural consolidation, multiple or confluent B-lines (interstitial disease picture), which can be localised or diffuse, pleural line irregularities and pleural effusion[27,28]. Two studies which compared LUS findings in children with clinical signs of ALRI to healthy controls found that sub-pleural consolidation, interstitial disease picture, pleural line irregularities or pleural effusion were all significantly associated with infection[28,29]. There were also a positive correlation between clinical and laboratory markers of disease severity and frequency of abnormal sonographic findings[29,30]. Further, follow-up studies of pneumonia cases have reported resolution of these findings following the illness[29,31,32]. In contrast, one study comparing pneumonia cases to controls with *upper respiratory symptoms only*, showed a significant overlap in sonographic findings of both interstitial picture and consolidation, although the clinical case definition used for pneumonia in this study may have contributed to some misclassification of cases and controls[33]. Few, isolated B-lines were equally present in both mild disease cases and healthy controls and is not considered an abnormal finding[29].

Meta-analysis of test accuracy

Meta-analytic methodology was used to pool accuracy results and assess methodological factors which may influence accuracy. Using the specified eligibility criteria 22 studies totalling 2756 participants were included. Characteristics of included studies are summarised in Table 1. The reference standard used could broadly be classified into two groups: those using CXR findings alone (16 studies)[34–48] and those using an *ex post* final diagnosis of pneumonia (6 studies)[25,27,49–52]. Of the latter, 3 studies[27,49,52] used purely clinical, standardised criteria (British Thoracic Society guidelines), while the remaining 3 studies[25,50,51] used all available evidence (laboratory, CXR results and response to treatment) in a non-standardized way (expert opinion). Diagnostic endpoint definitions also varied considerably, both for the index test and reference standard. For example, sonographic consolidation considered the definitive feature of pneumonia on LUS, was limited to lesions containing air-bronchograms in 9 studies[30,39,41,45,46,49,52–54] presumably to distinguish alveolar consolidation from collapse, while the rest of the studies did not make this distinction. Also, very small sonographic consolidations (diameter less than 1cm or 1 intercostal space) were excluded (or at least analysed separately) in only 4 studies [46,48,52,54]. This cut-off was chosen because lesions smaller than 1cm is typically not visible on CXR though frequently detected on LUS[39], which will lead to decreased specificity of LUS if CXR is considered

the reference standard, despite LUS actually detecting lesion missed by CXR. Similarly, only 6 studies considered sonographic interstitial disease pattern (without consolidation) diagnostic of pneumonia[27,32,41,49,51,55]. In contrast, interstitial pattern on CXR was considered diagnostic of pneumonia in 13 studies[27,30,55–57,32,34,36,41,51–54]. The WHO standardized interpretation methodology for CXR reporting, aimed at minimising inter-observer variation and standardized interpretation of findings, was applied in only 6 studies[39,41,45,55,56,58], while the rest either used non-standardized CXR reporting or did not state how CXR results were classified.

Overall pooled sensitivity of LUS was 95% (95% confidence interval (CI): 92%-97%) and pooled specificity was 88% (95% CI: 66%-96%) (Figure 1), which is in line with four similar, previously published meta-analyses[59–62]. However, meaningful comparison between LUS and CXR using these results are problematic as the majority of these studies used CXR as reference standard, which by default assumes 100% accuracy for CXR. The problem with this is two-fold: firstly, it is well established that the true accuracy of CXR is in fact not 100%, and secondly, the problem with using an imperfect reference standard is that it will negatively bias accuracy of the index test in cases with LUS-positive-CXR-negative discordant results, even though the true disease status in these cases are unclear and LUS may in fact be detecting cases missed by CXR. Another problem with these results is that some of the studies which used an *ex post diagnosis of pneumonia* as reference standard incorporated CXR, but not LUS findings into the final diagnosis, which are likely to bias accuracy results in favour of CXR.

As an alternative approach, concordance (agreement) between LUS and CXR was calculated for this subgroup of 16 studies which used CXR alone as reference standard (Table 2). This approach avoids the problems of an imperfect reference standard (CXR), while still allowing direct comparison between CXR and LUS. Pooled overall observed agreement (OOA) was 0.88 (95% CI: 0.87-0.89), with proportion positive agreement (PPA) = 0.90 (95% CI: 0.88-0.91), proportion negative agreement (PNA) = 0.86 (95% CI: 0.84-0.88) and Kappa=0.76 (95% CI: 0.73-0.78). In contrast, the 6 studies (496 participants) which calculated accuracy of both LUS (as index test) and CXR (as comparator test) against a common reference standard of *ex post diagnosis of pneumonia*[47–49,56,57] allowed for a different comparison. Pooled results of this subset of studies (Figure 2) found sensitivity (Se) was higher for LUS (Se=98%, 95% CI: 95%-99%) than for CXR (Se=92%, 95% CI: 86%-97%). Pooled specificity (Sp) for LUS was also higher (Sp=95%, 95% CI: 89%-99%) than for CXR (Sp=90%, 95% CI: 80%-97%). Although these differences were not found to be statistically significant, as is evident from the overlapping confidence intervals, this may be due to small sample size limitations (496 participants) rather than the lack of a true difference.

Methodological heterogeneity and subgroup analysis

Overall pooled results ignore the methodological differences between studies and the effect it may have on test accuracy. Exploratory subgroup (stratified) analysis was therefore performed to investigate the effect of several clinically important variable (additionally to the difference in reference standards already considered) on sensitivity and specificity of LUS. These included sonographic and radiographic endpoint definitions, different definitions of sonographic consolidation, level of sonographer expertise and number of CXR views used (Table 3). When considering different test endpoint definitions, specificity was notably higher when CXR positivity was defined as consolidation alone as compared to any abnormality (Sp: 91% vs 82%), while sensitivity was equal between subgroups (Se: 95% vs 95%). Both sensitivity and specificity were better when LUS positivity was defined as any abnormality as compared to sonographic consolidation alone (Se: 97% vs 94%; Sp: 91% vs 84%). With respect to different definitions for sonographic consolidation, a broad definition (any consolidation) yielded higher specificity compared to a restricted definition (excluding lesions <1cm and/or lesions without bronchograms) (Sp: 90% vs 85%) while sensitivity was not notably affected (Se: 96% vs 95%). When different levels of sonographer expertise were compared, expert operators yielded slightly higher sensitivity compared to non-experts (Se: 96% vs 92%), though sensitivity was excellent for both groups, while not showing any difference in specificity (Sp: 89% vs 89%). Sensitivity was not affected by the number of CXR views used (Se: 95% vs 95%), though specificity was higher when no lateral view was used. Though none of the reported subgroup differences in this exploratory analysis were statistically significant, as can be seen from the overlapping confidence intervals in Table 3, this should be viewed in the light of the sparsity of data (22 studies) rather than considering it a true lack of effect.

Considerations other than accuracy

Two studies which assessed point-of-care LUS use in the emergency department as a diagnostic tool for pneumonia in children reported significant cost and time savings when compared to CXR[63,64]. However, while these results reflect time savings for patients (time to discharge or definitive care), it is important to consider that for clinicians performing point-of-care scans, the procedure adds additional time spent examining patients to their workload. The typical duration of LUS has been reported as ranging from 5-20 minutes[46,48,49,55,65]. One of these studies, a pragmatic randomized clinical trial, also showed that the introduction of LUS decreased clinicians reliance on CXR, effectively decreasing use of CXR. The same study also investigated the impact of LUS on antibiotic prescription and found slightly increased antibiotic use in the investigational arm (LUS with optional CXR) compared to the control arm (CXR and LUS performed), but the clinical impact of this have not yet been robustly evaluated. In addition to diagnostic use, follow-up studies have also shown the usefulness of LUS to monitor disease resolution and response to treatment while avoiding repeated radiation exposure[29,31,32]. LUS is also able to detect complications including pleural

effusion, pneumothorax, atelectasis, lung necrosis and abscess[66]. In fact, LUS had been shown to be as sensitive as CT to detect effusion and superior to CT for characterization of effusions[67].

Limitations of LUS

There are also important limitations to the suitability of ultrasound for imaging of the lungs. Firstly, air in healthy lung tissue does not reflect ultrasound waves which makes direct visualisation of air-filled lung parenchyma and deep lung structures with overlying air by ultrasound impossible. Secondly, much of the lung surface is covered by calcified bone of the thoracic cage, which is impenetrable to ultrasound. These limitations mean ultrasound may potentially miss pneumonia not extending to the pleura or in areas covered by bone, such as the sub-scapular regions[31,32,56,68]. Another potentially limiting factor is the training requirements for clinicians with minimal prior ultrasound experience to achieve reliable results, as ultrasound findings are known to be operator dependent. However, evidence suggest that this can be achieved by relatively little training. In a recent meta-analysis[59] which compared results of expert and non-expert LUS practitioners, accuracy was found to be only slightly higher when scans were performed by experts compared to non-experts, while training in the included studies ranged between 1hr to 1 week, suggesting that LUS is a relatively simple skill to learn, but additional training is required nonetheless[33,53]. These results were echoed by the findings of the subgroup analysis of this review (Table 3). Several studies also found inter-rater agreement of LUS to be substantial to high (Kappa = 0.55-0.93)[52,53,65,69,70].

DISCUSSION

Pneumonia remains a global health priority in children. Clinical signs, including auscultation with a stethoscope, have limited diagnostic accuracy and imaging tests continue to have an important role in the diagnosis and management of pneumonia. CXR imaging is the current standard of care, but is not recommended for routine use in children due to concerns about radiation exposure and is frequently unavailable in settings where the burden of childhood pneumonia is the highest due to resource constraints. CT and MRI are also viewed as unsuitable for routine use for pneumonia in children due to limitations such as cost and perceived radiation risk.

In this review we used paired CXR and LUS data from 22 studies totalling 2756 participants to compare diagnostic accuracy of LUS using CXR as reference standard. Pooled results from all studies, ignoring methodological heterogeneity, found that LUS had sensitivity of 95% (95% CI: 92%-97%) and specificity of 87% (69%-97%). However, as CXR cannot be considered a true gold standard and due to the variation in diagnostic definitions used and other methodological heterogeneity, the validity of these overall pooled results is questionable and make meaningful comparison between LUS and CXR problematic. In an alternative

representation of the data, results from 16 studies all using CXR as reference standard found a high level of agreement between LUS and CXR, with the overall observed agreement = 0.88 (95% CI: 0.87-0.89), positive agreement = 0.90 (95% CI: 0.88-0.91), negative agreement = 0.86 (95% CI: 0.84-0.88) and overall inter-test agreement of Kappa=0.76 (95% CI: 0.73-0.78). In this subgroup of studies reporting sensitivity and specificity would not be meaningful, as it by default assume 100% accuracy for CXR as reference standard, which is not the case. Hence, concordance may be a better way to compare performance of LUS and CXR in this scenario. In a separate subgroup of 6 studies which separately compared both LUS and CXR respectively against a common reference standard (final ex post diagnosis of pneumonia), both sensitivity and specificity of LUS was found to be higher than CXR [Se: 98% (95% CI: 95%-99%) vs 92% (95% CI: 86%-97%); Sp: 95% (95% CI: 89%-99%) vs 90% (95% CI: 80%-97%). These results suggest that LUS may in fact be more sensitive and specific than CXR and studies using CXR as reference standard may therefore be underestimating accuracy of LUS.

This review also highlighted the significant methodological heterogeneity found across studies and investigated how several of these factors may affect accuracy of LUS. Results from exploratory subgroup analyses suggest that the reference standard used, imaging endpoint definitions (both radiographic and sonographic), definitions of specific sonographic findings, level of sonographic expertise and number of CXR views may all affect accuracy to a varying degree. However, sensitivity of LUS generally remains high (≥92%) across all subgroups, though specificity appears to be more affected by methodological variation with point estimates dropping as low as 77% in certain subgroups.

This overall high sensitivity and moderate to high specificity of LUS, as well as the high level of agreement between CXR and LUS, and the fact that the reasons for non-concordance are well-understood may be sufficient to make a rational argument for interchangeable rather than just complementary use of these two imaging modalities, while keeping in mind the fact that neither modality should be used in isolation for decision making without considering the broader clinical picture.

Areas requiring further research include the development and validation of standardized LUS interpretation methodology similar to the WHO standardized interpretation of CXR. Further research is also needed to clarify the defining features of clinically significant consolidation, as well as the clinical significance of interstitial disease picture without consolidation as these appear to be major points of contention. Additionally, further studies using CT as reference standard, where clinically and ethically justifiable, would be the ideal to investigate LUS accuracy. Lastly, pragmatic diagnostic randomised trials comparing the impact LUS and CXR on clinical outcomes, in a scenario where this is ethically justifiable, would be the ideal to inform policy on the potential substitution of CXR with LUS for diagnosis of pneumonia.

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Table 1: *Summary of important study characteristics and characteristics of the index test(s) and reference standard used of included studies.*

Study	Study design and population						Index test (LUS)				Comparator (CXR)		Reference standard
Author, year published	Data collection	Sampling method	Sample size (M : F)	Mean age (months)	Clinical setting	Main eligibility criteria	Operator expertise	Positive endpoint definition:			Views used	Positive endpoint definition:	
								Broncho-grams required	Conso-lidation size	Interstitial pattern included			
Copetti, 2008	Prospective	Convenience	79 (NR)	61	ED	Clinical suspicion of pneumonia	Expert	Unclear	Any size	Unclear	PA/AP only	Unclear	Ex post diagnosis of pneumonia (not using standardized guidelines)
Caiulo, 2013	Prospective	Convenience	102 (53:49)	60	Paediatric ward	Clinical suspicion of pneumonia and had CXR at discretion of attending physician	Expert	No	Any size	Yes	PA/AP only	Alveolar and/or interstitial pattern	Ex post diagnosis of pneumonia (using BTS guidelines)
Seif el Dien, 2013	Prospective	Consecutive	75 (36:39)	0.3	NICU	Neonates hospitalised with clinical suspicion of pneumonia (onset after 48hrs of life)	Expert	No	Any size	No	PA/AP only	Alveolar and/or interstitial pattern	Radiographic pneumonia as defined by CXR endpoint
Shah, 2013	Prospective	Convenience	200 (112:88)	36	ED	Clinical suspicion of pneumonia and had CXR at discretion of attending physician	Mixed	Yes	Any size	No	PA/AP & Lat	Alveolar and/or interstitial pattern	Radiographic pneumonia as defined by CXR endpoint
Esposito, 2014	Prospective	Consecutive	103 (56:47)	67	PICU	Hospitalised with clinically diagnosed pneumonia	Novice	Yes	Any size	Yes	PA/AP & Lat	Alveolar and/or interstitial pattern	Radiographic pneumonia as defined by CXR endpoint
Reali, 2014	Prospective	Consecutive	107 (61:46)	48	Paediatric ward	Clinical suspicion of pneumonia	Expert	Yes	Any size	Yes	PA/AP only	Unclear	Ex post diagnosis of pneumonia (using BTS guidelines)
Iorio, 2015	Retrospective	Consecutive	52 (NR)	42	Paediatric ward	Hospitalised with mild/uncomplicated respiratory sign & symptoms	Expert	No	Any size	No	PA/AP only	Alveolar pattern only	Ex post diagnosis of pneumonia (not using standardized guidelines)
Urbankowska, 2015	Prospective	Consecutive	106 (39:67)	53	ED	Clinical suspicion of pneumonia and had CXR at discretion of attending physician	Expert	No	Any size	No	Unclear	Alveolar and/or interstitial pattern	Radiographic pneumonia as defined by CXR endpoint
Guerra, 2016	Prospective	Consecutive	222 (108:114)	59	ED	Clinical suspicion of pneumonia: moderate to severe respiratory distress + high fever	Intermediate	Yes	Any size	No	Mixed	Alveolar and/or interstitial pattern	Radiographic pneumonia as defined by CXR endpoint
Ianniello, 2016	Retrospective	Consecutive	84 (44:40)	NR	ED	Clinical suspicion of pneumonia	Unclear	No	Any size	Yes	PA/AP & Lat	Alveolar and/or interstitial pattern	Radiographic pneumonia as defined by CXR endpoint
Samson, 2016	Prospective	Consecutive	200 (116:84)	30	ED	Clinical suspicion of pneumonia and had CXR at discretion of attending physician	Mixed	Yes	Any size	No	PA/AP only	Alveolar pattern only	Radiographic pneumonia as defined by CXR endpoint
Zhan, 2016	Prospective	Convenience	82 * (47:35)	18	ED	Clinical suspicion of pneumonia and had CXR at discretion of attending physician	Novice	Yes	>1cm	No	PA/AP only	Unclear	Radiographic pneumonia as defined by CXR endpoint
Boursiani, 2017	Prospective	Consecutive	69 (27:42)	54	ED	Clinical suspicion of pneumonia and had CXR at	Expert	No	Any size	Yes	PA/AP only	Alveolar and/or interstitial pattern	Ex post diagnosis of pneumonia (not using standardized guidelines)

						discretion of attending physician							
Claes, 2017	Prospective	Consecutive	143 (77:66)	31	Radiology department	Clinical suspicion of pneumonia and had CXR at discretion of attending physician	Expert	No	Any size	No	PA/AP only	Alveolar pattern only	Radiographic pneumonia as defined by CXR endpoint
Ellington, 2017	Prospective	Consecutive	421 (NR)	NR	Clinic, ED & ward	Clinically and radiologically defined pneumonia and healthy controls	Intermediate	No	>1 ICS	No	PA/AP only	Alveolar pattern only	Radiographic pneumonia as defined by CXR endpoint
Man, 2017	Retrospective	Consecutive	81 (42:39)	78	Paediatric ward	Hospitalised with clinical suspicion of pneumonia	Expert	No	Any size	No	PA/AP only	Alveolar and/or interstitial pattern	Radiographic pneumonia as defined by CXR endpoint*
Yadav, 2017	Prospective	Convenience	118 (65:53)	26	Paediatric ward	Hospitalised with clinically diagnosed pneumonia	Expert	No	Any size	Yes	Unclear	Alveolar and/or interstitial pattern	Radiographic pneumonia as defined by CXR endpoint
Yilmaz, 2017	Prospective	Convenience	149 (79:70)	16	ED	Clinical suspicion of pneumonia and had CXR at discretion of attending physcian	Expert	Unclear	Any size	Unclear	PA/AP only	Unclear	Radiographic pneumonia as defined by CXR endpoint
Biagi, 2018	Prospective	Consecutive	87 (43:44)	6	Paediatric ward	Clinical diagnosed bronchiolitis and clinical suspicion of concomitant pneumonia	Intermediate	Yes	Any size	No	PA/AP only	Alveolar and/or interstitial pattern	Ex post diagnosis of pneumonia (using BTS guidelines)
Iorio, 2018	Retrospective	Consecutive	47 (27:20)	48	Paediatric ward	Hospitalised with diagnosis of pneumonia	Expert	Yes	Any size	No	PA/AP only	Alveolar pattern only	Radiographic pneumonia as defined by CXR endpoint
Lissaman, 2018	Prospective	Consecutive	97 (50:47)	29	ED	Clinical suspicion of pneumonia and had CXR at discretion of attending physician	Novice	Yes	Any size	No	PA/AP only	Alveolar and/or interstitial pattern	Radiographic pneumonia as defined by CXR endpoint
Omran, 2018	Prospective	Convenience	50 (30:20)	6	Paediatric ward	Clinical defined pneumonia (BTS guidelines) and had CXR at discretion of attending physician	Expert	No	Any size	No	PA/AP only	Alveolar and/or interstitial pattern	Radiographic pneumonia as defined by CXR endpoint**

LUS = lung ultrasound, CXR = chest X-ray, NR = not reported, M = male, F = female, ED = Emergency Department, NICU = Neonatal Intensive Care Unit, PA = posterior-anterior, AP = anterior-posterior, Lat = lateral, BTS = British Thoracic Society, ICS = intercostal space

* LUS was also compared to clinical pneumonia, but CXR was not compared to the clinical reference standard, so no comparison was possible.

** Comparison to clinical pneumonia was also reported, but due to unclear methodology these results were not includable.

Table 2: *Summary of studies using CXR alone as reference standard showing both measures of accuracy and agreement.*

Study	Sample size	TP	FP	FN	TN	Se	Sp	OOA	PPA	PNA	Kappa
Seif el Dien, 2013	75	64	0	4	7	0.94	1.00	0.95	0.97	0.78	0.75
Shah,2013	200	31	18	5	146	0.86	0.89	0.89	0.73	0.93	0.66
Esposito, 2014	103	47	3	1	52	0.98	0.95	0.96	0.96	0.96	0.92
Urbankowska, 2015	106	71	0	5	30	0.93	1.00	0.95	0.09	0.92	0.89
Guerra, 2016	222	190	17	7	8	0.96	0.32	0.89	0.94	0.40	0.34
Ianniello, 2016	84	46	13	1	24	0.98	0.65	0.83	0.87	0.77	0.65
Samson, 2016	200	74	6	11	109	0.87	0.95	0.92	0.90	0.93	0.82
Zhan, 2016	164	33	7	49	75	0.40	0.91	0.66	0.54	0.73	0.32
Claes, 2017	143	44	8	1	90	0.98	0.92	0.94	0.91	0.95	0.86
Ellington, 2017	421	169	0	22	230	0.88	1.00	0.95	0.94	0.95	0.89
Man, 2017	81	57	5	15	4	0.79	0.44	0.75	0.85	0.29	0.16
Yadav, 2017	118	99	6	2	11	0.98	0.65	0.93	0.96	0.73	0.70
Yilmaz, 2017	149	127	15	5	2	0.96	0.12	0.87	0.93	0.17	0.11
Iorio, 2018	47	38	9	0	0	1.00	0.00	0.81	0.89	0.00	0.00
Lissaman, 2018	97	40	17	4	36	0.91	0.68	0.78	0.79	0.77	0.57
Omran, 2018	50	36	13	1	0	0.97	0.00	0.72	0.84	0.00	-0.04
Pooled value (95% CI)	**2260**	**1166**	**137**	**133**	**824**	**0.89 (0.88-0.91)**	**0.86 (0.84-0.88)**	**0.88 (0.87-0.89)**	**0.90 (0.88-0.91)**	**0.86 (0.84-0.88)**	**0.76 (0.73-0.78)**

TP = True positives, FP = False positives, FN = False negatives, TN = True negatives, Se = Sensitivity, Sp = Specificity, OOA = Overall observed agreement, PPA = Proportion positive agreement, PNA = Proportion negative agreement, Kappa = Cohen's kappa-coefficient

Table 3: *Comparison of sensitivity and specificity values for subgroups (stratified analysis).*

Study characteristics with subgroup		Sensitivity (95% CI)	Specificity (95% CI)
CXR endpoint definition			
	Consolidation alone	95% (84%-99%)	91% (21%-100%)
	Any abnormality	95% (92%-97%)	82% (54%-95%)
Sonographic endpoint definition			
	Consolidation alone	94% (89%-97%)	84% (48%-97%)
	Any abnormality	97% (94%-98%)	91% (72%-97%)
Sonographic consolidation definition			
	Broad (any consolidation)	96% (93%-98%)	90% (49%-99%)
	Restricted (excluding lesions <1cm or without bronchograms)	93% (84%-95%)	86% (57%-97%)
Sonographer expertise			
	Expert	96% (93%-98%)	89% (39%-99%)
	Non-expert	92% (82%-97%)	89% (71%-96%)
CXR views			
	PA & Lat	95% (91%-98%)	77% (46%-93%)
	PA only	95% (91%-98%)	91% (62%-98%)

Figure 1: *Forest plot showing LUS sensitivity and specificity for all included studies and overall pooled results.*

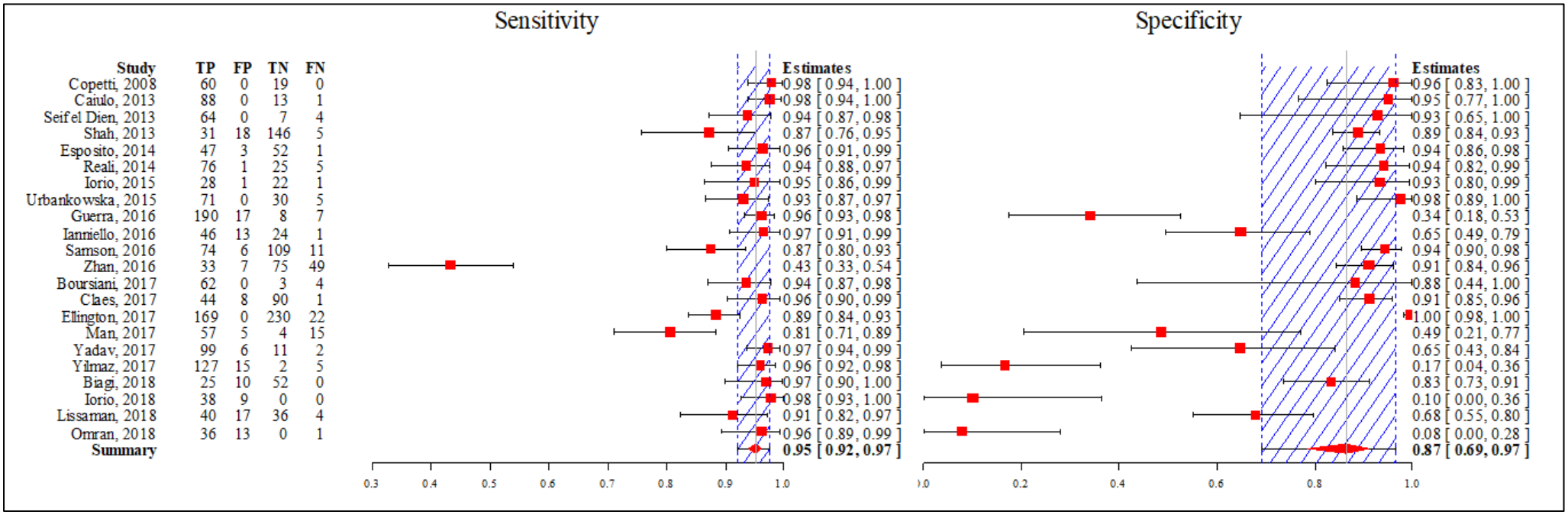
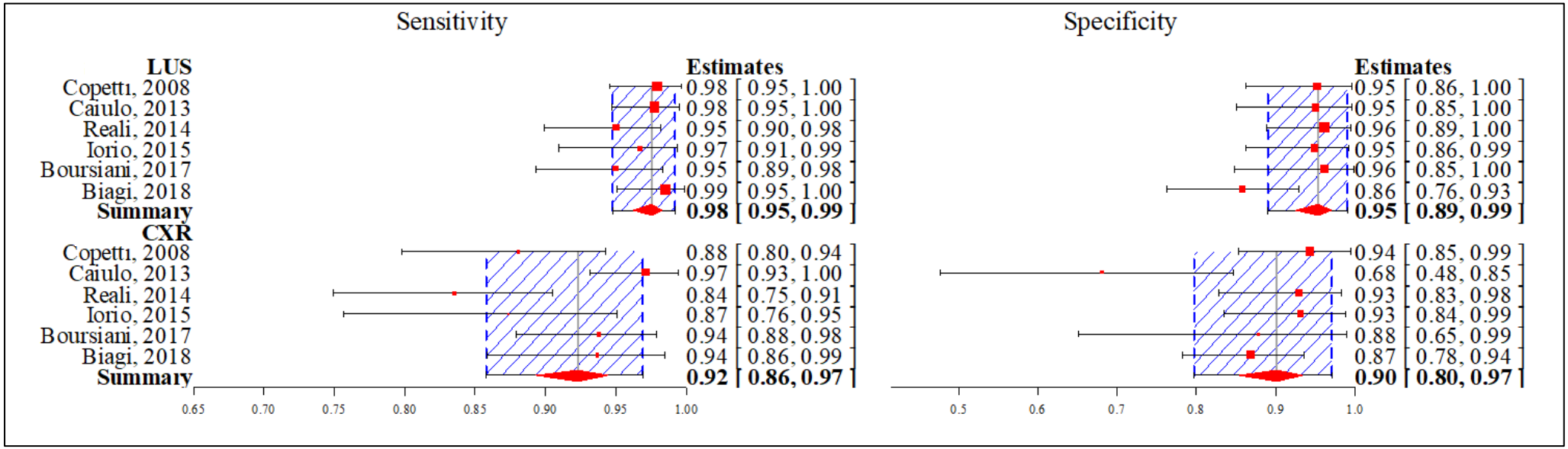


Figure 2: *Forest plot of 6 studies comparing sensitivity and specificity of both LUS (as index test) and CXR (as comparator test) against a common reference standard (ex post diagnosis of pneumonia).*



PART 3: Original Data Manuscript

Evaluation of the diagnostic performance of lung ultrasound compared to chest X-rays for the diagnosis of pneumonia in children in the Drakenstein Child Health Study.

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Abstract

Introduction: Lung ultrasound (LUS) is radiation-free and cheaper than and chest X-ray (CXR). The objective of this study was to investigate the diagnostic performance of LUS compared to CXR for pneumonia in children in a resource-constrained, African setting.

Methods: Children enrolled in the Drakenstein Child Health Study who presented with clinically defined pneumonia and had a CXR performed by the attending physician also had a LUS performed by a study doctor. Each modality was reported by two readers, using standardised methodology. Agreement between modalities, accuracy (sensitivity and specificity) of LUS and inter-rater agreement were assessed. Both c*onsolidation* and *any abnormality* (consolidation or interstitial picture) were considered as pneumonia endpoints.

Results: In 102 children (median age: 7.2 months; 56% male; 70% hospitalised), prevalence was 37% vs 39% for *consolidation* and 52% vs 75% for *any abnormality* on LUS and CXR respectively. Agreement was poor and not significantly higher than expected by chance, neither for *consolidation* (observed agreement (OA) 61%, Kappa=0.17, 95% confidence interval: -0.02-0.36) nor for *any abnormality* (OA=55%, Kappa=0.08, -0.09-0.29). Using CXR as reference standard, sensitivity (Se) of LUS was low, both for *consolidation* (Se=48%, 32%-0.64%) and *any abnormality* (Se=55%, 43%-66%), while specificity (Sp) was moderate for *consolidation* (Sp=69%, 56%-80%), but lower for *any abnormality* (Sp=56%, 35%-76%). Inter-rater agreement of LUS was substantial (Kappa=0.60, 0.47-0.74) and significantly higher than CXR (Kappa=0.25, 0.13-0.35).

Conclusion: Accuracy of LUS in non-ideal conditions may be considerably lower than suggested by recently published meta-analyses, but LUS has significantly higher inter-observer agreement than CXR.

Introduction

Pneumonia forms part of a spectrum of lower respiratory tract infections (LRTI). Despite a steady decline in mortality in recent decades, pneumonia remains the leading cause of death in children, accounting for over 700000 child deaths each year. Pneumonia is one of the most common reasons for healthcare visits in children with over 100 million episodes estimated to occur globally each year[1,2]. Over 90% of these deaths occur in low and middle income countries[2].

One modifiable factor which can potentially impact pneumonia outcomes is early and correct diagnosis. Diagnostic algorithms based on clinical features alone, as recommend by international evidence-based guidelines in mild disease cases[3–5], lacks specificity for bacterial pneumonia[6,7]. This may lead to antibiotic overuse and resistance. Addition of chest X-ray (CXR) imaging can improve specificity, but there are drawbacks such as radiation exposure, variability when interpreting results[8–10] and cost, specialized expertise and regulatory requirements of a radiology service. Even with all these factors aside, studies have failed to demonstrate a clear clinical benefit from routine CXR use in cases where mild, uncomplicated community-acquired pneumonia or viral aetiology is suspected[11], hence current guidelines reserve CXR for moderate to severe disease and hospitalized cases, even in well-resourced settings. Despite these limitations CXR remains the most widely used imaging modality for in children with suspected pneumonia, as alternatives such as computed tomography (CT) and magnetic resonance imaging (MRI) are perceived as having an unacceptable safety and cost profile.

The ideal diagnostic test for pneumonia should be safe, accurate, cheap, quick and simple to perform. Lung ultrasound (LUS) is a promising imaging modality which uses no radiation, is less costly than CXR and can improve the time to results[12] when used as a point-of-care tool by clinicians outside the radiology department. A number of published meta-analyses also reported high accuracy of LUS for the detection of pneumonia in children[13–17]. These characteristics make LUS an ideal option as a low risk, low cost screening test aimed at improving diagnosis and targeting treatment for paediatric pneumonia. Nonetheless, uptake of LUS in clinical practice is slow and several questions remain regarding real-world performance and requirements for achieving optimal results. The aim of this study was to evaluate the diagnostic performance of LUS compared to CXR in children presenting with clinically defined pneumonia in a low-resource, African setting and to identify factors which may be important for achieving optimal results.

Methods

The Drakenstein Child Health Study (DCHS) is a large, multi-year, population-based birth cohort study investigating the early life determinants of child health in Africa[18], taking place in Paarl, South Africa, a peri-urban town approximately 50km from Cape Town. Children enrolled in the DCHS who presented to the emergency department of the local public hospital with acute respiratory symptoms and signs matching the

World Health Organisation (WHO) clinical case definition for childhood pneumonia[4] and who received a CXR during clinical care, based on the discretion of the attending clinician, were identified and a LUS was performed as part of the study protocol. Cases were consecutively enrolled, and data was prospectively collected between August 2014 and December 2015. All scans were performed by the same study clinician, a general practitioner with minimal prior ultrasound experience, but who had undergone focused LUS training consisting of a theoretical training session with an experienced paediatric radiologist, followed by a number of practice scans which were reviewed with the radiologist. LUS was usually performed within 24 hours, but up to 72 hours from time of CXR. The sonographer was blinded to CXR findings at the time of performing the scan, but the indication for performing the scan was known. Scans were performed using a commercially available ultrasound machine (Mindray DP10, Mindray Bio-Medical Electronics Co. Ltd) with a micro-convex probe. Default machine settings (Frequency: 7.5MHz, Gain: 35, Depth: 4cm) were adjusted according to individual patient characteristics for optimal visualization. A standardized, systematic scanning protocol was used by dividing each hemi-thorax into four quadrants: anterior and posterior halves divided by the mid-axillary line, sub-divided into upper and lower quadrants at the level of the nipple line (Figure 1). Each quadrant was scanned diagonally by moving the probe from one intercostal space to the next while keeping the probe parallel to the ribs and a 5-10 second video clip was recorded of each quadrant and stored. Participants were scanned in sitting or lying position. Dependent areas were checked for pleural fluid collections. Considerable effort was made to keep children comfortable and calm during scans, often scanning children on the mother's lap while breastfeeding, as excessive movement from an uncooperative child negatively affected the performance and interpretability of scans. Each scan consisting of eight video clips was later reported independently by two reporters: the study clinician (general practitioner) who performed the scans and a paediatric radiologist, both blinded to CXR findings at the time of reporting the LUS. LUS findings were classified as *typical of pneumonia* (consolidation present), *interstitial syndrome* (focal or generalized pathological B-lines, but no consolidation) or *normal.* Definition details are summarised in Table 1 with Figure 2 showing characteristic examples of diagnostic categories.

A posterior-anterior (PA) CXR was done on all children and a lateral view was also attained in some at discretion of the attending clinicians. CXR images were reported independently by two experienced paediatricians blinded to LUS results, but aware of the indication for the CXR. CXR results were classified using the WHO standardized interpretation methodology for pneumonia in children.[19] For a final result, disagreement between LUS readers was resolved pragmatically by accepting the read of the paediatric radiologist, while CXR disagreement was adjudicated by using a third independent reader and accepting the result on which the majority readers agreed. CXR findings in keeping with pneumonia (radiographic pneumonia) were considered the reference standard for calculating accuracy. Radiographic pneumonia was defined in terms of WHO radiographic reporting categories (Table 1) and accuracy was calculated separately considering both *consolidation* and *any abnormality* (other infiltrates included) as diagnostic endpoints for

pneumonia. Despite recognition of the limitations of CXR as reference standard, this choice allows for comparison of results with other studies using similar methodology.

Data collection was performed using REDCAP electronic data capturing platform (Vanderbilt University, Nashville, Tennessee, USA) and statistical analysis was performed using STATA version 15 statistical software package (StataCorp Inc, College Station, Texas, USA). Categorical variables were expressed as simple frequencies (n), percentages (%) or proportions, while continuous variables were summarised using median and interquartile range (IQR). Sensitivity (Se) and specificity (Sp) were calculated as measures of test accuracy using 2x2 tables classifying LUS and CXR as positive or negative for specified findings. As CXR is considered an imperfect reference standard, the same 2x2 tables were used to calculate concordance between LUS and CXR (inter-test agreement) as an alternative way of comparing LUS and CXR findings. As proposed by Cicchetti et al[20] multiple measures of agreement were reported concurrently rather than a single omnibus index: overall observed agreement (OOA) = (LUS&CXR positive + LUS&CXR negative)/total cases; proportion positive agreement (PPA) = (2*LUS&CXR positive)/(total LUS positive + total CXR positive); proportion negative agreement (PNA) = (2*LUS&CXR negative)/(total LUS negative + total CXR negative) and Cohen's Kappa. 95% confidence intervals (95% CI) were calculated for statistical inference. There were no equivocal test results in our data.

The study was approved by the Human Research Ethics Committee of the University of Cape Town and written consent was given by a parent or legal guardian of all children at enrolment in the study and again annually. Assent was not sought, as all children were below 5 years of age at the time of data collection.

Results

Between August 2014 to December 2015, 529 clinically defined pneumonia cases were observed in the DCHS cohort, of which 134 (25%) had a CXR done based on the discretion of the treating clinicians. Cases of neonatal respiratory distress with onset directly following delivery were excluded (n=11), as these were unlikely to represent true pneumonia. Of the remaining 123 cases with a CXR, 102 also had LUS results available (Figure 3). Demographic, clinical and imaging characteristics of the 102 analysed cases are summarised in Table 2. The median age was 7.2 (IQR: 15.7) months, 56% (n=57) of participants were male and 70% (n=71) required inpatient hospitalisation while the rest received outpatient care only. Hypoxia (oxygen saturation <92%) were document in 25% (n=25) and 31% (n=32) received supplemental oxygen of which 6 also required non-invasive ventilatory support. No cases required invasive ventilation and no fatalities occurred. Prevalence of HIV exposure was 23% (n=23), but there were no HIV infected cases. The majority (85%, n=83) had both PA and lateral CXR views available.

Sonographic *consolidation* was present in 37% of cases compared to 39% radiographic consolidation (Table 2). However, when comparing the presence of consolidation (Table 3), agreement between LUS and CXR was poor and not significantly different from what would be expected by chance (OOA = 61%, PPA=49%, PNA=68%, Expected agreement = 53%, Kappa = 0.17, 95% CI: -0.02-0.36). Using radiographic consolidation as reference criterion, the sensitivity of LUS was low (Se=0.48, 95% CI: 0.32-0.64) and specificity was moderate (Sp=0.69, 95% CI: 0.56-0.80). Prevalence of *any abnormality* (both consolidation and interstitial disease picture without consolidation) was higher on CXR (75%) than on LUS (52%) compared. When comparing *any abnormality* on LUS and CXR (Table 4), agreement again was poor on and not significantly better than what could be expected by chance (OOA=55%, PPA=65%, PNA=38%, Expected agreement=51%, Kappa=0.08, 95% CI: -0.09-0.29). When considering *any abnormality* as a positive result, instead of *consolidation* alone, sensitivity LUS improved from 48% for consolidation to 56% for *any abnormality*, but specificity decreased from 69% for *consolidation* to 56% for *any abnormality*. Ultrasound found no abnormality (no consolidation or interstitial picture) in almost half (48%) of cases compared to only 25% on CXR with the probability of both tests finding no abnormality also being low with PNA = 0.38 (0.24-0.52). No pleural effusions or pneumothoraxes were identified on either modality.

Overall inter-observer agreement (IOA) of CXR (Table 5), interpreted by two experienced paediatricians, was poor in this study (Kappa=0.25, 95% CI: 0.13-0.35) and was statistically significantly lower than for LUS (Table 6) interpreted by a general practitioner and a paediatric radiologist (Kappa=0.60, 95% CI: 0.47-0.74). When comparing different LUS findings (Table 7), IOA was substantial for consolidation (Kappa=0.69, 95% CI: 0.54-0.83), but moderate for interstitial picture (Kappa=0.43, 95% CI: 0.24-0.61). When comparing IOA for each type of finding across modalities LUS had better IOA than CXR for all categories of findings, showing a statistically significant difference for consolidation (Kappa=0.69, 95% CI: 0.54-0.83 vs Kappa=0.32, 95% CI: 0.14-0.51), as can be seen from the non-overlapping confidence intervals (Table 7).

Discussion

Pneumonia remains a global health priority in children. Diagnostic imaging has an important role to play in improving pneumonia outcomes. CXR remains the first line and most widely used option when imaging is required but has significant limitations, including availability, cost, requirement for radiologic services and equipment, interpretation variability, and exposure to radiation. LUS overcomes some of these limitations and current evidence suggests that LUS may have accuracy similar to CXR [13-17]. In this study we compared the diagnostic performance of LUS to CXR in a real world, resource-constrained scenario: we applied LUS in a diverse spectrum of disease, using relatively low-end ultrasound equipment and a simplified scanning protocol, performed by a general practitioner with minimal prior experience and training. Contrary to the bulk of current literature, sensitivity and specificity of LUS in this study were low to moderate and did not

change considerably, whether pneumonia was defined as *consolidation alone* or *any abnormality*. Caution should be taken when interpreting sensitivity and specificity determined by using an imperfect reference standard such as CXR, as true disease status remains in question in cases when results of the index test and reference standard are discordant. As an alternative method of comparing test performance, this study reported concordance between CXR and LUS findings. Agreement between modalities was found to be only slightly better than what may have been expected by chance (Kappa=0.08-0.17), independent of which endpoint definition was used. Inter-observer agreement was statistically significantly better for LUS than for CXR (Kappa, 95% CI: 0.25 (0.06-0.40) vs 0.60 (0.49 - 0.74), despite CXR being interpreted by specialist clinicians using a standardized interpretation method, highlighting this inherent weakness of CXR.

There were notable limitations to our study, some which may have contributed to the difference in the observed results as compared to other literature. Not unique to this study was the lack of a true gold standard, which may have negatively affected accuracy measures. Our approach to this was to report multiple measures of concordance also, rather than accuracy only. We postulate that one of the major factors contributing to lower than expected accuracy was the learning curve for the relatively inexperienced general practitioner who was the sole sonographer in this study. This is supported by the observation that sensitivity calculated for the first thirty scans done was 36% compared to 70% for the last thirty scans. A second possible factor is that ultrasound results were based on retrospective interpretation of eight video clips of 5-10 seconds each. It is possible that the diagnostic yield may have been better if video clips were longer or reported in real time by the person performing them, taking into consideration the full scan and not just short video segments. We also used a simplified scanning protocol as compared to that describe by Copetti et al [21] which divides the chest into anterior, posterior and lateral regions, nor did we include a trans-abdominal approach shown by Lovrenski et al [7] to increase diagnostic yield. We also did not measure the size of consolidations. It has been shown by several studies that consolidations smaller than 1-1.5cm is typically not visualized on CXR and diagnostic accuracy of LUS is improved if these are excluded when using radiographic consolidation as reference standard[22–24]. These limitations are highlighted may serve as valuable learning points for future studies and clinical practice.

Conclusion

In this study LUS for the detection of pneumonia had low sensitivity and specificity, although this was determined using an imprecise reference standard, as is evident from the large proportion of CXR-negative-LUS-positive cases and the significantly lower inter-observer agreement of CXR. Considering the poor concordance between LUS and CXR and the well-understood limitations of each, it is appropriate to conclude that neither should be used as reference standard for the other and to question the validity of the reported accuracy measures this study and other studies using similar methodology. What is needed instead, are

studies comparing both CXR and LUS against a strong gold standard, ideally CT, under conditions where this is ethically justifiable. Perhaps, when considering where pneumonia ranks amongst causes of childhood mortality, the obvious limitations of CXR and the significant reduction in radiation dose achievable for chest CT today, it is worth asking if the justifications for NOT using CT are still as valid as previously judged? Otherwise we may end up substituting one inaccurate test with another and later find that there was little to gain. For now, we can only conclude that in a setting where no other form of imaging is available, there is no doubt that LUS will add value, but in the context where CXR is readily available, the role of LUS remains less clear. Ultimately, once the question of accuracy, first under ideal circumstance then real-world conditions have been adequately addressed, the role of LUS will best be clarified by randomised studies evaluating how LUS affects patient outcomes compared to other modalities. For clinicians who have already started or are planning to start using ultrasound as part of their diagnostic armamentarium, it may be worth keeping in mind that, as with CXR, it should not be used in isolation for decision making without considering the broader clinical picture.

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Table 1: *Standardized classification system used for reporting of LUS and CXR findings.*

	Category	Definition
Lung ultrasound	Typical of pneumonia	Any air-space consolidation with or without air-bronchograms. Includes associated pleural effusion.
	Interstitial syndrome	Pathological B-lines (>3 B-lines in a single frame or confluent B-lines), but no airspace consolidation or pleural effusion.
	Normal	A-line pattern with lung sliding present, with or without occasional, isolated B-lines; AND absence of consolidation/interstitial syndrome/effusion.
Chest X-ray	Primary endpoint pneumonia	Dense or fluffy opacity that occupies a portion or the whole of a lobe or the entire lung with or without air-bronchograms; OR pleural effusion.
	Other infiltrates	Linear and patch densities in a lacy pattern involving both lungs; includes minor patch infiltrates that is not sufficient to constitute endpoint consolidation.
	No pneumonia	Absence of consolidation infiltrates or effusion

Table 2: *Demographic, clinical and imaging characteristics of study participants.*

Variable	All Participants (N=102)
Age (months)	7.2 (15.7)
Male sex	57 (56)
HIV exposed	23 (23)
Clinical features	
Fever (≥38°C)	42 (41)
Oxygen saturation (lowest) <92%	25 (25)
Wheeze present	43 (42)
Chest wall indrawing present	85 (83)
Supplemental oxygen given	32 (31)
Non-invasive ventilation given	6 (6)
Blood results	
C-reactive protein (mg/L)	7.4 (25)
Total white cell count (x 10^9/L)	12.5 (7.4)
Disposition	
Admitted to hospital	71 (70)
Outpatient treatment	31 (30)
LUS findings	
Typical of pneumonia	38 (37)
Interstitial syndrome	15 (15)
Normal	49 (48)
CXR findings	
Primary endpoint pneumonia	40 (39)
Other infiltrates	37 (36)
No pneumonia	25 (25)
CXR views	
PA only	15 (15)
PA and lateral	85 (85)

Data are n (%) for categorical variables and median (IQR) for continuous variables.

Table 3: *Comparison of consolidation on LUS and CXR, with CXR as reference standard.*

	LUS		
CXR	Positive	Negative	Total
Positive	19	21	40
Negative	19	43	62
Total	38	64	102

Se (95% CI)	Sp (95% CI)	PPA (95% CI)	PNA (95% CI)	Kappa (95% CI)
0.48 (0.32 - 0.64)	0.69 (0.56 - 0.80)	0.49 (0.35-0.62)	0.68 (0.59-0.77)	0.17 (-0.02 - 0.36)

Se = Sensitivity; Sp = Specificity; PPA = Proportion positive agreement; PNA = Proportion negative agreement

Table 4: *Comparison of any abnormality (both consolidation and interstitial disease picture without consolidation) on LUS and CXR, with CXR as reference standard.*

	LUS		
CXR	Positive	Negative	Total
Positive	42	35	77
Negative	11	14	25
Total	53	49	102

Se (95% CI)	Sp (95% CI)	PPA (95% CI)	PNA (95% CI)	Kappa (95% CI)
0.55 (0.43 - 0.66)	0.56 (0.35 - 0.76)	0.65 (0.55-0.74)	0.38 (0.24-0.52)	0.08 (-0.09 - 0.29)

Se = Sensitivity; Sp = Specificity; PPA = Positive agreement; PNA = negative agreement

Table 5: *Inter-observer agreement of CXR findings between two paediatricians.*

	Reader 2			
Reader 1	No pneumonia	Other infiltrates	Endpoint Pneumonia	Total
No pneumonia	9	10	3	22
Other infiltrates	7	20	8	35
Endpoint pneumonia	2	19	24	45
Total	18	49	35	102

Kappa (95% CI) = 0.25 (0.13 – 0.35)

Table 6: *Inter-observer agreement of LUS findings between a general practitioner and radiologist.*

	Reader 2			
Reader 1	Normal	Interstitial syndrome	Typical of pneumonia	Total
Normal	37	2	4	43
Interstitial syndrome	11	13	9	33
Typical of pneumonia	1	0	25	26
Total	49	15	38	102

Kappa (95% CI) = 0.60 (0.47 – 0.74)

Table 7: *Comparison of inter-observer agreement between CXR and LUS for different imaging finding separately and overall.*

Imaging finding	**CXR** Kappa (95% CI)	**LUS** Kappa (95% CI)
Consolidation	0.32 0.14 - 0.51)	0.69 (0.54 - 0.83)
Interstitial picture	0.13 (-0.06 - 0.31)	0.43 (0.24 - 0.61)
No abnormality	0.32 (0.10 - 0.54)	0.65 (0.50 - 0.79)
Overall	0.25 (0.06 - 0.40)	0.60 (0.49 - 0.74)

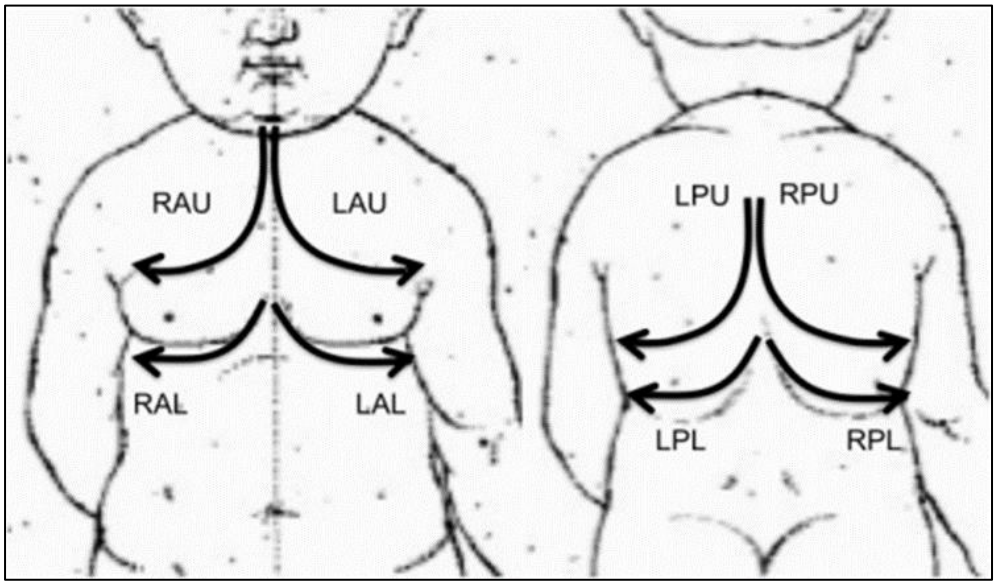

Figure 2: *Diagrammatic representation of simplified ultrasound scanning protocol.*

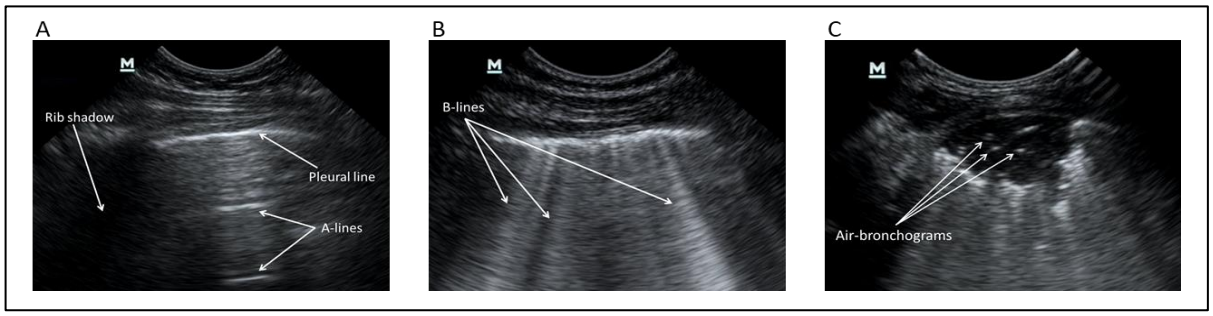

Figure 2: *Examples of characteristic sonographic findings in pneumonia: (A) healthy lung characterized by a smooth pleural line with parallel running A-lines, but no (or minimal) B-lines; (B) interstitial disease picture characterized by an irregular pleural line with multiple or confluent B-lines; (C) air-space consolidation characterized by a sub-pleural hypoechoic lesion with loss of the over-lying pleural line, irregular ("shredded") deep borders, and internal hyper-echoic punctate lesion indicating air-bronchograms.*

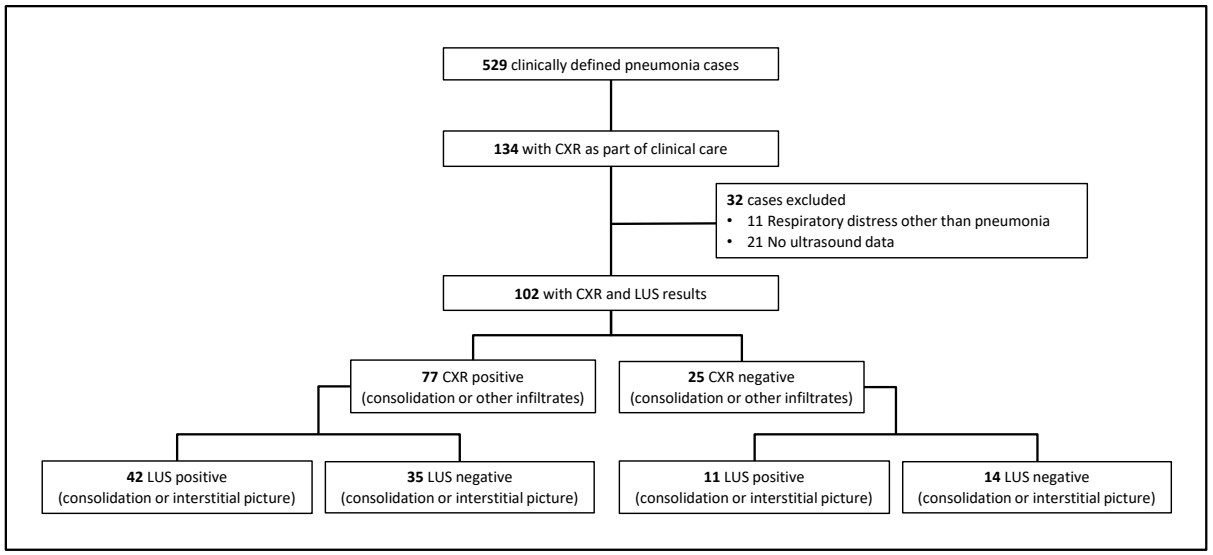

Figure 3: *Flow chart of study participants and results of imaging tests.*

Appendices

Appendix A: Ethics Approval Letter

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

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Groote Schuur Hoapltal
Observatory 7925
Telephone [021] 406 6492
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23 August 2018

HREC REF: 510/2018

A/Prof M Lesosky
Division of Epldemiology & Biostatistics
Level 3, Public Health & Family Medicine
Falmouth Bullding-FHS

Dear A/Prof Lesosky

PROJECT TITLE: EVALUATION OF THE DIAGNOSTIC PERFORMANCE OF LUNG ULTRASOUND COMPARED TO CHEST X-RAYS FOR THE DIAGNOSIS OF PHEUMONIA IN CHILDREN (Sub-study llnked to 401/2009) (MASTERS CANDIDATE - DR J. STADLER)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee (HREC) for review.

It Is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval Is granted for one year until the 30 August 2019.

Please submit a progress form, using the standardised Annual Report Form If the study continues beyond the approval period. Please submit a Standard Closure form If the study Is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

We acknowledge that the student: Dr,acob Stadler will also be involved In this study.

Please quote the HREC REF In all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responslbllty of the principal Investigator.

Please note that for all studies approved by the HREC, the prlnclpal Investigator m.llll obtain appropriate Institutional approval, where necessary, before the research may occur.

Yours sincerely

Signature Removed

PROFESSOR M.&LOCKMAN
CHAIRPERSON_FHS.HUMAN.RESEARCH.ETHICS.COMMITTEE

Federal Wide Assurance Number: FWA00001637.
Institutlonal Review Board (IRB) number: IRB00001938

This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP), South African Good Clinical Practice Guidelines (DoH 2006), based on the Association of the British Pharmaceutical Industry Guidelines (ABPI), and Dedaration of Helsinki (2013) guidellnes.

The Human Research Ethics Committee granting this approval Is In compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

Appendix B: Informed Consent Form

DRAKENSTEIN CHILD LUNG HEALTH STUDY
CONSENT AND INFORMATION SHEET FOR MOTHERS – MAIN COHORT
August 2015

CONSENT FORM AT YEAR 1

You and your child are invited to continue to take part in a study that is being done in the Drakenstein sub-district, in collaboration with the Universities of Cape Town and Stellenbosch. The following information describes the study for the second year and you and your child's role. Please read this carefully and feel free to ask any questions.

Why is this study being done?
Lung infections and chest problems are common in young children. This study is being done to find out the effect of chest infections in the early years of life on the development of lung disease in children. The study will also look at a number of other factors that may affect your child's health.

You and your child will continue to attend occasional scheduled visits at your primary health care clinic and at Paarl Hospital. During these visits, we will assess the health of you and your child by using questionnaires and doing tests. Should your child get sick with a chest infection, then he/ she will be carefully investigated to try and find out the cause of this infection. This study will help us to better understand why children get chest illness and may help to improve child health.

What must I do if I agree to continue in the study?
If you agree to continue in this study, we will follow you and your child regularly to assess his/ her health. We will see you and your child at Paarl hospital when your child is about 1 year of age and again at about 2 years of age. We will also schedule a visit at 1 year of age and at 18 months at the primary health care clinic. We will ask you some questions about your child's health, nutrition, growth and development, and any chest illnesses. We will do regular tests to watch these.

At study visits in the next year, you will be asked some questions about you and your child's health. Your child will be examined. Tests will be done on you and your child to assess whether there is any chest problem. The tests that may be done on your child are:

1. Blood tests - these will be to test for allergies or blood problems.
2. A test of the mucus from the nose (nasopharyngeal swab) to test for infection.
3. Saliva will be collected to check for germs which may cause pneumonia
4. A skin test for tuberculosis infection.
5. A urine test for smoke exposure.
6. A stool test to check what germs are in the stool.
7. A set of developmental measures in a subset of infants.
8. At 1 year and 2 years of age a breathing test will be done while your child is sleeping, to measure the air moving in and out of his/her lungs.
9. A skin test if your child has a rash

The tests YOU will be asked to complete are:

1. Questionnaires about your socioeconomic status and your levels of emotional distress, stress, life events, and drug and alcohol use. If a mental health condition or abuse is suspected, you will be referred to the appropriate local services. You may also be invited to return to undergo more thorough follow-up. This voluntary follow-up session will involve a clinical/psychiatric interview; and a neuropsychological assessment that tests your memory, problem-solving skills, and your attention.
2. A questionnaire and an interview about your experiences while in the Drakenstein Child Lung Health Study.

We will only share your test results with primary health care staff if it indicates that you or your child require treatment or further follow up. For some assessments, study staff may follow up with you and provide you with information on where you can seek help, if necessary.

Should your child get sick with a chest infection, then additional tests will be done to try and find out the cause of your child's illness. The tests that will be done will depend on how sick your child is and what the illness is. These tests may include:

1. Blood tests to test for infections, at the time of the illness, and again 4-6 weeks afterwards
2. A test of the mucus from the nose (nasopharyngeal swab) to test for infection
3 A skin test for tuberculosis infection.
4 A test of the mucus from the lungs (induced sputum test) for chest infection.
5 A urine test for smoke exposure
6 Chest X-ray
7 Breathing test
8 A ultrasound test of the lungs

If your child is enrolled in the study and is admitted to hospital, he/she will be followed up in hospital by a member of the study team. The study member will ask you questions about your child's illness, and some tests may be done, including a nose swab and an induced sputum. All of these tests are usual for investigating the cause of pneumonia.

What are the benefits of my child being in the study?

You and your child will be closely followed for the first few years of your child's life. Any medical illness or problem should be found soon after it develops. Your child's growth and development will be carefully followed. If an illness or problem is found then your child will be promptly investigated and treated. If your child gets sick you will be able to take him/ her to your usual health facility, where additional tests to find out the cause of your child's illness may be done, depending on how sick your child is. If your child requires hospitalisation, then he/ she will be hospitalised at Paarl hospital as is usually done. If your child is hospitalised, then one of the study staff will see your child in hospital and additional investigations may be done to try and find out the cause of the illness. Therefore the study offers an opportunity for your child to receive appropriate medical care. The study will also help us to better understand the causes of illness in children, and identify the things that may harm their health. We hope that this will lead to improvements in child health.

What are the risks to my child?

There are no major risks to your child. There may be some discomfort associated with some of the tests we will do. These tests are listed below:

(1) Blood tests

Your child may feel sore when blood samples are taken with a needle. Where possible an anaesthetic cream will be used to dull the pain from the needle. Some bruising may occur, but this is not harmful and will disappear. Only a small amount of blood (not more than 3 teaspoons) will be taken from your child at any time

(2) Nasopharyngeal swab

A sample of mucus will be taken from your child's nose, to test for germs that can cause chest infections and to monitor which germs are usually in your child's nose. Your child may experience minor discomfort when the nasal swab is done. Occasionally it can cause bleeding from the nose, but this is not serious, and usually stops by itself.

(3) TB skin test

A small injection is made on your child's arm. This is to test whether your child has TB or not, and will be done at regular visits. Your child will experience minor discomfort due to the needle, with

the skin test. There may also be irritation of the skin if the test is positive (reactive). This test will need to be checked 2-3 days after the injection is given.

(4) Induced sputum

Your child will be given salt-water through a nebulizer to loosen the mucous in the lungs. Then a sample of that mucus will be suctioned, or your child will be asked to cough up the mucus. Your child may experience a little discomfort while the sputum test is done. He/ she may develop some coughing or have a small amount of bleeding from the nose after this. These are not serious. Occasionally this test can cause the airways of the lungs to close. If this occurs your child will be given medicine through an inhaler/nebulizer to open the airways.

(5) Breathing test

This test is done after a child recovers from pneumonia, and at the 1 year and 2 years visits at Paarl Hospital, while your child is asleep and should not cause any discomfort. While your child is asleep a mask will be put on his/ her face and the air going in and out of his/ her lungs while breathing will be recorded.

(6) Stool test

This test may be done monthly on your child and then every 6 months after 1 year. Study staff will collect stool from your child's nappy if passed during a study visit. If there is no stool available, a small tube will be inserted into your child's bottom and some stool will be sucked out with a syringe. The tube is thin and bendable and is only put in 1-2 centimeters to reach stool. There is a very small chance of bleeding at the rectum right where the tube goes is.

(7) Ultrasound test of the lungs

This test will be done if your child develops pneumonia so as to better see how the infection is affecting your childs lungs. This is a very safe procedure and there are no side effects.

What are the risks to you?

There are no major risks to you. Some of the questionnaires ask for sensitive information relating to mental health and this may cause some emotional distress or discomfort. Where significant issues are identified, and if you agree, study staff will offer referal to mental health support. You may also choose not to answer certain questions and still remain in the study. You will be able to take breaks, if you need to, and you will be free to terminate or reschedule the interview should the need arise.

Will I be paid to participate in the study?

No, you will not be paid to participate in this study. If you agree to take part, we will reimburse your transport costs for visits that are not part of your well child clinic visits.

Will there be any cost to participate in the study?

No, there will be no cost to you.

How long will my child be in the study?

This consent form is for permission for you and your child to participate in the study from 1 to 2 years of age. However, your child will be involved in the study for at least 2 years, with the routine clinic visits, as well as hospital visits at 1 year and 2 years of age. Each year we will ask you again to sign permission for you and your child to continue in the study for another year.

Will my child's participation in the study be confidential?

All information that you provide will be considered confidential, and no mention of you or your child's name will appear on the stored samples or in any publication in connection with this study. No persons other than the health care workers overseeing your child's care and the study nurses and doctors will have access to any information that identifies your child personally. All your test results will not be disclosed to anyone other than for the purpose of treating you if there is a problem.

Does my child have to be in the study?

You can choose not to take part in the study. This will not affect the quality of care your child receives. You will be able to decline to participate at any time should any part of the study be unacceptable to you, you may still take part in the rest of the study.

What do I do if I have any questions?

If you have any questions about this study, you can ask study staff, the Principal Investigator or the lung study doctor at: 021 860 2802. For questions about your rights as a study participant call the Human Research Ethics Committee, Faculty of Health Sciences, University of Cape Town, Tel: 021-4066492

Informed Consent

1. **I, _____ understand the information contained in this consent form, as explained to me in a language that I understand. I am prepared to participate in this study and give consent for my child to participate in this study.**

I agree to allow study staff to access my medical and hospital records as well as those of my child during the course of the study.

2. To be completed by mother:

Child's Name:_____

Mother's Name:_____

Mother's Signature: _____

Date: _____

3. Study staff providing information:	**Study staff confirming consent:**
Name: _____	Name: _____
Role in Study:_____	Role in Study:_____
Signature: _____	Signature: _____
Date: _____	Date: _____

4. If the mother is unable to read or write the entire counselling process must be observed by an independent witness who can then confirm the procedure once the mother has given consent.

Fingerprint of mother:

Witness: I confirm that I am independent of the study and that I witnessed the entire enrolment counselling process in the home language of the mother.

Name:_____

Signature: _____

Date: _____

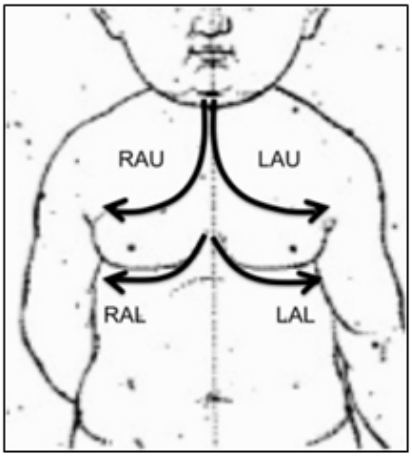
Appendix C: Case Report Forms

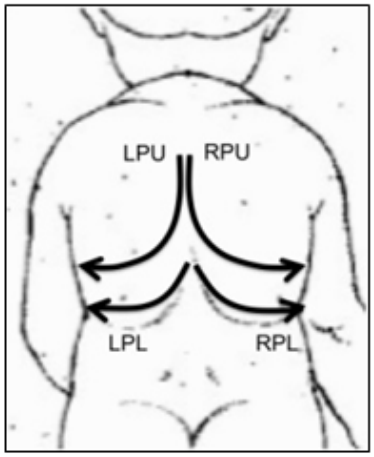
POC Chest Ultrasound

Select reader:	◯ Attie ◯ Savvas ◯ Karen ◯ David
Enter infant PID:	_____
Scan date:	_____
Pneumonia episode date:	_____
Episode time point:	◯ At diagnosis ◯ At follow-up (4-6 weeks)
Start time:	_____
End time:	_____
Scanning / technical difficulties:	◯ Yes ◯ No
If yes, please specify:	◯ Excessive patient movement ◯ Obesity ◯ Very small infant /neonate ◯ Equipment problem ◯ Other
If equipment problem, please specify:	_____
If other, please specify:	_____

LUNG ULTRASOUND

Lung ultrasound anatomical zones:





RAU

	Yes	No	Not evaluated
Lung sliding	○	○	○
A-lines	○	○	○
B-lines	○	○	○
Pathological B-lines	○	○	○
Airspace consolidation	○	○	○
Air-bronchograms	○	○	○
Pleural effusion	○	○	○
Pneumothorax	○	○	○

RAL

	Yes	No	Not evaluated
Lung sliding	○	○	○
A-lines	○	○	○
B-lines	○	○	○
Pathological B-lines	○	○	○
Airspace consolidation	○	○	○
Air-bronchograms	○	○	○
Pleural effusion	○	○	○
Pneumothorax	○	○	○

LAU

	Yes	No	Not evaluated
Lung sliding	○	○	○
A-lines	○	○	○
B-lines	○	○	○
Pathological B-lines	○	○	○
Airspace consolidation	○	○	○
Air-bronchograms	○	○	○
Pleural effusion	○	○	○
Pneumothorax	○	○	○

LAL

	Yes	No	Not evaluated
Lung sliding	○	○	○
A-lines	○	○	○
B-lines	○	○	○
Pathological B-lines	○	○	○
Airspace consolidation	○	○	○
Air-bronchograms	○	○	○
Pleural effusion	○	○	○
Pneumothorax	○	○	○

RPU

	Yes	No	Not evaluated
Lung sliding	○	○	○
A-lines	○	○	○
B-lines	○	○	○
Pathological B-lines	○	○	○
Airspace consolidation	○	○	○
Air-bronchograms	○	○	○
Pleural effusion	○	○	○
Pneumothorax	○	○	○

RPL

	Yes	No	Not evaluated
Lung sliding	○	○	○
A-lines	○	○	○
B-lines	○	○	○
Pathological B-lines	○	○	○
Airspace consolidation	○	○	○
Air-bronchograms	○	○	○

Pleural effusion	◯	◯	◯
Pneumothorax	◯	◯	◯

LPU

	Yes	No	Not evaluated
Lung sliding	◯	◯	◯
A-lines	◯	◯	◯
B-lines	◯	◯	◯
Pathological B-lines	◯	◯	◯
Airspace consolidation	◯	◯	◯
Air-bronchograms	◯	◯	◯
Pleural effusion	◯	◯	◯
Pneumothorax	◯	◯	◯

LPL

	Yes	No	Not evaluated
Lung sliding	◯	◯	◯
A-lines	◯	◯	◯
B-lines	◯	◯	◯
Pathological B-lines	◯	◯	◯
Airspace consolidation	◯	◯	◯
Air-bronchograms	◯	◯	◯
Pleural effusion	◯	◯	◯
Pneumothorax	◯	◯	◯

MEDIASTINAL ULTRASOUND

Was a mediastinal ultrasound done?
- ◯ Yes
- ◯ No

TRANSVERSE views (MT) done?
- ◯ Yes
- ◯ No

What was the image quality?
- ◯ Adequate
- ◯ Sub-optimal
- ◯ Uninterpretable

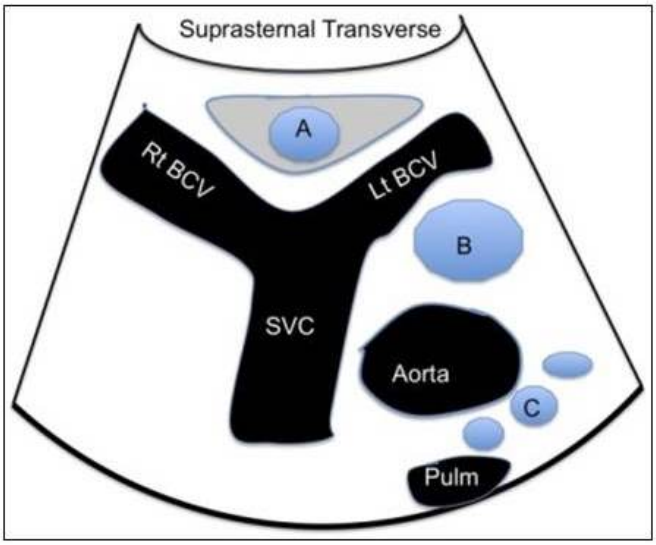
Was lymphadenopathy present?
- ◯ Yes
- ◯ No
- ◯ Not sure

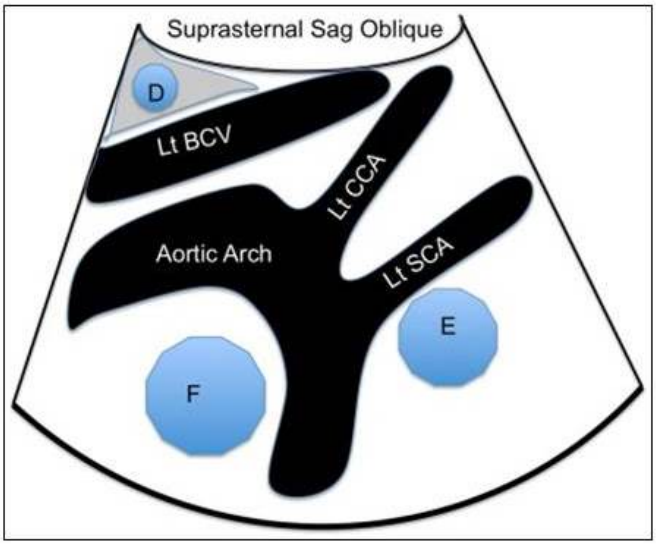
OBLIQUE scan (MO) done?
- ◯ Yes
- ◯ No

If yes, what was the image quality?
- ◯ Adequate
- ◯ Sub-optimal
- ◯ Uninterpretable

Was lymphadenopathy present?	◯ Yes ◯ No ◯ Not sure
Indicate location of adenopathy if present.(See image below for lymphnode zones.)	☐ A ☐ B ☐ C ☐ D ☐ E ☐ F

Mediastinal Lymphnode Zones





Conclusion

Image quality:	◯ Adequate ◯ Sub-optimal, but interpretable ◯ Uninterpretable
Conclusion:	◯ Normal examination ◯ Typical of pneumonia* ◯ Interstitial syndrome** (* Typical of pneumonia: Airspace consolidation with or without air-bronchograms or pleural effusion. ** Interstitial syndrome: Pathological B-lines, but no airspace consolidation or pleural effusion.)
Other pathology:	☐ None ☐ Pneumothorax ☐ Pleural effusion ☐ Mediastinal lymphadenopathy ☐ Other
If other, please specify:	_____

Additional comment

WHO CXR Report Form

Select reader:	◯ Attie (AS) ◯ Dave (DLR) ◯ Eckart (EVD) ◯ Consensus
CRF completion date:	_____
Infant PID:	_____
Date X-ray taken:	_____
Time of X-ray:	_____
Tick if time not recorded:	☐ Not recorded
What is the date of admission / date of the episode?	_____
What is the nature of this event?	◯ Pneumonia ◯ Congenital event (HMD, meconium aspiration, etc) ◯ Other
If 'other' event, please specify:	_____
Is this the initial or a follow-up X-ray?	◯ Initial ◯ Follow-up while admitted ◯ Follow up after discharge
Chest X-ray views available:	☐ AP ☐ Lateral ☐ Decubitus ((Tick all that are available.))

For the following questions use the WHO standardised radiological pneumonia definitions below:

	Finding	Definition
Film quality	Uninterpretable	Features of the image are not interpretable with respect to presence or absence of "primary end-point" without additional images
	Suboptimal	Features allow interpretation of primary end-point, but not of other infiltrates or findings; no entries were made for "other infiltrates" for such images
	Adequate	Features allow confident interpretation of end-point as well as other infiltrates
Classification of findings	Significant pathology	Refers specifically to the presence of consolidation, infiltrates or effusion
	End-point consolidation[a]	A dense or fluffy opacity that occupies a portion or whole of a lobe or of the entire lung, that may or may not contain air-bronchograms[b]
	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; 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 may be difficult to distinguish from consolidation
	Pleural effusion	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
Conclusions	Primary end-point pneumonia	The presence of end-point consolidation (as defined above) or pleural effusion that is 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
	Other 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

[a] The choice of the term "end-point" refers to this being the end-point of interest for trials of bacterial vaccines against pneumonia.
[b] Atelectasis of an entire lobe that produces a dense opacity and a positive silhouette sign with the mediastinal border was considered to be an end-point consolidation.

Quality of image:

- ◯ Adequate
- ◯ Suboptimal
- ◯ Uninterpretable

Does the film contain significant pathology?
(According to WHO pneumonia scoring system.)

- ◯ Yes
- ◯ No
- ◯ Unknown

If significant pathology present, please indicate type & location (tick side if present):

	RIGHT lung	LEFT lung
Primary end-point consolidation:	☐	☐
Other consolidation / infiltrate:	☐	☐
Pleural fluid:	☐	☐

Conclusion / Interpretation:

Conclusion:

◯ Primary end-point consolidation or pleural effusion
◯ Other consolidation / infiltrate
◯ No consolidation / infiltrate / effusion

CXR interpretation (Tick all that apply):

☐ Normal
☐ Abscess
☐ Air bronchogram
☐ Alveolar infiltrate
☐ Atelectasis
☐ Bronchial thickening/peribronchial cuffing
☐ Cardiomegaly
☐ Consolidation
☐ Hyperinflation
☐ Interstitial infiltrate
☐ Lymphadenopathy or mass
☐ Pleural effusion
☐ Pneumatocoele
☐ Pneumothorax
☐ Pulmonary edema
☐ Reticulonodular infiltrate
☐ Other
((Tick all that apply):)

If 'other' interpretation / finding, please specify:

_____

CRF completed by:

_____

Date of reading:

_____

Appendix D: Author Guidelines

Pediatric Pulmonology

Author Guidelines

- APPEALS PROCESS
- PRODUCTION QUESTIONS
- QUESTIONS ABOUT YOUR SUBMISSION
- CONTACT THE EDITOR-IN-CHIEF

SCOPE OF JOURNAL

Pediatric Pulmonology publishes the results of original clinical or laboratory research, state of the art reviews, exceptionally instructive or unique case reports, and letters to the Editor (and responses), pertaining to the specialty.

Reports on meetings, conferences and symposia may be published after consultation with the Publisher and the Editor-in-Chief.

Preliminary brief communications will be considered if the articles contain information which would be considered a major breakthrough in the field.

We do not publish research funded by tobacco companies.

As the field is continually evolving, our Journal has seen an increase in the number of submissions over the past few years, and, as a result, our rejection rate is climbing.

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We accept submissions of the following types of articles. Please note the specific guidelines for each type:

Original Research Articles

Original Research Articles should follow the standard structure of abstract, introduction, methods, results, discussion, and references, and may include up to six tables and/or images when appropriate. Original Research Articles should be limited to 3,500 words (not including the abstract or references). The abstract should not exceed 250 words, and references should be limited to forty (40).

Reviews/State of the Art Papers

Editors generally commission Reviews and State of the Art papers, but uninvited submissions are also welcome, particularly if the submission outlines an important and topical subject with a focus on recent advances. Reviews should be limited to 4,000 words, while State of the Art papers should be limited to 5,000 words (not including the abstract or references). We ask that the abstracts for these manuscript types do not exceed 250 words. There is no set limit on images, tables, or references for these types of manuscripts.

Case Reports

NOTICE TO AUTHORS OF CASE REPORTS: Pediatric Pulmonology is temporarily closing submissions of Case Reports. We will not consider new case report manuscripts during the period of July 15, 2017 to October 15, 2017. Case Report submission will re-open on October 15, 2017.
Pediatric Pulmonology will review case report manuscripts that present unique, paradigm-changing, or novel accounts of infantile or childhood disorders. Priority for selection for publication will be given to the following categories:.

1. Novel therapies and outcomes for cystic fibrosis
2. Novel disorders or outcomes of ChILD, NEHI, ABCA3 disorders, and surfactant disorders
3. Novel congenital malformations
4. Novel genetic disorders
5. Novel therapies or outcomes for other disorders

There is not a related format for a case series. Manuscripts of this nature will be treated as original articles or reviews and will compete with other manuscripts in these categories.
Case reports should be concise (a maximum of 1,000 words, not including the abstract or references), and contain a maximum of two images and/or tables. The summary/abstract should not exceed 100 words. Case Reports should contain no more than five (5) references. Authorship of case reports shall be limited to three (3). Physicians who participated in the care, but did not contribute to the writing of the manuscript may be listed under acknowledgements. Informed consent must be documented. Authors should note that most accepted Case Reports will be published online only, and not in a print edition.

Editorials (Commentaries)

Editors and members of the Editorial Board may make editorial comments on individual articles or on a group of articles published in the same issue. Editorials (including pro/con debates) from authors who are not part of the editorial team are also welcome as submissions to the Journal. These narrowly focused articles should discuss an article that was recently published, or that is soon to be published. The commentary should discuss specific issues within a subject area rather than the whole field, while explaining the implications of the article and putting it in context. Opinions must be factually based. These types of manuscripts should be limited to 1,500 words (not including the abstract or references). There is no limitation on the number of tables, images or references for these types of manuscripts.

Letters to the Editors

We encourage letters that offer criticism of published material in an objective, constructive, and educational manner conducive to further exchanges. Such letters will only be considered if they are in reference to an article published within the previous six months. Letters may also discuss matters of

general interest pertaining to the field of pediatric pulmonology, or may consist of brief reports of truly unique cases. Note that we do not publish original, previously unpublished data as letters. If appropriate, a copy will be sent to the author(s) referred to in the letter, so that they may respond. Letters to the Editor should not exceed 1,000 words (not including the abstract or references), and may contain a small table or single image. Letters should contain no more than five (5) references.

Top of Page

PRIOR TO SUBMITTING

Prior to submitting a manuscript through ScholarOne, prepare the text and images according to the instructions found below. You may enter and exit the manuscript submission process at the completion of each step, and you may save an unfinished draft in the system to work on later. However, once you submit your manuscript though the system, you will not be able to access it for editing. If you have any questions about this process please contact us at edsupport@wiley.com

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COMPONENTS OF ARTICLES/FILE PREPARATION

Please make note of the following when preparing your submission:

Main Document

All manuscript types must include a title page, abstract, text and references in the Main Document. Standard, double-spaced manuscript format, in 12 point font is requested. Number all pages consecutively.

Title page: The title should be brief (no more than 100 characters in length including spaces) and useful for indexing. All authors' names with highest academic degree, affiliation of each, but no position or rank, should be listed. For cooperative studies, the institution where research was primarily done should be indicated. In a separate paragraph, specify grants, other financial support received, and the granting institutions (grant number(s) and contact name(s) should be indicated on the title page). If support from manufacturers of products used is listed, assurances about the absence of bias by the sponsor and principal author must be given. Identify meetings, if any, at which the paper was presented. The name, complete mailing address, telephone number, fax number, and e-mail address of the person to whom correspondence and reprint requests are to be sent must be included. Keywords should also be noted on the title page. For usage as a running head, provide an abbreviated title (maximum 50 characters) on the bottom of the title page.

Summary/Abstract: In accordance with the structure of the article, with or without separate headings, outline the objectives, working hypothesis, study design, patient-subject selection, methodology, results (including numerical findings) and conclusions. The Summary should not exceed the word counts outlined above. If abbreviations are used several times, spell out the words followed by the abbreviations in parentheses.

Acknowledgements: Technical assistance, advice, referral of patients, etc. may be briefly acknowledged at the end of the text under "Acknowledgements."

Informed Consent: Informed consent statements, if applicable, should be included in the Methods section.

References/citations: References may be included at the end of your text, or uploaded as a separate file. Ensure your references are up to date, and include a critical selection from the world literature. References should be prepared according to CSE (Council of Science Editors) citation-sequence style. Refer to the *Scientific Style and Format: The CSE Manual for Authors, Editors, and Publishers*, 8th edition (University of Chicago Press). Start the listing on a new page, double-spaced throughout.

Number the references in the sequence in which they first appear in the text, listing each only once even though it may be cited repeatedly.

When citing a reference in the text, the style advocated by CSE suggests numbers appear in superscript, and appear before punctuation marks (commas or periods). In the **citation-sequence** system, sources are numbered by order of reference so that the first reference cited in the paper is [1], the second [2], and so on. If the numbers are not in a continuous sequence, use commas (with no spaces) between numbers. If you have more than two numbers in a continuous sequence, use the first and last number of the sequence joined by a hyphen, for example [2,4,6-10].

In the references, list the first ten authors of the cited paper. If there are more than ten authors, list the first 10 authors followed by 'et al'.

Journals' names should be shown by their abbreviated title in *Index Medicus*.

Manuscripts in preparation or submitted for publication are not acceptable references. If a manuscript "in press" is used as a reference, a copy of it must be provided with your submission.

Sample references:

Standard journal article
Landau IL, Morgan W, McCoy KS, Taussig LM. Gender related differences in airway tone in children. Pediatr Pulmonol 1993;16:31-35.

Book with authors
Voet D, Voet JG. 1990. Biochemistry. New York: John Wiley & Sons. 1223 p.

Book with editors
Coutinho A, Kazatch Kine MD, editors. Autoimmunity physiology and disease. New York. Wiley-Liss; 1994. 459 p.

Chapter from a book
Hausdorf G. Late effects of anthracycline therapy in childhood: evaluation and current therapy. In: Bricker JT, Green DM, D'Angio GJ, editors. Cardiac toxicology after treatment for childhood cancer. New York: Wiley-Liss; 1993. p 73-86.

For a book reference only include the page numbers that have direct bearing on the work described.

Keywords: On the title page, supply a minimum of 3 to 5 keywords, exclusive of words in the title of the manuscript. A guide to medical subject heading terms used by PubMed is available at http://www.nlm.nih.gov/mesh/MBrowser.html

Abbreviations: Define abbreviations when they first occur in the manuscript and from there on use only the abbreviation. Whenever standardized abbreviations are available use those. Use standard symbols with subscripts and superscripts in their proper place.

Drug names: Use generic names. If identification of a brand name is required, insert it in parentheses together with the manufacturer's name and address after the first mention of the generic name.

Eponyms: Eponyms (diseases or biologic entities named for persons) should not be used when standard descriptive terminology is available. Examples include club cells (formerly known as Clara cells); and granulomatosis with polyangiitis (formerly known as Wegener's granulomatosis). It is permissible to use

the eponym in parenthesis at the first mention of the term in cases in which the eponym is still in common use.

Formatting Specific to Original Research Articles: Divide article into: Title Page, Summary/Abstract, Introduction, Materials and Methods, Results, Discussion, and References, starting each section on a new page. All methodology and description of experimental subjects should be under Materials and Methods; results should not be included in the Introduction. Please ensure the following appears in the appropriate section of your manuscript:

- a concise introductory statement outlining the specific aims of the study and providing a discussion of how each aim was fulfilled;
- a succinct description of the working hypothesis;
- a detailed explanation of assumptions and choices made regarding study design and methodology;
- a description of the reasons for choosing the type and number of experimental subjects (patients, animals, controls) and individual measurements; if applicable, information about how and why the numbers may differ from an ideal design (e.g., the number required for achieving 90% confidence in eliminating Type II error);
- specifics about statistical principles, techniques and calculations employed and, if applicable, methods for rejecting the null hypothesis;
- a concise comparison of the results with those of conflicting or confirmatory studies in the literature;
- a brief summary of the limitations of the scientific methods and results; and
- a brief discussion of the implications of the findings for the field and for future studies.

- **Tables**

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