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Computerized lung sound analysis to improve the specificity of pediatric pneumonia diagnosis in resource-poor settings: A case-control study

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ARTICLE FOCUS

- We seek to characterize lung sounds associated with different respiratory illnesses in children using electronic auscultation and determine whether these sounds can be differentiated from normal through computerized lung sound analysis.
- We summarize the study design and methods with standardized protocols for electronic auscultation and chest ultrasound in children.

KEY MESSAGES

- We aim to develop a protocol for increased specificity of pediatric pneumonia diagnosis in developing countries.

STRENGHTS AND LIMITATIONS

- Our study is limited by the case definitions available. With no gold standard for many pediatric respiratory diseases, we will rely on clinical exam findings and chest radiography.
- By investigating a number of novel and commonly used diagnostic tools for a variety of respiratory diseases in children, we will gain valuable information regarding the diagnostic potential of each, with a main focus on the electronic stethoscope.

ABSTRACT

Introduction: The World Health Organization (WHO) case management algorithm for pediatric pneumonia relies solely on symptoms of shortness of breath or cough and tachypnea for treatment and has poor diagnostic specificity, tends to increase antibiotic resistance. Alternatives, including oxygen saturation measurement, chest ultrasound, and chest auscultation exist but with potential disadvantages. Electronic auscultation has potential for improved detection of pediatric pneumonia but has yet to be standardized. We aim to investigate the use of electronic auscultation to improve the specificity of the current WHO algorithm in developing countries.

Methods: Our study is designed to test the hypothesis that pulmonary pathology can be differentiated from normal using computerized lung sound analysis (CLSA). We will record lung sounds from 600 children aged ≤5 years, 100 each with consolidative pneumonia, diffuse interstitial pneumonia, asthma, bronchiolitis, upper respiratory infections, and normal lungs at a children's hospital in Lima, Peru. We will compare CLSA with the WHO algorithm and other detection approaches, including physical exam findings, chest ultrasound, and microbiologic testing to construct an improved algorithm for pneumonia diagnosis.

Ethics and dissemination: Approval was obtained from the Ethics Committees of A.B. PRISMA, Instituto Nacional de Salud del Niño and Johns Hopkins School of Medicine. Dissemination will include publications following the study and the development of a free online library of lung sounds for improvement of CLSA, future research, and clinical education.

Discussion: This study will develop standardized methods for electronic auscultation, and chest ultrasound, and compare their utility for detection of pneumonia to standard approaches. Utilizing signal processing techniques, we aim to characterize lung sounds and through machine

learning, develop a classification system to distinguish pathologic sounds. Data will allow a better understanding of the benefits and limitations of novel diagnostic techniques in pediatric pneumonia.

INTRODUCTION

Acute lower respiratory infection (ALRI) is the leading cause of death in children under 5 years of age. Pneumonia alone is responsible for killing 1.6 million children worldwide. The World Health Organization (WHO) developed a case management algorithm that relies solely on symptoms of shortness of breath or cough, an elevated respiratory rate, and chest indrawing for the diagnosis of pneumonia and administration of antibiotics and/or referral in resource-poor areas (Table 1). Where successfully implemented, this algorithm has resulted in a 30-40% reduction in case mortality[1] but has moderate sensitivity and poor specificity, ranging from 16% for children presenting with wheeze[2] and 49% for nonsevere pneumonia to 95% for very severe pneumonia[3]. Hazir and colleagues demonstrated that over 80% of children with WHO-defined non-severe pneumonia had normal chest radiographs (CXR)[4] and that the resulting case management was equivalent to no treatment in a randomized clinical trial[5], only further increasing concern for global antibiotic resistance.

Table 1. WHO Classification of ALRI in Children Presenting with Cough and/or Difficult Breathing

No pneumonia (cough and cold)	Respiratory rate, breaths/minute <50 (infants 2–11 months) <40 (children 12–59 months) No lower chest indrawing
Non-severe pneumonia	Respiratory rate, breaths/minute >50 (infants 2–11 months) >40 (children 12–59 months) No lower chest indrawing
Severe pneumonia	Lower chest indrawing ± rapid breathing
Very severe pneumonia	At least one of the following: Unable to feed Convulsions Lethargic Stridor at rest Clinically severe malnutrition

Pneumonia is a pathological process resulting in fluid-filled alveoli, and while there are multiple potential etiologies, most are infectious. Currently, there is no gold standard for detection of bacterial pneumonia requiring treatment. In areas where resources are readily available, chest radiography and clinical diagnosis serve as the standard of care for pneumonia

detection but these are not available in resource-poor settings around the world. Potential alternatives exist within aspects of the physical exam and imaging. Supplementing oxygen saturation measurements with the current WHO algorithm has been shown to increase specificity[6]; however, the normal range in healthy children varies with environmental factors like altitude[7]. Another promising alternative for detection of pediatric pneumonia is lung ultrasound. Ultrasound has the advantage of gathering information from multiple angles and the ability to detect air-fluid differences that are present with pneumonia. Studies suggest that this technique may be more sensitive than radiography and has the added benefit of lack of radiation; however, these studies have all lacked power due to small sample size[8-13]. Cost and availability of skilled ultrasound technicians may limit use in resource-poor settings. Chest auscultation is a valuable tool for detection of respiratory pathology and is used widely in clinical practice. However, limitations include inter-listener variability, subjectivity in the interpretation of lung sounds[14,15], and lack of trained personnel in resource poor settings. Electronic auscultation has the advantage of signal amplification and ambient noise reduction leading to increased signal-to-noise ratio along with its independence on human ear sensitivity to different acoustic frequencies. Furthermore, through computerized lung sound analysis (CLSA), this diagnostic method results in discrete values from a final reading, thereby facilitating standardization. With advancement in electronic stethoscopes and CLSA, there is great potential for improved diagnosis of pediatric pneumonia where multiple diagnostic tools are not readily available.

In acoustic signal processing, the two commonly studied lung sounds are crackles and wheezes, which constitute unique temporal and frequency characteristics. Crackles have been most commonly associated with pneumonia, whereas wheezes are often observed in patients

with asthma and bronchiolitis[16]. According to the Computerized Respiratory Sound Analysis (CORSA) Guidelines[17], the frequency of crackles is characterized in the spectrum of 200 to 2000 Hz, while wheezes have a frequency spectrum of 100 to 1000 Hz. Wheezes have continuous waveforms (>100 ms duration) with one or more tonal components and a dominant frequency greater than 400 Hz during the expiratory phase. Crackles are short (<20ms), non-periodic waveforms with transitory sharp peaks and broadband frequency content during mid-inspiratory phase. Time-frequency decomposition of lung sounds provides useful information in identifying and localizing adventitious lung sounds in a patient.

Translating the CLSA characterization of abnormal lung sounds to clinical practice has yet to be achieved. There are a few studies demonstrating potential, yet data is largely lacking, especially in the field of pediatrics. Our group conducted a systematic review and meta-analysis of studies using CLSA for the detection of a variety of respiratory disease in adults, which found an overall sensitivity and specificity of 80% and 85%, respectively, when compared to radiologically confirmed cases, with markedly limited results due to lack of quality and quantity of available data, as well as lack of standardization[16,18-22].

In this study, we seek to utilize electronic auscultation to record lung sounds of children with various clinical diagnoses: pneumonia (diffuse interstitial and lobar), asthma, bronchiolitis, and upper respiratory infection (URI) in a tertiary care center in Lima, Peru, and determine whether they can be differentiated from normal lung sounds using CLSA. In addition, we aim to compare with imaging modalities of chest radiography and ultrasound. We hypothesize that not only will the sounds profiles of each pulmonary disease pathology differ from normal, but due to unique characteristics of lung sounds associated with bacterial pneumonia versus asthma, bronchiolitis or URI, CLSA may allow differentiation of various acute lower respiratory disease

processes. With this information in conjunction with additional basic clinical information (i.e. temperature, respiratory rate, oxygen saturation), we believe that a much needed improvement in the detection and case management of pediatric pneumonia is possible.

METHODS

Study objectives

The primary objectives of this study are to characterize lung sounds associated with various clinical diagnoses: radiologically confirmed consolidative pneumonia and diffuse interstitial pneumonia, bronchiolitis, asthma, and upper respiratory infections, in a pediatric population; and, to determine if these diagnoses can be differentiated from normal through automated lung sounds analysis and compare with modalities of imaging, current WHO algorithm for ALRI case management, and microbiological testing. We then aim to then develop a clinical protocol pairing electronic auscultation with a CLSA algorithm to aid in pneumonia diagnosis.

Study design

Our design will be a cross-sectional study of lung sounds and other diagnostic modalities from children 2 to 60 months of age presenting with a primary respiratory complaint to the Instituto Nacional de Salud del Niño, a tertiary care hospital in Lima, Peru. Informed consent from parents will be obtained in the Emergency Department (ED), asthma ward, or pulmonary ward where all testing will be performed in a single visit. Parents will be asked to fill out a questionnaire while the physician reports relevant aspects of the physical exam. Electronic auscultation will then be performed, following by imaging and collection of blood, respiratory, urine, and stool samples.

During the initial phase, we will record lung sounds from 600 children from 2 to 59 months of age, 100 each with consolidative pneumonia, diffuse interstitial pneumonia, asthma, bronchiolitis, upper respiratory infections, and normal lungs. The second phase will consist of

completing our testing set for external validity and comparing CLSA with the current WHO algorithm and other diagnostic tools such as physical exam findings, chest ultrasound, and microbiologic testing, in order to construct an improved algorithm for pneumonia diagnosis.

Study population

Children from 2 to 59 months of age presenting to the ED or in the asthma or pulmonary ward without history of chronic lung disease, excluding asthma, or significant cardiac disease will be invited to participate in the study. Children with respiratory complaints will be invited to participate as potential cases, while those without respiratory complaints and no acute respiratory illness within one month of presentation will be invited to join the study as controls.

Children will be considered eligible if their parents or guardians are able to provide written informed consent, and they themselves do not require airway management or non-invasive ventilation. Children will be considered ineligible if they have chronic lung diseases other than asthma, such as cystic fibrosis, bronchiectasis, and chronic lung disease of prematurity or significant congenital heart disease. Patients will be considered ineligible post-consent if they were found to have more than one active respiratory diagnosis upon further testing. Group classification also may be modified post-consent and further enrollment required depending on chest x-ray (CXR) final readings and microbiological testing for diagnosis.

Outcomes and case definitions

Because there is no gold standard for diagnosis, we aim to compare our results with common case definitions and clinical diagnoses by experienced physicians. Secondary outcomes will

incorporate etiology information from standard culture and molecular techniques; however, these additional data will not serve as the gold standard.

Pneumonia will be initially categorized upon clinical diagnosis by examining pediatricians at El Instituto Nacional de Salud del Niño and further characterized as consolidative or diffuse interstitial pneumonia given final CXR reading by blinded radiologists from the Johns Hopkins University. Asthma will be defined by the presence of wheeze on physical exam, history of asthma, and improvement with bronchodilators. Bronchiolitis will be defined as the presence of wheeze and difficulty breathing on physical exam and viral symptoms (cough, rhinorrhea), no history of asthma, and little or no improvement with bronchodilators if attempted. URI will be defined as respiration rate less than 50 breaths per minute and associated with one or more of the following: clear nasal secretions, sore or red throat, or hoarseness.

Sample size

Our recruitment goal is 600 subjects, 100 each with consolidative pneumonia, diffuse interstitial pneumonia, asthma, bronchiolitis, URI, and normal lungs. Sample size was powered to improve specificity of the WHO algorithm upon the addition of electronic auscultation. To detect an improvement in diagnostic specificity from 50% (WHO algorithm for pediatric pneumonia) to 80% (CLSA and WHO algorithm) with 95% power and α of 0.05 between pneumonia and non-pneumonia cases, we require 70 patients per group in the training set. We will also recruit a test set consisting of an additional 30 patients per group (30% of total sample) to estimate areas under the curve for our diagnostic algorithm. Each group will be over-enrolled by twenty to account for post-consent ineligibility, for a total of 720.

Study organization

A.B. PRISMA in Lima, Peru, and Johns Hopkins University in Baltimore, USA, will provide administrative oversight for the study. There will be a research coordinator at a central location in Lima, Peru, who will provide logistical support and management of the study team. Instituto Nacional de Salud del Niño will provide a team of study nurses and physicians to carry out recruitment, physical examination, and collection of specimens. Hospital Edgardo Rebagliati Martins will provide an ultrasonographer for imaging at his institution and team member training to carry out chest ultrasonography at Hospital del Niño. A multidisciplinary team of clinicians, field epidemiologists, acoustical engineers, and biostatisticians from Johns Hopkins University, Tufts University, Cincinnati Children's Hospital, and Instituto Nacional de Salud del Niño will be involved with study design and conduct, statistical analysis, and reporting of results.

Questionnaire

We will ask the parent or guardian about the child's past medical history, environmental exposures, access to healthcare, and current respiratory symptoms. We will inquire about demographic information, nutrition, and vaccination history. We will ask about co-morbidities, family history, and developmental history. Environmental questions pertained to housing, number of children, rural versus urban living, parent occupations, smoke and allergen exposure, and sick contacts. Current respiratory symptoms were asked of the parent or guardian to answer subjectively and included rapid breathing, difficulty breathing, chest indrawing, cyanosis, cough, sputum production, audible breath sounds, and subjective fever.

Physical exam and laboratory testing

The initial set of vital signs will be recorded, including pulse oximetry. During the physical exam, a single examining physician from the larger group of study physicians will be responsible for recording findings for a given patient with emphasis on the respiratory exam. Chest retractions, nasal flaring, grunting, stridor, and accessory muscle use will be noted and characterized if present, along with any adventitious lung sounds appreciated by physician and study team member on chest auscultation. Degree of improvement after bronchodilators will also be recorded if administered. Additionally, signs of dehydration and malnutrition will be reported if present. Laboratory results will be recorded if evaluated by the ED and include complete blood count, electrolytes, and arterial blood gas.

Electronic Auscultation

Parents will be allowed to position the patient supine or upright. The study team member will listen to eight auscultation sites using a ThinkLabs ds32a Digital Stethoscope and mp3 recorder, for 10 seconds at each site, in the following order of placement: front top left and right, fronterolateral bottom right and left, back top right and left, and back bottom left and right (Figure 1). Auscultation will be performed at the participant's normal breathing patterns during recording without being asked to take deep breaths. We will allow only one repeat of auscultation if recording is interrupted for any reason or due to unacceptable signal quality of the first recording.

Lung ultrasound

All participants will receive bilateral lung ultrasonography carried out on SonoSite portable ultrasound machine with HFL38/13-6MHz and P17/5-1MHz MicroMaxx® transducers by a

single ultrasound technician who has been trained to the standardized protocol. Patients will be examined in the supine position with each hemithorax divided into six sections: 2 anterior, 2 lateral, and 2 posterior. The posterior area is defined from the posterior axillary line to the paravertebral line. Longitudinal and oblique scans will be obtained at each of the chest zones. Longitudinal scans allow visualization of the ribs with the pleural line under them[23]. Representative images from each section will be saved and later transferred to radiologists at an outside institution.

To assess for pneumonia, 2 of 3 radiologists must agree on the description of ultrasound images compatible with pneumonia. Consolidation will be determined by 1) the presence of hypo- or anechoic images with loss of distinct pleural lines and 2) an irregular shredded border of the pleural line that is distinct from the lung line, termed the "shred sign." Additional signs to be reported will include punctate hyperechoic images reflecting air bronchograms, decreased lung sliding, and homogenous, hypoechoic images in the pleural space corresponding to pleural effusions. Interstitial infiltrates will be determined by the presence of "lung rockets," which correlate to three or more B-lines in a longitudinal view between two ribs. Additional features to be reported include heterogenous echotexture, air and fluid bronchograms, lung pulse, and additional B-lines [23].

Chest radiography

All case participants will undergo chest radiography. We will attempt postero-anterior and lateral films but will allow an antero-posterior view if not possible. Digital images will be sent to a third party reading group blinded to clinical information. Using the WHO standardization of CXR interpretation for pediatric pneumonia [24], radiologists will comment on quality as adequate,

suboptimal, or unreadable and on the presence of pathology as consolidative or interstitial with or without pleural effusions. Radiographic evidence of pneumonia will be confirmed by agreement by 2 out of 3 radiologist reports for a given patient. Additional pathologic findings not previously characterized will also be recorded and reported to the patient's physician for further intervention if necessary.

Microbiological studies

Blood, urine, and nasopharyngeal samples will be collected according to our study design (Figure 2). Blood samples will be drawn for cultures and sensitivities. Urine will be tested for detection of pneumococcal antigen and stored for PCR. Nasopharyngeal swabs will be tested for respiratory viruses, along with culture and sensitivities. Respiratory pathogens tested by PCR will include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and respiratory syncytial virus.

Safety

In order to ensure safety, the researcher collecting data is experienced with providing care to children. The researcher will use this experience to minimize any discomfort the children may have. All blood samples will be collected by a skilled nurse or phlebotomist.

We will adhere to hospital procedures for avoiding hospital acquired infections. We will wash hands with soap and water or alcohol-based hand sanitizer before patient contact. We will wear gloves, gowns and mask when required. We will clean the devices using alcohol swabs before and after each use.

Data quality and management

Prior to data collection, a Manual of Operations will be developed to ensure standardization and reliability and contain detailed instructions for all study procedures and guidelines for data collection. The manual will be revised as needed and distributed to members of the study team.

All data are recorded first on paper case report forms and subsequently double-entered using Microsoft ACCESS. Data sets will be cross-validated and errors corrected. Electronic lung recordings will be transferred from the mp3 player to participant-specific files on the study computer at least every other day and backed-up weekly. Digital CXR images will also be uploaded to these files and backed-up similarly.

Analysis of lung sounds and statistics

An important first step in CLSA is using common signal processing techniques to investigate high and low frequency information using methods such as the Short-time Fourier Transform (STFT), wavelet transforms, and P-spline bases. The second step will be extracting signal processing features to train the classifier.

Based on preliminary recordings to date performed by our group in Baltimore (Figure 3), we anticipate that wheeze can be characterized using features from the Fourier transform, such as the existence and temporal stability of tonal peaks in the 300-1000 Hz range, while crackles could be recognized using features such as amplitude, the presence of broad-band energy and the duration of this energy. Features such as the decrease in signal energy with frequency can characterize movement sounds. We have previously used time-frequency descriptors such as Mel-frequency cepstral coefficients as features and anticipate they will be useful for CLSA but may require temporal information as well. We will use the extracted features from signal processing analyses for classification using machine learning algorithms including: nearest

neighbor methods, support vector machines, random forests, and gradient boosting. Primary analysis will consist of a five-fold cross validation on the training set to calculate expected prediction errors. The training set will additionally be used to estimate areas under the curve for our diagnostic algorithm, including CLSA, WHO algorithm, imaging, and physical exam findings. Secondary analysis will include calculating sensitivities and specificities of experimental diagnostic US for detection of pneumonia when compared to gold standards (clinical diagnosis and CXR reading). Performance will be measured using logistic and multinomial regression, receiver operating characteristic curves, and area under the curve.

ETHICS AND DISSEMINATION

Approval was obtained from the Ethics Committees of A.B. PRISMA in Lima, Peru, El Instituto Nacional de Salud del Niño in Lima, Peru, and the Johns Hopkins University School of Medicine in Baltimore, MD. Written informed consent will be obtained from a parent or guardian. Any clinical information gained from participation in this study that could possibly change management will be given to the child's physician for his/her discretion. All data and sensitive information will be protected by being kept on encrypted devices or accessible only to study members.

Plans for dissemination include final publication following completion of the study following the STARD guidelines for reporting diagnostic accuracy[25]. We aim to develop a free online library of lung sounds for further enhancement of CLSA and the machine learning algorithm, as well as for future research and clinical education.

DISCUSSION

This study aims to investigate alternatives to improve the specificity of the WHO algorithm for pediatric pneumonia, namely electronic auscultation and chest ultrasonography. Utilizing electronic auscultation, we intend to characterize and analyze lung sounds associated with consolidative pneumonia, diffuse interstitial pneumonia, bronchiolitis, asthma, and upper respiratory infections, to determine if these diagnoses can be differentiated from normal through automated lung sounds, and to compare with chest ultrasound, WHO algorithm, and molecular testing for etiology. By reporting a protocol for CLSA, we hope to encourage standardization and expansion of recorded lung sounds via an online library for continued enhancement of machine learning as well as for continued scientific research and clinical education.

We foresee our greatest challenge in maximizing the quality of recorded lung sounds. To begin the study, we will utilize a commercial electronic stethoscope for recordings, which is identical in design to standard clinical stethoscopes. However, through sound processing using time-frequency analysis methods such as the Short-time Fourier Transform (STFT) and Continuous Wavelet Transforms (CWT), we hope to enhance the signal-to-noise ratio for data analysis and characterization. By examining additional features such as amplitude, we may also be better able to identify crackles and consolidation. We also plan to test alternative recording devices using piezoelectric microphones covered with a thin polymer that may be able to better capture lung sounds. Based on our recordings to date, we anticipate that wheeze can be differentiated from normal breath using features such as the existence and temporal stability of tonal peaks in the 300-1000 Hz range, while crackle should be recognizable using features such as the presence of broad-band energy and the duration of this energy. Features such as the

decrease in signal energy with frequency can characterize movement sounds. We have previously used time-frequency descriptors borrowed from speech processing (Mel-frequency cepstral coefficients and their time derivatives) and cough-specific time-domain features such as signal rise time and event duration and anticipate they will be useful for CLSA. We will use the extracted features from signal processing analyses for classification using machine learning algorithms such as nearest neighbor methods, support vector machines, or random forests.

The largest challenge in regards to lung ultrasound will likely be obtaining adequate quality of images and inter-user variability. To reduce variability, the study technician will be trained to systematically scan each subdivided hemithorax for pathologic findings described previously [9,23], and if possible, we will attempt lung ultrasound twice for each patient. Ultrasound also takes substantially longer compared to chest radiography because all areas must be adequately explored; therefore, it may be difficult for a child to be cooperative for that length of time. Through our large sample size and detailed methods, we aim to improve standardization of pediatric chest ultrasound and further define pathologic findings associated with disease, which may also lead to more efficient and faster scanning.

Limitations to this study center mostly on our case definitions for clinical diagnoses. As mentioned previously, there are no precise gold standards and as with many pediatric diseases, diagnosis is clinical. As such, our end points are determined by clinical exam findings by single examining physicians with additional confirmation via radiology for pneumonia cases only. We acknowledge the variability of observed findings among physicians but also accept that this is the mechanism of diagnosis in most clinical settings.

The WHO algorithm for case management of pediatric pneumonia lacks diagnostic specificity. While clinical information such as elevated heart rate and decreased oxygen

saturation may aid in degree of illness and monitoring, these data also lack specificity required to drastically improve case management. Lung ultrasound is also a promising tool and offers portability that is not available for radiography. Ultrasound has the added benefit of pleural effusion detection, which may prove an important adjunct to the electronic auscultation algorithm. However, cost and availability of skilled technicians may greatly hamper its utility in resource-poor settings, similar to microbiologic testing. Electronic auscultation is a simple, inexpensive tool that could have great diagnostic impact on ALRI in children worldwide. Through further research, we foresee utilizing this tool with pre-programmed computerized analysis to improve case management in developing countries.

COMPETING INTERESTS

All authors in the study report no competing interests.

AUTHORS' CONTRIBUTIONS

All authors were involved in the study design and writing of the manuscript, and all reviewed the final manuscript before submission. Laura Ellington directly contributed to study design, and is responsible for supervision of data gathering at the children's hospital in Lima, electronic auscultation and chest ultrasound recordings, data management, analysis, and writing of this manuscript. Robert Gilman provided mentorship to Laura Ellington and technical support for the study. James Tielsch and Mark Steinhoff contributed to the concept and study design. Dante Figueroa will serve as study physician, provide supervision and administrative oversight on site, and perform physical testing. Shalim Rodriguez contributed to study design and was responsible for developing and training the study technician to a standardized chest ultrasound protocol. Brian Caffo contributed to study design and will contribute to statistical analysis. Brian Tracey, Mounya Elhilali, and James West contributed to study design and will contribute significantly to signal processing and data analysis. William Checkley had ultimate oversight over study design and administration, and was equally responsible writing of the manuscript, and serves as mentor to Laura Ellington throughout the conduct of the study.

REFERENCES

1 Sazawal S, Black RE. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. *The Lancet Infectious Diseases* 2003;**3**:547–56.

2 Cardoso M-R a, Nascimento-Carvalho CM, Ferrero F, *et al.* Adding fever to WHO criteria for diagnosing pneumonia enhances the ability to identify pneumonia cases among wheezing children. *Archives of disease in childhood* 2011;**96**:58–61.

3 Puumalainen T, Quiambao B, Abucejo-Ladesma E, *et al.* Clinical case review: a method to improve identification of true clinical and radiographic pneumonia in children meeting the World Health Organization definition for pneumonia. *BMC infectious diseases* 2008;**8**:95.

4 Hazir T, Nisar YB, Qazi S a, *et al.* Chest radiography in children aged 2-59 months diagnosed with non-severe pneumonia as defined by World Health Organization: descriptive multicentre study in Pakistan. *BMJ (Clinical research ed)* 2006;**333**:629.

5 Hazir T, Nisar YB, Abbasi S, *et al.* Comparison of oral amoxicillin with placebo for the treatment of world health organization-defined nonsevere pneumonia in children aged 2-59 months: a multicenter, double-blind, randomized, placebo-controlled trial in Pakistan. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2011;**52**:293–300.

6 Madico G, Gilman RH, Jabra A, *et al.* The role of pulse oximetry: its use as an indicator of severe respiratory disease in Peruvian children living at sea level. *Archives of Pediatrics and Adolescent Medicine* 1995;**149**:1259.

7 Schult S, Canelo-Aybar C. Oxygen saturation in healthy children aged 5 to 16 years residing in Huayllay, Peru at 4340 m. *High altitude medicine & biology* 2011;**12**:89–92.

8 Iuri D, De Candia a, Bazzocchi M. Evaluation of the lung in children with suspected pneumonia: usefulness of ultrasonography. *La Radiologia medica* 2009;**114**:321–30.

9 Parlamento S, Copetti R, Di S. Evaluation of lung ultrasound for the diagnosis of pneumonia in the ED. *European Respiratory Journal* 2009:379–84.

10 Yang PC, Luh KT, Chang DB, Yu CJ, Kuo SH WH. Ultrasonographic Evaluation of Pulmonary Consolidation. *American Review of Respiratory disease* 1992;**146**:757–62.

11 Su YH, Wang M, Block TM, *et al.* Transrenal DNA as a diagnostic tool: Important technical notes. *Annals of the New York Academy of Sciences* 2004;**1022**:81–9.

12 Gehmacher o, Mathis G, Kopf A, *et al.* Ultrasound imaging of pneumonia. U*ltrasound in med & biol* 1995;**21**:1119–22.

13 Lichtenstein D, Lascols N, Mezière G, *et al.* Ultrasound diagnosis of alveolar consolidation in the critically ill. *Intensive care medicine* 2004;**30**:276–81.

14 Murphy R, Vyshedskiy A, Charnitsky V, *et al.* Automated lung sound analysis in patients with pneumonia. *Respiratory Care* 2004;**49**:1490–07.

15 Grenier M, Gagnon K, Genest J, *et al.* Clinical comparison of acoustic and electronic stethoscopes and design of a new electronic stethoscope. *American Journal of Cardiology* 1998;**81**:653–6.

16 Gurung A, Scrafford C, Tielsch J, *et al.* Computerized lung sound analysis as a diagnostic aid for the detection of abnormal lung sounds: A systematic review and meta-analysis. *Respiratory Medicine* 2011;**doi:10.101**.

17 Abaza A a, Day JB, Reynolds JS, *et al.* Classification of voluntary cough sound and airflow patterns for detecting abnormal pulmonary function. *Cough (London, England)* 2009;**5**:8.

18 Reichert S, Gass R, Brandt C, *et al.* Analysis of respiratory sounds: state of the art. *Clinical medicine Circulatory, respiratory and pulmonary medicine* 2008;**2**:45–58.

19 Lu X, Bahoura M. An integrated automated system for crackles extraction and classification. *Biomedical Signal Processing and Control* 2008;**3**:244–54.

20 Marshall A, Boussakta S. Signal analysis of medical acoustics sounds with applications to chest medicine. *J Franklin Institute* 2007;**344**:230–42.

21 Taplidou S, Hadjileontiadis L, Kitsas I, *et al.* On applying continuous wavelet transform in wheeze analysis. *IEEE EMBS* 2004;:3832–5.

22 Saeed S, Body R. Auscultating to diagnose pneumonia. *EMJ* 2007;**24**:294–6.

23 Volpicelli G, Silva F, Radeos M. Real-time lung ultrasound for the diagnosis of alveolar consolidation and interstitial syndrome in the emergency department. *European Journal of Emergency Medicine* 2010;**17**:63–72.

24 Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children World Health Organization Pneumonia Vaccine Trial Investigators ' Group DEPARTMENT OF VACCINES. *World Health* 2001.

25 Bossuyt PM, Reitsma JB, Bruns DE, *et al.* Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ (Clinical research ed)* 2003;**326**:41–4.

Figure 1. Order of auscultation by electronic stethoscope. The study team member will listen to each site, starting with "A" for 10 seconds each.

Figure 2. Microbiology testing schematic.

Figure 3. Preliminary data suggest a difference in spectral analysis between children with and without wheeze. Short-time FFT analysis was utilized to visualize spectrograms of a normal control (A) and asthmatic child with active wheeze (B). Representative sample is from preliminary recordings taken from the Emergency Room at the Johns Hopkins Hospital in Baltimore, MD.

Figure 2. Microbiology testing schematic.
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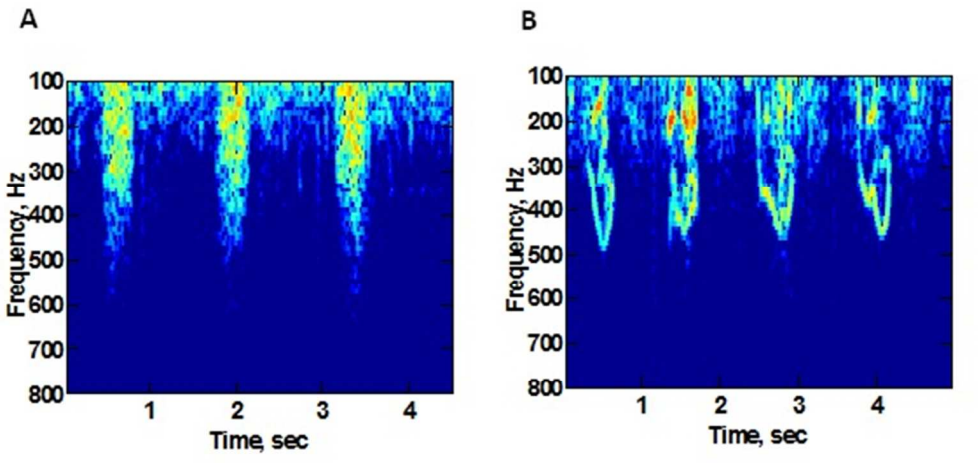

Figure 3. Preliminary data suggest a difference in spectral analysis between children with and without wheeze. Short-time FFT analysis was utilized to visualize spectrograms of a normal control (A) and asthmatic child with active wheeze (B). Representative sample is from preliminary recordings taken from the Emergency Room at the Johns Hopkins Hospital in Baltimore, MD.
151x74mm (96 x 96 DPI)

STARD checklist for reporting of studies of diagnostic accuracy

(version January 2003)

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	1,2
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	8,9
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	11
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	11
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	11
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	10
Test methods	7	The reference standard and its rationale.	11,12
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	14-16
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	14-16
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	11-12, 14-16
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	11-12
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	18
	13	Methods for calculating test reproducibility, if done.	N/A
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	N/A
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	N/A
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	N/A
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	N/A
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	N/A
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	N/A
	20	Any adverse events from performing the index tests or the reference standard.	N/A
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	N/A
	22	How indeterminate results, missing data and outliers of the index tests were handled.	N/A
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	N/A
	24	Estimates of test reproducibility, if done.	N/A
DISCUSSION	25	Discuss the clinical applicability of the study findings.	N/A

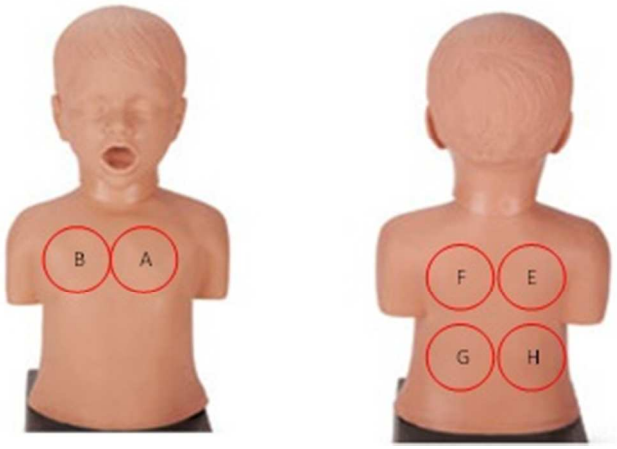

Figure 1. Order of auscultation by electronic stethoscope. The study team member will listen to each site, starting with "A" for 10 seconds each.
82x60mm (96 x 96 DPI)

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Computerized lung sound analysis to improve the specificity of pediatric pneumonia diagnosis in resource-poor settings: Protocol and methods for an observational study

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Computerized lung sound analysis to improve the specificity of pediatric pneumonia diagnosis in resource-poor settings: Protocol and methods for an observational study

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ARTICLE FOCUS

- We seek to characterize lung sounds associated with different respiratory illnesses in children using electronic auscultation and determine whether these sounds can be differentiated from normal through computerized lung sound analysis.
- We summarize the study design and methods with standardized protocols for electronic auscultation and chest ultrasound in children.

KEY MESSAGES

- We aim to develop a protocol for increased specificity of pediatric pneumonia diagnosis in developing countries.

STRENGHTS AND LIMITATIONS

- Our study is limited by the case definitions available. With no gold standard for many pediatric respiratory diseases, we will rely on clinical exam findings and chest radiography.
- By investigating a number of novel and commonly used diagnostic tools for a variety of respiratory diseases in children, we will gain valuable information regarding the diagnostic potential of each, with a main focus on the electronic stethoscope.

ABSTRACT

Introduction: The World Health Organization (WHO) case management algorithm for pediatric pneumonia relies solely on symptoms of shortness of breath or cough and tachypnea for treatment and has poor diagnostic specificity, tends to increase antibiotic resistance. Alternatives, including oxygen saturation measurement, chest ultrasound, and chest auscultation exist but with potential disadvantages. Electronic auscultation has potential for improved detection of pediatric pneumonia but has yet to be standardized. We aim to investigate the use of electronic auscultation to improve the specificity of the current WHO algorithm in developing countries.

Methods: Our study is designed to test the hypothesis that pulmonary pathology can be differentiated from normal using computerized lung sound analysis (CLSA). We will record lung sounds from 600 children aged ≤5 years, 100 each with consolidative pneumonia, diffuse interstitial pneumonia, asthma, bronchiolitis, upper respiratory infections, and normal lungs at a children's hospital in Lima, Peru. We will compare CLSA with the WHO algorithm and other detection approaches, including physical exam findings, chest ultrasound, and microbiologic testing to construct an improved algorithm for pneumonia diagnosis.

Ethics and dissemination: Approval was obtained from the Ethics Committees of A.B. PRISMA, Instituto Nacional de Salud del Niño and Johns Hopkins School of Medicine. Dissemination will include publications following the study and the development of a free online library of lung sounds for improvement of CLSA, future research, and clinical education.

Discussion: This study will develop standardized methods for electronic auscultation, and chest ultrasound, and compare their utility for detection of pneumonia to standard approaches. Utilizing signal processing techniques, we aim to characterize lung sounds and through machine learning, develop a classification system to distinguish pathologic sounds. Data will allow a

better understanding of the benefits and limitations of novel diagnostic techniques in pediatric pneumonia.

INTRODUCTION

Acute lower respiratory infection (ALRI) is the leading cause of death in children under 5 years of age. Pneumonia alone is responsible for killing 1.6 million children worldwide. The World Health Organization (WHO) developed a case management algorithm that relies solely on symptoms of shortness of breath or cough, an elevated respiratory rate, and chest indrawing for the diagnosis of pneumonia and administration of antibiotics and/or referral in resource-poor areas (Table 1). Where successfully implemented, this algorithm has resulted in a 30-40% reduction in case mortality[1] but has moderate sensitivity and poor specificity, ranging from 16% for children presenting with wheeze[2] and 49% for nonsevere pneumonia to 95% for very severe pneumonia[3]. Hazir and colleagues demonstrated that over 80% of children with WHO-defined non-severe pneumonia had normal chest radiographs (CXR)[4] and that the resulting case management was equivalent to no treatment in a randomized clinical trial[5], only further increasing concern for global antibiotic resistance.

Table 1. WHO Classification of ALRI in Children Presenting with Cough and/or Difficult Breathing

No pneumonia (cough and cold)	Respiratory rate, breaths/minute <50 (infants 2–11 months) <40 (children 12–59 months) No lower chest indrawing
Non-severe pneumonia	Respiratory rate, breaths/minute >50 (infants 2–11 months) >40 (children 12–59 months) No lower chest indrawing
Severe pneumonia	Lower chest indrawing ± rapid breathing
Very severe pneumonia	At least one of the following: Unable to feed Convulsions Lethargic Stridor at rest Clinically severe malnutrition

Pneumonia is a pathological process resulting in fluid-filled alveoli, and while there are multiple potential etiologies, most are infectious. Currently, there is no gold standard for detection of bacterial pneumonia requiring treatment. In areas where resources are readily available, chest radiography and clinical diagnosis serve as the standard of care for pneumonia detection but these are not available in resource-poor settings around the world. Potential

alternatives exist within aspects of the physical exam and imaging. Supplementing oxygen saturation measurements with the current WHO algorithm has been shown to increase specificity[6]; however, the normal range in healthy children varies with environmental factors like altitude[7]. Another promising alternative for detection of pediatric pneumonia is lung ultrasound. Ultrasound has the advantage of gathering information from multiple angles and the ability to detect air-fluid differences that are present with pneumonia. Studies suggest that this technique may be more sensitive than radiography and has the added benefit of lack of radiation; however, these studies have all lacked power due to small sample size[8-13]. Cost and availability of skilled ultrasound technicians may limit use in resource-poor settings. Chest auscultation is a valuable tool for detection of respiratory pathology and is used widely in clinical practice. However, limitations include inter-listener variability, subjectivity in the interpretation of lung sounds[14,15], and lack of trained personnel in resource poor settings. Electronic auscultation has the advantage of signal amplification and ambient noise reduction leading to increased signal-to-noise ratio along with its independence on human ear sensitivity to different acoustic frequencies. Furthermore, through computerized lung sound analysis (CLSA), this diagnostic method results in discrete values from a final reading, thereby facilitating standardization. With advancement in electronic stethoscopes and CLSA, there is great potential for improved diagnosis of pediatric pneumonia where multiple diagnostic tools are not readily available.

In acoustic signal processing, the two commonly studied lung sounds are crackles and wheezes, which constitute unique temporal and frequency characteristics. Crackles have been most commonly associated with pneumonia, whereas wheezes are often observed in patients with asthma and bronchiolitis[16]. According to the Computerized Respiratory Sound Analysis

(CORSA) Guidelines[17], the frequency of crackles is characterized in the spectrum of 200 to 2000 Hz, while wheezes have a frequency spectrum of 100 to 1000 Hz. Wheezes have continuous waveforms (>100 ms duration) with one or more tonal components and a dominant frequency greater than 400 Hz during the expiratory phase. Crackles are short (<20ms), non-periodic waveforms with transitory sharp peaks and broadband frequency content during mid-inspiratory phase. Time-frequency decomposition of lung sounds provides useful information in identifying and localizing adventitious lung sounds in a patient.

Translating the CLSA characterization of abnormal lung sounds to clinical practice has yet to be achieved. There are a few studies demonstrating potential, yet data is largely lacking, especially in the field of pediatrics. Our group conducted a systematic review and meta-analysis of studies using CLSA for the detection of a variety of respiratory disease in adults, which found an overall sensitivity and specificity of 80% and 85%, respectively, when compared to radiologically confirmed cases, with markedly limited results due to lack of quality and quantity of available data, as well as lack of standardization[16,18-22].

In this study, we seek to utilize electronic auscultation to record lung sounds of children with various clinical diagnoses: pneumonia (diffuse interstitial and lobar), asthma, bronchiolitis, and upper respiratory infection (URI) in a tertiary care center in Lima, Peru, and determine whether they can be differentiated from normal lung sounds using CLSA. In addition, we aim to compare with imaging modalities of chest radiography and ultrasound. We hypothesize that not only will the sounds profiles of each pulmonary disease pathology differ from normal, but due to unique characteristics of lung sounds associated with bacterial pneumonia versus asthma, bronchiolitis or URI, CLSA may allow differentiation of various acute lower respiratory disease processes. With this information in conjunction with additional basic clinical information (i.e.

temperature, respiratory rate, oxygen saturation), we believe that a much needed improvement in the detection and case management of pediatric pneumonia is possible.

METHODS

Study objectives

The primary objectives of this study are to characterize lung sounds associated with various clinical diagnoses: radiologically confirmed consolidative pneumonia and diffuse interstitial pneumonia, bronchiolitis, asthma, and upper respiratory infections, in a pediatric population; and, to determine if these diagnoses can be differentiated from normal through automated lung sounds analysis and compare with modalities of imaging, current WHO algorithm for ALRI case management, and microbiological testing. We then aim to then develop a clinical protocol pairing electronic auscultation with a CLSA algorithm to aid in pneumonia diagnosis.

Study design

Our design will be a cross-sectional study of lung sounds and other diagnostic modalities from children 2 to 60 months of age presenting with a primary respiratory complaint to the Instituto Nacional de Salud del Niño, a tertiary care hospital in Lima, Peru. Informed consent from parents will be obtained in the Emergency Department (ED), asthma ward, or pulmonary ward where all testing will be performed in a single visit. Parents will be asked to fill out a questionnaire while the physician reports relevant aspects of the physical exam. Electronic auscultation will then be performed, following by imaging and collection of blood, respiratory, urine, and stool samples.

During the initial phase, we will record lung sounds from 600 children from 2 to 59 months of age, 100 each with consolidative pneumonia, diffuse interstitial pneumonia, asthma, bronchiolitis, upper respiratory infections, and normal lungs. The second phase will consist of completing our testing set for external validity and comparing CLSA with the current WHO

algorithm and other diagnostic tools such as physical exam findings, chest ultrasound, and microbiologic testing, in order to construct an improved algorithm for pneumonia diagnosis.

Study population

Children from 2 to 59 months of age presenting to the ED or in the asthma or pulmonary ward without a history of chronic lung disease, excluding asthma, or significant cardiac disease will be invited to participate in the study. Children with respiratory complaints will be invited to participate as potential cases, while those without respiratory complaints and no acute respiratory illness within one month of presentation will be invited to join the study as controls.

Children will be considered eligible if their parents or guardians are able to provide written informed consent, and they themselves do not require airway management or non-invasive ventilation. Children will be considered ineligible if they have chronic lung diseases other than asthma, such as cystic fibrosis, bronchiectasis, and chronic lung disease of prematurity or significant congenital heart disease. Patients will be considered ineligible post-consent if they were found to have more than one active respiratory diagnosis upon further testing. Group classification also may be modified post-consent and further enrollment required depending on chest x-ray (CXR) final readings and microbiological testing for diagnosis.

Outcomes and case definitions

Because there is no gold standard for diagnosis, we aim to compare our results with common case definitions and clinical diagnoses by experienced physicians. Secondary outcomes will incorporate etiology information from standard culture and molecular techniques; however, these additional data will not serve as the gold standard.

Pneumonia will be initially categorized upon clinical diagnosis by examining pediatricians at El Instituto Nacional de Salud del Niño and further characterized as consolidative or diffuse interstitial pneumonia given final CXR reading by blinded radiologists from the Johns Hopkins University. Asthma will be defined by the presence of wheeze on physical exam, history of asthma, and improvement with bronchodilators. Bronchiolitis will be defined as the presence of wheeze and difficulty breathing on physical exam and viral symptoms (cough, rhinorrhea), no history of asthma, and little or no improvement with bronchodilators if attempted. URI will be defined as respiration rate less than 50 breaths per minute and associated with one or more of the following: clear nasal secretions, sore or red throat, or hoarseness.

Sample size

Our recruitment goal is 600 subjects, 100 each with consolidative pneumonia, diffuse interstitial pneumonia, asthma, bronchiolitis, URI, and normal lungs. Sample size was powered to improve specificity of the WHO algorithm upon the addition of electronic auscultation. To detect an improvement in diagnostic specificity from 50% (WHO algorithm for pediatric pneumonia) to 80% (CLSA and WHO algorithm) with 95% power and α of 0.05 between pneumonia and non-pneumonia cases, we require 70 patients per group in the training set. We will also recruit a test set consisting of an additional 30 patients per group (30% of total sample) to estimate areas under the curve for our diagnostic algorithm. Each group will be over-enrolled by twenty to account for post-consent ineligibility, for a total of 720.

Study organization

A.B. PRISMA in Lima, Peru, and Johns Hopkins University in Baltimore, USA, will provide administrative oversight for the study. There will be a research coordinator at a central location in Lima, Peru, who will provide logistical support and management of the study team. Instituto Nacional de Salud del Niño will provide a team of study nurses and physicians to carry out recruitment, physical examination, and collection of specimens. We have also established prior training by an experienced ultrasonographer to conduct chest ultrasonography. A multidisciplinary team of clinicians, field epidemiologists, acoustical engineers, and biostatisticians from Johns Hopkins University, Tufts University, Cincinnati Children's Hospital, and Instituto Nacional de Salud del Niño will be involved with study design and conduct, statistical analysis, and reporting of results.

Questionnaire

We will ask the parent or guardian about the child's past medical history, environmental exposures, access to healthcare, and current respiratory symptoms. We will inquire about demographic information, nutrition, and vaccination history. We will ask about co-morbidities, family history, and developmental history. Environmental questions pertained to housing, number of children, rural versus urban living, parent occupations, smoke and allergen exposure, and sick contacts. Current respiratory symptoms were asked of the parent or guardian to answer subjectively and included rapid breathing, difficulty breathing, chest indrawing, cyanosis, cough, sputum production, audible breath sounds, and subjective fever.

Physical exam and laboratory testing

The initial set of vital signs will be recorded, including pulse oximetry. During the physical exam, a single examining physician from the larger group of study physicians will be responsible for recording findings for a given patient with emphasis on the respiratory exam. Chest retractions, nasal flaring, grunting, stridor, and accessory muscle use will be noted and characterized if present, along with any adventitious lung sounds appreciated by physician and study team member on chest auscultation. Degree of improvement after bronchodilators will also be recorded if administered. Additionally, signs of dehydration and malnutrition will be reported if present. Laboratory results will be recorded if evaluated by the ED and include complete blood count, electrolytes, and arterial blood gas.

Electronic Auscultation

Parents will be allowed to position the patient supine or upright. The study team member will listen to eight auscultation sites using a ThinkLabs ds32a Digital Stethoscope and mp3 recorder, for 10 seconds at each site, in the following order of placement: front top left and right, fronterolateral bottom right and left, back top right and left, and back bottom left and right (Figure 1). Auscultation will be performed at the participant's normal breathing patterns during recording without being asked to take deep breaths. We will allow only one repeat of auscultation if recording is interrupted for any reason or due to unacceptable signal quality of the first recording.

Lung ultrasound

All participants will receive bilateral lung ultrasonography carried out on SonoSite portable ultrasound machine with HFL38/13-6MHz and P17/5-1MHz MicroMaxx® transducers by a

single ultrasound technician who has been trained to the standardized protocol. Patients will be examined in the supine position with each hemithorax divided into six sections: 2 anterior, 2 lateral, and 2 posterior. The posterior area is defined from the posterior axillary line to the paravertebral line. Longitudinal and oblique scans will be obtained at each of the chest zones. Longitudinal scans allow visualization of the ribs with the pleural line under them[23]. Representative images from each section will be saved and later transferred to radiologists at an outside institution.

To assess for pneumonia, 2 of 3 radiologists must agree on the description of ultrasound images compatible with pneumonia. Consolidation will be determined by 1) the presence of hypo- or anechoic images with loss of distinct pleural lines and 2) an irregular shredded border of the pleural line that is distinct from the lung line, termed the "shred sign." Additional signs to be reported will include punctate hyperechoic images reflecting air bronchograms, decreased lung sliding, and homogenous, hypoechoic images in the pleural space corresponding to pleural effusions. Interstitial infiltrates will be determined by the presence of "lung rockets," which correlate to three or more B-lines in a longitudinal view between two ribs. Additional features to be reported include heterogenous echotexture, air and fluid bronchograms, lung pulse, and additional B-lines [23].

Chest radiography

All case participants will undergo chest radiography. We will attempt postero-anterior and lateral films but will allow an antero-posterior view if not possible. Digital images will be sent to a third party reading group blinded to clinical information. Using the WHO standardization of CXR interpretation for pediatric pneumonia [24], radiologists will comment on quality as adequate,

suboptimal, or unreadable and on the presence of pathology as consolidative or interstitial with or without pleural effusions. Radiographic evidence of pneumonia will be confirmed by agreement by 2 out of 3 radiologist reports for a given patient. Additional pathologic findings not previously characterized will also be recorded and reported to the patient's physician for further intervention if necessary.

Microbiological studies

Blood, urine, and nasopharyngeal samples will be collected according to our study design (Figure 2). Blood samples will be drawn for cultures and sensitivities. Urine will be tested for detection of pneumococcal antigen and stored for PCR. Nasopharyngeal swabs will be tested for respiratory viruses, along with culture and sensitivities. Respiratory pathogens tested by PCR will include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and respiratory syncytial virus.

Safety

To ensure safety, the researcher collecting data is experienced with providing care to children. The researcher will use this experience to minimize any discomfort the children may have. All blood samples will be collected by a skilled nurse or phlebotomist.

We will adhere to hospital procedures for avoiding hospital acquired infections. We will wash hands with soap and water or alcohol-based hand sanitizer before patient contact. We will wear gloves, gowns and mask when required. We will clean the devices using alcohol swabs before and after each use.

Data quality and management

Prior to data collection, a Manual of Operations will be developed to ensure standardization and reliability and contain detailed instructions for all study procedures and guidelines for data collection. The manual will be revised as needed and distributed to members of the study team.

All data are recorded first on paper case report forms and subsequently double-entered using Microsoft ACCESS. Data sets will be cross-validated and errors corrected. Electronic lung recordings will be transferred from the mp3 player to participant-specific files on the study computer at least every other day and backed-up weekly. Digital CXR images will also be uploaded to these files and backed-up similarly.

Analysis of lung sounds and statistics

An important first step in CLSA is using common signal processing techniques to investigate high and low frequency information using methods such as the Short-time Fourier Transform (STFT), wavelet transforms, and P-spline bases. The second step will be extracting signal processing features to train the classifier.

Based on preliminary recordings to date performed by our group in Baltimore (Figure 3), we anticipate that wheeze can be characterized using features from the Fourier transform, such as the existence and temporal stability of tonal peaks in the 300-1000 Hz range, while crackles could be recognized using features such as amplitude, the presence of broad-band energy and the duration of this energy. Features such as the decrease in signal energy with frequency can characterize movement sounds. We have previously used time-frequency descriptors such as Mel-frequency cepstral coefficients as features and anticipate they will be useful for CLSA but may require temporal information as well. We will use the extracted features from signal processing analyses for classification using machine learning algorithms including: nearest

neighbor methods, support vector machines, random forests, and gradient boosting. Primary analysis will consist of a five-fold cross validation on the training set to calculate expected prediction errors. The training set will additionally be used to estimate areas under the curve for our diagnostic algorithm, including CLSA, WHO algorithm, imaging, and physical exam findings. Secondary analysis will include calculating sensitivities and specificities of experimental diagnostic US for detection of pneumonia when compared to gold standards (clinical diagnosis and CXR reading). Performance will be measured using logistic and multinomial regression, receiver operating characteristic curves, and area under the curve.

ETHICS AND DISSEMINATION

Approval was obtained from the Ethics Committees of A.B. PRISMA in Lima, Peru, El Instituto Nacional de Salud del Niño in Lima, Peru, and the Johns Hopkins University School of Medicine in Baltimore, MD. Written informed consent will be obtained from a parent or guardian. Any clinical information gained from participation in this study that could possibly change management will be given to the child's physician for his/her discretion. All data and sensitive information will be protected by being kept on encrypted devices or accessible only to study members.

Plans for dissemination include final publication following completion of the study following the STARD guidelines for reporting diagnostic accuracy[25]. We aim to develop a free online library of lung sounds for further enhancement of CLSA and the machine learning algorithm, as well as for future research and clinical education.

Funders have had no role in study design, nor will they have a role in the collection, management, analysis, and interpretation of data; manuscript preparation; and future

publications. The principal investigator will have ultimate authority over these aspects of research.

DISCUSSION

This study aims to investigate alternatives to improve the specificity of the WHO algorithm for pediatric pneumonia, namely electronic auscultation and chest ultrasonography. Utilizing electronic auscultation, we intend to characterize and analyze lung sounds associated with consolidative pneumonia, diffuse interstitial pneumonia, bronchiolitis, asthma, and upper respiratory infections, to determine if these diagnoses can be differentiated from normal through automated lung sounds, and to compare with chest ultrasound, WHO algorithm, and molecular testing for etiology. By reporting a protocol for CLSA, we hope to encourage standardization and expansion of recorded lung sounds via an online library for continued enhancement of machine learning as well as for continued scientific research and clinical education.

We foresee our greatest challenge in maximizing the quality of recorded lung sounds. To begin the study, we will utilize a commercial electronic stethoscope for recordings, which is identical in design to standard clinical stethoscopes. However, through sound processing using time-frequency analysis methods such as the Short-time Fourier Transform (STFT) and Continuous Wavelet Transforms (CWT), we hope to enhance the signal-to-noise ratio for data analysis and characterization. By examining additional features such as amplitude, we may also be better able to identify crackles and consolidation. We also plan to test alternative recording devices using piezoelectric microphones covered with a thin polymer that may be able to better capture lung sounds. Based on our recordings to date, we anticipate that wheeze can be differentiated from normal breath using features such as the existence and temporal stability of tonal peaks in the 300-1000 Hz range, while crackle should be recognizable using features such as the presence of broad-band energy and the duration of this energy. Features such as the decrease in signal energy with frequency can characterize movement sounds. We have

previously used time-frequency descriptors borrowed from speech processing (Mel-frequency cepstral coefficients and their time derivatives) and cough-specific time-domain features such as signal rise time and event duration and anticipate they will be useful for CLSA. We will use the extracted features from signal processing analyses for classification using machine learning algorithms such as nearest neighbor methods, support vector machines, or random forests.

The largest challenge in regards to lung ultrasound will likely be obtaining adequate quality of images and inter-user variability. To reduce variability, the study technician will be trained to systematically scan each subdivided hemithorax for pathologic findings described previously [9,23], and if possible, we will attempt lung ultrasound twice for each patient. Ultrasound also takes substantially longer compared to chest radiography because all areas must be adequately explored; therefore, it may be difficult for a child to be cooperative for that length of time. Through our large sample size and detailed methods, we aim to improve standardization of pediatric chest ultrasound and further define pathologic findings associated with disease, which may also lead to more efficient and faster scanning.

Limitations to this study center mostly on our case definitions for clinical diagnoses. As mentioned previously, there are no precise gold standards and as with many pediatric diseases, diagnosis is clinical. As such, our end points are determined by clinical exam findings by single examining physicians with additional confirmation via radiology for pneumonia cases only. We acknowledge the variability of observed findings among physicians but also accept that this is the mechanism of diagnosis in most clinical settings.

The WHO algorithm for case management of pediatric pneumonia lacks diagnostic specificity. While clinical information such as elevated heart rate and decreased oxygen saturation may aid in degree of illness and monitoring, these data also lack specificity required to

drastically improve case management. Lung ultrasound is also a promising tool and offers portability that is not available for radiography. Ultrasound has the added benefit of pleural effusion detection, which may prove an important adjunct to the electronic auscultation algorithm. However, cost and availability of skilled technicians may greatly hamper its utility in resource-poor settings, similar to microbiologic testing. Electronic auscultation is a simple, inexpensive tool that could have great diagnostic impact on ALRI in children worldwide. Through further research, we foresee utilizing this tool with pre-programmed computerized analysis to improve case management in developing countries.

COMPETING INTERESTS

All authors in the study report no competing interests.

AUTHORS' CONTRIBUTIONS

All authors were involved in the study design and writing of the manuscript, and all reviewed the final manuscript before submission. Laura Ellington directly contributed to study design, and is responsible for supervision of data gathering at the children's hospital in Lima, electronic auscultation and chest ultrasound recordings, data management, analysis, and writing of this manuscript. Robert Gilman provided mentorship to Laura Ellington and technical support for the study. James Tielsch and Mark Steinhoff contributed to the concept and study design. Dante Figueroa will serve as study physician, provide supervision and administrative oversight on site, and perform physical testing. Shalim Rodriguez contributed to study design and was responsible for developing and training the study technician to a standardized chest ultrasound protocol. Brian Caffo contributed to study design and will contribute to statistical analysis. Brian Tracey, Mounya Elhilali, and James West contributed to study design and will contribute significantly to signal processing and data analysis. William Checkley had ultimate oversight over study design and administration, and was equally responsible writing of the manuscript, and serves as mentor to Laura Ellington throughout the conduct of the study.

REFERENCES

1 Sazawal S, Black RE. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. *The Lancet Infectious Diseases* 2003;**3**:547–56.

2 Cardoso M-R a, Nascimento-Carvalho CM, Ferrero F, *et al.* Adding fever to WHO criteria for diagnosing pneumonia enhances the ability to identify pneumonia cases among wheezing children. *Archives of disease in childhood* 2011;**96**:58–61.

3 Puumalainen T, Quiambao B, Abucejo-Ladesma E, *et al.* Clinical case review: a method to improve identification of true clinical and radiographic pneumonia in children meeting the World Health Organization definition for pneumonia. *BMC infectious diseases* 2008;**8**:95.

4 Hazir T, Nisar YB, Qazi S a, *et al.* Chest radiography in children aged 2-59 months diagnosed with non-severe pneumonia as defined by World Health Organization: descriptive multicentre study in Pakistan. *BMJ (Clinical research ed)* 2006;**333**:629.

5 Hazir T, Nisar YB, Abbasi S, *et al.* Comparison of oral amoxicillin with placebo for the treatment of world health organization-defined nonsevere pneumonia in children aged 2-59 months: a multicenter, double-blind, randomized, placebo-controlled trial in Pakistan. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2011;**52**:293–300.

6 Madico G, Gilman RH, Jabra A, *et al.* The role of pulse oximetry: its use as an indicator of severe respiratory disease in Peruvian children living at sea level. *Archives of Pediatrics and Adolescent Medicine* 1995;**149**:1259.

7 Schult S, Canelo-Aybar C. Oxygen saturation in healthy children aged 5 to 16 years residing in Huayllay, Peru at 4340□m. *High altitude medicine & biology* 2011;**12**:89–92.

8 Iuri D, De Candia a, Bazzocchi M. Evaluation of the lung in children with suspected pneumonia: usefulness of ultrasonography. *La Radiologia medica* 2009;**114**:321–30.

9 Parlamento S, Copetti R, Di S. Evaluation of lung ultrasound for the diagnosis of pneumonia in the ED. *European Respiratory Journal* 2009:379–84.

10 Yang PC, Luh KT, Chang DB, Yu CJ, Kuo SH WH. Ultrasonographic Evaluation of Pulmonary Consolidation. *American Review of Respiratory disease* 1992;**146**:757–62.

11 Su YH, Wang M, Block TM, *et al.* Transrenal DNA as a diagnostic tool: Important technical notes. *Annals of the New York Academy of Sciences* 2004;**1022**:81–9.

12 Gehmacher o, Mathis G, Kopf A, *et al.* Ultrasound imaging of pneumonia. U*ltrasound in med & biol* 1995;**21**:1119–22.

13 Lichtenstein D, Lascols N, Mezière G, *et al.* Ultrasound diagnosis of alveolar consolidation in the critically ill. *Intensive care medicine* 2004;**30**:276–81.

14 Murphy R, Vyshedskiy A, Charnitsky V, *et al.* Automated lung sound analysis in patients with pneumonia. *Respiratory Care* 2004;**49**:1490–07.

15 Grenier M, Gagnon K, Genest J, *et al.* Clinical comparison of acoustic and electronic stethoscopes and design of a new electronic stethoscope. *American Journal of Cardiology* 1998;**81**:653–6.

16 Gurung A, Scrafford C, Tielsch J, *et al.* Computerized lung sound analysis as a diagnostic aid for the detection of abnormal lung sounds: A systematic review and meta-analysis. *Respiratory Medicine* 2011;**doi:10.101**.

17 Abaza A a, Day JB, Reynolds JS, *et al.* Classification of voluntary cough sound and airflow patterns for detecting abnormal pulmonary function. *Cough (London, England)* 2009;**5**:8.

18 Reichert S, Gass R, Brandt C, *et al.* Analysis of respiratory sounds: state of the art. *Clinical medicine Circulatory, respiratory and pulmonary medicine* 2008;**2**:45–58.

19 Lu X, Bahoura M. An integrated automated system for crackles extraction and classification. *Biomedical Signal Processing and Control* 2008;**3**:244–54.

20 Marshall A, Boussakta S. Signal analysis of medical acoustics sounds with applications to chest medicine. *J Franklin Institute* 2007;**344**:230–42.

21 Taplidou S, Hadjileontiadis L, Kitsas I, *et al.* On applying continuous wavelet transform in wheeze analysis. *IEEE EMBS* 2004;:3832–5.

22 Saeed S, Body R. Auscultating to diagnose pneumonia. *EMJ* 2007;**24**:294–6.

23 Volpicelli G, Silva F, Radeos M. Real-time lung ultrasound for the diagnosis of alveolar consolidation and interstitial syndrome in the emergency department. *European Journal of Emergency Medicine* 2010;**17**:63–72.

24 Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children World Health Organization Pneumonia Vaccine Trial Investigators ' Group DEPARTMENT OF VACCINES. *World Health* 2001.

25 Bossuyt PM, Reitsma JB, Bruns DE, *et al.* Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ (Clinical research ed)* 2003;**326**:41–4.

Figure 1. Order of auscultation by electronic stethoscope. The study team member will listen to each site, starting with "A" for 10 seconds each.

Figure 2. Microbiology testing schematic.

Figure 3. Preliminary data suggest a difference in spectral analysis between children with and without wheeze. Short-time FFT analysis was utilized to visualize spectrograms of a normal control (A) and asthmatic child with active wheeze (B). Representative sample is from preliminary recordings taken from the Emergency Room at the Johns Hopkins Hospital in Baltimore, MD.

Computerized lung sound analysis to improve the specificity of pediatric pneumonia diagnosis in resource-poor settings: Protocol and methods for an observational ~~A case-control~~ study

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ARTICLE FOCUS

- We seek to characterize lung sounds associated with different respiratory illnesses in children using electronic auscultation and determine whether these sounds can be differentiated from normal through computerized lung sound analysis.
- We summarize the study design and methods with standardized protocols for electronic auscultation and chest ultrasound in children.

KEY MESSAGES

- We aim to develop a protocol for increased specificity of pediatric pneumonia diagnosis in developing countries.

STRENGHTS AND LIMITATIONS

- Our study is limited by the case definitions available. With no gold standard for many pediatric respiratory diseases, we will rely on clinical exam findings and chest radiography.
- By investigating a number of novel and commonly used diagnostic tools for a variety of respiratory diseases in children, we will gain valuable information regarding the diagnostic potential of each, with a main focus on the electronic stethoscope.

ABSTRACT

Introduction: The World Health Organization (WHO) case management algorithm for pediatric pneumonia relies solely on symptoms of shortness of breath or cough and tachypnea for treatment and has poor diagnostic specificity, tends to increase antibiotic resistance. Alternatives, including oxygen saturation measurement, chest ultrasound, and chest auscultation exist but with potential disadvantages. Electronic auscultation has potential for improved detection of pediatric pneumonia but has yet to be standardized. We aim to investigate the use of electronic auscultation to improve the specificity of the current WHO algorithm in developing countries.

Methods: Our study is designed to test the hypothesis that pulmonary pathology can be differentiated from normal using computerized lung sound analysis (CLSA). We will record lung sounds from 600 children aged ≤5 years, 100 each with consolidative pneumonia, diffuse interstitial pneumonia, asthma, bronchiolitis, upper respiratory infections, and normal lungs at a children's hospital in Lima, Peru. We will compare CLSA with the WHO algorithm and other detection approaches, including physical exam findings, chest ultrasound, and microbiologic testing to construct an improved algorithm for pneumonia diagnosis.

Ethics and dissemination: Approval was obtained from the Ethics Committees of A.B. PRISMA, Instituto Nacional de Salud del Niño and Johns Hopkins School of Medicine. Dissemination will include publications following the study and the development of a free online library of lung sounds for improvement of CLSA, future research, and clinical education.

Discussion: This study will develop standardized methods for electronic auscultation, and chest ultrasound, and compare their utility for detection of pneumonia to standard approaches. Utilizing signal processing techniques, we aim to characterize lung sounds and through machine learning, develop a classification system to distinguish pathologic sounds. Data will allow a

better understanding of the benefits and limitations of novel diagnostic techniques in pediatric pneumonia.

INTRODUCTION

Acute lower respiratory infection (ALRI) is the leading cause of death in children under 5 years of age. Pneumonia alone is responsible for killing 1.6 million children worldwide. The World Health Organization (WHO) developed a case management algorithm that relies solely on symptoms of shortness of breath or cough, an elevated respiratory rate, and chest indrawing for the diagnosis of pneumonia and administration of antibiotics and/or referral in resource-poor areas (Table 1). Where successfully implemented, this algorithm has resulted in a 30-40% reduction in case mortality[1] but has moderate sensitivity and poor specificity, ranging from 16% for children presenting with wheeze[2] and 49% for nonsevere pneumonia to 95% for very severe pneumonia[3]. Hazir and colleagues demonstrated that over 80% of children with WHO-defined non-severe pneumonia had normal chest radiographs (CXR)[4] and that the resulting case management was equivalent to no treatment in a randomized clinical trial[5], only further increasing concern for global antibiotic resistance.

Table 1. WHO Classification of ALRI in Children Presenting with Cough and/or Difficult Breathing

No pneumonia (cough and cold)	Respiratory rate, breaths/minute <50 (infants 2–11 months) <40 (children 12–59 months) No lower chest indrawing
Non-severe pneumonia	Respiratory rate, breaths/minute >50 (infants 2–11 months) >40 (children 12–59 months) No lower chest indrawing
Severe pneumonia	Lower chest indrawing ± rapid breathing
Very severe pneumonia	At least one of the following: Unable to feed Convulsions Lethargic Stridor at rest Clinically severe malnutrition

Pneumonia is a pathological process resulting in fluid-filled alveoli, and while there are multiple potential etiologies, most are infectious. Currently, there is no gold standard for detection of bacterial pneumonia requiring treatment. In areas where resources are readily available, chest radiography and clinical diagnosis serve as the standard of care for pneumonia detection but these are not available in resource-poor settings around the world. Potential

alternatives exist within aspects of the physical exam and imaging. Supplementing oxygen saturation measurements with the current WHO algorithm has been shown to increase specificity[6]; however, the normal range in healthy children varies with environmental factors like altitude[7]. Another promising alternative for detection of pediatric pneumonia is lung ultrasound. Ultrasound has the advantage of gathering information from multiple angles and the ability to detect air-fluid differences that are present with pneumonia. Studies suggest that this technique may be more sensitive than radiography and has the added benefit of lack of radiation; however, these studies have all lacked power due to small sample size[8-13]. Cost and availability of skilled ultrasound technicians may limit use in resource-poor settings. Chest auscultation is a valuable tool for detection of respiratory pathology and is used widely in clinical practice. However, limitations include inter-listener variability, subjectivity in the interpretation of lung sounds[14,15], and lack of trained personnel in resource poor settings. Electronic auscultation has the advantage of signal amplification and ambient noise reduction leading to increased signal-to-noise ratio along with its independence on human ear sensitivity to different acoustic frequencies. Furthermore, through computerized lung sound analysis (CLSA), this diagnostic method results in discrete values from a final reading, thereby facilitating standardization. With advancement in electronic stethoscopes and CLSA, there is great potential for improved diagnosis of pediatric pneumonia where multiple diagnostic tools are not readily available.

In acoustic signal processing, the two commonly studied lung sounds are crackles and wheezes, which constitute unique temporal and frequency characteristics. Crackles have been most commonly associated with pneumonia, whereas wheezes are often observed in patients with asthma and bronchiolitis[16]. According to the Computerized Respiratory Sound Analysis

(CORSA) Guidelines[17], the frequency of crackles is characterized in the spectrum of 200 to 2000 Hz, while wheezes have a frequency spectrum of 100 to 1000 Hz. Wheezes have continuous waveforms (>100 ms duration) with one or more tonal components and a dominant frequency greater than 400 Hz during the expiratory phase. Crackles are short (<20ms), non-periodic waveforms with transitory sharp peaks and broadband frequency content during mid-inspiratory phase. Time-frequency decomposition of lung sounds provides useful information in identifying and localizing adventitious lung sounds in a patient.

Translating the CLSA characterization of abnormal lung sounds to clinical practice has yet to be achieved. There are a few studies demonstrating potential, yet data is largely lacking, especially in the field of pediatrics. Our group conducted a systematic review and meta-analysis of studies using CLSA for the detection of a variety of respiratory disease in adults, which found an overall sensitivity and specificity of 80% and 85%, respectively, when compared to radiologically confirmed cases, with markedly limited results due to lack of quality and quantity of available data, as well as lack of standardization[16,18-22].

In this study, we seek to utilize electronic auscultation to record lung sounds of children with various clinical diagnoses: pneumonia (diffuse interstitial and lobar), asthma, bronchiolitis, and upper respiratory infection (URI) in a tertiary care center in Lima, Peru, and determine whether they can be differentiated from normal lung sounds using CLSA. In addition, we aim to compare with imaging modalities of chest radiography and ultrasound. We hypothesize that not only will the sounds profiles of each pulmonary disease pathology differ from normal, but due to unique characteristics of lung sounds associated with bacterial pneumonia versus asthma, bronchiolitis or URI, CLSA may allow differentiation of various acute lower respiratory disease processes. With this information in conjunction with additional basic clinical information (i.e.

temperature, respiratory rate, oxygen saturation), we believe that a much needed improvement in the detection and case management of pediatric pneumonia is possible.

METHODS

Study objectives

The primary objectives of this study are to characterize lung sounds associated with various clinical diagnoses: radiologically confirmed consolidative pneumonia and diffuse interstitial pneumonia, bronchiolitis, asthma, and upper respiratory infections, in a pediatric population; and, to determine if these diagnoses can be differentiated from normal through automated lung sounds analysis and compare with modalities of imaging, current WHO algorithm for ALRI case management, and microbiological testing. We then aim to then develop a clinical protocol pairing electronic auscultation with a CLSA algorithm to aid in pneumonia diagnosis.

Study design

Our design will be a cross-sectional study of lung sounds and other diagnostic modalities from children 2 to 60 months of age presenting with a primary respiratory complaint to the Instituto Nacional de Salud del Niño, a tertiary care hospital in Lima, Peru. Informed consent from parents will be obtained in the Emergency Department (ED), asthma ward, or pulmonary ward where all testing will be performed in a single visit. Parents will be asked to fill out a questionnaire while the physician reports relevant aspects of the physical exam. Electronic auscultation will then be performed, following by imaging and collection of blood, respiratory, urine, and stool samples.

During the initial phase, we will record lung sounds from 600 children from 2 to 59 months of age, 100 each with consolidative pneumonia, diffuse interstitial pneumonia, asthma, bronchiolitis, upper respiratory infections, and normal lungs. The second phase will consist of completing our testing set for external validity and comparing CLSA with the current WHO

algorithm and other diagnostic tools such as physical exam findings, chest ultrasound, and microbiologic testing, in order to construct an improved algorithm for pneumonia diagnosis.

Study population

Children from 2 to 59 months of age presenting to the ED or in the asthma or pulmonary ward without a history of chronic lung disease, excluding asthma, or significant cardiac disease will be invited to participate in the study. Children with respiratory complaints will be invited to participate as potential cases, while those without respiratory complaints and no acute respiratory illness within one month of presentation will be invited to join the study as controls.

Children will be considered eligible if their parents or guardians are able to provide written informed consent, and they themselves do not require airway management or non-invasive ventilation. Children will be considered ineligible if they have chronic lung diseases other than asthma, such as cystic fibrosis, bronchiectasis, and chronic lung disease of prematurity or significant congenital heart disease. Patients will be considered ineligible post-consent if they were found to have more than one active respiratory diagnosis upon further testing. Group classification also may be modified post-consent and further enrollment required depending on chest x-ray (CXR) final readings and microbiological testing for diagnosis.

Outcomes and case definitions

Because there is no gold standard for diagnosis, we aim to compare our results with common case definitions and clinical diagnoses by experienced physicians. Secondary outcomes will incorporate etiology information from standard culture and molecular techniques; however, these additional data will not serve as the gold standard.

Pneumonia will be initially categorized upon clinical diagnosis by examining pediatricians at El Instituto Nacional de Salud del Niño and further characterized as consolidative or diffuse interstitial pneumonia given final CXR reading by blinded radiologists from the Johns Hopkins University. Asthma will be defined by the presence of wheeze on physical exam, history of asthma, and improvement with bronchodilators. Bronchiolitis will be defined as the presence of wheeze and difficulty breathing on physical exam and viral symptoms (cough, rhinorrhea), no history of asthma, and little or no improvement with bronchodilators if attempted. URI will be defined as respiration rate less than 50 breaths per minute and associated with one or more of the following: clear nasal secretions, sore or red throat, or hoarseness.

Sample size

Our recruitment goal is 600 subjects, 100 each with consolidative pneumonia, diffuse interstitial pneumonia, asthma, bronchiolitis, URI, and normal lungs. Sample size was powered to improve specificity of the WHO algorithm upon the addition of electronic auscultation. To detect an improvement in diagnostic specificity from 50% (WHO algorithm for pediatric pneumonia) to 80% (CLSA and WHO algorithm) with 95% power and α of 0.05 between pneumonia and non-pneumonia cases, we require 70 patients per group in the training set. We will also recruit a test set consisting of an additional 30 patients per group (30% of total sample) to estimate areas under the curve for our diagnostic algorithm. Each group will be over-enrolled by twenty to account for post-consent ineligibility, for a total of 720.

Study organization

A.B. PRISMA in Lima, Peru, and Johns Hopkins University in Baltimore, USA, will provide administrative oversight for the study. There will be a research coordinator at a central location in Lima, Peru, who will provide logistical support and management of the study team. Instituto Nacional de Salud del Niño will provide a team of study nurses and physicians to carry out recruitment, physical examination, and collection of specimens. We have also established prior ~~Hospital Edgardo Rebagliati Martins will provide an ultrasonographer for imaging at his institution and team member~~ training by an experienced ultrasonographer to ~~carry out~~conduct chest ultrasonography ~~at Hospital del Niño~~. A multidisciplinary team of clinicians, field epidemiologists, acoustical engineers, and biostatisticians from Johns Hopkins University, Tufts University, Cincinnati Children's Hospital, and Instituto Nacional de Salud del Niño will be involved with study design and conduct, statistical analysis, and reporting of results.

Questionnaire

We will ask the parent or guardian about the child's past medical history, environmental exposures, access to healthcare, and current respiratory symptoms. We will inquire about demographic information, nutrition, and vaccination history. We will ask about co-morbidities, family history, and developmental history. Environmental questions pertained to housing, number of children, rural versus urban living, parent occupations, smoke and allergen exposure, and sick contacts. Current respiratory symptoms were asked of the parent or guardian to answer subjectively and included rapid breathing, difficulty breathing, chest indrawing, cyanosis, cough, sputum production, audible breath sounds, and subjective fever.

Physical exam and laboratory testing

The initial set of vital signs will be recorded, including pulse oximetry. During the physical exam, a single examining physician from the larger group of study physicians will be responsible for recording findings for a given patient with emphasis on the respiratory exam. Chest retractions, nasal flaring, grunting, stridor, and accessory muscle use will be noted and characterized if present, along with any adventitious lung sounds appreciated by physician and study team member on chest auscultation. Degree of improvement after bronchodilators will also be recorded if administered. Additionally, signs of dehydration and malnutrition will be reported if present. Laboratory results will be recorded if evaluated by the ED and include complete blood count, electrolytes, and arterial blood gas.

Electronic Auscultation

Parents will be allowed to position the patient supine or upright. The study team member will listen to eight auscultation sites using a ThinkLabs ds32a Digital Stethoscope and mp3 recorder, for 10 seconds at each site, in the following order of placement: front top left and right, fronterolateral bottom right and left, back top right and left, and back bottom left and right (Figure 1). Auscultation will be performed at the participant's normal breathing patterns during recording without being asked to take deep breaths. We will allow only one repeat of auscultation if recording is interrupted for any reason or due to unacceptable signal quality of the first recording.

Lung ultrasound

All participants will receive bilateral lung ultrasonography carried out on SonoSite portable ultrasound machine with HFL38/13-6MHz and P17/5-1MHz MicroMaxx® transducers by a

single ultrasound technician who has been trained to the standardized protocol. Patients will be examined in the supine position with each hemithorax divided into six sections: 2 anterior, 2 lateral, and 2 posterior. The posterior area is defined from the posterior axillary line to the paravertebral line. Longitudinal and oblique scans will be obtained at each of the chest zones. Longitudinal scans allow visualization of the ribs with the pleural line under them[23]. Representative images from each section will be saved and later transferred to radiologists at an outside institution.

To assess for pneumonia, 2 of 3 radiologists must agree on the description of ultrasound images compatible with pneumonia. Consolidation will be determined by 1) the presence of hypo- or anechoic images with loss of distinct pleural lines and 2) an irregular shredded border of the pleural line that is distinct from the lung line, termed the "shred sign." Additional signs to be reported will include punctate hyperechoic images reflecting air bronchograms, decreased lung sliding, and homogenous, hypoechoic images in the pleural space corresponding to pleural effusions. Interstitial infiltrates will be determined by the presence of "lung rockets," which correlate to three or more B-lines in a longitudinal view between two ribs. Additional features to be reported include heterogenous echotexture, air and fluid bronchograms, lung pulse, and additional B-lines [23].

Chest radiography

All case participants will undergo chest radiography. We will attempt postero-anterior and lateral films but will allow an antero-posterior view if not possible. Digital images will be sent to a third party reading group blinded to clinical information. Using the WHO standardization of CXR interpretation for pediatric pneumonia [24], radiologists will comment on quality as adequate,

suboptimal, or unreadable and on the presence of pathology as consolidative or interstitial with or without pleural effusions. Radiographic evidence of pneumonia will be confirmed by agreement by 2 out of 3 radiologist reports for a given patient. Additional pathologic findings not previously characterized will also be recorded and reported to the patient's physician for further intervention if necessary.

Microbiological studies

Blood, urine, and nasopharyngeal samples will be collected according to our study design (Figure 2). Blood samples will be drawn for cultures and sensitivities. Urine will be tested for detection of pneumococcal antigen and stored for PCR. Nasopharyngeal swabs will be tested for respiratory viruses, along with culture and sensitivities. Respiratory pathogens tested by PCR will include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and respiratory syncytial virus.

Safety

~~In order to~~To ensure safety, the researcher collecting data is experienced with providing care to children. The researcher will use this experience to minimize any discomfort the children may have. All blood samples will be collected by a skilled nurse or phlebotomist.

We will adhere to hospital procedures for avoiding hospital acquired infections. We will wash hands with soap and water or alcohol-based hand sanitizer before patient contact. We will wear gloves, gowns and mask when required. We will clean the devices using alcohol swabs before and after each use.

Data quality and management

Prior to data collection, a Manual of Operations will be developed to ensure standardization and reliability and contain detailed instructions for all study procedures and guidelines for data collection. The manual will be revised as needed and distributed to members of the study team.

All data are recorded first on paper case report forms and subsequently double-entered using Microsoft ACCESS. Data sets will be cross-validated and errors corrected. Electronic lung recordings will be transferred from the mp3 player to participant-specific files on the study computer at least every other day and backed-up weekly. Digital CXR images will also be uploaded to these files and backed-up similarly.

Analysis of lung sounds and statistics

An important first step in CLSA is using common signal processing techniques to investigate high and low frequency information using methods such as the Short-time Fourier Transform (STFT), wavelet transforms, and P-spline bases. The second step will be extracting signal processing features to train the classifier.

Based on preliminary recordings to date performed by our group in Baltimore (Figure 3), we anticipate that wheeze can be characterized using features from the Fourier transform, such as the existence and temporal stability of tonal peaks in the 300-1000 Hz range, while crackles could be recognized using features such as amplitude, the presence of broad-band energy and the duration of this energy. Features such as the decrease in signal energy with frequency can characterize movement sounds. We have previously used time-frequency descriptors such as Mel-frequency cepstral coefficients as features and anticipate they will be useful for CLSA but may require temporal information as well. We will use the extracted features from signal processing analyses for classification using machine learning algorithms including: nearest

neighbor methods, support vector machines, random forests, and gradient boosting. Primary analysis will consist of a five-fold cross validation on the training set to calculate expected prediction errors. The training set will additionally be used to estimate areas under the curve for our diagnostic algorithm, including CLSA, WHO algorithm, imaging, and physical exam findings. Secondary analysis will include calculating sensitivities and specificities of experimental diagnostic US for detection of pneumonia when compared to gold standards (clinical diagnosis and CXR reading). Performance will be measured using logistic and multinomial regression, receiver operating characteristic curves, and area under the curve.

ETHICS AND DISSEMINATION

Approval was obtained from the Ethics Committees of A.B. PRISMA in Lima, Peru, El Instituto Nacional de Salud del Niño in Lima, Peru, and the Johns Hopkins University School of Medicine in Baltimore, MD. Written informed consent will be obtained from a parent or guardian. Any clinical information gained from participation in this study that could possibly change management will be given to the child's physician for his/her discretion. All data and sensitive information will be protected by being kept on encrypted devices or accessible only to study members.

Plans for dissemination include final publication following completion of the study following the STARD guidelines for reporting diagnostic accuracy[25]. We aim to develop a free online library of lung sounds for further enhancement of CLSA and the machine learning algorithm, as well as for future research and clinical education.

Funders have had no role in study design, nor will they have a role in the collection, management, analysis, and interpretation of data; manuscript preparation; and future

publications. The principal investigator will have ultimate authority over these aspects of research.

DISCUSSION

This study aims to investigate alternatives to improve the specificity of the WHO algorithm for pediatric pneumonia, namely electronic auscultation and chest ultrasonography. Utilizing electronic auscultation, we intend to characterize and analyze lung sounds associated with consolidative pneumonia, diffuse interstitial pneumonia, bronchiolitis, asthma, and upper respiratory infections, to determine if these diagnoses can be differentiated from normal through automated lung sounds, and to compare with chest ultrasound, WHO algorithm, and molecular testing for etiology. By reporting a protocol for CLSA, we hope to encourage standardization and expansion of recorded lung sounds via an online library for continued enhancement of machine learning as well as for continued scientific research and clinical education.

We foresee our greatest challenge in maximizing the quality of recorded lung sounds. To begin the study, we will utilize a commercial electronic stethoscope for recordings, which is identical in design to standard clinical stethoscopes. However, through sound processing using time-frequency analysis methods such as the Short-time Fourier Transform (STFT) and Continuous Wavelet Transforms (CWT), we hope to enhance the signal-to-noise ratio for data analysis and characterization. By examining additional features such as amplitude, we may also be better able to identify crackles and consolidation. We also plan to test alternative recording devices using piezoelectric microphones covered with a thin polymer that may be able to better capture lung sounds. Based on our recordings to date, we anticipate that wheeze can be differentiated from normal breath using features such as the existence and temporal stability of tonal peaks in the 300-1000 Hz range, while crackle should be recognizable using features such as the presence of broad-band energy and the duration of this energy. Features such as the decrease in signal energy with frequency can characterize movement sounds. We have

previously used time-frequency descriptors borrowed from speech processing (Mel-frequency cepstral coefficients and their time derivatives) and cough-specific time-domain features such as signal rise time and event duration and anticipate they will be useful for CLSA. We will use the extracted features from signal processing analyses for classification using machine learning algorithms such as nearest neighbor methods, support vector machines, or random forests.

The largest challenge in regards to lung ultrasound will likely be obtaining adequate quality of images and inter-user variability. To reduce variability, the study technician will be trained to systematically scan each subdivided hemithorax for pathologic findings described previously [9,23], and if possible, we will attempt lung ultrasound twice for each patient. Ultrasound also takes substantially longer compared to chest radiography because all areas must be adequately explored; therefore, it may be difficult for a child to be cooperative for that length of time. Through our large sample size and detailed methods, we aim to improve standardization of pediatric chest ultrasound and further define pathologic findings associated with disease, which may also lead to more efficient and faster scanning.

Limitations to this study center mostly on our case definitions for clinical diagnoses. As mentioned previously, there are no precise gold standards and as with many pediatric diseases, diagnosis is clinical. As such, our end points are determined by clinical exam findings by single examining physicians with additional confirmation via radiology for pneumonia cases only. We acknowledge the variability of observed findings among physicians but also accept that this is the mechanism of diagnosis in most clinical settings.

The WHO algorithm for case management of pediatric pneumonia lacks diagnostic specificity. While clinical information such as elevated heart rate and decreased oxygen saturation may aid in degree of illness and monitoring, these data also lack specificity required to

drastically improve case management. Lung ultrasound is also a promising tool and offers portability that is not available for radiography. Ultrasound has the added benefit of pleural effusion detection, which may prove an important adjunct to the electronic auscultation algorithm. However, cost and availability of skilled technicians may greatly hamper its utility in resource-poor settings, similar to microbiologic testing. Electronic auscultation is a simple, inexpensive tool that could have great diagnostic impact on ALRI in children worldwide. Through further research, we foresee utilizing this tool with pre-programmed computerized analysis to improve case management in developing countries.

COMPETING INTERESTS

All authors in the study report no competing interests.

AUTHORS' CONTRIBUTIONS

All authors were involved in the study design and writing of the manuscript, and all reviewed the final manuscript before submission. Laura Ellington directly contributed to study design, and is responsible for supervision of data gathering at the children's hospital in Lima, electronic auscultation and chest ultrasound recordings, data management, analysis, and writing of this manuscript. Robert Gilman provided mentorship to Laura Ellington and technical support for the study. James Tielsch and Mark Steinhoff contributed to the concept and study design. Dante Figueroa will serve as study physician, provide supervision and administrative oversight on site, and perform physical testing. Shalim Rodriguez contributed to study design and was responsible for developing and training the study technician to a standardized chest ultrasound protocol. Brian Caffo contributed to study design and will contribute to statistical analysis. Brian Tracey, Mounya Elhilali, and James West contributed to study design and will contribute significantly to signal processing and data analysis. William Checkley had ultimate oversight over study design and administration, and was equally responsible writing of the manuscript, and serves as mentor to Laura Ellington throughout the conduct of the study.

REFERENCES

1 Sazawal S, Black RE. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. *The Lancet Infectious Diseases* 2003;**3**:547–56.

2 Cardoso M-R a, Nascimento-Carvalho CM, Ferrero F, *et al.* Adding fever to WHO criteria for diagnosing pneumonia enhances the ability to identify pneumonia cases among wheezing children. *Archives of disease in childhood* 2011;**96**:58–61.

3 Puumalainen T, Quiambao B, Abucejo-Ladesma E, *et al.* Clinical case review: a method to improve identification of true clinical and radiographic pneumonia in children meeting the World Health Organization definition for pneumonia. *BMC infectious diseases* 2008;**8**:95.

4 Hazir T, Nisar YB, Qazi S a, *et al.* Chest radiography in children aged 2-59 months diagnosed with non-severe pneumonia as defined by World Health Organization: descriptive multicentre study in Pakistan. *BMJ (Clinical research ed)* 2006;**333**:629.

5 Hazir T, Nisar YB, Abbasi S, *et al.* Comparison of oral amoxicillin with placebo for the treatment of world health organization-defined nonsevere pneumonia in children aged 2-59 months: a multicenter, double-blind, randomized, placebo-controlled trial in Pakistan. *Clinical infectious diseases: an official publication of the Infectious Diseases Society of America* 2011;**52**:293–300.

6 Madico G, Gilman RH, Jabra A, *et al.* The role of pulse oximetry: its use as an indicator of severe respiratory disease in Peruvian children living at sea level. *Archives of Pediatrics and Adolescent Medicine* 1995;**149**:1259.

7 Schult S, Canelo-Aybar C. Oxygen saturation in healthy children aged 5 to 16 years residing in Huayllay, Peru at 4340□m. *High altitude medicine & biology* 2011;**12**:89–92.

8 Iuri D, De Candia a, Bazzocchi M. Evaluation of the lung in children with suspected pneumonia: usefulness of ultrasonography. *La Radiologia medica* 2009;**114**:321–30.

9 Parlamento S, Copetti R, Di S. Evaluation of lung ultrasound for the diagnosis of pneumonia in the ED. *European Respiratory Journal* 2009:379–84.

10 Yang PC, Luh KT, Chang DB, Yu CJ, Kuo SH WH. Ultrasonographic Evaluation of Pulmonary Consolidation. *American Review of Respiratory disease* 1992;**146**:757–62.

11 Su YH, Wang M, Block TM, *et al.* Transrenal DNA as a diagnostic tool: Important technical notes. *Annals of the New York Academy of Sciences* 2004;**1022**:81–9.

12 Gehmacher o, Mathis G, Kopf A, *et al.* Ultrasound imaging of pneumonia. U*ltrasound in med & biol* 1995;**21**:1119–22.

13 Lichtenstein D, Lascols N, Mezière G, *et al.* Ultrasound diagnosis of alveolar consolidation in the critically ill. *Intensive care medicine* 2004;**30**:276–81.

14 Murphy R, Vyshedskiy A, Charnitsky V, *et al.* Automated lung sound analysis in patients with pneumonia. *Respiratory Care* 2004;**49**:1490–07.

15 Grenier M, Gagnon K, Genest J, *et al.* Clinical comparison of acoustic and electronic stethoscopes and design of a new electronic stethoscope. *American Journal of Cardiology* 1998;**81**:653–6.

16 Gurung A, Scrafford C, Tielsch J, *et al.* Computerized lung sound analysis as a diagnostic aid for the detection of abnormal lung sounds: A systematic review and meta-analysis. *Respiratory Medicine* 2011;**doi:10.101**.

17 Abaza A a, Day JB, Reynolds JS, *et al.* Classification of voluntary cough sound and airflow patterns for detecting abnormal pulmonary function. *Cough (London, England)* 2009;**5**:8.

18 Reichert S, Gass R, Brandt C, *et al.* Analysis of respiratory sounds: state of the art. *Clinical medicine Circulatory, respiratory and pulmonary medicine* 2008;**2**:45–58.

19 Lu X, Bahoura M. An integrated automated system for crackles extraction and classification. *Biomedical Signal Processing and Control* 2008;**3**:244–54.

20 Marshall A, Boussakta S. Signal analysis of medical acoustics sounds with applications to chest medicine. *J Franklin Institute* 2007;**344**:230–42.

21 Taplidou S, Hadjileontiadis L, Kitsas I, *et al.* On applying continuous wavelet transform in wheeze analysis. *IEEE EMBS* 2004;:3832–5.

22 Saeed S, Body R. Auscultating to diagnose pneumonia. *EMJ* 2007;**24**:294–6.

23 Volpicelli G, Silva F, Radeos M. Real-time lung ultrasound for the diagnosis of alveolar consolidation and interstitial syndrome in the emergency department. *European Journal of Emergency Medicine* 2010;**17**:63–72.

24 Standardization of interpretation of chest radiographs for the diagnosis of pneumonia in children World Health Organization Pneumonia Vaccine Trial Investigators ' Group DEPARTMENT OF VACCINES. *World Health* 2001.

25 Bossuyt PM, Reitsma JB, Bruns DE, *et al.* Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *BMJ (Clinical research ed)* 2003;**326**:41–4.

Figure 1. Order of auscultation by electronic stethoscope. The study team member will listen to each site, starting with "A" for 10 seconds each.

Figure 2. Microbiology testing schematic.

Figure 3. Preliminary data suggest a difference in spectral analysis between children with and without wheeze. Short-time FFT analysis was utilized to visualize spectrograms of a normal control (A) and asthmatic child with active wheeze (B). Representative sample is from preliminary recordings taken from the Emergency Room at the Johns Hopkins Hospital in Baltimore, MD.

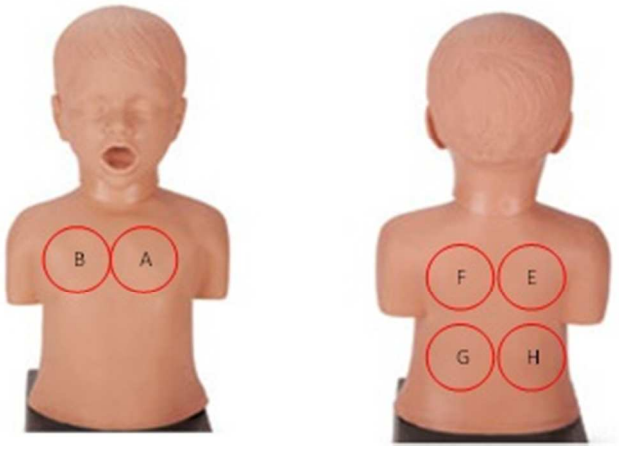
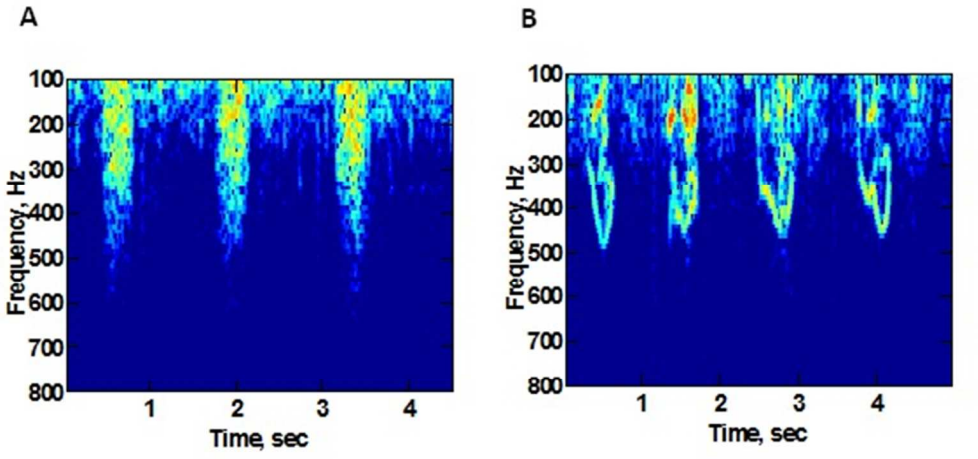


Figure 1. Order of auscultation by electronic stethoscope. The study team member will listen to each site, starting with "A" for 10 seconds each.
82x60mm (96 x 96 DPI)

Figure 2. Microbiology testing schematic.
165x218mm (96 x 96 DPI)



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151x74mm (96 x 96 DPI)

STARD checklist for reporting of studies of diagnostic accuracy

(version January 2003)

Section and Topic	Item #		On page #
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	1,2
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	8,9
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	11
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	11
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	11
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	10
Test methods	7	The reference standard and its rationale.	11,12
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	14-16
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	14-16
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	11-12, 14-16
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	11-12
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	18
	13	Methods for calculating test reproducibility, if done.	N/A
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	N/A
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	N/A
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	N/A
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	N/A
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	N/A
	19	A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	N/A
	20	Any adverse events from performing the index tests or the reference standard.	N/A
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	N/A
	22	How indeterminate results, missing data and outliers of the index tests were handled.	N/A
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centers, if done.	N/A
	24	Estimates of test reproducibility, if done.	N/A
DISCUSSION	25	Discuss the clinical applicability of the study findings.	N/A