



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

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3 **1 Computerized lung sound analysis to improve the specificity of pediatric pneumonia**
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5 **2 diagnosis in resource-poor settings: A case-control study**
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47
48 39 an electronic stethoscope, at discount.

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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.

STRENGTHS 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.

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6 60**ABSTRACT**

7
8 **Introduction:** The World Health Organization (WHO) case management algorithm for pediatric
9 pneumonia relies solely on symptoms of shortness of breath or cough and tachypnea for
10 treatment and has poor diagnostic specificity, tends to increase antibiotic resistance. Alternatives,
11 including oxygen saturation measurement, chest ultrasound, and chest auscultation exist but with
12 potential disadvantages. Electronic auscultation has potential for improved detection of pediatric
13 pneumonia but has yet to be standardized. We aim to investigate the use of electronic
14 auscultation to improve the specificity of the current WHO algorithm in developing countries.

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

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

26 **Discussion:** This study will develop standardized methods for electronic auscultation, and chest
27 ultrasound, and compare their utility for detection of pneumonia to standard approaches.
28 Utilizing signal processing techniques, we aim to characterize lung sounds and through machine
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3 82 learning, develop a classification system to distinguish pathologic sounds. Data will allow a
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6 83 better understanding of the benefits and limitations of novel diagnostic techniques in pediatric
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8 84 pneumonia.
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85

86 **INTRODUCTION**

87 Acute lower respiratory infection (ALRI) is the leading cause of death in children under 5 years
 88 of age. Pneumonia alone is responsible for killing 1.6 million children worldwide. The World
 89 Health Organization (WHO) developed a case management algorithm that relies solely on
 90 symptoms of shortness of breath or cough, an elevated respiratory rate, and chest indrawing for
 91 the diagnosis of pneumonia and administration of antibiotics and/or referral in resource-poor
 92 areas (Table 1). Where successfully implemented, this algorithm has resulted in a 30-40%

93 reduction in case mortality[1] but has

94 moderate sensitivity and poor specificity,

95 ranging from 16% for children presenting

96 with wheeze[2] and 49% for nonsevere

97 pneumonia to 95% for very severe

98 pneumonia[3]. Hazir and colleagues

99 demonstrated that over 80% of children

100 with WHO-defined non-severe pneumonia

101 had normal chest radiographs (CXR)[4]

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

102 and that the resulting case management was equivalent to no treatment in a randomized clinical
 103 trial[5], only further increasing concern for global antibiotic resistance.

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

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3 108 detection but these are not available in resource-poor settings around the world. Potential
4
5 109 alternatives exist within aspects of the physical exam and imaging. Supplementing oxygen
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8 110 saturation measurements with the current WHO algorithm has been shown to increase
9
10 111 specificity[6]; however, the normal range in healthy children varies with environmental factors
11
12 112 like altitude[7]. Another promising alternative for detection of pediatric pneumonia is lung
13
14 113 ultrasound. Ultrasound has the advantage of gathering information from multiple angles and the
15
16 114 ability to detect air-fluid differences that are present with pneumonia. Studies suggest that this
17
18 115 technique may be more sensitive than radiography and has the added benefit of lack of radiation;
19
20 116 however, these studies have all lacked power due to small sample size[8-13]. Cost and
21
22 117 availability of skilled ultrasound technicians may limit use in resource-poor settings. Chest
23
24 118 auscultation is a valuable tool for detection of respiratory pathology and is used widely in
25
26 119 clinical practice. However, limitations include inter-listener variability, subjectivity in the
27
28 120 interpretation of lung sounds[14,15], and lack of trained personnel in resource poor settings.
29
30 121 Electronic auscultation has the advantage of signal amplification and ambient noise reduction
31
32 122 leading to increased signal-to-noise ratio along with its independence on human ear sensitivity to
33
34 123 different acoustic frequencies. Furthermore, through computerized lung sound analysis (CLSA),
35
36 124 this diagnostic method results in discrete values from a final reading, thereby facilitating
37
38 125 standardization. With advancement in electronic stethoscopes and CLSA, there is great potential
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40 126 for improved diagnosis of pediatric pneumonia where multiple diagnostic tools are not readily
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42 127 available.
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50 128 In acoustic signal processing, the two commonly studied lung sounds are crackles and
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52 129 wheezes, which constitute unique temporal and frequency characteristics. Crackles have been
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54 130 most commonly associated with pneumonia, whereas wheezes are often observed in patients
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3 131 with asthma and bronchiolitis[16]. According to the Computerized Respiratory Sound Analysis
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5 132 (CORSA) Guidelines[17], the frequency of crackles is characterized in the spectrum of 200 to
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7
8 133 2000 Hz, while wheezes have a frequency spectrum of 100 to 1000 Hz. Wheezes have
9
10 134 continuous waveforms (>100 ms duration) with one or more tonal components and a dominant
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12 135 frequency greater than 400 Hz during the expiratory phase. Crackles are short (<20ms), non-
13
14 136 periodic waveforms with transitory sharp peaks and broadband frequency content during mid-
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16
17 137 inspiratory phase. Time-frequency decomposition of lung sounds provides useful information in
18
19 138 identifying and localizing adventitious lung sounds in a patient.

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21
22 139 Translating the CLSA characterization of abnormal lung sounds to clinical practice has
23
24 140 yet to be achieved. There are a few studies demonstrating potential, yet data is largely lacking,
25
26 141 especially in the field of pediatrics. Our group conducted a systematic review and meta-analysis
27
28 142 of studies using CLSA for the detection of a variety of respiratory disease in adults, which found
29
30 143 an overall sensitivity and specificity of 80% and 85%, respectively, when compared to
31
32 144 radiologically confirmed cases, with markedly limited results due to lack of quality and quantity
33
34 145 of available data, as well as lack of standardization[16,18-22].

35
36 146 In this study, we seek to utilize electronic auscultation to record lung sounds of children
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38 147 with various clinical diagnoses: pneumonia (diffuse interstitial and lobar), asthma, bronchiolitis,
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40 148 and upper respiratory infection (URI) in a tertiary care center in Lima, Peru, and determine
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42 149 whether they can be differentiated from normal lung sounds using CLSA. In addition, we aim to
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44 150 compare with imaging modalities of chest radiography and ultrasound. We hypothesize that not
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46 151 only will the sounds profiles of each pulmonary disease pathology differ from normal, but due to
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48 152 unique characteristics of lung sounds associated with bacterial pneumonia versus asthma,
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50 153 bronchiolitis or URI, CLSA may allow differentiation of various acute lower respiratory disease
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3 154 processes. With this information in conjunction with additional basic clinical information (i.e.
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6 155 temperature, respiratory rate, oxygen saturation), we believe that a much needed improvement in
7
8 156 the detection and case management of pediatric pneumonia is possible.
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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.

167

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

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3 180 completing our testing set for external validity and comparing CLSA with the current WHO
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5 181 algorithm and other diagnostic tools such as physical exam findings, chest ultrasound, and
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8 182 microbiologic testing, in order to construct an improved algorithm for pneumonia diagnosis.
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12 13 184 **Study population**

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15 185 Children from 2 to 59 months of age presenting to the ED or in the asthma or pulmonary ward
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17 186 without history of chronic lung disease, excluding asthma, or significant cardiac disease will be
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20 187 invited to participate in the study. Children with respiratory complaints will be invited to
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22 188 participate as potential cases, while those without respiratory complaints and no acute respiratory
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24 189 illness within one month of presentation will be invited to join the study as controls.

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27 190 Children will be considered eligible if their parents or guardians are able to provide
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29 191 written informed consent, and they themselves do not require airway management or non-
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31 192 invasive ventilation. Children will be considered ineligible if they have chronic lung diseases
32
33 193 other than asthma, such as cystic fibrosis, bronchiectasis, and chronic lung disease of prematurity
34
35 194 or significant congenital heart disease. Patients will be considered ineligible post-consent if they
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37 195 were found to have more than one active respiratory diagnosis upon further testing. Group
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39 196 classification also may be modified post-consent and further enrollment required depending on
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41 197 chest x-ray (CXR) final readings and microbiological testing for diagnosis.
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48 199 **Outcomes and case definitions**

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50 200 Because there is no gold standard for diagnosis, we aim to compare our results with common
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52 201 case definitions and clinical diagnoses by experienced physicians. Secondary outcomes will
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202 incorporate etiology information from standard culture and molecular techniques; however, these
203 additional data will not serve as the gold standard.

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

213

214 **Sample size**

215 Our recruitment goal is 600 subjects, 100 each with consolidative pneumonia, diffuse interstitial
216 pneumonia, asthma, bronchiolitis, URI, and normal lungs. Sample size was powered to improve
217 specificity of the WHO algorithm upon the addition of electronic auscultation. To detect an
218 improvement in diagnostic specificity from 50% (WHO algorithm for pediatric pneumonia) to
219 80% (CLSA and WHO algorithm) with 95% power and α of 0.05 between pneumonia and non-
220 pneumonia cases, we require 70 patients per group in the training set. We will also recruit a test
221 set consisting of an additional 30 patients per group (30% of total sample) to estimate areas
222 under the curve for our diagnostic algorithm. Each group will be over-enrolled by twenty to
223 account for post-consent ineligibility, for a total of 720.

224

225 **Study organization**

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

236

237 **Questionnaire**

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

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247 **Physical exam and laboratory testing**

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3 248 The initial set of vital signs will be recorded, including pulse oximetry. During the physical
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5 249 exam, a single examining physician from the larger group of study physicians will be responsible
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8 250 for recording findings for a given patient with emphasis on the respiratory exam. Chest
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10 251 retractions, nasal flaring, grunting, stridor, and accessory muscle use will be noted and
11
12 252 characterized if present, along with any adventitious lung sounds appreciated by physician and
13
14 253 study team member on chest auscultation. Degree of improvement after bronchodilators will also
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16 254 be recorded if administered. Additionally, signs of dehydration and malnutrition will be reported
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18 255 if present. Laboratory results will be recorded if evaluated by the ED and include complete blood
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20 256 count, electrolytes, and arterial blood gas.
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258 **Electronic Auscultation**

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

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

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3 271 single ultrasound technician who has been trained to the standardized protocol. Patients will be
4
5 272 examined in the supine position with each hemithorax divided into six sections: 2 anterior, 2
6
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8 273 lateral, and 2 posterior. The posterior area is defined from the posterior axillary line to the
9
10 274 paravertebral line. Longitudinal and oblique scans will be obtained at each of the chest zones.
11
12 275 Longitudinal scans allow visualization of the ribs with the pleural line under them[23].
13
14 276 Representative images from each section will be saved and later transferred to radiologists at an
15
16 277 outside institution.
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20 278 To assess for pneumonia, 2 of 3 radiologists must agree on the description of ultrasound
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22 279 images compatible with pneumonia. Consolidation will be determined by 1) the presence of
23
24 280 hypo- or anechoic images with loss of distinct pleural lines and 2) an irregular shredded border
25
26
27 281 of the pleural line that is distinct from the lung line, termed the “shred sign.” Additional signs to
28
29 282 be reported will include punctate hyperechoic images reflecting air bronchograms, decreased
30
31 283 lung sliding, and homogenous, hypoechoic images in the pleural space corresponding to pleural
32
33 284 effusions. Interstitial infiltrates will be determined by the presence of “lung rockets,” which
34
35 285 correlate to three or more B-lines in a longitudinal view between two ribs. Additional features to
36
37 286 be reported include heterogenous echotexture, air and fluid bronchograms, lung pulse, and
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39 287 additional B-lines [23].
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45 289 **Chest radiography**

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47 290 All case participants will undergo chest radiography. We will attempt postero-anterior and lateral
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49 291 films but will allow an antero-posterior view if not possible. Digital images will be sent to a third
50
51 292 party reading group blinded to clinical information. Using the WHO standardization of CXR
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53 293 interpretation for pediatric pneumonia [24], radiologists will comment on quality as adequate,
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3 294 suboptimal, or unreadable and on the presence of pathology as consolidative or interstitial with
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6 295 or without pleural effusions. Radiographic evidence of pneumonia will be confirmed by
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8 296 agreement by 2 out of 3 radiologist reports for a given patient. Additional pathologic findings not
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11 297 previously characterized will also be recorded and reported to the patient's physician for further
12
13 298 intervention if necessary.

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17 300 **Microbiological studies**

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20 301 Blood, urine, and nasopharyngeal samples will be collected according to our study design
21
22 302 (Figure 2). Blood samples will be drawn for cultures and sensitivities. Urine will be tested for
23
24 303 detection of pneumococcal antigen and stored for PCR. Nasopharyngeal swabs will be tested for
25
26 304 respiratory viruses, along with culture and sensitivities. Respiratory pathogens tested by PCR
27
28
29 305 will include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and respiratory syncytial virus.
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34 307 **Safety**

35
36 308 In order to ensure safety, the researcher collecting data is experienced with providing care to
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38 309 children. The researcher will use this experience to minimize any discomfort the children may
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40
41 310 have. All blood samples will be collected by a skilled nurse or phlebotomist.

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43 311 We will adhere to hospital procedures for avoiding hospital acquired infections. We will
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45 312 wash hands with soap and water or alcohol-based hand sanitizer before patient contact. We will
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48 313 wear gloves, gowns and mask when required. We will clean the devices using alcohol swabs
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51 314 before and after each use.

52 315

55 316 **Data quality and management**

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3 317 Prior to data collection, a Manual of Operations will be developed to ensure standardization and
4
5 318 reliability and contain detailed instructions for all study procedures and guidelines for data
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8 319 collection. The manual will be revised as needed and distributed to members of the study team.
9

10 320 All data are recorded first on paper case report forms and subsequently double-entered
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12 321 using Microsoft ACCESS. Data sets will be cross-validated and errors corrected. Electronic lung
13
14 322 recordings will be transferred from the mp3 player to participant-specific files on the study
15
16 323 computer at least every other day and backed-up weekly. Digital CXR images will also be
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18 324 uploaded to these files and backed-up similarly.
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23 24 326 **Analysis of lung sounds and statistics**

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26
27 327 An important first step in CLSA is using common signal processing techniques to investigate
28
29 328 high and low frequency information using methods such as the Short-time Fourier Transform
30
31 329 (STFT), wavelet transforms, and P-spline bases. The second step will be extracting signal
32
33 330 processing features to train the classifier.
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36 331 Based on preliminary recordings to date performed by our group in Baltimore (Figure 3),
37
38 332 we anticipate that wheeze can be characterized using features from the Fourier transform, such as
39
40 333 the existence and temporal stability of tonal peaks in the 300-1000 Hz range, while crackles
41
42 334 could be recognized using features such as amplitude, the presence of broad-band energy and the
43
44 335 duration of this energy. Features such as the decrease in signal energy with frequency can
45
46 336 characterize movement sounds. We have previously used time-frequency descriptors such as
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48 337 Mel-frequency cepstral coefficients as features and anticipate they will be useful for CLSA but
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50 338 may require temporal information as well. We will use the extracted features from signal
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52 339 processing analyses for classification using machine learning algorithms including: nearest
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3 340 neighbor methods, support vector machines, random forests, and gradient boosting. Primary
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5 341 analysis will consist of a five-fold cross validation on the training set to calculate expected
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8 342 prediction errors. The training set will additionally be used to estimate areas under the curve for
9
10 343 our diagnostic algorithm, including CLSA, WHO algorithm, imaging, and physical exam
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12 344 findings. Secondary analysis will include calculating sensitivities and specificities of
13
14 345 experimental diagnostic US for detection of pneumonia when compared to gold standards
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16
17 346 (clinical diagnosis and CXR reading). Performance will be measured using logistic and
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19 347 multinomial regression, receiver operating characteristic curves, and area under the curve.
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23 24 349 **ETHICS AND DISSEMINATION**

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27 350 Approval was obtained from the Ethics Committees of A.B. PRISMA in Lima, Peru, El Instituto
28
29 351 Nacional de Salud del Niño in Lima, Peru, and the Johns Hopkins University School of Medicine
30
31 352 in Baltimore, MD. Written informed consent will be obtained from a parent or guardian. Any
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33 353 clinical information gained from participation in this study that could possibly change
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35 354 management will be given to the child's physician for his/her discretion. All data and sensitive
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37 355 information will be protected by being kept on encrypted devices or accessible only to study
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39 356 members.
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43 357 Plans for dissemination include final publication following completion of the study
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45 358 following the STARD guidelines for reporting diagnostic accuracy[25]. We aim to develop a free
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47 359 online library of lung sounds for further enhancement of CLSA and the machine learning
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49 360 algorithm, as well as for future research and clinical education.
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5 362 **DISCUSSION**

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8 363 This study aims to investigate alternatives to improve the specificity of the WHO algorithm for
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10 364 pediatric pneumonia, namely electronic auscultation and chest ultrasonography. Utilizing
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12 365 electronic auscultation, we intend to characterize and analyze lung sounds associated with
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14 366 consolidative pneumonia, diffuse interstitial pneumonia, bronchiolitis, asthma, and upper
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16 367 respiratory infections, to determine if these diagnoses can be differentiated from normal through
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18 368 automated lung sounds, and to compare with chest ultrasound, WHO algorithm, and molecular
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20 369 testing for etiology. By reporting a protocol for CLSA, we hope to encourage standardization and
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22 370 expansion of recorded lung sounds via an online library for continued enhancement of machine
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24 371 learning as well as for continued scientific research and clinical education.

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27 372 We foresee our greatest challenge in maximizing the quality of recorded lung sounds. To
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29 373 begin the study, we will utilize a commercial electronic stethoscope for recordings, which is
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31 374 identical in design to standard clinical stethoscopes. However, through sound processing using
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33 375 time-frequency analysis methods such as the Short-time Fourier Transform (STFT) and
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35 376 Continuous Wavelet Transforms (CWT), we hope to enhance the signal-to-noise ratio for data
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37 377 analysis and characterization. By examining additional features such as amplitude, we may also
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39 378 be better able to identify crackles and consolidation. We also plan to test alternative recording
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41 379 devices using piezoelectric microphones covered with a thin polymer that may be able to better
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43 380 capture lung sounds. Based on our recordings to date, we anticipate that wheeze can be
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45 381 differentiated from normal breath using features such as the existence and temporal stability of
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47 382 tonal peaks in the 300-1000 Hz range, while crackle should be recognizable using features such
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49 383 as the presence of broad-band energy and the duration of this energy. Features such as the
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3 384 decrease in signal energy with frequency can characterize movement sounds. We have
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6 385 previously used time-frequency descriptors borrowed from speech processing (Mel-frequency
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8 386 cepstral coefficients and their time derivatives) and cough-specific time-domain features such as
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10 387 signal rise time and event duration and anticipate they will be useful for CLSA. We will use the
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12 388 extracted features from signal processing analyses for classification using machine learning
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14 389 algorithms such as nearest neighbor methods, support vector machines, or random forests.

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18 390 The largest challenge in regards to lung ultrasound will likely be obtaining adequate
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20 391 quality of images and inter-user variability. To reduce variability, the study technician will be
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22 392 trained to systematically scan each subdivided hemithorax for pathologic findings described
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24 393 previously [9,23], and if possible, we will attempt lung ultrasound twice for each patient.

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27 394 Ultrasound also takes substantially longer compared to chest radiography because all areas must
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29 395 be adequately explored; therefore, it may be difficult for a child to be cooperative for that length
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31 396 of time. Through our large sample size and detailed methods, we aim to improve standardization
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33 397 of pediatric chest ultrasound and further define pathologic findings associated with disease,
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35 398 which may also lead to more efficient and faster scanning.

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39 399 Limitations to this study center mostly on our case definitions for clinical diagnoses. As
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41 400 mentioned previously, there are no precise gold standards and as with many pediatric diseases,
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43 401 diagnosis is clinical. As such, our end points are determined by clinical exam findings by single
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45 402 examining physicians with additional confirmation via radiology for pneumonia cases only. We
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47 403 acknowledge the variability of observed findings among physicians but also accept that this is
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49 404 the mechanism of diagnosis in most clinical settings.

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53 405 The WHO algorithm for case management of pediatric pneumonia lacks diagnostic
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55 406 specificity. While clinical information such as elevated heart rate and decreased oxygen
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3 407 saturation may aid in degree of illness and monitoring, these data also lack specificity required to
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6 408 drastically improve case management. Lung ultrasound is also a promising tool and offers
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8 409 portability that is not available for radiography. Ultrasound has the added benefit of pleural
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10 410 effusion detection, which may prove an important adjunct to the electronic auscultation
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12 411 algorithm. However, cost and availability of skilled technicians may greatly hamper its utility in
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14 412 resource-poor settings, similar to microbiologic testing. Electronic auscultation is a simple,
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16 413 inexpensive tool that could have great diagnostic impact on ALRI in children worldwide.
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18 414 Through further research, we foresee utilizing this tool with pre-programmed computerized
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20 415 analysis to improve case management in developing countries.
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417 **COMPETING INTERESTS**

418 All authors in the study report no competing interests.

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4 420 **AUTHORS' CONTRIBUTIONS**

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7 421 All authors were involved in the study design and writing of the manuscript, and all reviewed the
8
9 422 final manuscript before submission. Laura Ellington directly contributed to study design, and is
10
11 423 responsible for supervision of data gathering at the children's hospital in Lima, electronic
12
13 424 auscultation and chest ultrasound recordings, data management, analysis, and writing of this
14
15 425 manuscript. Robert Gilman provided mentorship to Laura Ellington and technical support for the
16
17 426 study. James Tielsch and Mark Steinhoff contributed to the concept and study design. Dante
18
19 427 Figueroa will serve as study physician, provide supervision and administrative oversight on site,
20
21 428 and perform physical testing. Shalim Rodriguez contributed to study design and was responsible
22
23 429 for developing and training the study technician to a standardized chest ultrasound protocol.
24
25 430 Brian Caffo contributed to study design and will contribute to statistical analysis. Brian Tracey,
26
27 431 Mounya Elhilali, and James West contributed to study design and will contribute significantly to
28
29 432 signal processing and data analysis. William Checkley had ultimate oversight over study design
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31 433 and administration, and was equally responsible writing of the manuscript, and serves as mentor
32
33 434 to Laura Ellington throughout the conduct of the study.
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3 501 **Figure 1. Order of auscultation by electronic stethoscope.** The study team member will listen
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6 502 to each site, starting with “A” for 10 seconds each.
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10 504 **Figure 2. Microbiology testing schematic.**
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15 506 **Figure 3. Preliminary data suggest a difference in spectral analysis between children with**
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17 507 **and without wheeze.** Short-time FFT analysis was utilized to visualize spectrograms of a normal
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19 508 control (A) and asthmatic child with active wheeze (B). Representative sample is from
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21 509 preliminary recordings taken from the Emergency Room at the Johns Hopkins Hospital in
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Figure 2. Microbiology testing schematic. 165x218mm (96 x 96 DPI)

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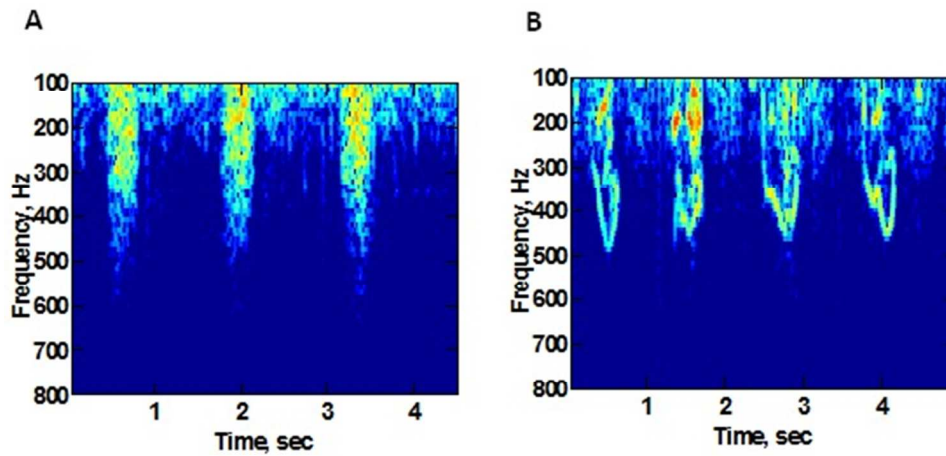


Figure 3. Preliminary data suggest a difference in spectral analysis between children with and without wheeze. Short-time FFT analysis was utilized to visualize spectrograms of a normal control (A) and asthmatic child with active wheeze (B). Representative sample is from preliminary recordings taken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

review only

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			
<i>Participants</i>	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
<i>Test methods</i>	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
<i>Statistical methods</i>	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			
<i>Participants</i>	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
<i>Test results</i>	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
<i>Estimates</i>	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

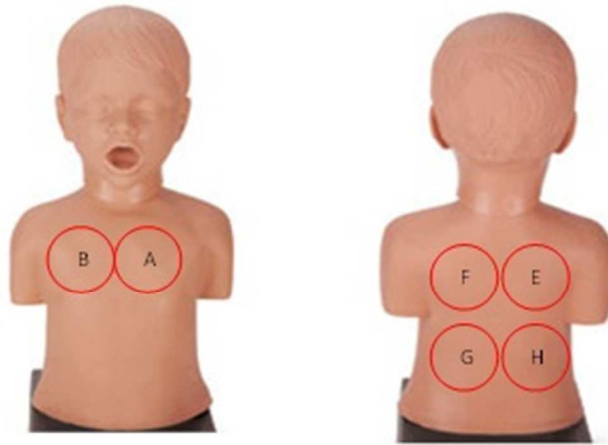


Figure 1. Order of auscultation by electronic stethoscope. The study team member will listen to each site, starting with "A" for 10 seconds each.
82x60mm (96 x 96 DPI)

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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

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2011-000506.R1
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Manuscripts

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3 1 **Computerized lung sound analysis to improve the specificity of pediatric pneumonia**
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5 2 **diagnosis in resource-poor settings: Protocol and methods for an observational study**
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10 4 Laura E Ellington (1), Robert H Gilman (2, 3), James M Tielsch (2), Mark Steinhoff (2, 4),
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12 5 Dante Figueroa (5), Shalim Rodriguez (6), Brian Caffo (7), Brian Tracey (8), Mounya Elhilali
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14 6 (9), James West (9), William Checkley (1).
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22 28 **Word count:** 3,887.
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27 30 **Keywords:** Electronic auscultation; sensitivity and specificity; pneumonia; diagnosis
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29 31 [subheading]; child
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44

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46

47 39 an electronic stethoscope, at discount.
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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.

STRENGTHS 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

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

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84 INTRODUCTION

85 Acute lower respiratory infection (ALRI) is the leading cause of death in children under 5 years
 86 of age. Pneumonia alone is responsible for killing 1.6 million children worldwide. The World
 87 Health Organization (WHO) developed a case management algorithm that relies solely on
 88 symptoms of shortness of breath or cough, an elevated respiratory rate, and chest indrawing for
 89 the diagnosis of pneumonia and administration of antibiotics and/or referral in resource-poor
 90 areas (Table 1). Where successfully implemented, this algorithm has resulted in a 30-40%
 91 reduction in case mortality[1] but has

92 moderate sensitivity and poor specificity,
 93 ranging from 16% for children presenting
 94 with wheeze[2] and 49% for nonsevere
 95 pneumonia to 95% for very severe
 96 pneumonia[3]. Hazir and colleagues
 97 demonstrated that over 80% of children
 98 with WHO-defined non-severe pneumonia
 99 had normal chest radiographs (CXR)[4]

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

100 and that the resulting case management was equivalent to no treatment in a randomized clinical
 101 trial[5], only further increasing concern for global antibiotic resistance.

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

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5 108 saturation measurements with the current WHO algorithm has been shown to increase
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8 109 specificity[6]; however, the normal range in healthy children varies with environmental factors
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10 110 like altitude[7]. Another promising alternative for detection of pediatric pneumonia is lung
11
12 111 ultrasound. Ultrasound has the advantage of gathering information from multiple angles and the
13
14 112 ability to detect air-fluid differences that are present with pneumonia. Studies suggest that this
15
16 113 technique may be more sensitive than radiography and has the added benefit of lack of radiation;
17
18 114 however, these studies have all lacked power due to small sample size[8-13]. Cost and
19
20 115 availability of skilled ultrasound technicians may limit use in resource-poor settings. Chest
21
22 116 auscultation is a valuable tool for detection of respiratory pathology and is used widely in
23
24 117 clinical practice. However, limitations include inter-listener variability, subjectivity in the
25
26 118 interpretation of lung sounds[14,15], and lack of trained personnel in resource poor settings.
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28 119 Electronic auscultation has the advantage of signal amplification and ambient noise reduction
29
30 120 leading to increased signal-to-noise ratio along with its independence on human ear sensitivity to
31
32 121 different acoustic frequencies. Furthermore, through computerized lung sound analysis (CLSA),
33
34 122 this diagnostic method results in discrete values from a final reading, thereby facilitating
35
36 123 standardization. With advancement in electronic stethoscopes and CLSA, there is great potential
37
38 124 for improved diagnosis of pediatric pneumonia where multiple diagnostic tools are not readily
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40 125 available.

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43 126 In acoustic signal processing, the two commonly studied lung sounds are crackles and
44
45 127 wheezes, which constitute unique temporal and frequency characteristics. Crackles have been
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47 128 most commonly associated with pneumonia, whereas wheezes are often observed in patients
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49 129 with asthma and bronchiolitis[16]. According to the Computerized Respiratory Sound Analysis
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3 130 (CORSA) Guidelines[17], the frequency of crackles is characterized in the spectrum of 200 to
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5 131 2000 Hz, while wheezes have a frequency spectrum of 100 to 1000 Hz. Wheezes have
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8 132 continuous waveforms (>100 ms duration) with one or more tonal components and a dominant
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10 133 frequency greater than 400 Hz during the expiratory phase. Crackles are short (<20ms), non-
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12 134 periodic waveforms with transitory sharp peaks and broadband frequency content during mid-
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14 135 inspiratory phase. Time-frequency decomposition of lung sounds provides useful information in
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16 136 identifying and localizing adventitious lung sounds in a patient.
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20 137 Translating the CLSA characterization of abnormal lung sounds to clinical practice has
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22 138 yet to be achieved. There are a few studies demonstrating potential, yet data is largely lacking,
23
24 139 especially in the field of pediatrics. Our group conducted a systematic review and meta-analysis
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26 140 of studies using CLSA for the detection of a variety of respiratory disease in adults, which found
27
28 141 an overall sensitivity and specificity of 80% and 85%, respectively, when compared to
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30 142 radiologically confirmed cases, with markedly limited results due to lack of quality and quantity
31
32 143 of available data, as well as lack of standardization[16,18-22].
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36 144 In this study, we seek to utilize electronic auscultation to record lung sounds of children
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38 145 with various clinical diagnoses: pneumonia (diffuse interstitial and lobar), asthma, bronchiolitis,
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40 146 and upper respiratory infection (URI) in a tertiary care center in Lima, Peru, and determine
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42 147 whether they can be differentiated from normal lung sounds using CLSA. In addition, we aim to
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44 148 compare with imaging modalities of chest radiography and ultrasound. We hypothesize that not
45
46 149 only will the sounds profiles of each pulmonary disease pathology differ from normal, but due to
47
48 150 unique characteristics of lung sounds associated with bacterial pneumonia versus asthma,
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50 151 bronchiolitis or URI, CLSA may allow differentiation of various acute lower respiratory disease
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52 152 processes. With this information in conjunction with additional basic clinical information (i.e.
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153 temperature, respiratory rate, oxygen saturation), we believe that a much needed improvement in
154 the detection and case management of pediatric pneumonia is possible.

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155 **METHODS**

156 **Study objectives**

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

165 **Study design**

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

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

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

180

181 **Study population**

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

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

195

196 **Outcomes and case definitions**

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

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3 201 Pneumonia will be initially categorized upon clinical diagnosis by examining
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5 202 pediatricians at El Instituto Nacional de Salud del Niño and further characterized as
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7 203 consolidative or diffuse interstitial pneumonia given final CXR reading by blinded radiologists
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9 204 from the Johns Hopkins University. Asthma will be defined by the presence of wheeze on
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11 205 physical exam, history of asthma, and improvement with bronchodilators. Bronchiolitis will be
12
13 206 defined as the presence of wheeze and difficulty breathing on physical exam and viral symptoms
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15 207 (cough, rhinorrhea), no history of asthma, and little or no improvement with bronchodilators if
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17 208 attempted. URI will be defined as respiration rate less than 50 breaths per minute and associated
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19 209 with one or more of the following: clear nasal secretions, sore or red throat, or hoarseness.
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27 211 **Sample size**

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29 212 Our recruitment goal is 600 subjects, 100 each with consolidative pneumonia, diffuse interstitial
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31 213 pneumonia, asthma, bronchiolitis, URI, and normal lungs. Sample size was powered to improve
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33 214 specificity of the WHO algorithm upon the addition of electronic auscultation. To detect an
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35 215 improvement in diagnostic specificity from 50% (WHO algorithm for pediatric pneumonia) to
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37 216 80% (CLSA and WHO algorithm) with 95% power and α of 0.05 between pneumonia and non-
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39 217 pneumonia cases, we require 70 patients per group in the training set. We will also recruit a test
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41 218 set consisting of an additional 30 patients per group (30% of total sample) to estimate areas
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43 219 under the curve for our diagnostic algorithm. Each group will be over-enrolled by twenty to
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45 220 account for post-consent ineligibility, for a total of 720.
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53 222 **Study organization**

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3 223 A.B. PRISMA in Lima, Peru, and Johns Hopkins University in Baltimore, USA, will provide
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5 224 administrative oversight for the study. There will be a research coordinator at a central location
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8 225 in Lima, Peru, who will provide logistical support and management of the study team. Instituto
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10 226 Nacional de Salud del Niño will provide a team of study nurses and physicians to carry out
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12 227 recruitment, physical examination, and collection of specimens. We have also established prior
13
14 228 training by an experienced ultrasonographer to conduct chest ultrasonography. A
15
16 229 multidisciplinary team of clinicians, field epidemiologists, acoustical engineers, and
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18 230 biostatisticians from Johns Hopkins University, Tufts University, Cincinnati Children's Hospital,
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20 231 and Instituto Nacional de Salud del Niño will be involved with study design and conduct,
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22 232 statistical analysis, and reporting of results.
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29 234 **Questionnaire**

30
31 235 We will ask the parent or guardian about the child's past medical history, environmental
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33 236 exposures, access to healthcare, and current respiratory symptoms. We will inquire about
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35 237 demographic information, nutrition, and vaccination history. We will ask about co-morbidities,
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37 238 family history, and developmental history. Environmental questions pertained to housing,
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39 239 number of children, rural versus urban living, parent occupations, smoke and allergen exposure,
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41 240 and sick contacts. Current respiratory symptoms were asked of the parent or guardian to answer
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43 241 subjectively and included rapid breathing, difficulty breathing, chest indrawing, cyanosis, cough,
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45 242 sputum production, audible breath sounds, and subjective fever.
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53 244 **Physical exam and laboratory testing**

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3 245 The initial set of vital signs will be recorded, including pulse oximetry. During the physical
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5 246 exam, a single examining physician from the larger group of study physicians will be responsible
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8 247 for recording findings for a given patient with emphasis on the respiratory exam. Chest
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10 248 retractions, nasal flaring, grunting, stridor, and accessory muscle use will be noted and
11
12 249 characterized if present, along with any adventitious lung sounds appreciated by physician and
13
14 250 study team member on chest auscultation. Degree of improvement after bronchodilators will also
15
16 251 be recorded if administered. Additionally, signs of dehydration and malnutrition will be reported
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18 252 if present. Laboratory results will be recorded if evaluated by the ED and include complete blood
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20 253 count, electrolytes, and arterial blood gas.
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27 255 **Electronic Auscultation**

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29 256 Parents will be allowed to position the patient supine or upright. The study team member will
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31 257 listen to eight auscultation sites using a ThinkLabs ds32a Digital Stethoscope and mp3 recorder,
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33 258 for 10 seconds at each site, in the following order of placement: front top left and right,
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35 259 fronterolateral bottom right and left, back top right and left, and back bottom left and right
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37 260 (Figure 1). Auscultation will be performed at the participant's normal breathing patterns during
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39 261 recording without being asked to take deep breaths. We will allow only one repeat of
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41 262 auscultation if recording is interrupted for any reason or due to unacceptable signal quality of the
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43 263 first recording.
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50 265 **Lung ultrasound**

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52 266 All participants will receive bilateral lung ultrasonography carried out on SonoSite portable
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54 267 ultrasound machine with HFL38/13-6MHz and P17/5-1MHz MicroMaxx® transducers by a
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3 268 single ultrasound technician who has been trained to the standardized protocol. Patients will be
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5 269 examined in the supine position with each hemithorax divided into six sections: 2 anterior, 2
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8 270 lateral, and 2 posterior. The posterior area is defined from the posterior axillary line to the
9
10 271 paravertebral line. Longitudinal and oblique scans will be obtained at each of the chest zones.
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12 272 Longitudinal scans allow visualization of the ribs with the pleural line under them[23].
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14 273 Representative images from each section will be saved and later transferred to radiologists at an
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16 274 outside institution.
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20 275 To assess for pneumonia, 2 of 3 radiologists must agree on the description of ultrasound
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22 276 images compatible with pneumonia. Consolidation will be determined by 1) the presence of
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24 277 hypo- or anechoic images with loss of distinct pleural lines and 2) an irregular shredded border
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27 278 of the pleural line that is distinct from the lung line, termed the “shred sign.” Additional signs to
28
29 279 be reported will include punctate hyperechoic images reflecting air bronchograms, decreased
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31
32 280 lung sliding, and homogenous, hypoechoic images in the pleural space corresponding to pleural
33
34 281 effusions. Interstitial infiltrates will be determined by the presence of “lung rockets,” which
35
36 282 correlate to three or more B-lines in a longitudinal view between two ribs. Additional features to
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39 283 be reported include heterogenous echotexture, air and fluid bronchograms, lung pulse, and
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41 284 additional B-lines [23].
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46 286 **Chest radiography**

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48 287 All case participants will undergo chest radiography. We will attempt postero-anterior and lateral
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50 288 films but will allow an antero-posterior view if not possible. Digital images will be sent to a third
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53 289 party reading group blinded to clinical information. Using the WHO standardization of CXR
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55 290 interpretation for pediatric pneumonia [24], radiologists will comment on quality as adequate,
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3 291 suboptimal, or unreadable and on the presence of pathology as consolidative or interstitial with
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6 292 or without pleural effusions. Radiographic evidence of pneumonia will be confirmed by
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8 293 agreement by 2 out of 3 radiologist reports for a given patient. Additional pathologic findings not
9
10 294 previously characterized will also be recorded and reported to the patient's physician for further
11
12 295 intervention if necessary.
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297 **Microbiological studies**

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20 298 Blood, urine, and nasopharyngeal samples will be collected according to our study design
21
22 299 (Figure 2). Blood samples will be drawn for cultures and sensitivities. Urine will be tested for
23
24 300 detection of pneumococcal antigen and stored for PCR. Nasopharyngeal swabs will be tested for
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26 301 respiratory viruses, along with culture and sensitivities. Respiratory pathogens tested by PCR
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28 302 will include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and respiratory syncytial virus.
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304 **Safety**

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36 305 To ensure safety, the researcher collecting data is experienced with providing care to children.
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38 306 The researcher will use this experience to minimize any discomfort the children may have. All
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40 307 blood samples will be collected by a skilled nurse or phlebotomist.
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43 308 We will adhere to hospital procedures for avoiding hospital acquired infections. We will
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45 309 wash hands with soap and water or alcohol-based hand sanitizer before patient contact. We will
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47 310 wear gloves, gowns and mask when required. We will clean the devices using alcohol swabs
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49 311 before and after each use.
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313 **Data quality and management**

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3 314 Prior to data collection, a Manual of Operations will be developed to ensure standardization and
4
5 315 reliability and contain detailed instructions for all study procedures and guidelines for data
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8 316 collection. The manual will be revised as needed and distributed to members of the study team.
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10 317 All data are recorded first on paper case report forms and subsequently double-entered
11
12 318 using Microsoft ACCESS. Data sets will be cross-validated and errors corrected. Electronic lung
13
14 319 recordings will be transferred from the mp3 player to participant-specific files on the study
15
16 320 computer at least every other day and backed-up weekly. Digital CXR images will also be
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18 321 uploaded to these files and backed-up similarly.
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23 24 323 **Analysis of lung sounds and statistics**

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27 324 An important first step in CLSA is using common signal processing techniques to investigate
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29 325 high and low frequency information using methods such as the Short-time Fourier Transform
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31 326 (STFT), wavelet transforms, and P-spline bases. The second step will be extracting signal
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33 327 processing features to train the classifier.
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36 328 Based on preliminary recordings to date performed by our group in Baltimore (Figure 3),
37
38 329 we anticipate that wheeze can be characterized using features from the Fourier transform, such as
39
40 330 the existence and temporal stability of tonal peaks in the 300-1000 Hz range, while crackles
41
42 331 could be recognized using features such as amplitude, the presence of broad-band energy and the
43
44 332 duration of this energy. Features such as the decrease in signal energy with frequency can
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46 333 characterize movement sounds. We have previously used time-frequency descriptors such as
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48 334 Mel-frequency cepstral coefficients as features and anticipate they will be useful for CLSA but
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50 335 may require temporal information as well. We will use the extracted features from signal
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52 336 processing analyses for classification using machine learning algorithms including: nearest
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3 337 neighbor methods, support vector machines, random forests, and gradient boosting. Primary
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5 338 analysis will consist of a five-fold cross validation on the training set to calculate expected
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8 339 prediction errors. The training set will additionally be used to estimate areas under the curve for
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10 340 our diagnostic algorithm, including CLSA, WHO algorithm, imaging, and physical exam
11
12 341 findings. Secondary analysis will include calculating sensitivities and specificities of
13
14 342 experimental diagnostic US for detection of pneumonia when compared to gold standards
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17 343 (clinical diagnosis and CXR reading). Performance will be measured using logistic and
18
19 344 multinomial regression, receiver operating characteristic curves, and area under the curve.
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23 24 346 **ETHICS AND DISSEMINATION**

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27 347 Approval was obtained from the Ethics Committees of A.B. PRISMA in Lima, Peru, El Instituto
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29 348 Nacional de Salud del Niño in Lima, Peru, and the Johns Hopkins University School of Medicine
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31 349 in Baltimore, MD. Written informed consent will be obtained from a parent or guardian. Any
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33 350 clinical information gained from participation in this study that could possibly change
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35 351 management will be given to the child's physician for his/her discretion. All data and sensitive
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37 352 information will be protected by being kept on encrypted devices or accessible only to study
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39 353 members.
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43 354 Plans for dissemination include final publication following completion of the study
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45 355 following the STARD guidelines for reporting diagnostic accuracy[25]. We aim to develop a free
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47 356 online library of lung sounds for further enhancement of CLSA and the machine learning
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49 357 algorithm, as well as for future research and clinical education.
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53 358 Funders have had no role in study design, nor will they have a role in the collection,
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55 359 management, analysis, and interpretation of data; manuscript preparation; and future
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360 publications. The principal investigator will have ultimate authority over these aspects of
361 research.

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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

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3 385 previously used time-frequency descriptors borrowed from speech processing (Mel-frequency
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5 386 cepstral coefficients and their time derivatives) and cough-specific time-domain features such as
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8 387 signal rise time and event duration and anticipate they will be useful for CLSA. We will use the
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10 388 extracted features from signal processing analyses for classification using machine learning
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13 389 algorithms such as nearest neighbor methods, support vector machines, or random forests.
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15 390 The largest challenge in regards to lung ultrasound will likely be obtaining adequate
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17 391 quality of images and inter-user variability. To reduce variability, the study technician will be
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20 392 trained to systematically scan each subdivided hemithorax for pathologic findings described
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22 393 previously [9,23], and if possible, we will attempt lung ultrasound twice for each patient.
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24 394 Ultrasound also takes substantially longer compared to chest radiography because all areas must
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27 395 be adequately explored; therefore, it may be difficult for a child to be cooperative for that length
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29 396 of time. Through our large sample size and detailed methods, we aim to improve standardization
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32 397 of pediatric chest ultrasound and further define pathologic findings associated with disease,
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34 398 which may also lead to more efficient and faster scanning.
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36 399 Limitations to this study center mostly on our case definitions for clinical diagnoses. As
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39 400 mentioned previously, there are no precise gold standards and as with many pediatric diseases,
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41 401 diagnosis is clinical. As such, our end points are determined by clinical exam findings by single
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43 402 examining physicians with additional confirmation via radiology for pneumonia cases only. We
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46 403 acknowledge the variability of observed findings among physicians but also accept that this is
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48 404 the mechanism of diagnosis in most clinical settings.
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50 405 The WHO algorithm for case management of pediatric pneumonia lacks diagnostic
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53 406 specificity. While clinical information such as elevated heart rate and decreased oxygen
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55 407 saturation may aid in degree of illness and monitoring, these data also lack specificity required to
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3 408 drastically improve case management. Lung ultrasound is also a promising tool and offers
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5 409 portability that is not available for radiography. Ultrasound has the added benefit of pleural
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7 410 effusion detection, which may prove an important adjunct to the electronic auscultation
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9 411 algorithm. However, cost and availability of skilled technicians may greatly hamper its utility in
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11 412 resource-poor settings, similar to microbiologic testing. Electronic auscultation is a simple,
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13 413 inexpensive tool that could have great diagnostic impact on ALRI in children worldwide.
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15 414 Through further research, we foresee utilizing this tool with pre-programmed computerized
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17 415 analysis to improve case management in developing countries.
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417 **COMPETING INTERESTS**

418 All authors in the study report no competing interests.

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3 420 **AUTHORS' CONTRIBUTIONS**
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6 421 All authors were involved in the study design and writing of the manuscript, and all reviewed the
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8 422 final manuscript before submission. Laura Ellington directly contributed to study design, and is
9
10 423 responsible for supervision of data gathering at the children's hospital in Lima, electronic
11
12 424 auscultation and chest ultrasound recordings, data management, analysis, and writing of this
13
14 425 manuscript. Robert Gilman provided mentorship to Laura Ellington and technical support for the
15
16 426 study. James Tielsch and Mark Steinhoff contributed to the concept and study design. Dante
17
18 427 Figueroa will serve as study physician, provide supervision and administrative oversight on site,
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20 428 and perform physical testing. Shalim Rodriguez contributed to study design and was responsible
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22 429 for developing and training the study technician to a standardized chest ultrasound protocol.
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24 430 Brian Caffo contributed to study design and will contribute to statistical analysis. Brian Tracey,
25
26 431 Mounya Elhilali, and James West contributed to study design and will contribute significantly to
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28 432 signal processing and data analysis. William Checkley had ultimate oversight over study design
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30 433 and administration, and was equally responsible writing of the manuscript, and serves as mentor
31
32 434 to Laura Ellington throughout the conduct of the study.
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3 501 **Figure 1. Order of auscultation by electronic stethoscope.** The study team member will listen
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6 502 to each site, starting with “A” for 10 seconds each.
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10 504 **Figure 2. Microbiology testing schematic.**
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15 506 **Figure 3. Preliminary data suggest a difference in spectral analysis between children with**
16
17 **and without wheeze.** Short-time FFT analysis was utilized to visualize spectrograms of a normal
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19 control (A) and asthmatic child with active wheeze (B). Representative sample is from
20 508
21 preliminary recordings taken from the Emergency Room at the Johns Hopkins Hospital in
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23 Baltimore, MD.
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4 1 **Computerized lung sound analysis to improve the specificity of pediatric pneumonia**
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6 2 **diagnosis in resource-poor settings: [Protocol and methods for an observational A-case-](#)**
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8 3 **~~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.

STRENGTHS 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

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

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85 INTRODUCTION

86 Acute lower respiratory infection (ALRI) is the leading cause of death in children under 5 years
 87 of age. Pneumonia alone is responsible for killing 1.6 million children worldwide. The World
 88 Health Organization (WHO) developed a case management algorithm that relies solely on
 89 symptoms of shortness of breath or cough, an elevated respiratory rate, and chest indrawing for
 90 the diagnosis of pneumonia and administration of antibiotics and/or referral in resource-poor
 91 areas (Table 1). Where successfully implemented, this algorithm has resulted in a 30-40%
 92 reduction in case mortality[1] but has

93 moderate sensitivity and poor specificity,
 94 ranging from 16% for children presenting
 95 with wheeze[2] and 49% for nonsevere
 96 pneumonia to 95% for very severe
 97 pneumonia[3]. Hazir and colleagues
 98 demonstrated that over 80% of children
 99 with WHO-defined non-severe pneumonia
 100 had normal chest radiographs (CXR)[4]

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

101 and that the resulting case management was equivalent to no treatment in a randomized clinical
 102 trial[5], only further increasing concern for global antibiotic resistance.

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

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3 108 alternatives exist within aspects of the physical exam and imaging. Supplementing oxygen
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5 109 saturation measurements with the current WHO algorithm has been shown to increase
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8 110 specificity[6]; however, the normal range in healthy children varies with environmental factors
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10 111 like altitude[7]. Another promising alternative for detection of pediatric pneumonia is lung
11
12 112 ultrasound. Ultrasound has the advantage of gathering information from multiple angles and the
13
14 113 ability to detect air-fluid differences that are present with pneumonia. Studies suggest that this
15
16 114 technique may be more sensitive than radiography and has the added benefit of lack of radiation;
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18 115 however, these studies have all lacked power due to small sample size[8-13]. Cost and
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20 116 availability of skilled ultrasound technicians may limit use in resource-poor settings. Chest
21
22 117 auscultation is a valuable tool for detection of respiratory pathology and is used widely in
23
24 118 clinical practice. However, limitations include inter-listener variability, subjectivity in the
25
26 119 interpretation of lung sounds[14,15], and lack of trained personnel in resource poor settings.
27
28 120 Electronic auscultation has the advantage of signal amplification and ambient noise reduction
29
30 121 leading to increased signal-to-noise ratio along with its independence on human ear sensitivity to
31
32 122 different acoustic frequencies. Furthermore, through computerized lung sound analysis (CLSA),
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34 123 this diagnostic method results in discrete values from a final reading, thereby facilitating
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36 124 standardization. With advancement in electronic stethoscopes and CLSA, there is great potential
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38 125 for improved diagnosis of pediatric pneumonia where multiple diagnostic tools are not readily
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40 126 available.

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48 127 In acoustic signal processing, the two commonly studied lung sounds are crackles and
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50 128 wheezes, which constitute unique temporal and frequency characteristics. Crackles have been
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52 129 most commonly associated with pneumonia, whereas wheezes are often observed in patients
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55 130 with asthma and bronchiolitis[16]. According to the Computerized Respiratory Sound Analysis
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3 131 (CORSA) Guidelines[17], the frequency of crackles is characterized in the spectrum of 200 to
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5 132 2000 Hz, while wheezes have a frequency spectrum of 100 to 1000 Hz. Wheezes have
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8 133 continuous waveforms (>100 ms duration) with one or more tonal components and a dominant
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10 134 frequency greater than 400 Hz during the expiratory phase. Crackles are short (<20ms), non-
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12 135 periodic waveforms with transitory sharp peaks and broadband frequency content during mid-
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14 136 inspiratory phase. Time-frequency decomposition of lung sounds provides useful information in
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16 137 identifying and localizing adventitious lung sounds in a patient.
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20 138 Translating the CLSA characterization of abnormal lung sounds to clinical practice has
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22 139 yet to be achieved. There are a few studies demonstrating potential, yet data is largely lacking,
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24 140 especially in the field of pediatrics. Our group conducted a systematic review and meta-analysis
25
26 141 of studies using CLSA for the detection of a variety of respiratory disease in adults, which found
27
28 142 an overall sensitivity and specificity of 80% and 85%, respectively, when compared to
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30 143 radiologically confirmed cases, with markedly limited results due to lack of quality and quantity
31
32 144 of available data, as well as lack of standardization[16,18-22].
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36 145 In this study, we seek to utilize electronic auscultation to record lung sounds of children
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38 146 with various clinical diagnoses: pneumonia (diffuse interstitial and lobar), asthma, bronchiolitis,
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40 147 and upper respiratory infection (URI) in a tertiary care center in Lima, Peru, and determine
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42 148 whether they can be differentiated from normal lung sounds using CLSA. In addition, we aim to
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44 149 compare with imaging modalities of chest radiography and ultrasound. We hypothesize that not
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46 150 only will the sounds profiles of each pulmonary disease pathology differ from normal, but due to
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48 151 unique characteristics of lung sounds associated with bacterial pneumonia versus asthma,
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50 152 bronchiolitis or URI, CLSA may allow differentiation of various acute lower respiratory disease
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52 153 processes. With this information in conjunction with additional basic clinical information (i.e.
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3 154 temperature, respiratory rate, oxygen saturation), we believe that a much needed improvement in
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6 155 the detection and case management of pediatric pneumonia is possible.
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156 **METHODS**

157 **Study objectives**

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

166 **Study design**

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

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

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

181

182 **Study population**

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

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

196

197 **Outcomes and case definitions**

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

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3 202 Pneumonia will be initially categorized upon clinical diagnosis by examining
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5 203 pediatricians at El Instituto Nacional de Salud del Niño and further characterized as
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8 204 consolidative or diffuse interstitial pneumonia given final CXR reading by blinded radiologists
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10 205 from the Johns Hopkins University. Asthma will be defined by the presence of wheeze on
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12 206 physical exam, history of asthma, and improvement with bronchodilators. Bronchiolitis will be
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14 207 defined as the presence of wheeze and difficulty breathing on physical exam and viral symptoms
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16 208 (cough, rhinorrhea), no history of asthma, and little or no improvement with bronchodilators if
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18 209 attempted. URI will be defined as respiration rate less than 50 breaths per minute and associated
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20 210 with one or more of the following: clear nasal secretions, sore or red throat, or hoarseness.
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27 212 **Sample size**

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29 213 Our recruitment goal is 600 subjects, 100 each with consolidative pneumonia, diffuse interstitial
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31 214 pneumonia, asthma, bronchiolitis, URI, and normal lungs. Sample size was powered to improve
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33 215 specificity of the WHO algorithm upon the addition of electronic auscultation. To detect an
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35 216 improvement in diagnostic specificity from 50% (WHO algorithm for pediatric pneumonia) to
36
37 217 80% (CLSA and WHO algorithm) with 95% power and α of 0.05 between pneumonia and non-
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39 218 pneumonia cases, we require 70 patients per group in the training set. We will also recruit a test
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41 219 set consisting of an additional 30 patients per group (30% of total sample) to estimate areas
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43 220 under the curve for our diagnostic algorithm. Each group will be over-enrolled by twenty to
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45 221 account for post-consent ineligibility, for a total of 720.
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53 223 **Study organization**

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3 224 A.B. PRISMA in Lima, Peru, and Johns Hopkins University in Baltimore, USA, will provide
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5 225 administrative oversight for the study. There will be a research coordinator at a central location
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8 226 in Lima, Peru, who will provide logistical support and management of the study team. Instituto
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10 227 Nacional de Salud del Niño will provide a team of study nurses and physicians to carry out
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12 228 recruitment, physical examination, and collection of specimens. [We have also established prior](#)
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15 229 [Hospital Edgardo Rebagliati Martins will provide an ultrasonographer for imaging at his](#)
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17 230 [institution and team member training by an experienced ultrasonographer to carry out conduct](#)
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20 231 chest ultrasonography [at Hospital del Niño](#). A multidisciplinary team of clinicians, field
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22 232 epidemiologists, acoustical engineers, and biostatisticians from Johns Hopkins University, Tufts
23
24 233 University, Cincinnati Children's Hospital, and Instituto Nacional de Salud del Niño will be
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26
27 234 involved with study design and conduct, statistical analysis, and reporting of results.
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31 32 236 **Questionnaire**

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34 237 We will ask the parent or guardian about the child's past medical history, environmental
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36 238 exposures, access to healthcare, and current respiratory symptoms. We will inquire about
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38 239 demographic information, nutrition, and vaccination history. We will ask about co-morbidities,
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40 240 family history, and developmental history. Environmental questions pertained to housing,
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42 241 number of children, rural versus urban living, parent occupations, smoke and allergen exposure,
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44 242 and sick contacts. Current respiratory symptoms were asked of the parent or guardian to answer
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46 243 subjectively and included rapid breathing, difficulty breathing, chest indrawing, cyanosis, cough,
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48 244 sputum production, audible breath sounds, and subjective fever.
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54 55 246 **Physical exam and laboratory testing**

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3 247 The initial set of vital signs will be recorded, including pulse oximetry. During the physical
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5 248 exam, a single examining physician from the larger group of study physicians will be responsible
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8 249 for recording findings for a given patient with emphasis on the respiratory exam. Chest
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10 250 retractions, nasal flaring, grunting, stridor, and accessory muscle use will be noted and
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12 251 characterized if present, along with any adventitious lung sounds appreciated by physician and
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14 252 study team member on chest auscultation. Degree of improvement after bronchodilators will also
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16 253 be recorded if administered. Additionally, signs of dehydration and malnutrition will be reported
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18 254 if present. Laboratory results will be recorded if evaluated by the ED and include complete blood
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20 255 count, electrolytes, and arterial blood gas.
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27 257 **Electronic Auscultation**

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29 258 Parents will be allowed to position the patient supine or upright. The study team member will
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31 259 listen to eight auscultation sites using a ThinkLabs ds32a Digital Stethoscope and mp3 recorder,
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33 260 for 10 seconds at each site, in the following order of placement: front top left and right,
34
35 261 fronterolateral bottom right and left, back top right and left, and back bottom left and right
36
37 262 (Figure 1). Auscultation will be performed at the participant's normal breathing patterns during
38
39 263 recording without being asked to take deep breaths. We will allow only one repeat of
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41 264 auscultation if recording is interrupted for any reason or due to unacceptable signal quality of the
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43 265 first recording.
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50 267 **Lung ultrasound**

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52 268 All participants will receive bilateral lung ultrasonography carried out on SonoSite portable
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54 269 ultrasound machine with HFL38/13-6MHz and P17/5-1MHz MicroMaxx® transducers by a
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3 270 single ultrasound technician who has been trained to the standardized protocol. Patients will be
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5 271 examined in the supine position with each hemithorax divided into six sections: 2 anterior, 2
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8 272 lateral, and 2 posterior. The posterior area is defined from the posterior axillary line to the
9
10 273 paravertebral line. Longitudinal and oblique scans will be obtained at each of the chest zones.
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12 274 Longitudinal scans allow visualization of the ribs with the pleural line under them[23].
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14 275 Representative images from each section will be saved and later transferred to radiologists at an
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16 276 outside institution.
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20 277 To assess for pneumonia, 2 of 3 radiologists must agree on the description of ultrasound
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22 278 images compatible with pneumonia. Consolidation will be determined by 1) the presence of
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24 279 hypo- or anechoic images with loss of distinct pleural lines and 2) an irregular shredded border
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26
27 280 of the pleural line that is distinct from the lung line, termed the “shred sign.” Additional signs to
28
29 281 be reported will include punctate hyperechoic images reflecting air bronchograms, decreased
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31 282 lung sliding, and homogenous, hypoechoic images in the pleural space corresponding to pleural
32
33 283 effusions. Interstitial infiltrates will be determined by the presence of “lung rockets,” which
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35 284 correlate to three or more B-lines in a longitudinal view between two ribs. Additional features to
36
37 285 be reported include heterogenous echotexture, air and fluid bronchograms, lung pulse, and
38
39 286 additional B-lines [23].
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46 288 **Chest radiography**

47
48 289 All case participants will undergo chest radiography. We will attempt postero-anterior and lateral
49
50 290 films but will allow an antero-posterior view if not possible. Digital images will be sent to a third
51
52 291 party reading group blinded to clinical information. Using the WHO standardization of CXR
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54
55 292 interpretation for pediatric pneumonia [24], radiologists will comment on quality as adequate,
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3 293 suboptimal, or unreadable and on the presence of pathology as consolidative or interstitial with
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6 294 or without pleural effusions. Radiographic evidence of pneumonia will be confirmed by
7
8 295 agreement by 2 out of 3 radiologist reports for a given patient. Additional pathologic findings not
9
10 296 previously characterized will also be recorded and reported to the patient's physician for further
11
12 297 intervention if necessary.
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15 298

17 299 **Microbiological studies**

20 300 Blood, urine, and nasopharyngeal samples will be collected according to our study design
21
22 301 (Figure 2). Blood samples will be drawn for cultures and sensitivities. Urine will be tested for
23
24 302 detection of pneumococcal antigen and stored for PCR. Nasopharyngeal swabs will be tested for
25
26 303 respiratory viruses, along with culture and sensitivities. Respiratory pathogens tested by PCR
27
28 304 will include *Streptococcus pneumoniae*, *Haemophilus influenzae*, and respiratory syncytial virus.
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34 306 **Safety**

36 307 ~~In order to~~To ensure safety, the researcher collecting data is experienced with providing care to
37
38 308 children. The researcher will use this experience to minimize any discomfort the children may
39
40 309 have. All blood samples will be collected by a skilled nurse or phlebotomist.
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43 310 We will adhere to hospital procedures for avoiding hospital acquired infections. We will
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45 311 wash hands with soap and water or alcohol-based hand sanitizer before patient contact. We will
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47 312 wear gloves, gowns and mask when required. We will clean the devices using alcohol swabs
48
49 313 before and after each use.
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55 315 **Data quality and management**

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3 316 Prior to data collection, a Manual of Operations will be developed to ensure standardization and
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5
6 317 reliability and contain detailed instructions for all study procedures and guidelines for data
7
8 318 collection. The manual will be revised as needed and distributed to members of the study team.
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10
11 319 All data are recorded first on paper case report forms and subsequently double-entered
12
13 320 using Microsoft ACCESS. Data sets will be cross-validated and errors corrected. Electronic lung
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15 321 recordings will be transferred from the mp3 player to participant-specific files on the study
16
17 322 computer at least every other day and backed-up weekly. Digital CXR images will also be
18
19 323 uploaded to these files and backed-up similarly.
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23 24 325 **Analysis of lung sounds and statistics**

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26
27 326 An important first step in CLSA is using common signal processing techniques to investigate
28
29 327 high and low frequency information using methods such as the Short-time Fourier Transform
30
31 328 (STFT), wavelet transforms, and P-spline bases. The second step will be extracting signal
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33 329 processing features to train the classifier.
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36 330 Based on preliminary recordings to date performed by our group in Baltimore (Figure 3),
37
38 331 we anticipate that wheeze can be characterized using features from the Fourier transform, such as
39
40 332 the existence and temporal stability of tonal peaks in the 300-1000 Hz range, while crackles
41
42 333 could be recognized using features such as amplitude, the presence of broad-band energy and the
43
44 334 duration of this energy. Features such as the decrease in signal energy with frequency can
45
46 335 characterize movement sounds. We have previously used time-frequency descriptors such as
47
48 336 Mel-frequency cepstral coefficients as features and anticipate they will be useful for CLSA but
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50 337 may require temporal information as well. We will use the extracted features from signal
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52 338 processing analyses for classification using machine learning algorithms including: nearest
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3 339 neighbor methods, support vector machines, random forests, and gradient boosting. Primary
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5 340 analysis will consist of a five-fold cross validation on the training set to calculate expected
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8 341 prediction errors. The training set will additionally be used to estimate areas under the curve for
9
10 342 our diagnostic algorithm, including CLSA, WHO algorithm, imaging, and physical exam
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12 343 findings. Secondary analysis will include calculating sensitivities and specificities of
13
14 344 experimental diagnostic US for detection of pneumonia when compared to gold standards
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16
17 345 (clinical diagnosis and CXR reading). Performance will be measured using logistic and
18
19 346 multinomial regression, receiver operating characteristic curves, and area under the curve.
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23 24 348 **ETHICS AND DISSEMINATION**

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27 349 Approval was obtained from the Ethics Committees of A.B. PRISMA in Lima, Peru, El Instituto
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29 350 Nacional de Salud del Niño in Lima, Peru, and the Johns Hopkins University School of Medicine
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31 351 in Baltimore, MD. Written informed consent will be obtained from a parent or guardian. Any
32
33 352 clinical information gained from participation in this study that could possibly change
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35 353 management will be given to the child's physician for his/her discretion. All data and sensitive
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37 354 information will be protected by being kept on encrypted devices or accessible only to study
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39 355 members.
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43 356 Plans for dissemination include final publication following completion of the study
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45 357 following the STARD guidelines for reporting diagnostic accuracy[25]. We aim to develop a free
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47 358 online library of lung sounds for further enhancement of CLSA and the machine learning
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49 359 algorithm, as well as for future research and clinical education.
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53 360 Funders have had no role in study design, nor will they have a role in the collection,
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55 361 management, analysis, and interpretation of data; manuscript preparation; and future
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362 | publications. The principal investigator will have ultimate authority over these aspects of
363 | research.

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3 364 **DISCUSSION**
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5 365 This study aims to investigate alternatives to improve the specificity of the WHO algorithm for
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8 366 pediatric pneumonia, namely electronic auscultation and chest ultrasonography. Utilizing
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10 367 electronic auscultation, we intend to characterize and analyze lung sounds associated with
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12 368 consolidative pneumonia, diffuse interstitial pneumonia, bronchiolitis, asthma, and upper
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14 369 respiratory infections, to determine if these diagnoses can be differentiated from normal through
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16 370 automated lung sounds, and to compare with chest ultrasound, WHO algorithm, and molecular
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18 371 testing for etiology. By reporting a protocol for CLSA, we hope to encourage standardization and
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21 372 expansion of recorded lung sounds via an online library for continued enhancement of machine
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23 373 learning as well as for continued scientific research and clinical education.
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27 374 We foresee our greatest challenge in maximizing the quality of recorded lung sounds. To
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29 375 begin the study, we will utilize a commercial electronic stethoscope for recordings, which is
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31 376 identical in design to standard clinical stethoscopes. However, through sound processing using
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33 377 time-frequency analysis methods such as the Short-time Fourier Transform (STFT) and
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35 378 Continuous Wavelet Transforms (CWT), we hope to enhance the signal-to-noise ratio for data
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37 379 analysis and characterization. By examining additional features such as amplitude, we may also
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39 380 be better able to identify crackles and consolidation. We also plan to test alternative recording
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41 381 devices using piezoelectric microphones covered with a thin polymer that may be able to better
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43 382 capture lung sounds. Based on our recordings to date, we anticipate that wheeze can be
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45 383 differentiated from normal breath using features such as the existence and temporal stability of
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47 384 tonal peaks in the 300-1000 Hz range, while crackle should be recognizable using features such
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49 385 as the presence of broad-band energy and the duration of this energy. Features such as the
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51 386 decrease in signal energy with frequency can characterize movement sounds. We have
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3 387 previously used time-frequency descriptors borrowed from speech processing (Mel-frequency
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5 388 cepstral coefficients and their time derivatives) and cough-specific time-domain features such as
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8 389 signal rise time and event duration and anticipate they will be useful for CLSA. We will use the
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10 390 extracted features from signal processing analyses for classification using machine learning
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12 391 algorithms such as nearest neighbor methods, support vector machines, or random forests.

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15 392 The largest challenge in regards to lung ultrasound will likely be obtaining adequate
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17 393 quality of images and inter-user variability. To reduce variability, the study technician will be
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19 394 trained to systematically scan each subdivided hemithorax for pathologic findings described
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21 395 previously [9,23], and if possible, we will attempt lung ultrasound twice for each patient.
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23 396 Ultrasound also takes substantially longer compared to chest radiography because all areas must
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25 397 be adequately explored; therefore, it may be difficult for a child to be cooperative for that length
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27 398 of time. Through our large sample size and detailed methods, we aim to improve standardization
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29 399 of pediatric chest ultrasound and further define pathologic findings associated with disease,
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31 400 which may also lead to more efficient and faster scanning.
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35 401 Limitations to this study center mostly on our case definitions for clinical diagnoses. As
36
37 402 mentioned previously, there are no precise gold standards and as with many pediatric diseases,
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39 403 diagnosis is clinical. As such, our end points are determined by clinical exam findings by single
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41 404 examining physicians with additional confirmation via radiology for pneumonia cases only. We
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43 405 acknowledge the variability of observed findings among physicians but also accept that this is
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45 406 the mechanism of diagnosis in most clinical settings.
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50 407 The WHO algorithm for case management of pediatric pneumonia lacks diagnostic
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52 408 specificity. While clinical information such as elevated heart rate and decreased oxygen
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54 409 saturation may aid in degree of illness and monitoring, these data also lack specificity required to
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3 410 drastically improve case management. Lung ultrasound is also a promising tool and offers
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5 411 portability that is not available for radiography. Ultrasound has the added benefit of pleural
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7 412 effusion detection, which may prove an important adjunct to the electronic auscultation
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10 413 algorithm. However, cost and availability of skilled technicians may greatly hamper its utility in
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12 414 resource-poor settings, similar to microbiologic testing. Electronic auscultation is a simple,
13
14 415 inexpensive tool that could have great diagnostic impact on ALRI in children worldwide.
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17 416 Through further research, we foresee utilizing this tool with pre-programmed computerized
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20 417 analysis to improve case management in developing countries.
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419 **COMPETING INTERESTS**

420 All authors in the study report no competing interests.

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3 422 **AUTHORS' CONTRIBUTIONS**
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5 423 All authors were involved in the study design and writing of the manuscript, and all reviewed the
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7
8 424 final manuscript before submission. Laura Ellington directly contributed to study design, and is
9
10 425 responsible for supervision of data gathering at the children's hospital in Lima, electronic
11
12 426 auscultation and chest ultrasound recordings, data management, analysis, and writing of this
13
14 427 manuscript. Robert Gilman provided mentorship to Laura Ellington and technical support for the
15
16 428 study. James Tielsch and Mark Steinhoff contributed to the concept and study design. Dante
17
18 429 Figueroa will serve as study physician, provide supervision and administrative oversight on site,
19
20 430 and perform physical testing. Shalim Rodriguez contributed to study design and was responsible
21
22 431 for developing and training the study technician to a standardized chest ultrasound protocol.
23
24 432 Brian Caffo contributed to study design and will contribute to statistical analysis. Brian Tracey,
25
26 433 Mounya Elhilali, and James West contributed to study design and will contribute significantly to
27
28 434 signal processing and data analysis. William Checkley had ultimate oversight over study design
29
30 435 and administration, and was equally responsible writing of the manuscript, and serves as mentor
31
32 436 to Laura Ellington throughout the conduct of the study.
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3 503 **Figure 1. Order of auscultation by electronic stethoscope.** The study team member will listen
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6 504 to each site, starting with “A” for 10 seconds each.
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10 506 **Figure 2. Microbiology testing schematic.**
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15 508 **Figure 3. Preliminary data suggest a difference in spectral analysis between children with**
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17 509 **and without wheeze.** Short-time FFT analysis was utilized to visualize spectrograms of a normal
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20 510 control (A) and asthmatic child with active wheeze (B). Representative sample is from
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22 511 preliminary recordings taken from the Emergency Room at the Johns Hopkins Hospital in
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24 512 Baltimore, MD.
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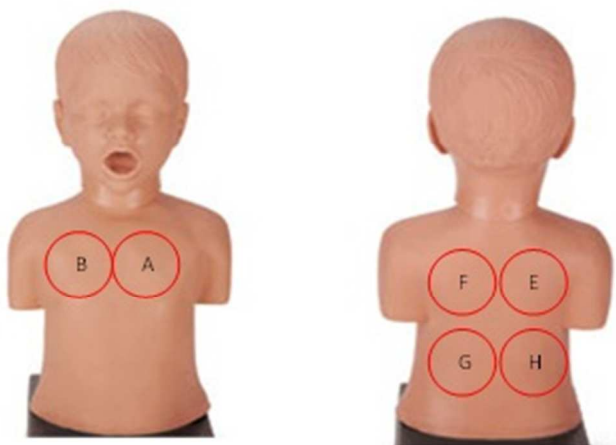


Figure 1. Order of auscultation by electronic stethoscope. The study team member will listen to each site, starting with "A" for 10 seconds each.

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Figure 2. Microbiology testing schematic.
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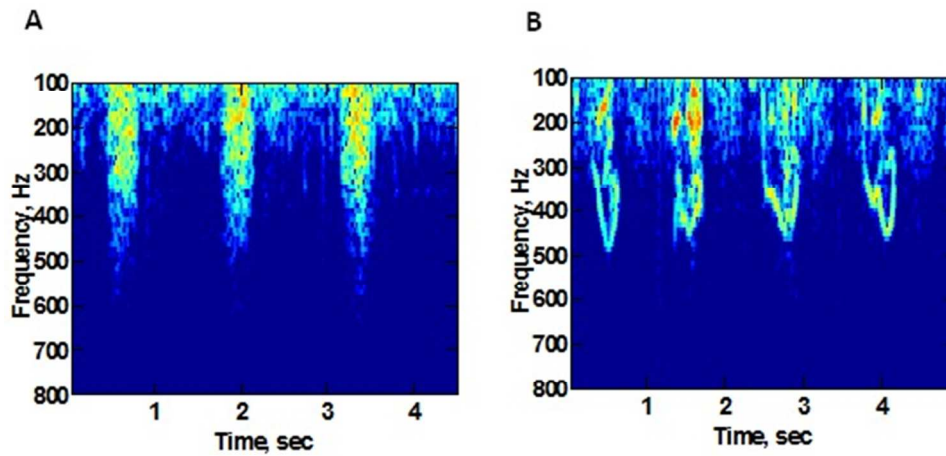


Figure 3. Preliminary data suggest a difference in spectral analysis between children with and without wheeze. Short-time FFT analysis was utilized to visualize spectrograms of a normal control (A) and asthmatic child with active wheeze (B). Representative sample is from preliminary recordings taken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

review only

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			
<i>Participants</i>	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
<i>Test methods</i>	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
<i>Statistical methods</i>	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			
<i>Participants</i>	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
<i>Test results</i>	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
<i>Estimates</i>	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