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Early View

Original article

Lung ultrasound patterns in pediatric pneumonia in Mozambique and Pakistan

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Title: Lung ultrasound patterns in pediatric pneumonia in Mozambique and Pakistan

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Take Home Message: We explored distinctive lung ultrasound patterns associated with pediatric community-acquired pneumonia in Mozambique and Pakistan and found reliable pattern recognition critical to identifying pneumonia.

Abstract

OBJECTIVE: Improved pneumonia diagnostics are needed, particularly in resource-constrained settings. Lung ultrasound (LUS) is a promising point-of-care imaging technology for diagnosing pneumonia. The objective was to explore LUS patterns associated with pediatric pneumonia.

METHODS: We conducted a prospective, observational study among children aged 2 through 23 months with World Health Organization Integrated Management of Childhood Illness chest-indrawing pneumonia and among children without fast breathing, chest indrawing or fever (no pneumonia cohort) at two district hospitals in Mozambique and Pakistan. We assessed LUS and chest radiograph (CXR) examinations, and viral and bacterial nasopharyngeal carriage, and performed a secondary analysis of LUS patterns.

RESULTS: LUS demonstrated a range of distinctive patterns that differed between children with and without pneumonia and between children in Mozambique vs Pakistan. The presence of LUS consolidation or interstitial patterns was more common in children with chest-indrawing pneumonia than in those without pneumonia. Consolidations were also more common among those with only bacterial but no viral carriage detected (50.0%) than among those with both (13.0%) and those with only virus detected (8.3%;p-value 0.03). LUS showed high interrater reliability among expert LUS interpreters for overall determination of pneumonia (κ=0.915), consolidation (κ=0.915), and interstitial patterns (κ=0.901), but interrater reliability between LUS and CXR for detecting consolidations was poor (κ=0.159,Pakistan) to fair (κ=0.453,Mozambique).

DISCUSSION: Pattern recognition was discordant between LUS and CXR imaging modalities. Further research is needed to define and standardize LUS patterns associated with pediatric pneumonia and to evaluate the potential value of LUS as a reference standard.

Key Words: lung ultrasound; pediatric pneumonia; pattern; low-resource settings

INTRODUCTION

Pneumonia remains the leading infectious killer of children;[1] effective and timely diagnosis is critical to saving lives. Pediatric pneumonia is difficult to diagnose, especially in resource-constrained settings.[2] Advantages of ultrasound (LUS), a point-of-care tool that can dynamically visualize lungs with promising diagnostic accuracy for pneumonia and greater sensitivity or specificity when compared with chest radiography (CXR), include lower cost, portability, ease-of-use, and absence of ionizing radiation.[3-5] Key to evaluating the use case of LUS in pneumonia diagnosis in resource-constrained settings is a better understanding of the LUS patterns associated with pediatric pneumonia. We conducted a pilot study in Mozambique and Pakistan to investigate use of LUS for diagnosis and found among children with World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) chest-indrawing pneumonia, expert LUS interpreters may achieve substantially higher interrater reliability (IRR) for LUS compared to CXR.[6] We chose to focus on non-severe chest-indrawing pneumonia rather than more severe pneumonia in this study since we believed it unlikely that LUS imaging would change initial management of severe pneumonia which is typically treated with intravenous antibiotics. In this secondary analysis, we explore distinctive LUS patterns associated with pediatric pneumonia and potential patterns associated with viral and/or bacterial nasopharyngeal carriage.

METHODS

Study design, setting and participants

Methods and primary results of this prospective, observational, facility-based cohort study were described previously.[6, 7] The primary objective was to provide evidence assessing whether the addition of LUS to current pneumonia care pathways improves identification of pneumonia in children presenting to district hospitals in Manhiça, Mozambique and Karachi, Pakistan. Secondary and exploratory objectives included identifying LUS patterns among children with and without chest-indrawing pneumonia and comparing those patterns to CXR patterns. We explored LUS patterns, and available biomarker and viral and bacterial nasopharyngeal carriage results.

Children aged 2 through 23 months meeting WHO IMCI chest-indrawing pneumonia case definition (chest-indrawing pneumonia cohort) in outpatient and/or emergency departments of the low-volume, rural Manhiça District Hospital in Manhiça, Mozambique and the high-volume, urban Sindh Government Children's Hospital–Poverty Eradication Initiative in Karachi, Pakistan were screened sequentially during working hours by study staff to determine eligibility (Table 1, Figure 1). A separate group of 40 children presenting with complaints of cough or difficulty breathing but without fast breathing, chest indrawing or fever (no pneumonia cohort) was also screened. Conducted in accordance with International Conference on Harmonisation, Good Clinical Practice and Declaration of Helsinki 2008, the study was approved by Western Institutional Review Board, Comité Nacional de Bioética para a Saúde (246/CNBS/17), Comite de Ética del Hospital Clínic de Barcelona (HCB/2017/0074), and Aga Khan University Ethics Review Committee, and registered with ClinicalTrials.gov (NCT03187067).

Study procedures

After enrollment on Day 1, eligible children underwent history, physical examination and LUS and CXR examinations. Enrolled children received local standard of care without the results of LUS examinations informing clinical care.

LUS examinations (longitudinal and oblique scans obtained of the anterior, lateral and posterior sides of the chest, Figure 2) with a linear probe were performed by 4 trained non-physician healthcare personnel (nurse and medical agent in Mozambique, and 2 radiology technicians in Pakistan) who received 1-day standardized training course and 3-day supervised practice. LUS interpretation using a standardized scoresheet targeted detection of typical lung consolidations, pleural effusions, interstitial patterns and obstructive atelectasis.[7, 8] Endpoint pneumonia using LUS was defined as the presence of consolidations or pleural effusions. At least 2 independent physicians expertly trained in LUS interpretation and blinded to clinical presentation interpreted each examination. If discordant, a designated expert LUS interpreter acted as arbiter. LUS operators at each site also interpreted LUS scans, independently from one another. All interpretations were performed in batches at a later time using the same standardized scoresheet.

Anteroposterior CXR images were collected based on standard practice at each study site. A CXR interpretation panel of 6 expert interpreters investigated radiographic indicators of WHO CXR standardized primary endpoint pneumonia.[9-12] At least 3 independent WHO CXR-trained physicians interpreted each CXR. Three interpretations were randomly selected, and if the first 2 interpretations were discordant, the third would act as tiebreaker.

Blood samples were tested for hemoglobin and C-reactive protein in Mozambique and Pakistan, and for procalcitonin, malaria and HIV in Mozambique. Nasopharyngeal aspirates and/or swabs

were tested for respiratory viral PCR in Mozambique and Pakistan, and bacterial PCR in Mozambique using commercial multiplex tests.

Statistical analysis

Chi-squared tests, Fisher's exact tests, and t-tests were used to compare baseline characteristics of children by country and cohort. Tests were 2-sided with alpha=0.05. Multiple comparison adjustments were not made, given the exploratory aims of the analyses. IRR among expert LUS interpreters and among expert CXR interpreters were estimated by cohort using Cohen's kappa (κ). All analyses were performed using R (version 3.5.1; R Foundation for Statistical Computing).

RESULTS

Enrollment began in August 2017 in Mozambique and October 2017 in Pakistan. The last visits were completed in June 2018 in Mozambique and April 2018 in Pakistan. Baseline LUS videos were available for 98 out of 100 and 128 out of 130 children with chest-indrawing pneumonia in Mozambique and Pakistan, respectively (Figure 1a), and all 40 in the no pneumonia cohort (Figure 1b), with baseline characteristics by cohort and country provided in Table 2. One child with an oxyhemoglobin saturation <90% was incorrectly enrolled in the chest-indrawing pneumonia cohort in Mozambique. The results reflect the available data from these 226 children in the chest-indrawing pneumonia cohort and 40 children in the no pneumonia cohort. Among children with pneumonia, there were more fevers (21.4% vs 8.6%,p=0.01), but less fast breathing (53.1% vs 64.6%,p=0.10) in Mozambique than Pakistan. One child had hypoxemia in Mozambique and none in Pakistan. C-reactive protein measurements were available for 93 and

128 children with pneumonia in Mozambique and Pakistan, respectively, and were on average lower in Mozambique than Pakistan (38.8 vs 109.9 ug/mL,p<0.01). Among children without pneumonia, C-reactive protein measurements were available in Mozambique, and on average were lower than those among children with pneumonia (18.2 vs 38.8 ug/mL,p=0.03). Procalcitonin measurements were available for 93 children with pneumonia and 20 children without pneumonia in Mozambique. Average levels were higher in the former group (1.7 ng/mL) than the latter (0.2 ng/mL) (p=0.07).

Nasopharyngeal viral carriage results were available for 98 children with pneumonia and 20 children without pneumonia analyzed from Mozambique, and 100 children with pneumonia analyzed from Pakistan (Appendix 1). Presence of any respiratory virus was similarly high across all tested children in both countries (91.8% Mozambique pneumonia; 84% Pakistan pneumonia; 95% Mozambique no pneumonia). However, average number of viruses per child was higher among children with pneumonia in Mozambique (1.67) than in Pakistan (1.08;p<0.01) or among children without pneumonia in Mozambique (1.25;p=0.01).

Streptococcus pneumoniae nasopharyngeal carriage results were available for 97 children with pneumonia in Mozambique, while remaining bacterial carriage results were available for all 100 children with pneumonia and 20 children without pneumonia in Mozambique. Most children with pneumonia in Mozambique tested positive for *S. pneumoniae* (86.6%); 3.1% were positive for *Bordetella pertussis* and 3.1% for *Mycoplasma pneumoniae* (Table 2). No children without pneumonia were positive for carriage of any of the tested bacterial strains.

Among 97 children with pneumonia in Mozambique for whom both viral and bacterial carriage results were available, 8 were positive for at least 1 bacterial but no viral carriage, 12 were

positive for at least 1 viral but no bacterial carriage, and 77 were positive for at least 1 of both; no children were negative for all tested strains of both (Table 5). Among viral-only positives, RSV and rhinovirus were the only strains that appeared without additional viruses in more than 1 child (3 and 2, respectively). Among mixed (both viral and bacterial) positives, RSV with *S. pneumoniae* (14 children), rhinovirus with *S. pneumoniae* (8 children), and adenovirus with rhinovirus with *S. pneumoniae* (7 children) were the 3 most common combinations present. Other combinations were each present in 4 or fewer children.

LUS patterns

Presence of any LUS consolidation was more common in children with chest-indrawing pneumonia than those without pneumonia (15.3% vs 0.0%,p=0.07,Mozambique; 45.5% vs 5.0%,p<0.01,Pakistan) as was presence of any LUS interstitial pattern (24.5% vs 10.0%,p=0.24,Mozambique; 62.5% vs 30.0%,p=0.01,Pakistan, Table 3). Neither LUS presence of pleural effusion nor obstructive atelectasis was significantly different between those with and without pneumonia in Mozambique (0.0% throughout) or Pakistan (1.6% vs 0.0%,p>0.99; 2.3% vs 0.0%,p>0.99, respectively). Among those with pneumonia, LUS consolidation and interstitial patterns were significantly more common in Pakistan than Mozambique (p<0.01 for each comparison), though LUS effusion and obstructive atelectasis were not (p=0.51; p=0.26, respectively). Among those without pneumonia, consolidation and interstitial patterns were not significantly more common in Pakistan than Mozambique (p>0.99; p=0.24, respectively), and effusion and obstructive atelectasis patterns were absent in all children.

Expert LUS interpreters showed very high levels of IRR in overall determination of pneumonia (κ=0.915), consolidation (κ=0.915), effusion (κ=1), and interstitial patterns (κ=0.901) among

children with pneumonia; estimated IRR was lower, but still moderate to good for obstructive atelectasis (κ=0.746) (Table 4). Of note, the unusual κ=1 occurred because of very small numbers of children with pleural effusions.

When both expert LUS interpreters determined a given imaging pattern was absent for all children, the κ-value for that imaging pattern was undefined, as was true for children without pneumonia with respect to presence of effusion and obstructive atelectasis. Among children without pneumonia, IRRs for overall pneumonia and for consolidations were estimated to be 1, but these were due to the small number of children with any findings on LUS. IRR for interstitial patterns was moderate (κ=0.635), but again, numbers were small.

No additional patterns of differences in LUS results were evident when comparing children with and without viral nasopharyngeal carriage (data not presented). Among children with pneumonia in Mozambique for whom viral and bacterial nasopharyngeal carriage results were available, presence of consolidations differed significantly between bacterial-only, mixed positives, and viral-only (50.0% vs 13.0% vs 8.3%,p=0.03); other imaging patterns did not (Table 5).

CXR patterns

Differences in presence of CXR imaging patterns between cohorts within each country were not significant except for interstitial patterns in Pakistan. CXR interstitial patterns were common in both countries for children with pneumonia (36.1%) and less common among those without pneumonia in Mozambique (15.0%, p=0.12) and Pakistan (10.0%, p=0.04). Presence of CXR consolidation was more common in Mozambique than Pakistan in both chest-indrawing pneumonia and no pneumonia cohorts (18.6% vs 9.8%,p=0.09; 20.0% vs 0.0%,p=0.11,

respectively) (Appendix 2). Presence of effusion was detected by CXR in 1 child with pneumonia in Mozambique (1.0%), while obstructive atelectasis was detected by CXR in 1 child with pneumonia in Pakistan (0.8%).

Comparison of LUS and CXR patterns

In assessing concordance between expert LUS vs expert CXR interpretations regarding presence of consolidation in the chest-indrawing pneumonia cohort, κ=0.453 for Mozambique and κ=0.159 for Pakistan; for the no pneumonia cohort, 4 consolidations were detected by LUS but none by CXR in Mozambique, resulting in κ=0, and 1 was detected by CXR but none by LUS in Pakistan, also resulting in κ=0. (Appendix 3). Regarding presence of effusion in the pneumonia cohort (data not shown), although 2 were detected by LUS in Pakistan, none were detected by CXR, resulting in κ=0; likewise, 1 was detected by CXR in Mozambique but none by LUS, also resulting in κ=0. Corresponding κ-values were undefined for those without pneumonia because no effusions were detected by either modality.

DISCUSSION

In our pilot, LUS demonstrated a range of distinctive patterns that differed between children in the chest-indrawing pneumonia and no pneumonia cohorts and between children in Mozambique vs Pakistan. Presence of consolidation or interstitial patterns was more common in children diagnosed with chest-indrawing pneumonia based on WHO IMCI criteria than in those without pneumonia. Presence of pleural effusion or obstructive atelectasis patterns was not significantly different among those children with and without pneumonia, though this was based on small numbers of LUS effusions and obstructive atelectasis. In Pakistan, differences in

identification of consolidation and interstitial patterns between those with and without pneumonia were statistically significant. Rates of consolidation and interstitial patterns were significantly higher in Pakistan than Mozambique, possibly due to differences in severity of disease for those eligible and enrolled. Other possible explanations for the different LUS patterns observed among children with chest-indrawing pneumonia include differing epidemiologies of etiologic pathogens, presentations of disease, host susceptibility and environmental factors, healthcare seeking behaviors, and healthcare facility levels (low-volume, rural district hospital in Mozambique and high-volume urban hospital in Pakistan), among others.

Among children with chest-indrawing pneumonia, most children with consolidation also had interstitial patterns in one or both lungs (12/15 (80.0%),Mozambique and 54/57 (94.7%),Pakistan). Of those children with chest-indrawing pneumonia with interstitial patterns, 50% (12/24) in Mozambique and 32.5% (26/80) in Pakistan demonstrated interstitial patterns without consolidation. Thus, children with chest-indrawing pneumonia demonstrate a mix of LUS patterns.

Among children with chest-indrawing pneumonia in Mozambique, consolidations were detected at a higher rate in those with bacterial carriage only (no viral carriage), and more frequently but to a lesser extent among those with mixed bacterial and viral carriage, than among those with viral carriage only. Interstitial patterns were again most frequent among those with bacterial carriage, but least frequent among those with mixed bacterial and viral carriage. One could hypothesize that LUS might be able to assist with etiological detection although in the absence of microbiologic diagnosis and confirmation, more research would be

necessary. It is not surprising that we find a high percentage of nasopharyngeal carriage in children without pneumonia, but this also implies that these comparisons between carriage and disease are not necessarily indicative of clinical disease status or severity. In a study evaluating LUS use during the 2009 H1N1 influenza A pandemic, investigators defined viral pneumonia as the presence of small subpleural consolidations usually <0.5 cm and/or individual B-lines or confluent B-lines (interstitial pattern), and bacterial pneumonia as the presence of lung consolidation with air bronchograms, and based on 54 observations found that IRR for distinguishing viral from bacterial pneumonia was 0.82 (0.63 to 0.99).[13]

While some variability in LUS pattern findings exists, in our study, LUS appears to be consistent with clinical presentation in identifying consolidation (except for 1 child in the no pneumonia cohort in Pakistan identified with consolidation on LUS). In the no pneumonia cohort LUS appears to overdiagnose interstitial patterns (8 children) while CXR appears to overdiagnose both consolidation (4 children) and interstitial patterns (5 children). Abnormal imaging patterns in the absence of clinical disease could lead to overtreatment with antibiotics.

Based on our limited sample, IRR between LUS and CXR was poor in identifying consolidation and pneumonia. Using LUS, it appears there is significantly more disease in Pakistan than Mozambique; however, using CXR, the opposite seems true (although not significantly). Depending on which imaging modality is used, there is different recognition of disease. The fact that recognition of disease on imaging is in the opposite direction between the study sites by imaging modality may appear paradoxical; however, this may be due to chance or to a lack of an imaging gold standard, making unclear whether it is LUS or CXR that is performing poorly.

Because study populations and underlying epidemiologies were different between Mozambique and Pakistan, and sample sizes of enrolled children were relatively small at each study site, there were limitations in comparisons that could be made between sites, and between pneumonia and no pneumonia cohorts. Of note, of those screened, 81.8% in Pakistan vs 27.3% in Mozambique were not enrolled because they did not have chest indrawing. Possible explanations for this difference could include differences in healthcare seeking behavior at the 2 study sites and/or differences in screening procedures. Importantly, though, great care was undertaken to ensure that all eligibility criteria were met at both study sites. Enrollment in the pneumonia cohort in Mozambique was slower due to smaller presenting numbers than in Pakistan as evidenced by larger differences in those screened vs enrolled in Pakistan, and this may have led to sicker children being enrolled in Pakistan (as suggested by higher average C-reactive protein measurement, lower average oxyhemoglobin saturations, and more LUS consolidation and interstitial patterns in Pakistan).

Additional limitations related to imaging interpretation. For LUS interpretation, detailed expert consensus on what constitutes clinically relevant disease does not exist. While LUS videos were reviewed independently, our expert reviewers were not completely independent because one had been trained by the other. For CXR interpretation methodology, despite being used widely for epidemiologic and vaccine effectiveness studies, current WHO CXR interpretation methodology is not intended for clinical use; rather it is intended to serve as a research endpoint, and thus, our expert CXR interpretations may miss more subtle disease.

Difficult to obtain, time-consuming, expensive and exposing its subject to ionizing radiation, CXR is also not an ideal reference standard due to its high interrater variability.[2-4, 12, 14-19]

In our study, CXR had poor IRR, even among expert CXR interpreters. Pattern recognition was discordant between LUS and CXR imaging modalities. Despite this discordance, LUS imaging may be preferable in identifying patterns; however, further research is needed to define and standardize LUS patterns associated with pediatric pneumonia. In addition, while more data may be needed to support LUS as a reference standard, in favor of LUS as a preferred imaging modality for pediatric pneumonia is its high IRR among expert LUS interpreters for overall determination of pneumonia, consolidation and interstitial patterns. LUS pattern recognition and image analysis is a potential tool to allow machine-learning and artificial intelligence-assisted automatic diagnosis of pneumonia. More research is needed to define and standardize LUS patterns associated with pediatric pneumonia and to evaluate the potential value of LUS as a reference standard.

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Contributorship Statement: Dr. Ginsburg conceptualized the study, obtained research funding, designed the study and data collection instruments, coordinated and supervised data collection from the sites, interpreted the data, and drafted the manuscript. Ms. Lenahan designed the study and data collection instruments, and coordinated and supervised data collection from the sites. Drs. LaMorte and Volpicelli provided input on the design of the study and designed the lung ultrasound methodology. Drs. Jehan and Bassat provided input on the design of the study and supervised teams that acquired the data. Among the authors, Drs. Vitorino, Valente, Balouch, and Nisar and Ms. Qasim conducted the clinical procedures and acquired the data. Mr. Hwang and Dr. May performed the statistical analyses and interpreted the data, and drafted sections of the manuscript. Dr. Almagro conducted laboratory analyses from Mozambique. All authors worked collaboratively to review and revise the manuscript and agree to be accountable for the work.

Conflict of Interest: The authors have no real or perceived conflicts of interest to disclose.

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Table 1. Study definitions and eligibility criteria

Definitions	
Fast breathing for age	• Children 2 to <12 months of age: RR ≥50 breaths per minute • Children ≥12 months of age: RR ≥40 breaths per minute
Severe respiratory distress	Grunting, nasal flaring, and/or head nodding
WHO IMCI general danger signs	Lethargy or unconsciousness, convulsions, vomiting everything, inability to drink or breastfeed
Eligibility criteria	
Inclusion criteria	<u>Chest-indrawing pneumonia cohort</u> • 2 through 23 months of age • Cough <14 days or difficulty breathing • Visible indrawing of the chest wall with or without fast breathing for age • Ability and willingness of child's caregiver to provide informed consent and to be available for follow-up for the planned duration of the study, including accepting a home visit if he/she fails to return for a scheduled study follow-up visit <u>No pneumonia cohort</u> • 2 through 23 months of age • Cough <14 days or difficulty breathing • Ability and willingness of child's caregiver to provide informed consent and to be available for follow-up for the planned duration of the study, including accepting a home visit if he/she fails to return for a scheduled study follow-up visit
Exclusion criteria	<u>Chest-indrawing pneumonia cohort</u> • Resolution of chest indrawing after bronchodilator challenge, if wheezing at screening examination • Severe respiratory distress • Arterial SpO_2 <90% in room air, as assessed non-invasively by a pulse oximeter • WHO IMCI general danger signs • Stridor when calm • Known or possible tuberculosis (history of a cough ≥14 days) • Any medical or psychosocial condition or circumstance that, in the opinion of the investigators, would interfere with the conduct of the study or for which study participation might jeopardize the child's health • Living outside the study catchment area

	<u>No pneumonia cohort</u> • Axillary temperature ≥38° C • Fast breathing for age • Visible indrawing of the chest wall • SpO_2 <95% in room air, as assessed non-invasively by a pulse oximeter • WHO IMCI general danger signs • Stridor when calm • Known or possible tuberculosis (history of a cough ≥14 days) • Any medical or psychosocial condition or circumstance that, in the opinion of the investigators, would interfere with the conduct of the study or for which study participation might jeopardize the child's health • Living outside the study catchment area

IMCI: Integrated Management of Childhood Illnesses; RR: respiratory rate; SpO_2: oxyhemoglobin saturation; WHO: World Health Organization.

Table 2. Baseline characteristics of enrolled and analyzed children by cohort and country

	Chest-indrawing pneumonia cohort			No pneumonia cohort			Between-cohort comparison p-value	
	Mozambique n = 98	Pakistan n = 128	Between-country comparison p-value	Mozambique n = 20	Pakistan n = 20	Between-country comparison p-value	Mozambique	Pakistan
Age (months)								
Mean (SD)	10.9 (6.0)	6.8 (4.8)	< 0.01	11.0 (6.1)	7.6 (4.8)	0.06	0.91	0.45
< 12 months, n (%)	55 (56.1%)	111 (86.7%)	< 0.01	12 (60.0%)	15 (75.0%)	0.50	0.94	0.18
Female, n (%)	39 (39.8%)	34 (26.6%)	0.049	14 (70.0%)	12 (60.0%)	0.74	0.03	< 0.01
Temperature (°C)								
Mean (SD)	37.1 (1.1)	36.7 (0.8)	< 0.01	36.3 (0.6)	36.3 (0.6)	0.72	< 0.01	0.02
Fever (≥38°C), n (%)	21 (21.4%)	11 (8.6%)	0.01	0 (0.0%)	0 (0.0%)		0.02	0.36
Respiratory rate (breaths per minute)								
<12 months, mean (SD)	52.5 (11.4)	53.5 (7.9)	0.58	39.7 (7.1)	38.8 (4.8)	0.72	< 0.01	< 0.01
≥12 months, mean (SD)	44.3 (10.0)	47.6 (9.6)	0.23	34.4 (4.2)	32.2 (4.5)	0.41	< 0.01	< 0.01
Fast breathing, n (%)	52 (53.1%)	83 (64.8%)	0.10	0 (0.0%)	0 (0.0%)		< 0.01	< 0.01
Oxyhemoglobin saturation (%), mean (SD)	97.8 (2.6)	95.3 (2.2)	< 0.01	96.2 (1.5)	96.8 (1.6)	0.23	< 0.01	< 0.01
<90%, n (%)	1 (1.0%)	0 (0.0%)	0.43	0 (0.0%)	0 (0.0%)		> 0.99	
Hemoglobin (g/dL), mean (SD)	10.0 (1.3)	10.7 (1.3)	< 0.01	10.3 (1.0)	9.4 (1.5)	0.04	0.37	< 0.01
Positive HIV rapid diagnostic test, n (%)[1]	0 (0.0%)			0 (0.0%)			> 0.99	
Positive malaria rapid diagnostic test, n (%)[2]	1 (1.0%)			0 (0.0%)			> 0.99	
C-reactive protein (ug/mL), mean (SD)[3]	38.8 (49.8)	109.9 (199.7)	< 0.01	18.2 (33.9)			0.03	
Procalcitonin (ng/mL), mean (SD)[4]	1.7 (7.2)			0.2 (0.6)			0.07	
Streptococcus pneumoniae[5]	84 (86.6%)							

Bordetella pertussis[6]	3 (3.1%)			0 (0.0%)			> 0.99	
Chlamydophila pneumophila[6]	0 (0.0%)			0 (0.0%)				
Legionella pneumophila[6]	0 (0.0%)			0 (0.0%)				
Mycoplasma pneumoniae[6]	3 (3.1%)			0 (0.0%)			> 0.99	
Nasopharyngeal viral polymerase chain reaction[7]								
Mean number of viruses detected (SD)	1.67 (1.04)	1.08 (0.65)	< 0.01	1.25 (0.55)			0.01	
Any viruses detected, n (%)	90 (91.8%)	84 (84.0%)	0.14	19 (95.0%)			0.31	
1 virus detected, n (%)	41 (41.8%)	61 (61.0%)		13 (65.0%)				
2 viruses detected, n (%)	30 (30.6%)	22 (22.0%)		6 (30.0%)				
3+ viruses detected, n (%)	19 (19.4%)	1 (1.0%)		0 (0.0%)				

SD = standard deviation

[1] HIV testing only conducted in Mozambique; missing for 55 children with chest-indrawing pneumonia.

[2] Malaria testing only conducted in Mozambique; missing for 2 children with chest-indrawing pneumonia.

[3] C-reactive protein missing for 5 children with chest-indrawing pneumonia in Mozambique; in Pakistan, only measured for children with chest-indrawing pneumonia.

[4] Procalcitonin only measured in Mozambique; missing for 5 children with chest-indrawing pneumonia.

[5] *S. pneumoniae* carriage only tested for 97 children with chest-indrawing pneumonia in Mozambique.

[6] *B. pertussis*, *C. pneumophila*, *L. pneumophila, M. pneumoniae* carriage only tested in Mozambique. All children with *B. pertussis* were also positive for *S. pneumoniae*, and 2 of the 3 children with *M. pneumoniae* were also positive for *S. pneumoniae*; no children were positive for both *B. pertussis* and *M. pneumoniae*.

[7] Viral carriage in Pakistan only tested in 100 analyzed children with chest-indrawing pneumonia.

Table 3. Baseline lung ultrasound imaging patterns of children by cohort and country

	Chest-indrawing pneumonia cohort			No pneumonia cohort			Between-cohort comparison p-value	
	Mozambique n = 98	Pakistan n = 128	Between-country comparison p-value	Mozambique n = 20	Pakistan n = 20	Between-country comparison p-value	Mozambique	Pakistan
Any consolidation, n (%)	15 (15.3%)	57 (44.5%)	< 0.01	0 (0.0%)	1 (5.0%)	> 0.99	0.07	< 0.01
Peripheral, n (%)	11 (11.2%)	51 (39.8%)		0 (0.0%)	1 (5.0%)			
Lobar, n (%)	5 (5.1%)	18 (14.1%)		0 (0.0%)	0 (0.0%)			
Present in both lungs, n (%)	4 (4.1%)	18 (14.1%)		0 (0.0%)	0 (0.0%)			
Any pleural effusion, n (%)	0 (0.0%)	2 (1.6%)	0.51	0 (0.0%)	0 (0.0%)			> 0.99
Simple, n (%)	0 (0.0%)	2 (1.6%)		0 (0.0%)	0 (0.0%)			
Complex, n (%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)			
Present in both lungs, n (%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)			
Any interstitial pattern, n (%)	24 (24.5%)	80 (62.5%)	< 0.01	2 (10.0%)	6 (30.0%)	0.24	0.24	0.01
Focal, n (%)	24 (24.5%)	64 (50.0%)		2 (10.0%)	6 (30.0%)			
Multifocal, n (%)	1 (1.0%)	28 (21.9%)		0 (0.0%)	1 (5.0%)			
Present in both lungs, n (%)	8 (8.2%)	46 (35.9%)		0 (0.0%)	4 (20.0%)			
Any obstructive atelectasis, n (%)	0 (0.0%)	3 (2.3%)	0.26	0 (0.0%)	0 (0.0%)			> 0.99
Present in both lungs, n (%)	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)			

Table 4. Interrater reliability among lung ultrasound experts

	Chest-indrawing pneumonia cohort (n = 226)	No pneumonia cohort (n = 40)
	Kappa	Kappa
Overall pneumonia	0.915	1†
Consolidation	0.915	1†
Pleural effusion	1†	
Interstitial pattern	0.901	0.635
Obstructive atelectasis	0.746	

† - Based on small counts for 1 of the 2 possible categories of interrater reliability, with 2 or fewer children in the smaller category.

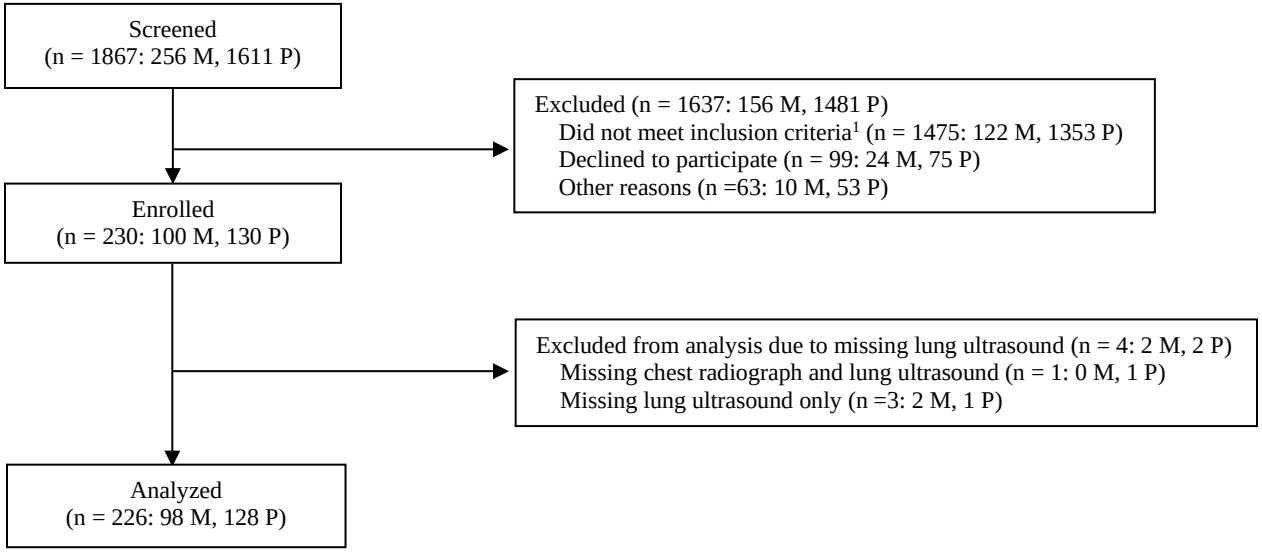
Note: Testing of kappa only signifies that the level of interrater reliability differs from what would occur by chance (kappa 0). Thus, p-values are not noted for kappa results.

Table 5. Baseline lung ultrasound pattern by nasopharyngeal carriage in the chest-indrawing pneumonia cohort in Mozambique[1]

	Chest-indrawing pneumonia cohort in Mozambique			
	Bacteria but no viruses detected n = 8	**Viruses but no bacteria detected** n = 12	**Both bacteria and viruses detected** n = 77	**Carriage type comparison p-value**
Any consolidation, n (%)	4 (50.0%)	1 (8.3%)	10 (13.0%)	0.03
Peripheral, n (%)	2 (25.0%)	1 (8.3%)	8 (10.4%)	
Lobar, n (%)	2 (25.0%)	1 (8.3%)	2 (2.6%)	
Present in both lungs, n (%)	1 (12.5%)	1 (8.3%)	2 (2.6%)	
Any pleural effusion, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Any interstitial pattern, n (%)	4 (50.0%)	4 (33.3%)	16 (20.8%)	0.14
Focal, n (%)	4 (50.0%)	4 (33.3%)	16 (20.8%)	
Multifocal, n (%)	1 (12.5%)	0 (0.0%)	0 (0.0%)	
Present in both lungs, n (%)	1 (12.5%)	2 (16.7%)	5 (6.5%)	
Any obstructive atelectasis, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	

[1] Both bacterial and viral carriage assessed in Mozambique. Pakistan did not have bacterial carriage testing conducted.

Figure 1a. Flow of children with chest-indrawing pneumonia by country: Mozambique (M), Pakistan (P)



[1] 70 children in Mozambique (27.3% of screened) and 1318 children in Pakistan (81.8% of screened) met the "no chest indrawing" exclusion criterion.

Figure 1b. Flow of children with no fast breathing, no chest indrawing and no fever by country: Mozambique (M), Pakistan (P)

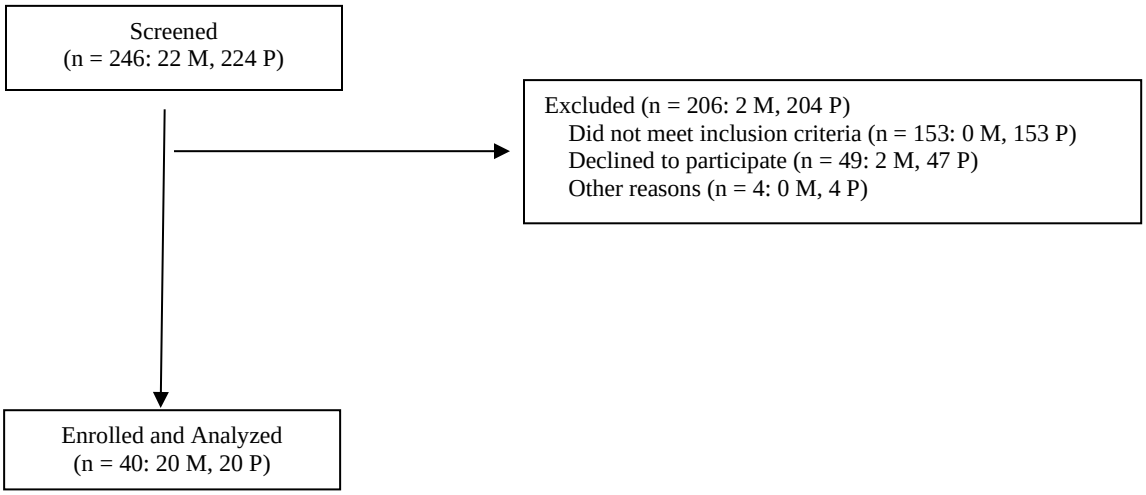
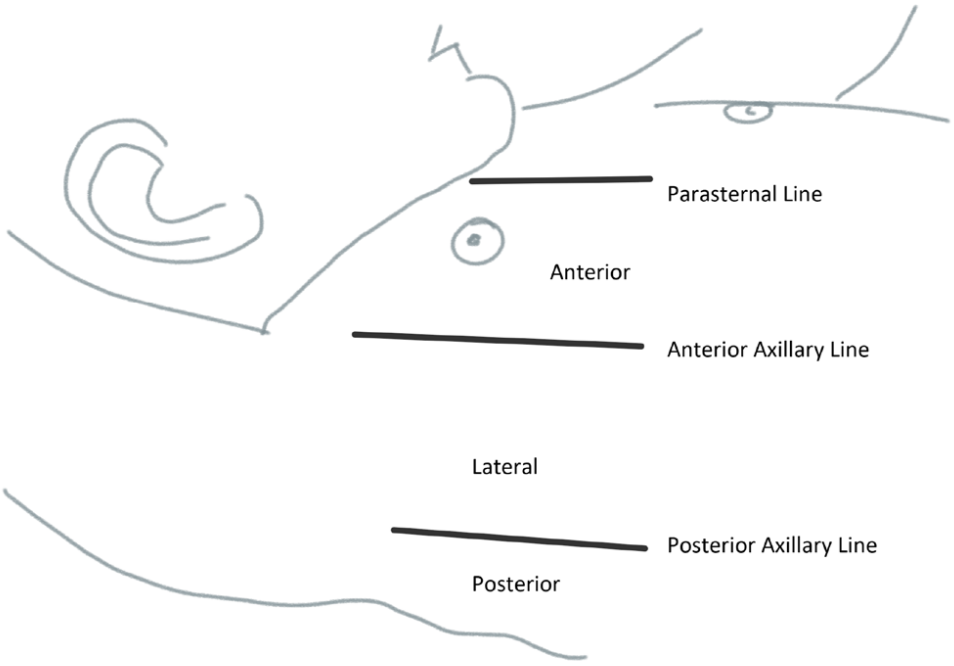
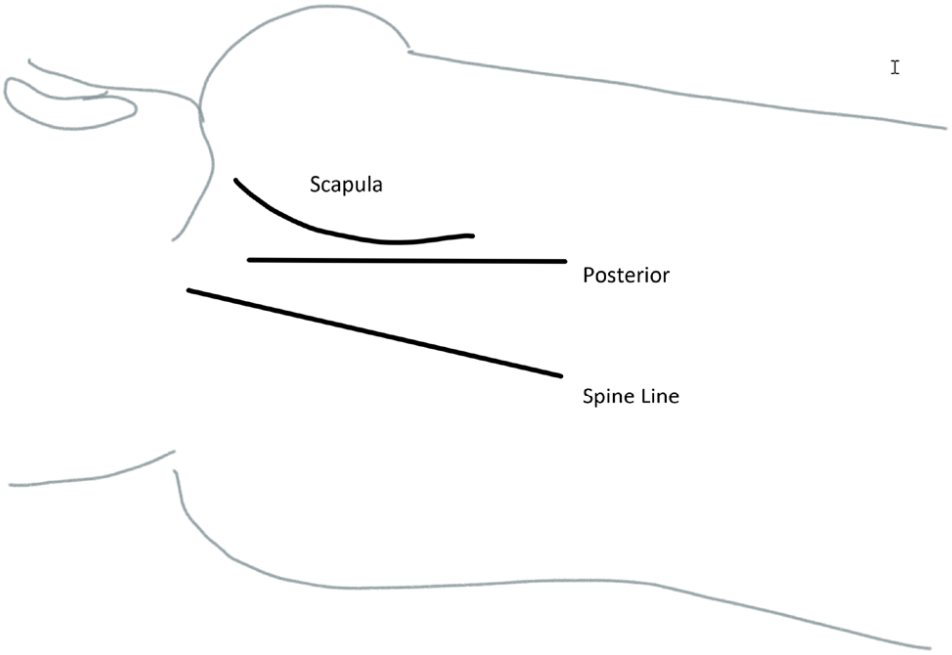


Figure 2. Lung ultrasound examinations consisted of longitudinal and oblique scans obtained of the anterior, lateral, and posterior sides of the child's chest.




Scapula
Posterior
Spine Line

Appendix 1. Nasopharyngeal carriage of viruses tested in enrolled and analyzed[1] children by cohort and country

	Chest-indrawing pneumonia cohort			No pneumonia cohort	Mozambique
Virus, n (%)	Mozambique n = 98	Pakistan n = 100	Between-country comparison p-value	Mozambique n = 20	Between-cohort comparison p-value
Adenovirus	22 (22.4%)	2 (2.0%)	< 0.01	3 (15.0%)	0.56
Bocavirus	13 (13.3%)	8 (8.0%)	0.33	2 (10.0%)	0.73
Coronavirus 229E	0 (0.0%)	0 (0.0%)		0 (0.0%)	
Coronavirus HKU1	0 (0.0%)	1 (1.0%)	> 0.99	0 (0.0%)	
Coronavirus NL63	1 (1.0%)	1 (1.0%)	> 0.99	4 (20.0%)	< 0.01
Coronavirus OC43	0 (0.0%)	7 (7.0%)	0.01	1 (5.0%)	0.17
Human metapneumovirus AB	16 (16.3%)	5 (5.0%)	0.02	2 (10.0%)	0.73
Influenza A H1N1pdm09	7 (7.1%)	2 (2.0%)	0.10	1 (5.0%)	> 0.99
Influenza A H1	0 (0.0%)	0 (0.0%)		0 (0.0%)	
Influenza A H3	0 (0.0%)	0 (0.0%)		0 (0.0%)	
Influenza B	0 (0.0%)	1 (1.0%)	> 0.99	0 (0.0%)	
Parainfluenza virus 1	2 (2.0%)	0 (0.0%)	0.24	0 (0.0%)	> 0.99
Parainfluenza virus 2	2 (2.0%)	0 (0.0%)	0.24	0 (0.0%)	> 0.99
Parainfluenza virus 3	12 (12.2%)	7 (7.0%)	0.31	6 (30.0%)	0.08
Parainfluenza virus 4	2 (2.0%)	1 (1.0%)	0.62	0 (0.0%)	> 0.99
Respiratory syncytial virus	35 (35.7%)	17 (17.0%)	< 0.01	0 (0.0%)	< 0.01
Rhinovirus	52 (53.1%)	56 (56.0%)	0.79	6 (30.0%)	0.10

[1] - Viral carriage in Pakistan tested in 100 children in the chest-indrawing pneumonia cohort.

Regarding viral strains that were present in at least 10% of children with chest-indrawing pneumonia either in Mozambique or Pakistan, adenovirus was more common in Mozambique than Pakistan (22.4% vs 2.0%;p<0.01), as were bocavirus (13.3% vs 8.0%;p=0.33), human metapneumovirus AB (16.3% vs 5.0%;p=0.02), parainfluenza virus 3 (12.2% vs 7.0%;p=0.31), and respiratory syncytial virus (RSV) (35.7% vs 17.0%;p<0.01); rhinovirus was similarly common among children with chest-indrawing pneumonia at both sites (53.1% in Mozambique vs 56.0% in Pakistan,p=0.79). Among children in the no pneumonia cohort in Mozambique, adenovirus (15.0%), bocavirus (10.0%), human metapneumovirus AB (10.0%), parainfluenza virus 3 (30.0%), and rhinovirus (30.0%) appeared similarly common compared to children with chest-indrawing pneumonia in Mozambique, but coronavirus NL63 was more common in the no pneumonia cohort (20.0% vs 1.0%,p<0.01), while RSV was less common (0.0% vs 35.1%,p<0.01).

Appendix 2. Baseline chest radiograph imaging patterns of children by cohort[1] and country

	Chest-indrawing pneumonia cohort[1]			No pneumonia cohort			Between-cohort comparison p-value	
	Mozambique n = 97	**Pakistan** n = 123	**Between-country comparison p-value**	**Mozambique** n = 20	**Pakistan** n = 20	**Between-country comparison p-value**	**Mozambique**	**Pakistan**
Any consolidation, n (%)	18 (18.6%)	12 (9.8%)	0.09	4 (20.0%)	0 (0.0%)	0.11	> 0.99	0.22
Any pleural effusion, n (%)	1 (1.0%)	0 (0.0%)	0.44	0 (0.0%)	0 (0.0%)		> 0.99	
Any interstitial pattern, n (%)	35 (36.1%)	44 (36.1%)[2]	> 0.99	3 (15.0%)	2 (10.0%)	> 0.99	0.12	0.04
Any obstructive atelectasis, n (%)	0 (0.0%)	1 (0.8%)	> 0.99	0 (0.0%)	0 (0.0%)			> 0.99

[1] Chest-indrawing pneumonia cohort is limited to 97 children in Mozambique and 123 children in Pakistan with both lung ultrasound and chest radiograph imaging.

[2] Presence of interstitial pattern was indeterminate for 1 child in the chest-indrawing pneumonia cohort in Pakistan.

Appendix 3. Baseline chest radiograph consolidation imaging patterns by cohort[1] and country

			CXR consolidation determination			Kappa
			Negative	Positive	Total	
Chest-indrawing pneumonia cohort[1]	Mozambique: LUS consolidation determination	Negative	73	9	82	0.453
		Positive	6	9	15	
		Total	79	18	97	
	Pakistan: LUS consolidation determination	Negative	65	2	67	0.159
		Positive	46	10	56	
		Total	111	12	123	
No pneumonia cohort	Mozambique: LUS consolidation determination	Negative	16	4	20	0†
		Positive	0	0	0	
		Total	16	4	20	
	Pakistan: LUS consolidation determination	Negative	19	0	19	0†
		Positive	1	0	1	
		Total	20	0	20	

[1] Chest-indrawing pneumonia cohort is limited to 97 children in Mozambique and 123 children in Pakistan with both lung ultrasound and chest radiograph imaging.

† Based on few children in the smaller positive/negative category for one imaging modality, and no children in one category for the other imaging modality.