Implementation of Lung Ultrasound in Low-to-Middle Income Countries: a new challenge global health?

Danilo Buonsenso[1,2,3]*, MD; Cristina De Rose[1], MD

[1] Department of Woman and Child Health and Public Health, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy

[2] Dipartimento di Scienze Biotecnologiche di Base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Rome, Italy

[3] Global Health Research Institute, Istituto di Igiene, Università Cattolica del Sacro Cuore, Roma, Italy

***Corresponding author:**

Danilo Buonsenso,

Largo A. Gemelli 8, 00168, Roma, Italy.

Email: danilobuonsenso@gmail.com

Tel: 0039 063015 4390

Twitter: @surf4children

Conflicts of interest: None of the participants has any conflict of interest to declare.

Funding: Nothing to declare.

Running head: Lung Ultrasound in Low-to-Middle Income Countries

Key words: lung ultrasound, LUS, Low-to Middle Income Countries, LMICs, challenge, global health

Abstract

Pneumonia remains the leading cause of death globally in children under the age of five. The poorest children are the ones most at risk of dying. In the recent years, Lung Ultrasound has been widely documented as a safe and easy tool for the diagnosis and monitoring of pneumonia and several other respiratory infections and diseases. During the pandemic, it played a primary role to achieve early suspicion and prediction of severe COVID-19, reducing the risk of exposure of healthcare workers to positive patients. However, innovations that can improve diagnosis and treatment allocation, saving hundreds of thousands of lives each year, are not reaching those who need them most. In this paper, we discuss advantages and limits of different tools for the diagnosis of pneumonia in low-to-middle income countries, highlighting potential benefits of a wider access to lung ultrasound in these settings and barriers to its implementation, calling international organizations to ensure the indiscriminate access, quality and sustainability of the provision of ultrasound services in every setting.

Background

Each year, approximately 920,000 children die from acute lower respiratory tract infections (ALRTIs) before age 5.[1] A substantial reduction in estimated deaths from pneumonia in recent decades (0.9 million in 2015 vs 1.7 million in 1990) reflects not only economic development, improved nutrition and reduced household crowding, but also improvements in specific interventions such as better case management, including empirical antibiotic treatment, and vaccination campaigns against the main pathogens of pneumonia.[2,3]

However, pneumonia remains the leading cause of death globally in children under the age of five, accounting for about 12.8% of annual deaths beyond the neonatal period.[1]

Pneumonia continues to disproportionately affect children in impoverished areas with both short-term and long-term consequences. The latter are linked to the spread of antibiotic-resistance, which represents a major threat to global health especially for low- and middle-income countries (LMICs).[1,4,5]In fact, although viruses represent the most frequent cause of LRTIs, most children with suspected or confirmed pneumonia are still treated with empirical and often unnecessary antibiotics[6], contributing to the spread of antibiotic resistance. In the Centers for Disease Control and Prevention Etiology of Pneumonia in the Community cohort, only 15% of hospitalized children with radiographic pneumonia had a detectable bacterial etiology; however, 88% received antibiotics.[7] Current guidelines do not help the physician on how to approach to an optimized strategy for prevention, diagnosis, and treatment of disease for each single child with LRTIs, based on his or her unique characteristics, but mainly suggest a general approach to pediatric pneumonia.[8.9]

Current challenges in diagnosis and management of pneumonia in LMICs

In primary care settings in low-income communities, the diagnosis of pneumonia is mainly clinical and guided by the Integrated Management of Childhood Illnesses (IMCI) approach of the World Health Organization (WHO).[8] WHO guidelines classify acute LRTIs as “absence of pneumonia”, “mild pneumonia” (with tachypnea or chest wall retraction), or “severe pneumonia with danger signs” (stridor when the patient is calm, hypoxia, inability to feed, persistent vomiting, convulsions, and decreased level of consciousness).[8]Although all guidelines state that clinical examination is sufficient for the diagnosis of pneumonia, studies have clearly showed the low sensitivity and specificity of this approach.[10]In fact, most practitioners seek support in radiological confirmation, when accessible.[11]

With the rationale that pneumonia has a bacterial cause in a substantial percentage of children, current guidelines emphasize sensitivity over specificity, suggesting in LMICs a diagnosis of pneumonia in children with tachypnea and cough. In these cases (eg “chest-indrawing pneumonia”), the WHO recommends a 5-day course of oral amoxicillin as first-line treatment in children younger than 5 years of age.[8,12,14] This clinical approach mainly relies on expert opinion and weak evidence, having poor sensitivity for both the diagnosis of pneumonia and its etiology.[13,14]

However, the epidemiological characteristics of pneumonia are changing also in LMICs following vaccination against the main pathogens such as *Haemophilus influenzae* type B and *Streptococcus pneumoniae*[5,15-17] with viral pathogens now cause of most LRTIs.[18]

Recent trials further supported these data. Ginsburg et al. in Malawi[15] demonstrated that a 3-day course of amoxicillin was not inferior to a 5-day course. Jehan et al in Pakistan[16] showed that more than 93% of Pakistani children who were randomly assigned to receive placebo recovered quickly without relapse. The number of children with pneumonia and tachypnea who should have been treated with amoxicillin to prevent treatment failure was 44. This finding suggests, on one hand, that a significant number of ALRTIs were of viral origin and did not require antibiotics.[16] On the other, this number of patients is relatively high to suggest that antibiotics may not be guaranteed for large numbers of children in these resource-constrained countries.[19]Also, it is possible that a number of children clinically diagnosed with pneumonia did not have pneumonia. These concepts suggest that there are subgroups with a clinical phenotype severe enough to warrant antibiotic therapy and identifying these subgroups for targeted treatment can limit unnecessary use of antibiotics.

The effect of excessive treatment on the community should not be neglected in the era of increasing antimicrobial multi-resistance. Resistance to beta-lactam antibiotics is at epidemic levels in some parts of LMICs[20], and antibiotic prescription appropriateness is the only sure way to prevent further extension of cephalosporin and carbapenem resistance.

These data highlights that in LMICs there is a worrying gap in the appropriate diagnosis and treatment allocation of children with suspected pneumonia. While in the past decades global health efforts focused in providing ***greater*** access to care (mainly vaccines and antibiotics) in LMICs, time has probably come to focus on providing ***appropriate*** and ***effective*** care. The flattening curve of reduced pneumonia-related deaths during the last years, and the increasing threats of antibiotic resistance, should highlight the need of a more modern, globalized, respectful and sustainable approach in global health. The next step to sustainably reduce pneumonia mortality should be based on the concepts "*how can we improve the accuracy of pneumonia diagnosis in LMICs?*" and "*how can we better allocate to antibiotic treatment each child with pneumonia*?". Approaches focusing on mass antibiotic distribution, although in the short-term showed efficacy in reducing child mortality, were associated with increased antibiotic resistance and are not economically sustainable and are impossible to achieve for millions of children.[20,21]

If such an approach would never be considered in richer settings, why should it be supported in LMICs, if a better diagnostic and treatment process can be accomplished?

A further limitation of mentioned studies[15,16,22,23],common challenge in daily practice in LMICs, is related to the lack of opportunities for clinical-imaging monitoring of those patients with suspected pneumonia, thanks to whom a clinician would better decide how to manage a child, according to its improvement/worsening during the following days. This limitation is mainly due to the unsustainability of traditional radiological/microbiological equipment in LMICs. Is this really an unsolvable problem?

Limits of traditional tools for the clinical and etiological diagnosis of pneumonia in LMICs

The microbial diagnosis of pneumonia in children is not easy to establish without invasive procedures, which in addition to being inaccessible in LMICs countries, are only rarely performed in this age group.[24]

To date, both *clinical findings*[25]and *laboratory results*[26,27]failed to accurately distinguish viral, bacterial and atypical pneumonia. Even studies that report differences in laboratory biomarkers could not determine reliable thresholds for differentiating bacterial pneumonia from viral pneumonia[28], since normal tests do not always exclude bacterial pneumonia.[8,9]Moreover, routine performance of blood tests in LMICs is difficult in terms of costs, risk of parenteral infections (eg HIV), waste storage and disposal, need of infrastructures and their maintenance, including electricity and running water.[8]

Radiologically, the "gold standard" for the diagnosis of CAP is the chest Computed Tomography (CT) scan, however its routine use in children is not ethical and is expensive.[30] Chest x-ray (CXR) is not necessary to confirm the diagnosis of acute LRTIs in milder cases and is also associated with radiation exposure.[28]Moreover, CXR cannot reliably establish the microbial diagnosis of pneumonia[29] and the interpretation of radiographic images varies significantly among the observers.[30] Furthermore, only 220 million people - for a population of over five billion people - (both individually and at the level of the hospital units) in LMICs have access to traditional radiology services. The WHO estimates that 60% of the world's population does not have access to CXR, CT, or other imaging tools in their local health centers.[31]Traditional radiological areas require expensive equipment, large areas, continuous use of electricity and heavy maintenance, which is not feasible in most LMICs settings, particularly in peripheral ones.

The role of lung ultrasound in the diagnosis of LRTIs in children

In recent years, lung ultrasound (LUS) use has been widely studied as an alternative diagnostic tool for pneumonia of both bacterial and viral origin, proving to have high specificity and sensitivity for the diagnosis and follow-up of pneumonia in children[32-34]. Moreover, LUS has several advantages over CXR, particularly useful for the pediatric population: radiation-free, lower cost, possibility of follow-up examinations, ability to monitor treatment, easy accessibility in all settings, fast, easily learnable, and can be used immediately as a point-of-care method. LUS results are immediately available to the clinician, allowing decisions about the initial empirical treatment.[29,32-35]

The first decade of LUS studies focused on the role of LUS in detecting pneumonia. A recently performed meta-analysis confirmed high sensitivity (96%) and specificity (93%) of LUS for detecting pneumonia in children.[36] The accuracy of LUS for the diagnosis of pneumonia has been confirmed worldwide and there is international agreement on this, including during the COVID-19 pandemic.[37,38]

In this context, recognizing bacterial pneumonia from a viral or atypical pneumonia using LUS at patient's bedside would allow to offer a more focused approach and treatment to each child, responding to a modern medical concept that each patient is a unique one and requires a personalized approach.

First studies showed specific LUS patterns to diagnose viral LRTIs and bronchiolitis in children.[39,40] Buonsenso and colleagues[33,34] showed that specific LUS patterns on diagnosis and after 48 hours of treatments (bronchograms, consolidation size, characteristics of pleural effusion) were predictive of antibiotic response in children with pneumonia, more than clinical data and laboratory results. Berce et al[29]evaluated 147 children hospitalized because of CAP, showing that LUS detected consolidations in viral CAP were significantly smaller, with a median diameter of 15mm, compared to 20mm in atypical bacterial LRTIs ($p = 0.05$) and 30 mm in bacterial LRTIs ($p <0.001$). Other authors also highlighted that consolidation size or distribution can support the diagnosis of viral bronchiolitis, Influenza pneumonia and COVID19 pneumonia.[29,37-40]A recent prospective study performed by Buonsenso et al[35]found that air bronchograms were more common in bacteria and atypical pneumonia but, importantly, fluid bronchograms were almost exclusively described in bacterial cases. Also, complicated pleural effusions were never described in viral pneumonias. Vertical artefacts, which gained more interest during the last year and in particular since LUS has been routinely used in COVID-19 pneumonia[32,37,38], also played a significant role, since in bacterial pneumonia were mainly located in proximity of the main consolidation , while in the others were mostly diffuse and bilateral.[35]Conversely, clinical parameters, including fever, chest pain and main auscultation features, and laboratory were not able to significantly distinguish between these groups of pneumonia. CXR, despite being still widely used, was the less useful tool in this discrimination.[35]

The ultrasound power in LMICs

During this period of rapid globalization, technology has had its greatest impact in the provision of health services.[41] One of the most important technological tools in the provision of quality health services is ultrasound, the application of which is increasingly wide. Already in 1985, WHO stated that there are "very real benefits to be gained from the use of ultrasound" and noted its potential for "better patient management and individual care" in developing areas (eg where ultrasound may represent the only useful radiological service).[42,43]

Ultrasonography is considered a sustainable type of technology for developing countries, due to its relatively low purchase cost, low cost of maintenance and supplies, portability and durability compared to other imaging modalities.[44]The most recent devices (whose development have been accelerated by the COVID-19 pandemic when point-of-care ultrasound was found particularly useful in this context) can be linked directly to a smartphone.

Additionally to known benefits, ultrasound (LUS in particular) can be readily learned by a variety of medical professionals, not just radiological, to allow for rapid assessment and treatment in a variety of settings. Ultrasound devices can be used by a single operator, handheld and can provide diagnostic capabilities at a much lower cost than other imaging tools such as CT or magnetic resonance imaging (MRI) and, in rural regions of LMICs, also compared with to traditional radiology.[45] These features make ultrasound an attractive option for clinical use in LMICs for both inpatient and outpatient use.

Several studies have demonstrated the diagnostic utility of ultrasound in the medical, surgical and obstetric fields in LMICs.[46,47]This has led to the increase in point-of-care ultrasound (POCUS) in LMICs[45], which is done by the doctor in real time and at the bedside.[48]Studies have shown that doctors and other healthcare professionals can perform effective and accurate scans after 3 hours of teaching and about 5 hours of practice.[49]

Several studies[45-50] have shown that POCUS can represent an important diagnostic tool in rural areas of low-income countries, which often lack radiological facilities. Ultrasound has been shown to change the initial diagnostic hypothesis in a considerable part of cases, thus improving patient management.[49,50] Kolbe et al[51]showed that POCUS performed on 132 Nicaraguan patients led to a new diagnosis in 52% of them and in 48% of cases it changed the therapeutic management.

Regarding lung ultrasound (LUS) in particular, there are not many studies evaluating its use in LMICs because its application is still scarce in these countries. However, LUS can be an important tool for the development of health services in LMICs, especially when it is compared with traditional radiological investigations, which are mostly inaccessible in LMICs, cannot be routinely suggested and used in children, and are unable to provide a reliable etiological diagnosis. Other than this logistic/economic advantages, particularly when is used in adjunction to clinical data, LUS can accurately diagnose pneumonia and support the etiological (viral/bacterial) of pneumonia and offer a personalized approach to patients. If further confirmed, this approach can also support antibiotic stewardship programs.

Furthermore, considering the recent literature data[29,35-40,52]which show the proven ability of LUS to detect pneumonia, cardiogenic edema and inflammatory interstitial lung disease, the potential for application of LUS in poor countries can certainly increase. In particular, respiratory distress is common in patients with malaria or sepsis. A major cause of life-threatening respiratory distress in these common infectious diseases in LMICs includes acute respiratory distress syndrome (ARDS).[53] Early bedside detection of life-threatening ARDS can guide therapy, which could possibly improve outcomes. In previous studies, LUS has been shown to outperform chest X-ray in detecting pulmonary edema.[54] Recently, a modification of the international consensus definition of ARDS (the Berlin definition) has been proposed to facilitate a diagnosis of ARDS based on lung ultrasound and SpO2 / FiO2 (SF) ratios in resource-limited settings.[55,56]A recent observational study in an intensive care unit in the Netherlands found a high diagnostic agreement between the Berlin definition and the new Kigali modification.[57]

Furthermore, a recent study[53]demonstrates the great potential advantage of point-of-care LUS in the early diagnosis of pulmonary manifestations of malaria and sepsis by describing the patterns of LUS aeration. The study results highlight the difficulties of diagnosing ARDS in a resource-limited hospital according to conventional criteria and show the potential for adapted LUS-based ARDS criteria to be used for the triage of high-risk patients. In the absence of other imaging facilities, or where the quality of available CXR is poor, the availability of an ultrasound machine can accelerate the underlying diagnosis of severe respiratory distress in LMICs.

Also in this cases, without wasting unsustainable resources, it is possible to optimize patient care both at the time of diagnosis and during follow-up.

Challenges, inequalities and difficulties in accessing ultrasound in LMICs

A review shows that research studies on the use of ultrasound and POCUS in LMICs have increased by nearly 60% and expanded geographically by 20% over the past decade.[45] However, the evidence also suggests that most of the ultrasound studies were conducted at tertiary care centers (over 70%

of all ultrasound studies) in middle-income countries, demonstrating broader problems such as lack of access to health care in low-income economies and especially in rural areas.[45]

This reflects what happens in clinical practice and the inequality of supply, training and acquisition of medical equipment within the LMICs themselves.

The social reality in LMICs directly influences the training and acquisition of medical equipment. For example, it is still thought that ultrasound is the exclusive portfolio of the radiologist and some very specific specialists such as in emergency intensive care, gynecology-obstetrics and cardiologists. Outside of this niche, the other specialties and professionals are navigating a limbo where there is no one to support, regulate and train them as potential users of ultrasound at the point of care. However, a similar scenario happened in the United States and Europe, where recently protocols and procedures have been clarified and ultrasound techniques became accessible to other specialists and is currently are taught in several medical schools.

The accessibility of the equipment by suppliers, whether by government agencies or the self-purchase of the equipment by the same user, is still complicated in Latin America as well as in other LMICs. For example, the salary of a general practitioner in Mexico ranges from 400 to 720 euros per month in the best of cases, a pocket ultrasound with acceptable characteristics is around 1,900 euros, which some professionals cannot afford easily. Therefore, there remains their acquisition by private or government organizations that must be convinced that investing in portable ultrasound equipment will also save costs.[57,58]

Two areas have major implications on the access, quality and sustainability of ultrasound service delivery wherever it is established: ultrasound equipment maintenance and training. Indeed, ensuring the sustainability of ultrasound programs in settings with limited resources will also require the implementation of successful training programs for local professionals and the development of quality assurance markers. The lack of qualified ultrasound scanners, most likely due to poor conditions in a developing world, has been an obstacle to the implementation of clinical examination with ultrasound assessment, but the training of local health workers in developing countries is possible, more ethical, and could allow effective use of ultrasound.

In fact, training is also fundamental for the sustainability, quality and reliability of any service, in particular ultrasound services. Since the quality of ultrasound depends on the operator, both theoretical and practical training must be combined to enrich the operator's experience and ensure quality of service. Mindel supports the strengthening of local training programs[59], which can be more sustainable and cheaper than sending doctors abroad[60] or quality assurance.[50,58]

In circumstances where quality local training is not available, the alternative remains foreign training or the rotation of visiting experts considering that teaching POCUS and LUS to medical and non-medical health professionals is possible with an intensive training of a couple of weeks which includes practical-theoretical courses.[50]To ensure continuity, however, constant telematics collaborations should also be established with foreign institutions and ultrasound schools.

Additionally, the use of portable ultrasound machines can improve access in remote rural areas. Since many hospitals in these areas do not have reliable power supplies, the use of solar panels can provide relief from the challenge of inadequate power supply to keep the system running in rural areas of LIMCs.

An effective referral system between primary and specialized centers should also be established, and protocols should be developed. This will allow patients to be referred to specialists whenever there are doubts about certain results.

A call for action of global health to finance access to ultrasound services and training in LMICs

Pneumonia remains a neglected disease both nationally and globally.[61] Pneumonia deaths are decreasing but more slowly than other leading causes of infant mortality[62], and too slowly to reach the sustainable development goal of ending preventable infant deaths by 2030.[62-64]

Pneumonia today can be considered the disease of poverty. The poorest children are the ones most at risk of dying. Innovations that can improve diagnosis and treatment allocation, saving hundreds of thousands of lives each year, are not reaching those who need them most.[62-64] The early successes of wider antibiotic access in LMICs, which contributed to reduce pneumonia mortality during the last decades, is now becoming an indiscriminate access to antibiotics, and is fueling the spread of antibiotic resistance globally and in LMICs. This is not contributing in further decrease in mortality and, ultimately, this will end in increased mortality during the next decades.[65-66]

Therefore, time has come to shift *from better access to care, to access to better care*. Recent developments in technological innovation can easily allow this, and LUS can support this process in LMICs, if global health institutions pose the proper attention and interests on this issue.

The WHO programs are aiming to achieve the Sustainable Development Goal (SDG) 3.2 by 2030, through the support of greater inclusion of pneumonia control in the main global health policies, programs and initiatives. Among the initiatives, the program mention the collaboration with partners and ministries of health; and a call to governments and international development agencies to issue vaccines, diagnostic tests, pulse oximetry, antibiotics and oxygen delivery in LMICs.[63-64,67]

The acquisition of these goals requires a multidisciplinary collaboration on different levels, not easily linked. Conversely, improving the proper diagnosis and treatment of pneumonia is much easier and feasible in the short time, and would be the primary step to achieve the final goal of reduced childhood mortality (figure 1). LUS is not the solution, but can play a primary role in the fight against pneumonia and can be easily implemented in the short time but with long lasting benefits, since it is already well established in richer countries.

In conclusion, we believe that in the programs of the WHO and its partners it is essential to include and ensure the access, quality and sustainability of the provision of ultrasound services of POCUS and LUS through the supply of equipment, maintenance and training of their users.

In remote health centers or even where there are none, geographic areas with high social inequality that affect the health of children, POCUS and LUS add incalculable value to the diagnosis and management of patients, ultimately saving lives.

REFERENCES

1. Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. *Lancet* 2015;385:430-40.
2. Feikin DR, Flannery B, Hamel MJ, Stack M, Hansen PM. Vaccines for Children in Low- and Middle-Income Countries. In: Black RE, Laxminarayan R, Temmerman M, Walker N, eds. *Reproductive, Maternal, Newborn, and Child Health: Disease Control Priorities, Third Edition (Volume 2).* Washington (DC): The International Bank for Reconstruction and Development / The World Bank; April 5, 2016.
3. Lee LA Franzel L Atwell J et al. The estimated mortality impact of vaccinations forecast to be administered during 2011–2020 in 73 countries supported by the GAVI Alliance. *Vaccine* 2013;31: B61-B72
4. Nair H, Simões EA, Rudan I, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *Lancet* 2013;381:1380-90
5. Leung DT, Chisti MJ, Pavia AT. Prevention and control of childhood pneumonia and diarrhea. *Pediatr Clin North Am* 2016;63:67-79
6. Lipshaw MJ, Eckerle M, Florin TA, et al. Antibiotic Use and Outcomes in Children in the Emergency Department With Suspected Pneumonia. Pediatrics. 2020;145(4):e20193138
7. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med* 2015;372(9):835-845
8. Revised WHO classification and treatment of childhood pneumonia at health facilities. Geneva: *World Health Organization* 2014
9. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by

the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2011;53(7):e25-e76

10. Shah SN, Bachur RG, Simel DL, Neuman MI. Does This Child Have Pneumonia?: The Rational Clinical Examination Systematic Review. *JAMA* 2017;318(13):1284
11. Andronikou S, Lambert E, Halton J, et al. Guidelines for the use of chest radiographs in community-acquired pneumonia in children and adolescents. *Pediatr Radiol* 2017;47(11):1405-1411.
12. Grant GB, Campbell H, Dowell SF, et al. Recommendations for treatment of childhood non-severe pneumonia. *Lancet Infect Dis* 2009;9:185-96
13. Das RR, Singh M. Treatment of severe community-acquired pneumonia with oral amoxicillin in under-five children in developing country: a systematic review. *PLoS One* 2013;8(6):e66232-e66232.
14. Grimwood K, Fong SM, Ooi MH, Nathan AM, Chang AB. Antibiotics in childhood pneumonia: how long is long enough? *Pneumonia (Nathan)* 2016;8:6-6
15. Ginsburg AS, Mvalo T, Nkwopara E, McCollum ED, Phiri M, Schmicker R, Hwang J, Ndamala CB, Phiri A, Lufesi N, May S. Amoxicillin for 3 or 5 Days for Chest-Indrawing Pneumonia in Malawian Children. *N Engl J Med* 2020 Jul 2;383(1):13-23.
16. Jehan F, Nisar I, Kerai S, Balouch B, Brown N, Rahman N, Rizvi A, Shafiq Y, Zaidi AKM. Randomized Trial of Amoxicillin for Pneumonia in Pakistan. *N Engl J Med* 2020 Jul 2;383(1):24-34.
17. Wahl B, O'Brien KL, Greenbaum A, et al. Burden of Streptococcus pneumoniae and Haemophilus influenzae type B disease in children in the era of conjugate vaccines: global, regional, and national estimates for 2000-15. *Lancet Glob Health* 2018;6(7):e744-e757
18. Picot VS, Bénet T, Messaoudi M, et al. Multicenter case-control study protocol of pneumonia etiology in children: Global Approach to Biological Research, Infectious

diseases and Epidemics in Low-income countries (GABRIEL network). *BMC Infect Dis* 2014;14:635-635

19. Zhang S, Sammon PM, King I, et al. Cost of management of severe pneumonia in young children: systematic analysis. *J Glob Health* 2016;6:010408
20. Fink G, D'Acremont V, Leslie HH, Cohen J. Antibiotic exposure among children younger than 5 years in low-income and middle-income countries: a cross-sectional study of nationally representative facility-based and household-based surveys. *Lancet Infect Dis* 2020;20(2):179-187.
21. Doan T, Worden L, Hinterwirth A, et al. Macrolide and Nonmacrolide Resistance with Mass Azithromycin Distribution. *N Engl J Med* 2020;383(20):1941-1950.
22. Greenberg D, Givon-Lavi N, Sadaka Y, Ben-Shimol S, Bar-Ziv J, Dagan R. Short-course antibiotic treatment for communityacquired alveolar pneumonia in ambulatory children: a doubleblind, randomized, placebo-controlled trial. *Pediatr Infect Dis J* 2014;33:136-42.3.
23. Pneumonia Etiology Research for Child Health (PERCH) Study Group. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. *Lancet* 2019;394:757-779.
24. Tramper-Stranders GA. Childhood community-acquired pneumonia: A review of etiology- and antimicrobial treatment studies. *Paediatr Respir Rev* 2018;26:41-48.
25. Korppi, M., Don, M., Valent, F. & Canciani, M. The value of clinical features in differentiating between viral, pneumococcal and atypical bacterial pneumonia in children. *Acta Pediatr* 2008;97,943-947.
26. Berg AS, Inchley CS, Fjaerli HO, Leegaard TM, Lindbaek M, Nakstad B. Clinical features and inflammatory markers in pediatric pneumonia: a prospective study. *Eur J Pediatr* 2017;176(5):629-638.

27. Stockmann C, Ampofo K, Killpack J, et al. Procalcitonin Accurately Identifies Hospitalized Children With Low Risk of Bacterial Community-Acquired Pneumonia. *J Pediatric Infect Dis Soc* 2018;7(1):46-53.
28. O'Grady KF, Torzillo PJ, Frawley K, Chang AB. The radiological diagnosis of pneumonia in children. *Pneumonia (Nathan)* 2014;5(Suppl 1):38-51.
29. Berce V, Tomazin M, Gorenjak M, Berce T, Lovrenčič B. The Usefulness of Lung Ultrasound for the Aetiological Diagnosis of Community-Acquired Pneumonia in Children. *Sci Rep* 2019;9(1):17957.
30. Elemraid MA, Muller M, Spencer DA, et al. Accuracy of the interpretation of chest radiographs for the diagnosis of paediatric pneumonia. *PLoS One* 2014;9(8):e106051
31. Mindel S. Role of imager in developing world. *Lancet* 1997;350(9075):426–429
32. Musolino AM, Supino MC, Buonsenso D, et al. Roman Lung Ultrasound Study Team for Pediatric COVID-19 (ROMULUS COVID Team). Lung Ultrasound in Children with COVID-19: Preliminary Findings. *Ultrasound Med Biol* 2020;46(8):2094-2098.
33. Musolino AM, Tomà P, Supino MC, et al. Lung ultrasound features of children with complicated and noncomplicated community acquired pneumonia: A prospective study. *Pediatr Pulmonol* 2019;54(9):1479-1486.
34. Buonsenso D, Brancato F, Valentini P, Curatola A, Supino M, Musolino AM. The Use of Lung Ultrasound to Monitor the Antibiotic Response of Community-Acquired Pneumonia in Children: A Preliminary Hypothesis. *J Ultrasound Med* 2020;39(4):817-826.
35. Danilo Buonsenso, Annamaria Musolino, Valentina Ferro, Cristina De Rose, Rosa Morello, Chiara Ventola et al. Role of Lung Ultrasound for the etiological diagnosis of community-acquired pneumonia in children: a prospective study. *MedRxiv* 2020.10.31.20223867.
36. Pereda MA, Chavez MA, Hooper-Miele CC, et al. Lung ultrasound for the diagnosis of pneumonia in children: a meta-analysis. *Pediatrics* 2015;135(4):714-722.

37. Buonsenso D, Parri N, De Rose C, Valentini P; Gemelli-pediatric COVID-19 team. Toward a clinically based classification of disease severity for paediatric COVID-19. *Lancet Infect Dis* 2020;15:S1473-3099(20)30396-0.

38. Volpicelli G, Gargani L. Sonographic signs and patterns of COVID-19 pneumonia. *Ultrasound J* 2020;12(1):22.

39. Tsung JW, Kessler DO, Shah VP. Prospective application of clinician-performed lung ultrasonography during the 2009 H1N1 influenza A pandemic: distinguishing viral from bacterial pneumonia. *Crit Ultrasound J* 2012;4(1):16.

40. Buonsenso D, Musolino AM, Gatto A, Lazzareschi I, Curatola A, Valentini P. Lung ultrasound in infants with bronchiolitis. *BMC Pulm Med* 2019;19(1):159.

41. Aliyu LD, Kurjak A, Wataganara T, de Sá RA, Pooh R, Sen C, Ebrashy A, Adra A, Stanojevic M. Ultrasound in Africa: what can really be done? *J Perinat Med* 2016 Mar;44(2):119-23.

42. World Health Organization. Training in Diagnostic Ultrasound: Essentials, Principles and Standards. Report of WHO Study Group. *Geneva, Switzerland, WHO Technical Report Series 875* 1998.

43. World Health Organization. Future use of new imaging technologies in developing countries. Report of a WHO Scientific Group. *World Health Organ Tech Rep Ser* 1985;723:1–67.

44. Goldberg BB. International arena of Ultrasound education. *J Ultras Med* 2003;22:549–51

45. Stewart KA, Navarro SM, Kambala S, et al. Trends in Ultrasound Use in Low and Middle Income Countries: A Systematic Review. *Int J MCH AIDS* 2020;9(1):103-120. doi:10.21106/ijma.294

46. Kotlyar S, Moore CL. Assessing the utility of ultrasound in Liberia. *J Emerg Trauma Shock* 2008;1(1):10–14

47. Shah SP et al. Impact of the introduction of ultrasound services in a limited resource setting: rural Rwanda 2008. *BMC Int Health Hum Rights* 2009;9:4
48. Moore CL, Copel JA. Point-of-care ultrasonography. *N Engl J Med* 2011;364:749–757.
49. Flick D. Bedside ultrasound education in primary care. *J Ultrasound Med* 2016;35:1369–1371.
50. Sabatino V, Caramia MR, Curatola A, Vassallo F, Deidda A, Cinicola B, Iodice F, Caffarelli C, Sverzellati N, Buonsenso D. Point-of-care ultrasound (POCUS) in a remote area of Sierra Leone: impact on patient management and training program for community health officers. *J Ultrasound* 2020;23(4):521-527.
51. Kolbe Nina et al. Point of care ultrasound (POCUS) telemedicine project in rural Nicaragua and its impact on patient management. *J Ultrasound* 2015;18:179–185.
52. Soldati G, Demi M, Demi L. Ultrasound patterns of pulmonary edema. *Ann Transl Med* 2019;7(Suppl 1):S16.
53. Leopold SJ, Ghose A, Plewes KA, Mazumder S, Pisani L et al. Point-of-care lung ultrasound for the detection of pulmonary manifestations of malaria and sepsis: An observational study. *PLoS One* 2018; 12;13(12):e0204832.
54. Martindale JL, Noble VE, Liteplo A. Diagnosing pulmonary edema: lung ultrasound versus chest radiography. *Eur J Emerg Med* 2013;20:356–60.
55. The ARDS Definition Task Force. Acute Respiratory Distress Syndrome. *JAMA* 2012;307: 2526–2533.
56. Riviello ED, Kiviri W, Twagirumugabe T, Mueller A, Banner-goodspeed VM, Of L, et al. Hospital Incidence and Outcomes of the Acute Respiratory Distress Syndrome Using the Kigali Modification of the Berlin Definition. *Am J Respir Crit Care Med Vol* 2016;193:52–59.

57. Shefrin AE, Warkentine F, Constantine E, Toney A, Uya A, Doniger SJ, Sivitz AB, Horowitz R, Kessler D. Consensus Core Point-of-care Ultrasound Applications for Pediatric Emergency Medicine Training. *AEM Educ Train* 2019;14;3(3):251-258.
58. Sippel S et al. Review article: use of ultrasound in the developing world. *Int J Emerg Med* 2011;4:72
59. Aliyu LD, Kurjak A, Wataganara T, de Sá RA, Pooh R, Sen C, Ebrashy A, Adra A, Stanojevic M. Ultrasound in Africa: what can really be done? *J Perinat Med* 2016;44(2):119-23.
60. Shah SP et al. Impact of the introduction of ultrasound services in a limited resource setting: rural Rwanda 2008. *BMC Int Health Hum Rights* 2009;9:4
61. Watkins K, Sridhar D. Pneumonia: a global cause without champions. *Lancet* 2018;392: 718–19.
62. Murdoch DR, Howie SRC. The global burden of lower respiratory infections: making progress, but we need to do better. *Lancet Infect Dis* 2018;18(11):1162-1163.
63. Every Breath Counts. Fighting for breath: the Global Forum on childhood pneumonia. 2020. https://stoppneumonia.org/latest/global-forum/#sign (March 1, 2020).
64. WHO, UNICEF. Ending preventable child deaths from pneumonia and diarrhoea by 2025: the integrated Global Action Plan for Pneumonia and Diarrhoea (GAPPD). 2013. https://www.who.int/maternal_child_adolescent/documents/global_action_plan_pneumonia_diarrhoea/en/ (accessed Feb 14, 2020).
65. Allwell-Brown G, Hussain-Alkhateeb L, Kitutu FE, Strömdahl S, Mårtensson A, Johansson EW. Trends in reported antibiotic use among children under 5 years of age with fever, diarrhoea, or cough with fast or difficult breathing across low-income and middle-income countries in 2005-17: a systematic analysis of 132 national surveys from 73 countries. *Lancet Glob Health* 2020;8(6):e799-e807.

66. Fink G, D'Acremont V, Leslie HH, Cohen J. Antibiotic exposure among children younger than 5 years in low-income and middle-income countries: a cross-sectional study of nationally representative facility-based and household-based surveys. *Lancet Infect Dis* 2020;20(2):179-187.
67. UNICEF, Save the Children, Every Breath Counts. Every child's right to survive: an agenda to end pneumonia deaths. New York, NY: United Nations Children's Fund, 2020.

Figure Legend

Figure 1. Key characteristics of clinical examination, lung ultrasound and chest X-ray with traffic-light system signaling potential for achieving a comprehensive management of pneumonia in Low-to-Middle Income countries. We used a traffic-light system to identify factors or barriers to widespread global implementation of Lung Ultrasound in LMICs compared with clinical examination and traditional radiology, with red indicating high difficulty/barriers, amber medium, and green little or no difficulty/barriers to implementation. Colors were decided by the two authors according with available literature. Disagreements were resolved through discussion.