



## Review

## Respiratory infections in low and middle-income countries

Lisa Frigati<sup>a,\*</sup>, Leonore Greybe<sup>a</sup>, Savvas Andronikou<sup>b,c</sup>, Ernst Eber<sup>d</sup>,  
Shyam Sunder B. Venkatakrishna<sup>e</sup>, Pierre Goussard<sup>a</sup>



<sup>a</sup> Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg Hospital, Cape Town, South Africa

<sup>b</sup> Department of Pediatric Radiology, Children's Hospital of Philadelphia, Philadelphia, PA, USA

<sup>c</sup> Department of Radiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

<sup>d</sup> Division of Paediatric Pulmonology and Allergology, Department of Paediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria

<sup>e</sup> Department of Radiology, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

## Educational Aims

The reader will appreciate:

- the recent epidemiology and aetiology of childhood pneumonia and other lung infections in low and middle income countries (LMICs).
- the current evidence for diagnostic tools for paediatric pneumonia and other respiratory infections in LMICs.
- prevention and management approaches for children with respiratory infections in these settings.

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## ABSTRACT

**Objectives:** To investigate the epidemiology, aetiology, diagnostics and management of childhood pneumonia in low and middle income countries (LMICs).

**Design:** Review of published english literature from 2019 to February 2024.

**Results:** Lower respiratory tract infections (LRTIs) still result in significant mortality in children under 5 years of age in LMICs. Important studies have reported a change in the pathogenesis of LRTIs over the last 5 years with respiratory syncytial virus (RSV) resulting in a large burden of disease. SARS-CoV-2 had a significant direct and indirect impact in children in LMICs. *Mycobacterium tuberculosis* (MTB) remains a priority pathogen in all children. Nucleic acid amplification and rapid antigen tests have improved diagnostic accuracy for MTB and other bacterial pathogens. Point of care diagnostics may overcome some limitations, but there is a need for better cost-effective diagnostics. Access to shorter courses of TB treatment are now recommended for some children, but child friendly formulations are lacking. The role of chest X-ray in TB has been recognized and included in guidelines, and lung ultrasound to diagnose LRTI is showing promise as a lower cost and accessible option.

**Conclusion:** Advances in diagnostics and large multi-centre studies have provided increased understanding of the causative pathogens of LRTIs in LMICs. Increased access to preventive strategies such as vaccines, treatment modalities including antivirals, and addressing upstream factors such as poverty are essential if further declines in LRTIs in LMICs are to be realised.

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## INTRODUCTION

Lower respiratory tract infections (LRTIs) are still the most common cause of mortality in children under 5 years of age in low and middle income countries (LMICs) [1]. In 2019, 45 million episodes of pneumonia occurred in children less than 5 years of age globally resulting in more than 700 000 deaths [1]. The incidence of

\* Corresponding author at: Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, PO Box 241, Cape Town 8000, South Africa.

E-mail address: [frigati@sun.ac.za](mailto:frigati@sun.ac.za) (L. Frigati).

pneumonia in sub-Saharan Africa (SSA) is double that of high income countries and the mortality rate is 60 times higher [2].

Over the last 5 years studies have reported on respiratory pathogens in children to inform the most relevant preventive strategies [3–7]. Viral infections specifically respiratory syncytial virus (RSV) remains a large burden [6,7]. COVID-19 had a significant impact on children in less well resourced settings where access to oxygen and intensive care settings remain limited [8]. In addition, SARS-CoV-2 along with measures taken to restrict its spread, changed seasonal patterns of other viral and bacterial infections [9,10]. The reallocation of resources toward combatting COVID-19 has also resulted in a loss of progress made in other respiratory tract infections such as *Mycobacterium tuberculosis* (MTB) [11,12].

In addition to acute LRTIs, other respiratory infections cause a severe burden of disease in resource limited settings. MTB remains a significant cause of morbidity in both children living with HIV and those without HIV [12]. HIV related lung infections such as *Pneumocystis jirovecii* (PJP) and cytomegalovirus (CMV) remain a problem [13]. Helminth related lung disease remains prevalent and hydatid disease causes significant morbidity, mortality and requires costly surgical interventions [14,15].

Vaccination, specifically against *Bordetella pertussis*, *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and specific case management of pneumonia, including empirical antibiotic treatment and the provision of oxygen, as well as general economic improvements resulting in decreased household crowding, have helped to decrease the burden of LRTIs. However, many pathogens still need to be addressed and poor ventilation, second hand smoke, and unclean fuel usage contribute to an increased risk for pneumonia [16].

There is an urgent need for better cost-effective diagnostics, increased access to preventive strategies as well as treatment modalities for childhood LRTIs. For infections such as hydatid disease a one health approach needs to be implemented and addressing upstream factors such as poverty is essential if further declines in LRTIs in LMICs are to be realised.

## AETIOLOGY

### *Studies on respiratory pathogens causing morbidity and mortality in children living in LMICs*

The Pneumonia Etiology Research for Child Health (PERCH) group conducted a case-control study in nine countries in Asia and Africa and found that ten pathogens were responsible for 79–90 % of cases with severe pneumonia requiring hospital admission in HIV negative children younger than 5 years. Causes of pneumonia varied by age strata, severity status and geography [3]. Viruses accounted for 61.4 % and bacteria for 27.3 % and MTB for 5.9 % of the causes of pneumonia with respiratory syncytial virus (RSV) (31.1 %) having the greatest aetiological fraction of all pathogens. The top ten pathogens identified included RSV, human rhinovirus, human metapneumovirus A or B, human parainfluenza virus, influenza A and C, *S. pneumoniae*, MTB, *H. influenzae*, *Staphylococcus aureus* and PJP.

The Child Health and Mortality Prevention Surveillance (CHAMPS) Network conducted a study using postmortem minimally invasive tissue sampling (MITS) in deceased children aged 1 to 59 months at seven sites in SSA and South Asia over a six-year period (between December 2016 and December 2022) [4]. Pneumonia was attributable in the causal pathway of death in 415/1120 (40.6 %) children. Causative organisms were found in 377 (83 %) of the pneumonia deaths and of those, multiple organisms were indicated in 218/377 (60 %) of deaths. Common patho-

gens included *S. pneumoniae*, non-typeable *H. influenzae* and RSV, and in contrast to PERCH, *Klebsiella pneumoniae* and CMV were also documented as a cause of LRTIs [4]. Notably, there were no deaths from MTB in the CHAMPS study. However, it is important to note that the study populations were different, and antibiotics may have selectively prevented deaths from certain bacteria in the CHAMPS study. In addition, the diagnostic sampling was much more extensive in the CHAMPS study compared to PERCH. The study of pneumonia from CHAMPS also reported on causes of nosocomial pneumonia (deaths that occurred 72 h after hospital admission) with the commonest organism being *K. pneumoniae*, *Acinetobacter baumannii*, *S. pneumoniae* and *Pseudomonas aeruginosa* [4].

It may be difficult to differentiate a colonising organism from a pathogenic organism and severe LRTIs are often caused by co-infections of bacterial and viral organisms [17]. The CHAMPS study highlighted that co-infection occurred frequently with varying combinations including bacterial-bacterial (70.6 %), bacterial-viral (37.2 %), bacterial-fungal (11.9 %), fungal-viral (7.8 %), and viral-viral (7.3 %) [4].

Adenovirus, although not found commonly in the PERCH or CHAMPS studies, is another important pathogen that can cause severe pneumonia in children in LMICs [18,19]. Adenoviral pneumonia is often severe in children and can lead to a need for respiratory support and death in previously healthy children. The white cell count (WCC) and C-reactive protein (CRP) are raised, thus it may be confused with a bacterial infection. Adenovirus is by far the most common cause of post-infectious bronchiolitis obliterans (Fig. 1) in children. In these children mechanical ventilation is an independent risk factor to develop post-infectious bronchiolitis obliterans [20]. Adenovirus is commonly found in the lower airways of children with protracted bacterial bronchitis and bronchiectasis suggesting a role in the development of chronic lung disease in children without cystic fibrosis as well as a role in symptom exacerbation in children with established bronchiectasis [21].

COVID-19 has significantly impacted LRTIs in LMICs. In a cohort study of 469 children and adolescents hospitalised with COVID-19 in six SSA countries between March and December 2020, morbidity and mortality were substantially higher than reported among those in non-African settings and were independently associated with age younger than 1 year and non-communicable diseases [8]. Thirty-nine (8.3 %) children died compared to mortality rates of  $\leq 1$  % in high income settings [22].

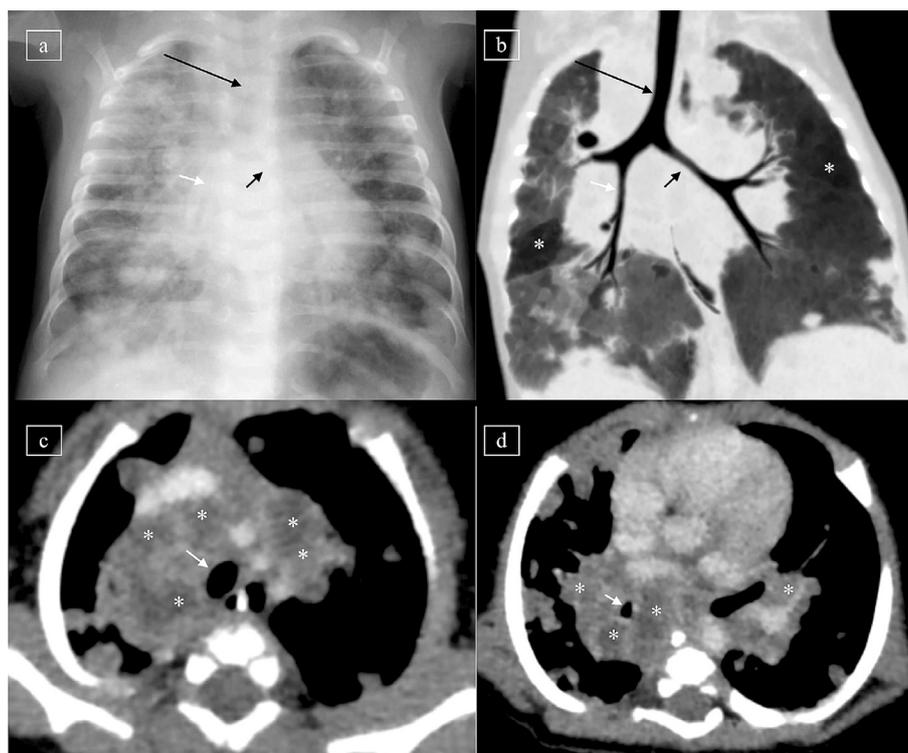
### *Other vaccine-preventable causes of pneumonia*

Other vaccine-preventable causes of pneumonia include measles virus, *B. pertussis*, and rarely *Corynebacterium diphtheriae* and varicella zoster virus. Latest estimations of Diphtheria Tetanus toxoid and Pertussis (DTP3) immunisation coverage in LMICs range between 70 and 85 %, but pertussis remains one of the most poorly controlled vaccine preventable bacterial infections in the world [23]. The surveillance of *B. pertussis* in LMICs is suboptimal and there is a resurgence of pertussis in LMICs with a disproportionate case fatality rate in young infants [24]. Higher rates of pertussis are detected in HIV infected, but also in HIV exposed and uninfected children [24]. Cases of *C. diphtheriae* have declined over the last few years, but the 4453 cases reported in 2022 exclusively occurred in LMICs [25]. Respiratory failure due to diaphragmatic paralysis and cardiac failure is common, but pneumonia caused by toxigenic and non-toxigenic strains is increasingly recognised in the literature [26].

In 2019, the measles case fatality rate in community-based settings in LMICs was estimated to be 3.03 % for those younger than



**Fig. 1.** 9-month-old boy with adenovirus pneumonia developing bronchiolitis obliterans. frontal chest radiograph at presentation with pneumonia demonstrates extensive, predominantly right-sided, confluent air-space disease (black arrows) requiring intubation and ventilation. (b) and (c) are sequential chest ct scan slices on lung window in the same child, 2 months after the presentation, demonstrating a mosaic attenuation, with low density areas (white arrows) representing focal air-trapping, in keeping with bronchiolitis obliterans.



**Fig. 2.** 2-month-old girl presenting with wheezing, with microbiologically confirmed TB. (a) Frontal chest radiograph demonstrates bilateral patchy air-space disease and multiple varying sized scattered nodules. The lower trachea is compressed and displaced left (long black arrow), and there is narrowing of the left main bronchus (short black arrow) and a poorly visualised bronchus intermedius (short white arrow). (b) Coronal reconstruction of the chest with a thick slab Minimum Intensity Projection technique on lung window, confirms the compression of the distal trachea (long black arrow) as well as the narrowing of the left main bronchus (short black arrow) and bronchus intermedius (short white arrow). There is resultant air-trapping in the left upper lobe and right middle lobe (asterisks). The CT also confirms the presence of both patchy air-space disease and varying sized interstitial nodules. (c and d) Axial sequential post contrast images on soft tissue window, demonstrates extensive low-density mediastinal, hilar and subcarinal lymphadenopathy (asterisks) causing the multifocal airway compressions (white arrows).

1 year with measles pneumonia, the most frequent cause of mortality [27]. In 2022, 40 million children missed a measles vaccine dose, with 102 330 cases of measles reported in large outbreaks in LMICs during the same year [25].

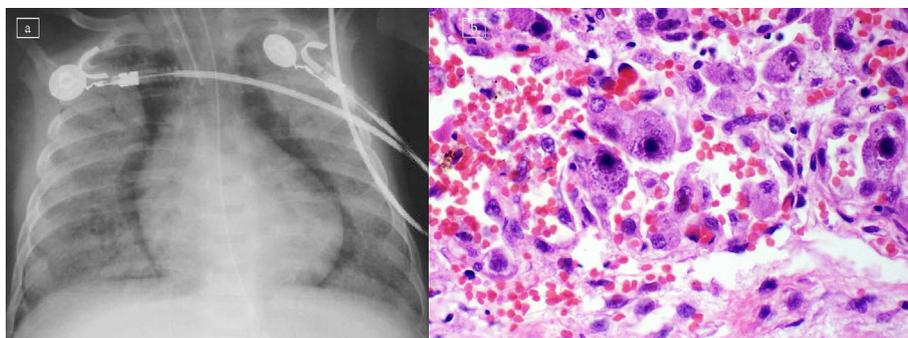
#### *Pneumonia in immunocompromised children*

In 2010, children living with HIV had 6.5 times (95 % CI 5.9–7.2) the odds of pneumonia that required hospitalisation and an increased risk of death (odds ratio 5.9, 95 % CI 2.7–12.7) [28]. Despite increased access to better tolerated antiretroviral therapy, children with HIV remain at increased risk of LRTIs due to MTB, CMV and PJP (Figs. 2–4) [29]. Rarer causes of pneumonia with a high mortality rate especially in immunocompromised children

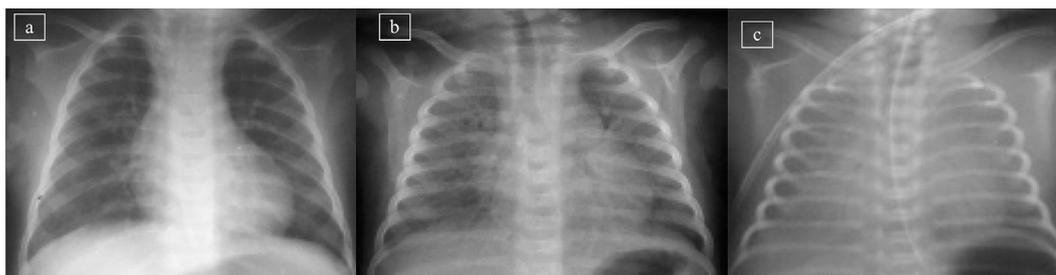
include varicella zoster virus (Fig. 5) and cryptococcal disease (Figs. 6 and 7) [30].

#### *Pneumonia caused by parasitic and neglected tropical diseases*

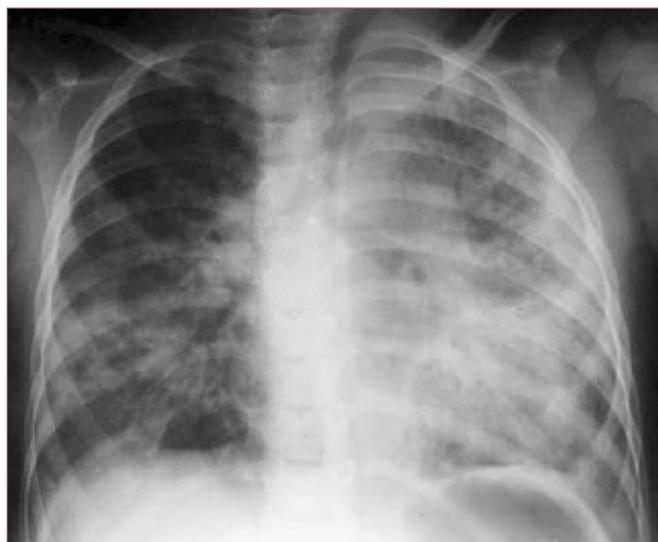
Pulmonary schistosomiasis, echinococcal cysts, and soil transmitted helminths and microfilariae causing eosinophilic pneumonia, all occur in LMICs especially in Southeast Asia, and SSA [31]. Parasitic infections can manifest with primary lung pathology such as effusions, cavitations, nodules or cysts or may cause blood and pulmonary eosinophilia. These conditions contribute to significant morbidity through the development of non-communicable lung disease and mortality where there is poor healthcare access [32].



**Fig. 3.** 3-month-old girl with hypoxic pneumonia and CMV confirmed histologically. (a) Chest X ray after 2 days of intubation and ventilation demonstrates the extensive bilateral diffuse air-space disease as well as bilateral medial pneumothoraces seen as a lucency outlining the cardio-mediastinal shadow. (b) Lung biopsy specimen with the histology showing the hallmark histologic feature of CMV of large intranuclear inclusions.



**Fig. 4.** A 2-month-old boy with HIV with hypoxic pneumonia was confirmed to have PJP with PCR on bronchoalveolar lavage. Consecutive-day chest X-rays, from day 1 to day 3 (a-c), demonstrate rapid development of diffuse parenchymal abnormality starting with air-trapping, progressing to a diffuse interstitial pattern and resulting in widespread confluent air-space disease with blurring of cardiac and diaphragmatic margins.



**Fig. 5.** An 8-year-old HIV positive boy presenting with chickenpox. Chest X-ray demonstrates bilateral asymmetric and patchy confluent air-space disease as well as underlying interstitial nodularity.

The presentation of cystic echinococcosis (CE) varies by age and pulmonary CE is the dominant site in the paediatric population [14]. Pulmonary cysts are first seen on chest X-ray (Fig. 8 a and b), either as an incidental finding or following respiratory symptoms after cyst rupture or secondary infection of the cyst. In children, pulmonary cysts have a broad differential diagnosis, and a definitive diagnosis relies on the combination of imaging, serology, and histology. In countries with high infectious burdens from diseases such as AIDS and TB, the diagnosis is even more challenging,

as atypical infections are more common. Pulmonary CE is treated with a combination of surgery and chemotherapy [14].

In a South African cohort of 35 children (mean age  $9 \pm 5.4$  years) the most frequent presenting symptoms were cough (93 %) and fever (70 %). Isolated pulmonary CE accounted for most cases, 74 % with left lower lobe predominance. Only 58 % had a positive indirect haemagglutination test, but a sizeable proportion exhibited chest computed tomography (CT) characteristics (Fig. 8c) consistent with complicated pulmonary CE. All children received medical treatment with 86 % requiring surgery. Prolonged mean hospitalisation of  $12.5 \pm 6.6$  days for complicated and  $6.8 \pm 1.5$  days for simple cysts are indicative of the significant healthcare burden of this neglected disease [32].

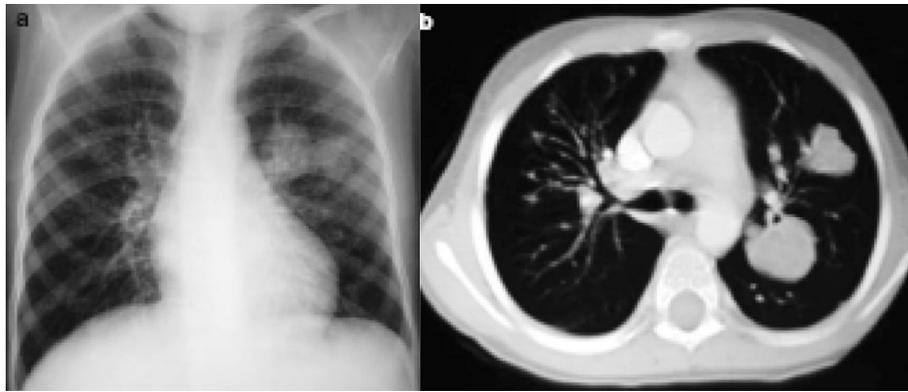
## DIAGNOSTICS

Table 1 summarises current diagnostic tools available to aid the aetiological diagnosis of pneumonia. The availability of many of these tests in LMICs is limited, but the development of point of care diagnostics, although still expensive, may overcome some of these limitations [33].

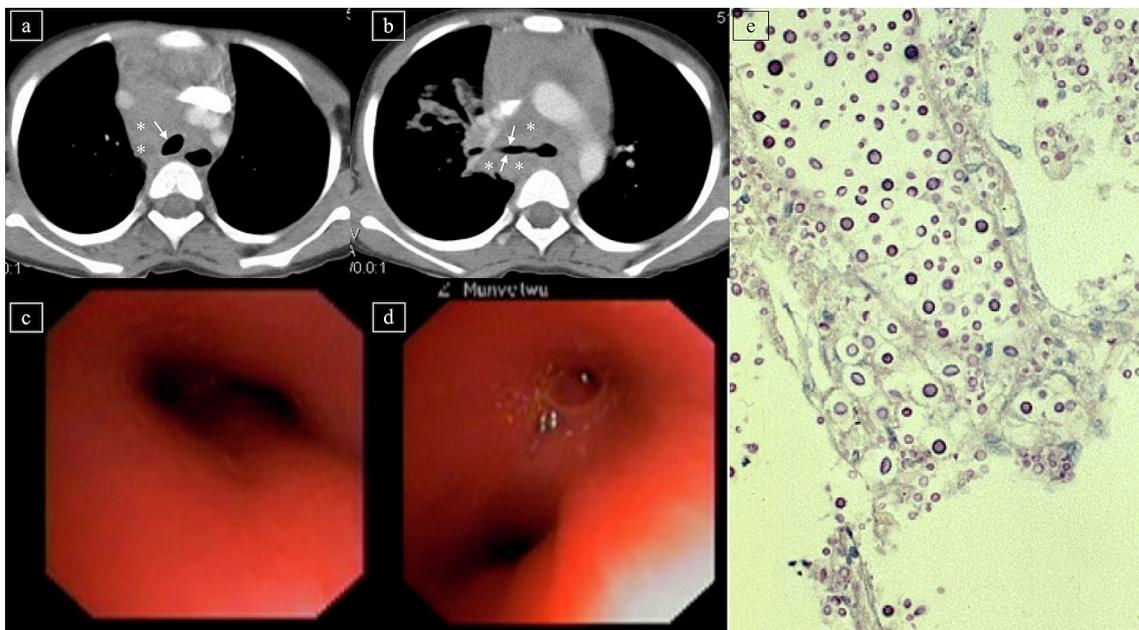
### Clinical scoring

Clinical scoring systems for TB in children living with HIV have been validated and diagnostic algorithms have been added to the WHO guidelines and may be used in settings with and without access to chest radiography [34,35].

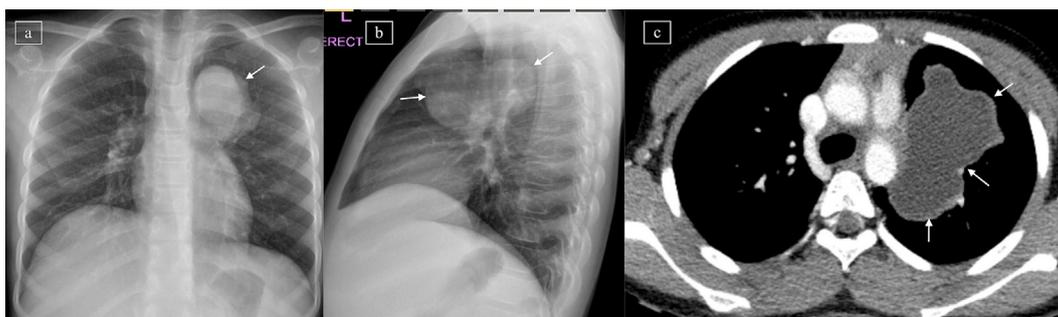
The use of modified diagnostic criteria suggested by the Global Pertussis Initiative (adding presence of coryza, apnoea, seizures or cyanosis as well as absence of fever, all without a specified duration), with presence of leucocytosis, may perform better than current WHO clinical criteria [36].



**Fig. 6.** A 9-year-old HIV positive girl presenting with cryptococcus meningitis and persistent cough. (a) Frontal plain chest X-ray and (b) axial CT scan slice on lung window demonstrate multiple, oval, large, well-margined nodules in the left upper lobe (arrows). CT-scan guided biopsy was done which confirmed cryptococcus.



**Fig. 7.** A 9-month-old HIV positive boy presenting with large airway obstruction. Post contrast CT scan at the level of trachea (a) and at the level of carina (b) demonstrates non-enhancing lymphadenopathy (asterisks) with central areas of low density involving the right paratracheal, the pre-carinal and azygo-oesophageal groups of nodes, causing compression of the trachea (arrow in a) and antero-posterior narrowing of the bronchus intermedius (arrows in b). There are resultant parenchymal changes in the right middle lobe. Bronchoscopy images: (c) at the level of the trachea demonstrating severe tracheal compression from the right and at the level of the opening of the right main bronchus showing complete occlusion of the right upper lobe bronchus and more than 75 % compression of the bronchus intermedius. (e) Specimen from enucleated nodes confirming cryptococcus.



**Fig. 8.** An 11-year-old boy presents with fever and cough. (a) AP and (b) lateral plain radiographs demonstrate a lobulated, well-margined dense mass (arrows) in the left upper lung abutting the left side of the mediastinum. (c) Post contrast CT scan at the level of the vena azygos confirms the presence of a left upper lobe mass (arrows) abutting the left mediastinal vascular structures and demonstrating a fluid density content and representing an uncomplicated hydatid cyst.

Imaging

Chest radiographs can demonstrate consolidation and the presence of effusions and cavities while lung ultrasound (LUS) can

accurately quantify pleural fluid volume and characterise the effusion [37]. LUS may also identify consolidation with a similar frequency to chest radiography, but with higher interobserver agreement than radiographs, making it an accessible and valuable

**Table 1**  
Current diagnostic tools for pneumonia in LMICs.

Methods/test	Microorganisms	Sample type
<u>Clinical scoring systems</u>		
PAANTHER Clinical Case Definition for Classification of Intrathoracic Tuberculosis <sup>i</sup>	MTB	—
WHO Treatment decision algorithm for settings access to CXR <sup>ii</sup>		
GPI modified pertussis diagnostic criteria <sup>iii</sup>	<i>Pertussis</i>	
<u>Microscopy and culture</u> (gold standard)	Bacteria Fungi	Blood LRS <sup>iv</sup>
<u>Nucleic acid amplification tests</u>		
Xpert <sup>®</sup> MTB/RIF	MTB	URS <sup>v</sup> LRS <sup>iv</sup>
Xpert <sup>®</sup> MTB/RIF Ultra		
Multiplex PCR	Viruses Bacteria	URS <sup>v</sup> LRS <sup>iv</sup>
Realtime PCR	CMV <i>B. pertussis</i> <i>P. jirovecii</i>	Blood URS <sup>v</sup> LRS <sup>iv</sup>
Biofire <sup>®</sup> Respiratory Panel	<i>Bacteria</i> <i>Viruses</i>	URS <sup>v</sup> , LRS <sup>iv</sup>
TaqMan Array Cards <sup>®</sup>	<i>Bacteria</i> <i>Viruses</i> <i>Fungi</i>	Blood URS <sup>v</sup> LRS <sup>iv</sup>
<u>Antigen detection</u>		
Alere LAM <sup>™</sup> ; Fujifilm SILVAMP TB LAM	MTB	Urine
Alere BinaxNOW <sup>®</sup>	<i>S. pneumoniae</i>	Urine
<u>MTB infection tests</u>		
Mantoux	MTB infection	Skin
IGRA	MTB infection	Blood
<u>Imaging</u>		
CXR	—	—
LUS		
CT chest		
Bronchoscopy	—	—

Abbreviations: *B. pertussis*, *Bordetella pertussis*; CT, computed tomography; CXR, chest X-ray; IGRA, interferon gamma release assay; GPI, global pertussis initiative; LAM, lipoarabinomannan; LRS, lower respiratory sample; LUS, lung ultrasound; MTB, *Mycobacterium tuberculosis*; NAAT, nucleic acid amplification testing; *P. jirovecii*, *Pneumocystis jirovecii*; *S. pneumoniae*, *Streptococcus pneumoniae*; URS, upper respiratory sample; WHO, World Health Organization;

<sup>i</sup> O. Marcy et al. Pediatrics (2019).

<sup>ii</sup> WHO operational handbook on tuberculosis; Module 5: management of tuberculosis in children and adolescents. (2022).

<sup>iii</sup> R. Muloiswa et al. PLoS One (2020).

<sup>iv</sup> Upper respiratory samples include nasopharyngeal aspirates, gastric aspirates.

<sup>v</sup> Lower respiratory samples include sputa, pleural fluid and bronchoalveolar lavage fluid.

**Table 2**  
Current preventive interventions for pneumonia in LMICs.

Intervention	Viral	Bacterial	Fungal
A. Infant/ Child Vaccination	Influenza Measles SARS-CoV-2 (child)	Whole cell pertussis Inactivated pertussis Pneumococcus <i>Haemophilus influenzae B</i> BCG	
B. Maternal Vaccination	RSV Pertussis Influenza		
C. Pharmacological	Monoclonal antibodies for RSV	TB preventive treatment -Rifapentine/INH for drug sensitive TB -levofloxacin for drug resistant TB	Cotrimoxazole prophylaxis for PJP ART to prevent PJP
D. Nutrition	Vitamin A for measles Breastfeeding Vitamin D Zinc		
E. Environmental	Facemasks Clean fuel		

Abbreviations: ART, antiretroviral therapy; INH, isoniazid; PJP, *Pneumocystis jirovecii* pneumonia; RSV, respiratory syncytial virus; TB, tuberculosis.

tool in low-resource settings where the infrastructure for radiography is limited [38].

Computed tomography of the chest is particularly helpful in scenarios where aggressive interventions such as video-assisted thoracoscopy (VATS) are considered and for detection of necrotising pneumonia and abscesses [39,40]. A CT scan can also help to diagnose bronchopleural fistula. In LMICs where complicated pneumonia is common, especially among children living with HIV and in TB-endemic settings, CT scan is increasingly employed to facilitate timely and appropriate management [39,40]. Cystic and nodular lesions which have a broad differential diagnosis may be more accurately visualised and characterised with CT [39,40].

### Bronchoscopy

Bronchoscopy with the ability for enucleation of paratracheal and subcarinal lymph glands is beneficial for the diagnosis of TB in complicated disease, in the presence of necrotic pneumonia, and to distinguish TB from other causes of lymphadenopathy and pulmonary nodules such as cryptococcal pneumonia [41]. Additionally, endoscopic therapeutic procedures in children with complicated TB may prevent thoracotomy with the advantage of a low complication rate [41].

### Next generation laboratory testing

Multiplex PCR for the detection of both viral and bacterial pathogens can significantly reduce turnaround times for microbiological identification and may prevent the use of unnecessary antibiotics where viruses are identified, although study results have been contradictory [33,42].

The use of polymerase chain reaction (PCR) tests for the diagnosis of pertussis has increased the sensitivity of detection to between 70–99 % when performed within the first four weeks of cough [43].

The use of Xpert<sup>®</sup> MTB/RIF Ultra (Cepheid<sup>®</sup>, Sunnyvale, CA) testing of sputum, gastric aspirate, nasopharyngeal aspirate or stool as an initial diagnostic test for TB is now part of WHO guidance [44]. Urinary lipoarabinomannan (Alere LAM<sup>™</sup>; Abbott, Chicago, IL, USA and Fujifilm SILVAMP TB LAM) has good specificity as a non-invasive point-of-care test to regularly screen symptomatic children living with HIV for TB [45].

## PREVENTION AND MANAGEMENT APPROACHES (TABLE 2)

### Treatment of uncomplicated community-acquired pneumonia (CAP)

A recent review confirmed that high-dose amoxicillin remains the treatment of choice for uncomplicated CAP in children in both the in- and outpatient settings [46]. Attempts at shortening the course of antibiotics in children with uncomplicated pneumonia and who may therefore represent a large group with viral aetiologies have been published [47,48]. This includes shortening antibiotic duration from 10 to 5 days and from 5 to 3 days [47,48]. A duration of three days was an effective treatment in HIV negative Malawian children with cough lasting for less than 14 days or with difficulty breathing and visible indrawing of the chest wall with or without fast breathing for age [48]. Withholding antibiotic therapy in children with non-severe pneumonia was not as successful, with treatment failure especially high in those who presented with fever and wheezing [49]. The pneumococcal vaccination rate was approximately 61 % in the study population [49].

### Preventative and empirical treatment

In LMICs household TB transmission remains common despite prevention strategies. Shorter courses of rifamycin based TB prevention have been introduced for adults and are being studied in children [50,51]. One study supported the safe implementation of one month of isoniazid and rifapentine (1HP) for children > 2 years old with household TB contacts in programmatic settings in Pakistan [52].

The 2022 WHO consolidated TB guidelines now recommend the use of 1 month of 1HP for children more than 13 years and 3 months of isoniazid and rifampicin in children > 2 years and up to 13 years, however there are still no child friendly formulations available [34]. The TB-CHAMP study showed that levofloxacin can be used to prevent drug resistant TB however, revised weight-band dosing guidelines with doses of >20 mg/kg are required to ensure adequate protection [53,54].

The SHINE study found that four months of a four-drug regimen including ethambutol is safe and effective to treat non-severe drug susceptible pulmonary TB [55]. Chest X-ray plays an important role in the classification of severe versus non-severe TB [56].

Empirical treatment of cytomegalovirus infection and tuberculosis in severe pneumonia in HIV infected infants is currently being studied in a randomised controlled trial in several African countries [57].

### Immunization

There are currently three strategies being explored to protect children against RSV: direct administration of antibodies to the infant, passive antibodies acquired from maternal vaccination in pregnancy and active vaccination of infants. The first strategy has resulted in the approval (in Europe) of Nirsevimab, a long-acting (150 day) single-dose monoclonal antibody to the RSV fusion protein that provides protection against medically attended RSV [58]. A phase 3 trial evaluated maternal vaccination using an RSV F protein nanoparticle vaccine and this unfortunately did not show efficacy against the endpoint of medically significant RSV infection [59]. However, an RSV pre-F vaccine administered during pregnancy was safe and effective against medically attended severe RSV pneumonia in infants [60]. Live-attenuated vaccines are in development for infants more than six months of age [61].

Vaccines for SARS-CoV-2 have been approved for children older than five years of age although there has been limited uptake and availability in LMICs [62].

Live attenuated influenza vaccines (LAIV) have the potential to be feasible and economical alternatives for influenza prevention in LMICs [63]. Efficacy studies of Serum Institute of India's low-cost, single-dose trivalent LAIV in Bangladesh and Senegal reported a maximum efficacy of 58 % but was not efficacious against A/H1N1 [64,65]. More recently, a cell-culture-derived quadrivalent influenza vaccine was shown to be efficacious in preventing laboratory confirmed influenza across three seasons in healthy children and adolescents between 2–18 years of age [66]. These important randomised controlled trials confirm the safety and variable efficacy of different influenza vaccines in children, but the next-generation vaccines are not currently economical for use in LMICs and the lack of clarity on efficacy and the need to update vaccines yearly still contribute to the underuse of vaccines in LMICs [67].

### Antivirals

The use of oseltamivir in children with influenza has been controversial [68]. A previous Cochrane review found that oseltamivir had a modest benefit of reducing the median duration of illness by 36 h (26 %,  $P < 0.001$ ) [69]. A subsequent large multicentre study of

children hospitalised with influenza favoured treatment with early oseltamivir, since it was associated with a shorter length of hospital stay (median of 1 day) and a lower readmission within seven days (OR 0.72), transfer to the ICU (OR 0.41) and in-hospital mortality (OR 0.63) [70]. Additionally, a post hoc pooled analysis of two open-label non-controlled studies of a single dose of baloxavir marboxil in paediatric outpatients showed time to improvement of influenza symptoms of 43.2 h for patients <six years and 45.4 h for patients  $\geq 6$ –12 years [71]. Although these agents are already in use in high-income countries, the use of antivirals in children in LMICs should be considered alongside vaccination efforts and tailored to local needs and capacities [72].

Treatment for adenovirus pneumonia is usually supportive but cidofovir has been shown to have some effect. Intravenous immune globulin can be considered in immune compromised children with conflicting data on its utility in immune competent children with severe pneumonia [73].

## CONCLUSION

Advances in diagnostics and large multi-country trials have improved our understanding of the causative organisms of LRTIs in LMICs. Newer diagnostic tools are becoming more accessible in many settings. Novel vaccines and monoclonal antibodies may decrease LRTIs in children in the near future and it is essential that LMICs have access to both new diagnostics as well as preventive interventions.

## DIRECTIONS FOR FUTURE RESEARCH

Future research should consider clarifying the pathogenesis of pneumonia and the role of co-infections in children and focus on the cost-effective implementation of preventative therapies and novel diagnostics in LMICs.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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