JIDC | THE JOURNAL OF INFECTION IN DEVELOPING COUNTRIES

Review

Multiplex PCR in pediatric LRTIs: challenges and opportunities in LMICs

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Abstract

Introduction: Lower respiratory tract infections (LRTIs) remain a leading cause of morbidity and mortality among children under five years of age, particularly in low- and middle- income countries (LMICs), where limitations in diagnostic capacity contribute to delayed and suboptimal clinical management. Conventional diagnostic methods are limited by slow turnaround time and reduced sensitivity, especially in mixed infections. This review synthesizes current evidence on the role of multiplex polymerase chain reaction (MxPCR) in the diagnosis and management of pediatric LRTIs, with emphasis on diagnostic accuracy, clinical impact, and implementation considerations in LMIC settings.
Methodology: A narrative review of published literature was undertaken, focusing on studies evaluating MxPCR diagnostic performance, clinical outcomes, epidemiological insights, and cost-effectiveness in pediatric respiratory infections, with cross-reference to LMIC specific health system constraints.
Observations: MxPCR consistently demonstrates high sensitivity and specificity for the detection of viral, bacterial, and mixed respiratory pathogens, enabling rapid and comprehensive pathogen identification. Evidence indicates improved antibiotic stewardship, reduced unnecessary investigations, and strengthened epidemiological surveillance. However, widespread adoption in LMICs remains limited by high per-test costs, infrastructure requirements, supply chain challenges, and limited local economic evaluation.
Conclusions: MxPCR represents a valuable diagnostic advancement for pediatric LRTIs. Sustainable integration in LMICs will require context-specific cost-effectiveness studies, appropriate panel selection based on local epidemiology, and feasible funding. Until these conditions are met, selective use in tertiary or high-dependency pediatric settings, or case-by-case application based on severity, remains the most practical approach.

Key words: healthcare; pneumonia; mortality; infectious diseases; antibiotics; childhood.

J Infect Dev Ctries 2026; 20(10):1430-1440. doi:10.3855/jidc.22952

(Received 22 January 2026 – Accepted 19 March 2026)

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Introduction

Respiratory infections remain a significant public health concern globally, in particular among children under 5 years of age. Lower respiratory tract infections (LRTIs) are the most severe subset of respiratory infections and were the leading infectious cause of death in 2019, responsible for an estimated 490 million cases and 2.5 million deaths worldwide [1].

The highest incidence and mortality rates were reported from South Asia and Sub-Saharan Africa, respectively, where the burden was several times greater than in high-income regions such as Western Europe and Australasia [1]. This striking regional disparity underscores the persistent inequity in the global distribution of LRTIs, with diagnostic capacity remaining a major limiting factor in timely and appropriate clinical management in low- middle income countries (LMICs).

The Pneumonia Etiology Research for Child Health (PERCH) study further demonstrated the complexity of LRTIs documenting that most childhood pneumonia cases are attributed to viral pathogens, followed by bacterial pathogens [2]. Pneumonia continues to be a major contributor to childhood mortality, accounting for approximately 40% of deaths, with multiple pathogen co-infections responsible for 60% of pneumonia-related case fatalities [2]. These findings highlight the need for rapid, sensitive, and comprehensive diagnostic tools capable of detecting both monomicrobial and mixed infections.

Despite this need, the routine use of multiplex polymerase chain reaction (MxPCR) platforms for respiratory pathogen detection in LMICs remains limited, with implementation largely confined to tertiary or research hospitals [3]. The coronavirus disease 2019 (COVID-19) pandemic highlighted both

the crucial importance of timely and accurate diagnostics and the widespread scarcity of such capacity, despite diagnostics being central to effective healthcare [4]. This diagnostics inequity aligns with findings from the "Lancet Commission on Diagnostics", which reported that only 19% of population in low- and lower-middle- income countries have access to basic diagnostics tests at the primary care level and only 60–70 % in hospital settings [4]. Importantly, the Commission emphasized that advancing three major global health priorities (universal health coverage, antimicrobial resistance, and global health security), is impossible without strengthening diagnostic capacity, underscoring the urgency of expanding access to molecular tools such as MxPCR.

Although the World Health Organization (WHO) introduced the "Essential Diagnostics List" (EDL) in 2023 to promote equitable access, broad syndromic respiratory multiplex panels are not included, reflecting their classification as specialized rather than essential diagnostics [5]. Collectively, these findings indicate that MxPCR, though valuable, is a non-routine diagnostic modality, constrained by cost, infrastructure, and policy prioritization, and is not yet a universal screening tool across LMIC healthcare systems.

This narrative review synthesizes current knowledge on the use of MxPCR for pediatric LRTIs and considers its potential impact within LMIC healthcare settings. By enabling rapid and comprehensive detection of respiratory pathogens, including mixed infections, MxPCR supports targeted therapy, particularly in ill patients, and informs judicious use of antibiotics, making it a valuable diagnostic tool for improving pediatric care in resource-limited settings.

Methodology

Search strategy

A structured literature search was conducted in PubMed and Google Scholar to identify relevant peer-reviewed studies. The search covered publications from January 2014 to December 2024, a period selected to capture the evolution of MxPCR platforms over the last decade. Earlier seminal reviews were included when necessary to contextualize the development of molecular diagnostics.

Keywords and combinations of MeSH terms included "molecular diagnostics", "multiplex PCR", "respiratory PCR panels", "lower respiratory tract infections", "LRTI", "children", "pediatrics", "low- and middle-income countries", "LMIC", "pneumonia", "coinfection", "antimicrobial stewardship", "cost effectiveness", "tropical settings", and "non-temperate countries".

During article review, certain in-text citations were followed up when they provided relevant context, clarification, or additional evidence. These reference studies were assessed using the eligibility criteria and included when appropriate.

While the primary focus was on LMIC settings, studies from middle income and selected upper middle-income countries were included when their findings were relevant or applicable to LMICs contexts.

Inclusion criteria

The inclusion criteria were: studies published between January 2014 and December 2024; research evaluating molecular diagnostics (including MxPCR) for LRTIs; studies reporting on diagnostic accuracy, turnaround time, co-infection detection, prevalence, antimicrobial stewardship, or cost-related outcomes; and peer-reviewed articles in English.

Exclusion criteria

The exclusion criteria were: studies evaluating only rapid antigen tests; non-English publications; conference abstracts, editorials, commentaries, and other non-peer-reviewed sources; studies focusing exclusively on *Mycobacterium tuberculosis*; and studies evaluating MxPCR exclusively in hospital-acquired pneumonias. Relevant reports and guidance documents from recognized international health organizations were considered separately for contextual information.

Study selection

The initial search yielded 713 records. After removing duplicates; and screening titles, abstracts, and full texts against the eligibility criteria, 69 peer-reviewed studies met the inclusion criteria. The final reference list was limited to 60 references in accordance with the journal's guidelines.

Molecular diagnostics for pediatric LRTIs

Traditional diagnostic approaches for LRTIs such as culture, microscopy, serology, and antigen detection are limited by slow turnaround times, variable diagnostic accuracy, and minimal ability to detect co-infection [6–10]. Immunofluorescence (IF) techniques offer incremental improvement but remain constrained by moderate sensitivity, narrow pathogen coverage, and the need for skilled personnel [8–11]. The introduction of nucleic acid amplification tests (NAATs),

particularly polymerase chain reaction (PCR), marked a major advancement in respiratory diagnostics by enabling rapid and sensitive detection of pathogens, including those present at low viral loads [8].

MxPCR, a PCR-based NAAT, further extends these capabilities by allowing simultaneous detection of multiple viral, bacterial, and, in some platforms, fungal pathogens within a single assay [7,8]. It detects pathogen-specific nucleic acids (DNA or RNA) with high analytical precision but requires specialized equipment and trained personnel, factors that influence feasibility in resource-limited settings [12]. This capability is especially valuable in pediatric LRTIs, where co-infections are common and clinical presentations often overlap, making syndromic differentiation challenging based on clinical assessment alone.

Advantages of molecular diagnostics in LRTI management

Rapid turnaround time: implications for clinical decision making

A major advantage of MxPCR over conventional diagnostic methods is its substantially shortened turnaround time (TAT). Traditional viral cultures may require 3–7 days, and rapid shell-vial culture typically requires at least 48 hours. In many LMIC settings, further delays arise from logistical constraints, batching practices, limited laboratory operating hours, and reliance on referral laboratories for respiratory testing, consistent with broader diagnostic system limitations [4,13].

In contrast, MxPCR panels provide results within 1–5 hours, depending on platform design and laboratory workflow. Comparative studies have demonstrated marked reductions in TAT, with MxPCR outperforming IF assays by 3 to 24 hours [14,15].

Evidence consistently demonstrates the clinical value of shortened TAT. Rapid pathogen identification supports earlier differentiation between viral and bacterial infections and enables more targeted antimicrobial and anti-viral decision making [14]. Faster diagnostic reporting has been associated with antibiotic de-escalation, more appropriate antiviral use, fewer unnecessary investigations such as chest radiographs, and shorter hospital stays; collectively improving clinical utility [16]. Additionally, early detection enhances infection control by facilitating timely isolation of transmissible pathogens such as respiratory syncytial virus (RSV) and influenza virus [15,17,18].

Overall, the markedly shorter TAT of MxPCR accelerates clinical decision making, improves healthcare utilization, reduces unnecessary antimicrobial exposures, and may lower the risk of healthcare-associated infections. These benefits are particularly relevant in LMICs, where diagnostics delays are common and timely management is crucial to improving pediatric LRTI outcomes.

Diagnostic accuracy and clinical relevance

Diagnostic accuracy reflects a test's ability to correctly distinguish true cases from non-cases, commonly assessed through parameters such as sensitivity, specificity, detection rate, predictive values, and predictive agreements. In pediatric LRTIs, where viral and bacterial pathogens often present with overlapping clinical features, relying solely on clinical findings risks both under- and overtreatment. Accurate identification of the causative pathogen is therefore critical to guide timely and appropriate therapy.

Conventional methods such as viral culture and IF remain constrained by low sensitivity and limited pathogen coverage. IF assays typically identify only a limited subset of viruses, potentially missing emerging or less common pathogens such as human rhinovirus (HRV) and human bocavirus (HBoV), which have been associated with severe pediatric pneumonia, including fatal mono-infections [19–21]. In contrast, MxPCR detects a broader spectrum of organisms, including those at low viral loads, substantially improving diagnostic yield.

In a study by Pan *et al*., MxPCR achieved a detection rate of 64%, more than 5 times higher than direct fluorescence assay (DFA) testing (12%) [14]. Similarly, Zhang *et al.* reported strong concordance between MxPCR and individual pathogen-specific PCR assays, particularly for HRV, adenovirus (AdV), and pandemic influenza A (pdmH1N1), confirming comparable sensitivity and specificity while enabling simultaneous multi-pathogen detection [22]. Lin *et al*. demonstrated a 1.5-fold higher detection rate using MxPCR (75%) compared with traditional antigen tests and viral cultures (48%) [23]. In the case of bacterial LRTIs, Collins *et al*. found MxPCR panels to have a positive percent agreement (PPA) of 97% and a negative percent agreement (NPA) of 99.9%, relative to quantitative culture, supporting excellent accuracy for bacterial pathogen detection [24].

Collectively, these findings indicate that MxPCR matches or exceeds the diagnostic accuracy of both conventional and single-pathogen PCR assays, while reducing diagnostic time. The ability to detect low abundance and multiple pathogens in a single assay

enhances clinical confidence, reduces missed diagnoses, and facilitates earlier, evidence-based management decisions. Conventional diagnostics are frequently limited to basic culture or IF in LMIC settings. In such cases, the higher sensitivity and multiplex capacity of MxPCR represent a critical step towards more equitable, accurate and efficient pediatric respiratory care.

Detection of co-infection and clinical decision making

Co-infection, the simultaneous detection of two or more respiratory pathogens, is a well-recognized feature of pediatric LRTIs and a key determinant of disease severity [25]. The Child Health and Mortality Prevention Surveillance (CHAMPS) study demonstrated that fatal pneumonias frequently involved multiple pathogens, most commonly bacterial-bacterial, followed by bacterial-viral, and viral-viral combinations [2]. These findings underscore that pediatric respiratory infections frequently involve polymicrobial rather than single-pathogen infections.

Co-infection arises from complex biological interactions that can amplify disease severity. Bacterial communities may interact co-operatively, such as through biofilm formation that enhances persistence and antibiotic resistance, or antagonistically, exemplified by the inhibitory effect of *Streptococcus pneumoniae* on *Staphylococcus aureus* [26]. Viral-bacterial interplay also shapes clinical outcomes: respiratory viruses such as RSV and influenza disrupt epithelial integrity and mucociliary clearance, predisposing to secondary bacterial infection [26]. Viral-viral interactions may involve synergy, interference, non-interference, collectively influencing viral replication dynamics and the clinical phenotype [27].

These mechanisms are reflected in global epidemiologic patterns. The most frequently identified viral components of co-infection across multiple studies were enterovirus/human rhinovirus (EV/HRV) and RSV, either detected together, or each independently in combination with other respiratory viruses [28–31]. In studies that distinguished EV from HRV, HRV consistently emerged as the predominant virus, followed by RSV [11,32–37]. Complementing these findings, Ito *et al* reported that HRV co-infections particularly HRV combined with RSV, HBoV, or human metapneumovirus (HMPV) were significantly associated with severe pneumonia [21], underscoring the clinical relevance of viral-viral interactions. Similarly, Caporizzi *et al.* found that children with HBoV co-infection were more likely to present with severe disease characterized by more pediatric intensive care unit (PICU) admissions, increased need for advanced respiratory support, and longer hospital stay [38].

These observations are consistent with broader evidence demonstrating the substantial clinical impact of co-infection. El Kholy *et al*. observed that 36% of children with severe acute respiratory infections (SARI) admitted to the intensive care unit (ICU) harbored multiple viral pathogens, and notably, 47% of RSV co-infected cases required PICU admission, suggesting a strong association between RSV-related coinfections and severe disease [32]. Similar patterns were reported in an Egyptian cohort, where a substantial proportion of viral-bacterial co-infected cases required ICU care, and a Mexican study in which viral-viral co-infection significantly increased the risk of severe pneumonia [28,39]. Collectively, these findings highlight the limitations of single-pathogen diagnostic approaches in children with LRTIs.

Bacterial-viral co-infection patterns were also notable in previous studies. *Mycoplasma pneumoniae* predominated among toddlers and preschoolers, while *Chlamydia trachomatis* was more frequently detected in infants, a pattern observed consistently in studies using panels incorporating atypical bacterial targets [33,34,37].

Co-infection was most prevalent in children under 3 years of age, with rates declining as immune maturity increased [11,25,30,32,34–37]. This age-related susceptibility is biologically well explained. Infants exhibit dysregulated innate antiviral responses, reduced cytotoxic/natural killer (NK) cell activity, limited B cell diversity and waning maternal RSV-specific immunoglobulin G (IgG) by 4 months. These immunologic limitations impair pathogen clearance and substantially increase vulnerability to multiple concurrent infections [40].

The principal value of MxPCR in co-infection lies not simply in detecting multiple pathogens, but in defining the broad and available pathogen profile at the time of presentation, including dominant viral agents, contributing co-pathogens, and atypical bacteria. This enables clinicians to better anticipate disease progression, identify children at heightened risk of severe pneumonia or SARI, and initiate timely escalation of care. Although some bacterial co-infections may emerge later in the course of illness, early identification of co-infection present at presentation remains critical for improving severity assessment and clinical outcomes in pediatric LRTIs.

The occurrence and clinical significance of co-

infection is increasingly being recognized, and underscores the need to understand the distribution and co-circulation patterns of local pathogens.

Prevalence and epidemiology of respiratory pathogens: insights from multiplex PCR studies

MxPCR has considerably strengthened epidemiologic understanding of pediatric lower respiratory tract infections by enabling the simultaneous detection of multiple viral, bacterial, and atypical pathogens. Unlike conventional methods where testing typically halts once a single organism is isolated, MxPCR platforms characterize the full spectrum of circulating pathogens, offering a more accurate representation of the disease burden, pathogen distribution, and temporal trends across different regions.

Table 1 summarizes key studies published over the last 10 years that have utilized MxPCR platforms to

Table 1. Epidemiological and prevalence studies of respiratory infections using multiplex PCR (MxPCR). The table summarizes epidemiological and prevalence studies of respiratory infections using MxPCR; and highlights the respiratory pathogens detected, associated age distribution, and seasonal variation across the study populations.

SI No	Citation no.	Country	Study population	Sample size	Prevalent respiratory pathogen	Detection rate	Age specific trend	Seasonal variation
1	[11]	Morocco	< 15 yrs	84	RSV 53.8%, RV 5.8%, Coronavirus 3.8% *S. aureus* 3.8% *S. pneumoniae*	≥1 respiratory pathogen 61.9%; co-inf 19.2%	RSV < 2 yrs 50%; 3-5 yrs 3.8%; 6-15 yrs 0%	Fall and winter all peak Winter RSV, RV, and AdV
2	[35]	Morocco	< 14 yrs	534	Viral 91.2%, Bacterial 8.8%, HRV 59.1%, RSV 36.5%, PIV 10.3%, IVA 8.5%, *Bordetella pertussis* 75.6% (among bacterial cases)	≥1 respiratory pathogen 72.5%; co-inf 23.3%	all age RV < 6 mths RSV < 6 mths *B. pertussis* 6 to 12 mths PIV 2-5 yrs IVA	Winter 82.5%, spring 68.9%, autumn 66.3%, summer 62%; HRV No RSV and IVA – winter; HMPV -Spring; *B. Pertussis* summer
3	[36]	India	1-12 mths	100	RSV 35.4%, RV 25.6%, AdV 22%, Hib 6%, C. pneumoniae 2.5%, Mp 2.5%	≥1 respiratory pathogen 82%; mono-inf 66% co-inf 34%		
4	[39]	Egypt	317	< 16 yrs	RSV: 63.8%, rhinovirus: 10%, influenza: 9.2%, bacterial: *Hemophilus non type B*: 75%, *S. pmeumoniae*: 25%	≥ 1 respiratory pathogen 72.2%; mono-inf: 90.8% co-inf 5.7% Bacterial: 3.5%	< 1 Year RSV 71% AdV 58.3% >1 year Influenza 71.4% RV 73.9%	
5	[42]	India	1-60 mths	997	RSV A/B (37.35%), RV 14.9%, AdV 11.11%	≥ 1 respiratory pathogen 76.73% Total viruses 59.98%, co-inf 22.24%, mono-inf 77.76% Total bacterial 41.85%	< 1 year RSVA/B, HRV, AdV, EV; 13-24 mths RSV A/B, RV, HMPV A/B, HPIV3; 1-2 years *S. pneumoniae* and *Moraxella catarrhalis*	Dec-Jan RSV A/B; Year-round (peaks in Mar, May, Dec) HRV; Feb HMPV and H1N1; higher Dec 2014 and 2015 ADV
6	[43]	Morocco	< 4 mths	86	RSV 51%, RV 23%, *Mp* 6%	83% at least 1 resp pathogen; Co-inf 31%		Autumn and winter RSV, winter influenzas, no variation RV
7	[46]	Egypt	1 mo to 16 yrs	75	RV/EV 32.1%; RSV 29.5%; AdV 11.5%	Total viral 73.4%, co-inf 46.7%	< 12 mths viral and co-inf, > 60 mths bacterial	Rainy winter season viruses, summer bacterial

The data are extracted from epidemiological and prevalence studies. Each study is cited in the "citation" column. AdV: adenovirus; co-inf: coinfection; *C. pneumoniae*: *Chlamydia pneumoniae*: Hib: *Haemophilus influenza* B; HMPV: human metapneumovirus; IVA: influenza virus A; mono-inf: monoinfection; Mp: *Mycoplasma pneumoniae*; mths: months; PIV: parainfluenza virus; RSV: respiratory syncytial virus; RV: rhinovirus; *S. aureus*: *Staphylococcus aureus*; *S. pneumoniae*: *Streptococcus pneumoniae*; yrs: years.

describe pathogen prevalence and circulation patterns, including seasonal fluctuations across diverse pediatric settings.

HRV, RSV, and combined HRV/EV have consistently emerged as the most frequently detected viral pathogens in children across studies conducted over the past decade [23,25–28,35]. RSV and HRV particularly predominate in infants and toddlers, reflecting age-related susceptibility [28,29,31,33,41]. MxPCR studies have also identified region-specific patterns: for example, in Egypt, RSV (47%) and adenovirus (83%) were more common in Giza, whereas HRV (70%) and influenza (57%) predominated in Gharbia [39]. These findings highlight the influence of local epidemiology on pathogen circulation.

Among the bacterial pathogens detected through multiplex panels, *Bordetella pertussis* remains an important cause of disease in infants under 6 months of age, accounting for approximately 76% of bacterial positive cohorts mirroring findings from Turkey and other LMIC settings [30,35]. Commonly identified bacterial organisms include *Streptococcus pneumoniae, Moraxella catarrhalis, Haemophilus influenzae type b (Hib), Staphylococcus aureus, Mycoplasma pneumoniae, and Chlamydia pneumoniae* [11,36,42,43]. The inclusion of atypical pathogens in several MxPCR platforms has also broadened epidemiologic understanding, revealing mixed viral-atypical infection patterns that may not have been fully appreciated previously [44,45].

Seasonality is a key determinant of respiratory pathogen circulation, but the pattern varies by climate. RSV and influenza peak during autumn and winter [35,42,46]. Pathogen circulation is less predictable in tropical and subtropical settings: HRV circulates year-round, while peak RSV and influenza often coincide with changes in humidity, rainfall, or transitional climatic periods [47–50]. Cross-wavelet analyses showed that shifts in temperature and humidity preceded RSV outbreaks in Vietnam, short-term increases in rainfall were associated with RSV surges in Malaysia and Zambia, and influenza peaks in Zambia's cool dry season aligned with declining humidity [47,49,50].

Understanding seasonal and regional patterns of peak pathogen activity assists clinicians in identifying the most likely causative agents by distinguishing the "driver" pathogen from incidental detections, especially in cases of co-infection. In settings where MxPCR testing is limited or where samples require referral to external laboratories, such epidemiologic data inform empirical treatment decisions while the results are pending. From a public health perspective, mapping local prevalence patterns also supports rational selection of multiplex panels tailored to regional pathogen profiles, thus optimizing diagnostic yield while maintaining cost-effectiveness.

Overall, MxPCR-based epidemiologic data reveal substantial geographic, seasonal, and age-specific variability in pediatric respiratory pathogens. This can facilitate more precise clinical decision making and can inform public health strategies, particularly in LMICs where pathogen distribution may differ from high-income settings and where empirical management remains common.

Multiplex PCR in the management of LRTIs: optimizing treatment and antibiotic stewardship

LRTIs are among the leading drivers of antibiotic overuse in children, largely because etiological organisms cannot be reliably distinguished on clinical presentation. Up to 50% of pediatric antibiotic prescriptions are initiated empirically without pathogen confirmation, a practice strongly linked to limited or delayed diagnostics in resource constrained settings. This diagnostic uncertainty fuels unnecessary and prolonged antibiotic use and inappropriate drug selection, particularly where clinicians rely on older, broad-spectrum agents in the absence of timely laboratory data. Ultimately, this pattern paves the way for accelerated antimicrobial resistance (AMR) [51].

MxPCR directly addresses these challenges by providing rapid and accurate pathogen identification. In a prospective randomized trial in Argentina, the use of MxPCR led to a 4-fold increase in significant clinical management changes, driven by a markedly shorter TAT [15].

The impact was especially notable in children, who had 8-fold higher odds of management modification, which was a reflection of the high clinical value of early, precise pathogen identification in pediatric care [15]. The key changes included substantial reduction in unnecessary antibiotic prescriptions and decreased reliance on complementary investigations such as chest radiographs and blood counts [15].

MxPCR also supports antimicrobial stewardship by enabling timely discontinuation of antibiotics once a viral etiology is confirmed. In the Philippines, 23.8% of children initially started on antibiotics had their treatment discontinued after MxPCR identified a viral pathogen, demonstrating the tool's ability to prevent avoidable antibiotic exposure [41]. Similar findings were observed in other cohorts with 43% of children

discontinuing antibiotics after receiving a confirmed viral diagnosis [52], and improved treatment precision and reduction in unnecessary antimicrobial use [53].

Beyond discontinuation, MxPCR contributes to smarter antibiotic optimization. MxPCR testing reduced the duration of intravenous antibiotic therapy by approximately 1 day, facilitated more frequent de-escalation within 72 hours, and reduced escalation between 72 hours and day 7 [54]. This resulted in fewer days of antimicrobial exposure and more rational antibiotic utilization.

In addition to optimizing antibiotic use, MxPCR also improves antiviral stewardship, particularly for influenza. MxPCR supports the timely initiation of antivirals by accurately detecting viral pathogens, where early administration within the first 48 hours offers the greatest benefits in reducing disease severity and complications [55]. Evidence from MxPCR guided management shows that antiviral therapy is used more appropriately when rapid viral confirmation is available, enabling initiation when influenza is detected and avoiding unnecessary treatment when it is not [15].

This diagnostic precision prevents both the overuse of antimicrobials and missed opportunities for timely antiviral interventions, reinforcing the broader stewardship benefits of MxPCR. These findings converge across multiple studies: rapid and accurate pathogen identification consistently reduced empirical antibiotic use, enabled early and appropriate de-escalation, improved the precision of antiviral therapy, and ultimately lowered downstream healthcare utilization [14,16,56].

Cost effectiveness

Although the clinical value of MxPCR is well established, its cost effectiveness remains an important consideration, particularly for LMIC healthcare systems where diagnostic investments must be carefully prioritized. Diagnostic practices for respiratory infections vary widely between regions: some facilities rely on rapid antigen tests (RATs) or DFA/IF, others use batched single-plex PCR, and many centers in LMICs have limited or no access to molecular diagnostics. These differences shape how the economic value of MxPCR is perceived, because cost effectiveness depends not only on the price of the test itself, but also on its downstream clinical and resource impacts, including effects on hospital admissions, antimicrobial use, imaging, isolation practices, and broader societal costs.

Cost effectiveness studies from high-income settings provide important early insights. Kitano *et al*. evaluated MxPCR versus RATs in hospitalized children in Japan where RATs are widely used and found that multiplex testing reduced hospital admission rates by 10%, shortened antimicrobial therapy by 4.26 days, and decreased length of stay (LOS) by 1.35 days. Despite higher per-test costs (USD 183.1 for MxPCR vs USD 39.3 for RATs), MxPCR achieved net savings of USD 14.9 per case by reducing total admission, hospitalization and social costs [57]. This demonstrates that higher upfront expenditure may be offset by reduction in treatment duration and hospital resource utilization.

Subramony *et al*. reported a similar finding in a large cohort of hospitalized pediatric patients. MxPCR testing was associated with fewer antibiotic days (median 4 vs 5), reduced chest radiography within the first 48 hours (59% vs 78%), and significantly lower odds of receiving $\geq$ 2 antibiotic days (OR 0.5) or undergoing chest radiographs (OR 0.4) [58]. Notably, MxPCR testing also increased the duration of isolation precautions due to the rapid identification of transmissible pathogens [58]. While this may raise hospital expenditure in high-income settings, its financial impact in LMICs is likely smaller due to generally lower isolation-related costs. Nonetheless, this finding highlights the need or context-specific cost assessments rather than direct extrapolation from high-income countries.

Evidence from MxPCR stewardship studies provides additional economic signals. In the Argentine trial, shorter turnaround time resulted in earlier clinical decision making, leading to reduced LOS in children and lower hospitalization costs [15]. Similarly, El-Nawawy *et al.* and other pediatric studies showed that reduced LOS and lower healthcare utilization followed early and accurate diagnostic clarification [46,54]. The consistent association between MxPCR and reduced imaging, antibiotic use, and unnecessary investigations further supports its potential to generate indirect cost savings, even when direct test costs are higher than traditional diagnostics.

Despite these promising findings, economic evaluations of multiplex testing in LMICs remain scarce, even though these regions experience the highest burden of morbidity and mortality from LRTIs [59]. The majority of cost effectiveness analyses for respiratory diagnostics have been conducted in high-income countries leaving a critical evidence gap for LMIC policy planning [59]. As health economic outcomes depend heavily on baseline diagnostic capacity, hospital cost structures, and epidemiological patterns, LMIC-specific studies are urgently needed.

Insights from the Foundation for Innovative New Diagnostics (FIND; 2023) market landscape provides further context for implementation. Near point of care (POC) molecular platforms showed substantial variation in price, with published ex-works instrument costs ranging from USD 10,000–72,000 and USD 7.90–90 per test for low and medium-plex assays (typically 2–8 targets) [13]. These figures excluded shipping, importation fees, distributor mark-ups, and service contracts; thus, real-world costs are substantially higher [13]. Very high multiplex systems (≥ 20 targets), such as BioFire FilmArray, QIAstat-Dx and Unyvero, cost USD 80–300 per test and are currently considered too costly for district hospitals and near-patient laboratories in most LMICs [13]. FIND further estimated that the near POC multiplex testing could meet a potential demand of 3.6 million tests annually across district-level facilities in LMICs, underscoring the need for affordable, sustainable, and scalable diagnostic options [13]. Although FIND's analyses focused on near POC technologies, the broader economic insights are directly relevant to understanding the financial consideration associated with adopting MxPCR in LMIC settings.

Given the economic realities and challenges, the adoption of high- or very-high-multiplex panels may be unrealistic for many LMIC hospitals. A more practical approach may involve implementing locally tailored multiplex panels focused on the most prevalent regional pathogens identified through epidemiological surveillance, thereby balancing diagnostic value with cost efficiency. Such an approach also aligns with antimicrobial stewardship priorities and maximizes diagnostic impact where resources are limited.

Limitations of the MxPCR

Although the MxPCR platforms generally demonstrate high sensitivity and specificity, performance can vary slightly across different assays and individual pathogen targets. Viruses such as human coronaviruses (HCoV) OC43, HCoV-HKU1, and hMPV have shown lower sensitivity or positive predictive value in some studies [60]. These variations reflect differences in the design of assays rather than inherent limitations of the MxPCR technology and can be mitigated through careful selection of platforms.

MxPCR performance is inherently linked to the predefined targets incorporated within each panel. Since panel composition varies across platforms, pathogens not included in a given assay will not be detected. Primer-probe sets also require periodic updates to ensure continued alignment with circulating strains, as emerging or mutated variants may otherwise escape detection. These features reflect assay design rather than performance limitations and underscore the importance of selecting panels aligned with local epidemiology and ensuring timely updates during periods of rapid viral evolution.

MxPCR panels are unable to distinguish between driver and passenger pathogens in co-detections or co-infections, which may reflect colonization, prolonged shedding, or a resolving infection. Therefore, interpretation occasionally requires consideration of the clinical picture, and, where appropriate, ancillary investigations to determine the significance of each detected pathogen. A proportion of patients with clinically suggestive respiratory infections may also have no identifiable pathogen on MxPCR, with reported rates of 17–30%, reflecting pathogens not included in the panel, low viral loads, suboptimal sampling, or non-infectious causes. In both scenarios, appropriate clinical decision making relies on clinician awareness and judgement.

Conclusions

LRTIs remain a major contributor to childhood morbidity and mortality in LMICs where diagnostic delays and limited access to definitive testing hinder timely management. This review highlighted the growing recognition of viral and bacterial co-infections, including pathogens previously considered low risk, and underscored the importance of early, accurate identification to guide appropriate clinical intervention. MxPCR offers a rapid, sensitive, and comprehensive diagnostic approach that is particularly valuable in settings where clinical presentations are heterogeneous and disease severity is difficult to predict.

Overall, the evidence suggests that MxPCR has the potential to substantially improve the diagnostic accuracy, clinical management, and broader public health response to pediatric LRTIs in resource-limited environments. Strategic and context-appropriate implementation could help LMICs move towards more precise, timely, and cost-effective respiratory illness management, ultimately improving outcomes for the most vulnerable children.

Recommendations

The successful implementation of MxPCR in LMICs will require alignment with national healthcare priorities and the careful selection of panels that reflect local epidemiology and burden of disease. Implementation may be most feasible in tertiary or high-dependency pediatric settings, where the need for rapid etiological clarification is the greatest and

diagnostic yield can meaningfully influence clinical decisions. Cost, infrastructure, and accessibility remain key hurdles; however, these can be addressed through phased deployment, public-private partnerships, and potential government subsidies to support equitable access.

Future economic evaluation should extend beyond assay pricing to include downstream costs such as transportation, staff training, maintenance, periodic probe updates, operational overheads, and institutional mark-ups. These analyses must also account for context-specific healthcare delivery models, as cost effectiveness will vary across LMICs based on local policies, reimbursement structure, and public sector procurement systems. Country-level economic studies are therefore essential to guide sustainable implementation strategies.

Acknowledgements
The authors acknowledge the use of ChatGPT to assist in refining grammar, improving the flow, and improving sentence structure. All intellectual content was developed by the authors, who take full responsibility for the manuscript.

Authors' disclaimer
We declare that this review is based on currently available evidence and does not endorse any specific diagnostic platform, diagnostic panel, or commercial products. The content of the review reflects the interpretation of peer reviewed literature.

Authors' contributions
KKT, KFN, CHL, and JR contributed to the study design. Study implementation was carried out by JR, who conducted the literature review and developed the manuscript framework. JR, KKT, KFN, and CHL contributed to the manuscript by providing substantial input and editing, including the discussion, epidemiological aspects, limitations, and recommendations. JR had the major contribution to writing, preparing the original draft and incorporating all feedback. All authors read and approved the final version of the manuscript. KKT and JR are guarantors of the work.

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Conflict of interest
No conflict of interest is declared.

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