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ToolCAP: a study protocol for a multi-country randomised controlled trial assessing a lung ultrasound-informed antibiotic prescribing strategy for paediatric community-acquired non-severe pneumonia

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Study protocol

Keywords: paediatric pneumonia, lung ultrasound, point-of-care ultrasound, antibiotic stewardship, IMCI, Sub-Saharan Africa

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Title {1a}

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Abstract

Background: Paediatric lower respiratory tract infections, including pneumonia, remain a leading cause of childhood morbidity and acute care attendance in low- and middle-income settings, and contribute substantially to mortality in sub-Saharan Africa. Management is commonly guided by the World Health Organization (WHO) Integrated Management of Childhood Illness (IMCI) pneumonia framework, which prioritises sensitivity and feasibility but relies on clinical signs alone. As these signs do not reliably distinguish bacterial pneumonia from viral or other self-limiting respiratory illness, IMCI-based management may contribute to substantial antibiotic overuse. Lung ultrasound (LUS) is a promising, non-invasive, point-of-care imaging modality that may improve pneumonia risk stratification and support antibiotic stewardship.

Methods: ToolCAP (Novel Tools to improve management of paediatric Community-Acquired Pneumonia) is a multi-country, open-label, individually randomised controlled trial comparing a LUS-informed IMCI-PLUS (Point-of-care Lung ultrasound) management strategy with routine IMCI-based care among children aged ≥60 days to <13 years presenting with WHO IMCI clinical pneumonia. Participants are randomised 1:1 to intervention or control across outpatient, emergency, district, regional, and tertiary facilities in South Africa, Tanzania, and Senegal. In the intervention arm, LUS is performed and interpreted by trained study personnel using a standardised scanning protocol and predefined IMCI-PLUS interpretation framework. A LUS report providing guidance for or against antibiotic treatment is shared with the treating clinician, who retains final responsibility for clinical management. Control arm participants undergo LUS for study purposes, but findings are not shared with treating clinicians and do not inform enrolment-visit management. The co-primary endpoints are: (1) proportion of participants prescribed antibiotics on Day 1 (superiority framework in terms of antibiotic prescription reduction); and (2) proportion of participants with clinical failure by Day 8 (non-inferiority framework). Secondary outcomes include antibiotic use by Day 8, adverse drug reactions, caregiver-reported cure rates, hospitalisation, diagnostic testing, deaths by Day 29, unscheduled health-seeking events, tuberculosis-related outcomes, and cost-effectiveness. The planned sample size is 3,500 participants.

Discussion: ToolCAP is designed as an efficacy trial to estimate whether standardised LUS interpretation, delivered under structured training, supervision, and quality-assurance conditions, can reduce antibiotic prescribing while preserving clinical safety in children with IMCI-defined pneumonia. The trial is not intended to evaluate routine, variably implemented “real-world” LUS use by frontline clinicians. By recruiting across diverse epidemiological contexts, levels of care, and provider settings in three SSA countries, ToolCAP will generate evidence on the potential role of LIS-informed IMCI-based management as an antibiotic

stewardship strategy. Further implementation and effectiveness research is planned within the EDCTP-funded IMCI-PLUS project to assess scalability, integration into routine care, and health system requirements for sustained use.

Trial registration: ClinicalTrials.gov: NCT06670833 (Registered 1st November 2024), https://clinicaltrials.gov/study/NCT06670833; Pan-African Clinical Trials Registry: PACTR20241282257G3G7 (Registered 9th December 2024), https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=32151

Keywords

paediatric pneumonia, lung ultrasound, point-of-care ultrasound, antibiotic stewardship, IMCI, Sub-Saharan Africa

Structured summary {1b}

Item	Description
Primary Registry and Trial Identifying Number {4}	ClinicalTrials.gov: NCT 06670833

Secondary Identifying Numbers	Pan-African Clinical Trials Registry: PACTR20241282257G3G7; South African National Clinical Trials Register: DOH-27-052025-7467
Source(s) of Monetary or Material Support	Swiss National Science Foundation EU Horizon/EDCTP
Primary Sponsor and contact information {3b}	École Polytechnique Fédérale de Lausanne (EPFL) IC IINFCOM LIGHT, INF 334, Station 14, 1015 Lausanne, Switzerland; kristina.keitel@epfl.ch
Role of sponsor and funder {3c}	The sponsor had oversight of the trial design, study management, regulatory compliance, and reporting. Funders have no role in trial design, trial conduct, analysis or reporting of results.
Contact for Public Queries	Prof. Kristina Keitel, EPFL IC IINFCOM LIGHT, INF 334, Station 14, 1015 Lausanne, Switzerland; kristina.keitel@epfl.ch
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Public Title	ToolCAP: Novel Tools to improve management of paediatric Community-Acquired Pneumonia - a randomised controlled trial
Scientific title	ToolCAP: Novel Tools to improve management of paediatric Community-Acquired Pneumonia - a randomised controlled trial
Countries of Recruitment	South Africa; Tanzania; Senegal
Health Condition(s) or Problem(s) Studied	Paediatric community-acquired pneumonia / lower respiratory tract infections (LRTI)
Intervention(s)	IMCI-PLUS (Point-of-care Lung ultrasound) clinical management algorithm using Lung Ultrasound (LUS) to guide antibiotic prescription decisions.
Key Inclusion and Exclusion Criteria	Inclusion: children ≥60 days to <13 years with WHO IMCI clinical pneumonia. Exclusion: severe clinical presentation (IMCI danger signs, severe respiratory distress, or need for ventilatory support), hypoxaemia meeting predefined thresholds, prior antibiotic use >48hr, non-acute or follow-up presentations for the same illness or recent enrolment within 28 days, high-risk underlying conditions (including comorbidities associated with increased risk of severe pneumonia or pneumonia of unusual aetiology), absence of caregiver consent.
Study Type	Prospective, open-label, individually randomised controlled trial with a superiority framework for antibiotic reduction and non-inferiority framework for clinical failure; allocation ratio 1:1.

Date of First Enrollment (planned)	09.04.25
Sample Size	3,500
Primary outcome(s)	Co-Primary Endpoints (1.1) Proportion of participants prescribed antibiotic treatment on D1. (1.2) Proportion of participants with clinical failure, defined as the development of any of the following criteria during the specified time periods after enrolment. Any time before or on D8: • WHO IMCI danger sign (inability to drink/breastfeed, vomiting everything, convulsions with this illness, lethargy/unconscious) • New or worsening severe respiratory distress (such as grunting, head nodding, severe chest indrawing) • Secondary Hospitalization (defined as a hospitalization occurring after discharge from in-patient admission or outpatient visit) related to a deterioration of the presenting complaint on D1 • Change in level of care (e.g., admission to intensive care unit, transfer to higher level of care) • Need for respiratory support (e.g., high flow nasal cannula, CPAP) • Death due to any medical cause (i.e., except trauma) At D8 outcome assessment: • Report from the caregiver of non-resolution / worsening of illness
Secondary outcome(s)	2.1) Evaluation of the effect of the intervention on: • The proportion of children prescribed an antibiotic by D8. • The proportion of adverse drug reactions related to routine antibiotic treatment by D8 (i.e., Anaphylactic reaction, severe diarrhoea, or generalised severe rash). • The proportion of patients cured (defined as caregiver reported recovery from illness) by D8 and D29. • The proportion and duration of inpatient admissions (by D8 and D29). • The proportion of patients undergoing a non-study related diagnostic test (including CXR, blood tests, urine tests, microbiological assays) on D1, and for those admitted on D1, tests conducted up until D8.

	• The proportion of deaths of any cause by D29. • The proportion of participants with any unscheduled health seeking events for any cause and/or hospital admission for any cause since D8 follow-up (at D29 follow-up). (2.2) Tuberculosis (TB) related endpoints: • The proportion of children with confirmed, unconfirmed or unlikely intrathoracic TB who were enrolled in the TB substudy. • The ability of LUS (and mediastinal US, if done) to distinguish TB from non-TB disease. • The diagnostic accuracy of LUS compared with CXR and computer aided detection (CAD), and within the context of TB Treatment Decision Algorithms. (2.3) Economic Evaluation endpoint: • Cost-effectiveness of integration of LUS into current IMCI-based management guidelines for pneumonia
Ethics Review	Switzerland • Bern Cantonal Ethics Committee, Switzerland 2023 01534 South Africa • University of the Witwatersrand Human Research Ethics Committee (HREC) (Medical) • Stellenbosch University Health Research Ethics Committee (HREC) Tanzania 1) Muhimbili University of Health and Allied Sciences (MUHAS) Institutional Review Board 2) National Institute for Medical Research (NIMR) Ethics Committee Senegal • Comité National d'Éthique pour la Recherche en Santé (CNERS)
Individual Trial Participant Data sharing statement	Deidentified individual participant data (IPD) will be made available upon reasonable request after publication, subject to data sharing agreements aligned with national regulations. Data will be shared for purposes of secondary analysis, meta-analysis, and reproducibility.

Protocol version {2}

Introduction

Background and rationale {9a}

In many low- and middle-income settings, lower respiratory tract infections (LRTIs), including pneumonia, remain a leading cause of childhood morbidity and a common reason for acute outpatient care [1]. Management of childhood pneumonia in these settings is commonly guided by the World Health Organization's (WHO) Integrated Management of Childhood Illness (IMCI) framework, which was first developed in the 1990s, when improving access to antibiotics for children with potentially serious bacterial infections was a major public health priority [2]. Under this approach, children meeting clinical criteria for pneumonia are generally all recommended antibiotic treatment.

However, IMCI pneumonia classification relies exclusively on clinical signs, including cough and/or difficulty breathing, age-specific tachypnoea, and/or lower chest wall indrawing [2], as evidence to include additional diagnostic tests into the IMCI approach has been lacking. These signs are intentionally sensitive but poorly specific and do not reliably distinguish bacterial infections from common, self-limiting viral infections in children [3]. Furthermore, recent evidence from SSA estimates the proportion of children with bacterial respiratory infection among those presenting with clinical LRTI may be substantially lower than the proportion treated with antibiotics. Recent studies in SSA, using composite reference standards have estimated bacterial respiratory infection in only 2-4% of children presenting in primary care [4,5], and 23.3-31.6% in secondary [6] care settings. These findings suggest that a large proportion of antibiotic courses recommended by current guidelines for children with LRTI may be unnecessary.

Although access to essential, quality-assured antibiotics remains limited for many populations in sub-Saharan Africa (SSA), inappropriate antibiotic use, including over-prescription in outpatient settings, is increasingly recognised as a key driver of antimicrobial resistance (AMR) [7–11]. Bacterial AMR is a major global threat, responsible for an estimated 1.27 million deaths globally in 2019 with the highest burden in SSA [12]; responsible for nearly as many deaths as malaria and HIV combined. In SSA, more than 50% of children who are sick receive antibiotics when visiting health facilities [13–18], with 80–90% of such antibiotics prescribed at the outpatient level [19]. A substantial proportion of this prescribing is considered

inappropriate[13,19], particularly for respiratory infections which are the most common indication for antibiotic use in children [13,19]. Antibiotic use and AMR are projected to increase over the coming years, underscoring the need for effective antibiotic stewardship strategies in SSA primary care settings [20–22]. Accordingly, WHO declared AMR as “one of the biggest threats to global health, food security and development today.” [7]. However, effective strategies remain limited, and improved diagnostic and management approaches are essential to reduce unnecessary antibiotic use while preserving access for children who are likely to benefit.

Lacking more effective tools to safely identify the minority of children likely to benefit from antibiotics, frontline clinicians in low resource settings often prescribe antibiotics broadly to children meeting clinical pneumonia critera, driving the above-described overuse and fuelling local AMR and significantly overtreating cases of viral pneumonia [3]. Besides the risk of AMR at the population level, reducing antibiotic prescriptions is also important for each individual patient. Unnecessary antibiotic exposure may also cause direct adverse drug reactions and observational studies have associated early-life antibiotic exposure with later childhood adverse health outcomes including allergic, autoimmune, metabolic, and neurodevelopmental conditions [23,24]. Improving the specificity of IMCI-based pneumonia management, while preserving safety, has therefore been identified as an important research and policy priority.

Several tools have been proposed (currently at different stages of diagnostic development) to improve both diagnostic pathways and appropriateness of antimicrobial prescriptions in Low and Middle-Income Countries (LMICs). These include the use of point-of-care biomarkers, comprehensive electronic decision support algorithms [4,25,26], and more novel applications of established technologies. Two such technologies are Lung Ultrasound (LUS) and Lung Auscultation (LAusc). LAusc, while widely used, has well-recognised limitations, including variable diagnostic accuracy and substantial inter-observer variability, particularly in distinguishing between respiratory pathologies in children [27]. These challenges have prompted renewed interest in digital and machine learning approaches to augment auscultation. Early studies suggest potential diagnostic utility of breath and cough sound analysis [28–30], although evidence remains limited and AI-assisted respiratory sound analysis has not yet been widely validated or implemented for routine paediatric pneumonia management in LMIC settings.

LUS, however, is a non-invasive, near consumable-free point-of-care imaging modality that has become increasingly accessible with the advent of portable, low-cost devices compatible with mobile platforms. These devices are increasingly available and utilised across sub-Saharan Africa (SSA) [31], while LUS is increasingly being integrated into outpatient respiratory assessment in high-resource settings [32–34].

A substantial body of evidence demonstrates that LUS can accurately detect lung consolidation in pneumonia, with high sensitivity and specificity reported in both adult and paediatric populations [35–37]. While some studies suggest potential for differentiating viral from bacterial aetiologies [38,39], interpretation remains limited by the lack of reliable microbiological reference standards in paediatric pneumonia more broadly [6,40,41]. Importantly, despite promising diagnostic accuracy and feasibility in low- and middle-income settings [42–46], there is currently limited evidence on whether LUS-guided management can safely reduce antibiotic use while maintaining favourable clinical outcomes in primary care settings, highlighting the need for interventional studies.

In TB-endemic settings, the interpretation of respiratory symptoms and LUS findings is further complicated by paediatric intrathoracic TB, where clinical presentations frequently overlap with acute pneumonia. Microbiological confirmation is often difficult in children, and reliance on clinical features alone can lead to both under- and over-treatment. In response, recent WHO guidance (Module 5) has introduced pragmatic treatment decision algorithms (Algorithm A and B) aimed at improving case detection and timely initiation of therapy in children with suspected TB [47]. However, these algorithms still depend heavily on non-specific clinical and radiographic features. Emerging evidence suggests that lung ultrasound (LUS), including assessment of pleural and mediastinal structures, may offer additional diagnostic value in this context, with growing data supporting its ability to identify features associated with paediatric TB [48]. Within this evolving diagnostic landscape, evaluating the potential role of LUS to support differentiation between TB and non-TB respiratory disease is of particular relevance.

We therefore hypothesise that integrating standardised LUS interpretation into the IMCI-based management of clinical pneumonia will improve identification of children likely to benefit from antibiotic treatment, reduce unnecessary antibiotic prescribing, and maintain favourable health outcomes.

Given the resource constraints faced by health systems in many LMICs, this study will also include an economic evaluation to assess the cost-effectiveness of LUS-informed IMCI-based pneumonia management. This will generate policy-relevant evidence to inform decisions on the potential scale-up of LUS-informed care.

Explanation for the choice of comparator {9b}

The comparator to the IMCI-PLUS (Point-of-care Lung Ultrasound) algorithm is IMCI as implemented in routine care practices. Routine care in South African, Tanzanian, and Senegalese primary care settings and District/Regional Hospitals is as per the National Standard Treatment Guidelines which are based on IMCI-guidelines that recommend antibiotic prescriptions for all cases of clinical pneumonia. The purpose of the study is to determine the added benefit of integrating LUS into the IMCI pneumonia management pathway; therefore, the appropriate comparison is the current routine care IMCI approach. Although IMCI may be implemented with variations across health systems, all participating recruitment sites apply IMCI-based outpatient pneumonia management as part of routine care.

Objectives {10}

Primary Objective

The primary objective of this study is to evaluate whether the integration of LUS into current IMCI-based management guidelines for pneumonia (intervention group):
(1.1) Reduces antibiotic treatment at D1
(1.2) Is non-inferior in terms of clinical failure by D8.
among children aged ≥60 days - <13 years with WHO IMCI clinical pneumonia, when compared to routine care (control group).

Secondary Objectives

(2.1) To assess the effect of the intervention (when compared to routine care) in children with WHO IMCI clinical pneumonia on:

- the proportion of children prescribed antibiotics by D8
- the proportion of adverse drug reactions related to routine antibiotic treatment by D8 (i.e.,

Anaphylactic reaction, severe diarrhoea, or generalised severe rash).

- the proportion of participants cured (defined as caregiver-reported recovery from illness) by D8 and D29 (for those not cured at D8)
- the proportion and duration of inpatient admissions by D8 and D29 (for those admitted on D1 only)
- the use of diagnostic tests (in addition to LUS) on D1, and for those admitted, by D8.
- death by D29
- the proportion of participants with any unscheduled health-seeking events for any cause and/or hospital admission for any cause since D8 follow-up at D29 follow-up

(2.2) To Investigate Tuberculosis (TB) in the context of acute pneumonia by:

- Determining the proportion of children in the TB substudy with confirmed, unconfirmed or unlikely intrathoracic TB according to the Classification of Intrathoracic Tuberculosis Case Definitions [49]
- Comparing specific LUS (and mediastinal US, if done) abnormalities that may distinguish TB from non-TB lung disease.
- Comparing LUS to both CXR and computer aided detection (CAD) of CXR as potential alternate imaging modalities, and within TB Treatment Decision Algorithms

(2.3) Estimate the cost-effectiveness of integration of LUS into current IMCI-based management guidelines for pneumonia

Exploratory Objectives:

(3.1) To compare, where available, the aetiological diagnoses (e.g., pulmonary TB, RSV bronchiolitis, confirmed bacterial pneumonia) between the intervention and control group (See Section 5.3.4 relating to relevant sample collection).

(3.2) To assess the effect of the intervention (when compared to routine care) in children with WHO IMCI clinical pneumonia on: the duration of antibiotic treatment between D1 and D8; and the proportion of participants with a change in antibiotic treatment strategy by D8 (including class switching, extension of spectrum)

(3.3) To assess the diagnostic and risk stratification potential of LUS and Lung Auscultation (LAusc) in comparison to clinical signs and symptoms, CXR and host biomarkers.

(3.4) To evaluate a LUS severity score in a cohort of patients with clinical pneumonia for risk stratification.

(3.5) To improve current risk stratification and management guidelines for clinical pneumonia, including

improved LUS feature thresholds to guide antibiotic prescription.

(3.6) To explore new generation host biomarkers and transcriptome signatures to identify patients with bacterial pneumonia or to predict adverse outcomes.

(3.7) To develop a flexible and interpretable multimodal deep learning algorithm to automate the interpretation of clinical signs (including LUS) and symptoms for the diagnosis and risk stratification of pneumonia.

(3.8) To optimize the diagnostic and risk-stratification pathway by identifying the most predictive combination, order, and number of variables.

(3.9) To review the LUS features detected on blinded retrospective expert LUS analysis in the control group

(3.10) In children enrolled in the TB substudy:

- To assess the role of novel biomarkers in the diagnosis of TB in children
- To assess the proportion with sole or concomitant extrapulmonary TB

Methods: Patient and public involvement, and trial design

Patient and public involvement {11}

Patients and members of the public were not involved in the design of the study protocol. However, patient and public involvement was integrated at each participating site through established community engagement mechanisms. These groups contributed to the development of the informed consent process and are providing input on trial implementation. During the trial, these community platforms will continue to be engaged, and a central patient and public involvement panel will be established to support broader engagement across sites. This panel will contribute to the reporting and analysis of trial findings and will be involved in the dissemination of results to participating communities.

Trial design {12}

This is an open-label, individually randomised controlled trial (RCT) with two arms, comparing lung ultrasound–informed pneumonia management to routine care. The allocation ratio is 1:1. The trial uses a superiority framework for assessing reduction in antibiotic prescriptions and a non-inferiority framework for evaluating clinical outcomes.

Methods: Participants, interventions and outcomes

Trial setting {13}

The study will be conducted as a multi-site trial across outpatient, emergency, district, regional, and tertiary care facilities in three countries where children with acute respiratory illness present for care. In South Africa, participating sites include: two District or Regional Hospitals in the Ehlanzeni District (Mpumalanga Province) and their feeder clinics, Khayelitsha Hospital and Tygerberg Hospital in the Western Cape Province and their feeder clinics. The Ehlanzeni District represents a rural population undergoing rapid epidemiologic transition, while Khayelitsha represents a densely populated peri-urban environment with high HIV and TB burden. In Tanzania, sites include 4–5 dispensaries/health centers or hospitals in the Temeke District of the Dar es Salaam Region, serving primary and secondary care. These sites will be selected to represent urban and peri-urban areas of Dar es Salaam with low malaria, TB, and HIV prevalence and will be chosen based on the number of children presenting with LRTI and available clinical staffing. In Senegal, the study will be conducted in one health center and one hospital in Dakar.

Characteristics of the people who are needed for the trial

Characteristic	**The people we would expect to see included**
Age	Children aged ≥60 days to <13 years Expected 90% of children aged ≥60 days to <5 years and 10% of children aged ≥5 years to <13 years.
Sex	Both male and female children will be included. No exclusions based on sex.
Gender	Gender is not assessed separately from sex in the protocol. Participants are expected to be identified as boys or girls, with no gender-based exclusions.
Race, ethnicity and ancestry	Participants will reflect the local populations of the recruitment areas. The trial does not define race/ethnicity categories but will include all children presenting to participating facilities.
Socioeconomic status	Participants are expected to represent low- and middle-income households typical of: rural Mpumalanga; peri-urban informal settlements in Khayelitsha; urban and peri-urban Dar es

	Salaam; and urban Dakar.
Geographic location	• South Africa: Rural Ehlanzeni District (Mpumalanga) and peri-urban Khayelitsha (Western Cape). • Tanzania: Urban and peri-urban Dar es Salaam Region. • Senegal: Urban Dakar.
Other characteristics relevant to the trial	The population is expected to have high prevalence of HIV/TB exposure in South African peri-urban and rural sites, and low HIV/TB prevalence and low to medium malaria prevalence in Tanzanian sites. In Senegal, prevalence of HIV/TB is low, and prevalence of Malaria is also low in urban aera in Dakar.

Eligibility criteria for participants {14a}

Inclusion Criteria:

(1) Children aged ≥60 days to <13 years

(2) Presenting for acute care to a study site

(3) WHO IMCI clinical pneumonia, defined as:

(3.1) Cough OR Difficulty Breathing

AND

(3.2) One of the below:

(3.2.1) Fast breathing (tachypnoea):

> 50/minute (≥60 days <1 year),

> 40/minute (≥1–<5 years),

> 25/minute (≥5-<13 years)

OR

(3.2.2) Lower chest wall indrawing

Exclusion Criteria:

1. Presenting for repeat visit/follow-up of a treated lower respiratory tract infection (index illness / non-acute) or enrolled in the study within the preceding 28 days.
2. Currently taking antibiotic treatment for more than 48 hours at the time of enrolment
3. WHO IMCI danger signs (inability to drink/breastfeed, vomiting everything, convulsions with this illness, lethargy/unconscious)

4. Presence of jaundice
5. Hypoxaemia with SpO_2<88%
6. SpO_2<90% (or country-specific / altitude-adjusted thresholds):
    a. With signs of severe respiratory distress (such as nasal flaring, grunting, etc.)
        OR
    b. In children < 6 months
7. Requiring non-invasive ventilatory support (i.e., high-flow, bi-PAP, CPAP)
8. Underlying disease associated with increased risk of severe pneumonia or pneumonia of unusual aetiology (e.g., WHO acute malnutrition requiring antibiotics as per local guidelines, severe immunodeficiency)
9. HIV positive participant that is either:
    a. less than 12 months old,
        OR
    b. requiring admission for this illness,
        OR
    c. known to be uncontrolled on treatment (with a documented VL >1000c/ml in the previous 6 months)
10. Caregiver unavailable at the time of enrolment, or unwilling, to provide informed consent

Children meeting all inclusion criteria, but meeting exclusion criteria 1-9, will be enrolled in an observational component of the study to obtain a more detailed understanding of all children presenting with IMCI pneumonia and in the TB substudy. Children enrolled in the RCT who are <2 years of age, living with HIV and/or with severe acute malnutrition, as well as those with clinical failure at Day 8 or persistent symptoms at D29 will also be considered for enrolment in the TB substudy.

Eligibility criteria for sites and those delivering interventions {14b}

The study will be conducted as a multi-site trial across outpatient, emergency, district, regional, and tertiary care facilities in three countries where children with acute respiratory illness present for care.

Who will take informed consent? {32a}

Informed consent will be obtained by trained study staff at each participating site, including study nurses, study clinicians, or delegated research personnel. Staff will screen presenting children during study hours,

provide caregivers with written and verbal information about the study, allow time for questions, and document consent before enrolment. For caregivers who cannot read, the consent form will be read aloud, and for those unable to sign, an independent witness will observe the process and co-sign the form. Assent will be obtained from children aged 7 to <13 years following an age-appropriate explanation; children who are unwilling to participate will not be enrolled. Caregivers receive a signed copy of the consent/assent documents, and originals are retained in the site file. Consent and assent materials will be translated and back-translated into relevant local languages at each site.

Additional consent provisions for collection and use of participant data and biological specimens {32b}

Collection of biological specimens for microbiological and biomarker analyses will require separate, study-specific consent. Residual samples may be stored for future ethically approved research only for participants whose caregivers provide optional consent for future use.

For the TB substudy, additional consent will be obtained for supplementary respiratory/stool samples, urine LAM (where applicable), chest radiography, venous blood collection for biomarker testing and an additional Week 8 telephonic follow-up visit.

Intervention and comparator

Intervention and comparator description {15a}

LUS will be performed at the D1 enrolment visit, immediately after clinical assessment and prior to participant randomisation, using a standardised scanning protocol. LUS will be conducted by trained nurses, clinicians, or study sonographers, depending on the site. All personnel performing LUS will be certified in the study-specific LUS acquisition and interpretation protocols. LUS findings will be interpreted using the IMCI-PLUS interpretation framework, a predefined study-specific framework developed through a structured process informed by literature review and expert consensus using Delphi methodology. The framework classifies LUS findings according to their likelihood of supporting bacterial pneumonia and provides corresponding guidance for or against antibiotic treatment (Interpretation Framework and Training Materials available upon request). Further details are provided in the protocol and supporting operational manuals. Standardised supervision, image review, and quality control procedures will be implemented to support consistency across sites.

Participants randomised to the intervention arm will receive routine clinical care supplemented by a LUS report generated by the trained study team. The LUS report will be integrated into the IMCI-PLUS algorithm and will provide the treating clinician with additional information to guide antibiotic prescribing decisions, including whether the LUS findings support or do not support antibiotic treatment. The LUS report is intended to support clinical decision-making; however, final responsibility for patient management, including the decision to prescribe antibiotics, remains with the routine treating clinician in accordance with clinical judgement and local standards of care.

Participants randomised to the control arm will also undergo LUS for study purposes, but the LUS findings and report will not be shared with the treating clinician and will therefore not inform clinical management at the enrolment visit. Control arm participants will receive routine care as provided by the treating clinician at participating facilities. Routine care is based on the IMCI framework as implemented in each health system and includes clinical assessment and management of pneumonia according to national standard treatment guidelines.

Criteria for discontinuing or modifying allocated intervention/comparator {15b}

The allocated study intervention or comparator will not restrict or delay any clinically indicated care. All clinical decisions, including escalation of care, hospital admission, initiation or modification of antibiotics, respiratory support, or other urgent management, will remain the responsibility of the routine treating clinician and will be made according to clinical judgement and applicable national standard treatment guidelines, irrespective of randomisation allocation.

Participants may therefore deviate from the allocated study pathway if the treating clinician determines that urgent or modified management is required. This may occur, for example, in the context of clinical deterioration, worsening respiratory distress, hypoxaemia, emergence of IMCI danger signs, poor response to first-line therapy, or any other clinical concern requiring reassessment or escalation of care. These examples are not intended to replace clinical judgement or define exclusive criteria for action.

In the intervention arm, participants with clinical deterioration, or those with poor response to first-line therapy at approximately 72 hours, may undergo repeat LUS in accordance with the protocol. Repeat LUS is intended to assess for new evidence of consolidation, progression of disease, or complications, and the

findings may be used to provide further LUS-based guidance to the treating clinician.

Caregivers may also request withdrawal from further study procedures at any time, which will result in discontinuation of the allocated intervention but allow continued collection of data unless the caregiver requests full withdrawal.

Strategies to improve adherence to intervention/comparator {15c}

LUS is performed by trained study personnel rather than by the routine treating clinicians, which is intended to ensure standardised image acquisition and interpretation across sites, and to reduce implementation barriers related to clinician workload, competing clinical priorities, or variable access to LUS expertise. Treating clinicians and relevant routine care staff receive orientation to the study objectives, procedures, local IMCI protocols, and the role of the IMCI-PLUS LUS report in supporting antibiotic prescribing decisions. In the intervention arm, the LUS-based recommendation is provided to the treating clinician in a standardised format to support consistent delivery of the intervention.
Final prescribing and management decisions remain the responsibility of the treating clinician. The study will document antibiotic prescribing decisions and assess concordance between the IMCI-PLUS recommendation and the clinician's management decision as part of routine trial procedures. Instances where clinician management differs from the LUS-based recommendation will be recorded and reviewed descriptively.

Concomitant care permitted or prohibited during the trial {15d}

All routine clinical care that is part of standard IMCI management and national treatment guidelines is permitted in both arms. This includes supportive care, referral, and hospital admission when clinically indicated. Additional diagnostic procedures outside the study protocol (e.g., CXR, blood tests, microbiology) are permitted when ordered by treating clinicians in routine care and these are monitored as a secondary outcome.

Ancillary and post-trial care {34}

Participants who experience clinical deterioration at any point during the trial will receive medical care according to local clinical guidelines and facility protocols, regardless of study allocation. The study will

support access to care through re-imbursing transport costs in case of deterioration before D8. Any study-related harms will be reported according to safety procedures defined in the protocol and appropriate insurance is purchased as per local regulations.

Outcomes {16}

Co-Primary Endpoints

(1.1) Proportion of participants prescribed antibiotic treatment on D1.

(1.2) Proportion of participants with clinical failure, defined as the development of any of the following criteria during the specified time periods after enrolment:

Any time before or on D8:

- WHO IMCI danger sign (inability to drink/breastfeed, vomiting everything, convulsions with this illness, lethargy/unconscious)
- New or worsening severe respiratory distress (such as grunting, head nodding, severe chest indrawing)
- Secondary Hospitalization (defined as a hospitalization occurring after discharge from in-patient admission or outpatient visit) related to a deterioration of the presenting complaint on D1
- Change in level of care (e.g., admission to intensive care unit, transfer to higher level of care)
- Need for respiratory support (e.g., high flow nasal cannula, CPAP)
- Death due to any medical cause (i.e., except trauma)

At D8 outcome assessment:

- Report from the caregiver of non-resolution/worsening of illness

Secondary Endpoints

(2.1) Evaluation of the effect of the intervention in children with clinical pneumonia on:

- The proportion of children prescribed an antibiotic by D8.
- The proportion of adverse drug reactions related to routine antibiotic treatment by D8 (i.e., Anaphylactic reaction, severe diarrhoea, or generalised severe rash).
- The proportion of patients cured (defined as caregiver reported recovery from illness) by D8 and D29.
- The proportion and duration of inpatient admissions (by D8 and D29)
- The proportion of patients undergoing a non-study related diagnostic test (including CXR, blood

tests, urine tests, microbiological assays) on D1, and for those admitted on D1, tests conducted up until D8.

- The proportion of deaths of any cause by D29.
- The proportion of participants with any unscheduled health seeking events for any cause and/or hospital admission for any cause since D8 follow-up (at D29 follow-up)

(2.2) Endpoints related to TB in the context of acute pneumonia include:

- The proportion of children with confirmed, unconfirmed or unlikely intrathoracic TB who were enrolled in the TB substudy
- The ability of LUS (and mediastinal US, if done) to distinguish TB from non-TB disease
- The diagnostic accuracy of LUS compared with CXR and CAD, and within the context of TB Treatment Decision Algorithms

(2.3) Cost-effectiveness of integration of LUS into current IMCI-based management guidelines for pneumonia

Harms {17}

The study will record and assess all adverse events (AEs) and serious adverse events (SAEs) according to definitions and procedures described in the protocol. Clinical deterioration events relevant to pneumonia management are captured as part of the trial's primary clinical failure outcome and are monitored throughout the study period. AEs and SAEs will be systematically assessed at enrolment and at each scheduled follow-up visit (Adverse Events will be collected until D8, death will be asked at the D29 follow-up), and unscheduled visits will also be reviewed for potential harms. Adverse drug reactions related to routine antibiotic treatment (e.g., anaphylaxis, severe diarrhoea, generalised severe rash) are prespecified secondary outcomes. LUS is non-invasive and not associated with direct clinical risk; therefore, no device-related harms are anticipated. All prespecified harms and SAEs will be reported in trial publications consistent with the outcomes and safety framework defined in the protocol.

Participant timeline {18}

1 *Table 1 Participant Timeline*

Time since enrolment (days)	**D1**	**D1**	**D2-7***	**D8**	**D29**	**Week 8**
Visit	*Enrolment*	*Clinical Visit*	*Unscheduled in-person Follow-up*	*1st Follow-up (telephone/ in-person)*	*2nd Follow-up (telephone/ in-person)*	*3rd Follow-up (telephone/ in-person)*
Windows				+4days	+4 days	+4days
Enrolment						
Eligibility screening	+					
Informed consent	+					
Demographic data collection	+					
Baseline clinical data collection	+					
LUS	+		+**	+^	+^	+^
LAusc	+					
Randomisation	+					
Sample collection		+	+^^	+^^	+^^	+^^
Interventions						
Control group: Routine care		+	+			
Intervention group: IMCI-PLUS algorithm and guidance on antibiotic use		+	+			
Assessments						
Antibiotic-related assessment		+	+	+		
Event-related data (Clinical Failure)			+	+	+	
Clinical signs	+	+	+	+^	+^	+^
Clinical management		+	+	+^	+^	+^
Survival			+	+	+	+
Adverse Events		+	+	+		
TB substudy only – Symptoms and TB exposure and/or treatment history				+	+	+

2 *For more detail regarding data points collected for Primary and Secondary outcomes, see Section 5.3.1 of protocol*

(Additional File 1)

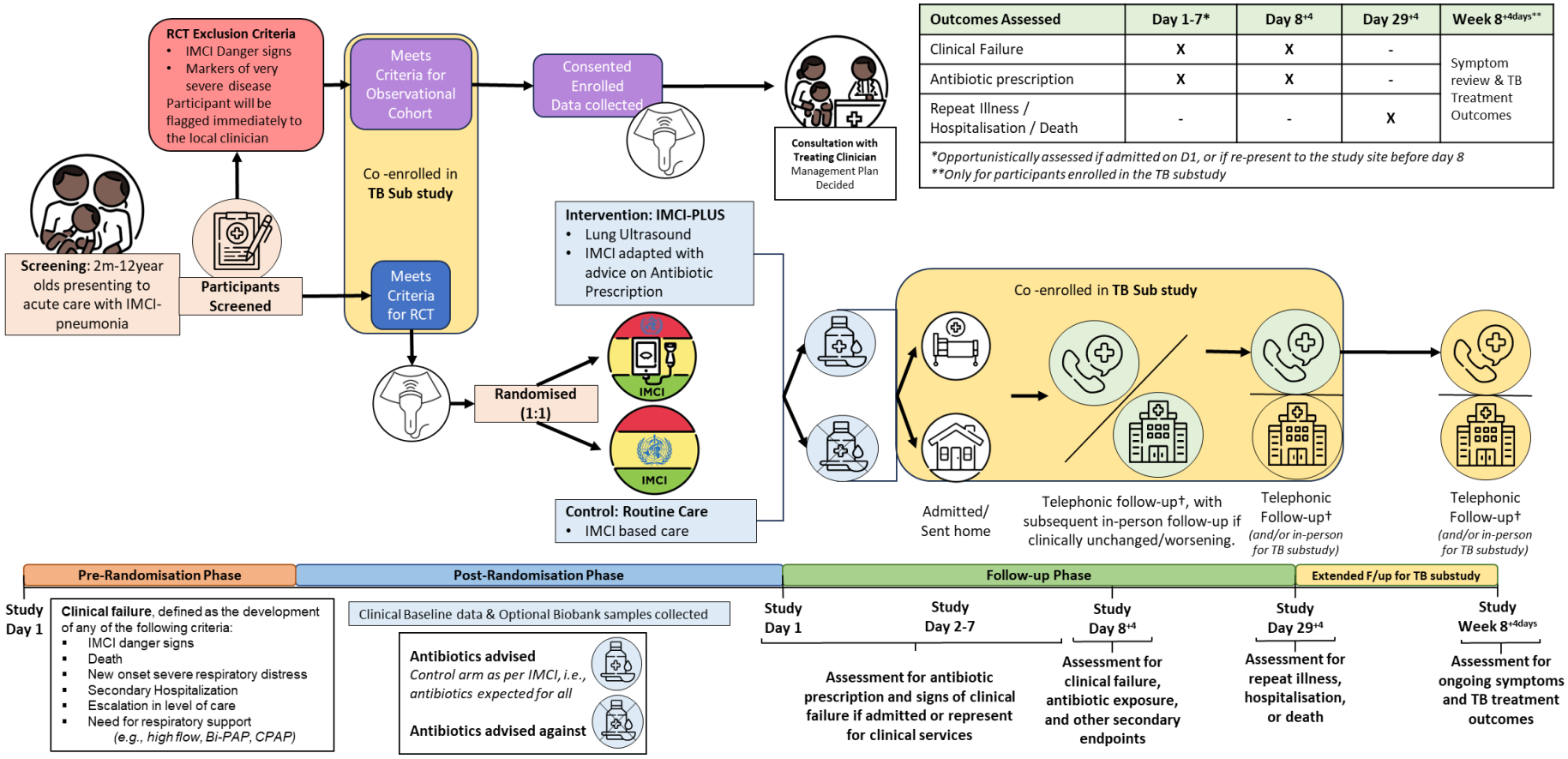
* *D2-7 refers to unplanned follow-up as a result of participants representing to the study site for the index illness AND/OR scheduled study visit for those sites where follow-up is routine care*

** *LUS performed at D2-7 follow-up visit if participant is:*

- *in the intervention group and clinically unchanged/ worsened and*
- *in the control group where possible/feasible*

^ *Only collected if in-person follow-up*

^^ *Sample collection after the D1 visit for the TB substudy only*



Outcomes Assessed	Day 1-7*	Day 8+4	Day 29+4	Week 8+4days**
Clinical Failure	X	X	-	Symptom review & TB Treatment Outcomes
Antibiotic prescription	X	X	-	
Repeat Illness / Hospitalisation / Death	-	-	X	

*Opportunistically assessed if admitted on D1, or if re-present to the study site before day 8
**Only for participants enrolled in the TB substudy

Figure 1 Flow Diagram of Study Procedures.

† If uncontactable, alternate strategies such as home-visits will be considered

Sample size {19}

With an assumed baseline proportion of clinical failure in the control group of 5% and using an acceptable clinical difference of 1.5x as a non-inferiority margin (therefore a delta of 2.5%) [50–54], the estimated sample size required across all sites would be 2730 (power 85%). This would equate to 1365 participants per group for the co-primary endpoints. We however aim to enroll a total of 3000 participants under the age of 5 years of age (power >85%) as this is the age group of greatest interest based on the current IMCI framework. However, due to limited data on paediatric pneumonia outcomes in the ≥5-<13years age group we wish to include these children as well. Considering approximately 90% of children presenting for acute respiratory care in the age group ≥60 days-<13 years are <5years, we would aim for a total sample size of 3500 participants, 1750 participants per group, to account for repeat visits of the same child within the enrolment period as well as potential differences in clinical failure rates between sites. Further details are provided in a separate Statistical Analysis Plan (SAP) [55].

Recruitment {20}

Study staff will screen all presenting paediatric patients during study operating hours. Screening logs will be maintained at each site to monitor recruitment efficiency and document reasons for non-enrolment. Sites were selected based on their high burden of paediatric LRTI and consistently large volumes of eligible children, as described in the protocol. Additional feeder clinics or hospitals may be added to support enrolment. Recruitment strategies include: presence of trained study staff on-site during operating hours to ensure continuous screening; collaboration with clinical teams at participating facilities to support identification and referral of potentially eligible participants; use of local languages and community engagement mechanisms to facilitate understanding of study participation; regular monitoring of enrolment numbers across sites and adaptive opening of feeder clinics.

Assignment of interventions: randomisation

Sequence generation: who will generate the sequence {21a}

The random allocation sequence will be generated by an independent statistician using an appropriate statistical software.

Sequence generation: type of randomisation {21b}

Randomisation will be individually based with a 1:1 allocation ratio between the intervention and control arms. The trial uses blocked randomization with varying block sizes, stratified by study site and age group (≥60 days to <5 years, ≥5 years to <13 years). Details of block sizes and random seed are not accessible to staff involved in enrolment or assignment.

Allocation concealment mechanism {22}

Allocation concealment will be ensured through electronic randomisation envelopes, hosted into a dedicated database, available online, in the same Electronic Data Capture (EDC) system used for participant data collection. The randomisation list is accessible only to the independent statistician and a restricted number of data managers until the end of the study.

Implementation {23}

Study staff at each site will screen, consent, and enrol participants. The randomisation assignment is displayed only after eligibility is confirmed and informed consent is obtained. The personnel conducting screening and enrolment do not have access to the randomisation sequence and cannot influence allocation.

Assignment of interventions: blinding

Who will be blinded {24a}

Because the intervention differs visibly from routine care, participants, caregivers, and treating clinicians will not be blinded to allocation. However, outcome assessors responsible for evaluating clinical failure at D8 and D29 will remain blinded to allocation status wherever feasible.

How will blinding be achieved {24b}

Blinding will be achieved through separation of outcome-assessment roles. Outcome assessors will, as much as possible, not participate in LUS procedures or routine-care decision-making and will conduct follow-up assessments without access to allocation data whenever feasible.

Procedure for unblinding if needed {24c}

As this is an open-label trial, unblinding is generally not required. No clinical circumstances require emergency unblinding, as treating clinicians already know the assigned intervention at the point of care.

Data collection and management

Plans for assessment and collection of outcomes {25a}

Outcome and resource use data will be collected at enrolment (D1), D8, and D29 using standardised electronic case report forms (eCRFs) within REDCap. All study staff undergo structured training in screening, clinical assessment, LUS procedures, and outcome evaluation. Data quality is supported through regular supervision, monitoring of data completeness, and validation rules embedded in REDCap. Clinical outcomes are assessed using WHO-defined clinical criteria. Adverse drug reactions and unscheduled visits are recorded at follow-up visits. For participants enrolled in the TB substudy, additional laboratory and imaging procedures are conducted using standardised methods. Unit costs for the economic evaluation will be obtained prospectively from country-specific sources (e.g. national fee schedules, procurement lists).
Data collection instruments and operational manuals are available upon reasonable request.

Plans to promote participant retention and complete follow-up {25b}

Study staff will encourage caregivers to remain available for scheduled follow-up and will provide clear verbal instructions at enrolment regarding the D8 and D29 follow-up procedures. Contact information is collected to enable reminder calls, telephone follow-up, and tracing where required.
The D8 follow-up will be conducted by telephone by default, unless the participant is admitted to hospital or returns to the facility in person. During the D8 telephone follow-up, study staff will assess the participant's clinical status and identify any concerns, including unchanged or worsening symptoms, adverse events, hospitalisation, or other clinically relevant outcomes. Participants whose condition is reported as unchanged or worsened may be asked to attend an in-person assessment according to study procedures and local clinical pathways.
For the D29 follow-up, caregivers will be reminded of the scheduled follow-up procedures and contacted as needed to support completion.
For participants who discontinue their trial participation or deviate from protocol procedures, all primary and secondary outcome data will be collected whenever possible, including clinical status, adverse events, hospitalisations, and follow-up outcomes.

Data management {26}

Data will be captured directly into REDCap using electronic case report forms with built-in validation rules, range checks, and logic constraints to ensure data accuracy. Access to REDCap is role-based and

password protected. Data are stored on secure servers with routine backup and audit trails.
Full details of data entry, coding, security, and storage procedures are provided in the Data Management Plan (DMP, available upon request).

Confidentiality {33}

Participant confidentiality will be protected by collecting only coded data within REDCap. Identifiers are stored separately from study data in secure, access-restricted systems. Access to identifiable information is limited to authorised site staff for follow-up and clinical safety purposes. All data will be handled according to local regulatory requirements and institutional policies to ensure confidentiality before, during, and after the trial.

Statistical methods

Statistical methods for primary and secondary outcomes {27a}

The first primary outcome, the proportion of children receiving antibiotics on D1, will be assessed for superiority using a logistic regression model, reporting odds ratios and a modified Poisson regression reporting risk ratios and risk differences and their respective 95% confidence intervals (CI). The second primary outcome, the proportion of children with clinical failure by D8, will be evaluated using a CI approach. Risk differences and their CI will be obtained from a modified Poisson regression model. If clinical failure in the intervention group is found to be non-inferior to the control, then it will be assessed for superiority. All models will be adjusted for the stratification factors of site and age group.
Binary secondary outcomes with sufficient events will be evaluated in the same way as the primary superiority outcome. Rare outcomes such as death will be compared across arms using non-parametric or small sample tests. The secondary outcomes of duration of hospitalization will be tested non-parametrically using a Wilcoxon rank-sum test.
Further details are provided in the Statistical Analysis Plan [55].

Who will be included in each analysis {27b}

The full analysis set (FAS) will include all randomised participants in their assigned arm. The per-protocol set (PPS) will exclude participants with relevant protocol deviations. Primary analysis of the co-primary outcomes will be performed on both FAS and PPS. Analysis of secondary outcomes will be performed on the

FAS only. Details of the analysis populations are defined in the SAP [55].

How missing data will be handled in the analysis {27c}

Multiple imputation with chained equations approach will be used to account for missing data under the assumption of data missing at random. More details are specified in the SAP (Additional File 2).

Methods for additional analyses (e.g. subgroup analyses) {27d}

Analyses will be presented stratified by age group (≥60 days to <5 years, ≥5 years to <13 years). In addition, a set of sensitivity analyses are planned for both co-primary outcomes and are described in the SAP.

Interim analyses {28b}

An interim analysis is planned after 50% of participants have been recruited to assess, among other things, sample size assumptions and conditional power for early stopping due to futility.

Protocol and statistical analysis plan {5}

The SAP was published at the start of the trial and is provided as Additional File 2. The study protocol is available as Additional File 1.

Oversight and monitoring

Composition of the coordinating centre and trial steering committee {3d}

The trial is sponsored and coordinated by the Sponsor/Coordinating Centre at EPFL with regional coordination across African sites supported by the Coordinating Investigator for Africa based at the University of the Witwatersrand, South Africa. National and site-level coordinating teams in South Africa, Tanzania, and Senegal oversee day-to-day study operations, training, and site support and meet regularly throughout the trial. A Trial Steering Committee (TSC) with >50% independent membership provides oversight of trial conduct, protocol adherence, and progress toward recruitment and data quality milestones. The TSC meets at least 6 monthly and reviews operational, ethical, and scientific issues.

Composition of the data monitoring committee, its role and reporting structure {28a}

An Independent Data Monitoring Committee (IDMC) oversees participant safety, study conduct, and interim analyses and provides recommendations to the Sponsor and TSC. The IDMC operates independently of the sponsor and funders. Its responsibilities, meeting schedule, conflict-of-interest statements, and reporting

structure are defined in the IDMC Charter (available upon request).

Trial monitoring {29}

The monitoring activities are coordinated by an external monitor and monitors are contracted to perform monitoring activities at local sites. The monitoring strategy is risk based in accordance with relevant regulations. The monitoring strategy (nature and extent of the monitoring activities) are described in a joint monitoring plan (available upon request). In principle, site initiation visits will be conducted on each site in order to ensure that all sites are ready to start the trial. Then interim monitoring visits will be performed remotely or on site depending on the situation and focusing mainly on safety, intervention adherence, and patient eligibility. Data from participant records (source documents) will be reviewed by local monitors against data reported in the eCRF in order to check completeness, validity, consistency, and adherence to protocol specifications. Queries regarding missing, questionable or inconsistent data will be documented. A (remote) closeout monitoring visit per study site will be performed at the end of the trial to ensure all pending actions are resolved and investigator site file is ready for archival.

Protocol amendments {31}

Any substantial amendments to the protocol will be communicated promptly to relevant Research Ethics Committees (RECs/IRBs), national regulatory authorities, trial registries, and study investigators. Updated protocol versions will be distributed to all sites and uploaded to the registries.

Dissemination policy {8}

Findings from the trial will be disseminated through peer-reviewed publications, presentations at scientific meetings, and communication with participating communities, healthcare providers, and Ministries of Health. Results will be reported in the trial registries, and a lay summary will be shared with caregivers and local partners. No personal identifying information will be included in any reports.

Discussion

ToolCAP (Novel Tools to improve management of paediatric Community-Acquired Pneumonia - a randomised controlled trial) addresses a critical evidence gap in the management of paediatric community-acquired pneumonia in sub-Saharan Africa by evaluating whether standardised lung ultrasound (LUS)

interpretation can be safely integrated into IMCI-based care to improve antibiotic stewardship. Existing IMCI pneumonia classifications prioritise sensitivity and feasibility in low-resource settings, but their limited specificity may contribute to substantial antibiotic overuse, particularly among children with viral or other non-bacterial respiratory illness. By testing whether a LUS-informed IMCI-PLUS algorithm can reduce unnecessary antibiotic prescribing while preserving non-inferior clinical outcomes, ToolCAP responds directly to the need for practical diagnostic and management strategies that reduce unnecessary antibiotic exposure without compromising child safety.

It is explicitly designed as an efficacy trial. The LUS component is delivered under structured conditions by trained and supervised staff, using a standardised scanning protocol and interpretation framework that is provided to the health care worker/clinician managing the child in routine care. This allows us to estimate the maximum achievable effect under controlled conditions. The trial is not intended to evaluate “real-world” LUS use as variably implemented by clinicians in routine practice. Future work is needed to understand how such an approach performs once embedded in usual health services with existing constraints on training, supervision, and workload. Further implementation and effectiveness research is planned within the EDCTP-funded IMCI-PLUS project (See Figure 2) [56] , which will explore how LUS-enabled decision support can be integrated into routine IMCI platforms, how providers adopt and sustain its use, and how health system factors influence impact at scale.

A strength of ToolCAP is the diversity of clinical settings and providers. These sites encompass a broad spectrum of epidemiological contexts (including varying prevalence of HIV, TB, and malaria), health system organisation, and provider cadres. This diversity allows assessment of the LUS-informed strategy across different levels of care and provider experience, which is important for interpreting potential generalisability.

Limitations of the trial design are its open-label design, as LUS cannot be masked to treating clinicians, which may introduce performance bias despite blinded outcome assessment where feasible. The structured training and close supervision associated with an efficacy design may not be fully replicable in routine health services and could overestimate the effect achievable under less supported conditions. In addition, while the trial spans several countries and settings, it remains focused on specific hospital and clinic networks, and findings may require contextual adaptation before adoption elsewhere.

Despite these limitations, ToolCAP is well positioned to provide robust data on whether integrating LUS into IMCI-based pneumonia management can substantially reduce antibiotic use without compromising safety. Combined with forthcoming implementation studies within IMCI-PLUS, the results will inform policy, guideline development, and investment decisions on the role of LUS and multimodal decision support for childhood pneumonia in resource-limited settings.

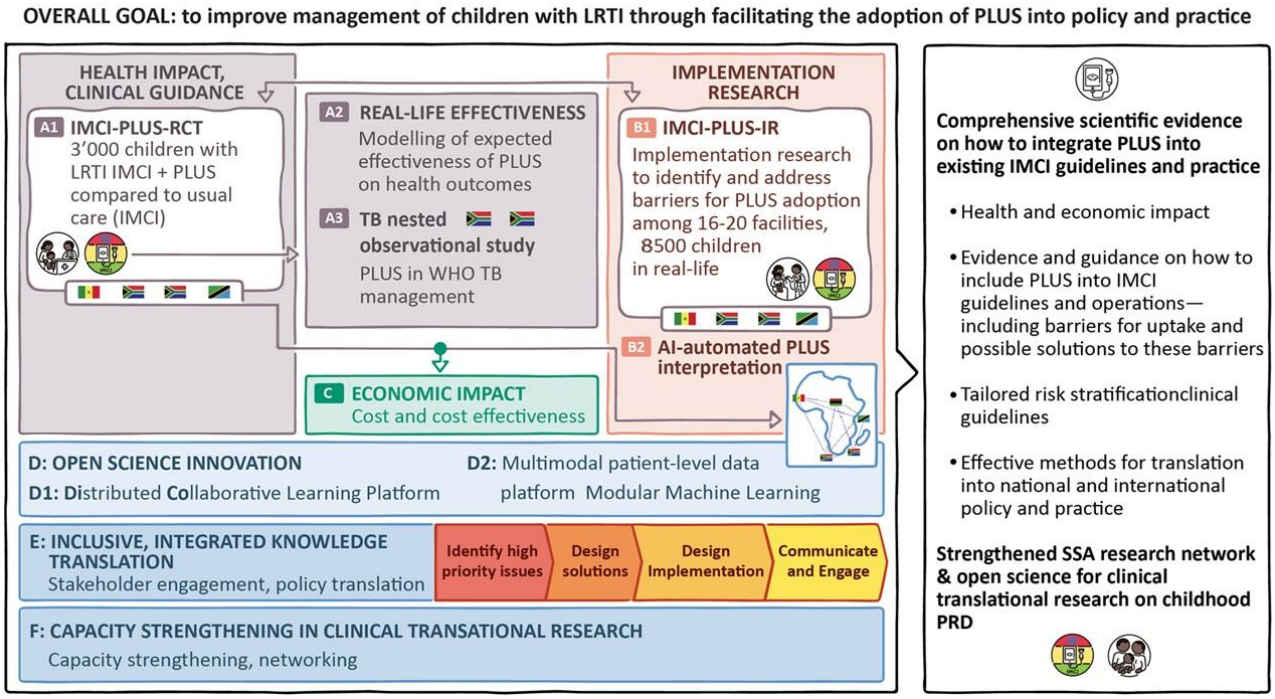


Figure 1 IMCI-PLUS project concept, scientific building blocks, and process map.

Trial status

ToolCAP Protocol, Version 3.0, 07 November 2025.

Recruitment started in April 2025, the trial is foreseen to recruit until June 2027.

Abbreviations

***AE**: Adverse event*

***AMR**: Antimicrobial resistance*

***CAD**: Computer-aided detection*

***CI**: Confidence interval*

***CPAP**: Continuous positive airway pressure*

***CRF**: Case report form*

***CXR**: Chest X-ray*

***D1, D8, D29**: Day 1, Day 8, Day 29*

***DMC / IDMC**: (Independent) Data Monitoring Committee*

***DMP:** Data management plan*

***EDC:** Electronic data capture*

***EDCTP**: European & Developing Countries Clinical Trials Partnership*

***eCRF:** Electronic case report form*

***EPFL:** École Polytechnique Fédérale de Lausanne*

***FAS:** Full analysis set*

***HIV:** Human immunodeficiency virus*

***HREC**: Health Research Ethics Committee*

***IHI**: Ifakara Health Institute, Tanzania*

***IMCI**: Integrated Management of Childhood Illness*

***IMCI-PLUS**: IMCI-based clinical management algorithm with enhanced decision support from PLUS*

***IPD**: Individual participant data*

***IRB / REC**: Institutional Review Board / Research Ethics Committee*

***LAM**: Lipoarabinomannan*

***LAusc**: Lung auscultation*

***LMIC**: Low- and middle-income country*

***LRTI**: Lower respiratory tract infection*

***LTFU**: Lost to follow-up*

***LUS**: Lung ultrasound*

***MUHAS**: Muhimbili University of Health and Allied Sciences*

***NIMR**: National Institute for Medical Research*

***PLUS:** Point-of-care Lung Ultrasound*

***PPS:** Per-protocol set*

***POCUS**: Point-of-care ultrasound*

***QMS**: Quality management system*

***RCT**: Randomised controlled trial*

***REDCap**: Research Electronic Data Capture*

***RSV:** Respiratory syncytial virus*

***SAE**: Serious adverse event*

***SAP:** Statistical Analysis Plan*

***SpO_2:** Peripheral oxygen saturation*

***SSA**: Sub-Saharan Africa*

***TB**: Tuberculosis*

***ToolCAP**: Novel Tools to improve management of paediatric Community-Acquired Pneumonia*

***TSC**: Trial Steering Committee*

***US:** Ultrasound*

***UCAD**: Université Cheikh Anta Diop de Dakar, Senegal*

***VL:** Viral Load*

***WITS**: University of Witwatersrand, South Africa*

***WHO**: World Health Organization*

Declarations

Acknowledgements

We would like to thank the children and families who participate in ToolCAP, and the clinical, nursing, and research teams at all participating sites in South Africa, Tanzania, and Senegal for their commitment to this study. We also acknowledge the contributions of the community engagement structures at each site, the national and local health authorities, and the members of the Trial Steering Committee and Independent Data Monitoring Committee for their oversight and guidance.

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1 *Listed alphabetically*

2 **Authors' contributions {3a}**

KK and JdT are coordinating investigators who conceived the study, led the proposal and protocol development. NB, RT, KM, PMF, MP, MAH, MAN, KR, and TRG contributed to study design and to development of the proposal.

TRG and SC contributed to drafting the protocol and led the development of the statistical analysis plan. FD, MB, JH, DJvH, WTM, JW contributed to the development of the study protocol. All authors read and approved the final manuscript. Artificial intelligence tools were used for language edits and proofreading.

Sources of funding and other support {7a}

This study is funded by the Swiss National Science Foundation and the EDCTP/EU Horizon programme. The funders support study implementation, including staff, equipment, and operational costs across all participating countries.

The funders had no role in the design of the study; they will not have any role in the collection, analysis, or interpretation of data; nor in the writing of the manuscript or the decision to submit it for publication.

Availability of data and materials {6}

Deidentified individual participant data (IPD) and the data dictionary underlying the published results will be made available upon reasonable request to the Sponsor after publication of the main trial findings, subject to data sharing agreements that comply with national regulations and ethics approvals. Access will be granted for purposes of secondary analyses, meta-analyses, and reproducibility.

The final trial dataset will be held by the Sponsor and the designated data management team; no contractual agreements restrict investigators' access to the cleaned trial dataset. Statistical code and core analysis scripts will be shared on request and/or via a public repository at the time of publication, where feasible.

Ethics approval and consent to participate {30}

Ethical approval for ToolCAP has been obtained from the Bern Cantonal Ethics Committee, Switzerland (2023 01534), the University of the Witwatersrand Human Research Ethics Committee (Medical), the Stellenbosch University Health Research Ethics Committee (M24/04/017), the Muhimbili University of Health and Allied Sciences (MUHAS) Institutional Review Board, the National Institute for Medical Research (NIMR) Ethics Committee in Tanzania, and the Comité National d'Éthique pour la Recherche en Santé (CNERS) in Senegal.

Written, informed consent to participate in the study will be obtained from all caregivers of participating children, and assent will be obtained from children aged 7 to <13 years as appropriate. Informed consent

forms are provided as additional file XX.

Consent for publication

Not applicable. This protocol does not contain individual person data in any form. If future publications include identifiable details, written informed consent for publication will be obtained from the relevant participants or their legal guardians.

Competing interests {7b}

The authors declare that they have no competing interests.

Authors' information (optional)

No relevant information

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