Effect of systematic tuberculosis detection on mortality in young children with severe pneumonia in countries with high incidence of tuberculosis: a stepped-wedge cluster-randomised trial

*Olivier Marcy, Eric Wobudeya, Hélène Font, Aurélia Vessière, Chishala Chabala, Celso Khosa, Jean-Voisin Taguebue, Raoul Moh, Juliet Mwanga-Amumpaire, Manon Lounnas, Veronica Mulenga, Sandra Mavale, Josina Chilundo, Dalila Rego, Bwendo Nduna, Perfect Shankalala, Uzima Chirwa, Agathe De Lauzanne, Bunnet Dim, Emeline Tiogouo Ngouana, Madeleine Folquet Amorrissani, Lassina Cisse, Flore Amon Tanoh Dick, Eric A Komena, Sylvie Kwedi Nolna, Gerald Businge, Naome Natukunda, Saniata Cumbe, Prossy Mbekeka, Ang Kim, Chanrithea Kheang, Sokha Pol, Elizabeth Maleche-Obimbo, James A Seddon, Tan Eang Mao, Stephen M Graham, Christophe Delacourt, Laurence Borand, Maryline Bonnet, for the TB-Speed Pneumonia Study Group**

Summary

Background Tuberculosis diagnosis might be delayed or missed in children with severe pneumonia because this diagnosis is usually only considered in cases of prolonged symptoms or antibiotic failure. Systematic tuberculosis detection at hospital admission could increase case detection and reduce mortality.

Methods We did a stepped-wedge cluster-randomised trial in 16 hospitals from six countries (Cambodia, Cameroon, Côte d'Ivoire, Mozambique, Uganda, and Zambia) with high incidence of tuberculosis. Children younger than 5 years with WHO-defined severe pneumonia received either the standard of care (control group) or standard of care plus Xpert MTB/RIF Ultra (Xpert Ultra; Cepheid, Sunnyvale, CA, USA) on nasopharyngeal aspirate and stool samples (intervention group). Clusters (hospitals) were progressively switched from control to intervention at 5-week intervals, using a computer-generated random sequence, stratified on incidence rate of tuberculosis at country level, and masked to teams until 5 weeks before switch. We assessed the effect of the intervention on primary (12-week all-cause mortality) and secondary (including tuberculosis diagnosis) outcomes, using generalised linear mixed models. The primary analysis was by intention to treat. We described outcomes in children with severe acute malnutrition in a post hoc analysis. This study is registered with ClinicalTrials.gov (NCT03831906) and the Pan African Clinical Trial Registry (PACTR202101615120643).

Findings From March 21, 2019, to March 30, 2021, we enrolled 1401 children in the control group and 1169 children in the intervention group. In the intervention group, 1140 (97·5%) children had nasopharyngeal aspirates and 942 (80·6%) had their stool collected; 24 (2·1%) had positive Xpert Ultra. At 12 weeks, 110 (7·9%) children in the control group and 91 (7·8%) children in the intervention group had died (adjusted odds ratio [OR] 0·986, 95% CI 0·597–1·630, p=0·957), and 74 (5·3%) children in the control group and 88 (7·5%) children in the intervention group had tuberculosis diagnosed (adjusted OR 1·238, 95% CI 0·696–2·202, p=0·467). In children with severe acute malnutrition, 57 (23·8%) of 240 children in the control group and 53 (17·8%) of 297 children in the intervention group died, and 36 (15·0%) of 240 children in the control group and 56 (18·9%) of 297 children in the intervention group were diagnosed with tuberculosis. The main adverse events associated with nasopharyngeal aspirates were samples with blood in 312 (27·3%) of 1147 children with nasopharyngeal aspirates attempted, dyspnoea or SpO_2 less than 95% in 134 (11·4%) of children, and transient respiratory distress or SpO_2 less than 90% in 59 (5·2%) children. There was no serious adverse event related to nasopharyngeal aspirates reported during the trial.

Interpretation Systematic molecular tuberculosis detection at hospital admission did not reduce mortality in children with severe pneumonia. High treatment and microbiological confirmation rates support more systematic use of Xpert Ultra in this group, notably in children with severe acute malnutrition.

Funding Unitaid and L'Initiative.

Lancet Infect Dis 2023; 23: 341–51

Published Online November 14, 2022 https://doi.org/10.1016/S1473-3099(22)00668-5

See Comment page 268

For the French translation of the abstract see Online for appendix 1

*Members listed in appendix 2

Inserm UMR 1219, IRD EMR 271, University of Bordeaux, Bordeaux, France (O Marcy MD, H Font PhD, A Vessiere PhD); **Makerere University–Johns Hopkins University Research Collaboration, Kampala, Uganda** (E Wobudeya MD, G Businge MD); **University of Zambia School of Medicine, University Teaching Hospital, Lusaka, Zambia** (C Chabala MD, V Mulenga MD, P Shankalala MD); **Instituto Nacional de Saúde, Marracuene, Mozambique** (C Khosa MD, S Cumbe MD); **Mother and Child Center, Chantal Biya Foundation, Yaoundé, Cameroon** (J-V Taguebue MD); **Teaching Unit of Dermatology and Infectiology, UFR of Medical Sciences, Felix-Houphouet Boigny University, Abidjan, Côte d'Ivoire** (R Moh MD, E A Komena MD); **Programme PAC-CI, CHU de Treichville, Abidjan, Côte d'Ivoire** (R Moh, E A Komena); **Epicentre Mbarara Research Centre, Mbarara, Uganda** (J Mwanga-Amumpaire MMED, N Natukunda MSc); **MIVEGEC, University of Montpellier, CNRS, IRD, Montpellier, France** (M Lounnas PhD); **Children's**

Introduction

Despite increasing awareness and progress in access to appropriate diagnostic services in many countries with high incidence of tuberculosis, childhood tuberculosis remains largely underdiagnosed. In 2020, of the estimated 1085700 childhood tuberculosis cases (in those younger than 15 years), only 408127 were notified to WHO, reflecting a major diagnostic gap.[1] Challenges to diagnosis

Hospital, University Teaching Hospital, Lusaka, Zambia (U Chirwa MD); Paediatrics Department, Maputo Central Hospital, Maputo, Mozambique (Prof S Mavale MD, J Chilundo MD); Paediatrics Department, José Macamo General Hospital, Maputo, Mozambique (D Rego MD); Arthur Davidson's Children, Ndola, Zambia (B Nduna MD); Epidemiology and Public Health Unit, Clinical Research Group, Institut Pasteur du Cambodge, Phnom Penh, Cambodia (A de Lauzanne MD, B Dim MD, L Borand PharmD); Byem Assi Hospital, Yaoundé, Cameroon (E Tiogouo Ngouana MD); Paediatrics Department, Cocody University Teaching Hospital, Abidjan, Côte d'Ivoire (Prof M Folquet Amorrissani MD); Paediatrics Department, Treichville University Teaching Hospital, Abidjan, Côte d'Ivoire (Prof L Cisse MD); Mother and Child Department, Angré University Hospital, Abidjan, Côte d'Ivoire (Prof F Amon Tanoh Dick MD); Jinja Regional Referral Hospital, Jinja, Uganda (P Mbekeka MD); Pulmonology Department, National Pediatric Hospital, Phnom Penh, Cambodia (Prof A Kim MD); Paediatrics Department, Kompong Cham Provincial Hospital, Kompong Cham, Cambodia (C Kheang MD); Paediatrics Department, Takeo Provincial Hospital, Takeo, Cambodia (S Pol MD); Department of Paediatrics & Child Health, University of Nairobi, Nairobi, Kenya (Prof E Maleche-Obimbo MD); Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Stellenbosch University, Stellenbosch, South Africa (J A Seddon MD); Department of Infectious Disease, Imperial College London, London, UK (J A Seddon); National Center for Tuberculosis and Leprosy, Ministry of Health, Phnom Penh, Cambodia (T E Mao MD); University of Melbourne Department of Paediatrics and Murdoch Children's Research Institute, Royal Children's Hospital, Melbourne, VIC, Australia (Prof S M Graham MD); International Union Against Tuberculosis and Lung Disease, Paris, France (Prof S M Graham);

Research in context

Evidence before this study

We searched PubMed for articles published between Jan 1, 2000, and March 1, 2022, with the terms "mortality" and "severe pneumonia" and "tuberc*" and "child*" and "diagn*". Several studies assessed factors around the causes of pneumonia and risk factors for mortality. A meta-analysis published in 2015 showed that in tuberculosis-endemic areas, up to 23% of children with pneumonia had tuberculosis diagnosed and 7·5% had culture-confirmed tuberculosis with variation across studies. More recent findings from an international case-control study on causes of pneumonia showed *Mycobacterium tuberculosis* as the cause in 5·9% of children with severe pneumonia. No study specifically assessed the question of the effect of tuberculosis screening at admission on mortality in children with severe pneumonia in countries with a high tuberculosis burden.

Added value of this study

This cluster randomised trial is the first large-scale international outcome-driven trial assessing the effect of using systematic molecular tuberculosis detection in children with severe pneumonia. Introducing systematic tuberculosis rapid molecular detection with Xpert MTB/RIF Ultra (Xpert Ultra; Cepheid, Sunnyvale, CA, USA) on one nasopharyngeal aspirate and one stool sample in addition to the WHO standard of care did not lead to a reduction in 12-week all-cause mortality in children with severe pneumonia. In the intervention group, tuberculosis detection and microbiological confirmation rates were higher, and the time to tuberculosis treatment initiation was shorter than in the control group. Hospital readmission rates were lower. However, this effect was explained by a higher prevalence of severe acute malnutrition in the intervention group, with these children at particularly high risk of tuberculosis. Mortality and tuberculosis diagnosis rates were four to five times higher in children with severe acute malnutrition. The study intervention based on the collection and testing of nasopharyngeal aspirates and stool samples was highly feasible and well tolerated in children with severe pneumonia and likely to be very beneficial for children with severe acute malnutrition.

Implications of all the available evidence

Globally, childhood tuberculosis remains largely undiagnosed, especially among highly vulnerable groups, such as children with severe pneumonia. Although our intervention, systematic molecular detection for tuberculosis in children with severe pneumonia, did not lead to decreased mortality as compared with the standard of care, the high rates of tuberculosis treatment initiation and microbiological confirmation in the intervention group would support the more systematic use of Xpert Ultra done on combined nasopharyngeal aspirates and stools in this vulnerable group. Analysis of data from children with severe acute malnutrition suggests a potential benefit of systematic molecular testing and tuberculosis assessment in this group. Our study results support the need for a paradigm shift in both paediatric tuberculosis and pneumonia guidelines emphasising the importance of tuberculosis as a cause in severe pneumonia and that the presentation of tuberculosis can be more acute in children with acute severe pneumonia, notably in those with malnutrition.

include the paucibacillary nature of childhood tuberculosis, difficulties in obtaining suitable respiratory samples for microbiological confirmation in younger children, and an absence of point-of-care testing.[2] Models suggest that 230 000 children die annually from tuberculosis; almost all are younger than 5 years and untreated.[3]

Worldwide, pneumonia is the leading cause of death in children younger than 5 years surviving preterm birth complications.[4] Increasing evidence indicates that tuberculosis is common in children with severe pneumonia. A 2015 meta-analysis found that in tuberculosis-endemic areas, up to 23% of children with pneumonia had tuberculosis and 7·5% had culture-confirmed tuberculosis.[5] More recent data from a large multicountry case-control study showed *Mycobacterium tuberculosis* as the cause of infection in 5·9% of children with severe pneumonia, ranging from 3·6% in Bangladesh to 12·8% in Zambia.[6,7]

As for adults, children with tuberculosis mostly develop chronic unremitting symptoms. Consequently, and in accordance with WHO childhood tuberculosis guidelines, most clinicians consider tuberculosis only in the context of prolonged symptoms, failure of wide-spectrum antibiotics, or a history of household tuberculosis exposure.[8] Autopsy studies show that tuberculosis is often missed, and inpatient case-fatality rate for pneumonia associated with tuberculosis ranged from 4% to 21% in four African studies reporting pathogen-related outcomes.[5,9] Most children presented with acute symptoms when symptom duration was reported.[5]

Following endorsement by WHO in 2013 for Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA), access to rapid molecular tuberculosis testing has expanded.[10,11] A more sensitive version, Xpert MTB/RIF Ultra (Xpert Ultra), has now been released but due to challenges in obtaining respiratory samples, young children (younger than 5 years) are seldom tested with Xpert Ultra.[12] In 2021 and 2022, WHO has recommended alternative samples for testing with Xpert Ultra, including nasopharyngeal aspirates and stool in children with presumptive tuberculosis. However, presumptive tuberculosis is mainly defined as a child with prolonged symptoms, and so most children with severe pneumonia are not tested.

Improving tuberculosis case detection could contribute to decreased mortality in children with severe pneumonia. We hypothesised that adding systematic rapid molecular detection on easily obtainable samples at hospital admission in children with severe pneumonia would increase tuberculosis case detection and reduce mortality in this clinically vulnerable group. We did an international pragmatic cluster-randomised trial to assess the effect on 12-week mortality of systematic Xpert Ultra testing on nasopharyngeal aspirate and stool samples, in young children with severe pneumonia, in addition to the WHO standard of care.

Methods

Study design and participants

We did a pragmatic, stepped-wedge cluster-randomised trial in 16 tertiary referral hospitals from six countries with high incidence of tuberculosis: Cambodia, Cameroon, Côte d'Ivoire, Mozambique, Uganda, and Zambia. The protocol with detailed design was published previously.[13] We enrolled newly hospitalised children aged 2–59 months presenting with WHO-defined severe pneumonia (appendix 2 p 3). We excluded children with a history of antituberculosis treatment in the preceding 6 months.

Parents or guardians of children meeting inclusion criteria were approached for consent. Once written informed consent was obtained, children were offered the strategy being implemented at the hospital (cluster) according to the cluster allocation. After an initial 5-week phase of WHO standard of care in all participating hospitals, hospitals were progressively switched in a randomly selected order, every 5 weeks (step), from the control, consisting of the WHO standard of care for severe pneumonia, to the intervention, consisting of the WHO standard of care plus systematic Xpert Ultra testing of one nasopharyngeal aspirate and one stool sample, without transition period.

The planned duration of enrolment into the trial was 80 weeks—ie, 16 time periods of 5 weeks, with the longest possible duration of the intervention of 75 weeks and the shortest of 5 weeks. Enrolment was interrupted between April, 1, and Oct 1, 2020, due to the COVID-19 pandemic lockdowns in study countries, per sponsor decision, and in agreement with the study independent data monitoring committee. The committee accessed blinded trial primary endpoint results, considered the enrolment rate in the trial as satisfactory and recommended closing enrolment as planned at the end the 16th period. Enrolment was discontinued in one hospital due to renovation (before the switch to intervention), and this hospital was replaced by another hospital located in the same capital city.

The study was approved by the WHO Ethics Review Committee, the sponsor's (Inserm) institutional review committee, the national ethics review committees of participating countries, and relevant national authorities and institutional review boards (appendix 2 p 2).

Randomisation and masking

The unit of randomisation was the cluster (hospital). Randomisation was stratified by the estimated country tuberculosis incidence rate, classified as either high (100–299 per 100 000 patient-years; Cameroon, Côte d'Ivoire, and Uganda) or very high (≥300 per 100 000 patient-years; Cambodia, Mozambique, and Zambia).[1] The trial statistician at the University of Bordeaux, France, established the randomisation sequence before the start of the trial, using a computer-generated random sequence. The research teams and hospitals were masked to the randomisation order up to 5 weeks before the switch date.

Procedures

Any child aged between 2–59 months presenting to the emergency units, intensive care unit, or paediatric departments of the selected hospitals with signs and symptoms of pneumonia were screened for trial eligibility. Eligible children had a clinical history taken, including details of symptoms suggestive of tuberculosis and history of tuberculosis exposure. Investigations in all children included a digitalised chest x-ray, a complete blood count, and testing for HIV and malaria.

In both trial groups, children received the WHO standard of care for severe pneumonia that consisted of broad-spectrum intravenous antibiotics and oxygen therapy if their peripheral oxygen saturation (SpO_2) was less than 90% or if they presented with signs of hypoxia, and airway management, symptomatic fever treatment, bronchodilators or steroids (if needed), appropriate maintenance fluids, nutritional support in case of malnutrition, and access to specific therapies for comorbidities such as HIV. Before the onset of the trial, we did refresher trainings on the WHO standard of care, and sites were equipped, if needed, with oxygen concentrators and pulse oximeters. As per the standard of care, children with suggestive tuberculosis symptoms, exposure history, or persistent signs of pneumonia despite adequate antibiotic treatment, could be evaluated for tuberculosis using routine procedures, which could include Xpert MTB/RIF or Xpert Ultra testing on routine specimens.

During the intervention, in addition to the WHO standard of care, children underwent systematic Xpert Ultra used on one nasopharyngeal aspirate and one stool sample, as soon as possible after hospitalisation. Nasopharyngeal aspirates were done without previous nasal instillation with a battery-operated suction machine connected to mucus aspirators to collect a 1–2 mL specimen, and under SpO_2 monitoring by pulse oximetry with access to oxygen therapy if required. Stool samples were obtained as soon as possible after admission.

Xpert Ultra testing was done on nasopharyngeal aspirates either at the hospital laboratory with the standard GeneXpert platform, or in the ward or side laboratory next to the ward using a one-module

Burnet Institute, Melbourne, VIC, Australia (Prof S M Graham); **Department of Paediatric Pulmonology, Necker University Teaching Hospital, Paris, France** (Prof C Delacourt MD); **IRD UMI233, Inserm U1175, University of Montpellier, Montpellier, France** (M Bonnet MD, S Kwedi Nolna PhD)

Correspondence to: Dr Olivier Marcy, Université de Bordeaux, Bordeaux Population Health Centre U1219, Bordeaux 33076, France **olivier.marcy@u-bordeaux.fr**

See **Online** for appendix 2

GeneXpert G1 Edge (Cepheid, Sunnyvale, CA, USA), to reduce the turnaround time to less than 3 h. Xpert Ultra testing on stool, which requires prior processing due to the presence of PCR inhibitors in the specimen, was done at the hospital central laboratory. Stool samples were processed using a sucrose flotation method.[14,15] All sites underwent external quality assessment of Xpert Ultra testing using half-yearly proficiency testing panels. All external quality assessment scores were above 87·5% corresponding to only one error or less. Turnaround time between sample collection and receipt of results by clinicians was monitored. Antituberculosis drugs were available at the inpatient ward to enable prompt initiation of treatment.

Each child was followed up for 12 weeks, with four protocol visits at day 3 or at hospital discharge, 2 weeks after discharge, and 12 weeks after enrolment. Each visit comprised a detailed clinical evaluation, an assessment of adherence, and tuberculosis drug dispensation for children initiated on treatment. Parents or guardians were invited to bring their child back to the hospital in case of new symptoms. At the 12-week visit, a digital chest x-ray was done, and an assessment of tuberculosis treatment response for those initiated on treatment.

Adverse events occurring during nasopharyngeal aspirates were monitored by trained study nurses using adverse events reporting questionnaires; clinicians were involved in cases of severe or life-threatening adverse events. Severity was graded with the 2017 Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events.[16] No adverse events were expected from stool sample collection. Serious adverse events were notified to the sponsor for all children in the study and included deaths, grade 4 clinical adverse events, and serious adverse events related to naso-pharyngeal aspirate collection.

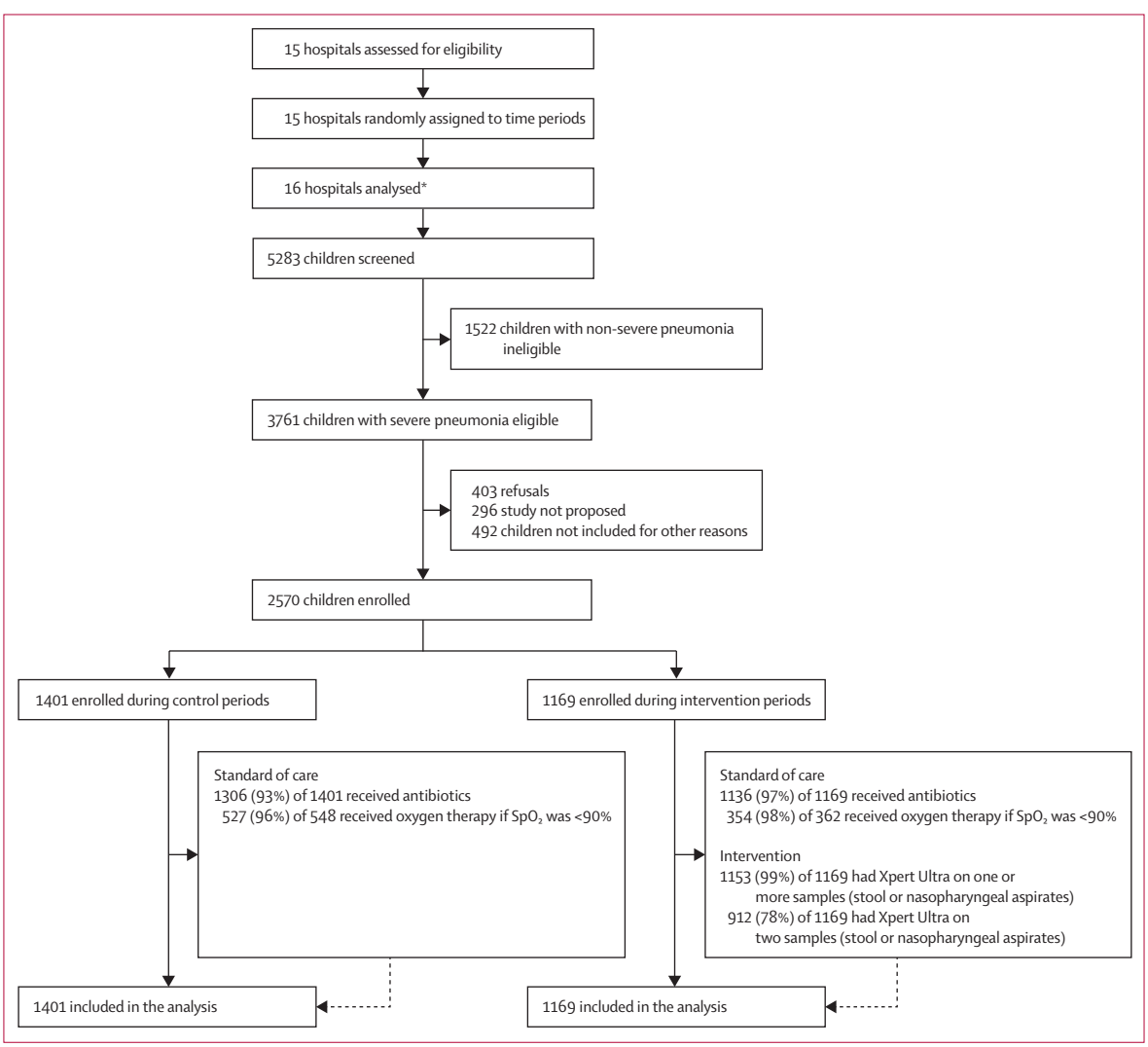

Figure 1: **Trial profile**
SpO_2=peripheral oxygen saturation. *One hospital was closed down for renovation and replaced by a similar site in the same city.

During the COVID-19 pandemic, when enrolment was interrupted, sites were instructed to have follow-up visits at the study clinic whenever possible, ensuring that staff had adequate personnel protective equipment in line with country regulations and level of risk. Alternatively, follow-up visits were done by study nurses by phone. As much as possible, families were instructed to bring the child to the nearest health facility, where appropriate vital signs measurements and clinical assessments could be made. Participants with safety concerns were referred to the nearest facility for assessment and care. In such cases, study teams were instructed to establish direct contact with the clinician or health-care worker at the facility, provided authorisation was given by the parent or guardian.

Outcomes

The primary outcome was all-cause mortality from enrolment to 12 weeks, a delay that would be appropriate to assess the effect on mortality of tuberculosis treatment empirically started in children with poor clinical progress during the first weeks of follow-up, in a context where mortality due to severe pneumonia (related or not to tuberculosis) is expected to occur early. If children were not seen at the week 12 visit, parents or guardians were contacted by phone, or home visits were done, to collect the child's vital status. Secondary endpoints were: tuberculosis diagnosis; tuberculosis treatment initiation; time to tuberculosis treatment initiation; duration of tuberculosis treatment at end of trial; inpatient deaths; duration of initial hospitalisation; readmission following discharge; weight gain at 12 weeks; and adverse events during nasopharyngeal aspirate collection in the intervention group only.

Statistical analysis

We assumed an overall mortality of 15% in the control group, in line with mortality associated with severe pneumonia observed in previous studies, and that the intervention would lead to a 30% reduction in the overall mortality rate (10·5%).[17,18] Using these estimates, with an alpha of 0·05, a power of 80%, an intra-cluster correlation coefficient of 0·005, and 1% of incomplete data, the sample size for our study was 3780 children, with a design effect of 2·16.[19]

We described and compared baseline characteristics, intervention uptake, and study follow-up across study groups using Pearson χ^2 or Wilcoxon tests, as relevant. The primary analysis used the intention-to-treat approach. We compared all-cause mortality at 12 weeks in the control versus intervention group using a generalised linear mixed effects model with binomial function. In the model, we included the study groups and time as fixed effects, and we included the hospital and country as nested random effects to account for clustering.[20] We controlled for severe acute malnutrition and SpO_2 at admission as these variables differed between the groups and were known to be associated

	Control (N=1401)	Intervention (N=1169)	p value
Age, months	11 (5–20), n=1400	11 (6–20), n=1169	0·866
Sex			
Female	610/1400 (43·6%)	492/1169 (42·1%)	0·449
Male	790/1400 (56·4%)	677/1169 (57·9%)	0·449
Body temperature, °C	37·2 (36·7–38·0), n=1400	37·3 (36·7–38·0), n=1168	0·521
Respiratory rate at admission, breaths per min	50 (38–60), n=1400	46 (38–56), n=1168	0·0001
Peripheral oxygen saturation at admission, %	92% (87–96), n=1397	94% (88–97), n=1165	<0·0001
Central cyanosis	65/1400 (4·6%)	42/1168 (3·6%)	0·186
Grunting	511/1400 (36·5%)	357/1168 (30·6%)	0·0015
Nasal flaring	1048/1400 (74·9%)	795/1168 (68·1%)	0·0001
Severe or very severe chest indrawing	422/1400 (30·1%)	667/1168 (57·1%)	<0·0001
Stridor	131/1400 (9·4%)	79/1168 (6·8%)	0·017
Wheezing on auscultation	420/1400 (30·0%)	399/1168 (34·2%)	0·024
Bodyweight, kg	8·0 (6·1–10·0), n=1400	7·8 (6·1–10·0), n=1168	0·166
Weight for height Z score of <2*	299/1393 (21·5%)	298/1152 (25·9%)	0·010
Severe acute malnutrition†	240/1401 (17·1%)	297/1169 (25·4%)	<0·0001
Previous tuberculosis disease	7/1399 (0·5%)	2/1167 (0·2%)	0·285
History of contact with adult tuberculosis case (any)	51/1400 (3·6%)	22/1168 (1·9%)	0·012
Contact with smear or Xpert + case	13/51 (25·5%)	9/22 (40·9%)	0·188
History of fever for >2 weeks	86/1399 (6·1%)	100/1168 (8·6%)	0·019
History of cough for >2 weeks	117/1400 (8·4%)	133/1168 (11·4%)	0·010
History of weight loss for >2 weeks	101/1400 (7·2%)	139/1168 (11·9%)	<0·0001
HIV positive	73/1384 (5·3%)	59/1167 (5·1%)	0·874
Malaria test positive	107/1393 (7·7%)	94/1167 (8·1%)	0·517
Asthma diagnosed before the study	22/1395 (1·6%)	21/1168 (1·8%)	0·665
Cardiac disorders diagnosed before the study	40/1400 (2·9%)	26/1167 (2·2%)	0·316
Sickle cell disease diagnosed before the study	24/1397 (1·7%)	17/1161 (1·5%)	0·611
Vaccination status			
Vaccination book available	921/1400 (65·8%)	746/1167 (63·9%)	0·325
BCG vaccination	898/915 (98·1%)	715/729 (98·1%)	0·926
Pneumococcal conjugate vaccination	795/916 (86·8%)	680/744 (91·4%)	0·0030
Haemophilus influenzae B vaccination	617/916 (67·4%)	500/741 (67·5%)	0·959
Measles, mumps, and rubella vaccination	501/912 (54·9%)	395/740 (53·4%)	0·528
Tetanus, diphtheria, and pertussis vaccination	785/915 (85·8%)	655/746 (87·8%)	0·230
BCG vaccine scar in those without vaccination book	425/478 (88·9%)	385/420 (91·7%)	0·166

Data are n/N (%) or median (IQR), unless otherwise specified. There was a total of 1401 children in the control group and 1169 in the intervention group, but N is the actual size of the study population in which the variable has been measured or is available. *Weight for height Z score is a WHO standard to compare a child's weight to the weight of a child of the same height and sex; a Z score of less than 2 indicates moderate acute malnutrition. †Defined as weight for height Z score of less than –3 SD, midupper arm circumference of less than 115 mm, or bilateral pitting oedema.

Table 1: **Baseline characteristics**

	Control (N=1401)	Intervention (N=1169)	p value
WHO standard of care for severe pneumonia			
Antibiotics	1306/1401 (93·2%)	1136/1169 (97·2%)	<0·0001
Oxygen therapy if oxygen saturation is <90%	527/548 (96·2%)	354/362 (97·8%)	0·173
Therapeutic feeding in those with severe acute malnutrition	97/240 (40·4%)	139/297 (46·8%)	0·138
Antiretroviral treatment in children living with HIV	58/73 (79·5%)	38/59 (64·4%)	0·054
Malaria treatment in those with positive malaria tests	104/107 (97·2%)	92/94 (97·9%)	0·759
Routine tuberculosis microbiological testing other than Ultra on NPA and stools	80/1401 (5·7%)	4/1169 (0·3%)	..
Intervention			
Xpert MTB/RIF Ultra performed on NPA	2/1401 (0·1%)	1132/1169 (96·8%)	..
Xpert MTB/RIF Ultra performed on stools	1/1401 (0·1%)	922/1169 (78·9%)	..
Xpert MTB/RIF Ultra performed on at least one sample	2/1401 (0·1%)	1152/1169 (98·5%)	..
Xpert MTB/RIF Ultra performed on both	1/1401 (0·1%)	902/1169 (77·2%)	..

Data are n/N (%). There was a total of 1401 children in the control group and 1169 in the intervention group, but N is the actual size of the study population in which the variable has been measured or is available. NPA=nasopharyngeal aspirates.

Table 2: **Intervention uptake (WHO standard of care and TB-Speed molecular detection)**

with the primary endpoint, which was death. The effect of the intervention was presented as odds ratios (ORs) with 95% CIs.

We did several sensitivity analyses: (1) per-protocol restricted to children who had received intravenous antibiotics and oxygen therapy if SpO_2 was below 90% in both groups and had Xpert Ultra tested on at least one sample in the intervention group; (2) considering missing final status and loss to follow-up as deaths; (3) adding HIV status and age younger or older than 12 months as covariates (as both had been previously associated with death in low-resource settings); (4) adding outside air temperature and precipitation as covariates to control for seasonal effect on pneumonia occurrence; (5) an evaluation before and after the COVID-19 pandemic break.[21] We also did sensitivity analyses using different model specifications. None improved the model quality and none are reported here.[22] All sensitivity analyses were done with the study groups, time, severe acute malnutrition, and SpO_2 at admission as fixed effects, and the hospital and country as nested random effects.

Binary secondary endpoints were compared between groups using similar models, as for the primary analysis. Weight gain at 12 weeks and duration of first hospitalisation were compared between groups using linear mixed effects models. Time-to-event endpoints were compared between groups with mixed effects Cox models. All secondary analyses were done using the same fixed and random effects as the primary analysis. The proportion of children with adverse events during nasopharyngeal aspirates was described in the intervention group.

To further understand study results, we separately assessed primary and secondary endpoints post hoc in the two groups of children with and without severe acute malnutrition, which was strongly linked to both mortality and tuberculosis diagnosis.

A significance level of 0·05 was used for all analyses. Analyses were done using the R software (version 4.1.1). An independent data monitoring committee reviewed overall safety and efficacy data. This study is registered with ClinicalTrials.gov (NCT03831906) and the Pan African Clinical Trial Registry (PACTR202101615120643).

Role of the funding source

The study funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 21, 2019, and March 30, 2021, 5283 children were screened, 3761 of whom presented with severe pneumonia; 2570 children were enrolled, including 1401 in the control group and 1169 in the intervention group (figure 1). Overall, demographic characteristics were similar in the control and the intervention groups with a median age of 11 months (IQR 5–20; table 1). Pneumonia was more severe in the control group with a lower median SpO_2 (92% [IQR 87–96] *vs* 94% [88–97]; p<0·0001) and with a higher median respiratory rate at admission (50 breaths per min [IQR 38–60] *vs* 46 breaths per min [38–56]; p=0·0001). There were more children with severe acute malnutrition in the intervention group than in the control group (25·4% *vs* 17·1%, p<0·0001). The proportion of children living with HIV was 5·1% overall, with no difference between trial groups.

There was a higher proportion of children receiving antibiotics in the intervention group than in the control group (97·2% *vs* 93·2%, p<0·0001; table 2). There was no difference between the two groups regarding oxygen therapy for children who had hypoxaemia (SpO_2<90%), antiretroviral therapy for children who were HIV-positive and therapeutic feeding for those with severe acute malnutrition. Children were hospitalised for a median duration of 5 days [IQR 4–8] with no difference between the study groups.

In the intervention group, nasopharyngeal aspirates were successfully collected in 1140 (97·5%) of 1169 children and stool in 942 (80·6%) children (figure 2). Xpert Ultra results were obtained with a median turnaround time of 2·63 h (IQR 1·73–4·25) for nasopharyngeal aspirates, and 4·92 h (IQR 2·64–23·40) for stool samples. Xpert Ultra was positive on nasopharyngeal aspirates in 21 (1·8%) of 1169 children and stools in 16 (1·4%) children. Overall, 1153 (98·6%) of 1169 children had at least one sample and 912 (78·0%)

children had both samples collected and tested with Xpert Ultra. 24 (2·1%) of 1169 children had a positive Xpert Ultra test on either sample. Combined samples testing with Xpert Ultra increased the yield over single sample testing. Stool testing increased the yield of nasopharyngeal testing by 14·3%; nasopharyngeal testing increased the yield of stool testing by 50%.

After 12 weeks, 110 (7·9%) of 1401 children had died in the control group and 91 (7·8%) of 1169 in the intervention group (unadjusted p=0·989, table 3). In addition, 40 (2·9%) of 1401 children in the control group and 41 (3·5%) of 1169 in the intervention group were lost to follow-up, and 11 (0·8%) of 1401 children in the control group and nine (0·8%) of 1169 in the intervention group withdrew from the trial. Mortality occurred at a median of 6 days (IQR 2–18) after inclusion in the study. 59 (29·3%) deaths occurred within 48 h of admission and 139 (69·2%) deaths occurred before hospital discharge. Of the 201 children who died, 27 (13·4%) had been initiated on tuberculosis treatment. Overall, 110 (20·5%) of 537 severely malnourished children with severe pneumonia died compared with 91 (4·5%) of 2033 children without severe acute malnutrition.

The analysis with the generalised linear mixed effects model showed that there was no effect of the intervention on the risk of death at 12 weeks with an adjusted OR of 0·986 (95% CI 0·597–1·630, p=0·957) in the intention-to-treat analysis (table 3; appendix 2 p 8). All sensitivity analyses were consistent with the primary analysis result.

In addition to the 24 children with positive Xpert Ultra on nasopharyngeal aspirates or stools in the intervention group, 65 (5·6%) of 1169 were clinically diagnosed on the basis of clinical or radiological features, or Xpert on other microbiological samples (table 3). Overall, 74 (5·3%) of 1401 children in the control group and 88 (7·5%) of 1169 children in the intervention group were diagnosed with tuberculosis (unadjusted p=0·020; table 3). The adjusted analysis did not show an effect of the intervention on tuberculosis diagnosis (adjusted OR 1·238, 95% CI 0·696–2·202, p=0·467). All children diagnosed with tuberculosis, except one in the intervention group, were initiated on tuberculosis treatment. In unadjusted analyses, tuberculosis treatment was initiated earlier (median 2 days [IQR 1–8] *vs* 5 days [IQR 2–10]; p=0·042), and there were fewer rehospitalisations following discharge (50 [4·3%] *vs* 100 [7·2%]; p=0·0026) in the intervention group versus the control group. However, the multivariate generalised linear mixed effects model did not show an effect of the intervention on these two endpoints. There was no difference between the two groups on the other secondary endpoints. In children with severe acute malnutrition, mortality rates were 23·8% in the control group and 17·8% in the intervention group, and tuberculosis diagnosis rates were 15·0% in the control group and 18·9% in the intervention group (table 4).

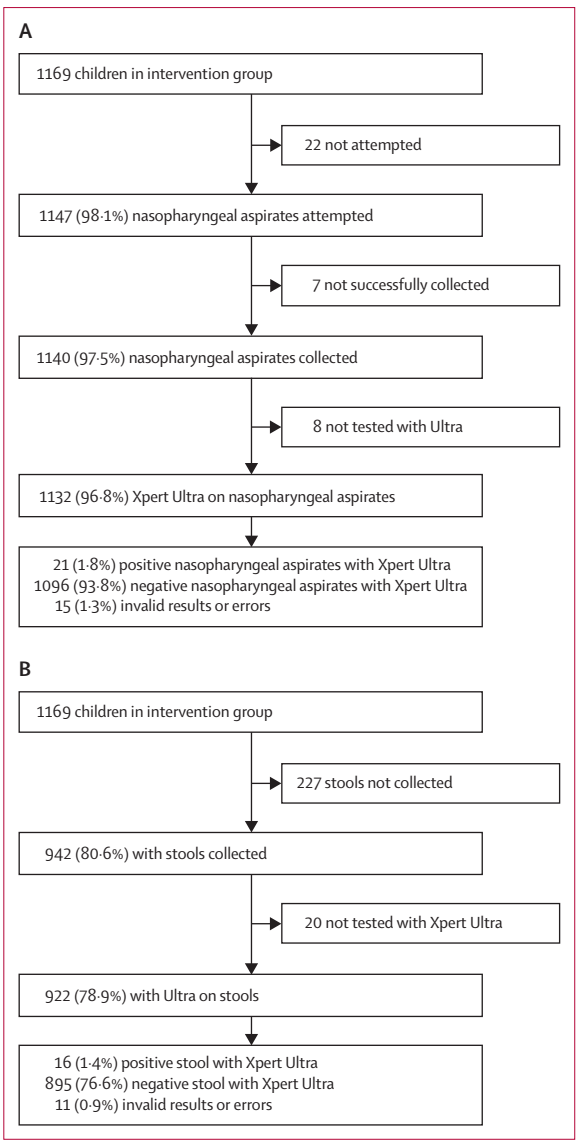

Figure 2: **Sample collection, testing, and results flow chart for nasopharyngeal aspirates (A) and stool samples (B)**

The main adverse events reported associated with nasopharyngeal aspirates were samples with blood in 312 (26·7%) of 1169 children, dyspnoea or SpO_2 less than 95% in 134 (11·4%) of 1147 children with nasopharyngeal aspirates attempted, and transient respiratory distress or SpO_2 less than 90% in 59 (5·2%) children (appendix 2 p 9). All other adverse events occurred in less than 5% of children and were mild. There was no serious adverse event related to nasopharyngeal aspirates reported during the trial. In addition to deaths that were reported as serious adverse events, 28 (2·0%) of 1401 children in the control group and 11 (0·9%) of 1169 children in the intervention group had serious adverse events reported (p=0·029).

	Control (n=1401)	Intervention (n=1169)	Unadjusted p value	Adjusted OR (95% CI)*	p value
Primary outcome					
Deaths in ITT analysis	110/1401 (7·9%)	91/1169 (7·8%)	0·989	0·986 (0·597 to 1·630)	0·957
Sensitivity analyses for the primary endpoint					
Missing means failure (lost to follow-up and withdrawal) in ITT analysis	161/1401 (11·5%)	141/1169 (12·1%)	0·655	0·967 (0·625 to 1·496)	0·879
Death in per protocol analysis†	94/1250 (7·5%)	82/1070 (7·7%)	0·896	0·852 (0·508 to 1·429)	0·543
Deaths in ITT analysis including additional covariates (HIV and age less than 12 months)	110/1401 (7·9%)	91/1169 (7·8%)	0·989	0·919 (0·553 to 1·526)	0·743
Deaths in ITT analysis controlling for seasonality	110/1401 (7·9%)	91/1169 (7·8%)	0·989	1·004 (0·606 to 1·665)	0·987
Analysis before COVID-19	101/1321 (7·6%)	43/619 (6·9%)	0·587	..	..
Analysis after COVID-19	9/80 (11·2%)	48/550 (8·7%)	0·527	..	..
Secondary outcomes					
Children diagnosed with tuberculosis by week 12‡	74/1401 (5·3%)	88/1169 (7·5%)	0·020	1·238 (0·696 to 2·202)	0·467
Tuberculosis based on microbiological confirmation§	13/1401 (0·9%)	26/1169 (2·2%)	0·0074	1·920 (0·630 to 5·853)	0·251
Tuberculosis based on clinical or radiological suspicion	61/1401 (4·3%)	62/1169 (5·3%)	0·261	1·033 (0·534 to 1·999)	0·922
Children with tuberculosis treatment initiated at any time during follow-up	73/1401 (5·2%)	88/1169 (7·5%)	0·016	1·229 (0·691 to 2·187)	0·483
Time to tuberculosis treatment initiation, days	5 (2–10), n=73	2 (1–8), n=88	0·042	HR 1·26 (0·69 to 2·30)	0·445
Duration of tuberculosis treatment at week 12, days	80 (39–87), n=73	85 (61–90), n=88	0·264	HR 0·942 (0·290 to 3·063)	0·921
Inpatient deaths (during first hospitalisation)	78/1401 (5·6%)	61/1169 (5·2%)	0·697	0·934 (0·531 to 1·643)	0·813
Duration of initial hospitalisation¶	5 (4–8), n=1401	5 (4–8), n=1169	0·846	β –0·031 (–0·104 to 0·043)	0·409
Children readmitted following discharge	100/1394 (7·2%)	50/1149 (4·3%)	0·0026	0·725 (0·397 to 1·323)	0·294
Weight gain at week 12 (as compared to weight at inclusion), kg	1·0 (0·5–1·8), n=913	1·0 (0·5–1·6), n=753	0·237	β –0·040 (–0·214 to 0·133)	0·647

Data are n/N (%) or median (IQR), unless otherwise specified. OR=odds ratio. HR=hazard ratio. β=linear regression parameter. ITT=intention to treat. All models used for analysis included study group, time, severe acute malnutrition, and oxygen saturation at admission as fixed effects, and hospital and country as random effects to account for clustering. *Intervention effect (reference=control) is described by adjusted OR (95% CI) for binary outcomes, β (95% CI) for continuous outcomes, and HR (95% CI) for duration outcomes. †Definition of per-protocol population is that the WHO standard of care is applied—ie, antibiotics and oxygen therapy if SpO_2 is less than 90% and Xpert Ultra on at least one sample. ‡Defined as tuberculosis treatment initiated or tuberculosis diagnosis or Xpert MTB/RIF Ultra positive. §Due to convergence issue, random effects have been simplified (country effect removed) and steps have been combined by pairs. ¶Log transformation was used to normalise the variable.

Table 3: **Primary outcome, sensitivity analyses, and secondary outcomes**

	Children with severe acute malnutrition		Children without severe acute malnutrition	
	Control (N=240)	Intervention (N=297)	Control (N=1161)	Intervention (N=872)
Deaths	57/240 (23·8%)	53/297 (17·8%)	53/1161 (4·6%)	38/872 (4·4%)
Withdrawn	1/240 (0·4%)	3/297 (1·0%)	10/1161 (0·9%)	6/872 (0·7%)
Lost to follow-up	9/240 (3·8%)	11/297 (3·7%)	31/1161 (2·7%)	30/872 (3·4%)
Children diagnosed with tuberculosis by week 12*	36/240 (15·0%)	56/297 (18·9%)	38/1161 (3·3%)	32/872 (3·7%)
Tuberculosis based on microbiological confirmation	3/240 (1·3%)	14/297 (4·7%)	10/1161 (0·9%)	11/872 (1·3%)
Tuberculosis based on clinical or radiological suspicion	33/240 (13·8%)	42/297 (14·1%)	28/1161 (2·4%)	21/872 (2·4%)
Children with tuberculosis treatment initiated at any time during follow-up	35/240 (14·6%)	56/297 (18·9%)	38/1161 (3·3%)	32/872 (3·7%)
Time to tuberculosis treatment initiation, days	4·0 (2·0–9·0), n=36	2·0 (1·0–10·0), n=56	5·5 (3·3–10·5), n=38	2·0 (1·0–6·0), n=32
Inpatient deaths (during first hospitalisation)	40/240 (16·7%)	35/297 (11·8%)	38/1161 (3·3)	26/872 (3·0%)
Duration of initial hospitalisation	8·0 (6·0–13·0), n=200	9·0 (6·0–13·0), n=262	5·0 (3·0–7·0), n=1123	5·0 (3·0–7·0), n=846
Children readmitted following discharge	21/240 (8·8%)	5/297 (1·7%)	79/1161 (6·8%)	45/872 (5·2%)
Weight gain at week 12 (as compared to bodyweight at inclusion), kg	1·3 (0·7–2·1), n=130	1·3 (0·7–2·0), n=168	1·0 (0·51·8), n=783	1·0 (0·5–1·5), n=587

Data are n/N (%) or median (IQR), unless otherwise specified. There was a total of 240 children with severe acute malnutrition in the control group and 297 in the intervention group, and a total of 1161 children without severe acute malnutrition in the control group and 872 in the intervention group, but N is the actual size of the study population in which the variable has been measured or is available. *Defined as tuberculosis treatment initiated or tuberculosis diagnosis or Xpert MTB/RIF Ultra positive.

Table 4: **Details of trial outcomes in children with and without severe acute malnutrition**

Discussion

This trial provides original data of the effect of using systematic molecular tuberculosis detection in children with severe pneumonia. Adding systematic Xpert Ultra testing, at the time of hospital admission, to the WHO standard of care did not lead to a reduction in 12-week

all-cause mortality in children with severe pneumonia. In the intervention group, the overall tuberculosis detection and microbiological confirmation rate were higher, and the time to tuberculosis treatment initiation was shorter and there were fewer hospital readmission rates. However, these differences became less significant after adjusting for severe acute malnutrition that was more frequent in the intervention group. This can be explained by an increased likelihood of tuberculosis among children with severe acute malnutrition.[23]

Respiratory specimen collection is a challenge in young children, and even more so if they have respiratory distress. For our study intervention, we selected a combination of two samples (nasopharyngeal aspirates and stools) for microbiological evaluation that have been shown to be highly feasible in children with presumptive tuberculosis and a typically stable respiratory condition, and to have a performance for tuberculosis detection similar to that of gastric aspirates and expectorated sputum, the sample collection methods recommended by WHO since 2014.[8,14,24] In our study, children had severe acute respiratory symptoms and 35% required oxygen; however, feasibility of nasopharyngeal aspirates was very high, with 97% of children having samples collected. Safety was good with a low rate of adverse events and the absence of serious adverse events related to nasopharyngeal aspirates. Uptake of stool sample collection was not as high as that of nasopharyngeal aspirates, with successful stool samples collected in 81% of the children, despite a median of 5 days in hospital. Testing these combined samples with Xpert Ultra increased the yield over single sample testing, consistent with results from previous studies combining nasopharyngeal aspirates and stool samples.[14,24] The low rate of indeterminate results and errors in both type of samples and short turnaround time confirmed the feasibility of these interventions in this population of children.

The yield of our microbiological testing strategy was lower than we had hypothesised based on data from the 2015 meta-analysis showing tuberculosis prevalence rates of up to 23% in children with pneumonia and 7·5% culture-confirmed tuberculosis.[5] In the intervention group, 7·5% of children were diagnosed with tuberculosis and 2·0% were microbiologically confirmed. These findings are consistent with data from the PERCH multicountry case-control study, which estimated that *M tuberculosis* was the cause of severe pneumonia in 5·9% of children.[6,7] The 29% microbiological confirmation rate in the intervention group is consistent with other tuberculosis diagnostic studies in children.[25] Overall, the rate of tuberculosis diagnosis was higher than we originally hypothesised in the control group. Capacity building for the trial might have substantially contributed to increased tuberculosis awareness among clinicians, including in highly skilled tertiary referral hospitals. Additionally, by systematically collecting tuberculosis exposure history and symptoms as part of the standardised data collection for the trial, we might have triggered identification of some presumptive tuberculosis cases that would have been missed under routine conditions.

Differences observed between the intervention and the control groups in terms of time to diagnosis, and yield of tuberculosis diagnosis, were in line with the expected impact mechanisms for our intervention. However, our multivariate analysis showed that these differences were instead related to differences in the proportion of children with severe acute malnutrition between study groups. Children with severe acute malnutrition are particularly susceptible to tuberculosis because they are at high risk of developing disease when infected because of the malnutrition-induced immunodeficiency; tuberculosis symptoms have lower sensitivity and specificity and hence can be difficult to diagnose; and they are at high risk of death due to tuberculosis and malnutrition.[23,26] Reasons explaining the difference between both study groups in terms of malnutrition prevalence are not clear but might include the social effect of the COVID-19 pandemic restrictions, as a large proportion of children in the intervention group were recruited during the acute phase of the pandemic—during the partial lockdowns, when transport was scarce, and when families were affected by the major economic changes. In addition, weight loss, failure to thrive, and ultimately severe acute malnutrition are also known suggestive tuberculosis symptoms that might have contributed to diagnosis in children without typical chronic respiratory symptoms.

Although the study was not powered, and not designed, to compare mortality and tuberculosis diagnosis rates in the intervention and the control groups in children with severe acute malnutrition, detailed outcomes by malnutrition status provide insight into the possible effect of the intervention in this clinically vulnerable group. Mortality and tuberculosis diagnosis rates were globally four to five times higher in children with severe acute malnutrition than in other children. Furthermore, microbiological confirmation nearly tripled with the intervention in the severe acute malnutrition group but did not increase in other children. In children with severe acute malnutrition, mortality rates between the control and intervention phase changed from 24% to 18%, and 15% to 19% for tuberculosis diagnosis rates. In contrast, mortality rates (around 4·5%) and tuberculosis diagnosis rates (around 3·5%) were stable between both phases in children without severe acute malnutrition. This might indicate that the intervention has little effect in the overall paediatric population but could have a strong effect and be very beneficial for children with severe acute malnutrition, which is of major public health importance given the prevalence of this condition in children from low-income and middle-income countries.

Mortality was lower in the study overall than we had hypothesised. Globally, mortality due to pneumonia has

fallen over the past 10–15 years in the context of increased access to pneumococcal conjugate and haemophilus influenzae B vaccines.[4,27] The 7·8% mortality rate in children with severe pneumonia from our study is in line with other data; the 30-day case fatality rate in severe pneumonia in PERCH was 6·4%.[6] Capacity building, which included both the training on the standard of care for severe pneumonia and the supply of oxygen concentrators, might have contributed to the overall lower mortality in the study sites. Death occurred early in our trial with almost a third of deaths occurring within 48 h of inclusion and two-thirds before hospital discharge, consistent with previous studies showing high inpatient case fatality rates in children hospitalised with severe pneumonia.[18] In children with such a severe clinical condition, accurately diagnosing and treating tuberculosis might not be sufficient to prevent early deaths.

Our study has several limitations. First, in some participating hospitals, we were unable to enrol patients with very severe symptoms at early stages due to a challenging enrolment process in intensive care units. This possibly contributed to excluding from the trial children with very severe forms of tuberculosis-associated pneumonia who might have benefited from the intervention. Second, to maximise external validity of our study findings, we selected sites from countries with a wide range of tuberculosis incidences and malnutrition, and HIV prevalence rates. This might have biased our results toward a lower difference than if targeted at settings with higher tuberculosis incidence and malnutrition, and HIV prevalences, such as from Zambia. Third, we were unable to document routine tuberculosis screening and diagnostic practices before our initial capacity building and systematic tuberculosis screening. Fourth, implementation of our trial was severely affected by the COVID-19 pandemic, and the stepped-wedge design led to most of the control periods occurring before the pandemic and most of the intervention periods occurring during the pandemic, which might have worsened unobserved differences hampering the comparability of the trial groups. Fifth, our intervention relies on molecular tests that have imperfect sensitivity to detect culture-confirmed tuberculosis, which in turn is a poorly sensitive reference standard, and did not include other criteria, such as tuberculosis exposure, and clinical and radiological feature. However, we hypothesised that we would increase case-detection of children with high bacillary loads and severe disease. Last, lower mortality in the control group, and lower enrolment than planned per protocol due to the stepped-wedge design, reduced the power of our study to detect an effect if existing. However, we were conservative in estimating our study design effect as compared with previous cluster trials, and the absence of overall difference between study groups did not seem linked to a lack of power.

Although systematic rapid molecular detection for tuberculosis did not lead to decreased mortality when compared with symptom screening and targeted microbiological testing, as recommended by WHO in children with severe pneumonia, the high tuberculosis treatment initiation and microbiological confirmation rate linked to the intervention support the more systematic use of Xpert Ultra testing in children admitted for severe pneumonia, and notably among the group with severe acute malnutrition. The applicability of the intervention is supported by the good feasibility of both nasopharyngeal aspirates and stool collection in this clinically vulnerable child population. Further research is required to integrate this microbiological testing strategy in comprehensive treatment decision algorithms with specific approaches for highly clinically vulnerable groups. Our study results support previous findings on the prevalence of tuberculosis in children admitted with severe pneumonia in countries with high tuberculosis incidence and calls for a paradigm shift in both paediatric tuberculosis and pneumonia guidelines emphasising the importance of tuberculosis as a cause of severe pneumonia and the fact that the presentation of tuberculosis can be more acute in young children.

Contributors

OM, MB, EW conceived and designed the study. AV coordinated and contributed to the development of the trial protocol. OM, MB, EW, HF, LB, CC, CKho, SM, RM, VM, JM-A, J-VT, TEM, CD, JAS, ML, and SMG contributed to the development of the trial protocol. OM, MB, and EW led the study at international level. LB and TEM led the study in Cambodia, J-VT and MB led the study in Cameroon, RM and FADT led the study in Côte d'Ivoire, CKho and SM led the study in Mozambique, EW and JM-A led the study in Uganda, CC and VM led the study in Zambia. AV coordinated study implementation at international level, ML coordinated laboratory aspects at international level, ADL and BD coordinated study implementation in Cambodia, SKN coordinated study implementation in Cameroon, EAK coordinated study implementation in Côte d'Ivoire, SC coordinated study implementation in Mozambique, NN and GB coordinated study implementation in Uganda, PS coordinated study implementation in Zambia. SMG, CD, EM-O, and JAS provided scientific guidance and expertise for the study, through the Scientific Advisory Board. CC, J-VT, VM, JC, DR, BN, UC, ETN, MFA, LC, FATD, GB, PM, AK, CKhe, and SP implemented the study and enrolled participants. HF did the statistical analysis. OM and HF accessed and verified the data, and prepared the report. OM, AV, LB, HF, MB and EW contributed to the interpretation of the results. OM wrote the first draft and all authors reviewed and approved the final version of the report and the manuscript. OM, MB, EW were responsible for the decision to submit the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Study data will not be publicly available. Data could be made available by the sponsor (Inserm) to any researcher interested. Deidentified participant data and a data dictionary can be made available and shared under a data transfer agreement. Requests for access to the TB-Speed Pneumonia study data should be sent to the corresponding author. The study protocol, statistical analysis plan, and informed consent forms are available in appendix 2.

Acknowledgments

Findings from this study were presented at the TBScience-Late Breaker session during the 52nd Union World Conference on Lung Health, that was held virtually on Oct 19–22, 2021, as abstract TBS-LB-05. This study was funded by Unitaid and l'Initiative. Inserm (Pôle de Recherche Clinique), Paris, France, was the sponsor of the trial. We thank the Ministries of Health and National Tuberculosis programmes of

participating countries for their support. We are grateful to the late Laurence Adonis-Koffy for her support throughout the trial and commitment. We thank the members of the independent data monitoring committee, Valeriane Leroy (Chair, Inserm, Toulouse, France), Marion Caseris (Hopital Robert Debré, AP-HP, Paris, France), Andrew Copas (University College London, London, UK), Victor Musiime (Mulago Hospital, Kampala, Uganda) and the other members of the TB-Speed Scientific Advisory Board who gave technical advice on the design of the study and approved the protocol: Anneke Hesseling (Stellenbosch University, Cape Town, South Africa), Luis Cuevas (Liverpool School of Tropical Medicine, Liverpool, UK), Malgorzata Grzemska and Sabine Verkuijl (WHO, Geneva, Switzerland), Philippa Musoke (Makerere University, Kampala, Uganda), Mark Nicol (University of Western Australia, Perth, WA, Australia). We thank all the children and their families who participated to the trial, and the health-care workers of the participating hospitals and laboratories.

References

1 WHO. Global tuberculosis report 2021. Geneva: World Health Organization, 2021.
2 Perez-Velez CM, Marais BJ. Tuberculosis in children. *N Engl J Med* 2012; **367:** 348–61.
3 Dodd PJ, Yuen CM, Sismanidis C, Seddon JA, Jenkins HE. The global burden of tuberculosis mortality in children: a mathematical modelling study. *Lancet Glob Health* 2017; **5:** e898–906.
4 Liu L, Oza S, Hogan D, et al. Global, regional, and national causes of under-5 mortality in 2000–15: an updated systematic analysis with implications for the Sustainable Development Goals. *Lancet* 2016; **388:** 3027–35.
5 Oliwa JN, Karumbi JM, Marais BJ, Madhi SA, Graham SM. Tuberculosis as a cause or comorbidity of childhood pneumonia in tuberculosis-endemic areas: a systematic review. *Lancet Respir Med* 2015; **3:** 235–43.
6 Pneumonia Etiology Research for Child Health (PERCH) Study Group. Causes of severe pneumonia requiring hospital admission in children without HIV infection from Africa and Asia: the PERCH multi-country case-control study. *Lancet* 2019; **394:** 757–79.
7 Seidenberg P, Mwananyanda L, Chipeta J, et al. The etiology of pneumonia in HIV-infected Zambian children: findings from the Pneumonia Etiology Research for Child Health (PERCH) study. *Pediatr Infect Dis J* 2021; **40:** S50–58.
8 WHO. Guidance for national tuberculosis programmes in the management of tuberculosis in children, 2nd edn. Geneva: World Health Organization, 2014.
9 Bates M, Shibemba A, Mudenda V, et al. Burden of respiratory tract infections at post mortem in Zambian children. *BMC Med* 2016; **14:** 99.
10 WHO. WHO consolidated guidelines on tuberculosis: module 3: diagnosis: rapid diagnostics for tuberculosis detection, 2021 update. Geneva: World Health Organization, 2021.
11 WHO. Rapid communication on updated guidance on the management of tuberculosis in children and adolescents. Geneva: World Health Organization, 2021.
12 Oliwa JN, Gathara D, Ogero M, van Hensbroek MB, English M, Van't Hoog A. Diagnostic practices and estimated burden of tuberculosis among children admitted to 13 government hospitals in Kenya: an analysis of two years' routine clinical data. *PLoS One* 2019; **14:** e0221145.
13 Vessière A, Font H, Gabillard D, et al. Impact of systematic early tuberculosis detection using Xpert MTB/RIF Ultra in children with severe pneumonia in high tuberculosis burden countries (TB-Speed pneumonia): a stepped wedge cluster randomized trial. *BMC Pediatr* 2021; **21:** 136.
14 Marcy O, Ung V, Goyet S, et al. Performance of Xpert MTB/RIF and alternative specimen collection methods for the diagnosis of tuberculosis in HIV-infected children. *Clin Infect Dis* 2016; **62:** 1161–68.
15 Lounnas M, Diack A, Nicol MP, et al. Laboratory development of a simple stool sample processing method diagnosis of pediatric tuberculosis using Xpert Ultra. *Tuberculosis (Edinb)* 2020; **125:** 102002.
16 Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US Department of Health and Human Services. Division of AIDS table for grading the severity of adult and pediatric adverse events. Maryland, USA: Division of AIDS, 2017.
17 Ngari MM, Fegan G, Mwangome MK, et al. Mortality after inpatient treatment for severe pneumonia in children: a cohort study. *Paediatr Perinat Epidemiol* 2017; **31:** 233–42.
18 Sutcliffe CG, Thea DM, Seidenberg P, et al. A clinical guidance tool to improve the care of children hospitalized with severe pneumonia in Lusaka, Zambia. *BMC Pediatr* 2016; **16:** 136.
19 Hemming K, Taljaard M. Sample size calculations for stepped wedge and cluster randomised trials: a unified approach. *J Clin Epidemiol* 2016; **69:** 137–46.
20 Hussey MA, Hughes JP. Design and analysis of stepped wedge cluster randomized trials. *Contemp Clin Trials* 2007; **28:** 182–91.
21 Constable L, Davidson T, Breeman S, et al. How to deal with a temporary suspension and restarting your trial: our experiences and lessons learnt. *Trials* 2020; **21:** 765.
22 Hemming K, Taljaard M, Forbes A. Analysis of cluster randomised stepped wedge trials with repeated cross-sectional samples. *Trials* 2017; **18:** 101.
23 Vonasek BJ, Radtke KK, Vaz P, et al. Tuberculosis in children with severe acute malnutrition. *Expert Rev Respir Med* 2022; **16:** 273–84.
24 Song R, Click ES, McCarthy KD, et al. Sensitive and feasible specimen collection and testing strategies for diagnosing tuberculosis in young children. *JAMA Pediatr* 2021; **175:** e206069.
25 Zar HJ, Workman LJ, Prins M, et al. Tuberculosis diagnosis in children using Xpert Ultra on different respiratory specimens. *Am J Respir Crit Care Med* 2019; **200:** 1531–38.
26 Chisti MJ, Salam MA, Shahid ASMSB, et al. Diagnosis of tuberculosis following World Health Organization-recommended criteria in severely malnourished children presenting with pneumonia. *Glob Pediatr Health* 2017; **4:** X16686871.
27 Liu L, Villavicencio F, Yeung D, et al. National, regional, and global causes of mortality in 5–19-year-olds from 2000 to 2019: a systematic analysis. *Lancet Glob Health* 2022; **10:** e337–47.