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Designing a community intervention for tuberculosis household child contact management and assessing the feasibility of its evaluation in Cameroon and Uganda

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THÈSE POUR OBTENIR LE GRADE DE DOCTEUR DE L'UNIVERSITÉ DE MONTPELLIER

En Biologie de la Santé
École doctorale CBS2
Unité de recherche UMI 233 TransVIHMI

Designing a community intervention for tuberculosis household child contact management and assessing the feasibility of its evaluation in Cameroon and Uganda

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Le 08 décembre 2021**

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Abbreviations

BCG	Bacille Calmette Guerin
CAD	Computer Aided Detection
CaP TB	Catalyzing Pediatric Tuberculosis Innovations
CFU	Colony Forming Units
CHW	Community Health Worker
CI	Confidence Interval
CXR	Chest X-Ray
DALY	Disability Adjusted Life Year
DOTS	Directly observed treatment, short course
E	Ethambutol
EGPAF	Elizabeth Glaser Pediatric AIDS Foundation
FDC	Fixed Dose Combination
FGD	Focus Group Discussion
FUN	France Université Numérique
GDG	Guideline Development Group
H	Isoniazid
HIV	Human Immunodeficiency Virus
IDI	In-depth Interview
IFN- γ	Interferon gamma
IGRA	Interferon Gamma Release Assay
LAM	Lipoarabinomannan
LJ	Lowenstein Jensen
LOD	Limit of Detection
LTBI	Latent Tuberculosis Infection
MDR	Multi Drug Resistant
MGIT	Mycobacteria Growth Indicator Tube
MOOC	Massive Open Online Course
MRC	Medical Research Council
NTM	Non-tuberculous Mycobacteria
NTP	National Tuberculosis Program
PABAK	Prevalence Adjusted Bias Adjusted Kappa
PCR	Polymerase Chain Reaction

PHC	Primary healthcare
POC	Point of Care
R	Rifampicin
RA	Research Assistant
RCT	Randomized Clinical Trial
SAC	Scientific Advisory Committee
SOP	Standardized Operating Procedure
TB	Tuberculosis
TFP	Tuberculosis Focal Person
ToC	Theory of Change
TPT	Tuberculosis Preventive Therapy
TST	Tuberculin Skin Test
UN	United Nations
WHO	World Health Organization
Z	Pyrazinamide

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Résumé long

Introduction

La tuberculose (TB) est une maladie infectieuse causée par *Mycobacterium tuberculosis* qui se transmet par voie aérienne, avec un tropisme particulier pour le poumon. Après une phase d'infection, le risque de développer la maladie est le plus élevé dans la première année qui suit l'exposition et chez les enfants en bas âge ou les personnes immunodéprimées.

L'organisation mondiale de la santé (OMS) estime que 10 millions de personnes ont été malades de TB en 2019. Les enfants représentent 15 à 20 % des cas de TB dans les pays à forte prévalence mais beaucoup ne sont pas traités, notamment les enfants de moins de 5 ans en raison des difficultés de diagnostic de la TB chez l'enfant et de l'absence de dépistage systématique de la TB bien que recommandé par l'OMS, notamment chez les enfants de moins de 5 ans ou VIH-positifs vivant dans le foyer d'une personne malade. En effet, lorsque les enfants sont exposés à la TB dans leur foyer, il est demandé aux parents de les ramener au centre de santé pour un dépistage de la TB. Après avoir écarté une TB maladie, un traitement préventif de la tuberculose (TPT) est proposé pour les enfants, avec une priorité donnée aux enfants de moins de 5 ans et à ceux vivant avec le VIH, quel que soit leur âge. Dans les pays à forte endémie, un des obstacles majeurs à cette approche, est que les parents n'amènent pas leurs enfants au centre de santé en raison du coût du transport, de problèmes de stigma éventuels, et d'incompréhension voire d'autres priorités des parents, quand les enfants sont bien portants, ce qui est le cas de la plupart des enfants contact. Ceci ne permet pas d'identifier les enfants au stade précoce de la maladie et de prévenir la maladie chez ceux qui sont infectés.

Une approche communautaire qui permettrait le dépistage des enfants contacts au sein du foyer avec la référence des enfants chez qui il y a une suspicion clinique de tuberculose maladie vers le centre de santé et l'initiation de la TPT chez ceux qui n'ont pas de symptômes évocateurs de la TB pourraient répondre à cette problématique et améliorer la prise en charge de ces populations vulnérables dans les pays à forte endémie. C'est ce que propose d'évaluer l'essai CONTACT au Cameroun et en Ouganda. Pour mettre en œuvre une intervention communautaire complexe, il est important de s'assurer des certains critères de faisabilité, des conditions de sa mise en œuvre pour en assurer une bonne acceptabilité et réalisabilité et des méthodes d'évaluation de son efficacité. Ce travail doctoral couvre ces différents aspects avec comme objectif principal le développement de l'intervention communautaire et l'évaluation de la faisabilité de l'étude qui teste l'efficacité de cette intervention. Les objectifs spécifiques se déclinent en 1) la revue des preuves existantes pour l'utilisation au niveau communautaire d'un outil symptomatique simplifié pour le dépistage de la TB chez les enfants contacts ; 2) le

développement de l'intervention et l'écriture du protocole d'étude ; et 3) l'évaluation de la faisabilité de l'étude qui teste l'efficacité de l'intervention communautaire.

Etudes

Article 1 : Dépistage de la TB basé sur les symptômes versus la radiographie pulmonaire pour les enfants contact : revue systématique et méta-analyse

Une étape incontournable avant l'initiation du TPT est l'exclusion de la TB maladie. Les outils pour exclure la maladie chez les enfants contact sont principalement le dépistage des symptômes et la radiographie thoracique. Le dépistage des symptômes de la tuberculose tel que proposé par l'OMS sur les symptômes évocateurs de tuberculose tels que : toux > 2 semaines, fièvre persistante, perte de poids sur les 3 derniers mois, sueurs nocturnes, manque d'appétit, perte d'enjouement. La radiographie thoracique est difficile à obtenir dans beaucoup de centres de santé des pays à ressources limitées en raison de son absence ou du coût. De plus, outre des problèmes de qualité son interprétation notamment chez les enfants est difficile et peu de cliniciens sont formés à l'interprétation de la radiographie thoracique de l'enfant dans les pays à haute prévalence de TB. Dans le contexte d'un accès limité à la radiographie, l'OMS ne recommande pas systématiquement la radiographie thoracique pour exclure la tuberculose avant l'initiation du TPT chez les enfants contacts à haut risque (< 5 ans et 5-15 ans séropositifs) et recommande l'utilisation d'un dépistage symptomatique. Seul ce type de dépistage pourrait être utilisé dans une approche communautaire mais il n'y a pas de revue systématique sur l'efficacité du dépistage symptomatique. Nous avons réalisé une revue systématique ayant pour objectif de comparer le dépistage symptomatique à la radiographie thoracique chez les enfants contacts dans les pays à ressources limitées. L'analyse a été réalisée par groupes d'âge (0-4 ans et 5-14 ans) en incluant dans la méta-analyse des études avec une double lecture de la radiographie thoracique et des définitions similaires d'une radiographie thoracique suggestive de TB. La concordance a été analysée en utilisant le PABAK (prevalence adjusted bias adjusted kappa), la valeur 0 représentant un désaccord total et la valeur 1, un accord parfait entre les deux tests. Le risque de biais a été évalué avec l'outil QUADAS-2.

Le PABAK de concordance entre le dépistage symptomatique et la radiographie pulmonaire varie entre 0,09 et 0,97 chez les enfants de moins de 5 ans et chez les enfants de 5 à 14 ans, entre 0,22 et 0,98. La valeur prédictive négative combinée des études incluses est de 98.7% (95% intervalle de confiance (IC) [96.9–99.8]) pour les enfants de moins de 5 ans et 98.1% (95% IC [93.8–100]) pour les enfants de 5-14 ans. Pour les études avec une double lecture de la radiographie pulmonaire et des définitions similaires de radiographie suggérant une TB, la

valeur prédictive négative combinée était de 99,3% (95% IC [97,5-100,0]) pour les enfants de moins de 5 ans. Cinq des 10 études incluses ont rapporté la proportion d'enfants asymptomatiques qui ont développé une TB en cours de suivi. Chez les enfants contacts de moins de 5 ans, 0 à 2 % des enfants ont développé une maladie tuberculeuse et 0 à 20,6 % chez les enfants de 5 à 14 ans. Il y avait une hétérogénéité dans les études incluses en raison des différentes définitions de la radiographie et des symptômes utilisés pour le dépistage.

Ces résultats soutiennent les recommandations de l'OMS pour les enfants de moins de 5 ans et suggèrent en outre que le dépistage basé sur les symptômes soit utilisé dans des modèles de soins alternatifs tels que le dépistage communautaire des contacts et la dispensation du TPT, réduisant le fardeau de la tuberculose dans les pays à faibles ressources. Ils montrent aussi le manque de données chez les enfants plus âgés, nécessitant des études supplémentaires avant de pouvoir recommander le dépistage symptomatique chez les enfants > 5 ans VIH-négatifs.

Le travail du doctorant a consisté à écrire le protocole de revue systématique, le déposer dans un registre en ligne (PROSPERO) et avec un autre auteur de la revue faire la recherche des articles éligibles et contacter les auteurs des articles pour extraire les données. Le doctorant a réalisé la méta-analyse en utilisant le logiciel R et a écrit l'article de la revue systématique.

Article 2 : Intervention communautaire pour le dépistage et traitement préventif de la TB chez les des enfants contacts : protocole d'étude pour un essai contrôlé randomisé parallèle en grappes

L'étude CONTACT est un essai contrôlé randomisé en grappes au Cameroun et en Ouganda. Cette étude fait partie d'un grand projet d'implémentation, nommé CaP TB, financé par Unitaid. L'objectif principal de l'étude CONTACT est de comparer une intervention communautaire de dépistage de la TB et dispensation du TPT chez les enfants contacts avec le standard des soins. Vingt grappes (centres de santé ou groupement de centre de santé avec diagnostic et traitement de la TB au sein du projet CaP TB) sont randomisées entre les 2 modèles de soins avec une stratification sur le pays. La taille d'échantillon est de 1500 enfants éligibles au TPT. Le critère de jugement principal est représenté par les enfants en dessous de 5 ans ou 5-14 ans porteurs du VIH déclarés par les cas index de TB.

L'étude se décline en trois phases : phase initiale, phase d'intervention et phase d'évaluation.

La phase initiale est dédiée à l'évaluation de la faisabilité de l'intervention communautaire et collecte des informations de base sur les sites d'intervention. L'inclusion et le suivi des participants se déroulent pendant la phase d'intervention. La phase d'évaluation comprend l'analyse des résultats de l'essai, l'analyse coût-efficacité et l'évaluation de l'acceptabilité et

des processus de mise en œuvre de l'intervention.

Dans le modèle de standard de soins, les enfants sont dépistés au niveau du centre de santé (Cameroun et Ouganda) ou du foyer (Ouganda) par le point focal TB du centre de santé. L'initiation et la dispensation du TPT durant le suivi sont effectués au niveau du centre de santé par le point focal TB.

Dans le groupe d'intervention (modèle communautaire), les enfants contact sont examinés dans le ménage par un agent de santé communautaire (ASC). Les contacts présentant des symptômes évocateurs de TB sont référés au centre de santé pour des investigations diagnostiques de la TB. Les contacts présentant des symptômes non évocateurs de TB sont réévalués après deux semaines. Les enfants contact asymptomatiques issus de groupes à haut risque (< 5 ans ou infectés par le VIH de 5-14 ans) sont mis sous traitement préventif dans le ménage. La dispensation de TPT est effectuée dans les communautés par l'ASC. Les symptômes de la tuberculose, l'observance du TPT et la tolérance sont évalués à chaque visite de suivi et en cas de suspicion de TB ou de mauvaise tolérance, l'enfant est référé au centre de santé pour évaluation.

Le régime de TPT utilisé dans les 2 modèles de soin est le régime de 3 mois d'isoniazide-rifampicine ou 6 mois d'isoniazide pour les enfants VIH-positifs.

Le travail du doctorant a consisté à rechercher dans la littérature et en interaction avec l'équipe méthodologique et le conseil scientifique de l'essai, la méthodologie la mieux adaptée à l'évaluation de cette approche communautaire, aboutissant à l'écriture et la publication du protocole de l'essai.

Article 3 : Faisabilité d'une intervention communautaire pour le dépistage de la TB et le traitement préventif chez les enfants contacts et de son évaluation dans un essai pragmatique au Cameroun et en Ouganda

Les études de faisabilité sont utilisées pour estimer les paramètres nécessaires à la conception de l'étude principale. Une intervention communautaire pour le dépistage de la TB et le traitement préventif des enfants contacts est une intervention complexe car elle est composée de plusieurs activités effectués par du personnel soignant et communautaire, dans des contextes locaux différents. Il est important d'évaluer la faisabilité d'une telle intervention avant sa mise en œuvre.

L'objectif de cette étude est d'évaluer la faisabilité d'une intervention à base communautaire pour le dépistage de la TB chez les enfants contacts et le traitement préventif des enfants asymptomatiques au sein du foyer et les conditions de son évaluation dans un essai randomisé en grappes pragmatique (étude CONTACT) dans deux pays à forte charge et à ressources limitées, le Cameroun et l'Ouganda.

Pour évaluer la faisabilité nous avons utilisé des méthodes mixtes en nous basant sur un modèle adapté dans la littérature. Nous avons évalué trois dimensions de la faisabilité : 1) Capacité de recrutement des sites de l'étude ; 2) Acceptabilité de l'intervention par les bénéficiaires et les prestataires ; 3) Adaptation, intégration et ressources pour la mise en œuvre de l'étude CONTACT. La capacité de recrutement a été évaluée par une cohorte rétrospective des patients TB enregistrés dans les registres TB des sites d'étude l'année avant le début des inclusions. L'acceptabilité pré-intervention a été évaluée par des discussions de groupe avec les patients TB et des entretiens semi-dirigés avec des soignants, des ASC et des membres de la communauté. Le besoin d'adaptation a été évalué par un questionnaire du personnel de santé et du projet CaP TB sur les pratiques TB de routine dans chaque centre, l'intégrations avec les services VIH et les systèmes de référence entre centres de santé.

Nos résultats ont montré qu'une intervention communautaire était considérée acceptable par les patients TB, les soignants et les représentants de la communauté mais a surtout permis d'ajuster l'intervention au contexte local et de définir les conditions de sa mise en œuvre, notamment en ce qui concerne la sélection et formation des agents communautaires, l'approche des familles et la préparation des visites. Les données de la cohorte rétrospective et la revue de la fiabilité des données collectées nous ont rassuré sur les capacités de recrutement et la possibilité d'utiliser les registres nationaux comme documents source pour l'essai. L'évaluation des pratiques via l'enquête transversale a permis d'intégrer au mieux les outils de l'étude dans l'organisation du système de santé.

Les résultats qualitatifs et quantitatifs ont permis à l'équipe de prendre des décisions opérationnelles importantes concernant la mise en œuvre de l'étude CONTACT.

Le travail du doctorant a consisté à analyser les données de la cohorte rétrospective et de l'enquête transversale des pratiques TB ; à conduire des discussions de l'enquête qualitative, coder les données et réaliser l'analyse. Les discussions avec les partenaires clés et la revue de la littérature ont permis au doctorant d'intégrer ces résultats pour analyser la faisabilité de l'étude CONTACT. Le doctorant a écrit l'article communiquant l'évaluation de la faisabilité.

Discussion

La revue systématique a confirmé la possibilité d'utiliser un outil simple de dépistage symptomatique dans l'étude CONTACT au niveau communautaire. Le dépistage des symptômes conçu pour l'étude CONTACT est basé sur celui proposé par l'OMS et mis en forme d'une simple liste avec des cases à cocher, facile à utiliser pour les ASC.

Le caractère pragmatique de l'étude permet l'évaluation de l'intervention en situation réelle et sa mise en œuvre rapide dans un contexte programmatique par la suite. Le choix de deux contextes différents en Afrique subsaharienne augmente la représentativité et la généralisation

des résultats de l'étude, néanmoins, il apporte également le défi d'une organisation différente des services de lutte contre la tuberculose et le besoin d'adaptation au contexte local. Les résultats de l'étude de faisabilité ont été essentiels à la mise en œuvre de l'étude CONTACT. L'évaluation qualitative a apporté des éléments importants à l'acceptabilité de l'intervention par les bénéficiaires et par les soignants et les membres de la communauté, comme la préparation de la visite, la communication et le respect de la confidentialité. En outre, la sélection, la formation et la motivation des ASC sont des éléments clés de la faisabilité de l'intervention communautaire.

Pendant l'implémentation de l'essai, l'équipe a rencontré plusieurs défis en lien avec la recherche, l'intervention et la pandémie COVID-19. Les défis en lien avec la recherche concernent principalement les amendements au protocole dues au changement du contexte local. Les défis en lien avec l'intervention sont causés principalement par des limites des systèmes de santé comme les délais d'acheminement des médicaments TB pour les adultes ou le personnel qui change régulièrement dans les centres de santé. Les défis en lien avec le COVID-19 affectent principalement les inclusions dans l'étude, soit car les cas index consultent moins, soit parce qu'ils ne vivent plus avec leurs enfants, la présence des enfants dans le foyer étant un critère d'inclusion. En outre, les moyens diagnostiques de la TB ont été parfois déviés vers le diagnostic COVID et les mesures alternatives de suivi en distanciel et dispensation des TPT pendant les périodes de confinement ont affecté la mise en œuvre des modèles de soin durant cette période.

L'étude CONTACT est en passe d'achever ses inclusions (décembre 2021). A la suite des inclusions, une analyse coût-efficacité et une évaluation des processus seront réalisées ayant pour but d'enrichir les conclusions de l'analyse principale.

Les résultats de l'étude CONTACT seront potentiellement utilisés pour formuler des nouvelles recommandations sur le dépistage de la TB chez les enfants contacts et leur initiation au TPT ayant pour but à long terme de diminuer le fardeau de la TB pédiatrique dans les pays à ressources limitées. Le modèle communautaire en cours d'évaluation et les premiers retours d'expérience ont été partagés avec l'OMS pour le manuel opérationnel d'implémentation qui accompagne la révision du guide pédiatrique en cours de finalisation.

Abstract

The World Health Organization estimates that 10 million people had tuberculosis (TB) in 2019. Children are estimated to represent 15-20% of TB cases in high-prevalence countries but many go untreated, especially children under 5 years of age, due to difficulties in diagnosing TB in young children and poor implementation of routine TB screening in contact children. When children are exposed to TB in their homes, parents are asked to take them to a health center for TB testing. After ruling out TB, preventive tuberculosis treatment (TPT) is offered for children at high risk of developing severe forms, such as children under 5 or children living with HIV, regardless of their age. Many exposed children go undetected due to barriers such as cost of transport, other competing priorities, especially when children are well, and lack of communication between health workers and TB patients.

My PhD thesis focuses on the design of a community-based approach for TB screening and TPT dispensing in contact children and on the conditions for its evaluation in the context of an international comparative study in two countries with a high prevalence of TB. and resource-poor sub-Saharan Africa, Cameroon and Uganda.

We first confirmed the possibility of using a simplified symptom screening tool for the exclusion of TB before TPT initiation. I performed a systematic review and meta-analysis comparing symptomatic screening with radiological screening in contact children in resource-limited settings. The combined negative predictive value of the included studies is 98.7% (96.9–99.8) for children under 5 years and 98.1% (93.8–100) for children 5-14 years. These results confirmed our choice of a simple symptomatic screening tool at the community level. We developed the research protocol for a randomized controlled trial in clusters including a total of 20 clusters (health centers or hospitals and their catchment area) distributed between the 2 countries, the main objective of which was to compare the community intervention for TB contact investigation and TPT management with the standard of care. The sample size is 1,500 children eligible for TPT. The project is composed of three phases: initial phase, intervention phase and evaluation phase.

During the initial phase of the project, we carried out a feasibility study to assess (1) the recruitment capacity into the study by a retrospective cohort, (2) the acceptability of the community intervention by TB patients, caregivers and community representatives through focus group discussions and in-depth interviews and (3) the adaptation and integration of study tools and procedures into existing TB services through a cross-sectional survey. Our results showed that a community intervention was considered acceptable by TB patients, caregivers and community representatives, made it possible to adjust the intervention to the local context and define the conditions for its implementation. In particular, we identified key elements like

the selection and training of community health workers, ways of approaching families and visit preparation. The data from the retrospective cohort and the register checks reassured us about the recruitment capacity and the possibility of using the national registers as source documents for the study. The evaluation of TB services via the cross-sectional survey made it possible to better integrate the tools of the study into the organization of the local health system.

This preliminary work enabled the implementation of the trial which began in October 2019.

Résumé

L'organisation mondiale de la santé estime que 10 millions de personnes ont été malades de tuberculose (TB) en 2019. Les enfants représentent 15 à 20 % des cas de TB dans les pays à forte prévalence mais beaucoup ne sont pas traités, notamment les enfants de moins de 5 ans, en raison des difficultés du diagnostic de la TB chez les jeunes enfants et d'une faible mise en œuvre du dépistage systématique de la TB chez les enfants vivant au contact d'un adulte. Lorsque les enfants sont exposés à la TB dans leur foyer, il est demandé aux parents de les amener vers un centre de santé pour un dépistage de la TB. Après avoir écarté une TB, un traitement préventif de la tuberculose (TPT) est proposé pour les enfants à haut risque de développer des formes graves, comme les enfants de moins de 5 ans ou les enfants vivant avec le VIH, quel que soit leur âge. Des nombreux enfants exposés ne sont pas dépistés en raison d'obstacles tels que le coût de transport, d'autres priorités des parents, notamment quand les enfants sont bien portants, et le manque de communication entre le personnel de santé et les patients.

Mon travail doctoral a porté sur le développement d'une approche communautaire de dépistage de la TB et dispensation du TPT chez les enfants contacts et sur les conditions de son évaluation dans le cadre d'une étude comparative internationale dans deux pays à forte prévalence de TB et à faibles ressources d'Afrique subsaharienne, le Cameroun et l'Ouganda.

Dans un premier temps, nous avons confirmé les possibilités d'utilisation d'un outil simplifié de dépistage des symptômes pour l'exclusion de la TB. J'ai réalisé une revue systématique et une méta-analyse comparant le dépistage symptomatique avec un dépistage radiologique chez les enfants contact dans des pays à ressources limitées. La valeur prédictive négative combinée des études incluses est de 98.7% (96.9–99.8) pour les enfants de moins de 5 ans et 98.1% (93.8–100) pour les enfants de 5-14 ans. Ces résultats nous ont conforté dans le choix d'un outil simple de dépistage symptomatique au niveau communautaire.

Nous avons développé le protocole de recherche pour un essai contrôlé randomisé en grappes avec un total de 20 grappes (centres de santé ou hôpitaux et leur population) distribués entre les 2 pays, dont l'objectif principal était de comparer l'intervention communautaire de dépistage de la TB et dispensation du TPT avec le standard des soins. La taille d'échantillon est de 1500 enfants éligibles au TPT. Le projet se décline en trois phases : phase initiale, phase d'intervention et phase d'évaluation.

Durant la phase initiale du projet, nous avons réalisé une étude de faisabilité afin d'évaluer (1) la capacité de recrutement dans l'étude par une cohorte rétrospective, (2) l'acceptabilité de

l'intervention communautaire par les patients TB, les soignants et les représentants de la communauté par des discussions de groupe et des entretiens semi-dirigés et (3) la nécessité d'adapter et d'intégrer les outils et procédures d'étude dans les services TB existants par une enquête transversale. Nos résultats ont montré qu'une intervention communautaire était considérée acceptable par les patients TB, les soignants et les représentants de la communauté mais a surtout permis d'ajuster l'intervention au contexte local et de définir les conditions de sa mise en œuvre, notamment en ce qui concerne la sélection et formation des agents communautaires, l'approche des familles et la préparation des visites. Les données de la cohorte rétrospective et la revue de la fiabilité des données collectées nous ont rassuré sur les capacités de recrutement et la possibilité d'utiliser les registres nationaux comme documents source pour l'essai. L'évaluation des pratiques via l'enquête transversale a permis d'intégrer au mieux les outils de l'étude dans l'organisation du système de santé.

Ce travail préliminaire a permis la mise en œuvre de l'essai qui a débuté en octobre 2019.

1. Introduction

1.1. Tuberculosis

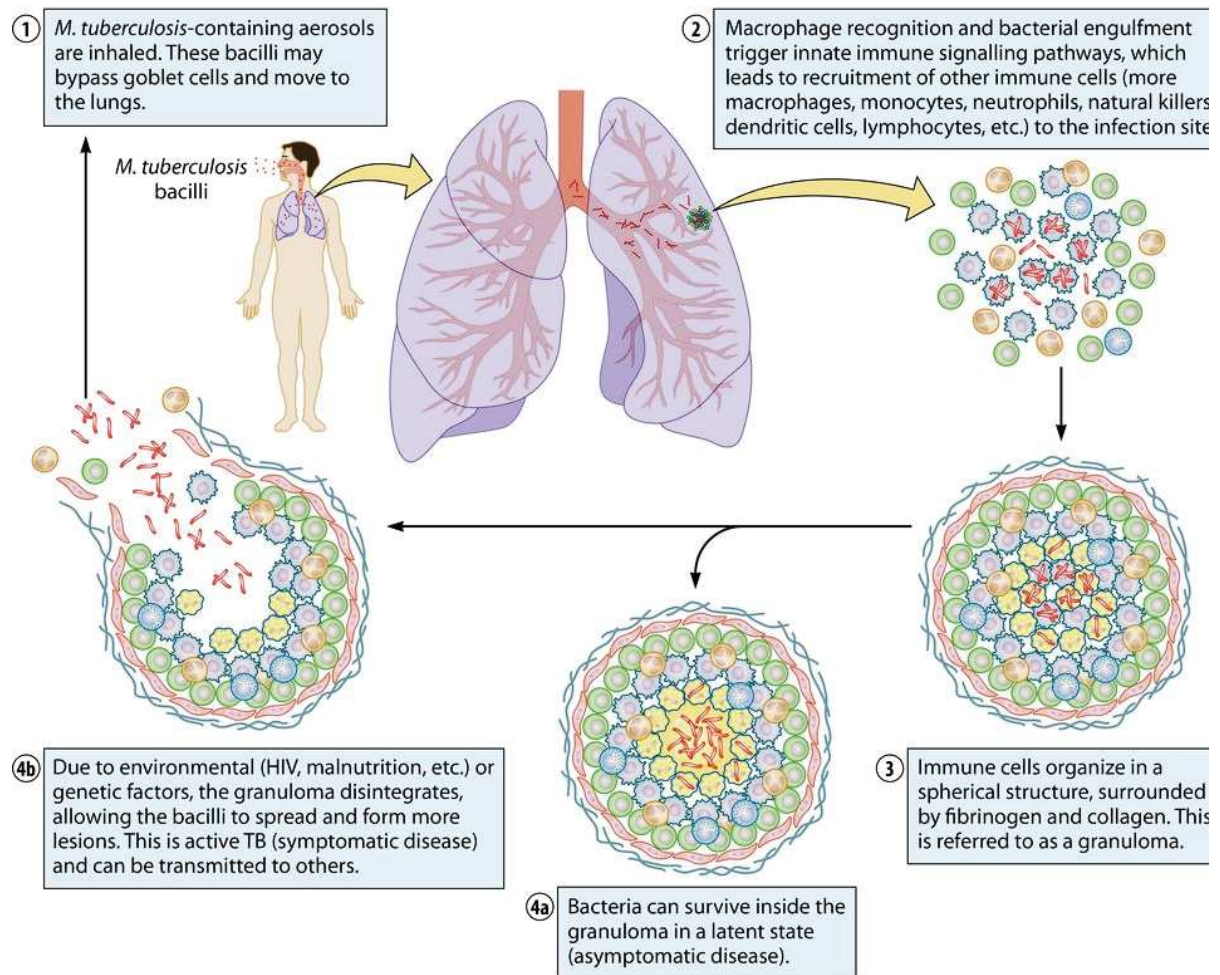
Tuberculosis (TB) is an airborne infectious disease caused by *Mycobacterium (M) tuberculosis*, a pathogen in the *M. tuberculosis* complex that also contains closely related species, such as *M bovis*, which mainly infect animals, and *M africanum*, mainly prevalent in West Africa(1). TB is one of the oldest infectious diseases known to man since prehistoric times(2).

1.1.1. Pathophysiology of tuberculosis transmission

TB transmission occurs when a person with TB disease releases the bacilli droplets in the air, mainly through coughing, but speaking, singing, or spitting could contribute to transmission as well. These droplets travel through the respiratory tract, where most of the bacilli become trapped by mucus-secreting goblet cells, which usually block entry and remove foreign entities. In some cases, however, these droplets can bypass this first-line defense system, allowing them to reach the upper, more oxygenated parts of the lungs. At this point during infection, the host's innate immune mechanisms come into action, and alveolar macrophages phagocytose the infecting bacilli and attempt to destroy them using various proteolytic enzymes and cytokines released by dendritic cells (TNF, IL-1, IL-12). This reaction signals T lymphocyte transfer to the infected area, initiating a cell-mediated immune response, which may either eliminate the infecting organism or result in granuloma formation(3). This initial immune process continues for 2 to 12 weeks; the microorganisms continue to grow until they reach sufficient numbers to fully elicit the cell-mediated immune response, which can be detected by a skin test.

A granuloma is a formation specific to pulmonary TB and can be defined as a mass of immune cells (macrophages, dendritic cells, monocytes, neutrophils, natural killer cells, etc.) aimed at restricting microbial spread. As the granuloma develops, macrophages differentiate resulting in a stratified structure with a layer of lymphocytes aggregated outside a fibrous layer(4). This represents a stable granuloma which, although unable to eliminate the germs, suppresses progression to active disease in immunocompetent individuals. However, *M. tuberculosis* still proliferates in these lesions as the bacilli avoid death by modulating the host immune system. This process creates a favorable environment within the granulomas for the bacilli to persist in a nonreplicating or slowly replicating state, where they may survive for decades(5). The granuloma illustrates the duality of *M. tuberculosis* infection: from the host's perspective, the granuloma is a bacterial restriction, with the potential to contain the infection from the rest of the body; however, from the bacterial perspective, it is a growing collection of cells to infect and replicate within(6). Some granulomas show an increased accumulation of caseum in their

center, subsequently losing the rigid integrity and rupturing due to necrosis, not only releasing the contagious bacteria but also forming a cavity in the airway wall, contributing to the lung damage observed in TB patients



Following *M. tuberculosis* infection, the bacilli reach the lungs (step 1), provoking a host immune response (step 2). This in turn leads to granuloma formation (step 3), which typically suppresses the infection in its latent state (step 4a). However, reactivation can occur, resulting in active disease which can spread to other individuals (step 4b).

Figure 1. The pathophysiology of M. tuberculosis infection

Source: Luies, *Clin Microbiol Rev*, 2020 (4)

Some of the people presenting granulomas will eventually progress and develop active pulmonary disease, which can lead to the release of *M. tuberculosis* from granulomas that have eroded into the airways. This progression can take place in weeks or in decades and for factors that are not clearly identified. HIV coinfection is considered the primary cause of TB activation, other conditions, such as malnutrition, chronic renal failure, uncontrolled diabetes mellitus, sepsis, malignancy, chemotherapy, uncontrolled alcohol use, smoking, drug

addiction, and the immunosuppressive medication administered following organ transplants, may also trigger disease conversion(3,6). If discharge is disseminated into the vascular system, the person will likely develop extrapulmonary tuberculosis. The risk of getting extrapulmonary tuberculosis increases with immunodeficiency. The most serious location is the central nervous system, where infection may result in meningitis. If not treated, tubercular meningitis is fatal in most cases. Bacilli can also drain into the lymphatic system and collect in the tracheobronchial lymph nodes of the affected lung(3).

There are some particularities of disease pathophysiology in children(7). First of all, the macrophages, which are the first line of cells to encounter the bacilli, have diminished chemotaxis(8) and reduced numbers(9), therefore they don't act as efficiently in phagocytosing the bacilli as they do in adults. Furthermore, the dendritic cells, which are the main producers of cytokines, have low numbers and diminished capacity to produce TNF, IL-1 and IL-12(10). These molecules are highly involved in recruiting T cells and their low numbers implicitly signal low activation for T cells transfer to the infected tissue(11). The adaptative immune response is also delayed in children, further diminishing the immune response to *M. tuberculosis*(12). Due to these factors, children don't form effective granulomas that contain the infection and they progress often towards TB disease. Progression to disease is determined, among other factors, by age, and very young children are prone to disease with severe manifestations and complications.

There is a new paradigm for a dynamic continuum of *M. tuberculosis* infection which suggests that additional stages of infection can be defined between latent infection and TB disease. This new paradigm especially applies to children. The different definitions proposed by Drain et al. are presented below(13):

Eliminated TB infection corresponds to prior exposure to *M. tuberculosis*, which either has been cleared by innate or acquired immune responses or has been cured of the infection with tuberculosis preventive treatment (TPT). This individual no longer has viable *M. tuberculosis* bacilli but may still have immunological evidence of prior infection.

Latent TB infection (LTBI) is an infection with viable *M. tuberculosis* for which progression to TB disease is not expected to occur in the near future in the absence of any important immunological deficiency.

Incipient TB infection is an infection with viable *M. tuberculosis* bacteria that is likely to progress to active disease in the absence of further intervention but has not yet resulted in clinical symptoms, radiographic abnormalities, or microbiologic evidence consistent with TB disease.

Subclinical TB disease is disease due to viable *M. tuberculosis* bacteria that do not cause clinical TB-related symptoms but causes other abnormalities that can be detected using

existing radiologic or microbiologic assays.

TB disease is disease due to viable *M. tuberculosis* that causes clinical symptoms with radiographic abnormalities or microbiologic evidence consistent with TB disease.

Following the establishment of latent infection, the pathways by which disease may naturally progress include: latency (the most common course, which encompasses persistent or eliminated disease burden), rapid or slow progression through incipient and subclinical disease to TB disease, or a period of cycling through incipient and subclinical states that may precede the development of symptomatic disease or eventual disease resolution(13) (Figure 2).

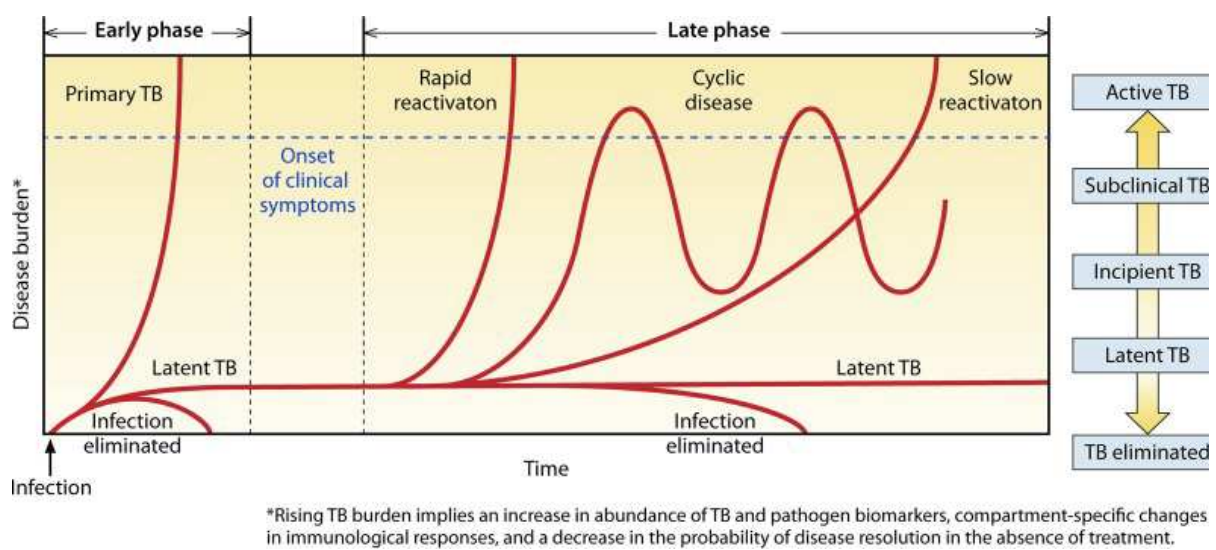


Figure 2. Pathways of tuberculosis disease progression

Source : Drain et al., *Clin Microbiol Rev*, 2018 (13)

TB disease in young children is usually the result of the rapid progression of a recent infection often following TB exposure in the household(14). Identifying tuberculosis exposure and infection is particularly urgent in young children as they are at high risk for infection once exposed, and for progression to disease, once infected. A recent meta-analysis reported that around 35% of household child contacts aged less than 5 years will be infected and 10% will have TB disease at the time of screening(15). A study from Guinea Bissau reported an increase in overall child mortality in households with a TB case compared to households in the same community without a TB case, and that increased risk of mortality was particularly marked (eight-fold increase) if the TB case was the child's mother(16). Contact tracing for children in high-burden settings is able to identify a large number of TB cases, and potentially reduce TB related mortality in children(17). Contact screening allows also for the identification of children with LTBI who could receive a preventive therapy to reduce their risk of developing TB disease.

1.1.2. Epidemiology and global tuberculosis policy

The World Health Organization (WHO) estimates there are 10 million (95% confidence intervals (CI) [8.9-11 million]) people who suffered from TB in 2019, which is equivalent to 130 cases (95% CI [116-143]) per 100,000 population. Out of these estimates, 44% of cases occurred in South-East Asia, 25% in Africa, 18% in the Western Pacific, 8.2% in Eastern Mediterranean, 2.9% in the Americas and 2.5% in Europe (see Figure 3). The burden and severity of the TB epidemic vary widely around the world and 30 countries account for 86% of the TB incidence worldwide(18).

Multi-drug resistant (MDR) TB, which is defined by the resistance to two main antituberculosis drugs (rifampicin and isoniazid), is estimated to represent 3.3% (95% CI [2.3–4.3%]) of new TB cases and 18% (95% CI [9.7–27%]) of previously treated cases and isoniazid resistance is estimated to occur in 13.1% (95% CI [9.9–16.9%]) of new cases and 17.4% (95% CI [0.5–54%]) of previously treated cases.

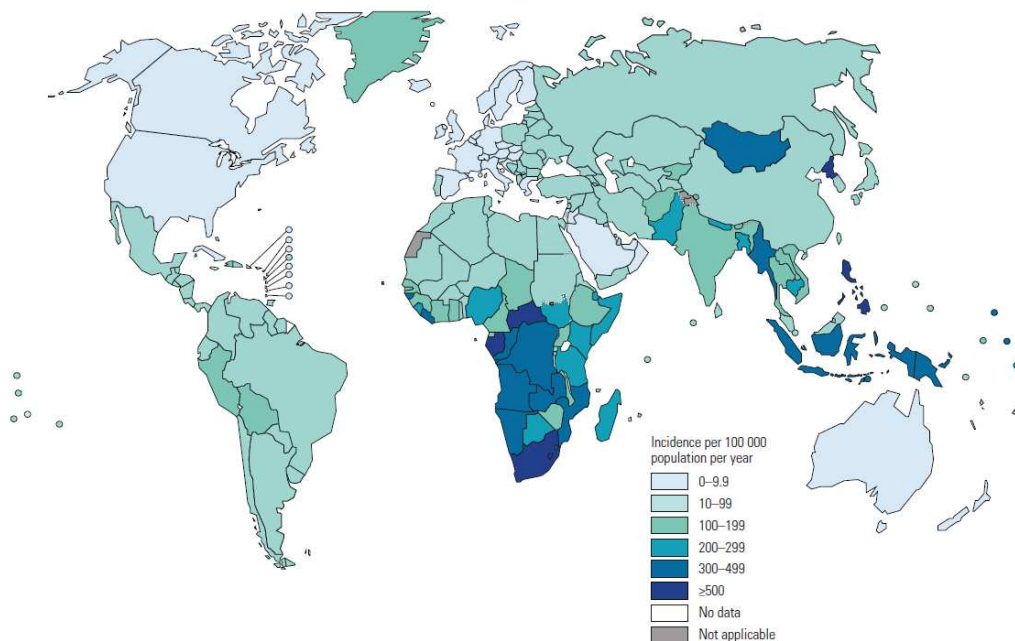


Figure 3. Estimated TB incidence rates, 2019.

Source: WHO Global Tuberculosis Report, 2020(18)

Most of the TB cases occur in men (56%), whereas women account for 36% of cases and children for 12% of cases globally. People with HIV (PLHIV) represented 8.2% (95% CI [7.0 – 9.5%]) of annual TB cases in 2019. The risk of developing TB among the 38 million people living with HIV was 18 (95% CI [15–21]) times higher than in the rest of the global population.

TB is the 10th leading cause of death worldwide and, since 2007, it has been the leading cause

of death from a single infectious agent. In 2019, there have been 1.2 million deaths attributed to TB. Out of these deaths, 83% occurred in the WHO African and South-Asian regions, and India alone accounted for 36% of global TB deaths among HIV-negative people. Globally in 2019, 53% of the HIV-negative people who died from TB were men, 31% were women and 16% were children. The higher share for children deaths compared with their estimated share of cases (12%) suggests poorer access to diagnosis and treatment(18).

Children aged <15 years represented 12% of the new TB cases that were notified in 2019 worldwide, according to the WHO 2020 report(18) (Figure 4). However, a modelling study estimated that in high-burden countries pediatric TB represents 15-20% of the TB case load(19) which indicates that most of the pediatric TB cases are undetected and/or unreported. The detection gap is largest in young children, 65% of children under 5 being not detected for TB. Detecting TB in children who present themselves at the health facility is a challenge in itself, due to the paucibacillary nature of TB disease in children, as presented previously. The undetected children go untreated, which increases their risk of death. Of more than 200000 estimated TB deaths in children, the vast majority occurred in untreated children mainly due to under-diagnosis(18). The mortality in untreated children has been estimated to be 21.9%, reaching 43.6% in children under 5 years(20).

Children of low age are particularly at risk of developing severe disease(21). This risk can be lowered by immunization with the BCG vaccine. BCG is the oldest vaccine in current use, being administered for the first time in 1921. In 100 years-time, no other vaccine has been developed and approved for any part of TB care, from prevention to disease(22). Despite questionable efficacy against pulmonary TB, BCG has consistently shown high protective efficacy against disseminated forms of TB, including TB meningitis and miliary TB in children under 2 years old(23,24). In addition, evidence from more recent studies suggest that BCG also protects against TB infection and progression from infection to disease(25).

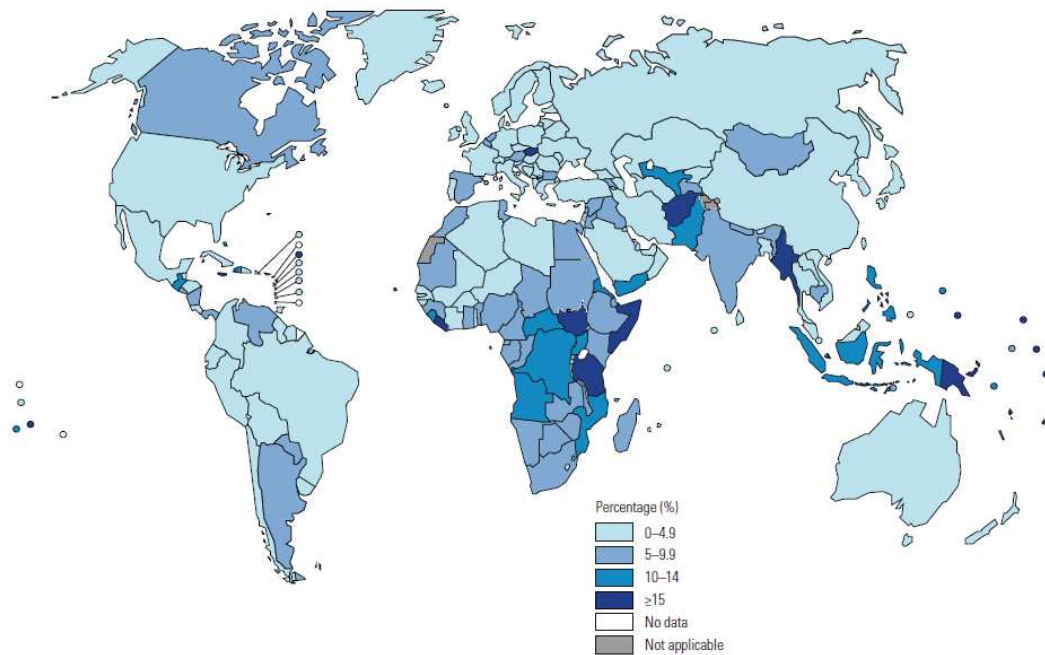


Figure 4. Percentage of new and relapse cases in children aged <15 years, 2019

Source: WHO Global Tuberculosis Report, 2020(18)

The WHO listed TB as a global health emergency in 1993 and since that time, many goals have been set for the reduction of the TB burden worldwide. In addition, TB is listed as a major health challenge in the Sustainable Development Goals (SDGs) as stated in Goal 3.3: “by 2030, end the epidemics of HIV/AIDS, TB, Malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases.” SDG 3 includes a target to end the global TB epidemic by 2030.

The WHO End TB Strategy includes targets of a 90% reduction in TB deaths and an 80% reduction in the TB incidence rate between 2015 and 2030; the 2020 milestones are reductions of 35% and 20%, respectively(26). Globally, as stated above, the reduction in TB incidence between 2015 and 2019 was 9% (from 142 to 130 new cases per 100 000 population), less than halfway to the 2020 milestone. The global reduction in the number of TB deaths between 2015 and 2019 was 14%(18). The Global Plan to End TB outlines the steps and resources needed to achieve the End TB Strategy’s goals and is periodically updated by the Stop TB Partnership (an international network of public and private entities working to eliminate TB)(27).

In September of 2018 at the UN General Assembly, the heads of States adopted the “Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis,” which called for a united and urgent global response to fight the epidemic and outlined concrete actions for increased investments and innovation. With the endorsement from the highest level of authorities by UN member states, the global commitment to fight the

epidemic has never been higher. The Political Declaration also articulated commitments on TB research and innovation, and the Global Strategy for Tuberculosis Research and Innovation was adopted by governments at the 2020 World Health Assembly. There is a strong political momentum at the global level for ending the TB epidemic by 2030.

Improving childhood TB case detection and access to treatment is a prerequisite to achieve the goal of zero deaths from tuberculosis in the Roadmap for Childhood Tuberculosis and the Sustainable Development Goals(28). The specific objectives of the high-level United Nations (UN) meeting on TB are to diagnose and treat 3.5 million children with TB and to provide TPT to 4 million children under 5 by 2022.

1.1.3. Clinical manifestations of tuberculosis disease

Approximately 10% of the infected persons will develop TB disease, which usually manifests with non-specific symptoms like cough, fever, weight loss and wasting, night sweats, fatigue.

TB is described as a sub-acute disease, and the persistence of symptoms is often suggestive of TB, meaning the symptoms are less pronounced but more prolonged than in an acute disease.

Symptoms can be classified in local (organ symptoms) and systemic (general symptoms).

Local symptoms of TB are due to the physiological changes and damage in the organ affected by TB, which is the lung tissue in more than 80% of cases. Extrapulmonary TB is most often seen in children and it can touch any organ, symptoms varying according to the affected organ. Manifestations include cervical lymphadenopathy, meningitis, pleural effusion, abdominal TB, military (disseminated) TB(29).

One of the main *systemic* manifestations of TB is fever. Although it is largely unclear why TB-related fever occurs primarily during the night, this occurrence has been associated with the body's circadian rhythm: the body temperature is normally lower in the predawn hours (36.1°C) and rises in the afternoon (37.4°C)(4).

Another systemic symptom is cachexia, or wasting. Wasting is due to the lack of appetite and the altered metabolism associated with the inflammatory and immune responses. Wasting involves the loss of both fat and lean tissue and the decreased muscle mass contributes to the fatigue. Nevertheless, it is important to note that the clinical symptoms of pulmonary TB are often nonspecific, and in approximately 5% of all adult cases and 60% of all pediatric cases, signs of the disease are completely absent(4).

TB in children can be asymptomatic or present a range of sub-clinical signs. The most common

manifestations are pulmonary or lymphatic. Small children (under 2 years old) progress more quickly to severe disease or to extrapulmonary TB(21). Adolescents are more likely to be symptomatic(29) and to presenting adult-like disease with clear symptoms like cough, fever or night sweats. Children living with HIV represent an additional challenge due to the fact that other HIV-related respiratory conditions mimic clinical and radiological findings of TB.

TB is a known cause of comorbidity in acute severe pneumonia(30). The clinical presentations overlap and response to antibiotics should not exclude a concurrent diagnosis of TB in children.

Undernourished and malnourished children are predisposed to TB disease and are associated with poor treatment outcomes(31). The population attributable fraction of tuberculosis due to undernutrition in 22 countries with a high tuberculosis burden was 26.9%(32).

1.1.4. Tuberculosis diagnosis

1.1.4.1. Latent tuberculosis infection diagnosis

There is no gold standard test for LTBI and its presence is assessed by a positive host immune response to stimulation by *M. tuberculosis* antigens. For this purpose, there are two tests which can be used, tuberculin skin test (TST) and Immunoglobulin Gamma Release Assay (IGRA). These tests are *indirect*, in the sense that they do not detect the presence of *M. tuberculosis* in the body, but the body's response to the bacilli.

The TST elicits a delayed-type hypersensitivity reaction to an intradermal injection of purified protein derivative which contains antigens from *M. tuberculosis*, non-tuberculous mycobacteria (NTM) and the *M. bovis* Bacillus Calmette–Guerin (BCG) strains. Its interpretation is dependent on the person's risk of recent TB infection and risk of progression to TB disease if infected. Moreover, this test requires the person to come back for reading after 48 to 72 hours and tuberculin needs to be refrigerated, limitations which makes it hard to implement in low-resource countries. In addition, vaccination with BCG could induce a false positive reading of the TST. In the specific case of PLHIV or other immunocompromised individuals, there is a risk of getting false negative results(33).

The IGRAs are in vitro blood tests which measure the amount of interferon gamma (IFN- γ) produced by CD4+ T lymphocytes (QuantiFERON-TB) or number of IFN- γ -producing T cells (T-SPOT.TB) after overnight stimulation with *M. tuberculosis* specific antigens ESAT-6 and CFP-10. These antigens are encoded in the RD-1 genomic region of *M. tuberculosis* that is absent from BCG strains and most NTM species, making IGRAs more specific in detecting LTBI than TST. The main limitation of this test is that it is costly and requires specific equipment

and expertise. In PLHIV there is the big advantage of the nil or the negative control which allows the reader to interpret the test in case of immunocompromised patients.

The WHO recommends the use of either TST or IGRAs in high-income and upper middle-income countries with estimated TB incidence less than 100 per 100 000 and in low-income countries, due to poor access and high cost, IGRAs should not replace TST(34).

TST and IGRA have numerous limitations and most notably they are not useful in discriminating latent infection from active disease, cannot be used to determine treatment response and are unable to distinguish recently infected persons who are at higher risk for early progression to TB disease from those who acquired their infection in the past(35).

1.1.4.2. Tuberculosis disease diagnosis

The confirmation of TB disease is made by the detection of the bacilli, mycobacteria or its DNA in patient's specimen using smear-microscopy, mycobacterial culture and more recently molecular diagnostic tests.

The most widely-used method in low-resource countries is acid-fast bacilli microscopy. Its main advantages consist in the rapid turnover time of about an hour and in the minimal equipment required to perform the test. However, microscopy has a poor sensitivity and specificity especially in PLHIV and children(36). Moreover, a positive result by microscopy does not discriminate between the *Mycobacterium* species.

The gold standard for the diagnosis of tuberculosis requires the identification of *M tuberculosis* in a culture of a diagnostic specimen. The most frequent sample used from a patient with a persistent and productive cough is sputum. Because most mycobacteria grow slowly, 3 to 6 weeks may be required for detectable growth on specific culture media. The most common methods include liquid media like Mycobacteria Growth Indicator Tube (MGIT) and solid media like Lowenstein Jensen (LJ). For obvious reasons, this diagnostic method raises many challenges to the practicality of TB diagnosis. Firstly, because the presumptive TB case might not be able to produce an adequate sputum sample. This is specifically the case of children or critically ill patients. Secondly, in resource limited settings, the lack of appropriate laboratory infrastructure, with good infection control measures, limits its use and reduces access to the test. Thirdly, due to a long turnaround time (3 weeks), TB treatment decision cannot wait for culture results, especially in immunocompromised patients.

Huge advance has come from the identification of the *M. tuberculosis* genome(37) and the gene sequencing of the main resistance genes(38). Molecular diagnostic methods can provide the data needed more rapidly. Xpert MTB/RIF has been rolled out in high burden and resource limited countries with the advantage of using an automated system integrating the specimen

preparation, amplification and detection allowing its use at low level of health care facility without the polymerase chain reaction (PCR) technology and to detect simultaneously both *M. tuberculosis* and rifampicin resistance within 2 hours after starting the assay. Moreover, the WHO is now recommending Xpert MTB/REF as the go-to rapid test for TB in low-resource countries(39). The next-generation Xpert MTB/RIF assay, Xpert MTB/RIF Ultra (Ultra), has a limit of detection (LOD) of 16 colony forming units (CFU)/mL (compared to 114 CFU/mL achieved by Xpert MTB/RIF). This lower LOD is similar to the detection level of culture and should improve the diagnosis of paucibacillary disease. Initial studies report Ultra sensitivities between 64% and 75% for sputum and high specificity (97% to 100%) compared to culture(40). The implementation of Xpert MTB/RIF Ultra is undergoing in limited-resource countries through funding from different implementors like Global Fund or Unitaid.

Microbiological testing is not a 100% sure bet and particularly in the case of children, a negative microbiological result does not exclude TB disease. Therefore, for the diagnosis of TB, it is highly important to rely on clinical elements in addition to the microbiological results.

Imaging is also used for the diagnosis of TB, more specifically chest radiography (CXR). CXR has high sensitivity. TB suggestive features on CXR are classically the presence of cavitation and infiltrates in the upper lobes, pleural effusion, peri-hilar or mediastinal adenopathy and miliary. Many of CXR findings are also non-specific for TB as they could also be found in other pulmonary pathologies, giving a poor specificity to CXR as a diagnostic test for TB disease. In addition to these limitations, CXR is highly dependent on the expertise of the reader, making it subject to human error in diagnosis. Another shortcoming for CXR is the poor access, as the necessary infrastructure is not available in lower levels of health facilities, and the patients have to pay to benefit of a CXR in health systems without universal health coverage.

Antigen detection assays based on lipoarabinomannan (LAM), a lipopolysaccharide component of the *M. tuberculosis* cell wall, have shown promise and have been commercially developed into point-of-care formats. The sensitivity of urine LAM detection is considered insufficient for screening of unselected TB suspects but has clinical utility among HIV-infected TB suspects with low CD4 cell counts(41).

Based on these tests, the WHO classifies TB cases into bacteriologically confirmed or clinically confirmed. Nevertheless, these tests perform differently for each of the stages of the TB spectrum and depending on the bacterial load, as shown in Figure 5 below.

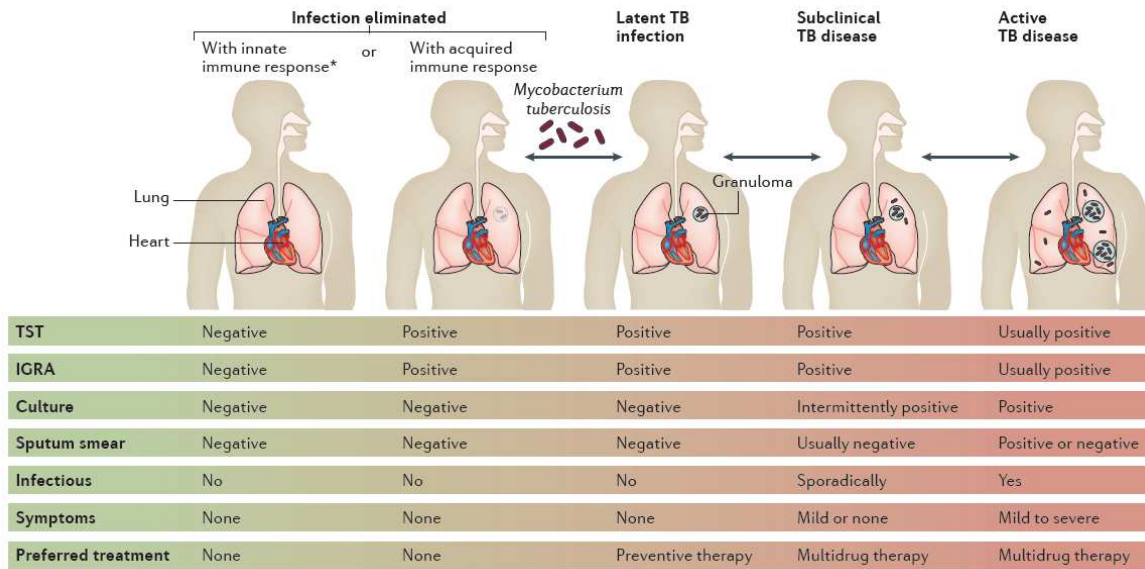


Figure 5. The spectrum of TB from exposure to disease and associated tests

Source: Pai et al., Tuberculosis, Nat. Rev. Dis. Pri. 2016(6)

1.1.4.3. Tuberculosis diagnosis in children

The WHO recommends the use of Xpert MTB/RIF as a frontline test in children with presumptive TB and there have been huge efforts to ensure the rollout of Xpert in high burden countries. Unfortunately, its impact on childhood TB detection remains limited by the difficulty of children to produce sputum samples and the operational challenges of using alternative specimen collections like induced sputum or gastric aspirate in limited resource countries(42). Induced sputum is a procedure helping patients produce sputum by inhaling saline solution. Gastric aspirate is an invasive procedure used to collect bronchial secretions which have been swallowed by the patient. All these procedures require special training, infection control measures and material, which are not often available in high-burden, low-resource settings. Nevertheless, Xpert MTB/RIF remains very relevant in the pediatric TB diagnosis due to the identification of possible resistant strains and to the rapid turnover of results avoiding diagnostic delays and risk of patient’s dropout during the course of investigations.

Increasing evidence shows that stool samples can be relevant specimens for the diagnosis of intra-thoracic TB using XpertMTB/RIF. Stools are easier to obtain compared to respiratory samples and more acceptable for patients than induces sputum or gastric aspirate. Stool samples rely on the detection of mycobacteria from respiratory secretions which have been swallowed In a systematic review of Xpert MTB/RIF testing on stool specimens, the pooled sensitivity and specificity were 67% (52-79) and 99% (98-99), respectively against culture(43).

Xpert Ultra has a sensitivity of 64% (95% CI ;[48-77%]) in gastric aspirates and 53% (95% CI [35-70%]) in stool samples. The specificity of Xpert Ultra was 95% (95% CI [84-99%]) in gastric aspirates and 98% (95% CI [93-99%]) in stool(44).

Urine LAM is recommended for the diagnosis of TB in PLHIV and the recommendations have been extended to children as well. In case the patient has a very low CD4 count (< 100cells/mm) or is seriously ill, the urine LAM test is recommended even in the absence of TB symptoms(45). The new urine FujiLAM test has a sensitivity of 60% and a specificity of 95% compared to Xpert MTB/RIF, which make it a promising point of care test for TB diagnosis in children(46). Its performances are higher in malnourished children or living with HIV(47).

The lower sensitivity of microbiological test in children as compared to adults is mostly explained by the paucibacillary nature of pediatric TB, which results in a very low bacterial load in respiratory specimens(48,49). This implies that a negative test result is not a confirmation of the absence of disease, but most probably indicates a low bacterial load. In addition, children, especially young children, are more likely to present disseminated or extra-pulmonary forms of TB that are poorly diagnosed from respiratory specimens(49). Therefore, the majority of children treated for TB are treated empirically based on an association of TB suggestive symptoms, history of exposure and radiological features suggestive of TB for children who had access to CXR. The chest X-ray (CXR) is a sensitive test but has poor specificity, especially in young children and HIV-infected children(49) and its use is hampered by the lack of training of clinicians to interpret CXR, the low access and poor quality of radiography in low resource settings(50–52). Some of these shortcomings could be addressed by the computer aided detection (CAD) technology which is still under evaluation for children in several research projects.

Treatment decisional algorithms and scoring systems can play a role in standardizing application of common criteria for rapid diagnosis and treatment initiation but most of the proposed algorithms did not go through proper prospective evaluation. The WHO is currently evaluating the use of treatment decision algorithms for paediatric diagnosis, and updated guidance is expected at the end of 2021(44).

1.1.5. Tuberculosis treatment

1.1.5.1. Treatment of latent tuberculosis infection

Prevention of TB disease by treatment of LTBI is a critical component of the WHO End TB Strategy(26,53). The efficacy of currently available treatments ranges from 60% to 90%(54).

Isoniazid monotherapy for 6 months is the standard prophylaxis used in adults and children with good efficacy based on several randomized clinical trials(55). Despite its affordability and overall good tolerability, adherence may be an issue due to its long duration. According to the literature, treatment completion rate ranges between 0 and 100%(56,57). The coverage of TPT among children <5 years can be found in Figure 6.

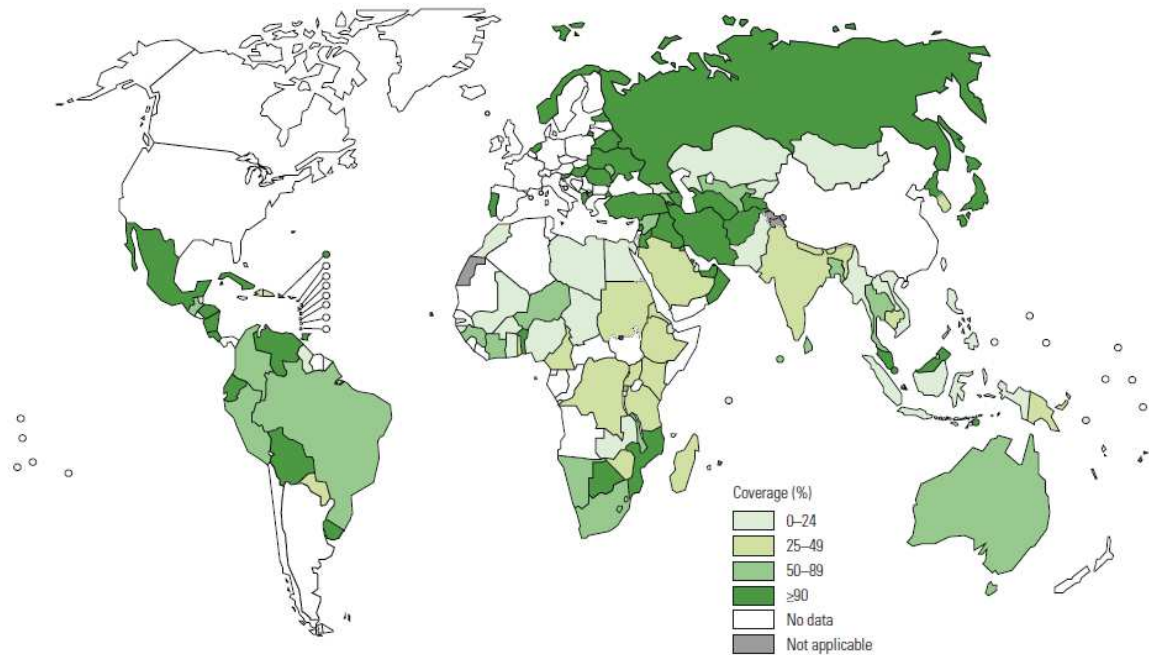


Figure 6. Coverage of TPT among eligible children aged <5 years, 2019

Source: WHO Global Tuberculosis Report, 2020(18)

Shorter combinations of isoniazid and rifampicin taken daily for a duration of 3 months have similar efficacy and safety compared to 6 months isoniazid(55,58). One randomized clinical trial (RCT) and 2 observational cohort studies comparing 3HR with 6/9H in children, reported a lower risk of adverse events (RR 0.33, 95%CI 0.20-0.56) and high adherence rate (RR 1.07, 95%CI 1.01-1.14) in the RCTs, with similar results in the 2 cohort studies(59–61). Daily rifampicin for 3 or 4 months has also been proven to have a similar efficacy to the 6 months of isoniazid(58).

A weekly treatment with rifapentine and isoniazid for 3 months (3HP) is also available and a systematic review regrouping 4 research studies(62–65) has shown that there was no difference in the occurrence of TB disease in the 3HP group versus 6H or 9H. The 3HP group had less hepatotoxicity and a higher completion rate than the standard of care.

The shortest available treatment is one month of daily rifapentine and isoniazid for children 13

and above, living with HIV. This regimen has proven its non-inferiority in a randomized trial comparing it to 9H in the population previously cited(66). Rifapentine is not yet accessible for wide distribution due to its high cost. Also, the large sized pill is difficult for children to ingest. Studies are underway to evaluate dosing in children aged less than 2 years, but significant delays are expected in the commercial availability of a water-dispersible formulation due to the nitrosamine impurity recently identified in all rifamycins

WHO is now recommending shorter regimens if available, and is still recommending the 6 months isoniazid TPT(56).

Table 1. TPT available regimens

Regimen	Duration (months)	Interval	Doses	Age	Child friendly
Isoniazid	6	Daily	182	All ages	Yes
Isoniazid+Rifapentine	3	Weekly	12	≥ 2 years	No
Isoniazid+Rifampicin	3	Daily	84	All ages	Yes
Rifampicin	4	Daily	120	All ages	No
Isoniazid+Rifapentine	1	Daily	28	> 12 years	No

source: WHO guidelines, Module 1: Prevention(56)

Both isoniazid and rifampicin are associated with a risk of hepatotoxicity. Isoniazid is also associated with a risk of peripheral neuropathy requiring the prescription of pyridoxine as adjunctive treatment. Most of these reactions are minor and occur rarely, therefore the WHO does not recommend monitoring the liver function using blood test, but specific attention needs to be given to signs of hepatotoxicity and neuropathy. In a recent review of safety of short TPT, Cruz et al reported that adverse events were more common in the longer regimen (9H) compared to the shorter 3-4 months regimens (OR 2.51, 95% confidence interval (CI): 1.48-4.32)(61).

In PLHIV, due to the pharmacological interactions between rifampicin (potent enzyme inducer) and antiretroviral drugs (nevirapine, dolutegravir, protease inhibitors)(67), precaution is recommended when using these drugs together.

1.1.5.2. Treatment of tuberculosis disease

Without specific treatment, TB disease is deadly in about 70% of cases(68). Standard treatment for drug-sensitive TB is ensured by four anti-microbials: isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). The current recommendation is for patients to take EHRZ for 2 months (intensive phase) and then HR for another 4 months (continuation phase). The long duration of this treatment regimen is a barrier to adherence and has a significant negative impact on tuberculosis control. Luckily, the regimen used to treat TB in children is in dispersible format which can be easily assimilated by children. The recommended dosage in children is of 10mg/kg for H, 15mg/kg for R, 35mg/kg for Z, and 20 mg.kg for E(69).

A recent study has shown the non-inferiority of a 4 months regimen(70) using high-dose rifapentine, a long-acting rifamycin and moxifloxacin instead of ethambutol, in combination with H and Z. This breakthrough is likely to improve adherence and make the burden of TB treatment more bearable for patients. The WHO released a communication preparing the implementation of this short regimen for the treatment of active disease in adults(71). The WHO is preparing the release of new recommendations for the management of pediatric TB in December 2021, and one of the researches which was taken into account for the guideline update is the SHINE trial(44,72). This trial showed the non-inferiority of a 4-month (2HRZE 2RH) using standard doses as compared to the standard 6-month regimen for treatment of non-severe, smear-negative TB. Although these results are likely to improve the management of children with TB, the implementation of this regimen is limited by the need of CXR to identify children with limited form of intra-thoracic TB.

1.2. Child contact management in high-burden countries

When a person is diagnosed with TB (also called index case), it is very important to identify all people in that person's circle who might have been exposed to TB (also called contact cases). It is widely accepted that 5-10% of contacts will develop TB in the first year after exposure. In order to prevent this from happening, the WHO recommends screening all close contacts in a short time span after the diagnosis of the index case. Contact investigation is defined by the WHO as: *"a systematic process for identifying previously undiagnosed people with TB disease and TB infection among the contacts of an index TB patient and/or other comparable settings where transmission occurs. Contact investigation consists of identification, clinical evaluation and/or testing and provision of appropriate anti-TB therapy (for people with confirmed TB) or TB preventive treatment (for those without TB disease)."*(34).

TB screening prioritizes child contacts and traditionally includes symptomatic and growth

assessment, CXR and tuberculin skin test (TST), if available. Children under 5 or PLHIV are particularly targeted for screening and initiating TPT because they have a higher risk of progression to TB disease and once diseased, they present more severe forms. The purpose of TB screening is to detect early forms of TB and to identify children eligible to TPT. Despite strong evidence of effectiveness and almost universal adoption by National Tuberculosis Programs (NTPs) of WHO recommendations to screen household contacts for TB and offer TPT to eligible contacts like children aged less than 5 years or HIV-infected of any age once TB disease is excluded(73), these recommendations are poorly implemented in high TB burden and resource limited countries(74,75) deepening the gap between estimated and notified child TB cases. Reasons for this include a lack of recognition of childhood TB as a public health problem, system and human resource constraints to do screening, and challenges in establishing a diagnosis of TB in children(75,76). A major challenge is availability and utility of TST and CXR (76).

In recognition of lack of tuberculin availability, strict temperature requirements and operational challenges in relation of TST that requires a 2nd visit after 48h for reading of TST result, diagnosis of LTBI is not a prerequisite to offer preventive therapy to young children and HIV infected household child contacts after exclusion of TB disease(77). Particular concerns relate also to the inability to confidently exclude TB disease without the use of CXR, which is generally unavailable in most low-resource settings, to allow for the safe use of TPT(52,76). Several studies have shown that the use of a symptom-based screening was safe and effective in selecting out the small proportion of child TB contacts requiring further evaluation for TB disease, allowing prompt initiation of TPT for the rest(78–81). Considering the risk of developing severe forms of active disease in exposed children who are either younger than 5 years or HIV-infected, the current WHO guidelines recommend using a symptom-based screening for screening these groups of household child contacts and to initiate TPT in those who are asymptomatic(56). This strategy has been proven to be the most cost-effective in children under 2 years(82) and the preferred strategy in children <5 years(82) to prevent TB in this high risk population. However, there was no published systematic review to assess the level of evidence to support this recommendation.

The symptom-based screening includes the most common TB-related symptoms which are: persistence of cough, fever, not eating well/anorexia, weight loss/failure to thrive, fatigue, reduced playfulness and decreased activity(73). There is good evidence for the use of symptomatic screening in children <5 years(48,57,82) and the benefits gained from rapid detection of symptomatic cases and preventive therapy for contact children with a negative screening largely outweigh the risk of missing a TB case. Nevertheless, there is not enough data in children ≥ 5 years in order to make the same assumption. Children 5-14 years old

without HIV, which are household contacts to a TB patient could be eligible to TPT if TB disease is excluded.

For HIV-infected children, the best combination of symptoms is current cough, fever or failure to thrive with a negative predictive value of 99%, but WHO considers this recommendation to have a low quality of evidence(73,83). The major challenge represented by symptomatic screening is that the clinical presentation of the TB disease mimics other common childhood pathologies like HIV, pneumonia and malnutrition; and that some symptoms cannot be properly assessed in children with some comorbidities such as fatigue or reduced playfulness which are also symptoms of severe malnutrition.

People living with HIV (PLHIV) are considered at high risk of developing TB disease if exposed to an index case. Therefore, if the index case is a PLHIV, the WHO recommends that all household contacts (irrespective of age) should be tested for HIV and counselled(73). It has been shown that in PLHIV, when exposed to a case of TB, they have a 33% lower risk of developing the disease if they are under TPT(83).

In most programs in low resource countries, index cases are asked to bring their child contacts to the facility for screening. Often, parents/guardians are hesitant to bring a child who is well to the hospital, or they did not understand the benefits of TB screening, as shown by many studies focused on contact screening(33–35). TB stigma is also a factor influencing parents in their decision to bring contact children for TB screening(84,85). Transport cost and distance influence the parents' decision as well(86). Sometimes even the health worker is reluctant to apply these recommendations for children who are not sick(87–89). TPT stockouts, lack of proper tools, lack of TB prevention prioritization and management are also barriers to TB screening and TPT implementation(84,86,90,91). According to a systematic review, the proportion of child contacts screened can range between 2.7 and 100% in high-burden settings (57).

The WHO recommends, in its most recent guidelines, the screening of all close contacts of a diagnosed TB case(73), irrespective of their age. Therefore, it is particularly important to support countries in achieving the target of the new WHO End TB Strategy of 90% of LTBI treatment coverage of household child contacts by 2025(18). In high-income countries this recommendation is easily implemented, however in resource-limited countries there are multiple obstacles that lead to a poor implementation in these specific settings, as healthcare infrastructure, human resources, high workload and poor access.

The many gaps observed in the cascade of care of child contacts occur mostly in the screening, TPT initiation and completion steps(57) and the main drivers of these gaps are considered to

be the health system infrastructure, limited worker resources and parents' reluctance to bring their children to the facility for screening. There would be great advantages of using a symptom-based screening at community level where only the symptomatic contacts are referred to hospital for further evaluation and asymptomatic contacts are started on TPT in the community(52,76). Household or community-based screening is likely to improve the uptake and acceptability of child contact screening and management as well as adherence to TPT and to reduce cost and workload at facility level(92).

The main challenges in TB contact tracing are lowering the gap in the identification of child contacts, their screening and also maintaining good treatment retention. A meta-analysis showed that in 41% of the analyzed studies, screening rates were less than 50%(57) and the pooled proportion of treatment completion was 18.8%. The authors identified the main challenges as being represented by the health system infrastructure, knowledge gaps, stigma, access to care and drugs and competing priorities of the NTP and the families(87,88,93,94).

1.3. Community interventions for tuberculosis care

In 2006, the new 6-pillar WHO Stop TB Strategy included a new component: *"Empower people with TB, and communities"*. This component spelt out the need to promote advocacy, communication and social mobilization in order to influence policy changes and sustain commitment and to facilitate community participation in TB care. A community consists of people living together in some form of social organization and cohesion. Although it may vary significantly in size and socioeconomic profile, its members usually share social, cultural, economic characteristics as well as common interests, including health.

Community-based TB activities represent a range of activities contributing to TB case notification, treatment adherence and improved outcomes. They also include activities for health promotion including generation of demand for TB prevention, diagnosis and treatment services. Communities, by sharing responsibilities with the health system, may often suggest an approach to these interventions that is more adequate for the local context. Community-based approaches help in empowering each community to deal with its own problems and also provides patient with a greater degree of autonomy and satisfaction with the treatment regimen(95).

A recent systematic review found mixed results that active case-finding is effective at initially increasing tuberculosis detection when measured by case notification rates, and that active case-finding could reduce community prevalence of tuberculosis if delivered with sufficient intensity and coverage(96).

Community-based delivery of directly observed treatment, short course (DOTS) may be more feasible and effective for TB case detection and treatment as community workers are familiar with the layout of community and have community member's trust which healthcare officials would have to develop(97). A systematic review found that community-based interventions for TB prevention and case detection showed significant increase in TB detection rates (RR: 3.1, 95% CI: 2.92, 3.28) with non-significant impact on TB incidence. The same approach for treating patients with TB disease showed an overall improvement in treatment success rates (RR: 1.09, 95% CI: 1.07, 1.11)(97). Community-based TB treatment delivery through community health workers (CHW) not only improved access and service utilization but also contributed to capacity building and improving the routine TB recording and reporting systems. There is evidence in the advantages of community interventions for TB contact screening, but no research reported so far results of the implementation of TPT initiation and follow-up in the community. More evidence is needed in this area.

WHO formulated recommendations for TB community activities and identified eight specific areas that should be considered to promote and implement the involvement of people with TB and communities in TB care and prevention and to strengthen their empowerment in health interventions(95): (1) policy guidance, initial implementation and scale-up, (2) advocacy and communication, (3) capacity-building, (4) addressing special challenges in controlling TB, (5) ensuring the quality of services provided at the community level, (6) budgeting and financing, (7) establishing a plan for monitoring, evaluation and supervision and (8) operational research.

1.4. Evaluation of complex interventions

1.4.1. Definition of complex interventions

An intervention is defined as a set of actions with a coherent objective to bring about change or produce identifiable outcomes. Public health interventions are intended to promote or protect health or prevent ill health in communities or populations. They are distinguished from clinical interventions, which are intended to prevent or treat illness in individuals.

In healthcare, education or social policy alike, there are many interventions which have several different components that influence the final outcome. These interventions are called *complex*, due to the fact that there is not one clearly identifiable element which is the main determinant of effectiveness for that intervention. The greater the difficulty in defining precisely what are the “active ingredients” of an intervention and how they relate to each other, the greater the likelihood that the intervention is complex(98).

The origin of the word complexity is the Latin *complexus*, where *com* means ‘together’ and *plectere* means ‘to wave’ or ‘braid’, meaning it has to do with “how things are connected with each other, and how these interactions work together”(99).

Generally, all activities can be classified in three categories: simple, complicated and complex. Simple activities, like following a recipe, may encompass some basic issues of technique and terminology, but once these are mastered, following the recipe carries with it a very high chance of success. Complicated activities contain subsets of simple activities, but are not merely reducible to them. Their complicated nature is often related not only to the scale of an activity, like sending a rocket to the moon, but also to issues of coordination or specialized expertise. Complex activities carry with them large elements of ambiguity and uncertainty that are in many ways similar to the activities associated with raising a child, where the degree of uncertainty of outcomes is very high and the behaviors can change abruptly(100).

A complex system is one that is adaptive to changes in its local environment, is composed of other complex systems (for example an integrated care unit), and behaves in a non-linear fashion (change in outcome is not proportional to change in input)(101). Complicated interventions can take on the characteristics of complex systems, since it is impossible to separate the intervention from the human resources required for its delivery.

In healthcare, complexity is a feature of many aspects: the intervention, the disease, the patient-group, the system, and the context in which the intervention is implemented. In addition, the investigation of interventions can be described as complex, and place many responsibilities on the shoulders of the researchers conducting interventions. For example, in TB care there

might be an intervention focused on TB treatment. Nevertheless, the context in which the treatment is delivered can highly influence the outcomes. In addition, the outcomes can be moderated by the person delivering the treatment, by factors related to the patient like socioeconomic status or by national healthcare policies. The research question itself may also be complex because it may not be confined to a single intervention but may relate to a package of interventions, and the evidence to answer that question may be difficult to locate and synthesize. Interactions between intervention components and their effects on outcomes are not always linear or obvious, and they are influenced by several factors which include the number of interacting components, the intensity of behavior change required by those delivering or receiving the intervention, the number of groups or organizational levels targeted by the intervention and the complexity of outcomes, as well as the context in which interventions are implemented(102). Community interventions can be complex due to the many interacting factors which can act like free electrons in a community and influence the intervention.

Campbell et al., citing the management of a stroke unit, points to variation among units in staff characteristics, clinical practices, management protocols, and infrastructure. This makes it difficult to specify what the intervention is, what is most effective, or how to replicate the intervention beyond the original trial(103). This applies to TB units as well, where care is highly dependent on the person delivering it and it has been shown that there is a healthcare workforce crisis related to TB services(104). In addition, there are different infrastructures and local practices that can influence TB services worldwide. This aspect should not be discouraging, as all systems of society are complex, but rather should inform the researchers in carrying a comprehensive evaluation of the intervention. Only by addressing these matters can we build a cumulative understanding of causal mechanisms, design more effective interventions and apply them appropriately across different setting.

The Medical Research Council (MRC) guidance(98) for developing and evaluating complex interventions identifies clear dimensions of complexity:

- Number of and interactions between components within the experimental and control interventions
- Number and difficulty of behaviors required by those delivering or receiving the intervention
- Number of groups or organizational levels targeted by the intervention
- Number and variability of outcomes
- Degree of flexibility or tailoring of the intervention permitted

1.4.2. Frameworks for complex intervention development and evaluation

There are several guidelines and frameworks available for the development and evaluation of complex interventions. The most widely used framework is the one proposed by the MRC in 2000(98,103) and 2008(105). Collins et al. proposed a multiphase optimization strategy (MOST)(106) for achieving the dual goals of program optimization and program evaluation in the behavioral intervention field. There is also the normalization process theory(107) which explains how new technologies, ways of acting, and ways of working become routinely embedded in everyday practice, and has applications in the study of implementation processes. Walker et al. proposes a framework for choosing a theoretical basis for interventions, called PRIME(108). Other frameworks are specifically focused on intervention mapping or modeling only(109–111). There is also the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework(112), first published in 1999, which indeed evaluates different steps of implementation evaluation, but is designed for health promotion interventions and programs. RE-AIM provides a functional starting point for determining the public health impact of strategies involved in health promotion by guiding the assessment of: reach, which captures the percentage of people from a given population who participate in a program and describes their characteristics; effectiveness, which refers to the positive and negative outcomes of the program; adoption, which is generally defined as the percent of possible settings (e.g., organizations) and staff that have agreed to participate in the program; implementation, which is an indicator of the extent to which the program was delivered as intended and its cost; and maintenance, which, at the individual level, reflects maintenance of the primary outcomes (>6 months). At the organizational level, maintenance captures the sustainability of the delivered programs.

According to the MRC guidance(113), the process from development through to implementation of a complex intervention may take a wide range of different forms. Figure 7 summarizes the main stages and the key functions and activities at each stage:

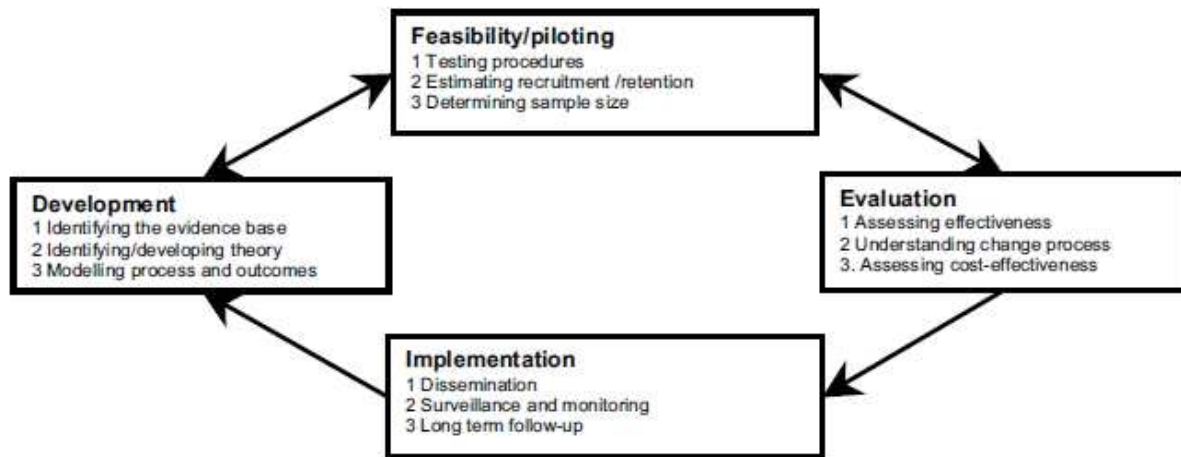


Figure 7. Key elements of the development and evaluation process

Source : MRC Complex Intervention Guidelines (113)

Best practice according to MRC(113) is to develop interventions systematically, using the best available evidence and appropriate theory, then to test them using a carefully phased approach, starting with a feasibility study targeted at each of the key uncertainties in the design, and moving on to an exploratory and then a definitive evaluation, as seen in Figure 7.

Researchers need to consider carefully the importance of the intervention, and the value of the evidence of effectiveness that can be gathered given the constraints which present themselves in complex interventions.

The guidance details each step of the development and evaluation process.

Step 1: Developing a complex intervention

The first step refers to the theoretical basis of the intervention and how it suggests that the intervention could have the desired effect. This phase is composed of 3 parts:

- Identifying the evidence base through a review of the available literature or by conducting a systematic review of the literature.
- Identifying or developing an appropriate theory by developing a theoretical understanding of the likely process of change, by drawing on existing evidence and theory and if necessary, by conducting new research, for example interviews with stakeholders.
- Modelling process and outcomes refers to understanding of the intervention and its possible effects.

Step 2: Piloting and assessing feasibility

This step is focused on the following practical concepts:

- testing for acceptability
- estimating the likely rates of recruitment and retention of subjects
- calculation of appropriate sample sizes.

Step 3: Effectiveness and process evaluation

For the effectiveness and cost-effectiveness evaluations, there are five types of experimental designs proposed by the MRC guidelines(98):

- individual randomized trials: Individuals are randomly allocated to receive either an experimental intervention, or an alternative such as standard treatment, a placebo or remaining on a waiting list. Such trials are sometimes dismissed as inapplicable to complex interventions, but there are many variations of the basic method.
- cluster randomized trials: groups such as patients in a GP practice or tenants in a housing scheme are randomly allocated to the experimental or a control intervention.
- stepped-wedge designs: this design may be used to overcome practical or ethical objections to experimentally evaluating an intervention for which there is some evidence of effectiveness, or which cannot be made available to the whole population at once. At the end of the study the whole population receives the intervention, but with randomization built into the phasing of implementation.
- preference trials/randomized consent designs: Practical or ethical obstacles to randomization can sometimes be overcome by the use of non-standard designs. Where patients have very strong preferences among treatments, basing treatment allocation on patients' preferences, or randomizing patients before seeking consent, may be appropriate
- N-of-1 designs: in this design individuals undergo interventions with the order or scheduling decided at random, can be used to assess between and within person change, and to investigate theoretically predicted mediators of that change.

A process evaluation is often highly valuable, providing insight into why an intervention fails unexpectedly or has unanticipated consequences or why a successful intervention works and how it can be optimized. Process evaluation nested within a trial can also be used to assess fidelity and quality of implementation, clarify causal mechanisms and identify contextual factors associated with variation in outcomes. Process evaluations should be conducted to the same high methodological standards and reported just as thoroughly as evaluation of outcomes.

An economic evaluation should be included, if at all possible, as this will make the results far

more useful for decision-makers. Ideally, economic considerations should be taken fully into account in the design of the evaluation, to ensure that the cost of the study is justified by the potential benefit of the evidence it will generate, appropriate outcomes are measured, and the study has enough power to detect economically important differences.

Step 4: Scale-up

First of all, the findings of the trial need to be made available to the policy-makers through means they would usually access. It has already been recognized that passive strategies are ineffective at getting evidence into practice(114) and active strategies are recommended like reaching out to local opinion leaders and involving decision-makers in dissemination workshops.

1.4.3. Developing a complex intervention

Existing evidence

Consulting the relevant literature may highlight important issues that modify or reassure the researchers in designing the complex intervention. If the evidence has not been synthesized in the literature, an important step is to conduct a systematic review, the results of which would help refine the intervention processed or even its outcomes. In addition, maintaining the process of checking the existing literature is a good practice even during the inclusions in the trial, but many researchers skip updating the literature review once the intervention has started.

Theory

Understanding the public health intervention's underlying theory of change (ToC) and its related uncertainties may improve the evaluation of complex health interventions. ToC is a theory of how and why an initiative works, which can be empirically tested by measuring indicators for every expected step on the hypothesized causal pathway to impact(115). It is visually represented in a ToC map, which is a graphic representation of the causal pathways through which an intervention is expected to achieve its impact within the constraints of the setting in which it is implemented.

A review(116) by the Comic Relief organization defines ToC as: *An ongoing process of reflection to explore change and how it happens – and what that means for the part organizations play in a particular context, sector and/or group of people.*

Piana et al. define ToCs as *“an outcomes-based approach which applies critical thinking to the design, implementation, and evaluation of initiatives and programs intended to support change in their context”*

A ToC accounts for the complexity of change, the wider systems and actors that influence it,

and is often presented in diagrammatic form with an accompanying narrative summary.

ToCs can be used to strengthen RCTs by building theories that are then empirically tested and allow for a detailed explanation of assumptions and pathways of change of the intervention.

The ToC is often developed using a backward mapping approach which starts with the long-term outcome and then maps the required process of change and the short- and medium-term outcomes required to achieve this [9]. During this process, the assumptions about what needs to be in place for the ToC to occur are made explicit as well as the contextual factors which influence the ToC. Additional elements of a ToC can include beneficiaries, research evidence supporting the ToC, actors in the context, sphere of influence, strategic choices and interventions, timelines and indicators.

Modeling

This involves describing the components of the complex intervention and how they interact with each other or how they influence the final outcome. The model can be done by very simple methods like paper modelling, or by computer modelling or economic evaluation. A paper model of the intervention, using diagrams or flowcharts, may be a useful starting point to identifying the key relations among components, and potentially some of the vulnerabilities of the intervention. Diagramming the components (nature, timing, frequency, duration, of inputs, including skills, organizational arrangements, setting) may highlight potential weak points and bottlenecks.

1.4.4. Assessing feasibility

Feasibility studies are studies designed to build the foundation for the planned intervention study. The primary purposes of a feasibility study are to ensure that study implementation is practical and to reduce threats to the validity of the study's outcomes(117).

A significant amount of funding resources, including participants' and researchers' time, may be wasted if feasibility has not been carefully examined and assured prior to conducting a pilot study or a RCT. For studies conducted in preparation for a RCT assessing the effect of a therapy or intervention, three distinct types of study come under the umbrella of feasibility studies: randomized pilot studies, non-randomized pilot studies, feasibility studies that are not pilot studies.

The British National Institute for Health Research's (NIHR) Evaluation, Trials and Studies Coordination Centre (National Institute for Health Research, 2012) makes a distinction between feasibility and pilot studies. According to them, a feasibility study focuses on

conducting research to examine whether the study can be done, whereas pilot studies are “smaller versions of the main study used to test whether the components of the main study can all work together”.

An important distinction between feasibility and pilot studies, especially for new interventions, is that feasibility studies are iterative, formative, and adaptive, whereas pilot studies are mini-RCTs. Feasibility studies focus on the process of developing and implementing an intervention and result in preliminary examination of participant responses to the intervention. Pilot studies more clearly focus on outcomes, rather than process, and include a more controlled evaluation of participant responses to the intervention. When data collected during the pilot study is used in the main trial, it is referred to as an internal pilot study and if data is analyzed and set aside, it is called an external pilot study. All pilot studies are feasibility studies, but not all feasibility studies are pilot studies(118). Feasibility studies that are not pilot studies are those in which investigators attempt to answer a question about whether some element of the future trial can be done but do not implement the intervention to be evaluated or other processes to be undertaken in a future trial, though they may be addressing intervention development in some way(118).

There have been several frameworks proposed in the literature to assess feasibility. Eldridge et al.(118) proposed a general conceptual framework based on the distinction between randomized pilot studies, non-randomized pilot studies and feasibility studies. Nevertheless, it gives little guidance on how exactly to conduct one of these studies. The MRC guidelines state that pilot and feasibility studies are highly recommended but don't provide clear steps to follow in order to conduct this type of study.

Orsmond and Cohn propose a framework for assessing feasibility(119) and state that the main objectives of feasibility studies focus on the:

- Obj 1: evaluation of recruitment capability and resulting sample characteristics,
- Obj 2: evaluation and refinement of data collection procedures and outcome measures,
- Obj 3: evaluation of the acceptability and suitability of the intervention and study procedures,
- Obj 4: evaluation of the resources and ability to manage and implement the study and intervention,
- Obj 5: preliminary evaluation of participant responses to intervention.

A concise list of focused questions to address each objective is provided to guide the feasibility phase of the intervention process. These questions are specific to the feasibility phase and are important to address before study implementation.

Acceptability

The 3rd objective of this framework focuses on acceptability, which is a necessary, but not sufficient condition for intervention effectiveness. Previous frameworks cite acceptability but offer no clear guidance on how to assess acceptability. Sekhon et al. propose a specific framework for acceptability assessment prior to conducting complex interventions(120). They define acceptability as being “a multi-faceted construct that reflects the extent to which people delivering or receiving a healthcare intervention consider it to be appropriate, based on anticipated or experiential cognitive and emotional responses to the intervention”.

Figure 8 below shows the framework proposed by Sekhon et al.

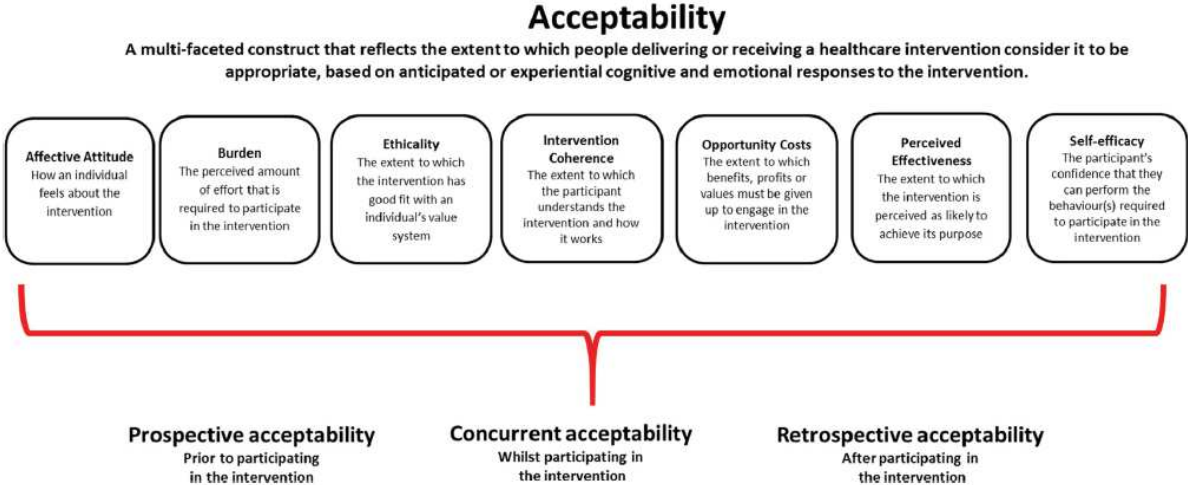


Figure 8. Acceptability framework with definitions

Source: Sekhon 2017, BMC Health Services Research(120)

Assessment of anticipated acceptability prior to participation can highlight which aspects of the intervention could be modified to increase acceptability, and thus participation in the intervention.

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2. Justification and objectives

2.1. Justification

Many challenges to TB contact investigation in resource-limited countries have been described in the previous sections. The use of community-based intervention avoiding the need for parents to bring their children to health facilities, especially when they are healthy, could increase the uptake of TB screening and TPT in high burden and resource limited countries. For TB screening, one condition would be to be able to use a simple symptom screening tool by community health workers. Therefore, only the symptomatic child contacts will need to be referred to health facility for further evaluation and asymptomatic contacts could be started on TPT in the community(76). Household or community-based screening is likely to improve the acceptability of child contact screening and management as well as adherence to TPT and to reduce cost and workload at facility level(92).

The WHO recommended that dedicated resources should be allocated, including human resource development and service delivery in the community to improve the uptake of contact screening and that epidemiological research should integrate community-based approaches.

So far, no RCT evaluated the impact of interventions that include both identification of children with signs suggestive of TB disease and referral for further diagnostic work up and preventive treatment initiation at community level on the cascade of care for children with active and latent TB, as compared to facility-based interventions.

The gold-standard of intervention evaluation is considered to be the RCT as this design allows for identification of casual relationship between variables(121).

The CONTACT study is a multicenter, cluster randomized trial conducted in two TB high-burden resource-limited countries comparing tuberculosis contact tracing and intervention at community level model to facility-based standard of care.

The CONTACT study is implemented under the frame of the Catalyzing Pediatric TB Innovation (CaP TB) Project, funded by UNITAID and implemented by the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF). EGPAF is the sponsor of the CONTACT study. The goal of CaP TB is to improve the pediatric TB morbidity and mortality by catalyzing the wide uptake of the new first-line fixed dose combination (FDC) drugs for children and optimizing the use of these drugs through improved case detection and innovative models of care.

This thesis work aimed at developing a community intervention which would be acceptable by providers, beneficiaries and their communities. This intervention should also be feasible and adapted to the specific local contexts of Cameroon and Uganda, respecting the local modus operandi of the health facilities, and should be able to recruit a statistically significant sample size. The study protocol is the transformation of these findings in a scientific format which would bring a high level of evidence for the effectiveness evaluation of its objectives.

2.2. Thesis Objectives

2.2.1. General objective:

The general objective of the thesis is to develop a cluster randomized trial evaluating a complex, pragmatic, community intervention for tuberculosis active contact screening and TPT management, and assess its feasibility in Cameroon and Uganda.

2.2.2. Specific objectives:

1. To assess the available evidence for the use of a simple tool for household child contact TB screening at community-level in low-resource countries
2. To develop the research protocol for the evaluation of the community intervention for TB screening and TPT management of household child contacts in Cameroon and Uganda.
3. To assess the feasibility of a randomized clinical trial evaluating a community intervention for household child contact TB screening and TPT management in Cameroon and Uganda.

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3. Method

3.1. Study setting and population

Cameroon and Uganda vary in their health systems and in particular in their experience with community approaches for TB child contact screening.

Cameroon had a TB incidence of 179 cases per 100000 population in 2019 and a HIV-TB incidence of 48 cases per 100000 population. In Cameroon, for contact screening and preventive therapy the current recommendation by NTP is: index cases are asked to bring their contacts to the TB diagnostic and treatment facility (district hospital mostly) where the screening is done by a TB nurse (TB focal person) using symptom-based screening. The TB focal person mainly asks the index case to bring child contacts under 5 years. Symptomatic children are referred to pediatric TB hospitals or regional referral hospitals for diagnosis. The diagnosis is done at the facility level if the child is able to produce sputum. No contact tracing register from the NTP is in use and therefore the number of child and adolescent contacts and their eligibility to TPT treatment is not captured in any form or register. Children initiated on PT and their outcomes are registered in a preventive therapy register. Only child and adolescent contacts started on preventive therapy are registered. The recommended TPT is 6 months isoniazid and the target children group are the child contacts below 5 years old and HIV-infected children of any age(122). Despite the recommendation, only 27% (25-30) of eligible children under 5 were started on TPT in 2019 according to the 2020 WHO TB report(18). There is a model of care for HIV case management that could serve as framework for the TB community interventions.

Uganda is a high-burden country with 200 new TB cases per 100000 population and an incidence of HIV/TB coinfection of 78 new cases per 100000 population. A similar approach is recommended for screening and preventive therapy of child TB contacts as in Cameroon. However, there have been previous research studies focused on community interventions in Uganda(17,74,123). In the DETECT Child TB project(124), children were screened in their communities and referred for TPT initiation at the facility. There were 72% of children who were initiated on TPT and 87% of children initiated on TPT with complete follow-up finished treatment. Following the DETECT Child TB pilot project, community activities for management of pediatric TB were scaled up in 2017 and include: contact (adults and children) symptom screening with collection of sputum in the household if possible, or referral of the symptomatic contact to the facility for further investigations; referral of asymptomatic child contacts at high risk of TB (<5years and HIV infected 5-14years) to the facility

to initiate TPT and for treatment refill. The recommended TPT is 6 months isoniazid and 3RH, but 3RH is not yet available in the country. Community activities include also TB treatment follow-up at home. The diagnosis of pediatric tuberculosis is done at district hospitals or health centers level 4. The Western region of Uganda is supported by the USAID-funded RITHES projects implemented by EGPAF. However, only 29% (26-31) of eligible children under 5 were initiated on TPT in 2019 according to the WHO 2020 TB report(18).

The contact study is implemented in these two sub-Saharan African countries because they have a similar burden of TB and TB/HIV coinfection, they have similar national guidelines but the level of decentralization of TB services is different. Implementation in different settings broadens the external validity of the study and the generalizability of its results.

Study clusters were selected from two regions (Centre and Littoral) in Cameroon and one region (South West) in Uganda (Figure 9).

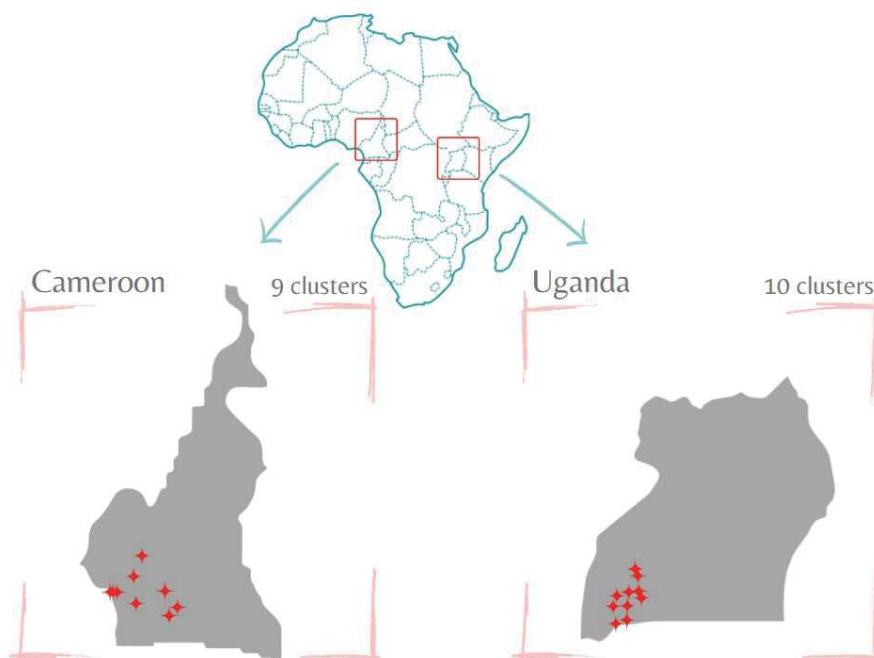


Figure 9 Geographical setting of the CONTACT study and its clusters

3.2. Study design

Overall, this thesis encompasses multiple designs, from systematic review and meta-analysis, cluster randomized trial, retrospective cohort, cross-sectional survey and qualitative discussions.

In order to assess if a simplified symptom screening tool would be enough for exclusion of TPT prior to initiating TPT, we performed a systematic review and meta-analysis of symptom screening compared to chest radiography in middle- and low-income countries, as defined by the World Bank. The simplified tool can be easily implemented at community level by trained staff as part of a community intervention for TB screening and TPT management.

The best evidence for the evaluation of an intervention is the randomized controlled trial. We have defined and developed a cluster randomized trial for the evaluation of a community intervention for TB screening and TPT management in Cameroon and Uganda. This study is designed as a pragmatic trial, meaning the intervention is evaluated under a real-life setting. Two parallel arms compare on one side, the community intervention and on the other side, the standard of care existing in the study clusters. A cluster design was chosen due to the fact that this community intervention cannot be delivered from the same health facility without contamination of study data between the study arms.

In order to prepare and fine-tune the proposed community intervention to the local setting and assess its acceptability, we used mixed methods comprising a retrospective cohort, a cross-sectional survey and a qualitative assessment.

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4. Studies

4.1. Symptom based screening versus chest radiography for TB child contacts: a systematic review and meta-analysis

4.1.1. Background

Investigation of TB exposed children is a highly important activity aiming at the timely detection of TB disease in this specific population and also at selecting children eligible for TPT. Ideally, all contact children should be tested for LTBI and only those found positive should be initiated on TPT to prevent onset of TB disease. As discussed in previous chapters, there are many operational and financial barriers to LTBI testing in resource-limited settings and the WHO has recommended initiating TPT in high-risk groups without prior LTBI testing(56). Still, a crucial step before TPT initiation is exclusion of TB disease. The molecular tests (Xpert MTB/RIF and Ultra) have a very poor sensitivity in children at early stage of the disease as it would be expected for child TB contacts. They are used for TB diagnosis, but not for excluding TB disease. Therefore, the most commonly used tools to exclude TB disease are the symptom screening with clinical examination and CXR.

CXR is more challenging to obtain in resource limited settings due to access and cost barriers. Even if a CXR is done, interpretation shortcomings arise if the readers are not well trained or if the CXR is not of good quality(52). CXR abnormalities commonly found in young children with TB include hilar lymphadenopathy, lobar or segmental parenchymal disease, pleural effusion and miliary pattern(125). These descriptions are commonly reported from high-burden countries in passive case-finding settings and are therefore likely to reflect a more advanced spectrum of disease than by active child TB contact screening(126).

While it is generally accepted that CXR has an important role in child contact screening, its feasibility in resource-limited settings remains a barrier.

TB symptom screening as proposed by the WHO is a simple clinical assessment inquiring on symptoms like: chronic cough, long lasting fever, weight loss, night sweats, poor appetite, loss of playfulness, hemoptysis. The notion of cough and fever duration is important in making the difference between other acute infections and TB.

Although recommended by WHO for excluding TB disease before TPT initiation in high-risk child contacts (< 5 years and 5-15 years HIV-positive) in the context of limited access to CXR, there was no systematic review to gather all the available evidence of the effectiveness of symptom screening and no recommendations for the 5-14 years HIV-negative children.

The primary objective of this systematic review is to compare CXR to a symptom screen to rule out TB disease in household child contacts under fifteen in low/medium income countries.

The secondary objectives are:

- To assess the accuracy of a symptom screening using double independent reading CXR as a reference standard.
- To assess the proportion of children with negative symptom screening who develop TB disease during follow-up

4.1.2. Methods

Two reviewers independently assessed titles and abstracts from PubMed, EMBASE, Medline, Cochrane, WHO Global Index Medicus, using a standardized research equation (available in the Supplementary Material of article 1). The review population was represented by children under the age of fifteen who are contacts of a person diagnosed with TB in their household and who live in a low/middle income country as classified by the World Bank in 2019(127).

The primary outcomes were the concordance between symptom screening and CXR to identify a negative case (proportion of children with both symptom and CXR screening negative) and the kappa coefficient. The secondary outcomes were the negative predictive value, and the sensitivity of symptom-based screening when compared to CXR reference standard read by two independent experts. An additional secondary outcome was the assessment of pediatric contacts who develop TB disease during prospective follow-up after a negative symptom screening.

The statistical analysis consisted of accuracy assessment calculating the sensitivity, specificity, negative predictive value and positive predictive value. We calculated the concordance between symptom screening and CXR using the PABAK (prevalence adjusted bias adjusted kappa). Only studies using same definition of TB suggestive chest X-ray were included in the meta-analysis to reduce risk of heterogeneity. A random effects model for pooled proportions was performed for studies using the same definition of CXR results using the R software(128) to account for both within and between study variance (Freeman Turkey Arcsin transformation using the “metaphor”

and “meta” packages). Analyses were stratified by two age groups: < 5 years and 5-14 years old. The reviewers assessed risk of bias using the QUADAS-2 scale(129), designed specifically for diagnostic accuracy studies(130). The systematic review protocol was registered on PROSPERO(131) and its reporting follows the PRISMA guidelines(132).

4.1.3. Results

We included 10 articles out of 639 screened. In children under 5 years, the PABAK varied between 0.09 and 0.97 and in children 5-14 years, it varied between 0.22 and 0.98, where 0 represents no agreement at all and 1 represents perfect agreement. The pooled proportion of children with both non-TB suggestive symptoms and chest radiography findings was 98.7% (95% CI [96.9–99.8]) in children less than 5 years and 98.1% (95% CI [93.8–100]) in children of age 5–14 years. For studies with double CXR reading and similar definitions of TB-suggestive CXR, the pooled negative predictive value was 99.3% (95% CI [97.5-100.0]) for children under 5. Five of the 10 included studies reported on the proportion of asymptomatic children who developed TB disease under follow-up. In child contacts under 5 years, 0-2% of children developed TB disease and 0-20.6% in children 5-14 years. There was heterogeneity in the included studies due to different definitions for a TB suggestive CXR and the symptoms used for symptom screening, but the general risk of bias was low.

4.1.4. Discussion

In children under 5 years there is indeed a very high negative predictive value of symptom screening compared to CXR, which implies that symptom screening alone can be used to rule out TB in high-burden resource-limited settings. The main methodological challenge is represented by the fact that there is no gold standard for TB diagnosis in children, therefore using CXR as a reference standard was imperfect. The standard case definitions of intra-thoracic childhood TB proposed for research were developed for evaluating diagnostic tests in children with presumptive TB and are not adapted to child contacts(133). In addition, they include symptoms (index test) and it would imply an incorporation bias and a flawed interpretation of results. Another shortcoming is represented by the fact that there is a high study heterogeneity linked firstly to the symptoms used for TB screening and their duration, but also to the timing of the screening, as some studies performed a prospective screening, others a post-hoc screening. Secondly, the heterogeneity was also identified in CXR definitions and reading, but this issue

was addressed in the secondary analysis by selecting only studies with a double CXR reading and similar TB-suggestive definitions.

In conclusion, these findings support the WHO recommendations for children under 5 years and furthermore suggest that the symptom-based screening can be used in alternative models of care like community-based contact screening and TPT delivery, hopefully reducing the TB burden in low-resource countries. For children ages 5-14 years, there is not enough evidence in order to conclude to CXR exclusion based on our systematic review and meta-analysis.

4.1.5. Involvement in this work

I have developed the systematic review protocol along with the other main author of the review, under the guidance of the coordinating authors. I have submitted the protocol to the PROSPERO online register for systematic review studies. With the other main author, we have screened the scientific databases using a standardized search equation and we included studies which responded to the inclusion criteria. We split between ourselves the list of authors to contact and each sent emails to half of the authors we needed data from. Upon receipt of data, I performed the concordance analysis, the accuracy analysis and the meta-analysis using R. I wrote the paper of this research with the help of the other main author, using valuable guidance from the coordinating authors.

4.1.6. Scientific communications:

Article:

- Vasiliu A, Abelman RA, Casenghi M, Cohn J, Bonnet M. Symptom-based Screening Versus Chest Radiography for TB Child Contacts: A Systematic Review and Meta-analysis. *The Pediatric Infectious Disease Journal*

Scientific conferences:

- 51st Union World Conference on Lung Health, Sevilla, 2020
- CBS2 Days 2021

ORIGINAL STUDIES

Symptom-based Screening Versus Chest Radiography for TB Child Contacts: A Systematic Review and Meta-analysis

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Jennifer Cohn, MD, MPH, ¶|| and Maryline Bonnet, MD, PhD*

Background: Accessibility to chest radiography remains a major challenge in high burden and low-income countries. The World Health Organization (WHO) guidelines acknowledge that for child contacts under 5 years, a negative symptom-based screening is sufficient to exclude active tuberculosis (TB), but in child contacts older than 5 years, a chest radiograph should be considered. We performed a systematic review and meta-analysis to assess the performance of symptom-based screening compared to chest radiography in household contacts under 15 years in low-income and middle-income countries.

Methods: Screening articles published prior 1 October 2020 and data extraction were performed by 2 independent reviewers. The primary outcome was the concordance between symptom screening and chest radiography using the prevalence adjusted bias adjusted kappa coefficient (PABAK) and the proportion of asymptomatic children with negative chest radiography. The analysis was stratified by age group.

Results: Of 639 identified articles, 10 were included. PABAK varied between 0.09 and 0.97 and between 0.22 and 0.98, in children less than 5 years and 5–14 years, respectively. The pooled proportion of children with both non-TB suggestive symptoms and chest radiography findings was 98.7% (96.9–99.8) in children less than 5 years and 98.1% (93.8–100) in children of age 5–14 years.

Conclusions: Despite low concordance between symptom-based screening and chest radiography, most children without TB suggestive symptoms did not have chest radiography findings suggestive of TB. These results suggest that a negative symptom screening is sufficient to rule out active TB, supporting the WHO recommendation to use symptom-based screening alone when chest radiography is not available.

Key Words: pediatric tuberculosis, contact investigation, symptom screening, chest radiography, systematic review

(*Pediatr Infect Dis J* 2021;XX:00–00)

INTRODUCTION

Tuberculosis (TB) is the ninth leading cause of death worldwide, with an estimated 10 million cases in 2019, with children

representing about 10% of cases.¹ Children are at highest risk for infection when living in the same household as a patient with active TB. Children under 5 years of age and those living with HIV are particularly vulnerable, and once infected have an increased risk of rapid progression of disease and increased disease severity.² For this reason, household child contact investigation and use of TB preventive therapy (TPT) is recommended by the World Health Organization (WHO) with a high priority for children under 5 years of age and for all children living with HIV.³ The effectiveness of TPT has been shown to be 63% in all exposed children.²

However, child contact investigation and initiation of TPT remain poorly implemented in high-burden countries with only 33% of eligible household child contacts (1.3 million) being started on TPT in 2019.¹ To determine which children should be started on TPT, active TB should first be excluded using symptom-based screening in addition to chest radiography. Symptom screening was introduced by the WHO guidelines of 2006⁴ and then updated in 2014⁵ as an alternative to TST and chest radiography given their associated challenges in excluding active TB. The inclusion of chest radiography in the screening algorithm for active TB can provide implementation challenges in many high burden and low-income countries due to poor access to quality radiography, lack of trained personnel in reading chest radiographies in children and potentially prohibitive costs for the patient's family. WHO guidelines have taken these practical challenges into consideration and acknowledge that for child contacts under 5 years of age, symptom-based screening is sufficient to exclude active TB prior to TPT initiation and that for children over the age of 5 years, chest radiography is recommended in addition to symptom-based screening, only if available.⁶ However, there has never been a published systematic review of the evidence for this recommendation in household child contacts in high burden and low-income countries.

We conducted a systematic review and meta-analysis to compare symptom-based screening with chest radiography to rule out active TB prior to TPT initiation among household child contacts in low-income and middle-income countries.

METHODS

Selection Criteria and Outcome Measures

Our review included randomized control studies, cohort and cross-sectional studies that reported data on symptom-based screening and chest radiography in children under the age of 15 years who live in a low/middle income country per the World Bank classification list of 2019.⁷

The primary outcome was the concordance to exclude active TB between symptom-based screening and chest radiography. One of the secondary outcomes was the accuracy of symptom-based screening when compared to chest radiography. We used chest radiography as a reference standard only in studies with 2 independent readers. Another secondary outcome was the proportion of child contacts without TB-suggestive symptoms who developed active TB during follow-up. Both TB-suggestive symptoms and TB-suggestive radiography findings were based on the definitions

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Dr. Anca Vasiliu and Dr. Rebecca A. Abelman contributed equally to the research. Dr. Jennifer Cohn and Dr. Maryline Bonnet contributed equally to the coordination of the research.

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provided in each respective study. TB-suggestive symptom screening should contain at least one of the following symptoms: cough, fever, weight loss and fatigue (regardless of duration). For studies reporting only abnormal versus normal chest radiography results, abnormal chest radiography was considered as TB-suggestive chest radiography.

Search Strategy, Data Extraction and Quality Assessment

Searches were conducted on PubMed, EMBASE, MEDLINE, Cochrane, WHO Global Index Medicus, English-language articles from the Latin American and Caribbean Health Science Information database, and in the grey literature through Open Grey. The search terms are listed in Supplemental Digital Content 1; <http://links.lww.com/INF/E483> (Table). The search was restricted to English or French within dates of 1 January 1980 and 1 October 2020. We checked reference lists of the included studies manually to identify additional sources.

The 2 review authors (A.V. and R.A.) independently screened study titles and abstracts for eligibility. Full text manuscripts of potential eligible studies were independently reviewed by R.A. and A.V. and reasons for exclusion were documented. Discrepancies in full-text review were resolved through discussion with M.B., M.C. and J.C. Final study selection was confirmed by consensus. The authors were contacted for missing data and further clarification. Extracted data were entered into Microsoft Excel for analysis.

The risk of bias was assessed by 2 independent reviewers (R.A. and A.V.) using the modified Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2).⁸ A specific data extraction form, including the modified QUADAS 2 tool, was developed (see Table, Supplemental Digital Content 2; <http://links.lww.com/INF/E483>). The chest radiography reference standard was evaluated based upon whether there was clear criterion for it being TB-suggestive. Applicability of the reference standard was whether there were 2 independent readers of the chest radiography. Applicability of the index test, the symptom-based screening, was determined by whether the study used a pre-defined symptom screening or if symptom identification was performed as a post-hoc analysis. Discrepancies were resolved through discussion with authors M.B., M.C. and J.C.

Statistical Analysis

Analyses were stratified by 2 age groups (less than age 5 years and 5–14 years). Symptom-based screening (suggestive of TB and not suggestive of TB) and chest radiography results (suggestive of TB and not suggestive of TB) were tabulated to construct a 2 × 2 contingency table per study. For the concordance analysis, the proportion of children with both non-TB suggestive chest radiography findings and non-TB suggestive symptoms and the prevalence adjusted bias adjusted kappa (PABAK) were calculated. We used the *epiR* package in the R software for the PABAK⁹ and the Landis and Koch recommendations for its interpretation.¹⁰ For the accuracy analysis, sensitivity, specificity, and positive and negative predictive values of the symptom-based screening compared to chest radiography were calculated with their 95% confidence intervals (95% CI) for studies with 2 independent readers. Forest plots of the proportion of child contacts without TB-suggestive symptoms nor TB-suggestive chest radiography, the sensitivity and negative predictive value of symptom screening were generated using the “forestplot” package in the R software. A meta-analysis was performed on studies that used a similar definition of TB-suggestive symptoms and TB-suggestive chest radiography findings to reduce the heterogeneity of the included studies. This was done using a random effects model for pooled proportions to

account for both within and between study variance (Freeman Turkey Arcsin transformation using the “metaphor” and “meta” packages in the R software).⁹

The study protocol was available on PROSPERO prior to data extraction.

RESULTS

Selection and Characteristics of Studies

Of 637 articles screened, 35 were eligible for full-text review and 10 were included in the systematic review (see Figure, Supplemental Digital Content 3; <http://links.lww.com/INF/E483>).^{11–20} Seven were prospective cohorts, 1 was a randomized controlled trial and 2 were cross-sectional studies.^{11–20} Four were conducted in sub-Saharan Africa,^{11–13,15} 3 in South Asia,^{16–18} 2 in South-East Asia^{19,20} and 1 in Armenia.¹⁴ All studies reported data for child contacts younger than 5 years old and 6 studies included children between 5 and 14 years of age. Only 5 studies had 2 independent chest radiography readers (see Table, Supplemental Digital Content 4; <http://links.lww.com/INF/E483>).^{11–13,19,20} In one study, 89% of contact children were already on TPT at the time of symptom and chest radiography screening.¹¹

Primary Endpoints

The PABAK coefficient varied between 0.09 (slight agreement) and 0.98 (almost perfect agreement) in the less than 5 years of age group and between 0.22 (fair agreement) and 0.98 (almost perfect agreement) in the 5–14 years of age group (Table 1).

The proportion of children with a chest radiography that was not-suggestive of active TB among children with a negative symptom-based screening ranged between 54.5% and 100% in the less than 5 age group and between 84.6% and 100% in the 5-to-14 years of age group (Table 1; see Figure, Supplemental Digital Content 5; <http://links.lww.com/INF/E483>). A meta-analysis was conducted among studies using similar definitions for TB-suggestive chest radiography. The pooled proportion of children with a non-TB suggestive chest radiography among those with a negative symptom-based screen was 98.7% (95% CI: 96.9–99.8) and 98.1% (93.8–100) in the groups of child contacts less than 5 years and 5–14 years old, respectively (Fig. 1). Therefore, less than 2% of both age groups of child contacts with negative symptom-based screen had a TB-suggestive chest radiography.

Secondary Endpoints

The sensitivity of TB symptom-based screening as compared with a chest radiography read by 2 independent readers ranged between 40.0% and 100% in the less than 5 years of age group and 39.1% and 100% in the group of age 5–14 years (Table 2; see Figure, Supplemental Digital Content 6; <http://links.lww.com/INF/E483>). The negative predictive value ranged from 70.8% to 100% for the age group <5 years (see Figure, Supplemental Digital Content 7; <http://links.lww.com/INF/E483>) and 84.6% and 100% in the 5–14 years of age group. Pooled analysis from the 3 studies using same definition of TB-suggestive chest radiography findings was only feasible for the negative predictive value in the subgroup of child contacts less than 5 years old. The pooled negative predictive value was 99.3% (97.5–100.0) (Fig. 2).

Of 7 studies using a prospective cohort design, only 5 reported the proportion of children without TB-suggestive symptoms at initial screening who consequently developed active TB during follow-up. Between 0% and 2% of child contacts less than 5

TABLE 1. Prevalence Adjusted Bias Adjusted Kappa Coefficient (PABAK) Results for Concordance Between Symptom-based Screening and Chest Radiography

Study	Age Group	Negative SS With		PABAK	95% Confidence Intervals	Agreement
		Negative CXR/Negative SS (%)				
Srivastava et al	<15	97.6		0.92	0.86 to 0.98	Almost perfect
	<5	97.6		0.92	0.81 to 1.00	Almost perfect
	5–14	97.6		0.92	0.85 to 0.99	Almost perfect
Kumar Dolla et al	<15	57.9		0.14	0.02 to 0.26	Slight
	<5	66.7		0.27	0.01 to 0.51	Fair
	5–14	55.4		0.10	–0.04 to 0.24	Slight
Hurega et al	<15	98.7		0.97	0.94 to 1.00	Almost perfect
	<5	98.3		0.97	0.90 to 1.00	Almost perfect
	5–14	98.9		0.98	0.93 to 1.00	Almost perfect
Birungi et al	<15	100		0.69	0.59 to 0.79	Good
	<5	100		0.51	0.33 to 0.69	Moderate
	5–14	100		0.84	0.74 to 0.93	Almost perfect
Malik et al	<15	93.5		0.57	0.52 to 0.62	Moderate
	<5	97.4		0.35	0.27 to 0.43	Fair
	5–14	87.5		0.89	0.84 to 0.93	Almost perfect
Fox et al	<15	99.6		0.97	0.97 to 0.98	Almost perfect
	<5	99.7		0.98	0.96 to 0.99	Almost perfect
	5–14	99.5		0.97	0.96 to 0.97	Almost perfect
Bonnet et al	<5	97.4		0.22	0.10 to 0.33	Fair
	0–14	78.5		0.16	0.04 to 0.28	Slight
	<5	70.8		0.09	–0.08 to 0.27	Slight
Triasih et al	5–14	84.6		0.22	0.06 to 0.38	Fair
	<5	54.5		0.23	0.05 to 0.40	Fair
	<5	97.1		0.52	0.41 to 0.63	Moderate

CI indicates confidence intervals; CXR, chest radiography; PABAK, prevalence adjusted bias adjusted kappa coefficient; SS, symptom-based screening.

years old (all on TPT) and 0–20.6% of children of age 5–14 years (not on TPT) developed active TB (see Table, Supplemental Digital Content 8; <http://links.lww.com/INF/E483>).

Risk of Bias

Patient selection had a low risk of bias across all but one study.¹⁴ Bias risk and applicability for the index test was unclear for 2 studies^{13,14} as the symptom-based screening used was not specified in the article, and was high risk for applicability for one study due to a post-hoc review of symptoms rather than a prospective symptom-based screening.¹⁷ There were higher risks for bias and applicability with the reference standard due to lack of specification of what qualified as a positive chest radiography in 3 studies^{13,16,17} as well as the absence of 2 independent readers for 5 studies.^{11,12,14,19,20} The full QUADAS-2 is in Table, Supplemental Digital Content 9; <http://links.lww.com/INF/E483>.

DISCUSSION

To our knowledge, this is the first systematic review evaluating the concordance and accuracy of symptom-based screening when compared to chest radiography in the exclusion of active TB in pediatric household contacts in high burden and income limited countries. Our analysis reveals a high pooled proportion in children in both age groups (97.7% [96.2–98.9] for children less than 5 years and 97.3% [90.6–100] for 5–14 years of age group) with both a non-TB suggestive chest radiography and symptom-based screening, suggesting that symptom-based screening alone is a reliable tool for excluding active TB. The 95% CI was wider for the older age group as fewer studies were included in the meta-analysis.^{11,13,17,18,20} The high negative predictive value in the group of children under 5 years of age (98.7% [96.5–99.9]) in addition to the low percentage of children in this age group with a negative symptom-based screening who later developed active TB

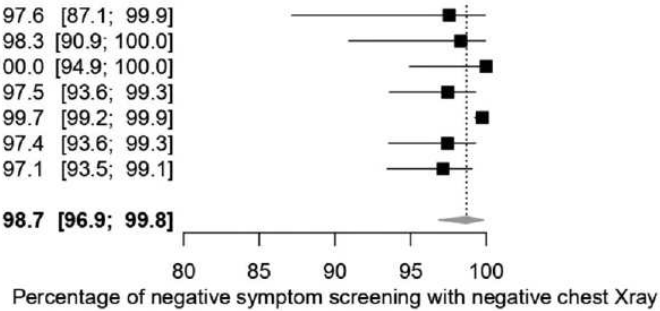
(0%–2%) supports that symptom-based screening alone is likely sufficient to exclude active TB in this population. In a low TB burden country, 2.6% of asymptomatic children had a TB suggestive chest radiography.²¹

It is worth remarking that in all studies conducting follow-up, all children under 5 years were started on TPT and that in one study,¹¹ most of the screened children were already receiving TPT at the time of screening. This was notably not the case in the 5–14 years of age group. Overall, our analysis supports the WHO recommendation that in settings without easy access to chest radiography, child contacts below 5 years of age with a negative TB symptom screening can safely be started on TPT without chest radiography.

Unfortunately, due to a lack of data, the pooled analysis of the negative predictive value could not be done in the older age group of child contacts. In the 3 studies where children of age 5–14 years with a negative initial symptom screening were followed prospectively for development of active TB, there was significant heterogeneity in results. In 2 of the studies, very few children developed active TB during follow-up. In the study by Srivastava et al, 20.6% of children in this age group developed active TB during follow-up.¹⁸ The difference between the 3 studies might be explained by difference in TB exposure and prevalence of TB infection among child contacts but this is poorly documented. For example, in the Srivastava et al study, tuberculin skin test was performed at initial screening, but there is no information if children who later developed TB during follow-up were from the group of infected children. Furthermore, in this study several children who were asymptomatic and had also negative chest radiography at enrollment developed a positive TST during follow up, suggesting that both infection and disease during the follow-up period may in part be due to on-going exposure to a positive household TB patient. As in the majority of children primary disease occurs within 1 year of primary infection, these findings further emphasize the importance of TPT initiation in all age groups of child contacts.²² In the latest WHO guidelines,²³ for the management of older HIV-negative children who are less at

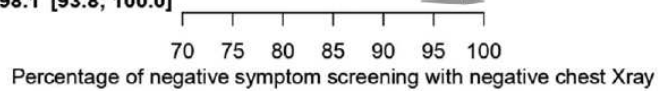
A 0-4 subgroup*

Study (0-4 years)	Cases	Total	Prevalence	95% C.I.
Srivastava 2020	40	41	97.6	[87.1; 99.9]
Hurega 2012-2016	58	59	98.3	[90.9; 100.0]
Birungi 2015-2016	71	71	100.0	[94.9; 100.0]
Malik 2014-2016	153	157	97.5	[93.6; 99.3]
Fox 2010-2015	1151	1154	99.7	[99.2; 99.9]
Bonnet 2012-2014	152	156	97.4	[93.6; 99.3]
Kruk 2004	170	175	97.1	[93.5; 99.1]
Random effects model	1813		98.7	[96.9; 99.8]
Heterogeneity: $I^2 = 73\%$				



B 5-14 subgroup

Study (5-14 years)	Cases	Total	Prevalence	95% C.I.
Srivastava 2020	80	82	97.6	[91.5; 99.7]
Hurega 2012-2016	89	90	98.9	[94.0; 100.0]
Birungi 2015-2016	108	108	100.0	[96.6; 100.0]
Malik 2014-2016	91	104	87.5	[79.6; 93.2]
Fox 2010-2015	3318	3333	99.5	[99.3; 99.7]
Random effects model	3717		98.1	[93.8; 100.0]
Heterogeneity: $I^2 = 90\%$				



* articles by Kumar Dolla, Triasih and Fortunato were excluded from the meta-analysis due to lack of information on the chest radiography definition (Kumar Dolla and Fortunato) and due to a different definition of positive chest radiography (Triasih)

FIGURE 1. Meta-analysis results of the proportion of child contacts without TB suggestive symptoms and chest radiography findings. CI indicates confidence interval.

risk of developing severe form of TB if infected, there is still a preference for chest radiography in addition to symptom screening to rule out active TB and evidence of infection before initiating TPT, if routinely available.

The high degree of variability in study design and in case definitions used by the different studies contributed to the heterogeneity of results. The PABAK coefficient varied across studies, and in some studies revealed a low concordance between symptom-based screening and chest radiography. However, these results are difficult to generalize given the variance in symptom screenings and what was defined as TB suggestive chest radiography in addition to discordance between symptoms and radiographic findings. While some studies did not conduct a prospective evaluation of symptoms with a pre-determined symptom-based screening, the variability was mostly due to either lack of standardization of the symptom-based screening, inter-study variability of the screening used, or the screening was not described in the manuscript. Similarly, several studies did not define what determined TB-suggestive chest radiography or definitions varied across studies. As some studies simply used a normal versus abnormal chest radiography in their analysis, the sensitivity and negative predictive value were likely lower than if more circumscribed criteria for chest radiography results were

used. Only 4 studies had 2 independent readers of the radiographies, also contributing to variability in the interpretation of chest radiographies in this population.

This review has several limitations. Only a small number of studies were included in the review, with even fewer including the 5-14 years of age group. This is largely due to the small number of studies published on screening of pediatric TB contacts using chest radiography and symptom-based screening. However, several studies were excluded given insufficient information available to tabulate the symptom-based and chest radiography results. Both the information bias and the small number of studies may affect the representativeness of the findings of this review. The symptom-based screening evaluated in this study depended on the authors' definitions (see table, Supplemental Digital Content 4; <http://links.lww.com/INF/E483>) and even if generally a prospective symptom-based screening based on the WHO recommendations was used, in some articles the type of screening was not clear or it was performed post-hoc after a general clinical examination. Moreover, when a prospective symptom-screening was used, the notion of symptom duration was not consistently evaluated. As with all studies evaluating screening and diagnostic approaches for pediatric TB, this analysis is limited by the lack of

TABLE 2. Accuracy of Symptom-based Screening Compared to Chest Radiography

Study	Age Group	Sensitivity (n/N)	95% Confidence Interval	Specificity (n/N)	95% Confidence Interval	Negative Predictive Value (n/N)	95% Confidence Interval	Positive Predictive Value (n/N)	95% Confidence Interval
Hurega et al	<15	33.3 (1/3)	0.8–90.6	100 (148/148)	97.5–100	98.7 (148/150)	95.3–99.8	100 (1/1)	2.5–100
	<5	50 (1/2)	1.2–98.7	100 (59/59)	93.9–100	98.3 (58/59)	91.1–99.9	100 (1/1)	2.5–100
	5–14	–	–	100 (89/89)	95.9–100	98.9 (89/90)	93.9–99.9	–	–
Birungi et al	<15	100 (0/4)	39.76–100	84.4 (179/212)	78.8–89.0	100 (179/179)	–	10.8 (4/37)	8.1–14.2
	<5	–	–	75.5 (71/94)	65.6–83.8	100 (71/71)	–	–	–
	5–14	100 (0/4)	39.76–100	91.5 (108/118)	84.9–95.9	100 (108/108)	–	28.6 (4/14)	18.1–41.9
Fox et al	<15	14.3 (3/21)	3.0–36.3	99.1 (4469/4509)	98.8–99.3	99.6 (4469/4487)	99.4–99.8	7.0 (3/43)	1.5–19.1
	<5	–	–	99.4 (1151/1158)	98.8–99.8	99.7 (1151/1154)	99.2–99.9	–	–
	5–14	16.7 (3/18)	3.58–41.41	99.0 (3318/3351)	98.6–99.3	99.5 (3318/3333)	99.2–99.7	8.3 (3/36)	1.7–22.5
Bonnet et al	<5	81.8 (18/22)	59.72–94.81	59.1 (152/257)	52.9–65.2	97.4 (152/156)	93.9–98.9	14.6 (18/123)	11.8–17.9
Triasih et al	<15	39.6 (35/58)	27.05–53.36	63.4 (128/202)	56.3–70.0	78.5 (128/163)	74.3–82.2	23.7 (23/97)	17.7–30.9
	<5	40.0 (21/35)	23.87–57.89	60.7 (51/84)	49.5–71.2	70.8 (51/72)	63.8–76.9	29.8 (14/47)	20.7–40.8
	5–14	39.1 (14/23)	19.71–61.46	65.2 (77/118)	55.9–73.8	84.6 (77/91)	79.4–88.7	18.0 (9/50)	11.1–27.9

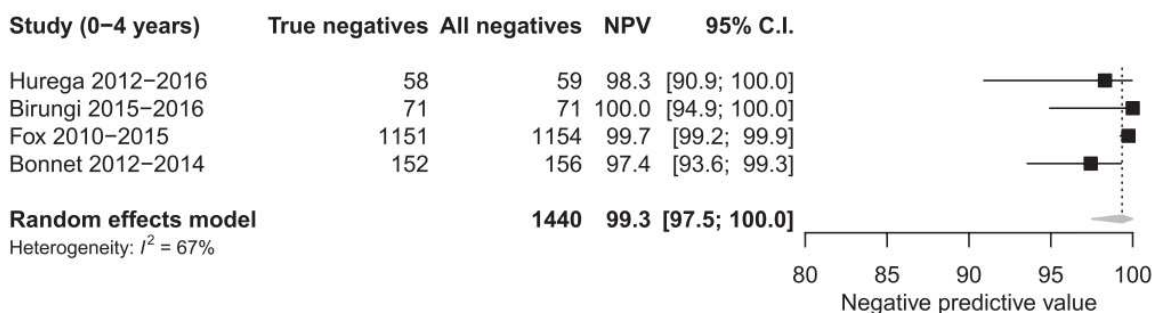


FIGURE 2. Meta-analysis of the negative predictive value of symptom-based screening versus chest radiography. CI indicates confidence interval. NPV, negative predictive value.

an adequate reference standard for the diagnosis of TB.^{23,24} This is especially true for the evaluation of TB screening tools in child contacts given the limited performance of microbiological tests in this patient population, especially during early stages of disease. Additionally, the consensus composite reference standard using uniformed case definitions of TB that has been developed for evaluation of diagnostic assays in children could not be considered as it is not applicable to presumptive TB pediatric population identified through active case finding activities.²⁵ Given these challenges, we chose chest radiography as the reference standard, but accuracy was only evaluated with studies using independent review by readers blinded to the clinical features.²² However, chest radiography remains imperfect due to discrepancy between different readers' interpretation, inconsistent quality and overall poor specificity for TB diagnosis, in particular in situation with co-existence of multiple co-morbidities like viral respiratory infections and possible reactive airways disease that could mimic TB-suggestive chest radiography findings.^{22,25,26}

In conclusion, despite the high heterogeneity between studies and the few studies available, our findings support the WHO recommendation for symptom-based screening alone when evaluating for active TB in household child contacts, especially for young children. Although the studies included in this review suggest a similar approach may be taken for children between 5 and 14 years of age, further data are still needed for this group. These results suggest that community-based symptom-based screening of child contacts can be used to determine children eligible for TPT, ideally facilitating increased TPT uptake and decreasing active TB progression in high-risk groups.

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Supplemental Digital Content

Table S1. PubMed research equation

#12	Search Filters: Publication date from 1980/01/01; English; French
#11	Search Filters: English; French
#10	Search (#6 OR #8 OR #9)
#9	Search (#6 NOT #4)
#8	Search ((#1 AND #2 AND #3 AND #4)) Filters: Child: birth-18 years
#7	Search ((#1 AND #2 AND #3 AND #4))
#6	Search (#1 AND #2 AND #3 AND #4 AND #5)
#5	Search (" child " OR " childs " OR " children " OR " childhood " OR " infant " OR " infants " OR " infancy " OR " neonatal " OR " neonate " OR " neonates " OR " adolescent " OR " adolescents " OR " adolescence " OR " pediatric " OR " pediatrics " OR " paediatric " OR " paediatrics ")
#4	Search Anorexia [Mesh Terms] OR "Body Weight" [Mesh Terms] OR "Carrier State" [Mesh Terms] OR "Child Behavior"[Mesh Terms] OR Cough [MeSH Terms] OR "Diagnosis"[Mesh Terms] OR "diagnosis" [Subheading] OR "Early Diagnosis"[Mesh Terms] OR "Fatigue"[Mesh Terms] OR Fever [MeSH Terms] OR "Growth Disorders"[Mesh Terms] OR Hemoptysis [MeSH Terms] OR Lethargy[MeSH Terms] OR Malnutrition [MeSH Terms] OR "Nutrition Disorders "[Mesh Terms] OR "Play and Playthings"[Mesh Terms] OR "Signs and Symptoms"[Mesh Terms] OR "Sweating"[Mesh Terms] OR "Weight Loss"[Mesh Terms] OR anorexia OR anorexic OR asthenia OR behavior OR behaviour OR behaviors OR behaviours OR behavioral OR behavioural OR carrier OR carriers OR Cough OR diagnosis OR diagnoses OR diagnostic OR fatigue OR fever OR "Growth Disorders" OR Hemoptysis OR Haemoptysis OR Lethargy OR Lethargic OR Malnutrition OR Malnourished OR "night sweat" OR "night sweats" OR pallor OR pale OR playful OR playfulness OR stunted OR stunting OR Sweating OR symptom OR symptoms OR symptomatology OR weight OR undernourished
#3	Search " Mass Chest X-Ray " [MeSH Terms] OR " Mass Screening "[MeSH Terms] OR " Radiography "[MeSH Terms] or " Radiography, Thoracic "[MeSH Terms] OR " CXR "[Title/Abstract] OR " Chest xray "[Title/Abstract] OR " chest x ray "[Title/Abstract] OR " chest xrays "[Title/Abstract] OR " chest x rays "[Title/Abstract] OR " chest radiography "[Title/Abstract] OR " thoracic radiography "[Title/Abstract] OR " lung

	radiography][Title/Abstract] OR “chest film”][Title/Abstract] OR “chest films”][Title/Abstract] OR “chest image”][Title/Abstract] OR “chest images”][Title/Abstract] OR “chest imaging”][Title/Abstract] OR “screening”][Title/Abstract] OR ”radiology”][Title/Abstract] OR ”radiography”][Title/Abstract]
#2	Search "Community-Acquired Infections" [Mesh Terms] OR "Contact Tracing" [Mesh Terms] OR "Environmental Exposure" [Mesh Terms] OR Family [Mesh Terms] OR Friends [Mesh Terms] OR "School Teachers" [Mesh Terms] OR Schools [Mesh Terms] OR "Social Environment" [Mesh Terms] or "Students" [Mesh Terms] OR “concentric circle” OR “concentric circles” OR Contact OR contacts OR household OR households OR "stone in the pond" OR brother OR brothers OR community OR communities OR environment OR environmental OR environments OR family OR families OR father OR fathers OR friend OR friends OR grandfather OR grandfathers OR grandmother OR grandmothers OR grandparent OR grandparents OR mother OR mothers OR playground OR playgrounds OR sibling OR siblings OR sister OR sisters OR student OR students OR teacher OR teachers
#1	Search ("Tuberculosis, Pulmonary" [MeSH Terms] OR "pulmonary tuberculosis"][Title/Abstract] OR ("lung"][Title/Abstract] OR "lung" [MeSH Terms]) AND ("tuberculosis"][Title/Abstract] OR "tuberculosis" [MeSH Terms]))

Table S2. Data extraction form

Title
Author
Included / Excluded
Exclusion criteria
Inclusion criteria
Year
Country
Study Type
Amount of time followed
Type of Patients
Age of patients
Type of symptom screening performed
Symptoms used
Symptom screening results
Definition of positive chest radiography
Chest radiography performed
Chest radiography result
2 chest radiography readers (Y/N)
% of children who developed TB after negative symptom screen
% of HIV positive children
Sample Size
TP
FN
FP
TN
Comments

Table S3: General characteristics of the studies included in this systematic review

Study	Year	Country	Study type	Age group	Sample size	Chest radiography definition	TB suggestive symptoms	Type of Symptom Screening Performed
Srivastava et al	2020	India	Cohort	0-14	152	Suggestive of TB / not suggestive of TB	fever, cough, poor appetite, weight loss, glandular swelling in any part of the body	Symptom-based screening performed prospectively
				0-4	50			
				5-14	102			
Kumar Dolla et al	2019	India	Cohort	0-14	277	Suggestive of TB / not suggestive of TB	Not defined	Unclear
				0-4	204			
				5-14	63			
Hurega et al	2012-2016	Armenia	Cohort	0-14	150	Normal/Abnormal Suggestive of TB/Abnormal not suggestive of TB (*)	cough more than 3 weeks, fever, failure to thrive, night sweats, wheeze/stridor, chest pain, weakness during the last 3 weeks	Symptom-based screening performed prospectively
				0-4	60			
				5-14	90			
Birungi et al.	2015-2016	Rwanda	Cross-sectional	0-14	216	Suggestive of TB / not suggestive of TB (*)	cough for ≥ 2 weeks, haemoptysis, fever, failure to gain weight, absence of appetite, fatigue, and the presence of lymphadenopathy	Symptom-based screening performed prospectively
				0-4	94			
				5-14	122			
Malik et	2014-	Pakistan	Cross-	0-14	906	Suggestive of TB	cough for ≥ 2	Symptom-based

al.	2016		sectional	0-4	529	/ not suggestive of TB	weeks, glandular swelling, fever lasting ≥ 2 weeks, night sweats and inappropriate weight loss (or failure to thrive)	screening performed prospectively
				5-14	377			
Fox et al.	2010 - 2015	Vietnam	Randomized control trial	0-14	4530	Normal/Abnormal Suggestive of TB/Abnormal not suggestive of TB (*)	WHO symptom screen	Symptom-based screening performed prospectively
				0-4	1161			
				5-14	3369			
Bonnet et al.	2012-2014	Uganda	Cohort	0-4	279	Normal/Abnormal Suggestive of TB/Abnormal not suggestive of TB (*)	cough, fever < 2 weeks, weight stagnation, reduced playfulness	Post-hoc symptom-based screening performed
Triasih et al.	2010-2012	Indonesia	Cohort	0-14	260	Normal/ abnormal (*)	cough, fever, poor appetite, weight loss, failure to thrive, hemoptysis, fatigue, night sweats	Symptom-based screening performed prospectively
				0-4	119			
				5-14	141			
Fortunato et al.	2007-2009	Angola	Cohort	0-4	124	No clear definition given	clinical examination	Unclear
Kruk et al.	2004	South Africa	Cohort	0-4	252	Certain TB/ Uncertain TB/ Certain not TB	fever, cough, wheezing, reduced playfulness, unusual fatigue, neck mass, weight loss	Symptom-based screening performed prospectively

**These articles had a chest radiography reading by two independent reviewers*

TB: tuberculosis

Table S4. TB disease occurrence during follow-up

Study	Follow-up duration	TB disease 0-4 n/N*(%)	TB disease 5-14 n/N*(%)
Srivastava et al.	9 months	1/ 50 (2.00 %)	21/102** (20.59%)
Hurega et al.	12 months	0/60 (0)	0/90 (0)
Bonnet et al.	9 months	1/279 (0.36%)	-
Triasih et al.	12 months	0/119 (0)	2/141 (1.41%)
Kruk et al.	12 months	2/252 (0.80%)	-

*the sample size shown here corresponds to the baseline, there were a few children lost to follow-up

**it is not clear whether all these children had a negative symptom screening and a negative chest radiography at baseline

Table S5. Risk of bias using the QUADAS-2 assessment tool

Study	Risk of bias				Applicability concerns		
	Patient selection	Symptom screening	Chest radiography	Flow and timing	Patient selection	Symptom screening	Chest radiography
Srivastava et al.	low	low	high	low	low	low	high
Hurega et al.	low	low	low	low	low	low	low
Birungi et al.	low	low	low	low	low	low	low
Malik et al.	low	low	high	unclear	low	low	high
Fox et al.	low	low	low	low	low	low	low
Bonnet et al.	low	low	low	low	low	high	low
Triasih et al.	low	low	low	low	low	low	high
Fortunato et al.	high	unclear	high	low	high	unclear	high
Kruk et al.	low	low	low	high	low	high	high
Kumar Dolla et al.	low	unclear	high	low	low	unclear	high

Figure S1. PRISMA flow diagram of the included articles

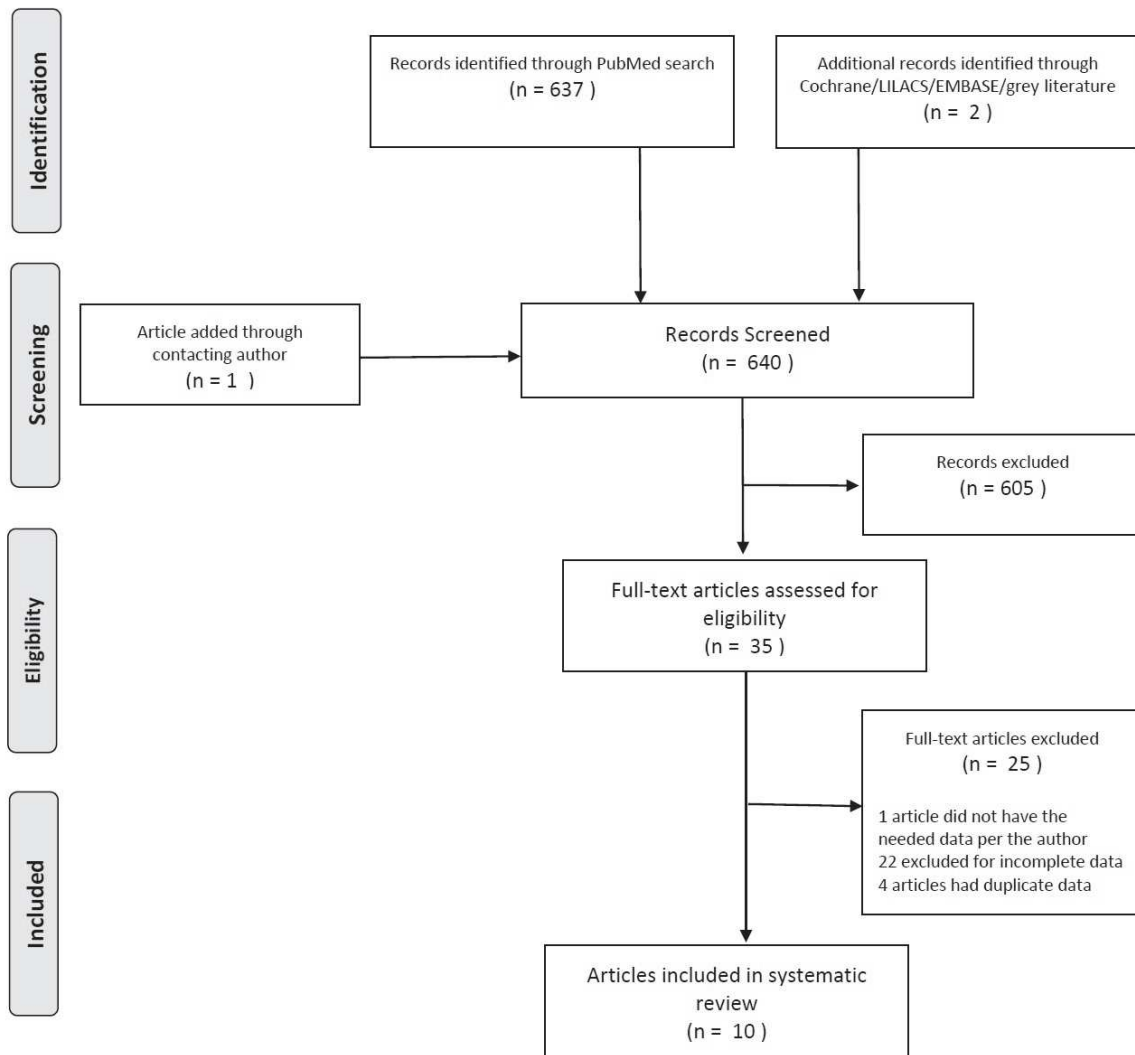


Figure S2. Forest plot for the proportion of negative symptom screening and with negative chest radiography in all studies

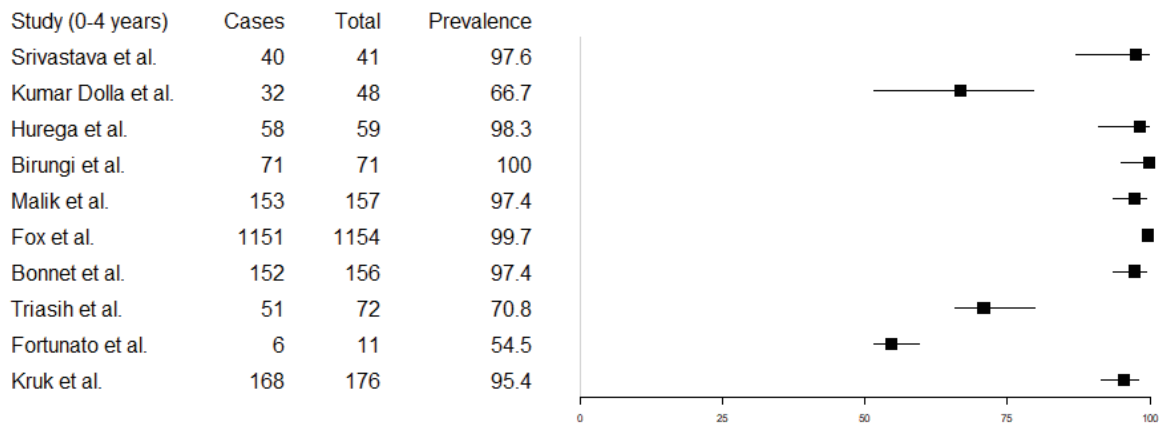


Figure S3. Forest plot for Sensitivity in the 0-4 age group (only studies with a double chest radiography reading and similar definitions of a TB-suggestive chest radiography)

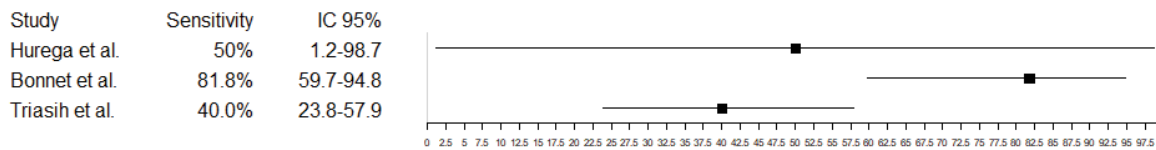
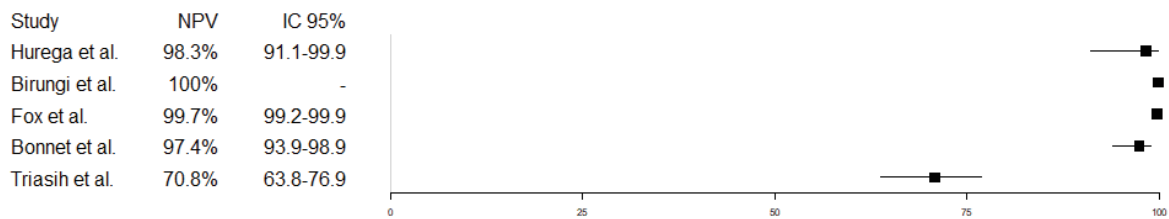


Figure S4. Forest plot for the negative predictive value in the 0-4 age group



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Oral abstract sessions, Saturday, 24 October S341

dren identified with active TB. Among all identified, 490 (98%) started treatment. The private sector yielded 37% of total child patients. The mean age for children diagnosed with TB was ten years, and 258 (51%) of them were female. Pulmonary and extra-pulmonary TB detected were 329 (66%) and 167 (34%), respectively. The number needed to screen was 433, and the number needed to test was 10. A 96% increase in child TB detection from the baseline in Mymensingh district was achieved through ACF.

Conclusions: Facility-based ACF intervention in both public and private settings can act as an effective mechanism for increased child TB detection to minimize the notification gap in Bangladesh.

OA-41-749-24 Role of urban DOTS approach on tuberculosis case finding among infertile women in Kabul: a document review

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Background and challenges to implementation: In 2019, totally 52,770 all form of TB cases detected. 57% (29873) of all cases of TB were among women. Of all TB cases, 13,720 (26%) were extra pulmonary (EP) TB, makes 37 cases per 100,000. Considering diagnostic limitation of EP TB, the actual EPTB could be higher than reported. The USAID-funded STAR project supported NTP to sustain urban DOTS approach in 26 private hospitals in Kabul including Shefajo private hospital. This hospital attended infertile women and tested them for TB. We evaluated the yield of TB among infertile women.

Intervention or response: We signed a memorandum of understanding with obstetrics & gynecology (Ob/Gyn) Shefajo hospital and conducting a baseline assessment. The NTP trained medical staff on: TB SOPs, improved supervision, monitoring, and feedback; and conducting active screening to identify presumptive TB patients. The staffs collected cervix swab and tested by GeneXpert or PCR technology. The NTP technical team reviewed data collected from 2017-2019 using standard NTP reporting tools.

Results/Impact: From 2017-2019, approximately, 2,400 Ob/Gyn patients attended this hospital and of them, 270 (11.2%) were infertile that tested for genital TB. The mean age was 25 years with average infertility duration of 5years. Finally, 190(70%) of them were diagnosed as TB. All were put on standard NTP treatment regimen. The hospital followed all for monthly check up and follows up tests. Among all on TB treatment, 91(48%) became pregnant at the end of TB treatment. The yield of TB was 7600 in 100,000 among infertile women that is 40 times higher than estimates of 189 in 100,000 for general population.

Conclusions: Urban DOTS services in Ob/Gyn private hospital in Kabul made significant improvements in case finding among women and recommend engaging other Ob/Gyn private hospital in TB service provision. Further, the yield of genital TB among women particularly infertile is higher than TB among general population.

OA-41-750-24 Systematic Review of Symptom-Based Screening and Added Value of Chest Radiography in Screening Pediatric Contacts for Tuberculosis in High-Incidence Countries

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Background: The WHO recommends tuberculosis (TB) preventive therapy in child contacts of confirmed index cases after exclusion of active TB. Symptom-based screening remains the most feasible approach to exclude TB, however its capacity to rule out TB compared to chest radiography in different age bands has been questioned.

We performed a systematic review to assess the performance of symptom-based screening as compared to chest radiography in household child contacts below 15 years in the WHO high-burden countries.

Design/Methods: Screening of manuscripts published prior February 2019, followed by data extraction was performed by two independent reviewers. Primary outcomes are the concordance between symptom-based screening and chest radiography using the prevalence adjusted bias adjusted kappa coefficient (PABAK) and the proportion of asymptomatic children with negative chest radiography. Secondary outcomes include negative predictive value (NPV) and sensitivity of symptom-based screening against chest radiography read by two independent experts and the proportion of asymptomatic children who developed TB during follow-up. Subgroup analysis in children below or above 5 years was performed.

Abstract at the Union World Conference on Lung Health 2020 (2/2)

S342 Oral abstract sessions, Saturday, 24 October

Results: Of 577 identified articles, 30 were assessed for full text eligibility and six met criteria for inclusion. Overall, PABAK varied between 0.16 (95 % confidence interval (CI) 0,04–0,28) and 0.69 (0,59–0,79) and the percentage of asymptomatic children with a negative chest radiography ranged between 54.5–100% (Table).

Study, year	Country	Age group	Sample size	SS- with CXR-/SS+	PABAK (95% CI)	Agreement	Sensitivity (95% CI)	NPV (95% CI)
Birung et al. 2015-2016	Rwanda	0-4	94	100,0%	0,51 (0,33 – 0,69)	moderate	100,0%	100,0%
		5-14	122	100,0%	0,84 (0,74 – 0,93)	almost perfect	100,0%	100,0%
Melik et al. 2014-2016	Pakistan	0-4	529	97,8%	0,35 (0,27 – 0,43)	fair	one radiography reviewer	
		5-14	377	87,5%	0,89 (0,84 – 0,93)	almost perfect		
Bornel et al. 2012-2014	Uganda	0-4	279	97,4%	0,22 (0,10 – 0,33)	fair	81,8% (59,72%–94,81%)	97,4% (93,9%–98,9%)
Tineoh et al. 2010-2012	Indonesia	0-4	119	70,8%	0,09 (-0,06 – 0,27)	slight	40,0% (23,87%–57,9%)	70,8% (63,8%–76,9%)
		5-14	141	84,6%	0,22 (0,06 – 0,38)	fair	39,1% (19,7%–61,5%)	84,6% (79,4%–88,7%)
Fortunelo et al. 2007-2009	Angole	0-4	124	54,5%	0,23 (0,05 – 0,40)	fair	one radiography reviewer	
Kruk et al. 2004	South Africa	0-4	252	95,5%	0,59 (0,49 – 0,69)	moderate	one radiography reviewer	

[Table. *SS- with CXR-/SS- = proportion with negative symptom screening (SS) and negative chest radiograph (CXR) out of all children with negative symptom screening.]

In three studies with follow-up data, only 0.4-1.2% of asymptomatic children developed TB.

Conclusions: Despite low concordance between symptom-based screening and chest radiography, most studies showed that symptom-based screening alone is effective in classifying children unlikely to have tuberculosis, suggesting that they don't need chest radiography. Lack of standardization in chest radiography reporting and use of different definitions could explain low performance in some studies.

OA-41-751-24 A systematic review of Xpert MTB/RIF and Xpert Ultra diagnostic accuracy for detection of active pulmonary tuberculosis and rifampicin resistance in children

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Background: Xpert MTB/RIF and Xpert Ultra are World Health Organization (WHO)-recommended molecular tests that detect tuberculosis in children with signs and symptoms of tuberculosis. We performed a systematic review on the diagnostic accuracy of these tests in children (< 15 years) with presumed pulmonary tuberculosis for an updated WHO policy on molecular assays intended as initial tests for diagnosis of pulmonary and extrapulmonary tuberculosis and rifampicin resistance.

Design/Methods: Searched multiple databases to 29 April 2019 without language restriction for studies that evaluated Xpert MTB/RIF and Xpert Ultra in sputum, gastric aspirate, stool, or nasopharyngeal specimens. For tuberculosis detection, reference standards were culture and a composite reference standard. Two review authors independently extracted data and assessed study quality using QUADAS-2. We used the bivariate model to estimate pooled sensitivity and specificity with 95% confidence intervals (CIs).

Results: We included 49 studies, which provided 299 data sets (68,544 participants) for pulmonary tuberculosis. Xpert MTB/RIF pooled sensitivity (defined by culture) was 64.6% (55.3 to 72.9) for sputum, 45.7% (27.6 to 65.1) for nasopharyngeal aspiration, 73.0% (52.9 to 86.7) for gastric aspiration specimens, 61.5% (44.1 to 76.4) for stool specimens. Pooled specificity ranged between 98.1% and 100%. Xpert Ultra pooled sensitivity (defined by culture) was 72.8% (64.7 to 79.6) for sputum and 45.7% (28.9 to 63.3) for nasopharyngeal aspirates. Pooled specificity was > 97.5% for both specimen types. Risk of bias was low for all domains, except unclear for the reference standard, because many studies collected only one specimen for culture.

Conclusions: We found Xpert MTB/RIF sensitivity to vary by specimen type, with gastric aspirate specimens having the highest sensitivity, followed by sputum and stool, and nasopharyngeal specimens the lowest; specificity in all specimens was > 98%. Compared with Xpert MTB/RIF, Xpert Ultra had higher sensitivity and slightly lower specificity for sputum and nasopharyngeal specimens.

Symptom screening is a good tool for excluding tuberculosis disease in household contact children in low resource countries

Context

Tuberculosis preventive therapy (TPT) is used in order to avoid the onset of tuberculosis (TB) disease in household contact children. Chest radiography is recommended to exclude TB disease prior to initiating TPT, but accessibility is limited in low resource countries. In this specific context, the World Health Organization (WHO) guidelines acknowledge that for child contacts under five years, a negative symptom-based screening is sufficient to exclude active TB, but in child contacts older than five, a chest radiography is still recommended due to lack of data.

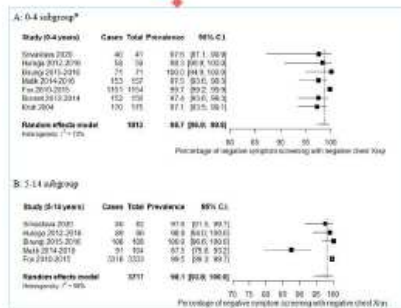
We performed a systematic review and meta-analysis to assess the performance of symptom-based screening compared to chest radiography in household contacts under fifteen in low and middle-income countries.

Methods

- Articles were screened before Oct 2020
- 2 independent reviewers
- Standardized data collection tool
- Inclusion criteria:**
 - Randomized controlled trials, cohorts, cross-sectional studies
 - Reports TB symptom screening and chest radiography
 - In children (0-14)
 - In low/middle income countries
- Outcomes:**
 - Percentage of negative symptom screening with negative chest radiography
 - Concordance (prevalence adjusted bias adjusted kappa - PABAK)
 - % TB disease under follow-up
- Risk of bias:** QUADAS-2
- Analysis:**
 - 2 subgroups: 0-4 years (A), 5-14 years (B)
 - Meta-analysis on studies that used similar definitions of symptom screening and chest radiography; random effects model

Key Results

- 640 records were screened and 10 included
- PABAK: 0-4 years: 0.09 - 0.97
- Heterogeneity in TB symptom screening definitions and in CXR definitions
- Meta-analysis

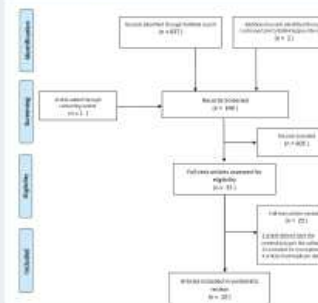


- TB disease during follow-up:
 - A: 0-2% in the 0-4 subgroup (all on TPT)
 - B: 0-20.6% in the 5-14 subgroup (not on TPT)

Conclusion

A negative symptom screening is sufficient to rule out TB disease, supporting the WHO recommendation to use symptom-based screening alone when chest radiography is not available. The main limitation is the absence of a robust reference standard for evaluation of TB screening tools in children.

Flow diagram



Characteristics of included studies

Study	Country	Year	Study type	Age group	Sample size	Chest radiographic definition	TB negative symptoms	TB disease during follow-up	Taxonomy
Shindeva et al.	India	2020	Cohort	0-4	133	Suggestive of TB (not suggestive of TB)	None, cough, weight loss, pleuritic chest pain, fever, night sweats, hemoptysis, loss of appetite, weight loss, night sweats, loss of appetite, weight loss, loss of appetite, weight loss	0-2%	Symptom screen positive
Hwang et al.	India	2016	Cohort	0-4	209	Suggestive of TB (not suggestive of TB)	None, cough, weight loss, pleuritic chest pain, fever, night sweats, hemoptysis, loss of appetite, weight loss, night sweats, loss of appetite, weight loss	0%	Not defined
Hwang et al.	Indonesia	2012, 2016	Cohort	0-4	46	Suggestive of TB (not suggestive of TB)	None, cough, weight loss, pleuritic chest pain, fever, night sweats, hemoptysis, loss of appetite, weight loss, night sweats, loss of appetite, weight loss	0%	Symptom screen positive
Hwang et al.	Indonesia	2012, 2016	Cohort	0-4	99	Suggestive of TB (not suggestive of TB)	None, cough, weight loss, pleuritic chest pain, fever, night sweats, hemoptysis, loss of appetite, weight loss, night sweats, loss of appetite, weight loss	0%	Symptom screen positive
Hwang et al.	Indonesia	2012, 2016	Cohort	0-4	122	Suggestive of TB (not suggestive of TB)	None, cough, weight loss, pleuritic chest pain, fever, night sweats, hemoptysis, loss of appetite, weight loss, night sweats, loss of appetite, weight loss	0%	Symptom screen positive
Shindeva et al.	India	2020	Cohort	0-4	43	Suggestive of TB (not suggestive of TB)	None, cough, weight loss, pleuritic chest pain, fever, night sweats, hemoptysis, loss of appetite, weight loss, night sweats, loss of appetite, weight loss	0%	Symptom screen positive
Fai et al.	Indonesia	2015	Randomized controlled trial	0-4	1180	Suggestive of TB (not suggestive of TB)	None, cough, weight loss, pleuritic chest pain, fever, night sweats, hemoptysis, loss of appetite, weight loss, night sweats, loss of appetite, weight loss	0%	Symptom screen positive
Hwang et al.	Indonesia	2012, 2016	Cohort	0-4	279	Suggestive of TB (not suggestive of TB)	None, cough, weight loss, pleuritic chest pain, fever, night sweats, hemoptysis, loss of appetite, weight loss, night sweats, loss of appetite, weight loss	0%	Not defined
Shindeva et al.	Indonesia	2020	Cohort	0-4	43	Suggestive of TB (not suggestive of TB)	None, cough, weight loss, pleuritic chest pain, fever, night sweats, hemoptysis, loss of appetite, weight loss, night sweats, loss of appetite, weight loss	0%	Symptom screen positive
Shindeva et al.	Indonesia	2020	Cohort	0-4	133	Suggestive of TB (not suggestive of TB)	None, cough, weight loss, pleuritic chest pain, fever, night sweats, hemoptysis, loss of appetite, weight loss, night sweats, loss of appetite, weight loss	0%	Symptom screen positive
Shindeva et al.	Indonesia	2020	Cohort	0-4	133	Suggestive of TB (not suggestive of TB)	None, cough, weight loss, pleuritic chest pain, fever, night sweats, hemoptysis, loss of appetite, weight loss, night sweats, loss of appetite, weight loss	0%	Symptom screen positive

Symptom-Based Screening Versus Chest Radiography for TB Child Contacts: A Systematic Review and Meta-analysis

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4.2. Community intervention for child tuberculosis active contact investigation and management: study protocol for a parallel cluster randomized controlled trial

4.2.1. Background

Contact investigation is a cornerstone element for diminishing the burden of TB in low-resource settings. It is defined as a systematic process for identifying previously undiagnosed people with TB among the contacts of an index case. The main challenge this activity is facing at the moment is that TB screening is offered mainly at health facilities. TPT initiation and follow-up are offered exclusively at the health facility under programmatic guidance. In spite the fact that TB treatment and TPT are provided free of charge, the index cases do not always bring their children to the health facility for screening and TPT initiation. Therefore, many household child contacts remain undiagnosed for TB and many do not benefit from TPT. There are many barriers to facility-based screening that can be classified in patient-related and health-system-related. Patient-related challenges include transport cost, stigma, competing priorities and the perception that children in apparent good health don't need to consult. One solution to many of these barriers could be offering contact screening and TPT in the household, and this has the potential of increasing the timely detection of TB cases and the uptake of TPT. Up to this date there has been no randomized controlled trial evaluating community-based TB screening and TPT management for contact children. The purpose of this work was to develop the study protocol which would bring a high level of evidence for the effectiveness of a community intervention for TB contact investigation and TPT management. The CONTACT study is a research study part of the CaP TB project, funded by Unitaid and implemented by EGPAF. The study is overseen since its conception by a scientific advisory committee composed of experts in pediatric TB, pragmatic TB interventions, statistical analysis.

4.2.2. Study protocol

Objectives

The primary objective of the study is to compare the proportion of household child TB contacts eligible for TPT (<5 years or 5-14 HIV-positive) who initiate and complete TPT under a facility-

based standard of care and under a decentralized community-based intervention model of care for contact screening and management.

The secondary objectives compare the community and facility models in terms of

- cascade of care of TPT initiation and completion in child contacts < 5 years or children living with HIV 5–14 years
- cascade of care for TB detection and treatment in all included contacts
- tolerability and adherence in children initiated on TPT
- acceptability and feasibility of the two models by the parents/guardians, health personnel, and community
- the effect of the community-based intervention on the number of adult contacts diagnosed with TB; and the cost-effectiveness

The number of children and adults diagnosed with TB and the number of children initiated on TPT will be also compared before and after the intervention.

Design

This research is designed as an international cluster randomized controlled trial. The cluster randomization was chosen because the intervention touches the TB services of a whole health facility and the communities in the afferent catchment area, therefore an individual randomization would not have been adapted. A cluster is defined by a health facility and its catchment area. Twenty clusters are stratified by country and ten are randomized to the community-based group and ten to the facility-based group.

The study contains three phases:

1. Baseline phase – assessment of study feasibility
2. Intervention phase – participant recruitment and study data collection
3. Explanatory phase – effectiveness analysis, cost-effectiveness analysis, post-intervention acceptability and process evaluation.

Setting

The CONTACT study is implemented in two sub-Saharan African countries with different programmatic delivery of TB services. In Cameroon, TB services are offered in secondary level health facilities. In Uganda, TB services are decentralized to primary healthcare (PHC) level and

community activities for TB care have already been implemented by the NTP.

Intervention description

In the facility-based model (standard of care), children are screened at facility (Cameroon and Uganda) or household level (Uganda) by the TB focal person. TPT initiation and refills are only done at facility level by the TB focal person. Adherence and tolerability assessments are part of the follow-up visit procedures.

In the intervention group (community-based model), child contacts will be screened in the household by a CHW/community nurse. Contacts with symptoms suggestive of TB are referred to the facility for TB investigations. Contacts with symptoms not suggestive of TB will be reassessed after two weeks. Asymptomatic child contacts from high-risk groups (<5 years or HIV infected 5-14 years) are initiated on preventive therapy (3 months isoniazid-rifampicin or 6 months isoniazid) in the household. Refills of TPT are done in the communities by the CHW/community nurse. TB symptoms, TPT adherence and tolerability are evaluated at each follow-up visit and in case of suspicion of TB, or safety issues, the child is referred to the health facility for evaluation.

Population

Index cases are newly bacteriologically confirmed TB cases, less than a month since diagnosis, 15 years or older, who report child contacts and who are willing to participate. The study excludes prisoners, MDR-TB cases and index cases whose household has already been screened under the study.

Contact cases are all contacts of index cases who respond to the WHO definition of TB contact case (see section). In the facility-based model in Cameroon, all self-referred contacts are included (the NTP recommends only for children < 5 years or HIV infected/exposed 5-14 years) to come back to the health facility. Contacts already on TB treatment or TPT are excluded.

Cluster selection and sample size

All clusters have been selected from facilities supported by the CaP TB program on TB diagnosis and treatment. A median of 75 index cases per cluster was necessary to reach the desired sample size of 1500 child contacts. With an intra-cluster variability of 50%, health facilities with a minimum of 50 TB patients per year were included. Priority was given to rural, semi-rural, or semi-urban facilities, but urban facilities were also included due to lack of clusters with the necessary recruitment capacity. In each country, 10 clusters are selected. The randomization is stratified by country in order to have 5 clusters with the community-based intervention and 5 with the facility-

based SOC. In Cameroon clusters are selected in the Center and Littoral regions. In Uganda, they are selected in the South West region.

Statistical analysis

The denominator for the analysis of the primary endpoint is the number of child contacts < 5 years and HIV-infected 5–14 years declared by the index case at the facility during the inclusion visit. Sensitivity analysis will be performed, taking into account the included children. The main analysis will be under an intention to treat approach, as the results of this study will potentially be used for real-life scaled-up implementation. The statistical analysis will be done using a generalized linear mixed model with a binomial distribution and a logit link function.

Ethics

The study protocol has been approved by the WHO Ethics Research Committee, the Advarra Institutional Review Board and by the two local ethics committees: Cameroon National Ethics Committee for Human Health Research and Research Ethics Committee of the Mbarara University of Science and Technology in Uganda. In addition, administrative approvals were needed from the Direction for Operational Research from the Ministry of Health in Cameroon and the Ugandan National Council for Science and Technology in Uganda.

All participants sign an informed consent prior to inclusions and children older than 7 years in Cameroon and 8 years in Uganda sign an assent form.

4.2.3. Discussion

This research will bring the needed evidence for alternative TB services which have the potential of being more convenient for the patient and his family in a patient-centered care perspective.

Main strengths of the study include the randomized controlled design, mixed methods assessments of feasibility and process evaluation, cost-effectiveness evaluation and the pragmatic implementation in two countries with similar burden of TB, but different healthcare services organization. The different study settings ensure a higher external validity of the study results.

Limitations include the low number of clusters and the improved standard of care model under CaP TB, which does not fully represent the existing standard of care. Operational challenges inevitably arise for this type of pragmatic study and they include national guidelines requiring protocol amendments, stock-outs of TB drugs and Xpert MTB/RIF cartridges, concurrent

community-based interventions, TB staff workload and turnover.

This is a first step in curbing the TB epidemic, but household contact investigation alone will not solve all existing gaps in TB care. A comprehensive community-wide approach integrating household contact investigation could be one of the directions future TB strategies could employ.

4.2.4. Involvement in this work

I participated in stakeholder and scientific advisory committee discussions on how to best develop a community intervention in Cameroon and Uganda. In addition to these elements, I have used findings from the literature to write the study protocol under the guidance of Dr Maryline Bonnet. I have prepared the first protocol submission package for the different Ethics Research Committees and I have followed up each protocol amendment, making the necessary changes in the new versions of the protocol. I have trained the country study teams on research procedures from the protocol and on the intervention and standard of care model. I presented the study protocol to the TB Research Forum, a recurrent research meeting organized by the NTP in Uganda, in March 2019 and I wrote the protocol article.

4.2.5. Scientific communications:

Article:


- Vasiliu A, Eymard-Duvernay S, Tchounga B, Atwine D, de Carvalho E, Ouedraogo S, et al. Community intervention for child tuberculosis active contact investigation and management: study protocol for a parallel cluster randomized controlled trial. *Trials*. 2021;22:180.

STUDY PROTOCOL

Open Access



Community intervention for child tuberculosis active contact investigation and management: study protocol for a parallel cluster randomized controlled trial

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Abstract

Background: There are major gaps in the management of pediatric tuberculosis (TB) contact investigation for rapid identification of active tuberculosis and initiation of preventive therapy. This study aims to evaluate the impact of a community-based intervention as compared to facility-based model for the management of children in contact with bacteriologically confirmed pulmonary TB adults in low-resource high-burden settings.

Methods/design: This multicenter parallel open-label cluster randomized controlled trial is composed of three phases: I, baseline phase in which retrospective data are collected, quality of data recording in facility registers is checked, and expected acceptability and feasibility of the intervention is assessed; II, intervention phase with enrolment of index cases and contact cases in either facility- or community-based models; and III, explanatory phase including endpoint data analysis, cost-effectiveness analysis, and post-intervention acceptability assessment by healthcare providers and beneficiaries. The study uses both quantitative and qualitative analysis methods. The community-based intervention includes identification and screening of all household contacts, referral of contacts with TB-suggestive symptoms to the facility for investigation, and household initiation of preventive therapy with follow-up of eligible child contacts by community healthcare workers, i.e., all young (< 5 years) child contacts or older (5–14 years) child contacts living with HIV, and with no evidence of TB disease. Twenty clusters representing TB diagnostic and treatment facilities with their catchment areas are randomized in a 1:1 ratio to either the community-based intervention arm or the facility-based standard of care arm in Cameroon and Uganda. Randomization was stratified by country and constrained on the number of index cases per cluster. The primary endpoint is the proportion of eligible child contacts who initiate and complete the preventive therapy. The sample size is of 1500 child contacts to identify a 10% difference between the arms with the assumption that 60% of children will complete the preventive therapy in the standard of care arm.

(Continued on next page)

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Discussion: This study will provide evidence of the impact of a community-based intervention on household child contact screening and management of TB preventive therapy in order to improve care and prevention of childhood TB in low-resource high-burden settings.

Trial registration: ClinicalTrials.gov [NCT03832023](https://clinicaltrials.gov/ct2/show/study/NCT03832023). Registered on 6 February 2019

Keywords: Contact tracing, Preventive therapy, Pediatric tuberculosis, Community intervention, Tuberculosis symptom screening, Cluster randomized controlled trial

Background

Tuberculosis (TB) is an infectious disease causing incident cases of disease in around 10 million people worldwide in 2018 [1]. The World Health Organization (WHO) estimated that 11% of the TB cases in 2018 were in children (< 15 years). However, a modeling study has estimated that the pediatric caseload in high-burden countries is as high as 15–20% of all TB cases [2]. The mortality rate in undetected untreated children is estimated to be 21.9% for children of all ages and rises to 43.6% in young children of less than 5 years [3]. Improving case detection and treatment of this high-risk group of young children is particularly challenging due to diagnostic limitations and clinical overlap with other common severe diseases of infants and young children in resource-limited settings.

Research has consistently shown that TB disease in young children usually occurs soon after exposure and infection, that the risk of disease if infected is high, and that TB preventive therapy (TPT) can significantly reduce the risk of disease following exposure and infection [4]. A meta-analysis reported that 10% of young child contacts had TB disease at the time of screening, and 35% had evidence of infection [5]. A recent individualized participant meta-analysis found that the effectiveness of tuberculosis preventive treatment (TPT) was 63% (95% CI 53–70%) among all exposed children and 85% (95% CI 80–89%) among those with evidence of infection [4]. Therefore, the rapid identification and management of exposed children in the households of TB disease cases is a critical opportunity to detect, treat, and prevent TB. Although recommended for decades, household child contact screening and TPT have been poorly implemented in high-burden and resource-limited countries. For many years, children were considered lower priority due to being less infectious and therefore contributing less to TB transmission than adults [6].

The WHO End TB Strategy and ambitious targets for coverage of screening and TPT in the Global Plan to End TB demonstrate political will and provide renewed opportunity to close the wide policy-practice gap [7, 8]. The policy-practice gaps observed

in the screening and management of child contacts are driven by health system and human resource challenges as well as the many challenges faced by families in bringing their children to the health facility [9–13]. In most low-resource countries, the index case is asked to bring all child contacts to the health facility for TB screening, and yet many barriers arise when applying this recommendation such as scheduling or financial challenges, transport costs, long waiting periods in settings with risks of further exposure, and families or even healthcare workers' reluctance to apply these guidelines as they do not always understand the rationale, potential benefits, or risks when the child is well [13–17]. Community-based household contact screening of children in the household is likely to improve TB disease case detection [8, 18–20].

The use of classical tuberculin skin test (TST) to identify child contact with TB infection who will benefit from the TPT and the need of chest radiography (CXR) in addition to symptom screening to exclude TB disease before initiation of TPT have both operational challenge that contributes to the lost proportion of child contacts initiated on TPT for a long time [13]. However, there is evidence that the additional yield of TB disease detection from CXR in asymptomatic child contacts is extremely low [9, 21–23]. In addition, WHO has recommended since 2006 that high-risk child TB contacts—young (< 5 years) or are living with human immunodeficiency virus (HIV) of any age—receive TPT after exclusion of TB disease without systematically confirming TB infection with TST [24, 25]. Therefore, a symptom-based approach that does not require further investigations for asymptomatic child contacts could facilitate a more decentralized, community-based implementation to initiate TPT in asymptomatic children [8]. In addition, the recent WHO recommendations [6] that include shorter TPT combination regimens (isoniazid and rifampicin or rifapentine for 3 months) are associated with improved adherence compared to the standard TPT regimen of isoniazid monotherapy for at least 6 months and provide an important opportunity for increasing completion of TPT [9, 26, 27]. Further, follow-up of children receiving TPT at the household could further improve TPT completion

rates and could be easily integrated with activities to support treatment of TB disease of the index cases in the household.

There is no published study that has evaluated the impact on the cascade of care of pediatric TB case detection and preventive therapy management of a community-based approach compared to a facility-based standard of care. We therefore aim to evaluate the implementation of a community-based approach to child TB contact screening and management in two TB-endemic African countries.

Methods

Study objective and endpoints

The primary objective of this study is to compare the proportion of household child TB contacts eligible for TPT who initiate and complete TPT under a facility-based standard of care and under a decentralized community-based intervention model of care for contact screening and management.

The corresponding primary endpoint is the proportion of child TB contacts < 5 years of age and HIV-infected children of 5–14 years of age who are declared by the index case and who initiate and complete the TPT.

The secondary objectives compare the aforementioned models in terms of (i) cascade of care of TPT initiation and completion in child contacts < 5 years or HIV-positive children 5–14 years; (ii) cascade of care for TB detection and treatment in all included contacts; (iii) tolerability and adherence in children initiated on TPT; (iv) acceptability and feasibility of the two models by the parents/guardians, health personnel, and community; (v) the effect of the community-based intervention on the number of adult contacts diagnosed with TB; and the cost-effectiveness. The number of children and adults diagnosed with TB and the number of children initiated on TPT will be also compared before and after the intervention.

The secondary endpoints of the study are presented in Table 1.

Study design

This is a two-arm parallel cluster randomized study comparing two models of care for TB contact investigation and management. This study contains three phases:

1. Baseline phase (phase I) in which retrospective data collection and register quality checks were done in order to assess if the facility registers could be a reliable source of documents for the study. During this phase, there was also a baseline qualitative assessment with adult TB patients who are parents and stakeholders to better prepare the intervention

phase and assess the acceptability and feasibility of the proposed activities.

2. Intervention phase (phase II) includes implementation and participant recruitment in the two models of care and study data collection.
3. Explanatory phase (phase III) contains the endpoint analysis and reporting, a cost-effectiveness analysis, and a post-intervention qualitative assessment with adult TB patients who are parents and cluster stakeholders to collect the acceptability of the implemented package.

This research is known under the name of CONTACT study (Community Intervention for Tuberculosis Active Contact Tracing and Preventive Therapy) and represents a research project embedded in a multi-country pediatric TB implementation program called Catalyzing Pediatric TB Innovations (CaP TB) led by the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) and funded by Unitaid.

Study setting

This study is conducted in two high TB incidence, resource-limited African countries: Cameroon located in West Africa and Uganda in East Africa, with important differences in programmatic delivery of TB services. In Cameroon, TB care and management is centralized. Only secondary-level health facilities have TB laboratory diagnostic facilities and TB patients can only access care and drugs from these health facilities. In Uganda, TB management is decentralized to the primary healthcare level. In both countries, national guidelines [28, 29] at the time of this study development recommended contact investigation and screening as well as TPT with 6 months of daily isoniazid (6H) for eligible children. However, coverage of TPT for eligible children below 5 years is low in both countries. WHO recently reported that only 24% and 15% of eligible children were initiated on TPT in 2018 in Cameroon and Uganda respectively [1].

Description of the intervention

Facility-based model

This model implements a “passive” approach to the screening and management of household contacts (see definition in the “Study population” section) at the facility level as per current practice. Implementation follows current National Tuberculosis Program (NTP) recommendations, except that a 3-month regimen of daily rifampicin-isoniazid (3RH) as a fixed-dose combination (FDC) is offered as TPT to eligible child contacts. In the context of the study, sites also benefit from additional data collection and trainings with follow-up support for the facility staff.

Table 1 Secondary endpoints of the CONTACT study

General secondary endpoints	Detailed secondary endpoints
Cascade of care for the initiation and completion of TPT of child contacts < 5 years or HIV-infected 5–14 years and reasons of dropouts at different steps of the cascade	Number of screened children and proportion of children screened among child contacts < 5 years or HIV-infected 5–14 years declared by the index case Proportion of children potentially eligible for TPT: TB disease excluded Proportion of children eligible for TPT after exclusion of contraindication to TPT Proportion of children started on TPT among those eligible for TPT Proportion of children who did not complete TPT among those started on TPT and reasons of interruptions
Cascade of care for TB detection of child contacts	Proportion of children with symptoms suggestive of TB: presumptive TB Proportion of presumptive TB cases investigated for TB Proportion of children diagnosed with TB Proportion of children with TB diagnosis who are started on TB treatment
Cascade of care for TB detection of adult contacts	Number of adults screened and proportion of adults screened among household identified adult contacts Proportion of adults with symptoms suggestive of TB: presumptive TB cases Proportion of adults presumptive TB cases diagnosed with TB
Safety and treatment adherence for children under TPT	Proportion of children with serious adverse events Proportion of children with adverse events of interest: peripheral neuropathy, clinical hepatotoxicity Ratio of dose taken as indicated (ticked) on the treatment card by the parent/guardian over the total number of doses to be taken by prescription
Endpoints at 6 months	Treatment outcomes of children started on TB treatment Proportion of children diagnosed with TB after initiation of TPT: during and after TPT Proportion of children diagnosed with TB among those who were not started on TPT and were not diagnosed with TB at baseline assessment
Before-after comparison for TB adult and pediatric cases and for TPT initiation and completion from health facility registers	Number of patients diagnosed with TB and registered Proportion of children among all patients diagnosed with TB and registered TB treatment outcomes of patients (adults and children) diagnosed with TB and registered Number of children started on TPT
Acceptability and feasibility of the intervention	Completion rate of children started on TPT Attitudes, willingness, and motivation to have a visit in their household Myths, anticipated fears, stigma, and risks of having a visit in their household Actual experiences with household visits Perception of the disease, its risk, and the notion of prevention, including TPT Description of critical events during house visits and how these were dealt with Identification of main constraints

Table 1 Secondary endpoints of the CONTACT study (*Continued*)

General secondary endpoints	Detailed secondary endpoints
Fidelity of the study	Proportion of delivered activities compared to the intended activities of the model
Cost-effectiveness of the intervention	Costs of CHW/community nurse assessment and treatment
	Costs of facility-based assessment and treatment
	Other facility costs (overheads, diagnosis, hospitalizations)
	Direct parent/guardian costs (related to care)
	Indirect parent/guardian costs (unrelated to care, e.g., dissaving, travel costs)

When a person is diagnosed with bacteriologically confirmed pulmonary TB (index case), the facility staff in charge of TB (TB focal person) asks the index case to bring all household contacts with TB-related symptoms, all young (< 5 years) child contacts or older (5–14 years) child contacts living with HIV or exposed to HIV, irrespective of symptoms, to the health facility for evaluation for TB disease or for eligibility for TPT. This facility-based model is currently implemented in district hospitals in Cameroon for child contacts under 5 years old, but poorly applied for child contacts 5–14 living with HIV. In Uganda, the NTP allows household contact tracing when feasible but evaluation, TPT initiation, and follow-up are required to be done at the facility. In practice, due to lack of transport, the household contact tracing was poorly implemented. In both countries, at facility, TB investigations include clinical examination, sample collection for smear microscopy or Xpert MTB/RIF testing, and CXR when available and indicated, i.e., Xpert is negative or not done. Any contact diagnosed with TB is commenced on TB treatment, registered, and provided with treatment support and follow-up as per NTP guidelines. All sites are supported by the CaP TB program reducing the risk of heterogeneity of diagnosis and treatment of pediatric TB between sites and the two countries. Asymptomatic children who are eligible to receive TPT as 3RH (or 6H if drug-drug interactions with antiretroviral therapy preclude the use of rifampicin) are initiated at the facility with monthly follow-up (Fig. 1). The schedule of the facility-based model is presented in Table 2.

Community-based model

The intervention model is a decentralized, “active” approach to the screening and management of household

contacts and is community-based. When an index case is diagnosed with bacteriologically confirmed pulmonary TB, the TB focal person asks whether s/he has child contacts in the household, and if so, then asks whether s/he is willing to receive a team in his/her household for contact symptom screening. If they agree, then an appointment is made and a team comprising a trained community health worker (CHW) and a research assistant goes in the household to screen all contacts (children and adults). If the index case does not have contact children in their household, then s/he is not included in the study, but contact investigation is done under routine care by the TB focal person. During the contact screening visit, the contacts who present symptoms of TB are referred to the health facility for TB investigations. Those who are asymptomatic and eligible for TPT (i.e., < 5 years irrespective of HIV status or 5–14 years and living with HIV) receive another visit by the TB focal person or TB nurse to initiate 3RH (or 6H if drug-drug interactions with antiretroviral therapy preclude the use of rifampicin). The follow-up is done at the household by the CHW after 1 week, 2 weeks, and then monthly in order to rapidly identify the children who develop TB symptoms in the community. The CHW collects the TPT at the health facility before each household visit and brings the remaining pills and documents back to the facility after the visit. During the follow-up visits, the CHW repeats the TB symptom screening, assesses the child’s TPT tolerability and adherence, and assesses the presence of any critical sign. If the child presents critical danger signs, tolerability problems, or TB symptoms, s/he is immediately referred to the health facility for a clinician to consult them (Fig. 2). The schedule of the community-based model is presented in Table 2.

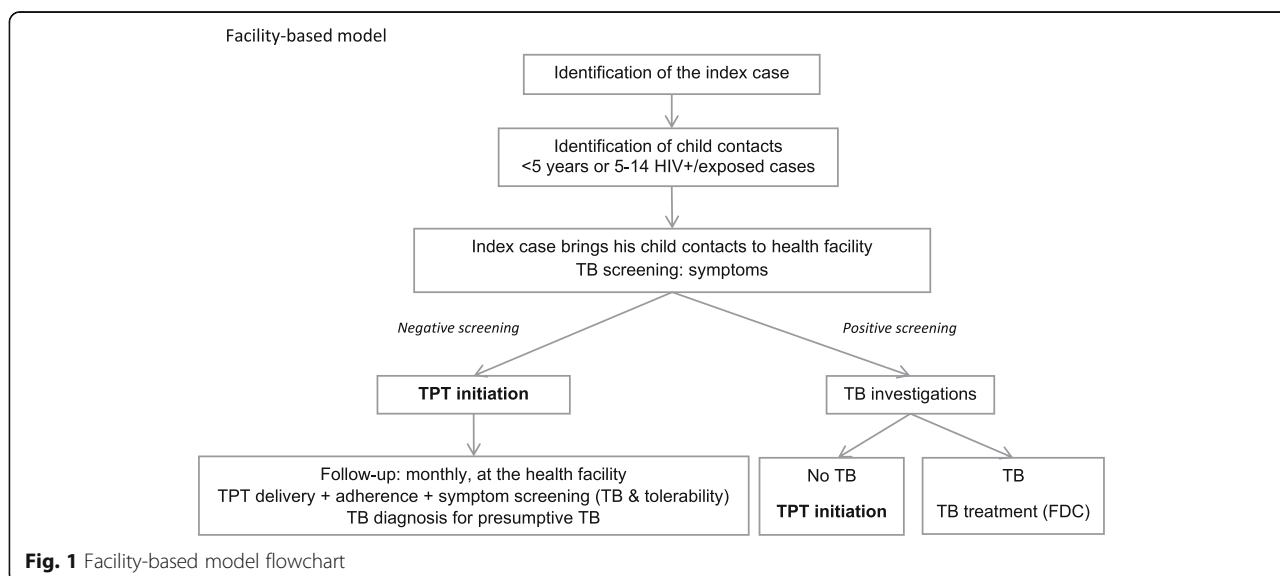


Fig. 1 Facility-based model flowchart

Table 2 SPIRIT study schedule

	Baseline phase		Intervention phase					Evaluation phase		
	Allocation*	Site assessment**	Enrolment of index cases	Enrolment of contact cases	Follow-up				End of study	
Timepoint			-2 W	0	W1	W2	W4	W8	W12***	W24
Enrolment										
Eligibility screen			X	X						
Informed consent			X	X						
Allocation	X									
Interventions										
Facility-based arm			X	X			X	X	X	X
Community-based arm			X	X	X	X	X	X	X	X
Qualitative assessment		X								X
CEA						X				
Assessments										
Identification of contact children			X							
Children started on TPT				X						
Children completed TPT								X	X	
Acceptability of the intervention		X								X
TPT cost						X				

Abbreviations: W week, CEA cost-effectiveness analysis, TPT TB preventive therapy
 *Allocation takes place before the intervention begins as the clusters are randomized and not the individuals
 **The baseline phase takes place 3 months before the intervention phase
 ***Children started on 6 months of isoniazid have 2 additional follow-up visits at week 16 and week 20

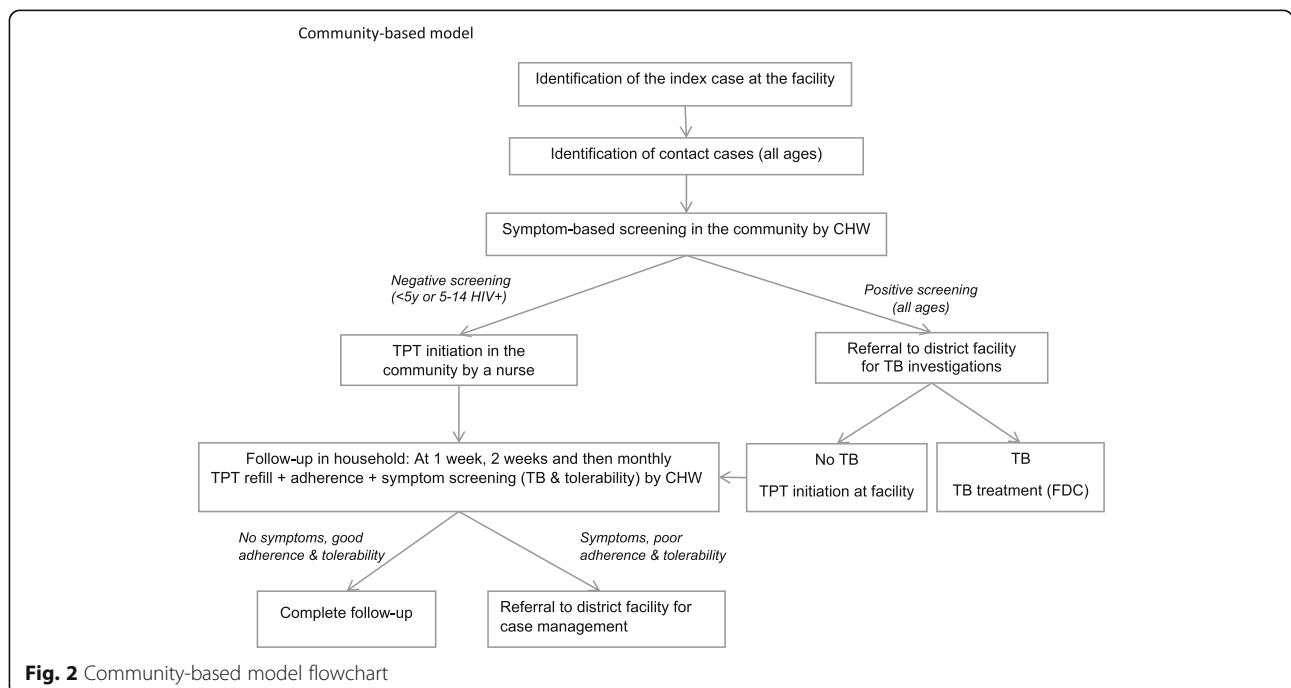


Fig. 2 Community-based model flowchart

Study population

Bacteriologically confirmed (by smear microscopy, Xpert MTB/RIF, or TB loop-mediated isothermal amplification (TB-LAMP) assays) index cases, ≥ 15 years old who have been diagnosed less than a month prior to inclusion and declaring child contacts in the study catchment area, are eligible. Exclusion criteria are known multi-drug resistance (MDR), the index case being a prisoner, or TB patients from an already screened household from the study.

Contacts sharing the same enclosed space for frequent or extended periods of time with the index case or having slept in the same bed during the last 3 months as per the WHO definition of a contact case [24] are eligible unless they are already on TPT or on TB treatment.

For the qualitative assessment, the study population is represented by key informants (facility managers, health staff, community health workers, and community leaders) and by male and female TB patients, who are parents/guardians.

Cluster selection and randomization

The study clusters are health facilities supported by the CaP TB Program with TB diagnostic and treatment capacity after an initial assessment taking into consideration the number of bacteriological index cases identified from January to December 2018 (minimum of 50). Priority was given to rural, semi-rural, or semi-urban facilities as there is less population movement than in an urban setting with relatively easy access. In Cameroon, there were mainly district hospitals because TB diagnosis is mainly done at the secondary healthcare level, with ten clusters selected from two regions (Central and Littoral regions). In Uganda, as TB services are decentralized at the primary healthcare level, the ten clusters were primary health centers in four districts in the South West region, some with two facilities per cluster in order to reach the minimum of 50 index cases per year.

The randomization was stratified by country, and in each country, the 10 clusters have been allocated to one of the study models by a covariate-constrained randomization [30] taking into account the number of bacteriologically confirmed TB cases from that cluster the previous year. The randomization was performed by a statistician from the central research team 3 months prior to the start of inclusions. Participants, healthcare providers, study staff, and investigators are not blinded to the allocation of the health facilities.

The cluster list can be found in the [Supplementary Material](#).

Criteria to discontinue the allocated intervention to a cluster are the absence of recruitment in a cluster for more than 2 months or if the NTP proposes a similar intervention that would bias the outcomes of the study.

TPT

The 3RH regimen uses the child-friendly formulation of rifampicin (R) 75 mg/isoniazid (H) 50 mg as a FDC [31] for eligible child contacts of < 25 kg. This formulation is procured and provided by the CaP TB project, as the NTP has not yet recommended this regimen, but has approved its use in the context of the study. Prescription is based on the body weight dose range as recommended by WHO [32]. The body weight is measured at the TPT initiation visit and at the TPT outcome visit for both models, and in the facility-based model, it is measured at every follow-up visit. For children of 25 kg or more, the adult RH tablet is provided. For children receiving an antiretroviral treatment with protease inhibitors (as lopinavir/ritonavir), nevirapine or dolutegravir, 6H is used to avoid the drug-drug interaction between R and these antiretrovirals. Along with the TPT, 10 mg of daily pyridoxine (vitamin B6) is given to each child to prevent peripheral neuropathy.

Study procedures

Symptom screening

Both models use the following symptoms [33] to assess if the contact child has presumptive TB or not:

- Persistent non-remittent cough > 2 weeks
- Reported persistent fever > 10 days
- Reduced playfulness/lethargy/fatigue
- Wheezing > 2 weeks
- Night sweats > 2 weeks
- Documented or reported weight loss, loss of appetite, or no weight gain (failure to thrive) in the last month
- Malnourishment using Mid-Upper Arm Circumference below 125 mm in children 6 months–5 years old

The presence of at least one of these symptoms requires TB investigations at the health facility.

For HIV-positive children, symptoms of any duration are suggestive of TB and the child is immediately referred to the clinic. HIV testing is proposed for 5–14-year-old children with unknown status using two rapid tests, as per national HIV testing guidance. In the community model, the first test is done in the household and if positive, the confirmation test is done at the health facility as per national guidance.

In case a child presents a sign that is not yet suggestive of TB due to its duration (ex: cough for less than 2 weeks), the screening is repeated after 2 weeks' time.

In addition to the screening for TB symptoms, CHWs have been trained to identify critical signs for urgent referral in case the child needs to be seen urgently by a

clinician. These signs are recommended by the Integrated Management of Childhood Illness Handbook of the WHO [34] and include lethargy or unconsciousness, chest indrawing, difficulty breathing, sunken eyes, drinking poorly or not drinking, seizures, severe wasting, severe pallor, and edema of both feet.

Adherence assessment

The adherence is assessed at each follow-up visit in both models of care using specific questions on how many doses were missed in the last 4 days, by counting the number of doses taken reported by the parent/guardian in a TPT treatment card introduced by the study and by verifying empty drug blister packs. Parent/guardian received treatment adherence counseling at TPT initiation and during follow-up based on treatment adherence.

Safety assessment

At each follow-up visit, the children are assessed for TPT tolerability by CHW using a standard check list of signs suggestive of hepatitis, peripheral neuropathy, and rash that are classically associated with HR (nausea, loss of appetite, vomiting, jaundice, dizziness, tingling, or burning sensation in the extremities). In every cluster facility, a clinician was trained to act as a safety monitor and examine children with problems of tolerability identified by the CHW. In case of serious adverse events, the safety monitor immediately notifies the event to the country principal investigator who informs the sponsor and the ethics committee of the respective country. All adverse events and serious adverse events are coded using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary (version 22.1, September 2019). On a 6-month basis, a safety data review is done by the study management team that is then reported to the sponsor and scientific advisory committee.

Sample size calculation

For the sample size calculation, we used an estimated 60% completion rate among the eligible children in the facility-based arm based on a recent systematic review [35] and a 10% difference in the community-based arm, considered to be the minimal clinically relevant difference. We considered a cluster coefficient variability of 50% based on the variation in the number of bacteriologically confirmed index cases between the 20 clusters in the year prior to the intervention. An intra-cluster correlation of 0.01 was used. With these parameters, we would need to include at least 1500 declared child contacts by the index case who would be eligible to the TPT to have a power of 85%. With a minimum of 1500 enrolled child contacts, we could maintain at least 80% of power to detect a difference of 10% in the primary outcome between the two arms assuming the proportion

with the primary outcome in the control arm ranges from 60 to 70% and of the cluster coefficient variability varies from 50 to 70%. The type I error rate α is conventionally fixed at 0.05%. Based on national household statistics per country [36–38], we make the hypothesis of one child under 5 years per household. Looking at the index case TB registrations in the year prior to the intervention, we estimate that it would be possible to include 1500 contact children in a 15-month period. Research assistants in each cluster supervised that all bacteriologically confirmed index cases registered in the NTP treatment register were screened for study eligibility to achieve adequate participant enrolment to reach sample size.

Data collection

Mixed methods of data collection, quantitative and qualitative, are used. There were no specific plans to promote participant retention to avoid biasing the trial outcomes that the cascade of cares for contact screening and management. The study reimburses participant's transportation in case for safety reasons only.

Quantitative data

Other than the facility registers, study-specific source documents are used. The data for the primary and secondary objectives are collected by the TB focal person in the health facilities and community health workers in the community. There is one research assistant assigned to each cluster health facility who enters data onto tablets using the Research Electronic Data Capture (REDCap) mobile application version 4.9.1, 6 February 2020. Patients' cost data are collected by research assistants in the REDCap mobile application using an adapted version of the patient cost tool developed by the WHO [39]. At the health system level, data are collected through literature, source documents from the Ministry of Health, primary expenditure analysis, and procurement records by the cost analysis researchers.

Qualitative data

The data for the qualitative assessment is collected by the social researchers through in-depth interviews and focus group discussions in English, French, or local language with the help of a local qualitative research assistant. Participants' confidentiality and privacy are respected throughout the study. During the baseline phase of the study, a qualitative assessment of social determinants has been performed to identify the perceptions of TB, prevention for child contacts, and obstacles for treatment, acceptability, and feasibility of the proposed intervention. Focus group discussions have been organized with TB patients and in-depth interviews have been conducted with health staff, facility managers,

CHW, and community leaders. During the implementation phase, data on concurrent acceptability is assessed through periodic supervision meetings of the CHW. A second qualitative assessment will be performed at the end of the intervention focusing on the acceptability and lessons learned. These activities are planned in both models of care implemented in the study.

Process data

In the baseline phase, sites were assessed in terms of quality of data collection in the registers and specific practices that would require adjustments for study organization of those sites. During the implementation phase, recruitment logs are filled in by research assistants to document study screening and enrolment process with reasons of refusal.

Data management

A central data manager coordinates with local data managers to ensure the data entry and verification according to a Data Management Plan. There are three levels of data checking and quality control: at data entry using restricted value set or compulsory fields, at country-level data management running weekly checks, and at central-level data management with a monthly consistency data check. The collected data is anonymized by the use of unique study identification numbers and followed by the investigators through a dashboard system developed at the central level. The tablets used for the study are password-protected and have an individual identification for each research assistant. The tablet data is encrypted when sent to the server. The study database is on a web-based platform provided by REDCap [40, 41], protected by password, encrypted, and hosted at the Institut de Recherche pour le Développement in Montpellier, France. The back-up of the database is done on a daily basis on the server of the Institut de Recherche pour le Développement in Montpellier.

Quality management

Each country research team is composed of one study coordinator, one clinical research assistant, and 8 research assistants. All staff is trained on good clinical practices, protocol, and study standard operating procedures. Training of the country research teams took place before the baseline phase and was done by the central research team. CHW were selected based on criteria regarding their education, experience with community activities, and acceptability by the community and capacity for study activities. The site teams (TB focal person, TB nurse, CHW, and safety monitor) were trained before the intervention phase by the country research teams. Each facility cluster has a clinician safety monitor trained to consult children with tolerability complaints and

report adverse events. Standard operating procedures, country-specific manuals of procedures (to take into account the implementation specificities of each country), and a quality management plan were developed by the central research team. Clinical research assistants perform internal data monitoring from the eCRF against source documents on a monthly basis, and central site monitoring is done every 3–4 months. In addition, the sponsor performs a yearly site monitoring.

The study is overseen by a steering committee involving all investigators including representatives of the national TB program with monthly calls to discuss study inclusions, challenges, and decisions on study implementation and a scientific advisory committee composed by experts in the field of pediatric tuberculosis and randomized controlled trials with meeting twice a year to discuss study progress, challenges, and safety review. A country community advisory board is constituted to give guidance on the implementation of the community activities and support the study team on patient information and communication.

Statistical analysis

Primary analysis

The denominator for the analysis of the primary endpoint is the number of child contacts < 5 years and HIV-infected 5–14 years declared by the index case at the facility during the inclusion visit. Since discrepancies can be expected between what is declared by the index case and what is observed during contact screening, a sensitivity analysis will be performed using as denominator the number of children < 5 years of age and HIV-infected children of 5–14 years of age identified during the screening. An additional sensitivity analysis will be performed including only participants that followed all study procedures (per-protocol approach) among the declared and then enrolled child contacts. Dropping out of the cascade of cares and potentially being lost to follow-up can be the consequence of the models of care under evaluation. Therefore, lost to follow-up will be kept in the primary outcome analysis. They will be removed from the sensitivity per-protocol analysis.

A generalized linear mixed model with a binomial distribution and logit link function will be used to perform individual-level analysis adjusting for clustering. The regression model will include the fixed effect of treatment assignation and country and one random-effect for the cluster. A degree-of-freedom correction will be applied (between-within method) to deal with the type I error inflation due to the small number of clusters. The primary analysis will focus on the difference between the two study arms adjusted for country, and a secondary analysis will add an adjustment for unbalanced factors (urban/rural, district size) identified in the baseline

assessment. For the analysis of the secondary outcomes, a similar mixed model will be used with the same random effects and correction method, focusing on each endpoint of the cascade of care for initiation and completion of TPT and each endpoint of the cascade of care for TB detection. The same model will be applied for the sensitivity analyses.

The proportion of children notified in the facility TPT register among all notified cases during the intervention period will be compared between the two models of care and will also be compared with the same proportions before intervention for the same time period (data collected during the baseline assessment). The proportion of confirmed TB among all pediatric notified cases and the proportion of treatment completion will also be compared between the two models and with the pre-intervention period.

Qualitative assessment analysis

All transcripts from the in-depth interviews and focus group discussions are transcribed in French if the activity was conducted in French and in English if the activity was conducted in the local language or English. For the analysis, an interim analysis process will be used. Major themes from the interviews and focus groups will be listed according to the objectives of the study before starting the analyses (a priori codes) and will be enriched if other themes will be found to be relevant to the study objectives (inductive codes). The analysis will be done using the software ATLAS.ti 8 2017.

Cost-effectiveness analysis

The two models of care will be analyzed and their cost-effectiveness in each country assessed.

The analysis will be from the healthcare system's and the primary analysis will generate an incremental cost per Disability-Adjusted Life Year averted for the intervention model of care vs the standard of care, with a mathematical model used to extrapolate effects observed in the trial to a lifetime time horizon. Additional analyses will include reporting of patient costs incurred during illness and care-seeking, and an asset-based wealth quintile of participants, and generation of additional measures of health impact (deaths and TB cases averted).

Ethical aspects

Protocol approval

The study protocol has been submitted and approved by two central Institutional Review Boards (IRBs): Advarra IRB from the USA, which is the sponsor's institutional IRB, and WHO Ethics Research Committee. In addition, the protocol was submitted and approved by the local IRBs: Cameroon National Ethics Committee for Human

Health Research and Research Ethics Committee of the Mbarara University of Science and Technology in Uganda. In Cameroon, it has also been approved by the Direction for Operational Research from the Ministry of Health and in Uganda by the Ugandan National Council for Science and Technology. Any change in the protocol or to the informed consent form that affects the scientific questions and study design or may affect a subject's willingness to continue participation in the study were considered as amendment and are submitted to all previously described ethics committees after approval from the scientific committee and the sponsor.

Informed consent

All consent forms used for the CONTACT study have previously been approved by the central and local ethics committees. Written informed consent is obtained from index cases and contacts, who are informed of the study objectives, procedures, and their risks and benefits. In addition, children older than 7 years in Cameroon and 8 years in Uganda provide written informed assent. Participants with incapacity consent through their legal representative and illiterate participants consent through a witness who is not part of study staff. Country-specific informed consent forms are developed to allow for different standard of care specificities. For index cases, the TB focal person collects the informed consent at the inclusion visit. For contacts in the facility-based model, the TB focal person, assisted by the research assistant, collects the informed consent. In the community-based model, only the research assistant can collect the informed consent. Consent for HIV testing is included in the study consent form.

Individual consent is obtained by the researchers during qualitative activities: focus group discussions and in-depth interviews and also during the patient cost collection for the cost-effectiveness analysis.

Handling withdrawals

At any moment, a contact case can withdraw their consent without any consequence for their care and their data prior to the date of withdrawal are kept for analysis. Their case management continues under the NTP guidelines.

Confidentiality

Each participant has a unique study code. No directly identifying data is entered into the database. An identification log allows the research assistants to make the link between the code and the name if needed and this log is kept separately in locked study cabinets on site.

Dissemination

The trial results will be published in peer-reviewed medical journals, preferably open access or guarantying an open access according to international guidelines for authorship. After approval by the scientific committee, the final trial report will be sent to the sponsor, Unitaaid, the World Health Organization, and NTP officials.

Discussion

The CONTACT study has several strengths and limitations.

Strengths

Methodologically, the use of a randomized cluster-controlled design ensures a good level of evidence. The inter-cluster variability is taken into consideration by the use of a covariate-constrained randomization of the number of index cases per cluster. In addition, the study is using a comprehensive mixed-methods approach that looks at the study goal from different perspectives: quantitative, qualitative, and cost-effectiveness.

The intervention package was conceptualized in a very pragmatic and realistic manner after discussion with end-users, national TB program, and community representative to ensure that it could be implemented by the NTP at the end of the research period. In addition, the intervention is evaluated in two countries with similar TB burden, but very different health system organization and level of community engagement that increases the representativeness of the study results. In Cameroon, the national system is very centralized whereas in Uganda lower level health facilities are capacitated to do TB diagnosis and follow-up. In Uganda, over the last 2 decades, there have been several HIV-related interventions, many of which have been implemented in the communities. The population is used to community activities and a system of CHW is in place (called Village Health Teams) and articulated by the Ministry of Health. The package proposed by the CONTACT study has been inspired by the HIV and malaria community activities [42, 43] and integrates very well in the Ugandan context. Finally, all cluster facilities are supported by the CaP TB program for TB diagnosis and treatment, which reduces the risk of heterogeneity between the clusters and TB detection endpoint assessment bias.

The study is constructed on the framework already existent in the health facilities and uses the health personnel of these health facilities. The main strength is represented by their training and experience in working with TB, and the fact that they are already integrated in the national system, no study additional staff was hired for this purpose. The TB focal person and safety monitor receive an incentive for filling study-specific documentation that is outside their usual work.

Limitations

Because the cluster sites were limited to the facilities supported by the CaP TB project, it was not possible to select more than 20 clusters. It was impossible to avoid urban facilities, which increases the inter-cluster variability and may increase the risk of cluster contamination due to the more complex system of patients' reference in cities as compared to rural settings. The proportion of urban clusters is higher in Cameroon as the two selected regions where the CaP TB project takes place include the two biggest cities of the country. In Uganda, some clusters comprise two health facilities to allow for the necessary recruitment capacity and this operational limitation may introduce more heterogeneity in the measurement of the outcomes.

Another limitation is the reliability of source documents from facility registers as compared to study-specific source documents, which can induce an information bias and risk of missing data. To minimize this limitation, a register data quality check was done during the baseline period and in sites where inconsistencies were found, a training on data collection was recommended.

The training of facility personnel on the study procedures, the reinforcement of the study source documents, and the presence of research assistants is likely to increase the quality of the facility-based as compared to routine conditions and may have an effect on the expected difference of primary endpoint between the community-based and the facility-based models. Also, because the duration of the TPT is known to influence the completion of the TPT, which is part of the primary endpoint measure and because NTP was expected to change their guidelines in the coming months, we introduced the 3-month regimen in the facility-based model as well. Therefore, the study standard of care does not fully represent the current standard of care used in both countries. The choice of a very operational and pragmatic adherence measure likely to be well accepted by NTP (recording of the dose intake on a treatment card) relies on the parent/guardian's understanding and reliability in recording the dose intake and could potentially introduce information bias or desirability bias. To prevent this risk, the CHW and research assistants are asked to systematically reconcile what is recorded by the parent/guardian on the treatment card with the pills remaining in the blisters. In the community-based model, two extra visits after 1 and 2 weeks after starting TPT were requested by the NTP to ensure that no child with TB disease was missed by the symptom screening done by CHW and to verify the tolerability. This results in more frequent assessments of treatment adherence and tolerability as compared to the monthly follow-up in the facility-based model and could introduce an

observation bias that could affect the comparison of adherence and safety between the two models.

Challenges

This is an implementation research which is highly dependent on the health system policy and organization. One of the many challenges to be taken into account is the change of the country guidelines during the implementation of the protocol as these changes require most of the time a protocol amendment with implications on study procedures and organization. Other challenges are related to shortages of TB medication, stock-outs of Xpert MTB/RIF cartridges that affect the identification of bacteriologically confirmed index cases at facility level and staff availability or turn over. The 3RH and 6H TPT drugs were provided by the study to prevent the risk of shortage. One cluster in Cameroon had to be changed after approval of the study protocol due to an unanticipated concurrent community-based intervention that could bias the study outcome measure. Additionally, in both countries, following the request from the NTP that TPT should be initiated by a nurse, the implementation of the intervention package could not rely on CHW only as initially planned and has to involve facility nurses moving to patients' household. The same applies to HIV testing that cannot be done by trained CHW in Cameroon.

Constant communication with the CaP TB program team and the NTP team at higher and lower levels is crucial to anticipate any operational issue and find solutions to ensure the continuity of study activities according to the protocol. It also reinforces the level of ownership by the NTP and prepares the future scale-up of the intervention. The cost-effectiveness and qualitative research components focusing on acceptability and potential barriers such as stigma around tuberculosis and its association to HIV bring crucial information for future scale-up.

The CONTACT study will bring new evidence of alternative ways for tuberculosis contact management in a more convenient manner for children and their families with an expected impact on TPT uptake, treatment completion, and increase of case detection.

Study status

The study completed the first phase and participants' enrolment started on 14 October 2019. Enrolment is expected to be completed in December 2021. The current study protocol version is version 3.0: 24 June 2019.

Abbreviations

3RH: 3 months of rifampicin and isoniazid daily; 6H: 6 months of isoniazid daily; CaP TB: Catalyzing Pediatric TB Innovations; CHW: Community health worker; CONTACT (study acronym): Community Intervention for Tuberculosis Active Contact Tracing and Preventive Therapy; CXR: Chest radiography;

EGPAF: Elizabeth Glaser Pediatric AIDS Foundation; FDC: Fixed-dose combination; H: Isoniazid; HIV: Human immunodeficiency virus; IRB: Institutional Review Board; MedDRA: Medical Dictionary for Regulatory Activities; MDR TB: Multidrug-resistant TB; NTP: National Tuberculosis Program; R: Rifampicin; REDCap: Research Electronic Data Capture; TB: Tuberculosis; TB-LAMP: TB loop-mediated isothermal amplification; TPT: Tuberculosis preventive therapy; TST: Tuberculin skin test; WHO: World Health Organization

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13063-021-05124-9>.

Additional file 1. List of participating clusters.

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Authors' contributions

AV participated in the design of the study, protocol writing, and writing of the manuscript. SED participated in writing the statistical details of the protocol. SO participated in the data management aspects of the protocol writing, and BT and DA participated in the study design and data collection. EdC participated in the data collection and quality control. MK, PT, ST, and AKK participated in the study design, and GT participated in the design and data collection for the qualitative assessment. PJD participated in the study design for the cost-effectiveness assessment. SG, MC, and JC participated in protocol writing and study design. MB is the Coordinating Investigator and supervised the protocol writing, data collection, and writing of the manuscript. All authors read and approved the final manuscript.

Authors' information

Not applicable

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Availability of data and materials

The research team at the IRD (Institut de Recherche pour le Développement) in Montpellier, France, will have access to the final trial dataset from both countries.

Ethics approval and consent to participate

The CONTACT study has been approved by the WHO Ethics Research Committee, Advarra Institutional Review Board, and each local Research Committee from Cameroon and Uganda. The approval letters are attached to the submission. Informed consent will be obtained from all study participants.

Consent for publication

Not applicable

Competing interests

The authors declare no competing interests.

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Supplemental material

No	Facility Name	District	Population (2016)	Adult TPB+	Level of facility	Urban/rural
Cameroon						
1	HD Log-Baba	Logbaba	213 224	123	District Hospital	Urban
2	HD Mbalmayo	Mbalmayo	156 597	121	District Hospital	Semi-Urban
3	HD Bonassama	Bonassama	337 007	106	District Hospital	Urban
4	CMA Delangue	Edea	154 244	94	CMA	Urban
5	HD Okola	Okola	69 194	90	District Hospital	Semi-Urban
6	HD New Bell	New Bell	860 913	177	District Hospital	Urban
7	St Jean de Malte	Njombe Penja	42 749	69	District Hospital	Rural
8	HR Nkongsamba	Nkongsamba	160 880	61	Regional Hospital	Urban
9	HD Mfou	Mfou	72 235	61	District Hospital	Semi-Urban
10	HD Yoko	Yoko	33 519	53	District Hospital	Rural
Uganda						
1	Ishongororo HC IV	Ibanda	249,625	71	Health Center IV	Rural
2	Ruhoko HC IV	Ibanda	249,625	95	Health Center IV	Rural
3	Bubaare HC III + Bwizibwera HC IV	Mbarara	472,629	50	Health Center IV Health Center III	Rural
4	Mbarara Municipal Council HC IV +	Mbarara	472,629 (195,160 ^a)	60	Health Center IV	Urban

	Kakoba HC III				Health Center III	
5	Bwongyera HC III + Rwashamaire HC IV	Ntungamo	483,841	59	Health Center IV Health Center III	Rural
6	Itojo Hospital	Ntungamo	483,841	50	District Hospital	Rural
7	Ntungamo Ngoma HC III + Rubaare HC IV	Ntungamo	483,841	50	Health Center IV Health Center III	Rural
8	Kitwe HC IV	Ntungamo	483,841	75	Health Center IV	Rural
9	Kitagata Hospital	Sheema	207,343	70	District Hospital	Rural
10	Kabwohe Clinical Research Center HC II + Kabwohe HC IV	Sheema	207,343	50	Health Center IV Health Center II	Urban

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4.3. Feasibility of a randomized clinical trial evaluating a community intervention for household tuberculosis child contact management in Cameroon and Uganda

4.3.1. Background

Feasibility studies are used to estimate important parameters needed to design the main study(109). Conducting a feasibility study is a developmental learning process in which the study procedures and intervention can be adapted as necessary to achieve the most promising and coherent outcomes, specifically tailored for the setting they are deployed in. It is crucial to assess feasibility in case of (1) activities needing any sort of community involvement and partnership, (2) when the data available in the literature are scarce regarding a specific technique or intervention, (3) when the population has specific socio-cultural differences and specificities, and (4) when available literature is described in different settings.

The CONTACT study aims at implementing a community intervention in a research field with scarce literature data and in two settings with high socio-cultural heterogeneity and therefore ticks three boxes of the previously mentioned cases where feasibility evaluations are essential.

The objective of this study is to assess the feasibility of a community-based intervention for TB household child contact management and the conditions for its evaluation in a pragmatic cluster randomized trial (CONTACT study) in two high-burden, resource-limited countries, Cameroon and Uganda.

4.3.2. Methods

We used the framework proposed by Orsmond and Cohn to evaluate the feasibility of the CONTACT study. There are three dimensions of feasibility that we have assessed in this study: 1) Recruitment capability of the study sites; 2) Acceptability of the intervention by beneficiaries and providers; 3) Adaptation, integration and resources for the implementation of the CONTACT study. The methods associated to each dimension are presented in Table 2 below:

Table 2 The feasibility dimensions and associated methods

	RECRUITMENT CAPABILITY	ACCEPTABILITY	ADAPTATION, INTEGRATION, RESOURCES
Objective	Evaluating the number of TB bact+ per cluster Identifying how many children <5 per household	Assessing the perceptions and opinions of the people receiving and delivering the intervention	Assessing existing pediatric TB activities and possibilities of integration of the intervention Assessing the availability of optimal resources for a successful intervention
Methods	Retrospective cohort Document review	FGD IDI	Cross-sectional survey Expert discussions Document review
Population	TB patients DHS population	TB patients Community leaders, CHW, TB focal persons, health facility managers	Study sites NTP representatives CaP TB stakeholders
Analysis	Descriptive analysis Document data extraction	Axial coding Thematic analysis	Descriptive analysis Document data extraction

TB= tuberculosis, bact+ = bacteriologically confirmed, NTP = National TB Program, FGD = focus group discussion, IDI= in-depth interview, CaP TB = Catalyzing Pediatric Tuberculosis Innovations; DHS= Demographic Health Survey; CHW= Community Health Worker

We used a convergent mixed methods design based on concurrent quantitative and qualitative data collection and analysis. Quantitative data were collected from a retrospective cohort and a cross-sectional survey in all CONTACT study clusters. A qualitative assessment was designed to document the perspectives of providers and patients on the proposed intervention. Stakeholder discussions and document review informed the team on best approaches to

implement the community intervention. After independent analysis of each type of research, the data interpretation and subsequent decision-making was done in an integrated way, taking all results into consideration (Figure 10).

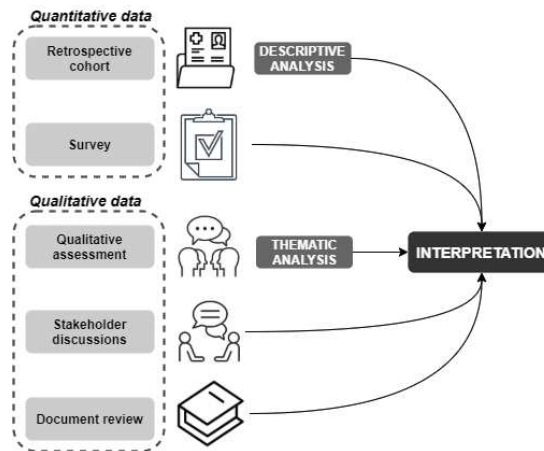


Figure 10 Schematic representation of the methods used for the feasibility assessment

4.3.3. Results

Recruitment capability. As there was no data on child contacts < 5 years old per household, we used both the index cases and the number of children <5 years per household according to national statistics as proxy for household child contacts < 5 years old. We identified 0.85 children <5 years per household in Cameroon and 0.81 in Uganda. The retrospective cohort identified that the one cluster from Cameroon and three clusters in Uganda will not reach the sample size in the 12 months initially considered for study completion.

The **acceptability** qualitative assessment showed that the community intervention is acceptable and coherent for both beneficiaries and providers. The main benefits of acceptability are not spending transport cost to get contacts to the health facility for screening, the opportunity to insist on TB health education, the opportunity to discuss other health problems while in the household. Nevertheless, some conditions emerged for the successful implementation of the community model like the visit preparation, the team conduct, the explanations about the scope of the household visit, respect of confidentiality and CHW training and motivation. An important theme that completely emerged from discussions with health providers, without specific questions on this aspect, was the sustainability of the project, highlighting the importance of ensuring the NTP

or other partners continue the project at the end of the research study.

In the **adaptation, integration and resources** dimension we found that contact investigation is recommended in the two countries and implemented at the health facility by the TB focal person. In Uganda, if funding allows, the health workers do contact screening in the community. There were existing registers for TPT initiation and outcomes, but no contact screening registers and no tools to assess adherence or safety. Presumptive TB investigations like clinical and microbiological assessments are free in both countries, but the parents need to pay for other investigations like CXR. HIV testing at the health facility is provided in both countries, and in Uganda it is also done in the communities.

The missing data rate and error rate in the TB registers, which are used as a source document for index case identification in the study, was very small, with 0.3% median rate of missing data (interquartile range (IQR) [0%-3%]) in Cameroon and 0.4% (IQR [0%-0.6%]) in Uganda. The median error rate was 1.1% (IQR [0.6%-1.4%]) in Cameroon, and 0.0% (IQR [0%-0%]) in Uganda.

The human resources at the health facility are similar in the two countries. Ugandan CHWs are used to TB community activities, whereas in Cameroon, CHWs were mainly working on HIV, family planning, malaria prevention, but have never worked on TB. The qualitative assessment informed the research team on the specific selection criteria for CHWs performing activities in the intervention model and close attention is paid to CHWs' competence and training.

4.3.4. Discussion

The proposed community intervention was acceptable by TB patients, healthcare providers and community leaders alike. Key elements of acceptability are visit preparation, good communication and respect of confidentiality. Moreover, one of the main conditions for feasibility of the community model is represented by CHW selection and training.

Both qualitative and quantitative findings allowed the team to take important operational decisions regarding the implementation of the CONTACT study. First of all, the inclusion period was extended from 12 to 15 months and index cases were chosen as a proxy for contact children under 5, indicator which was used for the sample size calculation. Secondly, as in Uganda TB services are decentralized to lower-level health facilities, and as sites were having a lower

recruitment potential, the team decided to regroup two sites in the same cluster. Due to the low level of missing data and errors in the TB registers in both countries, the source data for index case information was the TB register. Transport and communication were ensured for CHWs and a procedure with clear selection criteria was developed. The CHWs received training on all study procedures and benefit from job mentorship by the TB focal person and the RA. The TB focal person was instructed to plan the household visit according to the index cases' convenience, as highlighted by the qualitative assessment. Research activities and intervention activities were separated as much as possible with research assistants implementing research activities and health facility staff performing intervention activities.

Being able to implement community activities can have a high impact on the communities by bringing the needed TB prevention services at their doorstep. In addition to this, the health system could benefit of the CHW structure already in place.

4.3.5. Involvement in this work

I have analyzed the data from the retrospective cohort and presented it to the Scientific Advisory Committee of the CONTACT study. In addition, I analyzed the missing data and error rates in the TB registers and data from the cross-sectional survey on TB services. This information was corroborated with findings from the qualitative assessment to formulate clear solutions and adaptations for the successful implementation of the CONTACT study.

Along with the qualitative research expert, we conducted the pre-intervention qualitative assessment, when we both conducted focus group discussions and in-depth interviews in Cameroon and Uganda. In Cameroon we performed the visit together and in Uganda I have done the visit with a qualitative research assistant. I have verified the French transcriptions against the audio files and cleaned them accordingly. In addition, I have coded the discussions and performed the analysis using ATLAS.ti. I discussed the results with the study qualitative research expert.

I wrote the feasibility study article and presented the acceptability component to the Union World Conference on Lung Health, 2021.

4.3.6. Scientific communications:

Article:

- Vasiliu A, Tiendrebeogo G, Mbunka Awolu M, Akatukwasa C, Tchakounte BY, Ssekyanzi B, Tchounga BK, Atwine D, Casenghi M, Bonnet M, on behalf of the CONTACT study group. Feasibility of a randomized clinical trial evaluating a community intervention for household tuberculosis child contact management in Cameroon and Uganda. Pilot and Feasibility Studies, - submitted

Scientific conferences:

- 52nd Union International Conference on Lung Health, Virtual Event, 2021

Feasibility of a randomized clinical trial evaluating a community intervention for household tuberculosis child contact management in Cameroon and Uganda

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Abstract

Background: One of the main barriers of the management of household tuberculosis child contacts is the necessity for parents to bring healthy children to the facility. We assessed the feasibility of a community intervention for tuberculosis (TB) household child contact management and the conditions for its evaluation in a cluster randomized controlled trial in Cameroon and Uganda.

Methods: We assessed three dimensions of feasibility using a mixed method approach: (1) recruitment capability using retrospective aggregated data from facility registers; (2) acceptability of the intervention using focus group discussions with TB patients and in-depth interviews with healthcare providers and community leaders; and (3) adaptation, integration and resources of the intervention in existing TB services using a survey and discussions with stakeholders.

Results: Reaching the sample size is feasible in all clusters in 15 months with the condition of regrouping 2 facilities in the same cluster in Uganda due to decentralization of TB services. Community health worker (CHW) selection and training and simplified tools for contact screening, tolerability and adherence of preventive therapy were key elements for the implementation of the community intervention. Healthcare providers and patients found the intervention of child contact investigations and TB preventive treatment management in the household acceptable in both countries due to its benefits (competing priorities, transport cost) as compared to facility-

based management. TB stigma was present, but not a barrier for the community intervention. Visit schedule and team conduct were identified as key facilitators for the intervention

Conclusions: This study shows that evaluating a community intervention for TB child contact management in a cluster randomized trials is feasible in Cameroon and Uganda.

Trial registration: ClinicalTrials.gov, NCT03832023. Registered on February 6th 2019

Keywords: pediatric tuberculosis, community intervention, tuberculosis preventive therapy, tuberculosis screening, active contact investigation, feasibility, acceptability, mixed methods, cluster randomized trial, complex intervention

Key messages regarding feasibility

1) What uncertainties existed regarding the feasibility?

We were uncertain about the possibility to recruit the necessary sample size from the study clusters in 12 months. We did not know if a community intervention for tuberculosis screening and preventive therapy management would be acceptable by providers, beneficiaries and their communities. We wanted to better integrate this complex intervention into existing tuberculosis services in order to facilitate its programmatic scale-up at the end of the research study.

2) What are the key feasibility findings?

We found that we would need to extend the recruitment period to 15 months in order to reach the sample size. Discussions with patients, health staff and community showed that the community intervention is acceptable as long as confidentiality is respected, counseling is provided and the staff delivering the intervention is well trained. Findings from the tuberculosis services survey allowed us to better adapt and integrate study activities into existing services.

3) What are the implications of the feasibility findings for the design of the main study?

We used the findings of the feasibility study to fine-tune the community intervention in order to implement it and evaluate it in a manner which is respectful to the local context and can easily be scaled-up

Background

Tuberculosis (TB) is a preventable and curable disease. Nonetheless, the World Health Organization (WHO) estimates that more than one million children develop TB disease every year, representing 12% of the global TB burden(1). Africa carries a high burden of TB disease, with 25% of global new cases occurring in this region. The majority (80%) of children dying from TB are younger than five years old(2), and mathematical models show that 96% of them die before treatment mainly because they were not diagnosed with TB (2). One of the main transmission pathways for children takes place in the household, usually from a caregiver or another adult present in the household(3,4). When infected, children progress more rapidly towards TB disease and often present with severe forms of TB, especially if they are young (less than 5 years) or HIV-positive (5,6).

To increase early detection, WHO recommends for all children living in the same household with a bacteriologically confirmed adult TB patient, to be screened using at least a symptom-based screening. Those with a negative TB screening, with a priority given to young or HIV-positive children could then be initiated on tuberculosis preventive therapy (TPT) to prevent progression to TB disease(7,8). Nevertheless, WHO estimates that only 33% of estimated eligible contact children were started on TPT in 2019 (1). Health system and patient-related challenges(9–12) have already been described regarding contact screening and TPT initiation in resource-limited settings. Among them, one major challenge is the necessity for caregivers to bring children who may not have any symptoms to the health facility for TB screening and to bring them back on regular appointments for follow-up if they were initiated on TPT, knowing they are healthy children.

Previous findings from the literature show that community interventions have improved TB treatment outcomes(13,14) and that involving community healthcare workers (CHW) had a great impact on TB case finding (15–17). Community interventions can also increase the coverage of TB screening and initiation on TPT among household child contacts. There has not been any randomized controlled trial (RCT) comparing the effectiveness of a community intervention for

TB screening and TPT management to facility-based intervention. Our research group is conducting a pragmatic cluster RCT (cRCT) evaluating a community intervention for household child-contact management in Cameroon and Uganda. The CONTACT study (**C**ommunity **i**ntervention for **T**B **A**ctive **C**ontact **T**racing and preventive therapy management) is part of the CaP TB Project (Catalyzing Pediatric Tuberculosis Innovations), a multi-country project aimed at improving pediatric TB case finding and access to TPT through a multipronged approach including implementation of decentralized and integrated models of care, capacity building of front line health care workers on management of pediatric TB, improved access to timely and accurate diagnosis and effective treatment for active TB disease and TB prevention(18).

Under the CONTACT study, household child-contacts of bacteriologically confirmed index cases are being screened for TB at the household, and children under 5 years old or HIV-positive are also initiated on TPT if asymptomatic and followed-up in the household by CHW. Only symptomatic children or children facing safety issues with TPT are referred to the facility. More information can be found in the previously published study protocol(19).

Complex interventions are like black boxes more often than not and important processes and decision-making in the early stages of intervention development are seldom reported(20). Before evaluating a complex(21) community intervention, it is crucial to assess the feasibility of the proposed intervention to orient and prepare the investigators for full-scale research (22,23). This is particularly essential in case of (1) activities needing any sort of community involvement and partnership, (2) when the data available in the literature are scarce regarding a specific technique or intervention, (3) when the population has specific socio-cultural differences and specificities, and (4) when available literature is described in different settings (eg. high-income countries)(23). The first three criteria apply to the proposed community intervention of the CONTACT study.

Therefore, the objective of this study was to assess the feasibility of a community intervention for TB household child contact management and the conditions for its evaluation in a cRCT in two high-burden, resource-limited countries, Cameroon and Uganda.

Methods

Study design

This feasibility study used a convergent design based on concurrent quantitative and qualitative data collection and analysis, including with focus group discussions (FGD) and in-depth interviews (IDI), retrospective cohort, survey, document review and expert discussions (Table 1). We evaluated three dimensions of feasibility, adapted from Orsmond and Cohn(24): 1) Recruitment capability of study sites, 2) Acceptability of the intervention by beneficiaries and providers of the intervention. 3) Adaptation, integration and resources of the community intervention in the health system organization in each country.

Data were collected concurrently during the preparation phase of the CONTACT study, 3 months before the start of inclusions from July to September 2019.

Table 1 Description of different dimensions of the feasibility evaluation

	RECRUITMENT CAPABILITY	ACCEPTABILITY	ADAPTATION, INTEGRATION AND RESOURCES
Objective	Evaluating the number of TB B+ per cluster Identifying how many children <5 per household	Assessing the perceptions and opinions of the people receiving and delivering the intervention	Assessing existing pediatric TB activities and possibilities on integration of the intervention Assessing the availability of optimal resources for a successful intervention
Methods	Retrospective cohort Document review	FGD IDI	Cross-sectional survey Expert discussions Document review
Population	TB patients	TB patients	Study sites

	DHS population	Community leaders, CHW, TB focal persons, health facility managers	NTP representatives CaP TB stakeholders
Analysis	Descriptive analysis Document data extraction	Axial coding Thematic analysis	Descriptive analysis Document data extraction

TB= tuberculosis, B+ = bacteriologically confirmed, NTP = National TB Program, FGD = focus group discussion, IDI= in-depth interview, CaP TB = Catalyzing Pediatric Tuberculosis Innovations; DHS = demographic health survey; CHW = community health worker

Study setting

Both countries are high TB burden countries with a TB incidence of 179 and 200/100000 population for Cameroon and Uganda, respectively. The healthcare system and TB service provision are different in the two countries. TB services in Cameroon are delivered mainly in centers for diagnosis and treatment in district or regional hospitals, whereas in Uganda, TB services are decentralized down to primary health centers (PHC). Community activities are common in Uganda for TB patients' treatment follow-up, whereas in Cameroon, TB activities are mainly facility-based and community interventions are mainly on HIV, family planning and malaria. In Cameroon and Uganda in 2019, there were an estimated 27% and 29% of household contact children <5 years on TPT, respectively (1).

The CONTACT study is implemented in 20 clusters, 10 in each country. A cluster is defined as a health facility being part of the CaP TB Project and its catchment area to ensure the availability of similar diagnostic tools for presumptive TB children across clusters sites. In Cameroon, the clusters are district hospitals identified in 10 districts from two regions (Centre and Littoral) and in Uganda, clusters are 13 PHCs and 2 hospitals (more than one facility per cluster) in 4 districts from one region (South-West). Rural or semi-urban clusters are the main focus of the intervention (19). The primary outcome of the CONTACT study is the proportion of child contacts <5 years of adult bacteriologically confirmed TB cases (TB B+) who initiate and complete TPT with a sample size of 1500 contact children <5 years, which represents a minimum of 75 participants per cluster.

Taking into account a cluster size variability of 50%, a minimum of 50 participants per cluster was requested with an objective to complete enrolment in 12 months.

Recruitment capability

In the absence of information about the expected number of contact children < 5 years in the study sites, we chose a proxy for estimating the study population size. The most practical proxy was to estimate the number of children <5 years per adult index case TB B+. We searched the relevant data from the Demographic Health Surveys (DHS)(25,26) of each country and the relevant literature on TB patients' household sizes(27).

To estimate the number of index cases per cluster, study research assistants (RAs) retrospectively collected aggregated data from the National Tuberculosis Program (NTP) registers from March 2018 to April 2019 in all study cluster facilities using a REDCap data collection tool(28). Information about the type of TB (pulmonary or extrapulmonary), bacteriological confirmation, age of TB patients, their HIV status and their treatment outcomes were collected following a standardized operating procedure, and data was monitored at the end of the activity. We compared these data with aggregated data provided by NTP from 2017 from the same cluster facilities to assess potential variability in TB detection throughout the years.

Acceptability

We conducted a qualitative assessment in 4 clusters of two regions (Centre and Littoral) in Cameroon and 2 clusters of one region (South-West) in Uganda. We used a standardized discussion guide in both countries which was tested before the qualitative activities. Focus Group Discussions (FGDs) with a minimum of 6 TB patients with household child contacts were conducted separately among women and men. In-depth interviews (IDIs) were conducted with TB focal persons, health facility managers, community leaders and community healthcare workers. FGD participants were randomly selected from the TB registers by the facility TB focal person (TFP) by selecting retrospectively every 5th registered patient until nine (maximum

number) participants accepting to come to the health facility for the FGD. Participation was voluntary and all participants signed an informed consent form before discussions or interviews.

FGDs and interviews were conducted in French in Cameroon, and in English or Runyankole in Uganda. The qualitative research team recorded all discussions and verbatim transcriptions were done for all recordings and validated by a different researcher for consistency against audio files. Data coding and analysis were done using the ATLAS.ti software version 9.0.

Adaptation and integration

TB services and existing tools

Study RAs and CaP TB programmatic officers collected data using a standardized questionnaire about (1) child contact investigation, TB screening and diagnosis in cases of presumptive TB and TPT services (drugs, dosages and mode of delivery), (2) TB/HIV management (integration of services), (3) the referral system between different levels of health care facilities, (4) drug management, and (5) TB case recording tools used under routine and implemented by the CaP TB project (see Additional File 1 for the data collection tool).

Data quality check

To assess if the NTP facility TB registers represent a reliable source of data collection for index cases, we quantified missing data and errors between May 1st 2018 and Oct 31st 2018 on key variables. RA verified the TB register for the following fields: registration date, TB registration number, sex, age, type of TB, type of patient (new/retreatment) and HIV status, using a standardized data collection tool according to a SOP and all data were monitored. Missing data was any field which was not filled in and error was erroneous data after verification of the source of the information in patients' files, treatment cards and laboratory registers.

Resources and Procedures

This part of the feasibility assessment was focused on identifying eventual logistic, programmatic or financial gaps with possible solutions, and then ensuring that all human resources, operational and logistical prerequisites were met for an optimal implementation of the intervention. For procedure development, the team reviewed the National Guidelines on TPT management(29,30), National TB or pediatric TB guidelines (29,31), WHO Integrated Management of Childhood Illness guidelines(32), WHO latent TB guidelines(7,33) and WHO pediatric TB guidelines(8).

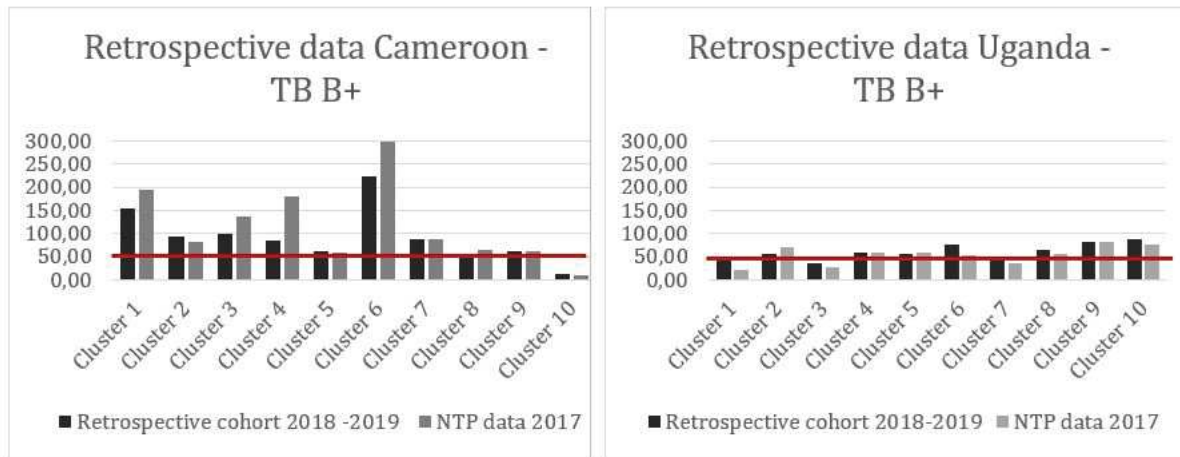
Ethics

This feasibility study was part of the main cRCT protocol that has been approved by the WHO Ethics Research Committee, the Advarra Institutional Review Board and by the two local ethics committees: Cameroon National Ethics Committee for Human Health Research and Research Ethics Committee of the Mbarara University of Science and Technology in Uganda. In addition, administrative approvals were needed from the Direction for Operational Research from the Ministry of Health in Cameroon and the Ugandan National Council for Science and Technology in Uganda.

Results

Recruitment capability

The review of the DHS data(25,26) in Cameroon identified 16.9% children <5 years per household and a mean of 5 household members, which would represent 0.85 children <5 years per household. In Uganda there are 18% children <5 years per household, with a mean of 4.5 household members, which corresponds to 0.81 children <5 years per household. Yuen et al. has looked into the household composition of TB patients for all countries and estimated 0.83 (95% confidence interval (CI) 0.80-0.86) children <5 years per household in Cameroon and 0.93 (0.89-0.96) in Uganda(27). Therefore, the assessment of the cluster facilities' capacity to enroll child contacts <5 was made using data on the number of index cases from TB registers, assuming there was one index case per household and one child contact <5 years per index case.



The red line marks the minimum of 50 bacteriologically confirmed TB cases necessary for sample size
 NTP = National Tuberculosis Program, TB B+ = bacteriologically confirmed tuberculosis

Figure 1. Retrospective data of tuberculosis bacteriologically confirmed cases in Cameroon and Uganda.

From Figure 1 we observe that the clusters facilities in Cameroon had enough TB patients to meet the minimum number of 50 TB B+ patients per cluster per year to reach the study sample size within 12 months, except for one cluster (cluster 10). In Uganda there were 3 clusters that did not meet the minimum of 50 bacteriologically positive TB patients (cluster 1, cluster 3 and cluster 7). Despite some fluctuations, data were consistent between the 2017 NTP reports and data collected retrospectively from TB registers between April 2018 and March 2019.

Acceptability

The team conducted 11 FGD with 42 men and 32 women. The mean FGD duration was 105 minutes for women and 128.5 minutes for men. One FGD with women in the Littoral region of Cameroon was not done as the required minimum number of 6 participants was not reached. Twenty-four IDI were conducted with providers and community leaders. (Additional Table 3). We discussed contextual and perceived barriers to facility-based TB child contact management, perceived benefits of a community intervention, and prerequisites for its implementation.

Barriers to facility-based TB screening

All TFP in both countries stated they ask TB patients to bring back their children to the health facility for TB screening as requested by national TB guidelines. In their overall assessment based on experience, patients' adherence to such a request is poor. During the FGDs, some TB patients confirmed they were indeed requested to bring their children to the facility for TB screening, among them, few did comply. Others declared that they were never asked to bring their children to the health facility for screening, stating they might have done so if requested.

The main reasons cited or anticipated by TB patients for not bringing their children to the health facility were financial, sociocultural or stigma-related. As illustrated below, facility-based child contact TB screening carries financial costs that make child-contact screening less financially and geographically accessible, especially transport costs for those living far away from the facility and those who have many children <5 years to bring for screening and more generally, the poor. This is corroborated by health personnel who did understand parents may face challenges when they cannot afford the transport cost and other costs such as buying food for children while waiting for the screening procedures.

"I need to get transport to transport about 8 people to come back and forth. For starters coming here and going back home alone, they take me for 3000 shillings. So I have to spend 3000 for each of the eight people to come here at the health facility and also spend 3000 shillings to transport them back, so transport would strain me" – Male participant, Uganda

"When you ask a parent to transport his 5 kids and bring them to the health center, he's going to ask: "Are you paying for transport?"" – CHW, Cameroon

While these practical and objective facts played a role in parents' non adherence to healthcare providers' recommendations, some FGD participants believed non-adherence was rather a form of child neglect and pointed at the sociocultural aspects such as gender roles in childcare religion that prevent men from attending health centers when a child is sick. Traditional beliefs about diseases and TB causation (witchcraft) associated with mistrust in "modern medicine" or

confidence in traditional medicine or religious prayers, negatively and strongly influence help- and health-seeking behaviors and trajectories, as well as treatment itineraries.

“You know, African families really like going to healers in the neighborhood. He [the TB patient] will look for herbs before going to the hospital. We, African families, love the healers.” – male participant - Cameroon

“There are some people who think that they have been bewitched especially when that person has a persistent cough. The person may even start to blame the neighbor whom they had a quarrel with for being responsible for the cough” – Community leader, Uganda

Whether associated to HIV or a stand-alone determinant of TB non-disclosure, TB stigma was ever-present in all FGDs and emerged as a barrier to TB health facility-based screening. Overt stigma was of particular concern and played an important role in how patients live with the disease.

“People fear to disclose that they have TB because they might lose their jobs, they might lose their relationships; it may cause people to be isolated” – male participant, Uganda

“They think this [TB] is a shameful disease and that people will mock them” – male participant, Cameroon

“After I was diagnosed with TB, my husband threatened me “I do not want to hear anyone discussing this with anyone.” And I have never told anyone [...] and it hurts me inside” – female participant, Uganda

Healthcare providers shared similar views regarding financial shortcomings, stigma and sociocultural norms. In addition, TFP highlighted the centrality of the initial encounter (or counseling) with the index case in helping patients understand the importance of TB prevention, including the need for child-contact TB screening and TPT. Indeed, provision of TB literacy and the rapport that is built during this initial visit are essential for a good follow-up during treatment. When such initial visit is rushed due to a high workload and patients queuing at the health center,

the information is not passed to the patient and in consequence, this important step is overlooked. As explained in one instance by a doctor and facility manager, health worker's priority is to cure patients who present themselves at the facility, not to manage the contacts.

"They [TB patients] are not coming back with the children not because they don't want to, but because maybe they did not understand an important part [of the health education]" – CHW, Cameroon

"The health facility is overwhelmed by the services here. You get here and you find many people here and that means that on that day you will not be attended to and might need to return the following day. That means that you will have lost two days of work, the child has also missed school. And you know many of us earn an income by the day" – male participant, Uganda

Conditions for acceptability of a community intervention

From the patients' perspectives the proposed intervention (19) was acceptable and made sense in both countries, as it will be helpful to many in overcoming the main barriers to facility-based child-contact TB screening, and in particular, transport costs that many TB patients cannot afford.

Besides removing distance and related transport costs, patients noted further benefits of the household visit, including the confirmation of the child's good health (not TB infected) and ensuring through TPT that a parent's TB infection will not be passed to the children.

"I would accept because I had it [TB]... and I need to make sure my children are healthy" – female patient, Cameroon

Additionally, parents get the opportunity to address other health or environmental problems with the CHW that might come up during the home visit discussions.

"Many people cannot afford to go to the health facility. When you go to the home, you can teach many things and they are able to know and understand better rather than spend the whole day at the health facility with a child in the back" – CHW, Uganda

All participants welcomed the community intervention. Only one male TB patient participant in Cameroon stated he preferred taking his children to the health center for TB screening because all investigations are available there as opposed to the limited knowledge or diagnostic means in the community intervention model. Indeed, the discourses of some other participants showed the obstacles they went through from district hospitals to the capital city on their diagnosis itinerary.

Elsewhere, many participants raised concerns about unintended disclosure and subsequent stigma from the other community members following home visits. The proposed approach to home visit did not include enquiries and screening of other children <5 years living in the same compound, participants were ambivalent when asked about the opportunity to also screen such children as the risk of stigma increases. Those who would agree to the screening of children playing together with their own children, preferred to inform their parents themselves based on past positive relationship and their living together experience.

“They [the family of the index case] need to check if the neighbors are not sick. It will be difficult, but if the family has accepted their fate [having TB], they can help the others [the neighbors] accept as well” – CHW, Cameroon

“Some clients do not want their neighbors to know because they know that the moment these know that they are having TB, they will either be chased from their place where they are renting or sometimes they may be isolated” – TB focal person, Uganda

From the providers' points of view, the intervention was coherent and welcome though they questioned its sustainability.

One CHW even highlighted the fact that many research projects test interventions in the communities and when they finish the project and remove the means, there is no benefit left for the community:

“You [implementing organizations] come, you tell us what has to be done, you teach us what to do, it [the project] starts well and after a certain time it stops. And we don’t understand why it stopped.” – CHW, Cameroon.

Prerequisites of feasibility of community TB screening and TPT management

Both patients, community leaders and health staff agreed that the cornerstone of this community intervention is the explanation given and the counseling offered by the TFP at the first visit with the index case. During this visit, TB education should be done, rapport should be created through demonstrating empathy, providing options, and ensuring confidentiality.

“During the first visit is when the rapport is created. Once the patient gets to know that you are friendly and you will keep their information, you will not release it to any other person; through my experience, these clients are willing to welcome you to their homes”
– TB focal person, Uganda

This was echoed by healthcare personnel, especially in Uganda, where TFP and CHWs stressed successful implementation depends on thorough information given to the index case. Of paramount importance is the quality of the initial counseling, and therefore on CHWs’ training, experience and acquired legitimacy.

“I think that if we explain very well to the patient, it will be acceptable. [...] when it is well explained, the patient understands the benefit [of the community intervention] from the explanation” – health facility manager, Cameroon

“At the beginning I told you, if you give them information on the initiation day, if you give them the information, they can give the medicine [to their children].” – TB focal person, Uganda

The opinions of the patients converged towards their need to be informed well in advance of the timing of the home visit so that they can ensure that their children are at home at the time of the visit or that they have informed their partner -if they have not yet done so- or relevant people

based on need-to-know. These conditions provided, the team is welcome to come and perform the screening and even take time to discuss other family health needs or concerns.

Creating rapport was also essential for CHW and they should be trained on this subject. The legitimacy and training of a CHW was also an important determinant of feasibility according to patients and stakeholders. Some respondents and interviewees were skeptical regarding the implication of CHWs because of past negative experiences with careless CHWs who would spread information about people they visit, which shows a lack of confidentiality.

Generally, FGD participants preferred trained CHWs who are polite and explain well all activities that will take place. There was no preference for gender, as long as the person is well trained.

“The most important thing is if you send a health worker with the expertise in whatever he or she is going to do. It does not matter if it is a doctor or a nurse, as long as they have the expertise in whatever they are going to do. It does not matter whether the health worker is male or female” – male participant, Uganda

Even with the best intentions in mind, unintentional disclosure cannot be totally ruled out due to the specific local context, and some participants expressed their concern. Others were not at all worried about disclosure and subsequent consequences.

“They [the neighbors] will maybe spread this [the information] everywhere. “Oh, she has this, she has that”. It’s difficult, it’s very difficult [to disclose]” – female participant, Cameroon

“For me it’s not a problem. It’s my house, my family” – female participant, Cameroon

An essential point discussed only by the health staff and community leaders is the CHWs’ motivation. This is a term historically referring to money used to compensate CHWs for their time and transport. Motivation is always requested when doing any kind of research activity in both countries as highlighted by the qualitative assessment:

“If we have enough staff and there are [financial] resources, it [TB screening] can be improved” – community leader, Uganda

“If there is motivation, they [the CHW] will do the work” – community leader, Cameroon

Adaptation and integration

TB services and available tools

In all cluster facilities contact investigation was done by a health care worker (nurse, clinician), for children <5 years in both countries. HIV-positive contact children were also screened in Uganda. Both countries had registers recording child contacts initiated on TPT and their TPT outcome. At the time of assessment, National TB Programs were about to introduce in both countries a contact screening register to record all household contacts per index cases with the results of their TB screening. None of the two countries had tools to monitor TPT adherence and tolerability. In Uganda, TB contact screening could be done at community level by the facility TFP. In practice, this activity was done only with support from implementing partners to cover transport cost. At the time of the site assessment, no registered data were available about the number nor age of household child contacts in both countries.

Six months isoniazid prophylaxis was used in all facilities and was delivered monthly at the facility by the TFP. All study facilities were expecting to introduce the 3 months isoniazid rifampicin (3RH) TPT under the CaP TB Project. TB screening, clinical and microbiological diagnosis for children with presumptive TB and drugs and treatment monitoring were free of charge. Families had to pay for further TB investigations like chest X-ray. Drug-resistant cases and complicated cases were referred to higher-level health facilities.

HIV testing was provided at the health facility in all study sites, in close collaboration but in separate units of the same department in Cameroon with the exception of two clusters facilities where TB and HIV services were fully integrated, and integrated in the same department in Uganda.

In all study sites TB drugs were stored at the TB clinic at room temperature in a locked cabinet and in two health facilities at the facility pharmacy.

A reference and counter-reference system between the CHW and the PHC staff or higher-level health facilities was set in the Ugandan clusters but almost inexistant or not functional in the Cameroon clusters.

Table 2 below summarizes practices and available tools under the standard of care in the two countries.

Table 2: Practices and tools in the routine system

Activity	Cameroon	Uganda
Index case identification	By the TFP at the health facility using the TB register	By the TFP at the health facility using the TB register
Contact investigation	At the health facility. Contact tracing register about to be introduced	Possibility of household contact investigation by the TFP Contact register about to be introduced
Symptom screening	At the health facility, no tool	Possibility of household screening, intensified case finding tool (checklist)
HIV testing of child contacts	Only medical personnel at the health facility	Possibility of HIV testing by CHWs or healthcare staff
TPT initiation	6H, at the health facility, recorded in the TPT register by the TFP	6H, at the health facility, recorded in the TPT register by the TFP
TPT follow-up: adherence and tolerability	Adherence and tolerability not assessed. No tool for TPT adherence. TPT register used for follow-up at the health facility	Adherence and tolerability not assessed. No tool for TPT adherence. TPT register used for follow-up at the health facility
Safety management	At facility. No tool for safety evaluation	At facility. No tool for safety evaluation
PT outcome assessment	According to national TB guideline: completed, death, lost to follow-up. At the health facility by the TFP	According to national TB guideline: completed, death, lost to follow-up. At he health facility by the TFP

<p>TB diagnosis</p>	<p>TB investigations at the health facility or referral at a higher-level facility</p> <p>Available tools: CXR, sputum collection, NPA, XpertMTB/RIF testing</p> <p>Laboratory results in the lab register</p>	<p>TB investigations at the health facility or referral at a higher-level facility</p> <p>Available tools: CXR, sputum collection, XpertMTB/RIF testing. Laboratory data collected in the lab register</p>
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TFP = tuberculosis focal person, CXR = chest radiography, NPA = nasopharyngeal aspirate, H = isoniazid; TB = tuberculosis

Checking data quality

A total of 1091 TB patients, out of which 708 were B+, have been registered between May 1st, 2018, and Oct 31st, 2018, in the TB registers of the cluster sites. The overall median rate of missing data was 0.3% (interquartile range (IQR) [0%-3%]) in Cameroon, ranging from 0 to 8.6% and 0.4% (IQR [0%-0.6%]) in Uganda, ranging from 0 to 1.4%. The median error rate was 1.1% (IQR [0.6%-1.4%]) in Cameroon, ranging from 0.3% to 3.6% and 0.0% (IQR [0%-0%]) in Uganda. The biggest rate of missing data was for the registration date, with a maximum of 8.2% in cluster 6. The biggest rate of errors was for the type of TB, with a maximum of 2.1% in cluster 5. (see Additional Tables 1 and 2).

Resources and procedures for the community intervention

The type of human resources at facility level was similar in the two countries. The community intervention involved mainly TFP and in addition, one clinician was identified as a safety monitor for referred children with TPT tolerability concerns and was trained for safety assessment. Regarding CHWs, in Uganda, village health team were already involved in TB activities at facility level within the CaP TB project (called Linkage facilitators). It was proposed to identify CHW for the community intervention among the linkage facilitators. In Cameroon, since there was no CHW involved in TB activities, they were identified among existing CHW involved in other community health activities (COSA - Comité de Santé (health committee)). Based on literature review of community interventions, findings of the acceptability survey and discussion with stakeholders in

both countries, a procedure for selection of the CHW was proposed including the following criteria: having experience with community work, living in the same community, medium level of education, time to perform the tasks, accepted and respected by the communities. In Cameroon there were 3 CHW per intervention site, with a total of 15 CHW and in Uganda there were 2 CHW per intervention site for HC IV and one CHW for HC III, with a total of 12 CHW. In both countries, it was proposed that CHW will report to the facility TFP.

Taking into consideration the absence of research experience of CHW, to guaranty good quality of data and to ensure that a clear distinction could be made between activities related to the intervention and activities related to research, it was proposed that RAs will accompany CHWs to households and will be in charge of the informed consent procedure for contacts and data entry in the electronic case report form (eCRF) from source documents filled by the CHW.

Transport cost for the community activities was identified as a barrier by both TB patients and providers in the acceptability survey and by stakeholder during study preparation. It was proposed that the study will cover the transport cost but that existing public transport will be used as much as possible to ensure the sustainability of the intervention and avoid stigmatization. Good communication between facility TFP and CHW was also identified as a very important factor justifying the allowance of small budget for communication (airtime). Therefore, to ensure sustainability and to comply with existing practices, it was proposed that CHWs will not receive a salary, but will be compensated for their time and transport.

Finally, working with CHW on a new intervention implied to develop simple tools and check lists for TB symptom screening, adherence and tolerability assessment. These tools were developed in coordination with country TB stakeholders (see Additional Table 4 for symptom screening checklist). These tools were incorporated in simple standard operating procedures used for the training of the CHWs. CHWs were also trained to recognize potential severe symptoms or signs that would justify urgent reference of the child to the facility that could be related to other disease than TB. Although the initial aim of the study was that CHW will initiate child contact on TPT in the household, both National TB Programs of Cameroon and Uganda requested that initiation be done by a nurse in the household and that the CHW will be in charge of the follow-up on his own.

They also requested a more frequent follow-up by the CHW, one and two weeks after initiation instead of 4 weeks as done at facility by TFP.

In Cameroon, due to national guidelines, HIV testing could only be performed by a nurse, therefore HIV testing in the community was done by a nurse. Cascade training was organized by country research team in each cluster facility sites followed by supervision by the RAs.

Discussion

Main results and implications for implementation

The qualitative results showed that community activities were well accepted by beneficiaries and healthcare providers alike in both countries. The emerging barriers to health facility TB contact investigation and TPT management were coherent with the literature findings and support the proposed community intervention(10,35,36). A study conducted in Uganda identified the following barriers to TB contact investigation: stigma, limited knowledge about TB among contacts, insufficient time and space in clinics for counselling, mistrust of health center staff among index patients and contacts, and high travel costs(36). Our qualitative assessment identified similar barriers for child TB contact investigation. Stigma and disclosure play an essential role firstly in the diagnosis of TB patients and secondly in the acceptability of the community intervention. Stigma and disclosure influence how TB patients accept a team coming to their household for TB contact investigation.

Both beneficiaries and providers insisted on the importance of proper selection, training and support of CHW in charge of the household visits and how important it is to build confidence with beneficiaries. Although CHW have been involved in TB community activities, their involvement in the TPT management was quite unique in the CONTACT study (37) (15).

A deductive approach for acceptability based on the acceptability framework proposed by Sekhon et al (34) combined with inductive theorizing can be used to propose a model which is specific for community TB investigation and TPT management, as illustrated in Figure 2. This framework contains 7 concepts: burden, affective attitude, ethicality, intervention coherence, opportunity cost, effectiveness and self-efficacy. Concepts like TB stigma and disclosure that emerged from

the discussions relate to the affective attitude, burden and ethicality components of acceptability. TB knowledge and experience with other community activities influence the affective attitude of the participants towards the intervention and reveals the coherence of the community intervention. Nevertheless, through experience from other community activities, participants anticipate the burden this kind of intervention could represent. TB patients anticipated the added health benefit of a community intervention through the possibility of discussing other health problems, which are related to the intervention coherence and the opportunity cost. Initial counseling and TB education for the index case is essential for acceptability and in the proposed framework these aspects influence the affective attitude of the participants, the opportunity cost and the effectiveness of the intervention. Finally, CHW legitimacy and training have a role to play in the effectiveness of the intervention and in the self-efficacy component of acceptability.

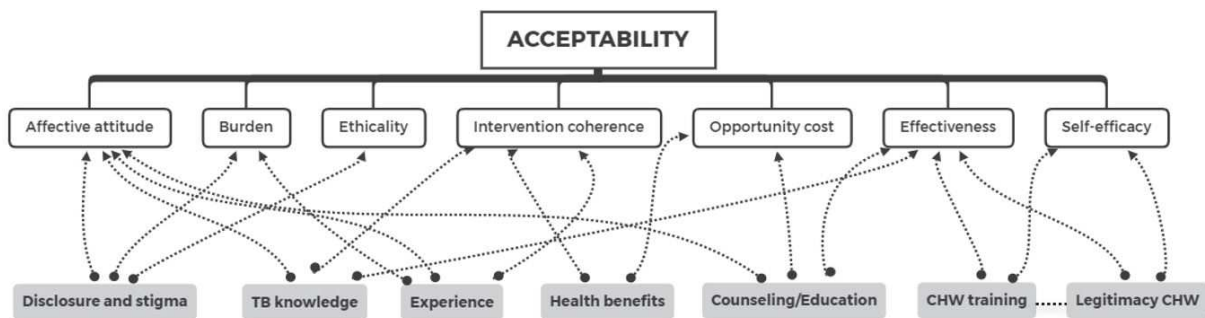


Figure 2. Acceptability components and emerging themes

The findings of the qualitative assessment were used to formulate recommendations on recruitment of CHWs, training curricula for CHWs, adapt team transportation for field visits and concentrate efforts on key elements that were important to the participants (like preparing the initial visit). Financial and non-financial means are known to improve performance of CHWs for the community activities (38), and close attention is paid to CHW competence and training. Kok et al identified the specific activities that led to a better performance of CHWs and frequent supervision and continuous training were main influencers(39). The CONTACT study ensured both these elements by close supervision of the CHWs by the RAs and TFPs and job mentorship by TFPs. It was indeed very important to ensure good communication and linkages between CHW and TFP and empowering CHWs in performing their activities, as dully noted in the Astana

declaration on primary health care: “Investment must encompass the empowerment of individuals and communities, with recognition of the importance of skills, local context and health needs”(40). Although incentives were not provided per se, transport and communication costs were covered by the study. This is an important aspect to be taken into account for sustainability purposes, as CHW transportation needs to be ensured in order for this type of community project to succeed(40).

Community intervention evaluated in the CONTACT study

Under the CONTACT study, all study drugs are kept at the health facilities under the responsibility of the TFP who prepares the necessary drug packages before each study visit. CHWs ensure the delivery of the drugs prepared and packed by the TFP to the contact children, according to the study visit procedures. The research team assessed TB services in the standard of care and the existing tools to ensure a smooth integration of study activities and source documents into current practice and to avoid disruption of routine activities by the CONTACT study. This part of the feasibility study is crucial to the sustainability of the proposed intervention beyond the end of the CONTACT study. It is challenging to integrate both the intervention and tools to evaluate the outcome of the intervention in a health system that may be weakened by lack of resources, turnover of personnel and high workload. The burden that the proposed intervention is putting on the health providers is an essential element of knowledge to practice translation. This feasibility assessment allowed us to identify which existing tools could serve as source documents and which additional tools will need to be introduced, keeping an adaptation to each country’s specificities. Integrating research and practice is a core element of translating the proposed intervention, if proven effective, into current practice. Selecting sites from the CaP TB Project is an asset for the study because of capacity reinforcement for pediatric TB case management and improvement of data collection tools. Also, distinguishing intervention activities from research activities and ensuring that these last ones will be covered by RA and not routine facility personnel or CHW was very important for the sustainability of the intervention and was emphasized by the WHO ethics research committee at the time of first protocol submission.

Table 3 presents the activities included in the intervention following the feasibility assessment and adapted to each country context.

Table 3: Activities proposed in the intervention model of care per country

Activity	Place	Cameroon	Uganda
Index case identification	Facility	TB register (NTP tool)	TB register (NTP tool)
Contact investigation	Community	Contacts table (study tool) by CHW	Contact tracing register is used (NTP tool) by CHW
Symptom screening	Community	Screening form (study tool) by CHW	Screening form (study tool) by CHW
HIV testing of child contacts	Community	1 st test done by community nurse. Confirmatory test at facility	Done by CHW
TPT initiation	Community	TPT initiation form (study tool) filled by community nurse	TPT initiation form (study tool) filled by TFP
TPT follow-up	Community	TPT follow-up form (study tool) by CHW	TPT follow-up form (study tool) by CHW
Adherence	Community	TPT card (study tool) filled by care giver	TPT card (study tool) filled by care giver
Safety management	Community	Tolerability checklist (study tool) filled by CHW	Tolerability checklist (study tool) filled by CHW
	Facility after referral	Safety form (study tool) filled by clinician	Safety form (study tool) filled by clinician
TPT outcome assessment	Community	TPT outcome form (study tool) by community nurse	TPT outcome form (study tool) by TB focal person
TB diagnosis	Facility after referral	Cap TB pediatric form filled by TFP	Cap TB pediatric form filled by TFP
Referral	Community	Referral form (study tool) filled by CHW	Referral form (study tool) filled by CHW

NTP = National Tuberculosis Program, CHW = community health worker; TFP = Tuberculosis focal person; TPT = Tuberculosis preventive therapy

In the context of few available cluster sites within the CaP TB Project, the retrospective data collection of bacteriologically-confirmed TB cases and comparison with NTP reports was extremely useful in informing the study team on potential problematic sites and adjusting the recruitment period from 12 to 15 months. This step was essential for activity planning and budget review(41).

Limitations

TB services have been assessed through a survey and discussions with health providers, nevertheless, there was no observation of practices by the research team. Indeed, collecting data through a survey could induce a declaration bias of the person filling in the survey. However, conducting observations would have been limiting for the feasibility study as some health facilities have very low patient flows, meaning the events to be observed would be rare. In addition, it is well known that observations could induce the Hawthorne effect, when subjects perform better because they know they are observed(42).

It is worth mentioning that during the qualitative assessment, participants could have been inclined to declare that they did certain activities because of social desirability bias, meaning they wanted to be perceived in a positive way by the researchers(43). The team tried to minimize this bias by always reassuring the participants that there is no right or wrong answer, that the discussions were not part of an evaluation by their hierarchy and by using the technique of indirect questioning (i.e. “Why don’t people in general bring children back to the health facility for TB screening”).

Conclusion

This study has identified a feasible community intervention for TB screening and TPT management for further evaluation in the context of two high TB burden and resource –limited countries. Being able to implement community activities is highly important due to the positive impact these interventions could make on the communities by bringing the needed TB prevention services at

their doorstep. In addition, the health system could benefit of the CHW structure already in place and ensures that other these activities are integrated with other community activities.

All activities occurring after the start of inclusions in October 2019 are assessed under an undergoing process evaluation that will support the interpretation of the CONTACT study effectiveness. Capturing what is delivered in practice, with close reference to the theory of the intervention, can enable the researchers to distinguish between the adaptations made to fit different contexts and changes that undermine intervention fidelity altogether(44). In addition, a qualitative assessment of post-intervention acceptability by child contact parents, facility personnel, CHWs and stakeholders will be repeated at the end of the study.

List of abbreviations

CaP TB = Catalyzing Pediatric Tuberculosis Innovations, CHW = community health worker, CXR = chest radiography, DHS = demographic health survey, FGD = focus group discussion, H = isoniazid, IDI = in-depth interview, NPA = nasopharyngeal aspirate, NTP= National Tuberculosis Program, TB = tuberculosis, TB B+ = bacteriologically confirmed tuberculosis, TFP = tuberculosis focal person, TPT = tuberculosis preventive therapy, WHO = World Health Organization

Declarations

Ethics approval and consent to participate

This feasibility study was part of the main cRCT protocol approved by the WHO Ethics Research Committee, the Advarra Institutional Review Board and by the two local ethics committees: Cameroon National Ethics Committee for Human Health Research and Research Ethics Committee of the Mbarara University of Science and Technology in Uganda. In addition, administrative approvals were needed from the Direction for Operational Research from the Ministry of Health in Cameroon and the Ugandan National Council for Science and Technology in Uganda.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. The survey used for TB services is found in the Additional File 1.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

AV and MB conceptualized the feasibility study. GT conceptualized the pre-intervention qualitative assessment. AV, GT, MMA and CA collected qualitative data, MMA and CA transcribed the qualitative data, AV coded the qualitative data and analyzed it with input from GT. BKT, DA, BYT and BS coordinated and supervised data collection for the retrospective cohort and the survey. AV analyzed the retrospective cohort and the survey data. MC coordinated linkage with CaP TB activities, MB coordinated all study activities. AV wrote the manuscript with valuable input from MB, GT, MC, BKT and DA.

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Additional Files

Additional File 1 Cluster assessment form

CONTACT TRACING AND MANAGEMENT

District name: _____

Facility name: _____

1. Who are the child contacts screened? Child contacts living in the same household, index case children only, child contacts < 5 years, HIV+ child contacts, none

a. Where is recorded the information about identified contacts? Form, log, note book, no records

b. Who is in charge of following up with TB index case and make sure children living in his/her household are brought to the facility for screening?

c. How is the follow-up done? (Phone calls, SMS...)

2. Who is in charge of the screening of contacts? _____

a. Is screening performed using a standardized questionnaire?

b. Is result of TB screening recorded? If yes where?

3. Who does the prescription of preventive therapy and where (facility/community)?

a. Is there counselling about tolerability and adherence during initiation and follow-up of preventive therapy?

b. Are there tools using to assess tolerability and adherence? (Questionnaire, visual scale, calendar.....)

c. Who delivers the preventive therapy? TB focal person, TB nurse, pharmacy

d. How is the treatment delivered and where (facility/community)? Individual tablets drugs blisters, boxes of drugs

e. Is pyridoxine systematically prescribed and delivered? _____

4. Are there services costs/fees that the patients/caregivers must pay during the process of TB screening, clinical assessment of eligibility for IPT initiation, IPT and follow-up? If Yes, please detail

REFERRAL SYSTEM

Number of health centres that refer children to this cluster facility: _____

Maximum distance (Km or time) between the furthest health centre and the cluster facility? _____

Referral from the cluster facility to reference centres

1. List the reasons for referral : _____

2. Is there a referral form? Type of document (form, log, register...) and MOH or facility form

If yes, is a copy kept at the cluster facility? _____

3. Is there a direct communication between the cluster facility and the referral centre? (telephone, SMS, other):

4. Does the cluster facility receive feedback from the referral centre? (how?)

Referrals from peripheral health centres to the cluster facility

5. Is there a referral form? Type of document (form, log, register...) and MOH or facility form

If yes, does the cluster facility keep a copy of the referral? Which document (form, log,...)

6. Does the cluster facility send a feedback to the centre? _____

7. Is the cluster facility contacted by the referral centre before referral? How (telephone, SMS):

8. Does the cluster facility involve the peripheral centres for contact screening? If yes, how?

9. Are there meetings between the cluster facility and peripheral centres? frequency?

TB/HIV INTEGRATED SERVICES

Prevention and treatment of HIV-infected child contacts

Name of district: _____

Name of facility: _____

1. Is there a HIV clinic in the facility? _____ ; if yes
- a. What is the relation between TB and HIV clinics? (same department, same clinician, none)

- b. Which clinic is in charge of HIV for TB-HIV co-infected patients?

2. Are children tested for HIV at the TB clinic? _____

If yes, who is tested? (Different options possible)

- All patients with presumptive TB
- All patients with TB diagnosis
- All child contacts
- Only child contacts of HIV+ TB index cases
- Other (detail) : _____

3. Where is done the TB screening of HIV+ child TB contacts? TB clinic HIV clinic

4. Where is initiated preventive therapy in HIV+ child TB contacts? TB clinic HIV clinic

5. Where is done the preventive therapy follow-up of HIV+ child TB contact? TB clinic HIV clinic

6. Where is filled the preventive therapy register for HIV+ child TB contacts? TB clinic HIV clinic

7. Where is done the TB diagnosis of HIV+ child TB contacts? TB clinic HIV clinic

8. Where are registered HIV+ child TB contacts with TB? TB clinic HIV clinic

9. How and when is initiated preventive therapy and ART for HIV+ child TB contacts

10. At the HIV clinic if an HIV+ adult is diagnosed with TB:

- a. Where is TB treatment initiated? TB clinic HIV clinic

- b. Where is registered the patient? TB clinic HIV clinic

- c. Where is done the screening of contacts? TB clinic HIV clinic

MANAGEMENT OF ANTI-TUBERCULOSIS DRUGS

1. If the preventive therapy is delivered at the TB clinic

- a. When and how is organised the supply of preventive therapy? Frequency (fixed days or when needed) and procedure of request
-

- b. Is there a stock management? describe the stock cards or logs
-
-

- c. Where and how are stored the drugs? In terms of security, temperature, humidity
-

2. At the facility pharmacy

- a. Is there a stock management? ask to see the stock cards or logs
-

- b. Where and how are stored the anti-tuberculosis drugs? Security conditions (locked key board, cool area, humidity)
-

Name and function of the person collecting the information: _____

Additional Table 2 Missing rate for TB register checks

Country	Cluster	Registered TB patients	Bacteriologically confirmed TB	date	register nb	sex	age	type of TB	type of patient	HIV status	Missing total	Missing rate total
Cameroon	Cluster 1	113	75	0	0	0	0	1	0	0	1	0,1%
	Cluster 2	85	51	0	0	0	0	0	0	1	1	0,2%
	Cluster 3	75	52	2	0	0	0	0	0	0	2	0,4%
	Cluster 4	98	42	23	0	0	0	0	0	1	24	3,5%
	Cluster 5	40	32	0	0	0	0	0	0	0	0	0,0%
	Cluster 6	157	101	90	1	0	0	0	1	2	94	8,6%
	Cluster 7	51	36	0	0	0	0	0	0	0	0	0,0%
	Cluster 8	40	27	0	0	0	0	0	0	4	4	1,4%
	Cluster 9	46	29	3	2	0	0	0	0	7	12	3,7%
	Cluster 10	19	9	0	0	0	0	0	0	0	0	0,0%
Uganda	Cluster 1	30	14	0	0	0	0	0	0	0	0	0,0%
	Cluster 2	32	25	0	0	0	0	0	0	0	0	0,0%
	Cluster 3	22	6	0	0	0	0	0	0	1	1	0,6%
	Cluster 4	48	23	2	0	0	0	0	0	0	2	0,6%
	Cluster 5	37	28	0	0	0	0	0	0	0	0	0,0%
	Cluster 6	28	28	0	0	0	0	0	0	1	1	0,5%
	Cluster 7	7	7	0	0	0	0	0	0	0	0	0,0%
	Cluster 8	35	32	0	0	0	0	1	0	0	1	0,4%
	Cluster 9	62	49	6	0	0	0	0	0	0	6	1,4%
	Cluster 10	66	42	2	0	0	0	0	0	0	2	0,4%

Additional Table 3 Error rate for TB register checks

Country	Cluster	Registered TB patients	Bacteriologically confirmed TB	date	register nb	sex	age	type of TB	type of patient	HIV status	Error rate total	Error rate total
Cameroon	Cluster 1	113	75	0	0	0	0	8	3	0	11	1,4%
	Cluster 2	85	51	0	0	0	0	1	6	0	7	1,2%
	Cluster 3	75	52	0	0	0	0	1	4	0	5	1,0%
	Cluster 4	98	42	2	0	0	0	0	0	0	2	0,3%
	Cluster 5	40	32	2	0	0	0	6	2	0	10	3,6%
	Cluster 6	157	101	0	0	0	0	6	0	0	6	0,5%
	Cluster 7	51	36	0	0	0	0	0	4	0	4	1,1%
	Cluster 8	40	27	0	0	0	0	1	0	0	1	0,4%
	Cluster 9	46	29	0	0	0	0	2	2	0	4	1,2%
	Cluster 10	19	9	2	0	0	0	0	0	0	2	1,5%
Uganda	Cluster 1	30	14	0	0	0	0	0	0	0	0	0,0%
	Cluster 2	32	25	0	0	0	0	0	0	0	0	0,0%
	Cluster 3	22	6	0	0	0	0	0	0	0	0	0,0%
	Cluster 4	48	23	0	0	0	0	0	0	0	0	0,0%
	Cluster 5	37	28	0	0	0	0	0	0	0	0	0,0%
	Cluster 6	28	28	0	0	0	0	0	0	0	0	0,0%
	Cluster 7	7	7	0	0	0	0	0	0	0	0	0,0%
	Cluster 8	35	32	0	0	0	0	0	0	0	0	0,0%
	Cluster 9	62	49	0	0	0	0	0	0	0	0	0,0%
	Cluster 10	66	42	0	0	0	0	0	0	0	0	0,0%

Additional Table 4 Characteristics of participants and discussion duration for FGD and IDI

Country	FGD participants				IDI participants
	Male	Duration (min)	Female	Duration (min)	
Cameroon					
Cluster 1 SOC model (Centre)	7	92	5	71	4
Cluster 2 ITV model (Centre)	8	100	6	141	4
Cluster 3 SOC model (Littoral)	7	127	.*	-	4
Cluster 4 ITV model (Littoral)	7	101	7	134	4
Uganda					
Cluster 1 SOC model	6	144	8	104	4
Cluster 2 ITV model	7	113	6	106	4
TOTAL	42	677	32	556	24

*one FGD in the littoral region could not be done due to lack of participants

Additional Table 5 Checklist of symptoms assessed by CHWs during TB symptom screening

Cough	Yes ☐	No ☐
If yes, for how long?	> 2 weeks ☐	≤ 2 weeks ☐
Fever	Yes ☐	No ☐
If yes, for how long?	> 10 days ☐	≤ 10 days ☐
Lethargy/reduced playfulness/ fatigue	Yes ☐	No ☐
Weight loss/appetite loss or failure to thrive during the last 3 months	Yes ☐	No ☐
Night sweats	Yes ☐	No ☐
If yes, for how long?	> 2 weeks ☐	≤ 2 weeks ☐
MUAC <125mm (if <5 years)	Yes ☐	No ☐

Neck swelling	Yes <input type="checkbox"/>	No <input type="checkbox"/>
Wheeze	Yes <input type="checkbox"/>	No <input type="checkbox"/>
If yes, for how long?	> 2 weeks <input type="checkbox"/>	≤ 2 weeks <input type="checkbox"/>

Poster presentation at the Union World Conference on Lung Health, 2021


The Union

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Acceptability and feasibility of household child contact TB screening and preventive therapy management in Cameroon and Uganda

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Check out the study protocol of the
CONTACT cluster randomized trial

Household child contact TB screening and TPT management is perceived as **acceptable** by both providers and beneficiaries alike based on the pre-intervention assessment

The **CONTACT** cluster randomized trial is currently evaluating the impact of a community-based approach for TB screening and TPT management

Main conditions for implementation:

- Visit preparation
- Clear explanations of the scope of visit
- Team conduct
- Unlabelled cars, no uniforms
- Respecting confidentiality
- CHW transport/motivation
- CHW training and counseling skills

Quotes

- Barriers to health facility screening
"When you ask a parent to transport his 5 kids and bring them to the health center, he's going to ask: "are you paying for transport?" – community health worker, Cameroon
- Acceptability of the community intervention by the patients
"some people cannot afford the transport to come to the health facility so this program that you are going to start of visiting the homes will be helpful for most of us" – Female patient, Uganda
- Main conditions prior to implementation
"when it is well explained, the patient understands the benefit [of the community intervention] from the explanation" – health facility manager, Cameroon
- *"if we have enough staff and there is a resource, it [TB screening] can be improved" – community leader, Uganda*
- *"So we have to emphasize on the issue of rapport and confidentiality, if it is well emphasized, it is a very good approach" – TB focal person, Uganda*

Intro

The uptake of TB child contact screening and TB preventive therapy (TPT) is limited by the necessity to bring children to the facility in high-burden countries.
We conducted a pre-intervention assessment of the acceptability of household child contact TB screening and TPT management.

Methods


We conducted 11 focus group discussions with 74 TB patients and 24 in-depth interviews with healthcare providers, community health workers and community leaders.
Main topics were: TB knowledge, perceptions on stigma and barriers to facility screening, acceptability and feasibility of a community-based TB intervention. Transcripts were coded and analyzed using ATLAS.ti 9.

Results

Transport cost, waiting time were main barriers to facility screening. Patients found household child contact screening by community health workers to be convenient and helpful in ensuring their children access screening and TPT and in providing the opportunity to address other family health problems, but confidentiality is essential. Providers also highlighted the benefits of integrated community care and on the importance of index case counseling

Conclusion

Community TB screening and TPT management is acceptable with some specific conditions for its feasibility.



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5. Discussion

5.1. Main findings of the thesis studies

The first article of the thesis is focused on the comparison between TB symptom screening and CXR in excluding TB for child contacts in high-burden and low-resource settings. This is an important research topic as in order for TB screening to be easily deployed in community settings, there needs to be a simple screening tool available to health providers and even more so, to CHWs. A simple symptom screening formatted as a checklist is very practical and easy to implement in these settings and used at community level, whereas a CXR demands infrastructure, maintenance, is only available at secondary health care facilities in resource limited countries and very few clinicians are trained on CXR interpretation. The findings suggest that symptom screening is sufficient in excluding TB disease for contact children under 5 years, confirming the WHO recommendations. The data for older contact children are scarce and even if we have identified a very high negative predictive value, few studies were included. The performance of symptom screening was compared to CXR which is an imperfect reference standard for TB disease. Nevertheless, the imperfect reference standard is counterbalanced by a low percentage of children 5-14 years developing TB disease after a negative symptom screening and without having received TPT. This finding would also support the use of symptom screening in older child contacts to exclude TB disease. However, more research is necessary in this specific age group and currently WHO still recommends the use of CXR to exclude TB disease in child contact older than 5 years old, unless they are HIV-positive.

These results support to use of a simple symptom screening tools in the CONTACT study at community level. The symptom screening designed for the CONTACT study is based on the symptom screening recommended by the WHO and national TB program guidelines from Cameroon and Uganda. A child contact with presumptive TB is a contact presenting one or more symptoms during screening. The list of symptoms used in the CONTACT study uses the following signs and symptoms: cough (yes/no and if yes, > 2 weeks); fever (yes/no and if yes, > 10 days), lethargy/reduced playfulness/fatigue, weight loss or failure to thrive, night sweats (yes/no and if yes, > 2 weeks), MUAC <125mm (if < 5 years), neck swelling and wheezing (yes/no and if yes, > 2 weeks).

CHW were trained on the symptom screening tool and to prevent any risk of erroneously initiating on TPT a symptomatic child. The same symptom screening during contact investigation was repeated the following 2 weeks for child contacts with symptoms of short

duration. Prior to TPT initiation a nurse was also checking that the child was correctly screened as asymptomatic. In the context of the study both NTPs in Cameroon and Uganda requested that nurses initiate eligible children on TPT in the household. In the CONTACT study we are using this tool to assess all child contacts under 15, but only child contacts under 5 years and child contacts 5-14 years living with HIV are eligible for TPT initiation. The CONTACT study has a study follow-up visit 6 months after the initial contact screening, for all contact children under 15, regardless of TPT initiation. This will provide very useful data on the safety of the symptom screening in children older than 5 years, under the assumption that there is no TB disease development within the 6 months follow-up. Indeed, the risk of developing TB disease is high in children during the first 6 months after exposure.

The findings of the literature review were important for writing the study protocol. The choice of a cluster randomized controlled trial can bring the best level of evidence when comparing health interventions. The pragmatic nature of the study allows the evaluation of the intervention in a real life setting and its rapid implementation under a programmatic context thereafter. The choice of two different settings in sub-Saharan Africa increases the representativity and generalizability of study results, nevertheless, it also brings the challenge of different TB service organization and the need for adaptation to the local context. An advantage of the study was that the study clusters were part of the CaP TB program sites. This ensures a good diagnosis capacity and homogenous offer of TB service among the study sites but limits the choice of clusters. In addition, the sites involved in the CaP TB program have an improved standard of care for pediatric TB than what is routinely available and might reduce the representativeness of the study results.

The CONTACT study is structured in three phases: baseline, intervention and post-intervention (explanatory). The baseline phase is concentrated on assessing the acceptability and feasibility of the study. The intervention phase is focused on participant recruitment and active response to challenges. The post-intervention phase is composed of the efficacy analysis, cost effectiveness analysis, process evaluation and acceptability assessment.

The baseline phase of the CONTACT study was essential in assessing the feasibility and acceptability of the proposed community intervention in the two study countries. Indeed, the community intervention for TB screening and TPT management is complex because it has multiple parts which depend on healthcare staff but also trained CHWs, it proposes a model of care which involves sending teams into communities and requires interpersonal skills from the staff delivering it. In addition, there were very few published experiences of TB screening at community level for child contacts and almost no publication on TPT management at community level.

When interventions involve communities, when there is no literature data on TPT delivery in this setting and when the evaluated interventions are complex with many parts that depend on different human resources like facility and also community health staff, it is crucial to be able to assess the feasibility in the specific context where the interventions will be evaluated. Additionally, this context is different due to the country specific level of decentralization of TB services. The feasibility evaluation of the CONTACT study uses mixed methods to get a comprehensive perspective on how to best integrate the intervention in the local context and how to ensure its acceptability by the community and by the health providers. The qualitative assessment brought essential elements for the acceptability intervention by both beneficiaries and healthcare providers, like visit preparation, communication and respect of confidentiality. In addition, CHW selection, training and motivation emerged as key components of the feasibility of the community intervention. The integration of existing tools within study tools ensured that only missing information was additionally collected, and the review of national registers allowed their use as source data. The availability of transport means for community activities emerged as a key element for the successful implementation of the intervention from the qualitative assessment and from the discussions with stakeholders, therefore the study ensured transport for all community activities, highlighting the fact that public transport was preferred. This specific aspect is arguably one of the most concerning for the sustainability of the project as other than reorganization, training or tools deployment, it involves a budgetary aspect.

5.2. CONTACT study – updates from the field

The CONTACT study has started inclusions in October 2019 and will stop inclusions on 31st December 2021. A 6-month follow-up period will last until June 2022. The study duration was increased from the initially expected 15 months, by the inevitable COVID-19 pandemic and the afferent lockdown periods. During the implementation of the study, we have encountered many challenges of different natures.

5.2.1. Ongoing challenges

We could classify the challenges we encountered in three categories: (1) research-related, (2) intervention-related, and (3) COVID-related.

5.2.1.1. Research related challenges

The research related challenges contain all study adaptations and protocol amendments, mainly to adapt the study implementation to changes in the local context. The study protocol benefited of three major amendments. The first protocol amendment was necessary right before the start of inclusions in order to change a study cluster which was not compatible with the intervention evaluation, as another organization was implementing community TB contact investigation in the same district, which could have biased the results. The health facility which was added after this protocol amendment was not in the initial randomization, but due to the limited availability of eligible study sites, we had to choose an urban site in another region. This was a potentially problematic choice because in urban settings care services are diversified and referral systems are complex. The protocol amendment was done prior to the feasibility assessment allowing for the feasibility criteria to be evaluated in the newly added study cluster. Changes in inclusion and exclusion criteria based on feedback from the study sites, determined the submission of the second protocol amendment. These changes allowed for the inclusion of self-referred adult contacts in the facility-based model and the exclusion of index cases whose household has already been screened because they were contacts of other index cases. The third protocol amendment was submitted to allow for the study team to perform the last study visit by phone instead of waiting for the contact to come back to the health facility and because of a change in the standard of care in Uganda. This is justified by the fact that for many children not started on TPT, only one study visit was performed, 6 months after the inclusion visit and many participants have moved. Also, the COVID restrictions and national measures made it difficult to retrieve the information for some participants. The NTP in Uganda issued a letter allowing TB focal persons to initiate TPT in communities if the parents cannot bring their children to the health facility for screening. If implemented, this recommendation could seriously bias the standard of care model. All protocol amendments have been approved by the SAC.

An important recurrent challenge of the CONTACT study is making the difference between research activities and intervention activities. For example, the informed consent procedure is timely and represents an important part of the first screening visit in the community with an impact on visit duration. Implementing a study in a pragmatic way and also ensuring a good level of research quality is not an easy endeavor and requires flexibility and creativity from the research team.

We have tried as much as possible to reduce the number of research-related challenges by delegating all research tasks to RAs and intervention tasks to health facility staff.

5.2.1.2. Intervention related challenges

The intervention related challenges arise mostly due to health system shortcomings. The study sites experienced national TB drug stockouts for adults or important delays in drug delivery to sites, which influenced the index case inclusions and implicitly the contact case inclusions. Also, the staff turnover in the health facilities demanded numerous trainings for different persons all along the implementation of the study. In Uganda, laboratory renovations and long sample referral times made bacteriologically confirmed index cases a rare sight in some of the study registers, with major implications on inclusion. In both countries, the community-based sites carry a higher burden of contacts per index case, which is expected, and implicitly a higher workload for the RAs who sometimes had to do multiple household visits in order to collect data from all contacts. In addition, another challenge is the high number of index cases declaring they don't have child contacts. This was a global problem but more pronounced in Cameroon where there were more cluster sites in urban or semi-urban setting. The study team did not anticipate this issue that had an effect on the enrolment of child contacts in the study.

5.2.1.3. COVID-19 related challenges

In addition to all these challenges which could occur in any TB community intervention implemented at any point in time, we had the additional challenge of conducting a research study during the COVID-19 pandemic. When the complete lockdown from the first wave was announced, all inclusions were put on hold from March 27th to August 27th 2020 in both countries. The research team made sure all children under TPT received their complete treatment by making home visits to deliver the remaining doses of their TPT. This activity, while necessary, will induce a bias in the standard of care model because those children should have come monthly to the health facility to receive their treatment. The research team considered that the most important aspect is for the previously TPT initiated children to receive their treatment until completion. Follow-up visits were done by phone to make sure the children don't manifest TB symptoms nor adverse events. All phone calls done during the COVID study interruption were entered in a log which has been monitored locally for completion. The second COVID wave of February 2020 in Cameroon, while very steep, had no influence on inclusions. In Uganda though, the second COVID wave brought a second complete lockdown which imposed another study interruption for the country, from June 18th to August 11th 2021. The same mitigation measures were applied during this lockdown period. These differences in the models of care will be taken into account in a sensitivity analysis planned in the statistical analysis plan. The lockdown periods impacted TB attendance to the health facilities and a lower level of inclusions was experienced after study restarted. Public transport cost has

increased in both study sites. In addition, due to the fact that schools were closed, children were sent to the villages to live with grandparents and this influenced the lost-to-follow-up in the study, but also the proportion of index cases declaring children in their household. The study interruption periods introduced a non-negligible delay in inclusions which led the research team to demand a no cost extension from the funder, which was approved. Nevertheless, personal protective equipment was provided for study staff and health facility staff, having an impact on the study budget. Study staff and health facility staff experienced different levels of COVID symptoms which influenced their involvement in the study. At national level, Xpert machines were repurposed for COVID detection, instead of TB detection, especially in Uganda. The study team delivered PPE to study health facilities and this had a non-negligible influence on the study budget.

It is important to reflect on how the CONTACT study was influenced by the COVID pandemic and its restrictions. The change of behaviors, population movement, differences in the delivery of the model of care, raise questions to the generalizability of the study results in a non-COVID context.

All these challenges are well documented by the research team and they will be assessed at the end of the implementation phase through a process evaluation with the scope and methodology described in the Perspectives section.

5.3. Perspectives for TB contact investigation

5.3.1. Short term perspectives

The most important short-term goal would be for the intervention to be effective from a statistical point of view.

When study results are obtained, the team will communicate them to the NTPs of each country with the aim of recommending the inclusion of community TB screening and community TPT initiation and follow-up in the national guidelines.

In addition to the effectiveness analysis, there will be a cost-effectiveness analysis and a process evaluation of the CONTACT study.

A restitution seminar will be organized at the end of the study with the national stakeholders and the members of the scientific advisory committee (SAC). During this seminar, the team will share the intervention package with strengths, limitations and main challenges. The research team will submit a publication in a peer review journal and share the results with the

scientific community.

Cost-effectiveness analyses are very important for national programs to take decisions on scale-up of the proposed interventions. The cost-effectiveness assessment of the CONTACT study includes a patient cost perspective, with data collected through individual surveys with parent/guardians using an adapted WHO cost data tool. This evaluation took place in March 2021 in both countries on a sample of 80 households from both models. Data analysis will generate an incremental cost per disability adjusted life year (DALY) for the two models. In addition, health system cost data is collected through document review and stakeholder discussions with the aim of evaluating the health system financial burden of community TB investigation and TPT management. This evaluation is ongoing.

Process evaluation is defined as a study which aims to understand the way an intervention works, by examining implementation, mechanisms of impact, and contextual factors(134). Process evaluation comes as a complimentary analysis explaining the outcomes of the complex intervention, but it is not a substitute to the study's main analysis.

Intervention fidelity is a part of process evaluation. Complex interventions usually undergo changes and adaptations when implemented in different local contexts. Documenting what is delivered in practice and also keeping a close reference to the theory of the intervention, will enable evaluators to distinguish between adaptations to make the intervention fit different contexts and changes that influence and undermine intervention fidelity(135).

The processes involved in the CONTACT study will be evaluated at the end of the implementation phase. The process evaluation will follow the MRC guidelines for process evaluation of complex interventions. In the MRC guidelines, the key components of a process evaluation are: context, implementation and mechanisms of impact:

Context – factors external to the intervention which may influence its implementation, or whether its mechanisms of impact act as intended. For the CONTACT study, the context is represented by the changes in the NTP guidelines and the COVID pandemic restrictions.

Implementation – the process through which interventions are delivered, and what is delivered in practice. Key dimensions of implementation include:

- Implementation process – the structures, resources and mechanisms through which delivery is achieved

- For the CONTACT study, this would be the description of the implemented package
- Fidelity – the consistency of what is implemented with the planned intervention
 - Protocol deviations and notes to file will be assessed
- Adaptations – alterations made to an intervention in order to achieve better contextual fit
 - Meeting minutes with important decisions on adaptation will be reviewed
- Dose – how much intervention is delivered
 - All reasons for lost to follow-up will be described
- Reach – the extent to which a target audience comes into contact with the intervention
 - The evaluation of screening failures for both index cases and contact cases will be performed.

Mechanisms of impact – the intermediate mechanisms through which intervention activities produce intended (or unintended) effects. The study of mechanisms may include:

- Participant responses – how participants interact with a complex intervention
 - The FGDs with TB patients from the second qualitative assessment will inform this part
- Mediators – intermediate processes which explain subsequent changes in outcomes
 - The IDIs with healthcare providers from the second qualitative assessment will inform this part
- Unintended pathways and consequences
 - Analysis of before and after TB case detection (aggregated data will be compared with pre-intervention data)

In the Figure 11 below, the relations between the process evaluation components and study design and outcomes are shown:

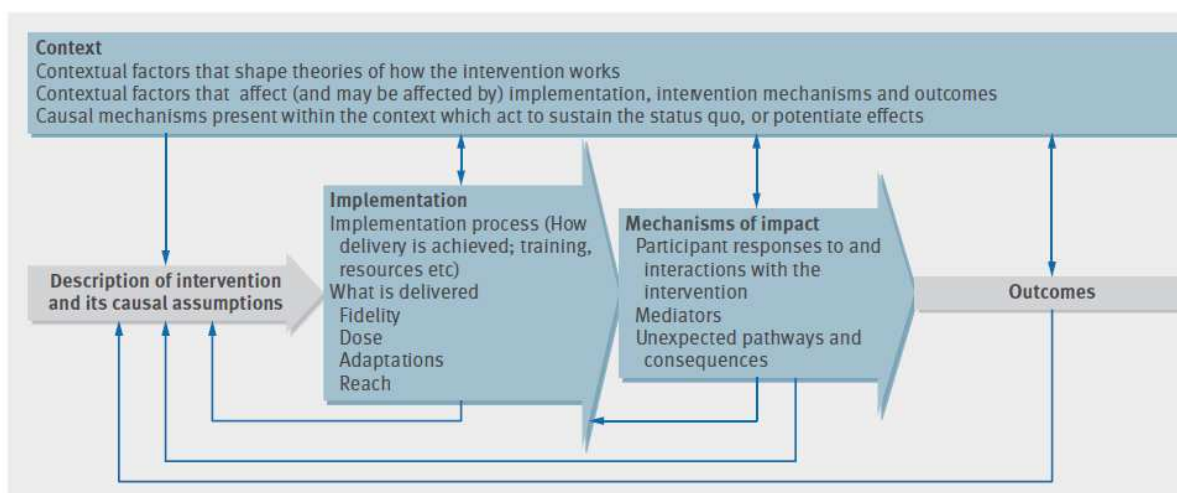


Figure 11. Key functions of process evaluations and the relations among them

Source: Moore 2015 (135)

At an international level, study results are presented to the WHO at every scientific advisory committee (SAC) meeting, as WHO members are part of the SAC. In addition, the study progress was presented to NTPs during the yearly WHO and Unitaid stakeholder meeting on child and adolescent TB. The WHO is preparing a long-awaited revision of the guidelines on child contact management. The CONTACT study will contribute to the WHO operational handbook by sharing the community model description with strengths and weaknesses in terms of implementation and lessons learnt from implementing a complex TB community intervention.

The following information was shared with the WHO for the operational handbook which will accompany the revised guideline of pediatric TB (Table 3 and Figure 12):

Table 3 WHO operational handbook contribution: lessons learnt from the CONTACT study

Strengths	Challenges
Flexible visit organization	Difficult to carry the scale (for TPT dosage) by nurses
Opportunity to screen the whole household	Households hard to reach in rainy season
Opportunity to discuss other health issues	Risk of delayed or non-done TB investigations due to referrals. This requires careful recording and follow-up of symptomatic children
Possibility of integrated care for contact and index	Refusal due to stigma: eg. If an index case did not disclose within household

Time and financial savings for the household	Need for human resources and financial support
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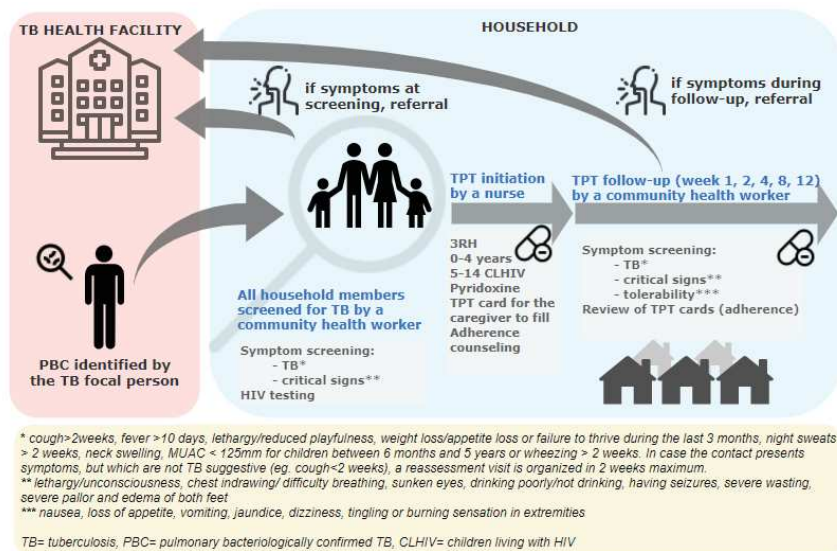


Figure 12 WHO operational handbook contribution: schematic representation of the community intervention

5.3.2. Long term perspectives

Other than the short-term goals, the CONTACT study has long term goals aligned with the *Roadmap towards ending TB in children and adolescents*(136), focused on reducing the gap between estimated and detected TB cases, reducing burden of TB pediatric cases and increasing the uptake of TPT.

In order for these long-term goals to be attained, more innovative approaches are called for. An electronic data capture system using smartphones would facilitate data collection in the communities and its rapid transfer at national and international levels. Challenges like network coverage and tablet delivery to CHWs would need to be overcome in order for this data collection system to be implemented. Even if we identified symptom screening as an easy and performant tool to exclude TB disease, the development of new tools to assess CXR like computer-aided-detection (CAD)(137) and portable CXR could bring this tool closer to the people and their communities and could remove the interpretation challenges. In addition to the tool used for contact screening, a more extended TB contact investigation could be recommended in schools and workplaces. More data is nevertheless needed for the use of this tool in children under 4 years old.

Shorter TPT regimens have the potential of improving adherence and being more convenient to the patient. Several short regimens are available and recommended by the WHO, with both daily and weekly modes of delivery. Weekly regimens have a higher completion rate and could accelerate TB prevention in low-burden countries, once cost and availability challenges are surpassed.

Another improvement would be TB contact investigation of all contacts in the household, indifferent of age, and delivering TB services in a patient-centered way. Community TB activities could very well be integrated with other services which would be coherent for the patient. This last point is especially important because the TB world is behind other infectious diseases like HIV or malaria in community activities. TB researchers and implementors could learn from what has been done for HIV and apply the lessons learnt to TB care. An example would be using patient experts at health centers for TB education or for TB health talks in the community. Patient ambassadors could train as community health workers and continue the work proposed by the CONTACT study.

6. Conclusion

In order to design mindful interventions which can be scaled-up after the research study is finished, adaptation and flexibility in design are essential. The pragmatic nature of the CONTACT study aims for the intervention package to be used by NTPs and the WHO in recommending community interventions for TB contact investigation and TPT management.

The findings of this thesis work show that community interventions can be feasible in two high-burden low-resource countries in sub-Saharan Africa. If deemed successful and if implemented by NTPs in similar contexts, a logical next step would be the evaluation of the community intervention under a programmatic leadership.

Further research based on integrated care and patient-centered approaches should be developed to propose the best services adapted to the needs of TB patients.

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PhD Portfolio

Scientific communications

- Scientific articles :
 - Vasiliu A, Eymard-Duvernay S, Tchounga B, Atwine D, de Carvalho E, Ouedraogo S, et al. Community intervention for child tuberculosis active contact investigation and management: study protocol for a parallel cluster randomized controlled trial. *Trials*. 2021; 22:180.
 - Vasiliu A, Abelman RA, Casenghi M, Cohn J, Bonnet M. Symptom-based Screening Versus Chest Radiography for TB Child Contacts: A Systematic Review and Meta-analysis. *The Pediatric Infectious Disease Journal*, online only, to be published in December 2021
 - Vasiliu A, Tiendrebeogo G, Mbunka Awolu M, Akatukwasa C, Tchakounte BY, Ssekyanzi B, Tchounga BK, Atwine D, Casenghi M, Bonnet M, on behalf of the CONTACT study group. Feasibility of a randomized clinical trial evaluating a community intervention for household tuberculosis child contact management in Cameroon and Uganda. *Pilot and Feasibility Studies*, - submitted
 - Vasiliu A, Trajman A, Salazar-Austin N, Lestari T, Majumdar S, Bonnet M, Casenghi M. Contact Investigation – a major policy-practice gap in high-burden countries. *Pathogens (Special Issue on TB)* - in writing
- Congress presentations
 - Vasiliu A, Abelman RA, Casenghi M, Cohn J, Bonnet M. Symptom-based Screening Versus Chest Radiography for TB Child Contacts: A Systematic Review and Meta-analysis, 51st Union World Conference on Lung Health, 2020, oral presentation
 - Vasiliu A, Abelman RA, Casenghi M, Cohn J, Bonnet M. Symptom-based Screening Versus Chest Radiography for TB Child Contacts: A Systematic Review and Meta-analysis. *CBS2 Days, Montpellier*, poster presentation
 - Vasiliu A, Tiendrebeogo G, Mbunka Awolu M, Akatukwasa C, Tchakounte BY, Ssekyanzi B, Tchounga BK, Atwine D, Casenghi M, Bonnet M. Acceptability and feasibility of household child contact TB screening and preventive therapy management in Cameroon and Uganda. 52nd Union World Conference on Lung Health, 2021, virtual event, poster presentation
 - Failla G, Croci R, Ferrari C, Antinozzi M, Bellini A, Traglia F, Caterina M, Caminiti M, Peyre-Costa D, Alonso A, Barone F, Vasiliu A. Assessing COVID-19-related depression, anxiety and stress among European public health residents. 14th European Public Health Conference, 2021, virtual event, oral presentation

Training

- *Votre thèse: du chaos des idées à un texte structuré*, Université de Montpellier
- *Comment rédiger une bonne revue de littérature?*, University of Montpellier
- *Principe et méthodes de la recherche interventionnelle en santé des populations (phase théorique)* Inserm – Bordeaux
- *Principe et méthodes de la recherche interventionnelle en santé des populations (phase pratique)* Inserm – Bordeaux
- Massive Open Online Course (MOOC) *Intégrité scientifique dans les métiers de la recherche*, plateforme France Université Numérique (FUN)
- MOOC *Ethique de la recherche*, plateforme FUN
- MOOC *Introduction to Systematic Review and Meta-Analysis* Johns Hopkins University, Baltimore USA, Coursera
- MOOC *How to Write and Publish a Scientific Paper (Project-Centered Course)* Ecole Polytechnique, Coursera
- *Master In-Demand Professional Soft Skills*, LinkedIn Learning
- *Une méthodologie pour écrire plus rapidement et augmenter ses chances de publication*, Inserm, Montpellier
- MOOC *Qualitative Data Collection Methods*, Emory University, Coursera
- *Advanced TB Diagnostics*, Summer Institute in Infectious Diseases and Global Health, McGill University
- *Qualitative Methods in Global Infectious Diseases Research*, Summer Institute in Infectious Diseases and Global Health, McGill University
- *European Advanced Course in Clinical Tuberculosis*, Research Center Borstel
- *Advanced TB Research Training Course*, University of Washington

Teaching

- September 2018: Practical seminar for the Principles of Clinical Research class of the Masters in Public Health from the Mbarara University of Science and Technology
- September 2019: Practical seminar for the Principles of Clinical Research class of the Masters in Public Health from the Mbarara University of Science and Technology

- The classes were suspended in 2020 and 2021 due to the COVID pandemic restrictions

Reviewing

- Scientific Reports: “One dollar incentive improves tuberculosis treatment outcomes in programmatic settings in rural Uganda: a quasi-experiment”
- International Journal of Tuberculosis and Lung Disease: “Effectiveness of a community-based intervention to prevent childhood TB in Lesotho: A cluster randomized trial”

Grant application

- Initiative 5%, Expertise France: “Implementation of a new Strategic TB Case-Finding, Treatment and Prevention Public Health Pack in Thailand”
- (I had a support role and wrote parts of the application)

Supervision & guidance

- European Network of Medical Residents in Public Health, mental health research group
 - Survey of depression, anxiety and stress related to COVID-19 among medical residents in public health in 4 European countries: France, Italy, Spain, Portugal
 - (I offered guidance for Public Health interns in setting study objectives, finding the appropriate tools, data collection, data analysis, data interpretation and scientific writing)
 - Abstract accepted at the 14th European Public Health Conference
 - Article in writing

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About the author

I am a medical doctor specialized in Public Health, with a vivid interest in research. During medical school in Romania, I wanted to broaden my horizon and have a different teaching experience. Therefore in 2009, I obtained an Erasmus scholarship in Tours, France for my third year of medical school. After 10 months in Tours, I returned to Romania for 3 more years, to finish medical school. With my mind set on France, I passed the Epreuves Classantes Nationales in 2012 and choose a Public Health residency in Rouen, Normandy. During my residency, I obtained a Masters 1 in Public Health degree from the Kremlin-Bicêtre Paris-Sud Faculty of Medicine. I then chose to follow the classes of the Specialized Masters in Public Health from the Pasteur-Cnam School of Public Health and did the master's internship at the Pasteur Institute of Cambodia, where I analyzed the performance of IGRAs in children living with HIV who were identified with presumptive TB (PAANTHER project). After the Pasteur Institute in Cambodia, I went to its Parisian counterpart to focus on hepatitis C research. There, I had the opportunity to go to Egypt to train the local team and roll out a research study on mathematical modelling of hepatitis C in a University Hospital in Cairo. During my Public Health internship in Rouen, I was constantly feeling curious and eager to learn what my European peers were doing and I joined the European Network of Medical Residents in Public Health, where I could exchange ideas and collaborate with colleagues from other European countries. My residency in Rouen allowed me to discover epidemiology work at the Invs regional cell of Normandy (now Santé Publique France), nosocomial infection control in the hygiene unit of the Rouen Hospital, more nosocomial infection control at the ARLIN (Antenne Régionale de Lutte contre les Infections Nosocomiales), clinical research at the Centre d'Investigations Cliniques of the Rouen Hospital, medical financing in the Département d'Information Médicale, and biostatistics in the Biostatistics Unit of the Rouen Hospital. When I finished my Public Health residency in Rouen in 2017, and still thirsty for new adventures, I came to Uganda to experience sub-Saharan Africa, and I am doing so ever since. In Uganda I was fortunate enough to meet Maryline who offered me the opportunity to work on the CONTACT study and start a PhD under her supervision. All my roaming and wandering brought me here, to the moment when I am writing these lines at the end of my PhD thesis, incredibly happy for everything I achieved and looking forward to what the future will bring.

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