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Contact tracing and Isoniazid preventive therapy for prevetion of childhood tuberculosis in The Gambia: an analysis of the challenges and opportunities

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Title of PhD Thesis

Contact tracing and Isoniazid preventive therapy for prevention of childhood tuberculosis in The Gambia: an analysis of the challenges and opportunities

I. Key Words

Childhood tuberculosis

Contact tracing

Isoniazid preventive therapy

Adherence

Confirmed tuberculosis

Clinically diagnosed tuberculosis

Symptom screening

Xpert MTB/RIF

II. Abstract

Background

Tuberculosis is a major public health problem worldwide and is characterized by a high incidence in The Gambia. Children acquire infection primarily from adults in their households, and especially young children are at higher risk of progressing to disease and death. In The Gambia, childhood tuberculosis is poorly addressed in the routine national TB program activities; contact tracing and isoniazid preventive therapy (IPT) are not implemented. The burden of childhood TB is therefore poorly characterized and the operational challenges of implementing IPT are not well understood.

Methods

TB symptoms screening questionnaire and tuberculin skin testing were administered in the community to child contacts of adults recently diagnosed with TB. Those with TB suggestive symptoms and/or positive TST result were further evaluated in a dedicated clinic with physical examination, chest x ray, sputum induction and examination with smear, Xpert MTB/RIF and culture. Adherence to IPT was measured by pill count and IsoScreen test.

Results

Co-prevalent TB disease was detected in child contacts both within and outside immediate household of the adult index TB case. Altogether, 1.6% of all child contacts screened had co-prevalent TB disease. 42.2% of the co-prevalent TB cases were among asymptomatic but TST positive child contacts. A combination of Xpert and culture was positive in 32.3% of all children diagnosed with TB, an increase of 9.7 – 22.6% over the yields from microscopy, Xpert and culture alone as individual tests. 255/328 (77.7%) children completed each of six months of IPT with good adherence.

Conclusions

Contact tracing restricted to symptom screening and immediate households would have missed nearly half of all co-prevalent TB disease in child contacts in this setting.

A combination of Xpert and mycobacterial culture had incremental benefit for the bacteriological confirmation of TB disease in actively traced child contacts. Uptake of, and adherence to, IPT were high among the eligible child contacts.

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IV. Abbreviations

AFB	Acid fast bacilli
AIDS	Acquired Immune Deficiency Syndrome
BCG	Bacille-Calmette-Guerin
DOTS	Directly Observed Treatment Short course
GBA	Greater Banjul area
HIV	Human immunodeficiency virus
INH	Isoniazid
IPT	Isoniazid preventive therapy
M.Tb	*Mycobacterium tuberculosis*
MRC	Medical Research Council
NLTP	National Leprosy Tuberculosis Control Program
NTPs	National Tuberculosis Programs
PPD	Purified protein derivative
RIF	Rifampicin
TB	Tuberculosis
TST	Tuberculin skin test
WHO	World health organization

1. Introduction

1.1 Brief history and global epidemiology of tuberculosis

Tuberculosis (TB) is an ancient disease. It was believed to have been present in Egypt from the early dynastic times and was well recognised and clearly described by Hippocrates (1). However, the study of TB began during the Renaissance period when Italian scientist Girolamo Fracastoro recognised the contagious nature of TB (2). Concerted efforts to fight TB began only in late 19th century following Robert Koch's report of the isolation of *Mycobacterium tuberculosis (M.Tb)* which established the communicable nature of TB (3). Since there was no definitive treatment, control efforts involved mainly bed rest, nutritional therapies, exposure to sunlight and isolation of patients in sanatoriums, which were located in rural areas(4).

The discovery of anti-TB drugs in the 5th decade of the last century represented a watershed in the history of TB, with a huge drop in mortality and morbidity attributable to tuberculosis in the developed countries (5). However, with time, National TB Programs de-prioritized TB as a public health concern, due to the massive progress made as a result of use of anti-TB drugs and improvement in living standards, education, nutrition and industrialization. Additionally, the advent of HIV/AIDS in the 1980s led to a dramatic increase in the number of TB cases worldwide especially in sub-Saharan Africa where TB was already a major public health concern (6). As a result, the gains slowed and TB resurged leading to the declaration by the World Health Organization (WHO) in 1993 that TB had become a global public health emergency (7). Today, TB still remains a major global health problem, with around 9 million new cases and nearly 2 million deaths every year (8). Though all countries are affected, 85% of all TB cases occur in Africa and Asia alone, with only 22 countries accounting for 80% of the global TB burden (9). TB recently ranked as the 8th leading cause of death in low- and middle-income countries, and in those aged 15 – 59 years, ranks as the 3rd cause of death after HIV/AIDs and Ischaemic heart disease (10).

1.2 Tuberculosis in Children

TB in children is regarded as a sentinel event as children with TB are usually recently infected in their households by adults with sputum smear positive TB (11). Childhood TB is therefore a marker of ongoing TB transmission in the community. Of the 9 million TB cases occurring globally every year, around 1 million cases are estimated to be among children aged less than 15 years. In countries with low TB burden, childhood TB constitutes approximately 5% of the TB case load (12). In developing countries, on the other hand, little accurate information about childhood TB is available because of difficulty in confirming the diagnosis and inadequate data recording. However available data indicate that childhood TB may constitute 20 – 40% of the TB caseload in these countries (13, 14). Furthermore, the HIV epidemic led to a marked increase in incidence of TB and decrease in peak age prevalence of infectious TB; therefore most cases now occur in young adults who are usually parents of young children (15).

Pulmonary parenchymal disease and intrathoracic lymphadenopathy are the commonest clinical manifestations of childhood TB and account for about 60 – 80% of cases (16). Among the extrapulmonary manifestations, lymphadenopathy occurs most commonly. Other forms of extrapulmonary TB in children include central nervous system involvement, pleural, pericardial, miliary and skeletal tuberculosis.

Diagnosis of childhood TB is a huge challenge. The clinical symptoms are non-specific and sputum samples are difficult to obtain, especially in younger (<8 years) children. Furthermore, the disease is paucibacillary and, therefore, even when sputum samples are obtained, microbiological confirmation remains very low rarely exceeding 30% in most places (17). The overwhelming majority of childhood TB are therefore clinically diagnosed and this has traditionally relied on the triad of close contact with a known infectious TB case, positive tuberculin skin test result (TST) and suggestive abnormalities on chest radiograph (18). These criteria, however, have limited applicability in the resource poor, high TB burden, settings such as The Gambia; case detection is not a routine programmatic activity and transmission is not limited to the household. There is therefore a glaring need for better control strategies for childhood TB especially in the developing countries with high TB burden.

1.3 Childhood TB in The Gambia

The Gambia is located on the west coast of Africa with an area of around 11,300 square kilometers. It is bounded entirely by Senegal in the north, east and south and by the Atlantic Ocean in the west. The population stands currently at 1.98 million with the majority of the population located in the coastal areas of the country (Gambian bureau of statistics). Life expectancy at birth is estimated at 60 years. The Gambia is a resource-limited country with gross national income is 460 US dollars and poverty headcount ration of 48.5% (19).

In The Gambia, like in other developing country settings, childhood TB is low on the priority of the National Leprosy and TB Program (NLTP), diagnostic capabilities are inadequate and trained personnel are scarce. There is therefore paucity of data in childhood TB. Since 2006, the WHO has recommended that childhood TB be reported in age bands 0 - 4 years and 5 – 15 years (20). Age disaggregation of TB data began in 2009 and only 4.4% of all cases of TB reported were children (NLTP Gambia data). Majority of the childhood TB cases are smear positive cases diagnosed in older children (>=10years) among whom sputum specimen are relatively easier to collect whilst extrapulmonary TB constitute the majority of TB cases among the younger children.

1.4 Control of Childhood TB

The strategy adopted for the control of childhood Tuberculosis in endemic countries focuses on the identification and treatment of infectious adult TB cases and the Bacillus-Calmette Guerin (BCG) vaccination (21). However these methods alone remain insufficient to control childhood TB (22). Identification and treatment of infectious adults is the major focus of the Directly Observed Treatment short course (DOTS) strategy, which relies heavily on demonstration of *M.Tb* in sputum smears. However, as TB in children is paucibacillary and sputum specimen is difficult to obtain, the DOTS approach remains suboptimal in childhood TB control. In addition, children are thought to not contribute to the epidemic since they play little or no part in TB transmission in the community. Childhood TB therefore remains relatively neglected and accorded low priority by national TB Programs. The Bacille-Calmette-Guerin (BCG) vaccine, a live attenuated vaccine derived from *Mycobacterium bovis*, was developed in the 1920s and is in use in many countries. This vaccine does not protect against transmission and studies have reported a widely varying range of 0 – 80% protective efficacy against pulmonary TB (23). It has no proven protective effect in HIV-infected children and might lead to BCG-disseminated disease, which is why it is now contraindicated in this group of children (24). Furthermore, though BCG has been shown to

protect against miliary TB and meningitis (25), a large randomized controlled trial enrolling over 350,000 infants in southern India showed that BCG did not protect against adult pulmonary TB (26). In the absence of a better protective vaccine, prevention of TB through chemoprophylaxis of exposed individuals or treatment of latent infection with isoniazid (INH) represents the other feasible and beneficial approach.

According to WHO recommendations, IPT is delivered to all children under the age of 5 who are evaluated during contact screening and found not to have any signs and symptoms of active TB. Some of these children would have evidence of latent TB infection and would receive IPT as curative therapy, whilst others would have no signs of M.Tb infection and would receive IPT purely on a prophylactic basis to prevent M.Tb infection. Given that in resource-poor settings asymptomatic children would not be further investigated routinely to distinguish between the need for treatment of latent infection or purely prophylactic administration of isoniazid, the term IPT is therefore used interchangeably in this thesis, in line with the WHO and programmatic public health practice.

The trials of treatment for latent TB infection carried out in the 1960s by Ferebee and colleagues showed clearly that daily administration of INH for 6 – 9 months was effective in preventing TB in adults and children with latent TB infection (27). More recently, a clinical trial of IPT among HIV infected children showed a marked reduction in TB incidence among those who received INH compared to those who received placebo (28). Effective contact tracing is required not only for early diagnosis of TB disease in child contacts but also for identification of those eligible for IPT. The WHO has therefore recommended that all NTPs screen household child contacts for TB disease and offer IPT to children <5 years in contact with adults with sputum smear positive TB (29), but this is currently not being done in The Gambia and most other resource-poor settings.

2. Rationale and Objectives

2.1 Rationale

TB is a major public health problem in the Gambia, a country with a predominantly young population and high TB incidence rates. A recent TB prevalence study showed a national prevalence of TB of 128/100,000 population and incidence of 175/100,000 population (30). Like in most other similar settings, childhood TB is poorly addressed in the routine national TB program activities. The burden of childhood TB is not well characterized, the reporting is extremely patchy and resources for diagnosis and management are scarce in the public health sector. As shown in other settings, household contact tracing and IPT among children under 5 would likely be of significant public health impact but are currently not being implemented by the Gambian National Leprosy and Tuberculosis Program (NLTP). The current global drive to eliminate tuberculosis has increased the focus on childhood TB and it has now become crucial to implement the WHO recommendations especially in resource-poor high TB burden countries. The resources required to administer IPT to a large cohort of *M.Tb* exposed children have never been estimated in this setting and the logistical and operational challenges are not understood. At present, no data exists to objectively assess the challenges, such as adherence and provide an estimate of the costs of IPT implementation in high TB burden settings such as The Gambia. However, in order to implement the WHO recommendations, such analyses are urgently required.

2.2 General objective

The general objective of this PhD is therefore to implement contact tracing in households of adults recently diagnosed with sputum smear positive TB in the Greater Banjul Area of the Gambia (GBA) in order to identify co-prevalent TB cases and initiate IPT among the children aged less than five years in whom TB has been ruled out.

2.3 The specific objectives are

1. To describe the burden of childhood TB among children in contact with adult cases of sputum smear positive TB in households in the GBA of The Gambia

2. To define the population of under-5 children potentially eligible for IPT and initiate therapy.

3. To determine adherence to IPT using the Urine Isoscreen test

3. Methods

3.1 Symptoms screening, mantoux testing, clinical examination and procedures

Adults diagnosed with smear positive TB and reported to the NTP at the 5 leading health centers in the GBA were approached for consent to visit their homes and screen all children in the household. When consent was obtained field workers visited the homes and administered a standard TB symptom screening questionnaire and tuberculin skin test (TST) to all contacts <15years. TST was performed by the Mantoux method using 2 Tuberculin Units of purified protein derivative (PPD RT23 Statens Serum Institut, Copenhagen) and size of induration was read 48 – 72 hours later. A positive TST was defined, for all children, as induration of ≥10mm measured transversely, in line with WHO recommendations (20). All symptom positive and / or TST positive (> 10 mm) children were brought to a dedicated child TB clinic at the MRC Unit for clinical examination, chest x ray, sputum examination and HIV testing. In the clinic, detailed symptoms review, physical examination and anthropometric measurements were performed. Sputum was obtained from all symptomatic children and all asymptomatic children with abnormal chest x ray. Older (>8years) children provided spontaneous sputum while sputum induction was performed in younger children and all other children who were unable to expectorate. Trained nurses performed sputum induction after pre-medication with nebulized salbutamol.

3.2 Laboratory procedures

Sputum was collected in sterile containers and sent immediately to the TB laboratory for smear microscopy, GeneXpert and culture. Auramine-phenol staining was used for fluorescent microscopy and mycobacterial culture was done with both the MGIT^{TM} liquid culture system (BD, Sparks, MD, USA) and the Lowenstein-Jensen solid media. For the Xpert assay, 1.5ml of Xpert sample reagent was added to 0.5ml of re-suspended specimen sample and processed according to the manufacturer's guidelines.

3.3 Anti-TB treatment, isoniazid preventive therapy and adherence monitoring

All children diagnosed with TB disease (probable or confirmed) were referred to the TB clinic in their catchment areas and were treated according to the national guidelines. They were followed up at the MRC child TB clinic at the end of intensive phase of treatment and at the end of treatment. All those seen in the clinic without TB disease were treated appropriately. All children under-5 in the same household as the adult index case and without

TB disease were placed on IPT at 10mg/kg/day for 6 months. INH was provided to eligible children in monthly packages and daily administration was captured in a specially designed INH card. Field workers delivered the INH to homes of children, asked about INH side effects, recorded weights on the INH card and completed risk factor questionnaire at each visit. Adherence was assessed by pill count and by the Isoscreen urine test method among the children recruited in the first year of the study.

All child contacts in the household without TB disease were followed up 3 monthly for a period of one year, independent of age.

4. Results

4.1 Study 1

Identifying children with tuberculosis amongst household contacts in The Gambia

Egere U, Togun T, Sillah A, Mendy F, Otu J, Hoelscher M, Heinrich N, Hill PC, Kampmann B (Published - International Journal of Tuberculosis and lung disease 2017; 21: 46 - 52)

Abstract:

Background: The Gambia is a high TB burden country but childhood TB is under recognised because of difficulties with diagnosis and low priority accorded to it by the TB Program.

Methods: We implemented contact tracing to identify co-prevalent tuberculosis among child contacts of adults with smear positive tuberculosis in the Greater Banjul Area of the country where over 70% of all TB cases are diagnosed. Symptoms screening and tuberculin skin test (TST) were performed in the community. All symptomatic and/or TST positive child contacts were brought to the dedicated childhood TB clinic at the MRC where physical examination, chest x ray and sputum examination were performed.

Results: Altogether, 4042 child contacts were enrolled in the study following screening in the community; 1772 were aged less than 5 years whilst 2270 were aged 5 years and above. Of the 4042, 82.6% (3339/4042) were diagnosed as TB exposed but not infected, 15.8% (639/4042) were latently infected and 1.6% (64/4042) had co-prevalent TB disease. Of the 64 TB cases, 19 (29.7%) were bacteriologically confirmed while 45 (70.5%) were clinically diagnosed. Fifty (78.1%) of the 64 TB cases were diagnosed among child contacts in the same household as the adult index case whilst 14 (21.9%) were outside the household. Of 630 asymptomatic but TST positive child contacts evaluated in the clinic, 27(4.3%) had co-prevalent TB disease, comprising 42.8% of all TB cases diagnosed. Symptom screening alone would have detected only 57.8% of co-prevalent cases.

Conclusion: This study showed that in our community setting, contact tracing detected co-prevalent TB cases among child contacts both within and outside the household of the adult index case. Contact tracing restricted to symptom screening and to the index cases' households would have missed nearly half of all co-prevalent TB disease in child contacts.

4.2 Study 2

Contribution of Xpert MTB/RIF to the diagnosis of pulmonary tuberculosis among TB-exposed children in The Gambia

Togun TO, Egere UE, Sillah AK, Ayorinde A, Mendy F, Otu J, Antonio M, Sutherland J, Hill PC and Kampmann B. (Published – International Journal of Tuberculosis and Lung Disease; Vol 19, 9, 1 September 2015; pp 1091 – 1097)

Abstract:

Background: The WHO has recently endorsed the Xpert MTB/RIF assay for the rapid diagnosis of pulmonary TB and detection of rifampicin resistance. To understand the performance and added value of GeneXpert testing when routinely used in the context of active case finding among an exclusively paediatric population of TB contacts in a low income country, we evaluated the Xpert in children with known household exposure to a sputum smear positive adult TB case in The Gambia, a low HIV setting.

Methods: One induced sputum sample was obtained from all symptomatic child contacts and also from asymptomatic TST positive child contacts with abnormal chest x ray. Sputum sample underwent fluorescent microscopy, culture and Xpert MTB/RIF assay. All the child contacts had HIV testing,

Results: Four hundred and eighty seven (95%) of 514 children evaluated in the clinic had complete sputum smear microscopy, Xpert and culture results. Smear microscopy was positive in 6 (1.2%), Xpert was positive in 12 (2.5%) while culture was positive in 14 (2.9%) of all samples. None of the children was HIV infected. Using culture as a reference standard, Xpert was positive for Mycobacterium tuberculosis in 6/14 culture positive and 6/473 culture-negative children. This gives a sensitivity and specificity, respectively, of 42.9% (95%CI 17.7 – 71.1) and 98.7% (95%CI 97.2 – 99.5). Using a composite reference standard, "all TB diagnosis and treatment, combined Xpert and culture tests were positive for M. tuberculosis in 20/62 children with TB disease (32.3%, 95%CI 20.9 – 45.3) and this was comparable to the combined yield from microscopy, culture and Xpert (33.9%, 95%CI 22.3 – 47.0) but significantly higher than individual yields from each test.

Conclusion: This study shows that the number of TB cases detected by Xpert and culture among all children diagnosed with TB disease was comparable. While the sensitivity of the Xpert test is low in actively traced child contacts, a combination of Xpert and mycobacterial culture has incremental benefit for the bacteriological confirmation of TB disease.

4.3 Study 3

Isoniazid preventive treatment among child contacts of adults with smears positive tuberculosis in The Gambia

Egere U, Sillah AK, Togun TO, Kandeh S, Cole F, Adama J, Able-Thomas, A, Hoelscher M, Heinrich N, Hill PC and Kampmann B (Published – Public Health Action 2016;6(4):226-231)

Abstract

Background: The World Health Organization recommends IPT for young children in contact with infectious adult TB cases. Despite its proven efficacy, IPT is not implemented in most high burden settings where it is needed most. We developed a home-based IPT programme among child contacts of adults recently diagnosed with sputum smear positive TB in The Gambia and assessed its impact on uptake, adherence and completion of treatment.

Methods: Child contacts of adults with sputum smear positive TB were screened for TB using symptoms screening questionnaire and TST. Clinical evaluation with chest x ray and sputum examination was conducted to exclude TB disease. All contacts aged less than 5 years without TB disease and in same household as the adult index case were provided isoniazid in their homes at 10mg/kg/day for 6 months. Adherence was measured both by pill count and a urine point of care colorimetric test, IsoScreen.

Results: Of 404 under-5 contacts screened in the community, 368(91.1%) were offered IPT of whom 328 (89.4%) consented and commenced IPT. Altogether, 255/328 children (77.7%; 95% CI 73.2 – 82.2) completed all 6 months with good adherence. Among those tested with IsoScreen, 85.3%% of all tests among those defined as having good adherence by pill count were positive, compared to 16% among those defined as having poor adherence ($p<0.001$). Mothers were responsible for administering prophylaxis in 92.3% (303/328) of the cases. Eighteen children dropped out of prophylaxis whilst 310 children remained on prophylaxis at the end of the 6th month. The 'cascade of care' analysis showed, for all child contacts including those who did not start prophylaxis, an overall completion rate with good adherence of 61%.

Conclusion: The study found that home-delivered IPT among child contacts of adults with smear positive TB in The Gambia achieved a verifiable high uptake and adherence rates. At national level, factors related to the system and not patient, are likely to determine success of IPT.

5. Discussion

The WHO recommends contact tracing for control of childhood tuberculosis but this is rarely done in most high burden countries. However, with the new ambitious goal of eliminating TB by the year 2035, the need to implement contact tracing has become urgent. Our first study reports, to the best of our knowledge, the largest single child contact tracing study in Africa with over 4,000 children successfully visited and screened for TB in 812 households. Sixty-four (64) co-prevalent were diagnosed among the child contacts, giving a prevalence of 1583 per 100,000 population of child contacts in this setting. Childhood TB is thus a huge public health problem in The Gambia and requires urgent control. A major opportunity from this study was the coverage of different subgroups of child contacts and analysis of various screening scenarios to provide a broad spectrum of informed choices for programmatic implementation of contact tracing in The Gambia and similar epidemiologic settings.

While the WHO recommends symptom based screening for identification of children with TB in resource-poor settings (31), our study found that around 40% of all co-prevalent TB cases diagnosed were asymptomatic at the time of screening. This group of children could have been missed if a solely symptom based approach was adopted and TST was not performed. Symptoms of childhood TB can be non-specific and up to 50% of children may be asymptomatic at the early stages of disease (32). In The Gambia, members of the extended family usually live together in a cluster of homes or building located in the same piece of land referred to as ‘compound’. In this setting, the adult TB index case is in contact with children both from within and outside his immediate household. We found 14 of the 64 (21.7%) of the co-prevalent child TB cases outside the immediate household of the adult index case suggesting that, for maximum impact, contact tracing in this setting must include all children in the compound of the index case, even if they belong to a different household. Again, this group of children with TB would have been missed if contact tracing were limited to the immediate household of the adult TB Index case. Though a ‘compound’ contact tracing is likely to be resource intensive, our data provides evidence to guide implementation and scaling up of contact tracing as resources become more available. For instance, since there is no added benefit in administering TST to children already symptomatic at the time of screening, TST could therefore be limited to the asymptomatic household contacts as more resources become available to the National TB Program.

Diagnosing childhood TB is very challenging mainly because of difficulty in obtaining sputum specimen and the low bacillary burden in children (33). In the light of the endorsement by the WHO in 2010 of the Xpert MTB/RIF assay for rapid diagnosis of pulmonary TB and detection of rifampicin resistance (34), our second study investigated the performance and added value of Xpert in the context of contact tracing among an exclusively paediatric population. The sensitivity of Xpert testing of one induced sputum sample was 42.9% relative to culture-confirmed TB and this was lower than 79% and 75% respectively reported in hospital-based studies from Uganda (35) and Tanzania (36), both of which are TB high burden countries with an HIV prevalence of >40%. In South Africa, a hospital-based study reported a sensitivity of Xpert relative to culture-confirmed TB of 74.3% similar to those from Uganda and Tanzania (37) but a study in a primary care setting reported a sensitivity of 43.3%, similar to ours (38). Xpert thus appears to have much lower sensitivity in ambulant paediatric populations. This is consistent with the assumption that children with TB in ambulant populations have less severe disease and lower bacillary load than those hospitalized with TB (38, 39) but has strong implications for use as a diagnostic tool for TB among children in this context. However, using a composite reference standard of 'all TB diagnosis and treatment' which has a higher sensitivity than culture alone, we found a significantly higher incremental bacteriological yield with an increase of 9.7 – 22.6% over yields from microscopy, Xpert and culture alone as individual tests. A combination of microscopy with culture did not result in a significant incremental yield over culture alone, and a combination of all 3 tests – microscopy, Xpert and culture – was not significantly different from using Xpert and culture alone. These results support the WHO recommendation that Xpert be used in place of microscopy as the initial diagnostic test for children being investigated for TB in high burden settings (40).

Given the high burden of childhood TB in The Gambia and the challenges associated with making both clinical and confirmed diagnosis, IPT remains a powerful tool for control of childhood TB. Given the high burden of childhood TB in The Gambia and the challenges associated with making both clinical and confirmed diagnosis, IPT remains a powerful tool for control of childhood TB. In the 3rd study, we implemented and evaluated a home-based IPT program in the greater Banjul area of The Gambia. Overall, using the pill count, 77.7% of all children initiating IPT completed 6 months of IPT with good adherence similar to the adherence of 76% in a study in Guinea Bissau where IPT was also delivered at home(41). However, adherence was much lower in other studies from other high burden countries –

24% in South Africa(42), 25.6% in Indonesia (43) and 32.5% in southern Ethiopia(44). Interestingly, in the Ethiopian study where IPT was delivered at home, adherence was very poor with only 33% of children taking their medications for up to 4 months. Therefore, while the home delivery approach achieved high adherence in The Gambia, more site-specific research is required to identify the best locally applicable approach to optimized adherence. In The Gambia, home delivery of IPT is feasible as the health system relies heavily on community health workers and assistants living in the villages. These health workers could be trained to deliver and monitor IPT at homes of the child contacts. Since adherence is a major determinant of IPT efficacy(45), we conducted a point of care urine test for adherence, the Isoscreen test, which detects metabolites of isoniazid in urine, to confirm the adherence obtained by pill counts. The excellent agreement between the adherence results from pill count and IsoScreen testing suggests the reliability of pill count as a means of determining adherence to IPT in Gambian children and increases our confidence that IPT would result in control of childhood TB in The Gambia. To identify where improvements may be needed in the continuum of care of child contacts eligible for IPT, we applied a 'cascade of care' analysis to account for all losses down the line of care which showed that approximately 61% of the estimated original number of contacts eligible for IPT completed 6 months of IPT with good adherence. This provides insight into the potential public health impact of the program, namely that system, and not patient, factors are likely to be the main determinants of success when IPT is fully taken over by the NLTP and that there are opportunities for improvement if IPT program is to have maximum public health impact in The Gambia.

The results of these studies provide the much-needed epidemiological, clinical and public health baseline data to support programmatic implementation of contact tracing and other child TB control measures in The Gambia. Additionally, since childhood TB control efforts are context specific, these data could largely be generalized to other similar contexts both within the West African sub-region and elsewhere.

6. Conclusions

Contact tracing in The Gambia detected co-prevalent TB in child contacts within and outside the household of the adult index cases well as among asymptomatic but TST-positive contacts. A symptoms-only based contact tracing would miss about 40% of all co-prevalent paediatric TB cases within the compound of the adult index case.

The sensitivity of Xpert MTB/RIF is much lower among actively traced child contacts with TB disease compared to hospitalized children with TB disease. The Xpert MTB/RIF and culture detected a comparable number of TB cases among all children diagnosed with active TB disease. A combination of Xpert and mycobacterial culture gave a significantly higher incremental bacteriological yield over the yields from microscopy, Xpert and culture alone as individual tests.

Uptake of, and adherence to, home delivered IPT were high by international standards among TB exposed Gambian children eligible for prophylaxis. IPT was highly acceptable to caregivers and children in The Gambia. System, not patient, factors will likely be the main determinants of success when IPT is transferred to be fully operational under the National TB Program.

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8. Publications

8.1 Publication 1

Identifying children with tuberculosis among household contacts in The Gambia

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Identifying children with tuberculosis among household contacts in The Gambia

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SUMMARY

SETTING: Greater Banjul Area of the Gambia.

OBJECTIVES: To identify co-prevalent tuberculosis (TB) among child contacts of adults with smear-positive TB.

DESIGN: Child contacts aged <15 years in the immediate household and compound were prospectively enrolled and evaluated for TB disease using screening questionnaires and the tuberculin skin test (TST). Symptomatic and/or TST-positive (⩾10 mm) contacts were further investigated.

RESULTS: Of 4042 child contacts who underwent symptom screening and TST, 3339 (82.6%) were diagnosed as TB-exposed but not infected, 639 (15.8%) were latently infected and 64 (1.6%) had co-prevalent TB. Of the 64 TB cases, 50 (78.1%) were from within the immediate household of the index case, and 14 (21.9%) from within the same compound. Of the 27 asymptomatic but TST-positive children diagnosed with TB, 7 were microbiologically confirmed. The median age of the TB cases was 4.4 years (interquartile range 1.9–6.9); 53.1% were aged <5 years. Of the 4042 child contacts, 206 (5%) slept in the same bed as the index case; 28.1% of all TB cases occurred in this group. Symptom screening alone would have detected only 57.8% of the co-prevalent cases.

CONCLUSION: In our community setting, if contact tracing is restricted to symptom screening and immediate households only, nearly half of all co-prevalent TB disease in child contacts would be missed.

KEY WORDS: contact tracing; tuberculin skin test; prevalence

CHILDREN acquire *Mycobacterium tuberculosis* infection primarily from adults or adolescents with smear-positive tuberculosis (TB) living in the same household.[1] Those aged <5 years and those with immune deficiency such as human immunodeficiency virus (HIV) infection are at especially high risk of developing TB disease, usually within the following 2 years.[2] The World Health Organization (WHO) therefore recommends tracing and screening of household child contacts to identify co-prevalent TB cases and prescribe prophylactic treatment to those aged <5 years.[3,4] Although this recommendation is commonly adopted, its implementation has been inadequate. Apart from financial issues associated with contact tracing, confirming TB diagnosis in children remains a challenge,[5,6] and many children continue to miss out on preventive or curative measures.

In 2009, children aged <15 years comprised 4.4% of the total number of TB cases notified in The Gambia (National TB & Leprosy Programme [NTLP] data), much lower than the expected 10–25%.[7] In line with WHO recommendations, the Gambian NTLP guidelines recommend contact tracing within the immediate household; however, this is not implemented. Unlike in resource-rich settings, the tuberculin skin test (TST) does not form part of the screening strategy. Screening efforts in The Gambia are also further complicated by the fact that members of the extended family commonly live together on the same piece of land (compound) in separate but closely located houses, with significant social mixing. TB cases are therefore in close contact with a large group of children within and outside their immediate household.

We aimed to estimate the co-prevalence of TB disease in child contacts of adult TB cases across

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Gambian compounds beyond the immediate household using an established community-based TB case contact platform[8] and symptom screening and the TST in the community.

METHODS

Study site

The study was carried out from February 2012 to December 2014 in the Greater Banjul Area (GBA) of the Gambia, a mixed peri-urban, urban and rural area, including Banjul, the capital city (population approximately 700 000). About 70% of all TB cases in the country are diagnosed in this area.[9]

Participants

Ethical approval for the study was obtained from the joint Medical Research Council (MRC)/Gambian government ethics committee, Banjul, The Gambia (ref L2012.E01). Child contacts aged <15 years living in the same compound with sputum smear-positive adult TB cases were recruited. A compound was defined as a cluster of homes or buildings often owned by members of the same family,[10] and a household as a group of individuals living in the same building and eating from the same pot.

Symptom screening and tuberculin skin testing

After obtaining informed consent, a standard TB symptom screening questionnaire was administered to all children or their care givers in the compound. Persistent unremitting cough of at least 2 weeks' duration, with at least one other symptom such as weight loss, failure to gain weight, fever or night sweats, was regarded as suggestive of TB, and contacts fulfilling these criteria were considered symptomatic. Child contacts not fulfilling these criteria were classified as asymptomatic. Bacille Calmette-Guérin status was evaluated by the presence of a typical scar. The TST was performed using the Mantoux method (2 tuberculin units, PPD RT23 Statens Serum Institut, Copenhagen, Denmark), and the size of the induration was read 48–72 h later. A positive TST was defined for all children as an induration of ⩾10 mm measured transversely, in line with WHO recommendations.[11] TST-negative children without symptoms of TB disease were classified as TB-exposed but not infected.

Clinical examination and investigations

All child contacts with symptoms suggestive of TB and/or a positive TST result were referred to a dedicated childhood TB clinic and examined by a paediatrician. Vital signs and anthropometric measurements were obtained. All referred children underwent chest X-ray (CXR) and HIV testing. CXRs were read independently by two study clinicians, one of whom was a paediatrician, with any discordant report assessed by a third senior paediatrician who was blinded to the clinical data. Sputum was obtained if the child was symptomatic and/or had an abnormal CXR, either spontaneously or induced in children who were unable to expectorate.[12] All children diagnosed with TB were referred for DOTS treatment, in line with the Gambian NLTP guidelines. TB was defined according to WHO proposed case definitions of bacteriologically confirmed and clinically diagnosed TB (Table 1).[13] TB was excluded if the CXR was normal, there was no microbiological confirmation and symptoms cleared spontaneously or with conventional short-course antibiotic treatment, regardless of TST results. TST-positive children who were not diagnosed with TB were classified as latently infected. All children with alternative diagnoses were managed as appropriate.

Table 1 Diagnostic classification according to the revised WHO case definitions[13]

Confirmed TB	Detection of AFB using microscopy of secretions, or identification of *M. tuberculosis* on culture, or identification of *M. tuberculosis* using Xpert
Clinically diagnosed TB*:	Does not fulfil criteria for bacteriological confirmation, but: appearance on chest X-ray suggestive of TB, and favourable response to specific anti-tuberculosis treatment ± positive tuberculin skin test ± histological appearance on biopsy material suggestive of TB

* TB cases with symptoms and signs suggestive of TB that did not fulfil the criteria for bacteriological confirmation of disease, had suggestive appearance on chest X-ray and failed to respond to empirical broad-spectrum antibiotics. Favourable response to anti-tuberculosis treatment was an integral part of the clinical TB diagnosis.
WHO = World Health Organization; TB = tuberculosis; AFB = acid-fast bacilli;

Isoniazid prophylaxis

All contacts aged <5 years living in the same household as the index case and in whom TB disease was excluded were provided with isoniazid (INH) prophylaxis at 10 mg/kg/day for 6 months, irrespective of TST result, in line with WHO recommendations.[3]

Follow-up

All contacts not diagnosed with TB disease were re-screened for symptoms every 3 months over 1 year of follow-up in the community. Children with new symptoms suggestive of TB were investigated as above.

Data analysis

Categorical data were reported as frequency and proportions. Medians and interquartile ranges (IQRs) were calculated for non-normally distributed contin-

uous data. Proportions of outcomes were compared between groups using the χ^2 test. $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of child contacts

Of 617 newly diagnosed adults with smear-positive TB, 551 (89.3%) consented to contact tracing of children in their households and compound; 4070 child contacts from 812 households in 346 compounds were screened, giving an average of 5 child contacts per household and 7–8 child contacts per index case. Of these, 4042 (99.3%) had complete screening data and were included in the analysis. The median age was 5.9 years (IQR 2.8–9.7); females constituted 50.8% of child contacts; 43.8% were aged <5 years (Table 2). Of the 705 (17.5%) TST-positive contacts, 480/2025 (23.7%) were resident in index case households compared to 225/2017 (11.2%) found outside of the household ($P < 0.001$). Of the 4042 child contacts, 206 (5.1%) shared the same bed with the index case. Following screening in the community, 940/4042 (23.8%) child contacts were referred for clinical evaluation, 909 of whom (96.6%) attended. Only 3/909 (0.3%) children tested HIV-positive among those examined at the clinic. After baseline evaluation and clinical examination, 82.6% (3339/4042) of contacts were classified as exposed but not infected, 15.8% (639/4042) were latently infected and 1.6% (64/4042) had TB disease.

Co-prevalent disease in contacts, overall and by age group

Overall, 64/4042 (1.6%) contacts were diagnosed with TB: 19 (29.7%) were confirmed bacteriologically and 45 (70.3%) were diagnosed clinically. Cough (27/45) and weight loss (23/45) were the most common symptoms among clinically diagnosed cases, while nearly all (42/45) had an abnormal CXR. The median age of the TB cases was 4.4 years (IQR 1.9–6.9); 34 (53.1%) were female (Table 2 and Figure 1A). Sixty-one TB cases completed anti-tuberculosis treatment; 2 died while on treatment and 1 was lost to follow-up after 2 months of treatment.

The data were analysed according to two age groups, in line with WHO reporting standards (Figure 1B and C). Of the 1772 contacts aged <5 years who underwent investigation at the clinic, 34 (9.8%; 2% of all contacts) were diagnosed with TB disease, and 8 were microbiologically confirmed. Two of the 184 asymptomatic but TST-positive TB cases were diagnosed on the basis of hilar lymphadenopathy alone. Of the 2270 contacts aged ⩾5 years investigated at the clinic, 30 (5%; 1.3% of all contacts) were diagnosed with TB disease, 11 of whom were microbiologically confirmed.

Table 2 Characteristics of child contacts of adult smear-positive TB screened in the community

Characteristics ($n = 4042$)	*n* (%)
Age, years, median [IQR]	5.9 [2.8–9.7]
Females	2056 (50.9)
Symptomatic	310 (7.6)
Contacts aged <5 years	1772 (43.8)
BCG scar present ($n = 1637$)	1418 (86.6)
TST ⩾ 10 mm	705 (17.5)
Relationship to index case	
Child	540 (13.4)
Sibling	301 (7.5)
Other relation	2118 (52.4)
Not related	1083 (26.8)
Proximity to index case	
Separate house	2017 (49.9)
Same house but separate room	1448 (35.8)
Same room but separate bed	371 (9.2)
Same bed	206 (5.1)
Attended clinic	909 (22.5)
TB diagnosis	64 (1.6)
Bacteriological confirmed	19 (0.5)
Clinically diagnosed	45 (1.1)
Not TB	830 (20.5)

TB = tuberculosis; IQR = interquartile range; BCG = bacille Calmette-Guérin; TST = tuberculin skin test.

Prevalence of TB disease according to age and proximity to index case

The prevalence of TB disease was 0.7% (14/2017) among children living in a separate house, while it was 1.2% (17/1448) for those in the same house but in separate rooms, and nearly 9% (18/206) in children sleeping in the same bed as the adult index case (P for trend <0.001). Of the 64 TB cases, 50 (78.1%) were diagnosed in the adult index case's household, while 14 (21.9%) additional cases lived in the compound (Figure 2).

TB prevalence according to possible approaches to contact tracing

Overall TB prevalence was 11.9% (95%CI 8.3–15.5; Table 3) among symptomatic contacts, with the highest prevalence (14.4%, 95%CI 9.1–19.7) among symptomatic contacts aged <5 years. When stratified by household, prevalence of TB disease was 2.5% (95%CI 1.8–3.2) among child contacts within the household compared to 0.7% (95%CI 0.3–1.1) of cases diagnosed outside the household of the index case. TB was diagnosed in 6.2% (44/705) of all TST-positive children, compared to 0.6% (20/3337) of TST-negative children. Among asymptomatic but TST-positive contacts, TB prevalence was 4.3% (95%CI 2.7–5.9).

Three-monthly follow-up

Of 3102 initially asymptomatic and TST-negative child contacts, 46 (1.5%) developed symptoms during follow-up and 3 were clinically diagnosed with TB disease: 2 at the first follow-up (in a 21-month-old female who was not eligible for IPT and a

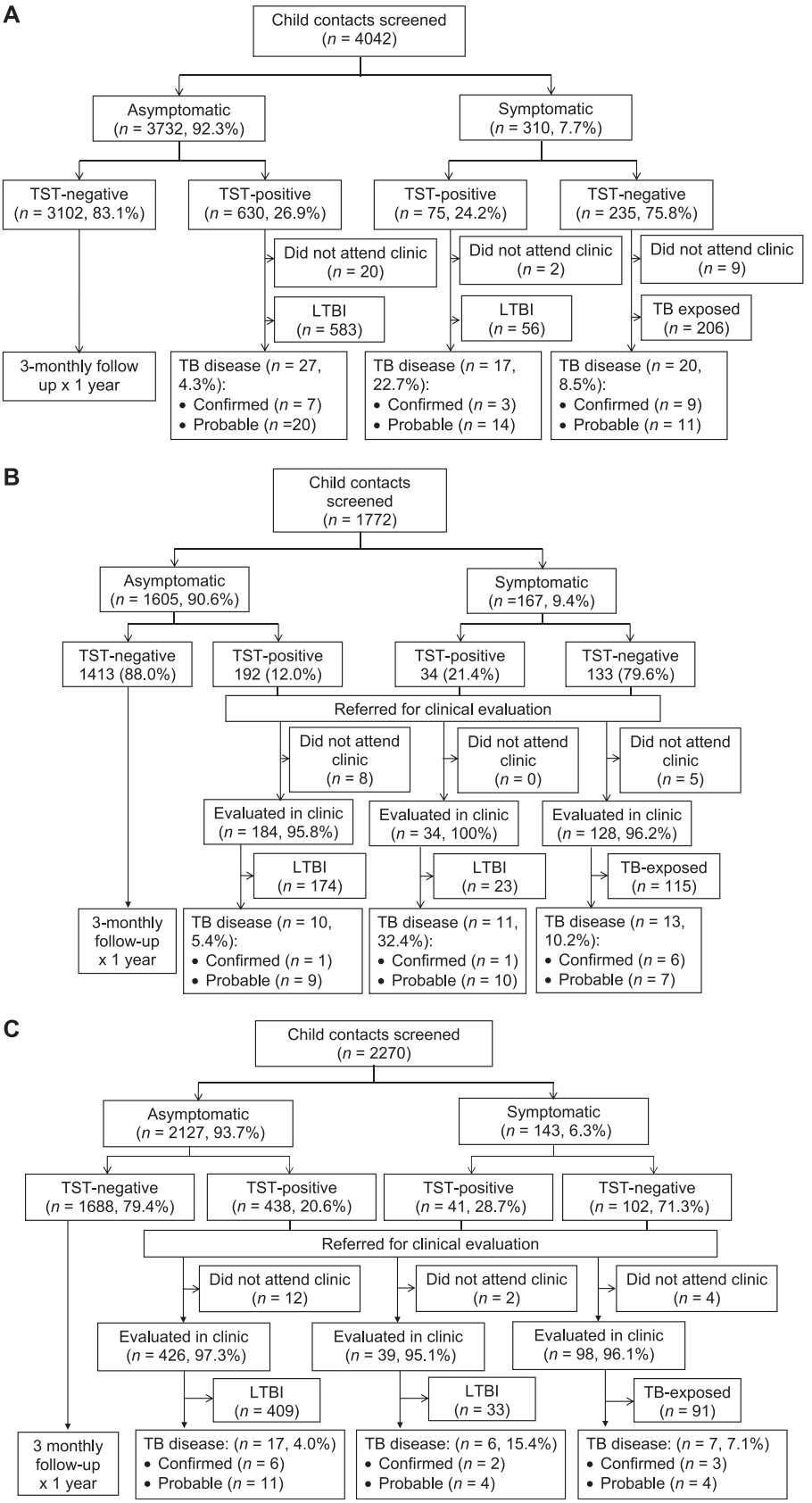

Figure 1 **A)** Flow chart of baseline screening, clinical examination and outcome of all child contacts. **B)** Flow chart of baseline screening, clinical examination and outcome of child contacts aged <5 years. **C)** Flow chart of baseline screening, clinical examination and outcome of child contacts aged ⩾5 years. TST = tuberculin skin test; LTBI = latent tuberculous infection; TB = tuberculosis.

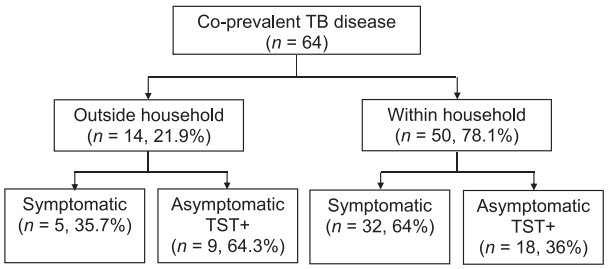

Figure 2 Distribution of co-prevalent cases within the compound. TB = tuberculosis; TST+ = tuberculin skin test-positive.

34-month-old male who was prescribed but did not undergo IPT), and an 11-year-old boy in the last month of follow-up.

DISCUSSION

To the best of our knowledge, this is the largest child contact tracing study reported from Africa, with over 4000 child contacts from 812 TB-affected households, enabling in-depth analysis of different subgroups and screening scenarios. Overall, 15.8% of contacts were latently infected and 1.6% had TB disease. There were 64 co-prevalent and three incident cases. While TB disease was more prevalent among symptomatic contacts regardless of age, 40% of the TB cases were nevertheless diagnosed among asymptomatic child contacts who were referred for further investigations due to TST positivity. Over three quarters of the co-prevalent TB cases were among contacts who lived in the immediate household of the adult index case. A third of cases arose from young child contacts who shared a bed with the index case. These findings might call into question an exclusively symptom-based approach to contact tracing in children and help policy makers define priorities for contact screening.

Only 1.6% of the study child contacts were found to have TB, increasing to 2.3% in contacts living within the index case households. These percentages are lower than the 7% reported from a pooled analysis of contact studies in middle- and low-income countries,[14] but comparable to our previous study from The Gambia.[15] A study from Indonesia found TB disease in 7.8% of child contacts, but none were bacteriologically confirmed,[16] while in Uganda, 10% of the contacts were diagnosed with TB; all child contacts were investigated in the clinic and 3% of children were HIV-positive (as opposed to 0.3% in our cohort in The Gambia).[17] Our rate of microbiological confirmation among diagnosed cases (29.7%) was similar to those found by other investigators.[18,19]

Symptom-based screening as recommended by the WHO[3] facilitates the identification of TB in children in resource-poor settings and has a high negative predictive value for TB disease.[16,20] Nearly 60% of all co-prevalent TB cases identified in our study were symptomatic. However, 40% of co-prevalent TB cases occurred in asymptomatic children, and sole reliance on a symptom-based approach would have missed these entirely.

Symptoms of childhood TB can be non-specific, and up to 50% of children may be asymptomatic in the early stages of the disease.[21] The TST led to the identification of 630 asymptomatic but TST-positive child contacts in our study, 4.3% of whom were diagnosed with TB, including seven who were bacteriologically confirmed. In a much smaller contact tracing study from South Africa also employing TST and CXR, microbiologically confirmed TB was diagnosed among 1.4% (9/644) of children aged <5 years, 7 of whom were asymptomatic but had an

Table 3 Prevalence of TB disease by approach to contact tracing

Approach to screening	n	TB cases n	Prevalence (95%CI)	Prevalence/100 000 population
All child contacts	4020	64	1.6 (1.2–1.9)	1583.4
Symptomatic	310	37	11.9 (8.3–15.5)	11935.5
Asymptomatic TST-positive	630	27	4.3 (2.7–5.9)	4285.7
Within household	2025	50	2.5 (1.8–3.2)	2469.1
Outside household	2017	14	0.7 (0.3–1.1)	694.1
Asymptomatic TST-negative	3102	0	0	
Aged <5 years				
All	1772	34	1.9 (1.3–2.6)	1918.7
Symptomatic	167	24	14.4 (9.1–19.7)	14371.3
Asymptomatic TST-positive	192	10	5.2 (2.1–8.3)	5208.3
Within household	898	29	3.2 (2.1–4.4)	3118
Outside household	874	5	0.6 (0.1–1.1)	572.1
Aged ⩾5 years				
All	2270	30	1.3 (0.9–1.8)	1321.5
Symptomatic	143	13	9.0 (4.4–13.7)	9090
Asymptomatic	438	17	3.9 (2.1–5.0)	3881
Within household	1127	21	1.9 (1.1–2.7)	1863
Outside household	1143	9	0.8 (0.3—1.3)	787

TB = tuberculosis; CI = confidence interval; TST = tuberculin skin test.

abnormal CXR.[22] Although the TST was performed in 94% of these children, TB prevalence in TST-positive vs. TST-negative children was not reported in that study. In our study, TB disease was 10 times more common in TST-positive than in TST-negative children.

The size of our cohort enables us to provide robust estimates of the yield from different screening approaches in the community, assuming the availability of TST. First, there is no added benefit from conducting TST in children who are already symptomatic at the time of screening, as they will be investigated for disease anyway. A negative TST does not exclude TB disease.[3] Second, noting the very low yield during the 12-month follow-up, there is little or no benefit from screening asymptomatic children who are TST-negative any further for TB disease. Restricting screening to the immediate household of the adult index case yielded 78% of the co-prevalent TB cases in our study. Independent of household or compound, restricting screening to children who shared a bed with the index case would have yielded 28% of the TB cases.

Given the ambitious new WHO End TB Strategy, which includes early detection and treatment of all patients with TB,[23] adequately resourced TB programmes may consider screening children outside of the immediate household of an index case, especially in a setting such as The Gambia. Here we have provided estimates of the yield from such screening approaches, with 21% of all co-prevalent cases found among contacts in the wider compound who would not have been included had contact tracing exclusively focused on the immediate household. While the prevalence rate in the wider compound was less than a third that found in the immediate households, we estimate that it was at least three times that in the general community (2014 NLTP TB prevalence survey data, personal communication), making these children a relatively high-risk, high-yield group for active case finding.

Our study had some limitations. As no further routine investigations of asymptomatic TST-negative contacts were conducted, the actual burden of childhood TB in this population may have been underestimated. Unlike recommendations in some European guidelines,[24] we did not perform a repeat TST in TST-negative children in any group. Second, our definition of suggestive symptoms was very restrictive and may have precluded eligible children from further evaluation. However, as outlined above, the regular follow-up of the entire cohort would most likely have picked up incident cases, as 90% of TB disease in children is known to develop within the first 12 months of a significant household exposure.[25]

In conclusion, contact tracing in this West African setting helped detect TB in child contacts both within and outside the household of the adult index case, and a significant proportion of co-prevalent TB was found among asymptomatic but TST-positive contacts. In settings such as The Gambia, a symptoms-only based contact tracing approach targeting only child contacts within the immediate household of the adult index case could detect the majority of co-prevalent child TB cases, but would miss about one fifth of all co-prevalent TB within the compound. Our data support the view that where TST is available as a screening tool, it should be applied to asymptomatic household contacts only. Further studies are now required to assess the cost-effectiveness of such a contact tracing strategy in The Gambia and similar settings.

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Conflicts of interest: none declared.

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RESUME

CONTEXTE : Région du Grand Banjul en Gambie.
OBJECTIF : Identifier la tuberculose (TB) co-prévalente parmi des enfants contacts d'adultes atteints de TB à frottis positif.
SCHÉMA : Les enfants (âge <15 ans) contacts dans la famille immédiate et dans la concession ont été enrôlés de façon prospective et évalués vis-à-vis de la TB grâce à des questionnaires de dépistage et un test cutané à la tuberculine (TST). Les contacts symptomatiques et/ou ayant un TST positif (⩾10 mm) ont bénéficié d'autres investigations.
RÉSULTATS : Ont eu un dépistage 4042 enfants contacts basé sur les symptômes et un TST. Parmi eux, 3339 (82,6%) ont été considérés comme exposés à la TB mais pas infectés, 639 (15,8%) avaient une infection latente et 64 (1,6%) avaient une TB co-prévalente. Sur les 64 cas de TB, 50 (78,1%) ont été diagnostiqués dans la famille immédiate du cas index et 14 (21,9%) au sein de la concession. Vingt-sept enfants asymptomatiques mais ayant un TST positif ont eu un diagnostic de TB, dont sept ont été confirmés par la microbiologie. L'âge médian des cas de TB a été de 4,4 (intervalle interquartile 1,9–6,9) ans ; 53,1% avaient moins de 5 ans. Cinq pour cent ($n = 206$) des contacts dormaient dans le même lit que le cas index et 28,1% de tous les cas de TB sont survenus dans ce groupe. Le dépistage des symptômes seul aurait détecté seulement 57,8% des cas co-prévalents.
CONCLUSION : Dans le contexte de notre communauté, la recherche de contacts restreinte au dépistage des symptômes dans la famille immédiate aurait laissé passer près de la moitié des cas de TB maladie co-prévalente chez les enfants contacts.

RESUMEN

MARCO DE REFERENCIA: La zona del Gran Banjul en Gambia.
OBJETIVOS: Detectar la prevalencia concomitante de tuberculosis (TB) en los niños que son contactos de los adultos con TB y baciloscopia positiva.
MÉTODO: Se investigó la presencia de enfermedad tuberculosa en los niños (menores de 15 años) que tenían un contacto inmediato o en el complejo domiciliario con un caso de TB, mediante cuestionarios de tamizaje y la prueba cutánea de la tuberculina (TST). Los contactos sintomáticos o con un resultado positivo de la TST se examinaron de manera más completa.
RESULTADOS: Se practicó la detección sistemática mediante la investigación de los síntomas y la TST en 4042 niños definidos como contactos. Se puso en evidencia una exposición a la TB sin infección en el 3339 (82,6%), una infección tuberculosa latente en el 639 (15,8%) y el 64 (1,6%) de los niños presentó TB. De los 64 casos de TB, 50 (78,1%) se diagnosticó en el domicilio inmediato del caso inicial y 14 (21,9%) en el complejo domiciliario. Se diagnosticó TB en 27 niños asintomáticos, pero con un resultado positivo de la TST, de los cuales se logró la confirmación bacteriológica en siete casos. La mediana de la edad de los casos de TB fue 4,4 años (intervalo intercuartil 1,9–6,9); el 53,1% era de edad de <5 años. El 5% de los contactos ($n = 206$) dormía en la misma cama del caso inicial y el 28,1% de todos los casos de TB ocurrió en este grupo. La investigación exclusiva de los síntomas solo habría detectado el 57,8% de los casos prevalentes concomitantes.
CONCLUSIÓN: En el entorno de la comunidad estudiada, una investigación de contactos limitada a la detección de síntomas y al domicilio inmediato habría pasado por alto cerca de la mitad de los casos concomitantes de enfermedad tuberculosa en los niños que son contacto de un caso adulto.

8.2 Publication 2

Contribution of Xpert MTB/RIF to the diagnosis of pulmonary tuberculosis among TB-exposed children in The Gambia

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Contribution of Xpert® MTB/RIF to the diagnosis of pulmonary tuberculosis among TB-exposed children in The Gambia

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SUMMARY

SETTING: Greater Banjul Area, The Gambia.

OBJECTIVE: To conduct a pragmatic evaluation of the Xpert® MTB/RIF assay in the diagnosis of tuberculosis (TB) among child contacts.

DESIGN: In this prospective study, one induced sputum sample was obtained from TB contacts aged <15 years and tested using fluorescent microscopy, culture and Xpert. The diagnostic accuracy of the microbiological tests was evaluated against culture and 'all TB diagnosis and treatment' as separate reference standards.

RESULTS: Using culture as a reference standard, Xpert was positive for *Mycobacterium tuberculosis* in 6/14 culture-positive and 6/473 culture-negative children, giving a sensitivity and specificity of respectively 42.9% (95%CI 17.7–71.1) and 98.7% (95%CI 97.2–99.5). With 'all TB diagnosis and treatment' as a composite reference standard, combined Xpert and culture tests were positive for *M. tuberculosis* in 20/62 children with TB disease (32.3%, 95%CI 20.9–45.3), which was comparable to the yield from microscopy, culture and Xpert combined (33.9%, 95%CI 22.3–47.0), but significantly higher than individual yields from each test.

CONCLUSION: The sensitivity of Xpert is low in actively traced child contacts, but a combination of Xpert and mycobacterial culture has incremental benefits for the bacteriological confirmation of TB disease.

KEY WORDS: accuracy; Xpert® MTB/RIF; child contacts

EACH YEAR, AROUND HALF a million children aged <15 years become ill with tuberculosis (TB), resulting in up to 70 000 deaths.[1] However, the true burden of disease remains unknown, mostly due to difficulties with the diagnosis of TB in children. Childhood TB mimics other diseases such as pneumonia, human immunodeficiency virus (HIV) infection and malnutrition.[2] Younger children rarely produce good quality respiratory specimens, and TB is associated with a low bacillary burden in children.[3,4] The bacteriological confirmation of TB disease in children therefore seldom exceeds 30%,[5,6] and the diagnosis of childhood TB is mostly presumptive.[7]

In 2010, the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) was endorsed by the World Health Organization (WHO) for the rapid diagnosis of pulmonary TB and detection of rifampicin (RMP) resistance;[8] however, data on its diagnostic accuracy in children are still emerging. In adult studies, the specificity of Xpert is comparable to that of liquid culture, while its sensitivity is relatively higher in smear- and culture-positive TB than in smear-negative, culture-positive TB cases.[9,10] Studies in children, mostly hospital-based, have reported variable sensitivity and high specificity of the Xpert test in the detection of *Mycobacterium tuberculosis*.[11–18] Given emerging concerns about the feasibility and cost-effectiveness of decentralised Xpert testing in high TB burden settings,[19] understanding the added value of Xpert testing when used routinely in a variety of contexts is important.[20,21]

Children exposed to adults with sputum smear-positive TB have a high likelihood of developing active TB themselves, and should be investigated for TB.[22] Although recommended, screening of child contacts is rarely performed in resource-constrained, high TB burden countries.[23] As far as we are aware, no study has investigated the performance and added value of Xpert in an active case-finding study among an exclusively paediatric population of TB contacts in a low-income country. We therefore evaluated Xpert in children with known household exposure to a sputum smear-positive adult TB case in a low HIV prevalence setting in West Africa.

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STUDY POPULATION AND METHODS

Study setting

This prospective study was conducted at the Medical Research Council (MRC) Unit – The Gambia, located in the urban Greater Banjul Area (GBA), from where an estimated 80% of all TB cases in the country are notified. In 2013, TB incidence rate in The Gambia was 173 cases per 100 000 population, while HIV prevalence among adults aged 15–49 years was 1.3%.[24,25]

Ethics approval for the study was obtained from the Gambia Government/MRC Joint Ethics Committee, Banjul, The Gambia.

Contact tracing and clinic procedure

Paediatric household contact tracing was conducted from February 2012 to July 2014. Consecutively diagnosed adult smear-positive index TB cases, identified within the Gambia National TB Control Programme (NTCP), were visited in their compounds for the screening of household contacts aged <15 years. Following written informed consent from the parent/guardian of the respective child, children were recruited and screened for disease using a standardised symptom screening questionnaire and tuberculin skin test (TST). In the clinical screening algorithm, symptoms suggestive of TB were defined as unremitting cough of >14 days and at least one of either fever, weight loss/failure to thrive, malaise/fatigue, haemoptysis, night sweats or enlarged cervical lymph nodes. A positive TST was defined as transverse skin induration ⩾10 mm, regardless of bacille Calmette-Guérin vaccination status, measured 48–72 h after intradermal injection of 0.1 ml of two tuberculin units of purified protein derivative (Statens Serum Institute, Copenhagen, Denmark) in the volar aspect of the left forearm. All children aged <15 years with symptoms suggestive of TB and/or positive TST results were referred to the MRC childhood TB clinic for further evaluation.

Evaluation at the clinic by study paediatricians included a detailed symptom review, physical examination and anthropometric measurements that included calculation of the height-for-age *Z*-score (HAZ) using the WHO 2007 reference standards.[26] All children referred to the clinic underwent HIV testing and a chest X-ray (CXR) that was read independently by two study physicians, with any discordant report assessed by a third senior clinician who was blinded to the clinical data. Sputum induction was requested for all children aged ⩾3 months with symptoms suggestive of TB and/or an abnormal CXR. A single induced sputum sample was requested per patient, taking into consideration the practical issues of the procedure, including the cost of materials and the extent of discomfort for the children. A trained study nurse performed sputum induction using nebulised hypertonic saline (3%) after fasting for at least 3 h and premedication with nebulised salbutamol, obtaining a sample of at least 2.5 ml. Sputum samples were collected in sterile containers and sent immediately to the onsite TB diagnostic laboratory for pathogen detection tests. TB disease was defined according to the case definitions proposed by the WHO, comprising bacteriologically confirmed or clinically diagnosed TB cases (Table 1).[27] All subjects diagnosed with TB disease were referred for standard 6-month anti-tuberculosis treatment according to national guidelines.[28] Children without bacteriological confirmation or radiological signs of TB disease and with resolution of symptoms either spontaneously or with conventional short-course antibiotic treatment were treated for respiratory infections other than TB.

All child contacts were followed up at home by trained field workers at 3-month intervals for 12 months, with repeated symptom screening and clinic visits if the child became unwell. Children initially diagnosed with TB disease underwent clinic follow-up at 2 months and at the end of anti-tuberculosis treatment, with evaluation of their response to treatment.

Laboratory procedures

Induced sputum samples were processed within 2 h of collection by trained laboratory technicians blinded to the clinical data (Appendix).* Briefly, samples were digested and decontaminated as previously described,[29] and the concentrated sediments were re-suspended in 1.5 ml of phosphate buffer. The re-suspended sediments were simultaneously processed for fluorescence microscopy after auramine-phenol staining and mycobacterial culture with both MGIT™ liquid culture system (BD, Sparks, MD, USA) and Löwenstein-Jensen (LJ) solid media using standard laboratory procedures as previously described.[30] For the Xpert assay, 1.5 ml of the Xpert sample reagent was added to 0.5 ml of re-suspended sediment sample and processed according to the manufacturer's guidelines.[31]

Statistical analysis

The diagnostic accuracy of the microbiological tests, including Xpert, was assessed by comparing the results with mycobacterial culture as the primary reference standard, and with a composite reference standard of 'all TB diagnosis and treatment' based on clinical, radiological and microbiological findings, comprising both bacteriologically confirmed and clinically diagnosed TB cases. The data were analysed on a per-patient basis: the results of all pathogen

* The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2015/00000019/00000009/art00018

Table 1 TB disease according to the revised WHO case definitions

Bacteriologically confirmed TB	Detection of AFB using microscopy of secretions; or Identification of *M. tuberculosis* using culture; or Identification of *M. tuberculosis* using a WHO-approved rapid diagnostic such as Xpert® MTB/RIF
Clinically diagnosed TB*	Does not fulfil criteria for bacteriological confirmation; but Suggestive appearances on chest X-ray; and Favourable response to specific anti-tuberculosis treatment; and/or Positive tuberculin skin test; Suggestive histological appearances on biopsy material

* Clinically diagnosed TB cases had symptoms and signs suggestive of TB, did not fulfil the criteria for bacteriological confirmation of disease, had suggestive appearance on chest X-ray and failed to respond to empirical broad spectrum antibiotics. A favourable response to anti-tuberculosis treatment was an integral part of the clinical TB diagnosis.
TB = tuberculosis; WHO = World Health Organization; AFB = acid-fast bacilli.

detection tests for each patient were combined into a single test result that was deemed positive when at least one positive result was obtained for a specific microbiological test. The McNemar's test was used to compare the performance of the microbiological tests individually or in combination. All statistical analyses were carried out using STATA, version 13 (Stata Corp, College Station, TX, USA). $P < 0.05$ (2-sided) was considered statistically significant.

RESULTS

Overall, 3298 child contacts of 622 consecutive adult index TB cases were recruited and screened in 952 households. Of these, 873 contacts were seen and investigated at the MRC childhood TB clinic (Figure 1). One induced sputum sample was obtained from 514 children with symptoms suggestive of TB or with an abnormal CXR, of which 487 (95%) with complete sputum smear microscopy, Xpert and culture results were included in this analysis.

The median age of the 487 child contacts was 6 years (interquartile range 3–9); none were HIV-infected (Table 2). Smear microscopy was positive in 6 (1.2%), Xpert was positive in 12 (2.5%) and culture was positive in 14 (2.9%). Overall, 62 patients were diagnosed with active TB disease and started on standard anti-tuberculosis treatment: 21 (4%) were bacteriologically confirmed, while 41 (8%) were clinically diagnosed with TB with no positive microbiological tests. Four hundred and twenty-five contacts (88%) were diagnosed and treated for other respiratory diseases. Using culture as reference standard, smear microscopy was positive for acid-fast bacilli in 4/14 culture-positive cases (28.6%, 95% confidence interval [CI] 8.4–58.1), while Xpert was positive for *M. tuberculosis* in 6/14 culture-positive and 6/473 culture-negative patients, giving a sensitivity and specificity of respectively 42.9% (95%CI 17.7–71.1) and 98.7% (95%CI 97.2–99.5) (Table 3). Xpert detected all four smear- and culture-positive cases and 3/10 (30%, 95%CI 7–65) smear-negative, culture-positive TB cases.

When using 'all TB diagnosis and treatment' as a composite reference standard, the sensitivity of Xpert was 19.4% (95%CI 10.4–31.4), significantly higher than that of smear microscopy (9.7%, 95%CI 3.6–19.9, $P = 0.042$), but comparable to that of culture (22.6%, 95%CI 12.9–35.0, $P = 0.598$) (Table 4). Figure 2 depicts the yields from smear microscopy, Xpert and culture as individual tests and in combinations. Xpert and culture combined were positive for *M. tuberculosis* in 20/62 children with active TB disease, giving a sensitivity of 32.3% (95%CI 20.9–45.3), which was significantly higher than the sensitivity of smear microscopy ($P < 0.001$), Xpert ($P = 0.005$) and culture ($P = 0.031$) when used as individual tests (Table 4). The bacteriological yield from combining the results of smear microscopy and culture was not significantly different from culture alone ($P = 0.157$), while the yield from the combination of the three tests (smear microscopy, Xpert and culture) was not significantly different from using only Xpert and culture together ($P = 0.317$). No RMP resistance was detected in any of the samples analysed.

DISCUSSION

In this study, we report the evaluation of Xpert among TB-exposed children identified from a household contact tracing project in The Gambia. Xpert testing of one induced sputum sample had a sensitivity of 42.9% relative to culture-confirmed TB, with a specificity of 98.7% among children without TB, while its sensitivity was 19.4% when compared to a composite reference standard of 'all TB diagnosis and treatment'.

In line with previous reports, the sensitivity of Xpert in our study was higher than that of smear microscopy, with relatively higher sensitivity in smear- and culture-positive TB cases than in smear-negative, culture-positive TB cases. However, we found that the sensitivity of Xpert relative to culture was lower than that reported in hospital-based studies from other high TB burden settings such as Uganda and Tanzania, where Xpert detected 79% and 75% of culture-confirmed TB, respectively, in populations with an HIV prevalence of >40%, while another hospital-based paediatric cohort from South

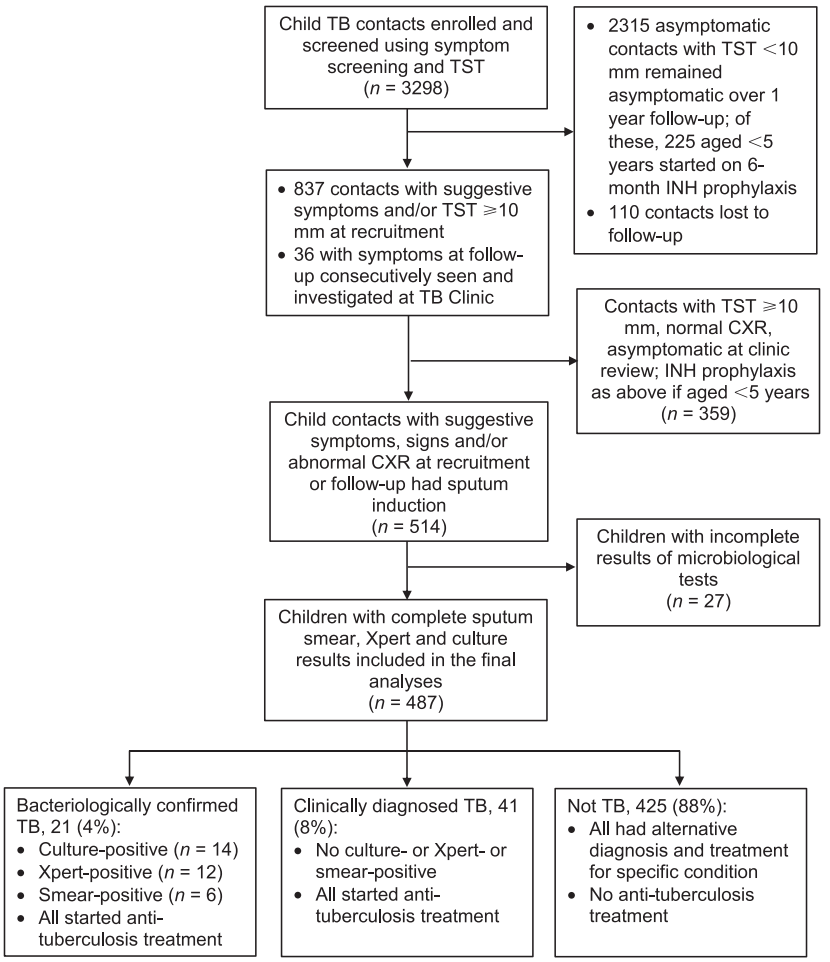

Figure 1 Study profile: recruitment and diagnostic classification of study subjects. TB = tuberculosis; TST = tuberculin skin test; INH = isoniazid; CXR = chest X-ray.

Africa similarly reported a sensitivity of 74.3% for Xpert testing of at least one induced sputum sample.[11,13,14] The sensitivity of Xpert in our study is comparable to the findings from another paediatric South African study that reported a sensitivity of 43.3% with Xpert relative to culture in a primary care setting,[18] while a recent systematic review of 15 studies on Xpert accuracy in children reported a pooled sensitivity of 48% in out-patient studies compared to 70% in in-patient studies.[32] Taken together, these figures are consistent with the assumption that children with TB in ambulant populations have less severe disease and lower bacillary load than children hospitalised with TB.[18,19] The sensitivity of Xpert thus appears to be substantially lower in ambulant populations, which has strong implications for its use as a diagnostic tool for TB among children in this context. This conclusion is

Table 2 Demographic and clinical characteristics stratified by diagnosis (confirmed, clinically diagnosed TB and not TB)

Characteristics	Total (*n* = 487) *n/N* (%)	Confirmed TB (*n* = 21) *n/N* (%)	Clinically diagnosed TB (*n* = 41) *n/N* (%)	Not TB (*n* = 425) *n/N* (%)	*P* value
Age, years, median [IQR]	6 [3–9]	6 [3–11]	3.8 [2–6]	6 [3–9]	0.020*
Male sex	259/487 (53)	6/21 (29)	22/41 (54)	231/425 (54)	0.069
Cough and/or fever ⩾2 weeks	374/487 (77)	21/21 (100)	34/41 (83)	319/425 (75)	0.019*
Chest X-ray abnormal	358/482 (74)	17/21 (81)	38/41 (93)	303/420 (72)	0.013*
BCG scar present	332/460 (72)	14/20 (70)	29/40 (73)	289/400 (72)	0.975
TST ⩾10 mm	243/398 (61)	8/16 (50)	26/35 (74)	209/347 (62)	0.174
Anthropometry					
BMI-for-age *Z*-score <−2 SD	137/480 (29)	10/21 (48)	12/41 (29)	115/418 (27)	0.137
Height-for-age *Z*-score <−2 SD	63/481 (13)	2/21 (10)	5/41 (12)	56/419 (14)	0.864

* Statistically significant.
TB = tuberculosis; IQR = interquartile range; BCG = bacille Calmette-Guérin; TST = tuberculin skin test; BMI = body mass index; SD = standard deviation.

Table 3 Accuracy of microbiological tests with mycobacterial culture as reference standard

Diagnostic test	Sensitivity *n/N* (%) (95%CI)	Specificity *n/N* (%) (95%CI)	PPV *n/N* (%) (95%CI)	NPV *n/N* (%) (95%CI)
Sputum smear microscopy	4/14 (28.6) (8.4–58.1)	471/473 (99.6) (98.5–100.0)	4/6 (66.7) (22.3–95.7)	471/481 (97.9) (96.2–99.0)
Xpert® MTB/RIF	6/14 (42.9) (17.7–71.1)	467/473 (98.7) (97.2–99.5)	6/12 (50.0) (21.1–78.9)	467/475 (98.3) (96.7–99.3)

CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

further supported by the overall Xpert and culture positivity rates of respectively 2.5% and 2.9% in our study, which were much lower than the 14–17% reported for both microbiological tests in hospital-based studies.[11,14] We also reported six Xpert-positive but culture-negative cases who were classified and treated as bacteriologically confirmed TB cases. The six cases had symptoms suggestive of TB, abnormal CXR, no past history of anti-tuberculosis treatment and a high background risk of disease, given their recent exposure to an adult with infectious TB in the household setting. These factors, taken together with the very high specificity of Xpert in children without TB, makes them very likely to be true-positive TB cases, and this is supported by the fact that at least five of the six children (one missed the 2-month follow-up) had an increase in weight of at least 5% after 2 months of anti-tuberculosis treatment.

The fact that culture has generally low sensitivity in children due to the paucibacillary nature of childhood TB makes it an imperfect reference standard, as recently discussed in detail by Cuevas et al.[33] We therefore chose to also assess the sensitivity and specificity of the microbiological tests using a composite reference standard of 'all TB diagnosis and treatment', which will have a higher sensitivity than culture alone. We found that the combination of Xpert and culture was positive in 32.3% of all children diagnosed with TB, giving a significantly higher incremental bacteriological yield, with an increase of 9.7–22.6% over the yields from microscopy, Xpert and culture alone as individual tests. It should be noted that combining microscopy with culture gave no significant incremental yield over culture alone, and the yield from the combination of the three tests (microscopy, Xpert and culture) was not significantly different from that using only Xpert and culture together. These results support the recent WHO recommendation that Xpert be used in place of smear microscopy as the initial diagnostic test for investigating children presumed to have TB in high-burden settings.[34] Although the impact of Xpert from an operational perspective is best addressed in large cohort studies, preferably within national TB programmes, our results suggest that in settings where presumptive treatment of TB in children is common, combining Xpert testing with culture methods has strong incremental value for bacteriological confirmation of TB diagnosis in children, and should be encouraged where feasible.

While Xpert testing of multiple similar or different specimens has been shown to increase the bacteriological yield in children presumed to have TB in research settings,[11,13,17,18] studies on the feasibility and cost-effectiveness of such an approach in resource-limited settings are required. Our study has some limitations. We identified a relatively small number of culture-confirmed TB cases from investigating almost 500 children, as reflected by the broad 95%CIs of test sensitivity compared to culture; however, this also emphasises the challenge of bacteriological confirmation of disease in children. Furthermore, the inclusion of the microbiological tests under investigation in the composite reference standard could result in incorporation bias that may

Table 4 Accuracy of microbiological tests using 'all TB diagnosis and treatment' as a composite reference standard

Diagnostic test	Sensitivity *n/N* (%) (95%CI)	Specificity *n/N* (%) (95%CI)	PPV *n/N* (%) (95%CI)	NPV *n/N* (%) (95%CI)
Sputum smear microscopy	6/62 (9.7) (3.6–19.9)	425/425 (100) (99.1–100.0)	6/6 (100) (54.1–100.0)	425/481 (88.4) (85.2–91.1)
Xpert® MTB/RIF	12/62 (19.4) (10.4–31.4)	425/425 (100) (99.1–100.0)	12/12 (100) (73.5–100.0)	425/475 (89.5) (86.4–92.1)
Culture	14/62 (22.6) (12.9–35.0)	425/425 (100) (99.1–100.0)	14/14 (100) (76.8–100.0)	425/473 (89.9) (86.8–92.4)
Sputum smear microscopy+culture	16/62 (25.8) (15.5–38.5)	425/425 (100) (99.1–100.0)	16/16 (100) (79.4–100.0)	425/471 (90.2) (87.2–92.8)
Xpert+culture	20/62 (32.3) (20.9–45.3)	425/425 (100) (99.1–100.0)	20/20 (100) (83.2–100.0)	425/467 (91.3) (88.4–93.6)
Sputum+Xpert+culture	21/62 (33.9) (22.3–47.0)	425/425 (100) (99.1–100.0)	21/21 (100) (83.9–100.0)	425/466 (91.2) (88.3–93.6)

TB = tuberculosis; CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value.

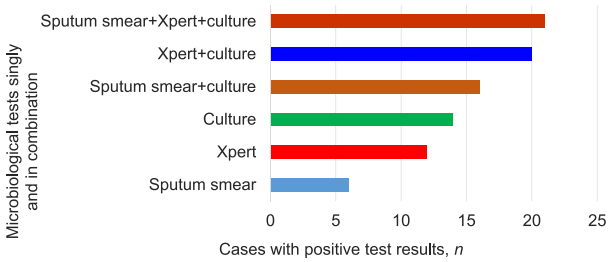

Figure 2 Incremental value of bacteriologically confirming tuberculosis diagnosis among all children started on anti-tuberculosis treatment using microbiological tests alone and in combination. This image can be viewed online in colour at http://www.ingentaconnect.com/content/iuatld/ijtld/2015/00000019/00000009/art00018

have overestimated test performance. However, even with possible overestimation, the sensitivity of Xpert and culture as standalone tests relative to the composite reference standard was only 19.4% and 22.6%, respectively. Furthermore, we obtained only one induced sputum sample per child and as such could not assess the incremental value of multiple testing.

CONCLUSION

The sensitivity of Xpert and the overall bacteriological yield, known to be generally lower in children than in adults, were even lower in actively traced child contacts than in hospital-based studies. Xpert and culture detected a comparable number of TB cases among all children diagnosed with active TB. Culture of respiratory specimens is still advisable if available because, unlike smear microscopy, it has incremental benefits when combined with Xpert testing.

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APPENDIX

LABORATORY PROCEDURES

Induced sputum samples were processed within 2 h of collection by trained laboratory technicians. Samples were digested and decontaminated using *N*-acetyl-L-cysteine and sodium hydroxide (1% final concentration), as previously described by Kent and Kubica,[25] with a contact time of 15 min; the concentrated sediments were resuspended in 1.5 ml phosphate buffer. An aliquot of the concentrated sediments was simultaneously prepared for fluorescent acid-fast smear microscopy following auramine-phenol staining, as well as both liquid and solid mycobacterial culture, as previously described.[26] For liquid culture, 0.5 ml of re-suspended sediment was inoculated into Mycobacteria Growth Indicator Tube (MGIT™) (BD, Franklin Lakes, NY, USA), supplemented with 0.8 ml of BD PANTA™ (BD, Sparks, MD, USA) antibiotic mixture and incubated into the BACTEC® MGIT 960MB (BD) instrument using standard procedures. Primary identification of *Mycobacterium tuberculosis* complex was performed on confirmed positive MGIT tubes using Capilia TB Neo (TAUNS Laboratory Inc, Shizuoka, Japan), according to the manufacturer's instructions. Each positive liquid culture was confirmed by Ziehl-Neelsen (ZN) stain and on blood agar plate to check for contamination. Pure isolates were subcultured into two Löwenstein-Jensen (LJ) slants, one of which contained sodium pyruvate, and then incubated at 37°C for 8 weeks. Growth on LJ slants were confirmed as *M. tuberculosis* complex by colonial morphology, ZN stain and standard biochemical tests. Pure colonies were then harvested in tryptone soya broth and stored at –70°C. LJ slants with no growth after 8 weeks' incubation were discarded. All mycobacterial cultures were identified and confirmed as *M. tuberculosis* using standard laboratory procedures.

For the Xpert® MTB/RIF assay, 1.5 ml of Xpert MTB/RIF Sample Reagent (SR) was added to 0.5 ml of re-suspended sediment sample and processed according to the manufacturer's guidelines.[27] The diluted sample mixture was shaken 10–20 times and incubated at room temperature for a total of 15 min. The mixture was then transferred using a sterile pipette into the open port of a pre-labelled Xpert cartridge, which was then loaded onto the Xpert machine. After a 2-h cycle, the results of the Xpert assay were read and reported as either *M. tuberculosis* ± rifampicin resistance detected or *M. tuberculosis* not detected.

The Medical Research Council TB Diagnostics Laboratory holds a Good Clinical Laboratory Practice Accreditation (ISBN 978-1-904610-00-7), serves as reference laboratory for the Gambia National TB Reference Laboratory and subscribes to the UK National External Quality Assessment Service.

RESUME

CONTEXTE : Région du grand Banjul en Gambie.
OBJECTIF : Conduire une évaluation pragmatique du test Xpert® MTB/RIF dans le diagnostic de la tuberculose (TB) parmi des enfants-contacts.
SCHÉMA : Dans cette étude prospective, un échantillon de crachats induits a été obtenu de contacts TB âgés de <15 ans et testé par microscopie fluorescente, culture et Xpert. L'exactitude du diagnostic des tests microbiologiques a été évaluée contre la culture et « tous les diagnostics et traitements de TB » comme standard de référence séparés.
RÉSULTATS : En utilisant la culture comme standard de référence, l'Xpert a été positif pour *Mycobacterium tuberculosis* dans 6/14 cas à culture positive et chez 6/473 enfants à culture négative, soit une sensibilité et une spécificité de respectivement 42,9% (IC95% 17,7–71,1) et 98,7% (IC95% 97,2–99,5). En utilisant comme référence composite standard « diagnostic et traitement de toutes les TB », l'Xpert et la culture combinés ont été positifs pour *M. tuberculosis* chez 20/62 enfants ayant une TB maladie (32,3% ; IC95% 20,9–45,3), ce qui était comparable au rendement de la combinaison de la microscopie, de la culture et de l'Xpert (33,9% ; IC95% 22,3–47,0), mais significativement plus élevé que le rendement de chacun des tests réalisé isolément.
CONCLUSIONS : La sensibilité de l'Xpert est faible chez les enfants contacts bénéficiant d'un dépistage actif, mais la combinaison de l'Xpert et de la culture mycobactérienne augmente les bénéfices en termes de confirmation bactériologique de la TB maladie.

RESUMEN

MARCO DE REFERENCIA: La zona metropolitana de Banjul en Gambia.
OBJETIVO: Practicar una evaluación práctica del uso de la prueba Xpert® MTB/RIF en el diagnóstico de los contactos pediátricos de los pacientes con tuberculosis (TB).
MÉTODOS: En el presente estudio prospectivo se obtuvo una muestra de esputo inducido de los contactos de edad de <15 años de pacientes tuberculosos, con la cual se practicó un examen en microscopio de fluorescencia, un cultivo y la prueba Xpert. Se evaluó la exactitud diagnóstica de las pruebas microbiológicas, tomando como patrones de referencia independientes el cultivo y una medida compuesta de 'todos los casos de diagnóstico y tratamiento de TB'.
RESULTADOS: Al usar el cultivo como referencia, la prueba Xpert fue positiva para *Mycobacterium tuberculosis* en seis de 14 casos con cultivo positivo y en seis de 473 niños con cultivo negativo y aportó una sensibilidad de 42,9% (IC95% 17,7–71,1) y una especificidad de 98,7% (IC95% 97,2–99,5). Al usar 'todos los casos de diagnóstico y tratamiento de TB' como patrón de referencia compuesto, la prueba Xpert y el cultivo combinados fueron positivos para *M. tuberculosis* en 20/62 niños con enfermedad tuberculosa (32,3%; IC95% 20,9–45,3) y exhibieron un rendimiento comparable al de la combinación de la microscopia, el cultivo y la prueba Xpert (33,9%; IC95% 22,3–47,0), pero significativamente superior al rendimiento de cada prueba utilizada de manera individual.
CONCLUSIÓN: La sensibilidad de la prueba Xpert es bajo en la investigación activa de los contactos pediátricos, pero una combinación de la prueba Xpert y el cultivo de micobacterias ofrece ventajas en la confirmación bacteriológica de la enfermedad tuberculosa.

8.3 Publication 3

Isoniazid preventive treatment among child contacts of adults with smear positive tuberculosis in The Gambia

Public Health Action

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Health solutions for the poor

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Isoniazid preventive treatment among child contacts of adults with smear-positive tuberculosis in The Gambia

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Setting: Greater Banjul area of The Gambia.
Objectives: To evaluate uptake, adherence and completion of treatment among tuberculosis (TB) exposed children in The Gambia when isoniazid preventive treatment (IPT) is delivered at home
Design: Child (age <5 years) contacts of adults with smear-positive TB were prospectively enrolled. Following symptom screening, tuberculin skin testing and clinical evaluation where indicated, those without disease were placed on daily isoniazid, provided monthly at home. Adherence was assessed by pill counts and IsoScreen™ urine test.
Results: Of 404 contacts aged <5 years, 368 (91.1%) were offered IPT. Of the 328 (89.4%) for whom consent was received and who commenced IPT, 18 (5.5%) dropped out and 310 (94.5%) remained on IPT to the end of the 6-month regimen. Altogether, 255/328 children (77.7%, 95%CI 73.2–82.2) completed all 6 months, with good adherence. The IsoScreen test was positive in 85.3% (435/510) of all tests among those defined as having good adherence by pill count and in 16% (8/50) of those defined as having poor adherence ($P < 0.001$). A cascade of care analysis showed an overall completion rate with good adherence of 61% for all child contacts.
Conclusion: Home-delivered IPT among child contacts of adults with smear-positive TB in The Gambia achieved verifiable high uptake and adherence rates. System rather than patient factors are likely to determine the success of IPT at national level.

The current elimination goals for tuberculosis (TB) include a focus on individuals who are latently infected with *Mycobacterium tuberculosis* to reduce the number of new TB cases and subsequent *M. tuberculosis* transmission.[1] This strategy requires isoniazid preventive therapy (IPT) or an alternative regimen. Initial targets are those at most risk of disease progression, such as young children and human immunodeficiency virus (HIV) infected individuals in contact with an infectious adult with TB.[2]

The above World Health Organization (WHO) recommendations have not, however, been implemented in most of the high-burden TB settings where IPT is most needed. In many places where IPT has been implemented and evaluated, the impact is suboptimal and the operational challenges are formidable.[3–6] Considering the cascade of care as a whole, it is estimated that, even where IPT is part of routine practice, only a minority of eligible children complete a course of treatment.[7] Not only is uptake poor, but adherence rates tend to be less than 30% among those who do commence IPT.[8,9] The measurement of adherence can also be unreliable, relying heavily on reports from care givers, how often care givers return for more medication, and pill counts.[10,11] Furthermore, interventions to improve IPT delivery frequently do not result in improved uptake, adherence and treatment completion.[12] A recent meta-analysis of the cascade of care for treatment of latent tuberculous infection (LTBI), which indicated where patients get lost in the system for various reasons, focused primarily on adults.[13]

As IPT implementation now has a higher priority within the agenda for TB control,[14] and as implementation via TB clinics appears to be challenging, we developed a home-based IPT programme among child contacts of recently diagnosed adult sputum smear-positive TB cases and assessed its impact on uptake, completion and adherence within the cascade of care in The Gambia. We also measured the isoniazid (INH) metabolites in urine to assess the reliability of our adherence measures.

METHODS

Study sites

The study was carried out in the Greater Banjul area of The Gambia between November 2013 and May 2015. This is a mixed urban-to-rural area, including the capital city of Banjul, and has a population of approximately 700 000. The setting has been described elsewhere.[15]

Participants

Child contacts aged <5 years living in the same household as adult sputum smear-positive TB cases were recruited. A household was defined as a group of individuals eating from the same pot and living in the same building.[16]

Symptom screening, tuberculin skin testing and clinical evaluation

Adults with newly diagnosed sputum smear-positive TB were identified at the National Leprosy/TB Control Programme (NLTP) clinics and were asked for their consent to a household visit. After the project was explained to the parents/care givers, written informed consent was obtained. A standard symptom-screening questionnaire for TB was then administered to ascertain if any child living in the same household had a cough of ⩾2 weeks' duration in association with at least one of the following symptoms: weight loss, fail-

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ure to gain weight, fever or night sweats. The tuberculin skin test (TST) was performed using the Mantoux method (2 tuberculin units of purified protein derivative RT23, Statens Serum Institute, Copenhagen, Denmark) and read 48–72 h later. A positive TST was defined as an induration of ⩾10 mm, in line with WHO recommendations.[17] Child contacts with symptoms suggestive of TB and/or a positive TST were referred to a dedicated childhood TB clinic for further evaluation. All children diagnosed with TB disease were referred to the TB clinics of the NLTP for DOTS-based treatment.

Isoniazid prophylaxis and follow-up

All child household contacts aged <5 years in whom TB disease was excluded were provided with IPT at 10 mg/kg/day for 6 months, as recommended by the WHO,[2] regardless of their TST result. Field workers delivered the IPT to the homes of the children on a monthly basis and administered a brief questionnaire to capture missed doses, the reasons for missed doses and any adverse events from the medication. To measure adherence, pill counts were performed for all children. An IPT card was specifically developed to record the child's weight and the number of unconsumed doses of medication. All children were assessed every 3 months for 1 year; those with new symptoms suggestive of TB were referred to the childhood TB clinic at the Medical Research Council (MRC) unit. A final home visit was made 1 year after INH completion to ascertain post-IPT status.

IsoScreen testing

In the first year of the study, consecutively recruited children on IPT were asked to provide a monthly urine sample for a qualitative assessment of adherence using the IsoScreen™ test (GFC Diagnostics Ltd, Oxfordshire, UK), a point-of-care colorimetric assay that detects INH and its metabolites utilising a disposable plastic test device and the Arkansas method for metabolite detection.[18] Two ml of collected urine was injected into a reaction chamber and mixed with the reagents contained in an effervescent tablet for about 10 s. Dark blue/purple colouration appearing within 5 min indicates a positive result, i.e., the individual has taken INH within the previous 24–48 h. If no INH has been taken, the colour of the urine remains unchanged, indicating a negative result. Care givers were informed about the monthly visits, but the actual days of the visit were unannounced. The results of the IsoScreen testing were recorded on the child's INH card.

Ethics approval

Ethics approval for the study was obtained from the joint Medical Research Council/Gambian government ethics committee (Ref. L2012.E01), Banjul, The Gambia.

Data analysis

Data were double-entered into an Access database (Microsoft Corp, Redmond, WA, USA) and verified using consistency checks. All analyses were performed using STATA/IC 13.1 (StataCorp, College Station, TX, USA). IPT implementation was assessed using a cascade of care approach. To provide a denominator for the uptake component of the cascade, the number of contacts of those TB cases who refused a home visit and the number of children with TB disease among those who had not been assessed in the clinic were estimated. This was performed by simple extrapolation of the average number of child contacts per case and the rate of disease in those assessed to a rate of disease in those not assessed, rounded to the nearest whole number.[13] Adherence was divided into three categories: good, reasonable and poor, if respectively >80%, 60–80% or <60% of the pills delivered each month had been taken.[19] Treatment completion was defined as consuming >80% of all pills prescribed in each of the 6 months of prophylaxis.[20] The proportion of children with a positive IsoScreen test result was compared among the adherence categories using the χ^2 test. The data are presented in frequencies, proportions and percentages with their 95% confidence interval (CI).

RESULTS

IPT uptake and characteristics of those commenced on IPT

Over the study period, 301/330 adults with sputum smear-positive TB consented to contact tracing in their households. Altogether 404 children aged <5 years and living in the same household as an adult index case were screened at community level. Of these, 163 symptomatic and/or TST-positive children were referred for further evaluation in the clinic, and 153/163 (94%) attended the appointment. Of this group, 26 (16.9%) were diagnosed with active TB. The remaining 368 children were eligible for IPT and consent was sought from their parent or legal guardian, of whom 25 refused, 14 moved out of the study area after consenting and one child died of a brief febrile illness thought to be malaria in the first month of prophylaxis (Figure 1). Of 328 children initiated on IPT, 50.6% were females; the median age (interquartile range [IQR]) at recruitment was 2.3 years (IQR 1.3–3.4) (Table 1).

Completion of IPT

Of the 328 children commenced on IPT, 318 (96.9%) started within 1 month of the diagnosis of their respective index cases. IPT was administered by the mothers in 92.3% (303/328) of the cases, by the fathers in 2.4% (8/325), and by grandmothers and siblings in 0.9% of cases each.

Eighteen of the 328 children dropped out of IPT, leaving 310 children remaining on prophylaxis at the end of 6 months. There was no difference in the characteristics of those who dropped out and those who completed prophylaxis. A final 255 of the 328 children (77.7%, 95%CI 73.2–82.2) completed the 6 months of IPT with good adherence.

Adherence to treatment

During the study period, 59 040 doses of IPT were dispensed, of which 53 573 (90.7%) were consumed. Based on pill counts, 78.9% (95%CI 74.5–83.2) of all medications were consumed by children with good adherence, 15.4% (95%CI 11.5–19.3) by children with

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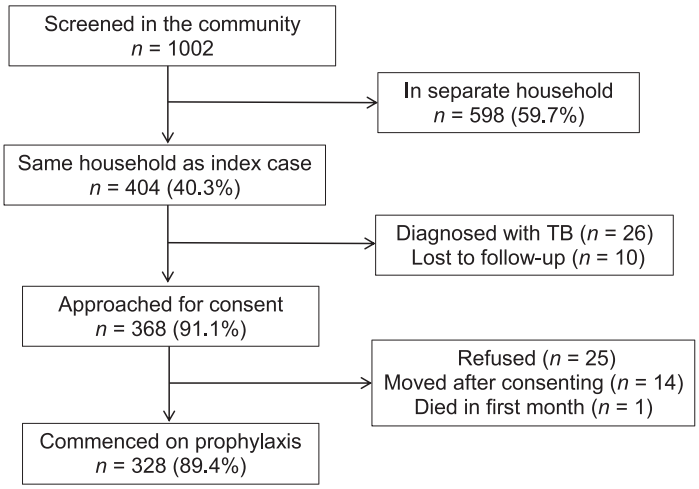

FIGURE 1 Flow chart of screening and recruitment of children on INH prophylaxis. INH = isoniazid; TB = tuberculosis.

reasonable adherence, and 5.6% (95%CI 3.1–8.1) by children with poor adherence. Table 2 shows the monthly adherence of children on IPT as determined by pill count. Less than 10% of children on prophylaxis in any month had poor adherence. Overall, the proportion of children with positive IsoScreen test results was similar to the proportion with good adherence: good adherence by pill count was 77.4% (95%CI 74.2–80.6) compared to 76.6% (95%CI 73.4–79.8) with positive urine test results.

The proportion of children with good adherence remained high, at 76.2% in the first month, and increased gradually over time to 83% in month 6. Spot urine samples were collected from the first 141 children recruited into the study, and 658 episodes of pill counts and urine tests were carried out simultaneously. Among these children, 85.3% (435/510) of all tests among those defined as having good adherence by pill count were positive, compared to 16% (8/50) of tests among those defined as having poor adherence ($P < 0.001$). Over the 6 months of IPT, 80.6–93.3% of those with good adherence by pill count were also positive by IsoScreen, compared to 0–25.0% of those with poor adherence (Table 3). Across the three adherence categories there was a significant trend in IsoScreen positivity ($P < 0.002$) in each month of IPT.

TABLE 1 Characteristics of children placed on INH prophylaxis

Characteristics	*n* (%)
Age at recruitment, years, median [IQR]	2.3 [1.3–3.4]
Weight at recruitment, kg, median [IQR]	11.3 [9–13.3]
Females	167 (50.9)
TST result	
Negative (<10 mm)	265 (80.8)
Ethnicity	
Mandinka	155 (47.3)
Fula	58 (17.7)
Jola	59 (18.0)
Wolof	27 (8.2)
Other	29 (8.8)
Relationship to index case	
Child	108 (33.2)
Sibling	18 (5.5)
Other*	166 (51.1)
Not related	33 (10.2)

*Includes cousin, nephew, niece or other extended family member.
INH = isoniazid; IQR = interquartile range; TST = tuberculin skin test.

Of 314 responses to the adherence questionnaire administered among care givers, 247 (78.7%) stated that the main reason for failure to administer the pills was forgetfulness. The second major reason, given by 30 (9.6%) of the care givers, was travel. Other reasons included the child being sick (11 [3.5%]), refusing medication (7 [2.2%]) and misplacement of the medications (5 [1.6%]).

Side effects

No side effects were reported throughout the study period.

One-year follow-up

Of the 310 children who completed their course of IPT, 12 (3.9%) were lost to follow-up at 1 year after IPT. One child aged 18 months died of a sudden febrile illness not related to INH or TB. One child who dropped out of IPT in the first month developed clinically diagnosed TB by the ninth month of follow-up. All the other children remained well.

Cascade of care summary analysis

To identify where improvements may be needed in the continuum of care of child contacts eligible for IPT, we used a cascade of care approach, as summarised in Figure 2. We estimated uptake and completion of IPT among all eligible children in the households of the 330 adults with TB approached during the study. After excluding 27 children with TB disease (26 diagnosed after clinical evaluation and one estimated from among those who failed to attend the clinic), 418 children remained eligible for IPT, of whom 328 (78.5%) accepted IPT and 255 (61%) completed 6 months of IPT with good adherence.

DISCUSSION

In this study, we implemented and evaluated a home-based IPT programme in The Gambia. Uptake of IPT was high (78%), and 77.7% of all child contacts who initiated IPT completed the 6-month course with good adherence. A further 15.4% had reasonable adherence, and 5.6% had poor adherence. We also found that pill count reliably reflected adherence in this population. The most frequent reason for non-adherence was forgetfulness. The cascade of care analysis showed that approximately 61% of the estimated original number of contacts eligible for IPT completed 6 months of IPT with good adherence, and provides insight into the potential public health impact of the programme.

Adherence is a major determinant of efficacy of IPT.[21] High IPT uptake in The Gambia is encouraging as the country moves to expand these services nationwide. In high TB burden countries, the proportion of those commencing and completing at least 4 months of IPT is approximately 15%,[6,7] and even in research conditions adherence to unsupervised IPT in high-burden countries has been relatively low. Good adherence to IPT was achieved by approximately 24% in South Africa,[4,22] 25.6% in Indonesia[8] and 32.5% in Southern Ethiopia.[9] In contrast, in another research study conducted in Guinea Bissau, West Africa, where IPT was also delivered to the homes of child contacts for 9 months, the proportion achieving good adherence according to pill counts was 76%,[20] similar to our study. Interestingly, when INH was delivered at home to children in Ethiopia, adherence was very poor, with only 33% of children taking their medications for up to 4

TABLE 2 Adherence to INH prophylaxis determined by monthly pill count

Month	Patients on IPT at end of month *(N = 328)* *n*	Good adherence *n* (%)	Reasonable adherence *n* (%)	Poor adherence *n* (%)
1	323	246 (76.2)	49 (15.2)	28 (8.8)
2	316	245 (77.5)	49 (15.5)	22 (6.9)
3	316	245 (77.5)	53 (16.8)	18 (5.7)
4	302	235 (77.8)	51 (16.9)	16 (5.3)
5	311	252 (81.0)	52 (16.7)	7 (2.3)
6	310	259 (83.6)	36 (11.6)	15 (4.8)

INH = isoniazid; ITP = isoniazid preventive therapy.

months.[9] More site-specific research is required to identify the best locally applicable approach to optimise adherence.[23]

The understanding and willingness shown by carers, especially mothers, to administer IPT provides a potential solid base for programmatic home-delivered IPT. As the project is now being transferred to the government programme, the priority is to enable sustained delivery of INH to homes of child contacts. In the current organisation of the health system in The Gambia, community health workers and assistants living within the communities play a major role in public health. It is intended to provide training for this group to deliver IPT—and monitor IPT delivery—to homes of contacts at minimal or no additional cost to the NTP, as they are already involved as TB treatment supporters to the index cases.

The use of IsoScreen enabled us to objectively assess whether pill counts are a reliable way to assess adherence in The Gambia, and we found excellent agreement. Our results should be interpreted with caution, however, as some of the negative test results came from individuals with good adherence by pill count but who had missed doses only in the most recent days. The sensitivity of the IsoScreen test decreases with the passage of time from ingestion of the medication.[24] Similarly, some poorly adherent individuals may have taken IPT prior to their IsoScreen test. As the day for IsoScreen testing was not announced in advance, however, it is unlikely that differential bias was introduced. A negative IsoScreen result has been reported in fast acetylators;[25] we did not assess acetylator status.

In summary, the uptake of and adherence to IPT in our study were high by international standards, suggesting that system rather than patient factors will be the main determinants of success when IPT management is transferred to be fully operational under the NLTP. IPT was highly acceptable to care givers and children in The Gambia, and home delivery will present an opportunity for health education on TB and other topics of public health importance, such as malnutrition, sanitation and oral rehydration. Training of health workers in childhood TB and IPT will be required to ensure success.[26,27] The cascade of care summary showed that there are opportunities for improvement for the IPT programme to have maximal public health impact. Further studies could explore the reasons why some households do not uptake IPT and whether an intervention to reduce care giver forgetfulness, such as cell phone text reminders,[28] could be beneficial.

TABLE 3 Adherence by pill count and urine test result in the IsoScreen™ cohort

Month of prophylaxis*	Adherence category	Patients *N* (%)	Positive IsoScreen *n/N* (%)
1 (*n* = 120)	Good	97 (80.7)	82/97 (85.5)
	Reasonable	11 (9.2)	4/11 (36.4)
	Poor	12 (10.1)	2/12 (16.7)
2 (*n* = 141)	Good	105 (74.5)	90/105 (85.7)
	Reasonable	25 (17.7)	14/25 (56.0)
	Poor	11 (7.8)	1/11 (9.1)
3 (*n* = 134)	Good	103 (76.9)	83/103 (80.6)
	Reasonable	19 (14.2)	12/19 (63.2)
	Poor	12 (8.9)	4/12 (33.3)
4 (*n* = 107)	Good	87 (81.1)	74/87 (85.1)
	Reasonable	14 (13.2)	9/14 (64.3)
	Poor	6 (5.7)	0/6 (0)
5 (*n* = 96)	Good	75 (78.1)	66/75 (88.0)
	Reasonable	16 (16.7)	13/16 (81.3)
	Poor	5 (5.2)	0/5 (0)
6 (*n* = 60)	Good	45 (75)	42/45 (93.3)
	Reasonable	11 (18.3)	8/11 (72.7)
	Poor	4 (6.7)	1/4 (25.0)

*The IsoScreen test was used only during the first 12 months of the study in the same children; the number of children willing to give urine declined substantially despite the dropout rate remaining very low.

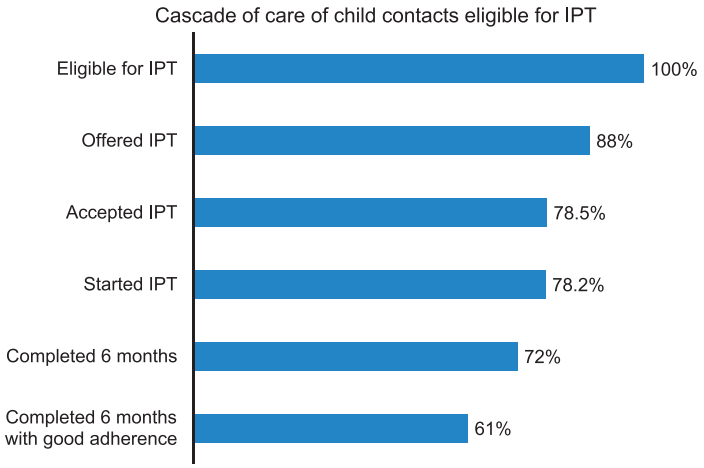

FIGURE 2 Cascade of care of child contacts eligible for IPT. IPT = isoniazid preventive therapy.

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Contexte : Région du Grand Banjul en Gambie.
Objectifs : Evaluer la couverture, l'adhésion et l'achèvement du traitement parmi des enfants exposés à la tuberculose (TB) en Gambie quand le traitement préventif par isoniazide (TPI) est donné à domicile.
Schéma : Les enfants âgés de <5 ans, contacts d'adultes atteints de TB à frottis positif, ont été enrôlés de manière prospective. Après dépistage sur les symptômes, test cutané à la tuberculine et évaluation clinique quand cela était indiqué, les enfants non malades ont été mis sous isoniazide, fourni une fois par mois à domicile. L'adhésion a été évaluée par un comptage des comprimés et par un test urinaire IsoScreen™.
Résultats : Sur 404 contacts âgés de <5 ans, 368 (91,1%) ont été invités à bénéficier du TPI, et 328 (89,4%) ont consenti et commencé le TPI. Sur ces 328 enfants, 18 (5,5%) ont abandonné et 310 (94,5%) sont restés sous TPI jusqu'à la fin du 6e mois. Au total, 255/328 enfants (77,7% ; IC95% 73,2–82,2) ont achevé les 6 mois de traitement avec une bonne adhésion. Le test IsoScreen a été positif chez 85,3% (435/510) de tous les tests parmi ceux définis comme ayant une bonne adhésion par le comptage des comprimés et chez 16% (8/50) de ceux définis comme ayant une adhésion médiocre ($P < 0,001$). L'analyse de la « cascade des soins » a montré, pour tous les enfants contacts, un taux de bonne adhésion d'ensemble de 61%.
Conclusion : L'administration à domicile du TPI à des enfants contacts d'adultes atteints de TB à frottis positif en Gambie a abouti à une bonne couverture et à un bon taux d'adhésion, tous deux vérifiables. Ce sont les facteurs de système plutôt que ceux liés au patient qui sont susceptibles de déterminer le succès du TPI au niveau national.

Marco de referencia: La zona del Gran Banjul en Gambia.
Objetivos: Evaluar la aceptación del tratamiento preventivo con isoniazida (TPI), su cumplimiento y su compleción por parte de los niños expuestos en Gambia, cuando se suministra el tratamiento en los hogares.
Método: Se incluyeron en el estudio de manera prospectiva los niños menores de 5 años de edad que eran contactos de un adulto con diagnóstico de tuberculosis (TB) y baciloscopia positiva. Luego de la detección sistemática a partir de los síntomas, se practicaron la prueba cutánea de la tuberculina y la evaluación clínica cuando estaban indicadas; en caso de ausencia de enfermedad activa se inició el tratamiento diario con isoniazida, la cual se suministraba en el hogar cada mes. Se evaluó el cumplimiento en función del recuento de los comprimidos y la prueba IsoScreen™ en muestras de orina.
Resultados: En los 404 contactos menores de 5 años de edad, se ofreció el TPI a 368 niños (91,1%) y 328 lo aceptaron y comenzaron a recibirlo (89,4%). De este grupo, 18 niños abandonaron el tratamiento (5,5%) y 310 recibían aun el medicamento al final del 6 mes (94,5%). De los 328 niños, 255 terminaron los 6 meses de tratamiento, con un cumplimiento satisfactorio (77,7%; IC del 95% de 73,2 hasta 82,2). La prueba IsoScreen fue positiva en el 85,3% (435/510) de los casos definidos con cumplimiento adecuado según el recuento de comprimidos y en el 16% (8/50) de los casos cuyo cumplimiento se consideró deficiente ($P < 0{,}001$). El análisis de la trayectoria asistencial reveló que en todos los contactos la tasa global de compleción con cumplimiento satisfactorio fue 61%.
Conclusión: El TPI suministrado en el hogar a los niños que son contactos de un adulto con diagnóstico de TB y baciloscopia positiva alcanza altas tasas de aceptación y de cumplimiento que se pueden verificar. Los factores que determinan el éxito del TPI a escala nacional dependen del sistema de salud y no del paciente.

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Statement of contribution

I led a team of clinicians, nurses, field and laboratory staff who participated in the household contact tracing and tuberculin skin testing in the communities, clinical assessment in the clinic, sputum and blood sample collection and processing, administration and management of isoniazid prophylaxis, data management and follow up of the enrolled cohort of children. Specifically, I managed the field and clinical research activities on a day to day basis, conducted clinical examination on all child TB suspects referred from the field, read and interpreted chest X rays and made diagnosis of TB. I took personal responsibility for ruling out TB disease and prescribing isoniazid prophylaxis to eligible children. A junior research clinician, who also stood for me and managed the field and clinic activities when I attended the Modules in Munich, supported my work.

I collected qualitative and quantitative data, worked with the project data manager in cleaning and verification of the datasets, and conducted the analysis under the supervision of Prof Kampmann, Prof Hoelscher, Dr Heinrich and the additional available expertise at the MRC Unit in Epidemiology and data management.

After deciding on the papers to be published from our work with my supervisors, I undertook the analysis of the relevant data wrote up the first draft of the first author papers and managed the process of senior author review and reviewers' comments. I presented parts of my data at local and international conferences, as well as in MRC Unit academic seminars.

Throughout the period of the project, I represented the Childhood TB Program in meetings with the Gambian National TB Program.

10. Acknowledgements

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My gratitude also goes to my direct supervisor, Dr Norbert Heinrich for his invaluable inputs and guidance. He visited and spent sometime with me in the research field and maintained constant communication throughout the period of this PhD. He went the extra mile to liaise on my behalf, on many occasions, with the coordinating team at the CIH, whenever the need arose. He prioritized my research period reports and provided a timely review of manuscripts and the thesis summary. I drew a lot of encouragement from his personal messages to me in time of personal challenges. In the same vein, I thank Prof Michael Hoelscher, my habilitated supervisor, for the solid foundation he laid during the module blocks and for ongoing senior oversight he provided throughout the PhD.

My PhD would have been impossible without the solid support of my colleagues at the MRC Gambia. I thank Dr Abdou K Sillah for competently holding the fort at the Childhood TB program and ensuring the research project went on undisturbed during my module blocks in Munich. He continued to provide invaluable support in the field and clinic. I thank Dr Toyin Togun for his immense support especially in critical appraisal and analysis of data, manuscript critique and review, and for generally being there for me. I thank Dr Uduak Okomo who, apart from contributing to the critique of my research work, also supplied technical assistance with the preparation of various documents i worked with during this PhD, including this thesis summary. My colleague in the TB research platform, Dr Owolabi, was readily available for discussion and solving of various day to day clinic challenges and provided independent opinion on management of concurrent illnesses in the child contacts seen in the clinic.

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Finally, I give thanks to God for being, to me, 'the eye which never sleeps beneath the wings of night; the ear which never shuts when sink the beams of light".

11. Annex

Egere Uzochukwu

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20-Sep-2016

Dear Dr. Uzochukwu Egere

Thank you for sending us the revised version of your article entitled

"Identifying children with tuberculosis among household contacts in The Gambia" (Original Article)

and your reply to the reviewers' comments.

I am pleased to inform you that your manuscript has been accepted for publication in one of the forthcoming issues of the IJTLD, subject to the usual editorial revisions.

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Fellowship of the West African College of Physicians (Paediatrics), University College Hospital, Ibadan, Nigeria

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Social skills and competences

I have gained professional experience in Nigeria, The Gambia and Germany at both practical level in patient management and fieldwork as a Paediatrician and researcher as well as within academic environments of Nigerian Universities, The MRC Gambia, University of Tuebingen, Germany and the University of Otago – a mix of experience in different continents. I have participated in and directed clinical and research work as both junior doctor and senior clinician in these settings. These exposures have provided me the opportunity to develop the ability to interact and work together with people of diverse backgrounds.

List of Publications

Egere U, Togun T, Sillah A K, Mendy F et al: Identifying children with tuberculosis among household contacts in The Gambia. International Journal of Tuberculosis and Lung Disease 21 (1): 46 - 52

Toyin T, Egere U and Beate Kampmann. "Extrapulmonary manifestations of tuberculosis and tuberculosis in immunocompromised children" in European Respiratory Society (ERS) HERMES Handbook, *Paediatric Respiratory Medicine* (2013), Vol. 12; Chapter 8, pp 284-292

Toyin T, Egere U and Kampmann B. "Childhood tuberculosis: new tools and remaining challenges." *Recent Advances in Paediatrics* (2014), Vol 26; Chapter 1, pp 1-10

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Roca A, Hill PC, Townend J, Egere U et al: Effects of community-wide vaccination with PCV-7 on pneumococcal nasopharyngeal carriage in the Gambia: a cluster-randomized trial**.** PLoS Medicine 10/2011; 8(10):e1001107.

Egere U, Sillah A K, Togun T, Cole F et al: Isoniazid preventive treatment among child contacts of adults with smear positive tuberculosis in The Gambia. Public Health Action 2016; 6(4): 226 - 231