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Evaluating UK national guidance for screening of children for TB: a prospective multi-centre study

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Authorship Contributions

BK devised the original idea for the study and obtained its funding. All authors were involved in the development of the study protocol, enrolment of patients and data collection. BK led the data analysis and interpretation of the findings with input from all authors. BK, JAS, SW and JP drafted the first version of the article; all authors contributed to critical review and amendments and approved the final version. BK is the guarantor.

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Evaluating UK national guidance for childhood TB infection

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At a Glance Commentary

What is the current scientific knowledge on this subject?

The safest and most effective strategies for recognition and treatment of TB infection in children remain to be defined, and national recommendations vary between countries.

What does this study add to the field?

In the low prevalence setting of the UK and over a follow up period of 2 years, we saw no incident cases of TB disease in children over the age of two years who had a positive tuberculin skin test (TST) but remained interferon-gamma release assay (IGRA) negative and did not receive treatment for TB infection.

ABSTRACT

Rationale and Objective

In order to identify infected contacts of tuberculosis (TB) cases, the UK National Institute for Health and Care Excellence (NICE) recommended the addition of interferon-gamma release assays (IGRA) to the tuberculin skin test (TST) in its 2006 TB guidelines. Treatment for TB infection was no longer recommended for children screened TST-positive but IGRA-negative. We carried out a cohort study to evaluate the risk of TB disease in this group.

Methods

Children exposed to an infectious case of TB in their household were recruited from 11 paediatric TB clinics. TST and IGRA were carried out at baseline, IGRA repeated at 8 weeks and TST repeated if initially negative. Children were treated according to 2006 NICE guidelines and followed for 24 months.

Measurements and Main Results

Of 431 recruited children 392 completed the study. We diagnosed 48 (12.2%) cases of prevalent TB disease, 105 (26.8%) with TB infection and 239 (60.9%) without TB infection or disease. 18 children aged two years and above had a positive TST but persistently negative IGRA. None received TB infection treatment and none developed TB disease. 90 (26.1%) children qualified for TB infection treatment according to 2006 NICE guidelines. In contrast, 147 (42.7%) children would have qualified under revised NICE guidance, issued in 2016.

Conclusions

In this low prevalence setting we saw no incident cases of TB disease in children who were TST-positive but IGRA-negative and did not receive treatment for TB infection. Following the latest NICE guidance, significantly more children will require medication.

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INTRODUCTION

Latest estimates by the World Health Organization (WHO) suggest that around one million children globally develop tuberculosis (TB) disease every year, and 210,000 die of this potentially preventable and treatable infectious disease.[1] For most children, exposure to TB occurs through an adult in their household. Following exposure about half of household contacts become infected[2] and once infected, the risk of disease progression is highest in the first 12 months.[3] The risk is heavily influenced by the age of the child at the time of infection: the youngest children are at the highest risk.[4] For these reasons, the WHO recommends that treatment of TB infection (also known as preventive therapy, isoniazid preventive therapy or latent tuberculosis treatment) be provided to all children under the age of five years who have recently been exposed to an adult with infectious TB in their household.[5,6] The post-2015 WHO End TB Strategy provides a target to reduce, by 2035, the global TB incidence by 90% compared to current levels.[7] Modelling studies suggest that reductions of this magnitude will not be possible unless cases of TB infection are treated in addition to TB disease.[8,9]

In the UK, the public health services (Public Health England, PHE) and the National Health Service (NHS) function in an integrated fashion: all cases of potentially infectious TB disease are notified to PHE and screened by clinical TB nursing teams, who identify household and other close contacts within NHS facilities. In England, 5,758 cases of tuberculosis were reported in 2015.[10] National policy, for many years, has been that household members of these cases, together with other close contacts, should be screened to identify any additional cases of TB disease, as well as any individuals with TB infection who might benefit from TB infection treatment. However, there has been much debate on which screening tools to use, especially for children.[11-13] In 2006, the National Institute for Health and Care Excellence (NICE) in the United Kingdom (UK) issued guidelines for the screening of those exposed to TB, which, for the first time, introduced interferon-gamma release assays (IGRA), a then novel blood-based assay, into the screening algorithm.[14] Up until that point testing for

evidence of sensitisation to *M. tuberculosis* had been via the tuberculin skin test (TST). Unlike the TST, IGRAs are designed to distinguish between a "false-positive" TST, due to sensitisation by non-pathogenic mycobacteria including due to previous BCG vaccine, and "true" infection with *M. tuberculosis* by using antigens encoded by genes located within the region of difference 1 segment of the *M. tuberculosis* genome in the test,[15,16] leading to somewhat greater specificity.[17] In the 2006 NICE algorithm, IGRA tests were recommended in TST-positive individuals and only those found to be both TST- and IGRA-positive were to receive treatment for TB infection. BCG vaccination history was used to decide on the size of the TST induration that was required to classify the test as positive, therefore directly influencing which children would progress to IGRA testing. This algorithm was applied to all individuals older than 2 years of age, and, as a consequence, children who were found to be TST-positive but IGRA-negative no longer qualified for TB infection treatment. Given the lack of data on the performance of IGRAs in children, paediatricians conducting TB contact investigations in the UK were concerned as to whether this new policy was safe.[18]

In response to these concerns, we set up a multi-centre, multi-site study within the National Health Service (NHS), the **N**IHR-funded **I**GRA **K**ids **S**tudy (NIKS).[19] Our primary objective was to measure incident TB disease in TST-positive but IGRA-negative children over a 2-year follow up period. Our secondary objectives were to ascertain the percentage of children who were TST-negative but IGRA-positive at baseline and who would have been missed by the 2006 NICE screening algorithm, and to determine the proportion of children who converted their TST and/or IGRA from negative to positive between baseline and follow-up at 8 weeks in order to assess the added value of repeat screening. After NIKS completed recruitment but prior to data analysis, the NICE guidance was updated.[20] The 2016 version now recommends treating all children for TB infection if they have a TST result ≥5mm, independent of IGRA results and BCG vaccination history. Given the availability of our substantive dataset, we therefore also evaluated the implications of these latest recommendations for clinical practice.

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METHODS

Study Setting

Between 1st Jan 2011 and 31st Dec 2014, children were recruited from five paediatric TB clinics in London, together with paediatric TB clinics in Southampton, Bristol, Birmingham, Manchester, Glasgow and Newcastle. An identical protocol was used at all sites and children were followed for 24 months. The study was funded by the NIHR and Comprehensive Local Research Network (CLRN) support was provided at the different study sites.

Study procedures

Ethical Approval: The study was approved by the UK National Research Ethics Service (REC: 11/11/11). Parents of all children included in the study provided written informed consent, with additional assent in older children.

Recruitment: In line with national guidelines, all contacts are screened by history for potential TB symptoms or underlying susceptibility to TB, and are then invited for TST and/or IGRA screening. Detailed procedures of recruitment to the NIKS study have previously been described.[19] In brief, parents/guardians of children attending for contact screening were approached for entry into the NIKS study and referred to participating clinics where children were evaluated by the study paediatricians. Evaluations included history, examination, TST and IGRA tests, chest radiography, microbiology and HIV testing where appropriate. The decision to provide treatment for TB infection to contacts with evidence of TB infection was based on the 2006 NICE guidelines for children above the age of 2 years. As we aimed to evaluate the utility of TST and IGRA testing in child contacts, children with a prior history of a positive test of TB infection were not included. *BCG vaccination status:* If a BCG scar was present, children were classified as BCG-vaccinated. If no scar was seen, but there was clear documentation in paper or electronic records, or if the parents gave a clear history of vaccination, the child was classified as BCG-vaccinated. Otherwise the child was classified as BCG-unvaccinated. *Evidence of TB infection:* Both TST and IGRA were carried out simultaneously at the first screening visit. TST was placed

by experienced members of the TB nursing teams, by injecting two tuberculin units (purified protein derivative RT23, Statens Serum Institute) intradermally with results read within 48-72 hours. IGRA tests (either QuantiFERON-TB Gold In-Tube [Quiagen] or T-SPOT.TB [Oxford Immunotec Ltd] were carried out in clinical laboratories of the respective NHS Trusts, following routine practice in the Healthcare Trust and the relevant manufacturers' instructions for processing. IGRA testing was repeated in all children after 8 weeks, as was TST if initially negative. IGRA results were interpreted as positive, negative or indeterminate in line with the standard clinical laboratory reporting practice. A child was classified as IGRA-positive (classified as TB infected) if either the baseline or the 8-week IGRA were positive and there was no evidence of TB disease. All children with a negative IGRA at both timepoints were classified as TB exposed but uninfected. An IGRA which was indeterminate twice would also be assigned as negative, and the child classified as TB exposed but uninfected. TST was defined as positive if the transverse diameter of the induration was ≥6 mm in BCG-unvaccinated children and ≥15mm in previously vaccinated children, as per 2006 NICE guidance. TST conversion was defined, in BCG-vaccinated children, as a TST induration at 6-8 weeks of ≥15mm with an increase from baseline of >5mm; in BCG-unvaccinated children it was defined as a TST induration at 6-8 weeks of ≥6mm with an increase from baseline of >5mm. The differences between the 2006 NICE guidance, the NIKS protocol and the 2016 NICE guidance are summarised in the supplementary table 1.

Statistical analysis:

Data were entered into a secure online database in real-time and later checked centrally for entry errors. Data were analysed using STATA software (version 11; Stata Corp, College Station, TX). Missing data were excluded from analysis.

Clinical Management

Children with confirmed or clinically-diagnosed TB disease were managed according to standard treatment protocols.[21] All children younger than 1 year of age at the time of enrolment, found to not have TB disease, were offered three months of isoniazid and rifampicin, independent of BCG vaccination status or

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TST/IGRA results. All children aged between one and two years, were commenced, once TB disease had been excluded, on isoniazid and rifampicin, with medication stopped if they remained negative on repeat testing of both TST and IGRA after 6-8 weeks. If either of these tests became positive, they were re-evaluated clinically to exclude TB diseases, and completed three months of TB infection treatment. Children older than 2 years with evidence of TB infection as determined by a positive IGRA test were given treatment for TB infection with three months of isoniazid and rifampicin. Following the completion of baseline and 8 week screenings, all children identified as TB exposed but with persistently negative TST and IGRA were offered BCG vaccination, if not previously immunised. All children were observed for 24 months with 3-monthly appointments in year 1 and 6 monthly in year two.

Outcome Definitions

In the study protocol, prevalent TB was defined as TB disease diagnosed at the time of screening or within the subsequent 8 weeks. Incident TB was defined as TB disease diagnosed, in a child TB disease-free at baseline, at any time after the 8 week during the 2-year follow up. TB infection was defined by IGRA positivity in the absence of TB disease. Children without evidence of TB infection or disease were classified as TB exposed but uninfected.

RESULTS

In total, we enrolled 431 children; 357 (83%) were >2 years. Cohort details are summarised in **Table 1**. Data from 39 children were subsequently excluded as 32 withdrew after their first visit, 4 had a change of diagnosis and 3 were treated with isoniazid and rifampicin outside of the agreed protocol. All outcome measures reported subsequently therefore relate to the 392 children who completed the study. Demographic details of the children who withdrew were not significantly different from those who completed the study, and there were no significant differences in the clinic populations in potentially confounding parameters such as age and sex. We diagnosed 48 cases of prevalent TB disease (12.2%), 105 children with evidence of TB infection (26.7%) and 239 children

(60.9%) without any evidence of TB infection or disease. There were no cases of incident TB during the follow-up period. Of the 48 children with prevalent TB disease, all were diagnosed with pulmonary TB within the first 8 weeks of assessment; 33 (68.7%) had samples sent for microbiological testing with confirmation of *M. tuberculosis* in 13/33 (39.4%). The remaining 35 (72.9%) were diagnosed with TB disease on clinical criteria alone. **Table 2** summarises the baseline characteristics of the study participants, categorised according to final outcome. The management of the 239 children classified as TB exposed but not infected is indicated in **Table 3**.

Of 344 children without prevalent TB, 251 (72.9%) were IGRA-negative at baseline, 80 IGRA-positive (23.2%) and 13 (3.8%) had indeterminate results **(Figure 1).** In comparison, 249 were TST-negative (72.3%) and 95 were TST-positive (27.6%). Overall, IGRA and TST results were concordant in 287 of 344 children (83.4%). At baseline, 28 (29.5%) children were TST-positive and IGRA-negative, and 16 (6.4%) children were IGRA-positive and TST-negative **(Table 4).** Follow-up was undertaken at 8 weeks, and 311 of the 344 (90.4%) children had a repeat IGRA. The missing IGRA tests were primarily in the group of children already found to be IGRA positive at baseline. Of these 311 children, 273 (87.7%) did not show any differences in IGRA status between baseline and 8 weeks. A change from negative to positive was found in 18 (5.7%) children re-tested and from indeterminate to positive in 7 (2.2%). A change from positive to negative was noted in 8 (2.5%), and from indeterminate to negative in a further 6 (1.9%). The rate of indeterminate IGRA results was 3.8% (13/344) at baseline and 2.9% (9/311) at 8 weeks. Only one child had an indeterminate IGRA twice.

In line with the study protocol, TST was only repeated in children with a negative baseline TST; of 249 eligible children, 239 (96.0%) underwent the repeat procedure, with 25 (10.4%) found to have converted their TST to positive 8 weeks later. Ten (40%) of this group of children also converted their IGRA result from negative to positive. 28 children were TST-positive but IGRA-negative at baseline and 18 remained IGRA-negative on repeat screening; the remainder becoming IGRA-positive. Of these 18, three fell into the under-2 years of age

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category and were given isoniazid and rifampicin (either for the full 3 months, if under 1 year, or until re-testing, if between 1 and 2 years), hence their outcome data could not be included in the primary analysis. The other 15 did not receive any treatment and none developed TB disease during the 2 years of follow-up. In 16 of 249 children (6.4%), the baseline IGRA was positive while the TST was negative. 10 of these children received a second TST, of whom 5 had converted from negative to positive on repeat screening 8 weeks later.

Applying the 2006 NICE guidance algorithm, 90 (26.1%) children qualified for treatment of TB infection on the basis of their TST and subsequent IGRA results. Using the 2016 NICE guidance, 147 (42.7%) children would have been prescribed treatment for TB infection, based on their TST result. This represents a 63% increase. 52 (35.3%) of the 147 children in this group would have tested IGRA-negative. In the group with positive IGRA but a TST defined as negative, 12 out of 16 (75%) would have qualified for treatment of TB infection according to 2016 NICE guidance. However, 4/16 (25%) would still have remained undetected, as they were IGRA-positive with a TST below 5mm.

DISCUSSION

Our study set out to measure incident TB disease in TST-positive but IGRA-negative children who had documented exposure to a household contact with infectious TB, in order to estimate the negative predictive value of IGRA for the development of TB, following the 2006 NICE guidance. We also examine concordance between TST and IGRA in the low prevalence setting of the UK.
We enrolled the largest, prospectively recruited cohort of TB-exposed children in the UK to date. In comparison to other studies of IGRA testing in young children, we encountered a low rate of indeterminate results.[13,22] In this low prevalence setting, and over 24 months of follow up, we saw no incident cases of TB disease in 18 children older than two years who were TST-positive but remained IGRA negative and did not receive treatment. A large proportion of exposed children remained uninfected in our study, with only a small percentage of children being

TST positive but IGRA negative. This is in contrast to other studies reported in the literature, where the proportion of children found to have TB infection following household exposure has been described as anywhere between 16 and 76 percent, depending on criteria and TST cut-off used.[2] We believe that despite the size of the cohort, we ultimately had insufficient power to definitively answer the primary study question, given that we had a much smaller than anticipated cohort of children with a positive TST but negative IGRA, which was further reduced by employing a second IGRA screening assay.

Our results do not fully reflect the reality of screening procedures within national TB guidelines, where TST and IGRA are not usually used simultaneously. We deliberately chose this study design in order to assess the level of concordance between the two screening tests and to measure any potential "missed opportunities" where a step-wise approach of TST first, followed by IGRA (if TST-positive) was employed. Conducting IGRA and TST at the same time therefore enabled us to assess how many IGRA-positive children would have been missed if only those with a positive TST received a subsequent IGRA. At baseline screening, this result was 6.4 %, but with repeat screening, half of this group had converted their IGRA and therefore would have qualified for treatment of TB infection ultimately. Our data show high concordance between TST and IGRA and, importantly, that on repeat testing the majority of children who converted their TST also converted their IGRA. The value of contact tracing in TB-exposed children was confirmed by the high yield of prevalent TB disease at the time of contact investigations: 12.2% of child contacts were diagnosed with TB disease. This is also in the context of a very strict definition of prevalent TB. Other studies have used a longer time interval to define prevalent TB disease. The study by Anger and colleagues, similarly demonstrated the importance of contact investigation as an active case finding activity, though they used a longer time interval with to define prevalent cases with contacts diagnosed with TB disease as late as 9 months after the index case. [23]

Our study has some limitations. Since TB infection treatment is nationally recommended for children under the age of two years exposed to an infectious

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case of TB, it would not have been appropriate to withhold such an intervention. The positive predictive value of IGRA for progression to TB disease cannot be established in our cohort, given its size, nor has it been conclusively demonstrated for children, who have generally been excluded from studies evaluating IGRA to predict disease progression or represented only a very small proportion of participant.[24,25] Given our protocol, we identified a higher proportion of children who qualified for TB infection treatment than the 2006 NICE algorithm would have determined. We therefore may have prevented some of the incident cases than might have occurred otherwise. Additionally, we cannot comment on the negative predictive value of IGRA in children under the age of two years, as we uniformly gave TB infection treatment to this group, given their acknowledged vulnerability. However, these children only represented 10% of the cohort.

In January 2016, the NICE guidance for TB screening was revised and it was recommended that a history of BCG vaccination should no longer be taken into account in the interpretation of the TST result.[20] Despite certain operational advantages for the use of IGRA, such as no need for return to the clinic if the result is negative, the cost effectiveness evaluation in the UK now favours the use of TST in its last version of the national guidance. A lower universal cut-off of 5mm was introduced to define TST-positivity; any child with a TST equal to or greater than 5mm should now receive treatment for TB infection. IGRA testing was left to the discretion of the treating health care professionals. Applying this new guidance to the data from our cohort, 63% more children would have qualified for treatment, a significant increase in the need for medication and use of NHS resources, including TB nurse time. All of these additional children would have been IGRA-negative. Only four children in our cohort were IGRA-positive with a TST result below 5 mm and these would not have been picked up by the 2016 screening algorithm. Of 344 children in a low prevalence setting, this represents a relatively small at-risk group.

The WHO End TB Strategy aims for effective TB elimination and places a significant emphasis on the treatment of TB infection in addition to TB disease.[7]

Children, following household exposure, are at very high risk for TB infection and subsequent disease progression. They have been identified as a group that should be at high priority for evaluation and TB infection treatment [5] and the latest Stop TB plan for elimination of tuberculosis places particular emphasis on treatment of latent infection in children. The WHO currently recommends that following exposure to an infectious TB case all children under five years should be offered treatment for TB infection without any immune-based screening tests.[26] If TST is to be used, WHO advises a 10mm cut-off. In the UK, TB infection treatment is now offered to all individuals with evidence of TB infection up to the age of 65 years. The current NICE guideline does not distinguish between the management of adults and children, with the same protocol used for both groups. This is probably with the aim of facilitating the programmatic delivery of TB care. Whilst the previous NICE guidance was deemed over-complicated with its use of different TST cut-offs in BCG-vaccinated and -unvaccinated individuals, the revised version simplifies the approach significantly. Previously published data from the NIKS cohort showed the age-related impact of BCG vaccination on TST interpretation, with a cut off of 10 mm increasing specificity after the age of two years.[19] It could be argued that by introducing a 5mm TST cut-off, the use of IGRA testing is now obsolete. We might therefore have come full circle after years of discussing the merits of a more specific test for TB infection. However, an additional and ongoing challenge has arisen due to the limited availability of tuberculin internationally, and as a consequence many hospital trusts are currently using IGRA, despite NICE guidance.[27]

The current UK screening practice in otherwise well children with household exposure relies exclusively on TST, with a smaller cut-off than advised by other international guidance. This has the advantage of being a sensitive and straightforward approach from a screening program perspective, but it leads to increased numbers of children being treated, likely some unnecessarily. Recent guidance from the United States has moved towards an approach based almost entirely on the use of IGRA rather than TST.[27] Despite the somewhat limited study size, our data suggest a high reliability of IGRA testing in children above the age of two years. No screening test perfectly predicts risk of progression to disease, and it is important to invest effort in

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retention in screening and treatment programs as well as optimising the screening test. A pragmatic recommendation, supported by our data, would be simply to treat all children under the age of 2 for TB infection, following household exposure, once TB disease has been excluded. In children older than 2 who are otherwise healthy, our data support using IGRA without TST for screening, with treatment for TB infection restricted to those who have tested positive on IGRA alone.

In conclusion, in this low prevalence setting we saw no incident cases of TB disease in children above the age of two years who were TST-positive but IGRA-negative and did not receive treatment for TB infection. Following the latest NICE guidance, significantly more children will require medication.

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TABLES

Table 1: Demographic details and recruitment sites for children in contact with an infectious case of tuberculosis

Characteristic		***n***	***(%)***
Total		431	100
Age (median, IQR)		6 (2.5-11)	
Age (years)	**<1**	42	9.7
	1-2	32	7.4
	above 2	357	82.8
Gender	**Male**	224	51.9
	Female	207	48.1
Ethnicity	**White**	105	24.3
	Indian	59	13.7
	Pakistani	84	19.5
	Bangladeshi	40	9.3
	Black-Caribbean	3	0.7
	Black-African	91	21.1
	Black-Other	10	2.3
	Chinese	1	0.2
	Mixed / Other	38	8.8
Place of birth	**UK**	353	81.9
	Born abroad	78	18.1
Recruitment Site	**Barts, London**	39	9.0
	Birmingham	77	17.9
	Bristol	30	7.0
	Evelina, London	16	3.7
	Newcastle	74	17.2
	Newham	61	14.1
	Northwick Park, London	53	12.3
	Southampton	16	3.7
	St. Mary's, London	20	4.6

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	Manchester/ Royal Oldham	6	1.4
	Yorkhill, Glasgow	39	9.0

IQR=interquartile range

Table 2: Demographic data, TST and IGRA results of the study participants at baseline screening. Participants are classified according to final outcome category.

		All included contacts (N=, %)	**prevalent TB disease (N=, %)**	**TB Infection (N=, %)**	**TB-exposed and uninfected (N=, %)**
Total according to final outcome		392 *(100)*	48 *(12.2)*	105 *(26.8)*	239*(60.9)*
Age in years (median, IQR)		6 (2.5-11)	4.5 (2-12)	8 (5-11)	5 (2-10)
	<1	39 *(9.9)*	3 *(6.2)*	4 *(3.8)*	32 *(13.4)*
	1-2	31*(7.9)*	5 *(10.4)*	2 *(1.9)*	24 *(10.0)*
	>2	322 *(82.1)*	40 *(83.3)*	99 *(94.2)*	183 *(76.6)*
Gender	**Male**	200 *(51.0)*	25 *(52.0)*	51 *(48.6)*	124 *(51.9)*
	Female	192 *(49.0)*	23 *(48.0)*	54 *(51.4)*	115 *(48.1)*
Born in the UK		320 *(81.7)*	36 *(75.0)*	82 *(78.0)*	202 *(84.5)*
Born abroad		72 *(18.3)*	12 *(25.0)*	23 *(21.9)*	37 *(15.5)*
Previously BCG vaccinated		281 *(71.6)*	29 *(60.4)*	69 *(65.7)*	183 (75.7)
TST	**positive**	131 *(33.4)*	36 *(75.0)*	74 *(70.4)*	21(8.8)
	negative	261 *(66.6)*	12 *(25.0)*	31 *(29.5)*	218 *(91.2)*
IGRA	**Positive**	120 *(30.6)*	40 *(83.3)*	80 *(76.1)*	0 *(0)*
	Negative	258 *(65.8)*	7 *(14.6)*	21 *(20.0)*	230 *(96.2)*
	Indeterminate	14 *(3.6)*	1 *(2.1)*	4 *(3.9)*	9 *(3.8)*

TB: tuberculosis; IGRA: interferon-gamma release assay; TST: tuberculin skin test; IQR: interquartile range

Table 3: Clinical management of uninfected children that were exposed to TB

Management	Number (%)
Total number of TB exposed, uninfected	239 (100)
Preventive Therapy, no BCG given	47 (19.7)
Preventive Therapy, BCG given	15 (6.3)
No preventive therapy required, BCG given	20 (8.4)
No preventive therapy required, no BCG given	157 (65.6)

BCG: Bacillus Calmette–Guérin

Table 4: Concordance of TST and IGRA results in children evaluated as household contacts at baseline screening (cases of prevalent TB excluded)

	IGRA positive (n=80)	IGRA negative (n=251)	IGRA indeterminate (n=13)
TST positive (n=95)	64 *(67.4)*	28 *(29.5)*	3 *(3.1)*
TST negative (n=249)	16 *(6.4%)*	223 *(89.5)*	10 *(4.01)*

TST: tuberculin skin test; IGRA: interferon-gamma release assay

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Figure 1: Study design flow diagram

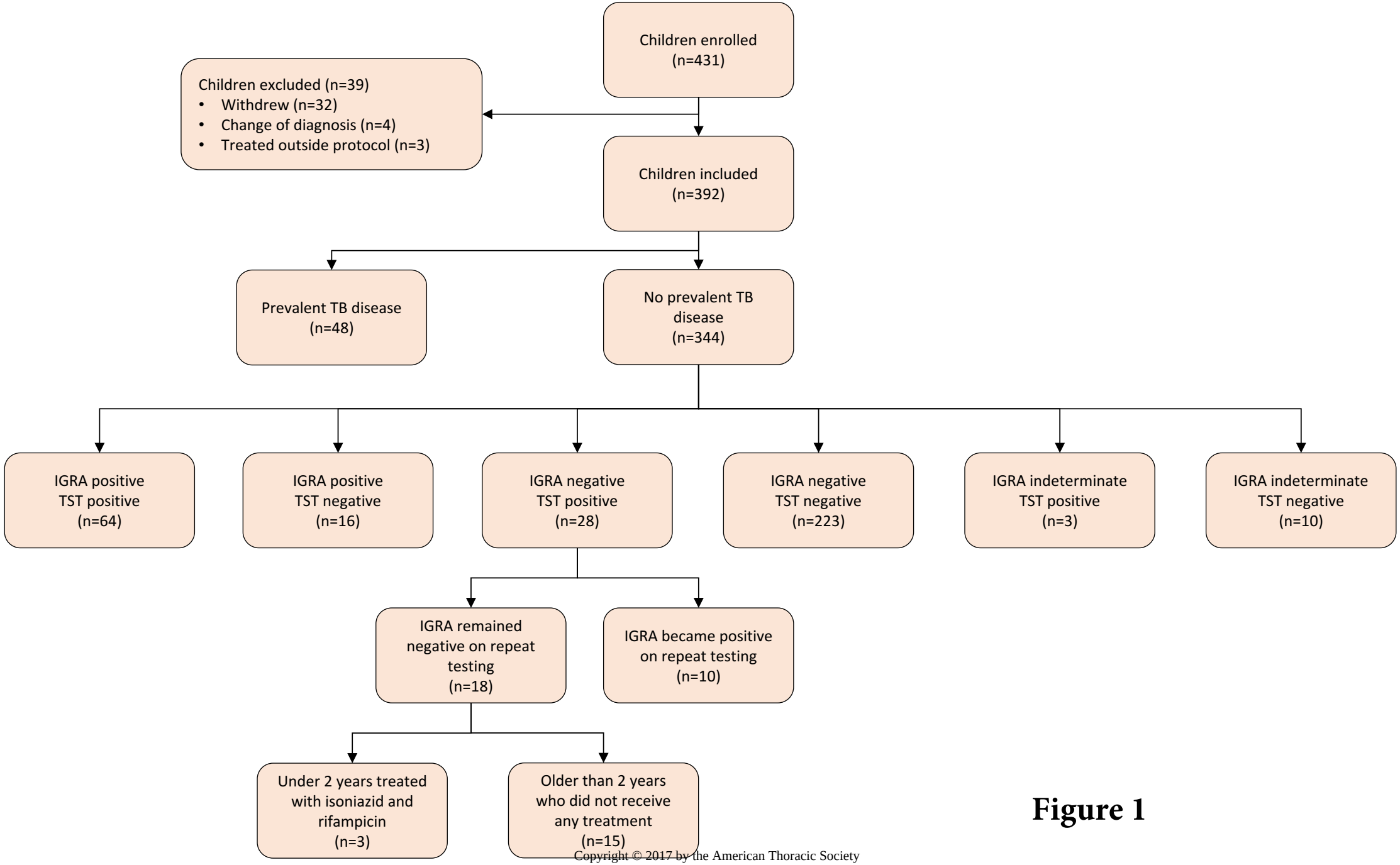

Figure 1

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SUPPLEMENTARY MATERIAL

Supplementary Table E1: Comparison of Nice guidelines 2006, 2016 and the NIKS study protocol overall (a) and by age-specific criteria (b), (c), (d)

E1a

Age-specific range	Protocol component	NICE 2006	NIKS Study Protocol	NICE 2016
All children except where specified.	Thresholds for TST	If BCG vaccinated, positive TST if ≥15mm If BCG unvaccinated, positive TST if ≥6mm		Positive TST if ≥5mm, independent of BCG status
	Index case definition	Smear positive pulmonary TB for contacts who are under 2 years of age. Active TB for paediatric contacts over 2 years of age.	Smear- and/or culture-positive pulmonary TB contact in either the same household or within other members of the family in direct social contact	Smear-positive pulmonary or laryngeal TB who have not had at least 2 weeks of anti-TB treatment If <2 years and index case smear negative refer to specialist.
	Clinical evaluation	At any point if symptomatic, TST positive, or IGRA positive, assess for active TB prior to decision to treat for latent TB infection		
	Regimen if treating for latent TB infection	6/12 INH or 3/12 INH/RIF	3/12 INH/RIF	3/12 INH/RIF (with pyridoxine) or 6/12 INH (with pyridoxine)

E1b

Age-specific range	Protocol component	NICE 2006		NIKS Study Protocol	NICE 2016
1 month to 12 months	Tests for latent TB infection	If BCG vaccinated	If not BCG vaccinated	Baseline: TST & IGRA 6-8 weeks: repeat TST and/or IGRA if initially negative (negative as defined per NICE 2006)	Baseline TST If baseline TST is negative (<5 mm), repeat TST at 6 weeks: if repeat TST is negative, consider IGRA.
		Baseline TST If baseline TST<15mm repeat after 6 weeks. If at 6 weeks TST≥15mm and has increased from baseline induration by >5mm, do IGRA.	Baseline TST If baseline TST<6mm repeat after 6 weeks. If at 6 weeks, TST≥6mm and has increased from baseline induration by >5mm, do IGRA.		
	Management	If BCG vaccinated	If not BCG vaccinated	All receive full treatment for latent TB infection. If 6-8 week TST-/IGRA-, BCG vaccinate (if no record) and discharge from follow-up after completion of treatment for latent TB infection.	Initiate treatment for latent TB in all. If baseline & 6 week TST and IGRA are negative, stop treatment for latent TB and give BCG vaccine if not given before. If baseline TST is positive complete treatment for latent TB. If baseline TST negative, but either 6 week TST or IGRA positive, complete treatment for latent TB.
		TST <15 mm at baseline and 6 weeks, discharge (no medication) If IGRA indicated and negative, discharge at 6 weeks. If IGRA indicated and positive, treat for latent TB infection	If BCG unvaccinated, start INH 5mg/kg and do TST. If≥6mm, complete 6/12 INH or 3/12 INH/RIF. If TST<6mm, continue INH and repeat TST at 6 weeks. If baseline and 6 week TST both negative, or 6 week IGRA indicated and negative, stop INH at 6 weeks and BCG vaccinate. If IGRA indicated and positive, treat for latent TB infection		

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E1c

Age-specific range	Protocol component	NICE 2006		NIKS Study Protocol	NICE 2016
1-2 years	Tests for latent TB infection	If BCG vaccinated Baseline TST If baseline TST<15mm repeat after 6 weeks. If at 6 weeks TST≥15mm and has increased from baseline induration by >5mm, do IGRA.	If not BCG vaccinated Baseline TST If baseline TST<6mm repeat after 6 weeks. If at 6 weeks, TST≥6mm and has increased from baseline induration by >5mm, do IGRA.	Baseline: TST & IGRA 6-8 weeks: repeat TST and/or IGRA if initially negative	Baseline TST If baseline TST is negative, repeat TST at 6 weeks: if repeat TST is negative, consider IGRA.
	Management	If BCG vaccinated TST <15 mm at baseline and 6 weeks, discharge (no medication) If IGRA indicated and negative, discharge at 6 weeks. If IGRA indicated and positive, treat for latent TB infection	If not BCG vaccinated If BCG unvaccinated, start INH 5mg/kg and do TST. If≥6mm, complete 6/12 INH or 3/12 INH/RIF. If TST<6mm, continue INH and repeat TST at 6 weeks. If baseline and 6 week TST both negative, or 6 week IGRA indicated and negative, stop INH at 6 weeks and BCG vaccinate. If IGRA indicated and positive, treat for latent TB infection	Initiate treatment for latent TB in all. If IGRA-/TST- or IGRA-/TST+ at 6-8 weeks, stop medication, BCG vaccinate (if no record). If IGRA+/TST+ or IGRA+/TST-, complete 3/12 INH/RIF (no BCG vaccine).	Initiate treatment for latent TB in all. If baseline & 6 week TST and IGRA are negative, stop treatment for latent TB and give BCG vaccine if not given before. If baseline TST is positive complete treatment for latent TB. If baseline TST negative, but either 6 week TST or IGRA positive, complete treatment for latent TB.

E1d

<table>
<tr><th>Age-specific range</th><th>Protocol component</th><th colspan="4">NICE 2006</th><th>NIKS Study Protocol</th><th>NICE 2016</th></tr>
<tr><td rowspan="4">>2 years</td><td rowspan="3">Tests for latent TB infection</td><td>If BCG vaccinated</td><td colspan="3">If not BCG vaccinated</td><td rowspan="3">Baseline: TST & IGRA
6-8 weeks: repeat TST and/or IGRA if initially negative</td><td rowspan="3">Baseline TST

If baseline TST negative (<5 mm), repeat TST and IGRA at 6 weeks.</td></tr>
<tr><td rowspan="2">Baseline TST
If TST≥15mm then baseline IGRA.</td><td>Baseline TST ≥6mm</td><td colspan="2">Baseline TST<6mm</td></tr>
<tr><td></td><td>If contact smear positive</td><td>If contact smear negative</td></tr>
<tr><td>Perform baseline IGRA.</td><td>Perform IGRA after 6 weeks.</td><td>No IGRA</td></tr>
<tr><td>Management</td><td>If BCG vaccinated</td><td colspan="3">If not BCG vaccinated</td><td rowspan="2">If IGRA+/TST+ or IGRA+/TST- at any point treat for latent infection.

If IGRA-/TST- BCG vaccinate (if no record) and discharge at 6-8 weeks without medication.

If IGRA-/TST+ follow up as per study protocol and finally discharge without medication or BCG vaccination.</td><td rowspan="2">If TST is positive (≥5mm), offer treatment for latent TB infection.</td></tr>
<tr><td>If TST positive & IGRA positive, with CXR + clinical exam not suggestive of active TB, treat for TB infection.

If initial TST negative, or TST positive but IGRA negative, inform and advise and discharge.

If TST<15mm, discharge</td><td>If IGRA negative, discharge.

If IGRA positive, treat for TB infection.</td><td>If IGRA negative, give BCG if not previously given and discharge.

If IGRA positive, treat for TB infection.</td><td>Give BCG if not previously given and discharge.</td></tr>
</table>