Evaluating UK National Guidance for Screening of Children for Tuberculosis

A Prospective Multicenter Study

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Abstract

Rationale: To identify infected contacts of tuberculosis (TB) cases, the UK National Institute for Health and Care Excellence (NICE) recommended the addition of IFN- γ release assays (IGRA) to the tuberculin skin test (TST) in its 2006 TB guidelines. Treatment for TB infection was no longer recommended for children who screened TST-positive but IGRA-negative.

Objectives: We performed 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 pediatric TB clinics. TST and IGRA were performed at baseline, with 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. Eighteen children aged 2 years and above had a positive TST but persistently negative IGRA. None received TB infection treatment and none developed TB disease. Ninety (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.

Keywords: childhood tuberculosis; diagnosis of tuberculosis infection; IFN- γ release assays

(Received in original form July 23, 2017; accepted in final form November 30, 2017)

Supported by a National Institute for Health Research (NIHR) Senior Research Fellowship (NIHR/SRF-2009-02-07) (B.K.). J.A.S. was supported by an NIHR Academic Clinical Lectureship and grants from the Academy of Medical Sciences and the Biomedical Research Centre. The research and D.K. were supported by the NIHR Biomedical Research Centre based at Imperial College Healthcare National Health Service Trust and Imperial College London. The funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Author Contributions: B.K. devised the original idea for the study and obtained its funding. All authors were involved in the development of the study protocol, enrollment of patients, and data collection. B.K. led the data analysis and interpreted the findings with input from all authors. B.K., J.A.S., S.B.W., and J.P. drafted the first version of the article. All authors contributed to critical review and amendments and approved the final version. B.K. is the guarantor.

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This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Am J Respir Crit Care Med Vol 197, Iss 8, pp 1058–1064, Apr 15, 2018

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Originally Published in Press as DOI: 10.1164/rccm.201707-1487OC on November 30, 2017

Internet address: www.atsjournals.org

At a Glance Commentary

Scientific Knowledge on the

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

What This Study Adds to the

Field: In the low-prevalence setting of the United Kingdom and over a follow-up period of 2 years, we saw no incident cases of TB disease in children over the age of 2 years who had a positive tuberculin skin test but remained IFN- γ release assay-negative and did not receive treatment for TB infection.

The 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. After exposure, about half of household contacts become infected (2); 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 5 years who have recently been exposed to an adult with infectious TB in their household (5, 6). The WHO End TB Strategy that was created after 2015 provides a target to reduce, by 2035, the global TB incidence by 90% compared with current levels (7). Modeling 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 United Kingdom, the public health services (Public Health England) and the National Health Service (NHS) function in an integrated fashion: all cases of potentially infectious TB disease are notified to Public Health England 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 issued guidelines for the screening of those exposed to TB, which, for the first time, introduced IFN- γ release assays (IGRA), a then-novel blood-based assay, into the screening algorithm (14). Up until that point, testing for evidence of sensitization 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 sensitization by nonpathogenic mycobacteria including due to a previous bacillus Calmette-Guérin (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 for 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, pediatricians conducting TB contact investigations in the United Kingdom were concerned as to whether this new policy was safe (18).

In response to these concerns, we set up a multicenter, multisite study within the NHS, the National Institute for Health Research (NIHR)-funded IGRA Kids Study (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 to assess the added value of repeat screening. After NIKS completed recruitment but before 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 ≥ 5 mm, 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.

Methods

Study Setting

Between January 1, 2011, and December 31, 2014, children were recruited from five pediatric TB clinics in London, together with pediatric 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 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 from 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 pediatricians. Evaluations included history, examination, TST and IGRA tests, chest radiography, microbiology, and HIV testing when 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 performed 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 performed in clinical laboratories at 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 the 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 infected with TB) 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 time points were classified as TB exposed but uninfected. An IGRA that was indeterminate on two occasions would also be assigned as negative, and the child would be 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 ≥ 15 mm 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 ≥ 15 mm with an increase from baseline of > 5 mm; in BCG-unvaccinated children it was defined as a TST induration at 6–8 weeks of ≥ 6 mm with an increase from baseline of > 5 mm. The differences between the 2006 NICE guidance, the NIKS protocol, and the 2016 NICE guidance are summarized in Table E1 of the online supplement.

Statistical Analysis

Data were entered into a secure online database in real time and later checked centrally for entry errors. Data were analyzed by using STATA Software (version 11; Stata Corp.). 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 enrollment, found to not have TB disease, were offered 3 months of isoniazid and rifampicin, independent of BCG vaccination status or TST/IGRA results. Once TB disease had been excluded, all children aged between 1 and 2 years received 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 reevaluated clinically to exclude TB diseases, and completed 3 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 3 months of isoniazid and rifampicin. After the completion of baseline and 8-week screenings, all children identified as TB exposed but with persistently negative TST and IGRA results were offered BCG vaccination, if not previously immunized. All children were observed for 24 months with an appointment every 3 months in Year 1 and every 6 months in Year 2.

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 weeks 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 older than 2 years. Cohort details are summarized in Table 1. Data from 39 children were subsequently excluded because 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

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), yr	6 (2.5–11)
Age	
<1 yr	42 (9.7)
1–2 yr	32 (7.4)
>2 yr	357 (82.8)
Sex	
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	
United Kingdom	353 (81.9)
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)
Manchester/Royal Oldham	6 (1.4)
Yorkhill, Glasgow	39 (9.0)

Definition of abbreviation: IQR = interquartile range.

^{*}Unless otherwise indicated.

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, pulmonary TB was diagnosed for all within the first 8 weeks of assessment; 33 (68.7%) had samples sent for microbiological testing with confirmation of *M. tuberculosis* in 13 out of 33 (39.4%). TB was diagnosed in the remaining 35 (72.9%) on clinical criteria alone. Table 2 summarizes the baseline characteristics of the study participants, categorized 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 were 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 who were retested, and 7 (2.2%) children had their result change from indeterminate to positive. 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

Table 2. Demographic Data and TST and IGRA Results of the Study Participants at Baseline Screening

	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, median (IQR), yr	6 (2.5–11)	4.5 (2–12)	8 (5–11)	5 (2–10)
Age				
<1 yr	39 (9.9)	3 (6.2)	4 (3.8)	32 (13.4)
1–2 yr	31 (7.9)	5 (10.4)	2 (1.9)	24 (10.0)
>2 yr	322 (82.1)	40 (83.3)	99 (94.2)	183 (76.6)
Sex				
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)
Place of birth				
United Kingdom	320 (81.7)	36 (75.0)	82 (78.0)	202 (84.5)
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)

Definition of abbreviations: BCG = bacillus Calmette-Guérin; IQR = interquartile range; IGRA = IFN- γ release assay; TB = tuberculosis; TST = tuberculin skin test.

Participants are classified according to final outcome category.

*Unless otherwise indicated.

converted their TST to positive 8 weeks later. Ten (40%) from this group of children also converted their IGRA result from negative to positive. Twenty-eight children were TST-positive but IGRA-negative at baseline, and 18 remained IGRA-negative on repeat screening; the remainder became IGRA-positive. Of these 18, three fell into the under-2-years-of-age category and were given isoniazid and rifampicin (either for the full 3 mo, if under 1 yr, or until retesting, if between 1 and 2 yr); 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, whereas the TST was negative. Ten 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. Of the 147 children in this group, 52 (35.3%) 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 out of 16 (25%) would still have remained undetected, as they were IGRA-positive with a TST below 5 mm.

Table 3. Clinical Management of Uninfected Children Who Were Exposed to TB

Management	n (%)
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)

Definition of abbreviations: BCG = bacillus Calmette-Guérin; TB = tuberculosis.

Figure 1. Study design flow diagram. IGRA = IFN- γ release assay; TB = tuberculosis; TST = tuberculin skin test.

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, and 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 United Kingdom.

We enrolled the largest, prospectively recruited cohort of TB-exposed children in the United Kingdom 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 2 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 after household exposure has been described as anywhere between 16% and 76%, depending on criteria and TST cutoff 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.

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 (%)]	IGRA-Negative [n (%)]	IGRA-Indeterminate [n (%)]
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)

Definition of abbreviations: IGRA = IFN- γ release assay; TB = tuberculosis; TST = tuberculin skin test.

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 to assess the level of concordance between the two screening tests and to measure any potential “missed opportunities” where a stepwise 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: TB was diagnosed in 12.2% of child contacts. 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 to define prevalent cases with contacts with TB diagnoses as late as 9 months after the index case (23).

Our study has some limitations. Because TB infection treatment is nationally recommended for children under the age of 2 years exposed to an infectious 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. In

addition, we cannot comment on the negative predictive value of IGRA in children under the age of 2 years, because 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 a return to the clinic if the result is negative, the cost-effectiveness evaluation in the United Kingdom now favors the use of TST in its last version of the national guidance. A lower universal cutoff of 5 mm was introduced to define TST-positivity; any child with a TST equal to or greater than 5 mm should now receive treatment for TB infection. IGRA testing was left to the discretion of the treating healthcare professionals. Applying this new guidance to the data from our cohort, 63% more children would have qualified for treatment and 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, after household exposure, are at very high risk for TB infection and subsequent disease progression. They have been identified as a group that should be a high priority for evaluation and TB infection treatment (5), and the latest Stop TB plan for elimination of TB places particular emphasis on the treatment of latent infection in children. The WHO currently recommends that after exposure to an infectious TB case all children under 5 years should be offered treatment for TB infection without any immune-based screening tests (26). If TST is to be used, WHO advises a 10-mm cutoff. In the United Kingdom, 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. Although the previous NICE guidance was deemed overcomplicated with its use of different TST cutoffs 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 cutoff of 10 mm increasing specificity after the age of 2 years (19). It could be argued that by introducing a 5-mm TST cutoff, 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 cutoff 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, some unnecessarily likely. Recent guidance from the United States has moved toward 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 2 years. No screening test perfectly predicts the risk of progression to disease, and it is important to invest effort in retention in screening and treatment programs as well as optimizing 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, after 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 2 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. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

Acknowledgment: The authors thank Neil Billingham, Debora Peddrasoli, and Ibrahim Abubakar at Public Health England for their support with the development of the study database and Olga Leonova for administrative support. They would also like to

thank the team of research nurses without whom this study would not have been possible: Lizzie Hutchison, Florence Manyika, Michael Browne, Jacqui Daglish, Jenni McCorkell, Laura Gebbie, Anne Barrett, Fiona Cook, Anjum Bahadur, and Gráinne O'Connor. Finally, they are grateful to the parents and children who agreed to participate in this study and undergo all of the involved procedures.

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