Increasing use of interferon gamma release assays among children 2 years of age in a setting with low tuberculosis prevalence

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Abstract

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US guidelines recommend interferon gamma release assays (IGRAs) for diagnosis of tuberculosis infection in children. In this retrospective cohort study, IGRA use in children 2–17 years of age increased substantially between 2015–2021. Testing in inpatient/subspecialty settings (vs primary care), public (vs private) insurance, lower age, and non-English preferred language were associated with increased odds of receiving an IGRA.

Keywords

latent tuberculosis; tuberculin; interferon gamma release assay; pediatric

Background

Interferon gamma release assay (IGRA) blood tests and tuberculin skin tests (TST) assess the adaptive immune response to tuberculosis (TB) antigens to test for TB infection. In the US, guidelines first recommended use of IGRAs to diagnose TB infection in children in 2005 (1); in May 2018, the American Academy of Pediatrics (AAP) decreased the age at which IGRAs were recommended to test children at low/intermediate risk of progression from 5 years to 2 years (2), which has been carried forward in newer guidance (3). Advantages of IGRAs include reduced inter-operator variability, lack of cross-reactivity with bacille Calmette-Guérin (BCG) vaccine antigens, and no need for a repeat visit to read a TST. These advantages have led some experts to call for "retirement" of the TST when IGRAs are available (4). Disadvantages of IGRAs include need for phlebotomy, laboratory infrastructure, and cost. Our objectives were to evaluate whether the testing approach for TB has changed since 2015 and examine predictors of TB test selection among clinicians providing care to children 5–17 years old.

Methods

We used electronic records to identify all IGRAs and TSTs completed by children in two Boston-area academic health systems between October 2015–January 2021. These health systems encompassed inpatient medical and surgical services, outpatient primary care, and outpatient subspecialty clinics (including clinics for children with immunocompromising conditions or receiving immune-depleting medications). We restricted our primary analyses to patients ages 2–17 years old, because IGRAs are not yet recommended for children <2 years old in our setting (2, 3). We recorded test type and date, patient age, family's preferred language, insurance type, and healthcare setting in which testing was ordered. We also recorded test results (positive, negative, or indeterminate/invalid/borderline [for IGRA tests]) when available. We were unable to determine indication for testing in our study; IGRAs and TSTs are used to test for both TB infection and for symptomatic TB disease in our setting.

In our primary analysis, we determined the proportion of total tests by month that were IGRAs and used Pearson correlation coefficients to examine changes over time. We stratified this analysis by age (2-<5 years old and 5 years old), given changing recommendations for IGRA testing for the younger age group during our study period.

We conducted two secondary analyses. First, given discrepancies in positivity rates between IGRA and TST, we conducted an exploratory concordance analysis of TST and IGRA results in the case of paired tests. We compared results when a TST or IGRA was followed by the opposite test within 28 days. The analysis was limited to tests with available results and excluded borderline/invalid/indeterminate IGRAs.

Second, after excluding tests missing demographic information, we assessed predictors of receiving an IGRA (vs TST) for each testing event, adjusting for month of testing. Because the AAP guidance change in May 2018 only affected children ages 2-<5 years old, we conducted separate analyses for children ages 2-<5 years old and for children 5 years old. For these analyses, we used generalized estimating equations with a logit link, exchangeable correlation structure, and robust standard errors to examine predictors of receiving an IGRA, hypothesizing that age, language, insurance, and testing setting would affect IGRA use. We conducted univariable and multivariable analyses, accounting for time. For children ages 2-<5 years old, we also hypothesized that time period (pre- vs post-AAP guidance change) would affect the odds of receiving an IGRA. To test this hypothesis, we included an indicator variable for pre- vs. post-AAP guidance change in the univariable and multivariable models for the 2-<5-year-old age group, to assess a change in the slope of the relationship between time and odds of receiving an IGRA when the AAP guidance was updated.

Because testing setting was missing for 24% of observations, we used multiple imputation for this variable, in a model with IGRA, age, month of test, insurance, language, and sex as predictors and 30 imputation sets. We also conducted a sensitivity analysis restricted to tests with known testing setting. Analyses were performed using Stata v17.0.

Results

We identified 20,267 tests obtained for 16,481 children 5–17 years old, and 5,118 tests obtained among 4,422 children ages 2-<5 years old (median tests per patient: 1 [interquartile range: 1–1]). Tests with known location were obtained from 78 primary care clinics, 216 subspecialty clinics, and 5 inpatient centers. Of all tests, 5,976 (29.5%) were TST and 14,291 (70.5%) were IGRA among children 5 years old; 2,325 (45.4%) were TST and 2,793 (54.6%) were IGRA among children 2-<5 years old. Prior to COVID-19, the number of tests per month increased from 204 in October 2015 to a maximum of 476 in October 2019 for children 5 years old (Figure 1A), and from 55 in October 2015 to a maximum of 147 in January 202 for children ages 2-<5 years old (Figure 1B). For children 5 years old, the proportion of tests that were IGRA increased from 48.5% in October 2015 to a maximum of 98.0% in April 2020 (Pearson correlation coefficient=0.92, P<0.001); for children ages 2-<5 years old, the proportion of tests that were IGRA increased from 7.2% in October 2015 to a maximum of 98.5% in August 2020 (Pearson correlation coefficient=0.96, P<0.001). A decrease in the number of tests per month was observed early in the COVID-19 pandemic.

Results were available for 21,711 of 25,385 tests (85.5%), of which 467 (2.2%) were positive, 21,045 (96.9%) were negative, and 199 IGRAs were indeterminate/invalid (1.3%

of all IGRAs with available results). Of the 6,433 TST with available results, 266 (4.1%) were positive; a total of 201 of 15,278 (1.3%) IGRAs were positive. Among 170 tests that were paired with an opposite test within 28 days, 93 (52.0%) results were concordant (Supplemental table 1). In this analysis, only 11/86 (12.8%) positive TSTs were accompanied by a positive IGRA.

In our predictor analysis of IGRA tests, 19,747 tests were included for children ages 5 years old (Supplemental table 2) and 4,937 tests were included for children ages 2-<5 years old (Supplemental table 3). Among children 5 years old, increasing age was independently associated with lower odds of receiving an IGRA; Spanish or other non-English language, public insurance and other insurance, and testing in an inpatient setting or subspecialty clinic were associated with higher odds of receiving an IGRA (Supplemental table 2). Among children 2-<5 years old, public insurance was associated with lower odds of receiving an IGRA; increasing age, other insurance and no insurance, and testing in an inpatient setting or subspecialty clinic were independently associated with higher odds of receiving an IGRA. In the model for 2-<5-year-olds, the interaction term between month of testing and AAP guidance time period was positive and significant (P<0.001), (Supplemental table 3).

The complete-case sensitivity analysis for both the 5 years old age group and the 2-<5 year old age group produced similar results (data not shown).

Discussion

From 2015–2021, the proportion of IGRA tests increased among children 2–17 years old in this low TB prevalence setting. Several factors could contribute to this finding. First, the change in testing among children 2-<5 years old likely demonstrates a response to updated AAP guidance in 2018. Additionally, increasing use of IGRA in both age groups may reflect growing comfort with IGRA testing for children and the appeal of tests that obviate return clinic visits, particularly during the COVID-19 pandemic. Although BCG vaccination status was unavailable, our findings may also reflect practice change in the context of evidence supporting IGRA use in low-prevalence settings where BCG-vaccinated children comprise a large proportion of children with TB infection risk (5, 6), despite concerns about IGRA sensitivity (7).

Previous research describing TB testing in North Carolina between 2010–2017 also noted increasing IGRA use over time and higher proportion of IGRA use among subspecialists, though pediatric patterns were not evaluated (8). The increasing TB test numbers we observed could reflect increasing numbers of foreign-born children from high-prevalence settings in Boston (9). The observed decrease in testing after the onset of the COVID-19 pandemic exemplifies recognized disruptions in TB health services globally (10).

We noted differences in positivity rate between TST (4.1%) and IGRA (1.3%), which may reflect differential specificity of these tests among BCG-vaccinated individuals or differences in indications for test use (which we were unable to measure). A large prospective study of IGRA and TST concordance in US children found an overall test agreement of 80% (5). The lower concordance rate in our study may arise from preferential

use of paired tests in the context of complicating clinical characteristics (e.g., BCG vaccination, immunocompromising conditions). The prior study found most discordant results occurred in patients with positive TST and negative IGRA (5), consistent with our findings. Furthermore, the overall rates of positive IGRAs align with findings from recent real-world observational cohorts (11).

We found that tests obtained for inpatients or patients in subspecialty clinics were more likely to be IGRAs than tests obtained in primary care practices, for both children 2-<5 years old and children 5 years old. This finding may indicate comfort or familiarity with IGRAs, access to phlebotomy and laboratory services, and availability of IGRA vs TST in specific clinics. Data on TST and IGRA availability throughout the health systems during our study period were unavailable; increasing IGRA availability and decreasing TST availability may have contributed to observed temporal trends, though changes in availability could also have reflected changing demand for these tests. These results also suggest a potential health system innovation to improve access to and use of IGRAs, given recommendations supporting IGRA use for children (3), and data supporting the cost effectiveness of IGRA versus TST to screen for TB infection (12). TSTs may continue to be preferred in settings where TSTs are available but access to laboratory services are limited (e.g. in many high-prevalence settings).

Insurance had different effects by age group. Among children 5 years old, the finding that publicly insured children had increased odds of receiving an IGRA could have been related to BCG vaccination and foreign-born status, although these data were unavailable, while decreased odds of IGRA testing among publicly insured children 2-<5 years old could be due to differential familiarity of guideline changes by providers in clinics serving these children. The finding that non-English language preference was significantly associated with increased IGRA use in both age groups may reflect increased use of IGRA among BCG-vaccinated children.

Among children 5 years old, we observed a small but significant association of decreasing IGRA use with increasing age. One potential driver of this finding is slow adoption of IGRAs for occupational TB infection screening for teenagers obtaining clearance to start jobs or volunteer positions. In contrast, odds of receiving an IGRA increased with increasing age among children 2-<5 years old, likely reflecting increased clinician comfort with IGRAs as children approached the pre-2018 AAP guideline threshold.

We found that IGRA use in children 2-<5 years old increased both before and after the 2018 AAP guidance change. Our interaction analysis demonstrated that the rate of change was significantly higher after the 2018 guidance update. This finding suggests that the guidance update accelerated a pre-existing trend towards increased adoption of IGRA use in this younger age group.

Limitations of our study include inability to determine TB testing indication or to evaluate specific reasons for selecting an IGRA or TST (e.g., BCG vaccination status; occupational screening protocols). Our data are restricted to hospitals and clinics reporting data within two health systems in a single low-prevalence urban setting. Information about clinicians'

training in performing and reading TSTs was unavailable, though differing levels of expertise could have contributed to the relatively low concordance rate between TST and IGRA. Additionally, demographic data were incomplete for some patients, necessitating exclusion of some patients and imputation of testing setting, but a complete case sensitivity analysis of predictors of IGRA testing produced similar effect estimates and overlapping confidence intervals for all predictors.

In this multicenter study encompassing inpatient and outpatient care in a low-prevalence setting, our findings suggest that the TST is being "retired". Education and support for primary care clinicians could improve equitable access to IGRA testing for children.

Supplementary Material

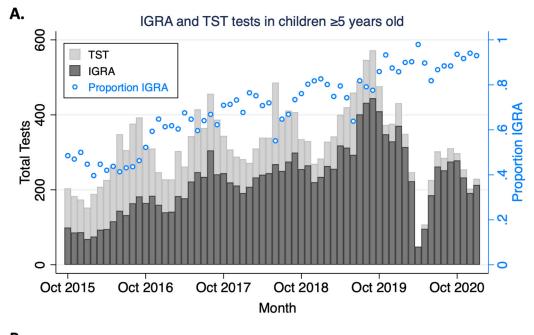Refer to Web version on PubMed Central for supplementary material.
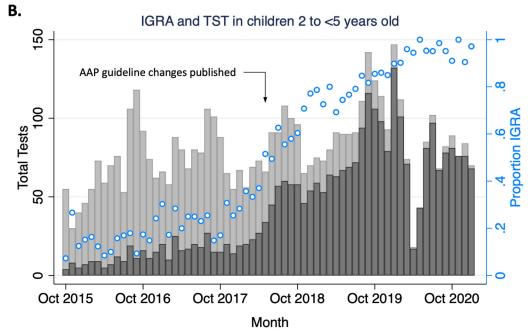
Acknowledgements

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A.

B.

Figure 1A and 1B.
Monthly number of TSTs, IGRAs, and proportion of tests that were IGRAs.
Abbreviations: IGRA – interferon gamma release assay, Oct – October, TST – tuberculin skin test