TITLE

Potential role for interferon-gamma release assays in tuberculosis screening in a remote Canadian community – A case study

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ABSTRACT

We undertook interferon-gamma release assays (IGRA) testing in a group of eleven children (14 years of age) from a small rural community in Canada. They all received the BCG vaccine as neonates. Seven had a positive TST (>10mm), and all had a negative TST at 4 years of age, with no potential exposures to or symptoms of active TB. IGRA testing with QuantiFERON gold was negative for all 7 of these children. Consideration should be given to the possibility that neonatal BCG may contribute to false positive TST performed at 14 years of age.
INTRODUCTION

Evidence that the Bacille Calmette-Guérin (BCG) vaccine can contribute to a false positive TB skin test (TST) has led to interferon-gamma release assays (IGRA) being a preferred option to identifying latent tuberculosis infection (LTBI) in vaccinated populations\(^1\). Because of the complexity of implementing IGRA testing, TST continues to be the predominant screening tool for LTBI in many Canadian jurisdictions\(^2-3\).

Although the BCG vaccine is not routinely used in most parts of North America, routine vaccination is still given in certain high TB incidence communities. Specifically in Canada, infants from some First Nations and Inuit communities receive the BCG vaccine as neonates (within first 28 days of birth). Current recommendations from the Canadian Tuberculosis Standards (7\(^{th}\) edition) state that the BCG vaccine, if given during infancy, should not be considered as a contributor to a false positive TST if the tested patient is now older than 10 years of age\(^2\). A growing body of evidence suggests that a proportion of positive TST results among those vaccinated may not be true positive. \(^4-8\).

False positive TST could potentially contribute to the unnecessary TB control activities and treatment for LTBI. We set out to examine the proportion of positive IGRA in a
group of 14 year olds who did not have an identifiable TB risk factor.

METHODS

A remote community north of Sioux Lookout, Ontario was the site of our investigation. Current policy supports BCG vaccine for neonates in this region, and children undergo routine TST for LTBI at 4 and 14 years of age. All children with a positive TST at age 14 years in one community with no identified exposure were considered for IGRA (4 were excluded; 1 prior BCG adenitis, 1 positive TST at age 4, 1 TST of 5mm, 1 unavailable). IGRA testing was done within 6 months of the positive TST.

QuantiFERON Gold tubes were used and shipped to nurses in the community. Once the blood samples were collected, they were flown the same day to a hospital, where they were incubated as per protocol and shipped to Ottawa for further processing. No samples were lost or ruined in transit.

BCG immunization history, previous TST results, active TB exposure and TB disease history were provided by the Sioux Lookout First Nations Health Authority. Consent for the TST and IGRA test was obtained from each child’s guardian by a nurse in the community. This work was part of a program evaluation and was done by the Sioux Lookout First Nations
Health Authority. Research ethics approval was obtained from Queen’s University in Kingston, Ontario.

RESULTS

Of the 7 children who were eligible, all were vaccinated and had a positive TST at 14 years of age, with no identifiable risk factors for TB exposure. Zero of the 7 tested positive with the QuantiFERON gold assay, and there were no indeterminate results. In addition, chest x-rays were all normal with no exhibited symptoms of active TB. No treatment for LTBI was initiated in these 7 children.

INTERPRETATION

With the addition of IGRA to routine TST screening, we provide evidence that neonatal BCG vaccination may contribute to a false-positive TST in youth at 14 years of age. The growing body of evidence supports that a more targeted application of treatment of LTBI can be accomplished in response to adding IGRA to the screening protocol.1,4-8.

The findings of this study are in agreement with other studies that have anchored IGRA as a more specific test than TST for BCG vaccinated individuals. The work of Katsenos et al. suggested that BCG vaccination after infancy contributed
substantively to a false positive TST \(^5\). Although evidence supports the idea that TST induration size is predictive of concordance with IGRA there remain a number of positive skin tests even at larger size that may we be false positive test. \(^4,6\). While these studies were all conducted on adults, Jacobs et al. performed a similar analysis on First Nations children in Alberta, Canada and once again documented false positive TST results with previous BCG vaccination\(^7\).

As outline previously, ensuring that samples were incubated in the appropriate setting and for the appropriate duration was logistically challenging in the small community. Careful organization of collection of samples and alignment with availability of the relatively limited shipping capabilities is necessary. A multidisciplinary approach involving numerous jurisdictions was required to coordinate IGRA testing in our investigation.

Most recently, Alvarez et al. conducted IGRA testing in Iqaluit, Nunavut (a remote Arctic community) and showed that such testing was feasible for 256 individuals\(^8\). Similar to previous studies, a high degree of discordance between TST and IGRA results was noted in previously BCG vaccinated individuals.

It should be noted that although the small community in question had a 10-year average incidence rate of smear
positive TB of 13.4 per 100,000\(^{10}\), our efforts to uncover any sick contacts (including active TB contacts) amongst the tested children all proved to be negative. It appears unlikely that recent contact with an active TB patient would have influenced the current study results.

**CONCLUSIONS**

There is a need for considering the role of IGRA testing in adolescents with positive TST who have received the BCG vaccine before infancy. Implementing such practices into First Nations communities must take into account the unique and remote conditions inherent to this population.

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References


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