

Potential role for interferon- γ release assays in tuberculosis screening in a remote Canadian community: a case series

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Abstract

Background: Current Canadian guidelines suggest that neonatal Bacille Calmette–Guérin (BCG) vaccination does not result in false-positive tuberculosis (TB) skin tests, despite a growing body of evidence that interferon- γ release assays may be a more specific alternative in identifying latent tuberculosis infections in vaccinated populations. We set out to evaluate the relationship between TB skin tests and interferon- γ release assays in patients who previously received neonatal BCG vaccine.

Methods: All children with a positive skin test at age 14 years in a remote community north of Sioux Lookout, Ontario, were considered for interferon- γ release assay testing.

Results: Of the 11 children who underwent routine screening at 14 years of age for latent TB infection, 7 had a positive TB skin test (≥ 10 mm). All 7 of these children had received the BCG vaccine as newborns and all had a negative TB skin test during their routine screening at 4 years of age. No potential exposure to active TB could be identified. Chest radiographs were normal, and none of the children had symptoms suggestive of active TB. The 7 children underwent interferon- γ release assay testing using QuantiFERON Gold. All 7 tests were negative.

Interpretation: With the addition of interferon- γ release assays to routine skin test screening, we provide evidence that neonatal BCG vaccination may contribute to a false-positive skin test in youth at 14 years of age. Consideration should be given to the possibility that neonatal BCG may contribute to false-positive TB skin tests.

Evidence that the Bacille Calmette–Guérin (BCG) vaccine can contribute to a false-positive tuberculosis (TB) skin tests has led to interferon- γ release assays being a preferred option for identifying latent TB infection in vaccinated populations.¹ Because of the complexity and cost of implementing interferon- γ release assay testing, TB skin tests continue to be the predominant screening tool for latent TB infection in many Canadian jurisdictions.^{2,3}

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

False-positive TB skin tests could potentially contribute to unnecessary TB control activities and treatment for latent TB

infection. We set out to examine the proportion of positive interferon- γ release assays in a group of 14 year old children who did not have an identifiable TB risk factor.

Methods

Setting

A remote community north of Sioux Lookout, Ontario, was the site of our investigation.

Study population

Current policy supports BCG vaccine for newborns in this region, and children undergo routine TB skin testing for latent TB infection at 4 and 14 years of age. All children with

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a positive skin test at age 14 years in 1 community with no identified exposure were considered for interferon- γ release assay testing. Interferon- γ release assay testing was done within 6 months of the positive skin test result.

Study design

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,⁹ then shipped to Ottawa for further processing. All testing was completed between March and August 2014.

Data sources

Vaccination history, previous TB skin test results, active TB exposure and TB disease history were provided by the Sioux Lookout First Nations Health Authority. All data are maintained on site at the health centres of local communities under the guidance of the health authority. The maintenance of these records follows standard clinical practice and is supervised by the TB control program of the health authority. Consent for the TB skin test and interferon- γ release assay 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.

Results

Among the children with a positive skin test at age 14 years, 4 were excluded from participating in the study: 1 with prior BCG adenitis, 1 with a positive TB skin test at age 4, 1 with a TB skin test wheal of 5 mm, and 1 who was unavailable to participate. Seven children were eligible to participate in the study, all of whom had received the BCG vaccine as newborns and had a positive TB skin test at 14 years of age, with no identifiable risk factors for TB exposure. None of the 7 had positive test results with the QuantiFERON Gold assay (0.00 IU/mL, 0.01 IU/mL, 0.00 IU/mL, 0.00 IU/mL, 0.00 IU/mL, 0.03 IU/mL, 0.02 IU/mL), and there were no indeterminate results. No samples were lost or ruined in transit. In addition, chest radiographs were all normal, and none of the children showed symptoms of active TB. No treatment for latent TB infection was initiated for these 7 children.

Interpretation

With the addition of interferon- γ release assays to routine skin test screening, we provide evidence that neonatal BCG vaccination may contribute to a false-positive skin test in youth at 14 years of age. The growing body of evidence supports that a more targeted application of treatment of latent TB infection can be accomplished in response to adding interferon- γ release assays to the screening protocol.^{1,4-8}

The findings of this study are in agreement with other studies that have anchored interferon- γ release assays as a more specific test than the skin test for people who have received the BCG vaccine. The work of Katsenos and col-

leagues suggested that BCG vaccination after infancy contributed substantially to a false-positive skin test.⁵ Although evidence supports the idea that induration size is predictive of concordance with interferon- γ release assays, there remain a number of skin tests even at larger size that may be false-positive results.^{4,6} Although these studies all involved adults, Jacobs and colleagues performed a similar analysis among First Nation children in Alberta, and once again documented false-positive skin test results with previous BCG vaccination.⁷

Ensuring that samples were incubated in the appropriate setting and for the appropriate duration was logistically challenging in this 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 interferon- γ release assay testing in our investigation. Most recently, Alvarez and colleagues conducted interferon- γ release assay testing in Iqaluit, Nunavut, and showed that such testing was feasible for 256 people.⁸ Similar to previous studies, a high degree of discordance between skin test and interferon- γ release assay results was noted in people who had previously received the BCG vaccine. Outside of Canada, Soborg and colleagues also presented data suggesting the potential for false-positive skin test results when the interferon- γ release assay is not used in the Inuit population.¹⁰

Limitations

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 100 000,¹¹ our efforts to uncover any sick contacts (including active TB contacts) among the children who underwent testing all proved to be negative. It appears unlikely that recent contact with an active TB patient would have influenced the current study results. However, the possibility of nontuberculous mycobacteria causing a positive skin test result cannot be ruled out with the current study's data. On the contrary, recent studies have documented some of the limitations of the interferon- γ release assay.¹² As with the TB skin test, the sensitivity of the interferon- γ release assay in immunocompromised patients has been questioned given that this population is most susceptible to latent TB infection.¹³ In addition, the interferon- γ release assay has been shown to be less accurate in younger children.¹⁴ Lastly, as mentioned in this current study, the costs and logistics of implementing interferon- γ release assay testing need to be considered when recommending its use in smaller communities.

Conclusion

There is a need for considering the role of interferon- γ release assay testing in adolescents with positive TB skin test results who have received the BCG vaccine as newborns. Implementing such practices into First Nation communities must take into account the unique and remote conditions inherent to these populations. The costs and logistics of implementing interferon- γ release assay testing need to be considered when recommending its use in smaller communities.

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