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Short Communication

Urine Xpert MTB/RIF for the diagnosis of childhood tuberculosis

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ABSTRACT

Introduction: Xpert MTB/RIF is recommended for the simultaneous detection of tuberculosis (TB) and rifampicin resistance directly from sputum specimens. Since young children cannot always expectorate, we assessed urine as a possible specimen source to diagnose TB in children using Xpert MTB/RIF.

Methods: During a field study to enhance childhood TB identification, spot urine samples were prospectively collected from consecutive ambulatory children aged 0 to 14 years presenting with presumptive pulmonary TB in community health centers. Urine Xpert MTB/RIF was performed by blinded technicians in 182 samples using 2 ml of unprocessed urine.

Results: The mean age of presumptive TB cases was 5.9 years (median 5.4, range 0.1 to 14.7) with more males (113, 62%) compared to females. All urine samples tested negative for Xpert MTB/RIF, regardless of whether concentration was performed or not. Out of these 182 presumptive TB cases, 50 (28%) were clinically diagnosed and 5 (3%) were bacteriologically diagnosed to have TB disease using either sputum or nasopharyngeal aspirate specimens.

Conclusions: In this community-based study, urine Xpert MTB/RIF does not appear to contribute to the diagnosis of childhood TB.

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Introduction

The Philippines is a country with high tuberculosis (TB) and multiple drug resistant TB (MDR-TB) burden. More than 70,000 Filipino children ≤ 14 years are estimated to have TB disease (WHO, 2017). However, the diagnosis of childhood TB remains problematic due to the paucibacillary nature of the disease and the difficulty of obtaining specimens for microbiologic confirmation (Marais et al., 2013).

Children, especially those less than 5 years of age, cannot expectorate and therefore sputum is not available for testing. Specimens like gastric aspirate and induced sputum require special equipment and are difficult to perform outside the hospital setting in most developing countries. Urine is a readily obtainable specimen in children that may be used for microbiologic detection

together with the use of newer tests like Xpert MTB/RIF. We explored the use of urine as a possible specimen source to diagnose TB in children in the community.

Methods

This study was prospectively conducted during a field study to enhance childhood TB identification in an urban municipality, Los Baños, Laguna and a predominantly rural municipality, San Juan, Batangas, both located in Southern Luzon island (Figure 1). As of the 2015 census, their respective populations were 112,008 and 108,585 (Philippine Statistics Authority, 2016).

After informed consent and assent were obtained, recruitment of at least 100 consecutive presumptive TB cases among ambulatory children aged ≤ 14 years of age was performed in local public health out-patient clinics. Sputum or nasopharyngeal aspirate (NPA) samples (performed whenever the child could not expectorate) were collected from all eligible children who assented (if applicable) and whose parents provided consent for participation. These specimens were sent for smear, Xpert MTB/RIF and mycobacterial culture using solid media. Sputum or NPA

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Figure 1. Study sites.

Footnote: Map created using Googlemaps.

specimens were processed for Xpert MTB/RIF following the manufacturer's recommended procedure. All specimens were stored at 2 to 8 °C for a maximum of 72 h.

Spot urine samples were concurrently collected at recruitment. Urine samples were stored at 2 to 8 °C for a maximum of 72 h or at –20 °C for a maximum of 5 days, before testing. Urine Xpert MTB/RIF was performed by blinded technicians using 2 ml of

unprocessed urine according to the manufacturer's recommended procedure for sputum samples except that the sample reagent was mixed at a 1:3 sample to reagent ratio. Urine was also concentrated for testing in 57 samples.

Data were collected in paper forms and entered into a custom-made mTB app using AppSheet (Seattle, WA, USA). Age, sex, sputum or NPA bacteriologic results were extracted from the

Table 1
Diagnosis of children who underwent urine Xpert MTB/RIF testing.

| Diagnosis | 0–4 yo | 5–9 yo | 10–14 yo | Total |
|-------------------------------|-------------------|-------------------|-------------------|-----------|
| | (n = 78) n (%) | (n = 78) n (%) | (n = 26) n (%) | n (%) |
| TB Disease | 25 (32.1) | 24 (30.8) | 6 (23.1) | 55 (30.2) |
| Clinically diagnosed | 22 (28.2) | 23 (29.5) | 5 (19.2) | 50 (27.5) |
| Bacteriologically confirmed | 3 (3.8) | 1 (1.3) | 1 (3.8) | 5 (2.7) |
| Latent tuberculosis infection | 0 | 1 (1.3) | 1 (3.8) | 2 (1.1) |
| Tuberculosis exposure | 30 (38.5) | 5 (6.4) | 2 (7.7) | 37 (20.3) |
| Not tuberculosis | 22 (28.2) | 48 (61.5) | 17 (65.4) | 87 (47.8) |
| Not evaluated | 1 (1.3) | 0 | 0 | 1 (0.5) |

database and tabulated using Microsoft Excel 2016. We assessed the performance of urine Xpert in comparison to clinical diagnosis and/or sputum or NPA bacteriologic tests (Xpert, smear or culture) following the standards for reporting of diagnostic accuracy studies protocol (STARD) (Cohen et al., 2016).

Results

From 17 February 2016 to 30 June 2017, we collected urine from 182 presumptive TB cases. The mean age was 5.9 years (median 5.4, range 0.1 to 14.7) with more males (113, 62%) compared to females. Fifty-five (30.2%) children were diagnosed with TB disease. Only five were bacteriologically confirmed using sputum or nasopharyngeal aspirate (Table 1). There was no case of extrapulmonary TB. All urine samples tested negative on Xpert.

One hundred sixty-four (164) children had sputum or NPA collected. Three had MTB and Rifampicin resistance detected, 1 had MTB but no Rifampicin resistance, 1 had MTB but Rifampicin resistance was indeterminate and 159 were negative on Xpert. One smear and Xpert positive participant was also positive on sputum culture.

Discussion

Out of 182 presumptive TB cases, all urine samples tested were negative on Xpert, even among the five patients who were bacteriologically confirmed TB.

A recent review showed that urine Xpert MTB/RIF may be helpful in confirming the diagnosis of genitourinary TB (Kohli et al., 2018). Screening using urine Xpert and urine lipoarabinomannan (LAM) increased the identification of TB by 50% among adult hospitalized patients with HIV (Gupta-Wright et al., 2018). The use of urine Xpert in pulmonary TB particularly in children remains limited (WHO, 2013). In our setting with HIV prevalence <1% (WHO, 2017), among ambulatory children, no urine was positive. Since we had no participant with disseminated or extrapulmonary TB, we were unable to assess the performance of urine Xpert MTB/RIF in those with more severe disease.

Other non-respiratory specimens have been tested using Xpert MTB/RIF in children. Previous studies have shown that stool Xpert has similar performance as gastric aspirate in HIV-infected children (LaCourse et al., 2018) and in those with severe pulmonary disease (Walters et al., 2017), however, processing of stool samples is tedious and may not be readily done in peripheral laboratories.

Conclusion

Among ambulatory children aged 0 to 14 years in our study, urine Xpert did not provide additional diagnostic utility for childhood pulmonary TB. Further studies may be conducted, particularly in children with more severe disease.

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Ethical approval

This study was approved by the University of the Philippines Manila Research Ethics Board.

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Author contributions statement

ALL, KNS and JGA prepared the protocol. ALL, JGA, JVD, MMD and AMS supervised and implemented the study. MCA, JVD, MMD and JGA conducted the laboratory testing. PS, JGA, MMD and ALL prepared the data entry system. MMD, PS and JGA cleaned the data for analysis. MMD and JNS analysed the data. ALL and MMD primarily wrote the manuscript. All authors reviewed and contributed to the manuscript.

Conflict of interest

The authors declare no conflict of interest.

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