Evaluation of Pulmonary Tuberculosis Case Detection Improvement with the Deployment of XpertMTB/Rif in the Tuberculosis Control Program of Cross River State, Nigeria

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Abstract

Objective/Background: Global indices show that Nigeria has the highest tuberculosis (TB)-related mortality rate. Overdependence on Ziehl–Neelsen (ZN) smear microscopy for diagnosis and human immunodeficiency virus (HIV)/AIDS has limited control efforts. The new polymerase chain reaction-based XpertMTB/Rif (Cepheid Inc., CA, USA), which detects Mycobacterium tuberculosis and rifampicin, was introduced in Cross River State in 2014. We evaluated the increment in pulmonary TB case detection following introduction of XpertMTB/Rif into the Cross River State TB control program. Materials and Methods: Data from three XpertMTB/Rif centers in Cross River were prospectively collected from June 2014 to December 2015. One spot specimen and one early morning sputum specimen were collected from each patient and tested using microscopy while one specimen was used for XpertMTB/Rif. Results: A total of 2326 patients comprising 47.4% (1103) males and 52.6% (1223) females were evaluated. Their mean age was 38.8 years (range 4–89 years); 42.6% (991) were HIV positive and 50.9% (1183) HIV negative, and for 6.5% (158) HIV status was unknown. XpertMTB/Rif detected M. tuberculosis in 22.9% (534) of patients, while 16.8% (391) were ZN smear positive. Smear microscopy missed 24.5% (131/534) of cases (P < 0.0001). When patients where categorized according to HIV status, XpertMTB/Rif detected 23.7% (280/1183) and ZN smear microscopy detected 18.5% (219/1183) of HIV-negative patients. XpertMTB/Rif detected 21.5% (213/991) and ZN smear 14.1% (140/991) of HIV-positive patients. TB case detection was significantly higher in HIV-negative patients than in HIV-positive patients when either XpertMTB/Rif and/or ZN was used (P = 0.018 and 0.012, respectively). Conclusion: The use of XpertMTB/Rif has significantly increased TB case detection and data in Cross River State. Scale-up of additional strategies such as culture is still required to improve TB detection in HIV patients.

Keywords: Acid-fast bacilli, genexpert, smear microscopy, tuberculosis, Ziehl–Neelsen

INTRODUCTION

Tuberculosis (TB), an ancient preventable and treatable disease, still remains a major public health problem despite concerted global efforts in controlling the disease. Current World Health Organization (WHO) indices showed that Nigeria had the sixth highest prevalence, fourth highest incidence, and the highest mortality rate globally.[1] TB diagnosis in Nigeria had continually depended on acid-fast bacilli detection by Ziehl–Neelsen (ZN) smear microscopy. This method had been shown to miss several cases at first presentation, particularly in patients with low bacilli numbers, such as human immunodeficiency virus (HIV)/AIDS-infected patients and children.[2]

The real-time polymerase chain reaction-based XpertMTB/Rif (Cepheid Inc.), which detects Mycobacterium tuberculosis and the rpoB, which encodes for rifampicin resistance, was rolled out as a panacea for diagnosis.[3] Many institutional-based studies have evaluated the sensitivity and specificity of this technology, but few have accessed the impact on TB programs.
in the field in high-TB-burden countries.\textsuperscript{14,3} This technology was introduced in Cross River State, Nigeria, in 2014. We evaluated the increment in pulmonary TB case detection following the introduction of XpertMTB/Rif in the Cross River State, Nigeria, TB control program.

**Materials and Methods**

We prospectively collated data following XpertMTB/Rif deployment in three centers in the state from June 2014 to December 2015. The protocol was reviewed and approved by the Cross River State Ministry of Health and University of Calabar Teaching Hospital Health Research Ethics Committees. Data collection commenced in Catholic Maternity Hospital Moniaya Ogoja in June 2014, University of Calabar Teaching Hospital in August 2014, and Dr Lawrence Henshaw Memorial Hospital Calabar in February 2015. Written informed consent was obtained from all patients. One spot specimen and one early morning specimen were collected from all patients who satisfied the criteria for XpertMTB/Rif testing, as provided in the Nigerian National Tuberculosis Control Program guidelines.\textsuperscript{9} These included all patients with relapse of disease, return after default, sputum smear positivity after intensive phase of treatment, and Category 1 treatment failure; all persons living with HIV/AIDS; and healthcare workers and children with symptoms of TB. Smears were prepared from the two specimens, stained with the ZN method, and viewed for acid-fast bacilli. One of the specimens was used by another technician for XpertMTB/Rif testing following the manufacturer’s instructions. This was done by mixing the Xpert extraction reagent with the specimen in a ratio of 2:1 in a specimen container. The container was agitated vigorously for up to 10 times and left to stand at room temperature for 10 min before another agitation and a 5-min waiting time. Finally, 2 mL of the mixture was transferred to the Xpert cartridge using a sterile DNA/DNase-free pipette. The cartridges were inserted into the Xpert real-time cycler, which ran automatically and generated results in about 2 h. All invalid or error results were repeated with the same mixture except where the repeat failed, in which case a new specimen was requested. All repeat samplings were not reregistered to avoid duplication of data.

Data were analyzed using Statistical Package for Social Sciences software, version 20.0. (SPSS Inc., Chicago, IL, USA). Categorical data are presented as % (n) when data are available for all participants and as % (n/sample size) when data are available only for a subset of the study population. The Chi-square test was used to compare categorical data between groups. All \( P \) values were two-sided, and \( P < 0.05 \) was considered to be statistically significant.

**Results**

A total of 2326 patients comprising 47.4\% (1103) males and 52.6\% (1223) females were evaluated. Their mean age was 38.8 years (range 4–89 years); 42.6\% (991) were HIV positive, and 50.9\% (1183) HIV negative, and for 6.5\% (158) HIV status was unknown. XpertMTB/Rif detected *M. tuberculosis* in 22.9\% (534) of patients, while 16.8\% (391) were ZN smear positive [Figure 1]. Smear microscopy missed 24.5\% (131/534) of cases (\( P < 0.0001 \)).

When patients were categorized according to HIV status, XpertMTB/Rif detected 23.7\% (280/1183) and ZN smear microscopy 18.5\% (219/1183) of HIV-negative patients [Figure 2a]. XpertMTB/Rif detected 21.5\% (213/991) and ZN smear 14.1\% (140/991) of HIV-positive patients [Figure 2b]. TB case detection was significantly higher in HIV-negative patients than in HIV-positive patients when either XpertMTB/Rif and/or ZN was used (\( P = 0.018 \) and 0.012, respectively).

**Discussion**

The age-long sputum smear has been the primary method of diagnosing pulmonary TB in low- and middle-income countries. It is simple, rapid, relatively inexpensive, and invaluable in monitoring treatment. It is, however, grossly compromised when bacilli number is <10,000/mL. With the continued dependence on ZN microscopy, several cases will still be missed, disease burden will be underestimated, and transmission will continue. In the majority of high-TB-burden countries, such as Nigeria, the XpertMTB/Rif technology is still not open to all presumptive TB patients, but limited to patients at the risk of drug resistance due to the high cost of cartridges.

A 24.5\% increment in this study is in keeping with a 23\% increment reported in a Cochrane review.\textsuperscript{7} The technology has also been shown to significantly reduce the time to initiation of therapy for drug-resistant TB.\textsuperscript{8} Total deployment of XpertMTB/Rif for all patients with presumptive TB will lead to a significant reduction in transmission.

Data suggest a higher TB incidence in HIV-negative patients in our program. However, with the depletion of CD4 cells,
HIV-positive patients are known to be more at risk of TB. Although there was a significant improvement in case detection with XpertMTB/Rif, there is still an obvious limitation in the detection of TB in HIV-positive patients. This could be resolved by concomitant deployment of cheap, rapid, WHO-recommended methods such as the microscopic observation drug susceptibility assay by national TB control programs in resource-limited settings.

In areas with a high burden of non-TB mycobacteria (NTM), ZN-positive XpertMTB/Rif-negative results may occur as XpertMTB/Rif does not detect NTM. There is, however, a yet to be determined burden of NTM infection in our locality. A study in Kaduna State, northern Nigeria, recorded an NTM prevalence of 15% of culture-positive mycobacterial infections in HIV patients, all of which were smear negative. Scale-up of complimentary phenotypic culture techniques is, therefore, still greatly needed to detect NTM-infected patients, as inappropriate treatment will result in avoidable mortalities.

**Conclusion**

In centers without access to XpertMTB/Rif that are still completely dependent on ZN smear microscopy to make a diagnosis of pulmonary TB, several cases of TB are still being missed. Decentralization of XpertMTB/Rif as a complementary protocol in national TB control programs will, therefore, greatly enhance TB detection toward a realization of the goals of the end-TB strategy of the WHO.

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**Conflicts of interest**

There are no conflicts of interest.

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