Diagnosis, strain patterns of drug-resistant tuberculosis and associated risk factors in Nairobi, Kenya

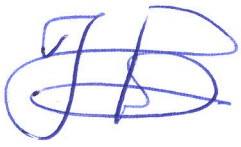
Thomas David Ogaro

A thesis submitted in partial fulfillment for the Degree of Doctor of Philosophy in Epidemiology in the Jomo Kenyatta University of Agriculture and Technology

2014

DECLARATION

This thesis is my original work and has not been presented for a degree in any other university.



Signature..... Date 24/04/2014

Thomas David Ogaro

This thesis has been submitted for examination with our approval as the University supervisors

Signature..... Date 25/04/2014

Dr Willie A. Githui

KEMRI, Kenya

Signature..... Date 24/04/2014

Dr Gideon M. Kikuvi

JKUAT, Kenya

ABSTRACT

The resurgence of tuberculosis (TB) has been associated mainly with Human Immuno deficiency Virus (HIV) and widespread poverty. The HIV pandemic and emergence of resistant strains of *Mycobacterium tuberculosis* threatens the success of patient treatment and TB control programs. The initial treatment of TB involves the administration of four drugs namely; isoniazid, rifampicin, pyrazinamide and either ethambutol or streptomycin. Isoniazid and rifampicin are critical in successfull treatment of TB. Resistance to any anti-TB drugs can develop spontaneously as a result of mutation then there after under selective pressure. Few epidemiological studies done in Nairobi have shown the presence of multidrug resistant TB (MDR TB) but none has determined the distribution of these cases and their potential causes. There is also limited information on the exact prevalence of resistance to anti-tuberculosis drugs in high density populations with high rates of tuberculosis and HIV co-infection such as those in Nairobi where there is great potential for spread. The objective of this study was to determine the magnitude, strain patterns and and identification risk factors associated with the resistance. This was a cross sectional study. Study sites were selected from each of the 8 districts in Nairobi and study subjects selected using weighted cluster sampling based on the patient population proportions of new smear positive cases notified in 2007. Eligible patients were enrolled in the study consecutively after consenting until the number allocated to each study site was achieved. Sputum samples were collected from patients before start of treatment in accordance with standard programme procedures

and transported to the central reference laboratory (CRL) where they were processed for culture and drug susceptability testing (DST) using the standard procedures. All culture isolates positive for *Mycobacterium tuberculosis* (MTB) were tested for susceptibility to first line anti-tuberculosis drugs namely; isoniazid, streptomycin, rifampicin and ethambutol using the conventional Mycobacterium Growth Indicator Tube (MGIT) medium. Spoligotying molecular method was used to identify isolates with strain families. Data was analysed using the SPSS software version 17. The standard chi-square test and Fishers exact test were used to compare 2 data points and a p-value of less than 0.05 was considered significant. The Mantel-Hansen test was used for odds ratios. A total of 691 TB patients were enrolled for study with mean age of 31.3 and median of 30 years. Among the patients, 438 (63.4%) were new smear positive TB cases from whom 368 *Mycobacterium tuberculosis* isolates were subjected to drug susceptiblity testing (DST) and 253 (36.6%) were previously treated smear positive TB cases from whom 199 MTB isolates were subjected to DST. Eeighty five percent and seventy seven percent of the MTB isolates from new patients and previously treated patients, respectively, were fully sensitive to all the drugs tested. Initial resistance (i.e. resistance among new patients) to isoniazid, streptomycin, ethambutol and rifampicin was 10.3%, 4.3%, 5.1% and 0.81%, respectively. Among previously treated patients resistance to isoniazid, streptomycin, ethambutol and rifampicin was 18.1%, 10.5%, 7.03% and 9.04%, respectively. The prevalence of MDR TB was 0.54% and 8.54% among new and previously treated patients respectively. No Extensive drug resistant TB (XDR TB) was identified in this population. The study found out that the TB disease in

Nairobi was caused by five main MTB strain sub-families namely; CAS1_KILI, T1, Beijing, LAM9 and LAM3 and S/Convergent which collectively contributed to 57 % of the TB cases in Nairobi. The levels of drug resistant TB in Nairobi was high compared to other previous studies done in the country and there was diverse array of *Mycobacterium tuberculosis* strain families which could be indicative of a cosmopolitant population with frequent migration suggesting that the dorminant strain families may have been present in the population for an extended period of time or on going transmision of closely related strain families. HIV status of the patient was not associated with any drug resistance. The proportion of isolates from patients who had previous treatment history (24.3%) was significantly higher than those from new patients (15.1%). History of previous treatment was therefore strongly associated with drug resistance ($p=0.007$ for any resistance and $p<0.0001$ for MDR TB). The study did not find any association between drug resistance and the Beijing or any other MTB strain family. However the overall proportional contribution to the TB disease in Nairobi by the Beijing strain family alone had increased from 8% to 12% over the last 5 years. This poses a serious threat to TB control due to its high virulence and frequent association with multidrug resistance. The National TB control program should therefore rapidly intensify the implementation of services for the diagnosis and treatment of MDR TB to control its transmission and carefully monitor the trends of anti-tuberculosis drug resistance to ensure the success of the TB control programme.