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Thibela TB: Design and methods of a cluster randomised trial of the effect of community-wide isoniazid preventive therapy on tuberculosis amongst gold miners in South Africa

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ABSTRACT

Background: South Africa has the third highest annual number of new tuberculosis (TB) cases globally. The resurgence of TB which has particularly affected gold miners in South Africa, is attributed to occupational risk factors for TB including silica dust exposure and high HIV prevalence. Isoniazid preventive therapy (IPT) is recommended for individuals at high risk to prevent both HIV-related TB and silicotuberculosis, but global uptake has been poor. We describe the design of a cluster randomised study, "Thibela TB", which compares routine IPT targeted to those identified as at higher risk of TB (due to HIV infection or silicosis) against a "community-wide" approach in which IPT is offered to all employees. The trial is registered with the Current Controlled Trials: Registration number ISRCTN63327174.

Methods: We describe the rationale for the intervention of community-wide IPT, drawing on studies conducted in 1950–1960s in the pre-HIV era. The design of the study, including the definition of the cluster, is presented and advantages and limitations of such a design are discussed.

Conclusion: If successful in reducing TB incidence and prevalence, this trial has potential to make a major contribution to TB control policy in high HIV settings, providing evidence concerning efficacy, and additionally safety and population-level effects on drug susceptibility patterns. Such rigorous evaluation is essential to provide policy makers with an evidence base to guide community-level TB prevention strategies.

1. Introduction

Southern Africa has been particularly hard-hit by the increase in tuberculosis (TB) cases attributable to the global HIV epidemic: in 2008, South Africa ranked third in terms of total number of incident TB cases; amongst an estimated 1.4 million HIV positive TB cases globally, 78% were in the African region [1]. Annual TB incidence rates now exceed 1% per year in urban populations. Standard approaches to TB control have failed to contain this explosive epidemic which, together with rapidly increasing rates of multi-drug resistant

Abbreviations: IPT, isoniazid preventive therapy;HIV, human immunodeficiency virus;MGIT, mycobacterial growth indicator tube;ART, antiretroviral therapy;DOTS, directly observation of therapy, short course;GM, geometric mean;ANOVA, analysis of variance.

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TB and recurrent TB episodes, presents an alarming public health emergency [2,3].

Since the early 1990s, the worsening TB epidemic has been more pronounced in the 147,000 strong gold-mining workforce than in the South African general population, due to high prevalence of both HIV infection (estimated at 29% in 2000 [4]) and silicosis: two of the strongest known risk factors for developing TB disease [5]. Silicosis is an occupational disease of gold miners that results from inhalation of silica dust generated during the mining process [6]. TB case notification rates rose to exceed 4000 per 100,000 per year in 1999 [7], despite an intensive TB control programme including active TB case-finding based on regular radiological screening of all employees, as well as more standard passive case-finding and treatment with short course rifampicin-based regimens, administered at the workplace as directly observed therapy using combination tablets.

Given this unprecedented background we explored options for large scale community-based interventions aimed at achieving rapid impact on TB incidence and transmission at the population level. Historical examples of intensive TB control efforts include two studies of community-wide isoniazid preventive therapy (IPT) by which we mean IPT is offered to the entire community regardless of being at higher risk of TB. In these studies IPT was offered to adults and children aged >2 months from the Inuit community of Alaska and adults in communities in the west coast of Greenland, conducted in the 1950s [8–11]. IPT has been shown to be effective in reducing TB incidence amongst HIV-positive [12], silicotic [13] and high-risk HIV-negative individuals [14], and is recommended as part of the World Health Organization's "Three Is" policy to reduce the burden of TB amongst people living with HIV. Current recommendations are for the use of targeted IPT, by which we mean IPT is restricted to those at higher risk of developing TB; however limited coverage of HIV testing has contributed to low uptake of IPT. The extraordinary epidemic of HIV-associated tuberculosis amongst gold miners in South Africa required extraordinary control measures, and this led us to propose a trial of community-wide IPT.

This paper describes the design of a cluster randomised study, Thibela TB ("Prevent TB"), which aims to investigate whether community-wide IPT, given after screening for TB and combined with standard facility-based TB control measures, can rapidly reduce TB incidence and undiagnosed infectious TB in a setting of high HIV prevalence. The study is registered with the Current Controlled Trials, registration number ISRCTN63327174.

2. Methods

2.1. Rationale for study design

2.1.1. Cluster randomised trials for infectious diseases

Cluster randomised trials are an appropriate study design for interventions for infectious diseases where the interest is in the effect of the intervention at the population level, therefore capturing both direct and indirect effects [15]. The impact of the intervention will be maximised when a large proportion of the target population receives the intervention and the cluster randomised design allows for such mass effects of the intervention to be captured. Small clusters are statistically more efficient but may not be the best design for infectious diseases where the transmission zone of the infection is of importance. Defining the cluster is therefore based on a geographical unit chosen to minimise transmission to or from individuals from outside the cluster (either individuals from other clusters or the wider community), thereby reducing "contamination" between clusters and other communities.

2.1.2. Mathematical modelling of various interventions

Various interventions aimed at the whole community were considered including community-wide IPT or targeted IPT where preventive therapy would be offered to all individuals in the community with known HIV infection or silicosis. At the planning stage mathematical modelling was used to gain a better understanding of the likely effect of these interventions on TB dynamics in our study population [16]. Using a deterministic model of TB infection and disease in gold miners, we assessed the impact of three interventions, taking into account issues relevant to our setting including HIV epidemiology and routine screening for TB. Results suggested that IPT offered to the whole community with high and rapid uptake of the intervention and pre-intervention screening for active disease had unusually high potential for TB control.

2.1.3. Community-wide isoniazid preventive therapy in the pre-HIV era

Community-wide IPT was assessed in the pre-HIV era in the 1950s in Alaska and Greenland where TB prevalence and incidence were high. The Alaskan study, conducted amongst Inuit communities, randomised households to receive isoniazid (300 mg daily) for 12 months and found TB incidence was 68% lower in households receiving isoniazid compared to those receiving placebo [8]. As the intervention was successful, approximately 5 years later all households received isoniazid, regardless of whether they received isoniazid or placebo the first time. The study area experienced a sustained reduction in TB incidence [9,10] though it was not clear whether this was entirely attributable to the intervention as other TB control interventions were implemented before and during the isoniazid intervention. The Greenland study randomised villages to receive a relatively low dose of isoniazid (400 mg taken two consecutive days each week for two periods of three months) and found an overall reduction in TB incidence of 29% over the six-year follow up period [11]. The smaller effect of isoniazid in this study compared to others was attributed to the smaller dosage and duration of isoniazid given.

Based on this we designed a cluster randomised trial to evaluate community-wide IPT, an intervention comprising screening for TB to exclude active TB disease, treatment of active TB cases identified, and nine months of IPT for those eligible. The effects of this type of intervention at the individual and community levels are potentially four-fold: transmission from undiagnosed active TB cases would be interrupted through TB screening and treatment of active cases; all individuals at high risk of reactivation of latent TB would be treated regardless of whether or not they are identified as being in a high risk group; potentially, protection