Factors Affecting the Spread of Tuberculosis in South Africa

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Abstract

Significant gains have been achieved in reducing AIDS mortality rates but the growing tuberculosis epidemic threatens to erode this progress. This study examines the relationship between poverty, AIDS treatment access and tuberculosis prevalence in South Africa. We use three years of tuberculosis test result data from the National Health Laboratory Service, which includes the majority of tuberculosis tests conducted nationwide. The rich data set includes patient demographic information, detailed test results and clinic location. Using geographic information we link these tuberculosis results to individual-level data from the South Africa Labour Force Survey as well as information on the timing of the rollout of publicly-provided AIDS treatment. In an event-study framework, we use exogenous variation induced by the rollout of ART to identify the causal impact of AIDS treatment on tuberculosis rates. This project exploits a wealth of medical and geographic data to inform health policy on tuberculosis and HIV in developed and developing countries.

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Motivation

South Africa has made significant gains in increasing life expectancy of AIDS patients but the growing tuberculosis epidemic threatens to erode the progress that has been made. Tuberculosis is a treatable, curable disease that has been brought under control in developed, and most developing, countries. With the advent of HIV/AIDS, however, tuberculosis rates have increased dramatically in the countries with the highest HIV prevalence rates. In South Africa, tuberculosis incidence rates nearly tripled between 1998 and 2007 (USAID).

In South Africa, about three-quarters of new tuberculosis cases are co-infected with HIV (USAID). AIDS and tuberculosis are inextricably linked because immune-compromised HIV-positive individuals are more susceptible to tuberculosis infection than HIV-negative individuals and less able to overcome the disease (Corbett et al. 2003). Tuberculosis is the first opportunistic infection to affect HIV-positive individuals as AIDS progresses. It progresses more quickly in HIV-positive individuals and is the leading cause of death among AIDS patients in developing countries (Friedland et al. 2004).

Despite the rising importance of tuberculosis as a cause of morbidity and mortality there has been relatively little recent research on the disease in South Africa. Tuberculosis research has been overshadowed by HIV/AIDS in terms of funding, research output and innovation in the past fifteen years. Lawn et al. (2011) make a compelling argument that the current strategy to fight tuberculosis, directly observed treatment short-course (DOTS), is inadequate to address the growing epidemic. Despite high co-morbidity rates, treatment programs for tuberculosis and HIV/AIDS are poorly integrated in South Africa. Ultimately, better integration will improve effectiveness in combating both diseases.

This project has the potential to influence both health policy and practice in combating tuberculosis and HIV/AIDS. A consideration of the role of AIDS treatment in fighting tuberculosis has been conspicuously absent from the health policy debate. Prior to August 2011, HIV-positive individuals were only eligible for anti-retroviral treatment (ART) for AIDS once their white blood cell (CD4) count, a measure of immune system functioning, dropped below 200 cells per cubic millimeter. In response to an active debate on the issue the eligibility cutoff was raised to a CD4 count of 350. This reduces AIDS mortality, increases life expectancy and helps to prevent opportunistic infections before they occur. One potential additional benefit of earlier ART is a reduction in the number of tuberculosis infections, which has largely been ignored in the policy debate. This study is designed to provide evidence of any reduction in tuberculosis incidence due to earlier treatment of AIDS.

This project highlights an important spillover of HIV/AIDS policy that directly affects the health of HIV-negative individuals. Tuberculosis is the only opportunistic infection to which even healthy HIV-negative individuals are susceptible. The resurgence of tuberculosis among HIV-positive people has led to a dramatic increase in tuberculosis prevalence among HIV-negative individuals as well. The dynamics of contagion between HIV-positive and HIV-negative individuals in South Africa are poorly understood. Our research design allows us to estimate the impact of loosening treatment eligibility criteria on individuals, both HIV-negative and HIV-

positive, that are not eligible or receiving treatment.

Contribution

The proposed large-scale, empirical study exploits a wealth of medical and geographic data from South Africa. It uses patient tuberculosis test results spanning 2004–2007 which we link to data from the South Africa Labour Force Survey as well as clinic-level data from the largest AIDS treatment program in the world. To our knowledge the tuberculosis data have never before been used for population-level research. It would be only the second study to examine the impact of the ART rollout at the national level. The population-level research design will fill the gap in knowledge between clinical studies using small cohorts and simulation studies that use mathematical modeling to extrapolate the results from small studies to the population level.

Related Literature

A number of recent clinical studies demonstrate the positive impact of ART on tuberculosis incidence. ART reduces the incidence of tuberculosis by as much as 80 percent in resource-limited environments (Badri et al., 2002; Santoro-Lopes et al. 2002) and the incidence continues to decrease for at least the first five years of ART (Lawn, Badri and Wood, 2005). Badri et al. (2002) find that the benefits of tuberculosis prevention do not extend to patients with CD4 counts above 350. However, Lawn et al. (2009) find that benefits extend to CD4 count levels of 500, and suggest using this cutoff would be the best way to minimize tuberculosis rates.

There is some skepticism about whether these positive results can be expanded to the population level in a resource limited environment. Williams and Dye (2003) argue that for ART to prevent tuberculosis at the community level, early treatment is necessary as are high levels of coverage and compliance to avoid any chance of infection. Lawn, Bekker and Wood (2005) doubt that ART would have an overall positive impact on tuberculosis incidence. They are concerned that ART enables HIV-positive individuals to live longer with sub-optimal immune responses, putting them (and those they come into close contact with) at risk for tuberculosis over a longer life span.

Currie et al. (2003) present a dynamic Bayesian model of the impact of HIV status on tuberculosis incidence, however the model is populated with parameters drawn from a number of different studies, which may have limited applicability in the South African context. In a related study, Williams et al. (2010) present a country-level model of the dynamics of tuberculosis infection and ART for sub-Saharan Africa.

By using a large, population level panel data set, this project will improve our understanding of the parameters that influence the incidence of tuberculosis in AIDS patients and contribute to the calibration of future models of these infection processes.

Data

This project uses a tuberculosis test result database that is managed by South Africa's National Health Laboratory Service (NHLS), the national network of about 265 pathology laboratories that provides diagnostic laboratory services for the country as a whole. The NHLS performs the majority of tuberculosis and HIV tests in South Africa so the comprehensive dataset includes detailed test results for over one million South African patients.

In addition to patient information on demographics and tuberculosis infection, the data include the location of the clinic where the tests were performed and results from tests for sensitivity to twenty common drugs used to combat tuberculosis. This geographic data allows us to link to any other data set that also includes geographic information which enables us to include community characteristics in our analysis. This data set confers a number of advantages, not least of which is its large size, allowing us to generate estimates for small geographic areas with great precision.

The South Africa Labour Force Survey is the most comprehensive source of national microeconomic data in South Africa and is therefore particularly suited for this analysis. The survey collects detailed information about the economic well-being of individuals aged 15-65 years, and basic information about children and seniors, in a nationally representative sample of approximately 30,000 households. The questionnaire includes questions about demographic characteristics; biographical information; activities related to work; unemployment and non-economic activities; agricultural activities and uncompensated activities.

Description of ART Rollout

We examine the impact of improved access to AIDS treatment on tuberculosis prevalence. We would expect to see a reduction in the number of tuberculosis cases subsequent to an ART clinic opening in a community as those accessing ART become less susceptible to tuberculosis infection.[1] We would expect tuberculosis incidence rates to fall not only among HIV+ individuals accessing treatment but also among HIV+ individuals not yet on ART and HIV- individuals due to a reduced prevalence in the population.

In 2004, the South African government began the rollout of free ART in public health clinics. The rollout was an ambitious government program that enabled 429 clinics to begin prescribing ART and enrolled over 500,000 patients on ART in the first four years. For most South Africans, especially those living in poverty, this represented the first time that ART was accessible. While some private treatment options existed, they were generally costly, conditional on employment, or both. A rollout of this size and scope presents an unprecedented opportunity to examine the effect of access to AIDS treatment on tuberculosis prevalence at the national level.

[1] There is a possible initial dip due to immune reconstitution inflammatory syndrome in which the body responds to ART with an inflammatory response to a pre-existing opportunistic infection that paradoxically makes the infection worse.

The national rollout of ART provides an exogenous source of geographic and temporal variation in ART access that we use to identify a plausibly causal effect. A unique feature of the rollout during this period is that a centralized DOH accreditation process acted as the main bottleneck in the rollout. There was high demand for accreditation once the process began and the small DOH accreditation team struggled to keep up with the demand.[2] The accreditation team acted autonomously to determine the timing of clinic opening, which, due to the opacity of the selection process, meant that it was not possible to anticipate the timing of clinic opening.

The government's stated goal was to provide "equitable" access to AIDS treatment within every locality so that every South African would have access to these services and historically underserved districts would receive the same standard of care as more advantaged districts (Mbewu and Simelela, 2003). So that lack of resources did not impede accreditation the government pledged that "additional financial and technical resources [would] be deployed to service points in resource-constrained or underserved areas" to help them meet the requirements for accreditation (Mbewu and Simelela, 2003).

In most cases, proposed ART treatment centers were already providing other HIV/AIDS care on-site so they were able to start enrolling patients from this pool in the ART program immediately following accreditation. Other HIV/AIDS care included HIV testing, counseling and treatment of tuberculosis and other opportunistic infections. This enables us to examine the impact of ART holding tuberculosis treatment constant.

As a result of the accreditation process, the access to ART improved at different times in communities that were otherwise similar, which allows us to control for confounders. In addition, previous work by McLaren shows that there are few good predictors of early access to ART, and once we control for time-invariant community characteristics the access to ART is close to randomly distributed.

Multivariate Regression Analysis of ART Impact

For our analysis, we aggregate individual test results into a panel of clinic-months to link to monthly measures of ART access. We create measures of ART access for areas around each tuberculosis clinic based on the distance to the nearest ART clinic and the patient capacity of that ART clinic.

Because we have three years of panel data with frequent measures of tuberculosis prevalence, we perform an event study methodology with fixed effects (FE) at the clinic/community level. The analysis examines pre-ART trends and post-ART trends in tuberculosis cases to determine whether the number of tuberculosis cases was reduced in communities after they obtained access to AIDS treatment.

[2] Ratshefola, personal communication, 29 July 2009.

We estimate the following equation for clinic i in community j at time t:

$$TB_{ijt} = \sum_{k=-48}^{-1} \pi_k D_j \mathbf{1}(t - T_j^* = k) + \sum_{k=1}^{48} \gamma_k D_j \mathbf{1}(t - T_j^* = k) + \phi' X_{ijt} + \alpha_j + \delta_{tj} + \epsilon_{ijt}, \quad (1)$$

where TB_{ijt} is the number of tuberculosis cases in the clinic population (or number of cases of resistance to a particular drug) and D_j is an indicator variable for a community that obtains access to ART during the period in question (2004-2007). The π_k coefficients capture the pre-access trends in TB cases and the γ_k coefficients capture trends once the community has obtained ART access, all relative to the month in which ART access was obtained ($t = 0$). The vector X includes the following clinic characteristics: number of patients tested, average age, percent female, percent Black African, percent in poverty, an indicator for whether the clinic is in a hospital or larger facility and an indicator for whether the clinic is in an urban area. We include a set of clinic fixed effects, α_j, and a set of interactions between survey wave and district, δ_{tj}, to control for district-specific time effects. Communities that did not receive ART access are included in the sample to identify the time and district effects. The γ_k coefficients estimate the impact of ART access and plot the time pattern of the effect. Because ART access was introduced at different places at different times, the inclusion of district-specific time effects, δ_{tj}, enables us to control for secular changes that took place in the district.

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