

Tuberculosis Control in Asia and the Western Pacific: A Role for Computer Modelling

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Abstract

Despite the availability of effective treatment, tuberculosis (TB) causes more deaths than any other infection. Most of the world's TB cases and deaths occur in Asia and the Western Pacific, and the growing prevalence of multiple drug-resistant TB and the spread of human immunodeficiency virus (HIV) present ever greater obstacles to effective TB control. The management of TB remains difficult, and epidemiologic studies to assess control programmes require significant time and expense and may not be generalizable to other regions. Computer models are powerful and relatively inexpensive tools for rapidly planning and evaluating TB control strategies.

Models have demonstrated the value of targeted chemoprophylaxis strategies for the prevention of TB among HIV-infected individuals, and programmes to ensure that all HIV-infected individuals receive TB chemoprophylaxis should be considered in Asia and the Western Pacific. Though directly observed therapy (DOT) is effective when designed to be attractive to patients, modelling has shown that DOT, if poorly accepted by patients, may lead to fewer patients seeking care and thus to paradoxical rises in TB case rates.

Models may be used to make accurate predictions of TB morbidity and programme costs using local epidemiologic and demographic inputs. The use of models in Asia and the Western Pacific offers a low-cost way to compare programmes, to improve the evaluation of programmes, to project future cases, and to examine programme needs while providing insights into TB control helpful to countries in and out of the region.

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Introduction

The Urgency and Complexity of the Tuberculosis Epidemic in Asia

Since the introduction of effective treatments over 40 years ago, tuberculosis (TB) has been a curable and potentially controllable disease. Yet, despite the widespread availability of efficacious therapy, TB remains unchallenged as the world's most lethal infection, responsible for more deaths than any other single infectious agent.¹ In the developing world, where 98% of fatalities from TB occur, this disease accounts for approximately one-fifth of all preventable adult deaths.^{2,3}

The tremendous impact of TB is particularly evident in Southeast Asia and the Western Pacific. Approximately 70% of all TB cases reported worldwide occur in these

regions which include over 60% of the world's population.⁴ The World Health Organization (WHO) estimates that only about half of all TB cases in these regions are treated, resulting in 1 million deaths per year.⁵ It is especially distressing that the TB epidemic in Asia will likely worsen because of the growing prevalence of multiple drug-resistant TB in areas with low TB programme cure rates,^{2,6,7} the rapid spread of human immunodeficiency virus (HIV) in these regions,^{5,8,9} and the increasing age of the population.^{4,5}

Of these factors, the most often discussed is the effect of the acquired immunodeficiency syndrome (AIDS) epidemic on TB incidence. Because HIV infection may increase the risk of progressing from latent to active TB by as much as 100-fold, even a low prevalence of HIV will be catastrophic in Asia and the Western Pacific

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regions where 1 billion people with TB infection live.¹⁰ In Bombay, 60% of AIDS cases present with TB; 10% of TB cases also have AIDS.⁹ Prospective data from Madras from 1991 to 1993 have shown a greater than 3-fold increase in HIV infection among pulmonary TB patients.¹¹ In the Chiang Rai province of Northern Thailand, where TB notification declined significantly in the 1980s, an unexpected resurgence in the overall incidence of TB during the early 1990s is attributed to the AIDS epidemic. By 1994, 45% of TB cases occurred in HIV positive patients.⁸ By extrapolating current trends in the HIV epidemic, the WHO predicts a two- to three-fold increase in the number of TB cases attributable to HIV in Southeast Asia during the last half of the 1990s with a seven-fold increase in HIV-associated TB cases overall since the beginning of the decade.⁵ By the end of the century, 15% or 600,000 out of 4 million TB cases in Southeast Asia will be attributable to HIV infection.

The prevalence of multiple drug resistance is another important determinant in planning TB control programmes. Multiple drug resistance, especially resistance to both isoniazid and rifampin, requires prolonged treatment with agents that are more expensive and associated with higher rates of toxicity than first line anti-tuberculous drugs.¹² Despite improved treatment response rates, multiple drug-resistant TB continues to have higher morbidity and mortality rates than drug sensitive TB.¹³⁻¹⁵

Multiple drug resistance has long been a problem in parts of Asia and the Western Pacific. In a study of patients with chest symptoms presenting for the first time to one of nine urban chest clinics throughout India in 1968, 15.8% of patients with culture positive *Mycobacterium tuberculosis* had bacilli resistant to both isoniazid and streptomycin. In the Calcutta chest clinic, resistance to both drugs was seen in 58% of patients with culture positive TB. Among patients with chest symptoms and no previous history of treatment for TB (primary resistance) presenting to the chest clinics, 22% of patients with culture positive TB had disease with bacilli resistant to isoniazid, streptomycin, or both.¹³ In contrast, in Australia at the same time, only 1.0% of patients with newly diagnosed TB had multiple drug-resistant bacilli, and primary isoniazid resistance was detected in only 1.8% of patients.¹⁴ Recent data from Korea showed that 4.7% of newly diagnosed patients with pulmonary TB at chest clinics had multiple drug-resistant disease, where multiple drug resistance was defined as resistance to ≥ 3 drugs. When patients with and without a history of treatment for TB were considered, 7.4% of patients diagnosed with pulmonary TB at chest clinics had multiple drug-resistant bacilli. Resistance to isoniazid and rifampin was found in 4.8% of all patients with pulmonary TB.¹⁵ At an outpatient hospital in Jaipur, India, between 1988 and 1991, primary multiple drug-resistant

disease was found in 3.2% of patients with smear positive pulmonary TB. Isoniazid and rifampin resistance was reported in 1.1% of patients.¹⁶

Tuberculosis Control and the Role of Computer Modelling

Even in countries with a low prevalence of TB, such as the United States, the management of TB remains a difficult problem. Proficient TB control programmes are essential for containing this epidemic, as demonstrated by the recent resurgence of TB in the US in locations where effective TB control programmes were lacking. However, there is disagreement even among experts as to what strategies are needed to constitute a good control programme. Programmes differ in their approaches to case-finding, emphasis on contact investigations, chemotherapy regimens for active TB, as well as in the frequency, duration, and location of treatment, and prevention measures used. While some of these differences may be attributable to disparities in resources or case rates, the majority are likely due to a lack of consensus on strategies to control TB. The management of patients with multiple drug-resistant TB or co-infection with HIV and the recent availability of new rapid diagnostic tests further complicate the issues which need to be considered when developing TB control programmes.

Epidemiologic studies remain the gold standard for the evaluation of TB control programmes. Unfortunately, these studies often require significant resources and time to conduct. In addition, epidemiologic studies are not practical for choosing among a large number of control strategies. For example, it would be difficult to design an affordable study to assess 10 different combinations of TB control strategies and ensure that each programme is conducted under similar conditions. Besides the logistics and costs associated with running 10 separate TB programmes, TB public health officers would have to wait for years to know which combination is the most effective. As a result of these cost and implementation hurdles, officials designing TB control programmes usually only consider a few strategies.

Because of the complexity of the TB epidemic and the myriad of possible control strategies, computer models are potentially powerful tools for the design of TB control strategies. Typically, national and local TB control policy is created by a panel of public health officials and TB experts who form a consensus based on a combination of their individual experiences, understanding of the literature, and interpretation of the current situation that needs to be addressed.¹⁷ However, TB control contains so many facets that it is not possible for a committee to recall all appropriate information necessary for developing a national strategy or to be able to assess the robustness of their conclusions across a range of reason-

able epidemiologic assumptions. Computer modelling addresses these issues and allows public health officials to make the best use of available epidemiologic data. Furthermore, patient and public preferences can and should be incorporated into control policies. Patients' attitudes towards a programme, which can significantly alter overall effectiveness,¹⁸ also may be weighed with the aid of models.

In addition to aiding in the design of control programmes, computer models can provide insights into how best to evaluate ongoing programmes with epidemiologic data. Models can be used to examine which parameters such as disease incidence, disease prevalence, disease specific mortality rates, or the percentage of patients completing treatment best predict the health of the population over time. A model may identify a sentinel indicator whose short-term changes portend long-term shifts in the desired outcome. By tracking the sentinel indicator, officials can assess the effectiveness of a programme sooner than could be done by following the final outcome of interest. Though useful for any programme, early indicators of programme effectiveness are especially helpful for programmes treating diseases like TB with potentially long latency or infectious periods.

Models can generate results which are broadly applicable as well as conclusions which are specific to the region for which the model was designed and from which the epidemiologic data was drawn. This paper will discuss both types of results.

General Insights from Tuberculosis Models

Though based on epidemiologic data from other regions, recent modelling work offers insights regarding links between TB and HIV and interactions between patient and control programmes applicable to TB control in Asia and the Western Pacific. In addition to helping make estimates of the impact of HIV on the demographics of TB, computer models have consistently demonstrated the value of targeted strategies for the prevention of TB among HIV-infected individuals. These results have held up across regions with very different prevalences of TB and HIV. For example, in a model using epidemiologic data from Africa, simulations show that the introduction of prevention strategies using isoniazid chemoprophylaxis could prevent many projected TB deaths attributable to a rise in HIV prevalence.¹⁹ Relying on US epidemiologic data, a separate model demonstrates that increases in isoniazid chemoprophylaxis use are likely to meaningfully lower TB mortality among HIV-infected persons.²⁰ Recent clinical data from yet another region further support the value of isoniazid chemoprophylaxis in reducing mortality in HIV-infected persons.²¹ Given the growing importance of HIV in the TB epidemic of Asia and the Western

Pacific, it is likely that the use of isoniazid prophylaxis may be an important control measure in areas where the HIV epidemic is currently taking hold or established.

Another area where modelling offers general insights is in assessing the impact of patients' attitudes on programme effectiveness. "DOTS", or directly observed therapy, short-course, is currently recommended as an essential component of TB control by some groups. WHO, for example, emphasizes "DOTS" for the control of TB.²² In areas with inadequate control programmes and/or inadequate resources, the implementation of "DOTS" with the provision of adequate supplies and personnel has led to reductions in TB cases and drug resistance rates.²³ However, if poorly designed, DOT could lead to decreases in the number of patients seeking care and thus to paradoxical rises in TB case rates. Studies have demonstrated that some patients avoid seeking care for TB altogether to avoid the risk of mandatory therapy, detainment,²⁴ or reporting to other authorities such as immigration officials.²⁵ Whether patients perceive DOT as a service or burden will influence the overall effectiveness of the programme. This issue, more generally stated as the impact of patient preferences on programme effectiveness, has been addressed using computer models. In the US, where reasonably effective self-administered programmes exist in most locations, small declines in programme acceptability with the introduction of universal DOT programmes quickly offset gains from improved treatment completion rates.²⁶ Universal DOT programmes are unlikely to add much in areas where efficacious self-administered programmes are in place.²⁷ In these locations, requiring DOT for all patients might paradoxically lead to declines in programme effectiveness by discouraging patients from seeking treatment.

Computer models also have generated insights into TB surveillance which hold across regions. Models have shown how a programme that successfully reduces TB mortality may transiently lead to an increase in TB cases.²³ Unless this rise has already been predicted through the use of computer modelling, programmes following case rates, but not mortality rates, might incorrectly conclude that the strategy is not effective. Thus, an effective strategy could be discarded needlessly. On the other hand, there are situations when surveillance may indicate that a control programme is successful when it is actually inducing detrimental effects. Increasing treatment entry rates while treatment completion rates decline or remain unchanged may lead to increasing numbers of drug-resistant TB cases.^{23,28} Programme officials monitoring TB treatment entry rates will see improvements in the number of patients starting treatment and may judge the programme effective. If they are not also monitoring treatment completion and effectiveness, they may miss an insidious climb in drug-resistant TB. With-

out properly-guided surveillance, this control strategy could unwittingly result in an increase in cases and mortality due to drug-resistant TB.

Finally, models can provide insights into the patterns epidemics follow. Models have shown that intrinsic properties of TB transmission result in epidemics which have natural periods of rise, plateau, and decline that occur over the course of a century or more. Appropriate or necessary control measures thus may depend on the stage in the natural history the TB epidemic that one is confronted with. In the earlier stages of an epidemic when incidence is rising, as may be the case in parts of Asia and Africa, a higher proportion of cases will occur in younger individuals. In the later stages of an epidemic, as incidence declines, as is happening in much of Europe and America, a higher proportion of cases develop in the older population.²⁹ These different demographic patterns, reflecting unique stages of the epidemic, require disparate control strategies.

Modelling Local Conditions and Implications for Tuberculosis Control

While models can provide important insights which are generalisable across regions, detailed projections of case or mortality rates, costs or programme needs, and derivations of diagnostic and treatment guidelines often require epidemiologic and cost inputs from the region being considered. To determine the threshold where empiric treatment with a regimen effective against multiple drug-resistant TB is more cost-effective than empiric treatment with four-drug therapy for US patients being evaluated for TB, epidemiologic data and costs from the US were used.³⁰ Similar thresholds for the empiric use of anti-tuberculous therapy for multiple drug-resistant disease can be determined for any country or region within Asia or the Western Pacific. For those locations where the costs and the epidemiology of TB differ from the US, national or regional inputs would be needed to ascertain meaningful treatment thresholds.

Short-course rifampin-based chemotherapy has been shown to lead to long-term savings when compared with standard therapy in three sub-Saharan countries.³¹ Epidemiologic and demographic data from the Indonesian Division of Communicable Disease Control was used to compare the cost-effectiveness of a rifampin-based short-course therapy, a standard treatment without rifampin, and a combined approach to chemotherapy for active TB in Indonesia. Based on the cost of the drugs in this country, short course chemotherapy has a higher initial cost, but results in the prevention of 1.8 million cases and savings of 61 million dollars compared with standard therapy over a 20-year period.³² The predicted aggregate of savings and number of prevented cases apply only to Indonesia or countries with

similar costs, population demographics and TB epidemiology.

Accurate predictions of TB morbidity and programme costs, invaluable for planning control policy, rely on the inputs derived from local epidemiologic and demographic studies. While epidemiologic and demographic information are often collected by public health organisations, there may be times when the appropriate local information is not available. Models also offer methods for making estimates in the absence of complete data. Using sensitivity analyses, where one or more model inputs are systematically varied across a range, models may be used to evaluate and compare control strategies when only partial local data is available.

Role for Tuberculosis Modelling in Asia and the Western Pacific

For mathematical modelling of TB to continue to be useful, it will have to address the issues that are most essential in determining the future course of the epidemic and provide solutions for disease control. Success in the global reduction of TB will hinge on what happens in Asia and the Western Pacific-home to the majority of the world's population and TB cases. For countries in these regions with limited resources, models offer a low cost way to compare programmes and design better methods for evaluating programme performance. Whether or not resources are limited, countries can benefit from using models to project future cases, evaluate strategies for the elimination of endemic TB, and examine programme needs. Besides the local benefits to the programmes using this technology, modelling TB control strategies in Asia and the Western Pacific will provide new insights which may be generalised to countries both in and out of the region. These insights are an additional way in which countries within the Western Pacific will continue to contribute to the improvement of TB control around the world.

With the careful use of existing data, mathematical models offer an improved method for prediction and planning. In the case of TB, modelling requires knowledge of TB epidemiology, and the current demographic status and trends of the population being studied. With the proper inputs, mathematical models improve our estimation and planning that otherwise relies on rough extrapolation or guessing.

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