REVIEW

Current issues in global tuberculosis control

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Summary   Despite attempts to standardize tuberculosis (TB) control strategies, there remains wide variation in the selection and implementation of control strategies within and among nations. Some of this variation is appropriate; based on wide variations in the available resources, the prevalence of TB infection, the incidence of TB disease, the relative contribution of reactivation versus recent transmission to incident cases, and the rate of HIV co-infection. This review will discuss three controversial questions relevant to global TB control: (1) What is the role of the treatment of latent TB infection in global TB control? (2) What are successful strategies to control immigrant TB in low incidence countries? (3) What are successful strategies to control TB in persons with HIV infection?

Introduction

Tuberculosis (TB) is the second leading cause of death worldwide, killing around 1.8 million persons annually.[1] TB rates vary widely by region (Table 1) with the highest case rates and mortality rates in Africa and the lowest rates in the Americas and Europe.[1] Large discrepancies exist among the countries in each region, and among different locations and demographic groups within each country. TB case rates have been falling steadily in many parts of the world. However, local and regional increases in TB cases have occurred due to limited resources, societal disruptions and an expanding HIV epidemic. Outbreaks due to multidrug-resistant tuberculosis (MDR-TB) have occurred in a number of locations, often in association with a breakdown in the health-care infrastructure. Despite attempts to standardize TB control strategies, there remains wide variation in the selection and implementation of control strategies within and among nations. Some of this variation is appropriate based on wide variations in the available resources, the prevalence of TB infection, the incidence of TB disease, the relative contribution of reactivation versus recent

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Table 1   Estimated TB incidence and mortality by region, 2002.

Region	Number of cases (thousands)		Cases per 100,000 population		Deaths from TB	
	All forms (%)	Smear-positive	All forms	Smear-positive	Number (thousands)	Per 100,000 population
Africa	2354 (26)	1000	350	149	556	83
The Americas	370 (4)	165	43	19	53	6
Eastern Mediterranean	622 (7)	279	124	55	143	28
Europe	472 (5)	211	54	24	73	8
South-East Asia	2890 (33)	1294	182	81	625	39
Western Pacific	2090 (24)	939	122	55	373	22
Global	8797 (100)	3887	141	63	1823	29

Data from World Health Organization[1]; Death statistics include TB deaths in persons infected with HIV.

transmission to incident cases, and the rate of HIV co-infection. This review will discuss three questions that are controversial and relevant to global TB control. The goal is to consider these issues in the context of global tuberculosis control. As a group, the authors have provided tuberculosis care in seven countries: Democratic Republic of Congo, Haiti, Rwanda, Saudi Arabia, Tanzania, United States and Zimbabwe. The authors currently practice in the United States, so their experience is weighted toward a North American perspective.

What is the role of the treatment of latent TB infection in global TB control?

Controversy

There are dramatic differences of opinion among providers in different nations related to the treatment of latent TB infection (LTBI). Treatment of LTBI has been a major component of TB control in the United States (US) for many decades, and is increasingly adopted in developing countries. However, the strategy has been greeted with skepticism in many countries and often generates resistance when offered to immigrants from developing countries. Most countries have adopted either BCG vaccination or treatment of LTBI as a primary strategy to prevent TB disease. The evidence for the efficacy of the treatment of LTBI will be reviewed, then its appropriate application as a component of global TB control based on local priorities and resources will be discussed.

Background

After infection, *Mycobacterium tuberculosis* (MTB) may remain latent for weeks to years before causing disease. Progression to symptomatic TB disease occurs only in a minority of those infected. The condition of clinical latency in the presence of infection with live MTB is described as latent TB infection (LTBI). LTBI is generally demonstrated by a positive reaction to a tuberculin skin test (TST). A purified protein derivative from killed MTB is injected intradermally, then induration is measured 48 to 72 hours later. Based on clinical and epidemiological factors, varied thresholds of 5 mm, 10 mm, and 15 mm are used to interpret the TST as positive or negative. The assumption that a positive TST represents infection with live MTB has been supported by the high rates of reactivation in TST-positive individuals who develop advanced immunosuppression due to HIV infection. The goal of treatment of LTBI is to decrease the likelihood that TB infection will progress to active TB disease. This treatment has previously been described as 'preventative therapy' or 'prophylaxis', but these terms are confusing since the therapy does not actually prevent infection. The goal of treatment of LTBI is eradication of an existing asymptomatic infection in order to prevent disease. The concept of treating LTBI has been considered most relevant in populations where repeated exposure to MTB is limited.

Efficacy of treatment for LTBI

Shortly after isoniazid was discovered to be bactericidal for MTB, interest surged in treating those with LTBI. A number of large clinical trials have demonstrated that treatment of LTBI reduces, but does not eliminate the risk of TB disease. Trials in otherwise healthy adults enrolled huge numbers of subjects since the background rate of progression to disease was relatively low (Table 2). More recent trials in persons with HIV infection have demonstrated benefit in small populations.[2,3] The relative benefit is similar, but the absolute benefit as measured by reduction in TB incidence is much higher in

Table 2 Efficacy of various durations of isoniazid treatment for persons with fibrotic lung lesions, International Union Against Tuberculosis Trial, 1969—1977.

Group	Five-year TB incidence per 1000 person-years (% reduction)			
	Placebo	12 weeks	24 weeks	52 weeks
All participants (*n* = 27,830)	14.3	11.3 (21)	5.0 (65)	3.6 (75)
Adherent participants (*n* = 21,635)	15	9.4 (31)	4.7 (69)	1.1 (93)
Fibrotic lesions <2 cm (*n* = 18,663)	11.6	9.2 (20)	4.0 (66)	4.2 (64)
Fibrotic lesions >2 cm (*n* = 8428)	21.3	16.2 (24)	7.0 (67)	2.4 (89)

Table from reference 4; Data from reference 112.

populations with a higher medical risk. Recent trials of treatment of LTBI in persons with HIV infection have also demonstrated the efficacy of a number of alternative regimens.[4] Isoniazid can be given daily or twice weekly using directly observed therapy (DOT). The preferred duration of isoniazid therapy for treatment of LTBI is now nine months in the US, although a six-month regimen is acceptable for adults without HIV infection or fibrotic lung lesions. Daily rifampin for four months is an acceptable alternative to isoniazid.[4] The combination of rifampin and pyrazinamide for two months is effective, but is associated with a substantial risk of hepatotoxicity.[5] This regimen is no longer recommended as routine treatment for LTBI, but it may be used when a longer isoniazid regimen is not feasible.[6]

Requirement for prolonged treatment

Most antituberculous medications target cell wall or protein synthesis, and are thus most active against actively metabolizing, cell wall-building bacteria. Bacterial replication appears to be markedly reduced during latent infection, so a latent tubercle bacillus is less amenable to killing than an actively replicating organism. Drug therapy for LTBI must be given over a prolonged time period to be effective. In persons with fibrotic lung lesions, 12 weeks of daily isoniazid therapy led to minimal reduction in TB disease (Table 2). Extending the duration to 24 weeks led to more reduction, but the best results were seen when therapy was extended to a full 52 weeks. The requirement for prolonged therapy dampens the enthusiasm for the treatment of LTBI. This therapy is further complicated by the challenge of encouraging a patient who feels well to take a drug for a potential future benefit. As demonstrated by the sub-group analysis in Table 2, adherent participants achieved a higher benefit than other participants. Drug efficacy (purely the drug's ability to have a certain effect) is substantially higher than the population effectiveness

(includes the drug efficacy with issues such as tolerability and compliance).

Groups with high risk of progression from LTBI to TB disease

The likelihood of progression from latent infection to active disease is highest in the first year after infection, steadily declining with the duration of latent infection (Table 3). It also varies greatly among hosts based on age and underlying medical conditions (Table 3). This has gradually diminished the one-size-fits-all approach, but in turn has led to more complicated criteria for the interpretation of the TST as a guide to the treatment of LTBI (Table 4). Populations with exceptionally high risk of progression to active disease include young children, those

Table 3 Incidence of active tuberculosis (TB) in persons with a positive tuberculin skin test, by selected risk factors.

Risk factor	TB cases/ thousand person-years
Recent TB infection	
Infection <1 year past	12.9
Infection 1—7 years past	1.6
Human immunodeficiency virus (HIV) infection	35.0—162
Injection drug use	
HIV seropositive	76.0
HIV seronegative or unknown	10.0
Silicosis	68
Radiographic findings consistent with prior TB	2.0—13.6
Weight deviation from standard	
Underweight by ≥15%	2.6
Underweight by 10—14%	2.0
Underweight by 5—9%	2.2
Weight within 5% of standard	1.1
Overweight by ≥5%	0.7

Table from reference 4.

Table 4 Criteria for tuberculin positivity, by risk group.

Reaction ≥ 5 mm induration	Reaction ≥ 10 mm induration	Reaction ≥ 15 mm induration
• HIV-positive persons	• Recent immigrants (i.e., within the last 5 years) from high prevalence countries	• Persons with no risk factors for TB
• Recent contacts of TB case patients	• Injection drug users	
• Fibrotic changes on chest radiograph consistent with prior TB	• Residents and employees of high risk congregate settings	
• Patients with organ transplants and other immunosuppressed patients	• Mycobacteriology laboratory personnel	
	• Persons with the following clinical conditions: silicosis, diabetes mellitus, chronic renal failure, leukemia, lymphoma, carcinoma of the head or neck and lung, weight loss of ≥10% of ideal body weight, gastrectomy, and jejunoileal bypass	
	• Children younger than four years	
	• Infants, children, and adolescents exposed to adults at high risk	

Table condensed from reference 4.

exposed in the preceding 1—2 years, and those with silicosis, HIV infection, or other immunosuppressive conditions (organ transplantation, treatment with TNF-α inhibitors, etc.). Due to a high rate of progression and greater severity of TB disease, the absolute benefit of LTBI for these groups is high. In settings where treatment of LTBI is ongoing, or being contemplated, there should be little disagreement about recommending treatment for LTBI in these cases.

Risks of treatment for LTBI

The US Public Health Service conducted a large trial in the 1960s showing a risk of isoniazid-associated hepatitis of about 1%.[7,8] A later meta-analysis revised the estimate to approximately 0.6% of latently infected subjects.[9] However, toxicity increases with age, concomitant active hepatitis B and alcoholism. Other adverse reactions have been given less attention in the literature, and include rash, GI intolerance, and headache. The fact that people who are otherwise well are being prescribed a medication with these side effects, which they are asked to take for 6—9 months, leads to poor completion of therapy. A recent study from a public health clinic in southern California found that 18% experienced an adverse effect and only 64% completed six months of treatment.[10] A shorter regimen combining rifampin and pyrazinamide for eight weeks was found to be effective in a population at great risk for TB, namely those with HIV or AIDS.[11] Assuming that the findings could be extrapolated to

the non-HIV-infected population, the regimen was recommended as an option by the US Centers for Disease Control (CDC).

When the rifampin/pyrazinamide regimen was used in persons without HIV, an excess risk of hepatotoxicity was observed compared to that seen in the HIV-positive cohort previously studied.[12—15] The incidence of hepatotoxicity when these two drugs are used to treat LTBI also exceeds that observed when four drugs including rifampin and pyrazinamide are used to treat active TB disease.[16] This paradox is the subject of much discussion within the TB control community and studies are needed to understand the basis of the apparent difference.[17]

In the meantime, the combination of rifampin and pyrazinamide is not recommended for routine use in the US for treatment of LTBI, but it may be considered when the more prolonged isoniazid treatment is not feasible.[6] This experience raised new questions about the mechanisms of drug-induced liver injury, and the balance between risk and benefit in persons with LTBI who do not have medical risk factors for progression to active TB.

BCG vaccine versus LTBI treatment

Administration of BCG vaccine early in life is recommended in many countries. This strategy makes sense when TB disease remains relatively common in the population, leading to unapparent exposure of young children. Because children under two years of age are at such high risk of life-threatening disseminated disease, the benefit of BCG given to

newborns in high-incidence settings is generally accepted. In addition, recent long-term follow-up of patients vaccinated in an Alaskan Eskimo community confirms that BCG decreases the risk of TB disease by a modest amount for many decades.[18] However, in populations with limited numbers of cases — such as in North America and Western Europe — and where most cases of TB are identified, a different approach has been taken. Rather than subject an entire population to the cost and the small but definable risks of BCG vaccine,[19] the focus is on testing for LTBI and on treating those who are identified.[4] These populations are generally also more likely to be able to afford the healthcare expenditure needed for testing and treating LTBI. Since vaccination with BCG complicates the interpretation of the TST, societies have tended to choose either BCG vaccination or the strategy of TST and treatment of LTBI. There is an increasing body of data indicating that TST remains informative in persons who have previously received BCG vaccine.[20] Recent trials of LTBI in persons with HIV infection who were previously vaccinated with BCG have demonstrated the validity of the TST in predicting the risk of TB disease in this group and the value of LTBI in reducing TB disease.[2,21,22] There is room for a dual strategy of universal BCG vaccination at birth for everyone followed by selective use of screening and treatment of LTBI in high risk populations. Screening and treatment for LTBI would be especially beneficial to TST-positive adults who are in the highest risk groups for progression to TB disease, including those with HIV infection.

Priorities for TB control programs

The highest priority for TB control programs worldwide must be to identify and effectively treat the most infectious (acid-fast-smear positive) TB cases.[23] In the authors' opinion, the next highest priority, especially in populations with a substantial prevalence of HIV infection, is to expand TB diagnostic capabilities. TB control programs need to be supported to develop the necessary infrastructure to provide patient-specific sputum culture and drug sensitivity results for patients suspected of having TB — both smear-positive and smear-negative cases. The initial investment may focus on re-treatment of apparent treatment failures, in order to curtail spread of MDR TB, but should promptly move toward including all TB suspects. In high incidence countries, widespread administration of BCG vaccine to newborns should continue to be considered a high priority and has likely saved many lives over the 80 years it has been in use. In populations where active TB is relatively rare and the majority of cases are

being found, identification and treatment of LTBI is next in the list of overall program priorities. Targeted testing and treatment of 'high risk' individuals, rather than mass screening, is the strategy of choice. Persons at high risk for progression to clinical TB disease include recent (<2 years) contacts to a person with pulmonary TB,[24] and children <4 years of age or who have underlying HIV infection or other conditions causing immunosuppression. Tracing contacts to infectious TB cases, identifying secondary active TB cases, and then testing and treating those with LTBI due to recent infection is the kind of high-priority, targeted activity that should speed the decline of TB in any community.

Summary

Individual recommendations for the treatment of LTBI must be made by balancing the risk of TB disease with the risk of treatment. At a countrywide or programmatic level, the priority must be on contacts to active cases, particularly those <4 years of age, and those with HIV infection. Programs still struggling with implementation of core TB activities — finding all cases of active TB, providing culture and susceptibility testing for the majority of suspect cases, including those that are AFB smear-negative, assuring a consistent supply of first- and second-line TB drugs, and maintaining educated staff to oversee prompt completion of therapy — probably need to focus on those activities prior to implementing targeted testing and treatment of LTBI.

What are successful strategies to control immigrant TB in low incidence countries?

Controversy

As TB rates have declined in developing countries, an increasing proportion of TB cases have been attributed to immigrants from high-incidence countries. Interventions that target recent immigrants can contribute to the health of the individual immigrants and to overall TB control in developing countries. However, such efforts may produce stigma and lead to resistance from immigrant populations. Here strategies will be discussed along with the evidence that they have provided benefit.

Volume of migration

Migration from the resource-poor developing world to the resource-rich developed world is occurring at

an astounding pace. Between 1995 and 2000, approximately 2.3 million persons per year migrated from the developing world to the developed world.[25] The US alone accepted over 1 million immigrants in 2002 from over 200 countries.[26] In 2000, approximately 1 in 13 persons residing in Europe was born elsewhere; this was true for 1 in 8 US residents and about 1 in 5 residents of Australia and New Zealand.[25,27] Many of these residents immigrated from the developing world; for example, 78% of foreign-born US residents emigrated from Latin America or Asia. In addition to immigrants, over 32 million persons entered the US for non-immigration visits in 2002 alone,[26] some of whom stayed for extended periods.

Impact of immigration on TB control

Immigration is a vital source of economic and cultural exchange, but also results in the importation of infectious diseases.[28] TB, in particular, is increasingly becoming an imported disease in the developed world. Eighty percent of the estimated 8 million new cases of TB worldwide each year occur in one of 22 high-burden developing nations.[29] When persons migrate from these nations, they often carry latent TB infection that may reactivate after arrival in the host country. Continuing migration, coupled with decreasing TB incidence among persons born in the developed world, has resulted in an increasing proportion of TB cases in the developed world attributable to persons born in the developing world (Figure 1). In 2003, foreign-born persons accounted for 53% of reported TB cases in the US,[30] compared with only 30% of reported cases in 1993.[31] Similar trends have been reported in Canada,[32] Western Europe,[33,34] and Australia.[35]
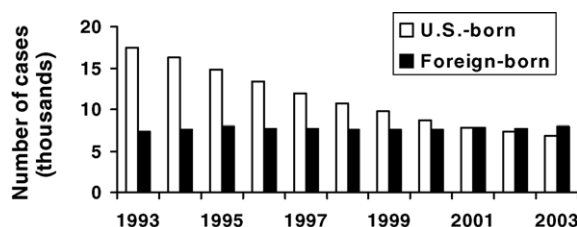

Figure 1   Number of US TB cases in US-born and foreign-born persons, 1993—2003. The absolute number of cases in foreign-born persons has remained constant while the number in US-born persons has fallen steadily. Successful TB control in the US requires strategies to control immigrant TB in the US and US participation in TB control in the countries of origin. Data from the Centers for Disease Control and Prevention (CDC).

Risk of TB disease among immigrants

TB disease rates among immigrants from developing countries are tightly correlated with rates in the country of origin.[32,36—38] For example, in some African immigrant communities, TB annual incidence may exceed 1000 cases per 100,000 population,[39,40] compared to an incidence rate of ten per 100,000 in many developing countries. The risk of progression to active TB is greatest soon after arrival; approximately half the TB cases among immigrants from endemic countries occur during the first five years after immigration.[40,41] However, the risk of progression to active TB in immigrants remains significantly higher than that of native-born persons, even up to 20 years after immigration from an endemic country.[42] Immigration therefore can have significant long-term impact on TB case rates in the new host country.[43]

TB diagnosis among immigrants

Diagnosis of TB among immigrants also presents significant challenges to TB control efforts. Foreign-born persons present with proportionately more extrapulmonary TB than native-born persons in developed countries.[31] In particular, African[44—46] and Asian[47,48] immigrants have had significantly higher rates of extrapulmonary TB than persons born in developed countries, with up to 40—50% of patients presenting with only extrapulmonary disease. A high prevalence of abnormal chest radiographs in certain immigrant populations may also complicate diagnostic efforts. For example, 51% of Tibetan refugees, 20% of Vietnamese refugees, 20% of Hmong refugees, and 13% of Russian refugees who emigrated to Minnesota between 1992—1995 had abnormal chest radiographs, and many of the abnormalities were compatible with active or prior TB.[49] Furthermore, among the Tibetan refugees, 21% were thought to have progressive changes when radiographs obtained in the US were compared to radiographs obtained in India prior to immigration. However, only 8.4% of Tibetan refugees in this study were diagnosed with active TB.

MDR-TB among immigrants

In addition to increased diagnostic challenges posed by a higher prevalence of extrapulmonary TB in foreign-born persons, the treatment of foreign-born TB cases is also more challenging because of a higher prevalence of drug-resistant isolates. Foreign-born patients reported between 1993—1998 in the US who had never previously been treated for TB had higher rates of resistance to isoniazid (11.6% vs.

5.7%) and higher rates of resistance to any first-line antituberculous drug (17.5% vs. 9.7%) than US-born patients. In one study in Texas (US) the rate of multi-drug resistant TB, defined as resistance to both isoniazid and rifampin, was significantly higher among foreign-born than native-born persons (2.4% vs. 0.7%).[50] A Spanish study demonstrated that immigrants with TB in Madrid who had no prior TB treatment had a 33% rate of resistance to any first-line antituberculous drug, compared with a 10.7% rate among all TB patients in Madrid.[46] Rates of drug resistance among immigrant populations reflect the rates in the countries of origin, which are significantly higher in many developing countries than in developed countries.[51]

Transmission vs. reactivation as a source of TB disease

TB among persons who recently immigrated from a developing nation most often represents reactivation of latent disease, with infection acquired in the country of origin. Molecular fingerprinting methods, primarily restriction fragment length polymorphism analysis of IS6110, have been used to assess the extent of transmission of particular TB isolates.[52] Isolates that have the same molecular fingerprint are presumed to be part of a cluster of recent transmission, with one or more persons in the cluster having transmitted infection to the others. These molecular fingerprinting methods have shown that most isolates from foreign-born persons who have immigrated to developed countries are not part of a cluster,[53—59] and likely represent reactivation of prior TB infection. The proportion of foreign-born cases who were not part of a cluster ranged from 55% in San Francisco[57] to 89% in Greater Vancouver.[54] This lack of clustering among foreign-born persons suggests that immigrants do not transmit disease to others as frequently as native-born persons. This suggestion is supported by an analysis of MTB transmission in San Francisco that used molecular fingerprinting combined with mathematical modeling.[57] The transmission index, which represents the average number of secondary TB cases caused directly or indirectly through recent transmission by a source case, was significantly lower for foreign-born persons (transmission index = 0.21) than for native-born persons (transmission index = 0.59).

A more complex association between foreign-born status and TB transmission was observed in a study in New York City examining patients diagnosed between 1990—1999.[60] In this study, foreign-born persons with TB were generally less likely to be part of a cluster (and thus have TB disease due to recent transmission) than native-born persons. However, this relationship was modified by human immunodeficiency virus (HIV) status. Foreign-born TB patients who were HIV-seronegative were less likely to be part of a cluster with increasing duration of residence in the US, while HIV-seropositive foreign-born TB cases were actually increasingly likely to be part of a cluster with increasing duration of residence in the US. Finally, most of the transmission that took place among the foreign-born in the previously mentioned studies was from one foreign-born person to another; transmission from foreign-born to native-born persons was extremely uncommon.

Not all studies have concluded that TB transmission from immigrants is uncommon. In some relatively closed immigrant communities, extensive transmission within the community has been detected. For example, among Senegalese immigrants in northern Italy, 43% of MTB strains were clustered and therefore associated with recent transmission.[61] In another study, 33% of presumed relapses among immigrants in northern Italy were found to be caused by exogenous reinfection.[62] As immigrant communities integrate further with their adopted societies, it would be expected that MTB transmission from the foreign-born to native-born persons will become increasingly common.[33,63]

Molecular fingerprinting methods are extremely useful tools to understand the epidemiology of TB, but these methods have limitations in assessing the extent of transmission among immigrant populations. For example, molecular fingerprinting is often unable to accurately assess TB transmission to young children because of a high proportion of clinical TB diagnoses without culture confirmation in the pediatric population.[64—66] Molecular fingerprinting also only captures transmission that results in secondary active cases of TB, and so underestimates the true extent of transmission.

TB screening among immigrants

It is clear from the preceding discussion that TB among immigrants from developing countries is an important issue on the agenda of TB control for the developed world. Screening of immigrants prior to immigration is one of the major methods used to attempt to find active TB cases early, and thus to limit subsequent morbidity and transmission to others. Many developed countries require TB screening for those coming from developing countries. This consists of chest radiography, followed in some countries by sputum microscopy for acid-fast bacilli if the chest radiograph is abnormal.[67—70] Persons with positive acid-fast smears are usually

not permitted to immigrate until they are no longer infectious, as documented by negative acid-fast smears of several consecutive sputum specimens. However, immigrants with abnormal chest radiographs but negative acid-fast sputum smears frequently have active TB that may become infectious after immigration. For example, in one study of refugees entering the US between October 1999 and September 2000, the incidence of active TB among persons with abnormal chest radiographs classified as having inactive TB was 3625 per 100,000 persons, and the incidence of smear-positive (more infectious) TB was 1000 per 100,000 persons.[71]

Another study of immigrants with abnormal chest radiographs but negative sputum smears in California reported that 3.5% of these persons presented with active TB within one year of arrival.[72] In the Netherlands, asylum seekers with an abnormal chest radiograph on entry had an incidence of 3704 TB cases per 100,000 person-years during a three-year surveillance period.[73] Screening on entry effectively reduced TB transmission in this population.[69] While it is clear that screening new immigrants for TB has a high yield, most immigrants who will develop TB are not captured by current screening measures. For example, in 1995 only 11% of TB cases diagnosed in Florida (US) among foreign-born persons were identified by overseas screening efforts.[74] Reasons for this may include the fact that an X-ray obtained for immigration purposes can be considered 'valid' for 1—2 years and it is not uncommon for immigrant hopefuls to arrive in the US, for example, months to years after the screening X-ray was obtained. In addition, in some countries there has been an active black market for 'normal' X-rays forged with immigrants' names.

Strategies for immigrant screening

Chest radiography has been shown to be a cost-effective method to screen for active TB in persons immigrating from high- to low-prevalence countries.[75] The tuberculin skin test (TST), which detects latent TB infection, is a considerably less cost-effective screening strategy, in part due to poor adherence to chemoprophylaxis recommendations.[76,77] TST to detect latent TB infection is also less cost-effective because most persons with latent TB infection will never develop active TB, so many persons need to be given chemoprophylaxis to prevent a single case of TB. On the whole, however, neither chest radiography nor the TST is likely to have a significant impact on TB case rates in immigrant populations. A significant proportion of immigrants with abnormal chest radiographs do not present for medical evaluation after arrival in the new host country.[78] Also, many foreign-born persons with TB who present in developed countries are either undocumented immigrants or nonimmigrant visitors[79] who would not be screened through the immigration process. Alternative strategies, such as specialized screening programs for undocumented immigrants,[80,81] targeted screening in general practice settings,[82] and prison-based screening programs,[83] have been suggested to target persons who would be missed by conventional immigration screening. However, given the enormous numbers of persons who migrate from the developing world to the developed world each year, immigrant screening programs based in the developed world are unlikely to have a major impact on TB incidence rates among immigrant populations.[84]

Responses to immigrant TB

TB has always been associated with stigma. Since immigrants from the developing world are also at risk for discrimination, the stigma attached to TB may raise formidable barriers to care. Immigrants may want to avoid care for TB, based on a fear that they will experience discrimination or isolation if they are associated with this contagious illness. Illegal immigrants may fear deportation if they are found to have TB.[85] Societal awareness of a high rate of TB in immigrants can provoke either xenophobia or compassionate activism. On the one hand, fear of immigrant TB may lead to fear of immigrants, provoking discrimination, deportation and attempts to screen out immigrants with TB or to reduce immigration generally.[86] All these approaches will motivate immigrants to avoid healthcare. On the other hand, awareness of TB in immigrants and their countries of origin may compel wealthier nations to devote resources to combating TB in the developing world. The responses of medical providers, whether leaning toward xenophobia or compassion, have major impact on societal responses to immigrant TB. The increased ease of international travel has led to increasing recognition that infectious diseases know no borders. Ultimately control of infectious diseases, including TB, will require a global not an insular response. The Global Fund to Fight AIDS, TB, and Malaria is an example of an effective and compassionate response to global infectious disease needs.[87,88]

Summary

TB is increasingly becoming an imported disease in the developed world. Imported TB poses significant challenges to clinicians, including increased diagnostic difficulty presented by a higher prevalence of

extrapulmonary disease and increased treatment difficulty caused by drug-resistant organisms. Efforts to control this disease in developed countries must recognize the changing epidemiology of TB and respond accordingly. While innovative screening strategies and shortened chemoprophylaxis regimens are certainly needed, these efforts are not likely to eliminate TB in the developed world.[89] In the long term, TB control in the developed world will only be achieved by controlling TB in the developing world.

What are successful strategies to control TB in persons with HIV infection?

Controversy

Persons with HIV infection are at increased risk for TB infection, TB disease, and more serious disease when compared to those without HIV infection. In addition to the impact on the individual patient, co-infection with HIV and TB may impact TB control in a population. Strategies that are effective in otherwise healthy populations do not always transfer directly to TB control in persons with HIV infection. Programs directed at HIV and TB may compete for precious resources in developing countries.

Background

It is estimated that 50% of the population of sub-Saharan Africa is latently infected with TB.[90] Once infected with MTB, progressive deterioration of cell-mediated immunity caused by HIV infection increases the risk of TB disease by a hundred-fold or more.[91,92] In 1999, the WHO estimated that 11.8 million people were living with HIV/MTB co-infection, the majority being in sub-Saharan Africa. Once active TB develops, MTB is a potent and virulent pathogen that spreads readily to others with HIV infection, even causing re-infection in those who have completed TB treatment.[93] TB is clearly the most significant AIDS-associated opportunistic infection that can be transmitted to those without HIV infection. Because the AIDS epidemic is most severe in regions of the world that also have the highest rates of TB latent infection, the TB epidemic is also expanding in these locations.

Impact of TB on HIV infection

TB hastens immune deterioration in those with HIV infection.[94] The timing of the initiation of antiretroviral therapy in patients with HIV/TB co-infection is also difficult. Rifampin, a pivotal part of TB treatment,[93] reduces the level of many antiretroviral drugs. Also, an immune reconstitution syndrome may occur with successful HIV therapy. The signs and symptoms of immune reconstitution resemble those of active TB disease, raising the specter of TB treatment failure.[95,96]

Impact of HIV infection on TB

HIV infection significantly increases TB-associated mortality.[97–99] Only rapid diagnosis and TB treatment can reduce this mortality. Those with active TB and HIV infection are more likely to develop drug-resistant TB.[100,101] Laboratory resources for rapid drug-susceptibility testing are particularly important for this group.

Edlin et al. described 18 AIDS patients with TB resistant to at least isoniazid and streptomycin.[102] Those who received appropriate therapy within two weeks of diagnosis had a survival of 86%, compared to 18% among those who did not ($p = 0.01$). Persons with HIV infection are also at risk for disseminated infection with *Mycobacterium avium* complex, *Mycobacterium kansasii*, and other nontuberculous mycobacteria (NTM). Unfortunately, laboratory resources for the diagnosis of MTB and the distinction between MTB and NTM are severely limited in the resource-limited countries most profoundly affected by TB and HIV co-infection. The vast majority of TB cases in the developing world are diagnosed on the basis of sputum smear microscopy alone. Reliance on the sputum smear alone may result in missing the diagnosis in up to 50% of TB patients who are smear-negative, or may lead to inaccurate treatment for TB in persons with HIV who have other mycobacterial pathogens.[103] Lack of laboratory diagnostic capacity leads to poor clinical outcomes, prevents epidemiologic assessment of mycobacterial disease in the region and may preclude initiation or participation in meaningful clinical or translational research.

Efficacy of the treatment of LTBI in persons with HIV infection

Treatment of LTBI has similar relative efficacy in patients with or without HIV. Treatment reduces the active TB rate in TST-positive HIV-infected adults by 60—80% (Table 5).[104] Since the absolute risk of active TB is much higher in persons with HIV infection, the absolute benefit in this population is high. Trials of treatment of LTBI in persons with HIV infection have been carried out in a wide variety of settings, including countries in which

Table 5 Prospective randomized trials of preventative TB therapy among persons infected with HIV.

Location (reference no.)	TST status of study subjects	Preventative treatment regimen	TB rate per 100 person-years	Relative risk of TB (95% CI)
Haiti[2]	TST positive (n = 25)	12 months of placebo; daily	10.0	5.8 (1.2—28.7)
	TST positive (n = 38)	12 months of INH; daily	1.7	1
	TST negative (n = 35)	12 months of placebo; daily	5.7	1.8 (0.4—9.2)
	TST negative (n = 20)	12 months of INH; daily	3.2	1
Haiti[105]	TST positive (n = 370)	6 months of INH; two times a week	1.7	1
	TST positive (n = 380)	2 months of RIF,PZA; two times a week	1.8	1.1
Uganda[3]	TST positive (n = 464)	6 months of placebo; daily	3.4	1
	TST positive (n = 536)	6 months of INH; daily	1.1	0.3 (0.1—0.8)
	TST positive (n = 556)	3 months of INH,RIF; daily	1.3	0.4 (0.2—0.9)
	TST positive (n = 462)	3 months of INH,RIF,PZA; daily	1.7	0.4 (0.2—0.9)
	Anergic (n = 323)	6 months of placebo; daily	3.1	1
	Anergic (n = 395)	6 months of INH; daily	2.5	0.7 (0.3—1.9)
Zambia[22]	TST positive (n = 60)	6 months of placebo; two times a week	9.8	1
	TST positive (n = 52)	6 months of INH; two times a week	2.3	0.3 (0.05—1.4)
	TST positive (n = 49)	3 months of RIF,PZA; two times a week	2.7	0.3 (0.05—1.4)
	TST negative (n = 166)	6 months of placebo; two times a week	3.1	1
	TST negative (n = 178)	6 months of INH; two times a week	2.5	0.9 (0.31—2.4)
	TST negative (n = 173)	3 months of RIF,PZA; two times a week	3.8	1.3 (0.50—3.2)
Kenya[21]	TST positive (n = 67)	6 months of placebo; daily	8.0	1
	TST positive (n = 69)	6 months of INH; daily	5.6	0.6 (0.2—1.6)
	TST negative (n = 235)	6 months of placebo; daily	2.7	1
	TST negative (n = 224)	6 months of INH; daily	3.3	1.2 (0.6—2.7)
United States[113]	Anergic (n = 257)	6 months of placebo; daily	0.9	1
	Anergic (n = 260)	6 months of INH; daily	0.4	0.5 (0.1—1.9)
Multinational[11]	TST positive (n = 792)	12 months of INH; daily	1.1	1
	TST positive (n = 791)	2 months of RIF,PZA; daily	0.8	0.72 (0.40—1.31)

Table updated from reference 114; CI, confidence interval; INH, isoniazid; PZA, pyrazinamide; RIF, rifampin; TST, tuberculin skin test.

BCG vaccination is administered routinely at birth. The TST remains informative in adults who received BCG vaccination as children. The rates of TB disease were higher in subjects with a positive TST than in those with a negative TST.[2,21,22] Furthermore, treatment of LTBI remains effective in lowering the rate of TB infection in adults with HIV infection and positive TST who received BCG as children. Several studies in persons with HIV infec-

tion demonstrate that two or three months of combination therapy with rifampin and pyrazinamide had equal efficacy to six or twelve months of isoniazid.[11] The combination of rifampin and pyrazinamide appears to have less hepatotoxicity in persons with HIV infection than in non-HIV-infected populations, based on comparisons between randomized controlled trials in persons with HIV infection and later clinical experience in persons

without HIV infection.[6,11,15,16,22,105] The rifampin/pyrazinamide regimen for treatment of LTBI is not recommended for routine use in the US either for HIV-positive or HIV-negative persons,[17] but it may be considered when the more prolonged isoniazid treatment is not feasible.[6]

Challenges to the use of LTBI in persons with HIV infection

There are a number of challenges associated with diagnosis and treatment of LTBI in patients with HIV infection. First, the diagnosis of LTBI using the TST is less sensitive when the CD4 count falls below about 200 cells $\times 10^6$/L at which time the person's cell-mediated immunity has often deteriorated to the point of anergy. New serum tests based on release of interferon-γ after in vitro stimulation with MTB specific antigens may help in this regard, but published studies have not yet demonstrated this. In countries where up to 50% of the population is thought to be infected with TB, some have advocated treating all patients with HIV infection for LTBI. However, as can be seen in Table 5, anergic patients and others with negative TST did not benefit significantly, and there are major program costs associated with this response. On the other hand, high TB incidence rates increase the likelihood of exogenous reinfection, raising the question of whether treatment of LTBI should be prolonged, either as a lifelong strategy or until antiretroviral therapy results in immune reconstitution.[106,107] Application of these strategies will depend on local TB incidence and the availability of resources. Treatment for LTBI in persons with HIV infection and a positive TST has clear value, but may not reach a high enough priority to warrant expenditures if core TB program activities have not been met.

Effect of highly-active antiretroviral therapy (HAART) on TB

HAART impedes HIV replication, leading to a reduction in HIV viral load. The degree of viral load suppression correlates with eventual immune reconstitution and an increase in CD4 lymphocyte count. Numerous studies have shown that the incidence of opportunistic infections due to both MTB and the *M. avium* complex declines dramatically as immune reconstitution becomes established.[108–110] Though of great importance to the individual patient, HAART alone has limited impact on the population incidence of TB disease among persons with HIV infection. Dye and colleagues used a cohort analysis approach to predict the effect of antiretroviral therapy as a means of TB control in a high-incidence region such as sub-Saharan Africa.[111] They found that HAART alone, if started at the currently-recommended CD4 count of 200 or less, would reduce the cumulative incidence of TB by only 22% over 20 years. Only by starting HAART at a much higher CD4 count, and combining it with treatment of LTBI could the TB incidence be reduced by an estimated 70% in HIV-infected persons.

Summary

Global TB control in 2004 relies on the same basic tools that have been used for decades: aggressive case-finding plus organized and consistently funded public health treatment centers that administer and closely monitor adherence to a 3- or 4-drug treatment plan. Components that are standard in developed countries need to be implemented in developing countries: sputum culture, susceptibility testing, and individual treatment plans that are guided by these results.

New challenges including global population mobility, HIV infection, limited resources, and drug resistance will require flexibility in the precise application of these TB control tools in different locales. TB control officers in different countries have much to learn from one another about strategies that succeed and those that do not. Effective TB control requires a mixture of medical expertise and compassionate activism.

Acknowledgements

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