Tuberculosis in the tropics
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This review focuses on the global importance, clinical epidemiology, and control of tuberculosis (TB) in tropical countries. Eighty percent of the global burden of tuberculosis is carried by 23 countries, nearly all of which are tropical [1]. Countries that are considered tropical are those in Central and South America, sub-Saharan Africa, South and Southeast Asia, and the adjacent islands. Not all of these areas are geographically in the tropics, but the regional tuberculosis problems they face are similar. It could be argued that Eastern Europe should be included because their socio-economic problems are similar to those of many developing countries. There are several unique aspects about the recent rise of tuberculosis in Eastern Europe, however, particularly the collapse of the state infrastructure and the resulting epidemic of multi-drug–resistant tuberculosis [2,3].

Mycobacterium tuberculosis is a highly infectious pathogen transmitted by the airborne route. A recent report documented transmission of \textit{M tuberculosis} on a passenger airliner [4]. TB has declined dramatically in industrialized countries, and their populations will become increasingly vulnerable. In several industrialized countries the majority of cases of TB are in foreign-born residents [2]—this is likely to become true in most industrialized countries. TB control thus has global importance. Experiences in resource-poor settings can benefit practitioners in resource-rich settings. Maximizing the yield of simple diagnostic tests will lead to more rapid diagnoses and reduce the need for invasive tests. Industrialized countries can learn from the innovative ways of delivering directly observed therapy developed over decades in developing countries.

\textbf{Epidemiology}

\textit{General patterns of tuberculosis epidemics}

TB has been present for thousands of years in humans [5]. The first epidemic, which started in Europe in the eighteenth century, was triggered by overcrowding and poverty associated with the industrial revolution. This led to increased transmission as well as greater susceptibility to disease due to factors such as malnutrition and alcohol abuse. Epidemics of TB span centuries due to the chronicity of the disease and the long period of clinical latency in most infectious cases (adults who present with pulmonary cavities). The initial phases of a TB epidemic are characterized by a high death rate, particularly among children and young adults [5]. Because mortality is high at or prior to the reproductive years, there is a powerful selection pressure favoring the survival of individuals who are able to contain the initial infection. As the epidemic progresses, mortality falls, older patients are affected, and eventually rates of TB gradually decline [5,6].

Europeans introduced TB into the interior of most tropical countries—in the mid-nineteenth century to Native Americans and at the beginning of the twentieth century in sub-Saharan Africa [5]. Urbanization and overcrowding has occurred more recently in tropical countries. Thus TB epidemics in tropical countries are a relatively recent phenomenon.

\textit{Epidemiology in children}

Accurate data for childhood tuberculosis are not available due to the low priority of the disease and the problem of accurate diagnosis. It is estimated that there is a global incidence of 1.3 million TB cases
with a mortality rate of 450,000 per year in children >15 years of age [7–9]. Developing countries carry the highest burden with >90% of cases and >95% of deaths.

The age distribution of TB from a high incidence community is shown in Fig. 1. Children <5 years of age are most affected, followed by a sharp drop until the mid-teens. The lifetime risk for developing TB after infection is 43% in infants, 24% in children aged 1 to 5 years, and 15% in adolescents [10], compared to immunocompetent adults, who have a lifetime risk of 5% to 10%. Younger children also experience more severe disease such as meningitis or disseminated disease [10,11].

A study of a South African community with a high incidence of TB found that the incidence in children was 3.5 times higher than in adults [12]. Children accounted for 39% of all cases. As TB incidence declines the proportion of childhood cases decreases, reaching 3% to 6% in developed countries [13,14].

Reactivation or re-infection?

Pulmonary TB in adults might occur many years after a primary infection as a result of either endogenous reactivation of the primary infection or a recent, exogenous re-infection. DNA fingerprinting is defining the role of these two mechanisms. It is not surprising that the immune suppression resulting from HIV infection leads to higher rates of exogenous re-infection [15–17]. A number of recent studies in populations with a low HIV burden have shown that exogenous re-infection plays an important role in adults [16–18]. The contribution of re-infection to the total caseload of “relapse” patients varies between 16% in a low incidence area [16] and more than 70% in a high incidence area [18]. It is hoped that these and future studies will provide evidence for the hypotheses of the models [19,20] that attempt to link the relative contribution of re-infection to the incidence of TB in an area. It is important to understand what this contribution is, especially in high incidence areas, and if an improved vaccine for TB is to be developed, researchers must understand why a first episode of TB does not provide lasting immunity.

Current global tuberculosis epidemics

In 1999 the World Health Organization (WHO) estimated that there were 8.4 million cases of TB compared to 8 million in 1997 [1]. The proportion of notifications by region is shown in Fig. 2.

The 5% global increase is largely due to a 20% increase in cases from sub-Saharan Africa [1,2]. TB
rates are relatively constant in Asia and Latin America but have been increasing steadily in sub-Saharan Africa for the last 2 decades [2]. Fig. 3 shows longitudinal notification rates in two tropical countries with HIV burdens that are high: Malawi, with 15.96% of adults HIV infected in 1999 [21], or low: Brazil, with 0.57% of adults HIV infected in 1999 [21]. The increased notification rates seen in Malawi are not likely due to poor control because 100% of their cases in 1999 were treated according to the WHO’s Directly Observed Therapy Short-course (DOTS) strategy, compared with just 7% in Brazil [1]. The increase in TB caseload in sub-Saharan Africa is largely due to the HIV pandemic.

Effect of HIV

HIV infection causes about a tenfold increase in TB incidence with a much higher risk in patients who have clinically advanced disease [22]. African countries with a low or intermediate HIV prevalence are able to contain the rise in incidence of TB provided they have reasonably functioning National Tuberculosis Programs [23]. Even countries with well-functioning national tuberculosis control programs have experienced dramatic increases in TB, however (Fig. 4).

HIV-infected individuals have much higher mortality while being treated for TB [24,25]. This increased mortality is largely due to HIV-related diseases other than TB. Declining mortality has been used as an indicator of TB control, but is difficult to use in areas with high HIV prevalence. This is illustrated by the example of the Central African country Malawi, where HIV infection was present in 72% of adults with smear-positive pulmonary TB in 1995 [26]. The WHO reports 22% mortality among new smear-positive cases in Malawi in 1999 with treatment success in 69% [1]; this represents good control despite an appallingly high mortality.

Silicosis

TB occurs with much greater frequency in patients with silicosis [27]. Due to inadequate dust control silicosis is common in many tropical countries, notably in Hong Kong [28] and the mines of Central and Southern Africa [27,29]. Silicosis multiplies the risk of TB in HIV-infected miners [29]. In Central and Southern Africa many hundreds of
thousands of migrant miners have acquired silicosis and subsequently developed TB when repatriated. Together with the secondary cases it is likely that silicosis has caused a significant proportion of TB in the region.

Possible role of helminth co-infection

A good cellular or Th1 immune response is necessary to contain *M. tuberculosis* infection. Helminthic infections induce a Th2 immune response.
that suppresses the Th1 response. It has been postulated that helminthic infections predispose patients to the development of TB [30]. PPD-specific immune responses are suppressed in young adults infected with helminths [31]. Helminthic infections are endemic in developing countries—where 95% of patients with TB live—and could predispose individuals to TB.

**Diagnosis in resource-poor settings**

Shortening the period of infectiousness is important in controlling TB [2]. In tropical countries access to health care centers is often difficult and late presentation is common. Further delays after presentation are frequently due to the slow turnaround time and low yield of diagnostic tests. The cornerstone of diagnosis in the tropics is the sputum smear. This is an inexpensive and rapid test that identifies the most infectious cases. Sputum microscopy on site is helpful in reducing diagnostic delay and is practiced widely in the tropics. Mycobacterial culture and histopathology are not widely available outside major urban centers; this leads to diagnostic problems in children and, increasingly, in HIV infection.

**Diagnosing tuberculosis in children**

The diagnosis of TB in childhood is notoriously difficult. TB in children is pauci-bacillary and therefore usually smear-negative. Bacterial confirmation of disease by positive cultures for *M tuberculosis* is achieved in only 10% to 30% of children treated for TB [8,32]. The diagnosis of TB in children is thus often a clinical diagnosis dependent on a constellation of symptoms, signs, history of contact with an infectious adult who has TB, tuberculin skin test, and chest radiography [33,34]. The most common radiographic features of childhood intrathoracic TB are mediastinal lymphadenopathy (49% to 70%), lobar opacification (56%), lobar or segmental collapse (17%), pleural effusion (12%), miliary opacification (6%), and lung cavities (6%) [32,34,35]. The diagnosis of TB in HIV-infected children appears to be similar to diagnosis in uninfected children [36].

**Limitations of tuberculin skin tests in adults**

Tuberculin skin testing is widely performed in industrialized countries as an aid in diagnosing TB. The test detects infection with TB but cannot distinguish latent infection from disease. In most African countries the majority of adults have been infected, so the test is of little value. Furthermore, Bacille Calmette-Guérin (BCG) vaccination, which is widely administered in the tropics, results in positive tuberculin skin tests that persist into adulthood [37]. A further limitation of skin testing in areas with high HIV prevalence is that the immune response, which forms the basis of a positive tuberculin skin test, becomes progressively impaired. For these reasons tuberculin skin testing is of little value as a diagnostic test in adults with suspected tuberculous disease in tropical countries, except for young adults presenting with primary TB. It is, however, the only test that can diagnose latent TB and is therefore necessary for detection in patients who are likely to benefit from preventive therapy.

**Diagnostic problems of HIV-associated tuberculosis in the tropics**

HIV infection in adults has led to an increase in the proportion of cases that are difficult to diagnose, either because they have extrapulmonary disease or are sputum smear-negative [38]. Diagnostic difficulties in tropical countries with a high HIV prevalence lead to under-diagnosis, which often has fatal consequences. An autopsy study found undiagnosed TB in 44% of HIV-infected patients dying with wasting [39]. *M tuberculosis* was the most common organism cultured from blood in another study, but it was often unrecognized before death [40]. Over-diagnosis of TB, with consequent wasting of precious resources in TB control programs, is also common.

The sputum smear is still the most common method of diagnosing HIV-associated TB [41]. The sensitivity of sputum smear examination can be improved and the time taken to examine the slide shortened by using fluorochrome staining [38]. Fluorescent microscopes are expensive, however, and are not widely available in tropical countries. A simple technique of sputum concentration improves the yield of sputum smear in patients with HIV infection [42]. Sputum induction with hypertonic saline is often positive if sputum is unobtainable or smear-negative [43]. Smears of lymph node needle aspirates have a high yield [41,44,45].

If the sputum or lymph node aspirate is smear-negative, assessment on the basis of clinical features and chest radiograph remains the mainstay of diagnosis because bronchoscopy is not widely available in the tropics and mycobacterial culture, when available, is slow. The chest radiographic features in HIV-associated TB differ from that seen in HIV-seronegative patients, with a significantly higher proportion having lymphadenopathy, pleural effusions, miliary
nODULES, AND CONSOLIDATION. A SIGNIFICANTLY LOWER PROPORTION OF PATIENTS HAVE CAVITATION ON THEIR CHEST RADIOGRAPHS [46]. THESE ATYPICAL FEATURES OF ADULT PULMONARY TB BECOME MORE APPARENT WITH ADVANCING IMMUNE SUPPRESSION [47].

THE WHO HAS PROPOSED A CASE DEFINITION FOR SMEAR-NEGATIVE PULMONARY TB BASED ON THREE NEGATIVE SPUTUM SMEARS, RADIOGRAPHIC ABNORMALITIES CONSISTENT WITH ACTIVE PULMONARY TB, AND NO RESPONSE TO A COURSE OF BROAD-SPECTRUM ANTIBIOTICS [48]. MOST PATIENTSfulfilling the case definition in a Malawian study were HIV-seropositive [48]. The final diagnosis was tuberculosis in 78%, but treatable conditions would have been missed in 14%, indicating the need for further refinement. Case definitions for extrapulmonary TB need to be developed.

**Therapy**

The most effective therapy for TB is a short-course (6 months) rifampin-based regimen. Supervised administration of short-course regimens leads to better completion rates and thus more success—this strategy is the so-called Directly Observed Therapy, Short-course (DOTS). The global success rates of DOTS for new sputum smear-positive cases in 1997 were 78% for DOTS and 38% for non-DOTS [1]. One of the main benefits of the DOTS strategy is minimizing the development of drug resistance [49]. It is estimated that 45% of the world’s population had access to DOTS in 1999 [1]. The targets set by the WHO of 70% case detection rate and 85% cure are likely to be achieved in 2013 at current rates rather than by 2005, as was previously hoped [1], because DOTS coverage has increased at a rate slower than anticipated.

HIV-infected patients with TB respond well to short-course therapy; relapse rates are low and similar to those of HIV-seronegative patients [24]. A recent study found that relapse rates were higher in patients with symptomatic HIV disease and suggested a role for secondary prophylaxis, however [50]. The increased mortality in HIV-infected patients treated for TB [24,25], largely due to opportunistic diseases other than TB, has been discussed above.

Unfortunately, rifampin is relatively expensive for the poorest countries, many of which reserve short-course therapy for sputum smear-positive patients. Patients who are sputum smear-negative or have extrapulmonary disease are treated with longer regimens that include streptomycin or thioacetazone [38]. These regimens are more toxic (especially those containing thioacetazone), which may cause severe and even fatal skin reactions in HIV-infected patients. These regimens are also less effective than rifampin-based regimens [38]. Fortunately most tropical countries are adopting short-course therapy for all patients.

**Delivering directly observed therapy**

In most areas directly observed therapy (DOT) is clinic-based with nurses supervising therapy, but the costs to patients in developing countries is high [51,52]. Several alternative models of DOT that are more convenient for patients have been tried in tropical countries. Trained community lay supervisors have proved successful [53] and this model is being widely applied in Southern Africa. Using patient-nominated family members as drug supervisors is even more convenient for patients. A recent Malawian study found improved adherence compared to health care worker drug supervisors [54].

**Multi-drug-resistant tuberculosis**

Multi-drug-resistant TB is defined by resistance to both isoniazid and rifampin. Therapy for multi-drug resistance is prolonged, toxic, expensive, and less effective than conventional therapy for drug-sensitive TB [55]. The expense of the regimen is beyond the reach of the poorest countries. Diagnosing multi-drug resistance is also expensive. A retreatment regimen consisting of rifampin, isoniazid, pyrazinamide, and ethambutol for 3 months (with streptomycin for the first 2 months) followed by rifampin, isoniazid, and ethambutol for 5 months has been devised for use in resource-poor settings with limited access to mycobacterial culture and sensitivity testing. A retrospective Nicaraguan study reported high success rates with this regimen in patients with multi-drug resistance [56]. The long-term strategy with multi-drug–resistant TB is to prevent its occurrence with DOTS.

**Prevention strategies**

**BCG in high prevalence communities**

BCG vaccination is very widely administered in tropical countries, yet its efficacy in preventing infectious cases of adult TB is questionable. Variable results have been obtained in clinical trials, with studies in tropical countries generally showing the most disappointing results [57]. Part of the reason for this may be exposure to environmental mycobacteria. BCG vac-
Citation does, however, protect against tuberculous meningitis and miliary TB, which are the most lethal manifestations in children [57]. It is thus worthwhile to continue administering BCG vaccination at birth in tropical countries. A more effective vaccine would make an enormous contribution to the reduction of the global TB epidemic [2].

Preventive therapy

In tropical countries preventive therapy has a role in high-risk cases only as the prevalence of infection (assessed by a positive tuberculin skin test) is very high. It is generally limited to young children who are close contacts of an infectious individual or HIV-infected patient.

Preventive therapy for HIV-infected patients

TB can be prevented in tuberculin skin test-positive adults with HIV infection [58,59]. The reduction in risk is around 60%. Identifying HIV-infected individuals is difficult in resource-poor settings. The development of voluntary counseling and testing centers is seen as an effective tool to promote safer sex through counseling and offering those with HIV infection interventions such as preventive therapy for TB. Early experiences with this approach in Uganda were disappointing; high dropout rates were reported [60]. Improved counseling and the development of rapid on-site HIV testing are yielding better results. It is unlikely, however, that enough HIV-infected individuals can be identified. Preventive therapy should therefore be seen as benefitting the individual rather than playing a major role in controlling TB in tropical countries with a high HIV prevalence. The relatively short-term benefit of preventive therapy is a further problem [61,62].

Prevention of nosocomial transmission in resource-poor settings

Preventing nosocomial transmission of an airborne pathogen such as TB requires sophisticated facilities, which are very expensive. Negative pressure ventilation and effective respiratory protection for health care workers are seldom available in tropical countries. Measures to limit nosocomial transmission of TB that are practical and affordable in resource-poor settings have been reviewed [63]. Admitting HIV-infected patients into TB hospitals exposes the patients to cases with multi-drug resistance. A recent outbreak occurred in South Africa with six HIV-infected patients admitted to a TB hospital with drug-sensitive tuberculosis—all developed multi-drug-resistant TB and died [64]. Recognition of outbreaks such as this requires sophisticated laboratory surveillance, which is seldom available in tropical countries. The extent of nosocomial transmission is unknown, but it is likely to be considerable.

Sequelae

Fibrotic changes following pulmonary TB in adults or endobronchial TB in children [65] can result in a number of permanent sequelae including aspergillomas, bronchiectasis, and chronic obstructive airway disease [66–68]. TB or its sequelae are the most common causes of life-threatening hemoptysis in tropical countries [69,70]. Because of the high incidence of TB and the frequent late presentation in resource-poor settings, sequelae of TB cause considerable morbidity in tropical countries. There is a surprising lack of research measuring the total burden of these tuberculous sequelae in tropical countries.

Summary

Tropical countries bear the brunt of the global TB burden. Young children are at high risk and suffer the most severe forms of TB; adults with pulmonary cavities are the main sources of transmission. The incidence in sub-Saharan Africa is increasing as a consequence of the HIV pandemic. Smear-negative TB, which is common in children and patients who have HIV infection, is becoming a major problem in resource-poor settings where access to mycobacterial culture and histopathology is limited. Clinical case definitions are being developed to address this problem. Short courses of rifampin-based therapy are not universally available, but access is increasing. DOTS is the main strategy that the WHO is promoting to improve TB control. This is particularly important for sputum smear-positive patients. Unfortunately, the DOTS targets set by the WHO have not yet been met. Innovative, low-cost ways of supervising therapy have been developed using family members or lay supervisors. Preventive therapy in tropical countries is limited to high-risk cases (young children and HIV-infected patients who are tuberculin skin test-positive). An improved TB vaccine would dramatically improve TB control.
References


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