Controversies and Unresolved Issues in Tuberculosis Prevention and Control: A Low-Burden-Country Perspective

Ibrahim Abubakar,[1,2] Helen R. Stagg,[1] Ted Cohen,[3] Punam Mangtani,[4] Laura C. Rodrigues,[4] Laura Pimpin,[1] John M. Watson,[1] S. Bertel Squire,[5] and Alimuddin Zumla[6]

[1]Respiratory Diseases Department, Health Protection Services Colindale, Health Protection Agency, London; [2]Department of Medicine, Norwich Medical School, University of East Anglia, United Kingdom; [3]Brigham and Women's Hospital and Harvard School of Public Health, Boston, Massachusetts; [4]Department of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine; [5]Liverpool School of Tropical Medicine; and [6]Department of Infections, Division of Infection and Immunity, University College London Medical School, United Kingdom

Despite declining incidence in most high-income countries, tuberculosis shows no signs of disappearing in the near future. Although surveillance data from most Western European countries show relatively stable declines in the rate of tuberculosis over the past several decades, some have reported either an increasing rate or a decelerating pace of reduction in recent years. The burden of disease now disproportionately affects high-risk groups such as migrants, homeless persons, and prisoners. In view of the concentration of cases in urban areas and high-risk deprived groups, interventions that may not be efficient when applied to the general population may be highly cost effective when targeted at high-risk groups. In this article, we examine some controversial elements of tuberculosis prevention and control in low-burden countries and recommend issues for further research. In particular, we assess current evidence on the duration of protection by BCG vaccine, the screening of migrants and hard-to-reach groups, and the use of preventive therapy for contacts of cases of infectious multidrug-resistant tuberculosis. This analysis is presented from the perspective of low-tuberculosis-burden, high-income countries attempting to eliminate tuberculosis.

Despite declining incidence in most high-income countries, tuberculosis shows no signs of disappearing in the near future [1]. Although surveillance data from most Western European countries show relatively stable declines in the rate of tuberculosis over the past several decades [2], some have reported either an increasing rate or a decelerating pace of reduction in recent years [3]. In the United States, an unexpected fall in the number of tuberculosis cases in 2009 [4] was followed by a return to the previous slow rate of decline [5]. Although high-income countries have low rates of disease compared with global averages, the burden of disease in these settings is heterogeneously distributed and remains stubbornly high in large urban centers. For example, a recent study indicated that 60% of US cities do not show a declining trend [6]. At the same time, the burden of disease now disproportionately affects high-risk groups such as migrants, homeless persons, and prisoners [7, 8]. Mathematical modeling suggests that even in settings where rates of tuberculosis are declining, localized outbreaks may occur as a result of the heterogeneity of contact networks [9]. In view of the concentration of cases in certain areas and groups of the population, interventions that may not be efficient when applied to the general population may be highly cost-effective when targeted at high-risk groups [10]. Further cost-effectiveness

DOI: 10.1093/infdis/jir886

research to inform tuberculosis control in high-risk groups would help to ensure the prioritization of resources to support this effort.

Tuberculosis elimination is a stated goal of US [11] and European Union [12] public health policies. However, current World Health Organization (WHO) projections indicate that no region is on track to achieve elimination, even by 2050 [1]. To "stop TB," even in these low-burden settings, significant resources must be applied in a concerted manner. Previous attempts to interrupt localized concentrations of disease in these low-burden settings have required substantial structural changes in the facilities available, in the organization of the program and financial investment [13]. As tuberculosis declines in the general population, increasingly it becomes a disease confined to hard-to-reach groups. These groups are often characterized by specific social characteristics or behaviors, for example, migration, substance abuse, incarceration, and homelessness. These are some convenient labels that imply separate social groupings, whereas in reality there is significant overlap among these groups. The overriding issues linking all of these groups are poverty and social deprivation. The diligent application of evidence-based interventions to ensure prompt diagnosis and improve treatment completion and infection control among these groups will be needed, but will require more investment per case than "routine" interventions.

In many countries, the improvement of living standards led to significant declines in tuberculosis rates in the early parts of the last century. Attention to the wider social determinants of tuberculosis and the socioeconomic factors hampering effective control remain important measures for reducing health disparities and protecting vulnerable groups that suffer outsize risks of infection and disease. There is overwhelming evidence that prompt diagnosis and treatment of active tuberculosis reduces disease burden in a population [14]. Historically, tuberculosis prevention and control programs in many countries have focused on this, together with BCG vaccination. In addition, contact investigation and the use of preventive therapies against latent *Mycobacterium tuberculosis* infection (latent tuberculosis) are widely applied control measures in low-burden countries. The use of some interventions for tuberculosis prevention and control is, however, more controversial. Interventions that lack a consensus on effectiveness and cost-effectiveness include screening of migrants from high-tuberculosis-incidence to low-incidence countries in order to detect active tuberculosis and latent tuberculosis, the identification and treatment of latent tuberculosis in hard-to-reach groups, the use of preventive therapy in persons who might be latently infected with drug-resistant *M. tuberculosis* strains, and the duration of protection of BCG vaccine, to name just a few.

In this article, we examine some controversial elements of tuberculosis prevention and control in low-burden countries and recommend issues for further research. In particular, we assess current evidence from the perspectives of a low-burden country attempting elimination, the duration of protection by BCG, screening of migrants and hard-to-reach groups for latent tuberculosis and active disease, and use of preventive therapy for contacting cases of infectious multidrug-resistant (MDR) tuberculosis.

BCG AND DURATION OF PROTECTION

What Is the Evidence of Effectiveness and Duration of Protection?

Several systematic reviews to date conclude that BCG vaccination of infants is very effective in preventing miliary tuberculosis and meningitis in children [15, 16]. Data on other forms of tuberculosis show that protection is more heterogeneous. Studies in locations farther from the equator find a higher level of protection compared with those at lower latitudes [17]. BCG has been part of the WHO Expanded Program on Immunization since 1974, and coverage is very high in high-burden countries. Implementation in low-burden countries has been variable. Several Western European countries have undertaken either infant or school-age vaccination programs, supported by major trials showing a high level of protection in UK schoolchildren in the 1950s, Norwegian nurses in the 1920s, and Native Americans in the 1930s [18]. The United States, Canada, Italy, and the Netherlands, however, have never utilized BCG vaccination on a population level, because US trials during this same period showed little protective effect. Zwerling et al developed a global map of current and past BCG vaccination policies [19]. The assessment of the contribution of BCG vaccination in tuberculosis control is made more difficult by the concurrent implementation of other effective measures, the possible reduction in protection at older ages when pulmonary disease is more predominant, and human immunodeficiency virus. Declining rates of tuberculosis, irrespective of national BCG vaccination policy, are consistent with a short-term impact at the population level, that is, the impact of BCG on tuberculosis transmission might have been modest. Nevertheless, national programs should consider BCG as part of a package of control measures in low-incidence countries for specific subgroups, such as immigrants from high-burden countries who are likely to be at a higher risk of subsequent exposure and staff who work with patients with drug-resistant tuberculosis.

In a systematic review published in 1998, it was concluded that the level of protection by BCG declines with time after vaccination, with very little evidence of protection lasting longer than 10 years [20]. More recently, results from long-term follow-up of individuals recruited to the 1930s study of Native Americans [21], and a small number of observational studies, suggest that BCG may protect for a longer period of time. The reasons for variation in the duration of protection relate, in

part, to the paucity of data beyond 10 years; too few studies have followed up participants or too few events have occurred to determine the significance of any observed difference.

Why Is This Important?

An understanding of the reason why the protection conferred by BCG differs between populations, as well as the duration of protection, is important. This understanding is significant not only to inform its use within national programs, but also for development of new vaccines, the correct timing of their administration in previously vaccinated persons, and the influence of the locality in which they are administered.

What Future Work Is Needed?

A systematic review of existing studies examining the duration of protection and analysis of factors that affect any observed variation would be valuable. Although very large randomized controlled trials and/or cohort studies with long follow-up periods would be the ideal method to investigate duration of BCG protection against tuberculosis, the ethical issues of denying vaccination to certain individuals and the need for an urgent resolution to this research question to inform the development of new vaccines means that a case-control study is the only practical approach [22].

Twelve new candidate vaccines have gone into clinical trials [23], including 3 recombinant BCG vaccines and a number of boosters of BCG-prime vaccination. It is likely that more vaccines will be developed, some of which may have the potential to reduce the incidence of active tuberculosis disease in individuals with latent tuberculosis. It is important to have an understanding of the impact of prior BCG vaccination on the protective efficacy of new vaccines. In addition, new trials should be designed to allow the subsequent measurement of the duration of protection conferred by the most efficacious candidates. Robust surveillance systems that can effectively monitor long-term trends will be necessary to confirm impact at the population level.

SCREENING AND TREATING TUBERCULOSIS IN HIGH-RISK GROUPS

Migrants From High-Tuberculosis-Burden Countries

Migrant screening for tuberculosis is usually designed to detect active disease. This permits the treatment of individuals and potentially averts transmission. In some countries, assessing at-risk healthy persons for evidence of latent tuberculosis and subsequent treatment is also utilized as a control policy. With >50% of tuberculosis now diagnosed in migrant communities in many low-prevalence countries and with most of these cases presumed to have been infected in their country of origin, the potential for identifying and treating latent infections becomes an attractive control measure. A question therefore exists of whether screening just for active disease is sufficient or whether migrants should also be tested for latent tuberculosis.

The setting in which migrant screening is undertaken also differs between countries and substantially influences the effectiveness of the program. For example, screening for active disease at the port of entry (as carried out in major UK airports) could only be effective at ensuring that active cases are fully diagnosed and treated if there is a reliable follow-up system. Screening after entry uses systems that are already linked to other local services and thus have been shown to have a low loss-to-follow-up rate. Migrants can also be screened and treated for active tuberculosis prior to leaving their country of origin, but this approach does not enable screening of others who enter the country, such as illegal immigrants and those whose original stated intention was to stay for a short period of time.

The extent to which low-burden countries have implemented widespread screening of migrants from high-burden countries has differed considerably. The United States has promoted the screening of immigrants, including testing for latent tuberculosis [11], but Western European countries have had variable levels of implementation of screening policies. A recent review of screening in low-burden countries highlights this variation [30]. Another important consideration for national tuberculosis control programs and policies makers is how focusing entirely on tuberculosis diagnosed within a country's borders compares to greater investment in the global effort to stop tuberculosis (the so-called enlightened self-interest approach) [24].

Is Screening for Latent Tuberculosis and Active Tuberculosis Disease in Immigrants Effective and Cost Effective at a Population Level?

Latent Tuberculosis

Screening for latent tuberculosis in migrants to low-burden countries is important because the majority of their tuberculosis arises through the reactivation of infections acquired abroad. A recent cost-effectiveness analysis suggested that in the United States, screening of migrants for latent infection with interferon-γ release assays (IGRAs) is more cost-effective than using the tuberculin skin test [25]. The National Institute for Health and Clinical Excellence (NICE), which is based in the United Kingdom, is responsible for providing national guidance advice regarding healthcare [26]. Their guidelines have shown that screening with either the tuberculin skin test followed by an IGRA, or with IGRA only, is cost-effective. These guidelines are not always followed [28]. The cost-effectiveness of latent tuberculosis screening programs is also dependent on the extent to which treatment is completed. It is important to note that even in low-tuberculosis-burden countries, the absolute quality of life improvement derived from the treatment of latent infection is limited due to the relatively low risk of progression for many individuals with a positive test for latent tuberculosis. It is therefore important

that the formulation of national guidelines always weigh the benefits of offering treatment against the probability of adverse effects [29] and the opportunity cost of widespread latent tuberculosis treatment.

Active Tuberculosis

Screening for active tuberculosis has largely been based on chest radiographic screening. The cost effectiveness of these programs is highly variable and likely to depend on a number of factors including site of screening (before, at, or after entry) and the yield of tuberculosis in immigrants to each country. In a systematic review of national programs in Europe, it was reported that the median yield for active tuberculosis was 0.18% (interquartile range, 0.10%–0.35%) [30]. A review of US, Canadian, and European literature suggested that chest radiographic

Table 1. Diagnostic Accuracy[a] and Cost Effectiveness of Diagnostic Tools for Tuberculosis Screening of Immigrants

Diagnostic Tool	Diagnostic Accuracy	Cost Effectiveness
Latent tuberculosis		
Tuberculin skin test		Screening less cost effective than single IGRAs, except as part of a 2-step approach
	Sensitivity: 77% (95% CI, 71%–82%) [35]	
	Specificity: 97% (95% CI, 95%–99%), non-BCG vaccinated populations [35]	
IGRA		Linas et al report that IGRAs are more cost effective; UK NICE guidelines identified a 2-step approach as the most cost-effective screening method [25, 26]. Other cost-effectiveness analyses support IGRAs as a more efficient tool for screening in Germany, France.
	QuantiFERON	
	Sensitivity: 76% (95% CI, 72%–80%) [35]	
	Specificity: 98% (95% CI, 96%–99%) [35]	
	TSPOT.TB	
	Sensitivity: 90% (95% CI, 86%–93%) [35]	
	Specificity: 93% (95% CI, 86%–100%) [35]	
Active tuberculosis		
Chest radiograph		The main tool used by most low-tuberculosis-burden countries to screen immigrants; conflicting cost-effectiveness data largely determined by the underlying prevalence of tuberculosis in screened groups
	Sensitivity: 59%–82% [36–38]	
	Specificity: 52%–99% [36–38]	
Smear and culture		Increased case detection as part of a package of tests in pre- and postentry screening
	Smear	
	Sensitivity: 50%–80% [39, 40]	
	Specificity: 95% [39, 40]	
	Culture × 3	
	Sensitivity: 80%–100% [39, 40]	
	Specificity: 98% [41]	
Molecular assays		Trial and cost-effectiveness data for immigrant screening limited; potentially cost effective as part of a diagnostic algorithm where individuals are first tested with smears [42]
	Gene Xpert	
	Sensitivity: 90% [33]	
	Specificity: 99% [33]	
	Other PCR assays	
	Sensitivity: 50–95% [44–46]	
	Specificity: 98% [44–46]	
	Line Probe Assay	
	Sensitivity: 82%–100% [34]	
	Specificity: 92%–100% [34]	

Abbreviations: CI, confidence interval; IGRA, interferon-γ release assay; NICE, National Institute for Health and Clinical Excellence; PCR, polymerase chain reaction.
[a] Defined using sensitivity and specificity. Presented as either a full range from published studies or, where a systematic review is available, a pooled point estimate with 95% CIs.

screening is not cost-effective and adds little to the improvement of public health [31]. The inclusion of sputum smears and culture, which may have greater diagnostic accuracy, has increased case detection [32].

New technologies for the diagnosis of active tuberculosis that may have a role in migrant screening are emerging (Table 1). Traditionally, molecular tests have had limited diagnostic accuracy compared with bacterial culture. However, recent progress has led to the introduction of a number of novel assays, such as improvements to nucleic acid amplification tests, immune-based assays, and skin patch tests. Research on these assays to date suggests variable effectiveness. Some of the tests that detect drug-resistant *M. tuberculosis* strains, discussed in an accompanying paper in this issue (see McNerney et al), have been endorsed by the WHO, for example, the Gene Xpert MTB/RIF assay [33] and the Line Probe assays [34]. None of these have yet been evaluated in trials in migrant screening. Furthermore, the high cost of molecular assays may preclude these tests as a cost-effective option for the first-line screening of migrants. Further research on the value of these tests in subgroups of migrants is warranted.

In the United States, preentry screening combined with subsequent in-country follow-up after arrival was found to be effective at identifying immigrants and refugees with tuberculosis [43]. An evaluation of preentry screening in the United States suggested that it might be enhanced by the addition of sputum cultures to existing algorithms that include chest radiography and smear examination [32]. A study from Israel also found evidence to support preentry screening [47]. Additional studies are needed to investigate whether preentry screening is cost-effective and how this compares with the enlightened self-interest approach of tackling tuberculosis in a migrant's country of origin, taking into account the inevitable differences between countries and migrant groups.

In the United Kingdom [28], there is considerable heterogeneity and deviation from national guidelines in the implementation of postentry screening for active tuberculosis, with many services showing poor yield. By contrast, the Dutch program of postentry screening was associated with a high yield [51]. Among various groups of immigrants considered to be at risk of tuberculosis, asylum seekers are recognized to have a very high incidence. A study in Norway suggests particular difficulties associated with the screening of asylum seekers due to high rates of loss to follow-up [48].

What Future Work Is Needed?
Strengthened control in the high-burden countries of origin for immigrants who migrate to low-incidence settings will ultimately have the biggest impact on the importation of tuberculosis. The perceived lack of effectiveness of internationally funded programs in developing countries needs to be tackled if tuberculosis is to be controlled. Where countries choose to screen for latent tuberculosis and/or active tuberculosis in migrants, it is important that evidence-based cost-effective measures be used to take into account overall health needs of migrants, subsequent exposure due to travel to home countries, and access to healthcare. Further research is needed to identify optimal tools for screening for latent tuberculosis and active tuberculosis in recent migrants, as well as settled migrants. In addition, shorter and less toxic treatment regimes for latent tuberculosis and active tuberculosis are required.

HARD-TO-REACH GROUPS

Many countries with a low tuberculosis burden have identified particular groups that are at high risk, including prisoners, homeless persons, and drug users [7, 8]. Interventions to identify and treat tuberculosis in these populations are often very expensive, partly because those who are hard to reach struggle to engage normal care and often because routine services fail to engage deprived groups [3]. Services that actively detect cases in these groups have been evaluated in trials. For example, a recent evaluation of active case finding with a mobile digital radiographic unit in London shows that this may be a cost-effective intervention [10]. A Dutch study demonstrated that mobile digital radiography could interrupt transmission [49]. Successful efforts to tackle tuberculosis in New York had a major component focused on these populations [50]. More controversial is the management of latent tuberculosis in these populations. Although the prevalence of latent tuberculosis is likely to be higher in these groups than in the general population, widespread drug use and coinfection with blood-borne viruses increase the probability of adverse reactions to prophylactic treatment. Furthermore, the hard-to-reach characteristics of these populations make completion of treatment difficult. Studies investigating novel approaches to improve treatment completion in these deprived populations will be invaluable. The specific groups with poverty-related and socioeconomically determined increased risk of tuberculosis will differ by country and sometimes by city. Therefore, evidence-based interventions need to be locally tailored and need to address disease in hard-to-reach groups as well as immigrant populations.

PREVENTIVE THERAPY FOR CONTACTS OF MULTIDRUG-RESISTANT TUBERCULOSIS

The treatment of persons exposed to infectious tuberculosis cases who become latently infected with *M. tuberculosis* has been an important element of tuberculosis control in low-burden countries. Although data on effective treatment regimens for those exposed to drug-sensitive tuberculosis are robust, evidence for the drug combinations to use during treatment of *M. tuberculosis*–infected contacts following exposure to drug-resistant strains of *M. tuberculosis* is limited. To date, no randomized controlled trials have been published on the

efficacy of recommended treatment combinations for latent infection or active disease [53]. Although the management of these individuals remains controversial, the low incidence of MDR tuberculosis in most low-tuberculosis-burden countries would suggest that this is a relatively low priority.

Why Is Preventive Therapy Used?

Contacts of patients with active pulmonary tuberculosis who have latent tuberculosis may progress to active disease. A reliable method to predict which individuals will progress does not currently exist, although developments have recently been made using transcriptional profiling [54, 55]. Despite the lack of a reliable predictor, preventive treatment of latent tuberculosis in exposed individuals remains an essential tool in the control of tuberculosis. US and European guidelines advise that treatment be considered for individuals who have evidence of latent tuberculosis from either an IGRA or tuberculin skin test [26, 56]. The guidelines differ in terms of the recommended application of these tests as well as which groups to treat. UK guidance recommends the treatment of latent tuberculosis in individuals who are ≤35 years of age due to concerns about increased incidence of toxicity in older persons [26], whereas US guidelines allow the treatment of latent tuberculosis irrespective of age [56]. Most guidelines recommend at least 6 months of isoniazid; however, some countries recommend a 3-month course of isoniazid and rifampicin treatment [26]. Recent research indicates that 3 months of treatment with rifapentine and isoniazid is equivalent to 9 months of treatment with isoniazid [57]. Because MDR tuberculosis is defined as resistance to isoniazid and rifampicin, these evidence-based regimens are not appropriate for contacts of MDR tuberculosis cases. Furthermore, the erroneous treatment of a person with active MDR tuberculosis thought to have only latent tuberculosis could lead to the development of additional resistance, thus restricting future treatment regimen options. This is particularly problematic for contacts of extensively drug-resistant tuberculosis cases. It is worrisome to note that whole genome sequencing data suggest that *M. tuberculosis* continues to mutate even among those with latent tuberculosis [58].

What Are the Options?

There are 3 main approaches to minimizing risk among contacts of drug-resistant cases. The first, which has been adopted by the UK NICE, is not to put these individuals on preventive treatment: "treatment for LTBI [latent tuberculosis] should not be started in close contacts of people with sputum smear-positive MDR-TB as no regimen is of proven benefit, and only a small proportion of people infected will develop the disease" [26]. The presumption is that if active disease occurs, it will be identified quickly and full multidrug treatment started accordingly. The second is to tailor the preventive treatment regime on a case-by-case basis, depending on the existing resistance profile. Several alternative regimens have been suggested [59–61]. The British Thoracic

Society and the Centers for Disease Control and Prevention (CDC) recommend a treatment regimen of 2–3 drugs for 6–12 months, although this can cause problems with drug toxicity [61, 62]. The third option is to assess the degree of drug resistance in order to determine if isoniazid can still be used. CDC guidelines categorize individuals by the likelihood of infection, risk of progression (eg, due to level of immunocompetence), and degree of resistance to isoniazid/rifampicin to determine which cases to treat and with which regimen [61]. For all 3 options, long-term vigilance for the development of active disease is recommended.

What Future Work Is Needed?

The development of new antituberculosis therapies to which there is no existing resistance is a key long-term goal, not only for the treatment of cases of active disease but also for prevention of progression in those with latent tuberculosis. This has particular relevance in the fight against a rising tide of global drug resistance.

The lack of efficacy data on alternatives to isoniazid or rifampicin prophylaxis has been highlighted as a key area of concern by several reviewers [53, 63–65]. With very young children, it is important to consider alternative approaches, including the use of high-dose rifampicin. Furthermore, a prospective cohort of childhood contacts of MDR tuberculosis cases suggested that tailoring treatment to the susceptibility profile of the source case is effective [66].

Large randomized control trials are essential to properly determine the best approach to treating those exposed to drug-resistant tuberculosis cases. Further trials are under way to investigate new drug regimens (see article by Lienhardt et al in this issue) [65]. The drug susceptibility profile of MDR tuberculosis cases differs; as a result, regimens for treatment of active disease or latent tuberculosis must often be tailored to the individual case to achieve optimal response. Although most novel tuberculosis drugs are being developed for treatment of disease (see article by Coxon et al in this issue), 1 potentially appealing approach would be to reserve a new drug for treatment of latent tuberculosis cases in close contacts of MDR tuberculosis cases in order to avoid potential perverse effects associated with selection for antibiotic resistance.

CONCLUSIONS

Tuberculosis control in low-burden countries requires efforts to tackle the disease in high-risk groups, as well as to ensure that the health system is able to diagnose cases, regardless of group, as early as possible. The latter can only be achieved with high levels of awareness among physicians of the possibility of tuberculosis in any patient. Although this article is not an exhaustive description of all the controversies surrounding the prevention and control of tuberculosis in low-incidence countries, the issues discussed illustrate the problems that exist. It is critical that each

country attempting elimination reviews all elements of their control program with a view to ensuring that a strategic approach is taken to address locally relevant issues. The parochial interests of each country may dictate that locally effective interventions, which may not be cost effective on the global scale, are used. Such tactics may not, in the long run, be in the interest of rich nations when compared with the enlightened self-interest approach [24] of addressing TB control in endemic countries. Infectious diseases do not respect international boundaries. Tuberculosis is a classic example of why all countries should join together and support the efforts needed to achieve global tuberculosis control.

Notes

References

1. World Health Organization. Global tuberculosis control 2010. http://www.who.int/tb/publications/global_report/2010/en/index.html. Accessed 23 June 2011.
2. Hollo V, Amato-Gauci A, Kodmon C, Manissero D. Tuberculosis in the EU and EEA/EFTA countries: what is the latest data telling us? Euro Surveill 2009; 14. http://www.ncbi.nlm.nih.gov/pubmed/19317981. Accessed 16 April 2011.
3. Abubakar I, Lipman M, Anderson C, Davies P, Zumla A. Tuberculosis in the UK—time to regain control. BMJ 2011; 343:d4281.
4. Winston C, Pratt R, Armstrong L, Navin T. Decrease in reported tuberculosis cases—United States, 2009. MMWR Morb Mortal Wkly Rep 2010; 59:289–94.
5. Pratt R, Price S, Miramontes R, Navin T, Abraham BK. Trends in tuberculosis—United States, 2010. MMWR Morb Mortal Wkly Rep 2011; 60:333–7.
6. Oren E, Winston CA, Pratt R, Robison VA, Narita M. Epidemiology of urban tuberculosis in the United States, 2000–2007. Am J Public Health 2011; 101:1256–63.
7. Story A, Murad S, Roberts W, Verheyen M, Hayward AC. Tuberculosis in London: the importance of homelessness, problem drug use and prison. Thorax 2007; 62:667–71.
8. Haddad MB, Wilson TW, Ijaz K, Marks SM, Moore M. Tuberculosis and homelessness in the United States, 1994–2003. JAMA 2005; 293:2762–6.
9. Colijn C, Cohen T, Murray M. Emergent heterogeneity in declining tuberculosis epidemics. J Theor Biol 2007; 247:765–74.
10. Jit J, Stagg H, Aldridge R, White P, Abubakar I. Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. BMJ 2011; 343:d5376.
11. Geiter L, ed; Committee on the Elimination of Tuberculosis in the United States, Division of Health Promotion and Disease Prevention. Ending neglect: the elimination of tuberculosis in the United States. Washington, DC: The National Academies Press, 2000:292.
12. ECDC. Framework action plan to fight tuberculosis in the European Union. Stockholm: ECDC, 2008.
13. Frieden TR, Fujiwara PI, Washko RM, Hamburg MA. Tuberculosis in New York City—turning the tide. N Engl J Med 1995; 333:229–33.
14. Wilson LG. The historical decline of tuberculosis in Europe and America: its causes and significance. J Hist Med Allied Sci 1990; 45:366–96.
15. Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. Lancet 2006; 367:1173–80.
16. Rodrigues LC, Diwan VK, Wheeler JG. Protective effect of BCG against tuberculous meningitis and miliary tuberculosis: a meta-analysis. Int J Epidemiol 1993; 22:1154–8.
17. Fine PE. Variation in protection by BCG: implications of and for heterologous immunity. Lancet 1995; 346:1339–45.
18. Fine PEM, Carneiro IA, Milstien J, Clements C. Issues relating to the use of BCG in immunization programmes: a discussion document. Geneva, Switzerland: World Health Organization, 1999.
19. Zwerling A, Behr MA, Verma A, Brewer TF, Menzies D, Pai M. The BCG World Atlas: a database of global BCG vaccination policies and practices. PLoS Med 2011; 8:e1001012.
20. Sterne JA, Rodrigues LC, Guedes IN. Does the efficacy of BCG decline with time since vaccination? Int J Tuberc Lung Dis 1998; 2:200–7.
21. Aronson NE. Long-term efficacy of BCG vaccine in American Indians and Alaska Natives: a 60-year follow-up study. JAMA 2004; 291:2086–91.
22. Rodrigues L, Mangtani P, Abubakar I. How does the level of BCG vaccine protection against tuberculosis decline with time? BMJ 2011; 343:d5974.
23. Kaufmann SH. Fact and fiction in tuberculosis vaccine research: 10 years later. Lancet Infect Dis 2011; 11:633–40.
24. Schwartzman K, Oxlade O, Barr RG, et al. Domestic returns from investment in the control of tuberculosis in other countries. N Engl J Med 2005; 353:1008–20.
25. Linas BP, Wong AY, Freedberg KA, Horsburgh CR Jr. Priorities for screening and treatment of latent tuberculosis infection in the United States. Am J Respir Crit Care Med 2011; http://www.ncbi.nlm.nih.gov/pubmed/21562129. Accessed 24 September 2011.
26. National Collaborating Centre for Chronic Conditions and the Centre for Clinical Practice at the National Institute for Health and Clinical Excellence. Tuberculosis (CG117). Clinical diagnosis and management of tuberculosis, and measures for its prevention and control. London, United Kingdom: Royal College of Physicians, 2011.
27. Pareek M, Watson JP, Ormerod LP, et al. Screening of immigrants in the UK for imported latent tuberculosis: a multicentre cohort study and cost-effectiveness analysis. Lancet Infect Dis 2011; 11:435–44.
28. Pareek M, Abubakar I, White PJ, Garnett GP, Lalvani A. Tuberculosis screening of migrants to low tuberculosis burden nations: insights from evaluation of UK practice. Eur Respir J 2010. http://www.ncbi.nlm.nih.gov/pubmed/21071474. Accessed 16 April 2011.
29. Menzies D, Long R, Trajman A, et al. Adverse events with 4 months of rifampin therapy or 9 months of isoniazid therapy for latent tuberculosis infection: a randomized trial. Ann Intern Med 2008; 149:689–97.
30. Klinkenberg E, Manissero D, Semenza JC, Verver S. Migrant tuberculosis screening in the EU/EEA: yield, coverage and limitations. Eur Respir J 2009; 34:1180–9.
31. Dasgupta K, Menzies D. Cost-effectiveness of tuberculosis control strategies among immigrants and refugees. Eur Respir J 2005; 25:1107–16.
32. Lowenthal P, Westenhouse J, Moore M, Posey DL, Watt JP, Flood J. Reduced importation of tuberculosis after the implementation of an enhanced pre-immigration screening protocol. Int J Tuberc Lung Dis 2011; 15:761–6.
33. Boehme CC, Nicol MP, Nabeta P, et al. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. Lancet 2011; 377:1495–505.
34. Morgan M, Kalantri S, Flores L, Pai M. A commercial line probe assay for the rapid detection of rifampicin resistance in *Mycobacterium tuberculosis*: a systematic review and meta-analysis. BMC Infect Dis 2005; 5:62.

35. Pai M, Zwerling A, Menzies D. Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: an update. Ann Intern Med **2008**; 149:177–84.

36. Abubakar I, Story A, Lipman M, et al. Diagnostic accuracy of digital chest radiography for pulmonary tuberculosis in a UK urban population. Eur Respir J **2010**; 35:689–92.

37. Markey AC, Forster SM, Mitchell R, Larson E, Smith H, Doré CJ. Suspected cases of pulmonary tuberculosis referred from port of entry into Great Britain, 1980–3. Br Med J (Clin Res Ed) **1986**; 292:378.

38. Barnes PF, Verdegem TD, Vachon LA, Leedom JM, Overturf GD. Chest roentgenogram in pulmonary tuberculosis. New data on an old test. Chest **1988**; 94:316–20.

39. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. This official statement of the American Thoracic Society and the Centers for Disease Control and Prevention was adopted by the ATS Board of Directors, July 1999. This statement was endorsed by the Council of the Infectious Disease Society of America, September 1999. Am J Respir Crit Care Med **2000**; 161:1376–95.

40. Toman K, Frieden T. World Health Organization. Toman's tuberculosis: case detection, treatment, and monitoring: questions and answers. Geneva, Switzerland: World Health Organization, **2004**: 358.

41. Burman WJ, Stone BL, Reves RR, et al. The incidence of false-positive cultures for *Mycobacterium tuberculosis*. Am J Respir Crit Care Med **1997**; 155:321–6.

42. Rajalahti I, Ruokonen EL, Kotomäki T, Sintonen H, Nieminen MM. Economic evaluation of the use of PCR assay in diagnosing pulmonary TB in a low-incidence area. Eur Respir J **2004**; 23:446–51.

43. Liu Y, Weinberg MS, Ortega LS, Painter JA, Maloney SA. Overseas screening for tuberculosis in U.S.-bound immigrants and refugees. N Engl J Med **2009**; 360:2406–15.

44. Abe C, Hirano K, Wada M, et al. Detection of *Mycobacterium tuberculosis* in clinical specimens by polymerase chain reaction and Gen-Probe Amplified *Mycobacterium tuberculosis* Direct Test. J Clin Microbiol **1993**; 31:3270–4.

45. Clarridge JE 3rd, Shawar RM, Shinnick TM, Plikaytis BB. Large-scale use of polymerase chain reaction for detection of *Mycobacterium tuberculosis* in a routine mycobacteriology laboratory. J Clin Microbiol **1993**; 31:2049–56.

46. Al Zahrani K, Al Jahdali H, Poirier L, René P, Gennaro ML, Menzies D. Accuracy and utility of commercially available amplification and serologic tests for the diagnosis of minimal pulmonary tuberculosis. Am J Respir Crit Care Med **2000**; 162:1323–9.

47. Mor Z, Lerman Y, Leventhal A. Pre-immigration screening process and pulmonary tuberculosis among Ethiopian migrants in Israel. Eur Respir J **2008**; 32:413–8.

48. Harstad I, Jacobsen GW, Heldal E, et al. The role of entry screening in case finding of tuberculosis among asylum seekers in Norway. BMC Public Health **2010**; 10:670.

49. de Vries G, van Hest RA, Richardus JH. Impact of mobile radiographic screening on tuberculosis among drug users and homeless persons. Am J Respir Crit Care Med **2007**; 176:201–7.

50. Paolo WF Jr, Nosanchuk JD. Tuberculosis in New York City: recent lessons and a look ahead. Lancet Infect Dis **2004**; 4:287–93.

51. Erkens C, Slump E, Kamphorst M, et al. Coverage and yield of entry and follow-up screening for tuberculosis among new immigrants. Eur Respir J **2008**; 32:153–61.

52. Alvarez GG, Gushulak B, Abu Rumman K, et al. A comparative examination of tuberculosis immigration medical screening programs from selected countries with high immigration and low tuberculosis incidence rates. BMC Infect Dis **2011**; 11:3.

53. Fraser A, Paul M, Attamna A, Leibovici L. Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis. Cochrane Database Syst Rev **2006**; (2):CD005435.

54. Berry MP, Graham CM, McNab FW, et al. An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. Nature **2010**; 466:973–7.

55. Maertzdorf J, Repsilber D, Parida SK, et al. Human gene expression profiles of susceptibility and resistance in tuberculosis. Genes Immun **2011**; 12:15–22.

56. Mazurek GH, Jereb J, Lobue P, Iademarco MF, Metchock B, Vernon A. Guidelines for using the QuantiFERON-TB Gold test for detecting *Mycobacterium tuberculosis* infection, United States. MMWR Recomm Rep **2005**; 54:49–55.

57. Sterling TR, Villarino ME, Borisov AS, et al. Three months of rifapentine and isoniazid for latent tuberculosis infection. N Engl J Med **2011**; 365:2155–66.

58. Ford CB, Lin PL, Chase MR, et al. Use of whole genome sequencing to estimate the mutation rate of *Mycobacterium tuberculosis* during latent infection. Nat Genet **2011**; 43:482–6.

59. Passannante MR, Gallagher CT, Reichman LB. Preventive therapy for contacts of multidrug-resistant tuberculosis. A Delphi survey. Chest **1994**; 106:431–4.

60. Trébucq A. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the literature. Int J Tuberc Lung Dis **1997**; 1:12–5.

61. Management of persons exposed to multidrug-resistant tuberculosis. MMWR Recomm Rep **1992**; 41:61–71.

62. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society. Thorax **1998**; 53:536–48.

63. Fraser A, Paul M, Attamna A, Leibovici L. Drugs for preventing tuberculosis in people at risk of multiple-drug-resistant pulmonary tuberculosis (Review). Cochrane Database Syst Rev **2009**; (3):1–9.

64. LoBue P. Extensively drug-resistant tuberculosis. Curr Opin Infect Dis **2009**; 22:167–73.

65. Lobue P, Menzies D. Treatment of latent tuberculosis infection: an update. Respirology **2010**; 15:603–22.

66. Schaaf HS, Vermeulen HA, Gie RP, Beyers N, Donald PR. Evaluation of young children in household contact with adult multidrug-resistant pulmonary tuberculosis cases. Pediatr Infect Dis J **1999**; 18: 494–500.