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Heemskerk D, Caws M, Marais B, et al. Tuberculosis in Adults and Children. London: Springer; 2015.

Chapter 6 Prevention

Prevention is the key to stop transmission of TB. It consists of early diagnosis and treatment of active TB to stop infectiousness, the prevention of active disease in exposed or known latently infected individuals and vaccination. Vaccination with the Bacillus Calmette-Guerin (BCG) vaccine is unfortunately largely ineffective in interrupting transmission. However a more powerful vaccine will have the potential to cause a major shift in the management of TB. In this chapter prophylactic treatment in latently infected and HIV infected patients is reviewed. Additionally the prevention of active disease in MDR-exposed persons and vaccine development will be discussed.

6.1. Prophylactic Treatment

TB transmission to susceptible contacts primarily occurs in enclosed, poorly ventilated locations. High risk locations for transmission are high density congregate living environments such as hospitals, care homes, prisons or student/migrant worker hostels. Transmission within institutional environments such as hospitals can be reduced by implementing effective infection control policies covering administrative, environmental and respiratory protection (refer to CDC guidelines for detailed recommendations: http://www.cdc.gov/tb/publications/guidelines/infectioncontrol.htm).

The standard regimen for treatment of latent TB infection is nine months isoniazid, also known as isoniazid prophylaxis therapy (IPT). Pyrodoxine should be given with isoniazid (Udani et al. 1971). In 2011 a trial of a novel 12 dose regimen of isoniazid and rifapentine showed higher completion rates and no loss of efficacy compared to the standard 9-month isoniazid treatment (Sterling et al. 2011). The 12-dose regimen has since been incorporated into US recommendations but is not recommended for children younger than 2 years of age, people with HIV/AIDS who are taking antiretroviral therapy (ART), people presumed to be infected with INH or rifampin-resistant *M. tuberculosis* or pregnant women, or women expecting to become pregnant while taking this regimen: http://www.cdc.gov/tb/publications/ltbi/treatment.htm.

A recent mass isoniazid prevention trial in South African mine workers showed no reduction in TB incidence and prevalence beyond the 9 months of IPT, suggesting that in high TB burden areas, transmission is not interrupted and the unchanged incidence is due to reinfection (Churchyard et al. 2014).

HIV is the strongest risk factor for developing TB in those with latent or recent *M. tuberculosis* infection, between 20 and 37 times the risk for those without HIV. To avoid treating an active TB case with monotherapy, HIV-infected individuals should be screened for active TB before the administration of IPT (Rangaka et al. 2014).

There is considerable debate around the duration of IPT in HIV-infected individuals since the trial data from South African miners who are heavily exposed showed that the protective effect of IPT quickly wanes, with the protective effect disappearing after one year. This is likely to be due to IPT clearing any latent infection, and therefore preventing reactivation disease, but not preventing re-infection after completion of therapy. WHO recommends extended IPT (36 months) for individuals living in areas with a high background prevalence of HIV and TB. There is concern that the widescale application of long-term IPT will lead to increases in isoniazid resistance and decrease in efficacy over time, but there is no evidence that this is occurring. Trials of long-term IPT are now underway in South Africa.

The reservoir of latently infected individuals is clearly a major barrier to eventual TB elimination, and shorter, less toxic regimens for latent TB will be a major boost to elimination efforts.

For more information on TB prevention: http://www.tbfacts.org/tb-prevention.html.

6.2. Prophylactic Treatment in Multi-drug Resistant Tuberculosis

Evidence to guide the choice of regimen for prophylatic treatment of the contacts of MDR and XDR TB patients is extremely limited. Derivation and testing of standardised regimens is complicated by the diverse spectrum of possible susceptibility patterns of an index case.

The American Thoracic Society (ATS) and the US Centers for Disease Control and Prevention (CDC) recommend prophylactic therapy for MDR TB contacts with the regimen to be used determined by the drug susceptibility profile of the potential source case. WHO and European guidelines [The International Standards for TB Care (ISTC) and European Union Standards for TB Care (ESTC)] favour careful clinical follow-up for a period of at least two years.

The European Centre for Disease prevention and control issued guidance on management of contacts of MDR and XDR patients in 2012 based upon systematic review of the available evidence: http://www.ecdc.europa.eu/en/publications/publications/201203-guidance-mdr-tb-contacts.pdf. The guidance recommends that each case must be considered individually with a comprehensive assessment of the likely risks and benefits of preventative therapy of unknown efficacy versus intensive clinical monitoring for signs of disease. The risk assessment should include consideration of any known individual risk factors for progression to active disease, the drug susceptibility pattern of the index case and any known risk factors for adverse events with the prophylactic regimen. A recent prospective observational study on an island in Micronesia, followed MDR-TB contacts who were offered 12-month preventive treatment with a fluoroquinolone. Among the 119 infected contacts, 15 refused, while 104 began treatment for MDR latent TB infection. None of the 104 contacts who undertook treatment with fluoroquinolones developed MDR-TB disease; however, 3 of 15 contacts who refused and 15 unidentified contacts developed MDR-TB disease (Bamrah et al. 2014). These data are compelling and warrant randomized studies, as the ability to prevent MDR-TB transmission would be the paradigm shift in MDR-TB management.

6.3. Vaccines

The only vaccine currently available for TB is the bacillus Calmette-Guerin (BCG) vaccine developed by serial passage of *Mycobacterium bovis* and introduced in 1921. BCG is the most widely used vaccine in the world but measures of effectiveness have varied widely, between 0 and 80 %. Studies have however, consistently shown a protective effect against the most severe forms of childhood TB, including TB meningitis. Meta-analysis of all published studies produced an estimate of 50 % for overall efficacy and 80 % efficacy in preventing TB meningitis (Colditz et al. 1994). BCG should not be administered to HIV-infected individuals (Nuttall and Eley 2011). Several theories have been proposed for the differences in observed effectiveness, including the use of different strains of BCG, variation in early exposure to non-tuberculous mycobacteria prior to vaccination, host genetic variation and pathogen genetic variation but none of these theories has strong supporting evidence to date.

Clearly, given the huge burden of global TB and the major barrier to elimination that the ‘silent’ reservoir of latently infected individuals represents, an effective TB vaccine would be a major advance in the battle to eradicate TB. However, the correlates of protective immunity in TB are not understood which represents a major hurdle to developing an effective vaccine. The most advanced vaccine candidate for a primary TB vaccine, MVA85A, failed to show any efficacy in a phase IIb trial in HIV-uninfected infants published in 2013 (Tameris et al. 2013). This trial should however provide valuable data to guide further development of novel vaccine candidates.

The current pipeline includes three distinct approaches to the development of a TB vaccine, known as Prime, boost or immunotherapy. An alternative strategy also being explored is post-infection vaccination. Vaccine types currently under-development include (1) modification of the BCG vaccine (recombinant BCG), (2) Boosting of BCG with adjuvants, (3) incorporation of TB antigen expression into vaccine vectors or (4) killed whole cell or extracts (Kaufmann et al. 2014).

6.4. Concluding Remarks

TB is a curable disease. The fact that it remains the most pressing public health problem for a significant proportion of the world, despite the availability of a cure and knowledge on prevention of transmission shows how medicine can fail without commitment at all levels of the community. The distribution of the TB pandemic painfully demonstrates the inequalities in health care delivery globally. Over 95 % of cases and deaths are in low and middle income countries. In general, prognosis of outcome is dependent on a multitude of factors: host factors (genetic variance, co-morbidities, HIV-coinfection, treatment adherence, access to healthcare) and pathogen factors (pathogen virulence, drug-resistance) and the site of the infection (pulmonary or extrapulmonary). The principle factor in a favourable outcome for all forms is early recognition and appropriate treatment. TB is the most common cause of death among HIV patients, estimated to cause a quarter of AIDS related deaths.

Drug resistant TB is a growing problem and threatens to reverse the recent gains in global TB control. In regions of the former soviet states MDR TB is found in over half of all new TB cases and threatens a return to untreatable strains

of TB disseminating globally without immediate and sustained action. Of the 34,000 MDR patients enrolled on treatment in 2010, only 48 % successfully completed treatment and 15 % died. Among 795 XDR cases, mortality was approximately 50 %.

The key to maintaining the momentum towards achieving the STOPTB target of global TB eradication by 2050 will be sustained commitment from donors, governments, national TB programmes, researchers and other stakeholders at all levels of society.

Table of useful online TB resources

Topic	Source	Website
Non-tuberculous mycobacterial disease	American Thoracic Society (ATS)	http://www.thoracic.org/statements/resources/mtpi/nontuberculous-mycobacterial-diseases.pdf
United States TB statistics	Center for Disease Control (CDC)	http://www.cdc.gov/tb/statistics/reports/2012/default.htm
Tuberculin skin test (TST) interpretation	CDC	http://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm
Novel tuberculosis diagnostics	Foundation for Innovative New Diagnostics (FIND)	http://www.finddiagnostics.org
Evidence-based TB diagnosis	McGill University	http://www.tbevidence.org
TB diagnostics; XpertMTB/RIF Roll-out	World Health Organisation (WHO)	http://who.int/tb/laboratory/mtbrifrollout/en/
Xpert MTB/RIF for diagnosis of pulmonary and extrapulmonary TB in adults and children Policy Update	WHO	http://tbevidence.org/wp-content/uploads/2013/11/WHOstat.pdf
IGRA for detecting infection with Mtb	CDC	http://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf
TB diagnostics and laboratory strengthening	WHO	http://www.who.int/tb/laboratory/en/
TB treatment guidelines	WHO	http://www.who.int/tb/publications/tb_treatmentguidelines/en/index.html
TB treatment in children	WHO	http://whqlibdoc.who.int/publications/2010/9789241500449_eng.pdf
Comprehensive treatment susceptible and drug resistant TB	CDC	http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm
Use of bedaquiline in MDR TB	WHO	http://www.who.int/tb/challenges/mdr/bedaquiline/en/index.html
Use of bedaquiline in MDR TB	CDC	http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm?s_cid=rr6209a1_e
TB infection control and prevention guidelines	CDC	http://www.cdc.gov/tb/publications/guidelines/infectioncontrol.htm
Management of contacts of MDR TB and XDR TB patients	European Centre for Disease prevention and Control (ECDC)	http://www.ecdc.europa.eu/en/publications/publications/201203-guidance-mdr-tb-contacts.pdf

Topic	Source	Website
TB vaccine resources	StopTB partnership	http://www.stoptb.org/wg/new_vaccines/documents.asp
Global Plan to stop TB 2006–2015	WHO	http://www.who.int/tb/features_archive/global_plan_to_stop_tb/en/
Tuberculosis treatment success rate	WHO	http://www.who.int/gho/tb/epidemic/treatment/en/

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