
TUBERCULOSIS INTERVENTIONS TO PREVENT TRANSMISSION OF INFECTION IN HEALTH CARE WORKERS: A SYSTEMATIC REVIEW

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PART A: PROTOCOL

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ABSTRACT

Background:

Tuberculosis is a major cause of morbidity and mortality as an estimated 8.6 million people developed TB and 1.3 million died from the disease in 2012. The number of deaths is high given that TB can be prevented. Health care workers are an at-risk group, since they are frequently in contact with infectious patients and/or work with infectious products. The World Health Organisation has declared the importance of finding innovative tools and strategies to prevent TB and implementing them successfully, especially for those with a high risk of TB transmission.

Methods:

This systematic review aims to undertake a quantitative review of tuberculosis interventions for health care workers in health care settings, so as to assess whether these interventions are effective in reducing the transmission of tuberculosis infection and disease. We will preferably include experimental studies, such as, randomised-controlled trials, but observational studies, such as controlled before and after studies and cohort studies will also be included in the absence of randomised-controlled studies. We will search databases, such as Medline, Scopus, Trip, LILACS and various trial registries. A hand search of reference lists of identified articles, abstracts, conference proceedings and campaign materials will be performed. Grey literature sites will also be used for the search. Data will be extracted using a single form. The quality of each study will be assessed in terms of selection bias, performance bias, attrition bias and detection bias. Thereafter a meta-analysis will be produced and subgroups will be analysed according to the three intervention types. Clinical and statistical significance will be determined for the included studies, and descriptive narratives of heterogeneous studies will be written.

Discussion:

Our results will be useful to policy-makers and public health officials for the prioritisation of those interventions identified as effective and critical.

Keywords:

Occupational tuberculosis, tuberculosis prevention, tuberculosis infection control, nosocomial transmission, health care workers, health care facilities.

BACKGROUND

Description of the condition

Tuberculosis (TB), an infectious disease caused by a mycobacterium, most often affects the lungs. A total of 8.6 million new TB cases were reported in 2012. TB can be transmitted from an infected person to a non-infected person via droplets from the throat or lung. These droplets can be spread from the infected person through coughing, sneezing, speaking, singing and laughing (World Health Organisation 2014).

There is a renewed focus on preventing and controlling occupationally acquired TB in low and middle income countries due to an increased risk of infection and disease. Health care workers, those at risk due to nosocomial exposure, include all occupations located within a health care facility, such as nurses, doctors, administrators and support staff. The risk of disease due to nosocomial exposure for health care workers in low- and middle-income countries ranges from 25 to 5361 per 100 000 per year. Also, the annual incidence of TB *infection* amongst health care workers in low income countries is approximately 5.3% compared to 1% in high income countries (Joshi et al. 2006).

In the South African context, approximately 948 out of 100 000 health care workers have active TB prevalence (Dheda 2011). TB incidence amongst health care workers is reported to be as high as 1 133 out of 100 000 at some hospitals in KwaZulu-Natal. There is also a higher incidence of MDR and XDR in HWCs than in the general population in South Africa. The reported annual incidence of MDR or XDR-TB in health care workers is 79.1 per 100 000 compared to 13.2 per 100 000 in the general population (Dheda 2011).

Health care workers caring for infectious TB patients are particularly at risk of infection, which may develop into disease. Non-existent or ineffective use of control measures enables TB transmission in health care facilities (South African Tuberculosis Control Guidelines 2004). The Treatment Action Campaign and the TB/HIV Association have criticised the government and policy-makers for failed implementation of interventions, referring e.g. to nurses and doctors who continued to work without masks.

Description of the interventions

Interventions for TB protection or prevention in health care have been commonly grouped into the following: administrative controls, environmental controls and personal respiratory protection (Claassens et al. 2013; South African Tuberculosis Control Guidelines 2004). Administrative controls include the management of TB disease by appointed personnel, the development of strategic plans to detect and treat TB disease timeously, the separation of infectious patients from others, the development of educational materials and the training of health care workers. Environmental controls include natural ventilation, open window policy, cross ventilation, propeller fans, exhaust ventilation systems, high-efficacy particulate air (HEPA) filters and ultraviolet (UV) lights. Personal respiratory protection includes a plan for respiratory protection, appropriate and available respirators for staff and training of staff to use the respirators (Claassens et al. 2013).

How the interventions might work

Early diagnosis, prompt isolation and treatment of potential infectious patients and health care workers are important practices. Risk assessments conducted in various high risk areas, such as TB wards, TB hospitals and laboratories etc., can guide the development of appropriate infection control plans. In dense areas where particles cannot be eliminated, environmental controls are useful. Open windows and doors, mechanical ventilators and exhaust ventilation systems ensure that air is circulated and mixed. UVGI are used to kill bacilli in a well-ventilated room. Personal respiratory protection refers to the use of masks or respirators to protect the wearer from inhaling bacilli. N95 respirators are recommended since they cover the mouth and nose and are fitted with a particular filter to filter out small particles (South African Tuberculosis Control Guidelines 2004).

Justification of the review

WHO has recommended several interventions for TB control in health facilities, which fall within the three groups discussed above. Although these recommendations have been adopted by various countries, there is no systematic evidence on the effectiveness of the recommended interventions (Cobelens et al. 2012).

A systematic review is therefore needed to evaluate the effectiveness of recommended interventions. Focus will be on interventions that prevent transmission of TB. The review will not include medical surveillance, BCG vaccination and isoniazid preventative therapy.

METHODS/DESIGN

The methods of the systematic review will be conducted along the methods of the Cochrane Collaboration (Higgins et al. 2009) and the protocol of the systematic review was registered with PROSPERO.

Criteria used in considering studies for this review

Types of study designs

Only randomised-controlled trials, clinically-controlled trials, quasi-randomised trials and controlled before and after studies will be included.

Types of participants

All health care workers who are at risk of TB infection in health care facilities are the targets of the interventions.

Types of interventions

The review will include interventions that are administered to health care workers in health care facilities in low- and middle-income countries. In the case of limited literature, studies from high-income countries will also be included and analysed as a subgroup. The following three types of interventions will be considered:

- Administrative controls, e.g. respiratory isolation and rapid TB diagnosis.
- Environmental controls, e.g. ultraviolet lights, ventilation and filtration.
- Personal respiratory protection measures, e.g. face masks and respirators.

Control: non-use, less intense or less frequent use of listed interventions.

Types of outcomes

The following outcome will be considered:

- Infection with or disease due to *Mycobacterium tuberculosis* (MTB), including multiple drug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB).

Search strategy for identification of studies

An extensive search will attempt to identify all relevant studies regardless of language and publication status. A librarian will be asked to assist with more advanced and complicated searches. Both peer-reviewed journals and grey literature (non-peer-reviewed, unpublished and internal papers) will be searched.

Electronic Searches

The following journal databases, but not limited to these, will be searched:

- Medline
- Trip
- Scopus
- LILACS

The following trial registries, but not limited to these, will be searched:

- Cochrane Central Register of Controlled Trials (CENTRAL)
- World Health Organisation International Clinical Trials Registry Platform (ICTRP)
- ClinicalTrials.gov

Keywords and medical subject heading (MeSH) terms will be used in different combinations depending on the database. The following is an example of how key words and MeSH terms will be used:

Tuberculosis OR (“TB”) AND (“infection control” OR “personal protection” OR “respiratory protective device” OR “respirator”) AND health care workers

Additional searches

A hand search of the reference lists of identified articles will be performed.

The following grey literature sites will also be searched for relevant articles:

- Stop TB Partnership
- Google and Google Scholar
- Networked Digital Library of Theses and Dissertation

DATA COLLECTION AND ANALYSES

Selection of studies

A standardised method will be used by review authors to search for relevant studies and screen titles and abstracts. Full articles will be obtained for those studies deemed potentially eligible. Then authors will again independently assess whether the full text articles meet the inclusion criteria. A third author will be asked for advice when discrepancies occur in the inclusion results of the two authors. Reasons will be provided for all excluded studies.

Data extraction and management

The data extraction form, attached as Appendix 1, will be used. Any uncertainties regarding the articles will be resolved through a discussion amongst the authors. The following information will be gathered from each included study:

- General details: trial registration number, title, authors, publication status, year in which the study was conducted and details of other relevant studies cited.
- Inclusion criteria: the investigator needs to verify whether the study meets the inclusion criteria of the proposed systematic review.
- Details of the study: type of study design, follow-up period and location of study.
- Details of participants: number of participants, baseline characteristics and evidence of participants working at a health care facility.
- Details of intervention: use of at least one of the three interventions that are the subject of of the systematic review.
- Details of control: non-use of interventions or use of an alternative intervention.
- Details of outcomes: tuberculosis infection or disease.
- Other important information from the study.

Assessment of risk bias in included studies

Information relating to the following aspects will be sought, so as to determine the risk of bias of each study:

- Selection of participants into studies, including random sequence generation and concealment of allocation in the case of randomised-controlled trials.
- Blinding of participants and assessors.
- Incomplete outcome data or missing data.
- Selective outcome reporting.
- Other biases.

Studies will be scored as having high, low or unclear risk of bias. Any disagreements in scoring will be resolved in a discussion involving all three authors.

Measures of intervention effect

Data will be analysed using Review Manager. The effectiveness of the interventions will be calculated as risk ratios and 95% confidence intervals.

Dealing with missing data

Wherever possible, authors will be contacted for full articles or missing data.

Assessment of heterogeneity

Heterogeneity between studies in each meta-analysis will be assessed using a chi-squared test (Higgins et al. 2009) and a low degree of heterogeneity will favour meta-analysis. We will determine a pooled effect for studies that are homogenous and use the fixed-effects model. However, as studies are likely to be of various intervention effects, a random-effects model will be presented. Alternatively, we will present a narrative summary of the results if included studies are heterogeneous. The three intervention types, that is, administrative controls, environmental controls and personal protection measures, will be analysed as subgroups of either low-and middle-income countries or separately high-income countries. Lastly, we will use the grading of recommendations assessment, development, and evaluation (GRADE) (Balslem et al. 2011) to assess the quality of evidence for the TB interventions as low, moderate or high.

Sensitivity analysis

A sensitivity analysis will be performed to determine the impact of the study design on the results of the meta-analysis, especially if studies are non-randomised. The review will also evaluate which meta-analysis model, i.e. random-effects or fixed-effects model, is appropriate for the studies included and the results.

Presenting and reporting of results

Our results will be prepared in various ways. Diagrams will be used to explain the sourcing and selecting of studies into the review. A list of excluded studies and reasons for exclusion will be provided. Forest plots will be used for interpreting the effects of homogenous studies, but where forest plots are not appropriate or possible, descriptive narratives will be produced.

ETHICS

No primary research will be conducted, nor will there be direct involvement with human participants. Systematic reviews draw on publicly available secondary data and, therefore do not require formal ethical review (Emanuel et al. 2004). It is noted that ethical research, even if secondary research, relies on scientific validity. The study will be guided by experts with knowledge of content and methodology. The protocol will be submitted to the University of Cape Town Departmental Research Committee for approval. The results of this review will be available online through the university library. The review will also be written up for submission to a peer reviewed journal.

DISCUSSION

Expected significance of the study

The systematic review will be useful for policy development, practice in health care facilities and research. The findings will be a basis on which recommendations can be made about the effectiveness of current interventions and for future improvements. The review will evaluate the evidence specifically in relation to low- and middle-income countries who bear most of the burden of TB (Global Tuberculosis Report 2013). The evidence is important for making cost-efficient decisions in relation to wide-scale implementation of interventions. At facility level, hospital managers will be concerned with which interventions to implement or prioritise in the case of limited resources, and with how to ensure compliance by health workers in line with labour laws and regulations. Lastly, the review will highlight areas for future research, for example, whether certain interventions are more suited to certain locations.

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PART B: OVERVIEW

OVERVIEW INTRODUCTION

Tuberculosis remains a hazard for health care workers even though a diverse range of TB infection control measures are available. The risk of TB transmission is especially high in health care facilities where high volumes of patients are being cared for. After mine workers, health care workers have the highest risk of acquiring TB at work. This overview broadly covers the epidemiology and pathogenesis of TB, the obstacles to TB control and prevention, and the risk of TB transmission in health care workers.

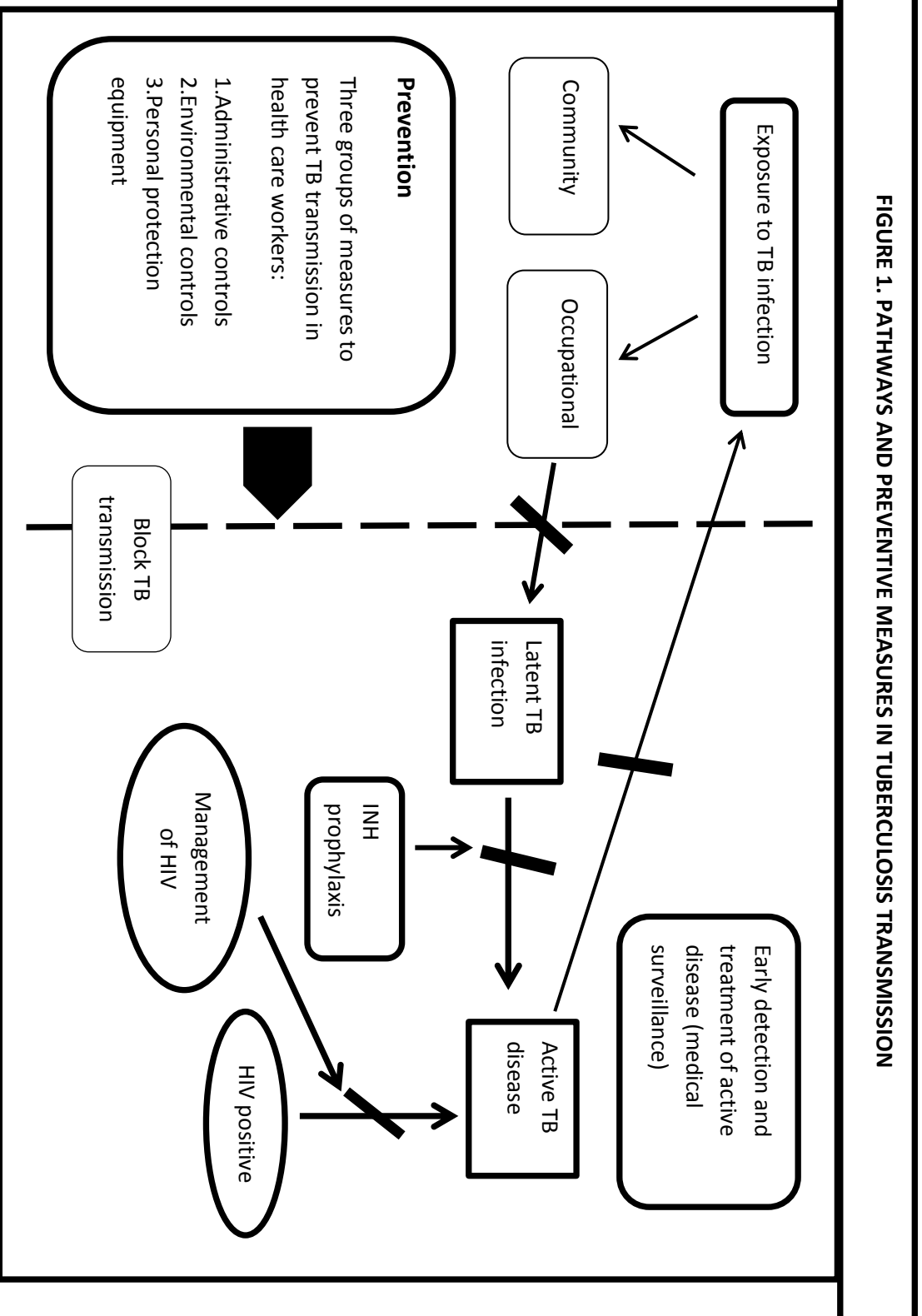
SECTIONS OF THE LITERATURE OVERVIEW

The overview precedes the systematic review and it is structured according to the following sections:

- The extent of the problem in health care settings, focusing on low- and middle-income countries with high TB burden.
- Factors translating into high risk transmission in health care workers, particularly inadequate protection measures, personal risk factors and non-compliance by health care workers with infection control measures.
- Prevention measures to stop TB transmission relevant to the systematic review, grouped as administrative control measures, environmental control measures and personal protection measures.
- Other interventions not relevant to the systematic review, that is, medical surveillance, isoniazid preventative therapy and BCG vaccination.
- The framework of a functioning health system and barriers within a health system that may interrupt TB prevention and control.

Figure 1 provides a summary of the pathway of TB after exposure. Community or occupational exposure to TB infection in susceptible individuals may lead to latent TB infection, or latent TB infection may progress to active TB disease. Preventative measures, that is, administrative controls, environmental controls and personal protection equipment, may block TB transmission between infectious and susceptible individuals. INH Prophylaxis may prevent latent TB infection from progressing to active TB disease and the management of HIV patients may also reduce the progression of TB disease. The management of HIV infected health care workers includes redeployment and preventative therapy, which prevent TB infection and active TB disease, rather than reduce the progression of disease. Early detection and treatment of active TB cases may limit exposure of susceptible individuals to infection in the community, as well as in health care services. In terms of health care workers, health services can only prevent TB infection in occupational settings, but not in community settings.

FIGURE 1. PATHWAYS AND PREVENTIVE MEASURES IN TUBERCULOSIS TRANSMISSION



SEARCH STRATEGY

A literature search was conducted through EbscoHost and the following databases were searched: Academic Search Premier, CINAHL, General Science Abstracts, Health Source (Nursing/Academic Edition) and MEDLINE. Various keywords, such as health care setting, health care worker, incidence, prevalence, risk, infection control, medical surveillance, IPT and BCG vaccination were searched in combination with tuberculosis to obtain relevant articles. Another search was performed using Google Scholar using the same keyword combinations. There were no limitations with regard to publication date, although recent articles were preferred.

Any journal article regardless of study design with TB data or information about TB control measures, particularly of low- and middle-income countries, were included. TB studies of health care workers or mine workers were of particular interest. Policy guidelines or healthy systems frameworks relating to health care workers or tuberculosis control were retrieved from the WHO website. Studies that did not provide information on TB or HIV were excluded.

BACKGROUND

TB is a global health problem, especially in high HIV prevalence and resource-limited settings. In health care facilities, health care workers are at risk of contracting TB infection and disease from infectious TB patients and other staff. In this background section, I provide an understanding of the epidemiology of *Mycobacterium tuberculosis*.

TB infection and TB disease

TB is caused by *Mycobacterium tuberculosis*, an acid-fast bacillus that is transmitted primarily via the respiratory tract. TB infection occurs mainly in the lungs, but can be spread to other organs once it gains access to the blood stream. There are various outcomes for a person encountering *M.tuberculosis* bacilli (Cohnheim 2013), including latent TB infection.

The distinction between latent TB infection and active TB disease is an important one. Individuals with latent TB infection are asymptomatic, but show a positive result on tuberculin skin tests (TST) and Interferon-Gamma Release Assays (IGRA) blood tests. There are an estimated 2 billion latently infected persons in the world, who represent an enormous reservoir of potential reactivation TB (Lin & Flynn 2010).

In cases where the initial TB infection is not controlled by the immune system, an individual may become symptomatic and develop primary progressive TB disease (Dye & Floyd 2006). Typical symptoms of TB disease include unexplained weight loss, loss of appetite, night sweats, and continuous coughing for three weeks or more.

Reactivation and Reinfection

Persons who are latently infected with *Mycobacterium tuberculosis* can develop TB through endogenous reactivation of the latent bacilli or exogenous reinfection with a second strain. TB reactivation results from the proliferation of a previously dormant endogenous bacterium of a primary infection. It occurs over the lifespan in 5 to 10 percent of those people with latent infection

and no underlying medical problems. There is an association between suppressed immune systems and TB reactivation, but it is not clear what host factors keep the infection latent and what factors cause the latent infection to become overt (Wani 2013). Reinfection may occur when a latently infected person is re-exposed to TB bacilli through repeated contacts with infectious individuals (Feng et al. 2000).

Health care workers in high TB burden settings are frequently in contact with infectious persons, thus making them an important risk group for both latent TB infection and TB disease (Joshi et al. 2006).

Pulmonary and extra-pulmonary TB

Another relevant distinction is between pulmonary and extra-pulmonary TB disease. Pulmonary TB may arise from exogenous reinfection or endogenous reactivation of a latent state from an initial clinical infection and involves the lung parenchyma and/or lymph nodes (Leung 1999). The classification of active TB for treatment purposes is based on a positive or negative sputum microbiology. A positive sputum is taken as indicative of being infectious; although such persons may or may not be symptomatic (Cramer & Frey 2006). In 2013, 109 630 pulmonary TB cases were bacteriologically confirmed and 148 658 pulmonary TB cases were clinically diagnosed, meaning that a total of 258 288 new pulmonary TB cases was reported (WHO 2014).

Extra-pulmonary TB occurs less commonly than pulmonary TB, but it sometimes occurs along with a pulmonary focus. It may affect many organs or tissues in the body other than the lungs, such as the meninges, extra-pulmonary lymph nodes, kidneys, intestines, bones and joint. HIV infection increases the occurrence of extra-pulmonary disease (Luetkemeyer 2013). In 2013, a total of 37 709 new extra-pulmonary TB cases were reported in South Africa (WHO 2014).

TB globally

Tuberculosis is a major health problem worldwide. In 2012, an estimated 8.6 million incident cases of TB and 1.3 million people died from the disease (including 320 000 deaths amongst HIV-positive people). This means the case fatality rate of TB is 15% which is the risk of death from TB among

people with active TB. Approximately one-third of the world's population is latently infected with *Mycobacterium tuberculosis*, of whom 10% are at lifetime risk of developing TB disease. Although the rate of TB incidence and the rate of TB mortality have fallen, the number of deaths is still high, especially considering that most are preventable (Global Tuberculosis Report 2013). Of the 8.6Asia accounted for 60% of new TB cases in 2012, while countries in sub-Saharan Africa carried the greatest proportion of new cases per population, that is, 255 new cases per 100 000. Looking at the incidence rate at country level there are substantial ranges, with around 1 000 or more cases per 100 000 in South Africa and Swaziland, and fewer than 10 cases per 100 000 in North America, Western Europe, Japan, Australia and New Zealand (Global Tuberculosis Report 2013).

TB in South Africa

As noted above, South Africa is amongst those countries with the highest incidence rate in the world, in fact, it has the second highest rate of new TB cases in the world. It also has the highest rate of drug-resistant TB in Africa, and the fourth highest prevalence of HIV/AIDS (Centers for Disease Control and Prevention 2011).

Even though TB control strategies were implemented as early as 1996, when TB was declared a national emergency, TB incidence and case–fatality rates have continued to increase in South Africa. (Weyer 2007). Weyer (2007) argued that determinants of the worsening TB epidemic in South Africa are diverse and multifactorial. South Africa has a legacy of poor management of patients and fragmented health services, and contemporary barriers to effective TB control are associated with deteriorating socioeconomic conditions, scarce human resources in the health-service sector, as well as the co-existence of HIV/AIDS in communities (Weyer 2007). The interaction between TB and HIV/AIDS is discussed next.

TB in the context of HIV/AIDS

TB is the most common infection in HIV positive individuals and it remains the most common cause of death in patients with AIDS worldwide. HIV infection has significantly increased TB incidence by producing a progressive decline in cell immunity and has modified the typical pathogenesis of TB, thus increasing the risk of active TB disease in HIV-infected individuals. The depletion of CD4+ T-cells

by AIDS is also an important contributor to the susceptibility of an individual to new *M.tuberculosis* infection (Pawlowski et al. 2012). The incidence of TB thus continues to climb in resource-limited countries where it is endemic.

Community risk of TB

In South Africa, health care workers are not only at risk of acquiring TB at work, but also in their communities. In mine workers, reactivation of inadequately treated latent TB infection or reinfection caused by high rates of on-going transmission within or outside the mines is a concern (Churchyard et al. 2014). It can be inferred that health care workers are also at risk of reactivation or reinfection both at work and in their communities.

A study by Wood et al. (2012) showed that there is an increase in non-home socialisation throughout age groups which is parallel to an increase in TB infection rates. Participants of all age groups reported transport use, and a number of TB contacts occurred while using transport, which provided the opportunity for inter-generational mixing, a pre-requisite for endemic TB (Wood et al. 2012). Wood et al. (2012) report that the working class in South Africa, as well as school going children, predominantly used minibus taxis, which are extremely overcrowded and poorly maintained. This means that health care workers are additionally at risk among social networks, as well as when using public transport.

The association between active TB disease and alcohol is widely documented as another contributing factor to transmission of TB in communities. A systematic review of published articles showed that recent transmission of TB and history of excessive alcohol consumption are associated (Cois & Ehrlich 2013). Health care workers who are drinkers or who are exposed to drinkers may be at increased risk of acquiring TB.

Occupational risk of TB

Health care workers are an important risk group, because of their frequent contact with infectious individuals. With the onset of the era of antibiotics in the 1950s, the risk of acquiring TB infection

amongst health care workers in high income countries declined (Sotgiu et al. 2008). This led to the relative neglect of TB infection control policies in hospitals (Sepkowitz 1994).

However, outbreaks associated with the HIV epidemic in the late 1980s changed views about the risk of TB in health care workers (Sotgiu et al. 2008). These outbreaks were indicative of the increased incidence of TB disease in European hospitals and the emergence of multiple drug-resistant strains of TB in hospitals all over the world. The presence of TB and HIV co-infection, even in countries with low incidence of both diseases, contributed to the changed views.

THE EXTENT OF THE PROBLEM IN HEALTH CARE SETTINGS

The problem of TB transmission in health care settings (nosocomial risk) is greater in low- and middle-income countries than in high-income countries.

A combined result of 51 analyses estimated that annual risk of latent TB infection ('incidence') among health care workers ranges from 0.5 to 14.3 percent per year in low- and middle-income countries (Joshi et al. 2006). The annual incidence range of TB disease in health care workers in high-income countries of 2 to 55 cases per 100 000 is much lower than the annual incidence range of TB disease in health care workers in low- and middle-income countries of 69 to 5 780 cases per 100 000 (Joshi et al. 2006).

Joshi et al. argue that the low staff-TB patient ratio in health care facilities in low- and middle-income countries is the cause of increased TB transmission to health care workers from infectious patients. Health care facilities in low- and middle-income countries have a median ratio of 36 health care workers per 100 TB patients compared to a median of 6 450 health care workers per 100 TB patients in high-income countries (Joshi et al. 2006). An individual health care worker in health care facilities in low- and middle-income countries is thus more likely to be repeatedly exposed to infectious TB patients and hence be at greater risk of acquiring active TB disease.

The study concluded that a higher risk of acquiring TB disease is associated with (a) certain work locations such as TB facilities, laboratories and emergency facilities, and (b) occupational categories such as patient attendants, paramedics, radiology technicians and nurses (Joshi et al. 2006).

Indian studies that investigated the risk of transmission in health care workers showed that the annual risk of TB infection is greater in health care workers than in the general population (Jesudas & Thangakunam 2013). The annual risk is about 5% per year in health care workers in comparison to the national average of 1.5%. The difference is attributed to nosocomial transmission (Pai et al. 2006). This finding is also observed in Brazil, where a study found that nurses working in a hospital emergency unit had a risk of latent TB of 12.6 greater than that of the city population (Pazin-Filho et al. 2008).

Similarly, in South Africa, a study conducted at 133 primary health care facilities in five provinces revealed that nosocomial transmission of TB is a serious problem among health care workers (Claassens et al. 2013). It was found that health care workers had double the incidence ratio of smear positive TB than the general population.

Moreover, the increasing prevalence of multiple drug-resistant (MDR) and extensively drug-resistant (XDR) TB poses a major threat to health care workers working in wards and outpatient clinics irrespective of HIV status (Jarand et al. 2010).

A study estimating the rates of MDR-TB and XDR-TB hospitalisations from 2003 to 2008 among health care workers in KwaZulu-Natal found that health care workers had a 5 to 6 fold increased rate of hospital admission with MDR- or XDR-TB compared to non-health care workers (O'Donnell 2010). Previous treatment for TB and HIV infection did not explain the increased drug-resistant TB hospitalisation rates in health care workers, as they did not report higher proportions of previous treatment of TB than did non-health care workers.

This growing burden of drug-resistant TB exacerbates the shortage of health care workers on duty, as those affected can often no longer continue with work while on treatment, at least until they are declared non-infectious (Jarand et al. 2010).

These studies are only a few of many that document the extent of TB risk amongst health care workers. In the next section, studies that argue that inadequate protection measures and personal risk factors contribute to the transmission risk of TB are reviewed, but first an explanation of the transmission process is necessary.

RISK

Transmission of TB

M. tuberculosis is carried by airborne droplets that are produced when infectious persons who have pulmonary TB disease cough, sneeze, sing, speak and shout. Depending on the environment these droplets can remain suspended in the air for hours (Centers for Disease Control and Prevention, 2014). The risk of infection is dependent on several factors such as the immune status of recipients, the closeness of contact, the bacillary load inhaled and the environment (Ahmad, 2010). The primary route of infection involves the lungs, where droplets are inhaled through the mouth or nasal passages.

In the case where a person inhales small droplets that cannot be stopped by the defences of the nose and throat, the droplets reach the alveoli in the lungs and multiply. The infection is generally limited to the Ghon focus, the first location affected in the lung. In most cases lymphocytes form granulomas to prevent the mycobacterium from propagating, which in turn provide the immune system cells with an environment in which to arrest the TB bacilli. In the granuloma the bacteria are suppressed to produce latent infection only. In cases where the immune system is impaired or overwhelmed, TB bacilli survive and multiply rapidly, causing TB disease to develop (Wikipedia 2014). Bacteria may also propagate to other parts of the body via the bloodstream or lymphatics.

Inadequate protection measures and personal risk factors

The pathogenesis of TB does not differ in health care workers from that in the general population. However, health care workers are at greater risk of acquiring TB in the workplace than persons in other occupations. A number of studies have investigated associations between personal risk factors and the risk of TB transmission in health care workers, but have yielded different results. A few of these studies are reviewed below.

A case-control study conducted by Jelip et al. (2004) examined whether age, duration of service, service in high risk procedures and non-use of personal protection were risk factors for TB among health care workers in Malaysia. For every one year increase in age, the risk of TB increased by 15%

in health care workers. Duration of service was categorised into 5-year intervals and those in the first 10 years of work had the highest risk of TB disease. High-risk procedures are those procedures that are cough-inducing, for example, bronchoscopy or drug administration by nebulization. Exposure to high-risk procedures did not significantly contribute to the risk of TB among health care workers, but those who did not use respiratory protection when carrying out such procedures were 3 times at higher risk to TB than their counterparts (Jelip et al. 2004).

A cross-sectional study in Iran enrolled 180 health care workers to investigate a list of personal risk factors for latent TB (Nassaji & Ghorbani 2012). As in the Jelip study above, the Iranian study explored whether age and employment duration were risk factors for latent TB infection. The Iranian study also obtained information about gender, history of BCG vaccination and type of work in relation to health care workers' risk of TB infection. All participants received a tuberculin skin test to determine TB infection status. Age and years of working as health care workers were assumed to reflect cumulative exposure to *M. tuberculosis*. A positive test result was more common in health care workers older than 40 years than in younger health care workers, that is, 21.1% versus 10.6%. Longer duration of work as a health care worker was significantly associated with a positive latent TB infection test result, with an odds ratio of 4.59 (95% CI 1.07 and 15.68). These results are consistent with other studies that have reported that increasing age and years of work in health care are associated with higher risk of latent TB infection in health workers (Mirtskhulava et al. 2008), although this is different from the Malaysian study above in which latent TB infection risk was highest in the early years of work.

Nassaji's study also showed that being female and having received BCG vaccination were associated with a greater latent TB infection risk. Laboratory staff and nurses were found to have higher tuberculin reactivity than other job categories, presumably because of a higher level of exposure to patients or human tissue or fluids (Nassaji & Ghorbani 2012).

In South India a nested case-control study enrolled 6 003 health care workers of whom 41 developed active TB during the study period. A high nosocomial risk of acquiring active TB was associated with frequent patient contact, lower than 19 kg/m² body mass index (BMI) scores, and being employed in medical wards and microbiology laboratories (Mathew et al. 2013). These risk factors are additional to those identified in the above studies.

The risk of TB transmission is further increased by inadequate protection measures, where use or provision of personal protection equipment, administrative controls and environmental controls is lacking for protecting health personnel.

Inadequacies in TB diagnosis and treatment of patients enhance risk of TB transmission. Nosocomial transmission is high when diagnosis of TB in patients is delayed, when patients do not receive adequate treatment and when drug resistance is unrecognised. In four cohort studies diagnosis was delayed in 40 to 50 percent of all patients with active TB, resulting in the exposure of 27 to 44 health care workers for each patient who was undiagnosed (Menzies 1995).

Ventilation is an environmental strategy in TB infection control to mix and circulate air. Poor ventilation is another factor that facilitates TB transmission. Open windows and doors allow for the natural flow of air current through wind, also known as natural ventilation. The alternative is mechanical ventilation, that is, the mixing and circulating of air using air conditioning and fans (McCarthy et al. 2009). A study investigating tuberculin conversion among health care workers in 17 hospitals of similar risk and size in Canada showed that tuberculin conversion was strongly associated with inadequate ventilation in general and non-isolation patient rooms (Menzies et al. 2000). The risk of tuberculin conversion was 3.4 times higher in those who worked in the general patient rooms with fewer than 2 air exchanges per hour on average, than those who worked in patient rooms with more than 2 air exchanges (Menzies et al. 2000). The problem with properly designed ventilation systems is that they increase energy costs and they require frequent inspection and maintenance in order to be effective (Menzies 1995).

Surgical masks were developed to prevent the inhalation of viable and total particles, but they are not effective in preventing the inhalation of small droplets with a diameter of 1 to 5 μm ; in fact they prevent less than 50% of such droplets from being inhaled and are thus ineffective (Menzies 1995). Instead high-efficacy particulate air filter (HEPA) masks can filter 99.7% of 0.3 μm particles. However, masks with higher efficacy result in increased difficulty in communication, shortness of breath and face-seal leakage unless health care workers are well trained and fit-tested (Menzies 1995).

Non-compliance of health care workers with infection control measures

Even though there are potentially effective TB infection control measures, lack of compliance by health care workers with protocols and guidelines remains an obstacle to reducing the risk of TB transmission in health facilities.

Recent studies, subsequent to the 2009 WHO review of the South African National Tuberculosis Control Programme, found that although health care workers may be aware of regulations and

guidelines relating to TB infection control, measures were not being used appropriately or consistently across facilities (Tudor et al. 2013).

A study by Engelbrecht & Rensburg (2013) explored the extent of TB and infection control measures at 127 primary health facilities across three districts in South Africa. The research identified that health care workers inconsistently complied with WHO policy. At 48.8% of the facilities coughing patients were not separated from other patients, at 35.4% of the facilities coughing patients were not provided with masks and only 18.9% of the clinics opened windows and doors for natural ventilation. On the other hand, coughing patients were screened for TB and staff participated in screening of signs and symptoms of TB at all facilities (Engelbrecht & Rensburg 2013).

From the literature it can thus be inferred that non-compliance by health care workers poses a threat to the reduction of TB risk in health care facilities. However, health care workers operate within specific health systems contexts. The influence of these health system factors are discussed at the end of the chapter.

PREVENTION

Interventions to stop TB transmission: administrative, environmental and personal measures

The three groups of interventions discussed in this section are those relevant to the systematic review. These infection control measures have the potential to reduce the risk of *M.tuberculosis* transmission even in resource limited settings (Bock et al. 2007). Bock et al. describe a 3-level hierarchy of controls, namely administrative (or work practice), environmental (or engineering) and personal protection equipment (or respiratory protection).

Administrative controls and work practice measures should be considered a first line of defence against TB transmission in health care facilities, especially in facilities caring for people with HIV infection as well (Bock et al. 2007; WHO/ILO 2010). Administrative controls and work practices include: early TB diagnosis and treatment protocols, an infection control plan, administrative support for procedures in the plan (including quality assurance), training of health care workers, education of patients and community awareness and coordination between TB and HIV programmes. Their goals are to prevent exposure to staff and patients by ensuring rapid and appropriate diagnosis and treatment for those suspected or known to have TB, which is best achieved when suspects are promptly recognised and separated out of waiting areas.

Environmental controls are the second line of defence against TB transmission in facilities that care for both TB and HIV patients, but administrative controls must be in place first in order for these controls to operate properly and be maintained. Environmental controls include natural and mechanical ventilation and room air cleaners (such as ultraviolet germicidal irradiation (UVGI) and air filters). Ensuring that overcrowding is reduced is both an administrative and environmental activity (Bock et al. 2007). It is important to note that some environmental control measures are technologically complex and expensive. However natural ventilation, which relies on the free movement of air by opening doors and windows, can reduce the risk of TB transmission. Fans or open ventilation channels may be useful in distributing air. In high-risk settings, UVGI may work when there is sufficient ventilation and when regular maintenance of the lights takes place.

The last strategy described by Bock et al. for the protection of health care workers is respiratory protection. Respirators can in theory reduce the transmission of TB by preventing face seal leaks

when fitted and used properly. Even a poor respirator or face mask that filters only half of the particles can in theory reduce transmission. The use of respirators is especially recommended for high-risk procedures such as sputum induction, bronchoscopy or post-mortem examinations (Bock et al. 2007).

Humphreys (2007) states that the evidence for the efficacy of controls to prevent the transmission of TB in health care facilities is not based on controlled trials (which are lacking in this area). Nonetheless the risks of transmission are generally lowered when all measures are combined together. All three TB infection control measures were implemented into a 1000-bed hospital in Atlanta after a policy for TB control was revised (Blumberg et al. 1995). The number of TB exposure episodes decreased from 4.4 per month to 0.6 per month and the tuberculin skin-test conversion rate decreased amongst health care workers from 3.3 to 1.7 percent (Humphreys 2007).

However, Humphreys warns that the implementation of all three groups of control measures may not be financially viable in resource limited settings. He argues that even when there are preventative measures for nosocomial transmission, compliance with or provision of all measures is a problem. Regular audit of the prevention measures and willingness to act on the results are also required.

A 10 year retrospective review of primary interventions for health care workers comes to the same conclusions as did Humphreys. The review was of Cook County Hospital, a large public hospital in Chicago and it included all three levels of TB infection controls (Welbel et al. 2009). From 1992 to 1997 personal, administrative and environmental measures were implemented and the results showed that the overall annual health care worker tuberculin skin-test conversion rate fell significantly when primary interventions were simple administrative and engineering controls. Welbel et al. (2009) showed that educating health care workers to quickly recognise TB case patients and having health care workers redirect TB suspects to isolation rooms were the two most effective infection control measures. A recent study by Nienhaus et al. (2014) also showed that early identification of cases and isolation are the two most effective measures.

The aim of the systematic review will be to assess the overall effectiveness of these identified strategies.

Other interventions: medical surveillance, INH therapy and BCG vaccination

The systematic review will not include intervention studies of medical surveillance, isoniazid prophylactic therapy (IPT) therapy or BCG vaccination. However, for completeness these interventions are considered in the context of South Africa.

Medical surveillance

South African occupational health legislation requires that *medical surveillance* (screening and monitoring of employees) be conducted in all hospitals since there is a risk of disease from “hazardous biological agents” (Wilson & Ndzungu 2011).

In a different context, a study by Churchyard et al. (2010) amongst South African miners compared 6-monthly and 12-monthly radiological screening for active tuberculosis case-finding. South African miners and health care workers are the largest at risk groups for occupationally-acquired TB. Case notifications exceeded 3 000 per 100 000 miners in 2008. The study found that compared with 12-monthly screening, 6-monthly screening detected more TB suspects, but not more TB cases (Churchyard et al. 2010). For mandatory screening to be effective, all TB suspects identified must be investigated for TB disease (Churchyard et al. 2010). Follow-up of TB suspects requires a well-functioning back up service.

Wilson & Ndzungu (2011) administered a questionnaire to health care workers working in a hospital in Johannesburg regarding their knowledge of TB symptoms and their attitudes towards regular medical surveillance. The authors found that of 200 staff available to participate; only 44% returned the questionnaires, with doctors and consultants noticeably missing. 85% of those who responded were in favour of routine medical surveillance and 48% were willing to disclose HIV status if early HIV treatment were provided. The study found that routinely administering a questionnaire is a cost effective means of medical surveillance and it can help identify those requiring investigation for TB (Wilson & Ndzungu 2011). The authors state that for medical surveillance to be effective, occupational health staff are needed to run the program, to ensure coverage of more health care workers and to provide training on health risks.

There is an important distinction that needs to be made between medical surveillance and public health surveillance. Medical surveillance, as stated above, is the monitoring of individuals who are

exposed to a pathogen or the detection of the early symptoms of disease. Public health surveillance refers to collection of information on disease occurrence on which public health actions can be based. It could also be used to monitor risk factors, such as non-compliance with TB guidelines, and it assists in the identification of areas that need intervention, research, policy change and impact evaluation (Heidebrecht et al. 2011).

Isoniazid preventative therapy (IPT)

Churchyard et al. (2014) recently published a cluster-randomised trial that evaluated an intervention to interrupt TB transmission in South African gold miners by means of mass screening for active TB or latent TB treatment. The intervention clusters received TB screening. Those who had active TB were referred for treatment, while the rest were offered 9 months of isoniazid preventative therapy (IPT). The study showed that the rates of TB were similar in the intervention and control clusters. The incidence of TB was 3.02 per 100 person-years in the intervention cluster and 2.95 per 100 person-years in the control clusters (Churchyard et al. 2014). Thus mass screening and treatment of latent TB had no significant effect on TB control in gold miners.

Community wide IPT in mine workers was not effective in reducing the incidence of TB because of post-treatment reinfection, within or outside mines (Churchyard et al. 2014). Individual protection of IPT may have been compromised due to reactivation of inadequately treated latent TB or reinfection caused by high rates of occupational and community TB. Additionally, the prevalence of HIV and other sexually-transmitted infections (STIs) is high amongst South African mine workers. STIs are strong risk factors for TB. ART may only reduce the risk of TB for an individual without having an effect for a population.

Wood & Bekker (2014) stated that in South Africa more than 50% of TB cases are diagnosed in HIV-infected people. The country has the largest anti-retroviral treatment (ART) programme in the world with 2 million people enrolled. The study thus investigated the effectiveness of IPT in the wider HIV-infected population, not limited to at risk groups such as miners and health care workers. The authors cited a combined analysis of randomised controlled trials of IPT in HIV-infected adults performed between 1962 and 1994. The analysis showed a 60% reduction in active TB in HIV-infected adults on IPT. A subsequent Cochrane meta-analysis of 12 randomised controlled trials of IPT in HIV-infected adults (mostly not on ART) showed a 62% reduction in TB amongst adults with positive tuberculin skin-tests (Wood & Bekker 2014).

In conclusion, IPT may be effective in individuals for an unknown period of time after treatment, but it is ineffective in populations with high TB incidence, due to reactivation and reinfection of TB.

BCG vaccination

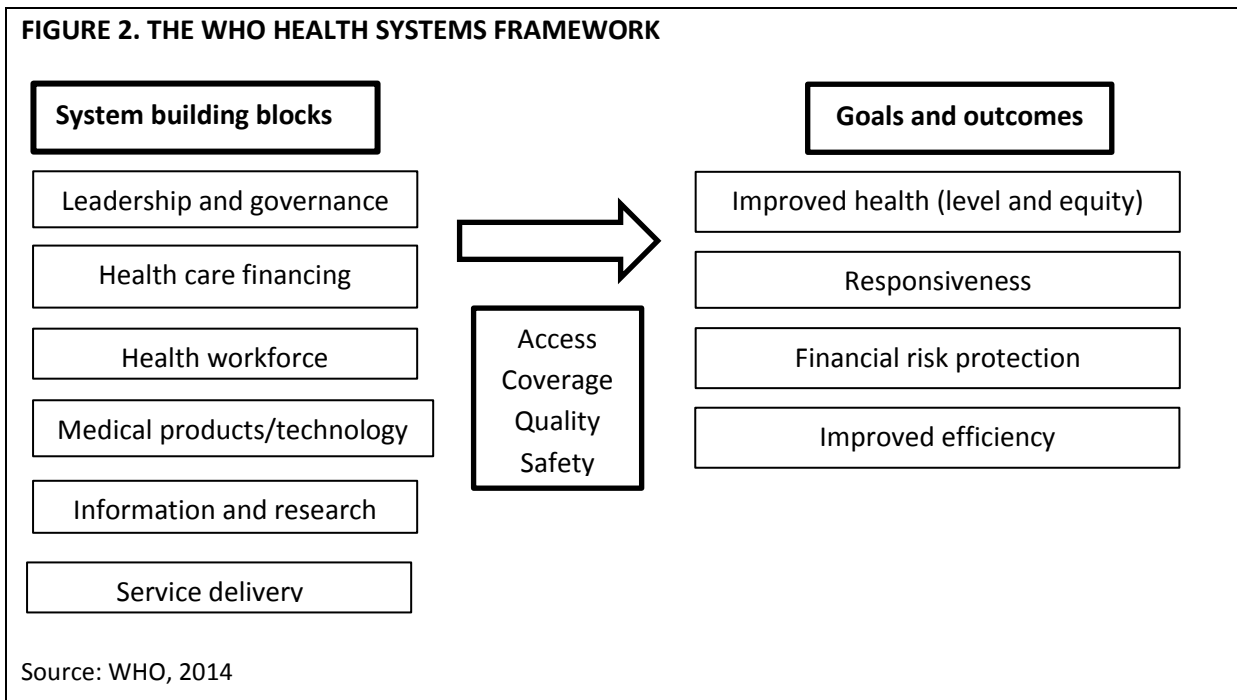
Although it provides good protection against disseminated forms of TB in children, such as TB meningitis, the protective efficacy of BCG vaccine for pulmonary TB in adults is uncertain (Centers for Disease Control and Prevention, 1996). The relative risk of BCG protection against TB disease in adults has a range of 0.20 to 1.56 and an average efficacy of 50% (relative risk of 1.5) which is significantly lower than that for infants (von Reyn & Vuola 2002). BCG vaccination is thus not administered to adults in South Africa and is not an option for health care workers at risk for occupationally acquired *M.tuberculosis*.

THE HEALTH SYSTEM

Building blocks of health systems

“A health system consists of all organizations, people and actions whose primary interest is to promote, restore or maintain health” (WHO 2014). WHO states six elements as the building blocks of a health system, that is, leadership and governance, health care financing, health workforce, medical products and technologies, information and research, and service delivery.

TB transmission in health care facilities is a dual threat, first, as a communicable disease and second as an occupational health hazard. The reduction of risk of TB in health care facilities is dependent on a functioning health care system. The six building blocks of a health system are shown in the figure below (WHO 2014).



Leadership and governance involves ensuring that policy frameworks exist and are being implemented. A good health financing system raises funds for needed services and ensures that people can use them. A well-performing workforce is able to work in ways that are responsive and efficient to achieve the best health outcomes given available resources. A well-functioning health system ensures that people have equitable access to good-quality, safe and effective medical products and technologies. A health information system collects, analyses and disseminates information on health determinants, health systems performance and health status. A health service functioning properly delivers effective, safe, timely and quality health interventions to those who need them with minimum waste of resources (WHO 2014).

Health systems barriers to reducing TB transmission

Similar elements to those of the WHO framework were identified in a cross-sectional study in 51 health facilities in Uganda (Buregyeya et al. 2013). Buregyeya et al. (2013) listed governance and stewardship, financing, infrastructure, procurement and supply chain management as important health systems elements. The lack of these elements resulted in poor TB infection control in some of the 51 facilities included in the Buregyeya study

Buregyeya et al. (2013) reported that half of the facilities did not have adequate ventilated waiting areas based on the proportion of the windows to the floor area and most facilities were crowded with no or little structural improvements. The authors also found that lack of managerial support in the form of funds for respirators, renovations and structural improvements resulted in poor TB control. Factors such as understaffing and heavy workload contributed to poor implementation of first line control measures.

A five country report by Corbett (2007a) identified different organisational barriers to TB prevention, testing and care. The report argues that lack of training and inadequate TB infection control guidelines for health care workers are obstacles to the reduction of occupational risk of TB. Additionally, lack of guidance to facilities about services and their implementation, and poor knowledge of available services and worker rights, limit TB infection among health care workers (Corbett, 2007a).

The report concluded that policies are needed to protect health care workers with TB and HIV from losing their jobs and experiencing stigma and discrimination in the workplace, and to protect their

career and training prospects if their TB and/or HIV status becomes known to their colleagues and employers. Health care workers from the five countries studied, namely Ethiopia, Kenya, Malawi, Mozambique and Zimbabwe, expressed the view that failure to acknowledge TB as an occupational hazard and denying them entitlement to leave and compensation led to mistrust, resentment and demotivation. Poor communication of policy and worker rights to health care workers and inadequate education on how to minimise and report occupationally acquired TB resulted in health care workers failing to access services or report occupational events (Corbett, 2007a).

In summary, health care systems are plagued by many difficulties in preventing TB among health care workers while health workers face increasingly risky working conditions. Interventions at the level of the health system thus have an important role to play in prevention, treatment and care to affected workers (WHO, 2006b).

The Joint WHO/ILO (2010) policy guidelines on improving health care access to prevention, treatment and care services for HIV and TB were designed to reinforce the implementation of best health practices for health care workers who are living with or are at risk of HIV and TB in the workplace. A list of 14 recommendations were developed for health systems and can be summarised into five categories: (a) implement supporting policies and strengthen structures, (b) provide training and codes of practices, (c) allocate funds for programs, materials and medicines, (d) provide compensation and (e) monitor structures, processes and outcomes with multi-stakeholder involvement from national to facility level.

CONCLUSION

After miners, health care workers are the largest at risk group for occupational TB in South Africa, with a higher incidence rate than the general population. Some personal factors such as employment duration and job category increase the risk of TB transmission, while behavioural factors such as compliance with personal protection and participation in administrative controls may decrease nosocomial risk. Health systems factors beyond the immediate control of health care workers shape the ability and willingness of health care workers to comply with protective measures.

However, these higher level activities are all predicated on the effectiveness of specific protective measures. The systematic review that follows will investigate the evidence for the effectiveness of measures aimed at reducing transmission of TB infection in health care workers.

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PART C: ARTICLE

PLAIN LANGUAGE SUMMARY

TB is a mycobacterium that is commonly transmitted via the respiratory tract. To reduce the risk of TB transmission to and among health care workers in contact with infectious TB patients at work, policies on the implementation of TB interventions are needed. In the field of public and occupational health these interventions are grouped into three levels as administrative controls, environmental controls and personal protection equipment. At each level, various measures are recommended to prevent the spread of TB in health facilities. This review aimed to compile a quantitative summary of the effectiveness of individual TB control measures at the three levels of TB prevention.

We analysed 15 observational studies (a majority with unclear methodological quality) that assessed the effectiveness of various combinations of TB interventions to prevent transmission. The research suggests that the implementation of multiple TB interventions at health facilities in low TB burden, high income countries may stop nosocomial transmission of TB. We are uncertain about the applicability of this evidence to high TB burden, low- and middle- income countries.

Given the lack of evidence for the effectiveness of a single TB intervention, we recommend that where possible, well-designed experimental studies be conducted in high TB burden, poorly resourced countries in order to identify effective TB interventions. Where trials are not practical or relevant, high quality observational studies need to be conducted in current contexts of nosocomial risk.

BACKGROUND

Description of the condition

Tuberculosis is a major global health problem. A total of 8.6 million people developed TB disease and 1.3 million died from TB in 2012 (Global Tuberculosis Report 2013). The historical record suggests that TB infection control was neglected during the 1980s. Since the early 1990s the effect of the HIV epidemic and upsurge of multidrug-resistant and extensively drug-resistant TB have resulted in a heightened recognition of the TB burden amongst various risk groups internationally (Glaziou et al. 2013). One focus is the prevention and control of nosocomial transmission of TB, especially in low- and middle-income countries. Most of the new TB cases in 2012 occurred in Asia (58%) and Africa (27%). In these regions, overcrowded and under-resourced health care facilities are a common site of TB transmission (Kompala 2013). Thus health care workers working in such facilities are constantly at risk of acquiring TB by being in contact with infectious TB patients (Eames et al. 2009).

Various studies (Joshi et al. 2006, Menzies et al. 2007a & Sotgiu et al. 2008) have demonstrated that TB infection rates are higher amongst health care workers than the general population in low- and middle-income countries. In South Africa, this is the case. A study in Kwa-Zulu Natal found that health care workers were 6 times more likely to be hospitalised with multidrug-resistant TB than the general population (O'Donnell 2010). The concern for health care workers is not only related to them being at risk of acquiring TB, but also to them having the potential to transmit TB to patients when unaware of or afraid to disclose their TB status. Nosocomial TB transmission may also worsen the short supply of trained nurses and clinical staff in the developing world (Kompala 2013).

The HIV pandemic has amplified the global burden of TB. 82% of the world's TB and HIV co-infected population lives in sub-Saharan Africa where 350 000 TB deaths were associated with HIV infection in 2010 (Gray & Cohn 2013). 15% of health care workers in South African are HIV positive (Dheda 2011).

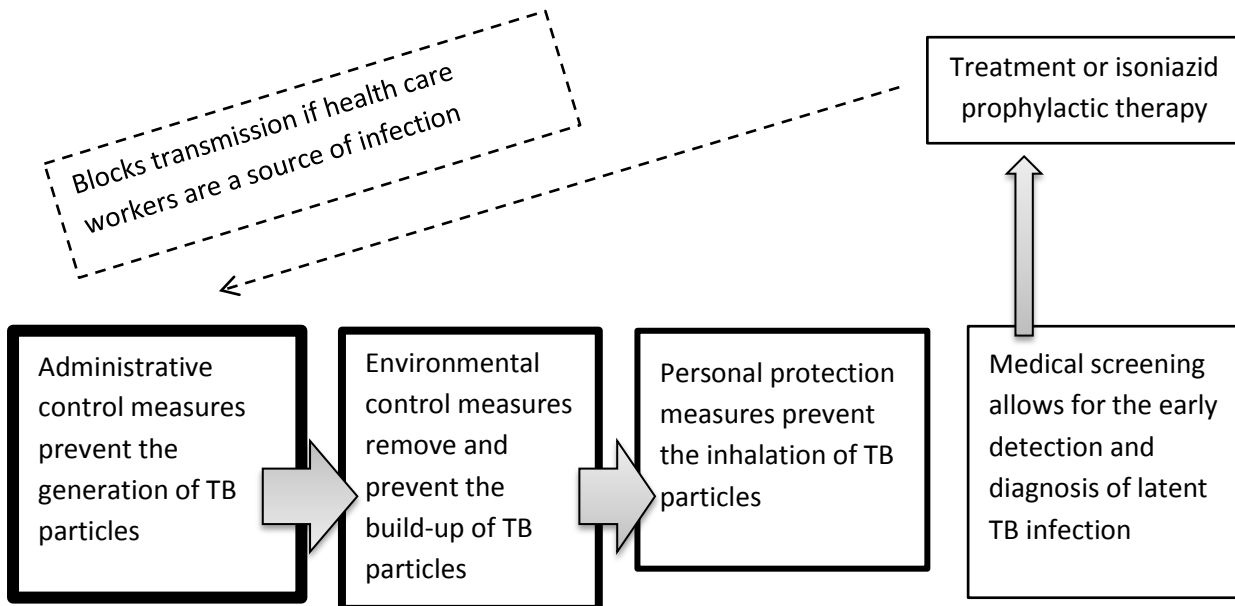
Description of the interventions

Effective TB control measures should prevent TB transmission between patient and health care worker, patient and patient, and health care worker and patient (Sotgiu et al. 2008) in health care facilities. The Centers for Disease and Infection Control (CDC) and the World Health Organisation (WHO) have established infection control guidelines suitable for poor and rich health care settings (WHO 2009). In the guidelines infection control measures are grouped at three levels: personal, administrative and environmental (Figure 1.). Personal protection is directed to patients, visitors and health care workers and includes a variety of measures such as cough hygiene, reduced contact, regular wearing of masks and respirators and a monitoring system that encourages routine use of respiratory protective devices (Eames et al. 2009). With regard to administrative controls, guidelines have been developed to provide information on worker education, patient triage, TB diagnosis, respiratory isolation of suspects, provision of care and referrals to appropriate TB services and programs. Environmental controls include the installation of ultraviolet (UV) lights and ventilation. Ventilation refers to the supply of fresh air to a building, naturally or mechanically, and its distribution within it. UV light (which includes sunlight) affects the survivability of infectious pathogens in the air (Eames et al. 2009). Medical screening of health care workers for TB infection or disease and early treatment of disease or provision of isoniazid prophylactic therapy can also be considered as measures to prevent transmission (Figure 1.). However, these will not be considered in this review.

How the intervention might work

Effective TB interventions should reduce the risk of TB transmission even in settings with limited resources (Bock et al. 2007). Administrative controls are the first line of transmission prevention, as these reduce the risk of exposure for health care workers and patients broadly and improve the quality of TB diagnosis and management (South African Tuberculosis Control Guidelines 2004). If the risk of TB transmission can be eliminated by administrative controls, there is no need for the other control measures. However, if the generation of airborne infectious particles cannot be eliminated, then environmental controls are used to remove them. Personal respiratory protection is a last resort when the other infection control measures have not or cannot eliminate risk of exposure (McCarthy 2009; South African Tuberculosis Control Guidelines 2004).

FIGURE 1. THREE LEVELS OF TUBERCULOSIS INTERVENTION TO PREVENT TRANSMISSION



Why is it important to do this review

Despite widespread but uneven use, the effectiveness of TB infection control practices is unclear. A few studies (Fennelly & Nardell 1998) have shown that the use of combined infection control measures is associated with reduced transmission. However, others have shown a non-significant decrease in TB disease incidence after implementing multiple measures (Harries et al. 2002). Discrepancies may be attributed to the inadequate evaluation of the effectiveness of multiple infection control measures (Kompala 2013) and the failure to evaluate single TB interventions at different levels (Claassens et al. 2013). Given the wide array of infection control measures that have been recommended, it is important to compile scientific evidence of the effectiveness of current infection control practices for policy makers and public health specialists. The evidence is most useful for low- and middle-income countries with a greater TB incidence than high-income countries. (Joshi et al. 2006)

OBJECTIVE

The objective of this dissertation was to undertake a systematic review to evaluate the effectiveness of TB interventions aimed at preventing transmission at three levels (administrative, environmental and personal) for health care workers working in health care facilities.

METHODS

Criteria for considering studies for this review

Studies that met the following criteria were included:

- Randomised controlled trials, clinically controlled trials, quasi-randomised trials, controlled before and after studies and cohort studies.
- Studies with participants whose occupations are located within health care facilities. Health care workers include nurses, doctors, laboratory staff, allied professionals and support staff.
- Studies that evaluated any type of TB intervention to prevent transmission against a control. Table 1 lists various types of TB interventions, and is adopted from the *Guidelines for Preventing the Transmission of Mycobacterium tuberculosis, 2005* document.
- Studies that defined a control as non-use, less frequent or less intense use of an intervention. In the absence of such studies, we also searched for studies that evaluated multiple components of TB interventions against an above-defined control.
- Studies that determined the effect of TB interventions on the risk of TB transmission, except for studies of medical screening or treatment of health care workers for latent TB infection.

TABLE 1: THREE LEVELS OF TB INTERVENTIONS

ADMINISTRATIVE CONTROLS

Involving health care workers: policy education

Involving patients: patient triage, rapid TB diagnosis, separation of TB suspects or isolation

Involving health system: risk assessment, policy implementation and guideline provision.

ENVIRONMENTAL OR

Mechanical and natural ventilation

ENGINEERING CONTROLS

UV lights

PERSONAL PROTECTION

Respirators and masks

Training in the use of personal respiratory protection

Hand hygiene

Fit-testing

Search methods for identification of studies

The electronic searches were conducted on publications dating to the end of May 2014. The search strategy included a combination of the following keywords: TB, tuberculosis, mycobacterium, health personnel, hospital personnel, respiratory protective device, mass screening, education, triage, patient isolation, early diagnosis, risk assessment, guideline, policy and controlled environment. The complete strategy is shown in Appendix 2. We developed a search strategy comprised of relevant medical subject headings (MeSH) and keywords relating to tuberculosis, health care workers, and tuberculosis interventions in Medline. We translated the Medline search strategy into Scopus, Trip, LILACS, Cochrane Central Register of Controlled Trials, World Health Organisation International Clinical Trials Registry Platform, and ClinicalTrials.gov, while making the necessary vocabulary adjustments. During the search we placed no limitations on date or language. Both published and unpublished studies were considered for inclusion. We looked over the reference lists of identified studies for additional studies. Relevant authors and experts in the field were contacted for unpublished and published work. A manual internet search, using Google, was performed at the end of the systematic search to identify relevant grey literature.

Data collection and analysis

Selection of studies

Two reviewers reviewed all titles and abstracts of identified references from the search. The full text articles of those references that seemed to meet the inclusion criteria were retrieved. Two reviewers, BS and ME, then verified whether the full text articles met the inclusion criteria. The three reviewers, one of whom is a subject expert, resolved any disagreements through discussion.

Data extraction and management

BS and ME extracted data independently of each other using a standardised data extraction form and then merged it. No measure of agreement was used, however the data extraction form was piloted numerous times, and any components that caused disagreement were revised. However, when discrepancies arose, they were resolved through discussion until consensus was reached, and the third reviewer was asked for advice when disagreements related to content. The extracted data were entered into a spreadsheet for final analysis. The following descriptive and outcome data were extracted from each study:

- Study identification details: authors, year of publication, country and relevance of cited references.
- Verification details: assessment whether the study met the inclusion criteria for the review.
- Study details: study design, follow-up period, study setting, study participants and number enrolled in the study.
- Details of intervention: type of intervention, and introduction and duration of intervention.
- Details of control: non-use, less frequent or less intense use of intervention.
- Details of the outcome measure: TB incidence or case notification rate
- Notes: study results and general comments.

Assessment of risk of bias in included studies

We assessed the risk of bias in included studies on the following criteria (Cochrane EPOC Group 2008):

- Selection of participants into studies, including random sequence generation and concealment of allocation in the case of randomised-controlled trials.
- Similar baseline outcome measures
- Similar baseline characteristics
- Complete outcome data
- Blinding or objective assessment of primary outcome
- Adequate protection from contamination
- No selective outcome reporting ; and
- No other risks of bias

Measures of treatment effect

Data were analysed in a spreadsheet where the estimates of the intervention effects reported by study investigators were recorded. Due to the heterogeneity among the included studies, a meta-analysis of the pooled effect was not possible. The results are therefore presented as a qualitative synthesis according to three subgroups of TB interventions.

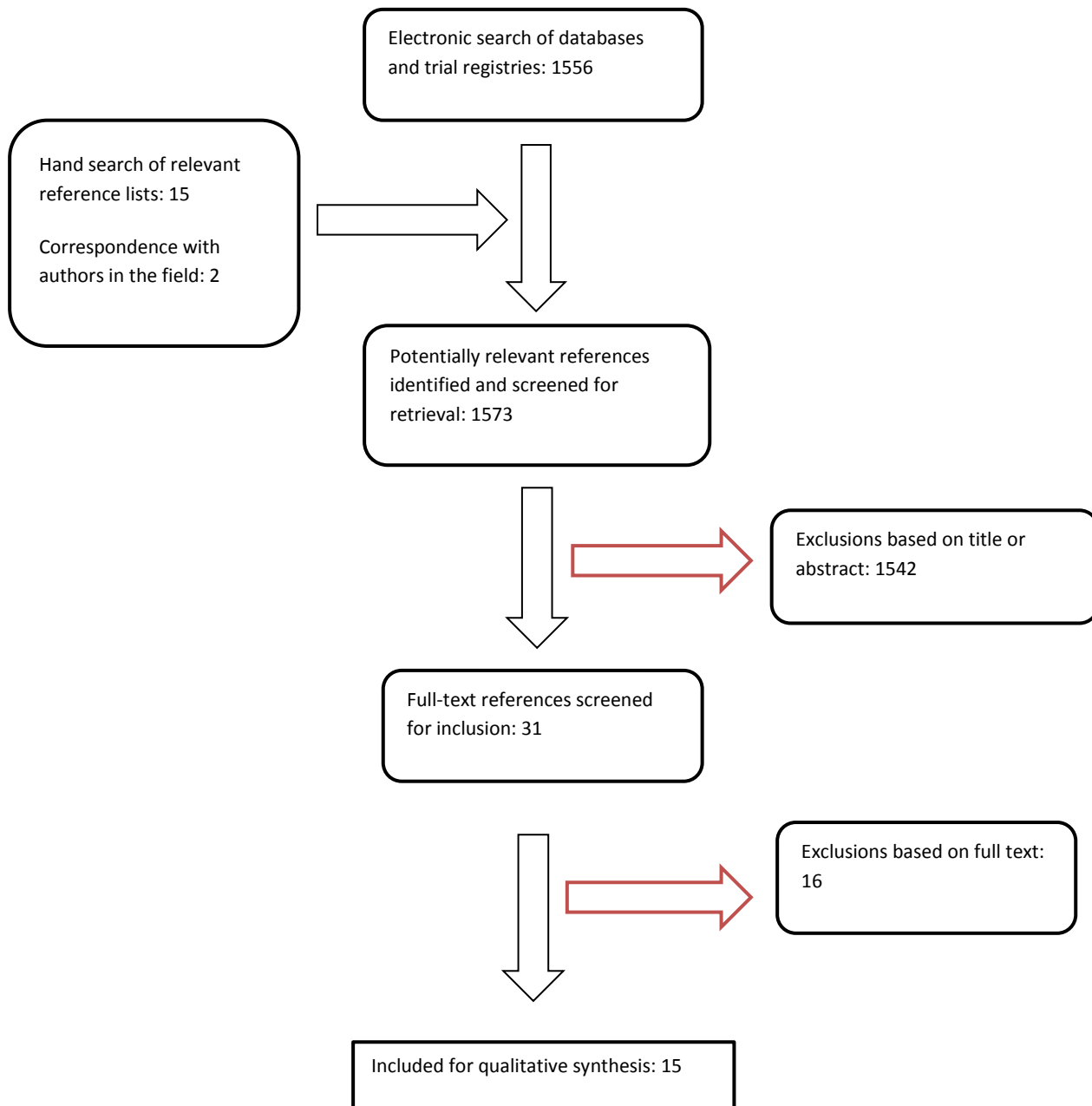
RESULTS

Description of studies

Results of the literature search

We obtained 1556 titles and abstracts from electronic databases and trial registries. All 1556 titles and abstracts were in the English language. We found 15 additional references through a hand search of relevant reference lists and by contacting relevant authors we obtained two additional references. A total of 1573 references were screened for retrieval, but only 31 full-text articles were retrieved as the other 1542 references were excluded on the basis of their titles and abstracts. Of the full-text articles, 15 articles met our inclusion criteria and the remaining 16 were excluded. Figure 1 shows a flow diagram of the search results.

FIGURE 2: RESULTS OF LITERATURE SEARCH



Characteristics of included studies

We included 15 observational studies (Wenger et al. 1995, Maloney et al. 1995, Fella et al. 1995, Bangsberg et al. 1997, Blumberg et al. 1995, Boudreau et al. 1997, Louther et al. 1997, Behrman 1998, Blumberg et al. 1998, Harries et al. 2002, Yanai et al. 2003, Roth et al. 2005, da Costa et al. 2009, Fridkin et al. 2014, Jarvis 1995) that compared the risk of TB transmission among health care workers for a period before and after multiple TB interventions were implemented. The characteristics and descriptions of the included studies are presented in Table 2 and Table 3. Most studies assessed the impact of multiple interventions implemented together.

TABLE 2: SUMMARY OF INCLUDED STUDIES

STUDY	DESIGN	PARTICIPANTS		INTERVENTION	OUTCOME MEASURE
		Pre-intervention	Post-intervention		
Bangsberg, 1997, USA	Prospective cohort study	88 HCWs	86 HCWs	Administrative, personal and environmental	TST conversion
Behrman, 1998, USA	Prospective cohort study	50 ED HCWs 2514 OHES	64 ED HCWs 3000 OHES	Environmental	TST conversion
Blumberg, 1995, USA	Descriptive case series	3579 HCWs	5153 HCWs	Administrative, personal and environmental	TST conversion
Blumberg, 1998, USA	Not stated*	2537 HCWs	2144 HCWs	Administrative, personal and environmental	TST conversion
Bourdreau, 1997, USA	Retrospective cohort study	249 HCWs	355 HCWs	Administrative, personal and environmental	TST conversion
da Costa, 2009, Brazil	Prospective cohort study	1336 HCWs	599 HCWs	Administrative	TST conversion
Fella, 1995, USA	Not stated*	145 HCWs	154 HCWs	Administrative, personal and environmental	TST conversion
Fridkin, 1995, USA	Cross-sectional study	52548 HCWs (masks)	29376 HCWs (masks)	Personal and environmental	TST conversion
		20296 HCWs (ventilation)	57600 HCWs (ventilation)		

STUDY	DESIGN	PARTICIPANTS		INTERVENTION	OUTCOME MEASURE
		Pre-intervention	Post-intervention		
Harries, 2002, Malawi	Not stated*	2697 HCWs	2979 HCWs	Administrative, personal and environmental	TST conversion
Jarvis, 1995, USA	Not stated*	174 HCWs	205 HCWs	Administrative and personal	TST conversion
Louther, 1997, USA	Not stated*	1303 HCWs	1303 HCWs	Administrative, personal and environmental	TST conversion
Maloney, 1995, USA	Retrospective cohort study	840 HCWs	727 HCWs	Administrative, personal and environmental	TST conversion
Roth, 2005, Brazil	Cross-sectional study	2990 HCWs (hospital A and B)	1764 HCWs (hospital C and D)	Administrative, personal and environmental	TST conversion
Wenger, 1995, USA	Not stated*	17 HCWs	27 HCWs	Administrative, personal and environmental	TST conversion
Yanai, 2003, Thailand	Prospective cohort study	Not stated	Not stated	Administrative, personal and environmental	TST conversion

ED=emergency department; HCWs=health care workers; OHES=other hospital employees; TST=tuberculin skin test

*Although the study designs of these articles were not stated, it can be inferred that before and after comparisons were conducted.

TABLE 3: DESCRIPTION OF INCLUDED STUDIES

Wenger, 1995	
Methods	Before and after comparison study in the HIV ward of a hospital in Miami, USA from June 1990 to September 1992.
Objective	To evaluate whether interventions reduced the risk of nosocomial transmission of TB from patients to health care workers. They compared the TST conversion rates among health care workers on the HIV ward in the initial and follow-up periods and the TST conversion rates among health care workers on the HIV ward and a control ward (where TB patients were not admitted).
Participants	Study population: health care workers in HIV ward. Number enrolled: 25 healthcare workers were included for analysis in the initial period and 27 in the follow-up period (17 in the early and 23 in the late follow-up periods).
Interventions	Implementation of similar measures recommended by the 1990 Centers for Disease Control and Prevention guidelines in HIV wards by June 1990. In September the efficacy of these control measures were evaluated.
Outcomes	Tuberculin skin-test conversions among health care workers.
Findings	The implementation of measures similar to the Centers for Disease Control and Prevention 1990 tuberculosis-control guidelines were effective in halting transmission of MDR-TB to healthcare workers and HIV-infected patients.
Maloney, 1995	
Methods	Retrospective cohort study at a teaching hospital in New York City, USA from January 1990 to August 1992.
Objective	To assess the efficacy of control measures in decreasing nosocomial transmission of MDR-TB.
Participants	Study population: health care workers. Number enrolled: 1567 TST were administered to health care workers (840 health care workers during the pre-intervention period and 727 during the post-intervention period).
Interventions	Implementation of prompt isolation and treatment of patients with TB, rapid diagnosis techniques, negative-pressure isolation rooms and moulded surgical masks for health care workers (Centers for Disease Control and Prevention 1990 guidelines).
Outcomes	Tuberculin skin-test conversions among health care workers.
Findings	Implementing TB infection control measures reduced nosocomial transmission of MDR-TB to health care workers

Bangsberg, 1997

- Methods** Prospective observational study at a university-based hospital in New York City, USA from June 1992 to June 1994.
- Objective** To assess the efficacy of infection control program as measured by TST conversion rates in medical house staff.
- Participants** Study population: medical house staff (health care workers who evaluate all non-trauma patient visits to the emergency room)
Number enrolled: 363 person years of exposure in the hospital.
- Interventions** An isolation policy was implemented at the hospital since May 1992. Negative pressure rooms with more than 6 air exchanges per hour were installed in the emergency room, which were operational since July 1992.
- Outcomes** Tuberculin skin-test conversion rates in medical house staff.
- Findings** Development of a multifaceted infection control program can decrease the risk of nosocomial tuberculosis infection in medical house staff.
-

Fella, 1995

- Methods** Prospective observational study at a hospital in New York City, USA from January 1991 to December 1993.
- Objective** To report on the impact of implemented control methods on the TST conversion rate among hospital employees.
- Participants** Study population: hospital employees
Number enrolled: numbers varied at every 6 month review: 145, 158, 219, 227, 249 and 154.
- Interventions** The implementation of broadened criteria for placement into respiratory isolation was constituted. Personal protective equipment (for e.g. shield masks) and ventilation systems were upgraded.
- Outcomes** Tuberculin skin-test conversion by 6 month interval among employees.
- Findings** Nosocomial spread of tuberculosis can be decreased by means of previously established, less costly methods.
-

Blumberg, 1995

Methods

Descriptive case series at a university-affiliated hospital in Atlanta, USA, from January 1992 to June 1994.

Objective

To study the efficacy of expanded TB infection control measures consisting primarily of administrative controls.

Participants

Study population: health care workers.

Number enrolled: numbers varied at every 6 month testing: 3579, 2975, 4715, 4775 and 5153.

Interventions

Introduction of expanded TB infection control measures (including an expanded respiratory isolation policy). Administrative controls and interim engineering controls were implemented by March 1992 and new masks were available to health care workers entering respiratory isolation rooms from June 1992.

Tuberculin skin-test conversion rates among health care workers.

Outcomes

Expanded infection controls resulted in the number of TB exposure episodes decreasing from 4.4 to 0.6 per month.

Boudreau, 1997

Methods

Retrospective cohort study at a hospital in the USA from January 1989 to December 1992.

Objective

To assess the risks of TST conversion over time during the changing conditions at the hospital, including the termination of the outbreak of MDR-TB and implementation of TB infection control measures.

Participants

Study population: hospital employees working on wards where TB patients and others were cared for.

Number enrolled: numbers varied at every annual review, but a total of 249 exposed workers (those working on TB wards) and 355 unexposed workers (those working on other wards) were included.

Interventions

Tuberculosis interventions were implemented at various times during the study period. In March 1990, tuberculosis drug therapy, respiratory isolation and worker education were improved. Ventilation systems were implemented and routine testing began in April 1990. Pentamidine procedures were revised in June 1990 and better masks were introduced in September 1990. Sputum induction booths were installed in January 1991 and UV lights were activated in September 1991.

Outcomes

The risk of tuberculin skin-test conversion among employees.

Findings

The cumulative incidence of TST conversion was significantly higher in the exposed than in the unexposed group.

Louther, 1997

Methods	Retrospective review of health records at a hospital in New York City, USA from 1991 to 1994.
Objective	To assess the relative contribution of community versus occupational risk. The authors reviewed the health records of persons employed from 1991 to 1994 at a hospital with a high tuberculosis case-rate. TB interventions were implemented during the study period, so the authors separately determined the effect of the interventions.
Participants	Study population: hospital employees. Number enrolled: 1303 persons employed at the hospital.
Interventions	The interventions studied were: increased isolation of TB suspects and patients, introduction of better masks and increased ventilation.
Outcomes	Rates of tuberculin skin-test conversion among health care workers.
Findings	After implementation of CDC guidelines, there was a significant improvement in the employee tuberculin conversion rate. Job category was strongly associated with risk of tuberculin conversion.

Behrman, 1998

Methods	Prospective interventional cohort study at a hospital in Philadelphia, USA from March 1993 to December 1996.
Objective	To measure tuberculosis conversion rates among staff of an urban emergency department (ED) with other hospital employees and to evaluate the effectiveness of new TB control measures.
Participants	Study population: hospital employees Number enrolled: 50 and 64 emergency department employees, and 2514 and 3000 employees in other departments in the pre- and post-intervention periods respectively.
Interventions	New ED department was constructed with TB respiratory isolation rooms, improved ventilation (with at least 25% fresh air in the entire ED area), non-recirculated air, and droplet shields were implemented.
Outcomes	Tuberculin skin-test conversion rates among ED employee and other hospital employees.
Findings	TB conversion rates were 5.9 times greater in ED staff members than OHEs before engineering controls were implemented. The ED TB conversion rate fell dramatically in the year following new TB controls.

Blumberg, 1998

Methods	Prospective observational study at a university-affiliated hospital in Atlanta, USA from July 1992 to June 1997.
Objective	To evaluate rates of tuberculin skin test conversion among house staff on a university-affiliate hospitals training program.
Participants	Study population: house staff (residents and fellows). Number enrolled: Over the 5 year study period there were 2537 physicians on the training program from various medical departments.
Interventions	An expanded respiratory isolation policy mandating the types of patients who required to be placed in isolation was implemented, a TB infection control nurse was hired and tuberculin skin testing of all health care workers was made mandatory. New respiratory isolation rooms that had >12 air changes per hour were put into use beginning August 1994. New masks were introduced in June 1992.
Outcomes	Tuberculin skin-test conversion rates among house staff on the training program.
Findings	TST conversion rates decreased significantly following full implementation of expanded infection control measures for tuberculosis and were low among U.S. medical school graduates despite their caring for large numbers of patients with tuberculosis at an inner-city public hospital.

Harries, 2002

Methods	Before and after comparison (of TB among health care workers) at a 40 district and mission hospitals in Malawi for 1996 and 1999.
Objective	To determine whether the guidelines were being implemented, the time between admission to hospital and the diagnosis of pulmonary TB had been reduced, and the annual case notification rates among health workers had fallen and were comparable to those of primary-school teachers.
Participants	Study population: health workers Number enrolled: TB case notifications for 2697 health care workers in 1996 and 2979 in 1999.
Interventions	Written guidelines were introduced by the Malawian National Tuberculosis Control Programme mid-1998: prioritise patients with chronic cough, rapid sputum specimen collection, transport and reporting, visitors kept to a minimum, chest x-rays taken at quiet times of the day, cough hygiene, improved ventilation, introduction of masks for TB patients when undergoing surgical procedures and introduction of staff counselling.
Outcomes	Tuberculosis case notification rate per annum among health workers.
Findings	The TB case notification rate for health workers in 1999 was 3.2%; this did not differ significantly from the value of 3.7% for health workers in 1996 but was significantly higher than that of 1.8% for primary-school teachers in 1999.

Yanai, 2003**Methods**

Prospective observational study at a hospital in Chiang Rai, Thailand from 1995 to 1999.

Objective

To describe the effectiveness of prevention strategies for nosocomial tuberculosis (TB).

Participants

Study population: health care workers

Number enrolled: 1325 health care workers were enrolled, but only 1202 were participants in the study after exclusions.

Interventions

The infection control measures included: 1) prevention interventions for HCWs; 2) prevention interventions related to patients; 3) prevention interventions through engineering control measures; and 4) development of standard operating procedures and an infection control plan.

Outcomes

Tuberculin skin-test conversion rates among health care workers

Findings

Implementation of nosocomial TB control measures in 1996 was followed by declining TST conversion rates, despite increasing exposure to active TB patients.

Roth, 2005**Methods**

Phase 1 and 2 of longitudinal study (cross-sectional surveys) at four general Brazilian hospitals from May 1998 to December 1999.

Participants

Study population: health care workers

Number enrolled: 4754 health care workers in total. 1023 workers at hospital A, 1967 workers at hospital B, 994 workers at hospital C and 770 workers at hospital D.

Interventions

At hospital A: rapid diagnosis and treatment, isolation rooms with closed doors, biosafety cabinets for laboratory and N95 respirators and surgical masks for patients until isolated. At hospital B: rapid diagnosis and treatment, isolation rooms with closed doors, HEPA filtration systems, biosafety cabinets for laboratory, N95 respirator and masks for patients until isolated. At hospital C: UVGI bulb for the laboratory when it is not being used. At hospital D: No interventions.

Tuberculin skin-test conversion rate among health care workers

Findings

Compared to Hospital A, participants working in Hospitals B, C, or D were more likely to have a positive TST.

da Costa, 2009

Methods	Prospective observational study at a teaching hospital in Rio de Janeiro, Brazil from 1998 to 2001.
Objective	To study the impact of administrative infection control measures on the risk for latent TB infection among HCWs in a resource-limited, high-burden country.
Participants	Study population: health care workers Number enrolled: 1336 health care workers were initially tested and 599 were retested.
Interventions	The following infection control measures were progressively implemented: isolation of TB suspects and confirmed TB inpatients, quick turnaround for acid-fast bacilli sputum tests and HCW education in use of protective respirators.
Outcomes	The number of tuberculin skin-test conversion per 1000 person-months among health care workers.
Findings	Administrative measures for infection control can significantly reduce latent TB infection among HCWs in high-burden countries and should be implemented even when resources are not available for engineering infection control measures.

Fridkin, 1995

Methods	Volunteer questionnaire to members of the Society of Healthcare Epidemiology of America in 1992-1993.
Objective	To assess the efficacy of current Mycobacterium tuberculosis control measures
Participants	Study population: health care workers Number enrolled: 52648 health care workers were enrolled from hospitals without respiratory protection and 29376 from hospitals with respiratory protection. 20296 health care workers were enrolled from hospitals not meeting ventilation criteria and 57600 from hospitals meeting ventilation criteria.
Interventions	The following TB infection control measures were reported: all four CDC 1990 TB guidelines, at least three specific criteria (negative pressure, exhaust directed outside, and single patient or cohorting of patients), at least the negative pressure criterion, or at least the direct outside exhausted air criterion.
Outcomes	Tuberculin skin-test conversion rates among health care workers.
Findings	Complete implementation of the 1990 CDC TB guidelines would decrease health care workers' risk of nosocomial transmission of TB in larger hospitals or those reporting more TB patients.

Methods

A review of three hospitals in the USA from August to September 1992.

Objective

To conduct investigations at three hospitals that experienced MDR-TB outbreaks to determine the impact of the implemented control measures and to assess the efficacy of the 1990 CDC tuberculosis guidelines.

Participants

Study population: health care workers

Interventions

Number enrolled: 174 workers at baseline and 205 during the intervention period.

The efficacy of the following infection control measures were assessed: increased respiratory isolation, increased treatment initiation, increased speed for AFB, the introduction of moulded surgical masks and the installation of window exhaust fans. Tuberculin skin-test conversion rates among health care workers.

Outcomes

The use of respiratory protective devices, administrative and engineering controls reduced the health care worker TST rate to baseline or eliminated all TB transmission to health care workers.

Findings

Description of TB interventions

The descriptions of TB interventions used are summarised in Table 4. Briefly, the majority of the 15 studies was conducted in high income countries, the exceptions being one Malawian, a Thai and two Brazilian studies . Eleven of the studies were published before 2000 while four were published after 2000. One study exclusively assessed administrative control measures and another, environmental control measures. The rest of the studies (n=13) assessed multiple interventions which combined administrative, environmental and personal measures.

Multiple interventions

Thirteen studies assessed multiple interventions implemented in various combinations. Ten studies compared the sputum conversion rate of health care workers working in hospitals in the pre- and post-intervention periods (Wenger et al. 1995, Maloney et al. 1995, Fella et al. 1995, Bangsberg et al. 1997, Blumberg et al. 1995, Boudreau et al. 1997, Louthier et al. 1997, Behrman 1998, Blumberg et al. 1998, Harries et al. 2002 & Yanai et al. 2003). Three studies compared the sputum conversion rate of health care workers in hospitals with preventative measures against that in hospitals without preventative measures (Fridkin et al. 2014, Jarvis 1995 & Roth et al. 2005).

Administrative control measures

A single study assessed administrative interventions. The TB infection control measures implemented and assessed in the da Costa et al. (2009) study were isolation of TB suspects and confirmed TB inpatients, quick turnaround for acid-fast bacilli sputum tests; and health care worker education in use of protective respirators. These infection control measures were implemented in October 1998 at a hospital in the north of Rio de Janeiro, resulting from the high health care worker tuberculin skin-test conversion rate of 5.9 per 1000 person-months compared to that of the general population in Rio de Janeiro of 0.83 per 1000 person-months.

Environmental control measures

Two studies assessed environmental interventions. In the first study (Behrman 1998) the following environmental mechanisms were implemented: four respiratory isolation rooms, 100% non-recirculated air in the trauma area, improved ventilation with at least 25% fresh air in the entire emergency department area and laminar flow and plastic droplet shields for health care workers. These TB infection control mechanisms were incorporated into the plans of a new emergency department facility which opened in January 1996. The second study by Fridkin et al. (2014) assessed ventilation within isolation rooms with the following criteria: a single occupancy or a group of patients; air exhausted directly outside; negative pressure relative to the hallway or other rooms; and greater than six air exchanges per hour.

Personal protection measures

A single study assessed personal protection interventions. The Fridkin et al. (2014) study assessed respiratory protective devices for health care workers. A diverse range of respiratory protection devices were included for evaluation, such as surgical masks, submicron surgical masks, particulate respirators and high efficacy particulate air filter respirators.

Description of TB outcomes

All studies reported on the change of risk of tuberculosis in health care workers, where this change was measured using tuberculin skin-tests. Two studies reported incidence rates of TB infection in person-months, while the rest of the studies reported the cumulative incidence of TB infection in percentages.

TABLE 4: RESULTS OF INCLUDED STUDIES

STUDY	INFECTION CONTROL MEASURES USED			TST conversion	
	ADMINISTRATIVE	PERSONAL	ENVIRONMENTAL	Pre-intervention	Post-intervention
<u>MULTIPLE</u>					
Bangsberg, 1997	Increased respiratory isolation	Respiratory masks	Negative pressure rooms in two wards; Upper air UV lights	9/88 (10.2%)	0/86 (0%)
Blumberg, 1995	Increased respiratory isolation	Medical screening of HCWs every 6 months; Respiratory masks	Window exhaust fans; Negative pressure rooms	118/3579 (3.3%)	23/5153 (0.4%)
Blumberg, 1998	Increased respiratory isolation; TB infection control nurse	Respiratory masks Medical screening of HCWs	Respiratory isolation rooms built	393/2537 (15.5%)	52/2144 (2.4%)
Bourdreau, 1997	Improved drug therapy; Increased respiratory isolation; Increased worker education;	Respiratory masks	Sputum induction booth; UV lights	36/249 (14.5%)	5/355 (1.4%)
Fella, 1995	Increased respiratory isolation	Respiratory masks	Window exhaust fans; Upper air UV lights	30/145 (21%)	9/154 (5.8%)
Harries, 2002	Triage for patients with chronic cough; Speed up TB diagnosis; Visitors kept to a minimum; Chest x-rays taken at quiet times	Proper cough hygiene; Respiratory masks worn by patients (when undergoing surgical procedures)	Improved ventilation; Inpatients spend more day-time outside; Windows left open	110/2979 (3.7%)	86/2697 (3.2%)

MULTIPLE

Jarvis, 1995	Increased respiratory isolation; Restricting patient movement; Worker education; Increased speed of AFB test turnaround	Some use of respiratory masks	None	Hospital A 7/29 (24%) Hospital B 2/22 (9%) Hospital C 15/123 (12%)	0/23 (0%) 6/33 (18%) 5/150 (3%)
Louther, 1997	Increased respiratory isolation	Respiratory masks	Increased ventilation	65/898 (7.2%)	47/971 (4.8%)
Maloney, 1995	Increased respiratory isolation; Increased treatment initiation; Increased speed of AFB test turnaround	Respiratory masks	Window exhaust fans	26/840 (3.1%)	22/727 (3.0%)
Roth, 2005	Rapid TB diagnosis and treatment; Isolation of TB patients	Respiratory masks for HCWs; HEPA filter in laboratory areas	Negative-pressure rooms; Safety cabinets in the laboratory	16 per 1000 person-months	7.75 per 1000 person-months
Wenger, 1995	Increased respiratory isolation; Increased speed of AFB test turnaround; Sputum induction in isolation rooms	Screening every 4 months; Respiratory masks in isolation rooms; Respiratory masks in isolation rooms	Automatic door closers on isolation room doors; Negative pressure isolation rooms	7/25 (28%)	3/17 (18%)
Yanai, 2003	Improved case detection, TB diagnosis and treatment initiation; Respiratory isolation of TB patients; One-stop service (all TB services) for outpatients	Respiratory masks for HCWs; HEPA filter area in laboratory areas	TB isolation rooms in wards; Increased ventilation in wards; Safety cabinets and UVGI system in laboratory	9.3 per 100 person-years	2.2 per 100 person-years

ADMINISTRATIVE

da Costa, 2009	Increased respiratory isolation; Increased speed for AFB; Worker education	None	None	5.8 per 1000 person- months	3.7 per 1000 person- months
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ENVIRONMENTAL

Behrman, 1998	None	None	4 respiratory isolation rooms built; Increased general ventilation; Droplet shields; Laminar airflow	Emergency department 12% Rest of departments 2%	0% 1.2%
Fridkin, 1995	None		Ventilation with 4 criteria: isolation rooms, negative pressure/inward flow, automatic door closers, ≥ 6 air changes per hour	383/20296 (1.9%)	348/57,600 (0.6%)

PERSONAL

Fridkin, 1995	None	Masks and respirators		497/52648 (0.94%)	289/29,376 (0.98%)
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Main results of included studies

Multiple interventions

Bangsberg et al. (1997) presented the findings of a study that investigated the efficacy of a multi-faceted infection control program for medical house staff at a hospital in New York, USA from June 1992 to June 1994. All patients with known HIV infection, HIV risk or homelessness who presented with evidence for pneumonia or tuberculosis were isolated. A total of four negative-pressure rooms with greater than 6 air changes per hour were installed in the hospital. Ultraviolet lights were installed in the emergency and patient care areas. Surgical masks were replaced with respirators and staff were fit-tested and instructed in the use of respirators. Medical staff were instructed to use 3M respirators in the care of all patients suspected of having TB under the isolation policy. TST conversions were measured every six months in the staff, so as to determine the effect of the interventions. The TST conversion rate decreased from 10.2% (9/88) at baseline to 0% (0/86) at the end of the 2.5 year study period.

In the Blumberg et al. (1995b) study the number of tuberculosis exposure episodes and the skin-test conversion rates of health care workers in a hospital in Atlanta, USA, were measured before and after the implementation of expanded control measures. The study took place from January 1992 to June 1994. The introduction of increased respiratory isolation, regular screening of staff for TB infection (every six months), sub-micron masks for staff and negative-pressure rooms with window exhaust fans resulted in the TST conversion rate dropping from 3.3% (118/3579) to 0.4% (23/5153) between the first and last study intervals of a 2.5 year study period.

Regarding study duration, the Blumberg et al. (1998) study evaluated the efficacy of an expanded infection control program over the longest study period of any of the included studies of 5 years (from January 1989 to December 1992). An isolation policy, the employment of a TB infection control nurse, new masks and the mandatory screening of all health care workers for TB infection were implemented by the end of the first year. New negative-pressure isolation rooms with greater than 12 air changes per hour were put in use two years after the study began. The TST conversion rate for medical staff pre-intervention was 15.5% (393/2573) and 2.4% (52 of 2144) post-intervention.

Boudreau et al. (1997) assessed the risk of TST conversion among health care workers at a hospital in the USA where TB interventions were implemented from January 1992 to June 1994. The TST

conversion was recorded at six month intervals. The following control measures were implemented during the study period: modified TB drug therapy for patients, increased respiratory isolation, increased worker education, introduction of better masks, sputum induction isolation and ultraviolet lights installation. The annual risk of TB infection in health care workers decreased from 6.9% before to 1.9% after control measures were implemented.

Fella et al. 1995 argued that many of the recommendations made by the Centers for Disease Control and Prevention (CDC) are expensive and unproven. The study thus reviewed the TST conversion rate among hospital employees by 6 month intervals from January 1990 to August 1992 while several TB control measures were implemented. Increased respiratory isolation, the placement of ultraviolet lights into patient rooms and common rooms, and the use of particulate and dust-mist-fume respirators led to the TST conversion rate falling from 20.7% (30/145) at baseline to 5.1% (9/154) at the end of the study.

A study by Jarvis (1995) that reviewed three hospitals in the USA from August to September 1992 assessed the efficacy of the 1990 CDC TB guidelines in regard to respiratory protection (some use of masks) and administrative control measures (isolation rooms, restricted patient movement, worker education and rapid diagnosis). At baseline the TST conversion rates were 24% (7/29), 9% (2/22) and 12% (15/123) among health care workers at hospital A, B and D respectively. The TST conversion rate of health care workers at hospital A and D declined significantly to 0% (0/23) ($p=0.01$) and 3% (5/150) ($p=0.01$) in the post-intervention period respectively. There was a non-significant increase to 18% (6/33) in the TB conversion rate of health care workers in hospital B in the post-intervention period.

Louther et al. (1997) reviewed the health records of persons employed at a hospital in New York, USA, from 1991 to 1994. The authors assessed the effect of TB interventions that were implemented during the study period. These included increased respiratory isolation, the introduction of better masks and increased ventilation. A total of 1303 health care workers were enrolled in the study. The conversion rate in the first study period was 7.2% (65/898), and decreased to 4.8% (47/971) in the second study period after TB interventions were implemented.

Another study assessed the efficacy of TB control measures recommended by the 1990 CDC TB guidelines at a hospital in New York, USA (Maloney et al. 1995). The efficacy of increased respiratory isolation, increased rate of treatment initiation, rapid AFB based diagnosis, the use of moulded surgical masks and the installation of window exhaust fans were evaluated from January 1990 to August 1992. The study found that the TST conversion rates in health care workers were similar before (26/840 = 3.1%) and after (22/727 = 3.0%) the control measures were implemented.

A more recent study by Roth et al. (2005) compared the TST conversion rates in health care workers at four hospitals in Brazil from May 1998 to December 1999. A total of 1023 health care workers were enrolled at hospital A, 1967 at hospital B, 994 at hospital C and 770 at hospital D. A varying degree of TB infection control measures were implemented at the hospitals. TST conversion at hospital A and B were compared to the TST rates of hospital C and D that had fewer or no control measures implemented. The TST conversion in hospitals with TB infection control measures was 16 per 1000 person-months, compared to the TST conversion in hospitals without TB infection control measures of 7.75 per 1000 person-months ($p=0.001$).

A before and after comparison was conducted at a hospital in Miami, USA, from June 1990 to September 1992 to evaluate whether TB interventions reduced the risk of TB transmission from infectious patients to health care workers (Wenger et al. 1995). The study by Wenger et al. (1995) showed that during the initial analysis period TST conversion was 28% (7/25) compared to 18% (3/17) during the early parts of the follow-up period.

Yanai et al. 2003 described the effectiveness of prevention strategies for nosocomial tuberculosis at a hospital in Chiang Rai, Thailand from 1995 to 1999. A total of 1202 health care workers were enrolled in the study. The interventions that were implemented targeted health care workers, hospitalised patients and the hospital environment. TST conversion rates decreased from 9.3% (before prevention) to 2.2% (after prevention) despite evidence of increasing exposure to active TB patients.

Administrative control measures

A Brazilian study by da Costa et al. (2009) conducted from 1998 to 2001 studied the impact of the following administrative infection control measures: increased respiratory isolation, more rapid TB diagnosis and worker education. A total of 1336 health care workers were tested during the pre-intervention period and 599 health care workers were retested during the post-intervention period. The number of TST conversions per 1000 person-months during and after the implementation of these measures was reduced from 5.8 per 1000 person-months to 3.7 per 1000 person-months ($p=0.006$).

Environmental control measures

Behrman (1998) studied the impact of four newly built respiratory isolation rooms, increased ventilation, laminar airflow and droplet shields at a hospital in Philadelphia, USA, from March 1993 to December 1996. The TST conversion rate among staff in the emergency department was compared with the rate of any staff working in other parts of the hospital. The conversion rate decreased from 12% ($n=50$) to 0% ($n=64$) among emergency department employees in the pre- and post-intervention periods respectively. The conversion rate decreased from 2% ($n=2514$) to 1.2% ($n=3000$) among employees working in the rest of the departments.

Fridkin et al. 2014 administered volunteer questionnaires requesting data on TB infection control measures and TST programs and results for 1992 and 1993. The study assessed the efficacy ventilation among hospitals in the USA. Ventilation was assessed with regards to four criteria: isolation rooms, negative-pressure or inward flow, automatic door closers and greater than 6 air changes per hour. There was a slight but significant difference ($p=0.02$) between the conversion rates of health care workers in hospitals that met all four ventilation criteria ($348/57600 = 0.6\%$) and conversion rates of health care workers in hospitals that did not meet all four ventilation criteria ($497/52648 = 0.94\%$).

Personal protection measures

Fridkin et al. (2014) assessed the efficacy of TB control measures amongst 359 hospitals in the USA for 1992 and 1993. The authors found that there was no significant difference ($p=0.98$) between the conversion rates of health care workers in hospitals with ($289/29376 = 0.98\%$) and without ($497/52648 = 0.94\%$) respiratory protection.

Methodological quality of included studies

Appendix 3 presents the criteria that were adopted to assess the risk of bias of all included studies. Figure 3 depicts a summary of the assessment of risk of bias of each study. Each risk of bias components were assessed as low risk, high risk or unclear. A majority of the studies provided limited information with regards to various components of risk of bias. Those studies were regarded as having unclear risk. Only two studies (Bangsberg et al. 1997 & Behrman 1998) provided substantial information relating to the nine criteria. The Bangsberg et al. (1997) study scored low risk for absence of selection bias, baseline outcome measurement and adequate protection against contamination and high risk for blinding or objective assessment of the primary outcome. The Behrman (1998) study scored low risk for similar baseline outcome measures, similar baseline characteristics and complete outcome data and high risk for objective assessment of the primary outcome and protection against contamination.

Characteristics of excluded studies

Sixteen studies were excluded for reasons stated in Table 5. The most common reason for exclusion was that the study participants were not health care workers.

FIGURE 3. RISK OF BIAS ASSESSMENT

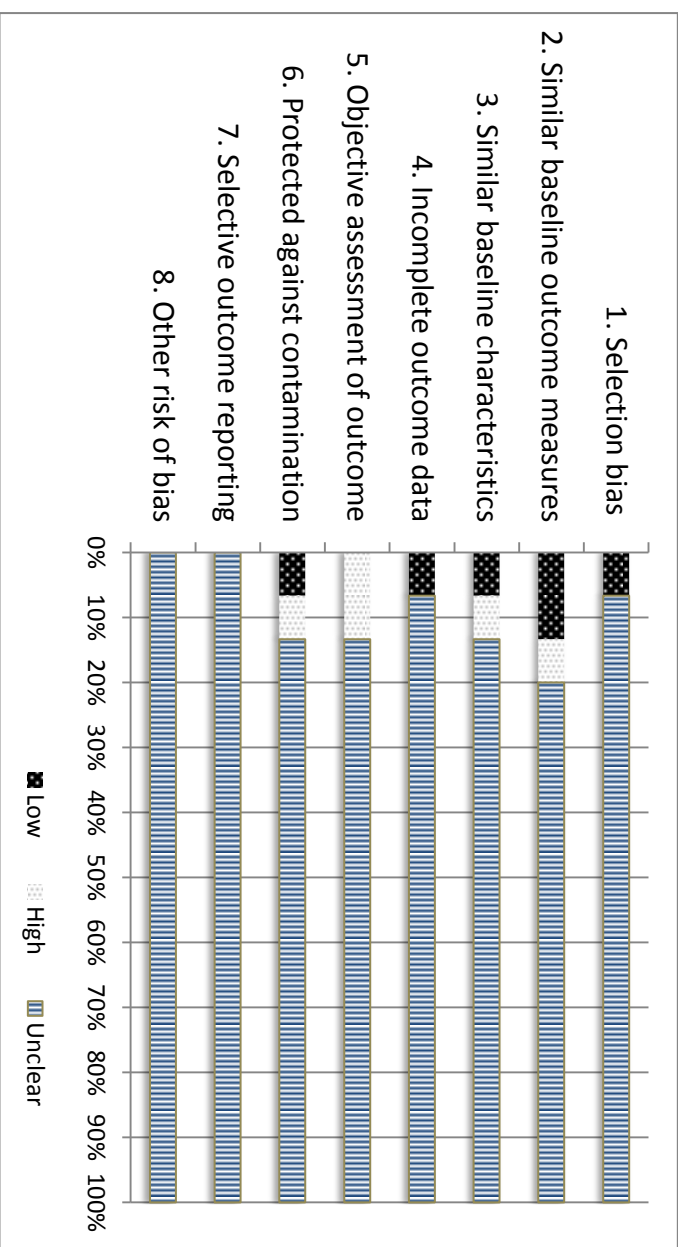


TABLE 5. CHARACTERISTICS OF EXCLUDED STUDIES

Authors	Study objective	Reason for exclusion
Holtton et al. 1997	To analyse tuberculosis programs in acute care hospitals (hospitals) categorized by size and risk of exposure to TB patients from 1989 to 1993.	Retrospective survey providing a situational analysis of Canadian hospitals.
Moro et al. 2000	To evaluate risk factors for transmission and the effectiveness of infection control measures.	Participants were not health care workers.
Tokars et al. 2001	To evaluate the implementation and efficacy of selected Centers for Disease Control and Prevention guidelines for preventing spread of Mycobacterium tuberculosis.	There were no tuberculin skin test results for health care workers before and after the implementation of selected infection control practices.
Lee et al. 2004	The article discussed the authors' strategy in selecting respirators from an initial array of seven NIOSH-certified Type N95 filtering face-piece devices for a respiratory protection program against Mycobacterium tuberculosis aerosol.	The study did not measure the effectiveness of fit-testing; rather it evaluated a strategy for selecting respirators.
Biscotto et al. 2005	To evaluate the use of personal respiratory protection by health care workers as a measure to reduce TB occupational risk.	The study did not measure the effectiveness of personal respiratory protection.
Balazy et al. 2006	To determine the performance of two types of N95 half-mask, filtering face piece respirators and two types of surgical masks.	Participants were not health care workers and the study results were not specific to tuberculosis.
Leonard et al. 2006	To determine whether a dedicated airborne infection isolation (AII) unit improves efficiency in "ruling-out" patients suspected of having pulmonary TB.	Participants were not health care workers.
Escombe et al. 2007	To investigate the rates, determinants, and effects of natural ventilation in health care settings.	The study population was not clearly defined and risk of TB infection was not measured.
Lee et al. 2008	To determine the short- and long-term efficacy of training for fit testing of N95 respirators in both untrained and trained healthcare workers.	The study did not measure the impact short- and long-term training for fit-testing of N95 respirators had on tuberculosis outcome in health care workers.

Torres Costa et al. 2010	To assess putative risk factors for latent TB infection.	No tuberculosis prevention measures were implemented; thus no measures of effect were reported.
Danyluk et al. 2011	To examine whether a user seal check is an appropriate surrogate for respirator fit-testing.	The study determined a model for user seal checks and respirator fit-testing.
Dharmadhikari et al. 2012	To quantify the efficacy of surgical face masks when worn by patients with multidrug-resistant TB.	Participants were not health care workers and the study involved animals.
MacIntyre et al. 2013	To compare three policy options for the use of medical masks and N95 respirators in healthcare workers.	The outcome measure was not tuberculosis.
Miller-Leiden et al. 1996	To evaluate the effectiveness of in-room air filtration systems, specifically portable air filters and ceiling-mounted air filters, in conjunction with dilution ventilation, for controlling TB exposure in high-risk settings.	The study conducted an experiment that did not involve the participation of health care workers.
Naidoo et al. 2012	To assess and describe current practices in infection control at local government primary health clinics.	The study did not assess infection control practices. There were minimal infection control measures implemented at the clinics.
Chughtai et al. 2013	To examine available policies and guidelines on the use of masks and respirators in HCWs and to describe areas of consistency between guidelines, as well as gaps in the recommendations, with reference to the WHO and the CDC guidelines.	Participants were not health care workers and the study results were not specific to tuberculosis.

DISCUSSION

Summary of main results

From a comprehensive literature search we identified 1 556 records of which 15 full-text articles met the inclusion criteria of the review. Eleven (73%) of the included studies were conducted in high-income countries in the USA, while the remaining four were conducted in low- and middle-income countries. All the studies reported on various TB interventions implemented together, including the Behrman (1998) and da Costa et al. (2009) that evaluated the impact of environmental and administrative control measures respectively. In all studies the primary outcome, mycobacterium tuberculosis infection, was measured using the tuberculin skin-test. The review suggests that the combination of administrative controls, environmental controls and personal protection measures reduces the risk of TB transmission in health care workers.

Applicability and quality of the evidence

Despite the attention given to TB control strategies in recent years and the large number of records obtained during the literature search, no studies have assessed the effectiveness of a single TB intervention in the absence of others. A few studies have dealt with the impact of implementing multiple interventions to prevent TB transmission in health care workers and were included in the review. We found only one additional study (da Costa et al. 2009) since the publication of the summary of TB control measures in low- and middle-income countries and high-income countries by Menzies et al. (2007).

The majority of the included studies were conducted in the USA which is a low TB endemic, high income country. Research on the effectiveness of TB interventions in high TB burden, low- and middle-income countries is limited. Much of the currently available literature on TB interventions is descriptive rather than evaluative, detailing the lack of TB interventions rather than robustly testing their effectiveness.

The absence of evidence to identify critical TB interventions, especially in the context of limited resources, is a concern. The WHO guidelines recommend administrative controls as the first line of TB prevention, followed by environmental controls and personal respiratory protection. Evidence to support this strategy is based on studies of multiple interventions, rather than studies of single interventions. Since no studies tested the effectiveness of each TB intervention alone, the systematic review found no evidence to support any single TB intervention. However, information on the effectiveness of multiple interventions should be useful. Included studies showed a reduction in the risk of tuberculosis with multiple interventions. However, these results are overshadowed by the methodological flaws of the studies.

Potential biases in the review

We minimised review bias by conducting comprehensive searches without date or language restrictions. In our protocol we made provision for the inclusion of observational studies, in the case that experimental studies did not meet our eligibility criteria.

Other studies on the effectiveness of TB interventions

Despite numerous recommendations on the use of TB interventions (WHO Best Practices in Prevention 2013)(WHO 2009a)(WHO 2007)(WHO 2009b), there is a shortage of studies that quantify the impact of single interventions on the prevention and transmission of TB.

In 2012 Cox et al. published a study that assessed the efficacy of wind-driven roof turbines, as an alternative to powered mechanical ventilation, compared to natural ventilation in primary care clinic rooms. Powered mechanical ventilation is expensive to install and maintain (Cox et al. 2012) for most resource-limited settings. Poor health facilities lack consistent electricity supply and skilled technicians to service ventilation systems. The study showed that the required rates of room ventilation recommended by the WHO (2007) may be achieved using wind-driven turbines. Although the study did not report on the impact of wind-driven turbines on tuberculosis outcomes at the clinics, the study showed that the simple, low cost technology is an equivalent-performing alternative to powered mechanical ventilation in windy cities, such as Cape Town.

A study by Dharmadhikari et al. (2012) evaluated the efficacy of surgical face masks worn by MDR-TB patients. Over 3 months, the 17 patients wore masks on alternate days and ward air was exhausted to two chambers, each housing 90 pathogen-free guinea pigs. Efficacy was based on differences in guinea pig infections in each chamber, as ward air was exhausted either when infectious patients wore masks (intervention group) or when they did not wear masks (control group). 69 of the 90 control guinea pigs became infected with TB compared to 36 of the 90 intervention guinea pigs. The study concluded that surgical face masks reduced TB transmission risk by 56%. From the Dharmadhikari et al. study it can be inferred that masks are protective against TB. However, risk was tested in animals rather than humans.

In a different occupational testing, a randomised-controlled trial conducted by Churchyard et al. (2010) of South African miner workers aimed to compare six-monthly and 12-monthly radiological screening for active TB. Mine workers at a gold mine were randomly assigned to a control and intervention group. Compared with routine screening, six-monthly 'intervention' screening detected more TB suspects, but not TB cases. There was attrition between screening and further investigation after the 'intervention' (Churchyard et al. 2010) The authors concluded that screening is an effective TB intervention in active case-finding and further investigation of TB suspects.

Similarly, a Portuguese study of health care workers argued that a screening programme had a positive indirect impact on the rate of active TB, by increasing the awareness of health care workers to take precautions (Torres Costa et al. 2010). It can be inferred from both studies that the risk of TB transmission in large at risk groups, such as miner workers and health care workers, can directly or indirectly be reduced by screening interventions.

Authors' conclusions

Implications for Practice

This review searched for currently available evidence on the effectiveness of interventions in reducing TB transmission among health care workers working in health care facilities. Observational studies of multiple interventions showed a reduction in the risk of occupational TB. Although the methodological quality of the evidence is unclear, the included studies are consistent with suggestions that the implementation of multiple TB interventions reduce the risk of TB transmission in health care workers in health facilities. Multiple TB interventions will need to be tailored to local settings and implemented within resource-constraints.

This review further identified that a majority of the studies were published before the 21st century. Most of the included studies were conducted in low TB burden, well-resourced countries. Thus rigorous evaluation of the effectiveness of TB interventions is required to determine the true and current impact of these interventions in high TB burden, poorly resourced countries. Rigorous evaluation will also inform policies and practices. The effectiveness of TB interventions is likely to be dependent on various risk factors (e.g. frequent use and complete implementation) with complex interactions which may vary across different settings.

Implications for Research

No studies employing a single intervention were identified. Studies to evaluate single TB interventions are not feasible. It may be difficult to eliminate the effect of other TB transmission 'blockers' during a single intervention trial. It may also be costly and time consuming to conduct numerous studies, each assessing the effectiveness of a single TB intervention.

To confirm or refute that multiple TB interventions are effective, well-designed studies in which bias and confounding are minimised need to be conducted. Although randomised-controlled trials are desirable in reducing selection bias, other designs such as controlled before and after studies may also be appropriate for determining the effectiveness of interventions to reduce TB transmission amongst health care workers in health facilities. Well-designed, high quality observational studies

can estimate the true effect of multiple TB interventions. Observational studies can also overcome ethical concerns of randomised trials.

In the absence of experimental studies, future studies evaluating TB interventions for health care workers, can consider mathematical modelling of available literature and secondary data sources. For example, a mathematical model can be used to simulate the risk of airborne TB transmission within a hospital's TB ward and amongst a susceptible community. Such a model should incorporate the rate of ventilation and duration of exposure etc. in order to simulate the risk of infection on an inpatient TB ward. A model using a compartmental approach can also describe the transitions made by TB-infected people as they move between TB states (Basu 2007).

Authors' contributions

BS developed the research question with the assistance of RE and ME. BS wrote the protocol, overview and article. BS and ME reviewed the titles, abstracts and full text articles. RE was involved during the selection of studies and he provided input with regard to the content of the dissertation. ME provided input with regard to the methods and data analyses of this dissertation.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Initially we expected that we would be able to calculate a pooled effect from various studies, but we found that a narrative synthesis was more suited to the data. As a result of heterogeneity of studies with regard to the interventions and study designs, a meta-analysis was not possible.

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APPENDICES

Appendix 1. Data extraction form

ORGANISATIONAL ASPECTS:

Reviewer ID:	Study ID:
Full Article Title:	
Author, year:	
Fate of article: Certain to include: <input type="checkbox"/> Certain to exclude: <input type="checkbox"/> Decision-pending: <input type="checkbox"/> Use for Discussion: <input type="checkbox"/> Check for useful references: <input type="checkbox"/>	
Notes/Comments:	

STUDY ELIGIBILITY:

Type of study:

Is the study design one of the following designs: Randomised-controlled trial (RCT), Clinically-controlled Trial (CCT), Controlled before and after study (CBA), Quasi-randomised, Cross-over study or a cohort study?

Yes: No: Unclear:

Note: Cohort studies will be analysed differently in the review, but will not be excluded in the data collection process.

Study setting:

Where was the study located?

Clinic: Hospital: Unclear: Neither:

Study participants:

Were the participants any of the following type of HCW? Please tick all applicable options.

Nurses: Doctors: Laboratory Staff: Support Staff*: Allied Professionals:
Unclear: None:

* Staff members who work within a health facility, but who do not provide health care to patients, such as catering and cleaning staff.

Study Interventions:

Was the intervention any of the following: personal protection equipment (PPE), an administrative control (AC) and/or an environmental control (EC)? (Please see the attachment for examples).

Yes	
Unclear	
If no, exclude	

Was there a control or comparison group?

No intervention: Less intense or less frequent use of the intervention:

Different intervention: Unclear:

Study outcomes:

Did the study report on one of the following outcomes?

Latent TB infection: Active TB disease: Bacterial respiratory disease: Unclear: Other:

Final decision (information about inclusion and exclusion criteria is attached to the form):

Include	
Exclude	
Uncertain-requires full text article	
Pending-study still in progress	

If the study is excluded please provide reasons for exclusion:

STUDY DETAILS:

Study aims:	
Outcome studied:	
Inclusion and exclusion criteria:	
Experimental intervention:	Type: PPE: <input type="checkbox"/> AC: <input type="checkbox"/> EC: <input type="checkbox"/>
What interventions? (First intervention)	<p><u>PPE:</u> Surgical or procedure masks: <input type="checkbox"/> N95 respirator: <input type="checkbox"/> Training to use PPE: <input type="checkbox"/> Hand hygiene: <input type="checkbox"/> Other: <input type="checkbox"/> _____</p> <p><u>AC involving HCWs:</u> Education or training for HCWs: <input type="checkbox"/></p> <p><u>AC involving patients (to protect HCWs):</u> Early diagnosis: <input type="checkbox"/> Triage: <input type="checkbox"/> Isolation or segregation of clinically symptomatic patients: <input type="checkbox"/></p> <p><u>AC involving health systems (to protect HCWS):</u> Risk assessment: <input type="checkbox"/> Policy implementation: <input type="checkbox"/> Guideline provision: <input type="checkbox"/></p> <p>Other AC: <input type="checkbox"/> _____</p> <p><u>EC:</u> Artificial ventilation system: <input type="checkbox"/> Open doors and windows: <input type="checkbox"/> Motorised or propeller fans: <input type="checkbox"/> UV lights: <input type="checkbox"/></p>
Details of the first intervention i.e. how was it performed?	

What interventions: (Second intervention)	<p><u>PPE:</u> Surgical or procedure masks: <input type="checkbox"/> N95 respirator: <input type="checkbox"/> Training to use PPE: <input type="checkbox"/> Hand hygiene: <input type="checkbox"/> Other: <input type="checkbox"/> _____</p> <p><u>AC involving HCWs:</u> Education or training for HCWs: <input type="checkbox"/></p> <p><u>AC involving patients (to protect HCWs):</u> Early diagnosis: <input type="checkbox"/> Triage: <input type="checkbox"/> Isolation or segregation of clinically symptomatic patients: <input type="checkbox"/></p> <p><u>AC involving health systems (to protect HCWS):</u> Risk assessment: <input type="checkbox"/> Policy implementation: <input type="checkbox"/> Guideline provision: <input type="checkbox"/></p> <p>Other AC: <input type="checkbox"/> _____</p> <p><u>EC:</u> Artificial ventilation system: <input type="checkbox"/> Open doors and windows: <input type="checkbox"/> Motorised or propeller fans: <input type="checkbox"/> UV lights: <input type="checkbox"/></p>
Details of the second intervention i.e. how was it performed?	
Control:	
Type of control:	PPE: <input type="checkbox"/> AC: <input type="checkbox"/> EC: <input type="checkbox"/> No intervention: <input type="checkbox"/>
Details of the control:	
Outcomes assessed:	Infection: <input type="checkbox"/> Disease: <input type="checkbox"/>
Outcome assessment method:	
Subgroups analysed:	
Confounders:	
Sample size:	
Length of follow-up(days, months, years):	Median (range): Mean:
Location (country):	
Economic status:	Low- or middle-income country: <input type="checkbox"/> High-income country: <input type="checkbox"/> (Low- or middle-income country as defined by the World Bank)
Method of randomisation:	

Method of concealment allocation:			
Was baseline comparability assessed?			
Who was blinded:	Participants: <input type="checkbox"/> Assessors: <input type="checkbox"/> None: <input type="checkbox"/>		
Results:	Outcome of interest (infection or disease) proportion in: Intervention group: 1. 2. 3. Control group:		
Analysis:	Intention to treat: <input type="checkbox"/> Per protocol: <input type="checkbox"/> Unclear: <input type="checkbox"/>		
LOSS TO FOLLOW-UP DETAILS:			
	Intervention (s)	Control	Total
Total number randomized			
No. available at follow-up			
No. loss to follow-up			
No. included in the analysis			
Is loss to follow-up different in study groups: No: <input type="checkbox"/> Yes: <input type="checkbox"/>			

PARTICIPANT CHARACTERISTICS:

Number of HCWs in trial

	Intervention	Control	Total
Number			
% of Total			100%

Gender of HCWs

	Intervention		Control		Total	
	N	%	N	%	N	%
Male						
Female						
Total						

Appendix 2. Search strategy developed in MEDLINE

- #1 Search ((TB) OR Tuberculosis) OR Mycobacterium
 - #2 Search (health personnel) OR hospital personnel
 - #3 Search respiratory protective device
 - #4 Search mass screening
 - #5 Search education
 - #6 Search triage
 - #7 Search patient isolation
 - #8 Search early diagnosis
 - #9 Search risk assessment
 - #10 Search guideline
 - #11 Search policy
 - #12 Search controlled environment
 - #13 Search (((TB) OR Tuberculosis) OR Mycobacterium) AND ((health personnel) OR hospital personnel)
 - #14 Search ((((((TB) OR Tuberculosis) OR Mycobacterium)) AND ((health personnel) OR hospital personnel)))) AND respiratory protective device
 - #15 Search ((((((TB) OR Tuberculosis) OR Mycobacterium)) AND ((health personnel) OR hospital personnel)))) AND mass screening
 - #16 Search ((((((TB) OR Tuberculosis) OR Mycobacterium)) AND ((health personnel) OR hospital personnel)))) AND education
 - #17 Search ((((((TB) OR Tuberculosis) OR Mycobacterium)) AND ((health personnel) OR hospital personnel)))) AND triage
 - #18 Search ((((((TB) OR Tuberculosis) OR Mycobacterium)) AND ((health personnel) OR hospital personnel)))) AND patient isolation
 - #19 Search ((((((TB) OR Tuberculosis) OR Mycobacterium)) AND ((health personnel) OR hospital personnel)))) AND early diagnosis
 - #20 Search ((((((TB) OR Tuberculosis) OR Mycobacterium)) AND ((health personnel) OR hospital personnel)))) AND risk assessment
 - #21 Search ((((((TB) OR Tuberculosis) OR Mycobacterium)) AND ((health personnel) OR hospital personnel)))) AND guideline
 - #22 Search ((((((TB) OR Tuberculosis) OR Mycobacterium)) AND ((health personnel) OR hospital personnel)))) AND policy
 - #23 Search ((((((TB) OR Tuberculosis) OR Mycobacterium)) AND ((health personnel) OR hospital personnel)))) AND controlled environment
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