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Systematic Review of Infection Prevention and Control Policies and Nosocomial Transmission of Drug-Resistant Tuberculosis

Aida Estebesova

ABSTRACT

Emerging multidrug-resistant tuberculosis (MDR/XDR-TB) has become a major public health problem, placing millions at risk. Further, nosocomial transmission of MDR/XDR-TB places both patients and healthcare workers at an even higher risk. Effective tuberculosis (TB) infection prevention and control (IPC) policies in high-risk settings must use evidence-based science and should be customized to the setting. However, the growing incidence of MDR/XDR-TB in some global settings raises questions about whether adequate healthcare-related TB IPC policies are in place and whether they are implemented effectively. The purpose of this systematic literature review was to catalogue healthcare-related TB IPC policy research conducted in high-prevalence settings and draw a picture of existing evidence-based TB IPC policies and their implementation, with a focus on preventing and controlling nosocomial transmission of MDR/XDR-TB.

Two databases (PubMed and Embase) were searched from 1990 – 2013 and outputs were categorized by region/country, income, MDR/XDR-TB incidence, level of IC intervention, and time period. None of the 20 captured research studies were conducted in TB high-prevalence, low-income settings. Most (12/20) were implemented within the Pan American Health Organization region, followed by the African (4/20) and European (4, 20%) regions. Most studies reviewed (70%) were undertaken because of an outbreak and most (70%) were published between 1990 – 2000.

This systematic literature review showed a gap in research on TB IPC policies addressing nosocomial transmission of MDR/XDR-TB in high-prevalence, low-income settings. TB IPC

policy development and implementation should be routinely undertaken as a part of effective and efficient public health practice. Development of TB IPC global best practices should be guaranteed and a concerted effort to promote, distribute, train, and implement these TB IPC best practices in low-resource countries would help mitigate the growing incidence of MDR/XDR-TB worldwide.

TITLE PAGE

SYSTEMATIC REVIEW OF INFECTION PREVENTION AND CONTROL POLICIES AND NOSOCOMIAL TRANSMISSION OF DRUG-RESISTANT TUBERCULOSIS

by

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APPROVAL PAGE

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CHAPTER I: INTRODUCTION

1.1. Overview

Despite globally adopted strategies to control tuberculosis (TB) and globally declining incidence and mortality rates of the disease over the years, it remains a major public health problem (WHO, 2012). TB was included by Stop TB Partnership in the Millennium Development Goals (MDG 6) to be achieved by 191 UN Member States by the year 2015 (STOP TB Partnership, 2010; United Nations, 2013). The TB epidemic is complicated by the multidrug-resistant/extensively drug-resistant tuberculosis (MDR/XDR-TB) which is a man-made disease and emerged as a result of inadequate TB treatment. It is defined as "caused by organisms that are resistant to isoniazid and rifampicin (MDR-TB); and by organisms that are resistant to isoniazid and rifampicin as well as any fluoroquinolone and any of the second–line anti-TB injectable drugs (amikacin, kanamycin or capreomycin)" (WHO, 2013b). Once developed, drug-resistant strains of TB can be transmitted directly from person to person as drug-sensitive TB. Treatment of drug-resistant TB is expensive, long-term (18-24 months), and complex requiring daily injections and involving serious side effects.

Globally MDR-TB is reported in 3.7 % of new TB cases and in 20% of previously treated TB, though these figures vary substantially from country to country (WHO, 2013b). Extensively drug-resistant TB comprises about 9% of MDR-TB cases and has been reported in at least 84 countries by March 2013. About 0.5 million new MDR-TB cases were estimated by WHO globally in 2011 with approximately 60% occurring in Brazil, Russian Federation, India, China and South Africa. There were 27 high MDR-TB burden countries (MDR-HBCs) estimated by WHO in 2008, defined as having had "at least 4000 MDR-TB cases occurring annually and/or at

least 10% of newly registered TB cases with MDR-TB". The highest proportions of MDR-TB among TB cases, however, are in the Eastern European and Central Asian countries. High-cost diagnosis and long treatment of drug-resistant TB put economic burden on health systems, governments and other payers globally. It is estimated that two billion USD will be required in 2015 to diagnose and treat MDR-TB (WHO, 2013b). Concerning is the fact that speed of MDR/XDR-TB propagation is much higher than slowly emerging treatment programs with less than 10% of the estimated cases with drug-resistant TB being treated (WHO, 2010).

Another challenge in addressing drug-resistant TB is its interplay with HIV. People living with HIV (PLHIV) and infected with TB have 20 times greater risk of developing active TB than HIV-negative persons (WHO, 2013a). Out of 1.4 million people who died from TB in 2012, 430,000 deaths were among PLHIV (WHO, 2012). There is evidence of significantly higher mortality rate and short survival associated with drug-resistant TB outbreaks among PLHIV.

2.2. Nosocomial Transmission

Inadequate TB treatment regimens leading to the lower levels of success and the higher rates of default or failure have long been considered driving factors for drug-resistant TB. However, over time, dynamics of factors responsible for drug-resistant TB have changed with about 40% of MDR-TB patients having a history of defaulted or failed treatment, and about 30% of them as new cases without previous treatment history (Figure 1)(WHO, 2011). Furthermore, recent studies show even higher proportions (about 50%) of new MDR-TB cases among people who never been treated for TB before, demonstrating direct transmission of drug-resistant strains (IOM, 2011). In addition, patients, who were previously treated for TB, acquire drug-resistant tuberculosis through transmission rather than as a consequence of non-adherence to the previous treatment. When transmission happens in healthcare setting it is considered as nosocomial.

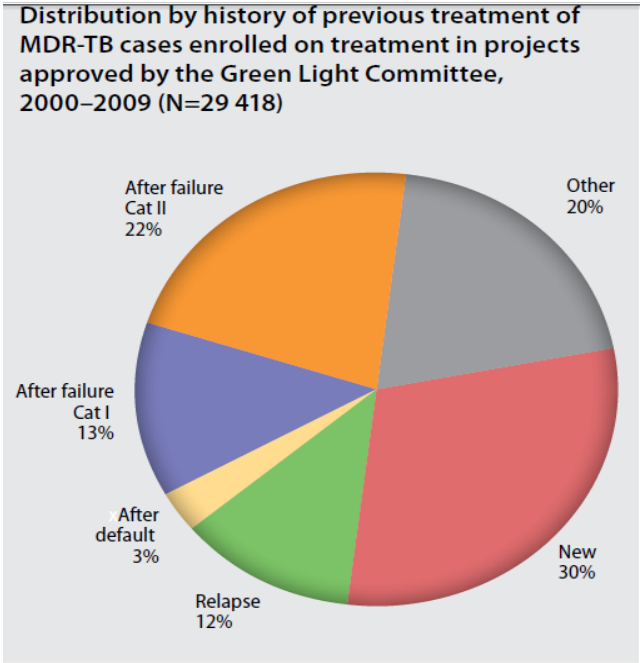

Figure 1. Distribution of MDR-TB Cases by History of Previous Treatment (*Source*: WHO, 2011).

European CDC (2008) defines nosocomial infections or "healthcare-associated infections" (HCAI) as "infections acquired during a stay in a healthcare setting which were neither present nor incubating at the time of admission in a healthcare setting …including occupational infections among staff of healthcare facilities". Nosocomial (healthcare-associated) transmission of drug-resistant TB has been documented in many countries including industrialized and has become a growing public health concern. It became one of the major contributing factors to MDR-TB and more recently the XDR-TB epidemic which threatens achievements in TB control and elimination globally (WHO, 2009). Numerous outbreaks of nosocomial transmitted drug-resistant TB since 1990s have been associated with limited-resource settings, high prevalence of HIV and lack of infection control policies, indicating a need for further and systematic examination of effective TB control strategies (Frieden TR, Sherman

L, Maw K, & et al, 1996); (Edlin et al., 1992); (Gandhi et al., 2013). The Center for Global Development has emphasized the following causes of drug-resistant TB: health system factors, including infection control; drug technology; and behavioral factors (Beith, 2008) (Figure 3).

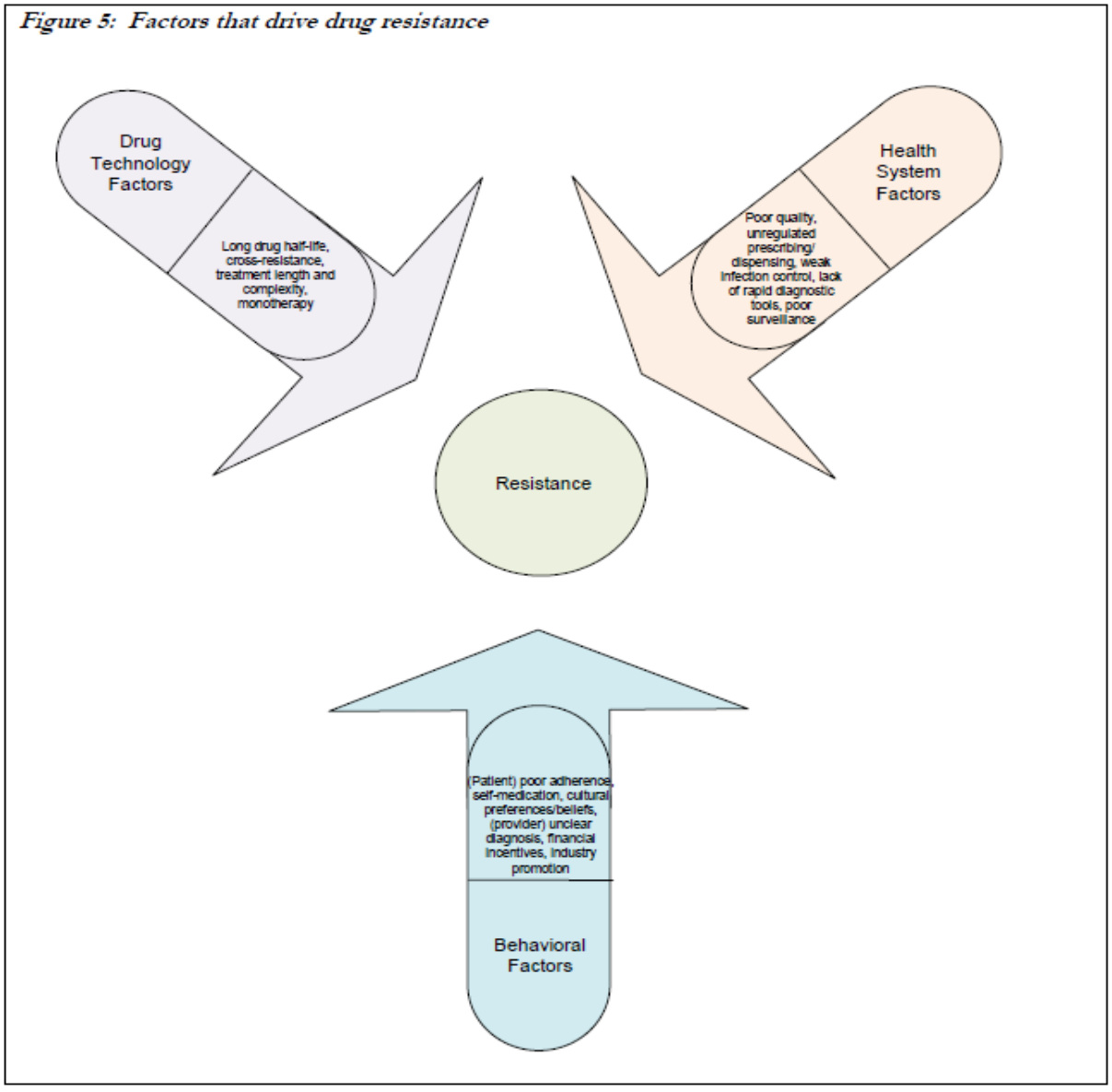

Figure 2. Factors that Drive Drug-resistance (*adopted from* CGD, 2008).

Some populations are of increased risk to nosocomial transmission of drug-resistant TB such as patients with HIV infection and healthcare workers. HIV-positive status is related to higher risk of exposure to MDR-TB patients, due to increased hospitalizations in healthcare settings with inadequate infection control (WHO, 2010). Nosocomial transmission among healthcare workers (HCWs) is of particular concern because of the documented increase in rates of TB in this population: higher attributable risk of TB in this group compared to the general population (ranged from 25 to 5,361 per 100,000 per year), high prevalence of TB (on average 54% (range 33% to 79%)), and increased risk of developing latent tuberculosis (from 0.5% to 14.3%) (Joshi, Reingold, Menzies, & Pai, 2006). HCWs are a valuable and often scarce resource, and their safety and protection from preventable TB exposure, morbidity and mortality should become an essential part of the IPC programs (WHO/CDC, 1999).

1.3.TB IPC

Rising demand from countries for guidance on TB transmission prevention and their need to understand policy gaps in TB IPC led to the development of TB IPC by WHO in 2009. The document defined TB IPC as "a combination of measures aimed at minimizing the risk of TB transmission within populations...[founded on] early and rapid diagnosis and management of TB patients" and included evidence-based recommendations on TB infection control in healthcare facilities, congregate settings and households (WHO, 2009). According to WHO (2009), there is evidence that implementation of IPC measures, including administrative and environmental controls and personal protection, reduces transmission of TB in healthcare facilities (Table 1). Important contributing factors of nosocomial transmission as delayed diagnosis, unrecognized multi-drug resistance, inadequate isolation and infection control practices, poor ventilation and air circulation, are addressed in the WHO document.

Table 1. Set of measures for healthcare facility-level TB infection control (WHO, 2009)

Facility-level measures
1. Implement the set of facility level managerial activities: a) Identify and strengthen local coordinating bodies for TB infection control, and develop a facility plan (including human resources, and policies and procedures to ensure proper implementation of the controls listed below) for implementation. b) Rethink the use of available spaces and consider renovation of existing facilities or construction of new ones to organize implementation of controls. c) Conduct on-site surveillance of TB disease among health workers and asses the facility. d) Address advocacy, communication and social mobilization (ACSM) for health workers, patients and visitors. e) Monitor and evaluate the set of TB infection control measures. f) Participate in research efforts.
Administrative controls
2. Promptly identify people with TB symptoms (triage), separate infectious patients, control the spread of pathogens (cough etiquette and respiratory hygiene) and minimize time spent in healthcare facilities. 3. Provide a package of prevention and care interventions for health workers, including HIV prevention, antiretroviral therapy and isoniazid preventive therapy (IPT) for HIV-positive health workers.
Environmental controls
4. Use ventilation systems. 5. Use ultraviolet germicidal irradiation (UVGI) fixtures, at least when adequate ventilation cannot be achieved.
Personal protective equipment
6. Use particulate respirators

Importantly, TB IPC was neglected for many years and has been recognized as a priority issue that should be incorporated into country-level policy. A majority of countries (66% of 199) reported having a policy on TB IPC, yet none of them had provided information on implementation of TB IPC measures (WHO, 2009). In 2011, less than half (41%) of the 27 MDR-HBCs reported having the national infection control plan (WHO, 2011).

1.4. Gap and Purpose of the Study

The growing global incidence of MDR/XDR-TB raises questions about whether adequate healthcare-related TB IPC policies are in place and whether they are implemented effectively. Continuing outbreaks of drug-resistant TB with recent high fatality XDR-TB highlight pitfalls in the progress of TB IPC implementation to reduce transmission of MDR and XDR TB in high HIV and TB burden countries (Gandhi et al., 2013). Many questions related to TB IPC and their implementation in high-burden and low-income countries, still have to be answered to be able to effectively address nosocomial transmission of drug-resistant TB: what works effectively and what is feasible in certain settings in terms of resources and policies; what are the barriers for development and adequate implementation of TB IPC; what are the gaps and variables that are not understood or taken into consideration in implementing TB IPC policies? WHO has recognized MDR-TB as one of "the greatest areas of unmet need for TB research", highlighting urgent need to scale up research as to provide evidence to countries to reach MDG and STOP TB Partnership goals (WHO, 2011).

Effective TB ICP in high-risk settings must use evidence-based science and should be customized to the setting. Synthesis of the current knowledge base and its distribution globally and in particular in the low-income MDR-HBCs might bring more understanding to the current challenges in control of drug-resistant TB. However, there have been a small number of published literature reviews on TB IPC and nosocomial transmission of MDR/XDR-TB. In addition, those reviews have number of limitations: available literature rarely gives global overview and many times analyses only one or some of the TB IPC measures, which provides a fragmented picture of TB IPC. Most importantly, methodology of the traditional literature review

carries more potential biases during selection and analysis and provides less reliable basis for decision making in comparison to the systematic review.

The purpose of this systematic literature review was to catalogue healthcare-related TB ICP policy research conducted in high-prevalence settings and draw a picture of existing evidence-based TB ICP policies and their implementation, with a focus on preventing and controlling nosocomial transmission of MDR/XDR-TB. Studies will be categorized by region (WHO regions), time period (1990-2000, 2001-2013), country income level (World Bank), level of intervention (WHO TB IPC levels), and study settings, involvement of HIV infection and outbreaks. The landscape of the published TB IC research related to nosocomial drug-resistant TB may contribute to an understanding of the global distribution of the knowledge base and existing gaps. It may also inform policy makers on research and resource allocation for research according to the needs and resources of the regions and countries.

CHAPTER II. REVIEW OF THE LITERATURE

2.1. Nosocomial transmission

Nosocomial transmission and re-infection by MDR/XDR-TB in congregate settings has been investigated and documented in numerous studies as an on-going factor contributing to the drug-resistant TB epidemic worldwide, especially in co-variance with HIV. A recent observational study, exploring hospital-associated epidemiologic links in XDR- TB outbreak in South Africa identified nosocomial transmission links for 82% of patients (Gandhi et al., 2013). Almost all of the patients (93%) were hospitalized while infectious (duration M =5 days; interquartile range: 10–25 days). The study reported multiple generations of nosocomial transmission due to a high degree of interconnectedness which was facilitated by poor infection control measures, high HIV prevalence and delayed diagnosis. These findings have been supported by a number of other studies in different countries establishing nosocomial transmission of drug-resistant TB due to inadequate infection control measures, delayed diagnosis, exacerbated by HIV infection among patients and healthcare workers (Fischl et al., 1992; Nodieva et al., 2010; Ritacco et al., 1997). Sissolak et al. (2010) has demonstrated that undetected cases contribute substantially to the MDR/XDR-TB pandemic due to the same factors, especially in high HIV-burden settings, emphasizing inadequate infection control measures and potentially infectious status of those patients during their hospitalization (Sissolak, Bamford, & Mehtar, 2010). Another study in Japan confirms ongoing community transmission of MDR/XDR- TB and underlines an urgent need to improve of infection control, including an isolation policy for patients with drug-resistant TB (Murase et al., 2010). DNA fingerprinting analysis of MDR/XDR-TB strains isolated from TB patients all over Japan in 2002 showed 38%

of the strains arranged into 9 clusters with geographic links. Moreover, there was a significant association found between the XDR-TB strains and clustering in comparison to non-XDR MDR strains (71% vs. 24%; p = 0.003), highlighting that transmission plays a critical role in the new incidence of XDR TB.

2.2. TB IPC, by levels of infection control

A systematic review was conducted to inform development of WHO TB IPC policy and indicated substantial gaps in knowledge of effectiveness and efficacy of TB IPC measures (WHO, 2009). General findings and policy recommendations for TB IPC were elaborated by the document; however, it didn't focus on IPC related to drug-resistant tuberculosis. Importantly, the critical need to scale up TB IPC research has been highlighted in the document. All TB IC recommendations in the document have specific notes on the level of recommendation and quality of evidence supporting it: almost all of them were indicated as strong recommendations with low-quality evidence. In addition to the conventional TB IPC measures the WHO policy document paid special attention to some new factors, such as selective administrative controls (minimize time spent in health-care facilities), design of buildings, provision of HCWs with HIV prevention and treatment package. Finally, integration of IPC efforts with other health-system work, monitoring and evaluation of TB IPC and involvement of civil society on all stages of infection control programs, were recommended.

According to WHO (2009), TB IPC policy with the goal to minimize the risk of nosocomial transmission of TB, should be a part of the national infection prevention and control policies (WHO, 2009). Managers on national, subnational and health facility levels are recommended to be directed by the developed set of four -level hierarchy infection controls with

administrative level as the most effective and the least expensive, followed by environmental and respiratory controls.

2.2.1. Facility-level control

Importance of the facility-level control, which includes on-site surveillance of TB among HCWs and assessment of the facility, was brought lately by increasing incidence of TB among this population. Nosocomial TB in HCWs is suggested as "the special issue" with median annual incidence 5.8% (range 0%-11%) in low- income and 1.1% (range, 0.2%-12%) in high-income countries (Shenoi, Escombe, & Friedland, 2010). Since IPC practices largely depend on HCWs, more behavioral research among this population is recommended by the authors. Higher risk for skin test conversion (25% vs 12.7%) among medical students on clinical training was associated with the smaller rooms, fewer windows and ineffective mechanical ventilation systems of healthcare settings in Lima, Peru (Nardell & Dharmadhikari, 2010). A study from South Africa demonstrated that HCWs in high HIV burden area were significantly more likely to be hospitalized with either MDR-TB or XDR-TB than were non-health care workers (O'Donnell et al., 2010). Incidence of MDR-TB hospitalization was estimated as 64.8 per 100,000 HCWs versus 11.9 per 100,000 non-HCWs (incidence rate ratio, 5.46 [95% CI, 4.75 to 6.28]). Incidence rate ratio of XDR-TB hospitalizations among HCWs versus non-HCWs was estimated as 6.69 [CI, 4.38 to 10.20]). HCWs with MDR-TB or XDR-TB were more likely to be female (78% vs. 47%; $P < 0.001$) and less likely to report previous tuberculosis treatment (41% vs. 92%; $P < 0.001$). High occupational risk of exposure and contracting drug-resistant TB emphasizes importance of regular surveillance on TB among HCWs and critical need for effective TB IPC programs.

2.2.2. Administrative level controls

Administrative level TB IPC measures aim to prevent generation of infectious droplets nuclei with *M. tuberculosis* and consequently reducing exposure of patients and HCWs to the infection (WHO/CDC, 1999). This level includes triage and isolation of infectious patients, control of the spread of *M. tuberculosis* through respiratory hygiene and cough etiquette, and reduction of time spent in hospital. Role of administrative IC level increases substantially when it comes to MDR-TB, which is associated with longer time of infectiousness compared to drug susceptible TB (Andrews, Shah, Gandhi, Moll, & Friedland, 2007). Administrative controls, in particular rapid diagnoses, are suggested as the most effective and least expensive interventions (Nardell & Dharmadhikari, 2010). Simple triage (based on acid-fast bacilli stain (AFB) for TB and rapid HIV test) and separation strategy from Haiti were demonstrated as a good practice of administrative controls that could be tailored to resource-limited settings.

Administrative controls should also ensure provision of prevention and care interventions for HCWs including HIV prevention, isoniazid preventive therapy (IPT) and antiretroviral therapy for HIV-positive HCWs (WHO, 2009). HIV- infection along with other factors as delayed diagnosis of tuberculosis and poor infection control has been proven to increase the risk of transmission of multidrug-resistant strains of TB (Gandhi et al., 2013; Laing, Ocampo, & Harris, 2010). O'Donnell et al. compared and found in the study in South Africa differences in HIV infection between HCWs and non-HCWs as not significant (55% vs. 57%), although comparison of HCWs to HIV-infected patients on antiretroviral therapy (ART) was significant and showed HCWs as being more likely to receive ART (63% vs. 47%; $P < 0.001$) (O'Donnell et al., 2010).

2.2.3. Environmental level controls

Over-crowded wards in resource-limited, high-burden settings are indicated as one of the main barriers to effective implementation of TB transmission control. Thus environmental controls are proposed to start with renovation or construction of buildings (Nardell & Dharmadhikari, 2010). Natural ventilation is also recommended in low-resource settings in a warm climate considering minimal hourly ventilation rates issued by WHO. It is recommended as a low cost, low maintenance and the most effective (when design of the building includes considerations for it) airborne infection control measure (Shenoi et al., 2010). Mechanical ventilation and mixed-mode systems in addition to natural ventilation are proposed by Nardell et al. (2010) when the latter does not sufficiently meet WHO standards.

Germicidal ultraviolet air disinfection could be a low-cost complementary system to the natural and mechanical ventilation, in particular an upper room ultraviolet germicidal irradiation (UVGI), which is highlighted as a highly effective disinfection mean (70-80%). UVGI addresses limitation of natural ventilation, being climate independent, and in addition of relatively low cost (Shenoi et al., 2010).Yet, UVGI has its certain limitations requiring proper installation that depends on availability of skilled engineers, architects, and good quality and lower cost UVGI fixtures (Nardell & Dharmadhikari, 2010).

2.2.4. Respiratory level controls

WHO (2009) recommends particulate respirators for use by HCWs when caring for infectious or suspected in being infectious patients. For patients surgical masks are recommended to reduce spread of pathogens. Respiratory protection is acknowledged as a complementary level of protection for HCWs after other strategies have been implemented, and recommendations made to elaborate low-cost, non-disposable, of better appearance respirators

allowing verbal communication with the patients (Nardell & Dharmadhikari, 2010). Respirators N95 and FFFP2 have been indicated as certified and the most widely used respirators in US and Europe respectively. Shenoi et al. argues that even though respirators N95 were recommended as a personal protection, however, no discussion of the costs and availability of this type of protection were provided (Shenoi et al., 2010). A comprehensive training program for HCWs on correct and routine use of particulate respirators was recommended by WHO (2009), however, some studies report that fit-testing program is neglected (Nardell & Dharmadhikari, 2010). Fit-testing for correct size and compliance to routine use of respirators were indicated as challenges to be addressed in personal protection.

2.3. Implementation and compliance to the TB ICP policy

Literature suggests that despite availability of TB IPC policies and some of the measures implemented, compliance to those policies and quality of implementation may be far from being adequate (Humphreys, 2007). Thus regular monitoring or audit of the provision of TB IC measures has been recommended. Examples of low compliance and inadequate implementation were found in different countries, including hospitals in resource-rich settings: 122 Belgian hospitals in 1995 were reported to isolate only 84% of patients suspected in infectious TB and to have 96% of HCWs wearing masks, although masks were adequate in only 24% of rooms they entered; UK hospitals with only 35% out of 144 surveyed, had more than one negative-pressure rooms and only 27% had continuous automatic monitoring system of negative pressure of isolation rooms. Study in several U.S. hospitals showed that day-to-day implementation of TB IPC policy was not adequate with observed improper use of respirators by 65% of the HCWs and lack of negative pressure in 19% of patient-rooms, suggesting need in regular monitoring of the equipment's performance (Sutton, Nicas, & Harrison, 2000).

Shenoi et al. (2010) have supported those recommendations pointing out existing gap in information on effectiveness and implementation of TB IPC in resource-limited high HIV and TB prevalence settings, and have indicated critical need to build such evidence (Shenoi et al., 2010). More resources are needed for research and implementation of comprehensive airborne IPC. Murphy (2008) has suggested that there is need in re-design of the current TB IPC protocols in South Africa, even though the country made some progress in addressing MDR/XDR-TB outbreaks, to prevent further spread of the epidemics to the neighboring countries that lack resources and have high HIV prevalence (Murphy, 2008).

2.4. Summary of literature review

The literature acknowledges the main findings and recommendations made by WHO TB IPC policy on the following points:

- hierarchy of the TB infection controls by levels of effectiveness
- substantial gaps in knowledge on efficacy and effectiveness of infection controls
- urgent need in scale up of TB IC research and its inclusion as a critical component of TB, HIV and overall infection control research agenda(WHO, 2009).

Importantly, the document has underscored that rapid implementation of TB IPC policy based on the adequately estimated and allocated resources for all its elements would define its success. In addition, monitoring of the implementation of TB IPC policies would need simple indicators to measure progress.

CHAPTER III: METHODS

This study employed a systematic review which refers to as "a review of the evidence on a clearly formulated question that uses systematic and explicit methods to identify, select and critically appraise relevant primary research, and to extract and analyze data from the studies that are included in the review" (Higgins JPT, 2011). Biases in selection and assessing literature for narrative or traditional literature reviews are not clear, thus might depend on the author's agenda and competence. Moreover, literature reviews are not replicable. Systematic review, in contrast, identifies, assesses and synthesizes all available literature relevant to the defined question, uses explicit methods, is open to external scrutiny, and can be replicated and updated. Importantly, systematic review ensures a reliable basis for decision making.

The author started the systematic review process with defining a research question which was "What is the current landscape of healthcare-related TB IPC research conducted in high-prevalence settings among HCWs and patients on TB ICP policies and their implementation, with a focus on preventing and controlling nosocomial transmission of MDR/XDR-TB?" (Table 2). A Protocol was developed with identification of inclusion and exclusion criteria (Table 3; Annex1). **Table 2. Research Question according to PICO**

Population	Question/Intervention	Outcome	Setting
MDR/XDR-TB patients (all, including PLHIV), HCWs (all, including PLHIV, excluding laboratory)	TB infection control measures (as defined by WHO TB IC policy)	Reduced MDR/XDR-TB incidence associated with nosocomial transmission	Healthcare settings: Any wards (excluding laboratory)

Key search words were developed with the support of a librarian of the public health school and then a search performed on two databases MEDLINE and EMBASE for published research papers on TB IPC interventions in the period from 1 January, 1990 to 31 August, 2013, based on a pre-established protocol (Table 3). The inclusion criteria was expanded to include mathematical modeling studies that might present interest for this research because of the lack of primary experimental human studies on TB infection control due to ethical issues. Only publications reporting on primary studies that were peer reviewed and published in English were included. Grey literature as well as case reports and qualitative studies were excluded from the review. PUBMED database was first searched employing pre-set key search words that were adapted then for EMBASE database search (Table 4). There was only one reviewer (the author) who manually screened, identified and selected the publications based on the established criteria from the list of titles with abstracts generated in the databases. Full texts were screened for the relevant titles with missing abstracts. Duplicates were removed in two steps: first, establishing a command for EMBASE database to exclude records from MEDLINE, which were already covered by PUBMED; secondly, manually during the screening process.

Additionally, five relevant reviews were identified and their lists of references were hand-searched to identify papers relevant to the research question and missing in the list of selected papers from the databases. Results for both databases and snowballing of the reviews are documented in a Flow Chart following the Cochrane standards (Figure 3) (Higgins JPT, 2011).

Table 3. Selection Criteria for Papers

Inclusion Criteria	Exclusion Criteria
• Full text papers reporting on human studies in any country • Title and abstract (or full text when abstract is missing) in English; publications in English • Papers reporting on mathematical modeling	• Case reports • Qualitative studies • Grey literature • Papers reporting equipment testing without human involvement • Papers related to laboratory infection control • Papers not in English • Papers with full texts not found after search efforts • Reviews

Data from all selected papers was extracted according to defined categories and entered into MS Excel database (Microsoft Corp). Categories were defined and evaluated by the author as levels of intervention (facility, administrative, environmental, personal), study design (comparative, non-comparative), setting, population (HCWs, patients), sample size, geographic location (WHO regional grouping applied), involvement of people living with HIV, and whether the studies were conducted during or after outbreaks (Table 5). Income level of the countries where the studies were conducted was included into categories to understand resources available at settings. Additional analysis of the selected articles was conducted to identify publications reporting on the same study and decide which papers were duplicate. This review did not intend to make summary of the results of the selected studies, therefore no quality assessments and meta-analysis were performed.

Table 4. Search Terms by Database, Date, Period and Number of Hits

Date of Search	Resource Used (database, search engine)	Years Searched	Search Terms or Strategies Used (note Limits, MeSH, etc.)	# of Hits/Results
8/28/2013	PubMed	1990-8/2013	("tuberculosis, multidrug-resistant"[MeSH Terms] OR ("tuberculosis"[All Fields] AND "multidrug-resistant"[All Fields]) OR "multidrug-resistant tuberculosis"[All Fields] OR ("drug"[All Fields] AND "resistant"[All Fields] AND "tuberculosis"[All Fields]) OR "drug resistant tuberculosis"[All Fields]) AND ("Cross Infection/transmission"[Mesh] OR "nosocomial transmission"[All Fields]) AND ("1990/01/01"[PDAT] : "2013/08/31"[PDAT])	119
8/28/2013	PubMed	1990-8/2013	(drug resistant tuberculosis) AND "Infectious Disease Transmission, Patient-to-Professional"[MeSH Terms]	58
8/28/2013	PubMed	1990-8/2013	("infection control"[MeSH Terms] OR ("infection"[All Fields] AND "control"[All Fields]) OR "infection control"[All Fields]) AND ("1990/01/01"[PDAT] : "2013/08/31"[PDAT])	151
8/28/2013	PubMed	1990-8/2013	(((drug resistant tuberculosis) AND (("Cross Infection/transmission"[Mesh]) OR "nosocomial transmission"))) OR ((drug resistant tuberculosis) AND "Infectious Disease Transmission, Patient-to-Professional"[Mesh]) AND infection control	111
9/4/2013	EMBASE	1990-8/2013	'drug resistant tuberculosis'/exp OR 'drug resistant tuberculosis'	4138
9/4/2013	EMBASE	1990-8/2013	nosocomial AND ('infection'/exp OR infection)	26606
9/4/2013	EMBASE	1990-8/2013	'infection control'/exp OR 'infection control'	94415
9/4/2013	EMBASE	1990-8/2013	('drug resistant tuberculosis'/exp OR 'drug resistant tuberculosis') AND (nosocomial AND ('infection'/exp OR infection) OR ('infection control'/exp OR	204

	'infection control')) AND (('cross infection'/exp OR 'cross infection')OR('infection transmission'/exp OR 'infection transmission'))

Table 5. Categorization Criteria of Studies

Category	Description of Category
Study publication date	Studies were categorized as published during two periods of time. First time period was defined as January 1990-December 2000. Second time period was defined as January 2001-August 2013.
Study setting	Studies were categorized according to the region and country where the study was undertaken. Regions were defined according to the WHO global grouping: European, African, Region of Americas, Eastern Mediterranean, South-East Asia, and Western Pacific. In addition, countries were defined according to the WHO/World Bank criteria as low-income, lower middle income, upper middle income, and high income.
Study design	Studies were categorized as comparative and non-comparative. Comparative studies were defined as studies comparing case-control groups or pre-post intervention with or without experimental design and randomization. Non-comparative studies were defined as cross-sectional, descriptive, or mathematical modelling studies that did not compare interventions.
Study location	Study locations were categorized as routine setting, research setting, or mixed routine/research settings. Research setting was defined as setting with strong laboratory and clinical research facilities; setting having routine clinical and laboratory facilities was defined as routine; mixed setting included combination of routine and mixed.
TB infection control levels	TB infection control measures involved in the studies were categorized by levels according to the WHO TB IC Policy (see Table 1): facility, administrative, environmental, and respiratory

CHAPTER IV. RESULTS

There were 20 studies included for the analysis from 315 titles and abstracts screened from the databases and additional sources (Figure 3; Table 5). Two hundred sixty five (265) titles and abstracts were excluded after screening as not relevant to the research question (infection control and nosocomial transmission of MDR/XDR-TB) and as not meeting pre-defined study selection criteria. Twenty duplicate publications found as overlapping in two databases were removed. Full texts of the rest 30 studies selected based on the title and abstract's relevance to the research question, were assessed for meeting eligibility criteria and 12 of them were excluded as reporting on the same study (2), irrelevant content (9) as related more to establishing nosocomial transmission of MDR-TB through genotyping, rather than looking into infection control interventions, and having no target population (1). Additional search of relevant studies which was performed by snowballing (handsearching) of the references of the selected five most relevant literature reviews, resulted in two studies that were found relevant and eligible for inclusion in analysis. In total, 20 studies were included in the systematic review.

The majority of them (65%) explored TB IC among both patients and HCWs, three (15%) studied only patients and the remaining four (20%) only HCWs. Most the studies (70%) were conducted in healthcare settings during or after a drug-resistant TB outbreak, and almost the same proportion of the studies (75%) reported HIV infection in the populations of interest (Table 5).

In terms of time, most of the studies (*n*=14) were published between 1992 and 2000, and one third of them (*n*=6) from 2001 to 2012. Geographically, studies were undertaken predominantly in the Americas region (12, 60%), Africa (4, 20%) and Europe (4, 20%). In the Americas region eleven studies (92%) originated from the U.S., one (8%) from Canada; all

studies (100%) in African region were from South Africa; reports from UK (25%), France (25%), Spain (25%) and one study from EU&CIS countries (25%) comprised findings from the European region (Figure 4). Seventy-five percent (n=15) of the studies were implemented in high income and low prevalence of MDR/XDR-TB countries.

Sixteen studies (80%) addressed three and more TB IC levels of intervention; two studies (10%) included only personal level, another one (5%) only administrative level and the last one (5%) both facility and administrative levels. Proportion of investigations for each level of TB IC didn't vary substantially, showing personal and administrative levels reported each in 14 studies (70%), environmental and facility levels in 12 (60%) and 13 (65%) studies respectively.

While one-third of the studies were implemented in the research settings (*n*=6), routine setting was used by most of researchers (*n*=12). About half of the studies were comparative.

Figure 3. Flow Chart for Selection of Studies on TB Infection Prevention and Control for Nosocomial Transmission of MDR/XDR-TB, 1990 – 2013

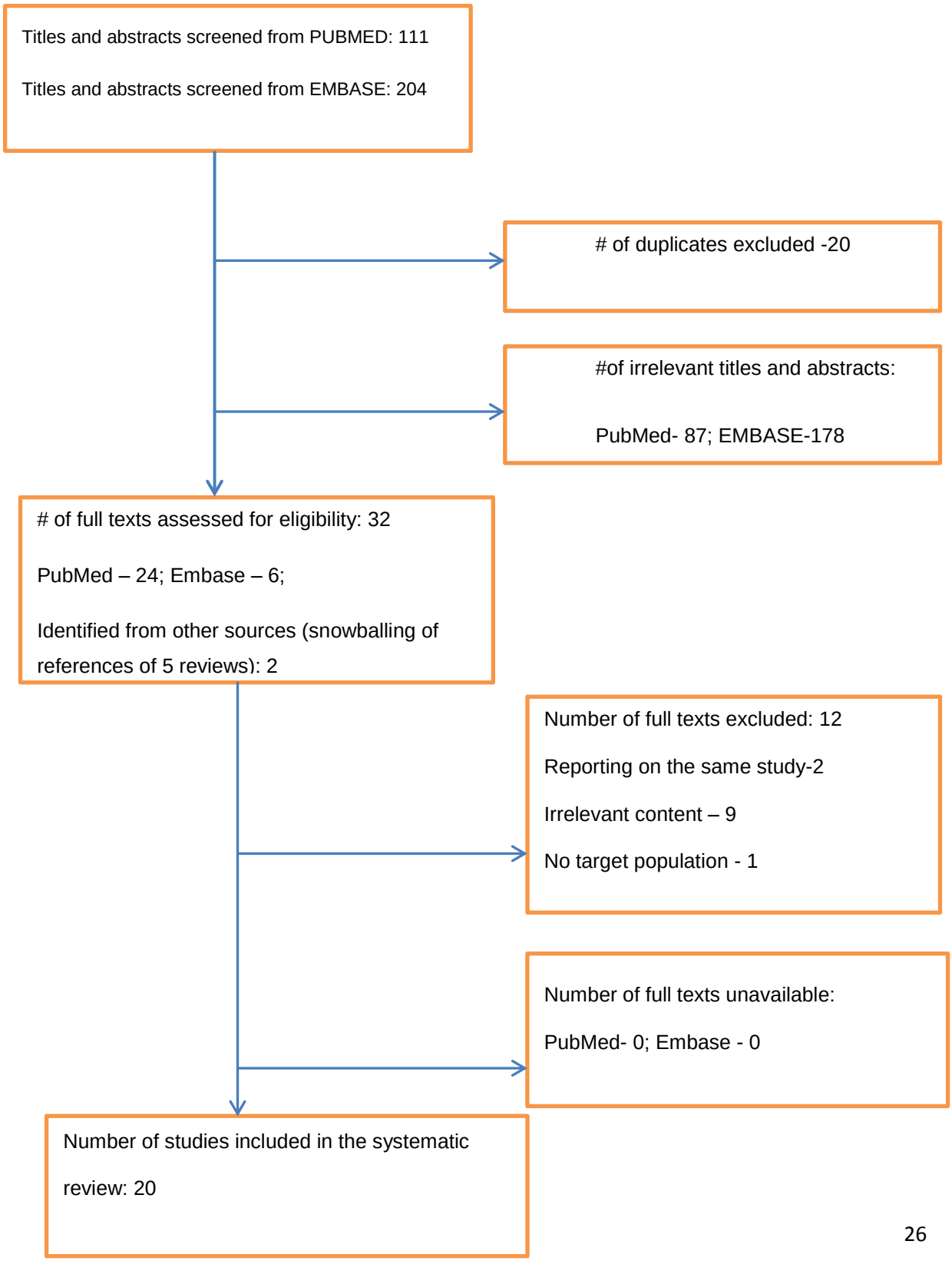

Table 5. Studies Included in the Systematic Review

Citation	Title	Study year	Region/ Country	Study design (comparative/ noncomparat)
(Farley et al., 2012)	A national infection control evaluation of drug-resistant tuberculosis hospitals in South Africa.	2009	African/South Africa	non-comparative
(Manangan et al., 2000)	Nosocomial tuberculosis prevention measures among two groups of US hospitals, 1992 to 1996.	1992-1996	Americas/US	comparative
(Dharmadhikari et al., 2012)	Surgical face masks worn by patients with multidrug-resistant tuberculosis: impact on infectivity of air on a hospital ward.	2010	African/South Africa	comparative
(Basu et al., 2007)	Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study.	2007-2012	African/South Africa	non-comparative
(Guerrero et al., 1997)	Nosocomial transmission of Mycobacterium bovis resistant to 11 drugs in people with advanced HIV-1 infection.	1993-1995	Europe/Spain	non-comparative
(Boudreau et al., 1997)	Occupational risk of Mycobacterium tuberculosis infection in hospital workers.	1989-1992	Americas/US	comparative
(Holton et al., 1997)	Comparison of tuberculosis infection control programs in Canadian hospitals categorized by size and risk of exposure to tuberculosis patients, 1989 to 1993 - Part 2	1989-1993	Americas/ Canada	non-comparative
(Kenyon et al., 1997)	A nosocomial outbreak of multidrug-resistant tuberculosis.	1994-1995	Americas/US	non-comparative.

	(Jarvis, 1995)	Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis.	1989-1992	Americas/US	comparative
	(Ikeda et al., 1995)	Nosocomial tuberculosis: an outbreak of a strain resistant to seven drugs.	1989-1992	Americas/US	comparative
	(Stroud et al., 1995)	Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis in a New York City hospital.	1989-1992	Americas/US	comparative
	(Wenger et al., 1995)	Control of nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis among healthcare workers and HIV-infected patients.	1990-1992	Americas/US	comparative
	(Maloney et al., 1995)	Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers.	1990-1992	Americas/US	comparative
	(Maloney et al., 1995)	The use of high-efficiency particulate air-filter respirators to protect hospital workers from tuberculosis. A cost-effectiveness analysis.	1990-1992	Americas/US	non-comparative
	(Bouvet et al., 1993)	A nosocomial outbreak of multidrug-resistant Mycobacterium bovis among HIV-infected patients. A case-control study.	1990-1993	Europe/France	non-comparative
	(Beck-Sague et al., 1992)	Hospital outbreak of multidrug-resistant Mycobacterium tuberculosis infections. Factors in transmission to staff and HIV-infected patients.	1988-1990	Americas/US	comparative

	(Sotgiu et al., 2011)	TB and M/XDR-TB infection control in European TB reference centres: The Achilles' heel?	2009-2010	Europe/EU and CIS countries (intermediate and low TB incidence)	non-comparative
	(Basu & Galvani, 2008)	The transmission and control of XDR TB in South Africa: An operations research and mathematical modelling approach	2006	African/South Africa	non-comparative
	(Fella, Rivera, Hale, Squires, & Sepkowitz, 1995)	Dramatic decrease in tuberculin skin test conversion rate among employees at a hospital in New York City.	1991-1993	Americas/US	comparative
	(Hannan et al., 2001)	Investigation and control of a large outbreak of multi-drug resistant tuberculosis at a central Lisbon hospital.	1996-1997	Europe/UK	comparative

Table 6. Results for Selected Studies

Appraisal	*n*=20	Country Income	MDR-TB prevalence
Year of publication			
1990-2000	14 (70%)		
2001-2013	6 (30%)		
Region			
European Region	4 (20%)		
African Region	4 (20%)		
Region of the Americas	12 (60%)		
Eastern Mediterranean Region	0		
South-East Asia Region	0		
Western Pacific Region	0		
By Country			
USA	*11 (55%)*	high-income	low-prevalence
Canada	*1 (5%)*	high-income	low-prevalence
South Africa	*4 (20%)*	middle-income	low-prevalence
Spain	*1 (5%)*	high-income	low-prevalence
EU&CIS countries	*1 (5%)*	mixed-income	mix-prevalence
France	*1 (5%)*	high-income	low-prevalence
UK	*1 (5%)*	high-income	low-prevalence
Study Design			
Comparative	11 (55%)		
Non-comparative	9 (45%)		
TB IC by levels			
Facility level	13		
Administrative	14		
Environmental	12		
Personal	14		

TB IC levels (<3) by study	16 (80%)
TB IC levels (>3) by study	4 (20%)
Personal	2
Facility &administr.	1
Administrative	1
Study location	
Research setting	6 (30%)
Routine setting	12 (60%)
Mixed (research-routine) setting	1 (5%)
Modelling (no setting)	1 (5%)
Population	
HCWs	4 (20%)
Patients	3 (15%)
Mixed	13 (65%)
HIV infection	15 (75%)
Outbreak of drug-resistant TB	14 (70%)

CHAPTER V. DISCUSSION

Despite the large number of studies establishing nosocomial transmission of drug-resistant TB among patients and HCWs and recommending improvement or introduction of TB IPC measures, the results of this review show a paucity of published evidence on infection control interventions to reduce or prevent nosocomial transmission of MDR/XDR-TB in high-prevalence low-income settings. These findings might be of importance for the policy makers on global, national and subnational levels, in the context of rapidly growing incidence of drug-resistant TB in specifically above-mentioned areas with high TB and HIV burden and low resources. Emerging drug-resistant TB epidemic signals on challenges and probably failures of the current health systems in those countries either to develop and adequately implement WHO's TB ICP policies, or possibly adaptation of these policies to the local context. Factors contributing to the nosocomial transmission of MDR/XDR-TB should be carefully investigated to understand current gaps, barriers and challenges in developing and implementing TB ICP policies.

The majority of the studies were undertaken during or after outbreaks in industrialized countries and South Africa. Geographical concentration of studies in three regions and countries with low prevalence and high or middle income and lack of studies in high burden and low-income countries demonstrates an existing gap and critical need for further research in the most affected regions. Although the highest burden of the drug-resistant TB is found in developing countries and in certain regions (China, India, South Africa, Russian Federation, Ukraine, Caucasus, Central Asia), there was only one study included in the review which was

conducted in the European Union and CIS countries and might have covered low-income, high prevalence country (WHO, 2013b). This raises questions on whether the findings are due to the language and publication bias, and/or possible lack of expertise and resources. If the latter is true there is a need for increase of awareness and political commitment of policy makers to strengthening health systems including IPC policies and adequate practices along with the capacity building and resource allocation for research.

The income level of countries seems to be related to how urgently and effectively nosocomial drug-resistant TB has been addressed, as well as availability of resources for research and development and implementation of infection control measures. For comparison, the estimated percentage of MDR TB among cases in 2012 in some high-income countries (e.g., United States) is 1% for new cases and 2.9 % for retreatment; in UK these values are 1.3% and 5.6% respectively; versus data from low-income high-burden countries such as Armenia (9.4% and 43%), Somalia (5.2%, 41%) and Kyrgyzstan (26%, 68%) (WHO, 2013c). Availability of in-country resources including technical expertise (CDC and research centers/universities) and funding has been critical in responding to drug-resistant TB outbreaks. Some studies following outbreaks in US showed that rigorous implementation of hierarchical TB IPC measures recommended by CDC were effective to control outbreaks; however, they require plentiful resources to implement those measures in a short period of time (Jensen, Lambert, Iademarco, & Ridzon, 2005). Experience from South Africa shows the possibility of collaboration with and attraction of expert teams to do research and establish evidence on causes of and identification of interventions that have been effective in other countries.

Guidelines were developed as a collaborative effort of WHO and CDC with focus on the resource-limited settings (WHO/CDC, 1999).

The trend in publications over time demonstrates that the majority of studies have been undertaken as a response to the outbreaks, highlighting a critical need in a systematic and routine studies on TB IC of nosocomial transmission of drug-resistant TB in high-burden and low-resourced areas. Similarly, regular monitoring and evaluation of implementation of TB IC measures remains essential in low MDR/XDR-TB prevalence regions. In addition, a few studies published in the recent years provide data on length of stay in the hospital, which has been identified by WHO as one of the important recommendations on reduction of time spent in the hospital as an administrative level measure to reduce risk of nosocomial transmission of drug-resistant TB.

Most of the studies reported significant reduction of drug-resistant TB and skin test conversions among HCWs after implementation of three and more levels of TB IC. This confirms importance of comprehensive though hierarchical implementation of TB IC measures, with the most effective and relatively less expensive administrative level, followed by environmental and complimented by personal levels, as indicated in previous reviews (Nardell & Dharmadhikari, 2010). Effectiveness of use of personal protection interventions alone (respirators for HCWs, surgical masks for patients) varied across studies with some suggesting their effectiveness, and others reporting high cost and low effectiveness.

Nosocomial transmission of drug-resistant TB to HCWs is indicated as a "special issue" by majority of the studies, supporting this observation from one of the previous reviews, with even higher skin test conversion rates (Shenoi et al., 2010). Some studies which compared

TST results pre and post-intervention demonstrated significant reduction of conversion after implementation of TB IPC measures. Other studies which compared risk of conversion of TST of HCWs in wards with or without exposure to drug-resistant TB patients showed varying results.

Studies suggest that in order to reduce nosocomial transmission of drug-resistant TB, the priority and focus of TB IPC should be placed on adequate implementation of effective and cost-effective measures, such as administrative (triage, isolation of infectious or suspected for being infectious patients), adequate environmental, and respiratory (using masks) to ensure protection of HCWs. Importantly, implementation of those policies should be stipulated by context. Political commitment of the leadership on the national, subnational and facility levels plays crucial role in resource allocation and proper implementation of TB IPC policies.

There is a need to implement, observe and learn about the effectiveness of TB IPC in addressing nosocomial transmission of MDR/XDR-TB in low-income, high-burden settings that are considerably different from high-income, low-burden settings where most research has occurred. Where the resource context differs, it seems reasonable to expect practices to differ also. As such, research in high-burden, low income countries could establish the effectiveness or (lack thereof) of current TB IPC recommendations. It is possible that such research may inform the establishment of new, context specific TB IPC and practice.

It is also concerning that less than one half of the 27 MDR-TB high-burden countries (41%) reported having a national infection control plan (WHO, 2011). This suggests that an important area for future research might be in identifying and understanding the underlying reasons for this gap. Cross-sectional survey studies in conjunction with qualitative research cis

needed to assess the factors that drive decision making in these countries, specifically focused on why so many have neglected to implement IC policies. Another fact is that none of the WHO reporting countries provided information on implementation of TB ICP policies, including countries which report to have the policy in place. This highlights the need for further research aimed at better understanding the policy implementation processes and dynamics, the impact these policies have on practices, and the outcomes that are produced from the policies and corresponding practice changes.

There is an opportunity for WHO and its technical group on infection control to increase and prioritize its focus on these issues, both in terms of resources and time dedicated to technical support to high burden, low income countries on development, implementation and monitoring of TB IPC policies and strategies. Capacity building among these countries on IPC policies and may contribute to the effective and consistent adoption and implementation of IC practices with appropriate consideration of the local context (resources, culture, level of awareness, stigma towards TB).

With globalization, health issues of some countries are no longer isolated. Further, they cross national boundaries. In the case of drug-resistant TB epidemic, success to reduce or stop its spread depends on the joint efforts of the global community. Efforts and resources should be united to address the disease locally based on evidence that should be collected in the settings with high TB burden, which are often low-resourced. More research on TB IPC and nosocomial transmission of MDR/XDR-TB should be undertaken in these countries to guide and inform locally feasible and effective policies and their implementation.

5.1. Limitations

There were several limitations of this study. Only one person (an author) performed all search and selection process that could result in selection bias. However, involvement of other person or persons for independent selection and evaluation was not feasible, since this work was done as a part of a graduate program thesis. There were two major databases searched (PubMed, Embase), the study may benefit from more expanded search. Another limitation of the review might be in a language bias, as only publications in English were included, that excluded relevant articles published in other languages. Publication bias might lead to availability of more studies with positive results of the interventions that tend to be submitted and published rather than those with negative results. Also, because of the nature of the issue considered, it was not possible to conduct rigorous selection of the studies (limited only to true experimental studies on human subjects), which lack in this field due to ethics concern.

5.2. Conclusion

This systematic literature review showed a gap in research on TB IPC policies addressing nosocomial transmission of MDR/XDR-TB in high-prevalence, low-income settings. TB IPC policy development and implementation should be routinely undertaken as a part of effective and efficient public health practice. TB IPC global best practices should be reviewed and a concerted effort to promote, distribute, train, and implement these TB IPC global best practices in low-resource countries would help mitigate the growing, global incidence of MDR/XDR-TB.

REFERENCES

Andrews, J. R., Shah, N. S., Gandhi, N., Moll, T., & Friedland, G. (2007). Multidrug-resistant and extensively drug-resistant tuberculosis: implications for the HIV epidemic and antiretroviral therapy rollout in South Africa. *Journal of Infectious Diseases, 196 Suppl 3*, S482-490. doi: 10.1086/521121

Basu, S., Andrews, J. R., Poolman, E. M., Gandhi, N. R., Shah, N. S., Moll, A., . . . Friedland, G. H. (2007). Prevention of nosocomial transmission of extensively drug-resistant tuberculosis in rural South African district hospitals: an epidemiological modelling study. *Lancet, 370*(9597), 1500-1507.

Basu, S., & Galvani, A. P. (2008). The transmission and control of XDR TB in South Africa: An operations research and mathematical modelling approach. *Epidemiology and Infection, 136*(12), 1585-1598.

Beck-Sague, C., Dooley, S. W., Hutton, M. D., Otten, J., Breeden, A., Crawford, J. T., . . . Jarvis, W. R. (1992). Hospital outbreak of multidrug-resistant Mycobacterium tuberculosis infections. Factors in transmission to staff and HIV-infected patients. *JAMA, 268*(10), 1280-1286.

Beith. (2008). Characterization Paper. Mapping Factors that Drive Drug Resistance (with a Focus on Resource-Limited Settings): A First Step Towards Better Informed Policy. Retrieved August 2013, 2013, from http://www.cgdev.org/doc/drug%20resistance/DRWG_Characterization_Paper_16%20July.pdf

Boudreau, A. Y., Baron, S. L., Steenland, N. K., Van Gilder, T. J., Decker, J. A., Galson, S. K., & Seitz, T. (1997). Occupational risk of Mycobacterium tuberculosis infection in hospital workers. *American Journal of Industrial Medicine, 32*(5), 528-534.

Bouvet, E., Casalino, E., Mendoza-Sassi, G., Lariven, S., Vallee, E., Pernet, M., . . . Vachon, F. (1993). A nosocomial outbreak of multidrug-resistant Mycobacterium bovis among HIV-infected patients. A case-control study. *AIDS, 7*(11), 1453-1460.

Dharmadhikari, A. S., Mphahlele, M., Stoltz, A., Venter, K., Mathebula, R., Masotla, T., . . . Nardell, E. A. (2012). Surgical face masks worn by patients with multidrug-resistant tuberculosis: Impact on infectivity of air on a hospital ward. *American Journal of Respiratory and Critical Care Medicine, 185*(10), 1104-1109.

Farley, J. E., Tudor, C., Mphahlele, M., Franz, K., Perrin, N. A., Dorman, S., & Van der Walt, M. (2012). A national infection control evaluation of drug-resistant tuberculosis hospitals in South Africa. *International Journal of Tuberculosis and Lung Disease, 16*(1), 82-89. doi: 10.5588/ijtld.10.0791

Fella, P., Rivera, P., Hale, M., Squires, K., & Sepkowitz, K. (1995). Dramatic decrease in tuberculin skin test conversion rate among employees at a hospital in New York City. *American Journal of Infection Control, 23*(6), 352-356. doi: http://dx.doi.org/10.1016/0196-6553(95)90265-1

Fischl, M. A., Uttamchandani, R. B., Daikos, G. L., Poblete, R. B., Moreno, J. N., Reyes, R. R., . . . Lai, S. (1992). An outbreak of tuberculosis caused by multiple-drug-resistant tubercle bacilli among patients with HIV infection. *Annals of Internal Medicine, 117*(3), 177-183.

Gandhi, N. R., Weissman, D., Moodley, P., Ramathal, M., Elson, I., Kreiswirth, B. N., . . . Shah, N. S. (2013). Nosocomial transmission of extensively drug-resistant tuberculosis in a rural hospital in South Africa. *Journal of Infectious Diseases, 207*(1), 9-17. doi: 10.1093/infdis/jis631

Guerrero, A., Cobo, J., Fortun, J., Navas, E., Quereda, C., Asensio, A., . . . Gomez-Mampaso, E. (1997). Nosocomial transmission of Mycobacterium bovis resistant to 11 drugs in people with advanced HIV-1 infection. *Lancet, 350*(9093), 1738-1742. doi: 10.1016/s0140-6736(97)07567-3

Hannan, M. M., Peres, H., Maltez, F., Hayward, A. C., Machado, J., Morgado, A., . . . Gazzard, B. S. (2001). Investigation and control of a large outbreak of multi-drug resistant tuberculosis at a central Lisbon hospital. *Journal of Hospital Infection, 47*(2), 91-97.

Higgins JPT, G. S. e. (2011). *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*: The Cochrane Collaboration, 2011.

Holton, D., Paton, S., Gibson, H., Taylor, G., Whyman, C., & Yang, T. (1997). Comparison of tuberculosis infection control programs in Canadian hospitals categorized by size and risk of exposure to tuberculosis patients, 1989 to 1993 - Part 2. *Canadian Journal of Infectious Diseases, 8*(4), 195-201.

Humphreys, H. (2007). Control and prevention of healthcare-associated tuberculosis: the role of respiratory isolation and personal respiratory protection. *Journal of Hospital Infection, 66*(1), 1-5. doi: 10.1016/j.jhin.2007.01.007

Ikeda, R. M., Birkhead, G. S., DiFerdinando, G. T., Jr., Bornstein, D. L., Dooley, S. W., Kubica, G. P., & Morse, D. L. (1995). Nosocomial tuberculosis: an outbreak of a strain resistant to seven drugs. *Infection Control and Hospital Epidemiology, 16*(3), 152-159.

Jarvis, W. R. (1995). Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis. *American Journal of Infection Control, 23*(2), 146-151.

Kenyon, T. A., Ridzon, R., Luskin-Hawk, R., Schultz, C., Paul, W. S., Valway, S. E., . . . Castro, K. (1997). A nosocomial outbreak of multidrug-resistant tuberculosis. *Annals of Internal Medicine, 127*(1), 32-36.

Laing, S. S., Ocampo, C., & Harris, J. R. (2010). Evaluating the relationships among psychological distress, executive cognitive function and economic factors on mammography use in unaffected African American women at risk for breast cancer. *Ethnicity and Disease, 20*(4), 467-473.

Maloney, S. A., Pearson, M. L., Gordon, M. T., Del Castillo, R., Boyle, J. F., & Jarvis, W. R. (1995). Efficacy of control measures in preventing nosocomial transmission of multidrug-resistant tuberculosis to patients and health care workers. *Annals of Internal Medicine, 122*(2), 90-95.

Manangan, L. P., Bennett, C. L., Tablan, N., Simonds, D. N., Pugliese, G., Collazo, E., & Jarvis, W. R. (2000). Nosocomial tuberculosis prevention measures among two groups of US hospitals, 1992 to 1996. *Chest, 117*(2), 380-384.

Murase, Y., Maeda, S., Yamada, H., Ohkado, A., Chikamatsu, K., Mizuno, K., . . . Mitarai, S. (2010). Clonal expansion of multidrug-resistant and extensively drug-resistant tuberculosis, Japan. *Emerging Infectious Diseases, 16*(6), 948-954.

Murphy, R. A. (2008). The emerging crisis of drug-resistant tuberculosis in South Africa: Lessons from New York City. *Clinical Infectious Diseases, 46*(11), 1729-1732.

Nardell, E., & Dharmadhikari, A. (2010). Turning off the spigot: reducing drug-resistant tuberculosis transmission in resource-limited settings. *International Journal of Tuberculosis and Lung Disease, 14*(10), 1233-1243.

Nodieva, A., Jansone, I., Broka, L., Pole, I., Skenders, G., & Baumanis, V. (2010). Recent nosocomial transmission and genotypes of multidrug-resistant Mycobacterium tuberculosis. *International Journal of Tuberculosis and Lung Disease, 14*(4), 427-433.

O'Donnell, M. R., Jarand, J., Loveday, M., Padayatchi, N., Zelnick, J., Werner, L., . . . Dheda, K. (2010). High incidence of hospital admissions with multidrug-resistant and extensively drug-resistant tuberculosis among South African health care workers. *Annals of Internal Medicine, 153*(8), 516-522. doi: 10.7326/0003-4819-153-8-201010190-00008

Ritacco, V., Di Lonardo, M., Reniero, A., Ambroggi, M., Barrera, L., Dambrosi, A., . . . de Kantor, I. N. (1997). Nosocomial spread of human immunodeficiency virus-related multidrug-resistant tuberculosis in Buenos Aires. *Journal of Infectious Diseases, 176*(3), 637-642.

Shenoi, S. V., Escombe, A. R., & Friedland, G. (2010). Transmission of drug-susceptible and drug-resistant tuberculosis and the critical importance of airborne infection control in the era of HIV infection and highly active antiretroviral therapy rollouts. *Clinical Infectious Diseases, 50 Suppl 3*, S231-237. doi: 10.1086/651496

Sissolak, D., Bamford, C. M., & Mehtar, S. (2010). The potential to transmit Mycobacterium tuberculosis at a South African tertiary teaching hospital. *International Journal of Infectious Diseases, 14*(5), e423-428. doi: 10.1016/j.ijid.2009.06.030

Sotgiu, G., D'Ambrosio, L., Centis, R., Bothamley, G., Cirillo, D. M., De Lorenzo, S., . . . Migliori, G. B. (2011). TB and M/XDR-TB infection control in European TB reference centres: The Achilles' heel? *European Respiratory Journal, 38*(5), 1221-1223.

STOP TB Partnership. (2010). The Global Plan to Stop TB 2011–2015

Stroud, L. A., Tokars, J. I., Grieco, M. H., Crawford, J. T., Culver, D. H., Edlin, B. R., . . . et al. (1995). Evaluation of infection control measures in preventing the nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis in a New York City hospital. *Infection Control and Hospital Epidemiology, 16*(3), 141-147.

Sutton, P. M., Nicas, M., & Harrison, R. J. (2000). Tuberculosis isolation: comparison of written procedures and actual practices in three California hospitals. *Infection Control and Hospital Epidemiology, 21*(1), 28-32. doi: 10.1086/501693

United Nations. (2013). Millenium Development Goals and Beyond 2015. Retrieved September 20, 2013, from http://www.un.org/millenniumgoals/aids.shtml

Wenger, P. N., Otten, J., Breeden, A., Orfas, D., Beck-Sague, C. M., & Jarvis, W. R. (1995). Control of nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis among healthcare workers and HIV-infected patients. *Lancet, 345*(8944), 235-240.

WHO. (2009). *WHO policy on TB infection control in health-care facilities, congregate settings and households*

WHO. (2011). Towards universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis by 2015: WHO progress report 2011. Retrieved October 24, 2013, from http://whqlibdoc.who.int/publications/2011/9789241501330_eng.pdf

WHO. (2012). Global tuberculosis report 2012.

WHO. (2013a). Management of tuberculosis and HIV coinfection (Clinical Protocol for the WHO European Region (2013 revision). 4. Retrieved September 20, 2013, from http://www.euro.who.int/__data/assets/pdf_file/0004/218515/Management-of-tuberculosis-and-HIV-coinfection-Eng.pdf

WHO. (2013b). Multidrug-resistant tuberculosis (MDR-TB). 2013 Update. Retrieved 09/18/13, 2013, from http://www.who.int/tb/challenges/mdr/MDR_TB_FactSheet.pdf

WHO. (2013c). Tuberculosis country profiles. Retrieved October 02, 2013, from http://www.who.int/tb/country/data/profiles/en/index.html

WHO/CDC. (1999). GUIDELINES FOR THE PREVENTION OF TUBERCULOSIS IN HEALTH CARE FACILITIES IN RESOURCE-LIMITED SETTINGS. Retrieved October 02, 2013, from http://www.who.int/tb/publications/who_tb_99_269.pdf