Chapter 2
Preventive Therapy for Multidrug Resistant Latent Tuberculosis Infection: An Ethical Imperative with Ethical Barriers to Implementation?

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Abstract Multidrug resistant tuberculosis (MDR-TB) has a substantial impact on individuals and communities globally, including lengthy, expensive and burdensome therapy with high rates of treatment failure and death. Strategies to prevent disease are well established for those who acquire latent tuberculosis infection (LTBI) after exposure to drug susceptible TB (DS-TB). However, there has been limited research or programmatic experience regarding the prevention of MDR-TB. Accordingly, while global recommendations strongly emphasize the need to deliver LTBI therapy after TB exposure, most programs do not do so where MDR LTBI is identified.

The paucity of prospective randomized trial evidence for the effectiveness of MDR LTBI therapy, and concerns regarding its adverse effects, have been used to justify a reluctance to scale up programmatic interventions to prevent MDR-TB, or to participate in research evaluating such strategies. However, such a response fails to adequately balance potential risks of therapy with the substantial harms associated with inaction. Furthermore, the cost of inaction falls disproportionately on the

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most vulnerable members of society, including children. Delays in implementing proven preventive strategies may also mask hidden programmatic concerns, particularly regarding the financial cost and other burdens of treating drug resistant infection. Reticence to engage with preventative therapy for MDR-TB, even in the absence of high-level evidence, may run counter to the best interests of individuals who have been exposed to MDR-TB.

This chapter will explore ethical tensions raised by expanding access to preventative therapies for MDR-TB, and consider how ethically optimal responses to this adverse condition may be evaluated. An ethical perspective on evidentiary burden will be addressed, emphasizing how MDR LTBI research may both offer, and be shaped by, paradigmatic insights into human research ethics more generally. Emerging research and illustrations from the authors programmatic engagement in Vietnam are offered as case examples, because social and community expectations and norms may challenge, or support, implementation of therapy for drug-resistant infection. Such circumstances prompt consideration of the broader questions of social impact, such as the potential for widespread preventive therapy to accelerate the development of antimicrobial resistance.

Keywords Bioethics · Infectious diseases · Public health · Social justice · Equality and human rights · Asian culture

2.1 Background

Multidrug resistant tuberculosis (MDR-TB) is a global pandemic disease, characterised as 'Ebola with wings' by public health experts due to its airborne transmission and significant patient mortality (Voelker 1998). With more than 450,000 cases reported in 2015, MDR-TB has become an established global health emergency (World Health Organization 2013a, 2015a, 2016; Hoang et al. 2015a). While treatment for drug-susceptible (DS)-TB typically involves multiple antibiotic tablets for a period of 6 months, standard MDR-TB treatment involves up to 2 years of both oral and injected antibiotics. These toxic regimens frequently cause nausea, liver damage and irreversible hearing loss, and may also require surgery or other invasive procedures (Fox et al. 2016; Torun et al. 2005). Despite the availability of these intensive regimens, MDR-TB therapy is successful in only around half of cases globally, with a high risk of treatment failure and death (Orenstein et al. 2009). In addition, the burden of MDR-TB extends far beyond its medical impact. The prolonged illness, and its associated treatment, has major financial implications for patients and their families - incurring significant financial and housing instability (Tanimura et al. 2014). In short, MDR-TB is costly, prolonged, and complex for both individuals and health care services (Keal et al. 2013).

As TB is a contagious infectious disease, those who live in close contact with affected individuals are themselves at a high risk of developing disease - around 10% of contacts with latent (asymptomatic) TB infection (LTBI) due to *M. tuberculosis* will subsequently develop disease (Marks et al. 2000). Current strategies to prevent the spread of MDR-TB mainly focus upon interrupting the transmission of

infection, by identifying and treating patients with active disease (World Health Organization 2011, 2013b; Fox et al. 2013a). Such strategies are important for individuals with MDR-TB, but have limited impact on preventing disease in those around them who are likely to have already been infected prior to the diagnosis of the treated patient. Transmission studies indicate that close contacts of MDR-TB patients have an elevated risk of infection. Not only are contacts exposed directly to the recognised patient, but they also share socio-economic determinants of disease (World Health Organization 2014; Grandjean et al. 2011; Fox et al. 2017a). This confers an increased risk of exposure to other affected individuals, and susceptibility to developing this dangerous and burdensome disease (Fox et al. 2013b).

Given the high risk of developing active disease after infection with either DS- or MDR-TB, interventions to reduce risk among close contacts are of considerable clinical and public health importance (Trauer et al. 2016). In cases of DS-TB exposure, international guidelines recommend screening of exposed contacts, and a period of antibiotic therapy to prevent progression for those at highest risk of disease progression – such as children under 5 years of age, or those with HIV infection (World Health Organization 2015b). The effectiveness of preventative chemoprophylaxis for DS-TB is well established, including through randomized controlled trials in a variety of global settings (Lobue and Menzies 2010; Sterling et al. 2011). The importance of strategies for preventing MDR-TB has recently been summarised in national and international guidelines for the programmatic management of drug-resistant TB based on the risks of transmission, high morbidity and mortality, and the further development of drug resistance (World Health Organization 2014, 2015c; Ministry of Health 2015; European Centre for Disease Prevention and Control 2012). However, most guidelines have not recommended the routine use of targeted chemopreventive therapy for contacts of MDR-TB (Fox et al. 2017b), citing insufficient evidence of effectiveness in preventing disease, instead recommending programmatic surveillance of contacts. While such surveillance may lead to earlier identification of those developing disease, it fails to reduce the risk of disease among infected contacts, and hence does not prevent the consequent social and economic hardship caused by drug-resistant disease. Thus, current approaches to MDR-TB contacts recognise the high risk of disease among contacts, but do not offer routine use of preventive therapy in most settings, including Vietnam.

2.2 Discussion

2.2.1 Ongoing and Proposed Clinical Trials to Evaluate Antibiotic Therapy to Prevent Drug-Resistant Infection

In this section, we will introduce ongoing and planned clinical trials that aim to establish the effectiveness of preventive therapy for MDR-TB in order to highlight ethical issues arising from this research and reflect upon possible solutions. The first of these is the V-QUIN MDR Trial - a randomised placebo-controlled trial among infected contacts of patients with MDR-TB. Contacts are recruited from district

tuberculosis clinics (DTUs) where MDR-TB treatment is delivered, throughout the Southeast Asian nation of Vietnam. The trial is underway within the Programmatic Management of Drug Resistant TB (PMDT) program at 132 clinics across 10 Provinces of the country. The primary aim of the VQUIN MDR Trial is to evaluate the effectiveness of levofloxacin (a fluoroquinolone antibiotic) in the prevention of active TB among household contacts of patients with MDR-TB with latent tuberculosis infection. Adult contacts will receive either levofloxacin or placebo daily for 6 months. In accordance with international recommendations, contacts will then be monitored for disease progression over a further 2 years to detect incident TB disease.

Vietnam has the twelfth highest TB burden in the world, and is listed among the top 27 countries with the highest burden of MDR-TB (WHO 2015). The country applies regimens recommended by WHO for the treatment of MDR-TB in Vietnam, including at least 19 months of treatment. This comprises, a minimum of 6 months of intensive phase treatment (including a second line injectable antibiotic, kanamycin or capreomycin) and 13 months of continuation phase therapy. Antibiotic treatment is provided free of charge for patients meeting the eligibility criteria for the program.

Despite having a nation-wide TB Program network and a structured, well-organized health service, and reporting impressive rates of treatment completion (WHO 2015), Vietnam still faces many challenges in implementing effective MDR-TB screening and treatment. Ongoing difficulties include a lack of communication and consistency in implementing policy changes, a lack of integration between general district hospitals and the National TB Program network, and limited resources. These health-system factors contribute to a significant gap between the estimated number of cases and the number of patients commencing treatment (Hoang et al. 2015b).

In the hope of gaining more data for evidence of effective regimens in MDR-TB contacts, two other clinical trials are planned, TB-CHAMP and PHOENIx (ACTG A5300) (Clayden et al. 2015; ACTG and IMPAACT Networks 2015). Similar to V-QUIN MDR Trial using levofloxacin and placebo for intervention and control groups, TB-CHAMP study is aimed to test levofloxacin as chemoprevention in children recruited from four clinical sites in South Africa. In this trial, children under five who are household contacts of MDR-TB patients are randomized into two groups taking levofloxacin or placebo every day for 6 months and followed-up for up to 2 years (Tuberculosis child multidrug-resistant preventive therapy: TB CHAMP trial 2016). PHOENIx (ACTG A5300) run by AIDS Clinical Trials Group (ACTG) and International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) presents another different approach in which it aims to assess the efficacy of delamanid which is a new TB drug treatment for MDR-TB and XDR TB (Xavier and Lakshmanan 2014) in treating LTBI for high risk groups of household contacts of MDR-TB patients by comparing its daily use in 6 months with isoniazid preventive therapy then follow up study subjects in 2 years. The trial is planned to be conducted in Africa, South America and Asia (ACTG and IMPAACT Networks 2015).

Observational studies of LTBI treatment are limited. The three randomized controlled clinical trials on LTBI treatment in MDR-TB contacts that we outline here could well be the only research projects currently designed to address this research gap (Mitnick et al. 2016). In the following section, we will present issues and challenges in more detail, informed by our work in Vietnam and discussion with other research teams and experts in the field. Programmatic and research ethics are contextual, and specific settings may provide useful insights into the range of issues which consideration of MDR LTBI generates. In this chapter, we aim to draw on Vietnamese experience to illustrate and reflect on key ethical issues, which may be more broadly applicable in other contexts.

2.2.2 Challenges in the Use of Antibiotics as a Research Intervention in LTBI Treatment

2.2.2.1 How to Balance Between Uncertainties and Risk of Harm: A Common Issue in Public Health Practice

Medical decision-making for LTBI is replete with medical uncertainty. Diagnostic tools with the capacity to identify resistance patterns in LTBI are unavailable. Similarly, diagnostic tools capable of identifying which cases of LTBI will progress to TB disease are lacking. Developing appropriate responses with this diagnostic repertoire requires reflective engagement with medical uncertainty and the ethical challenges of emerging practices (Mason 2014a; Mason 2014b). An effective treatment for LTBI may well be the best method to stop progression to active disease (World Health Organization 2011; Hill et al. 2008), but puzzling questions persist about who should receive treatment for LTBI. The problem is complex enough for LTBI cases where the index patient has drug sensitive TB, but even more complicated for MDR LTBI, where high risk of progression is recognized but uncertainty regarding potential side effects of the drugs and the impact of preventative therapy persists. For LTBI cases who have been exposed to MDR-TB, there is little consensus to guide clinicians and programs towards the risk/benefit of MDR LTBI treatment. In contexts where existing programmatic guidelines recommend against MDR LTBI treatment on the basis of such uncertainty, additional difficulties are faced for researchers seeking to establish a study protocol, which may not align to traditional clinical views and practices in a study country site even if evidentiary equipoise is present.

In the balance between benefits and harms to receivers of MDR-TB preventive treatment, a default approach of ‘surveillance’ is frequently assumed in which “strict clinical observation and close monitoring for the development of active TB disease for at least two years is preferred over the provision of preventive treatment for contacts with MDR-TB cases” (World Health Organization 2015c). However, such a conclusion perhaps does not follow reasonably from the available evidence and resource availability in resource-limited settings. First, strict observation and

close monitoring in order to early detect active TB disease requires many resources for TB screening, diagnosis and case follow-up at a community level over a long period of time. In resource-limited settings where there is a lack of healthcare staff, diagnostic tools and competency, this approach is likely neither feasible nor sustainable. Even if such an approach to surveillance were in place, some may argue in support of providing additional chemoprophylactic agents such as isoniazid (INH) for contacts exposed to MDR-TB patients, thus raising a question of ethical acceptability for study protocols which use a placebo as a control arm.

Based on the fact that INH or RIF has been proven to reduce the risk of developing active TB by at least 60%, and widely adopted in international and national guidelines for LTBI as a standard treatment for those exposed to TB (World Health Organization 2015c; Ministry of Health 2015), the argument in favour of giving INH for MDR-TB contacts involves three rationales. The first reason is that a proportion of contacts with LTBI will have been infected previously, or infected by another index patient, and so will benefit from the therapy. The second is that giving INH is recommended as the standard of care in many countries, and that it would be inappropriate to deprive people of that option because even if it is less effective, it still will be somewhat effective. The third reason is INH is a relatively safe drug, particularly for those under 35 years. For small children, on the balance of risks and benefits, using INH is preferred where the risk of untreated infection leading to disseminated disease is high. However, considering that equipoise may be present given the lack of evidence to guide LTBI treatment for MDR-TB contacts, randomized controlled trials using placebo with periodic follow-ups could be considered ethical for the following reasons: (a) INH is unlikely to be effective, given the most proximate exposure is with MDR-TB; (b) in settings where there is a high rate of INH resistant TB—for example, in Vietnam, at least 17% of all newly diagnosed TB is INH resistant (Nhung et al. 2015)—the effectiveness will be less even if the person has been infected by non-MDR-TB; (c) the current standard of care for adults is either passive case-finding or screening for prevalent TB, (d) INH has a degree of toxicity associated with its use (Denholm et al. 2014). If a drug is toxic, ineffective, and unlikely to benefit patients, then it cannot be ethically administered. Given the diagnostic and therapeutic tools available, serial follow-up by chest Xray is a preferable form of active intervention that exceeds the current standard of care, and will detect cases early enough to reduce serious consequences and allow referral for free treatment.

Recognising that MDR-TB preventive treatment is important, more efforts should be made in finding out effective therapies when there is no standard treatment, or when no proven effective and safe treatment is known to exist. This brings us to our second theme about assessing the effectiveness of LTBI treatment in MDR-TB contacts. Systematic reviews highlight the lack of data and limits of studies conducted in assessing the effectiveness of LTBI regimens available in relevant settings (Fraser et al. 2006; van der Werf et al. 2012). Small observational studies on LTBI regimens have reported promising results. In these studies, a combination of first and second-line TB medications, including a fluoroquinolone antibiotic, is prescribed to both adult and child contacts as preventive therapy from 2 to 12 months

with post treatment follow-up mean periods less than 2 years comparing with placebo or no intervention. High rates of treatment completion, low rates of incident TB disease with low rates of adverse events and good tolerability are reported from the studies (Lobue and Menzies 2010; Seddon et al. 2013; Bamrah et al. 2010). Put together, this evidence suggests that LTBI treatment may be beneficial and further research on LTBI alternative therapies is necessary in producing more comprehensive data on both effectiveness and safety on LTBI therapies.

As the risk of developing MDR-TB is acknowledged to be high in recent contacts, the risk of serious adverse effects from any preventative treatment would need to outweigh the potential benefits in order to justify withholding treatment. While sensible responses to identified MDR-TB exposure should prioritise those at highest risk, the institution of a surveillance strategy instead of provision of treatment with potential adverse effects would preferentially advantage those at lowest risk of developing disease. On this basis, despite imperfect objective estimation of the risks and benefits of different therapeutic options, we would argue that programs may default towards provision of potentially effective therapy for those with MDR LTBI, provided reasonable measures to minimize harms (such as pharmacovigilance programs to identify adverse effects) are in place. In parallel, however, it is also contingent on clinicians and programs continuing to strengthen knowledge of both risks and benefits associated with MDR LTBI therapy, so that future care may be optimally targeted and individuals appropriately informed.

2.2.2.2 Development of Acquired Drug Resistance during Preventive Therapy

Research collaborators and infectious disease clinicians participating in the VQUIN MDR-TB Trial raised valid concerns about administering drugs with unknown effectiveness and the potential harm of selecting new strains of drug resistant TB. The use of antibiotics whose effectiveness has not been demonstrated raises potential problems for individuals and the community. An ineffective regimen may fail to protect the individual, or even result in acquired drug resistance if taken infrequently. Consequently, acquired drug resistance, particularly fluoroquinolone resistance, may then lead to transmission of more advanced strains of drug resistant TB. In the case of the VQUIN MDR-TB Trial, concern hinged on two issues. First, fluoroquinolones (such as levofloxacin) are a part of the backbone of the standard regimen used to treat MDR-TB. Treatment of active TB requires effective multidrug therapy, in order to prevent resistance. If active disease is not excluded prior to commencing preventive therapy, single drug therapy could lead to acquired drug resistance. This concern underpins the reluctance of some physicians to use single-antibiotic preventive therapy in these patients. Second, in settings where LTBI is not routinely managed, clinicians and patients report reluctance to prescribe treatment in the absence of symptoms. In high-burden, low-income settings such as Vietnam, LTBI is not perceived as a disease or condition requiring treatment. Such concerns are compounded by lack of programmatic experience with the use of LTBI

therapies more generally in resource-limited settings, as clinicians have few opportunities to confidently exclude active disease and develop experience with preventative therapies.

Responding to perceptions of risk in relation to amplification of drug resistance is challenging, particularly when public health messaging regarding good antimicrobial stewardship emphasizes the need to avoid unnecessary antibiotic use to preserve drug effectiveness (Doron and Davidson 2011). Some evidence suggests that isoniazid monotherapy to treat drug-susceptible LTBI is unlikely to contribute to drug resistance (Balcells et al. 2006). In fact, modeling data suggest that preventive therapy may actually reduce the overall prevalence of resistance in a population by its secondary effect of reduced propagation among cases that would otherwise have been generated (Fox et al. 2015). One priority is clear: assisting clinicians and community members to appropriately distinguish active from latent TB is an important issue if preventive therapy is to be scaled up. This requires concerted efforts to provide education, clear guidelines and updated knowledge of TB management and research.

2.2.3 Challenge in Conducting Research Using Fluoroquinolone in Children

A significant challenge in conducting research using levofloxacin to treat LTBI in contacts of MDR-TB patients is that fluoroquinolones are generally contraindicated in children and growing adolescents by drug manufacturers and cautiously prescribed by doctors, due to theoretical concerns about the toxicity of the drug class (Goldman and Kearns 2011). In Vietnam, the study proposal to use levofloxacin to treat MDR LTBI in children under 15 years old has caused some controversy among local scientists and members of national ethics committee in considering appropriate assessment of risks and benefits to conducting the research on children. Scientifically, the debate mainly revolves around possible adverse effects of levofloxacin to tendon and musculoskeletal system of children. This concern originated from an association between fluoroquinolone use and irreversible joint cartilage defects in juvenile animals (Ingham et al. 1977) and reversible musculoskeletal events in children (Schaaf et al. 2006). Considering that children have an increased risk of both developing active disease and more severe disseminated forms of disease, and only indirect evidence for a link between fluoroquinolones and musculoskeletal harm exists, there is a strong argument for the inclusion of children in studies such as VQUIN. However, while strategies to deal with potential risks have been considered, including enhanced adverse effect monitoring of younger participants, at present the study has only been approved for adult contacts of MDR-TB.

2.2.4 *Poor Understanding about LTBI and the Use of Diagnostic Tests*

LTBI is generally poorly understood (Colson et al. 2010). Interviews with community members in a variety of contexts consistently identify confusion regarding the difference between latent and active TB, the extent of risk associated with infection, and the availability of treatment to prevent progression to disease (Wieland et al. 2012). A lack of knowledge about LTBI and its attendant risks of progression to disease presents difficulties for the introduction of preventative therapies, particularly where they involve prolonged treatment with some potential adverse effects.

Such uncertainty exists among healthcare workers as well as in the general community. In the research of LTBI therapy given to contacts of MDR-TB patients in Provincial Hospitals and District TB Units in Vietnam, we have identified particular issues including low level of knowledge of LTBI and a general lack of knowledge of treatment options for both active MDR-TB and suspected MDR LTBI. While TB is commonly known as a transmissible airborne infection, the pathways to active disease following exposure are still poorly understood by most healthcare staff. Uncertainties have been repeatedly expressed over the use of diagnostic tests for LTBI, the type and duration of LTBI treatment, presumably reflecting a lack of familiarity with preventative therapies in this context.

2.2.5 *Challenges in Obtaining Informed Consent and Following-up Study Participants*

The requirement to obtain informed consent is central to the ethical conduct of research involving human subjects. As clinical research has become more global, bringing with it a requirement to obtain consent in different places where many disparate values are held, the obtaining of valid consent increasingly raises a range of challenges. Consent practices in resource-limited settings may be impacted by time constraints for researchers to provide detailed research information, the lack of familiarity with medical research, traditionally paternalistic doctor-patient power dynamics and communication styles, involvement of family members and community members in the decision making process, conflict of duty of healthcare provider acting as researcher (Cheah and Parker 2014; Nguyen 2016), not to mention the significant cultural dimensions involved in adapting (and asserting) this research practice in settings where it is a foreign concept (Mason et al. 2017). Suffice to say that obtaining consent in research on LTBI treatment presents complex issues posed by its research context and clinical practice in addition to the complexities of explaining LTBI to a naïve audience.

Based on our experience in conducting research on LTBI therapy given to contacts of MDR-TB patients in Vietnam, we outline challenges generated by different understandings about research and preventive treatment. When the term "research" is translated directly into Vietnamese, it arouses commonly-held negative perceptions within the lay Vietnamese population. Healthcare workers also often express concerns that patients will decline to participate in research studies due to these negative associations, and prefer to avoid the term. An inability to refer to a study as being "research" may obstruct appropriate consent practices, since participants may not be aware of the experimental nature of the involved procedures. This difficulty is further complicated by differing understandings about LTBI and the appropriateness of preventive treatment.

The practical experience of obtaining consent in Vietnam for this study has been explored in series of research staff interviews, highlighting misperceptions about preventive therapy and the low priority people give to it. A staff member who worked on the community studies of the V-QUIN TB screening commented:

> "Our Vietnamese common perception is that "no disease, no treatment". Preventive treatment is not a priority to our people, especially people in farming regions. Their educational level is low so they don't think about preventive treatment. They only buy drugs when they get sick" (Study staff – N01).

With limited information about LTBI treatment in national guidelines, and specific recommendations against MDR LTBI treatment, challenges to effective consent and study participation are likely. In the traditionally hierarchical Vietnamese healthcare system, the existence of guidelines recommending against MDR LTBI treatment is a strong disincentive to both clinicians and community members' participation in research. Research into MDR LTBI treatment may be perceived as being in opposition to existing recommendations, despite the limited evidence on which they are based.

2.2.6 Stigmatization

The stigmatization of TB may impact upon the management of and research into LTBI. In research practice, we experienced that some MDR-TB patients are self stigmatised, or are isolated by their family members due to their disease status. Such patients may want to hide the disease from household contacts and neighbors (therefore prefer going to a private clinic to keep their privacy) and have poor medical adherence. Those most concerned about stigma may also avoid providing accurate information about their household contacts. Study staff in collaboration with local healthcare providers have to explore the information on household contacts by gradually building the relationship between patients and their care-giver, if there is any. This can be achieved through talking with them and providing them more information about TB, LTBI and preventive treatment in clinical assessments performed at hospitals or district tuberculosis clinics. The same stigma may drive healthy

household contacts with LTBI to avoid sharing their infection status with neighbors and friends. As a result, these infected individuals do not want any home visit made by NTP staff/study staff, and do not want to be contacted and asked about the patient. This can create difficulties and challenges in approaching potential study subjects who may participate in the research. It also impedes monitoring of drug adherence and post-treatment following up. As expressed by a study staff about stigmatization in TB:

> "TB is a social disease. It makes participant feel ashamed of getting infection, and thus not wanting to talk about their disease status or being followed up for a long period of time in the study to have their health checked. They also avoid their neighbors knowing about the disease" (Study staff – S01).

2.3 Solutions for Identified Ethical Problems and Challenges

So far, we have attempted to map out a range of issues arising in the prevention of MDR-TB, current approaches to MDR LTBI therapy and in the context of doing a randomized controlled trial in LTBI with our experiences in Vietnam as an exemplary case of high burden TB and limited resource countries. What we will propose as solutions in this chapter accordingly will be general solutions to be considered in providing LTBI treatment and in doing MDR LTBI research. They are put forward in light of the nature of the problems, challenges occurring in the research practice and practical conditions in the setting.

2.3.1 Developing a Comprehensive LTBI Research Agenda

Clinical studies are crucial in advancing medical care. They are needed to produce systematic information on pathogenesis, clinical course, potential interventions and response to treatment. Especially in LTBI, it is important to address a key ethical challenge which is balancing between uncertainties and risk of harm involved in screening and treatment provision, and from that to derive lessons and possible ways to scale up interventions at the community level. Any new scientific information or breakthroughs can bring about alterations to current accounts of scientific and ethical considerations about existing interventions. Concerns about how best to apply systematic screening of LTBI and its related accounts of risk and benefit with beneficiaries (Degeling et al. 2017) is an example which can be expected to be resolved via promising outcome of studies on new LTBI diagnostic methods and indicators of reactivation risk (Dodd and Schlesinger 2017). From our experience drawn in the setting as outlined above, we argue that systematic research, especially randomized clinical trials in evaluating the effectiveness of preventive therapy for LTBI in the contacts of patients with MDR-TB are imperative to better inform clinical decisions, to benefit future infected people and the public in general.

2.3.2 Collaboration

Efforts toward the elimination of tuberculosis call for wide collaboration of various stakeholders including, but not limited to, clinicians in both public and private sectors, public health practitioners (Hauck and Panchal 2009; Taylor et al. 2005), researchers of all groups of expertise, funders, research communities and the public (Sablan 2009). This would serve as a ground for developing a comprehensive and balanced research agenda to inform clinical and public health practice, and to create sustainable research and public health platforms with long term facilities and community support. This type of collaboration can be conducted through the format of national and international collaborative research networks, for example, The Tuberculosis Network European Trials group (TBNET) (Giehl et al. 2012), The Australasian Clinical Tuberculosis Network (ACTnet), The Union World Conference on Lung Health, and the involvement of research community, public and mass media. The primary aim of such collaborations is to engage relevant stakeholders from the beginning of a research initiative to translating research findings into practice in community level on the basis of mutual understanding of a shared account of vision and mission and benefit generating for afflicted population.

While collaborations are recognized as crucial to successful research schemes, effective collaborations, in our view, need to be characterized by 'openness' in which collaborative partners see each other having supplementary role rather competitors, and a shared common interest that is to contribute to the knowledge of the disease for the public good through sharing data and samples. Contributing to the framework of global health, such an open form of collaboration is aimed to protect the common interest towards the global health and stress on the duty to protect affected members of the public and the public good.

2.3.3 Provide Education and Raise Community Awareness of LTBI

Provide necessary scientific training to healthcare workers and study staff.

In order to help ensure success in LTBI treatment program and research initiatives, given the issues related to the lack of knowledge of current LTBI diagnostic methods and therapies which we have outlined above, training on scientific knowledge of LTBI and the role of research in producing systematic information to inform practice is necessary. It is importantly required for frontline health workers who directly provide healthcare to patients and communities where are most needed. These can include pharmacists, nurses, clinicians, and public health officers who serve in hospitals and community clinics. As the first and sometimes the only link to essential healthcare services in limited resource settings, this group of experts

hold great potential to make a direct impact on individual and community health through supporting research activities, delivering good healthcare services and community consultation. Studies and our experience have shown that interaction and communication between health workers/study doctors and patients/study participants brings significant effect to the level of recruitment, medication adherence and treatment outcomes (Horne 1999; Dwamena et al. 2012; Sumartojo 1993). In this case of LBTI and TB control, it is knowledge of current approaches for TB control and prevention available locally and internationally, important health implications of LTBI, the need to provide LTBI treatment, and associated adverse events and their management that needs to be provided and updated to health workers and study staff to equip them in delivering healthcare services at the best level and standard.

Public education.

When research participants are subject to possible sources of vulnerability, the consent process with consideration of some additional protections should aim to protect the safety and the rights of research participants and benefits of afflicted population. This duty should be taken on by ethics committees, physician-researchers, local and international research institutions and other entities involved in the research in designing, reviewing and implementing research projects. At the same time, the consent process should be developed in a way that will enhance "voluntary actions that are intended to help or benefit another individual or group of individuals" (Eisenberg and Mussen 1989a) of research participants, family members and community.

In addressing the key issues in consent and the awareness of LTBI and the role of MDR LTBI treatment in the prevention of TB, we propose that educating the public about the nature of research and its necessity for the improvement and advancement of science in medicine as an overarching plan to make people understand more about the meaning of research and therefore to encourage their participation. For the purpose of raising community awareness of LTBI and the importance of doing more research on this subject, along with the general public education as mentioned above, it also requires providing education programs about clinical research and LTBI to the population and disseminating information about LTBI treatment in the forms of national guidelines with references to international guidelines, health promotional materials and community consultation. This form of education should be carried out on a long term and regular basis. Specific aims of these plans would be (1) to change negative attitude towards research, e.g. 'being a Guinea Pig'; (2) to let people have a better understanding of research, scientific methods in treatment and healthcare, and the role of research in support of medicine; and (3) to maintain trust and nurture pro-social behavior that will enhance "voluntary actions that are intended to help or benefit another individual or group of individuals" in society (Eisenberg and Mussen 1989b) for research and public health agenda.

2.3.4 *Strengthen Communication Between Research Ethics Committees (RECs) and Researchers*

Facilitating cooperation between RECs and scientists/researchers is necessary for mutual understanding and a rapid response in LTBI research context. One way to achieve this is to establish and maintain communication between researchers and RECs throughout research scheme. On the part of RECs, effective communication strategies with researchers will help the RECs to improve transparency in their decisions, understand practical challenges in doing research in the local context, develop expertise in a particular topic area, understand researchers' perspectives and make researchers mutually understand the challenges and duties of RECs. This mutual understanding would eventually place both RECs and researchers in an engaged process whereby research participants are better protected and research can be conducted effectively without being subject to unnecessary delays, misunderstanding and uncertainties.

2.4 Conclusion

In this chapter, we have outlined key issues in preventative therapies for MDR-TB and challenges in conducting research to assess potentially effective MDR LTBI therapies. We have raised possible solutions, derived from our own work in the Vietnamese setting in juxtaposition with broader ethical considerations. We have argued that preventive therapy for MDR-TB should be a high priority. There is a need for appropriately conducted systematic research to address the spread of MDR-TB in limited-resource settings globally. Engagement with local cultural norms and priorities is critical for ensuring that such research is conducted in both ethical and effective fashion.

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