Editorial

DOI: 10.5582/ddt.2022.01029

Challenges in the screening and treatment of latent multidrug-resistant tuberculosis infection

Guofang Deng[§], Peize Zhang[§], Hongzhou Lu[*]

Department of Pulmonary Medicine and Tuberculosis, The Third People's Hospital of Shenzhen, China, The National Clinical Research Center for Infectious Diseases, Shenzhen, China.

SUMMARY Individuals in close contact with multidrug-resistant tuberculosis (MDR-TB) patients are subject to an elevated risk of infection, and may develop latent MDR-TB infection. Numerous studies have described latent tuberculosis infection (LTBI) as a reservoir of new TB disease. The screening and treatment of latent MDR-TB infection are challenging. Hereby, we reviewed the epidemiology, current management and prevention approach of LTBI in MDR-TB close contacts, to provide additional information for future research direction and policy design formulation to reduce the LTBI reservoir.

Keywords multidrug-resistant tuberculosis, latent tuberculosis infection, close contact, diagnosis, treatment

1. Introduction

The World Health Organization (WHO) global tuberculosis report reveals that 9.87 million people were newly diagnosed with tuberculosis in 2020, of which 490,000 were new multidrug-resistant TB (MDR-TB) cases. Meanwhile, 20.1% of these new cases were resistant to fluoroquinolones, a class of antibiotics which are key regimen components for patients with drug-resistant TB (*1*). China is in the second place in the global list of high burden countries for MDR-TB. Treatment success rate of MDR-TB is reported to be 54% only (*1*). The treatment of MDR-TB is difficult and is a huge challenge for disease control in China and many other high burden countries in the world (*2*).

Latent tuberculosis infection (LTBI) is defined as the presence of immune responses to *Mycobacterium tuberculosis* without clinical evidence of active tuberculosis (TB). Around 5-15% of people with LTBI will progress to active TB over their lifetime (*3*). The WHO recently advocated the urgency to address the problem of LTBI in order to contain and eliminate the tuberculosis epidemic, especially MDR-TB (*4*). Evidence-based studies have reported the effectiveness of LTBI treatment in preventing progression to active TB (*5*). However, only a small portion of population at risk have received preventive treatment (*6*). It is more complicated to assess and tailor an optimal regimen for individuals who have developed LTBI from being a close contact to an MDR-TB patient. Therefore, we reviewed the studies relevant to care and prevention of MDR-TB in close contacts and describe the problems faced by people at risk of MDR-TB disease.

2. Global burden of LTBI in MDR-TB close contacts

A study by Knight *et al*. (*7*) estimated that three out of 1,000 in the world population are latent MDR-TB infected, and the infection rate among individuals under the age of 15 is about 10 times higher than those over 15 years. If the current trend continues, the proportion of LTBI caused by MDR-TB will increase and become a serious challenge to TB management. We speculate that about 2 million people in the global population were already infected by the year 2015 (*i.e*. infection in 2013 or 2014) and this population is at an increased risk of progressing to active MDR-TB. The mathematical model developed by Mehra *et al*. (*8*) showed the prevalence of LTBI caused by MDR-TB was growing at a faster pace than those caused by drug-susceptible tuberculosis (DS-TB) in China. Moreover, compared with adults, children with LTBI are at an elevated risk of progressing to MDR-TB and their timely diagnosis and treatment is also more challenging (*9*). With the ongoing MDR-TB epidemic, the global burden of latent MDR-TB infection has become an obstacle to the End TB Strategy.

3. Diagnosis of LTBI in MDR-TB close contacts

There are no definite tests to accurately diagnose LTBI until now. Currently, the tuberculin skin test (TST) and tuberculosis interferon-gamma release assay (IGRA)

recommended by WHO are in use for the diagnosis of LTBI in close contacts (*4*). Nonetheless, both methods cannot assess the drug susceptibility profile of LTBI. Some studies suggested the use of prediction models combining epidemiological and clinical risk factors of the index cases and TST results of their contacts as effective index like biomarkers to predict and stratify risk of active TB progression (*10,11*). But the use of these tools to screen LTBI in practice is limited by different clinical settings. Before the introduction of novel diagnostic testing, TST and IGRA still are considered to be acceptable in contact tracing and LTBI management. Optimization of both tests may play a key role in the contact investigation strategy (*4*).

4. Treatment of LTBI in MDR-TB close contacts

The clinical trials of preventive treatment of LTBI in MDR-TB close contacts have begun in 2015. With emerging evidence from observational studies and the introduction of new drugs, treatment regimen design has evolved over the years (*4*). At present, levofloxacin is the key medicine for treatment of LTBI caused by MDR-TB and shows a good tolerability profile (*12*). However, 16.3% of multidrug-resistant strains were reported to be resistant to fluoroquinolone (*1*), which raised the concern of the feasibility of fluoroquinolone in the treatment of LTBI caused by a fluoroquinolone-resistant MDR-TB strain. A treatment regimen modelling by Holland *et al*. showed that fluoroquinolone prophylaxis treatments for latent MDR-TB infection could significantly save health care payments, lower mortality and improve the quality of patients' life (*13*). Although the pre-existing fluoroquinolone-resistance rate is as high as 85% in the total number of fluoroquinolone-resistant MDR-TB first-episode cases, the regimen still shows prospective results in lowering incidence of latent-to-active MDR-TB progression in close contacts (*13*). Therefore, prophylactic treatment of fluoroquinolones may be a cost-effective strategy. In 2020, Huang *et al*. had demonstrated good results of using isoniazid in reducing incidence of latent-to-active MDR-TB progression in patients under 19 years old (especially under 5 years old) (*14*). The main controversy of these studies is the lack of a clear and credible mechanism to explain the results. Still, the rigor of observation and detailed analysis are noteworthy and lays a foundation for further research and national strategies (*15*).

In recent years, several randomized clinical trials (RCT) of prophylactic drug treatment for latent MDR-TB infection showed that later-generation fluoroquinolones can be used either in a monotherapy or with a second drug. But an increasing incidents in its associated toxicity, adverse events, and discontinuation suggest that pyrazinamide should not be routinely used as a second drug (*9,16*). A systematic review from Marks *et al*. found that the most cost-effective regimen is fluoroquinolone combined with ethambutol, followed by fluoroquinolone alone, then pyrazinamide combined with ethambutol (*17*). Based on current evidence of treatment outcome for latent MDR-TB infection, the WHO recommends fluoroquinolones, such as levofloxacin or moxifloxacin, for the treatment of latent MDR-TB infection (*4*), but as there is a lack of RCT or cohort study, the recommendation is not based on robust evidence (*18*). Another important subject in debate is whether preventive treatment is necessary for all latent MDR-TB infections (*19*). More evidence from stratified studies in MDR-TB close contacts in different immune states are needed to find out prevalence and risk of progression from LTBI to active TB. The high cost and toxicity associated with active MDR-TB treatment should be taken into account in identifying an optimal preventive treatment design for latent MDR-TB infection to lower the incident rate of active TB.

5. Management of LTBI in MDR-TB close contacts

Contact tracing and LTBI management in MDR-TB close contacts should be monitored closely and constantly for 24 months to enable early detection of active MDR-TB (*20*). In addition, the vast majority of close contacts without evidence of latent MDR-TB infection should be followed up for possible onset of active TB within 24 months. Preventive treatment involving drugs with high intolerability profile should be avoided (*19*).

6. Conclusion

In conclusion, current studies have provided evidence on the importance of preventive treatment for LTBI in MDR-TB close contacts, which is also an essential step in containing the MDR-TB epidemic. However, it is necessary to explore new strategies for the diagnosis, treatment and management of LTBI in MDR-TB close contacts. More prospective studies in the area are needed to generate a larger data set and provide validation to formulate updated clinical guidelines and public health advice. Together we are moving in the direction of WHO's End TB goal by 2035.

Funding: None.

Conflict of Interest: The authors have no conflicts of interest to disclose.

References

1. World Health Organization. Global tuberculosis report 2021. Geneva. World Health Organization.
2. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022; 399:629-655.
3. Comstock GW, Livesay VT, Woolpert SF. The prognosis of a positive tuberculin reaction in childhood and

adolescence. Am J Epidemiol. 1974; 99:131-138.
4. World Health Organization. Latent tuberculosis infection: Updated and consolidated guidelines for programmatic management Background document on the 2019 revision. Geneva, WHO Global TB Programme.
5. Zenner D, Beer N, Harris RJ, Lipman MC, Stagg HR, van der Werf MJ. Treatment of latent tuberculosis infection: An updated network meta-analysis. Ann Intern Med. 2017; 167:248-255.
6. World Health Organization. Latent tuberculosis infection, updated and consolidated guidelines for programmatic management. Geneva; 2018.
7. Knight GM, McQuaid CF, Dodd PJ, Houben R. Global burden of latent multidrug-resistant tuberculosis: trends and estimates based on mathematical modelling. Lancet Infect Dis. 2019; 19:903-912.
8. Mehra M, Cossrow N, Kambili C, Underwood R, Makkar R, Potluri R. Assessment of tuberculosis burden in China using a dynamic disease simulation model. Int J Tuberc Lung Dis. 2013; 17:1186-1194.
9. Migliori GB, Tiberi S, Zumla A, *et al*. MDR/XDR-TB management of patients and contacts: Challenges facing the new decade. The 2020 clinical update by the Global Tuberculosis Network. Int J Infect Dis. 2020; 92s:S15-s25.
10. Li R, Nordio F, Huang CC, Contreras C, Calderon R, Yataco R, Galea JT, Zhang Z, Becerra MC, Lecca L, Murray MB. Two clinical prediction tools to improve tuberculosis contact investigation. Clin Infect Dis. 2020; 71:e338-e350.
11. Saunders MJ, Wingfield T, Tovar MA, Baldwin MR, Datta S, Zevallos K, Montoya R, Valencia TR, Friedland JS, Moulton LH, Gilman RH, Evans CA. A score to predict and stratify risk of tuberculosis in adult contacts of tuberculosis index cases: a prospective derivation and external validation cohort study. Lancet Infect Dis. 2017; 17:1190-1199.
12. Bamrah S, Brostrom R, Dorina F, Setik L, Song R, Kawamura LM, Heetderks A, Mase S. Treatment for LTBI in contacts of MDR-TB patients, Federated States of Micronesia, 2009-2012. Int J Tuberc Lung Dis. 2014; 18:912-918.
13. Holland DP, Sanders GD, Hamilton CD, Stout JE. Strategies for treating latent multiple-drug resistant tuberculosis: a decision analysis. PLoS One. 2012; 7:e30194.
14. Huang CC, Becerra MC, Calderon R, Contreras C, Galea J, Grandjean L, Lecca L, Yataco R, Zhang Z, Murray M. Isoniazid preventive therapy in contacts of multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2020; 202:1159-1168.
15. Schluger NW. Prevention of multidrug-resistant tuberculosis in close contacts. Back to the future? Am J Respir Crit Care Med. 2020; 202:1077-1078.
16. Nahid P, Mase SR, Migliori GB, *et al*. Treatment of drug-resistant tuberculosis. An official ATS/CDC/ERS/IDSA clinical practice guideline. Am J Respir Crit Care Med. 2019; 200:e93-e142.
17. Marks SM, Mase SR, Morris SB. Systematic review, meta-analysis, and cost-effectiveness of treatment of latent tuberculosis to reduce progression to multidrug-resistant tuberculosis. Clin Infect Dis. 2017; 64:1670-1677.
18. World Health Organization, WHO operational handbook on tuberculosis (Module 1 – Prevention): Tuberculosis preventive treatment. Geneva.
19. Moore DA. What can we offer to 3 million MDRTB household contacts in 2016? BMC Med. 2016; 14:64.
20. Shah NS, Yuen CM, Heo M, Tolman AW, Becerra MC. Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. Clin Infect Dis. 2014; 58:381-391.

Received April 3, 2022; Revised April 20, 2022; Accepted April 21, 2022.

[§]These authors contributed equally to this work.

**Address correspondence to:*
Hongzhou Lu, Department of Pulmonary Medicine and Tuberculosis, The Third People's Hospital of Shenzhen, China, The National Clinical Research Center for Infectious Diseases, No.29, Bulan Road, Longgang District, Shenzhen 518112, China.
E-mail: luhongzhou@fudan.edu.cn

Released online in J-STAGE as advance publication April 23, 2022.