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Latent tuberculosis infection among contacts of patients with multidrug-resistant tuberculosis in New South Wales, Australia

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Abstract

Background

Contacts of an individual with active tuberculosis (TB) disease, have a higher risk of developing latent TB infection (LTBI) or active TB disease. Contact tracing is a public health measure that seeks to identify exposed contacts, screen them for co-prevalent TB, and consider prophylactic treatment to prevent progression from LTBI to active TB disease. The investigators sought to determine the prevalence of LTBI and active TB disease amongst MDR-TB contacts in New South Wales (NSW).

Methodology

A retrospective cohort study was performed among the contacts of patients diagnosed with MDR-TB between 2000 and 2016, inclusive, at seven chest clinics. Medical records were used to identify eligible contacts. Outcomes of screening and prophylactic treatment regimens offered to MDR-TB contacts with LTBI were characterised. Collected data included demographic information, screening tests results, and initial management.

Results

A total of 247 MDR-TB contacts of 55 MDR-TB patients were identified. LTBI was identified in 105 (42.5%) contacts. Preventive treatment was received by 20 (32.3%) contacts with LTBI, in the form of various regimens, ranging from one to three antimicrobials, with various doses and durations. One contacts with LTBI, untreated, were noted to have progressed to active TB disease during the study period, according to clinic notes.

Conclusion

Contacts of MDR-TB have a high prevalence of LTBI. Management of these contacts varies substantially in NSW, reflecting a lack of definitive evidence for preventive therapy. Further research is required to determine the optimal management of this population.

Introduction

In 2018, an estimated 10 million people fell ill with tuberculosis (TB) worldwide [1 2]. Among these, almost half a million people develop multidrug-resistant tuberculosis (TB), defined as disease caused by *M. tuberculosis* that is resistant to both rifampicin and isoniazid[1 2 3 4]. A diagnosis of MDR-TB presents a major challenge for patients, owing to prolonged treatment and high incidence of adverse events, high mortality rates, and substantial costs of treatment [5 6] .

Tuberculosis is transmitted via droplets coughed up from infected patients to susceptible contacts. The World Health Organization (WHO) aims to eliminate this disease by 2035 [7]. In high-income countries with low rates of tuberculosis, contact tracing is the primary method used to find those at risk of developing tuberculosis. However, the prevalence of latent tuberculous infection (LTBI) and tuberculosis (TB) disease among contacts of patients with multidrug-resistant TB (MDR-TB) and drug-susceptible TB are not well understood. Systematic reviews and meta-analyses have showed that contacts of MDR-TB patients have a high risk of developing TB, with disease commonly diagnosed within 12 months of the index patient's diagnosis [8 9]. A recent prospective cohort study found a higher prevalence of latent tuberculosis infection among household contacts of MDR-TB patients than among contacts of patients with newly diagnosed TB that was presumed not to be drug resistant [10]. Accelerating the detection of disease among high-risk contacts for MDR-TB patients, could maximize the opportunity for identification and treatment of latent infection to prevent disease, and should be prioritised to achieve the End TB strategy [11].

Identifying MDR-TB contacts with LTBI, is clinically useful only if there is an approach to reducing the risk of potential development of active TB disease. This is the rationale for prophylactic treatment regimens for LTBI [12]. However, established consensus amongst global authorities and governments has yet to be reached with regards to management of LTBI in MDR-TB contacts [13 14 15]. In the absence of definitive guidelines in NSW, the provision of prophylaxis lies with a respiratory physician's clinical judgment, based upon the individual clinical features of each patient. A contact tracing study conducted in Victoria, Australia, reported substantial variability in prescribed prophylaxis for MDR-TB contacts, in terms of antimicrobial regimens, as well as treatment duration [16]. Current practices regarding

effective regimens to prevent TB among contacts of patients with MDR-TB have not yet been established [17] .

This study aimed to determine the prevalence of LTBI and active TB disease amongst contacts of patients with MDR-TB screened in NSW and characterise the current approach to management of LTBI in this population.

Methodology

Study design and setting

This retrospective cohort study was performed for contacts of patients with MDR-TB in NSW, between 2000 and 2016. MDR-TB were defined as patients with bacteriologically confirmed TB with resistance to isoniazid and rifampicin. Patients were excluded if they did not have bacteriologically confirmed MDR-TB (with proven isoniazid and rifampicin resistance). We collected quantitative data from the medical records of contacts of the MDR-TB index patients attending chest clinics within NSW. Variables of interest included demographic information, age, gender, country of birth and contact exposure to a person with known TB (an 'index' patient). We also recorded disease status of the contacts, and the outcomes of the contact screening. Tuberculin skin test (TST) and interferon gamma release assay (IGRA) tests results of the contacts were recorded. Immunological evidence of TB infection was defined as a TST reaction size of 10 mm or greater or positive IGRA, upon which LTBI status was determined and the use of prophylactic treatment regimens were reported. Contacts were defined to have completed screening if they completed TST or IGRA and clinical follow up at the TB clinic.

Participant identification

A list of all patients with a laboratory-confirmed diagnosis of MDR-TB in NSW from 1st January 2000 to -31st December 2016 were identified from the state-wide mycobacterial reference laboratory at the Institute for Clinical Pathology and Medical Research (ICPMR) Mycobacterium Mycobacterial Reference Laboratory. Fifty-five patients were identified from seven participating urban chest clinics in NSW where patients received treatment at

the TB clinics. We visited the Chest clinics of these seven hospitals to identify the records of these MDR-TB patients, which contained documentation of routine contact tracing performed for each case of active TB disease.

Contact tracing was managed differently across different chest clinics, where some kept paper records, and others documented via specialised computer software. For each MDR TB patient, generally a list of individuals would be identified as contacts and attempted to be screened and followed up by the chest clinic. The sample of MDR-TB contacts examined by this study included all individuals identified through chest clinic contact tracing programs and comprised the population of identifiable MDR-TB contacts. No identified contacts were excluded at the data collection stage. Existing electronic and hard copy contact records maintained by chest clinics were obtained and manually searched for relevant quantitative data.

Outcome measures

Outcomes of contact screening were also of interest. Contacts with positive TST results obtained from contact screening, without a prior history of LTBI or TB, were considered to have new LTBI. We also recorded the use of prophylactic treatment regimens, including the medications used, their doses, durations and documented adverse effects. Adverse events were evaluated based upon documentation by the treating physicians in the patients' medical records. The grade of adverse events was determined from the available clinical information by two researchers (VC and RL), according to standardised criteria [8]. Grade 1 adverse events comprised events with no symptoms or mild symptoms; Grade 2 events comprised adverse events for which local or non-invasive interventions were indicated; Grade 3 events were defined as those requiring hospitalization or resulting in disability; Grade 4 events comprised events with life-threatening consequences, and Grade 5 resulted in death. Adverse events leading to changes to treatment were documented.

Data analysis

Descriptive analyses were performed. Quantitative variables were summarised using frequency, percentage median (interquartile ranges (IQR)). Adverse events were stratified by organ or system. Proportions were based upon the number of non-missing values. Statistical analyses were performed using SPSS Statistics (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp).

Ethical considerations

Ethics approval for the study was granted by the Sydney Local Health District human research ethics committee (HREC)- LNR/17/CRGH/129. Site specific permission was obtained from each hospital prior to commencement of data collection.

Results

We reviewed the medical files of 55 MDR-TB patients within seven chest clinics in Sydney, NSW. through which 247 MDR-TB contacts were screened (Table 1). The number of contact cases per index patient ranged from 1 to 115 with a median of 2 contacts per case. Most of the contacts were overseas born 131/247 (53.0%). All the patients with presence of BCG scars 57/247 (23.1%) were overseas born.

247 contacts with chest clinic records were commenced screening, and 215 completed screening. TST was the predominant mode of TB exposure screening. Only three contacts were documented to have had an interferon gamma release assay (IGRA) test. Immunological evidence of TB infection was found in 105 (42.5%) contacts. 96 (38.9%) were diagnosed as LTBI by the specialist medical assessment. 62 (25.1%) contacts were classified as LTBI due to recent exposure and 34 (13.8) were classified as remote exposure. With the 62 (25.1%) of the newly diagnosed LTBI contacts, 11 (4.5%) were born in Australia/ New Zealand, 28 (11.3%) were born in Southeast Asia, 13 (5.3%) born in South Asia, 8 (3.2%) were born in East Asia, and 2 (0.8%) were born in Africa. One contact had co-prevalent extrapulmonary TB that was fully sensitive to first line antibiotics. The index case isolate had differing drug susceptibility test results than this contact. .Table 2 showed screening outcomes of contacts.

More than half of the contacts with newly diagnosed LTBI were offered prophylactic treatment (Table 3). Extensive variation was observed in the medications, doses and durations making up the prophylactic treatment regimens offered to contacts with LTBI. Table 4 reports the documented regimens used in the treating hospitals. In two contacts, Isoniazid preventive therapy were commenced before patients' drug susceptibility results were known. Treating clinicians stopped therapy once it was recognised to be ineffective. These two contacts went onto CXR surveillance. 14 of the index cases with MDR-TB had organisms that were susceptible to high level isoniazid, and 11 contacts were offered isoniazid as part of their prophylactic regimens. Adverse events from the prophylactic treatments were rarely reported..

Discussion

This retrospective cohort study found a high prevalence of LTBI among contacts of patients diagnosed with MDR-TB over a 16-year period. In low incidence countries, including Australia, have low background transmission rates of TB, among contacts born in Australia, transmission most likely resulted from the recognised exposure to a patient with MDR-TB.The calculated LTBI prevalence in our study was 96/247 (38.9%) which is comparable to a reported 52.6% prevalence of LTBI in a meta-analysis of contacts of MDR or XDR-TB patients in other high-income countries[8]. One contact had a concurrent extrapulmonary that was not drug resistant. More than half of the contacts with LTBI 33/62 (53.2%) were offered prophylactic treatment and only 20/62 (32.3) of the contacts accepted preventive therapies. Majority of the contacts 42/62 (67.7) accepted CXR surveillance.

Selecting an appropriate preventive therapy is a major challenge for treatment of contacts of patients with drug-resistant TB. It is often difficult to distinguish whether contact LTBI arose from transmission from the recognised index case, or due to a prior remote infection. For those born in Australia, a setting with a low incidence and low background transmission of *M. tuberculosis* in most cases of LTBI are likely to have occurred due to their close contact with active MDR-TB disease. However, in our study many contacts were overseas born, meaning that it was difficult to definitively exclude remote infection.

This study had several limitations. As this was a retrospective study, documentation in the medical records was sometimes incomplete. Relying on chest clinic records, the investigators were unable to exclude the possibility that some contacts were not documented in available records. Secondly, with the small number of contacts treated, the variation in regimens used, and the absence of a control group, we are unable to assess the effectiveness of different regimens to treat LTBI. The undertaking of this study has so far corroborated the utility of contact tracing programs demonstrated by the existing body of literature and characterised a substantial degree of contact transmission in NSW. Even if contacts do not receive treatment, they can be monitored for incipient disease following

their known exposure. This is likely to accelerate diagnosis of early disease and reduce potential ongoing transmission in the community.

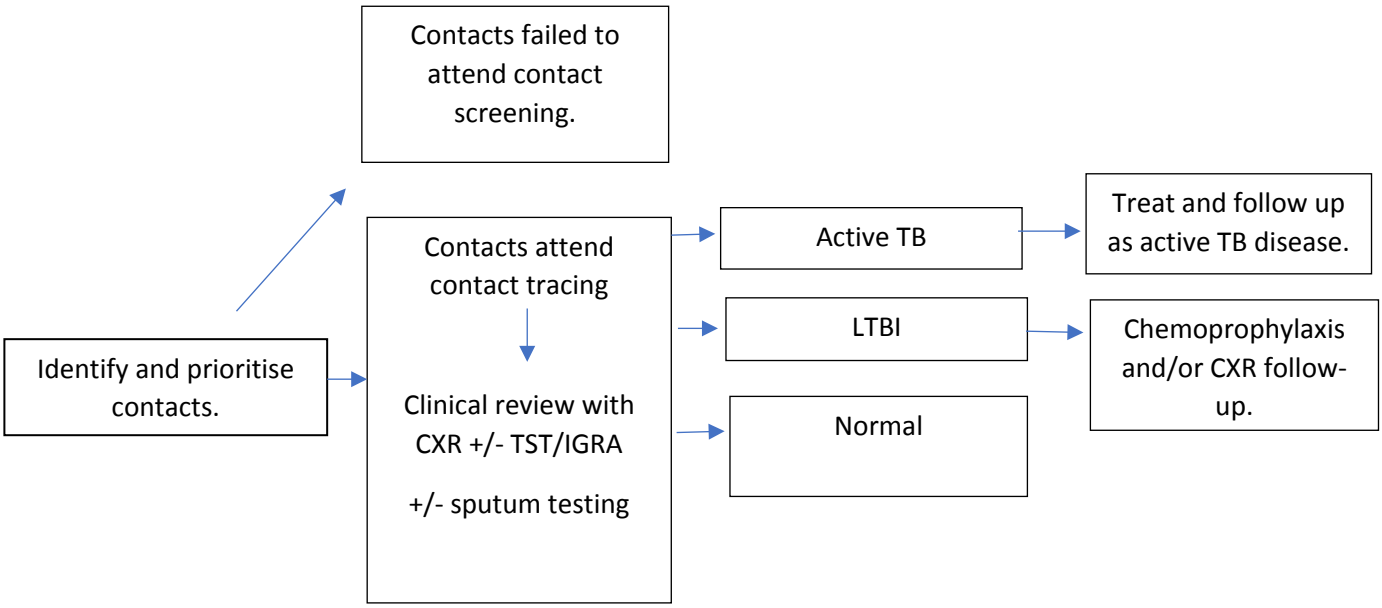
This study has important policy implications. Firstly, given the significant role of contact transmission in LTBI development, efforts to detect and treat contacts with MDR-TB infection plays an important role in the control of TB in this low-prevalence setting. LTBI poses a significant risk to developing infectious active TB disease. It often stated that the lifetime risk of developing active TB after an index infection is 5% to 10%, recent study has shown the 1,650-day cumulative hazard was up to 11.5% [19]. Hence identifying contacts and screening them for LTBI can effectively break the cycle of TB transmission. Prevention is especially important for those at risk of MDR-TB, given the difficulty of treating these cases once active MDR-TB disease is established. Secondly, identifying contacts with LTBI is clinically useful only if there is an approach to reducing the risk of potential development into active TB disease. Regular clinical and radiological surveillance accelerate diagnosis of early disease and reduce potential ongoing transmission in the community [1], but it is labour intensive and it does not reduce the risk of potential development into active TB disease. This is the rationale behind prophylactic treatment regimens for LTBI, however currently available guidelines for treatment of LTBI among MDR-TB contacts lack uniformity and are based upon limited evidence of effectiveness of the commonly used preventive therapies in this population [2 20 21]. Another important consideration unique to our population of MDR-TB contacts would be individualising therapy based upon the drug resistance profile of the index patient. Given the high likelihood of multidrug-resistance in strains responsible for LTBI amongst MDR-TB contacts, prophylactic treatment regimens should ideally be guided by drug susceptibility profiles of M. tuberculosis strains.

Conclusion

This study has characterised the current practice relating to contact investigation for MDR-TB in NSW, and it showed a high prevalence of LTBI in close contacts of patients with MDR-TB. Further research is required to shape clinical guidelines relating to the appropriate management of LTBI among MDR-TB contacts. Attention should be given to identifying

strategies to enhance uptake of screening, as well as chemoprophylaxis to advance the ambitious goal of TB elimination[7].

Figure 1: Algorithm for contact tracing and management in New South Wales, Australia



TB = tuberculosis, LTBI = latent tuberculosis infection; TST = tuberculin skin test; IGRA = interferon gamma release assay, CXR= chest XR, AFB= acid fast bacilli

Table 1: Demographics of contacts of patients with MDR-TB, New South Wales, Australia, 2000 – 2016

	Total n (%)
Total contacts commenced screening	247 (100)
Gender	
Male	107 (43.3)
Female	140 (56.7)
Age	
less than 18	27 (10.9)
18-24	16 (6.4)
25-34	76 (30.8)
35-44	43 (17.4)
45-54	38 (15.4)
55-64	29 (11.7)
65+	18 (7.3)
Country of Birth	
Africa	12 (4.9)
East Asia	18 (7.3)
South Asia	26 (10.5)
Southeast Asia	65 (26.3)
West Asia	4 (1.6)
Europe	4 (1.6)
South America	1 (0.4)
North America	1 (0.4)
Australia and New Zealand	81 (32.8)
Not documented	35 (14.2)
Employment status	
Working full time	87 (35.2)
Working part-time	91 (36.8)
Unemployed	23 (9.3)
Studying	31 (12.6)
Not stated	15 (6.1)
Smoking status	
lifelong non-smoker	185 (74.9)
Current smoker	12 (4.9)
Ex smoker	15 (6.1)
Not documented	35 (14.2)
Alcohol (etoh) usage	
Does not drink	159 (64.4)
Social usage	58 (23.5)

Excessive usage	8 (3.2)
Not documented	22 (30.9)
Intravenous drug user (IVDU)	
Non-IVDU	222 (89.9)
Current IVDU	0 (0)
Ex- IVDU	3 (1.2)
Not documented	22 (30.9)
Bacille Calmette–Guérin (BCG) scar	
Yes	57 (23.1)
No	30 (12.1)
Not documented	160 (64.8)
Medical comorbidities	
HIV	
Yes	0 (0)
No	221 (89.5)
Not documented	26 (10.5)
Diabetes mellitus	
Yes	30 (12.1)
No	209 (84.6)
Not documented	8 (3.2)
Immunosuppression	
Yes	0 (0)
No	231 (93.5)
Not documented	16 (6.5)
Types of contact	
Household	94 (38)
Institutional/ Health care	71 (28.7)
Other	10 (4)
Not documented	72 (29.1)

Table 2: Screening outcomes of contacts of patients with MDR-TB, New South Wales, Australia, 2000 – 2016

	Total n (%)
Total contacts commencing screening	247 (100)
Screening outcomes	
Completed screening (Total)	215 (87)
Total testing positive for LTBI	105 (42.5)
TST positive (10 mm or greater)	104 (42.1)
IGRA positive (0.35 or greater)	1 (0.4)
Total testing negative for LTBI	110 (44.5)
TST positive (less than 10 mm)	108 (43.7)
IGRA negative (less than 0.35)	2 (0.8)
Did not complete screening	32 (13.0)
Do not attend	26 (10.5)
Transferred out before completing screening	3 (1.2)
Deceased before completing screening	3 (1.2)
Chest X-ray findings	
Abnormal	8 (3.2)
Normal	207 (83.8)
Not documented	32 (13.0)
Final diagnosis	
LTBI	96 (38.9)
Newly diagnosed LTBI	62 (25.1)
Prior history of LTBI	34 (13.8)
Active TB disease	1 (0.4)
Previous inactive TB (treated or not treated)	8 (3.2)

TB = tuberculosis, LTBI = latent tuberculosis infection; TST = tuberculin skin test; IGRA = interferon gamma release assay

Table 3: Management of contacts diagnosed with LTBI.

	No. of contact n(%)
Contacts with newly-diagnosed LTBI	62 (100)
Preventive therapy offered	31 (50)
Contacts accepting preventive therapy	18 (29)
Contacts refusing preventive therapy	13 (21.0)
Preventive therapy not offered	31 (50)
Chest Xray surveillance offered	31 (50)*
Contacts accepting CXR surveillance**	44 (71.0)
Contacts refusing CXR surveillance	0
LTBI = latent tuberculosis infection.	

*Isoniazid preventive therapy were commenced before patients' drug susceptibility results were known and stopped by clinicians once it was recognised to be ineffective.

*These contacts went onto CXR surveillance.

**Including contacts refusing preventive therapy.

Table 4: Antibiotic treatment infected contacts of patients with MDR-TB

Regimen recommended by treating physicians	Contacts commencing treatment n (%)	Contacts completing recommended treatment n (%)	Contacts reporting adverse events during treatment n (%)
Total	18 (100)	18 (100)	1 (5)
1 drug			
Moxifloxacin			
6 months	7 (35)	7 (35)	0 (0)
2 drugs			
Isoniazid and Rifampicin	7 (35)	7 (35)	0 (0)
4 month	3 (15)	3 (15)	0 (0)
6 months	3 (15)	3 (15)	0 (0)
unknown duration	1 (5)	1 (5)	0 (0)
Isoniazid and Pyrazinamide			
9 months	2 (10)	2 (10)	1 (5)
3 drugs			
Isoniazid, Rifampicin and Pyrazinamide	2 (10)	2 (10)	0 (0)
5 months	1 (5)	1 (5)	0 (0)
6 months	1 (5)	1 (5)	0 (0)

Supplemental table

Table S1. LTBI rates in different age categories amongst contacts of patients with MDR-TB, New South Wales, Australia, 2000 – 2016

Final diagnosis based upon the specialist assessment	**Total n (%)**
LTBI	96 (100)
Age	
less than 18	10 (10.4)
18-24	12 (12.5)
25-34	36 (37.5)
35-44	10 (10.4)
45-54	4 (4.2)
55-64	16 (16.7)
65+	8 (8.3)
Newly diagnosed LTBI	62 (64.6)
Age	
less than 18	8 (8.3)
18-24	10 (10.4)
25-34	32 (33.3)
35-44	8 (8.3)
45-54	2 (2.1)
55-64	2 (2.1)
65+	0
Prior history of LTBI	34 (35.4)
Age	
less than 18	2 (2.1)
18-24	2 (2.1)
25-34	4 (4.2)
35-44	2 (2.1)
45-54	2 (2.1)
55-64	14 (14.6)
65+	8 (8.3)

References

1. Global tuberculosis report 2019. Geneva: World Health Organization; 2019.
2. WHO. Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Geneva, World Health Organization, 2014.
3. Mitchison DA. The Diagnosis and Therapy of Tuberculosis During the Past 100 Years. *American Journal of Respiratory and Critical Care Medicine* 2005;171(7):699-706. doi: 10.1164/rccm.200411-1603OE
4. Seddon JA, Garcia-Prats AJ, Purchase SE, et al. Levofloxacin versus placebo for the prevention of tuberculosis disease in child contacts of multidrug-resistant tuberculosis: study protocol for a phase III cluster randomised controlled trial (TB-CHAMP). *Trials* 2018;19(1):693. doi: 10.1186/s13063-018-3070-0 [published Online First: 2018/12/24]
5. Bastos ML, Hussain H, Weyer K, et al. Treatment outcomes of patients with multidrug-resistant and extensively drug-resistant tuberculosis according to drug susceptibility testing to first- and second-line drugs: an individual patient data meta-analysis. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America* 2014;59(10):1364-74. doi: 10.1093/cid/ciu619 [published Online First: 2014/08/07]
6. Ahmad N, Ahuja SD, Akkerman OW, et al. Treatment correlates of successful outcomes in pulmonary multidrug-resistant tuberculosis: an individual patient data meta-analysis. *The Lancet* 2018;392(10150):821-34. doi: 10.1016/S0140-6736(18)31644-1
7. WHO report to the World Health Assembly on the End TB Strategy and targets.
8. Fox GJ, Barry SE, Britton WJ, et al. Contact investigation for tuberculosis: a systematic review and meta-analysis. *The European respiratory journal* 2013;41(1):140-56. doi: 10.1183/09031936.00070812 [published Online First: 2012/09/01]
9. Shah NS YC, 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(3):381-91. Yield of contact investigations in households of patients with drug-resistant tuberculosis: systematic review and meta-analysis. Clin Infect Dis. 2014;58(3):381-91.

.

10. Fox GJ, Anh NT, Nhung NV, et al. Latent tuberculous infection in household contacts of multidrug-resistant and newly diagnosed tuberculosis. *The International Journal of Tuberculosis and Lung Disease* 2017;21(3):297-302. doi: 10.5588/ijtld.16.0576
11. Reichler MR, Khan A, Sterling TR, et al. Risk and Timing of Tuberculosis Among Close Contacts of Persons with Infectious Tuberculosis. *The Journal of Infectious Diseases* 2018;218(6):1000-08. doi: 10.1093/infdis/jiy265
12. 2018. WHOLtiUacgfpmGW.
13. van der Werf MJ SA, Manissero D. Management of contacts of multidrugresistant tuberculosis patients in the European Union and European Economic Area. Int J Tuberc Lung Dis. 2012;16(3):426.
14. 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. *Clinical Infectious Diseases* 2017;64(12):1670-77. doi: 10.1093/cid/cix208
15. 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. *International Journal of Infectious Diseases* 2020;92:S15-S25. doi: https://doi.org/10.1016/j.ijid.2020.01.042
16. Denholm JT, Leslie DE, Jenkin GA, et al. Long-term follow-up of contacts exposed to multidrug-resistant tuberculosis in Victoria, Australia, 1995-2010. *The international journal of tuberculosis and lung disease : the official journal of the International Union against*

Tuberculosis and Lung Disease 2012;16(10):1320-5. doi: 10.5588/ijtld.12.0092 [published Online First: 2012/08/07]
17. https://www.futuremedicine.com/doi/10.2217/fmb-2017-0236.
19. Trauer JM, Moyo N, Tay EL, et al. Risk of Active Tuberculosis in the Five Years Following Infection . . . 15%? *Chest* 2016;149(2):516-25. doi: 10.1016/j.chest.2015.11.017 [published Online First: 2016/02/13]
20. Rodriguez CA, Sasse S, Yuengling KA, et al. A systematic review of national policies for the management of persons exposed to tuberculosis. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2017;21(8):935-40. doi: 10.5588/ijtld.17.0061 [published Online First: 2017/08/09]
21. van der Werf MJ, Langendam MW, Sandgren A, et al. Lack of evidence to support policy development for management of contacts of multidrug-resistant tuberculosis patients: two systematic reviews. *The international journal of tuberculosis and lung disease : the official journal of the International Union against Tuberculosis and Lung Disease* 2012;16(3):288-96. doi: 10.5588/ijtld.11.0437 [published Online First: 2012/05/30]