IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
May 2024 Vol.:30, Issue:5
© All rights are reserved by Dr.Dipali S. Bolde et al.

Effect of Multi Drug Resistance Review: Tuberculosis (TB)

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

[1]Dr.Dipali S. Bolde, [2]Dr Balkrishna D. Tiwari, [3]Vaishnavi S. Raut, [4]Shreyash S. Sabban

[1]Assistant Professor, [2]Vice Principal. [3]Co-author. [4]Co-author, [1]Department of Pharmacology
[1]Amepurva Fourm's Nirant Institute of Pharmacy, Solapur, Maharashtra, India

Submitted: 22 April 2024
Accepted: 28 April 2024
Published: 30 May 2024

HUMAN JOURNALS
ijppr.humanjournals.com

Keywords: Tuberculosis (TB), MDRTB, Drugs, Infection.

ABSTRACT

The fast rise of multidrug resistance Mycobacterium tuberculosis (TB), which is immune to both isoniazid and rifampicin, has put efforts to reduce the worldwide incidence of tuberculosis (TB) in danger. Variable frequency rates of multidrug-resistant tuberculosis (MDR-TB) with related risk factors have been identified in Ethiopia by earlier research.[1]The treatment of tuberculosis (TB) is in danger due to the development of multidrug resistant tuberculosis (MDR-TB). Before to the 1994–1997 worldwide project on anti-tuberculosis drug resistance watching, which was started by the World Health Organisation (WHO) and International Union Against Tuberculosis and Lung Diseases (IUATLD), the precise scope of the problem of drug resistance to antituberculosis drugs was unknown. In 2014, the Global Tuberculosis Report estimated that MDR-TB was present in 20.5% of cases of TB that had previously been treated and 3.5% of newly diagnosed cases. According to estimates, MDR-TB caused 210,000 deaths and 480,000 new cases worldwide in 2013. According to estimations, the incidence of MDR-TB was 2.2% and 15%, respectively, among newly diagnosed and previously treated patients in India. According to estimates.[2]

Introduction:

Robert Koch discovered the tubercle bacillus, sometimes referred to as Mycobacterium tuberculosis (M. Tb), as the tuberculosis (TB) cause of infection in 1882 [43] Since his discovery, the global TB epidemic appears to be continuing continuously. One of the leading causes of death worldwide and a highly contagious airborne disease is tuberculosis [44] Extrapulmonary tuberculosis (TB) is the name given to the condition that can spread to other areas of the body, even though the disease usually affects the lungs [44].Since the early days of anti-TB chemotherapeutic introduction, drug resistant tuberculosis (TB) has been observed; however, multi-drug resistance tuberculosis (MDR-TB) has been a cause of issue.[2]Of considerable concern in recent times and a danger for worldwide efforts to kill tuberculosis. The World Health Organisation (WHO) and International Union Against Tuberculosis and Lung Diseases (IUATLD) started a global study on anti-TB drug résistance surveillance in 1994–1997 that helped determine the precise scope of the MDR–TB problem worldwide. The prevalence of MDR-TB is a good indicator of the effectiveness and functioning of TB control programmes as well as the community's practical approach to their administration.[3]MDRTB's development stays an important risk to public health, particularly in developing countries. The cost of MDR-TB presented difficulties to the country due to its increasing incidence and demanding course of treatment. It is important when little is available regarding the distribution of drug resistant tuberculosis.[4] Effective therapies are largely caused by the continued use of useless, costly, unsafe, and ineffective medications. Treatment plans for Mycobacterium tuberculosis strains that are multidrug resistant (MDR)—that is, those that are resistant in vitro to at least isoniazid and rifampicin—should be provided for a minimum of 18 months. Long-term drug exposure is linked to poor patient adherence, which is made better by the frequent, sometimes severe, and sometimes death drug-related adverse events that affect everyday quality of life and physical health [5] There has been and continues to be new research conducted on simpler, safe, and effective treatments.[6]

What is MDRTB?

Multidrug resistant tuberculosis (MDR-TB) is defined As disease due to Mycobacterium tuberculosis that is Resistant to isoniazid and rifampicin with or without Resistance to other drugs (the cult susceptibility test results being from an accredited.[2] The present review used the definition below according to with the MDR-TB guideline:[478]

Any first-line anti-tuberculosis medication will not cure drug-resistant tuberculosis (TB).

. •Patients who have never received TB treatment and those who show resistance to isoniazid and rifampin are considered to have MDR-TB among new cases (Primary drug resistance). This represents the spread of drug-resistant tuberculosis bacteria from person to person.

•Medical issues are simultaneous conditions that are discovered in tuberculosis patients as a secondary diagnosis.

Drugs used on tuberculosis:

anti tuberculous drugs, including first- and second line.

 1st line drug:

 Isoniazid ▪ Rifampin 2nd line drug

 Fluroquinolone

 Levofloxacin

❖ **Isoniazid:**

Moa: [45]

Isoniazid

↓

Inhibitions of mycolic acid (essential for component of tb bacteria)

↓

Distribution of cell wall formation and weakness the bacteria

↓

This distribution ultimately leads to death of tb bacteria.

Adverse drug reaction:[46]

- Cardiac disorder
- Endocrine disorder
- Hepatobiliary disorder

- Nervous system disorder
- Psychiatric disorder
- Skin and subcutaneous tissue disorder

Rifampin:

Moa: [47] Rifampin

Binds to ß-subunit bacteria DNA dependant RNA polymerase

Block the RNA synthesis in Mycobacterium

Cell death

Adverse drug reaction:[46]

- Immune system disorder
- Product Issue.
- Vascular disorder.
- Endocrine disorder.
- Cardiac disorder

Types of drug resistance:

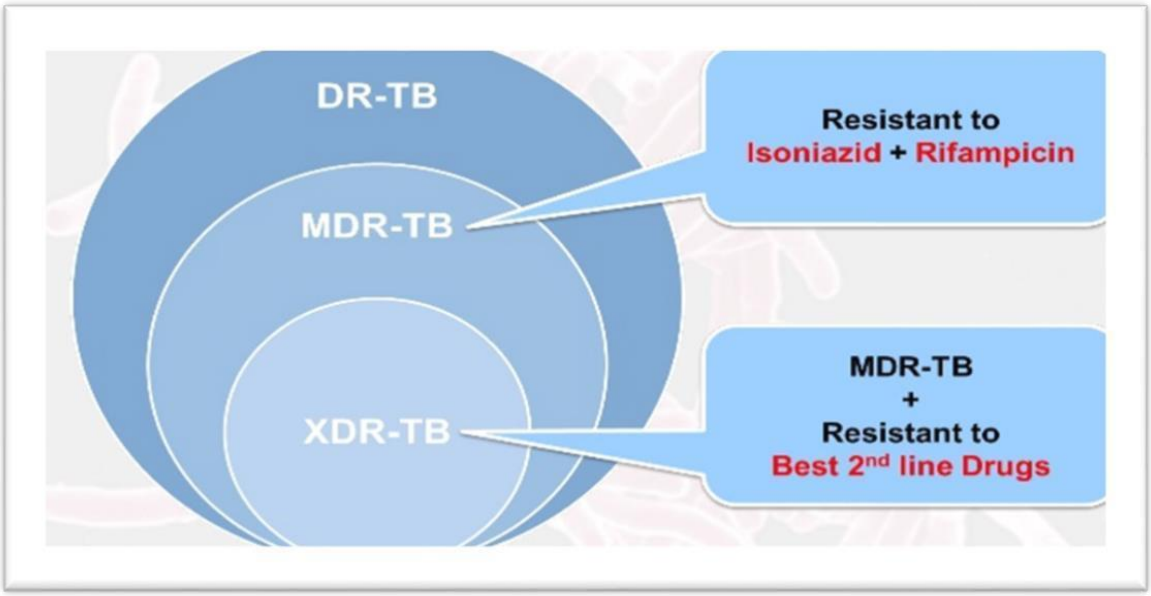

Fig.1 (multi- drug resistance)[16]

There are two categories of drug resistance: acquired and primary. Primar medication resistance is characterised by a patient's absence of response to recent. therapy against TB (ATT) in previous years. Acquired drug resistance refers to the resistance that appears in a patient who has had chemotherapy in the past. The terms "resistance in previously treated cases" and "resistance in new cases" have recently been suggested for use because it can be challenging to verify the accuracy of the patient's previous medical record. Initial drug resistance is the state in which it is unclear if the resistance is primary or acquired as a result of a hidden history of prior treatment or ignorance of prior therapy. As a result, initial resistance consists of both openly acquired resistance and primary resistance. The total of primary and acquired resistance is known as combined resistance.[2]

Risk factors of MDRTB:

A number of risk factors have been found to contribute to MDR-TB, with the three most significant ones being: previous ant tuberculosis medication treatment (which a high frequency of drug-resistant TB in the community and contact with a patient known to have multidrug resistant tuberculosis (MDRTB) may be unsuitable, partial, or irregular. The likelihood of developing MDR-TB was four to seven times higher in patients with a history of prior therapy than in those without such a history. Co-infection with HIV, socioeconomically disadvantaged populations in slums, cells, correctional facilities, day care

centres, intravenous drug abusers, and other immunocompromised states like transplant recipients, patients receiving anti-cancer therapy, and patients with diabetes mellitus are additional factors that may contribute to an increased risk of MDR. Scientifically, highly technological HIV.[9,10,11]

Control of MDR-TB:

The main goal of MDR-TB control is to stop the disease from ever starting in the first place. Directly Observed Therapy is one short-term method that can help with this. (DOTS), the most economical approach to treating and preventing MDR-TB. At the same time, cautious introduction of second-line medications to treat MDR-TB will be necessary to prevent additional transmission of such strains, as cases of MDR-TB react poorly to short-course chemotherapy. Upload the document To prevent MDR-TB from ever occurring in the first place is the primary objective of its control. One temporary solution for this is Directly Observed Therapy. (DOTS), the least expensive method of treating and guarding against MDR-TB. Furthermore, cautious introduction of second line drugs to treat.[12] [13]In 1998, WHO suggested a work plan to curb the spread of drug resistant tuberculosis and multidrugresistant tuberculosis. Previously referred to "DOTS-Plus," for which WHO had established the Green Light Committee, is now referred to as programmatic management of drug resistant tuberculosis[14] The committee's main objectives were to authorise, manage, and oversee pilot projects according to protocols for Launching trial programmes for "DOTSPlus." A thorough management approach for TB and MDR-TB control is called "DOTSPlus." 2006 saw the introduction of a new Stop TB Strategy in response to the successful deployment and execution of "DOTS-Plus" pilot projects for the treatment of drug-resistant tuberculosis between 2000 and 2005. The detection and treatment of drug-resistant tuberculosis are part of the new Stop TB Strategy.[15]

Effectiveness of DOT's therapy:

The primary goal of two recent surveys was treatment completion as a measure of DOT's efficacy [17] [18]While excellent tuberculosis control requires a high completion rate, completion does not ensure a permanent recovery. In an attempt to determine how frequently and why, we concentrate on failure and default (together with death and transfer, the opposite of completion) and relapse, a common indicator of regimen efficacy.[19,20,21] DOT's efficacy would ideally be evaluated by a randomised, controlled trial that contrasted it with concurrent unsupervised therapy in an otherwise The same configuration (blinding is not possible).

Practically speaking, the new assertion that DOT is preferable to unsupervised treatment is almost exclusively supported by comparisons with historical and/or uncontrolled data, coupled with common sense and clinical impressions[17] [22]- [28] of the 34 studies that were reviewed again, 25 do not discuss pre-DOT results in their districts, and none of them provide a cutting-edge evaluation of failure and relapse rates with DOT versus se With the start of DOT, the remaining nine all reported significant increases in completion and/or cure rates. DOT was first presented in 6 [29] -[34] as a component of a larger project called "DOTS." plan") to improve the program's infrastructure in a neglected area with insufficient tuberculosis control. Despite a sophisticated healthcare system, adherence to unsupervised therapy had been weak in the other three [35]-[37] Just two of these nine research include historical data that can be evaluated. The rates of total relapse, multidrug-resistant relapse, and acquired resistance were lowered to 26%, 15%, and 14% of their previous values, respectively, in metropolitan Texas with nearly systematic DOT use (90.5% of patients) [37] Thailand's DOT increased provincial completion and cure rates.[31]

The WHO presently recommends DOTS as a method for controlling tuberculosis. Treatment for DOTS entails a six-to nine-month course of medication consisting of INH, RIF, pyrazinamide (PZA), and ethambutol (EMB). To get the highest rates of cure, DOTS must be used for the duration of the therapy.[49]

Table:1:- Dose of drug [50]

Drugs	**Therapy per dose**	
	(Thrice a week)	
• Isoniazid.	>	10-15 mg/kg
• Rifampin.	>	10 mg/kg
• Pyrizinamide	>	35 mg /kg
• Ethanbutol	>	30 mg/kg

More multidrug-resistant antibiotics:

- Bedaquiline
- Pretomanid

- Moxifloxacin

❖ **Bedaquiline**:

The Food and Drug Administration (FDA) approved bedaquiline (TMC207 [BDQ]), a novel oral diarylquinoline antimycobacterial agent, in 2012.This makes it one of the newest medications used to treat MDR/XDR-TBBy blocking the proton pump of mycobacterial ATP synthase, BDQ exhibits bactericidal and sterilising effects on M.tb [51] -[54].Crucially, BDQ is efficient in suppressing dormant cell like those found in latent tuberculosis infectionsas well as actively proliferating cells [53]The presence of resistance mechanisms to other antiTB medicines does not affect the effectiveness of BDQ, which has a limited range of activity against mycobacteria [51] [53] [54].The advantages of adding BDQ to the typical second-line antiTB treatment in patients who test positive for MDR/XDR TB have been demonstrated by numerous clinical trials.In these trials, BDQ supplementation to conventional treatment has been shown to be effective in treating MDR/XDR-TB patients.[52] [55] [56]

BDQ has been shown to be effective in treating MDR/XDR-TB patients, but its potential is limited by adverse effects and unexplained elevated mortality rates [54]By lowering the necessary dosage, targeted inhalation of BDQ to the lungs as opposed to systemic oral delivery may help mitigate some of these side effects and improve patient compliance. [57, 59]

Table :2 dose of drug [60]

Drug	Dose
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards OR 200 mg daily for 8 weeks, then 100 mg daily
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	600 mg once daily
Moxifloxacin (400 mg tablet)	400 mg once daily

As BDQ is a solid-state drug product that can often be stored at room temperature and does not require the supervision of healthcare professionals (i.e., injectables), dry powder inhalers (DPIs) are an appealing delivery method that may make the drug more accessible to rural areas.

Adverse drug reaction:[46]

- Ear and labyrinth disorder
- Genetics disorder
- Metabolism disorder
- Nutrition disorder
- Headache
- Nausea.

Role of pharmacist in managing of tuberculosis:

The management of tuberculosis involves pharmacy staff. According to patient pathway studies, pharmacies serve as the main first aid centres for TB patients [38] [39]and may be a good place to find more cases of the disease. Hospital settings present a significant challenge for TB therapy because of the variety of severely ill individuals. Pharmacotherapeutic follow-up is crucial for these patients because they may be at higher risk for drug related problems (DRPs), particularly if they also have other co-occurring disorders. [40]

National pharmacy associations and national TB programmes should work together to implement TB programmes, according to a joint declaration from the World Health Organisation (WHO) and the International Pharmaceutical Federation (FIP) [41]But this hasn't been used in real life very often [40]Extensive research on practice models and characteristics associated with their successful adoption is necessary since enhancing the practice of health professionals entails intricate determinants [42]Insight into this can help design contemporary pharmaceutical care (PC) to enhance patient outcomes for tuberculosis and reduce medical expenses, particularly in nations with high tb burdens. In order to improve TB patient diagnosis and treatment outcomes, this study reviewed different pharmaceutical service models. Next, in order to successfully introduce PC services in TB, we examined future issues and challenges.

For any type of TB treatment to be effective, pharmacists must provide advice to all patients gaining these medications. Above all, they must stress how crucial it is to finish the antibiotic treatment even if they start to feel better. Health care providers may need to take appropriate action to prevent MDR-TB from spreading over the world.[48]

Conclusion:

The threat that multidrug resistant tuberculosis poses to tuberculosis control is a matter of considerable concern. An estimated 400,000 or more cases of MDR-TB are reported each year. Year due to insufficient treatment of drug-resistant and sensitive tuberculosis infections worldwide. Since MDR-TB is a man-made issue, early detection and successful treatment of all TB cases can stop it from spreading. A complete management approach to reduce multidrug-resistant tuberculosis (MDR-TB) is highlighted by the WHO's DOTS-Plus project, now knowns Programmatic management of drug-resistant tuberculosis(PMDT). According to the worldwide plan's aim, programme management of MDR-TB must be increased and laboratory services for correct and quick detection of the disease must be improved. It has to be.[2]

References:

1.Setegn Eshetie, Gemenchu Kumera , and Feleke mogas;multi drug resistance tuberculosis:in Ethiopian setting and associated with previous history of Anti -TB treatment;volume 17,article no.219,(2017),publish:20 March 2017.
2.Rajendra Prasad, Nikhil Guptaand Mandeep sing;multidrug-resistant tuberculosis:trend and control ;university of Delhi and department of medicine. ERA's Lucknow medical college of Lucknow (UP)India.
3. Jawahar MSS. Multidrug resistant tuberculosis. ICMR Bull 1999;29:105-14.
4.Tadele girum ,Ebrahim muktar ,;Epidemiology of multidrug resistance tuberculosis in Ethiopia ;publish 14 june 2018.
5.Michele Mondoni [1], Laura Saderi [2], Giovanni Sotgiu [3];Novel treatments in multidrug resistanttuberculosis;Volume 59, August 2021, Pages 103-115.
6.A.H. Diacon et al.14day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial Lancet (2012)
7.World Health Organisation global TB report 2017.genewa Switzerland:WHO press ;2017
8.World Health Organisation definition And reporting Framework for TB -2013 revision genewa :WHO press ;2013
9. Prasad R. Multidrug resistant tuberculosis and existing Health system in India (Editorial). Chest (IndianEdition)2011;3:65-7.
10. Kant S, Maurya AK, Kushwaha RA, Nag VL, Prasad R.Multi-drug resistant tuberculosis: an iatrogenic problem. Biosci Trends 2010;4:48-55.
11. Prasad R. MDR TB: current status. Indian J Tub 2005; 52:121-31.
12. Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, et al. Standard short course chemotherapy for Drug resistant tuberculosis: treatment outcome in six Countries. JAMA 2000;283:2537-45.
13. Prasad R. Multidrug and extensively drug-resistant TB(M/XDR-TB): problems and solutions. Indian J Tub
14 . DOTS-Plus and Green Light Committee. Available at:
www.who.int/gtb/policyrd /dotsplus.htm. Accessed on June 1, 2014.
15. The Global MDR-TB & XDR-TB response Plan 2007-2008.World Health Organization Document, 2007WHO/HTM/TB/2007.387.
16. https://images.app.goo.gl/cSVfi3V6T7ZfGCRf6
17.Bayer R, Stayton C, Desvarieux M, Healton C, Landesman S, Tsai W-Directly observed therapy and treatment completion for tuberculosis:in the United States: Is universal supervised therapy necessary? Am JPublic Health 88: 1052–8, 1998.

18.Chaulk CP, Kazandjian VA. Directly observed therapy for treatment completion of pulmonary tuberculosis. JAMA 279: 943–8, 1998.
19.owie RL, Brink BA. Short-course chemotherapy for pulmonary tuberculosis with a rifampicin-isoniazid-pyrazinamide combination tablet. S Afr Med J 77: 390–1, 1990.
20.Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tubercu-losis undertaken by the British Medical Research Council Tuberculo-sis Units, 1946–1886, with relevant subsequent publications. Int J Tu-berc Lung Dis 3: S231–79, 1999.
21.Hopewell P, Cynamon M, Starke J, Iseman M, O'Brien R. Evaluation ofnew antiinfective drugs for the treatment and prevention of tubercu-losis. Clin Infect Dis 15: S82–95, 1992.
22. Bal Subramanian VN, Oommen K, Samuel R. DOT or not? Direct observation of antituberculosis treatment and patient outcomes, KeralaState, India. Int J Tuberc Lung Dis 4: 409–13, 2000.
23.El-Sadr W, Medard F, Barthaud V. Directly observed therapy for tu-Berculosis: The Harlem Hospital experience. Am J Public Health 86:1146–9, 19969
24 Fujiwara PI, Larkin C, Frieden TR. Directly observed therapy in NewYork City: History, implementation, results, and challenges. Clin ChestMed 18: 135–48, 1997.
25.Mathema B, Pande SB, Jochem K, Houston RA, Smith I, Bam DS, Mc-Gowan JE. Tuberculosis treatment in Nepal: A rapid assessment of Government centers using different types of patient supervision. Int JTuberc Lung Dis 5: 912–9, 2001.
26. Ormerod LP. Directly observed therapy (DOT) for tuberculosis: Why, When, how and if?
Thorax 54(Suppl 2): S42–5, 1999.
27.Weis SE, Slocum PC, Blais FX, King B, Nunn M, Matney GB, Gomez E,Foresman BH. The effect of directly observed therapy on the rates ofDrug resistance and relapse in tuberculosis. N Engl J Med 330: 1179–84,1994.
28.Weis SE. Universal directly observed therapy. Clin Chest Med 18:155–63, 1997.
29.China Tuberculosis Control Collaboration. Results of directly ob-Served shortcourse chemotherapy in 112,842 Chinese patients withSmear-positive tuberculosis. Lancet 347: 358–62, 1996
30.Chowdhury AMR, Chowdhury S, Islam MN, Islam A, Vaughan JP. Con-Trol of tuberculosis by community health workers in Bangladesh.Lancet 350: 169–72, 1997.
31.Kamolratanakul P, Sawert H, Lertmaharit S, Kasetjaroen Y, Akksilp S,Tulaporn C, Punnachest K, Na-Songkhla S, Payanandana V. Random-Ized controlled trial of directly observed treatment (DOT) for patientsWith pulmonary tuberculosis in Thailand. Trans R Soc Trop Med Hyg93: 552–7, 1999.
32.Kumaresan JA, Ahsan Ali AKM, Parkkali LM. Tuberculosis control in Bangladesh: Success of the DOTS strategy. Int J Tuberc Lung Dis 2:992–8, 1998.
33.Neher A, Breyer G, Shrestha B, Feldman K. Directly observed inter-Mittent shortcourse chemotherapy in the Kathmandu valley. TubercleLung Dis 77: 302–7, 1996.
34.Zalesky R, Abdullajev F, Khechinashvili G, Safarian M, Madaras T,Grzemska M, Englund E, Dittmann S, Raviglione M. Tuberculosis con-Trol in the Caucasus: Successes and constraints in DOTS implementa-Tion. Int J Tuberc Lung Dis 3: 394–401, 1999.
35.Caminero JA, Pavon JM, Rodriguez de Castro F, Diaz F, Julia G, CaylaJA, Cabrera P. Evaluation of a directly observed six month fully inter-Mittent treatment regimen for tuberculosis in patients suspected ofPoor compliance. Thorax 51: 1130–3, 1996.
36.Schluger N, Ciotoli C, Cohen D, Johnson H, Rom WN. ComprehensiveTuberculosis control for patients at high risk for noncompliance. Am JRespir Crit Care Med 151: 1486– 90, 1995.
37.Weis SE, Slocum PC, Blais FX, King B, Nunn M, Matney GB, Gomez E,Foresman BH. The effect of directly observed therapy on the rates ofDrug resistance and relapse in tuberculosis. N Engl J Med 330: 1179–841994.
38.Lestari B.W., McAllister S., Hadisoemarto P.F., Afifah N., Jani I.D., Murray M., van Crevel R., Hill P.C., Alisjahbana B. Patient Pathways and Delays to Diagnosis and Treatment of Tuberculosis in an Urban Setting in Indonesia. Lancet Reg. Health West.
Pac. 2020;5:59. Doi: 10.1016/j.lanwpc.2020.100059. [PMC free article] [PubMed] [CrossRef] [Google Scholar]

39.Surya A., Setyaningsih B., Suryani Nasution H., Gita Parwati C., Yuzwar Y.E., Osberg M., Hanson C.L., Hymoff A., Mingkwan P., Makayova J., et al. Quality Tuberculosis Care in Indonesia: Using Patient Pathway Analysis to Optimize Public-Private Collaboration. J.
Infect. Dis. 2017;216:S724–S732. Doi: 10.1093/infdis/jix379. [PMC free article] [PubMed]
[CrossRef] [Google Scholar]
40.De Resende N.H., de Miranda S.S., Ceccato M.D.G.B., Haddad J.P.A., Reis A.M.M., da Silva D.I., Carvalho W.D.S. Drug Therapy Problems for Patients with Tuberculosis and HIV/AIDS at a Reference Hospital. Einstein. 2019;17:eAO4696. Doi:
10.31744/einstein_journal/2019AO4696. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
41.Nakatani H., Buchmann M. Working Together: WHO and FIP. FIP; Hyderabad, India: 2011. [Google Scholar]
42.Flottorp S.A., Oxman A.D., Krause J., Musila N.R., Wensing M., Godycki-Cwirko M., Baker R., Eccles M.P. A Checklist for Identifying Determinants of Practice: A Systematic Review and Synthesis of Frameworks and Taxonomies of Factors That Prevent or Enable Improvements in Healthcare Professional Practice. Implement. Sci. 2013;8:35. Doi:
10.1186/1748-5908-8-35. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
43.Kaufmann S.H., Schaible U.E. 100th anniversary of Robert Koch's Nobel Prize for the discovery of the tubercle bacillus. Trends Microbiol. 2005;13:469–475. Doi:
10.1016/j.tim.2005.08.003. [PubMed] [CrossRef] [Google Scholar]
44.World Health Organisation . Global Tuberculosis Report 2022. World Health Organization; Geneva, Switzerland: 2022. [(accessed on 1 February 2023)]. Licence: CC BY-NC-SA 3.0 IGO.
Available online:
https://www.who.int/publications/i/item/9789240061729 [Google Scholar]
45. https://images.app.goo.gl/2CLCM9TaTFsv81oX6
46.vigiaccess.
47. https://images.app.goo.gl/isCevPV38nLRzpjM6
48.Yuettec terric Rph ;the role of pharmacist in multidrug-resistant tuberculosis:Aug.1,2003
49.Leonard Moises..Anne's Degroot ;Mycobacterium tuberculosis;2009
50.https://images.app.goo.gl/kjafiBXnKh4EhMEi8
51.Chahine E.B., Karaoui L.R., Mansour H. Bedaquiline: A novel diarylquinoline for multidrug-resistant tuberculosis. Ann. Pharmacother. 2014;48:107–115. Doi:
10.1177/1060028013504087. [PubMed] [CrossRef] [Google Scholar]
52.Diacon A.H., Pym A., Grobusch M., Patienta R., Rustomjee R., Page-Shipp L., Pistorius C., Krause R., Bogoshi M., Churchyard G., et al. The diarylquinoline TMC207 for multidrugresistant tuberculosis. N. Engl. J. Med. 2009;360:2397–2405. Doi: 10.1056/NEJMoa0808427. [PubMed] [CrossRef] [Google Scholar]
53.Fox G.J., Menzies D. A review of the evidence for using bedaquiline (TMC207) to treat multi-drug resistant tuberculosis. Infect. Dis. Ther. 2013;2:123–144. Doi: 10.1007/s40121-
013-0009-3. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
54.Field S.K. Bedaquiline for the treatment of multidrug-resistant tuberculosis: Great promise or disappointment. Ther. Adv. Chronic Dis. 2015;6:170–184. Doi:
10.1177/2040622315582325. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
55.Diacon A.H., Pym A., Grobusch M.P., de los Rios J.M., Gotuzzo E., Vasilyeva I., Leimane V., Andries K., Bakare N., De Marez T., et al. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N. Engl. J. Med. 2014;371:723–732. Doi:
10.1056/NEJMoa1313865. [PubMed] [CrossRef] [Google Scholar]
56.Chesov D., Heyckendorf J., Alexandru S., Donica A., Chesov E., Reiman M., Crudu V., Botnaru V., Lange C. Impact of bedaquiline on treatment outcomes of multidrug-resistant tuberculosis in a high-burden country. Eur. Respir. J. 2020;57:2002544. Doi:
10.1183/13993003.02544-2020. [PubMed] [CrossRef] [Google Scholar]
57.Zhao Y., Li F., Liu Y., Shi Y., Li Z., Cao G., Zhu W. Comparison of efficacy of inhaled and intravenous corticosteroid on pregnant women with COPD and the effects on the expression of PCT and hs-CRP. Exp. Ther. Med. 2018;15:4717–4722. [PMC free article] [PubMed]

[Google Scholar]
58. Borghardt J.M., Kloft C., Sharma A. Inhaled therapy in respiratory diseases: The complex interplay of pulmonary kinetic processes. Can. Respir. J. 2018;2018:2732017. Doi: 10.1155/2018/2732017. [PMC free article] [PubMed] [CrossRef] [Google Scholar]
59.. Videira M.A., Llop J., Sousa C., Kreutzer B., Cossio U., Forbes B., Vieira I., Gil N., Silva-Lima B. Pulmonary administration: Strengthening the value of therapeutic proximity.
Front. Med. 2020;7:50. Doi: 10.3389/fmed.2020.00050. [PMC free article] [PubMed]
[CrossRef] [Google Scholar]
60.https://images.app.goo.gl/cv47jLZh921zrNYY7