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# Patterns of adverse drug reactions in patients with drug resistant tuberculosis in Eswatini: a retrospective cohort study

Alemayehu Lelisa Duga

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**Effets indésirables des médicaments de latuberculose pharmaco-  
résistante en Eswatini et comparaison des caractéristiques des EI  
avec la base de données mondiale de pharmacovigilance : études  
prospectives et rétrospectives**

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Sous la direction du Professeur Francesco Salvo (Directeur de thèse), Professeur Albert  
Figueras (Co-Directeur de thèse), et du Professeur Associé Alexander Kay (Co-Directeur  
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## **ABSTRACT**

Drug-resistant tuberculosis (DR-TB) is a critical public health concern, particularly in developing countries like Eswatini. The treatment of DR-TB requires the combination of several second-line TB medicines over several months, which can lead to adverse drug reactions (ADRs). Our thesis examined the safety profiles of DR-TB medicines at both global and national levels, using a multifaceted approach that provided a comprehensive understanding of the safety issues associated with these treatments. Firstly, we evaluated the magnitude and characteristics of DR-TB-related ADRs by analyzing reports from the World Health Organization (WHO) database (VigiBase). We then investigated the patterns of ADRs in patients with DR-TB in all treatment sites in the Kingdom of Eswatini. Finally, we analyzed ADRs associated with the use of repurposed medicines focusing on clofazimine (CFZ) and linezolid (LZD) in a prospective cohort study at one of the regions in Eswatini.

The analysis of individual case safety reports (ICSR) from VigiBase revealed that pyrazinamide was the most reported medicine associated with ADRs, followed by ethionamide and cycloserine. The study found that almost half of the reports required complete withdrawal of the suspected medicine(s), which significantly impacts treatment adherence and ultimately leads to drug resistance. The study underlines the urgent need to remain alert for potential ADRs throughout treatment, emphasizing the immediate action required to prevent treatment failure.

The retrospective cohort study provides crucial insights into the patterns of ADRs in 670 patients with DR-TB in Eswatini. The results reveal that 44% of patients experienced at least one ADR, with bedaquiline being associated with the highest number of ADRs. The study also identified age as a significant factor in the occurrence of peripheral neuropathy and arthralgia-related ADRs. These findings underscore the need for enhanced safety monitoring of patients undergoing DR-TB treatment to ensure prompt and appropriate ADR management, thereby reducing the risk of treatment failure.

The findings of the prospective cohort study indicate that 80% of patients treated with CFZ or LZD experienced adverse drug reactions (ADRs). CFZ was associated mainly with mild ADRs, whereas LZD was linked to more serious ADRs, such as anemia, peripheral neuropathy, and optic

neuritis. These findings underscore the importance of closely monitoring ADRs linked to these repurposed medicines throughout the duration of treatment.

This thesis significantly contributes to understanding DR-TB medicines' safety profiles in various contexts. The studies underscore the critical importance of closely monitoring ADRs linked to these medicines throughout the treatment duration to ensure patient safety and positive treatment outcomes. Adverse drug reactions, whether they are directly related to medicines or not, might lead to low treatment adherence and discontinuation. Such outcomes can further compromise the effectiveness of the treatment regimen, leading to incomplete eradication of the bacteria and drug resistance. Therefore, it is important to monitor DR-TB medicines' safety to ensure ADR management, thus lowering the chance of treatment failure. Understanding the impact of ADRs and taking proactive measures to address them will significantly contribute to more favorable treatment outcomes and facilitate the comprehensive eradication of DR-TB, a global health priority.

**Keywords:** pharmacovigilance, public health, Drug-Resistant Tuberculosis, Medicine safety, adverse drug reaction, safety surveillance

**Title:** Patterns of Adverse Drug Reactions in Patients with Drug-Resistant Tuberculosis in Eswatini and comparison of AE Reports characteristics with a worldwide database: A Prospective and Retrospective Studies

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## RÉSUMÉ

La tuberculose multirésistante (TB-MR) constitue un problème de santé publique important, en particulier dans les pays en développement comme l'Eswatini. Le traitement de la TB-MR nécessite la combinaison de plusieurs médicaments pendant plusieurs mois, ce qui peut entraîner des réactions indésirables médicamenteuses (ADR). L'objectif de cette thèse était de caractériser et de décrire une analyse complète des profils de sécurité des médicaments contre la tuberculose multirésistante utilisés dans le traitement de la TB-MR au niveau mondial et national. Tout d'abord, nous avons évalué l'ampleur et les caractéristiques des réactions indésirables médicamenteuses liées à la TB-MR grâce à une analyse des rapports de la base de données (VigiBase) de l'Organisation mondiale de la santé (OMS). Nous avons ensuite étudié les caractéristiques des ADR chez les patients atteints de TB-MR dans tous les sites de traitement du Royaume de l'Eswatini. Enfin, nous avons réalisé une analyse des ADR associées à l'utilisation de la clofazimine (CFZ) et de la linézolide (LZD) dans une étude de cohorte prospective.

L'analyse des rapports de sécurité individuels (ICSR) provenant de la VigiBase a montré que la pyrazinamide était le médicament le plus souvent associé aux ADR, suivie de l'éthionamide et de la cyclosérine. L'étude a révélé que près de la moitié des rapports nécessitaient le retrait complet du ou des médicaments suspectés, ce qui a un impact sur l'observance du traitement et conduit finalement à la résistance aux médicaments.

L'étude de cohorte rétrospective a analysé les profils des ADR chez 670 patients atteints de TB-MR en Eswatini. Les résultats ont montré que 44% des patients avaient au moins une réaction indésirable médicamenteuse (ADR), le bédaquiline étant associé au plus grand nombre d'ADR. L'étude a révélé que l'âge est un facteur significatif dans l'apparition des réactions indésirables médicamenteuses (ADR) liées à la neuropathie périphérique et à l'arthralgie. L'analyse de cet échantillon a montré que près de la moitié des patients présentaient au moins une réaction indésirable médicamenteuse, et que près d'un tiers d'entre eux étaient graves. L'étude souligne l'importance de renforcer la surveillance de la sécurité des patients traités pour la TB-MR pour garantir une gestion rapide et appropriée des ADR, réduisant ainsi le risque d'échec du traitement.

Les résultats de l'étude de cohorte prospective ont montré que 80% des patients traités par CFZ ou LZD ont développé des ADR. La CFZ était associée principalement à des ADR légers, tandis que



la LZD était associée à des ADR plus graves, notamment l' anémie, neuropathie périphérique et la neurite optique.

Cette thèse contribue à la compréhension des profils d'innocuité des médicaments contre la tuberculose pharmacorésistante dans différents contextes. Les études soulignent l'importance de surveiller de près les effets indésirables liés à ces médicaments tout au long de la durée du traitement afin de garantir la sécurité des patients et des résultats positifs du traitement. Les effets indésirables des médicaments, qu'ils soient directement liés aux médicaments ou non, peuvent entraîner une faible observance du traitement et l'arrêt du traitement. De tels résultats peuvent compromettre davantage l'efficacité du schéma thérapeutique, conduisant à l'éradication incomplète de la bactérie et à la résistance aux médicaments. Par conséquent, il est essentiel de surveiller l'innocuité des médicaments contre la tuberculose pharmacorésistante pour assurer la prise en charge des effets indésirables, réduisant ainsi le risque d'échec du traitement. Comprendre l'impact des effets indésirables et prendre des mesures proactives pour y faire face contribuera à des résultats thérapeutiques plus favorables et facilitera l'éradication complète de la tuberculose pharmacorésistante.

**Mots clés:** pharmacovigilance, santé publique, tuberculose multirésistante, sécurité des médicaments, réactions indésirables aux médicaments, surveillance de sécurité

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## LIST OF MAIN ABBREVIATIONS

ADR	Adverse Drug Reaction
aDSM	Active tuberculosis drug-safety monitoring and management
BDQ	Bedaquiline
BPaL	Bedaquiline, pretomanid and linezolid
CFZ	Clofazimine
CTCAE	Common Terminology Criteria for Adverse Events
DI	Drug interactions
DOT	Directly observed treatment
DR-TB	Drug-resistant Tuberculosis
DST	Drug susceptibility test
DTMGIT	Mycobacteria Growth Indicator Tube
ETO	ethionamide
FDA	Food Drug Administration
FDR	Fluoroquinolone drug-resistance
HIV	Human Immunodeficiency Virus
ICSRs	Individual Case Safety Reports
IPT	Isoniazid preventive therapy
KM	Kanamycin
LFX	Levofloxacin
LPA	Line Probe Assay
LTI	Latent TB infection
LZD	Linezolid
MAH	Marketing Authorization Holders
MDR	Multidrug resistance
MDR-TB	Multidrugresistant Tuberculosis
MFX	Moxifloxacin
NPC	National Pharmacovigilance Center
NTCP	National Tuberculosis Control Programme
PAS	Para-amino-salicylic acid
PIDM	Programme for International Drug Monitoring

PV	Pharmacovigilance
PZA	Pyrazinamide
RR	Rifampicin Resistance
RR-TB	Rifampicin Resistant Tuberculosis
SLDs	Second Line Drugs
SPSS	Statistical Package for Social Science
STR	Shorter treatment regimen
UMC	Uppsala Monitoring Centre
WHO	World Health Organization
XDR-TB	Extensively drug-resistant TB

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# **CHAPTER 1. INTRODUCTION**

## 1.1 BACKGROUND

Tuberculosis (TB) remains the world's leading cause of death, exceeding Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS).<sup>1,2</sup> Since the introduction of chemotherapy to treat *Mycobacterium tuberculosis* in 1943, the incidence of drug resistance has increased worldwide.<sup>3</sup> In 2022, an estimated 7.5 million people who developed TB were diagnosed and notified.<sup>4</sup> About 500,000 new cases of multidrug and rifampicin-resistant *tuberculosis* (MDR/RR-TB) are estimated to emerge annually, but only one in three cases were reported by countries in 2018.<sup>1</sup>

Multi-drug-resistant TB cases were first reported in Eswatini in 2006.<sup>5</sup> According to the 2022 TB annual report, the prevalence of DR-TB in new cases in Eswatini was 8.6%, while in previously treated cases, it was 18%. A total of 144 cases were notified in the kingdom in 2021.<sup>6</sup> However, according to the second nationwide anti-TB drug resistance survey (DRS) conducted in 2017/2018, there could be under-reporting of DR-TB cases due to the presence of a localized Rifampicin-resistant-TB mutant strain that cannot be detected by the currently existing diagnostic techniques, which are GeneXpert MTB/RIF, Line Probe Assay (LPA), and Mycobacteria Growth Indicator Tube(MGIT).<sup>6</sup>

The Kingdom also suffers a very high HIV burden, with recent figures showing a prevalence rate of 27.2% among the 15-49 years age group. However, between Swaziland HIV Impact Measurement Survey(SHIMS) 1 and 2 conducted in 2011 and 2017, respectively, the annual incidence rate of HIV has nearly halved, from 2.38% to 1.36%.<sup>7,8</sup> Regarding DR-TB, the HIV/DR-TB coinfection rate was 71% in 2021, while the DR-TB death/case fatality rate stood at 8%, and the percentage of patients lost to follow-up was 5%.<sup>6</sup>

Despite significant progress in the availability of improved diagnostics and more effective medicines for earlier detection and higher success rates among patients with MDR/RR-TB in several countries, the overall global treatment success rate reported in 2020 reached only 60% for MDR/RR-TB patients, this was an improvement from 60% in 2021 and up from 50% in 2012.<sup>4</sup> Regarding Eswatini, a significant increase in the DR-TB treatment success rate from 53% in 2013 to 79% in 2022 is documented in Eswatini.<sup>95</sup>

## 1.2 CAUSES OF DR-TB

Drug-resistant bacterial infections are estimated to be the cause of 1.3 million fatalities worldwide each year, making antimicrobial resistance (AMR) a serious global health and socioeconomic concern.

This problem afflicts people of all ages and places, but low- and middle-income nations are the most severely affected.<sup>10</sup> Antimicrobial resistance, in general, is a public health crisis mainly caused by the misuse and mismanagement of antibiotics. To address this challenge, a new resolution aimed at expediting both national and global solutions has been passed by Seventy-seventh World Health Assembly (WHA) delegates on May 30<sup>th</sup>, 2024, marking a significant step towards addressing the growing issue of AMR. In line with the WHO's operational and strategic aims for 2025–2035, the resolution promotes the prevention of infections; universal access to affordable, quality diagnosis and appropriate treatment of infections; strategic information, science, and innovation; and effective governance and financing of the human health sector response to AMR.<sup>11</sup>

The development and spread of antimicrobial resistance, including DR-TB, are accelerated when treatments are incorrect or inadequate treatment, such as the use of incorrect medicines, insufficient drug combinations/monotherapy, or poor adherence to treatments and transmission in communities and facilities.<sup>12–14</sup> Additionally, the rise in the prevalence of DR-TB is also attributed to factors such as poverty, vulnerability, and social risk.<sup>15</sup>

In countries with a high prevalence of DR-TB cases, primary resistance accounts for up to 75% of tuberculosis cases.<sup>16</sup> The primary resistance is the presence of drug resistance to one or more anti-tuberculosis drugs in a person who has received either no or less than one month of prior tuberculosis chemotherapy.<sup>17,18</sup> Secondary or acquired resistance, on the other hand, occurs due to insufficient treatment, leading to the selection of spontaneously resistant strains. It can only develop in patients who have received at least four weeks of anti-TB chemotherapy. The rate of initial drug resistance is seen as an indicator of treatment program quality, with a high rate suggesting a poor treatment program.<sup>16</sup>

Drug-resistant TB(DR-TB) cases are also classified into different types based on drug susceptibility testing (DST) of clinical isolates confirmed to be *M. tuberculosis*. According to the WHO 2018/2019 updated DR-TB guidelines, the classification based on the resistance type includes:<sup>19,20</sup> Mono-resistance- resistance to one first-line anti-TB drug only; poly-resistance: resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin together; multidrug resistance (MDR): resistance to at least both isoniazid and rifampicin; pre-XDR-TB- resistance to either fluoroquinolone or injectable in addition to MDR; Fluoroquinolone drug-resistance (FDR): resistance to any fluoroquinolone in addition to multidrug-resistance; XDR-TB- resistance- resistance to both



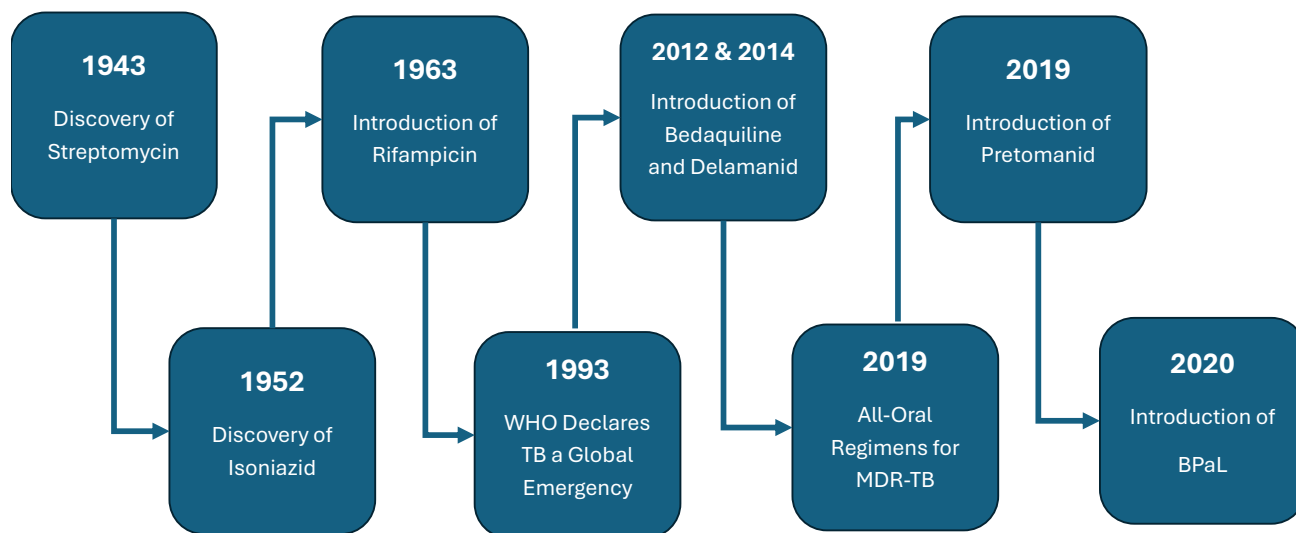
fluoroquinolone and injectable in addition to multidrug-resistance; Rifampicin Resistance (RR): resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin in the form of monoresistance, poly-resistance, MDR, Pre-XDR, and XDR. Presumptive DR-TB patient: Symptomatic patients with significant risk or with a history of contact with a patient diagnosed with DR-TB and has been started on treatment in the absence of confirmed laboratory diagnosis, more especially children.

### **1.3 EVOLUTION OF DR-TB TREATMENT**

The evolution of DR-TB treatment has been a complex journey marked by the introduction and removal of various medicines based on their benefits and risk profiles. The treatment of TB is an effective intervention in the control of TB epidemics globally. It saved 53 million lives globally between 2000 and 2016.<sup>21</sup> However, the journey of DR-TB treatment has faced many challenges. The discovery of streptomycin in 1945 marked a turning point in the fight against TB, but the rapid development of resistance undermined its effectiveness.<sup>22</sup> To combat this, para-aminosalicylic acid(PAS) was introduced in the same year and found to reduce the occurrence of drug resistance when combined with streptomycin.<sup>23</sup> Isoniazid, introduced in 1952, began the modern era of TB treatment due to its affordability and safety. Due to better tolerance, ethambutol replaced PAS in the early 1960s, and rifampin became a cornerstone of therapy in the 1970s. The addition of pyrazinamide(PZA) allowed for a reduction in treatment duration to six months.<sup>23</sup>

Despite these advancements, some strains of TB bacteria resisted standard TB medicines through genetic change. Effective treatment of this emerging threat requires prolonged use of multiple second-line medicines, which are more expensive and toxic than first-line medicines yet less efficacious.<sup>24,25</sup> In response to the growing crisis, three new anti-TB medicines have been developed and included in the treatment protocol between 2010 and 2020. Bedaquiline(BDQ) was approved by the FDA in 2012, the first new treatment for MDR-TB in 40 years.<sup>26</sup> Following BDQ, delamanid(DLM) was also granted conditional approval by the European Medicine Agency in April 2014 for treating DR-TB.<sup>27</sup> The third new DR-TB medicine joined the response mechanism was pretomanid, which was developed by the TB Alliance and approved by the U.S. FDA in August 2019.<sup>28</sup> The Nix-TB trial in South Africa tested a novel regimen (BPaL) consisting of BDQ, pretomanid, and linezolid(LZD), achieving a cure rate of 85–90% after a 6-month course of treatment.<sup>29</sup>

Pretomanid, in combination with BDQ and LZD, was recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of a specific limited population of adults with pulmonary extensively drug-resistant (XDR-TB) or treatment-intolerant or nonresponsive MDR-TB.<sup>30,31</sup> Even though data are not available on the efficacy, safety, and tolerability of BPaL, WHO recommends using a shorter, all-oral, BDQ-containing regimen instead of the standardized shorter regimen with an injectable for treatment-eligible MDR/RR-TB patients.<sup>31</sup>



*Figure 1: Key milestones of DR-TB medicine evolution (illustration by the author)*

The WHO has been actively strengthening drug resistance surveillance and promoting research and innovation to develop rapid diagnostics and treatments for DR-TB.<sup>32</sup> By 2017, at least 62 countries had introduced shorter regimens for MDR-TB treatment, and 68 countries had started using BDQ.<sup>29</sup> Updated WHO guidelines in 2019 changed the approach to MDR-/XDR-TB treatment, reflecting the evidence from new studies.<sup>19,31</sup>

According to WHO and Eswatini consolidated guidelines on DR-TB, the MDR-TB treatment regimens are currently organized into three levels for regimen construction, balancing efficacy and safety.<sup>19,33</sup>

*Table 1: Grouping of medicines recommended for use in longer MDR-TB regimens*

Groups and steps	Medicine	Abbreviation
Group A: Include all three medicines	Levofloxacin <b>OR</b>	LFX
	Moxifloxacin	MFX
	Bedaquiline	BDQ
	Linezolid	LZD
Group B	Clofazimine	CFZ
	Cycloserine <b>OR</b>	CS
	Terizidone	TRD
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used.	Ethambutol	E
	Delamanide	DLM
	Pyrazinamide	PZA
	Imipenem–cilastatin <b>OR</b>	IPM–CLN
	Meropenem	MPM
	Amikacin <b>OR</b>	AM
	(Streptomycin)	S
	Ethionamide <b>OR</b>	ETHO
	Prothionamide	PTO
	P-aminosalicylic	PAS

*Source: WHO consolidated guidelines on tuberculosis Module 4: Treatment Drug-resistant tuberculosis treatment 2022 update.*<sup>34</sup>

These are Group A (LFX, MFX, BDQ, LZD), Group B (CFZ, CS, TRD), and Group C (E, DLM, PZA, IMP-CLN, MPM, AM, S, ETO, PTO, PAS ).<sup>33</sup>

The principle of regimen design for MDR-TB treatment includes: Treatment regimen design is to be individualized to the extent possible guided by drug susceptibility test(DST) results before treatment initiation, TB treatment history, contact DST, and co-morbidities.<sup>19</sup> Having at least five effective TB medicines to be constituted (Group A Medicines to be prioritized; Group B Medicines to be added next; and Group C Medicines to be included to complete the regimens and when agents from Groups

A and B cannot be used).<sup>33,35</sup> It is noteworthy that Kanamycin and capreomycin are no longer among the recommended medicines for the treatment of DR-TB.<sup>19,20</sup>

Overall, the journey of DR-TB treatment has been one of continuous adaptation and improvement, supported by progressive research and development to control TB epidemics and save lives globally effectively.

#### **1.4 DR-TB TREATMENT-ASSOCIATED ADVERSE DRUG REACTIONS**

The growing public health threat posed by DR-TB and the complex nature of its treatment necessitate a closer look at safety and ADR management. Given the significant impact that ADRs can have on treatment outcomes and the overall effectiveness of tuberculosis control programs, establishing the safety profile of DT-TB medicines is critical.

Various studies have indicated that ADRs are highly prevalent among patients treated with second-line anti-TB drugs, ranging from 20% to 90%.<sup>36-38</sup> ADRs attributed to MDR-TB treatment can lead to the withdrawal of one or more drug regimens from about 21.1% of patients due to uncontrolled side effects.<sup>39</sup> Serious AEs may lead to refusal and discontinuation of treatment before smear conversion, which might lead to the transmission of resistant strains of *Mycobacterium tuberculosis* to the community.<sup>40</sup> Studies conducted in South Africa, Nigeria, China and India indicate that a higher proportion of patients required permanent discontinuation of the offending drug associated with ADRs.<sup>36,41-44</sup> According to another study conducted in Latvia, over two-thirds of MDR-TB cases require discontinuation of at least one drug due to ADRs.<sup>45</sup> According to DOTS-plus initiative data collected from five different DOTS-plus sites, only 2% of patients stopped treatment, but 30% required removal of the offending drug(s) from the regimen due to AEs.<sup>46</sup>

Common ADRs due to medicines used in the treatment of DR-TB are joint pain, nausea, hearing disturbances, gastrointestinal disturbance, depression, itching, hypothyroidism, dizziness, seizures, and hepatitis.<sup>37,41,47-49</sup> One of the controlled clinical trials conducted in India demonstrated that a therapeutic regimen without rifampicin was a risk factor for arthralgia and suggests that rifampicin can indirectly offer protection against arthralgia.<sup>50</sup> Another study shows that fluoroquinolones, CFZ, and BDQ had the lowest incidence of AEs leading to permanent treatment discontinuation. In contrast, second-line injectable medicines, aminosalicylic acid, and LZD had the highest incidence.<sup>51</sup>

Joint pain is considered as frequently associated with PZA and E due to their property to induce hyperuricemia.<sup>52</sup> Pyrazinamide is a potent urate retention agent, causing a greater than 80% reduction in renal clearance of uric acid at a 300-mg therapeutic daily dose.<sup>53</sup> Hyperuricemia has been reported in 43% to 100% of patients treated with PZA (alone or in combination).<sup>52,54</sup> Nausea and vomiting are common ADRs of ETO/PTO, BDQ, DLM, PAS, INH, E, and PZA. Persistent vomiting and abdominal pain may result from developing lactic acidosis and/or hepatitis secondary to medications.<sup>20,55</sup>

Various studies associate optic neuritis with LZD.<sup>39</sup>, it is also claimed that the toxicity of LZD is dose-dependent.<sup>56</sup> A retrospective study conducted to assess the safety and efficacy of LZD in DR-TB treatment indicated that twice-daily administration produced more side effects than once-daily dosing, with no difference in efficacy found.<sup>57</sup> In addition to LZD, ETO, E, and PTO can cause optic neuritis.<sup>33</sup>

Although generally well tolerated, DLM has been associated with QT prolongation, which is mainly dose-related.<sup>58</sup> Fluoroquinolones, CFZ, and BDQ are associated with the QTc interval prolongation as significant toxicities during usage.<sup>59</sup> ADRs like psychosis and other common psychiatric problems are associated with the usage of CS and TRD.<sup>20</sup> In Lesotho, 16% of patients with MDRTB experienced psychosis from CS.<sup>60</sup>

Serious ADRs are expected during the first six months of second-line TB treatment, and they are significantly associated with discontinuation, non-adherence to the treatments, and defaulter outcomes.<sup>42,44</sup> According to Petros I. *et al.*, 71%, 63%, and 40% of patients experienced one or more mild, moderate, or severe ADRs, respectively, among HIV/MDR-TB Co-infected patients receiving antiretroviral and second-line anti-TB concomitantly.<sup>60</sup> A study of ADRs in an Integrated Home-Based Treatment Program for MDR-TB and HIV in KwaZulu-Natal indicates that the most common severe ADRs were hypothyroidism (36%) and psychosis (5%).<sup>61</sup>

In patients receiving R and PZA for two months for the treatment of latent TB infection (LTBI), a much higher occurrence of hepatotoxicity than in patients receiving only isoniazid preventive therapy(IPT) was observed.<sup>62</sup> The combination of PZA and LFX appears to be a poorly tolerated regimen.<sup>63</sup> One of the retrospective study conducted in South Korea indicated that one or more side effects were observed in 37.1% of the patients, and these side effects led to the withdrawal of 1 or more medicines from the regimen of individualized treatment given for 17.2% of the patients.<sup>39</sup>

Furthermore, antiretrovirals and DR-TB medicines have overlapping toxicities, or in some cases additive, toxicities. The rates of ADRs in the concomitant treatment of DR-TB and HIV are not well known.<sup>20,64</sup> A systematic review and meta-analysis by G. Lazarus *et al.* indicated that HIV co-infection independently increased the risk of developing ADRs during DR-TB treatment by 12%.<sup>65</sup> Adverse drug reactions(ADRs) such as hearing loss, nephrotoxicity, and depression were notably higher in patients with HIV co-infection, with the concomitant use of antiretroviral rather than HIV-related immunosuppression.<sup>65</sup> Another systematic study conducted in high HIV prevalence settings found that nearly 83% of patients on DR-TB treatment experienced one or more ADRs. However, no significant association was found between HIV co-infection and the occurrence of ADRs.<sup>66</sup> Therefore, the concomitant treatment of HIV/TB co-infection presents a complex challenge due to overlapping and additive toxicities, highlighting the need for increased pharmacovigilance and further research into safer treatment regimens to improve patient outcomes.

**Table 2: Common ADRs of DR-TB medicines and suggested management**<sup>19,20,67</sup>

ADRs	Suspected medicines/associated medicines	Recommended management
Arthralgia	Z, BDQ, FQS, INH	<ul style="list-style-type: none"> <li>• Initiate therapy with analgesics</li> <li>• Reduce the dose of the suspected agent (most commonly pyrazinamide) if this can be done without compromising the regimen.</li> <li>• Discontinue the suspected agent if this can be done without compromising the regimen.</li> </ul>
Depression	CS/TRD, FQs, INH, ETO/PTO and PAS	<ul style="list-style-type: none"> <li>• Consider antidepressant therapy (if necessary)</li> <li>• Reduce the dose of the suspected medicines.</li> <li>• Discontinue the suspected agent if this can be done without compromising the regimen.</li> <li>• Stop CS and TRD if suicidal ideation is reported associated with CS or TRD</li> </ul>
Diarrhea and/ or flatulence	PAS, ETO/PTO	<ul style="list-style-type: none"> <li>• Fluid intake</li> </ul>

		<ul style="list-style-type: none"> <li>• Treat uncomplicated diarrhoea</li> <li>• Check serum electrolytes and act</li> </ul>
Gynaecomastia	ETO/PTO	<ul style="list-style-type: none"> <li>• Encourage the patient to tolerate this ADR.</li> <li>• Symptoms resolve when ETO or PTO is stopped.</li> </ul>
Hematological abnormalities (anemia, neutropenia and/or thrombocytopenia)	LZD	<ul style="list-style-type: none"> <li>• Stop linezolid if Myelosuppression (suppression of white blood cells, red blood cells, or platelets) occurs.</li> <li>• Consider restarting with a lower dose of linezolid (300 mg instead of 600 mg) if Myelosuppression resolves and if linezolid is essential to the regimen.</li> <li>• Consider blood transfusion for severe anemia</li> </ul>
Headache	CS/TRD, BDQ	<ul style="list-style-type: none"> <li>• Rule out more serious causes of headaches, including meningitis and other central nervous system infections.</li> <li>• Treat the headache with analgesics.</li> <li>• Encourage good hydration.</li> <li>• Consider low-dose tricyclic antidepressants for refractory headaches.</li> </ul>
Hearing loss	KM, AM, CM	<ul style="list-style-type: none"> <li>• Change the dosing of the injectable agent to the lowest dose for the patient's weight.</li> <li>• Discontinue the injectable agent if hearing loss continues despite dose adjustment and add additional medicines</li> </ul>
Hepatitis	Z, INH, R, PTO / ETO, PAS, FQs, BDQ	<ul style="list-style-type: none"> <li>• If enzymes are more than five times the upper limit of normal, stop all hepatotoxic medicines and continue with at least three non-hepatotoxic medications (for example,</li> </ul>

		<p>the injectable agent, fluoroquinolone, and Cs/Trd).</p> <ul style="list-style-type: none"> <li>• Avoid other potential causes of hepatitis</li> </ul>
Hypothyroidism	ETO/PTO, PAS	<ul style="list-style-type: none"> <li>• Treat the ADR with levothyroxine and monitor TSH every one to two months and increase the dose by 12.5–25 mcg until TSH normalizes</li> </ul>
Lactic Acidosis	LZD	<ul style="list-style-type: none"> <li>• Stop linezolid if lactic acidosis occurs.</li> </ul>
Nausea and vomiting	ETO, PTO, PAS, BDQ, INH, E, Z, AMX/CLV, CFZ, DLM	<ul style="list-style-type: none"> <li>• Assess signs of dehydration, electrolyte disturbances, and hepatitis.</li> <li>• Initiate rehydration therapy if indicated and correct any electrolyte disturbances.</li> <li>• Adjust medicine administration frequencies and timing without lowering the overall dose: Administer ETO/PTO at night; Give ETO or PAS twice or thrice daily; Give a light snack before the medicines; Give PAS two hours after other anti-TB medicines. <b>OR</b></li> <li>• Start antiemetic eg: Metoclopramide/ Ondansetron; promethazine. <b>OR</b></li> <li>• Decrease the dose of the suspected medicine (when necessary only)</li> </ul>
Optic neuritis	E, LZD, ETO/PTO, CFZ, INH	<ul style="list-style-type: none"> <li>• The most common medicine responsible for this is ethambutol, and it usually reverses with cessation of the medicine.</li> <li>• Improve diabetes control in Diabetic patients.</li> <li>• Stop ethambutol and linezolid.</li> <li>• Treat the case</li> </ul>



Peripheral Neuropathy	CS/TRD, LZD, INH, KM, AM, CM, H, FQS, PTO/ETO, E	<ul style="list-style-type: none"> <li>• Correct any vitamin or nutritional deficiencies.</li> <li>• Provide/Increase pyridoxine to the maximum daily dose (200 mg daily).</li> <li>• Dose adjustment/withdrawal of CS/TRD, LZD, and INH by assessing the severity of the ADR</li> <li>• Consider analgesics for pain management</li> </ul>
QTc prolongation	BDQ, DLM, FQS, CFZ	<ul style="list-style-type: none"> <li>• A QTc value greater than 500ms should be managed carefully.</li> <li>• BDQ and DLM should be stopped for QTc value greater than 500ms.</li> <li>• Check potassium, calcium, and magnesium levels and maintain the electrolyte levels</li> <li>• Measure thyroid stimulating hormone (TSH) and, if necessary, treat hypothyroidism.</li> </ul>
Rash, allergic reaction and anaphylaxis	Any medicine	<ul style="list-style-type: none"> <li>• If severe allergic reactions occur, stop all therapy pending the resolution of the reaction.</li> <li>• Rule out other potential causes of allergic skin reactions (like scabies or other environmental agents).</li> <li>• For minor dermatologic reactions- treat the condition</li> <li>• Suspend permanently any medicine identified to be the cause of a severe reaction</li> </ul>
Seizures	CS/TRD, INH, FQS	<ul style="list-style-type: none"> <li>• Hold CS/TRD, INH, and FQS pending resolution of seizures.</li> <li>• Initiate anticonvulsant therapy (carbamazepine, phenytoin or valproic acid are most used)</li> </ul>

		<ul style="list-style-type: none"> <li>• Increase pyridoxine to the maximum daily dose (200 mg per day)</li> </ul>
Vestibular toxicity (tinnitus and dizziness)	KM, AM, CM, CS/TRD, FQs, INH, ETO, LZD	<ul style="list-style-type: none"> <li>• Change the dosing of the injectable agent to the lowest acceptable for the patient's weight.</li> <li>• If tinnitus and unsteadiness worsen with the above adjustment, stop the injectable agent.</li> </ul>

### 1.5 TIME TO ONSET OF ADR AMONG DR-TB PATIENTS

The onset of reaction is critical to support the management of ADRs and improve treatment success in the treatment of DR-TB. With few exceptions, like a new signal recently detected in Eritrea with the development of alopecia, which has a delayed onset<sup>68</sup>, most of the medicines' ADRs started to appear within the first three months of treatment.<sup>69</sup>

Studies indicated that the average time elapsed from the initiation of anti-TB treatment to the development of drug-induced liver injury is estimated to be about 24 days.<sup>70,71</sup> This could be due to a significant reduction in the clearance rate of metabolized drug agents( in relation to age ) by the cytochrome P450 enzyme, changes in the hepatic blood flow distribution, and other factors affecting liver function.<sup>72</sup> Few studies indicate that long-term use of LZD is associated with optic neuropathy and hematological toxicity.<sup>73</sup> Pyrazinamide in monotherapy or combination therapy with INH and R for the management of patients with pulmonary tuberculosis resulted in progressive hyperuricemia in about 50% of the patients between the 6<sup>th</sup> and 8<sup>th</sup> weeks of treatment.<sup>54,74</sup> Gastrointestinal disorders such as uncontrolled diarrhea, nausea, or vomiting occurred at a mean of 5.9 months into treatment.<sup>39</sup>

According to one study in Egypt, liver enzyme and creatinine levels began to elevate from the third to sixth month after treatment.<sup>69</sup> In the same study, potassium levels among the studied cases did not significantly change throughout the follow-up period.<sup>69</sup> It is important to note and dispel the misconception that most ADRs manifest primarily at the beginning of treatment. Evidence indicates that ADRs can occur not only at the onset but throughout the duration of treatment.<sup>75</sup> Therefore, healthcare workers must stay vigilant about the side effects of medicines throughout treatment.

## 1.6 RISK FACTORS OF ADRS

In clinical practice, it's essential to consider various predictors and factors when evaluating the causes of ADRs. Regarding the treatment of DR-TB, several risk factors contribute to the occurrence of ADRs. Risk factors for ADRs associated with DR-TB medicines include age > 60 years, alcoholism, smoking, overweight/obesity status, anemia, and HIV co-infection, as well as sodium, iron, and albumin deficiency.<sup>44,76,77</sup> A review study on the Risk factors associated with ADRs to TB treatment medicines indicated that ADRs were significantly associated with age, gender, treatment regimen, alcoholism, HIV co-infection, genetic factors, and nutritional deficiencies.<sup>44</sup>

The susceptibility of older people to ADRs is considered secondary to extrinsic factors (prescribing and medication management) and intrinsic factors (pharmacokinetics and pharmacodynamics).<sup>72</sup> There is an increasing risk of developing ADRs due to TB medicines as age increases.<sup>77</sup> Additional findings also support the occurrence of any major side effects with age, especially amongst the elderly.<sup>78</sup> Overall, vulnerability to ADRs is more probable at older ages—especially at a hepatotoxic level—due to a significant reduction in the clearance rate of metabolized drug agents by the cytochrome P450 enzyme, changes in the hepatic blood flow distribution, as well as other factors affecting liver function.<sup>79</sup> Increasing age is correlated with increasing incidence of ADRs both in hospital and in the community.<sup>72</sup>

There are varying findings in studies regarding the correlation between HIV co-infection and ADRs during TB treatment. In patients with TB/HIV co-infection, ADRs are generally related to the immune system itself and are due to immunosuppression and drug metabolism pathways, which often generate toxic compounds.<sup>44</sup> Some of the AEs, like gastrointestinal disturbances, are associated with HIV co-infection.<sup>80,81</sup> Schnippel *et al.* indicated that there is no significant association between ADR and HIV coinfection.<sup>82</sup> Similarly, Breen *et al.* found no difference between groups of patients with and without HIV co-infection in terms of the incidence of hepatotoxicity.<sup>83</sup> Another study conducted in South Africa by Martha *et al.* strengthens the above two findings that being HIV-infected did not increase the occurrence of serious ADRs in patients on second-line anti-tuberculosis medicines.<sup>84</sup>

Regarding reactions related to hepatorenal cases, according to Mohammad A. and his colleagues, the frequency of nephrotoxicity, hepatotoxicity, and hypoalbuminemia were significantly higher in

diabetic than in non-diabetic cases.<sup>69</sup> Low body weight and diabetes mellitus increased the risk of the occurrence of ADRs during anti-TB treatment.<sup>85</sup>

Even though few studies point out alcohol as a major risk factor for ADRs, studies conducted in Ethiopia and a systematic review of studies retrieved from electronic databases indicated that alcoholism is a risk factor for the occurrence of ADRs, and it was associated with sleeping disturbance and anorexia.<sup>44,86</sup> Healthcare professionals can improve patient safety and treatment outcomes by better understanding the ADR risk factors. Additional study and comprehension of these risk variables will maintain improved DR-TB management and reduced treatment-related adverse responses.

### **1.7 ADVERSE DRUG REACTIONS IN DRUG-RESISTANT TUBERCULOSIS (DR-TB): DETECTION, MANAGEMENT AND REPORTING**

The detection, management, and reporting of ADRs related to DR-TB medicine is crucial in the clinical care of DR-TB and to ensure the success of public health program goals. In addition to the commonly used spontaneous pharmacovigilance system, early detection of ADRs through an active surveillance system can significantly improve treatment outcomes by allowing timely intervention and management of ADRs.<sup>87</sup> One of the most innovative active surveillance systems introduced to monitor the safety of DR-TB medicine was active drug monitoring systems (aDSM). Implementing aDSM allows for proactive surveillance of patients on new anti-TB drugs, novel MDR-TB regimens, or XDR-TB regimens, ensuring early intervention and appropriate management of suspected or confirmed drug toxicities. Active PV systems are more effective in detecting ADRs than passive reporting systems. For instance, a study comparing active and passive ADR reporting systems found that the active method identified four times more ADRs than the passive method, although it also had a higher rate of false reporting.<sup>88</sup>

Effective management of ADRs is essential to ensure treatment adherence and prevent treatment failure. The management strategies for ADRs in DR-TB include symptomatic treatment, dose adjustment, and, in severe cases, discontinuation of the offending drug.<sup>89</sup> Furthermore, understanding the genetic markers associated with ADRs can help predict patient-specific drug responses and tailor treatment accordingly.<sup>90</sup> This personalized approach can potentially reduce the incidence of ADRs and improve treatment outcomes.

More importantly, the practical analysis and communication of safety data are critical for understanding the patterns and risk factors associated with ADRs in DR-TB treatment. Current pharmacovigilance practice, specifically in developing countries, should encompass more than ADR identification and reporting. Methodological research and innovative studies are crucial for designing robust observational and post-approval safety studies that can effectively evaluate medicine safety in the real world.

## **1.8 PHARMACOVIGILANCE PROGRAMS AND DATA MANAGEMENT SYSTEM**

The World Health Organization (WHO) has defined PV as “the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems.”<sup>91</sup> The PV system aims to protect the public from medicines-related harm and continuously monitor and report ADRs. Countries worldwide have their pharmacovigilance centers to monitor the safety of medicines. Pharmacovigilance programs in each country collect Individual Case Safety Reports (ICSRs) of ADRs associated with medicinal products and contribute to VigiBase database.<sup>92</sup> The WHO Programme for International Drug Monitoring (PIDM)'s global database, VigiBase, is a central repository for adverse event reports from member countries.<sup>93</sup> As of July 2023, VigiBase contained over 35 million reports of ICASR, highlighting the extensive data collection and analysis efforts undertaken to safeguard patient health.<sup>94</sup> VigiBase is managed by the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre for PIDM.

The PIDM has grown significantly, with 157 full members and 23 associate members as of May 2024, demonstrating a widespread commitment to pharmacovigilance worldwide.<sup>94</sup> This expansion allows for a more comprehensive analysis of suspected harm patients suffer and facilitates preventing adverse events. VigiBase is managed by the UMC, the WHO Collaborating Centre for International Drug Monitoring. UMC collaborates with member countries in the development and practice of pharmacovigilance, focusing on reports of ICSRs from healthcare providers and patients in member countries. UMC maintains and develops pharmacovigilance tools and classifications, such as the WHO Drug Dictionary and VigiFlow, a program for case report management.<sup>94</sup>

Since 2013, after the introduction of two new TB medicines, WHO's Global Tuberculosis Programme has set up another global data management system known as aDSM to monitor the safety of patients who receive MDR-TB treatment with new medicines (e.g., BDQ and DLM), repurposed medicines

(e.g., LZD and CFZ), or new regimens, which don't have a well-established safety profile.<sup>95</sup> The overall objectives of aDSM are to reduce risks from drug-related harms in patients on treatment for DR-TB and to generate data to inform future policy updates on the use of such medicines. Active TB Drug Safety Monitoring and Management has three packages. The core package targets reporting serious adverse events; in the intermediate form, adverse events of special interest are added. In its most rigorous form, the advanced aDSM package targets all AEs of clinical interest, where all adverse events of a patient in a TB cohort are collected during treatment.<sup>95</sup>

Eswatini established its National Pharmacovigilance Center (NPC) in 2009 to coordinate all pharmacovigilance activities in the country. The NPC has evolved its reporting systems from spontaneous reporting to active surveillance systems for patients receiving TB and HIV medicines. The NPC is a member of the WHO PIDM and utilizes the web-based individual case safety report (ICSR) management system, VigiFlow, to collect, process, and share data for practical analysis.

## **CHAPTER 2. STATEMENT OF THE PROBLEM AND OBJECTIVES OF THE THESIS**

## 2.1 STATEMENT OF THE PROBLEM

Pharmacological interventions sometimes carry inherent significant risks, which include ADRs, drug interactions (DIs) and other consequences of inappropriate medicines use. "Despite the extensive research and focus on ADRs, they continue to present a significant challenge with a high incidence and prevalence in clinical settings." Due to the introduction of new drugs (NDs) and, shorter treatment regimens (STR), and increasing usage of repurposed medicines (LZD and CFZ) for the management of DR TB, there are major challenges with understanding and properly managing and predicting ADRs. Despite the continued updates and several studies being done around the treatment of DR-TB, the information on ADRs is inadequate to make an informed decision.

In Eswatini, limited published information on the safety of DR-TB treatment used and the absence of clear pharmacovigilance guidance adversely affected the practices of PV and hence, the safety of the patients. The safety profile of medicines used in patients with DR TB is not comprehensive, as these are complicated patients and often are treated in places where there are no pharmacovigilance systems, or they are poorly developed. Thus, this thesis contributes to PV knowledge by determining the magnitude of ADRs and associated risk factors among DR-TB patients on treatment. Additionally, we leveraged Vigibase® a global database of individual case safety reports (ICSRs), to assess the safety of DR-TB medicines reported globally.

This study will be the first pharmacovigilance investigation conducted in Eswatini on the toxicity of DR-TB treatment. It will also enhance the visibility of PV data for DR-TB patients in sub-Saharan Africa. Given the complexity of these patients and the treatment challenges they face, a comprehensive understanding of ADRs and their associated risks is crucial for improving patient safety and optimizing treatment outcomes.



## 2.2 OBJECTIVES OF THE THESIS

This thesis was developed to evaluate and describe the pattern and characteristics of ADRs in Eswatini patients with DR-TB and the comprehensive safety of DR-TB medicines globally. We conducted prospective and retrospective studies on local data to achieve these objectives and evaluated worldwide data extracted from Vigibase. These studies are presented as follows:

Study 1: Safety Profile of Medicines Used for the Treatment of Drug-Resistant Tuberculosis: A Descriptive Study Based on the WHO Database (VigiBase®). This study focused on assessing the safety profile of DR-TB medicines by utilizing ICSR data from the WHO Database (VigiBase®).

Study 2: Patterns of Adverse Drug Reactions in Patients with Drug-Resistant Tuberculosis in Eswatini: A Retrospective Cohort Study. The second study evaluated and characterized the safety profile of DR-TB medicine utilized across all DR-TB sites in the kingdom of Eswatini.





Study 3: Evaluation of Safety of Repurposed Drug-Resistant TB Medicines in Eswatini: A Prospective Pharmacovigilance Study. The last study included in this thesis evaluated the safety of repurposed medicines, focusing on LZD and CFZ.

## **CHAPTER 3. STUDY ONE**

### **SAFETY PROFILE OF MEDICINES USED FOR THE TREATMENT OF DRUG-RESISTANT TUBERCULOSIS: A DESCRIPTIVE STUDY BASED ON THE WHO DATABASE (VIGIBASE®)**

## Article

# Safety Profile of Medicines Used for the Treatment of Drug-Resistant Tuberculosis: A Descriptive Study Based on the WHO Database (VigiBase<sup>®</sup>)

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**Abstract:** Background: The introduction of new drugs that increase the usage of repurposed medicines for managing drug-resistant tuberculosis (DR-TB) comes with challenges of understanding, properly managing, and predicting adverse drug reactions (ADRs). In addition to the health consequences of ADRs for the individual, ADRs can reduce treatment adherence, thus contributing to resistance. This study aimed to describe the magnitude and characteristics of DR-TB-related ADRs through an analysis of ADRs reported to the WHO database (VigiBase) in the period from January 2018 to December 2020. Methods: A descriptive analysis was performed on selected reports from VigiBase on the basis of medicine-potential ADR pairs. The ADRs were stratified by sex, age group, reporting country, seriousness, outcome of the reaction, and dechallenge and rechallenge. Results: In total, 25 medicines reported to be suspected individual medicines or as a fixed-dose combination in the study period were included the study. Pyrazinamide ( $n = 836$ ; 11.2%) was the most commonly reported medicine associated with ADRs, followed by ethionamide ( $n = 783$ ; 10.5%) and cycloserine ( $n = 696$ ; 9.3%). From the report included in this analysis, 2334 (31.2%) required complete withdrawal of the suspected medicine(s), followed by reduction of the dose (77; 1.0%) and an increased dose (4; 0.1%). Almost half of the reports were serious ADRs mainly caused by bedaquiline, delamanid, clofazimine, linezolid, and cycloserine that are the backbone of the DR-TB treatment currently in use. Conclusions: A third of the reports required medication withdrawal, which impacts treatment adherence and ultimately leads to drug resistance. Additionally, more than 40% of the reports indicated that ADRs appeared two months after the commencement of treatment, thus it's important to remain alert for the potential ADRs for the entire duration of the treatment.

**Keywords:** drug-resistant tuberculosis; pharmacovigilance; VigiBase<sup>®</sup>; adverse drug reaction



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## 1. Introduction

Tuberculosis (TB) remains the world's leading cause of death from infectious agents, exceeding human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) [1,2]. Globally, the incidence of drug-resistant TB (DR-TB) has increased since the introduction of chemotherapy for the treatment of *Mycobacterium tuberculosis* in 1943 [3]. In 2018, 10 million people developed TB, and 1.5 million died from the disease at a worldwide level [1]. Moreover, about 500,000 new cases of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) are estimated to emerge annually; only one in three cases were reported by all countries in 2018 [1]. Despite significant progress in diagnostics, more effective medicines for earlier detection, and higher success rates among patients with MDR/RR-TB in a number of countries, the overall treatment success rate reached only 56% in 2018 [4].

### 3.1 SAFETY PROFILE OF MEDICINES USED FOR THE TREATMENT OF DRUG-RESISTANT TUBERCULOSIS: A DESCRIPTIVE STUDY BASED ON THE WHO DATABASE (VIGIBASE®)

#### ABSTRACT

**Background:** The introduction of new and repurposed medicines for the treatment of drug-resistant tuberculosis (DR-TB) comes with challenges in understanding and managing adverse drug reactions (ADRs). In addition to their health consequences, ADRs can also reduce treatment adherence, thereby contributing to resistance. This study aimed to analyze ADRs reported to the WHO database (VigiBase®) from January 2018 to December 2020 to describe the magnitude and characteristics of DR-TB-related ADRs.

**Methods:** A descriptive analysis was conducted on selected reports from VigiBase, focusing on medicine-potential ADR pairs. The study included stratification of ADRs by sex, age group, reporting country, seriousness, outcome of the reaction, and dechallenge and rechallenge.

**Results:** In total, 25 medicines reported to be suspected individual medicines or as a fixed-dose combination in the study period were included in the study. Pyrazinamide (n = 836; 11.2%) was the most reported medicine associated with ADRs, followed by ethionamide (n = 783; 10.5%) and cycloserine (n = 696; 9.3%). ADRs such as vomiting (n = 834; 11.16%), arthralgia (n = 331; 4.43%), and nausea (n = 275; 3.68%) were the most frequent ADRs reported. Most ADRs appeared in less than three months (a median time of 61 days, IQR: 14–161) and resolved in less than two weeks after the onset (median = 7 days, IQR: 3–14).

**Conclusions:** A high proportion of the medicines responsible for frequent ADRs are the backbone of the shorter DR-TB treatment regimens currently in use.

**Keywords:** drug-resistant tuberculosis; pharmacovigilance; VigiBase®, adverse drug reaction

## 3.2 INTRODUCTION

Tuberculosis (TB) remains the world's leading cause of death from infectious agents, exceeding human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) [1,2]. Globally, the incidence of drug-resistant TB (DR-TB) has increased since the introduction of chemotherapy for the treatment of *Mycobacterium tuberculosis* in 1943 [3]. In 2018, 10 million people developed TB, and 1.5 million died from the disease at a worldwide level [1]. Moreover, about 500,000 new cases of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) are estimated to emerge annually; only one in three cases were reported by all countries in 2018 [1]. Despite significant progress in diagnostics, more effective medicines for earlier detection, and higher success rates among patients with MDR/RR-TB in several countries, the overall treatment success rate reached only 56% in 2018 [4].

TB that is resistant to at least rifampicin (R) and isoniazid (INH) has posed a threat to all efforts to control TB [5]. DR-TB can occur when the drugs used to treat TB are misused or mismanaged [6], and it can be transmitted directly. Common causes of multidrug-resistant TB can also be related to the health care system, inadequate/poor treatment regimens, poor adherence, lack of information on treatment, primary transmission, and the side effects of treatment [7,8].

The management of multidrug-resistant TB requires multiple medicines for a longer duration of treatment with drugs that are more expensive and difficult to tolerate [9]. In recent years, two newly introduced (bedaquiline and delamanid) and two repurposed (clofazimine and linezolid) medicines have been introduced to treat DR-TB [10,11]. According to the WHO's consolidated guidelines on DR-TB, treatment regimens are organized into three groups to construct a regimen while balancing efficacy and safety [12,13]: Group A (levofloxacin, moxifloxacin, bedaquiline, and linezolid); Group B (clofazimine, cycloserine, and terizidone); and Group C (ethambutol, delamanid, pyrazinamide, imipenem-cilastatin, meropenem, amikacin, streptomycin, ethionamide, prothionamide, and p-aminosalicylic acid (PAS)) [12].

The principle of designing a regimen for treating DR-TB is to individualize it, guided by the results of a drug-susceptibility test (DST) prior to the treatment's initiation, the TB treatment history, a contact DST, and co-morbidities [13]. Regimens are designed with at least four to five effective TB medicines. Group A medicines are prioritized, followed by Group B; Group C medicines are added to complete the regimens when agents from Groups A and B cannot be used [14,15].

Pharmacological interventions sometimes carry inherent risks, which include adverse drug reactions (ADRs) and drug interactions (DIs). The incidence of ADRs due to DR-TB drugs ranges from 20% to 90% [16–18]. ADRs associated with DR-TB drugs include joint pain, nausea, hearing disturbances, gastrointestinal disturbances, depression, itching, hypothyroidism, dizziness, seizures, and hepatitis [17,20–23]. About one patient in five is withdrawn from DR-TB drugs because of ADRs [19].

Collectively, ADRs represent a clinically significant problem and burden with high incidence and prevalence. The safety profile of the medicines used in patients with DR-TB is not comprehensive, as these are complicated patients and often are treated in places where there are no pharmacovigilance systems or only ones that are poorly developed. We aimed to study the profile of ADRs of the medicines used in DR-TB patients reported to the global WHO pharmacovigilance database.

### 3.3 RESULTS

In VigiBase, 349,831 cases of ADRs potentially related to DR-TB drugs were identified using the predefined search criteria; of these, 342,357 ADRs were excluded because they were associated with concomitant (not suspected) and unspecified medicines, indications other than DR-TB cases, an unknown drug start date, and unknown ADR start date and ADRs not described in the report.

This study was, therefore, based on 7474 reports associated with 25 different DR-TB drugs that were reported as suspected individual medicines or as a fixed-dose combination. Most reports were from India (n= 5048; 67.5%), South Africa (446; 5.9 %), and Eswatini (304; 4.1%). The mean and median ages of the patients were 35.6 years (SD = 15.6) and 33 years, respectively, while the most-represented groups were male patients (4030; 53.9%) and those aged 19–64 years (6435; 86.1%).

Among the 25 medicines included in these reports, pyrazinamide (n = 836; 11.2%) was the most reported, followed by ethionamide (783; 10.5%) and cycloserine (696; 9.3%).

**Table 1. Characteristics of the 7474 reports of adverse drug reactions (ADRs) attributed to medicines used in the management of DR-TB.**

Indicators (n = 7474)		Frequency	%
Age group (years)	Children and adolescents (0–18)	652	8.7
	Adult (19–64)	6435	86.1

	Elderly (above 65)	387	5.2
Sex	Female	3444	46.1
	Male	4030	53.9
Seriousness of ADR (n = 7474)	Serious	3365	45.0
	Non-serious	4065	54.4
	Unknown	44	0.6
Route of administration	Oral	6013	80.5
	Intramuscular	568	7.6
	Intravenous	110	1.5
	Other	8	0.1
	Unknown	775	10.4
Dechallenge action	Does not changed	3568	47.7
	Drug withdrawn	2334	31.2
	Dose reduced	77	1.0
	Dose increased	4	0.1
	Unknown	818	10.9
	Not applicable	673	9.0
Dechallenge outcome	Reaction abated	3854	51.6
	Effect unknown	2006	26.8
	No effect observed	1274	17.1
	Fatal *	340	4.6
Rechallenge action	Unknown	6703	89.7

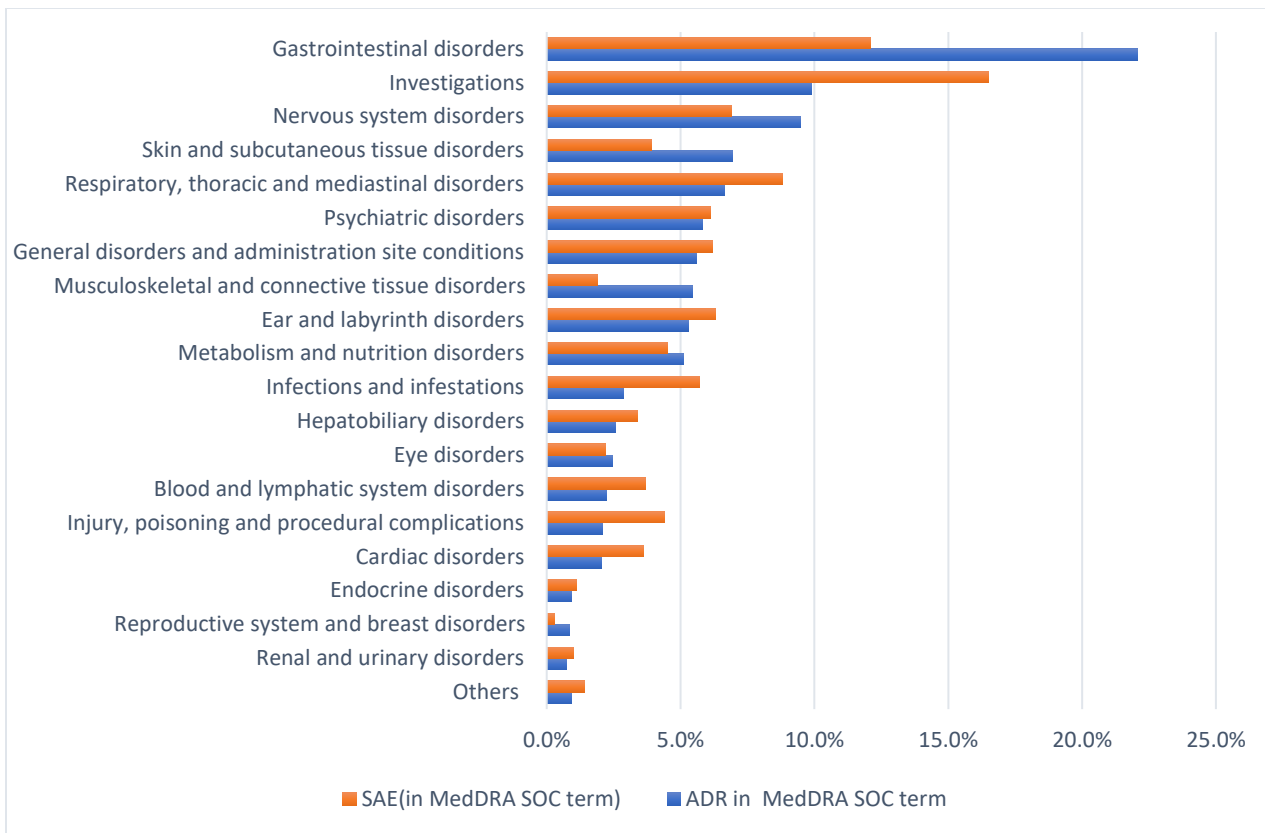
	Rechallenge	771	10.3
Rechallenge outcome	Effect unknown	7331	98.1
	No recurrence	104	1.4
	Reaction recurred	39	0.5
The outcome of the reaction	Recovered/resolved	2113	28.3
	Recovering/resolving	1901	25.4
	Recovered/resolved with sequelae	82	1.1
	Not recovered/not resolved	1332	17.8
	Fatal **	408	5.5
	Unknown	1638	21.9

***Fatal \**, fatal reaction outcome after withdrawal of the treatment; *Fatal \*\**, overall fatal outcome of the reaction.**

ADRs were firstly categorized according to the classifications of the System Organ Class MedDRA terms. Gastrointestinal disorders (n = 1650; 22.1%) and nervous system disorders (709; 9.5) were the most frequently reported ADRs grouped by system/organ (see Figure 1). It should be noted that 739 (9.9%) reports were described as “investigations.”

Regarding specific ADRs, vomiting (n=834; 11.6%) was the most frequently reported ADR, followed by arthralgia (331; 4.4%), nausea (275; 3.7%), peripheral neuropathy (216; 2.9%), and prolongation of electrocardiogram QT (204; 2.7%).





**Figure 1. The frequency of the 7474 reported ADRs and the proportion of SAE are determined according to the system/organ classification (SOC; MedDRA terms).**

**SERIOUSNESS OF ADRS**

Almost half of the reports (n = 3365; 45.1%) described serious ADRs. Seriousness was not different between men (4030; 53.9%) and women (3444; 46.1%). However, serious ADRs were more frequent in children and adolescents (n = 363; 55.7%) than in adults (2822; 43.8%) and older people (180; 46.5%) (chi-square = 34.9; p < 0.001).

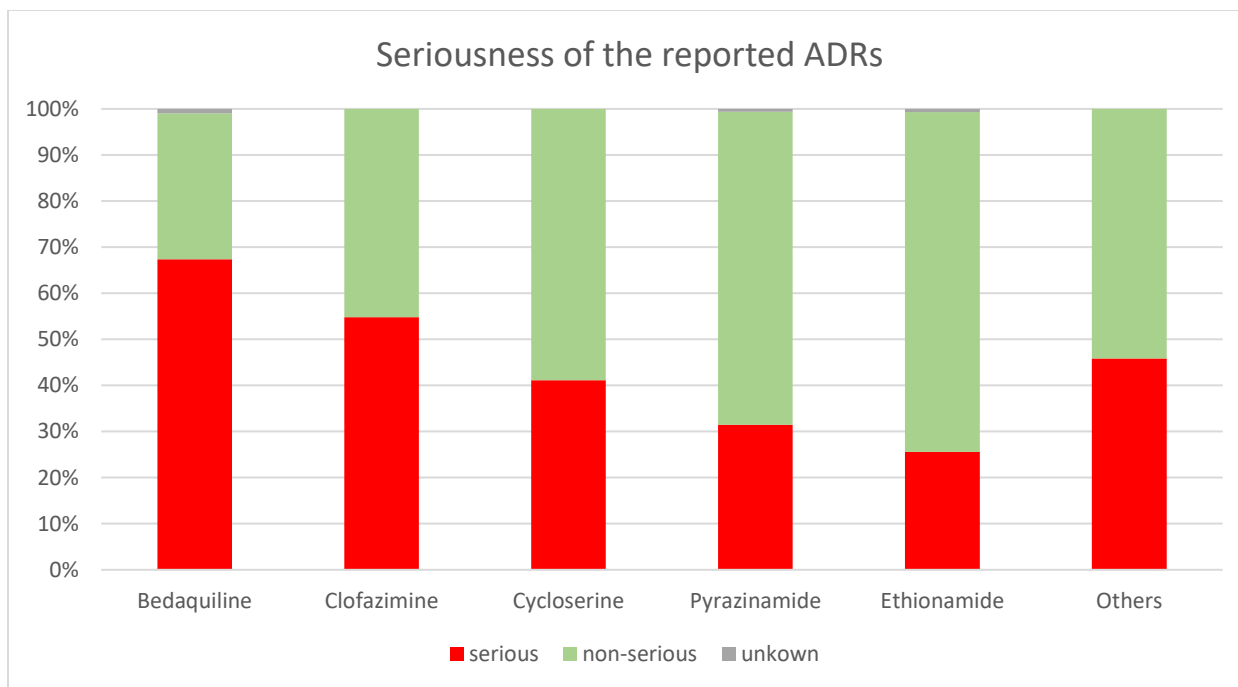
**Table 2. The seriousness of the 7474 reported ADRs is based on the suspected medicines, age group, and specific ADRs.**

Variables	Medicine	Seriousness					
		Yes (n = 3365)		No (4065)		Unknown (44)	
		N	%	N	%	N	%

Age group (years) *	Children and adolescents (0–18)	363	55.7%	287	44.0%	2	0.3%
	Adult (19–64)	2822	43.8%	3571	55.5%	42	0.6%
	Elderly (above 65)	180	46.5%	207	53.5%		0.0%
Top five ADRs according to the SOC MedDRA terms	Respiratory, thoracic, and mediastinal disorders (n = 496)	296	59.7%	200	40.3%	-	-
	Psychiatric disorders (n = 435)	206	47.4%	223	52.2%	6	1.4%
	Nervous system disorders (n = 709)	231	32.6%	471	66.4%	7	0.01%
	Skin and subcutaneous tissue disorders (n = 520)	131	25.2%	387	74.4%	2	0.01%
	Gastrointestinal disorders (n = 1650)	406	24.6%	1233	74.7%	11	0.6%
	Others (n = 3646)	2095	57.1%	1551	42.3%	18	0.5%

\* *chi-square* = 34.9456;  $p \leq 0.00001$ .

The majority of serious ADRs according to the terms of the MedDRA System Organ Class (SOC), were reported as gastrointestinal disorders (n = 406; 12.1%), followed by respiratory disorders (296; 8.8%), nervous system disorders (231; 6.9%), and ear and labyrinth disorders (212; 6.3%). Upon analyzing the seriousness of ADRs according to the preferred terms (PTs) of MedDRA, vomiting (n = 34; 11.2%), arthralgia (331; 4.4%), and nausea (275; 3.7%) were the top three reported serious ADRs. In terms of medicines, the majority of serious ADRs (n = 1846; 54.9%) were caused by bedaquiline (457; 67.4%), followed by delamanid (391; 11.6%), clofazimine (370; 11.0%), linezolid (342; 10.2%), and cycloserine (286; 8.5%). Ethionamide (577; 7.72%), pyrazinamide (568; 7.60%), cycloserine (410; 5.49%), levofloxacin (338; 4.52%), and ethambutol (335; 4.48%) caused non-serious reactions.



**Figure 2. Graphical representation of the top five reported medicines causing serious ADRs.**

Table 3 shows a cross-tabulation of the top five medicines against the top five reported serious ADRs based on the SOC.

**Table 3. The top five reported medicines, and the top five reported serious ADRs based on MedDRA SOCs for these medicines.**

	Gastrointestinal Disorders	Respiratory, Thoracic, and Mediastinal Disorders	Nervous System Disorders	Ear and Labyrinth Disorders	General Disorders and Administrative Conditions	Other	Total N (%)
Linezolid, n (%)	34 (9.9)	33 (9.6)	43(2.3)	-	22(6.4)	210 (61.4)	342 (100)
Delamanid, n (%)	33 (8.4)	44 (11.3)	23 (1.2)	3 (0.8)	34 (8.7)	254 (64.9)	391 (100)
Cycloserine, n (%)	26 (9.1)	18 (6.3)	25 (1.4)	4 (1.4)	14 (4.9)	199 (69.6)	286 (100)

<b>Clofazimin e, n (%)</b>	48 (13.0)	50(13.5)	24 (1.3)	1 (0.3)	26 (7.0)	221 (59.7)	370 (100)
<b>Bedaquilin e, n (%)</b>	40 (8.8)	59 (12.9)	25 (1.4)	1 (0.2)	32 (7.0)	300 (65.6)	457 (100)
<b>Others, 1519 (100)</b>	225 (14.8)	92 (6.0)	91 (5.9)	203 (13.3)	81 (5.3)	827 (54.4)	1519 (100)
<b>Total, 3365 (100)</b>	406 (12.1)	296(8.8)	231 (6.8)	212 (6.3)	209 (6.2)	2011 (59.7)	3365 (100)

Special mention must be made of the 554 (16.5%) reports describing investigations, which are diagnostic tests and results. As expected, most reports, including this term, were serious. Bedaquiline contributed to the most serious ADRs categorized under investigation-related SOC MedDRA terms. Prolonged QT, decreased hemoglobin, increased liver function test, increased aspartate aminotransferase, increased white blood cell count, and reduced blood sodium accounted for more than 50% of the serious ADRs (based on PT) under the investigation-related MedDRA SOC terms. The most frequent individual serious ADRs according to the MedDRA PT terms are described in Table 4.

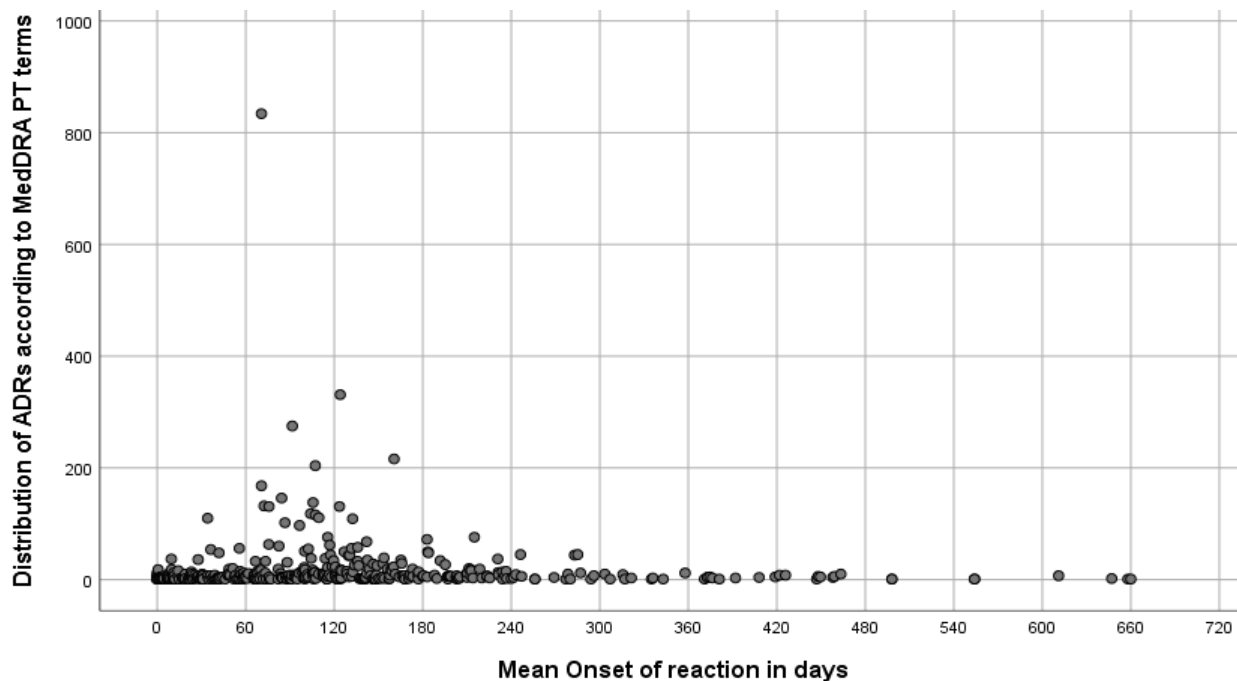
**Table 4. The reported serious ADRs are classified according to the MedDRA SOC and PT terms.**

Top Five Reported Serious ADRs Based on MedDRA SOC Terms (n = 3365)	The Most Frequent Individual ADRs Based on MedDRA PT Terms
Ear and labyrinth disorders (n = 212)	Deafness (100; 47.2%), tinnitus (31; 14.6%), hypoacusis (26; 12.3%), and others (55; 25.9%)
Gastrointestinal disorders (n = 406)	Vomiting (222; 54.6%), gastritis (63; 15.5%), nausea (40; 9.8%), and others (81; 19.9%)
Nervous system disorders (n = 140)	Peripheral neuropathy (70; 50%), headache (32; 22.8%), optic neuritis (28; 20%), and others (10; 7.1%)

Respiratory, thoracic, and mediastinal disorders (n = 296)	Dyspnea (93; 31.4%), respiratory failure (37; 12.5%), cough (30; 10.1%), and others (136; 45.9%)
General disorders and administration site conditions (n = 209)	Pyrexia (41; 19.6%), chest pain (37; 17.7%), asthenia (22; 10.5%), and others (100; 47.8%)
Others (n = 2011)	Electrocardiogram QT prolonged (135; 6.7%), anemia (91; 4.5%), psychotic disorders (73; 0.6%), and others (1712; 85.5%)

### DURATION OF THE REACTION AND TIME TO THE ONSET OF THE REACTION

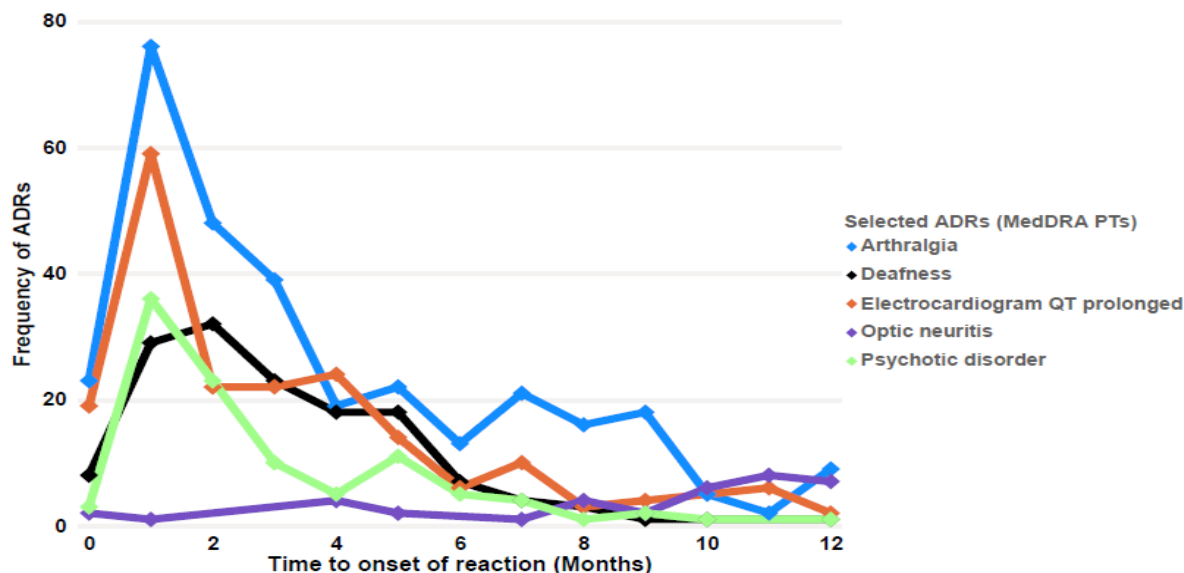
Regarding the timing of the ADRs' occurrence, most ADRs (n = 4438; 59.3%) appeared in less than three months (a median time of 61 days, IQR: 14–161) (Figure 3). The most frequent ADRs, such as vomiting (n = 834; 11.2%), arthralgia (331; 4.4%), and nausea (275; 3.7%), had a mean onset of the reaction of 71, 124, and 92 days, respectively. However, 3036 ADRs (40.7%) started between 3 and 24 months after the treatment onset; the most frequent late ADRs were heavy menstrual bleeding (n = 1; 0.01%), premature delivery (2; 0.02%), and chronic cholecystitis (2; 0.02%), with a mean onset of the reaction of 660, 658, and 647 days, respectively.



**Figure 3. Mean onset of the reactions in days (dots represent ADRs).**

The visual display of the time to the onset of the reaction for most ADRs had similar patterns, except for optic neuritis (n = 28); in this case, the reports slightly increased as the duration of treatment increased (see Figure 4). In this study, the time to the onset of optic neuritis had a median time of 302 days (IQR: 223–361). Most suspected medicines associated with optic neuritis were linezolid (n = 16; 35.5%) and ethambutol (8; 17.7%). The mean onset of optic neuritis associated with linezolid and ethambutol was 251 and 263 days, respectively.

The remaining ADRs showed a descending reporting pattern after an initial peak during the first two months after starting the treatment. Notwithstanding this, it should be noted that for arthralgia (n = 331 reports), after the initial peak, there were successive peaks around 5, 7, and 9 months after starting the treatment. The most frequently suspected medicines in these cases of arthralgia were pyrazinamide (n = 130; 39.3%) and levofloxacin (n = 68; 20.5%). Reports describing prolonged QT (n = 204) had an initial peak (n = 59 reports; 28.9%), followed by a plateau between the second and fourth months (n = 68; 33.3%) that greatly diminished after the fourth month (n = 58; 28.4%). Reports of deafness (n = 146 reports) peaked at the second month (n = 32; 21.9%) and maintained a slightly descending plateau until the fifth month (cumulative n = 59; 40.4%) and then almost disappeared after that moment.



**Figure 4. Time to the onset of the reaction of selected ADRs (based on MedDRA PT terms).**

In terms of duration, most ADRs resolved in less than two weeks after their onset (median: 7 days; IQR: 3–14). The most frequent ADRs, such as vomiting (n = 360; 19.2%), nausea (110; 5.8%), and pruritus (77; 4.1%), had a mean duration of less than two weeks. In contrast, the rarer reports describing a decrease in blood albumin, a decrease in blood calcium, and a decrease in weight (1 report each; 0.1%) took around 300 days to be resolved.

Concerning medicines, streptomycin (n = 1; 0.1%), PAS (7; 1.6%), and moxifloxacin (13; 5.8%) were associated with reactions that had a mean duration of less than seven days. Terizidone (n = 8; 0.4%), followed by the fixed-dose combination of ethambutol + isoniazid + pyrazinamide + rifampicin (1; 0.1%) and delamanid (137; 7.3%) were associated with reactions that had the most extended mean durations of 34, 37, and 61 days, respectively.

### OUTCOMES OF THE REACTIONS

The current study shows that almost one-quarter (n = 1740; 23.3%) of the ADRs were fatal or not resolved when they were reported, while 82 (1.1%) recovered/resolved with sequelae, and 1901 (25.4%) of the ADRs were still recovering/resolving. Further analysis of the reactions' outcomes about the medicines showed that bedaquiline, clofazimine, linezolid, delamanid, and pyrazinamide were responsible for the most fatal outcomes of the ADRs.

We further analyzed the outcomes of serious reactions; accordingly, 435 (2.9%) of the serious ADRs were not recovered/resolved when reported, while 404 (12.01%) were reported as fatal. The cross-tabulation of the ADRs' outcomes against the seriousness of the reaction in Table 5 shows that more fatal outcomes of the reaction were reported for serious reactions ( $\chi^2 = 1196.2$ ,  $DF = 10$ ,  $p < 0.001$ ).

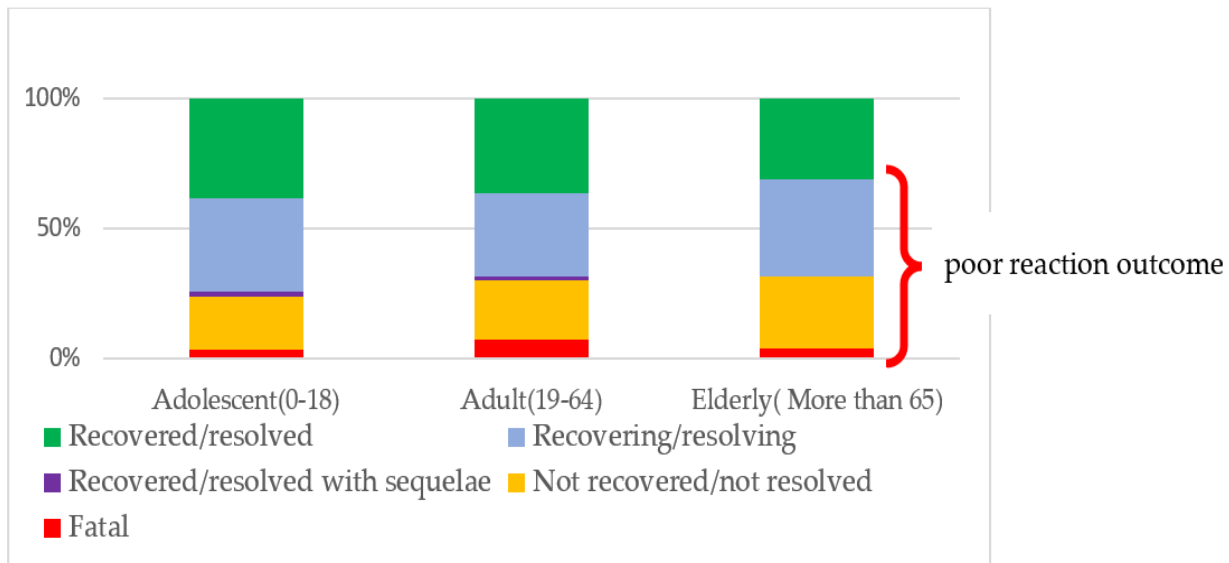
**Table 5. Cross-tabulation of ADR outcomes against seriousness of reaction.**

		The outcome of the Reaction					Total	
		Fatal	Not Recovered/ Not Resolved	Recovered/Resolved	Recovered /Resolved with Sequelae	Recovering/Resolving	Unknown	
Seriousness	Yes	404 (12.0%)	435 (12.9%)	705 (20.9%)	44 (1.3%)	641 (19.0%)	1136 (33.7%)	3365 (100%)
	No	4 (0.1%)	884 (21.7%)	1384 (34.0%)	38 (0.9%)	1260 (30.9%)	495 (12.2%)	4065 (100%)

Unknown	-	13 (29.5%)	24 (54.5%)	-	-	7 (15.9%)	44 (100%)
<b>Total</b>	408 (5.45)	1332 (17.82%)	2113 (28.2%)	82 (1.1%)	1901 (25.4%)	1638 (21.9%)	7474 (100)

The association between the reactions' outcome and sex was also analyzed. Fatal outcomes of the reaction (n = 263; 3.5%) and reactions that had not recovered when reported (730; 9.8%) were observed more often in male than female patients.

As indicated in Figure 5 below, fatal reactions were reported more frequently among adults (n = 383; 6.0%) than in children and adolescents (16; 2.5 %) and the elderly (9; 2.3%). Overall, elderly patients had the poorest outcomes relative to adolescents (0–18 years) and adults (19–64 years). With regards to the medicines, more than 50% of the fatal reactions reported were associated with bedaquiline (n = 77; 19.1%), clofazimine (63; 15.6%), linezolid (42; 10.4%), and delamanid (39; 9.7%) ( $\chi^2 = 822.684$ ,  $DF = 110$ ,  $p < 0.0001$ ).



**Figure 5. Outcomes of the reaction according to age group.**



## **DISCONTINUATION OF TREATMENT DUE TO ADRS**

Of the 7474 reports, 2334 (31.2%) required complete withdrawal of the suspected medicine(s), followed by a reduction of the dose (77; 1.0%) and an increased dose (4; 0.1%). Overall, kanamycin (315; 13.5%), cycloserine (296; 12.7%), and pyrazinamide (240; 10.3%) were the most frequent medicines withdrawn due to ADRs. In terms of medicine–reaction pair, ear, and labyrinth disorders were associated with kanamycin (185; 7.9%), and psychiatric disorders (181; 7.8%) and gastrointestinal disorders (93; 4.0%) were responsible for the withdrawal of cycloserine and ethionamide, respectively.

As indicated in the supplementary data in Table S1, we also analyzed the most frequently withdrawn medicines for different age groups. Accordingly, psychiatric disorders associated with cycloserine (168; 8.8%) were more prominent in adults than in adolescents and the elderly ( $X^2 = 1840.785$ ,  $DF = 25$ ,  $p < 0.0001$ ).

### **3.4 DISCUSSION**

The present study aimed to evaluate the magnitude and characteristics of DR-TB-associated ADRs by analyzing the ADRs reported in the global pharmacovigilance database (VigiBase®). It was the first of its kind to be carried out at the global level using VigiBase®. Studies conducted previously on the safety of DR-TB focused either on a few medicines or were extracted from a few countries' PV databases without considering the wider scope of DR-TB medicines used in different countries. In summary, the most relevant results found in this analysis were that half of the ADR reports of DR-TB medicines were attributed to pyrazinamide, ethionamide, cycloserine, bedaquiline, clofazimine, and linezolid. Among the most frequently reported ADRs, there were a few serious conditions, such as peripheral neuropathy or prolongation of QT (most cases were attributed to linezolid and bedaquiline). Furthermore, almost one-third of the reports described events that required withdrawal of the suspected medicine or a reduction in the dose; this affects adherence to the treatment and can indirectly trigger resistance. Finally, it should be highlighted that 40% of the analyzed reports of suspected events started more than two months after the onset of the treatment, which stresses the importance of remaining alert for the potential adverse effects of medicines, enabling their quick identification and thus avoiding as many treatment withdrawals as possible.

## **MEDICINES ASSOCIATED WITH THE MOST FREQUENT ADRs**

Of the 25 suspected individual medicine or fixed-dose combinations associated with ADRs, pyrazinamide, ethionamide, cycloserine, bedaquiline, clofazimine, and linezolid were responsible for more than 50% of the ADRs reported. This could be due to the new all-oral approach of WHO, the introduction of repurposed and new drugs, the removal of kanamycin and capreomycin [15,29,30], and the reduced use of amikacin, ethionamide/prothionamide, and PAS [29]. In contrast, linezolid is used more often due to its benefits despite its frequent and serious adverse events [30].

## **ADVERSE DRUG REACTIONS**

In the present study, vomiting was the most frequently reported ADR, followed by arthralgia, nausea, peripheral neuropathy, and prolongation of electrocardiogram QT, a finding that is more or less like the findings from previous studies [31–34]. The same sets of ADRs were also reported in a four-year retrospective study conducted by Arif et al. [35]. Similarly, gastrointestinal disturbances (18.4%), psychiatric disorders (5.5%), arthralgia (4.7%), and hepatitis (3.9%) were the top five ADRs reported by Tae et al. [36]. Slight differences in the frequencies of ADRs could be due to different factors, such as the sociodemographic background, which may contribute to the occurrence of ADRs [37].

Furthermore, we evaluated the timing of the ADRs' occurrence, revealing that most ADRs appeared in less than three months. The most frequent ADRs, such as vomiting, arthralgia, and nausea, had a mean reaction onset of less than 3 months. With few exceptions, such as a new signal recently detected in Eritrea with the development of alopecia, which has a delayed time to onset [38], most of the drugs' ADRs started to appear within the first 3 months of treatment [39]. Additionally, other studies also indicated that the average time from the initiation of the anti-TB treatment to developing drug-induced liver injury was estimated to be about 24 days [40,41]. This is like the results of a retrospective observational cohort study using pharmacovigilance data conducted in Nigeria by Avong et al. [23]. However, a study by Madan et al. on ADRs caused by second-line anti-tubercular drugs used in Nepal reported that the mean onset time of ADRs was 7.85 months [42]. Overall, it is possible to conclude that patients on DR-TB medicines mostly develop more frequent ADRs around the beginning of their treatment, and the ADRs will continue to appear throughout the duration of the treatment. Therefore, ADRs should be closely monitored for the entire duration of the treatment.

On the other hand, we also analyzed the seriousness of the ADR. Accordingly, almost half of the reports were serious ADRs mainly caused by bedaquiline, delamanid, clofazimine, linezolid, and

cycloserine. Significant numbers of these ADRs were not recovered/not resolved when they were reported, while 12.1% were fatal. This is worrying, as an important proportion of the medicines responsible for serious ADRs are the backbone of the DR-TB treatment currently in use [13–15], and the outcomes of these ADRs are not pleasant.

## **OUTCOMES OF THE REACTIONS**

The present study showed that almost one-quarter (23.3%) of the ADRs' outcomes were fatal or not resolved when reported, while 1.1% had recovered/resolved with sequelae, and 25.4% were still recovering/resolving. Based on the WHO's recommendations, it is very important to strictly monitor the unfavorable effects of medicines and put an effective PV system in place when administering new and repurposed DR-TB medicines [43,44]. As indicated in Figure 4, elderly patients have poorer reaction outcomes than adolescents and adults. The susceptibility of older people to ADRs is secondary both to extrinsic factors (prescription and management of medication) and intrinsic factors (pharmacokinetics and pharmacodynamics) [45]. Overall, vulnerability to ADRs is more probable at older ages—especially at a hepatotoxic level—due to a significant reduction in the clearance rate of metabolized drug agents by the cytochrome P450 enzyme, changes in the distribution of hepatic blood flow, and other factors affecting liver function [46].

Another key finding of this study showed that of the 7474 reports, 31.2% required complete withdrawal of the suspected medicine(s), followed by a reduction in the dose (1.03%) and an increase in the dose (0.05%). Overall, kanamycin (13.5%), cycloserine (12.7%), and pyrazinamide (10.3%) were the most frequent medicines withdrawn due to ADRs. In terms of medicine–reaction pairs, ear and labyrinth disorders were associated with kanamycin (7.9%), and psychiatric disorders (7.8%) and gastrointestinal disorders (4.0%) were responsible for the withdrawal of cycloserine and ethionamide, respectively. Similarly, studies conducted in South Africa, Nigeria, China, and India indicated that a significant proportion of patients required permanent discontinuation of the offending drug associated with ADRs [23,47–49]. A retrospective study conducted in South Korea indicated that PAS was withdrawn in 11.3% of the patients due to uncontrolled diarrhea, nausea, or vomiting [36]. According to Bhatt et al., cycloserine produced major adverse psychotic reactions, which led to the discontinuation of the treatment [32]. Early diagnosis and appropriate management of ADRs are important to improve patients' quality of life, tolerability, and thus treatment success. Serious ADRs may lead to poor adherence and discontinuation of the treatment before smear conversion, which might lead to the transmission of resistant strains of TB to the community [50].

## **STRENGTHS AND LIMITATIONS OF THE STUDY**

The strength of this study is the use of VigiBase as a data source, which included reports submitted by multiple countries. This makes it a valuable resource for identifying safety concerns with medications that may not be apparent in one country.

However, there are also some limitations. Firstly, VigiBase only includes data from reports submitted by the WHO's PIDM countries. This means that there may be significant gaps in the data, particularly from countries that are not members of the WHO's PIDM. Secondly, according to Hagggar et al. [51], ICSRs from Africa make up <1% of the global total reports in VigiBase, and another study was conducted to analyze the global patterns of ADRs submitted to VigiBase over a decade, highlighting those low-income countries reported relatively more ADRs for anti-infective cases (including DR-TB cases) than high-income countries [52]. These findings imply that low-income countries known to report ADRs for anti-infective cases are less visible in VigiBase globally; therefore, this study should be supplemented with other data sources to address this gap. Thirdly, the data in VigiBase are not always complete. Large reports were excluded because of missing information, such as the ADRs' start date, the medicine's start date, and unknown indications. This appears to be a challenge globally, as studies conducted in São Paulo (Brazil), western China, the Japanese AE database, Catalonia, the Midi-Pyrénées PV center (France), and Portugal on the completeness and quality of reporting showed similar trends [53–58]. Therefore, we strongly recommend that PIMD member countries and WHO-UMC work towards improving the quality of the reports. Lastly, VigiBase does not include all the possible ADRs collected by pharmacovigilance centers as countries decide on what information can be shared with VigiBase. Similarly, since there are no data on the exposure denominator, and only individual case safety reports (ISCsRs) of suspected adverse drug reactions (ADRs) that have already occurred are collected by the WHO Programme for International Drug Monitoring (PIDM)/UMC database, it is impossible to determine the risk associated with the suspected medicines. Given these limitations, it is important to consider additional sources of information when researching the safety of medicines.

## **METHODS AND MATERIALS**

### **Data Source**

This study was conducted using data obtained from VigiBase®, maintained by the WHO's Uppsala Monitoring Center (WHO-UMC), Uppsala, Sweden. VigiBase is the WHO's only global database of

the reported potential side effects of medicinal products. It is the largest database of its kind in the world, with over 32 million reports of suspected ADRs submitted since 1968 by the member countries of the WHO's Program for International Drug Monitoring (PIDM) [24]. It is a repository of individual case safety reports (ICSR) of ADRs collected by the national pharmacovigilance centers of about 152 member countries and 23 associate members [24].

VigiBase is linked to medical and drug classifications, including terminologies such as the WHO-ART/MedDRA and WHO ICD classifications, which are vital to effective and accurate analyses [24,25]. Thus, this study analyzed all the suspected ADRs associated with DR-TB medicines included in VigiBase. Each report represents an individual who may have experienced one or several ADRs simultaneously. As a result, the number of reported ADRs could be higher than the number of patients.

### **Variables and Definitions**

The following ADR report variables were included in the data analysis: medicines, country of origin, age, patients' age group, MedDRA preferred terms (PT) and system organ class (SOC), the seriousness of the ADR, the outcome of the reaction, and action taken. Reports with unknown information for a particular variable were included in the analysis to obtain a complete panorama of the data.

An adverse drug reaction (ADR) is a response to a medicinal product that is noxious and unintended. Adverse reactions may arise from using the product within or outside the terms of the marketing authorization or from occupational exposure. Uses outside the marketing authorization include off-label use, overdose, misuse, abuse, and medication errors [26].

An indication was defined as a DR-TB case that led to a treatment being recommended. The following indications/cases were included in the analysis: extensively resistant pulmonary tuberculosis, multidrug-resistant tuberculosis, rifampicin-resistant tuberculosis, multidrug-resistant pulmonary tuberculosis, mono-resistant tuberculosis, poly-resistant tuberculosis, mono-resistant pulmonary tuberculosis, poly-resistant pulmonary tuberculosis, and multidrug-resistant pulmonary tuberculosis.

Serious ADRs: According to the ICH E2A guidelines, a serious adverse event or reaction is an AE that either leads to death or a life-threatening experience, hospitalization or prolongation of hospitalization, persistent or significant disability, or a congenital anomaly or that is a medically important event or reaction [27].

The patient’s age group was the patient’s age at the ADR’s onset. The age groups in this study were categorized into children, adolescents (0–18 years old), adults (19–64 years old), and the elderly (above 65 years old). The MedDRA SOCs are the 27 groups of ADR terms at the top of the MedDRA hierarchy, which use groupings by etiology (e.g., infections and infestations), manifestation site (e.g., gastrointestinal disorders), or purpose (e.g., surgical and medical procedures) [25].

The MedDRA preferred terms (PTs) are discrete descriptors (single medical concepts) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, or medical, social, or family history characteristic [25].

According to the MedDRA SOC, an “investigation” is a clinical laboratory test (including biopsies), radiologic test, physical examination parameter, or physiologic test (e.g., a pulmonary function test).

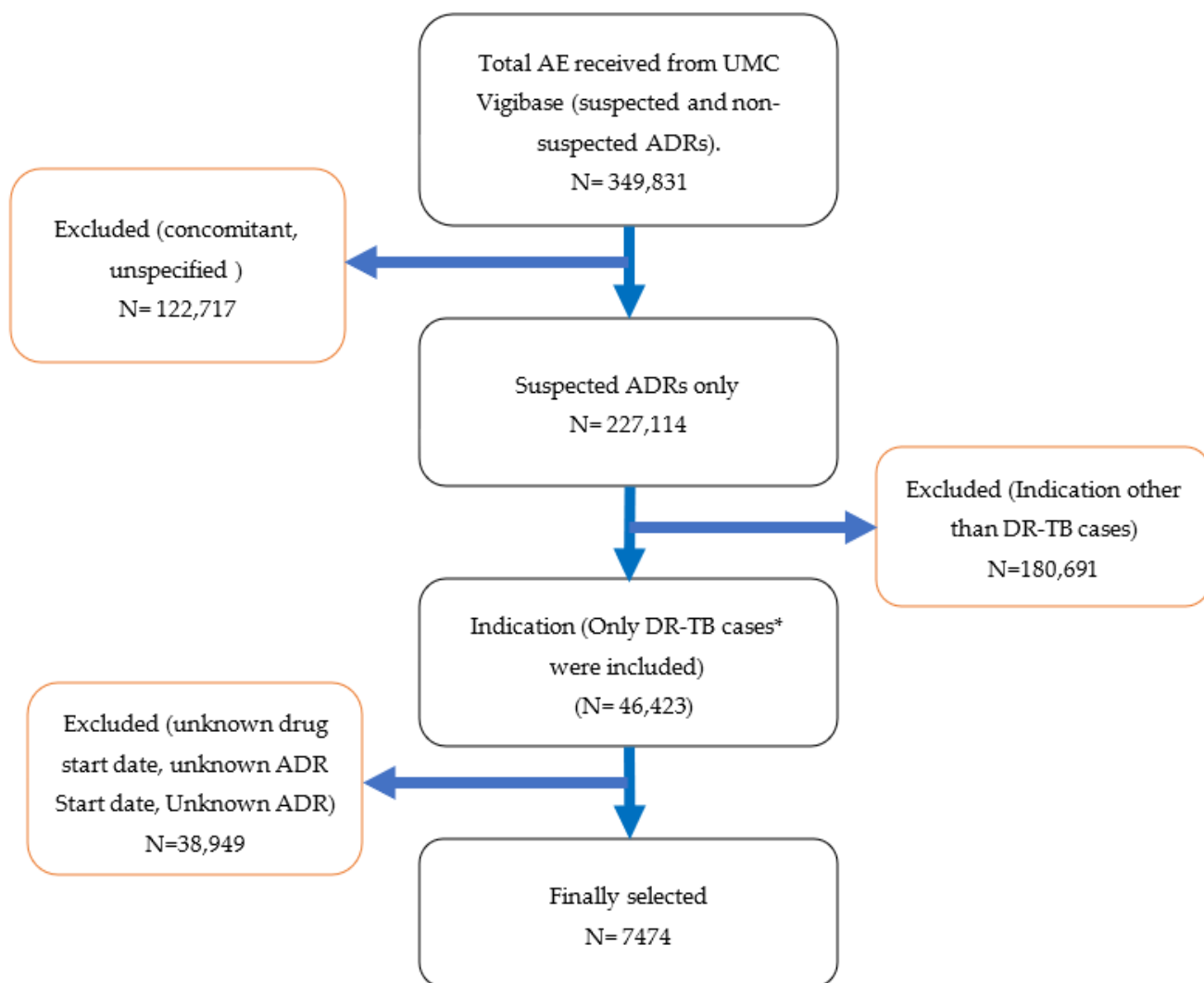
## SEARCH CRITERIA

**Table 6. Summary of search criteria used.**

Search Criteria	
Substance	Amikacin, PAS, bedaquiline, capreomycin, cilastatin-imipenem combination, clofazimine, cycloserine, delamanid, ethambutol, ethionamide, kanamycin, levofloxacin, linezolid, meropenem, moxifloxacin, protionamide, pyrazinamide, streptomycin, terizidone, isoniazid, rifampicin, amoxicillin–clavulanic acid combination, gatifloxacin, thioacetazone, ethambutol–isoniazid–pyrazinamide–rifampicin(RHZE),isoniazid–pyrazinamide–rifampicin(RHZ), isoniazid–rifampicin (RH), ethambutol–isoniazid (EH), and isoniazid–thioacetazone.
Drug involvement	Suspected
Terminology	MedDRA
Reactions	All
Country	All
Years	1 Jan 2018 to 31 December 2020

<b>Other</b>	<p>Search in indication and medical history (coded fields),</p> <p>Search terms (MedDRA):</p> <p>“extensively resistant pulmonary tuberculosis”, “multidrug resistant tuberculosis”, “rifampicin resistant tuberculosis”, “multidrug resistant pulmonary tuberculosis”, “mono-resistant tuberculosis”, “poly-resistant tuberculosis”, “mono-resistant pulmonary tuberculosis”, “poly-resistant pulmonary tuberculosis”, “multidrug resistant pulmonary tuberculosis”, “other respiratory tuberculosis, other”.</p> <p>Reports are selected if any of the terms above appear in the indication or medical history; additionally, reports where the indication is missing will be included.</p>
<b>De-duplicated dataset?</b>	Yes

For each report describing ADRs attributed to any of these medicines, detailed information regarding the patient’s demographics (age, sex, country, and medical history), drugs (an indication of use, route of administration, and start and end date), ADRs (date of onset, seriousness, outcome, outcomes of dechallenge and rechallenge, and causality), and administrative information (type and source of the report) was recorded. Figure 6 illustrates a graphic flowchart of ADR selection.



\*DR-TB cases: See the definition section

**Figure 6. Schematic diagram of the selection criteria of ADRs from Vigibase data used to filter the records.**

### Data Analysis

A descriptive analysis was performed on the eligible reports from Vigibase using prespecified indicators. The ADRs were stratified by sex (male or female), age group (< 18 years, 18–64 years, and ≥ 65 years), reporting country, seriousness (serious and non-serious), the outcome of the reaction (fatal, not recovered/not resolved, recovered/resolved, recovered/resolved with sequelae, and recovering/resolving), and dechallenge and rechallenge. A combination of Excel and SPSS data analysis software [28] was utilized for data cleaning and data analysis



### 3.5 CONCLUSIONS

In conclusion, 39 countries' reports were included in this study. Most of the reports were submitted by India, followed by South Africa and Eswatini. The results of this study confirmed that pyrazinamide, ethionamide, cycloserine, bedaquiline, clofazimine, and linezolid were responsible for more than half of the ADRs reported in VigiBase during the period from January 2018 to December 2020. Vomiting was the most frequently reported ADR, followed by arthralgia, nausea, peripheral neuropathy, and prolongation of electrocardiogram QT. Elderly patients (aged more than 65 years) had poorer outcomes of the reaction relative to adolescents (0–18 years) and adults (19–64 years). We want to emphasize that strict monitoring of the unfavorable effects of medicines and effective pharmacovigilance systems should be implemented, as a high proportion of the medicines responsible for serious ADRs are the backbone of DR-TB treatment currently in use.

**Supplementary Materials:** The following supporting information can be downloaded at <https://www.mdpi.com/article/10.3390/antibiotics12050811/s1> Table S1: Cross-tabulation analysis of the most frequent ADRs associated with the top five withdrawn medicines.

**Author Contributions:** All authors contributed to the study's conception and design. Conceptualization, A.L.D. and A.F.; methodology, A.L.D. and A.F.; validation, A.L.D., A.F., A.K., and F.S.; formal analysis, A.L.D. and A.F.; data curation, A.L.D.; writing—original draft preparation, A.L.D.; supervision, A.F., A.K., and F.S. All authors have read and agreed to the published version of the manuscript.

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**Data Availability Statement:** The datasets used during this study are not publicly available due to agreements between the data contributors to the database used (VigiBase) and the database's custodian. The national centers of the WHO's Program for International Drug Monitoring (PIDM) contribute data to VigiBase, and the Uppsala Monitoring Centre serves as the custodian in its capacity as a WHO collaboration center for international drug monitoring. On reasonable request, the corresponding author may make some subsets of the data available.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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### **3.6 KEY RESULTS AND RESEARCH PERSPECTIVE**

This first study of our thesis focused on ADRs associated with the treatment of DR-TB based on data extracted from the WHO database (Vigibase). We analyzed 25 medicines and their associations with ADRs.

The study identified important and notable findings. First, we discovered that the most associated medicines with ADRs were pyrazinamide, ethionamide, and cycloserine. Additionally, more than half of the recorded ADRs were caused by bedaquiline, clofazimine, and linezolid.

The current DR-TB treatment regimen's key medicines, such as bedaquiline, delamanid, clofazimine, linezolid, and cycloserine, are primarily responsible for serious ADRs. Furthermore, we observed that psychiatric disorders reported in relation to cycloserine were more common in adults compared to adolescents and the elderly. The most frequently reported ADRs included vomiting, arthralgia, nausea, peripheral neuropathy, and QT prolongation, which were consistent with findings from previous studies. Fundamental understanding regarding DR-TB management can be gained through recognizing these safety concerns and assessing the seriousness and frequency of the most prevalent ADRs. Our study emphasizes the importance of tracking and managing ADRs associated with DR-TB medicines to maximize positive treatment outcomes and ensure patient safety.

This work draws attention to two significant focus areas from a research perspective. Firstly, more than one-third of patients required complete withdrawal of suspected medicines due to serious ADRs. This highlights the necessity of regularly monitoring the safety of medicines and taking suitable measures as soon as possible to address these challenges. Secondly, we also observed that two out of five ADRs tended to appear two months after treatment initiation. This suggests the importance of closely monitoring patients during this critical period to detect and manage ADRs effectively.

This study significantly contributes to our knowledge of adverse drug reactions (ADRs) in the treatment of drug-resistant tuberculosis (DR-TB). The findings provide valuable insights into the relationship between specific medicines and adverse effects, which can inform the development of strategies to optimize treatment outcomes and enhance patient safety. However, further research is necessary to explore preventive measures and improve the management of ADRs in the context of DR-TB treatment, both globally and at the national level.

Building on these findings, the next step of our thesis focused on assessing the safety profile of DR-TB medicines specifically used in all DR-TB sites in Eswatini. We analyzed data collected from patients' chronic care files across all DR-TB sites to gain an understanding of the safety profile of these medicines and their impact on patients in a national-level context.



## **CHAPTER 4. STUDY TWO**

### **PATTERNS OF ADVERSE DRUG REACTIONS IN PATIENTS WITH DRUG RESISTANT TUBERCULOSIS IN ESWATINI: A RETROSPECTIVE COHORT STUDY**

#### 4.1 PATTERNS OF ADVERSE DRUG REACTIONS IN PATIENTS WITH DRUG RESISTANT TUBERCULOSIS IN ESWATINI: A RETROSPECTIVE COHORT STUDY

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##### **Abstract:**

**Background:** Drug-resistant tuberculosis (DR-TB) poses a significant challenge to global health, particularly in resource-limited countries, with an estimated 450,000 new cases of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) in 2021. DR-TB is caused by TB bacteria that are resistant to at least one first-line anti-TB medicine, necessitating the use of second-line medications, which are associated with higher toxicity.

**Methods:** A retrospective study analyzed 670 DR-TB patients treated in the DR-TB treatment sites between January 2018 and December 2020, focusing on the cohort's baseline characteristics and the adverse drug reactions (ADRs) encountered during treatment.

**Result:** A total of 670 patients enrolled in the treatment during the study period. The cohort was composed of 384 males (57.3%) and 286 females (42.7%) with an overall median age of 36 years [interquartile range (IQR): 29 - 45]. Most of the DR-TB patients (380; 56.7%) were never treated previously and 410 (61.2%) were co-infected with HIV. Out of 670 DR-TB patients, 295 (44.0%) had at least one ADR; the total number of ADRs reported in this sample was 484. Out of the 19 different medicines included in this report, bedaquiline was associated with the highest number of ADRs (79; 16.3% of the total ADRs), followed by ethionamide (75; 15.5%), pyrazinamide (69; 14.3%), terizidone (60; 12.4%) and linezolid (44; 9.1%). Arthralgia was the most reported ADR (66; 13.6% of the total ADRs), followed by nausea and vomiting (51; 10.5%), peripheral neuropathy (47; 9.7%), hypoacusis

(43; 8.9%), QTc prolongation on electrocardiogram (34; 7.0%) and optic neuritis (31; 6.4%). The analysis of this sample showed that age is a significant factor in the occurrence of peripheral neuropathy and arthralgia-related ADRs, with individuals aged 19-65 showing an increased risk compared to older age groups. Serious ADRs related to DR-TB medicines were identified in more than 30% of the patients. While two-thirds of these patients (n=308) recovered from their ADRs, 66 (13.6%) of the reactions were either not recovered or recovered with sequelae.

**Conclusion:** The analysis of the present cohort has shown that almost half of the patients showed at least one ADR, and almost one-third were serious. As ADRs can appear at any time during treatment and can interfere with adherence to the treatment, it is extremely important to strengthen the safety monitoring of patients being treated for DR-TB to ensure quick and appropriate ADR management, thus reducing the chance of treatment failure.

**Keywords:** Drug-Resistant Tuberculosis, Pharmacovigilance, Adverse Drug Reaction, Eswatini

## 4.2 INTRODUCTION

Drug-resistant tuberculosis (DR-TB) poses a significant challenge to global health, particularly in resource-limited settings like the Kingdom of Eswatini. DR-TB is caused by TB bacteria that are resistant to at least one first-line anti-TB medicine (1), necessitating the use of second-line medications, which are associated with higher toxicity. (2) Globally, there were an estimated 450,000 new cases of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB) in 2021. (3) DR-TB-resistant TB cases were first reported in Eswatini in 2006. (4) The kingdom faces a considerable multi-drug resistant TB (MDR-TB) burden with 8.6% prevalence of MDR-TB among new cases, 17.5% among previously treated, and 13% prevalence of any form of drug resistance. (5)

Treatment of DR-TB disease requires multiple medicines for many months, which requires more extended treatment regimens with medicines that are more expensive and increase the risk of adverse drug reactions (ADRs), posing significant clinical and public health challenges. (6) While the focus often lies on treatment successes and resistance patterns, the management of ADRs among DR-TB patients is equally critical. According to the CIOMS Cumulative Pharmacovigilance Glossary, an ADR is a noxious and unintended response to a medicinal product for which there is a reasonable possibility that the product caused the response. (7) ADRs are common during TB treatment, especially in the context of DR-TB, where patients are exposed to multiple medications for prolonged periods. (8) ADRs compromise treatment adherence and contribute to treatment failure, disease progression, and increased healthcare costs. (8,9) A comprehensive understanding of ADRs' nature, magnitude, and risk factors can significantly inform treatment protocols and improve patient outcomes.

Several studies have highlighted the substantial burden of ADRs among DR-TB patients, with prevalence ranging from 30 to 90% reported across different settings. (8,10–13) The severity of ADRs ranges from mild discomfort to life-threatening complications, necessitating close monitoring, timely intervention, and proactive management strategies to prevent treatment interruptions, regimen modifications, and poor treatment outcomes. (9,12,14)

Risk factors such as age > 60 years, alcoholism, smoking, overweight/obesity status, anemia, and HIV co-infection, as well as sodium, iron, and albumin deficiencies, have been associated with ADRs due to DR-TB medicines. (15–17)

In this article, we critically analyzed safety data collected retrospectively across 14 DR-TB treatment sites in Eswatini to elucidate the characteristics and determinants of ADRs in this vulnerable population.

## **METHODS**

### **Study design**

This was a retrospective cohort study that employed quantitative research methods among DR-TB patients receiving or who received treatment at the 14 DR-TB treatment sites of Eswatini before the COVID-19 pandemic. The study analyzed the longitudinal data of all eligible patients abstracted from the chronic care files/medical records, which involved reviewing the records of DR-TB patients enrolled in the treatment.

### **Study setting**

Eswatini has 14 treatment sites for managing DR-TB patients. (18) Secondary data were collected from patients' medical records and documented longitudinally. These sites are AHF Matsapha, Baylor Center of Excellence TB Clinic, Dvokolwako Health Center, Emkhunzweni Health Center, Good Shepherd Hospital, Hlatikhulu Hospital, Mankayane Government Hospital, Manzini TB Center, Matsanjani Health Center, Nhlanguano Health Center, Pigg's peak Hospital, Siphofaneni Clinic, Sithobela Health center, and National TB Hospital.

### **Exposure definition**

According to the Eswatini National Guidelines and the World Health Organization for the Medical Management of DR-TB(19), patients should be treated with at least four effective medicines constructed from groups of anti-tuberculosis second-line drugs. These are Group A (Levofloxacin, Moxifloxacin, Bedaquiline, Linezolid), Group B(Clofazimine, Cycloserine, Terizidone), Group C (Ethambutol, Delamanid, Pyrazinamide, Imipenem-cilastatin, Meropenem, Amikacin, Streptomycin, Ethionamide, Prothionamide, p-aminosalicylic acid). (19) Kanamycin(Km) and capreomycin(Cm) have been removed from the standardized regimen due to safety and effectiveness issues(2). Bedaquiline (Bdq) and Delamanid (Dlm) are recommended for 6 months, but extended use under off-label protocols is possible in special circumstances. (20) The Eswatini national guidelines at the time recommended treatment durations as follows: Longer MDR-TB regimen (18 to 20 months, all oral

regimen), Shorter MDR-TB regimen (9-12 months, existing regimen with Amikacin substituting Kanamycin) and Shorter MDR-TB regimen (9-12 months, all oral regimen) .

### **Study population**

The study population included all DR-TB patients who were enrolled in treatment between January 1, 2018, and December 31, 2020. These patients included those who were documented as having started, completed or were still on treatment. The study excluded all patients who died or lost to follow-up before being initiated on treatment.

### **Data collection**

Standardized data collection tools collected comprehensive information from patients' chronic care files. The tool captured patient demographic information, comorbidities, reaction details, medicine details on the suspected medicines, and baseline and follow-up laboratory tests. To ensure the validity of the data collection tools and to familiarize data collectors with both tools, a one-week field test (pilot study) was conducted on non-eligible patients following a one-day orientation workshop. In our analysis, we employed the Medical Dictionary for Regulatory Activities (MedDRA) to ensure consistent terminology and to code ADRs. We incorporated Preferred Terms (PT) and System Organ Class (SOC) classifications from MedDRA in our evaluation.

### **Outcome measures**

The current study measured ADRs encountered during the study period, their nature, seriousness, causality, outcome, management and/or treatment taken, and possible risk factors as primary outcomes. The association of risk factors with ADRs was evaluated using bivariate and multivariate logistic regression.

### **Data analysis**

Descriptive and analytical analyses were conducted using the Statistical Package for Social Science version 26 (SPSS-26). These include descriptive, univariate, bivariate, and multivariate analysis. The association between the identified major ADRs and possible risk factors (age, sex, exposure time, and comorbidities) was explored using the chi-square ( $\chi^2$ ) test. P-value and 95% confidence intervals (95% CIs) were used to test statistical significance. Results are presented as medians, percentile, frequencies, interquartile ranges, and odds ratios as appropriate. P-value < 0.05 was regarded as statistically significant.

## **Variables and Definitions**

The following ADR report variables were included in the data analysis: medicines, age, patient age group, MedDRA Preferred Term (PT), the seriousness of ADR, the reaction outcome, and action taken. Reports with information 'unknown' on a particular variable were included in the analysis to obtain the complete panorama of the data.

**Adverse Drug Reaction (ADR):** is a response to a medicinal product, which is noxious and unintended. Adverse reactions may arise from using the product within or outside the terms of the marketing authorization or from occupational exposure. Use outside the marketing authorization includes off-label use, overdose, misuse, abuse, and medication errors. (21)

**Serious ADR:** According to ICH E2A guideline, a serious ADR is an ADR that either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to persistent or significant disability; or to a congenital anomaly or is a medically important event or reaction. (22)

**The patient age group** is the patient age at ADR onset; the age group in this study was categorized into Children and Adolescents (0-18 years old), Adults (19-64 years old), and Elderly (above 65 years old)

**The MedDRA Preferred Terms (PTs)** are discrete descriptors (single medical concept) for a symptom, sign, disease diagnosis, therapeutic indication, investigation, surgical or medical procedure, and medical, social, or family history characteristics. (23)

### **Ethical considerations**

Ethical approval was obtained from The Eswatini Health and Human Research Review Board (EHHRB). All ethical and professional considerations were followed throughout the study to keep patient records strictly confidential, and patients' identifiers were anonymized and de-identified prior to analysis. As this was a retrospective study, informed consent was not obtained from patients and waived by EHHRB. In addition to the Ethical clearance letter, permission to collect data was requested through a formal letter from the European training program in pharmacovigilance and pharmacoepidemiology (Eu2P) and the researcher with ethical clearance to the management of each treatment site.

### 4.3 RESULT

#### Baseline Characteristics

The current study analysis included 670 patients enrolled in the treatment during the study period. The cohort was composed of (n=384;57.3%) males and (286;42.7%) females with a median age of 36 [interquartile range (IQR): 29 - 45]. The details are shown in Table 1 below. Most of the DR-TB patients were never treated for TB previously (380; 56.7%).

Table 3: Distribution of the DR-TB cohort according to the background characteristics

Background characteristics		N= 670 (%)
Sex	Male	384 (57.3)
	Female	286 (42.7)
Age	Mean age, years (+/- SD)	37.7 (14.5)
	0-18 =42(6.3%)	42 (6.3)
	19-64	586 (87.5)
	Above 65	42 (6.3)
HIV status	Reactive	410 (61.2)
	Non-reactive	260 (38.8)
TB Treatment History	Never treated	380 (56.7)
	Already Treated	289 (43.1)
	Unknown	1 (0.2)
Comorbidity	Patients without Co-morbidities	228 (34.1)
	Patients with at least one comorbidity	409 (61.1)
	Patients with more than two comorbidities	33 (4.9)



Type of comorbidities	Diabetes	32 (4.8)
	Asthma	6 (0.9)
	Pre-existing ECG abnormality	10 (1.5)
	Liver problem	10 (1.5)
	Abnormal thyroid	9 (1.3)
Alcohol abuse(>40ml)	YES	53 (7.9)
	NO	617 (92.1)
Types of Tuberculosis	Pulmonary	633 (94.6)
	Extra Pulmonary	53 (7.9)

Regarding HIV/TB co-infection, most of the patients were co-infected with HIV (410; 61.2%). As indicated in the below table 2, among individuals with HIV +ve status (410; 51.5% had not received prior anti-TB therapy, while 48.3% had a history of prior anti-TB treatment. Additionally, a negligible percentage (0.2%) had an unknown history of prior anti-TB therapy.

**Table 2: Table showing the distribution of TB treatment history and HIV status among the study population**

		Prior anti-TB therapy			Total
		No	Yes	Unknown	
HIV_status	Reactive	211(51.5%)	198(48.3%)	1(0.2%)	410(100%)
	Non-Reactive	169(65.0%)	91(35.0%)	0	260(100%)
Total		380(56.7%)	289(43.1%)	1(0.1%)	670(100%)

( $\chi^2= 12.29$ ;  $df= 2$ ;  $P= 0.0021$ )

#### 1.1. Characteristics of ADRs among DR-TB patients included in the cohort.

Out of 670 DR-TB patients in the cohort, (n=295;44.0%) had at least one ADR. The total number of reported ADRs was 484; 112 patients (16.7% of the sample) experienced more than one ADR simultaneously. With regards to specific ADRs, arthralgia (66 patients; 13.6%) was the most reported ADR, followed by nausea and vomiting (51; 10.5%), peripheral neuropathy (47; 9.7%), hypoacusis (43; 8.9%), QT prolonged on the electrocardiogram (34; 7.0%) and optic neuritis (31; 6.4%).

Among the 19 different medicines analyzed in this study, bedaquiline was associated with the highest number of ADRs (n=79, 16.3%) followed by ethionamide (75 ADRs; (15.5%), pyrazinamide (69; 14.3%), terizidone (60; 12.4%) and linezolid (44; 9.1%). Regarding the ADRs attributed to the DR-TB medicines in this cohort, QT prolonged on the electrocardiogram was the most prevalent ADR associated with bedaquiline (24;30.4%), followed by nausea and vomiting (12; 15.2%) and chest pain (8; 10.1 %). So, most of the ADRs associated with bedaquiline were cardiac, gastrointestinal, and neurological symptoms.

Mild gastrointestinal issues, specifically nausea and vomiting (19; 25.3%) and gastritis and dyspepsia (13; 17.3%) were predominantly linked with ethionamide. Optic neuritis (11;14.7 %) and hypothyroidism (4; 5.3%) were also frequently reported in relation to ethionamide.

Terizidone and linezolid also had high rates of specific ADRs, such as peripheral neuropathy (23; 38.3%) and optic neuritis (12; 27.3%), respectively.

### Seriousness of reaction

Of the identified ADRs, 146 (30.2%) were found to be serious. These 146 ADRs happened in 136 patients (20.2 % of the study sample). Among these serious ADRs, (70; 47.9%) were observed in males, while (76; 52.1%) were reported in females. In the 0–18 age group, 25.0% of reported ADRs were serious, and 75.0% were non-serious, while in the 19–64 age group, 32.3% were serious and 67.7% were non-serious; for those above 65 years, 17.2% of ADRs were serious, and 82.8% were non-serious. (see the following Table 3).

**Table 4: Seriousness of the reported ADRs according to the suspected medicines, sex, age group, and specific ADRs**

Variables		Seriousness				Total (N=484,100%)
		YES (n = 146)		No (n= 338)		
		N	%	N	%	
Age group (years)	Children and adolescents (0–18)	6	25.0	18	75.0	24 (100)

	Adult (19–64)	130	32.3	272	67.7	402 (100)
	Elderly (above 65)	10	17.2	48	82.8	58 (100)
TOTAL		146	30.1	338	69.8	484 (100)
Top five ADRs according to PT MedDRA terms	Arthralgia	2	3.0	64	97.0	66(100)
	Nausea and Vomiting	4	7.8	47	92.2	51(100)
	Neuropathy peripheral	11	23.4	36	76.6	47(100)
	Hypoacusis	38	88.4	5	11.6	43(100)
	Electrocardiogram QT prolonged	25	73.5	9	26.5	34(100)
	Optic neuritis	23	74.2	8	25.8	31(100)
	Others	43	20.3	169	79.7	212(100)
TOTAL		146	30.2	338	69.8	484(100)
Sex	Male	70	26.9	190	73.1	260(100)
	Female	76	33.9	148	66.1	224(100)
TOTAL		146	30.2	338	69.8	484 (100)

In terms of the seriousness of ADRs, peripheral neuropathy (11;23.4%), hypoacusis (38;88.4%) prolonged electrocardiogram QT (25;73.5%), and optic neuritis (23;74.2%) were the most frequent serious reported in the cohort). The medicines that are associated with these ADRs need to be monitored.

### **Mean onset of reaction and duration of reaction**

ADRs occurred at various points throughout the treatment duration, from treatment initiation to the last day of the treatment. Specifically, arthralgia exhibited the highest frequency of reported ADRs, with a mean onset of reaction occurring at 127.7 days (ranging from 33 to 560 days). Peripheral neuropathy had an average onset at 191.7 days (ranging from 42 to 479 days), hypoacusis at 96.8 days (ranging from 62 to 428 days), prolonged electrocardiogram QT at 115.3 days (ranging from 18 to 446 days), and optic neuritis at 233.5 days (ranging from 48 to 458 days). Furthermore, we noted several

ADRs that commonly appeared later in treatment. These included skin conditions like bronze skin and psoriasis, which appeared at around a mean duration of 370.0 days (ranging from 355 to 385 days). Unilateral blindness occurred at an average of 368.0 days (ranging from 76 to 330 days), hypothyroidism at 319.8 days (ranging from 14 to 486 days), and optic neuritis at 233.4 days (ranging from 48 to 458 days). It is important to note the wide variation in the induction period of these relevant ADRs.

Regarding the duration of reaction, the mean duration of ADRs across all observations is approximately 62.8 days [ranging from 1-240 days], indicating that, on average, ADRs persist for about two months.

### Reaction outcome

The current study shows that most ADRs were recovered/resolved (308;63.3%), followed by recovering/resolving (52;10.7%). Similarly, reactions recovered with sequelae and not recovered account for (61,12.6%). We also discovered that a total of 5 fatality cases were reported, involving 4 patients who experienced different ADRs. The seriousness of ADRs significantly varied with their outcomes ( $\chi^2=122.27$ ,  $df=5$ ,  $p<0.001$ )

*Table 5: Seriousness of reaction crosstab against the outcome of the reaction*

Reaction outcome	Seriousness of ADRs				Total
	YES	%	No	%	
Recovered/resolved	50	16.2	258	83.8	308
Recovering/resolving	27	51.9	25	48.1	52
Recovered with sequelae	17	39.5	26	60.5	43
Not recovered/resolved	14	77.8	4	22.2	18
Died	2	40.0	3	60.0	5
Unknown	36	62.1	22	37.9	58
TOTAL	146	30.1	338	69.8	484

( $\chi^2=122.27$ ,  $df=5$ ,  $p<0.001$ )

Concerning the reports of patients who died while receiving the treatment, there was not enough information to establish the relationship with the reported ADR or the causality association with the medicines taken by these patients. For a descriptive purpose, the adverse events presented by the patients who died included arthralgia (n=2) and edema, headache, and anemia (1 each). Concerning the events associated with medicines in these fatal cases, these were: arthralgia in a patient taking levofloxacin, edema in a patient taking bedaquiline, and headache and anemia in a patient taking rifampicin and linezolid, respectively (see Table 3). Looking at the seriousness of the reactions, 3 of the cases were non-serious reactions. As indicated in the following table 4, two of the reported fatal cases were attributed to a single patient undergoing treatment for a presumptive DR-TB case. Importantly, all 4 patients had co-infection of HIV and TB and were concurrently receiving treatment with HIV medicines, which were not included in the reports. In terms of sex, four of the five patients were females, and 3 out of 5 were less than 65 years old (see Table 3)

**Table 6: Distribution of suspected death cases identified while on treatment\***

Case	M/F	Age	Suspected medicine	Reason for use	Reported ADRs	Concomitant medicines	Observations
#1	M	66	Bedaquiline	Poly-resistance TB	Arthralgia	Bedaquiline, Linezolid, Terizidone, Tenofovir, Lamivudine, Efavirenz	
#2	F	27	Levofloxacin	Rifampicin Resistance	Arthralgia	Bedaquiline, Linezolid, Terizidone, Levofloxacin, Clofazimine, Tenofovir,	Optic Neuritis and Peripheral neuropathy were co-reported with Arthralgia.

						Lamivudine, Efavirenz	
#3	F	54	Rifampicin	Isoniazid resistance	Headache	Rifampicin, Isoniazid, Pyrazinamide, Ethambutol, Dolutegravir, lamivudine and tenofovir	
#4	F	52	Linezolid and Bedaquiline	Presumptive DR	Anemia; Oedema	Bedaquiline, Linezolid, levofloxacin, clofazimine, Cycloserine, Dolutegravir, lamivudine and tenofovir	The patient presented with two ADRs. Anemia and edema are suspected to be caused by Linezolid and Bedaquiline respectively

*\*: Death cases were identified while patients were on treatment, and Causality has not been fully established. Therefore, we cannot associate or completely rule out the association of the fatal cases with ADR outcomes.*

### **Factors associated with the occurrences of ADRs.**

We conducted univariate and multivariate analyses to assess the association between selected ADR occurrence and variables such as sex, age group, HIV status, and previous tuberculosis (TB) treatment. Crude odds ratios (OR) with 95% confidence intervals (CI) and adjusted ORs from multivariate analysis were calculated.

The bivariate and multivariate analysis showed that only age group is a significant factor in the occurrence of peripheral neuropathy and arthralgia, with individuals aged 19-65 showing an increased risk compared to older age groups. However, other variables such as sex, HIV status, and previous TB

treatment did not demonstrate significant associations with the occurrences of ADRs in the current analysis (See below Table 6).

**Table 7: Risk Factors for ADRs in Patients Undergoing DR-TB Treatment - Bivariate and Multivariate Analysis**

AD R	Risk factors	Variables	Presence of Adverse Drug Reactions				Univariate		Multivariate analysis	
			YES		NO		Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
			N	%	N	%				
Hypoaacusis	Sex	(Ref: Male)	22	5.7	362	94.3	ref	Ref	ref	ref
		Female	21	7.3	265	92.7	1.304(0.70-2.41)	0.4	1.314(0.705-2.452)	1.314
	Age Group	(0-18)	2	4.8	40	95.2	2.05(0.179-23.512)	0.564	2.215(0.191-25.628)	0.524
		(19-65)	40	6.8	546	93.2	3.004(0.403-22.4)	0.283	2.653(0.349-20.173)	0.346
		>65	1	2.4	41	97.6	ref	Ref	ref	ref
	HIV Status	YES	27	6.6	383	93.4	1.075(0.568-2.037)	0.824	0.9(0.466-1.739)	0.754
		NO	16	6.2	244	93.8	ref	Ref	ref	
	Previous TB treatment	(YES)	27	9.3	262	90.7	2.344(1/238-4.439)	<b>0.009</b>	2.285(1.193-4.326)	0.13
NO		16	4.2	364	95.8	ref	Ref			
Electrocardiogram QT prolonged	Sex	(Ref: Male)	17	4.4	367	95.6	ref	ref	ref	ref
		Female	17	5.9	269	94.1	1.364(0.684-2.721)	0.378	1.352(0.676-2.702)	0.393
	Age Group	(0-18)	2	4.8	40	95.2	0.475(0.82-2.746)	0.406	0.47(0.081-2.728)	0.4
		(19-65)	28	4.8	558	95.2	0.477(0.159-1.429)	0.186	0.478(0.154-1.485)	0.202
		>65	4	9.5	38	90.5	ref	Ref	ref	ref
	HIV Status	YES	21	5.1	389	94.9	1.026(0.504-2.086)	0.944	1.137(0.542-2.385)	0.73
		NO	13	5.0	247	95.0	ref	ref	ref	ref
	Previous TB treatment	(YES)	13	4.5	276	95.5	0.805(0.396-1.637)	0.549	0.823(0.399-1.699)	0.599
NO		21	5.5	359	94.5	ref	ref	ref	ref	
Optic neuritic	Sex	(Ref: Male)	18	4.7	366	95.3	ref	ref	ref	ref
		Female	13	4.5	273	95.5	0.968(0.466-2.010)	0.931	1.045(0.48-2.192)	0.908

	Age Group	(0-18)	2	4.8	40	95.2	ref	ref	ref	ref
		(19-65)	29	4.9	557	95.1	1.041(0.24-4.521)	0.957	2.060(0.267-15.8)	0.488
		>65	0	0.0	42	100.0	0.00(0.000-00)	0.998		0.988
	HIV Status	YES	21	5.4	366	94.6	1.350(0.625-2914)	0.445	1.136(0.517-2.495)	0.75
		NO	10	3.5	273	96.5	ref	ref	ref	ref
	Previous TB treatment	(YES)	13	4.5	276	95.5	1.008(0.48-2.16)	0.988	0.911(0.43-1.925)	0.808
NO		17	4.5	363	95.5	ref	ref	ref	ref	
Neuropathy peripheral	Sex	(Ref: Male)	26	6.8	358	93.2	ref	ref	ref	ref
		Female	21	7.3	265	92.7	1.091(0.61-1.981)	0.774	1.135(0.618-2.083)	0.683
	Age Group	(0-18)	2	4.8	40	95.2	0.250(0.49-1.285)	0.097	0.128(0.015-1.095)	0.061
		(19-65)	38	6.5	548	93.5	0.347(0.144-0.832)	0.18	0.308(0.124-0.770)	0.012
		>65	7	16.7	35	83.3	ref	ref	ref	ref
	HIV Status	YES	29	7.1	381	92.9	1.023(0.556-1.883)	0.941	1.007(0.528-1.92)	0.982
		NO	18	6.9	242	93.1	ref	ref	ref	ref
	Previous TB treatment	(YES)	25	8.7	264	91.3	ref	red		
NO		21	5.5	359	94.5	1.619(0.887-2.954)	0.117	1.705(0.917-3.170)	0.92	
Arthralgia	Sex	(Ref: Male)	41	10.7	343	89.3	ref	ref	ref	ref
		Female	25	8.7	261	91.3	0.801(0.475-1.352)	0.406	0.793(0.465-1.351)	0.393
	Age Group	(0-18)	0	0.0	42	100.0		0.997		0.997
		(19-65)	54	9.2	532	90.8	0.254(0.123-0.524)	0.000	0.229(0.107-0.489)	0.000
		>65	12	28.6	30	71.4	ref	ref	ref	ref
	HIV Status	YES	41	10.7	343	89.3	1.044(0.619-1.763)	0.871	1.161(0.664-2.03)	0.6
		NO	24	8.4	261	91.6	ref	ref	ref	ref
	Previous TB treatment	(YES)	31	10.7	258	89.3	ref	ref	ref	ref
NO		35	9.2	345	90.8	1.184(0.711-1.972)	0.515	1.221(0.720-2.672)	0.458	



#### 4.4 DISCUSSION

The current study retrospectively analyzed 670 DR-TB patients treated in the DR-TB treatment sites. We examined critical findings on the cohort's baseline and the ADR characteristics that patients encountered during treatment. The finding indicates that both new and previously treated patients are equally at risk of DR-TB. Furthermore, serious ADRs related to DR-TB medicines were present in more than 30% of the reports. While most patients recovered from the ADRs, a notable number of serious ADRs persist or lead to fatal outcomes.

The majority of the DR-TB patients (56.7%) had never received prior anti-TB therapy, which is in line with the national annual TB program report. (18) However, the current study output differs from other studies where the primary DR-TB was 14.7%, 24.5%, and 23.67% in the Central African Republic (CAR), China, and Nepal, respectively. (24–27) This suggests that primary resistance to TB medicines is a significant concern in Eswatini and underscores the need for more robust DR-TB surveillance.

The most common ADRs identified in this study included arthralgia, nausea and vomiting, peripheral neuropathy, hypoacusis, prolonged QT on electrocardiogram, and optic neuritis. These findings are also consistent with known side effects of DR-TB medicines and similar to findings from previous studies (28–31). In a four-year retrospective investigation, Arif D. et al. also reported the same groups of ADRs.(32) According to Tae W. Y. et al. et al. (33), the top 5 ADRs were hepatitis (3.9%), arthralgia (4.7%), mental disorders (5.5%), and gastrointestinal disturbances (18.4%). It's important to note that small variations in ADRs rates may result from a variety of variables, including sociodemographic background, which may influence the incidence of ADRs. (34)

Bedaquiline was associated with the highest number of ADRs among the 19 different medicines included in the study, with cardiac issues, gastrointestinal concerns, and neurological symptoms being the most prevalent, which is in line with a descriptive Study Based on the WHO Database (VigiBase®).(14) Along with clofazimine, levofloxacin, and delamanid, QTc prolongation was reported in association bedaquiline which is in line with other studies.(35–38)

In the current study, ethionamide was the most associated medication, following linezolid, with optic neuritis. Optic neuritis occurs when inflammation damages the optic nerve, all nerve fibers that transmit visual information from the eye to the brain. Common symptoms of optic neuritis include pain with eye movement and temporary vision loss in one eye. (39) Linezolid has a narrow therapeutic index, often dose-adjusted or discontinued due to intolerance or toxicity during treatment. (40,41)

However, since long-term use may cause optic neuropathy, the possibility of optic neuropathy should always be considered. If optic neuropathy is suspected, prompt medicine withdrawal is required, and reversible clinical changes can be expected. (42)

Hypothyroidism was one of the most frequent ADRs reported in association with ethionamide. Although hypothyroidism was previously believed to be rare in DR-TB treatment (43), recent reports suggest that it is more common. (44,45) This could be due to the enhanced awareness of healthcare workers about ADR detection practices and emerging safety evidence in DR-TB treatment protocols. It's therefore critical to conduct a thorough screening of hypothyroidism in DR-TB patients on Ethionamide-based treatment. (43)

Furthermore, 146 ADRs, constituting 30.2% of the identified cases, were considered serious. Interestingly, the seriousness of ADRs exhibited variations across different demographics, with 26.9% of males and 33.9% of females experiencing serious reactions. Age-wise, the study observed that 25.0% of ADRs in the 0–18 age group were serious, compared to 32.3% in the 19–64 age group and 17.2% in individuals above 65 years old. It's noteworthy that ADRs with higher seriousness rates are associated with medicines that are the backbone of DR-TB treatment currently in use. (2,19,46)

In addition, we explored time-related aspects of ADR occurrence - the mean onset and duration of reactions. Most gastrointestinal reactions had the earliest mean onset of reaction, whereas palpitations occurred with a late onset. Furthermore, the average duration of reactions was roughly 76.73 days. Our findings are consistent with previous findings of a retrospective observational cohort research conducted in Nigeria by Avong et al. Avong et al. (47). Conversely, the mean onset of reaction was 7.85 months in research by Madan et al. on ADRs brought on by second-line anti-tubercular medications used in Nepal. (48) We observed that patients taking DR-TB medications tend to experience more frequent ADRs around the beginning of their treatment and that these reactions will persist throughout the duration of the treatment. Consequently, ADRs must be carefully monitored throughout the duration of treatment. It should be noted that healthcare professionals and patients must be advised on the possibility of late-onset ADRs to avoid either treatment withdrawal due to discomfort or a late association between symptomatology and the causal medicine, which can cause a delay in finding the cause and healing patients or relieving their discomfort.

Regarding reaction outcomes, most ADRs were resolved or in the process of resolving when they were reported. Specifically, 308 ADRs were reported as recovered or resolved, with only 16.2% of the

reports being serious. While most ADRs had favorable outcomes, most serious ADRs persist or lead to fatal outcomes. Although serious ADRs are not always associated with the most serious outcomes, such as death, most non-serious ADRs tend to recover in a larger proportion than serious. In comparison, there is a greater proportion of not recovered at the time of reporting for serious ADRs as compared to ADRs that were not serious. The findings underscore the importance of being vigilant and patient support to mitigate the risks associated with ADRs in clinical settings.

We also analyzed factors associated with ADR occurrences, conducting univariate and multivariate analyses to assess their relationships with variables such as sex, age group, HIV status, and previous tuberculosis (TB) treatment. While the age group emerged as a significant factor in the occurrence of peripheral neuropathy and arthralgia-related ADRs, other variables such as sex, HIV status, and previous TB treatment did not demonstrate significant associations across various ADRs. This is not in line with a retrospective study conducted in Amhara regional state public hospitals where age, co-morbid conditions, and base-line hemoglobin were statistically significant predictors of major adverse events were significant predictors of major ADRs.(49) Similarly, a cross-sectional study design using a retrospective medical record conducted by Yimer et al., indicates that Co-morbid conditions of HIV/AIDS were identified as important predictors of ADRs which is different from our finding.(50) These differences could be attributed to various reasons, including differences in study design, population characteristics, or variations in healthcare settings and practices.

### **Strengths and limitations of the study**

Our study's strength is its retrospective review of medical records from all DR-TB treatment sites in the country. This all-inclusive strategy guarantees the incorporation of real-world data, offering insightful information about the safety of DR-TB treatments in clinical settings. While our longitudinal data assessment method makes exploring patterns and long-term consequences easier, the large sample size supports our findings' statistical robustness and application.

The primary limitation of the current study is the inability to detect ADRs; it relies on recorded ADRs by healthcare workers during their routine clinical practices- which may lead to an underestimation of certain ADRs. Second, ADRs that need laboratory diagnosis and the absence of tests and expertise could lead to a significant underreporting of these ADRs. Finally, some potential confounders were left unmeasured, which might introduce outcome misclassification bias.

In summary, while the study's retrospective and longitudinal approach provides valuable real-world insights into DR-TB treatment and its safety profile, the potential underreporting of ADRs and the limitations inherent in the use of secondary data highlight the need for cautious interpretation of the results and consideration of additional research to fill in the gaps.

#### 4.5 CONCLUSION

In conclusion, the present study's findings showed the high prevalence and seriousness of ADRs in patients with DR-TB, underscoring the significance of effective treatment approaches and comprehensive drug resistance safety monitoring. Overall, this study contributes significantly to the understanding of ADRs among DR-TB patients, emphasizing the importance of tailored interventions, continuous vigilant monitoring, and proactive management to mitigate the risks associated with ADRs in clinical settings, including early treatment withdrawal, which could lead to increased resistance.

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## 4.6 KEY RESULTS AND RESEARCH PERSPECTIVE

The findings of this study provided insight into specific challenges in the landscape of DR-TB treatment, allowing the development of tailored strategies to enhance the safety of DR-TB treatment in the country. This study is very important for developing country context-specific treatments that can effectively address the substantial burden of DR-TB in the kingdom of Eswatini.

Our research focused on the safety of DR-TB patients enrolled for treatment at all DR-TB sites in Eswatini from January 2018 to December 2020. The results showed that nearly half of these patients experienced at least one adverse drug reaction. Among the drugs, Bedaquiline had the highest number of adverse drug reactions, followed by ethionamide, pyrazinamide, terizidone, and linezolid. Additionally, we found that over 30% of the patients experienced serious adverse drug reactions linked to DR-TB medications, with some resulting in incomplete recovery or recovery with lingering effects. We also observed that age played a significant role in the occurrence of peripheral neuropathy and arthralgia-related adverse drug reactions, with individuals aged 19-65 facing a higher risk compared to older age groups. These findings emphasize the crucial need for careful monitoring of drug effects, patient-centered care, and the incorporation of newer, safer medications into treatment plans. The high incidence of adverse drug reactions among DR-TB patients in Eswatini highlights the necessity for improved monitoring and management to maintain treatment adherence and effectiveness.

Introducing new and repurposed medicines such as bedaquiline, delamanid, clofazimine, and linezolid has significantly improved cure rates and effectiveness, highlighting the potential benefits of updating treatment protocols with safer options. Subsequent steps should encompass developing and implementing targeted interventions to enhance ADR monitoring and management, specifically focusing on augmenting treatment adherence and patient safety.

Moreover, the findings of this study can be used to advocate for increased political and financial support, as well as the integration of PV into healthcare services to improve treatment outcomes. It is also important to share these findings within the global health community to have an impact on treatment guidelines and regimens worldwide. The insights garnered from this study underscore the critical need for strong PV, patient-centered care, and the integration of new, less toxic medicines into treatment regimens. These findings can guide strategies to enhance the safety and efficacy of DR-TB treatment, not only in Eswatini but also in other high-burden settings.

## **CHAPTER 5. STUDY THREE**

### **EVALUATING THE SAFETY OF REPURPOSED DRUG- RESISTANT TB MEDICINES IN ESWATINI: A PROSPECTIVE PHARMACOVIGILANCE STUDY**

## 5.1 EVALUATING THE SAFETY OF REPURPOSED DRUG-RESISTANT TB MEDICINES IN ESWATINI: A PROSPECTIVE PHARMACOVIGILANCE STUDY

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### **Abstract:**

**Introduction:** Drug-resistant tuberculosis (DR-TB) poses a serious global health threat due to the complex treatment regimens, higher cost, and toxicity. Additionally, the efficacy of current treatments is lower compared to first-line medicines. As a result, new repurposed medicines are being considered for inclusion among the recommended treatments. However, the safety profiles of these repurposed medicines, such as clofazimine (CFZ) and linezolid (LZD), in DR-TB treatment remain unclear. Considering this, we conducted a study to evaluate both medicines' reported adverse drug reactions (ADRs) in the context of Eswatini.

**Method:** We conducted a prospective cohort study from January 1 to December 31, 2022, at all DR-TB treatment sites in the Manzini region. Patients with confirmed DR-TB infection were enrolled starting on January 1st and continued for six months, allowing each patient to be followed for a maximum of six months. We evaluated the safety profiles of both CFZ and LZD.

**Result:** Our study included 29 patients, with an overall median age of 38 [interquartile range (IQR): 32–49]. During the study period, we identified a total of 56 ADRs. Notably, 19/29 patients presented two or more ADRs, and 4/29 showed one ADR. Only 6/29 patients did not develop any ADR during the study period. CFZ (27 patients treated) was associated with only five ADRs, mainly nausea and vomiting in 4 patients. In contrast, the 25 patients treated with LZD developed 16 ADRs, including anemia and peripheral neuropathy (3 each), arthralgia, unilateral blindness, blurred vision (2 each), optic neuritis, appetite decrease, ocular hyperemia, and myelosuppression (1 each). These findings underscore the need for immediate and extensive research into the safety profiles of these repurposed medicines in the context of DR-TB treatment in Eswatini.

**Conclusion:** In our cohort, 80% of the patients treated with CFZ or LZD developed ADRs. To ensure patient safety and treatment effectiveness, we recommend closely monitoring ADRs linked to these repurposed medicines throughout the treatment duration. ADRs can have profound implications and may potentially affect treatment adherence.

**Keywords:** pharmacovigilance, Eswatini, repurposed DR-TB medicines, Clofazimine, Linezolid

## 5.2 INTRODUCTION

Drug-resistant tuberculosis (DR-TB) poses a significant global health challenge. Eswatini has one of the highest burdens of MDR tuberculosis. (1) The country is heavily burdened by DR-TB, with 4.4% of new cases and 32% of previously treated cases, with the treatment success rate for DR-TB cases treated with second-line treatment was 78% in 2022. (2–4)

Effective treatment of DR-TB requires prolonged use of multiple second-line antituberculosis medicines, which are more expensive and toxic than first-line medicines. (5) With the current DR-TB medicines, their associated toxicities, and increasing resistance as well as controlling the disease has become more challenging. To address these challenges, some antimicrobials were initially used for other conditions but have been effective against *M. tuberculosis* and have been repurposed. WHO has approved five antimicrobial repurposed medicines for the treatment of DR-TB: clofazimine (CFZ), levofloxacin (LFX), linezolid (LZD), meropenem, and moxifloxacin (MFX). (6) The safety profiles of repurposed medicines used in multidrug regimens for extended periods are not yet fully understood. (7) This research will specifically focus on CFZ and LZD.

Linezolid (LZD) is an oxazolidinone-class antibacterial used in adults and children to treat infections caused by susceptible gram-positive bacteria.(8) However, new evidence from the ZeNix trial findings and the 2022 WHO rapid communication indicates that a daily dose of 600 mg for 26 weeks, along with other DR-TB medicines, has a favorable outcome with 24% neuropathy and 2% myelosuppression ADRs. (9–11) The most frequent and remarkable ADRs reported with LZD in this indication include neuropathy (24% of cases) and myelosuppression (2%). (9–11) Regarding CFZ, it is a phenazine originally used to treat leprosy. (12) It has not traditionally been used against TB treatment because it has little bactericidal activity. (13) However, recent studies have shown that it has sterilizing and treatment-shortening potentials, although the mechanism of action has yet to be elucidated fully. (14)

Given the novelty of this indication and the limited real-world experience, it is crucial to prioritize safety surveillance to effectively monitor and characterize the adverse drug reaction (ADR) profile.

## **Method**

A prospective cohort study was conducted between January 1 and December 31, 2022, at all DR-TB treatment sites in the Manzini region. The Manzini region has four DR-TB treatment sites: AHF Matsapha, Mankayane Referral Government Hospital, Manzini TB Center, and The Luke Commission. The study population and methods used in this study have been outlined in similar studies conducted in north-western Nigeria and India. (15,16) From the first of January, patients with confirmed DR-TB infection were enrolled and followed for a maximum of six months. Data was collected prospectively, and patients were closely monitored for the presence of ADRs.

### **Treatment Protocol**

Patients were treated according to the Eswatini National Guidelines for the Medical Management of DR-TB, WHO Rapid Communication, and WHO guidelines (17–19). The general principles of regimen design were based on an individualized treatment approach to the extent possible, guided by drug-susceptibility test (DST) (molecular and/or phenotypic) results before treatment initiation. TB treatment history, contact (source) DST, and co-morbidities were considered in treatment decisions.

### **Data Collection**

A validated, self-designed data collection tool was distributed to all study sites to collect comprehensive safety data. The tool captured patient demographic information, comorbidities, reaction details, medicine details on the suspected medicines, and baseline and follow-up laboratory tests. To ensure the validity of the data collection tools and to familiarize data collectors with both tools, a one-week field test (pilot study) was conducted on non-eligible patients following a one-day orientation workshop for the DR-TB treatment site physicians. On each monthly visit, patients were closely monitored and evaluated for any DR-TB medicines associated with ADRs by the treatment site TB physician and recorded in the data collection form. ADRs were deemed to exist when they could be confirmed by any laboratory value, assessed by the doctor using clinical criteria, or self-observed or patient-reported.

### **Data Analysis**

Data cleaning and analysis were performed using Excel and the statistical package for Social Science version 26 (SPSS-26). Descriptive statistics were employed using the mean, standard deviation (SD), median, and interquartile range (IQR).

### 5.3 RESULTS

#### Baseline Characteristics

A total of 29 patients (19 males, 10 females) with an overall median age of 38 [interquartile range (IQR): 32–49] were included in the analysis. Almost half of the patients enrolled in the study were diagnosed with Rifampicin Resistance (RR) (13/29), followed by Multidrug Resistance (MDRR) (9/29), Isoniazid Mono-Resistance (MONOH) (5/29) and poly drug-resistant (PDR) and extensively drug-resistant (XDR)(1 each) (see Table 1).

It should be noted that more than two-thirds of the patients (20/29) had HIV/TB co-infection. Regarding TB treatments, 27/29 patients in the cohort received regimens that included CFZ with or without LZD. Similarly, 25 of 29 patients received regimens that included LZD, with or without CFZ. Additionally, ancillary medicines and antiretroviral therapy (ART) depend on the individual. The most prescribed ART was TDF/3TC/DTG (14/20 patients) and ancillary medicines such as cotrimoxazole, vitamin B6, or amitriptyline.

Table 4: Distribution of the DR-TB cohort according to the background characteristics

Background characteristics		N=29 (%)
Sex	Male	19 (65.5)
	Female	10 (34.5)
Age	Mean age, years (+/- SD)	38 (13.0)
	0-18	0
	19-64	27 (93.1)
	Above 65	2 (6.1)
HIV status	Reactive	20 (69.0)
	Non-reactive	9 (31.0)

Types of resistance	RR	13 (44.8)
	MDR	9 (31.0)
	MONOH	5 (17.2)
	PDR	1 (3.4)
	XDR	1 (3.4)
	Total	29 (100)
HIV treatment	TDF/3TC/DTG*	14 (70.0)
	TDF/3TC/EFV*	4 (20.0)
	ABC/3TC/DTG*	2 (10.0)
	Total	20 (100)
Repurposed TB medicines	Regimen without LZD but CFZ	4 (13.7)
	Regimen without CFZ but LZD	2 (6.9)
	Regimens with both LZD and CFZ (The whole cohort)	29 (100)
Utilization of ancillary medicines	Vitamin B6	23(79.3)
	Cotrimoxazole	6(20.7)
	Other medicines for other infections and supplements	Salbutamol1(3.4), multivitamin 2(6.8), ferrous Sulfate1(3.4), metoclopramide1(3.4), acyclovir1(3.4), ciprofloxacin1(3.4), folic acid1(3.4), doxycycline1(3.4), metformin1(3.4), metronidazole1(3.4).

Abbreviations: TDF=Tenofovir; 3TC=Lamivudine; DTG=Dolutegravir; EFV=Efavirenz; ABC=Abacavir; MONOH=Isoniazid mono-resistance; RR=Rifampicin Resistance; XDR-TB=extensively drug-resistant TB; MDR=multidrug resistance

## Frequency of ADRs

In the present cohort, 56 ADRs were identified during the study period, with only six patients out of 29 not presenting any adverse outcome (4 males and 2 females). Overall, 19/29 patients were presented with two or more ADRs, while the remaining 4/29 had one ADR. The two patients who received LZD-containing regimens without CFZ experienced two or more ADRs each; similarly, of the 4 patients who received CFZ-containing regimens without LZD, 1 patient had one ADR, and 3 patients had two or more ADRs. Most patients develop two 2 or more ADRs in both genders.

Regarding HIV status, among the HIV-reactive patients in the cohort, five of the patients did not present with any ADRs, while 15/20 patients experienced one or more ADRs. Among the nine HIV non-reactive patients in the cohort, one patient did not develop any ADRs, while 8/9 reported two or more ADRs. In the CFZ alone group (2 HIV non-reactive patients), both showed 2 or more ADRs. None of the HIV non-reactive patients treated with Regimens without CFZ developed any ADRS. (see below Table 2)

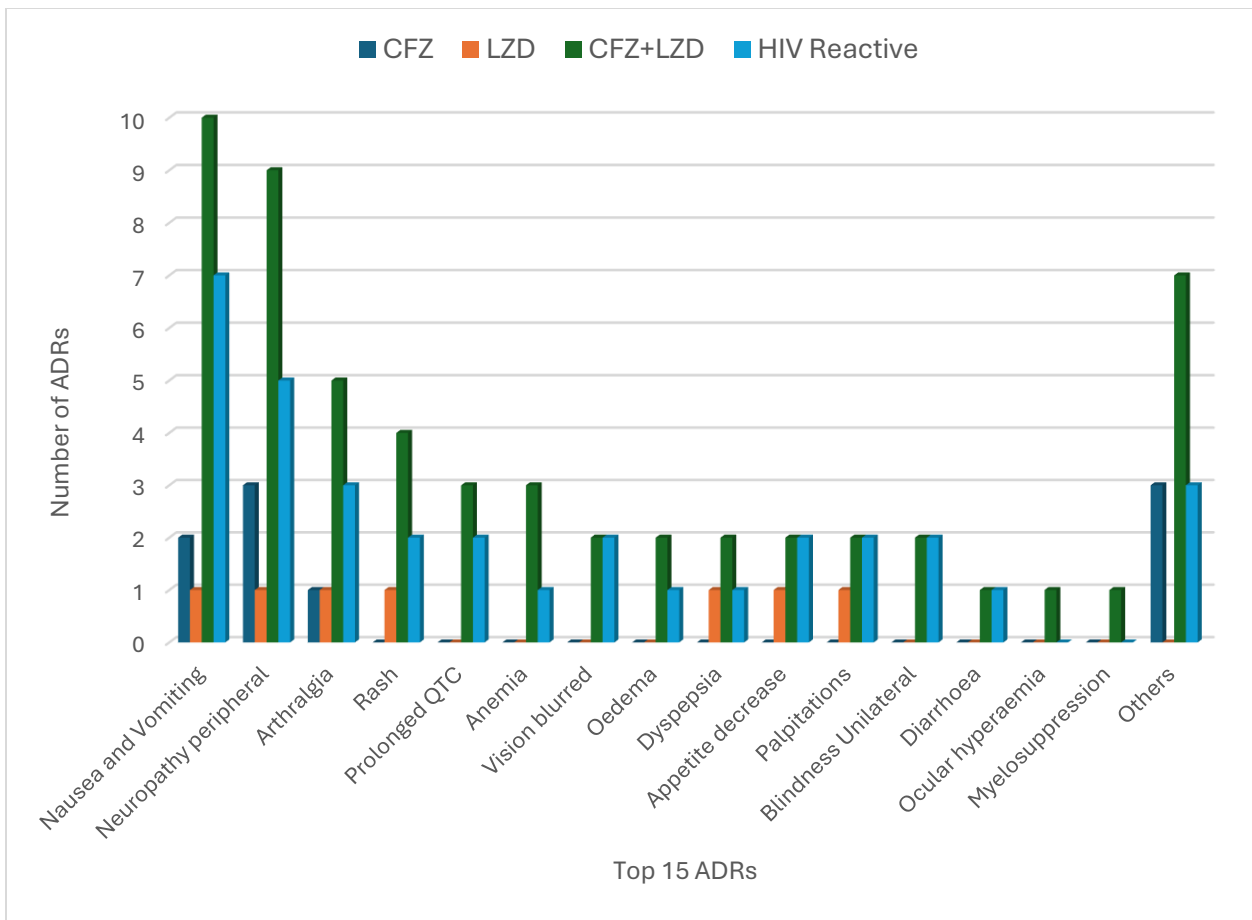
Table 5: Distribution of Patients According to Their Treatment and Reports of ADRs

Number of Patients	No ADR (N)	One ADR(N)	Two or more ADRs (N)	Total patients N= 29
<b>Sex</b>				
Male	4	3	12	19
Female	2	1	7	10
<b>Age group</b>				
18-64	5	4	18	27
65 and above	1	0	1	2
<b>Regimens with both LZD and CFZ(the whole cohort)</b>				
Regimens with both LZD and CFZ(the whole cohort)	6	4	19	29
<b>Regimens without CFZ but LZD</b>				
Regimens without CFZ but LZD	0	0	2	2



<b>Regimens without LZD but CFZ</b>	0	1	3	4
<b>HIV reactive</b>				
<b>Regimens with both LZD and CFZ (the whole cohort)</b>	5	4	11	20
<b>Regimens without CFZ but LZD</b>	0	0	2	2
<b>Regimens without LZD but LZD</b>	0	1	1	2
<b>HIV non-reactive</b>				
<b>Regimens with both LZD and CFZ(the whole cohort)</b>	1	0	8	9
<b>Regimens without CFZ but LZD</b>	0	0	0	0
<b>Regimens without LZD but CFZ</b>	0	0	2	2
<b>Types of resistance</b>				
<b>MonoH</b>	0	0	5	5
<b>MDR</b>	5	1	3	9
<b>PDR</b>	0	0	1	1
<b>RR</b>	0	3	10	13
<b>XDR</b>	1	0	0	1

With regards to specific ADRs, nausea and vomiting (10/56 ADRs) was the most reported ADR in the cohort, followed by peripheral neuropathy (9/56). We also presented the occurrence of ADRs in HIV-positive patients treated with regimens without CFZ and regimens without LZD. (see the following figure).



**Figure 2: Distribution of the Top 15 ADRs in HIV-positive Patients Treated with LZD & CFZ (the whole cohort), CFZ-containing regimens without LZD-alone, and LZD-alone regimens without CFZ**

Of the 56 ADRs identified in the cohort, (21, 37.5%) of the ADRs were attributed to both LZD and CFZ, while the remaining 62.5% of the ADRs were caused by other concomitantly administered medicines. CFZ was associated with only five ADRs (nausea and vomiting (4;80%) and prolonged QTC(1;20%)), while peripheral neuropathy (3;18.8%), anemia (3; 18.8%), arthralgia (2;12.5%), unilateral blindness (2; 12.5%), vision blurred (2; 12.5%), optic neuritis (1; 6.3%), appetite decrease ( 1; 6.3%), ocular hyperemia (1;6.3%) and myelosuppression( 1;6.3%) were reported in association with LZD.

In our study, we also found that a majority of PLHIV (34; 60.7%) experienced ADRs. Notably, among patients receiving LZD and /or CFZ regimens, most PLHIV receiving LZD were also treated with TDF/3TC/DTG (12; 71%). Similarly, for PLHIV receiving CFZ, the majority were concurrently treated with TDF/3TC/DTG (12; 67%). Additionally, we evaluated the frequency of concomitantly administered medicines such as isoniazid (INH), ethionamide (ETO), CS or TRD, LZD, and

fluoroquinolones that can potentially induce peripheral neuropathy. One of the peripheral neuropathies suspected to be caused by LZD was concomitantly administered with CS and LFX, while the remaining two were co-administered with terizidone and levofloxacin. It's worth noting that all three patients were given VitB6 as part of the country's treatment protocol.

### **Seriousness, timing, and outcome of the reaction**

The reporters classified the ADRs identified in the cohort (14; 25.0%) as serious. These 14 ADRs happened in 9 patients (31.65% of the study sample), with (3; 10.3 %) of the patients experiencing more than one serious ADR.

Regarding the timing of reactions associated with the two medicines of interest, the mean onset of reactions varies. The highest mean onset of reaction, 147.3 days (ranging from 134 to 166 days), was observed for peripheral neuropathy associated with LZD. On the other hand, a lower mean onset of reaction was observed at 63 days for appetite decreases. For CLZ, the two ADRs associated with it had different mean onsets of reactions. Nausea and vomiting had a mean onset of reaction of 106.75 (ranging from 14 to 152 days), while prolonged QTC had a mean onset of reaction of 113 days (see Table 2).

Regarding the outcome, out of the 21 reactions suspected to be caused by CFZ and LZD, 15 (71.5%) had recovered during the follow-up period. However, 6 (28.5%) were still in the recovery process or had not yet recovered by the end of the study period.

As indicated in Table 2, we also analyzed two types of ADRs that warrant attention, mainly in PLHIV. The two ADRs are neurological and hematological cases. Among HIV-positive patients, neurological reactions suspected to be caused by LZD were observed in 9 individuals, including peripheral neuropathy (n = 5; 55.6%), optic neuritis (1), unilateral blindness (2), and ocular hyperemia (1). Anemia was reported in 1 out of 3 cases (33.3%), while no myelosuppression cases were found in HIV-positive patients.

## **5.4 DISCUSSION**

In the present study, we conducted a prospective pharmacovigilance study to evaluate the safety of repurposed DR-TB medicines in Eswatini, focused on CFZ and LZD. In our analysis, 56 ADRs were

identified during the study period, with 20.6% of the patients presenting with one ADR, 34.4% presenting with two ADRs, and 31% presenting with more than two ADRs. Most of the ADRs were resolved with various patient support systems established by the TB program. The patient support system is a comprehensive psychosocial support package that includes transport allowance for patients to facilitate travel to healthcare facilities; nutritional support – food packages; treatment supporter stipend; and Video Observed Therapy (VOT)/virtual Directly Observed Therapy (vDOT) implemented during Covid-19 pandemic to maintain treatment adherence without the need for in-person visits. (4)

Adverse drug reactions such as nausea and vomiting, followed by peripheral neuropathy, arthralgia, prolonged QTC, unilateral blindness, and anemia, were the most frequently reported reactions in the cohort, which is in line with previous studies conducted in different settings. (20–23) Furthermore, the frequency of ADRs observed in the current study aligns with findings from published studies conducted in different countries. (24–27)

In the present study, we identified ADRs such as blood and lymphatic disorder, cardiac disorder, eye disorder, GI disorder, musculoskeletal and connective disorder, and nervous system disorder associated with LZD and CFZ presented as follows:

### **Blood and Lymphatic Disorder**

Linezolid (LZD) appears to be one of the most effective repurposed medications. However, it has often been linked to hematological toxicities, mainly myelosuppression, in both non-randomized studies and randomized controlled trials (RCTs), which has resulted in the termination of LZD in 6%–23% of patients. (6,28,29) Myelosuppression is when bone marrow activity decreases, resulting in fewer red blood cells, white blood cells, and platelets. (30) In our findings, anemia, and myelosuppression were among the reported blood and Lymphatic disorders to LZD, which is in line with other findings and the product's summary of product characteristics (SmPC). (31) However, due to the characteristics of the patients, iron deficiency anemia due to nourishment problems could not be ruled out. There is a high risk of developing several serious side effects while using LZD for an extended period. These include hyperlactatemia, lactic and metabolic acidosis, myelosuppression with thrombocytopenia and anemia, gastrointestinal issues, and peripheral or optic neuropathy that are mostly reversible upon dose reduction or withdrawal of the treatment. (32,33)

It's noteworthy that in a population with high TB/HIV co-infection, cotrimoxazole preventive therapy (CPT) is prescribed to reduce morbidity in HIV-positive TB patients by reducing the risk of opportunistic infections. (34–36) However, cotrimoxazole, like LZD, has been linked with anemia and myelosuppression. (37,38) As highlighted in the reaction weekly published case report, the combined use of cotrimoxazole and LZD is linked with an increased risk of anemia and myelosuppression. (39) Therefore, national and WHO guidelines for DR-TB treatment and SmPCs of the two medicines must incorporate guidance on the ADRs management and regimen design in a situation necessitating the combined use of both medicines, such as in cases of advanced HIV disease.

### **Peripheral neuropathy**

In our analysis, we observed that peripheral neuropathy was reported in a relatively comparable number of 16% to other findings reported in studies in Bangladesh (28%), Russia (13%), and India (18.75%).(40–43) Lower frequencies of peripheral neuropathy was reported in other studies. (27,44) It is essential to acknowledge that ADRs may not solely be attributed to a single suspected medicine. Peripheral neuropathy is one example of ADR that can be associated with multiple medicines such as INH, ETO, cycloserine(CS)or terizidone(TRD), and LZD, along with fluoroquinolones and ethambutol. (45) For example, in our study, for all peripheral neuropathy cases, CS/TRD along with LFX were concomitantly administered with LZD. Therefore, the possible effects of other combined medicines must be considered. For this reason, the Eswatini National DR-TB guideline recommends placing patients on pyridoxine (vitamin B6) as a routine part of anti-tuberculous therapy in co-infected patients. (18)

We also examined the neurological and hematological-related ADRs that are also known to occur in HIV-positive individuals linked to LZD. (46) In our study, anemia, peripheral neuropathy, optic neuritis, unilateral blindness, and ocular hyperemia were LZD-linked neurological and hematologic ADRs reported in PLHIV. Peripheral neuropathy is among HIV-associated neurological syndromes that happen when the nerves between the feet and, less commonly, hands and the spinal cord become damaged. (47) HIV can cause damage to nerves throughout the body, resulting in significant pain or weakness, resulting in neuropathy, which is most common in people with advanced HIV. (48,49) Similarly, myelosuppression and other wide range of hematopoietic abnormalities can be induced by direct and indirect effects of HIV infection.(50,51) Monitoring ADRs is critical when providing DR-TB treatments such as LZD to patients with TB/HIV co-infection, as the neurological and bone marrow dysfunction-related ADRs identified in this study were also caused by HIV infection. This warrants

more study to evaluate these relationships and inform individualized treatment methods for HIV/TB co-infected patients.

### **Other reactions**

In the present study, unilateral blindness (2), blurred vision (2), optic neuritis (1), and Ocular hyperemia (1) were eye disorders reported in relation to LZD. Optic neuropathy is a reversible complication related to the prolonged use of LZD, regardless of the dose.(40) Despite the low frequency of the ADR reported in our finding, the onset of reaction of the ADR was 98 days after initiating LZD treatment, which is in line with other studies. (52–54) This temporal aspect is crucial for clinical management, as it suggests that ocular complications may not manifest immediately, necessitating ongoing monitoring and follow-up even in patients who have been on LZD therapy for an extended period.

Regarding ADRs associated with CFZ reported in our study, gastrointestinal issues were the most frequent ADR, which aligns with a prospective, multicenter, Randomized Controlled Study conducted in China, other studies, and the FDA’s prescribing information (55,56). Nausea and vomiting in the present study had a mean onset of reaction of 136 days (ranging from 116 to 156 days).

### **5.5 CONCLUSION**

In conclusion, the repurposing of medicines for DR-TB treatment must be supported by evidence of their efficacy and safety, with pharmacovigilance playing a critical role in monitoring adverse events and optimizing treatment outcomes. Active pharmacovigilance, including aDSM and cohort event monitoring and safety surveillance studies on real-world evidence, are essential for managing the risks associated with new and repurposed medicines. Additionally, adequate clinical trials and individualized treatments based on susceptibility testing are vital to improving patient outcomes, with the potential for shorter treatment regimens on the horizon.

### **Limitations**

The study was conducted at only four health facilities, limiting the generalizability of the findings. The short follow-up period may have missed long-term adverse drug reactions. With a small sample size (n = 41), the study's findings may lack statistical power and generalizability. Future research with a larger, more representative sample is necessary to understand the influence of ADRs on the outcome variable.

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## 5.6 KEY RESULTS AND RESEARCH PERSPECTIVE

Following our retrospective study, we conducted a prospective study to characterize the safety profile of repurposed DR-TB medicines, focusing on CFZ and LZD in Eswatini. Given the novelty of the repurposed medicines and the limited real-world experience, it is important to monitor and manage the safety issues of these medicines. Our two studies taught us that the most serious ADRs were associated with clofazimine and linezolid, among other medicines. Patients receiving either CFZ and LZD or one of the two medicines were enrolled in the study and closely monitored for the presence of ADRs.

Reflecting on the most recent WHO guidance to manage DR-TB cases and emerging evidence, it is evident that repurposed medicines are becoming increasingly important components of treatment plans. According to our findings, a significant number of patients receiving these medicines have experienced serious ADRs, including anemia, peripheral neuropathy, and, in some cases, unilateral blindness. The complexity of DR-TB treatment, especially considering the high prevalence of HIV co-infection, requires tailored approaches that target the unique challenges that patients face. It's crucial to consider that HIV and its treatments could have also contributed to the occurrences of ADRs linked to these repurposed medicines. This overlap emphasizes the necessity of thorough investigation to identify the underlying mechanisms. Particularly, ADRs like optic neuritis and peripheral neuropathy, which have been linked to LZD and are also known complications in HIV infections, necessitate an in-depth understanding of this combination.

Moreover, the approach of home-based DR-TB treatment, led by trained community health workers and augmented by the implementation of thorough safety surveillance systems, is also key to a positive treatment outcome. Additional research is required to explore the entire range of ADRs linked to DR-TB medicines, including rare cases, with the aim of establishing evidence-based treatment guidelines for their management.

In summary, analyzing the safety profiles of DR-TB medicines is of utmost importance in countries with a high burden of TB and HIV, which presents unique challenges. The insights gained from our findings in Eswatini reinforce the necessity for effective pharmacovigilance, patient-focused care, and the inclusion of newer, less toxic drugs in treatment regimens. These findings can guide strategies to enhance the safety of DR-TB treatments, not just in Eswatini but also in other regions facing similar burdens.

# **CHAPTER 6. GENERAL DISCUSSION AND CONCLUSION OF THE THESIS**

## 6.1 GENERAL DISCUSSION AND RECOMMENDATIONS

The complexities of DR-TB treatments, which underscore the use of multiple medicines, underline the importance of evaluating the safety and effectiveness of these treatments. As DR-TB evolves fast, so must our approaches to contend with it, ensuring that patients receive the most effective and safe treatments. The WHO introduced significant changes to treating DR-TB protocols and guidelines to ensure less toxic and efficacious regimens. This thesis delves into the implications of these changes, evaluating the safety profiles of DR-TB medicine at both national and global levels. By analyzing the multifaceted aspects of DR-TB medications and the evolving treatment protocols, this work seeks to illustrate the current landscape of DR-TB treatment safety and identify potential opportunities for improvement.

It is noteworthy that various factors can affect the occurrence of ADRs, including social/lifestyle, genetic predispositions, and the concurrent use of other medicines.<sup>96-98</sup> These factors necessitate the analysis of a global safety database to generate reliable and comprehensive evidence across countries that share ICSR with UMC. We, therefore, started this thesis with a global safety database analysis, leveraging the WHO's VigiBase, the largest global medicine safety database, containing over 35 million ICSRs since 1968.<sup>94</sup> This database, which is continuously updated, allowed us to assess the magnitude and characteristics of DR-TB medicine-related ADRs reported between January 2018 and December 2020. Our findings highlighted that medicines such as pyrazinamide, ethionamide, and cycloserine were frequently associated with ADRs, with serious reactions often caused by the backbone of DR-TB treatment currently in use like bedaquiline, delamanid, clofazimine, linezolid, and cycloserine. We also observed that one-third of the reports in this study required the withdrawal of kanamycin, cycloserine, and pyrazinamide, the most frequently withdrawn medicines due to ADRs. Acknowledging the documentation and management of these ADRs through dose reduction, temporary/permanently suspending treatments, or continuing with the treatments by augmenting with ancillary medicines, it's also important to note that some of the medicines have been removed from the treatment guidelines and replaced with more effective and safe regimens. The 2019 and 2022 WHO DR-TB treatment guidelines recommended all-oral regimens and new medicines, emphasizing the use of newer medicines like bedaquiline and delamanid, and phasing out older injectable treatments such as removal of Kanamycin and capreomycin due to their toxicities and poorer treatment outcome.<sup>19,99</sup>

Following the global perspective, we conducted a retrospective analysis of safety data collected across 14 DR-TB treatment sites in Eswatini to elucidate the characteristics and determinants of ADRs in DR-TB patients. Here, we identified that bedaquiline was associated with the highest number of ADRs, followed by ethionamide, pyrazinamide, terizidone, and linezolid. Arthralgia was the most reported ADR, followed by nausea and vomiting, peripheral neuropathy, hypoacusis, QTc prolongation on electrocardiogram, and optic neuritis. 45% of patients showed at least one ADR and almost one-third were serious. Even though the medicines involved with the frequent ADRs are closely related to the first study, some highly toxic medicines like kanamycin were not reported in the second study. This is because kanamycin was withdrawn from Eswatini due to its lower safety and outcome benefits. Additionally, the second study addressed the limitations of the first study. In the first study, only ICSRs of suspected ADRs reported to vigibase were included in the analysis. This means that the first study did not have information on the number of people exposed to the suspected medicines. As a result, it was impossible to determine the risks associated with these medicines.

To deepen our understanding of the safety profile of repurposed medicines, a prospective study was conducted in all DR-TB facilities in the Manzini region of the Kingdom of Eswatini, focusing on CFZ and LZD. This study provided valuable insights into these treatments' usage and potential adverse effects.

Since the inception of this thesis, there have been substantial improvements in DR-TB treatment guidelines and regular updates of DR-TB medicine safety profiles. Through these three important global, national, and regional studies, we have contributed considerably to understanding medicine safety in DR-TB treatment. Our study provides critical insight for researchers, healthcare professionals, and policymakers to enhance patient care and provide safer, more efficient treatment strategies. To ensure this, we recommend the following key points:

- **Integration of PV activities into public health programs (PHPs) and other routine health care systems:** The country should integrate PV activities into PHPs to help monitor the safety profile of DR-TB medicines and other treatments. Given the high prevalence of TB-HIV co-infections, strengthening the PV system in both the TB and HIV/AIDS programs is critical. Close collaboration and coordination between these programs can enhance the understanding of potential ADRs of these medicines and improve treatment outcomes.

- **Introduce and implement innovative patient support mechanisms to ensure adherence to DR-TB treatment:** The patient support system is a comprehensive psychosocial support package that entails ensuring that TB treatment is taken by the correct/right patient, at the right time, the right dose, the right route, and the right frequency during treatment without interrupting the treatment to achieve good treatment outcomes. These include transport allowance for patients to facilitate travel to healthcare facilities; nutritional support – food packages; treatment supporter stipend; and Video Observed Therapy (VOT)/virtual Directly Observed Therapy (vDOT) to maintain treatment adherence without needing in-person visits.
- **Conduct country-wide and continental prospective PV studies:** A prospective study conducted in one of the regions in Eswatini provided valuable insights into the safety profile and usage of two repurposed DR-TB medicines, CFZ and LZD. Additional studies with larger sample sizes covering different settings should be conducted to obtain a more comprehensive panorama of the safety profile of the repurposed medicines.
- **Establishment of a PV department or sub-unit in each DR-TB treatment site:** All DR-TB treatment sites across the country should consider establishing a PV department or sub-unit to provide special attention and close monitoring for patients on MDR-TB treatments. These PV units can implement routine monitoring of the safety of medicines, ensure proper ADR detection, management, and reporting, and train and supervise healthcare providers to increase the reporting rate and quality of reports.
- **Improvement of reporting tools:** It is recommended that the ADR reporting mechanisms be streamlined. To help in reporting and lessen administrative burden, introducing and implementing electronic ADR reporting forms linked to electronic patient files should be considered.
- **Human Resources and Capacity Building:** Human resources with PV skills are needed for data analysis, causality assessment, signal detection, and risk communication. Strengthening the signal detection and communication process can enhance the overall pharmacovigilance efforts. Training, feedback, and regular communication with healthcare providers and patients should be provided to achieve this.
- **Moving beyond reporting to safety data analysis and risk communication:** As the WHO defines, PV encompasses important activities beyond detecting and reporting. It requires a shift from merely reporting safety data to a more holistic approach that includes analyzing and communicating the safety of medicines to all stakeholders. Therefore, it is recommended that



the PV center analyze the reported potential safety issues and communicate the findings to healthcare workers, regulatory bodies, and patients.

## 6.2 CONCLUSION

This thesis aims to evaluate and describe the pattern and characteristics of ADRs in Eswatini patients with DR-TB and assess the comprehensive safety profile of DR-TB medicines globally. To realize these objectives, we conducted prospective and retrospective studies on local data and analyzed worldwide data extracted from Vigibase.

In our global database study, the analysis of ICSRs from 39 countries indicated that PZA and ETO were responsible for most ADRs in DR-TB treatment, with elderly patients (aged more than 65 years) having poorer reaction outcomes. It highlighted the need for rigorous monitoring and an effective PV system as the most serious ADRs were reported to key medicines used in DR-TB therapy.

Regarding our retrospective study, we observed that almost half of the patients showed at least one ADR and nearly one-third were serious. Another common finding with the first study was that ADRs could appear at any time during the treatment and can interfere with adherence to the treatment; it is essential to strengthen the safety monitoring of patients being treated for DR-TB to ensure a quick and appropriate ADR management, thus reducing the chance of treatment failure.

In the end, we assessed the safety profile of repurposed DR-TB medicines, specifically CFZ and LZD, in one of the regions in Eswatini. We found that 80% of the patients treated with CFZ or LZD developed ADRs.

Overall, this thesis contributes significantly to the understanding of ADRs among DR-TB patients, emphasizing the importance of tailored interventions, continuous vigilant monitoring, and proactive management to mitigate the risks associated with ADRs in clinical settings, including early treatment withdrawal, which could lead to increased resistance.

**Keywords:** pharmacovigilance, public health, DR-TB, Medicine safety, adverse drug reaction, safety surveillance

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## DISCUSSION GÉNÉRALE ET RECOMMANDATIONS

Les complexités des traitements de la TB-MR, qui soulignent l'utilisation de plusieurs médicaments, mettent en lumière l'importance d'évaluer la sécurité et l'efficacité de ces traitements. Comme la TB-MR évolue rapidement, nos approches pour la combattre doivent évoluer également, en veillant à ce que les patients reçoivent les traitements les plus efficaces et sûrs. L'OMS a introduit d'importants changements dans les protocoles de traitement de la TB-MR et les lignes directrices pour garantir des schémas thérapeutiques moins toxiques et plus efficaces. Cette thèse explore les implications de ces changements, évaluant les profils de sécurité des médicaments contre la TB-MR aux niveaux national et mondial. En analysant les aspects multifacettes des médicaments contre la TB-MR et les protocoles de traitement évolutifs, ce travail cherche à illustrer le paysage actuel de la sécurité des traitements de la TB-MR et à identifier des opportunités d'amélioration potentielles.

Il est à noter que divers facteurs peuvent influencer la survenue des ADR, notamment les facteurs sociaux/lifestyle, les prédispositions génétiques et l'utilisation concomitante d'autres médicaments<sup>96-98</sup>. Ces facteurs nécessitent l'analyse de bases de données de sécurité mondiales pour générer des preuves fiables et complètes à travers les pays qui partagent des ICSR avec UMC. Nous avons donc débuté cette thèse par une analyse de base de données de sécurité mondiale, en exploitant la VigiBase de l'OMS, la plus grande base de données mondiale sur la sécurité des médicaments, contenant plus de 35 millions d'ICSR depuis 1968.<sup>94</sup> Cette base de données, qui est continuellement mise à jour, nous a permis d'évaluer l'ampleur et les caractéristiques des ADR liées aux médicaments contre la TB-MR signalées entre janvier 2018 et décembre 2020. Nos résultats ont mis en lumière le fait que des médicaments tels que la pyrazinamide, l'éthionamide et la cyclosérine étaient fréquemment associés à des ADR, les réactions graves étant souvent causées par l'épine dorsale du traitement de la TB-MR actuellement en cours d'utilisation comme le bédaquiline, le délamanide, la clofazimine, la linézolide et la cyclosérine. Nous avons également observé qu'un tiers des rapports dans cette étude nécessitaient le retrait de la kanamycine, de la cyclosérine et de la pyrazinamide qui étaient les médicaments les plus fréquemment retirés en raison des ADR. En reconnaissant la documentation et la gestion de ces ADR par la réduction des doses, la suspension temporaire/permanente des traitements ou la poursuite des traitements en les augmentant avec des médicaments auxiliaires, il est également important de noter que certains médicaments ont été retirés des directives de traitement et remplacés par des régimes plus efficaces et sûrs. Les directives de traitement de la TB-MR de l'OMS en 2019 et 2022 recommandent tous les régimes oraux et de nouveaux médicaments en mettant l'accent sur l'utilisation

de médicaments plus récents comme le bédaquiline et le délamanide, et la suppression des traitements injectables plus anciens comme la kanamycine et la capréomycine en raison de leurs toxicités et de leurs résultats thérapeutiques médiocres.<sup>19,99</sup>

Dans la perspective mondiale, nous avons mené une analyse rétrospective des données de sécurité collectées dans 14 sites de traitement de la TB-MR en Eswatini afin d'élucider les caractéristiques et les déterminants des ADR chez les patients atteints de TB-MR. Nous avons identifié que le bédaquiline était associé au plus grand nombre d'ADR, suivi par l'éthionamide, la pyrazinamide, la térizidone et la linézolide. L'arthralgie était l'ADR la plus signalée, suivie par les nausées et vomissements, la neuropathie périphérique, l'hypoacousie, la prolongation du QTc à l'électrocardiogramme et la neurite optique. 45 % des patients ont montré au moins une réaction indésirable médicamenteuse, et presque un tiers d'entre eux étaient graves. Même si les médicaments impliqués dans les ADR fréquentes sont étroitement liés à la première étude, certains médicaments très toxiques comme la kanamycine n'ont pas été signalés dans la deuxième étude. Cela est dû au retrait de la kanamycine de l'utilisation. De plus, la deuxième étude a abordé les limites de la première étude. Dans la première étude, seuls les ICSRs des ADR suspectées qui ont été signalées à vigibase ont été incluses dans l'analyse. Cela signifie que la première étude n'avait pas d'informations sur le nombre de personnes exposées aux médicaments suspects. Par conséquent, il était impossible de déterminer le risque associé à ces médicaments.

Pour approfondir notre compréhension du profil de sécurité des médicaments repositionnés, une étude prospective a été menée dans tous les établissements de TB-MR situés dans la région de Manzini du Royaume de l'Eswatini en se concentrant sur le CFZ et le LZD. Cette étude a fourni des aperçus précieux sur l'utilisation et les effets indésirables potentiels de ces traitements.

Depuis le début de cette thèse, il y a eu des améliorations substantielles dans les lignes directrices de traitement de la TB-MR et des mises à jour régulières des profils de sécurité des médicaments contre la TB-MR. Grâce à ces trois études importantes aux niveaux mondial, national et régional, nous avons contribué considérablement à la compréhension de la sécurité des médicaments dans le traitement de la TB-MR. Notre étude fournit des aperçus critiques pour les chercheurs, les professionnels de la santé et les décideurs, aidant à améliorer les soins aux patients et à fournir des stratégies de traitement plus sûres et plus efficaces. Pour garantir cela, nous recommandons les points suivants

- **Intégration des activités de pharmacovigilance dans les programmes de santé publique (PHP) et autres systèmes de soins de santé de routine:** Le pays devrait intégrer les activités de pharmacovigilance dans les PHP pour aider à surveiller le profil de sécurité des médicaments contre la TB-MR et d'autres traitements. Étant donné la forte prévalence des co-infections TB-VIH, il est crucial de renforcer le système de pharmacovigilance dans les programmes de TB et de VIH/sida. Une collaboration étroite et une coordination entre ces programmes peuvent améliorer la compréhension des ADR potentielles de ces médicaments et améliorer les résultats du traitement.
- **Introduction et mise en œuvre de mécanismes innovants de soutien aux patients pour garantir l'observance du traitement de la tuberculose multirésistante (TB-MR):** Le système de soutien aux patients est un ensemble complet de soutien psychosocial qui implique de s'assurer que le traitement de la TB est pris par le bon patient, au bon moment, à la bonne dose, par la bonne voie et à la bonne fréquence pendant le traitement sans interrompre le traitement pour obtenir de bons résultats de traitement. Cela comprend une allocation de transport pour les patients pour faciliter les déplacements vers les établissements de santé; un soutien nutritionnel - des colis alimentaires ; une allocation pour les accompagnateurs de traitement ; et une thérapie observée par vidéo (TOV) / thérapie directement observée virtuelle (TDOV) pour maintenir l'observance du traitement sans avoir besoin de visites en personne.
- **Réalisation d'études prospectives de pharmacovigilance à l'échelle nationale et continentale:** Une étude prospective menée dans l'une des régions de l'Eswatini a fourni des aperçus précieux sur le profil de sécurité et l'utilisation de deux médicaments repositionnés contre la TB-MR, le CFZ et le LZD. Des études supplémentaires avec des échantillons plus importants couvrant différents contextes devraient être menées pour obtenir un panorama plus large du profil de sécurité des médicaments repositionnés.
- **Établissement d'un département ou d'une sous-unité de pharmacovigilance dans chaque site de traitement de la tuberculose multirésistante (TB-MR):** Tous les sites de traitement de la TB-MR à travers le pays devraient envisager d'établir un département ou une sous-unité de pharmacovigilance pour accorder une attention particulière et surveiller de près les patients sous traitement de la TB-MR. Ces unités de PV peuvent mettre en œuvre une surveillance régulière de la sécurité des médicaments, garantir une détection, une gestion et une notification appropriées des

ADR, ainsi que la formation et la supervision des prestataires de soins de santé pour augmenter le taux de notification et la qualité des rapports.

- **Amélioration des outils de notification:** Il est recommandé de travailler à la rationalisation des mécanismes de notification des ADR. Pour faciliter la notification et réduire la charge administrative, l'introduction et la mise en œuvre de formulaires électroniques de notification des ADR liés aux dossiers électroniques des patients devraient être envisagées.
- **Ressources Humaines et Renforcement des Capacités:** Des ressources humaines formées avec des compétences en pharmacovigilance sont nécessaires pour l'analyse des données, l'évaluation de la causalité, la détection des signaux et la communication des risques. Renforcer le processus de détection des signaux et de communication peut améliorer les efforts globaux de pharmacovigilance. Pour cela, il devrait y avoir une formation continue, des retours d'information et une communication régulière avec les prestataires de soins de santé et les patients.
- **Aller au-delà du simple rapport aux analyses de données de sécurité et à la communication des risques:** Comme décrit dans la définition de l'OMS, la pharmacovigilance englobe des activités importantes au-delà de la simple détection et du rapport. Cela nécessite un passage d'une simple déclaration des données de sécurité à une approche plus holistique qui comprend l'analyse et la communication de la sécurité des médicaments à toutes les parties prenantes. Par conséquent, il est recommandé que le centre de pharmacovigilance analyse les problèmes de sécurité potentiels signalés et communique les résultats aux travailleurs de la santé, aux organismes de réglementation et aux patients.

## CONCLUSION

Cette thèse avait pour but d'évaluer et de décrire le profil et les caractéristiques des effets indésirables des médicaments chez les patients atteints de tuberculose résistante en Eswatini, ainsi que d'évaluer le profil de sécurité des médicaments contre la tuberculose résistante au niveau mondial. Pour atteindre ces objectifs, nous avons mené des études prospectives et rétrospectives sur des données locales et analysé des données mondiales extraites de Vigibase.

Dans notre étude de la base de données mondiale, l'analyse des CIRS de 39 pays a indiqué que le Pyrizinamide - PZA, l'éthambutol - ETO, le Cyclosérine -CS, le Bidaquiline - BDQ, le Clogazimine - CFZ et le Linézolide - LZD étaient responsables de la plupart des rapports de sécurité de cas

individuels dans le traitement de la tuberculose pharmacorésistante, les patients âgés (plus de 65 ans) ayant de moins bons résultats que les adolescents (0-18 ans) et les adultes (19-64 ans). Cette étude a mis en évidence la nécessité d'un suivi rigoureux et d'un système de PV efficace, car les rapports de sécurité de cas individuels les plus graves ont été signalés en relation avec des médicaments clés utilisés dans le traitement de la tuberculose pharmacorésistante.

En ce qui concerne notre étude rétrospective, nous avons observé que près de la moitié des patients présentaient au moins un effet indésirable et que près d'un tiers d'entre eux étaient graves. Il est donc extrêmement important de renforcer la surveillance de la sécurité des patients traités pour la tuberculose pharmacorésistante, afin de garantir une gestion rapide et appropriée des effets indésirables, réduisant ainsi le risque d'échec du traitement.

Enfin, nous avons évalué le profil de sécurité des médicaments contre la tuberculose réadaptés, en particulier le CFZ et le LZD, dans l'une des régions de l'Eswatini, où nous avons constaté que 80 % des patients traités par le CFZ et le LZD ont été satisfaits de leur traitement, ce qui a permis de réduire les risques d'échec du traitement.

**Mots clés:** pharmacovigilance, santé publique, tuberculose multirésistante, sécurité des médicaments, réactions indésirables aux médicaments, surveillance de sécurité

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  - Position: PhArmacoVigilance Africa (PAVIA) coordinator

PhD period: January 2020 – December 2024

SN	Short courses and training taken during the thesis period
1.	Substantiation and Quantification of Risks (6 ECTS credits), By European Programme for Pharmacovigilance and Pharmacoepidemiology (EU2P) July 2023
2.	Pharmacovigilance Regulatory Processes (3 ECTS credits), EU2, July 2022
3.	Regulatory aspects of pharmacovigilance, Uppsala Monitoring Centre, May 2022
4.	WHO Global Benchmarking Assessment Tool training, By Southern Africa Regulatory for Clinical Research (SEARCH) project, October 2021
5.	Drug-Induced Liver Injury E-learning Course Drug Induced Liver Injury E-learning Course; Uppsala Monitoring Centre, Issued May 2022



6.	Methods in Clinical Research, Pharmacoepidemiology and the assessment of the Efficacy of medicines, EU2P, July 2021
7.	Pharmacovigilance Risk evaluation and communication, The Lareb Pharmacovigilance Center, June 2021
8.	International Harmonisation Initiatives, EU2P, April 2020
9.	Statistical reasoning and algorithms in pharmacovigilance; Uppsala Monitoring Center; April 2020
<b>Publications during the Thesis period</b>	
1.	Schievano F, Mwamwitwa KW, Kisenge S, et al. Development, assessment, and educational impact of a blended e-learning training program on pharmacovigilance implemented in four African countries. <i>Frontiers in medicine</i> . 2024;11. doi: <a href="https://doi.org/10.3389/fmed.2024.1347317">https://doi.org/10.3389/fmed.2024.1347317</a>
2.	Alemayehu Lelisa Duga, Salvo F, Kay A, Figueras A. Safety Profile of Medicines Used for Drug-Resistant Tuberculosis: A Descriptive Study Based on the WHO Database (VigiBase®).
3.	Duga AL, Magongo S, Nhlabatsi S, Ladwar DO, Härmark L, Rolfes L. An evaluation of postmarketing reports of hyperglycemia associated with dolutegravir for treatment of HIV in Eswatini. <i>AIDS Res Ther</i> . 2022 Nov 24;19(1):54. Doi: 10.1186/s12981-022-00481-0. PMID: 36424607; PMCID: PMC9694599.
4.	Mutale Deluxe, Alemayehu Lelisa Duga, Girinshuti G, Ahmadi A, Eliseo D. Eswatini's formidable task of fighting against COVID-19. <i>Razi International Medical Journal</i> . 2021;1(1). doi: <a href="https://doi.org/10.56101/rimj.v1i1.12">https://doi.org/10.56101/rimj.v1i1.12</a>
5.	Tiemersma EW, Ibrahim A, Alemu A, et al. Baseline assessment of Pharmacovigilance activities in four sub-Saharan African countries: a perspective on tuberculosis. Published online April 19, 2021. doi:10.21203/rs.3.rs-422624/v1
6.	Koirala S, Borisov S, Danila E, et al. Outcome of treatment of MDR-TB or drug-resistant patients treated with bedaquiline and delamanid: Results from a large global cohort. <i>Pulmonology</i> . Published online March 2021. doi:10.1016/j.pulmoe.2021.02.006
7.	LESSONS AND BEST PRACTICES FROM THE PAVIA PROJECT: A blueprint for strengthening pharmacovigilance systems in resource-limited countries.

	[accessed 2024 Jun 1]. <a href="http://www.efda.gov.et/wp-content/uploads/2023/06/A-blueprint-for-strengthening-pharmacovigilance-systems-in-resource-limited-countries.pdf">http://www.efda.gov.et/wp-content/uploads/2023/06/A-blueprint-for-strengthening-pharmacovigilance-systems-in-resource-limited-countries.pdf</a> .
8.	Malaria Vaccine Rollout begins in Africa: The Need to Strengthen Regulatory and Safety Surveillance Systems in Africa [ <i>Submitted to BMJ Global health</i> ]
9.	A community engagement framework to accelerate the uptake of malaria vaccines in Africa [ <i>Accepted for publication at Nature Medicine</i> ]
10.	Innovative Vaccination Approaches and Risk Communication Strategies to Accelerate COVID-19 Vaccination in Africa[ <i>Submitted to BMJ Global Health</i> ]
<b>Membership and professional registration</b>	
1.	Registered as a Pharmacist by the Ministry of Health of the Federal Democratic Republic of Ethiopia since 12/8/2010
2.	Registered as a Pharmacist by Swaziland Dental and Medical Council in June,2012
3.	A member of the technical working group of the Safety of COVID-19 Vaccination in Children and Pregnancy in LMICs
4.	Member of The International Society of Pharmacovigilance (ISoP) since 2019
5.	Member of the International Association for Public Health Logisticians (IAPHL)
6.	Member of Ethiopian Pharmacy Association since 2015
7.	Member Of Swaziland Pharmacy Association, since 2012
8.	Safety Platform for Emergency Vaccines (SPEAC) Advisory Committee member (April 2024 to present )
9.	The International Society of Pharmacovigilance (ISoP), Regulatory and Practice TWG member
10.	Coordinator, Eswatini National Patient safety week Campaign (2021 and 2022)
11.	Eswatini Clinical Advisory Committee for TB sequencing member (November 2021-December 2022)
12.	Member of AEFI case investigation and causality assessment expert group in Eswatini. (January 2020-December 2022)

13.	Member of Eswatini National Patient Safety and Monitoring Committee (NPSMC) (Feb 2018 to December 2022)
14.	The Community Boosting Organization (CBO), PROACTIVE VOLUNTEER MEMBER (April 2023-present)[volunteer]
Abstract presentations	
1.	<b>Oral Presentation:</b> Development and Evaluation of a Blended Pharmacovigilance e-Learning Course in Africa - ProQuest. Proquest.com. Published 2022. Accessed May 30, 2024. <a href="https://www.proquest.com/openview/0720a483886031f574a7e7764c21fc98/1?pq-origsite=gscholar&amp;cbl=32187">https://www.proquest.com/openview/0720a483886031f574a7e7764c21fc98/1?pq-origsite=gscholar&amp;cbl=32187</a>
2.	<b>e-poster presentation:</b> An evaluation of post-marketing reports of hyperglycemia associated with dolutegravir for treatment of HIV in Eswatini [ <b>the BIPAI RAISE Symposium in 2021</b> ]
3.	<b>Oral presentation:</b> Surveillance of Adverse Events Following Immunization during mass vaccination campaigns in The Democratic Republic of Congo. [ <b>CPHIA2023 Conference-Zambia-Lusaka</b> ]
4.	<b>e-Poster presentation:</b> E. Tiemersma, F. Cobelens, A. Isah, B. Mmbaga, H. Tumwujukye, Teferi, Duga, L. Harmark; Four years of pharmacovigilance strengthening for drug-resistant TB in Eswatini, Ethiopia, Nigeria and Tanzania: Results from the PhArmacoVigilance in Africa (PAVIA) project [ <b>Union World Conference on Lung Health-Paris, France2023</b> ]
5.	<b>Poster presentation:</b> COVID-19 Vaccine Safety Surveillance: Phase 1 Implementation Achievements under the Saving Lives and Livelihoods Programme [ <b>CPHIA2023 Conference-Zambia-Lusaka</b> ]
6.	<b>Oral presentation:</b> The Process of Developing a Pharmacovigilance - ProQuest. 2021. Proquestcom. doi: <a href="https://doi.org/%22,.">https://doi.org/%22,.</a> [accessed 2024 Jun 1]. [ISoP Meeting] <a href="https://www.proquest.com/docview/2604881564?pq-origsite=gscholar&amp;fromopenview=true&amp;sourcetype=Scholarly%20Journals">https://www.proquest.com/docview/2604881564?pq-origsite=gscholar&amp;fromopenview=true&amp;sourcetype=Scholarly%20Journals</a> .
Blogs and Op-eds	
1.	COVID-19 Vaccine Hesitancy in Africa: Tackling Safety Concerns for Optimal Uptake   Think Global Health. Council on Foreign Relations. Published October 25,

	2023. Accessed June 1, 2024. <a href="https://www.thinkglobalhealth.org/article/covid-19-vaccine-hesitancy-africa-tackling-safety-concerns-optimal-uptake">https://www.thinkglobalhealth.org/article/covid-19-vaccine-hesitancy-africa-tackling-safety-concerns-optimal-uptake</a>
2.	Medication Without Harm: Implementing Pharmacovigilance. 2022 Sep 15. The Medicines, Technologies, and Pharmaceutical Services (MTaPs) Program. [accessed 2024 Jun 1]. <a href="https://www.mtapsprogram.org/news-blog/medication-without-harm-implementing-pharmacovigilance/">https://www.mtapsprogram.org/news-blog/medication-without-harm-implementing-pharmacovigilance/</a>
3.	Evolution of pharmacovigilance in the Kingdom of Eswatini. 2022. Uppsala Reports. [accessed 2024 Jun 1]. <a href="https://uppsalareports.org/articles/evolution-of-pharmacovigilance-in-the-kingdom-of-eswatini/#:~:text=To%20this%20end%2C%20the%20Ministry,of%20drugs%20on%20the%20market.">https://uppsalareports.org/articles/evolution-of-pharmacovigilance-in-the-kingdom-of-eswatini/#:~:text=To%20this%20end%2C%20the%20Ministry,of%20drugs%20on%20the%20market.</a>
<b>Hosted conferences and participations</b>	
1.	Hosted a side event at the 3 <sup>rd</sup> International Conference on Public Health in Africa (CPHIA 2023) on “Pharmacovigilance in Africa in the face of COVID-19 vaccination.”
2.	Patient safety date-Eswatini, September 2021
3.	As a speaker on PharmaReg AfriSummit 2021
4.	As a speaker on PharmaReg AfriSummit 2022
5.	Pharmacovigilance Meeting of the Members of the WHO programme for international drug monitoring and partners in Africa (Mar 2-3, 2023), Morocco.
6.	Participated on ‘Pharmacovigilance Journal Club’ webinar: 15 April 2021, organized by the International Society of Pharmacovigilance (ISoP) and the Journal of Drug Safety
7.	Good Clinical Practice training, by NIDA Clinical Trials Network, October 2021
8.	ISoP Symposium & Training for Eurasian Countries, June 2021
<b>Contributions to the development of Pharmacovigilance documents and tools</b>	
1.	Coordinated and developed the first-ever Eswatini National pharmacovigilance policy (December 2021)
2.	Coordinated and developed the Eswatini National Pharmacovigilance Road map (2019-2021)
3.	Coordinated and developed Eswatini PV guideline (July 2022)

<b>4.</b>	Developed National PV SoPs and Job Aids for Eswatini national PV center (June 2021)
<b>5.</b>	Developed a Pharmacovigilance training manual for the Republic of South Sudan
<b>6.</b>	Developed PV reporting tools and SOPs and trained healthcare workers in South Sudan
<b>7.</b>	Developed an E-module on pharmacovigilance to train healthcare workers in Eastern Africa
<b>8.</b>	Development and distribution of the semi-annual Medicines Safety newsletter in Eswatini [From 2019-2022]
<b>9.</b>	Contributed to the development of the Eswatini Field Guide on Surveillance of Adverse Events Following Immunization (AEFI) and Response (April 2022)
<b>10.</b>	Contributed to the development of Zambian Ministry of Health Guidelines for The Integration of Covid-19 Vaccination into Routine Immunization/ Primary Health Care
<b>11.</b>	Contributed into the development of the pharmacovigilance section of the Africa CDC Strategic Plan for the period 2023-2027.

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3. K B. Barriers to Reaching the Targets for Tuberculosis Control: Multidrug-Resistant Tuberculosis. *Bull World Health Organ*. 2007;85(5).
4. World Health Organization. Global Tuberculosis Report [Internet]. 2023 [cited 2024 May 19]. Available from: <https://www.who.int/teams/global-tuberculosis-programme/tb-reports/global-tuberculosis-report-2023/tb-diagnosis---treatment/drug-resistant-tb-treatment>
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6. The Kingdom of Eswatini M of H. National TB Control Programme (NTCP) Tb annual report 2022. 2022;
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## **CHAPTER 8. ANNEXES**

## Annex A: Support letter from the School

Ecole doctorale 545 Sociétés, Politique, Santé Publique,

### CERTIFICATION

I, the undersigned, Professor Bernard N'KAOUA, Director of the Doctoral School Societies, Politics, Public Health (ED SP2), certify that Mr. Alemayehu Duga is enrolled in the 1st year of the doctoral program "Pharmacology, option Pharmaco-Epidemiology, Pharmacovigilance" for the academic year 2020/2021. The doctoral student will have to apply annually for re-enrollment throughout the duration of his thesis (normally 3 years).

The study project is entitled "Patterns of Adverse Drug Reactions in Patients with Drug-Resistant Tuberculosis in Eswatini and comparison of AE Reports characteristics with a worldwide database: A Prospective and Retrospective Cohort Study" and is being developed within the Bordeaux Population Health laboratory, under the direction of Francesco Salvo, Albert Figueras and Alexander Kay.

Done in Bordeaux in order to assert what is right,

Bordeaux, December 9, 2020



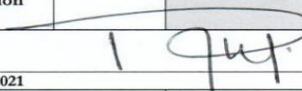
Professor Bernard N'KAOUA  
Director of EDSP2

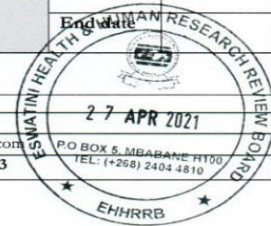
## Annex B: Ethical Clearance from Eswatini Health and Human Research Review Board



**ESWATINI  
HEALTH AND HUMAN  
RESEARCH REVIEW BOARD**  
MBANDZENI HOUSE, 3<sup>RD</sup> FLOOR, CHURCH STREET  
P.O. BOX 5, MBABANE, ESWATINI

### ONE YEAR RESEARCH PROTOCOL APPROVAL CERTIFICATE

BOARD REGISTRATION NUMBER	FWA 00026661/IRB 00011253				
PROTOCOL REFERENCE NUMBER	SHR327/2020				
Type of review	Expedited	<input checked="" type="checkbox"/>		Full Board	
Name of Organization	PHD student				
Title of study	Patterns of Adverse Drug Reactions in Patients with Drug-Resistant Tuberculosis in Eswatini and comparison of AE Reports characteristics with a worldwide database: A Prospective and Retrospective Cohort Study				
Protocol version	1.0				
Nature of application	New	<input type="checkbox"/>	Amendment	<input type="checkbox"/>	Renewal
		<input checked="" type="checkbox"/>		<input type="checkbox"/>	Extension
					CT updates
List of study sites	AHF Matsapha, Baylor Clinic COE, Dvokolwako Health Center, Emkhunzweni Health Center, Mankayane Government Hospital, Hlathikhulu Government Hospital, Nhlngano Health Centre, Manzini TB Center, Matsanjani Health Centre, Pigg's Peak Government Hospital, Sithobela Health Centre, Siphofaneni Clinic, National TB Hospital				
Name of Principal Investigator	Mr. Alemayehu Duga				
Names of Co- Investigators	Professor Albert Figueras, Associate Professor Alexander Kay				
Names of steering committee members in the case of clinical trials	N/A				
Names of Data and Safety Committee members in the case of clinical trials	N/A				
Level of risk (Tick appropriate box)	Minimal	<input checked="" type="checkbox"/>	More than minimal		High
Initial study Approval information	Approved	<input checked="" type="checkbox"/>	Study completion date	27/04/2022	Certificate expiry Date
	Approval date	27/04/2021			27/04/2022
Study renewal approval information	Renewal date				End date
Study amendment approval information	Amendment date				End date
Study extension approval information	Extension date				End date
Signature of Chairperson					
Signing date	27/04/2021				
Secretariat Contact Details	Name of contact officers	Babazile Shongwe			
	Email address	ehhrrbeswatini@gmail.com			
	Telephone no.	(00268) 2404 7751/9553			



### APPROVAL CONDITIONS

Ref.	Conditions	Indication of conditions (tick appropriate box)				
		Yr 1	Yr 2	Yr 3	Yr 4	Yr 5
1	Implementation of approved version of protocol					
2	Provide a specific insurance cover certificate in respect of this particular study within 14 days of receiving this Ethics Clearance certificate					
3	Update information on adverse events both on the addendum and the informed consent form to include measures for addressing life threatening adverse events that occur at home.					
4	Reporting of adverse events within 5 days of occurrence					
5	Submission of progress reporting for multi-year studies					
6	Submission of end of project report (Hard copy)	✓				
7	Submission of end of project report (Soft copy)	✓				
	Submission of data sets	✓				

### List of reviewed documents

Ref.	Documents	Reviewed documents (tick appropriate box)
1	Completed application form	✓
2	Cover letters	✓
3	Evidence of administrative permission to conduct the research by involved institutions/sites (where applicable)	✓
4	Detailed current resume or curriculum vitae of Principal Investigator/s including Principal investigators declaration	✓
5	Summary resume or biography for other investigator(s)	✓
6	Evidence of approval/rejection by other Ethics Committees, including comments and requested alterations to the protocol, where appropriate.	
7	Research protocol (see outline in Annex 1)	✓
8	Questionnaires and interview guides (with back-translated versions where applicable)	✓
9	Case report forms (CRFs), abstraction forms and other data collection tools	
10	Participant/subjects Information Statement(s) (where applicable)	
11	Informed consent form(s) including photographic and electronic media consent statements.	✓
12	Advertisements relevant to the study (where applicable)	
13	Source of funding and detailed budget breakdown including material and incentives to participants if applicable	✓
14	Notification form for adverse effects/events.	
15	Proof of payment	✓
16	Proof of insurance cover for research subjects in clinical trials or where applicable	
17	Any other special requirements should be stated, if applicable	N/A

*PC*

||



## Annex C: Permission letter from The Kingdom of Eswatini Ministry of Health

Telephone: (+268 24042431)  
Fax: (+268 2404 2092)



MINISTRY OF  
HEALTH  
P.O. BOX 5 MBABANE  
ESWATINI

### THE KINGDOM OF ESWATINI

Date: December 10, 2021

Uppsala Monitoring Centre  
WHO Collaborating Centre for International Drug Monitoring  
Sweden

Dear Sir/Madam,

#### **SUBJECT: PERMISSION FOR CUSTOMIZED VIGIFLOW DATA**

This letter serves to give permission to Mr. Alemayehu Duga who is currently pursuing his Ph.D. with EU2P in Pharmacovigilance and Pharmacoepidemiology. One of the objectives of his project is to investigate the Patterns of Adverse Drug Reactions (ADRs) in Patients with Drug-Resistant Tuberculosis from a worldwide database (VIGIFLOW) for a period of three years.

The aim of the study is to analyze the characteristics of globally reported ADRs and compare with local and continental data. This will help to identify the possible gaps in the country and continentally at large with regard to reporting as well as to investigate the characteristics of ADRs reported in these settings.

I therefore request your organization to offer Mr. Duga all possible assistance with regard to the above-mentioned subject matter.

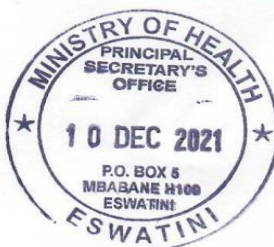
I thank you for your continued support and cooperation. For additional information and further action, please contact the following officers:

1. Mr. Siphesihle Nhlabatsi |Email: [ntinisphe@gmail.com](mailto:ntinisphe@gmail.com)
2. Mr. Alemayehu Duga |Email: [alexduga4@gmail.com](mailto:alexduga4@gmail.com)

Your sincerely

A handwritten signature in black ink, appearing to be 'S. M. Zwane'.

**Dr. S. M. Zwane**  
Principal Secretary  
Ministry of Health



## Annex D: Support letter from Eu2P

université  
de **BORDEAUX**

**Eu2P**  
EUROPEAN PROGRAMME IN  
PHARMACOVIGILANCE AND  
PHARMACOEPIDEMIOLOGY



Dr Karine Palin  
Eu2P Central office  
Université Bordeaux  
146, rue Léo Saignat  
33076 Bordeaux Cedex  
France

[eu2p.office@eu2p.org](mailto:eu2p.office@eu2p.org)  
Tel +33(0) 557579257  
Mob +33 (0) 630290029

Bordeaux, December 09<sup>th</sup>, 2020

**Subject:** Alemayehu Duga 's PhD registration within the University of Bordeaux

This is to certify, that Mr Alemayehu Duga, born on June 12<sup>th</sup> 1987 in Dawo, Ethiopia, is regularly registered to the Doctoral school of Public Health and Population at the University of Bordeaux and is working on a project entitled "Patterns of Adverse Drug Reactions in Patients with Drug-Resistant Tuberculosis in Eswatini and comparison of AE Reports characteristics with a worldwide database: A Prospective and Retrospective Cohort Study".

Dr Karine Palin  
Eu2P Programme Manager



Adresse postale  
Université de Bordeaux  
351 cours de la libération  
33405 Talence cedex  
[www.u-bordeaux.fr](http://www.u-bordeaux.fr)



## **Annex E: Informed consent statement [English Version]**

**Project title:** “Patterns of Adverse Drug Reactions in Patients with Drug Resistant Tuberculosis in Eswatini and comparison of AE Reports characteristics with worldwide database: A Prospective and Retrospective Cohort Study”.

**Study purpose:** To identify and describe the pattern and characteristics of ADR in patients with MDR-TB in Eswatini and compare them with a worldwide database

**Name of Principle Investigator:** Alemayehu Duga

**Name of institution:** The University of Bordeaux

**Name of supervisors:** Professor Albert Figueras

**Co-Supervisors:** Dr. Alexander Kay and Francesco Salvo

**This Informed Consent Form has two parts:**

- Information Sheet (to share information about the study with you)
- Certificate of Consent (for signatures if you choose to participate)

You will be given a copy of the full Informed Consent Form

### **Part I: Information Sheet**

#### **Introduction**

Dear Sir/Madam,

My name is Alemayehu Duga. I am a Student at The University of Bordeaux and currently conducting research on “Patterns of Adverse Drug Reactions in Patients with Drug-Resistant Tuberculosis in Eswatini and comparison of AE Reports characteristics with worldwide database.” This study is in partial fulfillment for PhD in Pharmacovigilance and Pharmacoepidemiology.

This study aims to identify and describe the pattern and characteristics of ADR in Eswatini patients with MDR-TB and compare them with a worldwide database. You have been selected as a respondent in this study.

The information you provide will be used for studies that will improve the Eswatini Health System and the globe. Before you decide whether to participate in the research, you can talk to anyone you feel comfortable with about it.

This consent form may contain words that you do not understand. Please ask me to stop as we review the information, and I will take time to explain. If you have questions later, you can ask me or another team member of this study.

#### **Purpose of the research**

Treatment of sickness with medicines may sometimes bring significant risks, which include side effects and other consequences of inappropriate medication use.

Due to the introduction of new drugs and increasing usage of repurposed medicines for the management of MDR TB, there are significant challenges with understanding, properly managing, and predicting side effects. Despite the continued updates and several studies being done around the treatment of MDR-TB, the information on adverse drug reactions is inadequate to make decisions. Therefore, this project will contribute to the knowledge by determining the extent of side effects, preventability, predictability, and associated risk factors among MDR-TB clients on treatment.

### **Type of Research Intervention**

This research will involve your participation in an interview using a structured data collection tool that will take about one hour for each visit.

### **Voluntary Participation/ Right to Refuse or Withdraw**

Your participation in this research is entirely voluntary. It is your choice whether to participate or not. Your choice will not affect the treatment or services you receive from this facility. You may change your mind later and stop participating even if you agreed earlier.

### **Procedures**

1. We are asking you to help us learn more about the side affects you may experience while taking MDR-TB treatment
2. Participate in an interview with your physician or Nurse.
3. If you do not wish to answer any of the questions during the interview, you may say so, and the interviewer will move on to the next question.
4. The information recorded is confidential, and no one else except your doctor, Nurse, and researchers will access the information documented during your interview

### **Duration**

The research takes place over 12 months. The interviews or data collection will be done during your regular visits. Each interview or data collection will last about one hour.

### **Risks and benefits of the study**

You will not be asked to visit facilities for this study and will not experience any benefits or harm related to being part of the study. In terms of benefits or harms for the community, the study will benefit patients currently in care and future patients. It will help improve DR TB management by identifying the treatment-limiting toxicities, their patterns, and risk factors associated with toxicities. Therefore, the findings and recommendations from this study will help improve DR-TB-related care and programs in Eswatini and inform policy and decision-makers in allocating resources for public health. In addition, this will be published and thus will also inform the international scientific community on DR-TB treatment toxicity characteristics.

**Confidentiality:** The data received from this study will be kept confidential. We will not share information about you with anyone outside the research team. The information that we collect from this research project will be kept private. Any information about you will have a number instead of your name. Only the researchers will know your number, and we will lock that information up with a lock and key.

## Sharing the Results

This study's findings will be shared with you and your community before it is made widely available to the public. Each participant will receive a summary of the results. Following the dissemination of the summary of the results, we will publish the results so that other interested people may learn from the study.

## Who to Contact

If you have any questions, you can ask them now or later. If you wish to ask questions later, you may contact the principal investigator:

- Name: Alemayehu Duga; Telephone number: +26878264522 or Email: [alexduga4@gmail.com](mailto:alexduga4@gmail.com)

This proposal has been reviewed and approved by Eswatini Human Health Research and Review Board (EHHRRB), a committee whose task it is to make sure that research participants are protected from harm. If you wish to find about more about WHHRRB, contact (26824044810)

## Part II: Certificate of Consent

I have read the foregoing information, or (it has been read to me). I have had the opportunity to ask questions about it, and any questions I have been asked have been answered satisfactorily. I consent voluntarily to be a participant in this study:

Print Name of Participant: \_\_\_\_\_

Signature of Participant: \_\_\_\_\_

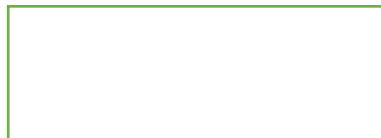
Date: \_\_\_\_\_

### For study participants who cannot read:

I have witnessed the potential participant's consent form being accurately read, and the individual has had the opportunity to ask questions. I confirm that the individual has given consent freely.

Print name of witness: \_\_\_\_\_

Thumbprint of participant:



Signature of witness: \_\_\_\_\_

Date: \_\_\_\_\_

**Statement by the researcher/person taking consent**

I have accurately read out the information sheet to the potential participant, and to the best of my ability, I will make sure that the participant:

- Will be fully briefed about the study
- Will be informed how long the study will take
- Will be briefed on the confidentiality of the information

I confirm that the participant was allowed to ask questions about the study, and all questions have been answered correctly and to the best of my ability. I confirm that the individual has not been coerced into giving consent, and the consent has been given freely and voluntarily. A copy of this informed consent form has been provided to the participant.

Print Name of Researcher/person taking the consent \_\_\_\_\_

Signature of Researcher /person taking the consent \_\_\_\_\_

Date \_\_\_\_\_

## **Annex E: Informed consent statement [Siswathi Version]**

### **Sengetetelo Sesibili: Inkhulumo Lesho Kuvuma**

**Sihloko:** “Tinkhomba tetindlela le bantfu babangayo uma bane TB legwamile eSwatini nane kucatsaniswa kwemapoti aka AE kunye naletinye tinombolo temhlaba: lucwaningo lolu chamuka emuva.”

**Inhloso yalolucwaningo:** Kubona nekuchaza tindlela le bantfu labagula nge-TB legwamile (MDR-TB) bangatondza ngayo uma badla emaphilisi ayo eSwatini, nekuticatsanisa netinombolo letikhona mhlaba wonkhe.

**Umcwaningi lomkhulu:** Alemayehu Duga

**Inyuvesi:** Inyuvesi yase Bordeaux

**Umbuyeketi lomkhulu:** Professor Albert Figueras

**Labanye Babuyeketi:** Dr. Alexander Kay, Francesco Salvo

### **Lelifomu leli lelisho kuvuma lingunayi imikhakha lemibili:**

- Liphepha lembiko (lapho lipha wena umbiko ngalolucwaningo)
- Liphephad lekuvuma (lapho ungasayina khona uma ukhetsa kuba yincenye yalolucwaningo)

Utawunikwa lakakho nawe lifomu.

### **Sicephu sekucala: Liphepha lembiko**

#### **Setfulo:**

Mnumzane/Nkhosikati,

Libito lami ngingu Alemayehu Duga, umfundzi wase Nyuvesi yase Bordeaux, lowenta lucwaningo ngetinkhomba tetindlela le bantfu babangayo uma bane TB legwamile eSwatini nane kucatsaniswa kwemapoti aka AE kunye naletinye tinombolo temhlaba. Lolucwaningo luyicenye yelugcwaliso lwemfundvo yebu Dokotela ka “Pharmacovigilance & Pharmacoepidemiology”.

Lolucwaningo lolu luhlose kutfolo nekuchaza tinkhomba te-ADR kutigulane letine MDR-TB eSwatini nekuticatsanisa naletinye tinombolo mhlaba wonkhe. Wena ukhetsiwe kutsi ube yincenye yalolucwaningo.

Letimphendvulo lowutawusipha tona titawusita kulamanye emacwaningo latawufukula Temphilo eSwatini na mhlaba wonkhe. Ungakakhetsi kutsi utoba ngiyo yini incenye yalolucwaningo, kumbe ungakhuluma nemuntfu lometsembako mayelana nalo.

Lelifomu leli kungenteka libe nemagama longawacondzi kahle. Uma kwenteka kuba kanjalo, uvumelekile kutsi ungibutisise, noma ubute noma ngubani-ke lomunye lesenta naye lolucwaningo.

### **Inhloso yalolucwaningo:**

Ngalesinye sikhatsi, kwelashwa ngemitsi tsite kungaletsa bungoti lobuphatsekako lobufaka imitsetela yekudla imitsi nje, nanalobubangwa-ke kungadli imitsi kahle.

## **Luhlobo lwelucwaningo**

Lolucwaningo lolu lutofaka kusebentisana nawe kakhulu, lapho khona wena sikubuta imibuto sisebentisa luhla lwemibuto loluhleliwe. Asikagadzi kutsi imibuto yetfu le itsatse ngetulu kweli-awa.

## **Kuvuma kutimbandzakanya nalolucwaningo/Lilungelo lekwala**

Kukhetsa kwakho kutimbandzakanya nalolucwaningo lolu kuyintsandvo yakho lephelele. Loko lotowutikhetsela kusitjela kona ngeke kube nemitselela kundlela lowutawuphatfwa ngayo ngitsi. Sisachubeka nalolucwaningo, ungayishintsha ingcondvo wale kuchubeka nekuba yincenye yalo, noma ngabe bowuvumile ekucaleni.

## **Indlela lekutokwentiwa ngayo**

1. Sikucela kutsi usisite sati kabanti ngemitselela longaba nayo usadla emaphilisi e-MDR-TB.
2. Sitawukhulumisana kabanti nana Dokotela wakho noma Nesi wakho.
3. Uma kukhona umbuto lova shengatsi awukhululeki kuwuphendvula ungasho, sitoweca lowo mbuto sendlulele kulolandzelako.
4. Timphendvulo losipha tona tiyimfihlo, futsi kute lomunye, ngaphandle kwa Dokotela wakho na Nesi wakho nebacwaningi, lovunyelwe kutati leto timphendvulo.

## **Budze belucwaningo**

Lolucwaningo lutotsatsa sikhatsi lesitinyanga letilishumi na mbili. Lemibuto lotobutwa yona itobutwa njalo uma ute esibhedlela, ngetikhatsi takho letijwayekile. Njalo uma ubutwa, kutovamisa kutsatsa sikhatsi lesingange li-awa.

## **Bungoti nenzuzo**

Ngeke kube khona tindzawo lotocelwa kutsi uye kuto kusentiwa lolucwaningo, futsi kute nalotakuzuza nalokutakulimata ngekutsi uvume kuba yincenye yalolucwaningo. Mayelana nebungoti nenzuzo yem'mango, lolucwaningo lolu lutozuza tigulane letikhona nyalo naletistoba khona ngoba lutawusita kufukula indlela lokwelashwa ngayo i DR-TB, ngekutsi itokwenta kubonakale bo shevu labangenta kutsi emaphilisi angasebenti ngendlela labhekeke ngayo.

Lokutawutfolakala kulolucwaningo lolu-ke, kutawusita kakhulu ku Temphilo eSwatini, eluhlangotsini lolubukene nekwelapha I DR-TB, kwente ne tishaya-mtsetfo tikhone kwati kahle kutsi loluhlangotsi lolu lwe Temphilo ludzinga timali letinganani. Lokunye-ke futsi, lolwati lolu lutoshicilelwa lusakatwe mhlaba wonkhe, ngako-ke, lutokhaliphisa kabanti nabo cwephesha bamhlaba wonkhe nge DR-TB nangekwelashwa kwayo.

## **Bumfihlo**

Timphendvulo letitokolekwa kulolucwaningo titoba yimfihlo. Kute imininingwane yakho lesitoyipha muntffu ngaphandle kwabo bona laba lesisebentisana nabo. Yonkhe imininingwane lesitoyitfolo kuwe itawukuba nenombolo lekhomba wena, hhayi ligama lakho. Kutoba bacwaningi kuphela labatokwati kutsi inombolo yakho itsini, futsi yonkhe imininingwane lotosipha yona itohlala ivalelwe yakhiyelwa.



### **Kutjengisana imiphumela yelucwaningo**

Imiphumela yalolucwaningo lolu itotjengiswa wena kunye nem'mango wakini ingaka tjengiswa live lonkhe nemhlaba wonkhe.

Nguloyo naloyo lotoba yincenye yalolucwaningo utonikwa sifinyeto salemiphumela. Emuva kwekuba sekukhishwe lesifinyeto, sitobese sishicilela lemiphumela khona wonkhe lowo lomunye longaba khona longafuna kuyifundza naye ayifundze.

### **Kutsintfwa bani?**

Uma ngabe kukhona imibuto longaba nayo, ungayibuta manje noma-ke ngalesinye sikahtsi. Uma ufuna kuyibuta ngalesinye sikhatsi, unagatsintsa umcwaningi lomkhulu lobhalwe lana ngentasi;

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Lesicelo lesi sekwenta lucwaningo sibukiwe sase siyavunyelwa baka Eswatini Human Health Research and Review Board (EHHRB), lekulibandla lelibukene nekucineseka kutsi labo labatimbandzakanya nalolo cwaningo lolwentiwako bavikelekile. Uma ufise kwati kabanti nga EHHRB, ungabantsitsa ku: +268 2404 4810.

### **Sicephu sesibili: Imvumo yekutimbandzakanya nalolucwaningo**

Sengikufundzile konkhe lolokubhalwe lapha ngenhla (noma ke sebangifundzele). Sengilitfolile nanelitfuba lekubuta imibuto ngako loku lokubhaliwe, futsi yonkhe imibuto lengibutwe yona iphendvulekile ngalokungenetisako. Ngekungaphocelelwa ngumuntu, ngiyavuma kutsi ngibe yincenye yalolucwaningo.

Libito: \_\_\_\_\_

Kusayina: \_\_\_\_\_

Lusuku: \_\_\_\_\_

### **Kulabo labangakhoni kufundza**

Ngiyavuma kutsi ngikubonile kufundzelwa kahle kwalesivumelwano kulomuntu lofise kuba yincenye yalolucwaningo, futsi lomuntu ulitfolile nanelitfuba lekubuta imibuto. Ngiyavuma kutsi lomuntu utivumele yena ngekutsandza kwakhe kutsi abe yincenye yalolucwaningo, akaphocelelwa ngumuntu.

Libito lemfakazi: \_\_\_\_\_

Sitfupha salofise kubayincenye yelucwaningo:

Kusayina kwemfakazi: \_\_\_\_\_

Lusuku: \_\_\_\_\_

### **Lokuvunywa Ngumkoleki Wemininingwane**

Ngiyavuma kutsi ngimfundzele kahle lomuntfu lofise kuba yincenye yalolucwaningo, ngakucacisa kahle konkhe ngalokusemandleni ami onkhe, futsi-ke ngitawuciniseka kutsi lomuntfu:

- utawuchazelwa kahle ngalolucwaningo
- utawutjelwa kutsi lolucwaningo lutotsatsa sikhatsi lesinganani
- utochazelwa nange bumfihlo bemininingwane lakatawusipha yona.

Ngiyavuma nanekutsi lomuntfu unikiwe nelitfuba lekubuta imibuto ngaloluphenyo, futsi yonkhe imibuto lekayibutile ngimuphendvule kahle ngalokusemandleni ami onkhe. Ngiyavuma kutsi lomuntfu akaphocelelwa ngumuntfu kutsi avume kuba yincenye yalolucwaningo, futsi utivumele yena. Lomuntfu naye unaso sona lesivumelwano lesi, lesihlala kuye.

Libito Lemkoleki: \_\_\_\_\_

Kusayina Kwemkoleki: \_\_\_\_\_

Lusuku: \_\_\_\_\_