Preventing and Minimizing Risks Associated with Antituberculosis Medicines to Improve Patient Safety

December 2013

USAID
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SIAPS
Systems for Improved Access to Pharmaceuticals and Services

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CONTENTS

ACRONYMS AND ABBREVIATIONS

AE	adverse events
AIDS	acquired immunodeficiency syndrome
anti-TB	antituberculosis
DOT	directly observed therapy
FDA	US Food and Drug Administration
HCW	health care worker
HIV	human immunodeficiency virus
ICH	International Conference on Harmonisation
IEC	information, education, and communication
MDR-TB	multidrug-resistant tuberculosis
MSH	Management Sciences for Health
PAS	para-aminosalicylic acid
PPI	patient package insert
RMP	risk management plan
SIAPS	Systems for Improved Access to Pharmaceuticals and Services
TB	tuberculosis
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

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BACKGROUND

More than 20 antituberculosis (anti-TB) medicines are being used today. These medicines are taken in different combinations simultaneously; they may also be taken concurrently with other medicines for management and treatment of comorbidities such as HIV/AIDS, diabetes, malaria, and cardiac-related illnesses. Although all these medicines have well-known adverse event (AE)—defined as any unfavorable or unintended sign, symptom, or disease that occurs temporally with use of a medicine that may or may not be caused by the medicine—profiles that have been published by the manufacturers and written on the medicine labels, new information on safety and tolerability of tuberculosis (TB) medicines that have been on the market for decades still continues to emerge because of comorbidities and complexities of treatment. Clinicians are increasingly aware of anti-TB medicines' associated risks, but there is still no guarantee or assurance of their safe use. Just like anti-TB medicines, other older medicines, such as acetaminophen (paracetamol), have safety problems. Just recently (August 2013), the US Food and Drug Administration (FDA) issued a safety alert about acetaminophen's association with a risk of rare but serious skin reaction. Two other safety alerts were issued by the FDA (July 2013): mefloquine hydrochloride was found to have risk of psychiatric and nervous system side effects, and a warning was issued that ketoconazole causes severe liver injuries, adrenal gland problems, and harmful drug interactions with other medicines. In September 2013, another alert was issued for fluoroquinolones, requiring a product label change to warn against rapid and potentially permanent nerve damage—peripheral neuropathy—from oral and injectable formulations. These examples stress the point that no medicine is completely safe, no matter how long it has been in use.

> **"Understand that 'lack of evidence is not evidence of lack.' That is, risks and safety data will accrue over time. The drug's best profile is on the day of launch. It is 'downhill' from there."**
>
> *—Cobert's Manual of Drug Safety and Pharmacovigilance,* 2nd ed.

Many countries are planning to introduce new anti-TB medicines and treatments. The World Health Organization (WHO) recently issued an interim policy guideline for the use of a new TB medicine, bedaquiline, and many other clinical trials are in the pipeline (such as STREAM trial, NC002, NC003, Nix TB, and Marvel TB trial) to assess optimal combinations of repurposed and new anti-TB medicines. New compounds are also currently in phase II and III trials in the development pipeline for TB treatment (such as Delamanid, Sutezolid, PA-824, SQ109, and AZD-5847). With the introduction of new medicines, assuring

patient safety becomes even more important since these medicines have not been tested in a wide population. The WHO practical handbook on pharmacovigilance for TB medicines clearly articulates the importance and need for good vigilance in TB programs to enhance TB patient safety.[1]

Again, all anti-TB medicines have inherent risk to the patients—some are avoidable whereas others are not. There are expected risks (already identified during clinical trials or postmarketing surveillance) and unexpected risks. Most clinical trials for medicines are tested only in limited populations; there are many unknowns regarding how a wider population (elderly, pediatrics, pregnancy, comorbid conditions, ethnic variations, etc.) will react to the same medicine. AEs are one of the main contributing factors that affect patient adherence to TB treatment, which in turn can increase morbidity and in some cases cause death.[2] They are also associated with defaulting,[3] affect TB program treatment outcomes, and in some instances promote development of drug-resistant TB strains, which require a lengthier, more toxic, and more expensive treatment.

The purpose of this document is to guide countries through the process of planning and implementing feasible strategies to minimize risks posed to TB patients on treatment. The main objectives of this document are to—

- Identify the main contributing risk factors to a successful TB treatment
- Categorize risks associated with each TB medicines in their order of importance
- Identify and prioritize feasible affordable interventions and tools for managing risks
- Describe strategies for implementing and monitoring interventions to achieve successful outcomes

The target audiences for the document are national TB control programs, national pharmacovigilance centers, organizations working to improve patient safety in developing countries, medicine therapeutic committees, and health care workers (HCWs). This document can be used to guide users on risk identification and minimization approaches for TB medicines. It could also be adapted and used for other essential medicines. This document also provides several reference resources and tools to guide minimization of risks to TB patients as a result of their treatment.

Factors Contributing to Medicine-Related Risk in Resource-Constrained Countries

Many factors contribute to patient safety risk in resource-constrained countries apart from AEs. These factors include—

- Poor access to trained physicians and HCWs
- Poor access to health care facilities and treatment
- Poor access to pharmacies or drug outlets with trained personnel
- Inadequate documentation of patient medical and medication history to identify potential risks such as drug interactions
- Poor implementation and enforcement of national policies and guidelines
- Poor use of national standard treatment guidelines in the private sector for TB treatment

- Lack of useful scientifically accurate information written specifically for patients, preferably in local languages
- Poor quality and substandard medicines[4]
- Medicine diversion—sometimes across country borders—which may compromise product quality[5]
- Poor storage practices for TB medicines affecting product integrity, effectiveness, and safety

Safety of Medicines in Children

A lot of the clinical trials for medicines do not include children. But after these products are approved for the adult population, doctors use these medicines off-label (unlicensed) in children, usually because there are no alternatives. Because the medicines have not been adequately studied in children to determine their effects in that population (no safety and efficacy data), monitoring these patients closely becomes even more critical to identify AEs early and provide appropriate care as needed.

Nevertheless, for first-line TB medicines, the safety and efficacy profile in children is known because of a long history of use; however, this is not the case for all second-line medicines. Because many of these medicines are used off-label in children and intolerable AEs are known to occur with these medicines, caregivers, HCWs, and the national TB control program must ensure that children are safe while taking their TB medicines. Measures should be put in place to prevent or minimize the risks that some of these medicines pose to children.

Another challenging area for pediatric treatment is the problem of how to adequately dose a child with the available adult medicine. Because no appropriate formulation for children exists for most second-line TB treatment, when a pediatric patient presents, the HCWs have to administer medicines to the patients. In some countries, the pharmacy compounds (changing the nature of the medicine from solid to liquid) the adult medicine for pediatric treatment. Often, this process is not standardized in the country because there is no national guidance about how to reformulate these medicines to ensure optimal dosing, quality, and safety of the preparation. Some of the risks posed are underdosing, which affects treatment outcomes and may promote resistance; overdosing, which may cause more AEs; and risk of contamination of preparation if not properly handled. Annex C presents a table showing available dosage forms for

Problems that affect medicine safety in children include—

- ✓ Administering wrong dosages, which can increase the toxicity of the medicine and cause more harm
- ✓ Limited or inappropriate formulations for children, particularly for second-line TB treatment
- ✓ Unavailability of appropriate dosage forms for younger children and limited guidance on how to translate adult dosages to minute volumes for this population
- ✓ Effect of other comorbid conditions
- ✓ Inadequate training of health care workers and doctors who treat children

pediatric use and recommended number of tablets for administration of second-line anti-TB medicines.

Relationship between Adverse Events and Treatment Adherence

In 2011, an estimated 8.7 million new TB cases were documented. Also in the same year, 1.4 million deaths occurred as a result of TB.[6] The highest burden of TB is found in Asia and Africa, with the latter accounting for 24 percent of TB cases worldwide. Although approximately 51 million people (according to WHO) have been successfully treated for TB in regions and countries where the WHO global TB strategy (1995 to 2011) was adopted, successful treatment of patients is difficult to achieve when good quality medicines are not accessible or when the medicine is not used appropriately. Only a 48 percent treatment success rate was reported by WHO for patients with multidrug-resistant tuberculosis (MDR-TB) enrolled on treatment in 2009.[7] The standard regimen for treating susceptible TB is 6 months and up to 24 months for the drug-resistant forms, which require multiple medications with commitment and attention to details. Nevertheless, as is the case with all medicines, risk is associated with the use of anti-TB medicines. These risks (AEs) commonly develop during TB treatment and are a serious threat to treatment outcome.

Drug-induced hepatitis is a common AE from some anti-TB medications. Its presence in a patient is usually confirmed by tests for liver enzymes that are more than three times the upper limit of normal. Most frequently, the enzyme level returns to normal following discontinuation of the causal medicine, but sometimes the patient's condition may worsen and even result in death. Isoniazid is reported to have a 5 percent hepatotoxicity-related mortality rate.[8] Severe AEs can equally be seen in the second-line anti-TB medicines.[9] An example is amikacin (an aminoglycoside), which causes increased kidney damage, especially in patients with both normal and preexisting renal failure at higher doses over a long period. It is reported that about 86 percent of patients being treated with these second-line medicines develop an AE.[10] A study conducted in Namibia by Sagwa et al. reported that 90 percent of TB patients on second-line TB treatment experienced varying severity of AEs, particularly tinnitus, hearing loss, gastrointestinal-related AEs, and joint pains.[11]

For children, the most severe AE reported is development of hepatotoxicity caused by isoniazid, pyrazinamide, or ethionamide. Ethambutol causes optic neuritis in children, usually at doses higher than the recommended dosage of 15 to 25 mg/kg/d.[12] Ethionamide can cause vomiting in children and ethionamide and para-aminosalicylic acid (PAS) taken concurrently can increase the risk for hypothyroidism. Even though studies claim that children tolerate second-line TB treatment and their AEs well,[13,14] this does not preclude the need to monitor these population groups to prevent or minimize the risks associated with their anti-TB medicine treatment.

Termination of first-line TB therapy because of AEs, such as hepatitis, dyspepsia, exanthema, and arthralgia, is estimated to occur in up to 23 percent of patients during the intensive phase of treatment.[15] Yet TB

patients are more tolerant to first-line medicines than second-line medicines. Tables 1 and 2 show proportion of patients with anti-TB medicine interruption due to AEs; more details can be found in annex D.

Table 1: Anti-TB Medicine Interruptions Caused by Adverse Events

Medicine	Percentage of treatment interruption frequency caused by AEs in studies	Study source
Rifampicin	3 % (n = 430)	Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med* 2003;167:1472–77.
Isoniazid	4 % (n = 430)	
Pyrazinamide	6 % (n = 430)	
Rifampicin	1.8% (n = 1,317)	Ormerod LP, Horsfield N. Frequency and type of reactions to antituberculosis drugs: observations in routine treatment. *Tuber Lung Dis* 1996;77:37–42.
Isoniazid	0.5% (n = 1,317)	
Pyrazinamide	4.9% (n = 1,317)	
Ethambutol	0.2 % (n = 1,317)	
Streptomycin	4.5 % (n = 1,317)	
Prothionamide	10.6% (n = 218)	Chiang CY, Enarson DA, Yu MC, et al. Outcome of pulmonary multidrug-resistant tuberculosis: a 6yr follow-up study. *Eur Respir J* 2006;28:980–85.
PAS	9.1% (n = 209)	
Cycloserine	9.8% (n = 51)	

Source of content: Caminero, JA, ed. *Guidelines for Clinical and Operational Management of Drug-Resistant Tuberculosis*. Paris: International Union Against Tuberculosis and Lung Disease; 2013.

Generally, AEs can lead to poor treatment adherence and to partially suppressive drug concentrations because of inadequate treatment. Interruptions in treatment compromise achievement of treatment outcomes. They can lead to development of more resistant strains of the infection. WHO reported that about 60 percent of drug-resistant TB occurs in Brazil, China, India, Russia, and South Africa. According to a 2012 publication by WHO,[16] 3.7 million new TB infections worldwide are the resistant form of the disease, with previously treated individuals reflecting an increase of approximately 20 percent over new ones. The exact prevalence cannot be established because of laboratories lacking equipment or not being adequately equipped to confirm diagnosis of extensively drug-resistant TB (XDR-TB). XDR-TB develops following mismanagement of MDR-TB; it is reported by WHO to make up approximately 9 percent of drug-resistant cases.[17]

Table 2: Anti-TB Medicine Discontinuation and Withdrawal Caused by Toxicity

	"Discontinuation rates for antituberculosis drugs" Chan et al. 2004[18]		"Drug toxicity leading to withdrawal of treatment" Goble et al. 1993[19]	
Drug	Number discontinued/ number given drug (%)[a]	Top reasons for discontinuation (number affected)	Number with reaction/ number given drug (%)	Reaction (number affected)[b]
Amikacin	9/70 (13%)	Ototoxicity (8)	2/6 (33%)	Hearing loss (1) Renal dysfunction (1)
Capreomycin	15/139 (11%)	Ototoxicity (4) Nephrotoxicity (3) Nausea (2) Rash (2)	11/108 (10%)	Renal dysfunction (5) Hearing loss (3) Vertigo, early (1) Rash (1) Vasculitis (1)
Kanamycin	14/105 (13%)	Ototoxicity (9)	12/70 (17%)	Renal dysfunction (1) Hearing loss, early in 1 (9) Vertigo, early (1)
Streptomycin	31/129 (24%)	Ototoxicity (18) Paresthesias (3) Rash (3)	0/16	—
Viomycin	—	—	3/14 (21%)	Renal dysfunction (1) Rash (1) Itching, early (1)
Clofazimine	4/58 (7%)	Abdominal pain (2)	2/17 (12%)	Liver dysfunction (1) Abdominal pain (1)
Cycloserine	21/183 (11%)	Psychosis, aggression, depression or suicidal thoughts (15) Nausea (2)	8/98 (8%)	Myoclonic seizures (1) Neurologic symptoms, early (1) Depression, early in 2 (5) Nightmares (1)
Ethambutol	10/195 (5%)	Hepatotoxicity (3) Rash (2) Vision (2)	1/62 (2%)	Visual problems (1)
Ethionamide	28/169 (17%)	Nausea (8), Hepatotoxicity (5) Anorexia (3)	10/126 (8%)	Liver dysfunction, early in 2 (3) Gastrointestinal upset, early in 2 (4) Gynecomastia (1) Arthritis (1) Fever, early (1)
Isoniazid	18/191 (9%)	Hepatotoxicity (8) Fever (3) Nausea (2)	3/45 (7%)	Liver dysfunction, early (2) Joint effusion, early (1)
Aminosalicyclic acid/PAS	15/151 (10%)	Diarrhea (6) Nausea (4)	7/50 (14%)	Gastrointestinal upset, early in 1 (5) Rash (1) Fever, early (1)

Drug	"Discontinuation rates for antituberculosis drugs" Chan et al. 2004[18]		"Drug toxicity leading to withdrawal of treatment" Goble et al. 1993[19]	
	Number discontinued/ number given drug (%)[a]	Top reasons for discontinuation (number affected)	Number with reaction/ number given drug (%)	Reaction (number affected)[b]
Pyrazinamide	17/193 (9%)	Hepatotoxicity (8) Nausea (3) Arthralgias (2)	10/101 (10%)	Liver dysfunction, early in 3 (8) Gastrointestinal upset (1) Gout (1)
Rifampin	14/188 (7%)	Hepatotoxicity (8) Nausea (3) Rash (2)	2/22 (9%)	Gastrointestinal upset, early (2)
Rifabutin	4/15 (27%)	Low white blood cell count (2)	—	—
Ciprofloxacin	8/99 (8%)	Nausea (2)	—	—
Clarithromycin	1/17 (6%)	Nephrotoxicity (1)	—	—
Ofloxacin	3/124 (2%)	Nausea (2)	—	—

Note: — No data.

a. In contrast to the prior National Jewish Medical and Research Center (NJMRC) study, Goble et al., in which the denominator included only those individuals who were prescribed the drugs, the denominators shown here included drugs administered from both past and NJMRC regimens.

b. "Early" denotes occurrence of reaction within three months after the beginning of treatment.

Some AEs are minor and can be adequately managed without withdrawing treatment if recognized early. Others are more serious and can be minimized or stopped if the dose is adjusted or the medicine is withdrawn completely. Some of the effects can also be permanent, such as the hearing loss caused by the aminoglycoside group of anti-TB medicines. But with good vigilance of HCWs and the patients, most of these AEs that affect adherence to treatment can be reduced or completely eliminated. However, one of the main challenges resource-constrained settings face in managing TB AEs is the problem of availability of the ancillary medicines for management. Some countries do not have a standardized approach for managing these AEs, and even when they do, the medicines required are not readily available and accessible. Countries also have difficulties determining the right quantity of the ancillary medicines to procure, mostly because of lack of the AE prevalence data to guide the medicine quantification process. Currently, the WHO has no global guidance for countries to estimate their AE prevalence for anti-TB medicines. Table 3 aggregates AE occurrence rate data from various studies. More detailed information about individual studies can be found in annex D. In the tools section of the document, you can also find information on the various ancillary medicines for treating AEs caused by anti-TB medicines.

Table 3: Aggregated Frequency of Adverse Events for Patients Receiving MDR-TB Treatment

	"Frequency of MDR-TB cases with specific adverse event and definitions of adverse events" Bloss et al.[20]	"Frequency of adverse events and suspected agents among 818 patients receiving MDR-TB treatment in Estonia, Latvia, Peru (Lima), the Philippines (Manila) and the Russian Federation (Tomsk Oblast)" Nathanson et al. 2004[21]	"Side effects of drugs" Torün et al. 2005[22]
	N = 1,027	N = 818	N = 263
Adverse event	Frequency of event	Affected number (%)	Patients experiencing each effect, number (%)
Nausea	598 (58.2%)	268 (32.8%)	—
Vomiting	402 (39.1%)		—
Abdominal pain	246 (23.9%)	88 (10.8%)	—
Dizziness/vertigo	241 (23.5%)	117 (14.3%)	—
Diarrhea	209 (20.4%)	173 (21.1%)	—
Hearing loss or ototoxicity	195 (19.0%)	—	110 (41.8%)
Hearing or vestibular disturbance	92 (9.0%)	98 (12.0%)	—
Arthralgia	138 (13.4%)	134 (16.4%)	30 (11.4%)
Psychiatric	136 (13.2%)	51 (6.2%) (depression only)	56 (21.3%)
Tinnitus	124 (12.1%)	42 (5.1%)	—
Hematologic	111 (10.8%)		—
Headache	98 (9.5%)	96 (11.7%)	—
Hepatitis	91 (8.9%)	18 (2.2)	12 (4.5%)
Itching	89 (8.7%)	—	—
Skin rash	88 (8.6%)	38 (4.6%)	—
Peripheral neuropathy or neuropathy	84 (8.2%)	65 (7.9%)	8 (3%)
Convulsions or Seizures	50 (4.9%)	33 (4.0)	—
Renal failure or renal toxicity	44 (4.3%)	9 (1.2) (renal failure/nephrotoxicity)	2 (0.7%)
Visual impairment/disturbance	33 (3.2%)	36 (4.4%)	—
Electrolyte imbalance/disturbances	29 (2.8%)	94 (11.5%)	—
Hyperurecemia	29 (2.8%)	—	—
Dermatitis or dermatological effects	21 (2.0%)	—	12 (4.5%)

	"Frequency of MDR-TB cases with specific adverse event and definitions of adverse events" Bloss et al.[20]	"Frequency of adverse events and suspected agents among 818 patients receiving MDR-TB treatment in Estonia, Latvia, Peru (Lima), the Philippines (Manila) and the Russian Federation (Tomsk Oblast)" Nathanson et al. 2004[21]	"Side effects of drugs" Torün et al. 2005[22]
	N = 1,027	N = 818	N = 263
Adverse event	Frequency of event	Affected number (%)	Patients experiencing each effect, number (%)
Hypothyroidism	8 (0.8%)	29 (3.5)	3 (1.1%)
Jaundice	5 (0.5%)	--	—
Sleep disturbance	—	95 (11.6%)	—
Anorexia	—	75 (9.2%)	—
Gastritis or gastrointestinal disturbance	—	70 (8.6%)	37 (14.0%)
Allergic reaction	—	42 (5.1%)	—
Central nervous system	—	—	26 (9.9%)
Leukopenia	—	—	7 (2.6%)
Psychosis	—	28 (3.4)	—

Note: — No data.

Many other factors contribute to poor adherence to treatment besides AEs. For example, comorbidities such as HIV and AIDS, diabetes, heart diseases, and others can contribute to nonadherence to treatment. According to the WHO (Global TB report 2012), TB coexists with HIV and AIDS in an estimated 1.1 million cases of the 8.7 million new cases of TB globally, and approximately 80 percent of these cases are found in Africa. Treatment of coinfected patients can be complicated because the AEs of the medicines used to manage both conditions and the potential for serious harm are magnified. Other factors that affect adherence are social and economic, such as level of education and social support structure; health care team and system related, such as weak systems to educate patients and follow-up

Why Risk Management?

"When a drug first reaches the market, its safety profile is not well characterized. Relatively few patients have been studied (especially with orphan drugs), and those who have been studied are usually patients with no other diseases, no or few co-medications, not too young or old, with tight inclusion and exclusion criteria in the clinical trials. Thus, 'real-world' patients have not taken the drug yet, and rare adverse drug reactions (ADRs) have not been detected."

—*Cobert's Manual of Drug Safety and Pharmacovigilance,* 2nd ed.

treatment; patient related, such as patient's knowledge, beliefs, and motivation about treatment. Other therapy-related factors include pill burden, which particularly affects TB patients on second-line treatment.

Besides good adherence to treatment by patients, national TB programs should ensure access to good quality and affordable medicines and ensure appropriate treatment and safe use to achieve desired treatment outcomes. Despite global and national TB treatment guidelines, in 2011, a report on 37 studies conducted on patients undergoing TB treatment showed that 67 percent received inappropriate treatment.[23] Promoting rational anti-TB medicine use through the application of WHO strategies for improving the use of medicines[24] will support efforts toward improving adherence and preventing the development resistance to anti-TB medicines.This document discusses risk management strategies and tools for identifying anti-TB medicine risks, feasible interventions and tools to minimize the risk, and measures to ensure interventions are effective after implementation.

RISK MANAGEMENT

In ensuring prevention of AEs related to the use of anti-TB medicines and other medicines, several strategies have been designed. Some are targeted at guideline development (treatment regimens, laboratory parameters to monitor for toxicity, contraindications) or at the pharmaceutical supply chain system (level of use, prescription or over-the-counter use, storage conditions, use of registers, etc.). All these strategies can be considered as ways of managing the identified risk incurred with the use of those medicines. In the context of this document, rational selection, prescription authorization, safe and rational use interventions, and other strategies are considered as a part of risk management strategies.

Risk management in this context is a continuous *process* of identifying; assessing; implementing interventions; and evaluating actual or potential risks associated with anti-TB medicines to prevent or minimize the risks and thereby improve patient treatment outcomes.

The main aims of conducting a risk management activity are—

- Early and better detection of AEs and characterization of risks in various patients and settings
- Better communication of known and unknown risks
- Minimization of morbidity and mortality—protecting the public health

A risk is the probability that an unwanted or unexpected medical event could result from a medical procedure or the use of a medical product. The risk could be known or unknown—some may have already been identified from clinical studies and some may not have been identified before approval for public use.

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), established by regulatory authorities of the European Union, Japan, and the United States in 1990 to address the safety, quality, and efficacy of medicines, developed several guidelines for medicine safety and the European Medical Agency in particular on risk management systems.

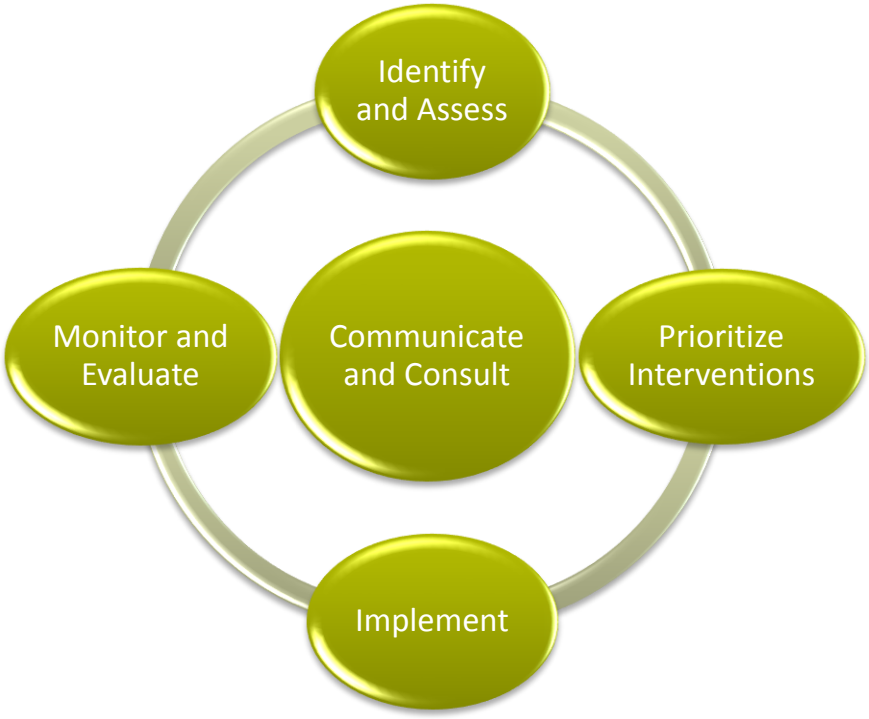
A ***risk management plan (RMP)*** is described by the FDA as *a strategic safety plan* that targets one or more safety-related health outcomes or goals and uses one or more risk minimization tools or measures to achieve those goals. A risk management plan entails—

- Identifying issues and putting them into context
- Assessing risks/benefits
- Identifying and analyzing options
- Selecting an appropriate strategy
- Implementing the strategy
- Evaluating results

Risk Management Cycle

Risk management is a continuous process to ensure a risk/benefit balance for the medicine. The entire process of a risk management plan involves four basic activities: risk identification and assessment, risk evaluation, risk communication, and risk minimization.[25] The risk management cycle in figure 1 illustrates the main processes that are described in this document.

Figure 1: Risk Management Cycle



Risk Identification and Assessment

Risk identification is the process of identifying and characterizing risks of anti-TB medicines. The outcome of risk identification is a list of risks to monitor. Risks can be identified through examination of data derived by several means, such as—

- Spontaneous reporting of AEs
- Interviews with HCWs and patients
- Data from patient files on AEs

After risks are identified, they should be grouped or characterized in like risks for easier management of the risks in the assessment phase.

Risk assessment evaluates the risk identified. This is a continuous process of assessing the nature, frequency, and severity of the risk associated with the use of anti-TB medicines. This step is critical for decision making and paves the way for identification and prioritization of feasible

interventions. It is also at this stage (risk identification and assessment) that the root cause of the problem is identified to guide identification of appropriate interventions.

The main steps in this process for risk identification and assessment are the following—

1. **Understand the context**
   - Research and review documents (national, regional, and global).
   - Develop an objective and define a structure for the analysis.
   - Establish a criteria to evaluate risks (see annex A).
2. **Identify risks**
   - Establish a list of anti-TB medicines to assess risk.
   - Identify reliable information sources to collect data about medicine risks (for example, manufacturer websites or labels, reference books, literature search for articles, publications, documents, WHO website, and international regulatory authorities internet sites).
   - Develop a matrix to analyze data using selected risk criteria.
   - Populate the matrix with information, such as: What can happen to the patient on this medicine (consequences)? Why will it happen (if known)?

In risk identification, you answer questions such as—

- ✓ What can happen to a patient on this medicine?
- ✓ At what point can this happen?
- ✓ Why will it happen? (Root cause)

3. **Analyze risks**
   - Establish a rating scale to define likelihood of risk occurring—for example, almost certain, likely, possible, unlikely, rare, yes, no.
   - Identify the likelihood of the risk occurring for patients taking that medicine, and rate the likelihood level using a scoring system.
   - Define risk levels to help determine at what point to take action. These levels can be color coded with red representing the highest level of risk—for example, minor, moderate, major, and extreme.
   - Categorize the risk according to the defined levels.

Illustrative Risk Identification and Assessment Process

Following is an illustrative process for carrying out risk identification and assessment for anti-TB medicines. This process should be adapted to local settings and context.

The *objective* is to identify anti-TB medicines that pose the most risk to patients during treatment and to develop feasible, affordable interventions to minimize the risks. *Risk criteria* related to public health issues for TB in resource-constrained settings were identified for assessment. The risk criteria were adapted mostly from the FDA safe use initiative report, which highlights different risk criteria, such as medication errors, intentional misuse or abuse of medicines, off-label use, AEs such as drug-drug interactions, and drug quality defects.[26] The European Medicines Agency *Guideline on Good Pharmacovigilance Practices*, "Module V—Risk management systems," updated June 2012, was also examined, and

risk factors were adapted from the guideline.[27] The users can select a set of risks that are prevalent in their environment for the anti-TB medicines selected. The five main risk criteria groups identified are—

- Known serious or severe adverse events
- Drug interactions
- Safe use indicators
- Drug integrity and supply chain
- Chronic medicine use risk

These risks touch on most of the factors that can affect safety of patients on anti-TB medicines, including medicine quality issues. Each risk group consists of subrisk elements that have been defined. Please refer to annex A for details on how each of these criteria was defined for this context.

A *tracer list* of anti-TB medicines was compiled from WHO treatment guidelines for susceptible and resistant TB treatment. (A tracer list of medicines, also known as index medicines, is a basket of representative items used to simplify data collection and analysis.[28]) *Information sources* for each medicine were collected through review of online literature, books, and medicine package inserts. The main source of medicine information used to compile data was medicine package inserts obtained from Facts and Comparisons, LexiComp online access, and the US National Institutes of Health DailyMed free online access. For other information not available in these reference sources, data were collected through a literature search for articles, publications, documents, manufacturers' websites, the WHO website, and international regulatory authorities Internet sites. Note that information quality and completeness from commercial drug information vendors such as LexiComp and DrugDex have been found questionable for several categories of information in published studies and surveys.[29,30,31,32] Therefore, source material should be limited to information from the medicine manufacturers, such as product labels, or from the most transparent government-regulated sources.

In risk analysis, you answer questions such as—

- ✓ What is the likelihood of this risk occurring in patients taking this medicine?
- ✓ What are the consequences of this risk?
- ✓ What is the risk level? Mild, moderate, or severe?
- ✓ What is the estimated number of people that will be affected?

A *matrix* was developed using Microsoft Excel spreadsheet software, and data were collected for each risk criterion selected for the tracer list anti-TB medicines. The matrix was populated with data from the information sources previously mentioned (see illustrative matrix in table 4).

Table 4: Illustrative Matrix on Risk Information

Risk criteria	Kanamycin	Levofloxacin	Ethionamide
Known class effect	Aminoglycosides: nephrotoxicity, neurotoxicity, ototoxicity	Fluoroquinolones: serious and occasionally fatal hypersensitivity and/or anaphylactic reactions	Anti-TB: may potentiate the adverse effects of other anti-TB drugs administered concomitantly.
Pregnancy category	Pregnancy category D (use only in life-threatening emergencies when no safer medicine is available)	Pregnancy category C (use with caution if benefits outweigh risks). To date, no specific teratogenic effect or increased pregnancy risk has been identified; however, because of concerns of cartilage damage in immature animals exposed to quinolones and the limited levofloxacin-specific data, levofloxacin should be used during pregnancy only if a safer option is not available.	Pregnancy category C. Teratogenic potential in rabbits and rats. Because of these animal studies, however, it must be recommended that drug be withheld from women who are pregnant, or who are likely to become pregnant while under therapy.
Known safety issues for pediatrics	Aminoglycosides should be used with caution in prematures and neonates because of the renal immaturity of these patients and the resulting prolongation of serum half-life of these drugs.	Musculoskeletal disorders (arthralgia, arthritis, tendinopathy, and gait abnormality) seen. Shown to cause arthropathy and osteochondrosis in juvenile animals. Safety in pediatric patients treated for more than 14 days has not been studied. Risk-benefit appropriate only for the treatment of inhalational anthrax (postexposure) and plague.	Should not be used in pediatric patients under 12 years of age except when the organisms are definitely resistant to primary therapy and systemic dissemination of the disease, or other life-threatening complications of TB, is judged to be imminent.
Drug-drug interactions	Potentially nephrotoxic or neurotoxic drugs, particularly polymyxin B, bacitracin, colistin, amphotericin B, cisplatin, vancomycin, and all other aminoglycosides should be avoided because of additive toxicity; kanamycin should not be given concurrently with potent diuretics (ethacrynic acid, furosemide, meralluride sodium, sodium mercaptomerin, or mannitol), because some cause ototoxicity. Increased nephrotoxicity reported with concomitant administration with some cephalosporins.	Antacids, sucralfate, multivitamins and other products containing multivalent cations, theophylline, warfarin, NSAIDs, drugs that prolong QT, live vaccines, corticosteroids	Cycloserine, isoniazid; may potentiate adverse effects of other anti-TB drugs.

Risk criteria	Kanamycin	Levofloxacin	Ethionamide
Off-label use (besides for TB and leprosy treatment)	Treatment of infections where the following pathogens are known or suspected: *E. coli, Proteus* species, *Enterobacter aerogenes, Klebsiella pneumoniae, Serratia marcescens, Acinetobacter* species	Diverticulitis, enterocolitis (Shigella spp), epididymitis (nongonococcal), gonococcal infections, complicated intra-abdominal infections (in combination with metronidazole), Legionnaires' disease, peritonitis, acute otitis media, community-acquired pneumonia, pelvic inflammatory disease	None
Action taken by regulatory authority or marketing authorization holder	FDA black box warning for potential toxicity	FDA black box warning for increased risk of tendinitis and tendon rupture in all ages. This risk is further increased in older patients usually over 60 years of age, in patients taking corticosteroid drugs, and in patients with kidney, heart, or lung transplants, and may exacerbate muscle weakness in persons with myasthenia gravis. Label change to warn against risk of irreversible nerve damage—peripheral neuropathy—which may occur soon after initiation.	None
WHO prequalification	No	Yes	Yes
Total number of manufacturers/ suppliers prequalified	0	7	4
Storage conditions	3 years	3 years	4 years

For *data analysis*, a predefined scoring system was used to quantify the data collected for each medicine in the matrix. This score can be defined in as many levels as needed. In this illustration, each criterion was defined by different levels of likelihood of occurrence and severity of the risk—for example, *Yes, No, Significant, Nonsignificant, Contraindicated*. Also note that in this exercise, each risk criterion has been allotted equal weighting (equal importance); while this may not be true for all risks, stakeholders and local expert committees should decide the most appropriate weighting for each criterion selected.

The scoring system was applied to each risk criterion, such as pregnancy or drug-drug interaction (table 5; definition of risk criteria can be found in annex A). This scoring system was used to quantify the qualitative data collected from medicine information sources in the matrix. Risk scores were tallied to come up with a total score (table 6). Based on this categorization, each anti-TB medicine was labeled according to the total risk score determined by the analysis.

Table 5. Illustrative Risk Criteria Rating Base

Risk	Rating[d]	Comments
Known serious and severe adverse event		
Known class effect	0[a] (no) 2[c] (yes)	
Known safety issues for renal impairment	0[a] (no) 1[b] (yes) 2[c] (unknown)	
Known safety issues for hepatic impairment	0[a] (no) 1[b] (yes) 2[c] (unknown)	
Known safety issues for elderly	0[a] (nonclinically significant) 1[b] (clinically significant) 2[c] (unknown)	
Pregnancy category[d]	0[a] (category A and B) 1[b] (category C and D) 2[c] (category X)	
Potential risk during lactation	0[a] (safe to use), 1[b] (known effect but doctor decision) 2[c] (contraindicated or unknown)	Contraindication was also defined as “discontinue drug” or “stop nursing” in this criterion.
Known safety issues for pediatrics	0[a] (non-clinically significant) 1[b] (clinically significant) 2[c] (unknown or contraindicated)	Medicine with no established safety profile for under the age of one was not considered in this criterion.
Interactions		
Drug-drug interactions	0[a] (nonclinically significant interaction) 1[b] (clinically significant)	This includes drug interaction with anti-TB and other medicines.
Drug-food interactions (excluding ethanol and smoking)	0[a] (none known, no interaction with food) 2[c] (known bioavailability interaction with food)	Known bioavailability with food is when the medicines need to be taken with food, without food, or with a specific type of food. Ethanol and smoking are excluded because almost all medicines will interact with them.
Drug-disease interactions	0[a] (none) 1[b] (yes)	Distinguish between drug-drug interactions and consider interactions other than renal and hepatic.
Safe use indicators		
Potential for medication error—look alike, sound alike	0[a] (no) 1[b] (yes)	Some of the brand or generic names for sound alike might not be available in all countries. Only considered generic name sound and look alikes.
Off-label use (besides for TB and leprosy treatment)	0[a] (no or unknown) 1[b] (yes)	
Experience with overdose	0[a] (yes) 1[b] (unknown)	A lower risk was allotted to medicines with established processes for treating overdose.
Potential for medication abuse (recreational abuse)	0[a] (no) 2[c] (yes)	No information was found for any anti-TB medicine. This will vary by country.

Risk	Rating[d]	Comments
Therapeutic window	0[a] (wide window) 2[c] (narrow window)	Narrow therapeutic window was considered when the medicine required monitoring of the peak and through levels.
Action taken by regulatory authority or marketing authorization holder	0[a] (withdrawal and no action) 2[c] (black box or REMS)	
New product	0[a] (no) 2[c] (yes)	
Drug integrity and supply chain		
WHO prequalification	0[a] (yes) 2[c] (no)	WHO prequalification website[e]
Total number of manufactures/suppliers prequalified	0[a] (if greater or equals 4 suppliers or if non prequalified) 1[b] (if 2-3 suppliers) 2[c] (if 1 or less)	WHO prequalification website
Short shelf life	0[a] (greater than 36 months) 1[b] (25–36 months) 2[c] (0–24 months)	Shelf life varies by manufacturer per WHO guideline. Donated products should not exceed 1-year shelf life.
Storage conditions	0[a] (stored at room temperature) 1[b] (store away from moisture or light) 2[c] (needs refrigeration)	Did not consider stability after reconstitution; only stability of original package in this criterion.
Substandard medicines	2[c] (no reports of substandard medicines) 1[b] (substandard medicines reported)	No data were found for anti-TB medicines in the literature search. However, we assumed that no records mean high risk.
Diversion	0[a] (low pilferage item) 1[b] (high pilferage item)	No data were found for anti-TB medicines in the literature search, so this was categorized as high risk for second-line medicines because they are more expensive with higher likelihood of profiting from sales. However, this will vary from country to country.
Chronic medicine use risk		
Population exposed to the medicine	1[b] (public health programs or part of top 20 medicines used in country) 2[c] (other)	
Adverse event with prolonged use	0[a] (no) 1[b] (yes)	Prolonged use was defined as treatment for more than 28 days.

a. Low Risk (score of 0)—defined in this context as acceptable risk; has minimal threat to the patient and does not require monitoring.
b. Medium Risk (score of 1)—also acceptable, but the threat posed requires regular monitoring to ensure it does not increase. Measures may also need to be implemented to reduce the risk.
c. High Risk (score of 2)—unacceptable risk because it can lead to life-threatening conditions. In this context, unknown risk is also categorized as high risk because the risk has not been studied. This requires mandatory monitoring and interventions to reduce or eliminate the risk. The general assumption made in this analysis is to consider "no data" for a particular risk criterion as high risk.
d. See annex 1 for description of pregnancy categories.
e. WHO list of prequalified medicinal products, http://apps.who.int/prequal/query/ProductRegistry.aspx. Accessed July 31, 2013.

Table 6a. Illustrative Summary Table of Risk Analysis for First-Line Anti-TB Medicines

Risk	Isoniazid	Rifampicin	Ethambutol	Streptomycin	Pyrazinamide
Known serious and severe adverse effect	2	5	6	7	5
Interactions	3	3	1	1	1
Safe use indicator	2	0	1	5	0
Drug integrity and supply chain	2	1	3	4	1
Chronic medicine use risk	2	2	2	2	2
Total[a]	11	11	13	19	9

a. Interpretation of risk scores

- Score of 0 to 19 is categorized as low risk.
- Score of 20 to 39 is categorized as high risk.

Table 6b. Illustrative Summary Table of Risk Analysis for Second-Line Anti-TB Medicines

Risk	Kanamycin	Amikacin	Capreomycin	Levofloxacin	Moxifloxacin	Gatifloxacin	Ofloxacin	Ethionamide	Prothionamide	Cycloserine	Terizidone	PAS	Clofazimine	Linezolid	Amoxicilline/Clavulante	Thioacetazone	Clarithromycin	Imipenem
Known serious and severe adverse effect	7	7	8	10	10	7	9	8	8	7	7	6	10	3	6	7	5	4
Interactions	1	1	1	1	1	2	1	1	1	4	4	3	3	4	3	2	3	1
Safe use	6	5	5	4	3	3	3	1	1	2	2	2	0	1	1	3	2	1
Drug integrity and supply chain	6	5	6	4	5	6	3	3	5	5	5	8	5	7	6	5	8	7
Medicine chronic use risk	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	22	20	22	21	21	20	18	15	17	20	20	21	20	17	18	19	20	15

a. Interpretation of risk scores

- Score of 0 to 19 is categorized as low risk.
- Score of 20 to 39 is categorized as high risk.

A final risk analysis was done to support an action plan decision. Two risk levels were defined based on the maximum risk score any product can attain—low risk and high risk (see table 7 for definition). To define the risk score range, the total possible score (maximum) and lowest score (minimum) from table 5 were determined. The mean score was then derived and rounded down to the nearest whole number. Each anti-TB medicine was then categorized for appropriate action based on its risk score range (see table 7).

Table 7: Risk Classification and Action

Risk level	Risk definition and action	Score range
Low risk	Acceptable risk; has minimal threat to the patient. **Action required**: Continue monitoring to further reduce or eliminate risk.	0 to 19
High risk	Elevated risk level; but the threat posed requires regular monitoring to ensure it does not increase. **Action required:** Implement risk minimization measures to reduce or eliminate risk. Prioritize interventions according to risk criteria that pose most risk to patients.	20 to 39

The score range for the risk levels should be defined during the initial planning phase before the analysis is performed. This score range can be adjusted according to the number of criteria selected for analysis and weight allocated to each criterion. The expert committee should be responsible for defining the score range and the different action levels. Interventions should be prioritized according to impact of risk to patients, availability of funding, and human resources required for implementation and monitoring.

Table 8: Illustrative Anti-TB Medicine Risk Classification

Low risk	High risk
Isoniazid	Kanamycin
Rifampicin	Capreomycin
Pyrazinamide	Moxifloxacin
Ethambutol	Levofloxacin
Linezolid	Clofazimine
Ethionamide/prothionamide	Gatifloxacin
Streptomycin	Amikacin
Ofloxacin	PAS
Thiacetazone	Cycloserine/terizidone
Imipenem	Clarithromycin
Amoxicilline/Clavulanate	Bedaquiline

In summary, this exercise for assessing risk can be subjective and may yield a different rating when conducted by different people because the qualitative information may be interpreted differently if the risk criteria are not well defined at the planning phase. However, if all the criteria are assessed, the score should be close to what was determined in table 6. Although bedaquiline was not included in table 6, when the FDA approved the medicine, certain stipulations were required as part of the manufacturer's postmarketing surveillance to promote safety of the medicine in patients. These stipulations include development of a patient registry and a drug interaction trial of bedaquiline and efavirenz to determine a safe and effective dose regimen for both medicines when they are coadministered in HIV coinfected MDR-TB patients. Because this medicine is new, it has to be closely monitored once countries adopt it in their treatment plans to ensure the benefits of use outweigh the risks. The same goes for the new anti-TB medicine delamanid, which has been recommended by the European Medicines Agency's Committee for Medicinal Products for Human Use to be granted a conditional marketing authorization. The expert committee should reach consensus on how to rate the risks and assign scores. The scores assigned to the risk criteria (table 5) may vary in different settings because of perceived risk; a decision might be reached to weight some criteria higher than others. The main purpose of this exercise is to illustrate a standardized approach to identify anti-TB medicines that pose heightened risks to patients. This can be achieved in other ways without going through this process, for example by—

- Reviewing the spontaneous reporting of AEs from anti-TB medicines (expected and unexpected AEs) including case reports and case series studies
- Identifying new safety information or increased occurrence of AEs through causality assessments
- Conducting active surveillance studies in which AEs data are routinely collected and analyzed

The process needs to be an inclusive one with all key stakeholders participating to come up with effective decisions on how to analyze and categorize anti-TB medicine risks.

Risk Intervention and Prioritization

Risk intervention is a risk control action guided by the risk assessment results and involves identification and selection of new or alternative approaches to minimize identified risk. These approaches should be targeted to the right audience to achieve favorable results. In this document, general examples of risk interventions and tools are listed that may or may not apply in your setting (see annex B, examples of interventions targeting HCWs and patients). Once the medicines that pose serious risks to patients are identified, appropriate public health–focused interventions should be selected that are feasible, cost-effective, and sustainable for your setting.

In risk intervention, you answer questions such as—

- ✓ What risk measures can be put in place to mitigate occurrence?
- ✓ What is the capacity (financial and human resources) to implement interventions?

Many types of risk minimization measures are already currently implemented in resource-constrained settings, such as use of registers to document dispensing and sales of narcotics and hypnotic medicines, storage of certain medicines in locked cabinets in the dispensing area or pharmacy to control diversion and misuse, and restriction of certain medicine availability and use to a particular health care delivery level that can manage it appropriately—for example, streptomycin injections not available at the lowest level of care. Focused risk studies to support effective safety decisions have also been conducted. Risk minimization measures are not new; they are already in place in many countries even though not always monitored and evaluated for success.

The main purpose of this phase is to identify feasible, cost-effective interventions for identified medicine risks and to define their level of priority. In the earlier exercise, risk levels were identified based on a set of risk criteria selected by the stakeholder committee. Risk measures should then be identified for each medicine, taking into consideration the most critical risk criteria that require prompt attention. To evaluate and prioritize in which risk areas to focus interventions, further categorization is required for each selected medicine (the medicines that have been identified for risk intervention) according to level of impact on TB patients. See illustrative categorization and prioritization of the risks (table 9), which uses the same medicines and examples as the previous illustrations. The parameters can be defined by the stakeholder committee, as appropriate. In this document, they were defined as follows: Minor—no immediate action required; Moderate—monitor, plan to implement risk minimization measures within a given time period; Major—immediate risk minimization action required. For the major activities that require immediate action, interventions can also be further categorized and prioritized according to funding and human resources capacity.

Table 9: Illustrative Categorization: Risk Impact of Anti-TB Medicines on the Population

Medicine	Minor	Moderate	Major
Kanamycin	• Known safety issues in pediatrics (not used in neonates and premature births in most countries)	• Off-label use • WHO prequalification • Total number of manufacturers/supplier prequalified • Storage conditions	• Class effect • Pregnancy category • Drug-drug interactions • Action taken by drug regulatory authority
Levofloxacin	• WHO prequalification • Total number of manufactures/supplier prequalified	• Pregnancy category • Known safety issues in pediatrics • Off-label use • Storage conditions	• Class effect • Drug-drug interactions • Action taken by drug regulatory authority
Ethionamide	• Off-label use • Action taken by drug regulatory authority • WHO prequalification	• Storage conditions • Total number of manufacturers/supplier prequalified	• Pregnancy category • Known safety issues in pediatrics • Class effect • Drug-drug interactions

Looking at the example in table 9, one might ask why WHO prequalification is considered low risk for levofloxacin and ethionamide and moderate risk for kanamycin. The answer is because WHO has no prequalified suppliers for kanamycin, unlike ethionamide and levofloxacin. The risk of procuring medicines with low quality is higher if the country does not have a rigorous regulatory authority and if there are no WHO prequalified manufacturers. Kanamycin and levofloxacin are considered moderate risk for off-label use because both medicines are indicated for other conditions, which can lead to diversion or even inappropriate use and thus promote development of resistant strains of TB, unlike ethionamide which has no off-label use. Use the matrix (table 4) and the risk criteria rating base (table 5) to interpret results.

The stakeholder committee should decide and agree on what specific actions are feasible and cost-effective to implement based on local context. The key to successful implementation of this process is communication of information, consultation with key stakeholders, and consideration of the wider country context.

Examples of stakeholders in this process under the leadership of the national TB control program include the following—

- Regulatory authorities
- Pharmacovigilance units
- National TB program
- TB clinical experts and other HCWs
- Nongovernmental organizations and TB implementing partners
- Community health workers for TB
- TB patients and advocacy groups
- WHO and donor partners
- Professional associations—doctors and pharmacists
- Academia

The stakeholders can be coordinated by the national TB control program using already existing committees or forums where anti-TB medicine risk management is a standing item in the agenda. The group can be tasked with exploring feasible strategies to reduce the risks caused by identified medicines. The group would have to decide what intervention or tool will be used to reduce risk, how the tool will be developed, who will implement it, and how it will be implemented.

The stakeholder committee should be tasked to—

- ✓ Explore feasible strategies to reduce risk
- ✓ Decide on appropriate interventions and tools to use
- ✓ Decide how tools will be developed, who will implement them, and how they will be implemented

Understanding the problem and its context is very important to identify the right intervention. Sometimes, existing measures may be in place but not be working. When designing risk minimization interventions, the team responsible should have clear answers to the following questions—

- What risk do you want to reduce?
- Why did the risk occur?
- What will you do to reduce risk?
- How will you know that risk was reduced?

At the end of the deliberation, an agreed summary list of actions or the action plan for risk minimization and prevention should be realized. The composition of the team for initial decision making should be manageable (relatively small); subcommittees may be formed to achieve varying tasks. Agreed-on decisions by the committee can then be presented to a larger group for ratification. After ratification, recommendations should be forwarded to the appropriate offices for implementation. A description of risk minimization activities and tools to improve safety of TB patients can be found in annex B and the "Risk Management Tools" section of this document.

Using the preceding illustration, consider drug-drug interaction. Many interventions can be implemented to minimize significant risks, such as the following—

- Formal communication to HCWs about the risk
  - "Dear health care professional" letters to inform about interactions
  - Medicine safety alerts about a risk
- Use of Information, education, and communication (IEC) strategies
  - Training prescribers and health care providers and providing information guides (see section on additional risk management tools for examples)
  - Using posters, flyers, and other IEC materials to raise awareness
  - Providing medication guides to patients to educate and empower them about risk
- Use of existing technology
  - Build checks and balances into electronic health records to minimize risks
  - Use SMS messaging (phone texting) to alert patients about how to space out administration of medicines that can interact with their TB treatments

Communication pieces must clearly state the purpose of the message, describe the risk and its implications, state facts about the medicine, indicate whether the fact is still valid or invalid and what action should be taken by patients and health care professionals. See figures 2 and 3, respectively, for a sample dear health care professional letter and a recent safety alert, both taken from the FDA website. In the United States, the manufacturers are required to send out the dear health care professional letters, whereas the FDA sends out safety alerts. The policy will differ from country to country. Following is the link for signing up for automatic updates from the FDA: http://www.fda.gov/aboutfda/contactfda/stayinformed/getemailupdates/default.htm.

Non-US safety communications can be found on the following websites:

- Australia: Medicines Safety Update (http://www.tga.gov.au/hp/msu.htm) and Safety alerts (http://www.tga.gov.au/safety/alerts.htm)
- Canada: Canadian Adverse Reaction Newsletter *in English and French* (http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/index-eng.php)
- Denmark: Danish Pharmacovigilance Update (http://laegemiddelstyrelsen.dk/en/service-menu/news/subscribe-to-our-newsletters.aspx)
- European Medicines Agency: Monthly reports of the CHMP Pharmacovigilance Working Party

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/document_listing/document_listing_000198.jsp&mid=WC0b01ac0580033aa1&murl=menus/about_us/about_us.jsp&jsenabled=true)

- France: Newsletter 'ANSM Actu' *in French* (http://ansm.sante.fr/Mediatheque/Publications/Bulletins-depliants-Newsletter-ANSM-Actu) and Actualité *in French* (http://ansm.sante.fr/?UserSpace=pro)
- Ireland: Drug Safety Newsletter (http://www.imb.ie/EN/Publications/Publications.aspx?categoryid=45&year=&letter=)
- Japan: Pharmaceuticals and Medical Devices Safety Information (http://www.pmda.go.jp/english/)
- Netherlands: Lareb News (http://www.lareb.nl/Nieuws/2013)
- New Zealand: Medsafe - Prescriber Update (http://www.medsafe.govt.nz/profs/PUarticles.asp)
- Singapore: Adverse Drug Reaction News Bulletin (http://www.hsa.gov.sg/publish/hsaportal/en/health_products_regulation/safety_information/adr_bulletin.html)
- Spain: Notas informativas *in Spanish* (http://www.aemps.gob.es/informa/notasInformativas/medicamentosUsoHumano/seguridad/home.htm)
- United Kingdom: MHRA - Drug Safety Update (http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/index.htm)

Figure 2: Sample Health Care Provider Letter

Norplant (levonorgestrel implants) Dear Healthcare Professional Letter July 2002

This is the retyped text of a letter from Wyeth. Contact the company for a copy of any referenced enclosures.

July 26, 2002
Important Norplant® System (levonorgestrel implants) Update
Back-up Contraception No Longer Required on Specified Lots

Dear Health Care Professional:

This letter is an update to both the August 10, 2000 and the September 13, 2000 letters from Wyeth that advised health care professionals to discontinue insertion of Norplant System kits from lots distributed beginning October 20, 1999 with expiration dates during 2004. These lots had atypically low levels of levonorgestrel release in routine shelf-life stability tests. Wyeth also advised that any patient who had received product from one of these specified lots should use back-up, nonhormonal contraception until the results of further testing could be evaluated. Women who had Norplant System insertions before October 20, 1999 were not affected.

After further evaluation, in conjunction with the Food and Drug Administration (FDA), we are very pleased to inform you that back-up contraception is no longer required in those patients who had previously been advised to use back-up, barrier, or other nonhormonal methods of contraception. Please communicate this information to women in your practice who may have been affected. A Patient Letter template is enclosed to assist you. Women who use barrier methods for other purposes, such as protection against STDs, should continue to use them.

Update
To address the problem of atypically low levels of levonorgestrel release, investigations were conducted by Wyeth in women with Norplant capsules from the specified lots. The data from these lots do not suggest less contraceptive effectiveness than that reported in clinical trials. Because of this new information, patients will no longer need to incur the inconvenience and expense of the back-up methods of contraception mentioned above. Wyeth will continue to pay for back-up, barrier, or other nonhormonal methods of contraception until December 31, 2002.

Norplant System Availability
Due to limitations in product component supplies, Wyeth does not plan to reintroduce the six-capsule Norplant® System (levonorgestrel implants). Therefore, your patients will need to consider other contraceptive options as they approach the five-year expiration dates of their Norplant Systems. If your patients would prefer to have the Norplant capsules removed, Wyeth will pay for removal procedures until December 31, 2002.

We sincerely appreciate your continued understanding and cooperation in this matter and realize that it may have caused inconvenience to you and your patients. If you or your patients want further information, please call the Norplant System Information Line at 1-800-364-9809.

Wyeth is committed to being a leader in women's health care and will continue to research and develop other contraceptive options, including implants, in the future.

Side Effects of Norplant System Use
The Norplant System is a reversible 5-year contraceptive. Commonly reported side effects include menstrual-bleeding irregularities, insertion site complications, weight gain, headache, nausea, nervousness, dizziness, and removal difficulties. These vary from woman to woman. The Norplant System does not protect against HIV and other STDs.

As part of the usual spontaneous reporting program, Wyeth requests that health care professionals continue to report pregnancy and adverse events that occur during Norplant System use.

Please see accompanying Prescribing Information.

Sincerely,
Victoria Kusiak, M.D.

Enclosures
Wyeth Pharmaceuticals
PO Box 8299
Philadelphia, PA 19101-8299

Excerpt from FDA website
http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm171071.htm. Accessed August 2013.

Figure 3: FDA Drug Safety Communication

FDA requires label changes to warn of risk for possibly permanent nerve damage from antibacterial fluoroquinolone drugs taken by mouth or by injection (August 15, 2013).

Safety Announcement

The U.S. Food and Drug Administration (FDA) has required the drug labels and Medication Guides for all fluoroquinolone antibacterial drugs be updated to better describe the serious side effect of peripheral neuropathy. This serious nerve damage potentially caused by fluoroquinolones (see Table for a list) may occur soon after these drugs are taken and may be permanent.

The risk of peripheral neuropathy occurs only with fluoroquinolones that are taken by mouth or by injection. Approved fluoroquinolone drugs include levofloxacin (Levaquin), ciprofloxacin (Cipro), moxifloxacin (Avelox), norfloxacin (Noroxin), ofloxacin (Floxin), and gemifloxacin (Factive). The topical formulations of fluoroquinolones, applied to the ears or eyes, are not known to be associated with this risk.

If a patient develops symptoms of peripheral neuropathy, the fluoroquinolone should be stopped, and the patient should be switched to another, non-fluoroquinolone antibacterial drug, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk. Peripheral neuropathy is a nerve disorder occurring in the arms or legs. Symptoms include pain, burning, tingling, numbness, weakness, or a change in sensation to light touch, pain or temperature, or the sense of body position. It can occur at any time during treatment with fluoroquinolones and can last for months to years after the drug is stopped or be permanent. Patients using fluoroquinolones who develop any symptoms of peripheral neuropathy should tell their health care professionals right away.

FDA will continue to evaluate the safety of drugs in the fluoroquinolone class and will communicate with the public again if additional information becomes available.

Facts about the fluoroquinolone drug class

- Antibacterial drugs approved for the treatment or prevention of certain bacterial infections.
- Approximately 23.1 million unique patients received a dispensed prescription for an oral fluoroquinolone product from outpatient retail pharmacies during 2011. Patients receiving a dispensed prescription for ciprofloxacin, levofloxacin, or moxifloxacin accounted for 70%, 28%, and 9% of the total number of patients, respectively, during 2011. Gemifloxacin, ofloxacin, and norfloxacin each accounted for less than 1% of total patients during 2011.[1]
- Within the hospital setting, there were approximately 3.8 million unique patients billed for an injectable fluoroquinolone product during 2011. Levofloxacin, ciprofloxacin, and moxifloxacin accounted for 63%, 28%, and 13% of total unique patients, respectively, during 2011; hospital billing for ofloxacin was not captured.[2]

Additional Information for Patients

- If you are taking a fluoroquinolone drug (see Table for a list) by mouth or by injection, know that it may cause symptoms in the arms or legs such as pain, burning, tingling, numbness, weakness, or a change in sensation to light touch, pain or temperature . These symptoms can occur early in treatment and may be permanent.
- Contact your health care professional right away if you take a fluoroquinolone drug and experience any of the above symptoms; it may be necessary to stop the fluoroquinolone and take another antibacterial drug, but do not do so without first talking with your health care professional.
- Carefully read the Medication Guide that comes with your fluoroquinolone prescription.
- Discuss any questions or concerns about fluoroquinolone drugs with your health care professional.
- Report any side-effects you experience to your health care professional and the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Additional Information for Health Care Professionals

- Make sure your patients know to contact you if they develop symptoms of peripheral neuropathy.
- Make sure your patients receive the Medication Guide with every prescription.
- If the patient develops symptoms of peripheral neuropathy, the fluoroquinolone should be stopped and an alternative non-fluoroquinolone antibacterial drug should be used, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk.
- Report adverse events involving fluoroquinolones to the FDA MedWatch program, using the information in the "Contact FDA" box at the bottom of the page.

Figure 3: FDA Drug Safety Communication (continued)

Data Summary

Peripheral neuropathy is an identified risk of fluroquinolones and was added to the *Warnings* or *Warnings and Precautions* sections of all the labels for systemic (oral and injectable) fluoroquinolone drugs in 2004. The risk of peripheral neuropathy is also described in the Medication Guides for these products. FDA has continued to receive reports of peripheral neuropathy even after the adverse reaction was added to the fluoroquinolone drug labels. The results of FDA's recent review of the Adverse Event Reporting System (AERS) database indicate that although the risk of peripheral neuropathy is described in the drug labels of each marketed systemic fluoroquinolone, the potential rapid onset and risk of permanence were not adequately described.

The recent AERS review evaluated cases of fluoroquinolone-associated peripheral neuropathy with an outcome of "disability," reported between January 1, 2003 and August 1, 2012. The review showed a continued association between fluoroquinolones use and disabling peripheral neuropathy. However, because AERS is a spontaneous reporting system, an incidence of peripheral neuropathy, especially permanent damage among patients exposed to these medications, cannot be calculated. The onset of peripheral neuropathy after starting fluoroquinolone therapy was rapid, often within a few days. In some patients the symptoms had been ongoing for more than a year despite discontinuation of the fluoroquinolone. Several patients were continued on the fluoroquinolone drug despite the occurrence of neuropathic symptoms.

FDA has not identified any specific risk factors for the development of peripheral neuropathy. Peripheral neuropathy appeared to be unrelated to the duration of therapy or the age of the patient.

FDA has required manufacturers of systemic fluoroquinolone drugs to make revisions to the drug labels (*Warnings/Precautions* and *Warnings and Precautions* sections) and the Medication Guides. These label changes are to better characterize the risk of peripheral neuropathy associated with the class of systemic fluoroquinolones. If a patient develops symptoms of peripheral neuropathy, the fluoroquinolone should be stopped, and the patient should be treated with an alternative non-fluoroquinolone antibacterial drug, unless the benefit of continued treatment with a fluoroquinolone outweighs the risk.

References

1. IMS Health Vector One®, National Total Patient Tracker. Extracted July 2012
2. ICHARUS®. Extracted July 2012.

Excerpt from FDA website, http://www.fda.gov/Drugs/DrugSafety/ucm365050.htm. Accessed August 16, 2013.

Appropriate interventions that are feasible and cost-effective should be selected, and each intervention should have a built-in evaluation strategy to determine whether the intervention is working. For example, to address the problem of protecting pregnant women from certain medicines that can cause harm, an intervention can be educating HCWs to ask the question "When was your last menstruation?" at every follow-up visit by the patient and to document the response in patient records. If the patient's response indicates she may be pregnant, the HCW must be trained to follow up appropriately by confirming the patient's condition and changing the patient's medicine if necessary. Another intervention is following country guidelines of prescribing a contraceptive for nonpregnant patients, and monitoring and documenting adherence to contraceptive treatment. However, contraceptives have to be easily accessible to the patients for this intervention to be effective. To determine whether the intervention worked, compare baseline and post baseline numbers, and modify the strategy as needed.

Risk Management Implementation

Implementation is the process of operationalizing the action plan. This process requires commitment (from key stakeholders involved in the process) to continuous implementation and monitoring of the plan. Risk intervention can be targeted to different audiences (for example, HCWs, patients, manufactures) to

improve systems that are associated with medicine risk problems. Interventions can take the form of education, communication, approved label revisions or updates, certification requirements, and the like.

Answers to the following questions will guide the development of an implementation action plan for risk minimization or prevention. This action plan should specifically define—

- What specific tasks should be done to minimize risk?
- Who must do it? (roles and responsibilities)
- By when should this be done?
- What is the capacity to implement identified tasks? (financial and human resources)
- Who will lead the process?
- What data should be collected and reported?
- What is the reporting mechanism and flow?
- What dates (timelines) should follow-ups occur?
- How to know intervention is working?

Depending on identified tasks, tools and standard operating procedures may need to be developed. The correct audience for the intervention should be targeted and trained to carry out required functions.

When implementing new interventions that require changes in attitudes and behaviors of HCWs, you may find out that some people are resistant to the change. The following tips for leading change to effectively implement a new intervention.

Leading Change Approaches
Work with the key stakeholders to plan and develop intervention
Communicate what change and why change is occurring to all affected
Find out what the resistance is (concerns) and address it
No blame games; seek to understand problems hindering change rather than judge
Communicate how the intervention will help stakeholders improve their work

Source: Adapted from the class "The Science of Safety in Health Care," Dr. Peter J. Pronovost, MD, PhD, FCCM, and Dr. Cheryl Dennison Himmelfarb, RN, ANP, PhD, FAAN, Johns Hopkins University, Baltimore, Maryland.

Risk Monitoring and Evaluation of Interventions

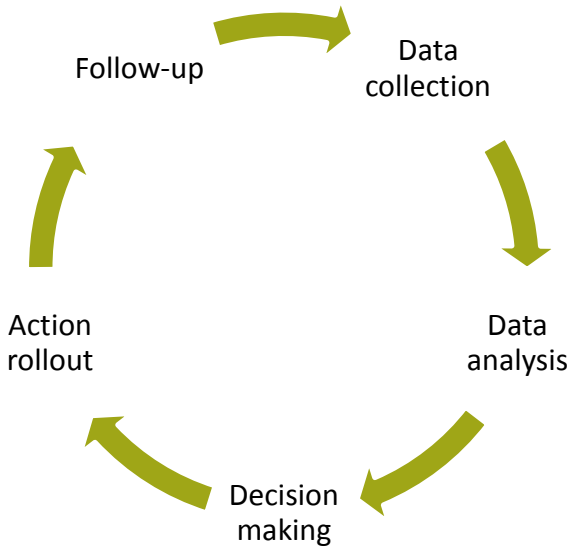
This phase answers the most important question: "How do we know the intervention is working?" This is also the most difficult part of any activity implementation because it is often forgotten and not planned for during the design phase of the intervention. To ensure effective risk minimization, a good monitoring process should be in place with formal procedures to report challenges and ensure corrective action. All risk minimization plans should have a review process and defined reassessment periods to keep the process dynamic and continuous. New risks identified in the process should also be addressed.

Risk Monitoring and Evaluation Process

- ✓ Develop framework to assess impact of action
- ✓ Define measurement variables
- ✓ Determine how variables will be measured
- ✓ Establish timelines for monitoring and evaluation of process

Figure 4 presents a framework for measuring the success of an intervention. The main components are data collection, data analysis, decision making, action rollout, and follow-up. This is a continuous process; one activity feeds into the next. Monitoring and performance indicators should be identified and incorporated in the intervention to evaluate how well the intervention is working to minimize risks. These indicators can either be qualitative or quantitative or a combination of both. Data to monitor performance should be collected regularly and assessed at defined periods to decide if the problem has improved. It is also important to investigate the reasons why the intervention did not work; having this information will help in the redesign of the intervention, so data collected should have information to determine this. After the redesign of the risk intervention, it should be implemented and evaluated again to make sure the risk has been reduced.

Figure 4. Framework to measure success of a risk intervention



When evaluating interventions to find out if risk has been reduced, baseline and follow-up data should be collected and compared. Any measure selected should address the risk and be meaningful and important to the target audience. Identified measures should collect enough information to identify problems and opportunities for improvement. Examples of quantitative indicators that can be monitored over time include the following—

- Percentage reduction in the number of AEs reported over a period of time
- Percentage increase in patient adherence to treatment during specified period
- Percentage reduction in use of contraindicated medicines by prescribers over a defined period
- Percentage decrease in drug-drug interactions reported over a period of time

- Percentage increase in frequency of required laboratory testing for a set of tracer medicines or one medicine
- Percentage increase in frequency of required clinical examination for a set of tracer medicines over a period
- Percentage of high-risk medicines that require registers with those registers in place at a given time
- Percentage of a set of tracer medicines stored appropriately on the day of visit
- Percentage of a set of tracer medicines reported to fail quality control tests during a specified period
- Percentage of prescriptions in accordance with the national treatment guidelines at a given time

Communication and Consultation

Communication is key in the entire process of risk management. This will provide an opportunity for all stakeholders to contribute to the process every step of the way. Consultation and proactive engagement of stakeholders involved in or affected by the decision or intervention will assist in bridging gaps between statistical evidence (if available) and actual perception of risk. Risk communication is also important to reconcile differing perceptions of risks and gain an appreciation of stakeholders' points of view.

The risk communication process involves team effort with multiple stakeholders to make decisions about how to improve the problem. It should be a two-way process where all stakeholders should be encouraged to provide feedback. Communication strategies should anticipate and respond effectively to public concerns and expectations. Table 10 lists illustrative tasks and required skills needed for effective communication in risk management activities.

Table 10: Illustrative Tasks and Skills Requirements of the Communication Committee

Communication tasks	Skills needed to achieve tasks
Plan and coordinate communication efforts	Active listening
Determine communication objective and have shared understanding of risks or problems	Respect and value others' opinions
Identify the right audience and how to gain their trust	Establish long-term relationships
Develop the right message and the right tools to communicate message effectively	Share expertise and insights
Solve problems collectively, build consensus, and resolve conflicts	Build trust and credibility
Ensure transparent decision making	Translate technical information to lay language
Implement effective two-way communication: information and feedback	Manage conflicts
Evaluate and improve communication strategy	Effectively deliver message to the right audience

Figure 5: Illustrative Example of a Risk Management Process

Problem: Reduction in treatment success rate for drug-resistant TB patients in certain regions of the country. Further investigation revealed the decrease could be attributed to nonadherence to treatment caused by rumors in the community that cycloserine causes mental health problems.

Assessment questions: (a) What is the context of this problem? And what objective do we want to achieve? Where did this problem start? When did it start? Why did it start? And how did it start?
(b) What is currently done to mitigate problem? Is it working?
(c) What other interventions can be put in place?
(d) Are sufficient resources (financial and human) and capabilities available to implement identified interventions?
(e) How will success of interventions be measured?

Findings: Revealed that rumors about cycloserine started as a result of a failed awareness campaign by a local organization in community A, district A. The information that cyloserine causes mental problems caused patients on treatment to stop taking their medicines. The health facilities have not implemented any action to correct the problem.

Interventions and implementation: Upon assessment of feasible, cost-effective options, the following interventions were identified targeting health care workers in TB clinics—

- ✓ Train health workers on good counseling techniques, messages, and follow-up actions for patients on cycloserine
- ✓ Develop standard procedures for prevention and management of cycloserine-related mental health issues and train health care workers accordingly
- ✓ Monitor administration (directly observed therapy—DOT) of cycloserine during intensive phase of treatment according to guidelines and document in patient records
- ✓ Monitor adherence to treatment during each patient visit to pick up medicines in continuation phase; use adherence tool to record if patient has adhered to treatment
- ✓ Use the new tool—"cycloserine assessment checklist"—during each patient encounter; document and report findings

A detailed action plan was developed and implemented at selected sites.

Monitoring and evaluation: The following indicators were monitored quarterly; the monitoring process was incorporated into the regular quarterly monitoring visits.

- ✓ Total number of days DOT was not done in intensive phase for MDR-TB patients on cycloserine: target 0 days
- ✓ Total number of days that patients did not adhere to their regimen during each monthly visit in continuation phase: target 0 days
- ✓ Total number of times cycloserine assessment checklist findings were not documented during each patient encounter: target 0 days
- ✓ Percentage of patients counseled on adverse events of cycloserine: target 100%
- ✓ Percentage increase in treatment success rate for MDR-TB patients: from baseline

If the indicators do not improve, review the process and make appropriate changes until the desired outcome is achieved.

CONCLUSION

No medicine is completely safe to patients. Some of the medicine effects are known and documented in the medicine labels, whereas others are unknown and will be known only after use of the medicine in a wide population. TB treatment is for a long duration (6–24 months), and anti-TB medicines, even though used for decades, are still intolerable for patients, causing AEs that can compromise adherence to treatment, result in antimicrobial resistance, and frustrate achievement of optimal treatment outcomes. The advent of new technologies (new medicines, repurposed medicines, and regimens recently available or still in the global development pipeline) reinforces the need for good vigilance to maximize their benefits while ensuring patient safety. A variety of factors, which include AEs, medicine interactions, treatment duration, appropriate use of medicines, and medicine quality, affect patient safety and adherence to treatment. Systematic planning, feasible approaches, and continuous monitoring of interventions are required to minimize risks to patients and to achieve desired results. The main purpose of this document is to guide countries through the process of planning and implementation of feasible strategies to minimize risks posed to TB patients on treatment. Risk management, which involves identification and assessment of risks, prioritization, implementation, and evaluation to measure success of interventions, is an example of an approach to achieve the desired goal of improving treatment outcomes and ensuring patient safety. Consultation, communication, and consensus building are key requirements throughout the risk management process. Practical cost-effective tools are also critical for documentation to support the monitoring and evaluation phase.

One may ask: “Whose responsibility is it to ensure TB patient safety?” Poor patient safety contributes to poor adherence to treatment and results in poor treatment outcomes. The national TB control program is responsible for minimizing spread and eliminating TB in the country. The responsibility will fall on the national TB control program to coordinate with key stakeholders and reach consensus on the most feasible and cost effective approaches required to minimize the risks caused by anti-TB medicines in the country. It is never too early to start; protect your community through implementing simple measures that can save their lives.

A: Adverse Event Management for Patients on Anti-TB Medicines

Types of AEs associated with anti-TB medicines	Medicines used to treat AEs	Dosing of medicines for AE treatment
Capreomycin		

• Peripheral neuropathy
• Electrolyte disturbance (hypokalemia and hypomagnesemia)
• Vestibular disturbance[1]
  ○ Nausea and vomiting[1,2]
  ○ Vertigo[1]
  ○ Ataxia[1]
  ○ Nystagmus[1]
• Depression[2]
• Hearing loss[2] and auditory damage[1]
• Renal failure and nephrotoxicity
	• **Peripheral neuropathy**
	  ○ Vitamin B6[1–3]
	  ○ Gabapentin[2]
	  ○ NSAIDs[3]
	  ○ Tricyclic antidepressant[2,3]
	• **Electrolyte disturbance**
	  ○ Potassium PO/IV
	  ○ Amiloride
	  ○ Spironolactone
	▪ **Nausea and vomiting**
	  ○ Anti-emetic 30 minutes before drug administration[2]
	  ○ Metoclopramide
	  ○ Dimenhydrinate[3]
	  ○ Prochlorperazine
	  ○ Promethazine[3]
	  ○ Bismuth subsalicylate[3]
	  ○ Ondansetron[3]
	• **Depression**
	  ○ Amitriptyline[3]
	  ○ Nortriptyline[3]
	  ○ Fluoxetine[3]
	  ○ Sertraline[3]
	  ○ Increase pyridoxine to 200 mg daily[2]
		• **Vitamin B6** (pyridoxine) 200 mg daily[2]
		• **Gabapentin** 300 mg/6 hourly initially then 600 mg every 3–7 days[2]
		• **Amiloride** 5–10 mg/8 hourly[2]
		• **Spironolactone** 25 mg/8 hourly[2]
		• **Metoclopramide** 10–20 mg PO/IV every 4–6 hours as required[4]
		• **Promethazine** 12.5–25mg PO/ IV PRN 30 minutes before administration of medicine and 8 hourly as required[4]
		• **Ondansetron** 8 mg PO 30 minutes before administration and repeated 8 hours after administration[4]

Cycloserine and Terizidone		

• Psychosis
• Peripheral neuropathy
• Seizures
• Tremors
• Depression
	• **Psychosis**
	  ○ Antipsychotics:
	  ○ Haloperidol[2]
	  ○ Risperidone[2]
	• **Peripheral neuropathy**
	  ○ Vitamin B6[1–3]
	  ○ Gabapentin[2]
	  ○ NSAIDs[3]
	  ○ Tricyclic antidepressant[2,3]
	• **Seizures**
		• **Vitamin B6** (pyridoxine) 200 mg daily[2]
		• **Gabapentin** 300 mg/6 hourly initially then 600 mg every 3–7 days[2]
		• **Haloperidol**:1–5 mg repeated hourly as required PO/IV/IM[2]
		• **Risperidone** 0.5–2mg PO 12 hourly[2]
		• **Phenytoin** 3–5 mg/kg/day[2]

Types of AEs associated with anti-TB medicines	Medicines used to treat AEs	Dosing of medicines for AE treatment
	○ Anticonvulsant therapy: ▪ Phenytoin ▪ Valproic acid ▪ Carbamazepine ▪ Phenobarbital ▪ Increase pyridoxine • **Tremors** ○ Anticholinergic: ▪ Benzotropine ▪ Biperiden • **Depression** ○ Amitriptyline[3] ○ Nortriptyline[3] ○ Fluoxetine[3] ○ Sertraline[3] ○ Increase pyridoxine to 200 mg daily[2]	• **Valproic acid** 750–1,250 mg/kg/day[2] • **Carbamazepine** 600–1,200 mg/day[2] • **Phenobarbital** 60–120 mg/day[2] • **Pyridoxine** 200 mg daily[2]
Fluroquinolones (levofloxacin, gatifloxacin, moxifloxacin, ofloxacin)		
• Arthralgia/arthritis • Depression • Psychosis • Peripheral neuropathy • Seizures • Nausea and vomiting • Diarrhea • Constipation • Dizziness • Headache • Vaginitis • Serum glucose disturbance • Confusion/ hallucination • Prolongation of QT interval	• **Arthralgia/arthritis** ○ NSAIDs[1,2] • **Depression** ○ Amitriptyline[3] ○ Nortriptyline[3] ○ Fluoxetine[3] ○ Sertraline[3] ○ Increase pyridoxine to 200 mg daily[2] • **Psychosis** ○ Antipsychotics: ▪ Haloperidol[2,3] ▪ Risperidone[2,3] ▪ Torazine[3] ▪ Benzotropine[3] ▪ Biperiden[3] • **Peripheral neuropathy** ○ Vitamin B6[1–3] ○ Gabapentin [2] ○ NSAIDs[3] ○ Tricyclic antidepressant[2,3] • **Seizures** ○ Anticonvulsant therapy: ▪ Phenytoin ▪ Valproic acid ▪ Carbamazepine ▪ Phenobarbital	• **Haloperidol** 1–5 mg repeated hourly as required PO/IV/IM[2] • **Risperidone** 0.5–2 mg PO 12 hourly[2] • **Vitamin B6** (pyridoxine) 200 mg daily[2] • **Gabapentin** 300 mg/6 hourly initially then 600 mg every 3–7 days[2] • **Valproic acid** 750-1,250 mg/kg/day[2] • **Carbamazepine** 600–1,200 mg/day[2] • **Phenobarbital** 60–120 mg/day[2] • **Pyridoxine** 200 mg daily[2] • **Metoclopramide** 10–20 mg PO/IV 4–6 hourly as required[4] • **Promethazine** 12.5–25 mg PO/IV PRN 30 minutes before administration of medicine and 8 hourly as required[4] • **Ondansetron** 8 mg PO 30 minutes before administration and repeated 8 hours after

Types of AEs associated with anti-TB medicines	Medicines used to treat AEs	Dosing of medicines for AE treatment
	▪ Increase pyridoxine • **Nausea and vomiting** ○ Anti-emetic 30 minutes before drug administration[2] ○ Metoclopramide ○ Dimenhydrinate[3] ○ Prochlorperazine ○ Promethazine[3] ○ Bismuth subsalicylate[3] ○ Ondansetron[3] • **Diarrhea** ○ Loperamide[3] • **Constipation** ○ Stool softeners • **Dizziness** ○ Meclazine[3] ○ Dimenhydrinate[3] ○ Prochlorperazine[3] ○ Promethazine[3] • **Headache** ○ Ibuprofen[3] ○ Acetaminophen[3] ○ Codeine[3] • **Vaginitis** ○ Topical or short-course oral antifungal medicine • **Serum glucose disturbance** ○ Oral hypoglycemic agent or insulin as required[3]	administration[4]
Ethionamide and Prothionamide		
• Gastritis[1,2] • Nausea and vomiting[1,2] • Diarrhea[2,3] • Hypothyroidism[2,3] • Depression[2,3] • Psychosis[3] • Peripheral neuropathy[3] • Seizures[3] • Hepatitis[3] • Optic neuritis[3]	• **Gastritis** ○ Antacids[2]: calcium carbonate, aluminum hydroxide, magnesium hydroxide ○ H_2-blockers[2]: ▪ Cimetidine ▪ Ranitidine ○ Proton pump inhibitors[2]: ▪ Omeprazole • **Nausea and vomiting** ○ Anti-emetic 30 minutes before drug administration[2]	• **Metoclopramide** 10–20 mg PO/IV 4–6 hourly as required[4] • **Promethazine** 12.5–25mg PO/IV PRN 30 minutes before administration of medicine and 8 hourly as required[4] • **Ondansetron** 8 mg PO 30 minutes before administration and repeated 8 hours after administration[4] • **Levothyroxine**[4] ○ Adults 100–150 µg daily

Types of AEs associated with anti-TB medicines	Medicines used to treat AEs	Dosing of medicines for AE treatment
	▪ Metoclopramide [3] ▪ Dimenhydrinate[3] ▪ Prochlorperazine [3] ▪ Promethazine[3] ▪ Bismuth subsalicylate[3] ▪ Ondansetron [3] • **Diarrhea** ○ Loperamide[3] • **Hypothyroidism** ○ Levothyroxine • **Depression** ○ Amitriptyline[3] ○ Nortriptyline[3] ○ Fluoxetine[3] ○ Sertraline[3] ○ Increase pyridoxine to 200 mg daily[2] • **Psychosis** ○ Antipsychotics: ▪ Haloperidol[2] ▪ Risperidone[2] • **Peripheral neuropathy** ○ Vitamin B6[1–3] ○ Gabapentin[2] ○ NSAIDs[3] ○ Tricyclic antidepressant[2,3] • **Seizures** ○ Anticonvulsant therapy: ▪ Phenytoin[2] ▪ Valproic acid, carbamazepine[2] ▪ Phenobrarbitol[2] ▪ Increase pyridoxine	○ Young healthy adults 75–100 µg daily ○ Geriatric patients: initiate therapy with 50 µg • **Haloperidol** 1–5 mg repeated hourly as required POo/IV/IM[2] • **Risperidone** 0.5–2 mg PO 12hourly[2] • **Vitamin B6** (pyridoxine) 200 mg daily[2] • **Gabapentin** 300 mg/6 hourly initially then 600 mg every 3–7 days[2] • **Phenytoin** 3–5 mg/kg/day • **Valproic acid** 750–1,250 mg/kg/day[2] • **Carbamazepine** 600–1,200 mg/day[2] • **Phenobarbital** 60–120 mg/day[2] • **Pyridoxine** 200 mg daily[2]
Aminoglycoside antibiotics (kanamycin and amikacin)		
• Peripheral neuropathy • Electrolyte disturbance • Hearing loss • Renal failure and nephrotoxicity	• **Peripheral neuropathy** ○ Vitamin B6[1–3] ○ Gabapentin[2] ○ NSAIDs[3] ○ Tricyclic antidepressant[2,3] • **Electrolyte disturbance** ○ Potassium PO/IV[2] ○ Amiloride[2] ○ Spironolactone[2]	• **Vitamin B6** (pyridoxine) 200 mg daily[2] • **Gabapentin** 300 mg/6 hourly initially then 600 mg every 3–7 days[2] • **Amiloride** 5–10 mg 8 hourly[2] • **Spironolactone** 25 mg 8 hourly[2]

Types of AEs associated with anti-TB medicines	Medicines used to treat AEs	Dosing of medicines for AE treatment
Para-aminosalicylic acid		
• Hypothyroidism • Gastritis • Nausea and vomiting • Hepatitis	• **Hypothyroidism** ○ Levothyroxine[3] • **Gastritis** ○ Antacids[2]: calcium carbonate, aluminum hydroxide, magnesium hydroxide ○ H_2-blockers[2]: ▪ Cimetidine[2] ▪ Ranitidine[2] ○ Proton pump inhibitors[2]: ▪ Omeprazole[2] • **Nausea and vomiting**: ○ Anti-emetic 30 minutes before drug administration[2]: ▪ Metoclopramide[3] ▪ Dimenhydrinate[3] ▪ Prochlorperazine[3] ▪ Promethazine[3] ▪ Bismuth subsalicylate[3] ▪ Ondansetron[3]	• **Levothyroxine**[4] ○ Adults 100–150 µg daily ○ Young healthy adults 75–100 µg daily ○ Geriatric patients: initiate therapy with 50 µg • **Metoclopramide** 10–20 mg PO/IV 4–6 hourly as required[4] • **Promethazine** 12.5–25 mg PO/IV PRN 30 minutes before administration of medicine and 8 hourly as required[4] • **Ondansetron** 8 mg PO 30 minutes before administration and repeated 8 hours after administration[4]
Streptomycin		
• Peripheral neuropathy • Electrolyte disturbance • Hypersensitivity reactions[3] • Neuromuscular blockade[3] • Diarrhea[3] • *Clostridium difficile*–associated diarrhea • Hearing loss • Renal failure and nephrotoxicity • Hepatitis and hepatotoxicity[3]	• **Peripheral neuropathy** ○ Vitamin B6[1–3] ○ Gabapentin[2] ○ NSAIDs[3] ○ Tricyclic antidepressant[2,3] • **Electrolyte disturbance** ▪ Potassium PO/IV[2] ▪ Amiloride[2] ▪ Spironolactone[2] • **Hypersensitivity reactions**[3] ▪ Antihistamine therapy[3]: ○ Diphenhydramine[3] ○ Chlorpheniramine[3] ○ Dimenhydrinate[3] ○ Corticosteroids[3]: ○ Prednisolone[3] ○ Methylprednisolone[3] ○ Hydrocortisone cream[3] ○ Calamine/Caladryl lotion[3]	• **Vitamin B6** (pyridoxine) 200 mg daily[2] • **Gabapentin** 300 mg/6 hourly initially then 600 mg every 3–7 days[2] • **Amiloride** 5–10 mg 8 hourly[2] • **Spironolactone** 25 mg 8 hourly[2] • **Diphenhydramine** 25–50 mg PO/IV/IM before administration and then 4–6 hourly as required[4] • **Chlorpheniramine** 4 mg PO before administration and then 4–6 hourly as required[4] • **Prednisolone** 10–20 mg daily for several weeks[4] • **Hydrocortisone cream** administered topically[4]

Types of AEs associated with anti-TB medicines	Medicines used to treat AEs	Dosing of medicines for AE treatment

	• **Neuromuscular blockade**[3]
	  ▪ Calcium salts[3]
	• **Diarrhea**[3]
	  ▪ Loperamide[3]
	• ***Clostridium difficile*–associated diarrhea**[3]
	  ▪ Fluid and electrolyte therapy[3]
	  ▪ Antibiotic treatment[3]
	  ▪ Protein supplementation[3]	

NB: The authors are not endorsing any of these treatments but have simply compiled information from available resources. Appropriate treatment selection should be evidence based, agreed upon by key stakeholders, and included in the national standard treatment guidelines for use in the country.

References:

1. Caminero JA, ed. 2012. *Guidelines for Clinical and Operational Management of Drug-Resistant Tuberculosis*. Paris: International Union Against Tuberculosis and Lung Disease.
2. Republic of South Africa Department of Health. *Management of Drug Resistant Tuberculosis: Policy Guidelines*. Pretoria: National Department of Health; 2011: 62–67. Available at: http://www.info.gov.za/view/DownloadFileAction?id=165278.
3. SIAPS. 2013. *Guidelines for Implementing Anti-Tuberculosis Drug Use Review Programs.* Submitted to the US Agency for International Development by the Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program. Arlington, VA: Management Sciences for Health, Annex A.
4. Curry International Tuberculosis Center and California Department of Public Health. *Drug-Resistant Tuberculosis: A Survival Guide for Clinicians, 2011.* 2nd ed. San Francisco, CA: Curry International Tuberculosis Center; 2011: 145–70.

B: Anti-TB Medicine Storage Requirements

Anti-TB medicine	Recommended storage requirements
Rifampin	25°C (77°F). Store in a dry place. Avoid excessive heat.
Isoniazid	15–30°C (59°–86°F). Protect from moisture and light. Dispense in a tight, light-resistant container with a child-resistant closure.
Pyrazinamide	Store in a well-closed container at controlled room temperature 15°–30°C (59°–86°F).
Ethambutol	20°–25°C (68°–77°F). Protect from light and moisture.
Streptomycin	Store dry powder under controlled room temperature 15°–30°C (59°–86°F).
Kanamycin	Store at 20°–25°C (68°–77°F).
Amikacin	Store at 20°–25°C (68°–77°F).
Levofloxacin	Store at 15°–30°C (59°–86°F) in well-closed containers.
Moxifloxacin	Store at 25°C (77°F). Avoid high humidity.
Ofloxacin	Store at 20°–25°C (68°–77°F). Dispense in a tight container.
Ethionamide	Store at 20°–25°C (68°–77°F). Dispense in a tight container.
Cycloserine	Store at 20°–25°C (68°–77°F).
PAS	PASER (without sodium compound). Store below 59°F (15°C) (in a refrigerator or freezer).
Linezolid	Store at 25°C (77°F). Protect from light and moisture.
Amoxicillin/clavulanate	Store at 20°–25°C (68°–77°F).
Clarithromycin	15°–30°C (59°–86°F) in a well-closed container. Protect from light.
Capreomycin	15°–30°C (59°–86°F) prior to reconstitution
Clofazimine	Store below 30˚C (86˚F). Protect from moisture.
Imipenem	Do not store above 25 °C.

Source: National Institutes of Health, DailyMed website. http://dailymed.nlm.nih.gov/dailymed/about.cfm.

C: Illustrative Patient's Adverse Event Documentation Form

<table>
<tr><th colspan="4">Section I</th></tr>
<tr><td colspan="2">Patient name</td><td rowspan="2">Address</td><td rowspan="2">Patient's telephone number</td></tr>
<tr><td colspan="2">Date of treatment initiation</td></tr>
<tr><td>Age</td><td>sex</td><td>Name of health care facility</td><td>Emergency telephone number</td></tr>
<tr><td colspan="2">Name of physician</td><td></td><td>Emergency telephone number</td></tr>
<tr><th colspan="4">Section II</th></tr>
<tr><td colspan="4">List of Medications</td></tr>
<tr><td colspan="2">Drug 1 (date prescribed)</td><td>Drug 2(date prescribed)</td><td>Drug 3(date prescribed)</td></tr>
<tr><td colspan="2">Major drug-related adverse reaction</td><td></td><td></td></tr>
<tr><td colspan="2">Drug 4 (date prescribed)</td><td>Drug 5(date prescribed)</td><td>Drug 6(date prescribed)</td></tr>
<tr><td colspan="2"></td><td></td><td></td></tr>
<tr><th colspan="4">Section III</th></tr>
<tr><td colspan="4">List of general adverse reactions requiring notification</td></tr>
<tr><td colspan="2">• No appetite
• Nausea
• Vomiting
• Yellowish skin or eyes
• Fever for 3 or more days
• Abdominal pain
• Tingling in the fingers or toes
• Pain in the lower chest or heart burn
• Feeling itchy
• Skin rash</td><td colspan="2">• Easy bruising
• Bleeding from gums
• Nose bleeding
• Urine becomes dark or brown in color
• Aching joints
• Dizziness
• Tingling or numbness around the mouth
• Blurred or changed vision
• Ringing in the ears
• Hearing loss</td></tr>
<tr><td>Days 1–31</td><td colspan="3">Adverse effects experienced by patient</td></tr>
<tr><td></td><td colspan="3"></td></tr>
<tr><td></td><td colspan="3"></td></tr>
<tr><td></td><td colspan="3"></td></tr>
<tr><td></td><td colspan="3"></td></tr>
<tr><th colspan="4">Section IV</th></tr>
<tr><td colspan="4">Document any action taken by patient</td></tr>
<tr><td>Days 1–31</td><td colspan="3"></td></tr>
<tr><td></td><td colspan="3"></td></tr>
<tr><td></td><td colspan="3"></td></tr>
<tr><td></td><td colspan="3"></td></tr>
<tr><td colspan="4">This section should be filled in by health care worker at each visit following review of information documented above by patient</td></tr>
</table>

Section V	
Plan of care for patient implementation	
Date	

Patients are provided with this document at the initiation visit and should present it to the physician/health care worker and pharmacist at all visits. An advantage of this tool is that it provides the opportunity for pharmacists to collaborate with clinicians on the best option for each individual patient to avoid harmful drug effects during care as well as improve patient treatment outcome.

Sections I, II, and V are filled in by staff at the health care (facility clinician, nurse, etc.).

Section I contains patient's biodata, name of treatment facility, and contact information. It should be completed at the facility of treatment before issuing to patient. **Section II** is a list of medications. All medicines prescribed for the patient are entered in this section. Major medicine-related adverse effects the patient is expected to experience are listed for each medicine. Documentation of the important major adverse effects will help increase the prescriber's alertness to the adverse effects most likely to occur. Ensure that additional empty fields are available in this section in case of medication change. **Section V** should include all advice given to patient, including the dos and don'ts for correctly taking the medicine. Also enter notes on when you expect the patient to return to the clinic.

Sections III and IV should be filled in by the patient.
Patients should be educated on how to enter the information in these sections. The importance of accurate entry of information according to treatment experience and outcome should be emphasized.

Section III describes the common side effects that require reporting. Contact information for the prescribing physician and treatment facility is provided in section I. This section is also meant for the patient to document any unpleasant or abnormal experience during treatment even if reported.

Section IV is where the patient should document whatever action was taken. If any intervention was implemented at home, it should be noted in this section.

A new form should be given to the patient every month.

To avoid errors in date, it is advisable to enter information corresponding to date. That is, adverse effects occurring on day 17 should be entered on the 17th date of the month. If patient management started at the middle or end of the month, patients should be provided with two set of forms.

D: Illustrative Physician Checklist and Adverse Event Risk Monitoring Tool

Section I Patient's Health History Review		
Patient education/counseling: provide each patient with generic education and briefly document any concerns	**List regimen and potential side effects for each drug**	
Section II		
Risks due to family history	**Risks caused by preexisting conditions**	**Potential risks from social habits**
Section III Contraindication Check		
Found on patient's adverse event record **List contraindications for patients based on medical history**		
Pregnancy/postpartum/breast-feeding (if applicable)		
Food (list any if applicable)		

Concomitant medication	Risk	No risk
List all concomitant medications (other than ARVs)		
HIV medication (if applicable)		

Section IV Adverse Reactions	
Dates	**Reactions**

Date	Laboratory abnormality	Comments	Dates for follow-up

Section V Referrals (if Applicable)		
Conditions mandating referral to specialist and follow-up notes		**Specialist's name and contact number**
Date	**Conditions and notes**	

This tool will alert physicians on impending risk to patients during treatment to avoid severe harmful outcomes.

Section I. This section ensures the patient receives adequate counseling at treatment initiation. Physicians are to take note of any concerns patients may have that need to be addressed. (Examples include nutritional or economic status that may affect continuation of treatment; communication barriers, family support system, and the like.) This section also contains the patient's regimen and the information on potential adverse events. Adverse events should be discussed at the beginning of each visit and at the end of the patient's evaluation.

Section II. Enter the list of all potential risks to the patient.

Section III. This section is based on the patient's medical and social history. Documentation of the risk will enable easier determination of contraindications that should be documented. (This includes contraindications for pregnancy and concomitant medication such as HIV medicines.)

Section IV. Laboratory results. Comments should include any action taken if normal or abnormal.

Section V. This section should contain information related to any reason for referrals and management provided.

E: Potentially Overlapping Toxicities of Antiretrovirals and Anti-TB Agents

Potential toxicity	Antiretroviral therapy	Anti-TB therapy
Peripheral neuropathy	Stavudine Didanosine	Cycloserine/terizidone Isoniazid Ethambutol Fluoroquinolones Streptomycin Kanamycin Amikacin Capreomycin Viomycin Ethionamide/prothionamide Linezolid
Psychiatric symptoms	Efavirenz	Cycloserine/terizidone Isoniazid Fluoroquinolones Ethionamide/prothionamide
Hepatitis	Nevirapine Ritonavir-boosted protease inhibitors Efavirenz Etravirine Maraviroc	Pyrazinamide Isoniazid Rifampicin/rifabutin *P*-aminosalicylic acid Fluoroquinolones
Gastrointestinal intolerance	Zidovudine Protease inhibitors Didanosine	Ethionamide/prothionamide *P*-aminosalicylic acid Pyrazinamide Isoniazid Rifampicin Ethambutol Clofazimine
Renal toxicity	Tenofofvir Indinavir	Streptomycin Kanamycin Capreomycin Amikacin Viomycin Rifampicin
Bone marrow toxicity	Zidovudine	Linezolid Rifampicin/rifabutin
Lactic acidosis	Stavudine Didanosine Zidovudine	Linezolid
Stevens-Johnson syndrome	Nevirapine Efavirenz Etravirine	Thioacetazone Cycloserine/terizidone Linezolid Ethambutol Streptomycin
Arrhythmias/QT prolongation	Atazanavir/ritonavir Saquinavir/ritonavir Lopinavir/ritonavir	Fluoroquinolones

Rash/pruritus	Nevirapine Efavirenz Etravirine Abacavir	Rifampicin/rifabutin Pyrazinamide

Source: World Health organization. 2011. *Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis*. http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf.

Additional Risk Management Resources

Lawrence Flick Memorial Tuberculosis Clinic. *Guidelines for the Management of Adverse Drug Effects of Antimycobacterial Agents*. Philadelphia, PA: Philadelphia Tuberculosis Control Program; 1998. http://www.uphs.upenn.edu/TBPA/treatment/managingsideeffects.pdf.

Mehta U, Clerk C, Allen E, et al. Protocol for a drugs exposure pregnancy registry for implementation in resource-limited settings. *BMC Pregnancy and Childbirth* 2012;12:89. http://www.biomedcentral.com/1471-2393/12/89

Partners in Health (PIH); Program in Infectious Disease and Social Change, Harvard Medical School; Division of Social Medicine and Health Inequalities, Brigham and Women's Hospital. *The PIH Guide to the Medical Management of Multidrug-Resistant Tuberculosis*. International ed. United States: Partners in Health; 2003: Appendix 5. http://www.pih.org/library/pih-guide-to-the-medical-management-of-multidrug-resistant-tuberculosis.

Rifamycins and Anti-Diabetic Agents: Drug-Drug Interactions. Chart developed by Kelly Bujnoch, PharmD Candidate 2011, with the assistance of Regina Tabor, RPh, DPh, Robert Petrossian and Barbara Seaworth, MD. http://www.heartlandntbc.org/products/Rifamycins%20and%20Anti-Diabetic%20Agents_2012.pdf. Accessed August 23, 2013.

US Food and Drug Administration website. Drugs, Drug Safety and Availability, Medication Guides. http://www.fda.gov/drugs/drugsafety/ucm085729.htm. Accessed August 23, 2013.

US Food and Drug Administration website. Drugs, Resources for You, Information for Healthcare Professionals (Drugs). "Communicating Benefits and Risk Information." http://www.fda.gov/Drugs/ResourcesForYou/HealthProfessionals/ucm365624.htm. Accessed August 23, 2013.

ANNEX A. IDENTIFICATION OF RISK CRITERIA FOR ANTI-TB MEDICINES

The following criteria are used for risk identification to determine which anti-TB medicines require risk management interventions based on the risk level. Not all the criteria will be useful in your setting; some are subjective and will need an expert committee from the key stakeholder group to agree on how best to define each selected criteria for your setting.

Expected Serious Adverse Event

A *serious adverse event or reaction* is defined[33] as any untoward medical occurrence that at any dose may—

- Result in death
- Be life threatening (patient was at risk of death at the time of the event)
- Require inpatient hospitalization or prolongation of existing hospitalization
- Result in persistent or significant disability or incapacity
- Cause a congenital anomaly or birth defect

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious AEs when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An *expected AE or reaction* is an event that is noted in the labeling package insert for the medicine. The term serious is based on an event outcome and used when an event poses a threat to the ability to conduct normal life functions or to a patient's life.

The following subcriteria were considered—

1. **Known pharmacological class effect:** These are identified or potential risks from clinical development and postauthorization experience that are believed to be common to a drug class.[34] For example, the aminoglycoside class of antibiotics, such as amikacin and kanamycin used for MDR-TB treatment, cause ototoxicity (damage to the auditory nerve). This means that taking two medicines in this pharmacologic class can increase the risk and effect of ototoxicity in patients. Only anti-TB medicines with known class effect from the tracer list of anti-TB medicines were considered in the medicine risk analysis.

2. **Known safety issues for renal impairment:** These medicines have identified or potential risks of causing renal impairment or kidney damage when administered at a normal therapeutic dose. The level of risk of a medicine that causes renal impairment is increased if the TB patient already has a kidney disease. For example, anti-TB medicines such as capreomycin should be avoided in patients with mild to severe kidney problems because of the increased risk of damage to the kidneys. Sometimes, the risk may exist but have not yet been recognized or reported by the patient. Only anti-TB medicines with known safety issues for renal impairment in normal patients at normal dose of medicine and for patients with kidney disease were considered in the medicine risk analysis.

3. **Known safety issues for hepatic impairment:** These are medicines with identified or potential risks of causing hepatic impairment or liver damage when administered at a normal therapeutic dose. Anti-TB medicines such as isoniazid and pyrazinamide can cause liver damage when taken at normal therapeutic dose, and the risk level increases if the patient already has a liver condition (whether recognized or unrecognized). Only anti-TB medicines with known safety issues for hepatic impairment in normal patients at normal dose of medicine and for patients with hepatic disease were considered in the medicine risk analysis.

4. **Known safety issues for elderly:** These are medicines with identified or potential risks of causing harm to elderly patients. The elderly represent a special group in pharmacology because they tend to have more diseases than younger people and therefore consume more medicines that can increase the risk of drug interactions. In addition, the rate and extent of absorption, distribution, metabolism, and elimination of medicines in the elderly may change, producing different effects from what will occur in younger population. Safety information available for the elderly during time of approval is limited, thereby increasing the risk potential. Anti-TB medicines with known clinically significant and unknown (no clinical information available) safety effects in the elderly were considered in the medicine risk analysis. The term “clinical significance” is subjective and difficult to interpret; there is no agreed upon definition for specific diseases. However, Kraemer et al. defined it as a change to normal functioning due to therapy.[35] Clinical significance is a subjective term without a precise definition based on external standards provided by clinicians, patients, or researchers and indicates when the effect of the drug makes enough difference to the provider and patient to justify changing it.

5. **Known safety issues for pediatrics:** These are medicines with identified or potential risks of causing harm to pediatric patients. Pediatric patients differ from adults in having still-developing body systems, so additional considerations may be involved. Very limited safety information is available on pediatric populations during approval of medicines, thus increasing the potential for risks. Information obtained online following the examination of more than 60,000 research trials from 2005 to 2010, using data entered into the US clinicaltrials.gov registry, showed that only about 8 percent of trials were designed for children younger than 18 years.[36] Key safety issues such as drug-drug, drug-food, and other safety-related issues in children are largely unknown, and most recommendations are based

on extrapolations from adult data. Professional labeling for pediatric patients for older medicines can be confusing when it says that the safety and efficacy have not been established. This can mean no studies have been done or that the medicine failed to show safety and efficacy in a pediatric population in clinical trials. A good resource to find more information for rigorously reviewed studies that may be unpublished is the US FDA website. Under the Best Pharmaceuticals for Children Act of 2012 and the Pediatric Research Equity Act of 2012, manufacturers of already marketed medicines are granted additional marketing exclusivity for conducting clinical trials in pediatric patients. The FDA posts the medical, statistical, and clinical pharmacology reviews of these trials at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm. Anti-TB medicines with known clinically significant and unknown (no clinical information available) safety effects in pediatric patients were considered in the medicine risk analysis.

6. **Pregnancy risk category:** These medicines cause harm to the fetus when taken by pregnant women at the normal recommended doses. The pregnancy categories considered in this document taken from FDA website are—
   - Category A: Generally acceptable. Controlled studies in pregnant women show no evidence of fatal risks.
   - Category B: May be acceptable. Either animal studies show no risk but human studies not available, or animal studies showed minor risks and human studies done and showed no risks.
   - Category C: Use with caution if benefits outweigh risks. Human data are lacking or not done, but animal studies are positive for causing fetal harm.
   - Category D: Use in life-threatening emergencies when no safer alternative is available. Human data show risk to fetus.
   - Category X: Do not use in pregnancy. Animal and human data are positive to cause harm to the fetus.

7. **Potential risk during lactation:** These medicines affect lactating mothers or can pass through breast milk to the baby, causing harm. Many medicines pass through the breast milk but the decision whether or not to take the drug should be determined by a risk/benefit analysis. Anti-TB medicines that produce the following effects were considered in the medicine risk analysis.
   - Medicines contraindicated during lactation
   - Medicines that need risk/benefit analysis
   - Medicines where effect on lactation is unknown

Interactions

Interactions discussed and considered as risk criteria in this document include—

1. **Potential for clinically significant drug-drug interactions:** Medicine interaction is the pharmacological result, either desirable or undesirable, of medicines interacting with themselves or with other medicines, with endogenous chemical agents, or with chemicals used in or resulting from diagnostic tests.[37] When the combined effect of two medicines equals the sum of each medicine given alone, it is called an additive effect. For example, use of cycloserine and isoniazid at the same time can cause an additive effect, increasing the toxicity and adverse effects of isoniazid. Interaction called a synergistic effect occurs when the combined effect exceeds the sum of the effect of each medicine given alone. A drug interaction is described as a potentiation effect when the medicine in the presence of another medicine creates a toxic effect. An antagonistic effect is the interference of one medicine with the action of another. Interactions also occur with herbal and traditional medicines. Drug-drug interactions considered in the medicine risk analysis are interactions that have been documented to be clinically significant, for example, interactions that either stimulate or inhibit the liver enzymes, which can result in overdosing or underdoing of one of the medicines administered. Only drug-drug interactions with clinical significance were considered in the anti-TB medicine risk analysis.

2. **Drug-food interactions:** Genser defined drug-food interactions as alterations of pharmacodynamics or pharmacokinetics (absorption, distribution, metabolism, elimination) of an agent as a result of its interaction with the nutritional or chemical components of food.[38] A food-drug interaction can cause changes in the efficacy and safety profile of an agent by altering its therapeutic effects and/or adverse effects. Simply described, it is the effect produced when some medicines and certain foods or beverages are taken at the same time. In the medicine risk analysis, only anti-TB medicines that interact with food (medicine taken on empty stomach, with a specific type of food, or with food in general) were considered as high risk.

3. **Drug-disease interactions:** According to Lindblad et al., these interactions are exacerbations of preexisting diseases, conditions, or syndromes caused by the use of multiple medications.[39] Examples include the following: a person with high blood pressure could experience an unwanted reaction (increased heart rate) from also using a nasal decongestant; patients with diabetes mellitus using gatifloxacin could experience disturbances of blood glucose—hyper- and hypoglycemia. All diseases that interact with an anti-TB medicine were considered in the medicine risk analysis.

Safe Medicine Use indicators

A *safe medical product* is one that has reasonable risk given the magnitude of benefits expected and the alternatives available.[40] The FDA notes that reasonable risk to individual research participants is defined as (a) requiring the least amount of intrusion into interests of participants that is necessary to facilitate sound scientific injury, and (b) consistent with an equal regard for the basic interest of study participants and the members of the larger community whose interest that research is intended to serve.[41]

The elements of safe use examined in this document include—

1. **Potential for medication error:** A *medication error* is any incorrect or wrongful administration of a medication, such as a mistake in dosage or route of administration, failure to prescribe or administer the correct medicine or formulation for a particular disease or condition, use of outdated medicines, failure to observe the correct time for administration of the medicine, or lack of awareness of adverse effects of certain medicine combinations.[42] Causes of medication error may include difficulty in reading handwritten orders and confusion between different medicines with similar names. Other types of error include improper dilution or improper administration techniques, which may result in nonoptimal dosing. For this document, only medication error caused by look-alike and sound-alike medicines was considered in the medicine risk analysis. Please note that this criterion will need to be adapted according to country relevance. Medicine brand names or brand generic names may differ by country. The analysis considered only generic names.

2. **Off-label use of medicines:** This occurs when marketed medicines are used to treat conditions that were not studied during clinical development of the product,[43] for example, when a particular medicine is not approved for pediatric use but used off-label in pediatrics. Uncertainty about benefits and risks usually exists because less information about the safety and efficacy of the medicine is available. However, if the medicine is approved for use in the particular country in question (not in the United States or European Union, for example) then it is not off-label use. For this document, only anti-TB medicines that have known off-label use (except for the treatment of TB as an off-label use) were considered in the medicine risk analysis. Off-label data used for the analysis are based on FDA approvals of medicines. This criterion should be adjusted according to country context.

3. **Experience with drug overdose or toxic levels:** These are medicines for which specific methodology or approaches for management of toxic effects or overdose in patients were defined. Overdose is a lethal or toxic amount of a drug. In the medicine risk analysis, medicines with defined approaches to handle overdose were considered as lower risk than medicines without any defined approach to control overdose.

4. **Potential for medication abuse:** Medication abuse is defined in this context as habitual use of the medicine to alter one's mood, emotion, or state of consciousness.[44] Review of literature did not show any information about any anti-TB medicine that has been used recreationally or abused. For the analysis, all medicines were considered as low risk.

5. **Therapeutic window:** The FDA defines narrow therapeutic ratio to be those medicines that have "less than a twofold difference in median lethal dose (LD50) and median effective dose (ED50), or those that have less than a twofold difference in minimum toxic concentration (MTC) and minimum effective concentration (MEC) in the blood and safe and effective use of the drug products requires careful dosage titration and patient monitoring."[45] Simply described, a therapeutic window is usually a short time interval (after a precipitating event)

during which a particular therapy can be given safely and effectively. For example, the peak therapeutic range for amikacin is 20.0–35.0 mcg/mL and the trough range is <8.0 mcg/mL. Clinical effects may not be achieved if the peak serum concentration is <20.0 mcg/mL. Toxicity may occur if, for prolonged periods of time, peak serum concentrations are maintained >35.0 mcg/mL, or trough concentrations are maintained at >10.0 mcg/mL.[46,47,48] Anti-TB medicines that required monitoring of peak and trough levels during treatment were considered as narrow therapeutic window.

4. **Action taken by regulatory authority or marketing authorization holder:** This includes any significant regulatory action in any market imposed due to safety concerns. Significant regulatory action includes a new or strengthened warning such as a black box warning or action to suspend or revoke a marketing authorization.[49] The regulatory authority considered in this analysis is the US FDA for actions taken after marketing authorization was issued to the manufacturer. This section may need to be adapted by the country as needed.

5. **New product:** A new product can be referred to as (a) a new preparation and presentation (new dose, generic formulation, and route of administration), (b) a new indication, and (c) a new population approved for use (pediatric, geriatric, or others).[50] Usually, the drug safety profile conducted by the manufacturer prior to preapproval of the medicine does not cover all special populations, such as pediatric, elderly, and pregnant women, and populations with racial or genetic predispositions. In addition, because the medicine is new, it may require more prolonged use in a larger population size before some of its adverse effects are detected. A new product in the context of this document is one that meets the preceding three criteria for anti-TB medicines within the last three years.

Drug Integrity and Supply Chain

Availability of good quality anti-TB medicines is important to ensure patients' safety and to ensure the medicine manages the condition effectively. Consequences of use of poor quality medicine include lack of therapeutic effect, which can prolong the illness or even cause death; induce adverse events that can be harmful to the patient; and waste scarce resources.

A stable drug product is one that can retain its properties within specified limits to be useful.[51] Stability is defined by the World Bank as "capabilities of a particular formulation of a pharmaceutical in a specified container/closure system to remain within specified physical, chemical, microbiological, therapeutic and toxicological specifications."[52] The period that a medicine can be stable is established by the manufacturer or sometimes by a country's drug regulatory authority; this period ends with the expiration date of the medicine.

The elements considered in these criteria include—

1. **WHO prequalification of medicines:** This is a service provided by WHO to ensure that medicines supplied by procurement agencies meet acceptable standards of quality, safety,

and efficacy. This service is specifically for TB, HIV/AIDS, malaria, reproductive health, and zinc supplementation. This service is used by international procurement agencies and increasingly by countries to guide bulk purchasing of medicines. In the context of this document, the WHO prequalification is considered as the first step of quality control for countries with weak regulatory systems to ensure safety of medicines. Medicines that are prequalified are categorized as having a lower risk than medicines that are not.

2. **Total number of manufacturers or suppliers prequalified:** Even though the WHO prequalification is considered a first step to quality control for countries with weak regulatory systems, not all anti-TB medicines have been prequalified. For the prequalified medicines, very few quality-assured sources are available, which can lead to a global stock-out for those medicines, thus making countries procure from non-quality-assured sources. Because of weak and nonfunctional regulatory systems to assure medicine quality, procuring from suppliers whose products and manufacturing plants have not been certified or prequalified by a strong regulatory authority increases the risk of the possibility that the medicine could be substandard. In addition, if a medicine has fewer suppliers, then a higher risk of manufacturer shortages exists if there is a problem with the manufacturing plant or if demand was not well forecast. The assumption made in this document and considered in the risk analysis is that the fewer suppliers are available for a prequalified medicine, the higher the risk of procuring substandard medicines from nonprequalified suppliers.

3. **Short shelf life:** Shelf life is the length of time that a medicine can be stored and still remain safe and effective for use by patients. Shelf life is sometimes used interchangeably with expiry date, which is defined by WHO as the date given on the individual container of a drug product up to and including which the product is expected to remain within specifications if stored correctly.[53] The main difference is that a medicine still within the expiry date period can be unstable if not properly stored. Regular inventory monitoring is required for medicines with short shelf life to ensure they are used before expiry and to dispose of them after expiry. Anecdotal evidence shows that some patients are sometimes given expired medicines because of lack of inventory monitoring. Expired products are less effective due to decreased potency. Countries may be forced to make emergency procurements when medicines are not properly monitored for expiry; depending on the emergency source, product quality may be compromised, thereby increasing the risk to patients. In this document, products with a shorter shelf life are considered a higher risk than products with longer shelf life. Short shelf life is defined as a period from 0 to 24 months.

4. **Storage conditions:** These are determined by the manufacturer after stability testing and represent the conditions under which a medicine should be stored to remain stable. In resource-constrained settings, medicines that require refrigeration will have a higher risk of being unstable because of reasons such as irregular power supply or poor temperature monitoring. Medicines that require reconstitution or compounding also have slightly higher risk than other medicines that do not because of risk of contamination during the preparation process. Medicines that need to be stored away from light and away from moisture have a higher risk of being unstable if not properly stored.

5. **Substandard medicines:** Substandard or counterfeit medicines may be contaminated or may not contain the right active ingredient or may not have any active ingredient at all. They may also have the right active ingredient but at the wrong dose. In a 2005 WHO draft document, counterfeit medicine was defined as a medicine that is deliberately and fraudulently mislabeled with respect to identity or source.[54] Substandard medicines are illegal and may be harmful to patient health; medicines with high cost and medicines used by a large market are usually targeted, as well as countries with weak regulatory enforcement for medicines. Medicines that have been reported to be substandard are allotted a higher risk score in this risk analysis.

6. **Diversion of medicines:** Medicines may be diverted from legal and medically necessary uses toward uses that are illegal and typically not medically authorized or necessary. In the context of this document, medicine diversion is defined as losses due to pilferage. Because of the economic situation in many resource-constrained settings, expensive medicines are sometimes lost or diverted either during transport to health facilities or from the health facility store and traded for personal gain. Medicines that have a high potential for diversion are allotted a higher risk profile than other medicines because medicine quality may be compromised during diversion.

Chronic Medicine Use Risk

1. **Population exposed to the medicine:** The target audience and size of its population is a risk determinant that has been considered in this analysis. The larger the population that is exposed to the medicine, the higher the number of casualties from an associated risk event. In this document, higher risk is attributed to medicines that are used for treatment in larger populations. In the context of this document, all medicines used for management of public health diseases (of which TB is one) are considered to constitute a higher risk than medicines used for treatment of nonpublic health diseases. This document also considered that medicines in the top-20 list of most used medicines in the country constitute a higher risk than other medicines.

2. **Adverse event at prolonged use:** As the length of time that a particular medicine is taken for the treatment of TB is increased, patients are at a higher risk of developing AEs that may be harmful to the body. In this document, a higher risk is allotted to all anti-TB medicines because they are used for more than 28 days—prolonged use.

ANNEX B. EXAMPLES OF RISK MANAGEMENT INTERVENTIONS

Interventions Targeting Health Care Workers

Communication Interventions

There are various means by which HCWs can be educated about medicine risks and how best to manage their patients on those medicines. Some practiced widely examples include—

- *Letter to health care providers:* "Dear doctor letters" are a useful tool used to communicate important new information related to any medicinal product to health care providers to mitigate injury from the product use. The letter covers medicine warnings and recommendations on steps to take, such as patient counseling, improving training programs on medication use, and where to report adverse reactions related to the medicine if suspected. This is a risk mitigation strategy that is widely used by developed countries.

- *Drug alerts or safety alerts:* New potential safety risks are communicated to health care providers in a timely manner through this medium. Prescribers can subscribe to alerts to keep updated on important safety information related to individual medicines and key factors to consider during treatment.

Mandating Education and Certification for Product Prescribers

Mandatory certification and recertification requirements for TB care providers may be required for products where the risk has not been reduced by use of other approaches, such as medication guides to patients and communications to health care providers. For this intervention, HCWs are required to undergo training (using the most cost-effective and sustainable approach) and receive certification for the medicine in question. In this training, the HCW may be required to demonstrate knowledge and skills in appropriate methods of treatment and care of TB patients using the product. The HCW should be able to understand the risks and benefits of using the medicine and the appropriate management of AEs to reduce the risk.

Certification of Treatment and Dispensing Facility

Depending on the product and the level of risk, certain facilities may be certified to treat patients with the product (for example, MDR-TB treatment may be done only in certain facilities). The certification will require training the HCW about the risks and the requirements for treatment and dispensing of that particular medicine in his or her facility. Certain measures may be put in place to achieve this, such as supplying medicines only to approved facilities, or requiring a preauthorization from a central, subdistrict, or health facility committee that will

approve use of the medicine for treatment. However, the latter approach will require additional monitoring to ensure that nonapproved patients are not started on treatment without prior authorization. Examples of other approaches include dispensing medicines only from certain enrolled prescribers, or requiring additional documentation from prescribers prior to dispensing proving that the patient meets requirement for treatment with that medicine.

Routine Laboratory Monitoring

Laboratory monitoring for patients is required for some anti-TB medicines to support proper management of AEs. These monitoring requirements are sometimes part of standard treatment guidelines and the HCWs receive training, but this is not always done. As a risk management intervention, trained dispensers may be required to see laboratory tests before dispensing particular medicines. They should have the knowledge to evaluate whether the values fall within the safe range before dispensing the medicine to the patient.

Drug Toxicity Charting Tools

These tools can be manual charts or computerized monitoring systems for tracking incidences of toxicities. Drug toxicity charting tools are used to match adverse events against offending medicines. An example is ototoxicity caused by aminoglycosides and ophthalmic toxicity by ethambutol. Additional information on steps to mitigate these toxicities may be described in a chart, for example, Snellen chart for visual acuity and color vision tests for severe reversible or irreversible damage to the eyes related to ethambutol; and a baseline audiometric test for aminoglycoside performed within 72 hours of treatment onset and then regularly throughout treatment.

Patient Adherence Interventions and Tools

Adherence to instructions on proper medicine use and effects is a key factor in ensuring treatment success and improved treatment outcomes. Some examples of approaches that can be used to improve adherence include—

- *Directly observed therapy (DOT):* This is an intervention recommended by WHO as part of the DOTS strategy and widely implemented in many countries. In this approach, the patient is observed by the HCW or caregiver when taking his or her medicines. This approach is implemented during the intensive phase of TB treatment. Studies show 86 to 90 percent success in patients completing treatment with DOT compared with 61 percent for those patients self-administering medicines.[55] This method has been shown to decrease the risk of drug resistance associated with incomplete treatment and the chances of treatment failure and relapse.

- *Patient reminder tools:* SMS (text message) messaging is used to alert patients of refilling and dispensing time to encourage patient adherence to treatment. Some existing examples that could be adapted are SIMpill (http://www.simpill.com/) and X Out TB (http://healthmarketinnovations.org/program/x-out-tb), which have been

effective in promoting patient adherence and preventing the development of drug resistance.

Templates and Information on Reporting Adverse Events

Documentation of anti-TB medicine–related AEs is useful only when the information is used by health authorities to guide decision making related to patient safety. Prescribers should have standardized templates or forms and information on the process for reporting suspected AEs (spontaneous reporting) to the pharmacovigilance unit or central level when they occur. Adverse events can also be closely monitored and reported (active surveillance) by the HCW to support effective decisions about patient safety.

Strengthening Quality Assurance Measures

The quality of medicines dispensed to patients is important because it can affect treatment outcomes. Poor quality medicines can lead to AEs, treatment failures, drug resistance, or even death. To assure the quality of medicines, WHO established a prequalification program for medicines; however, this process is not 100 percent efficient. Countries also procure anti-TB medicines from non-WHO-prequalified suppliers, and the integrity of medicines may be affected during storage and distribution in the country. Countries still need to perform quality control and quality assurance tests and equip their national testing laboratories where available to carry out this function. A postmarketing surveillance quality test is an example of an approach that can be undertaken to ensure that medicines in the supply chain are of good quality and safe to patients. The approach involves undertaking random testing of anti-TB medicine samples and determining where in the supply chain the integrity of the medicine was compromised. This approach can also help in the detection of counterfeit or substandard medicines, particularly in the private sector.

Packaging and Labeling at Dispensing Facilities

The type of package and labels for dispensing medicines to patients can be useful in enhancing patient safety. Many medications are packaged in containers with similar shapes and sizes. Changing the medicine's appearance, such as the selection of different colors for labeling, can help patients in distinguishing and identifying the appropriate medication, thereby avoiding medicine mix-up. The packaging labels must include the written order exactly as prescribed to avoid errors in administration that may pose harm to patients and be supplied in tamper-resistant packages to minimize the risk of accidental use in children.

Medication Storage

It is necessary to store and stock medications in a manner that reduces unintended errors. Storage areas should be able to accommodate medicines, and they should be stored under appropriate conditions to maintain their quality. There should be a process for reviewing and separating expired, recalled, and short-dated products so they are not dispensed to patients. A drug-expiry monitoring tool could be kept to support regular monitoring of medicine expiry dates. This tool could be either manual or electronic.

Interventions Targeting Patients

A Medication Guide or Patient Package Insert (PPI)

These are used when the information on the medicine label can affect AEs and patients' decisions to use the medicine. The Medication Guides and PPIs can also be given when the effectiveness of the medicine depends on the directions for use, because they contain written information on potential side effects to help patients make informed decisions about their treatment, instructions on product use to improve use and effectiveness of treatment, and information that can help prevent serious AEs. Both medication guides and PPIs are given to patients at the time of dispensing.

Patient Counseling

Patients should be counseled when they start treatment and every time their anti-TB treatment is refilled to give them important information about their medicines. Patient counseling should include information on the medicine's risks, benefits, and safe administration; the importance of continuing the medicine and not skipping doses; not sharing prescribed medicines; steps to avoid overdosing; and importance of reviewing the medication guide provided. For effective outcomes, counseling communication should be tailored to the audience; language barriers and education levels should be considered when developing counseling messages.

Outreach/Advocacy Programs

Some patients who have successfully completed their TB treatment and are considered cured can be used as advocates to educate other patients suffering from TB. These advocates can provide the support group that other patients need to alleviate their concerns about the AEs they are experiencing and the importance of adhering to their treatments.

Patient-Oriented Risk Communication

Promotional materials can educate patients on the risks and benefits of the medicines they are taking. Examples of approaches that have been implemented in countries include printed educational flyers; posters; media communication (TV, radio); outdoor placards, billboards, and signs; and in some countries, the Internet. These tools should be simplified for easy understanding by the local population to increase the effectiveness of the message.

Incentives to Promote Adherence

Providing incentives to patients, such as nutritional supplements, food, and acknowledgments, is an approach that can be used for improving adherence to treatment. A pilot study conducted by Lorvick et al. to test adherence to a six-month course of community-based directly observed preventive therapy showed an 89 percent completion rate and adherence to therapy among study participants.[56]

ANNEX C. PEDIATRIC SECOND-LINE TB MEDICINE DOSING AND ADMINISTRATION

Drug	Available dosage forms[1]	Pediatric dosing[3]	Recommended number of tablets based on weight (kg)[4,5,6]		Maximum daily dose[3,4]	Administration
Injectables						
Kanamycin	1 g/4 mL injectable solution	15–30 mg/kg QD	Not applicable		1,000 mg	
Amikacin	500 mg/2 mL injectable solution	15–22.5 mg/kg QD	Not applicable		1,000 mg	
Capreomycin	1 g powder for injection	15–30 mg/kg QD	Not applicable		1,000 mg	
Fluoroquinolones						
Levofloxacin	250 mg scored tablet	7.5–10 mg/kg QD	1–3	Not recommended	750 mg	Tablet can be taken with or without food. Antacids containing magnesium, aluminum, sucralfate, metal cations (iron), and multivitamins with zinc or didanosine should be taken at least two hours before or two hours after administration.[7]
			3–4.9	Not recommended		
			5–6.9	0.25 tablet (62.5 mg)		
			7–9.9	0.25–0.5 tablet (62.5–125 mg)		
			10–13.9	0.5 tablet (125 mg)		
			14–19.9	0.5–0.75 tablet (125–187.5 mg)		
			20–29.9	1 tablet (250 mg)		
			30–39.9	1.25 tablets (312.5 mg)		
			>40	1.5 tablets (375 mg)		

Drug	Available dosage forms[1]	Pediatric dosing[3]	Recommended number of tablets based on weight (kg)[4,5,6]			Maximum daily dose[3,4]	Administration
Moxifloxacin	400 mg film-coated tablet	7.5–10 mg/kg QD	1–3	Not recommended		400 mg	Moxifloxacin can be taken with or without food, but the tablets cannot be crushed or chewed. Antacids, antiretroviral drugs, and other preparations containing magnesium or aluminum, sucralfate, and agents containing iron or zinc should be administered at least four hours before or two hours after ingestion of oral dose.[8]
			3–4.9	Not recommended			
			5–6.9	Not recommended			
			7–9.9	Not recommended			
			10–13.9	0.25 tablet (100 mg)			
			14–19.9	0.5 tablet (200 mg)			
			20–29.9	0.5 tablet (200 mg)			
			30–39.9	0.75 tablet (300 mg)			
			>40	1 tablet (400 mg)			
Ofloxacin	200 mg scored tablet; 400 mg scored tablet	15–20 mg/kg BID		**200 mg**	**400 mg**	800 mg	Ofloxacin can be taken with or without food. Mineral supplements; vitamins with iron or minerals; calcium-, aluminum-, or magnesium-based antacids; sucralfate; or didanosine should not be taken within the two-hour period before or within the two-hour period after taking ofloxacin.[9]
			1–3	Not recom-mended	Not recom-mended		
			3–4.9	0.5 tablet (100 mg)	0.25 tablet (100 mg)		
			5–6.9	0.5 tablet (100 mg)	0.25 tablet (100 mg)		
			7–9.9	0.75–1 tablet (150–200 mg)	0.5 tablet (200 mg)		
			10–13.9	1 tablet (200 mg)	0.5 tablet (200 mg)		
			14–19.9	1.5 tablets (300 mg)	0.75 tablet (300 mg)		
			20–29.9	2 tablets (400 mg)	1 tablet (400 mg)		
			30–39.9	2.5–3 tablets (500–600 mg)	1.5 tablets (600 mg)		
			>40	4 tablets (800 mg)	2 tablets (800 mg)		

Drug	Available dosage forms[1]	Pediatric dosing[3]	Recommended number of tablets based on weight (kg)[4,5,6]			Maximum daily dose[3,4]	Administration
Bacteriostatics							
Ethionamide	250 mg scored tablet	15–20 mg/kg BID	1–3	Not recommended		1,000 mg	If ethionamide tablet is unscored, and the child needs a partial dose, the tablet can be frozen and then broken into smaller pieces in a small plastic bag. The fragments can be used over several doses to get an accurate dose in over the course of several doses.[6]
			3–4.9	0.25 tablet (62.5 mg)			
			5–6.9	0.5 tablet (125 mg)			
			7–9.9	0.5–0.75 tablet (125–187.5 mg)			
			10–13.9	1 tablet (250 mg)			
			14–19.9	1–1.5 tablet (250–375 mg)			
			20–29.9	1.5–2 tablets (375–500 mg)			
			30–39.9	2.5 tablets (625 mg)			
			>40	3 tablets (750 mg)			
Prothionamide	250 mg scored tablet	15–20 mg/kg BID	1–3	Not recommended		1,000 mg	
			3–4.9	0.25 tablet (62.5 mg)			
			5–6.9	0.5 tablet (125 mg)			
			7–9.9	0.5–0.75 tablet (125–187.5 mg)			
			10–13.9	1 tablet (250 mg)			
			14–19.9	1–1.5 tablet (250–375 mg)			
			20–29.9	1.5 – 2 tablets (375 – 500 mg)			
			30–39.9	2.5 tablets (625 mg)			
			>40	3 tablets (750 mg)			
Cycloserine	250 mg hard capsule	10–20 mg/kg QD or BID		**250 mg capsule**	**250 mg capsule in 10 mL water**	1,000 mg	Capsule can be broken and sprinkled on food or dissolved in 10 mL of water.[4]
			1–3	Not recom-mended	Not recom-mended		
			3–4.9	0.25 capsule (62.5 mg)	2.5 mL		
			5–6.9	0.5 capsule (125 mg)	5 mL		
			7–9.9	0.5–0.75 capsule (125–187.5 mg)	5–7.5 mL		

Drug	Available dosage forms[1]	Pediatric dosing[3]	Recommended number of tablets based on weight (kg)[4,5,6]			Maximum daily dose[3,4]	Administration
			10–13.9	0.75–1 capsule (187.5–250 mg)	7.5–10 mL		
			14–19.9	1–1.5 capsules (250–375 mg)	—		
			20–29.9	1.5–2 capsules (375–500 mg)	—		
			30–39.9	2.5 capsules (625 mg)	—		
			>40	3 capsules (750 mg)	—		
Terizidone	250 mg hard capsule	10–20 mg/kg QD		**250 mg capsule**	**250 mg capsule in 10 mL water**	1,000 mg	Capsule can be broken and sprinkled on food or dissolved in 10 mL of water.[4]
			1–3	Not recom-mended	Not recom-mended		
			3–4.9	0.25 capsule (62.5 mg)	2.5 mL		
			5–6.9	0.5 capsule (125 mg)	5 mL		
			7–9.9	0.5–0.75 capsule (125–187.5 mg)	5–7.5 mL		
			10–13.9	0.75–1 capsule (187.5–250 mg)	7.5–10 mL		
			14–19.9	1–1.5 capsules (250–375 mg)	—		
			20–29.9	1.5–2 capsules (375–500 mg)	—		
			30–39.9	2.5 capsules (625 mg)	—		
			>40	3 capsules (750 mg)	—		

Drug	Available dosage forms[1]	Pediatric dosing[3]	Recommended number of tablets based on weight (kg)[4,5,6]			Maximum daily dose[3,4]	Administration
P-aminosalicylic acid	4 g enteric-coated delayed-release granules in sachets	200–300 mg/kg/day[4]		**QD**	**BID**	12 g	Packet can be cut to approximate dose needed. Granules can be sprinkled on top of or mixed into small amount of soft food. Can give with acidic foods to enhance absorption.[6]
			1–2	Not recom-mended	Not recom-mended		
			3	0.75 sachet (750 mg)	0.25 and 0.75 sachets (250 and 750 mg)		
			4–5	1 sachet (1,000 mg)	0.5 sachet (500 mg)		
			6	1.5 sachets (1,500 mg)	0.75 sachet (750 mg)		
			7–8	2 sachets (2,000 mg)	1 sachet (1,000 mg)		
			9–10	2.5 sachets (2,500 mg)	1.25 sachet (1,250 mg)		
			11–13	3 sachets (3,000 mg)	1.5 sachet (1,500 mg)		
			14–16	4 sachets (4,000 mg)	2 sachets (2,000 mg)		
			17–20	5 sachets (5,000 mg)	2.5 sachets (2,500 mg)		
			2–24	6 sachets (6,000 mg)	3 sachets (3,000 mg)		
			25–28	7 sachets (7,000 mg)	3.5 sachets (3,500 mg)		
			29–30	8 sachets (8,000 mg)	4 sachets (4,000 mg)		
Miscellaneous agents							
Clofazimine	100 mg capsule	1 mg/kg QD[4]				200 mg	
Linezolid	600 mg film coated tablet[2]	10 mg/kg TID[4]				600 mg	

Drug	Available dosage forms[1]	Pediatric dosing[3]	Recommended number of tablets based on weight (kg)[4,5,6]	Maximum daily dose[3,4]	Administration
Amoxicillin/ clavulanate	500/125 mg coated tablet; 875/125 mg coated tablet	80 mg/kg/day divided BID[4]		4,000 mg amoxicillin; 500 mg clavulanate	
Clarithromycin	250 mg film-coated tablet; 500 mg tablet	7.5 mg/kg BID[4]		1,000 mg	Extended-release tablets cannot be crushed, broken, or chewed and should be taken with food.[10]

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ANNEX D. FREQUENCY OF ADVERSE EVENT OCCURRENCE IN TB PATIENTS

A: Adverse Events in the Treatment of Multidrug-Resistant Tuberculosis: Tesults from the DOTS-Plus Initiative

Citation: Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. *Int J Tuberc Lung Dis* 2004;8;1382–84.

Background: Adverse events associated with second-line drugs have been mentioned as obstacles in the management of MDR-TB. Data on AEs were collected from five DOTS-Plus sites in Estonia, Latvia, Peru (Lima), the Philippines (Manila), and the Russian Federation (Tomsk Oblast). The results show that among 818 patients enrolled on MDR-TB treatment, only 2 percent of patients stopped treatment, but 30 percent required removal of the suspected drug(s) from the regimen because of AEs.

Table A: Frequency of adverse events and suspected agents among 818 patients receiving MDR-TB treatment in Estonia, Latvia, Peru (Lima), the Philippines (Manila), and the Russian Federation (Tomsk Oblast)

Adverse event*	Suspected agent(s)†	Affected n (%)
Nausea/vomiting	PAS, TM, FQ	268 (32.8)
Diarrhea	PAS, TM	173 (21.1)
Arthralgia	FQ, TM, CS, AG	134 (16.4)
Dizziness/vertigo	CS, CM, AG, FQ	117 (14.3)
Hearing disturbances	CM, TM, AG	98 (12.0)
Headache	CS, FQ	96 (11.7)
Sleep disturbances	CS, FQ	95 (11.6)
Electrolyte disturbances	CM, TM	94 (11.5)
Abdominal pain	PAS, TM	88 (10.8)
Anorexia	PAS, TM	75 (9.2)
Gastritis	TM, PAS	70 (8.6)
Peripheral neuropathy	TM, AG, CS	65 (7.9)
Depression	CS	51 (6.2)
Tinnitus	CM, CS, AG	42 (5.1)
Allergic reaction	FQ	42 (5.1)
Rash	FQ, PAS	38 (4.6)
Visual disturbances	CS, TM	36 (4.4)
Seizures	CS	33 (4.0)
Hypothyroidism	TM, PAS	29 (3.5)

Psychosis	CS	28 (3.4)
Hepatitis	TM	18 (2.2)
Renal failure/nephrotoxicity	AG, CM	9 (1.2)

*Adverse events occurring in at least two projects and in more than 1 percent of the sample population are listed.

† To ensure consistency, only drugs suspected in at least two projects for a particular adverse event are presented.

PAS = para-aminosalicylic acid; TM = thioamides; FQ = fluoroquinolones; CS = cycloserine; AG = aminoglycosides; CM = capreomycin.

B: Adverse Events Related to MDR-TB Treatment, Latvia, 2000–2004

Citation: Bloss E, Kuks L, Holtz TH, Riekstina V, Skripconoka V, Kammerer S, Leimane V. Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000–2004. *Int J Tuberc Lung Dis* 2010;14:275–81.

Setting: Latvia has one of the highest rates of MDR-TB globally. Clinical management of MDR-TB requires lengthy multidrug regimens that often cause AEs.

Design: We retrospectively reviewed records of patients who began MDR-TB treatment between 2000 and 2004. Treatment-related AEs and factors associated with experiencing AEs were evaluated. We also examined the frequency of and reasons for changing drug regimens.

Table B: Frequency of MDR-TB cases with specific adverse event and definitions of adverse events (*N* = 1,027)

Adverse event	Frequency of event (%)	Definition
Nausea	598 (58.2)	Persistent nausea, causing anorexia or loss of appetite as reported by patient
Vomiting	402 (39.1)	Vomiting, ranging from mild (treated with anti-emetic) to moderate (treatable by adjusting treatment or with anti-emetic and/or proton pump inhibitors) to severe (uncontrolled vomiting with dehydration, requiring stopping treatment)
Abdominal pain	246 (23.9)	Patient complaint of pain associated with gastritis or abdominal gas
Dizziness	241 (23.5)	Patient complaint of dizziness or balance disturbances
Diarrhea	209 (20.4)	Watery bowel movements more than four times per day
Hearing loss	195 (19.0)	Hearing loss confirmed by audiometry
Arthralgia	138 (13.4)	Elevated uric acid or presence of joint pain, stiffness or swelling as reported by patient
Psychiatric	136 (13.2)	Presence of depression, anxiety and/or psychosis, as diagnosed by TB physician or by a psychiatrist
Tinnitus	124 (12.1)	Persistent ringing in the ears based on patient report
Hematologic	111 (10.8)	Anemia as measured by low hemoglobin levels, g/dL
Headache	98 (9.5)	Any patient report of headache
Vestibular	92 (9.0)	Balance and vestibular disturbances as diagnosed by neurologist
Hepatitis	91 (8.9)	Elevation of serum transaminases or serum bilirubin at least five times the upper limit of normal levels*

Itching	89 (8.7)	Patient report of pruritus
Skin rash	88 (8.6)	Signs of rash or dermatological reaction related to medication
Neuropathy	84 (8.2)	Symptoms and findings consistent with neuropathy as reported by patient and diagnosed by neurologist (e.g., numbness, tingling or pain in extremities)
Convulsions	50 (4.9)	Event consistent with seizure either reported by patient or witnessed by medical staff
Renal failure	44 (4.3)	Decrease of creatinine clearance <50 ml/min and elevation of at least one value of creatinine >141 mmol/L
Visual impairment	33 (3.2)	Presence of visual changes, including vision loss, pain on moving the eye, loss of color vision or presence of optic neuritis as reported by the patient and confirmed by an ophthalmologist
Electrolyte imbalance	29 (2.8)	At least one measure of serum potassium value of <3.5 mEq/L S (hypokalemia)
Hyperurecemia	29 (2.8)	At least one value of elevated uric acid level in blood serum*
Dermatitis	21 (2.0)	Severe skin inflammation as diagnosed by dermatologist
Hypothyroidism	8 (0.8)	At least one measure of serum thyroid stimulating hormone >10 IU/mL
Jaundice	5 (0.5)	Yellow discoloration of the skin, conjunctival membranes and other mucous membranes

* Normal range: AST (0.45–0.68 mmol/L), ALT (0.45–0.68 mmol/L), bilirubin (7.5–20.5 mEq/L), uric acid (125–488 µmol/L).
IU = International Unit; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

C: Adverse Events Associated with the Treatment of MDR-TB

Citation: Torun T, Gungor G, Ozmen I, Bolukbasi Y, Maden E, Bicakci B, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005;9:1383–77.

Setting: Süreyyapa a Centre for Chest Diseases and Thoracic Surgery, Istanbul, Turkey.

Objective: To report the frequency of treatment side effects in cases of MDR-TB.

Design: A retrospective review of the medical records of 263 patients who received individualized treatment for MDR-TB between April 1992 and June 2004.

Table C: Adverse Events of Anti-TB Medicines

Side effects	Patients experiencing each effect *n* (%)	Minor effects: do not need to withdraw the medicine *n* (%)	Major effects: needed to withdraw the medicine *n* (%)	Mean interval from start of therapy to withdrawal of any medicine from treatment month (±SD)
Ototoxicity	110 (41.8)	—	110 (41.8)	4.7 ± 1.7
Psychiatric	56 (21.3)	32 (12.1)	24 (9.1)	7.0 ± 5.1
Gastrointestinal disturbance	37 (14.0)	31 (11.7)	6 (2.3)	8.6 ± 7.5
Arthralgia/arthritis	30 (11.4)	30 (11.4)	—	—
Central nervous system	26 (9.9)	18 (6.8)	8 (3)	8.1 ± 9.1

Hepatitis	12 (4.5)	4 (1.5)	8 (3)	8.2 ± 5.7
Dermatological effects	12 (4.5)	12 (4.5)	—	—
Leukopenia	7 (2.6)	—	7 (2.6)	3.5 ± 3.9
Peripheral neuropathy	8 (3)	4 (1.5)	4 (1.5)	3.2 ± 2.2
Renal toxicity	2 (0.7)	—	2 (0.7)	3 ± 1.4
Hypothyroidism	3 (1.1)	3 (1.1)	—	—

SD = standard deviation.

D: Treatment and Outcome Analysis of 205 Patients with MDR-TB

Citation: Chan ED, Laurel V, Strand MJ, Chan JF, Huynh MLN, Goble M, et al. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2004;169:1103–9.

Background: MDR-TB, a disease caused by *Mycobacterium tuberculosis* strains that are resistant at least to rifampin and isoniazid, entails extended treatment, expensive and toxic regimens, and higher rates of treatment failure and death. We retrospectively analyzed the outcomes in 205 patients treated at our center for MDR-TB, with strains resistant to a median of six medicines, and compared the results with those of our previous series.

Table D: Discontinuation rates for antituberculosis medicines

Medicine*	Number discontinued/ Number given medicine (%)	Top reasons for discontinuation (number affected)
Rifabutin	4/15 (27)	Low white blood cell count (2)
Streptomycin	31/129 (24)	Ototoxicity (18), paresthesias (3), rash (3)
Ethionamide	28/169 (17)	Nausea (8), hepatotoxicity (5), anorexia (3)
Kanamycin	14/105 (13)	Ototoxicity (9)
Amikacin	9/70 (13)	Ototoxicity (8)
Cycloserine	21/183 (11)	Psychosis, aggression, depression or suicidal thoughts (15), nausea (2)
Capreomycin	15/139 (11)	Ototoxicity (4), nephrotoxicity (3), nausea (2), rash (2)
Para-aminosalicylic acid	15/151 (10)	Diarrhea (6), nausea (4)
Isoniazid	18/191 (9)	Hepatotoxicity (8), fever (3), nausea (2)
Pyrazinamide	17/193 (9)	Hepatotoxicity (8), nausea (3), arthralgias (2)
Ciprofloxacin	8/99 (8)	Nausea (2)
Rifampin	14/188 (7)	Hepatotoxicity (8), nausea (3), rash (2)
Clofazamine	4/58 (7)	Abdominal pain (2)
Clarithromycin	1/17 (6)	Nephrotoxicity (1)
Ethambutol	10/195 (5)	Hepatotoxicity (3), rash (2), vision (2)
Ofloxacin	3/124 (2)	Nausea (2)

In contrast to the prior National Jewish Medical and Research Center (NJMRC) study, in which the denominator included only those individuals who were prescribed the medicines there, the denominators shown here included medicines administered from both past and NJMRC regimens.

* Additional medicines not tabled because few persons received them are as follows: of two patients who received azithromycin, one discontinued it because of anorexia; of two patients who received sparfloxacin, one discontinued it because of myalgias and arthralgias; of nine patients who were treated with levofloxacin, there were no untoward adverse event to warrant discontinuation.

E: Treatment of 171 Patients with Pulmonary Tuberculosis Resistant to Isoniazid and Rifampin

Citation: Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh CR, Jr. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med* 1993;328:527–32.

Background and Methods: The frequency of infection with multidrug-resistant *Mycobacterium tuberculosis* is increasing. We reviewed the clinical courses of 171 patients with pulmonary disease due to *M. tuberculosis* resistant to rifampin and isoniazid who were referred to our hospital between 1973 and 1983. The patients' records were analyzed retrospectively. Their regimens were selected individually and preferably included three medications that they had not been given previously and to which the strain was fully susceptible.

Table E: Anti-TB medicine toxicity leading to withdrawal of treatment

Medicine	No. with reaction/No. given Medicine (%)	Reaction (No. affected)*
Amikacin	2/6 (33)	Hearing loss (1) Renal dysfunction (1)
Capreomycin	11/108 (10)	Renal dysfunction (5) Hearing loss (3) Vertigo, early (1) Rash (1) Vasculitis (1)
Kanamycin	12/70 (17)	Renal dysfunction (1) Hearing loss, early in 1 (9) Vertigo, early (1)
Streptomycin	0/16	
Viomycin	3/14 (21)	Renal dysfunction (1) Rash (1) Itching, early (1)
Clofazimine	2/17 (12)	Liver dysfunction (1) Abdominal pain (1)
Cycloserine	8/98 (8)	Myoclonic seizures (1) † Neurologic symptoms, early (1) Depression, early in 2 (5) Nightmares (1)
Ethambutol	1/62 (2)	Visual problems (1)
Ethionamide	10/126 (8)	Liver dysfunction, early in 2 (3) Gastrointestinal upset, early in 2 (4) Gynecomastia (1) Arthritis (1) Fever, early (1)
Isoniazid	3/45 (7)	Liver dysfunction, early (2) Joint effusion, early (1)
Aminosalicyclic acid	7/50 (14)	Gastrointestinal upset, early in 1(5) Rash (1) Fever, early (1)
Pyrazinamide	10/101 (10)	Liver dysfunction, early in 3 (8) Gastrointestinal upset (1) Gout (1)
Rifampin	2/22 (9)	Gastrointestinal upset, early (2)

*"Early" denotes occurrence of reaction within three months after the beginning of treatment.

† This patient also had alcoholism

F: DrugCite; AE Reports Submitted to the FDA

Citation: DrugCite, accessed on August 13, 2013, from: http://www.drugcite.com

Background: The table below shows the top five AEs reported to the FDA for each drug indicated, as well as related generic and/or brand-name drugs containing the same primary active ingredients, from Q1 2004 to Q3 2012. Adverse events are counted if the drug is flagged as a *suspect* drug causing the AE. **For each AE listed, percent (%) represents percentage of the AE to all AEs reported for the drug. Percent does not represent a rate related to drug use.**

Note: The following drugs were **not** included in DrugCite: capreomycin, kanamycin, p-aminosalicylic acid, prothionamide, terizidone, thioacetazone.

Medicine name	Adverse event	Count	Percent (of all reported AEs for the drug)
Amikacin	Drug rash with eosinophilia and systemic symptoms	60	1.64%
	Renal failure acute	57	1.56%
	Pyrexia	55	1.51%
	Renal failure	50	1.37%
	Acute respiratory distress syndrome	49	1.34%
Amoxicillin	Pruritus	1,200	1.81%
	Diarrhea	1,153	1.74%
	Pyrexia	1,130	1.70%
	Rash	1,099	1.65%
	Vomiting	845	1.27%
Ciprofloxacin	Arthralgia	941	1.66%
	Tendon rupture	715	1.26%
	Pain in extremity	714	1.26%
	Tendonitis	678	1.19%
	Pyrexia	627	1.10%
Clarithromycin	Drug interaction	1,040	4.14%
	Pyrexia	439	1.75%
	Diarrhea	348	1.39%
	Dyspnea	311	1.24%
	Vomiting	274	1.09%
Clofazamine	Drug ineffective	13	2.28%
	Diabetes mellitus	11	1.93%
	Hemoglobin decreased	11	1.93%
	Peptic ulcer perforation	11	1.93%
	Peritonitis	10	1.76%
Cycloserine	Hypothyroidism	10	3.44%
	Visual acuity reduced	10	3.44%
	Abdominal pain upper	9	3.09%
	Hepatic failure	9	3.09%
	Lactic acidosis	9	3.09%

Medicine name	Adverse event	Count	Percent (of all reported AEs for the drug)
Ethambutol	Pyrexia	122	2.49%
	Immune reconstitution syndrome	86	1.76%
	Drug rash with eosinophilia and systemic symptoms	59	1.21%
	Drug interaction	55	1.12%
	Vomiting	55	1.12%
Ethionamide	Hypothyroidism	8	2.99%
	Abdominal pain upper	7	2.61%
	Hepatic failure	7	2.61%
	Lactic acidosis	7	2.61%
	Pericarditis tuberculous	7	2.61%
Gatifloxacin	Hypoglycemia	188	11.01%
	Hyperglycemia	95	5.56%
	Blood glucose increased	37	2.17%
	Diarrhea	37	2.17%
	Blood glucose decreased	25	1.46%
Imipenem	Pyrexia	40	1.99%
	Convulsion	29	1.44%
	Renal failure acute	29	1.44%
	Pneumonia	26	1.29%
	Septic shock	25	1.25%
Isoniazid	Pyrexia	168	2.09%
	Jaundice	114	1.42%
	Hepatitis	107	1.33%
	Alanine aminotransferase increased	100	1.25%
	Nausea	96	1.20%
	Vomiting	95	1.18%
Levofloxacin	Drug interaction	204	1.39%
	Pyrexia	185	1.26%
	Tendon rupture	174	1.18%
	Arthralgia	172	1.17%
	Tendonitis	158	1.07%
Linezolid	Thrombocytopenia	178	3.79%
	Serotonin syndrome	155	3.30%
	Drug interaction	154	3.28%
	Anemia	99	2.11%
	Pancytopenia	85	1.81%
Moxifloxacin	Anaphylactic reaction	1,206	2.27%
	Dyspnea	1,151	2.17%
	Dizziness	1,096	2.06%
	Rash	1,048	1.97%
	Hypersensitivity	1,015	1.91%

Medicine name	Adverse event	Count	Percent (of all reported AEs for the drug)
Ofloxacin	Pyrexia	62	1.62%
	Drug interaction	56	1.46%
	Drug rash with eosinophilia and systemic symptoms	56	1.46%
	Corneal deposits	44	1.15%
	Thrombocytopenia	44	1.15%
Pyrazinamide	Hepatitis	89	2.42%
	Pyrexia	80	2.18%
	Acute hepatic failure	74	2.02%
	Jaundice	62	1.69%
	Alanine aminotransferase increased	51	1.39%
Rifabutin	Pyrexia	37	2.98%
	Uveitis	37	2.98%
	Diarrhea	22	1.77%
	Neutropenia	22	1.77%
	Decreased appetite	21	1.69%
	Thrombocytopenia	21	1.69%
Rifampicin	Drug interaction	186	2.73%
	Pyrexia	173	2.54%
	Vomiting	84	1.23%
	Jaundice	78	1.15%
	Nausea	77	1.13%
Streptomycin	Pyrexia	23	3.55%
	Immune reconstitution syndrome	13	2.01%
	Rash	13	2.01%
	Respiratory failure	11	1.70%
	Drug rash with eosinophilia and systemic symptoms	10	1.55%

ANNEX E. PATIENT RISK AWARENESS TOOLS

Does your body feel like this...

Tingling in your toes, your feet, your legs or arms?

No feeling in your hands, feet, legs and arms?

You can't walk and you feel like you are falling?

TALK TO YOUR HEALTH WORKER.

USAID FROM THE AMERICAN PEOPLE

SIAPS Systems for Improved Access to Pharmaceuticals and Services

Do You Feel...

Excited? Bothered? Angry? Confused? Sad?

Do you think about hurting yourself?

Are you tired all the time?

Is your body feeling weak, scratchy, burning, shaky?

Can you sleep at night?

Do you see things that others cannot see?

TALK TO YOUR HEALTH WORKER.
DO NOT DRINK ALCOHOL.

USAID
FROM THE AMERICAN PEOPLE

SIAPS
Systems for Improved Access to Pharmaceuticals and Services

Do You...

Feel pain in your stomach?

Not want to eat?

Want to throw up?

Need to use the toilet too often?

ALWAYS TAKE YOUR PILLS WITH FOOD.

If you don't feel better,
TALK TO YOUR HEALTH WORKER.

USAID FROM THE AMERICAN PEOPLE

SIAPS Systems for Improved Access to Pharmaceuticals and Services

NOTES

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