Adopting the Pharmacovigilance Monitoring System for the Philippines National Tuberculosis Program

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BACKGROUND

Drug-resistant tuberculosis (DR-TB) is a major threat to global health. The World Health Organization (WHO) estimated that, in 2015, about 480,000 people developed multidrug-resistant TB (MDR-TB) in the world, and that an additional 100,000 people with rifampicin-resistant TB were newly eligible for MDR-TB treatment. Furthermore, an estimated 9.5% of these cases were extensively drug-resistant TB (XDR-TB).[1] Currently, MDR-TB patients require daily treatment for 18 months or more with medicines that are usually more toxic and less effective than those used to treat drug-susceptible TB. This created the need for shorter and more effective treatment for latent TB infection to prevent the emergence of disease in and transmission from the estimated 1 billion people infected with TB in the world today.[2]

Over the past 10 years, much progress has been made in research and development of new drugs for TB. Specifically, two novel drugs, bedaquiline (BDQ) and delamanid for the treatment of MDR-TB, have been approved as part of combination therapy for adults with pulmonary TB when other alternatives are not available. Also, novel drug combinations to treat drug sensitive and/or DR-TB in a shorter timeframe (from 18 months down to 9 months), including new or repurposed drugs, are under investigation in a series of phase II and III trials.[3]

As with any new medicine, its safety must be closely monitored to identify and evaluate adverse effects, such as unexpected and serious adverse reactions, in the early post-marketing phase, particularly for medicines given conditional or expedited approval, as was the case with BDQ and delamanid. The purpose of the monitoring is to learn more about its safety profile and improve treatment protocols and outcomes.

Given limited knowledge about the safety of the new TB medicines and regimens, WHO recommended monitoring and evaluation, including pharmacovigilance (PV) and drug resistance surveillance.[2] Specifically, in 2012, WHO recommended that the use of shorter regimens for MDR-TB be accompanied by the collection of drug safety data within a framework of observational research. In 2013 and 2014, WHO recommended active PV as one of the five conditions to be met when using BDQ and delamanid to treat MDR-TB patients.[4]

In 2015, WHO came up with the essential requirements for active drug-safety monitoring and management (aDSM) applicable to patients on treatment with new anti-TB drugs, novel MDR-TB regimens, or XDR-TB regimens, in order to detect, manage, and report suspected or confirmed drug toxicities.[4] aDSM is intended to be an integral component of the programmatic management of drug-resistant TB (PMDT). aDSM is particularly useful for systematic collection and prompt analysis of safety data to learn more about the safety profile of new medicines in the early post-marketing phase and inform future policy on the use of these medicines. Although one of the main costs associated with active surveillance is the creation or adaption of a database, WHO highly recommends the use of an electronic tool to standardize and safe-keep data in active surveillance implementation.[5] The management of data in electronic format is indispensable and will facilitate data sharing as well as generation of indicators and analysis.[4]

PROJECT APPROACH

The Philippines, with 2.6% of its more than 286,000 new cases of TB being MDR-TB cases,[6] introduced the shorter treatment regimen (nine-month treatment regimen [9MTR]) in 2015 and BDQ in June 2016 under an operational research framework; implementation was scaled up under programmatic conditions in 2017. Delamanid had been registered in the country since September 2017. Under the operational research framework, the WHO recommended that:

- The protocol be approved by a national ethics review committee, ahead of patient enrollment
- Treatment be delivered under operational research conditions following international standards to assess the safety and effectiveness of the regimens
- Implementation be monitored by an independent monitoring board set up by and reporting to WHO

Using the PV system framework (figure 1) developed under the USAID-funded Strengthening Pharmaceutical Systems (SPS) Program, a PV structure (figure 2) was put in place to ensure active monitoring of patients enrolled in the program and facilitate systematic data collection.[7]

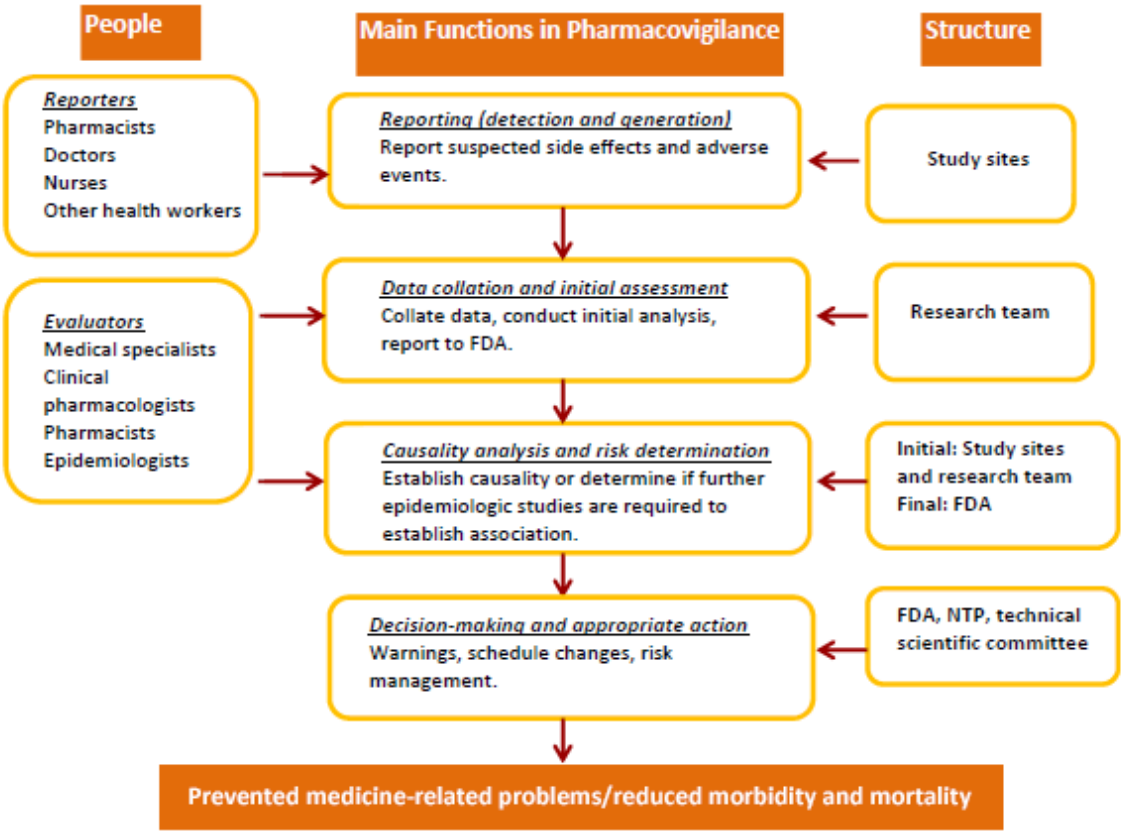
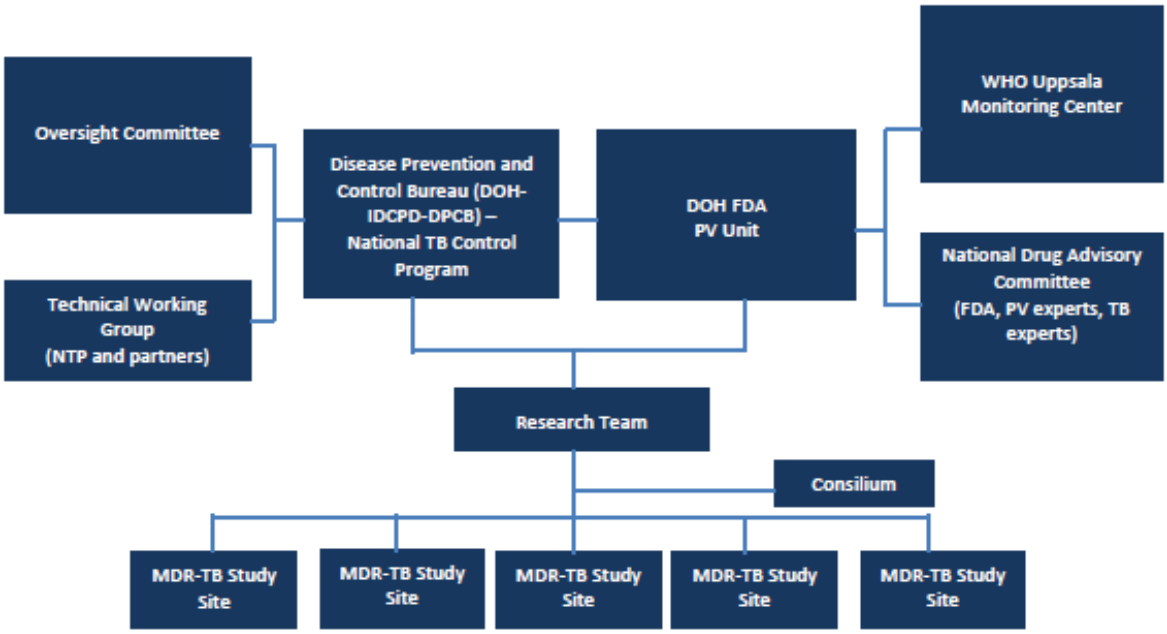


Figure 1. PV system framework[7]



Abbreviations: DOH = Department of Health; FDA = Food and Drug Administration; MDR-TB = multidrug-resistant tuberculosis; NTP = National Tuberculosis Control Program; PV = pharmacovigilance; 9MTR = 9-month MDR-TB treatment regimen; WHO = World Health Organization;

Figure 2. Structures and stakeholders involved in active PV surveillance for new medicines and novel regimens for TB under operational research[7]

PROJECT IMPLEMENTATION

The Department of Health-Pharmaceutical Division (DOH-PD) and National TB Program (NTP) in the Philippines adopted the web-based application Pharmacovigilance Monitoring System (PViMS) to ensure systematic data collection and simplify the analysis of medicine safety information.[8] PViMS is a free web tool developed by the USAID-funded Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program, implemented by Management Sciences for Health, to help clinicians, regulatory bodies, and implementing partners monitor medicine safety, specifically in resource-limited countries.[9] The SIAPS Program works to improve the availability and quality of information for decision making through the use of electronic tools combined with systems strengthening.[6, 8]

Prior to adoption of PViMS, the Lung Center of the Philippines-National Center for Pulmonary Research (LCP-NCPR), the research arm of the NTP that managed operational research, received scanned study forms through email from study sites. The data was subsequently entered into Microsoft Excel® files for data management and analysis. A total of 11 Excel files were created by LCP-NCPR, which represent the 11 study forms of the operational research. As more patients were enrolled in the program, the data became more complex and increasingly difficult to manage and analyze with Excel. Furthermore, data-entry personnel experienced difficulty in transcribing data from the scanned paper forms into the database. Recording adverse events (AEs) was not standardized. Given the number of patients receiving treatment under operational research and the number anticipated to be rolled into the programmatic phase of implementation, it became obvious that a robust electronic tool was required to collect, manage, and analyze safety data from active monitoring of patients on BDQ and 9MTR.

Through SIAPS, USAID supported the DOH-PD in implementing and operationalizing PViMS at the central and peripheral levels in the Philippines. To ensure effective implementation, SIAPS, NTP, the Food and Drug Administration (FDA), and LCP-NCPR collaboratively conducted a readiness assessment in 2016 to determine the current IT infrastructure, human resources, processes, data management, and quality control mechanisms available and to identify gaps in the PV recording and reporting of patients at the seven treatment facilities implementing the 9MTR for PMDT patients.[10] Results from the assessment were used to design the PViMS implementation plan. Data elements in PViMS were harmonized with those recommended by the WHO aDSM framework and local regulatory requirements for active safety monitoring of TB patients and new TB medicines. Furthermore, all the safety data collected by LCP-NCPR in Excel from July to December 2015 under the operational research framework were cleaned, validated, coded into medDRA,[11] and migrated to PViMS by SIAPS.

In preparation of programmatic implementation of the 9MTR and BDQ, SIAPS worked with Knowledge Management Information Technology Services (KMITS) to make PViMS interoperable with the country's national TB database. This allows seamless exchange of data between the two information systems and eliminates duplication of work. Finally, SIAPS trained key central-level staff on the clinical, reporting, publishing, and analytical functionalities of PViMS. The training was augmented with onsite mentoring visits by FDA, KMITS, LCP, and PD at 7 of the 10 implementing treatment facilities (table 1). Another important aspect was the inclusion of PViMS orientation as part of the 9MTR roll-out by NTP.

In 2017, NTP, PD, KMITS, LCP, and FDA created the *PViMS User Guide: Active Reporting of Adverse Events*[12] to further standardize the reporting of

aDSM data through PViMS. The DOH also released a department memorandum on issuing PViMS user accounts. In September 2017, SIAPS held a workshop for 63 central and regional NTP, PD, and FDA staff along with facility staff from the 10 implementing sites. During the workshop, regional coordinators from FDA, PD, and NTP in 9 regions worked collaboratively in planning programmatic implementation of standardized aDSM data recording and reporting in their respective regions.

The objectives of systematic data collection within an active drug monitoring program, such as aDSM, are to:

- Detect unknown adverse drug reactions (signals) early
- Better characterize known reactions
- Measure risk (incidence)
- Identify risk factors for important reactions so that appropriate measures can be taken to minimize the risk of harm and improve treatment outcomes[13]

PViMS is therefore expected to help the NTP achieve the stated objectives with respect to the new anti-TB medicines and novel TB treatment regimens. It will also help the Philippines comply with international standards for medicine safety monitoring and contribute to global efforts to better characterize the safety profile of these treatments.

RESULTS

PViMS has been implemented in 10 out of 94 facilities involved in the treatment of MDR-TB patients on new anti-TB medicines and/or 9MTR as of December 2017 (table 1) and in the LCP-NCPR as the 9MTR and BDQ operational research database. With implementation of PViMS, the Philippines has established the basic infrastructure for efficient safety-data collection in the NTP to ensure the new treatments are not only safe and effective, but the best possible health outcomes are attained for MDR-TB patients. Furthermore, aDSM data collected from treatment sites can be analyzed at the national level in collaboration with TB and drug safety monitoring authorities in-country to make quick evidence-based decisions to improve the safety of TB patients as recommended by WHO.[4]

Table 1. PMDT treatment facilities where PViMS is operational

Treatment facility	Location	Region
Lung Center of the Philippines	Quezon City, Metro Manila	National Capital Region
Dr. Jose N. Rodriguez Memorial Hospital	Caloocan City, Metro Manila	
Ilocos Training and Regional Medical Center	San Fernando, La Union	Region 1
Dr. Jose B. Lingad Memorial Hospital	San Fernando, Pampanga	Region 3
Batangas Medical Center	Batangas City, Batangas	Region 4A
Sorsogon Medical Mission Group Hospital	Sorsogon City, Sorsogon	Region 5
West Visayas Medical Center	Iloilo City, Iloilo	Region 7
Eversley Child Sanitarium	Cebu City, Cebu	Region 7
Zamboanga City Medical Center	Zamboanga City, Zamboanga	Region 9
Xavier University Community Health Care Center (Committee of German Doctors)	Cagayan de Oro, Misamis Oriental	Region 10

The ultimate purpose of systematic data collection within aDSM is to enable causality assessment for serious adverse events (SAEs), determine their frequency (rates), and detect signals.[4] Through PViMS, data collection, causality assessment, determining the frequency, and signal detection can be performed in a single platform. The line-listing and first review of all episodes, which is the first step in analysis of aDSM data, can be easily done in PViMS.

From January to September 2017, 1,184 patients were started on the new treatments under programmatic conditions (1,141 patients on the 9MTR and 43 patients on BDQ). Of these, 470 patients (39%) (made up of 460 patients on 9MTR and 10 patients on BDQ) were treated at 10 sites

that use PViMS; 23 of the patients treated at the 10 sites where PViMS is installed reported 32 SAEs involving 13 system organ classes from January 2017 to October 2017.

In addition, feedback from the operational research team noted the following positive results:

- Organization and encoding of reported AEs is easier using PViMS: LCP-NCPR is managing 329 9MTR and 75 BDQ patients' data; each patient had an average of 16 events and 25 clinical evaluations for the entire treatment duration
- Shorter time to prepare LCP-NCPR quarterly reports using PViMS: Previously about 15 calendar days (with no distractions) were required to complete the quarterly report (including mapping the reported SAEs to the affected system organ classes), but with PViMS it requires just 1 day
- Fewer keystrokes: Redundancies in data entry experienced with Excel, such as having to enter the patient study ID or medical record number each time there is a clinical evaluation, site visit, or event with the patient, have been eliminated
- Overview of patient's medical history: With PViMS, it is easy to view and follow a patient's medical history over time from a single page, whereas with Excel, the health workers has to look through 11 separate files

CHALLENGES AND LESSONS LEARNED

A major challenge being encountered in implementing PViMS is the slow Internet connection at the 10 sites implementing PViMS and LCP-NCPR. This makes it hard to access the website when needed, thus slowing down the pace of work. Patient demographics and treatment regimen data from the country's national TB database must be complete and updated to ensure that the data transferred to PViMS when the event occurred is accurate.

Due to the urgency of 9MTR and BDQ implementation under programmatic conditions, the drafting of policy and implementation of PViMS are being done simultaneously. Drafting of administrative policy will take longer because of multi-stakeholder involvement.

Collaboration with relevant stakeholders from the planning stage of PViMS ensured that the system complied with national regulatory requirements. Leadership is a critical success factor in PV. However, TB and drug safety monitoring authorities in-country lack sufficiently trained staff to undertake causality assessment and analyze data. In addition, there is no dedicated staff to routinely assess all reports received in PViMS in order to detect signals.

NEXT STEPS

With the planned expansion of 9MTR (known as standard shorter treatment regimen in programmatic implementation) and use of BDQ to all 163 (as of December 2017) treatment centers in the 17 regions of the country comes the need to also expand implementation of standardized aDSM data collection using PViMS. The more data that are available the better the reliability of the safety profile.[5] Plans are already underway for this. However, success will depend on availability of the following:

- A pool of trainers to train personnel at all treatment and satellite treatment centers in the expansion of PViMS use, eventually in all 17 regions
- Continuous supportive supervision and on-the-job mentoring to strengthen the capacity of staff to use PViMS
- Enhanced IT infrastructure of the DOH where PViMS is deployed to support the increase in the number of facilities that will use the software

- Periodic data quality checks in PViMS to ensure that valid data are collected so that clinical and regulatory decisions emanating from such data are also valid
- Field testing and finalizing the draft aDSM recording and reporting flow SOPs using PViMS at the central, regional, and peripheral levels

It is further envisaged that other DOH programs in the Philippines, such as malaria, HIV/AIDS, immunization, family planning, maternal and child health, and nutrition, will adopt PViMS while monitoring the safety of medicines used in these programs.

Finally, although initial steps on institutionalizing PViMS as the tool for collecting and managing drug safety data have been taken, a policy that supports PViMS implementation nationwide should be finalized and approved to strengthen the governance structure and ensure sustainability of the system.

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ABOUT SIAPS | The Systems for Improved Access to Pharmaceuticals and Services (SIAPS) program works to assure access to quality pharmaceutical products and effective pharmaceutical services through systems-strengthening approaches to achieve positive and lasting health outcomes. SIAPS is funded by the US Agency for International Development (USAID) and is implemented by Management Sciences for Health.

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