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REVIEWS

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Unfinished first-line tuberculosis treatment in primary care in Indonesia

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A – Study Design, **B** – Data Collection, **C** – Statistical Analysis, **D** – Data Interpretation, **E** – Manuscript Preparation, **F** – Literature Search, **G** – Funds Collection

Summary **Background.** Unfinished tuberculosis (TB) treatment has slowly but surely become an unexpected event in the disease's development into drug-resistant TB. Developing countries, mostly comprised of Asian and Eastern European countries, including Indonesia, have been overwhelmed in preventing drug-resistant TB outcomes and have also failed to avoid the development of this disease.
Objectives. This review discusses the current issue of an unfinished first-line TB treatment strategy in primary care in Indonesia, presenting some relevant strategies in developing countries.
Material and methods. A narrative review approach conducted on all existing evidence in selected scientific bibliographic sources. The researchers defined the keywords based on the research question as a search strategy.
Results. Scarce resources and limited access, alongside national policy on TB control and management, contribute in different ways to impede first-line TB treatment in Indonesia. Empowerment of TB patients and their families are considered the best ways to increase awareness on TB medication in a low- to middle-income setting. The role of the hospital and private practitioner networks in the treatment and management of TB patients is essential for developing active-case-finding-approach programs for TB suspects in primary care in an Indonesian setting. Contrarily, the potential misunderstandings in TB treatment have led to peculiar events affected by poor surveillance systems for TB investigation contacts to prevent TB incidences in large populations.
Conclusions. This study addressed the barrier of all stakeholders, particularly primary care, to achieve the Indonesian government's goals of TB elimination by 2030 and zero TB findings by 2050.
Key words: tuberculosis, drug resistance, Indonesia, developing countries, primary care.

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Background

Rationale

Multidrug-resistant tuberculosis (MDR-TB) has become a global social health problem, in which the disease is immune to first-line drugs, such as isoniazid and/or rifampicin [1]. MDR--TB has affected more developing countries than developed ones [2–4].

Unfinished first-line TB treatment has emerged as a large proportion of MDR-TB incidences, consisting of failure, default and relapse of TB treatment [3, 5]. Management of TB therapy on non-directly observed treatments (DOTs) at health facilities [3, 6], the lack of a gold standard of drug-susceptibility facilities for diagnosis [7, 8] and poor TB patient access to medication [5, 8–10] are the main determinant factors for MDR-TB control, which is more complex in an under-resourced country setting.

Several developing countries have been encouraging their central governments' activities and programs through the primary care policy related to this agenda [11], including any necessary efforts to prevent TB, such as bacille Calmette–Guerin (BCG) vaccination, which is still disputed [12]. Indonesia, which ranks 9th out of 27 countries in high-burden MDR-TB diseases [1], focused on this strategy by committing to a local government policy in four provinces in 2012. Previously, drug-resistant TB surveys began in 2006 in the Jawa Tengah Province, as the national TB policy resulting from the estimation of MDR-TB reached 1.8% of TB incidence and 17.1% of TB default [13]. Based on the National Action Plan on Programmatic Management of Drug Resistance Tuberculosis (*RAN*-PMDT), TB-drug resistance in Indonesia has been affected by (1) poor quality of implementation of DOTs in hospitals and any other health facilities except health centers, (2) increase in TB-HIV coinfection, (3) poor surveillance system, and (4) the lack of TB case management for TB-drug resistance facilities [14].

Objectives

This study aims to explore a developing country's strategy of unfinished first-line TB treatment in primary care. This narrative review particularly examines TB control and management in the Indonesian setting.

We examined recent literature on the current issue and prospects for the unfinished treatment of TB, with MDR-TB as a common outcome for treatment failure resulting from the government policy associated with adherence to TB therapy in numerous studies.

Material and methods

Eligibility criteria

We assemble all existing evidence relevant to TB mitigation and control in primary care in Indonesia to identify evidence gaps, all forms of literature, including published or unpublished scientific articles or government/institution reports, and other related eligible documents for review in Bahasa Indonesia or English. No publication date or publication status restrictions were imposed.

Evidence resources

In this review, we researched bibliographic sources, i.e. MEDLINE, EMBASE, CINAHL, Cochrane Library, Science Direct, ProQuest, WHO SEARO database, SCOPUS, Wiley Library, SAGE, Taylor & Francis, SpringerLink, Hindawi and Directory of Open Access Journals (DOAJ). We also researched literature not listed in the above bibliographic resources using the Indonesian Portal Indexing (IPI), and we examined recent literature on the current issue and prospects for the unfinished treatment of TB, with MDR TB as a common outcome for treatment failure of TB resulting from the government policy associated with adherence to TB therapy in numerous studies.

Search strategy

Two researchers defined the keywords based on the research question. No years of publication and language restriction were placed on the search strategy. The team researcher used the keywords to conduct the search and input the search results into the Mendeley library. Subsequently, we assessed all meta-data for each article, including the abstract and full-text, and discuss it to the meeting.

Results and discussion

Poor quality of implementation of DOTs in hospitals and in other health facilities

Insufficient implementation of DOTs, either in hospitals, public lung clinics and private health practice, has led to inadequate MDR-TB medication [15]. In 2007, assessment results of implementation of DOTs in 50 hospitals showed a default rate of TB patients reaching 10% to 20% of category 1 and 6% to 29% of category 2 (Table 1). Otherwise, the average success rate in the hospital was only at 60% out of the 85% national target, which is less for category 2 at 6.5%. Therefore, more than 90% of TB patients experiencing default in the hospital had a high risk of MDR-TB [16].

The low success rate of TB treatment was also affected by a poor case holding process that led to a poor compliance rate of TB patient treatment. There was also a lack of family support and insufficient internal networking between hospitals and external networking between hospitals and other healthcare facilities that implemented DOTs (hospital DOT linkage). Indeed, the level of knowledge, attitude and patient behavior also contributed to poor compliance of TB treatment [17].

Other factors related to inadequate implementation of DOTs in hospitals included the use of non-standardized TB drugs. One study on prescriptions for TB treatment in hospitals found free TB drugs from DOT programs in only 13% of prescriptions; the rest referred to generic brands of TB drugs [19]. The results of a clinical audit in hospitals that have implemented DOT treatment before also showed an equal pattern of TB drug utilization that is practically non-standardized. Furthermore, inappropriate deficiency criteria for doses of TB drugs were found in 69% to 100% of 387 audited hospital medical records [20].

Otherwise, the TB drug group that is usually given alongside first-line TB drugs is quinolone, particularly ciprofloxacin, which is available commercially. This study on hospital prescriptions showed a general pattern of TB drug combination HRE or HRZE prescription alongside ciprofloxacin (11.6% of category 1 regimen and 12.1% of category 2 regimen) or single-regimen ciprofloxacin (0.75% of category 1 and 7.9% of category 2) [18].

Another threat that surfaced was the unrestricted sale of at least three second-line TB drugs that are freely available on the commercial market: fluoroquinolone, kanamycin and amikacin. These drugs are freely accessible and are the most utilized by healthcare facilities in both hospitals and private practice, without any standard term and regulation practices. Other second-line TB drugs, consisting of ethionamide, protionamide, PAS and cycloserin, proved ineffective, more expensive and harder to manage as a short-term package, with worse side effects. It is essential to prevent resistance to second-line TB drugs. Several studies have found that in countries where this disease was en-

Table 1. TB cases found that potentially developed into MDR-TB in 20 hospitals and public lung health clinics [18]

	Hospitals				Lung Hospital				Public Lung Health Clinics			
	2006		2007		2006		2007		2006		2007	
No. of treated TB cases	1093		1694		451		266		269		167	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Category 1	731	66.9	1169	69.0	271	60.1	201	75.6	246	91.4	161	96.4
Failure	9	1.2	10	0.9	0	0.0	0	0.0	4	1.6	5	3.1
Default	149	20.4	143	12.2	0	0.0	0	0.0	27	11.0	17	10.6
Treatment result unrecorded	96	13.1	526	45.0	225	83.0	169	84.1	29	11.8	50	31.1
Category 2	29	66.9	11	69.0	28	60.1	16	75.6	17	91.4	3	96.4
Failure	5	17.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Default	5	17.2	0	0.0	0	0.0	0	0.0	1	5.9	1	33.3
Treatment result unrecorded	0	0.0	10	90.9	18	64.3	12	75.0	3	17.6	1	33.3
Relapse	21	72.4	9	81.8	10	35.7	6	37.5	17	100.0	1	33.3
Category 1 with smear positive after intermittent phase	13	1.2	7	0.4	1	0.2	1	0.4	11	4.1	10	6.0

The Public Lung Health Clinics (Balai Pengobatan Penyakit Paru-Paru – BP4).

demic, the tuberculosis potentially developed as a genetic mutation of *Mycobacterium tuberculosis* sp. with a new variant of TB affecting either first-line and second-line TB drug resistance: TB Extra Drug Resistant (XDR) [17].

Referral laboratory capacities for drug susceptibility tests

The laboratory capacity for MDR-TB is the essential component in facing the challenges of this disease from a diagnosis standpoint. Laboratory facilities have not been well developed or optimal, as the health system is still being strengthened in several under-resourced countries, including developing countries. The poor diagnosis system for MDR-TB is affected by the unavailability of a laboratory infrastructure, outdated laboratory guidelines and a quality assurance system fragmented by limited skilled laborers [21].

In Indonesia, only five laboratories are allowed to run drug susceptibility tests (DSTs), which have been certified by an international TB laboratory, the Institute of Medical and Veterinary Science (IMVS), Adelaide, Australia, which both diagnoses and leads the referral therapy for MDR-TB patients. These laboratories are the Microbiology Laboratory of the Faculty of Medicine, University of Indonesia; the Main Health Laboratory Clinic of Surabaya; the Microbiology Laboratory of Persahabatan Hospital; the Novartis Eijkmann Hasanuddin Clinical Research Initiatives (NEHCRI) Laboratory of the Faculty of Medicine, Hasanuddin University; and the Health Laboratory Clinic of Bandung. All these laboratories have undergone routine external quality assurance by IMVS for first-line and second-line TB drugs in the DST. The capacity of DST assessments is still low, i.e. less than 100,000 DSTs annually for all five laboratories. Their limited capacity was affected by running-out-of resources, either manpower or others [22].

TB management strategy

Patient-centered tuberculosis (PCT) is a promising strategy for TB medication [23]. It enables the patient to choose the treatment option or supervision model for drug consumption, whether in a healthcare facility under health professional supervision or at home with relatives who wish to supervise.

Options for treatment location, information related to medication and tuition from treatment supervisors should increase. Regular training is also needed for health workers to effectively supervise feasibility strengthening for a successful PCT approach.

Furthermore, PCT aims to gain access and compliance to TB treatment, as well as DOTs. TB patients, or their supervisors when they are unable to go to healthcare facilities, can procure the TB drugs every week in the incentive phase (within the first two months) and every two weeks in the advance phase (in the last four months). PCT eliminates the workload of health workers when they do not need to supervise the intake of TB drugs of their patients every day. It enables good quality of health professional care [23].

In conventional DOT approaches, TB patients are obligated to visit a healthcare facility every day for treatment. In many cases, this is hard for TB patients, as they are affected by their physical condition, distance from the facility and lack of either transportation or accommodation funds [24, 25]. Health workers, with an exceeded workload, tend to care for patients with unaffordable service. Meanwhile, it potentially decreases treatment adherence, since patients should be coming in every day [23].

Unfortunately, the PCT strategy lets patients identify passively. The period between realizing the symptoms and visiting healthcare facilities is missed. Therefore, access to healthcare is not affected by this approach. However, PCT enables health workers to consider newly diagnosed TB patients as TB incidences. Health workers also do not need to worry about being overwhelmed, which could happen when they serve all their TB patients. PCT supports the increase of access to diagnosis and the required medication indirectly, as it contributes to improving diagnostic procedures and assessments. The key to a PCT strategy lies in the option of a treatment location and supervision. Empowerment of TB patients and their families is essential to cover treatment care, which influences their compliance positively [26]. Prompt diagnosis and treatment leads to compliance and adequate medication based on effective TB control [23].

Limitations of the study and future research

This narrative review presents the current strategy of the Indonesian government in controlling first-line TB treatment as part of their national priority and strategy. The narrative review is not truly useful as scientific evidence, but it would be evidence-based [27]. This study was unable to clear the bias that caused the absence of systematic selection criteria, but it provides an evidence-based view of the current situation of unfinished TB treatment in developing countries. Thus, further studies are needed to set a more systematic approach to this issue, as well as its potential for MDR-TB disease development in developing countries.

Conclusions

The role of hospitals and private practitioner linkages in the treatment management of TB patients is critically required. It would be too late if TB control and management begins treatment only after the disease has developed into MDR-TB, particularly in under-resourced countries such as Indonesia. Healthcare facilities, which are not supported by the TB control strategy, tend to ignore the *International Standard TB Care* (*ISTC*) as its standard procedure for TB control. Poor accessibility by TB patients directly causes unfinished TB treatment. Further study is necessary to describe and analyze the pattern of unfinished TB patients, which is related to the potential of TB to develop into MDR-TB in developing countries.

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