Pharmacy Education (2022) 22(2) 270 - 274
https://doi.org/10.46542/pe.2022.222.270274

IAI SPECIAL EDITION

RESEARCH ARTICLE

Signal detection of adverse drug reaction to first line anti tuberculosis drugs using the Indonesian pharmacovigilance database

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Keywords
Adverse drug reaction
Anti tuberculosis drug
Pharmacovigilance
Signal detection

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Abstract

Introduction: Pharmacovigilance is a key component to identify risks associated with drug use. The safety of antituberculosis drugs (ATDs) is a concern. **Aim:** To detect first-line ATD signals in the Indonesian pharmacovigilance database. **Methods:** A retrospective cohort with a sample report of ADRs obtained from the National Agency of Drug and Food Control (NADFC) from 2012 to May 2018. The validity was seen from the completeness of the data. The signals found were verified against registered product labels, books, and reports from other countries' databases. **Results:** ATD ADRs reported was 5.3%. The ATD that met the requirements as a signal was rash maculopapular (PRR 4.53; ROR 6.19; IC 0.74 and *p*=035) for Rifampicin-Isoniazid-Pyrazinamide-Ethambutol (RHZE) and rash (PRR 2.94; ROR 4.23; IC 1.41 and *p*=0.046) for RH. **Conclusion:** Safety signals detected in the Indonesian pharmacovigilance database between 2012 and May 2018 were rash maculopapular.

Introduction

Pharmacovigilance is an extension of patient safety because it can identify risks and risk factors to prevent unwanted events (WHO, 2006; Andrews, 2014). According to the World Health Organisation (WHO) (WHO, 2015), pharmacovigilance covers adverse drug reactions (ADRs) or adverse drug events (ADE), medication error, fake and sub-standard drugs, low efficacy drugs, abuse and misuse, and drug interactions.

The traditional method for detecting security signals is a qualitative method by conducting a literature review, reviewing a series of cases that occur, and through Periodic Safety Update Report (PSUR) (Monaco *et al.,* 2017). A new method carried out with continuous monitoring of the side effect database uses statistical techniques (quantitative) to detect safety signals (Monaco *et al.,* 2017; Park *et al.,* 2017).

Tuberculosis (TB) was one of the top ten causes of death globally in 2015 (WHO, 2016). As many as 60% of cases occurred in six countries, ranked from India, Indonesia, China, Nigeria, Pakistan, and South Africa. Of the 10.4 million new incidents in 2015, only 6.1 million were reported to WHO. The difference between the estimation and cases notified to WHO was 4.3 million, half of which was a contribution from India, Indonesia, and Nigeria (WHO, 2016).

Indonesia has a pharmacovigilance database that collects ADR reports from health-service facilities and the pharmaceutical industry. The use of report data in the database has not been carried out optimally. Report data in the database can show ADR profiles or safety profiles of circulating drugs, safety signals that appear during drug use, and severe and life-threatening ADRs that need immediate follow-up (Badan POM RI, 2017a). Thus, this study aimed to detect the security

signals of first-line ATD in the Indonesian pharmacovigilance database.

Methods

Ethical approval was obtained from the Faculty of Public Health Universitas Airlangga in June 2018 (No: 502-KEPK). The research method used was a retrospective cohort with a sample of ADR reports in the Indonesian pharmacovigilance database based in the National Agency of Drug and Food Control (NADFC). Data were retrieved online and offline. Validity was seen from the completeness of the components, including patient sex and age and the reported ADRs.

Inclusion criteria were (1) ADR reports suspected from first-line antituberculosis drugs (ATDs), (2) reports received and recorded between 2012 to May 2018, (3) spontaneous reports originating from health workers at health-service facilities, (4) ADRs classified based on the Medical Dictionary for Regulatory Activity (MedDRA), and (5) complete reports. ADR reports from the pharmaceutical industry, including clinical trial data and periodic safety update reports (PSURs), were not included in the study sample to avoid duplication because some of the pharmaceutical industry reports were sourced from health workers at health-service facilities.

Data analysis to determine ADR report profiles was done by calculating the Proportional Reporting Ratio (PRR), Reporting Odds Ratio (ROR), and Informational Component (IC). The requirement applied was PRR> 2, ROR> 2 IC> 0, with more than three case samples, and the value of other ADR cases on the same drug not equal to 0 (zero). The signal found was verified against registered product labels, books, and reports from other countries' databases; it was confirmed if it had been listed in the literature and databases of other countries. Otherwise, it was referred to as a new safety signal of the prescribed drug (Andrews *et al.,* 2014; Böhm, 2015).

Results

Figure 1 presents the diagram of sampling, while Table I shows the number of reported ATD ADRs. Reports entered and recorded in the Indonesian pharmacovigilance database are spontaneous reports from health workers via the yellow form, drug program reports, and e-MESO online reports for 2014-2018. A drug program report is a copy of a report on the progress of ADRs cases from patients reported to the Ministry of Health by health-service facilities administering treatment programs (ATM), also reported by the public health office. There is a possibility of duplication in reporting these drug programs. There is also a possibility for the ATM report to be notified to provincial NA-DFC via the yellow form or e-MESO by health-service facilities. The ATM report also has not been coded according to MedDRA.

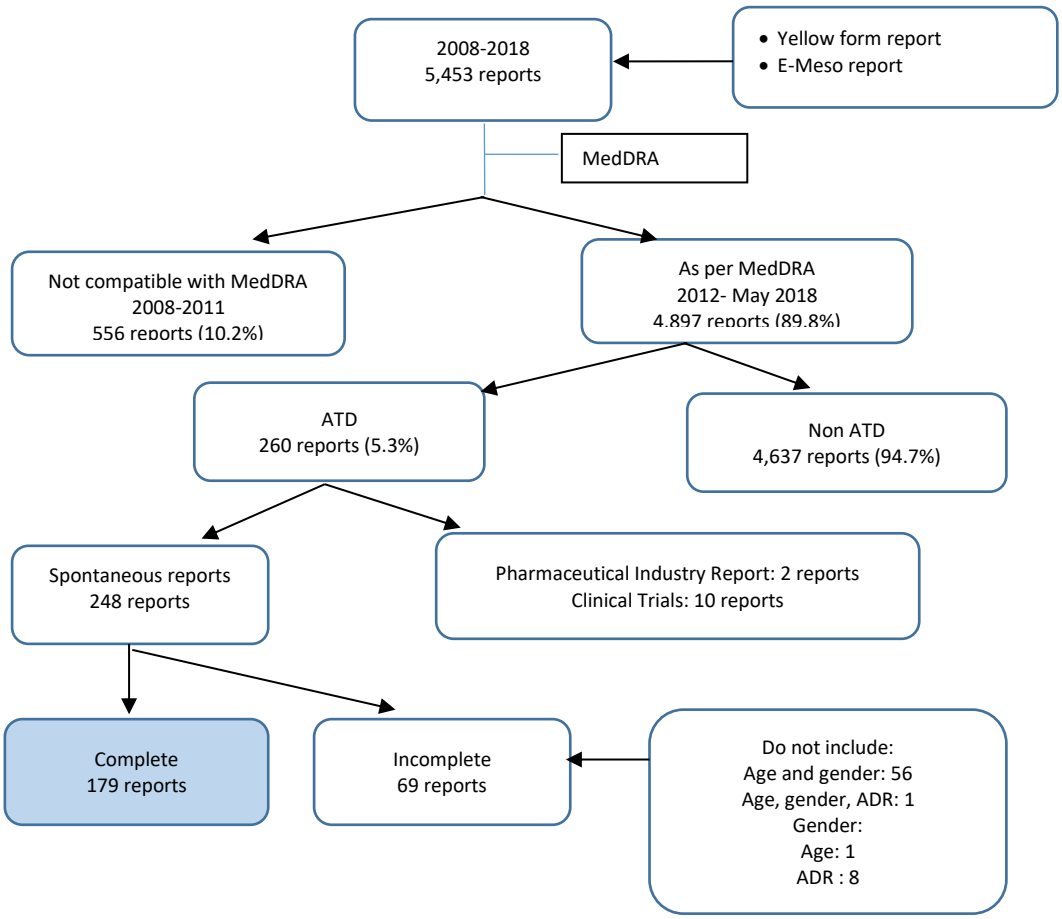
Table I: Anti tuberculosis drug (ATD) adverse drug reactions (ADRs) report in the Indonesian pharmacovigilance database from 2012 to May 2018

Year	Total ADRs report	ATD ADRs report n(%)		ATD ADRs report from spontaneous reporting
2012	193	18	(9.3)	
2013	341	4	(1.2)	
2014	395	20	(5.1)	17
2015	725	64	(8.8)	44
2016	900	82	(9.1)	62
2017	1,274	35	(2.7)	26
January to May 2018	1,069	38	(3.6)	30
Total	**4,897**	**260**	**(5.3)**	**179**

ATD: Anti-tuberculosis drug, ADR: Adverse drug reaction

Results showed that most TB patients with ADRs were males (96, 53.6%), with most patients aged between 20-40 years (n=76, 42.5%). Health professions reporting ATD ADRs were pharmacists, doctors, specialists, nurses, and other health workers. Pharmacists were the profession with the most reported ADRs (n=93, 52.0%). The report on ADRs of ATD consisted of ADRs of first-line, second-line, and ATD for MDR TB. The largest number of reported ATD ADRs was first-line ATD (n=124, 69.3%), followed by MDR TB ATD (n=39, 21.8%). The most widely used first-line treatment causing ADRs was the combination of Rifampicin-Isoniazid-Pyrazinamide-Ethambutol (RHZE) for 68.5% (85).

The results of the calculation of the security signal from the ADRs are listed in Table II. Signals found in Table II were verified by signalling the presence of ADRs on product labels registered in Indonesia, standard literature, and databases of other countries. Unexpected first-line anti tuberculosis drug adverse drug reactions are presented in Table III; the confirmed signal was a maculopapular rash.



ADR: Adverse drug reaction; ATD: Anti-tuberculosis drug; MeDRA: Medical Dictionary for Regulatory Activity

Figure 1: Sampling diagram

Table II: First-line anti tuberculosis drug detected signal

Drug Combination	ADRs	Parameters								
		p <0.05	χ2 (yates correction)	a	b	C	d	PRR	ROR	IC
RHZE	Nausea	0.404	0.19	15	19	70	15	0.87	0.85	-0.11
	Vomiting	0.489	0.06	11	11	74	11	1.11	1.12	0.07
	Hepatitis	0.154	2.18	4	1	81	4	4.42	4.59	0.75
	Rash	0.552	0.01	12	14	78	12	0.85	0.82	-0.04
	Rash Erythematous	0.063	3.49	7	2	78	7	3.87	4.13	0.71
	Rash maculopapular	0.035	4.33	8	2	78	8	4.33	4.67	0.74
	Pruritus	0.213	1.22	7	4	78	7	1.94	2.02	0.42
	Urticaria	0.154	2.18	4	81	1	4	1.72	4.59	0.75
	Hyperbilirubinaemia	0.063	3.49	7	2	78	7	3.87	4.13	0.71
	Drug-Induced Liver Injury	0.084	2.81	5	1	80	5	5.53	5.81	0.74
	Hepatitis	0.154	2.18	4	1	81	4	4.42	4.59	0.75
	SGOT Increased	0.430	0.23	6	5	79	6	1.33	1.35	0.19
	SGPT Increased	0.563	0.04	4	5	81	4	0.88	0.88	-0.09
RH	Rash	0.046	5.13	4	23	6	4	2.94	4.23	1.41

Description: ADRs is said to be 'signal' if values of $\chi^2 > 3.84$ or $p < 0.05$ and the PRR value> 2; ROR> 2, IC> 0
RHZE: Rifampicin-Isoniazid-Pyrazinamide-Ethambutol, RH: Rifampin-Isoniazid

Table III: Unexpected first-line anti tuberculosis drug adverse drug reactions signal

Drug Combination	ADRs expected as a signal	Parameters						
		WHO (2009)	BNF	PIONAS	Registered drug labels in Indonesia	FAERS	German Database	WHO vigibase
RHZE	Maculopapular rash	-	-	-	-	√	√	√
RH	Rash	√	√	√	√	√	√	√

Description: Verified signal is a signal that is not found on the registered label and standard book but has been reported on the PV database of another country.
RHZE: Rifampicin-Isoniazid-Pyrazinamide-Ethambutol, RH: Rifampin-Isoniazid

Discussion

Table I shows that TB patients with ADRs were mainly male patients with 53.6%; some studies showed the same results (Damasceno *et al.,* 2013; Athira et al., 2015; Maqusood *et al.,* 2016). In TB, gender is considered less influential on the incidence of ADRs than other risk factors, namely diabetes mellitus, malnutrition, and alcohol use (WHO, 2004; Wells *et al.,* 2009).

Pharmacists were the health professionals who reported the most ADRs (52.0%). A study found that only 25.7% of respondents who work as doctors had good knowledge of pharmacovigilance, and 20% had a good attitude about pharmacovigilance (Wangge and Akbar, 2016). Research conducted in the Netherlands on health professionals stated that the attitudes and knowledge of pharmacists and specialist doctors were better than that of non-specialist doctors (Piening *et al.,* 2012).

As Indonesia pharmacovigilance manager, NADFC carries out routine activities, including publishing the MESO bulletin, which can be accessed via e-MESO subsite or sent to hospitals and other health-service facilities. The dissemination of reporting methods and pharmacovigilance training for health workers is also carried out regularly to increase concern, awareness, and willingness to report (Badan POM RI, 2017b).

The highest number of ATD ADR reports is first-line ATD ADRs. The number of ADRs is quite influenced by the great use of first-line ATDs (Ye *et al.,* 2017). The second-largest ADR reports are ATD for MDR TB. The drugs used in MDR TB therapy are relatively new to attract health workers' attention to reporting. The desire to publish severe ADR findings from new drugs and be rewarded for reporting it can also increase the reporting rate for ADRs (Lopez-Gonzalez, Gupta, Pankaj; Audupa, 2011).

Table III shows that the confirmed signal was maculopapular rash. A maculopapular rash is not available in standard books but has been reported in pharmacovigilance databases from various countries as ADRs of first-line ATD. These ADRs are not listed on registered drug labels in Indonesia.

The maculopapular rash incident as ADR from ATD is very rare (Khayyam *et al.,* 2010). However, 95% of the incidence of cutaneous ADRs with first-line ATD is a maculopapular rash (Dheda, 2012). The use of combination ATD (RHZE) triggers this maculopapular rash (Ye *et al.,* 2017). The risk of maculopapular rash increases in patients with HIV (Boonyagars *et al.,* 2017).

The limitation of this study was the small amount of ATD ADRs data in the Indonesian Pharmacovigilance Database. In the process of calculating disproportionality, the potential for bias will increase with the limitation of the number of samples (van der Heijden *et al.,* 2002; Hammond *et al.,* 2007). The signal detection process also involves the quality of the reports used. Reports with an incomplete dataset will reduce the sample size and increase the possibility of bias due to unclear data (van Puijenbroek *et al.,* 2001). There was also no direct access to other countries' databases used for signal verification. Access was only obtained through the available web so that it was not possible to carry out further exploration. This access affects the validity of the data on signal verification (Hammond *et al.,* 2007).

Conclusion

It can be concluded that the new safety signal for First-Line Anti-Tuberculosis Drugs on the Indonesian Pharmacovigilance Database is maculopapular rash.

Acknowledgment

This article was presented at the 2021 Annual Scientific Conference of the Indonesian Pharmacist Association.

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