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A model for monitoring the medication rechallenge system in Queen Savang Vadhana Memorial Hospital

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ABSTRACT

A rechallenge process is crucial for patients who need to use drugs known to cause allergic reactions. Establishing a standardized rechallenge protocol is essential to protect patients and increase the likelihood of using effective medications. This study aimed to evaluate the outcomes of the rechallenge monitoring system implemented at Queen Savang Vadhana Memorial Hospital. In this retrospective study, rechallenges focused on two drugs categories: antimicrobial drugs and non-steroidal anti-inflammatory drugs. The confirmed rechallenge protocol was introduced in 2018, and data from October 2019 and November 2022 were extracted from the hospital's electronic database. The primary outcome measured was the number of adverse events during rechallenges. Trends in severe allergic reactions were documented, and descriptive statistics were used. Out of 81 total rechallenge events, with a history of 77 mild reactions (95.1%) and 4 serious events (4.9%), only 3 mild reaction (3.7%) occurred. A positive trend in successful rechallenges was observed following the implementation of the monitoring model, along with a decrease in medication error levels B and C. Importantly, no harmful levels D and E were detected. The rechallenge monitoring system improved the chance of safe medication use and reduced the occurrence of seriously adverse drug events.

Keywords: medication rechallenge; medication errors; adverse drug reactions; medication near miss

1. INTRODUCTION

A 'medical rechallenge' involves administering a treatment or medication to a patient who previously experienced an adverse effect or treatment failure with the same therapy. Rechallenges are commonly conducted in research settings to further assess the safety and effectiveness of a treatment or in clinical practice when alternative options are unavailable, and the potential benefits of the treatment outweigh its risks (Yothapitak, 2016, 2018; Ningsanon, 2006; Stanulovic´ et al., 2013).

Several factors should be considered when deciding to conduct a medical rechallenge, including the severity of the adverse effect or treatment failure, the potential benefits of the treatment, and the availability of alternative options. Rechallenges can help identify the cause of an adverse effect or treatment failure and determine which patients may be more or less likely to experience certain side effects (Mutair et al., 2021; Rattanadechsakul and Rattanadechsakul, 2017; Paulmann et al., 2017; The Healthcare Accreditation Institute, 2018; Ningsanon, 2006; Stanulovic´ et al., 2013). Furthermore, it is important to promptly identify and manage any adverse effects by carefully weighing the potential benefits and risks of a rechallenge and closely monitoring patients who undergo the procedure (Rattanadechsakul and Rattanadechsakul, 2017; Stanulovic´ et al., 2013).

As mentioned earlier, the rechallenge process is crucial for patients who need to use drugs with a history of causing allergies. A standardized rechallenge process is essential to save the lives and increase the opportunity to use effective medications. Consequently, Queen Savang Vadhana Memorial Hospital developed a model to monitor its rechallenge system, focusing on two groups of medications: antimicrobials and non-steroidal anti-inflammatory drugs (NSAIDs). Hospital data have indicated reports of allergic reactions to these two classes of medication, with several documented cases of patients experiencing allergies after using them. Therefore, this study aimed to evaluate the outcomes of this monitoring model concerning these medications.

2. MATERIALS AND METHODS

2.1 Rechallenge monitoring system

The confirmed rechallenge form was formulated in 2018. This form includes the reason for the rechallenge and requires consent from the patients and the physicians. After its introduction, physicians were instructed to use the form whenever they intended to rechallenge a medication. The rechallenge record form specially includes the following elements:

- Patient identification information, such as name and hospital number (HN)
- Patient's medication allergy history
- Patient's informed consent/signature
- Physician's confirmation
- Pharmacist's informed consent

Conditions

1. The rechallenge of medication/contrast media is part of the hospital's standard rechallenge procedure.
2. Rechallenge of medication or contrast media is not permitted in patients with severe hypersensitivity, except for antibiotics in case where the patient is being treated for an infection and the rechallenge is ordered by an infectious disease physician.

This system not only adheres to the definition of a rechallenge but also extends its application to include the medications that may cause hypersensitivity.

In the outpatient department (OPD) setting, the procedure begins when a physician prescribes a medication for which the patient has a documented allergic history. The physician records this information and informs the patient of the associated risks and benefits of undergoing a rechallenge. If the patient consents and signs the consent form, the pharmacist assesses the risk of adverse drug reactions (ADRs) using Naranjo's algorithm, following the standard guide for ADR assessment (Yothapitak, 2016) and documents the rationale for rechallenge. If the pharmacist approves, the computerized ordering system is alerted with a pop-up message, allowing the physician to order the rechallenged medication. However, if the pharmacist advises against the rechallenge, a consultation with the physician takes place. If the physician agrees to proceed, the pharmacist notifies the physician's staff, and upon their confirmation, unlocks the computerized ordering system. The physician is then informed that the system has been unlocked.

Once the physician completes the rechallenge record form, the documented information is stored in the pharmacy department for outcome monitoring. The rechallenged medication is then dispensed and successfully administered to the patient. After administration, the patient is closely monitored at the hospital for 1 h. If ADR occurs, the medication is discontinued, and the patient receives treatment for the adverse event. The pharmacist then locks the computerized ordering system, and the ADR is recorded. If no ADR is observed after 1 h, the pharmacist dispenses the medication and schedules a follow-up within 72 h.

In the event of an ADR, the patient is advised to discontinue the medication, and the pharmacist records this by selecting 'certain' in the computerized system, preventing further prescription of that medication to the patient. The completed rechallenge record form is stored in the medical record department for outcome monitoring (Figure 1). The inpatient (IPD) rechallenge process mirrors the OPD process, with the primary difference being the timing of the pharmacist's communication with the physician regarding the rechallenge confirmation order (Figure 2).

2.2 Study design and setting

The retrospective study focused on two groups of drugs commonly involved in rechallenges: antimicrobials and NSAIDs. However, any medication documented in the rechallenged confirmation form was also included. The rechallenge form was introduced in 2018, and data were collected from October 2019 to November 2022. The primary outcome measured was the number of adverse events during rechallenges, with a specific focus on trends in severe allergic reactions.

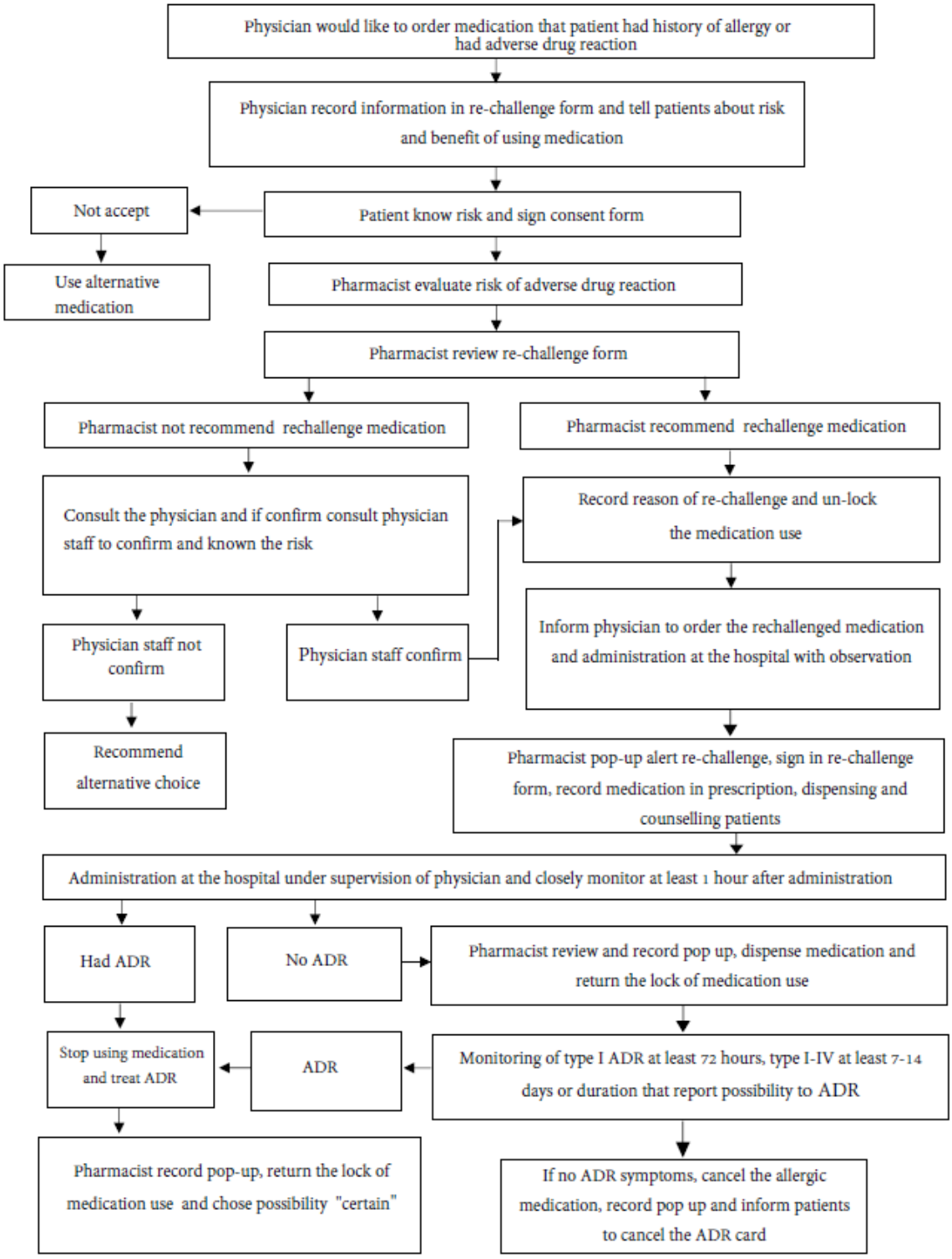

Figure 1. The rechallenge monitoring system applied in the OPD

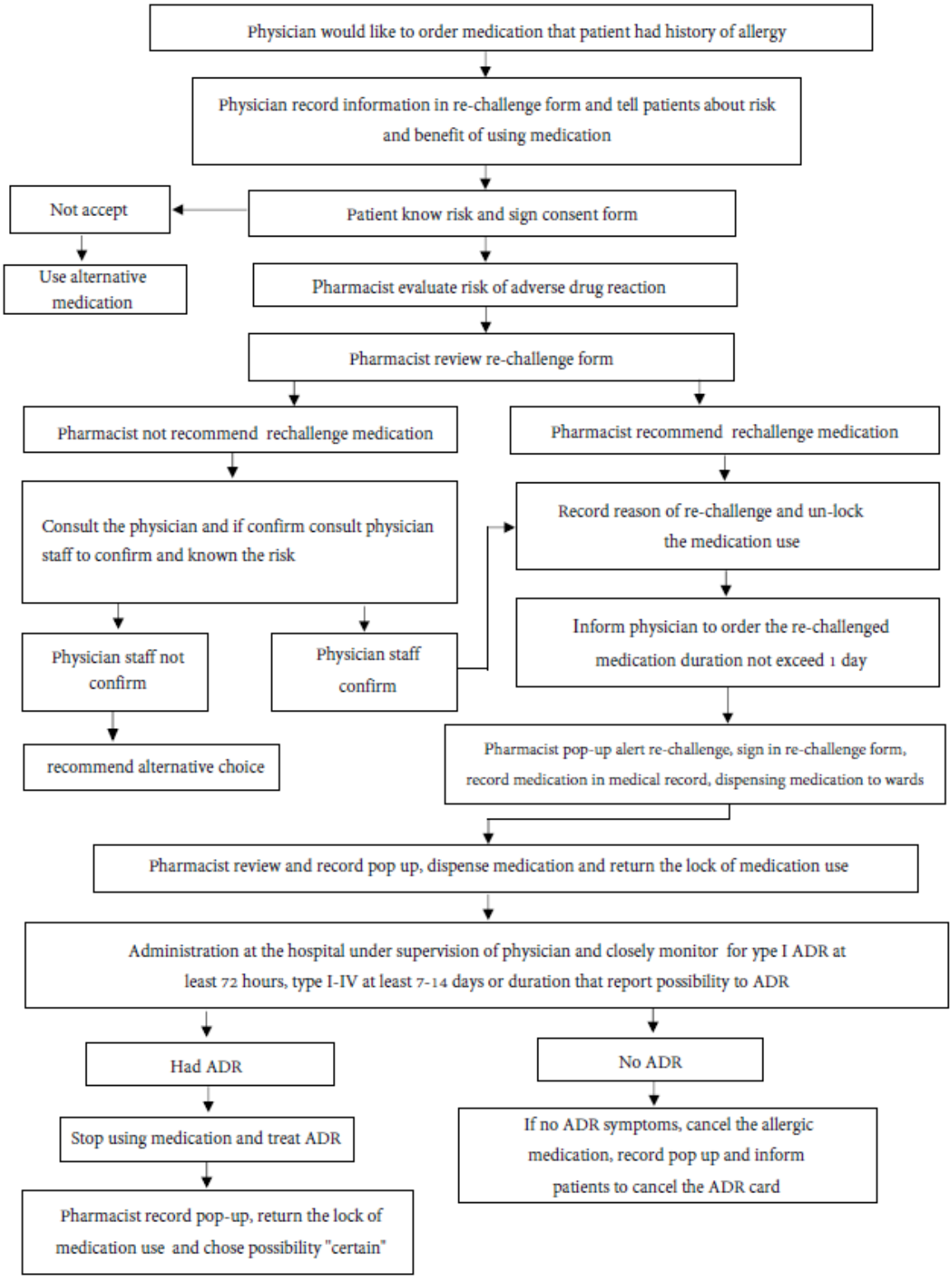

Figure 2. The rechallenge monitoring system applied in the IPD

2.3 Participants

All participants were patients who received medications listed in the rechallenge confirmation forms during the study period. The inclusion and exclusion criteria were as follows:

Inclusion criteria
- Rechallenge confirmation forms issued between 2018 and 2022
- Rechallenge confirmation forms signed by the patient, physician and pharmacist
- Rechallenge confirmation form with a completed medication order

Exclusion criteria
- Rechallenge confirmation forms with no completed medication order.

2.4 Data collection

Data were retrieved from the hospital's computerized database. The classification of ADRs was performed according to the guidelines established by the Association of Hospital Pharmacists (Thailand), which align with those of the Thai FDA and WHO (Yothapitak, 2016).

2.5 Outcome monitoring

The severity of ADR was classified as mild or severe based on the following definitions: Severe or high-risk ADRs include Steven-Johnson syndrome, toxic epidermal necrolysis, drug-induced hypersensitivity syndrome, drug rash with eosinophilia and systemic symptoms or acute generalized exanthematous pustulosis, as defined by the ADR monitoring guideline (Yothapitak, 2016).

The level of medication error was also recorded according to the criteria of the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP), classified from level A to I (Mutair et al., 2021). This classification is important because the implementation of a rechallenge system aims to decrease the unintentional prescribing of medications to patients with known allergy.

Successful rechallenges are defined as those in which patients are able to continue using the prescribed medication until the completion of the treatment course.

2.6 Data analysis

Patient characteristics are reported using descriptive statistics, including mean, standard deviation (SD) and percentage. The outcomes are reported as the percentage of patients who experienced ADRs during rechallenges. The trend of patients who had ADRs during rechallenge since 2019 is illustrated using a graph and trendline.

3. RESULTS

Table 1 presents the characteristics of the patient cohort, showing that females constitute the majority at 58.02% of the participants. The average age is 53.26±19.89 years. The predominant reason for rechallenging, as observed in 23.53% of cases, was that patients who were accustomed to the medication did not experience any allergic reactions. Table 2 illustrates the trend of patients undergoing rechallenges, revealing a significant increase in successful rechallenges over time. Table 3 provides a breakdown of medication types used for rechallenges, with beta-lactam drugs being the most common, accounting for 63%. Furthermore, Table 4 indicates that the majority of patients undergoing rechallenges (95%) manifested only mild hypersensitivity reactions.

Compared to the trends before the implementation of medication rechallenges (2018), the number of medications near-miss medication errors at level B has decreased, as shown in Figure 3. In addition, this model has reduced the occurrence of medication errors at levels C, D and E, indicating safer outcomes terms for patients with repeated medication allergies, as shown in Figure 4.

Table 1. Patient's characteristics

Characteristics	N (%)
Gender	
- Male	34 (41.98)
- Female	47 (58.02)
Age (Mean±SD)	53.26±19.89
The reason for rechallenging	
- Patient used to administer the medication and has no allergy	20 (23.53)
- Minor symptom	15 (17.65)
- Prophylaxis, surgery, empiric therapy	13 (15.29)
- Need to use, use with indication	13 (15.29)
- No reason	8 (9.41)
- Patient requested to use, or tolerate	6 (7.06)
- Physicians request to rechallenge	4 (4.71)
- Low incidence of cross-reaction	3 (4.71)
- No history of sulfa allergy	1 (1.18)
- Liver functions improve	1 (1.18)
- Consult ID physicians	1 (1.18)
Adverse drug reaction history	
- Mild reaction	77 (95.06)
- Severe reaction	4 (4.94)

Table 2. Number of patients with rechallenges (N = 81)

Year	Number (cases)	Success	Fail
2019	1	1	0
2020	10	9	1
2021	4	3	1
2022	66	66	0

Table 3. The type of medication rechallenges (N = 81)

Medication	N	%
Beta-lactam	52	64.2
- Ceftriaxone	15	18.5
- Ceftazidime	9	11.1
- Piperacillin/Tazobactam	8	9.9
- Meropenem	8	9.9
- Amoxicillin/Clavulanic, Amoxicillin	3	3.7
- Dicloxacillin/Cloxacillin	3	3.7
- Cefazolin	2	2.5
- Cefixime	2	2.5
- Cefdinir	1	1.2
- Penicillin	1	1.2
NSAIDs	13	16.1
- Naproxen	3	3.7
- Celecoxib	2	2.5
- Diclofenac	2	2.5
- Parecoxib	2	2.5
- Etoricoxib	1	1.2
- Indomethacin	1	1.2
- Ketorolac	1	1.2
- Meloxicam	1	1.2
Others	16	19.7
- Acriptega®	1	1.2
- Atorvastatin	1	1.2
- Bactrim®	2	2.5
- Betahistine	1	1.2
- Clarithromycin	1	1.2
- Ciprofloxacin	1	1.2
- Dapsone	1	1.2
- Dilantin	1	1.2
- Ethambutol	1	1.2
- Metronidazole	1	1.2
- Rifampicin	1	1.2
- Rosuvastatin	1	1.2
- Salbutamol	1	1.2
- Teevir®	1	1.2
- Ultravist®	1	1.2

Table 4. The type of adverse drug event after rechallenges (N = 3)

Adverse drug event	N	%
Mild reaction	3	100
Severe reaction	0	0

4. DISCUSSION

Based on the study results, the proposed rechallenge monitoring model effectively increase the opportunity for medication use in patients with a history of allergy to identified medications. In terms of medication error severity, this model significantly decreased the incidence of severe ADR events, leading to cost saving in ADR management.

Previous studies have reported successful rechallenges with immunotherapy, anti-tuberculosis and antipsychotic medications (Berroa et al., 2013; Chen et al., 2014; Gao et al., 2022; Hunt et al., 2017; Lin et al., 2022; Pathak et al., 2019; Senior, 2016; Thong et al., 2014), including cases of immune checkpoint inhibitor-induced pneumonitis and myasthenia gravis (Gao et al., 2022; Lin et al., 2022). However, only a few studies have focused on monitoring rechallenges for NSAIDs and antibiotics. For instance, one pediatric study found that up to 50% of patients with delayed allergies to penicillin could tolerate subsequent treatment with the same drug (Berroa et al., 2013). The current study demonstrates the effectiveness of this system in providing patients the opportunity to use necessary medications safely.

In line with Thailand's patient safety goals (The Healthcare Accreditation Institute, 2018), this study supported achieving patient outcomes under Item M: Medication and Blood Safety (Safe from Preventable ADRs) by reducing near-miss medication errors at level B. In addition, it decreased the occurrence of repeated medication allergy events (levels C, D, and E), highlighting the success of the medication rechallenge monitoring model, especially for level E, which is the most harmful to patients. Notably, there were no repeated medication allergy events at levels D and E during the budget year 2022, indicating an improvement in patient medication safety. Among the 4 cases with a history of severe ADR, 3 experienced only mild ADR after rechallenging. These 3 cases were appropriate managed (medication discontinued and antihistamine administered), and one patient continued using the drug until the treatment course was completed.

This study has a limitation due to the retrospective nature of the research, which may result in incomplete information that could affect the accuracy of the collected data, particularly in the OPD setting, which differ from the ADR monitoring process. Future studies should focus on assessing cost saving related to ADR management to further confirm the benefit of this medication rechallenge model. In addition, a prospective study is recommended for future research.

5. CONCLUSION

The rechallenge monitoring system proposed in this study effectively increased the opportunity for the medication use while reducing the incidence of serious ADR events.

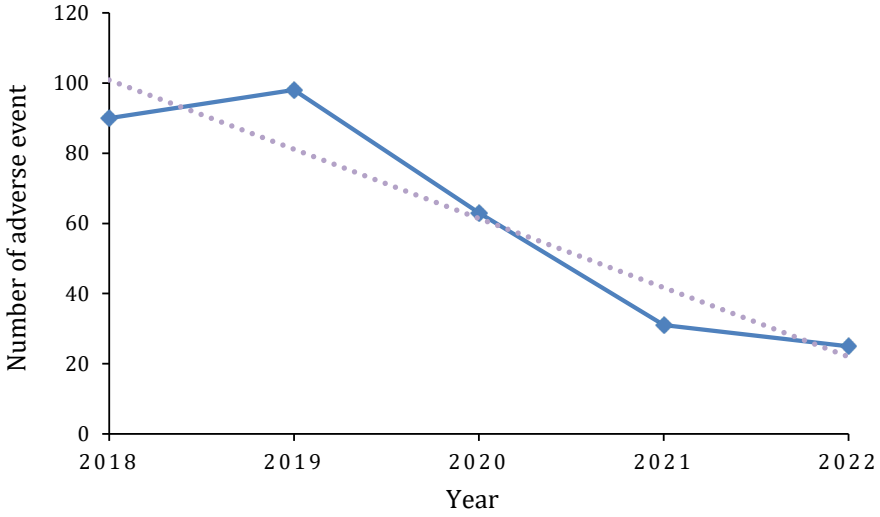

Figure 3. The trend of medication near-miss at level B during the budget year 2018–2022
Note: Near-miss level is definitely by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP, 2023).

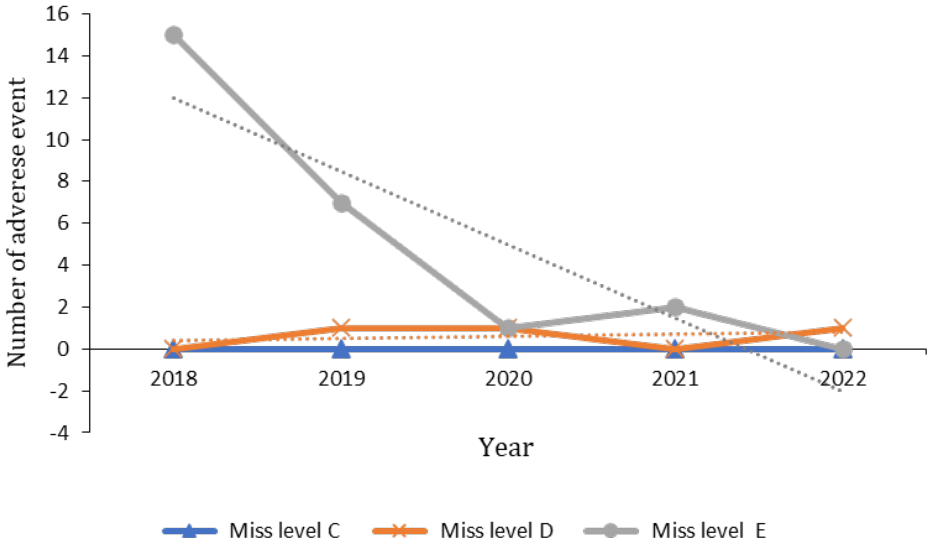

Figure 4. The trend of repeated medication allergies during the budget year 2018–2022
Note: NEAR MISS level is defined by the National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP, 2023).

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