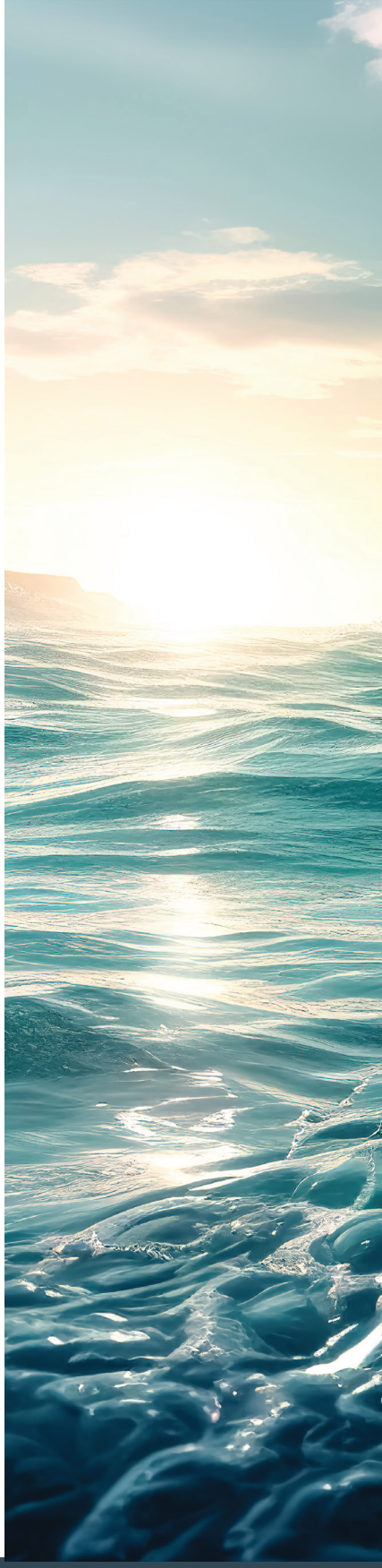
Ministry of Health Malaysia
National Pharmaceutical Regulatory Agency



2022
ANNUAL REPORT
NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING

Ministry of Health, Malaysia

NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING: ANNUAL REPORT 2022

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Our Purpose

Keeping medicines safe for the nation

This is what inspires and drives us as individuals and as a regulatory agency. This is how we contribute to the society by ensuring the safety of the products registered in Malaysia.

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Training, International Participation & Collaborations, and Other Pharmacovigilance Activities

The National Centre for Adverse Drug Reactions Monitoring

The National Centre for Adverse Drug Reactions Monitoring serves as a repository for all adverse drug reaction (ADR) reports and adverse events following immunisation (AEFI) reports received by the National Pharmaceutical Regulatory Agency (NPRA). The National Centre is housed within the Pharmacovigilance Section, Centre of Compliance & Quality Control, NPRA.

The National Centre plays an important role in managing and analysing information on suspected adverse reactions to medicines or vaccines. Based on the evaluation of a safety concern, NPRA may take regulatory action(s) to improve product safety and protect public health, such as updating product packaging information, restricting the use of the product, communicating new safety information to healthcare professionals and the public, or even removing a product from the market.

The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC)

The Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) was established in 1987 under the Drug Control Authority (DCA) to perform the function of monitoring safety profiles of medicinal products registered for use in Malaysia.

Appointment of MADRAC members are made every three (3) years, and the Pharmacovigilance Section, Centre of Compliance & Quality Control, NPRA is the Secretariat to the Committee. During MADRAC meetings held once every three months, causality verification is done for all local reports of ADR/AEFI and all pertinent drug safety issues are discussed to provide DCA with information and recommendations if required.

A total of **four (4) MADRAC meetings** were held in 2022.

Table 1: Members of MADRAC Session 2022-2024

Ex-officio	Chairman **YBrs. Dr. Roshayati binti Mohamad Sani** Director of NPRA
	Secretary to the MADRAC **YBrs. Dr. Noraida Mohamad Zainoor** Deputy Director, Centre of Compliance & Quality Control
	Secretary of the Drug Control Authority **YBrs. Pn. Rosilawati Ahmad** Deputy Director, Centre of Product & Cosmetic Evaluation
Commitee Members *(Alternate members)*	**YBhg. Datuk Dr. Noel Thomas Ross** Medical Consultant Hospital Kuala Lumpur *(YBrs. Dr. Marzilawati Abdul Rahman)*
	YBrs. Dr. Liza Mohd. Isa National Head of Rheumatology Services and Medical Consultant (Rheumatology), Hospital Putrajaya *(YBrs. Dr. Habibah Mohd Yusoof)*
	YBrs. Dr. Suganthi Thevarajah National Head of Dermatology Services and Consultant Dermatologist, Hospital Kuala Lumpur *(YBrs. Dr. Tang Min Moon)*

Commitee Members

(Alternate members)

YBrs. Dr. Sunita Bavanandan
Head of Department and Consultant Nephrologist,
Hospital Kuala Lumpur
(YBrs. Dr. Suryati Yakob)

YBrs. Dr. Mazni Mat Junus
Head of Department and Consultant Psychiatrist
Hospital Selayang
(YBrs. Dr. Chin Loi Fei)

YBrs. Dr. Farah Inaz Syed Abdullah
Consultant Paediatrician and Neonatologist,
Hospital Tunku Azizah
(YBrs. Dr. Lim Poi Giok)

YBrs. Dr. Mohd. Sapawi Mohamed
Consultant Cardiologist,
Hospital Raja Perempuan Zainab II
(YBrs. Dr. Siti Khairani Zainal Abidin)

YBrs. Dr. Voon Pei Jye
Medical Oncologist
Hospital Umum Sarawak
(YBrs. Dr. Ibtisam Muhamad Nor)

YBrs. Dr. Mohd Hanif Zailani
Vaccine Preventable Diseases and Food & Water Borne Diseases Sector
Disease Control Division
Ministry of Health
(YBrs. Dr. Jamiatul Aida Md. Sani)

YBrs. Prof. Madya Dr. Adyani Md Redzuan
Faculty of Pharmacy
National University of Malaysia
(YBrs. Dr. Norkasihan Ibrahim)

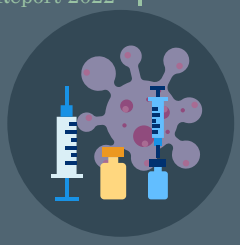
YBrs. Dr. Nur Sufiza Ahmad
Deputy Director
Formulary Management Branch
Pharmacy Practice & Development Division
(Pn. Rohana Hassan)

YBrs. Dr. Sivanaesan Letchumanan
Malaysian Medical Association (MMA)
(YBrs. Dr. Balachandran Krishnan)

YBrs. Dr. G. Shanmuganathan
Federation of Private Medical Practitioners' Associations Malaysia (FPMPAM)
(YBrs. Dr. Pearl Leong Yuet Mae)

Pn. Ho Wan Dien, Jemima
Malaysian Pharmaceutical Society (MPS)
(Pn. Syireen Alwi)

Pn. Eliza Basir
Association of Private Hospitals of Malaysia (APHM)
(Pn. Zarihasyum Wan Zein)



Highlights: Pharmacovigilance Work During the COVID-19 Pandemic

Safety Monitoring for New Oral Antivirals Treatments and Pre-Exposure Prophylaxis for COVID-19 Infections

The National Pharmaceutical Regulatory Agency (NPRA) remained committed to improve public access to medicines for the purpose of treatment or prevention of COVID-19 transmission in Malaysia by ensuring that they have met the NPRA's rigorous standard for quality, efficacy, and safety. In 2022, the Drug Control Authority (DCA) has granted a conditional registration for 3 oral antiviral products for the treatment of COVID-19 infection, namely Paxlovid (nirmatrelvir/ritonavir), Veklury (remdesivir), and Lagevrio (molnupiravir). The DCA has also conditionally approved Evusheld (tixagevimab/cilgavimab) for pre-exposure prophylaxis of COVID-19 in adults and adolescents who may not mount an adequate immune response to vaccination or for whom vaccination is not recommended.

The NPRA continuously reviewed safety-related documents submitted post-registration by product registration holders and closely monitored adverse drug reactions (ADRs) reported locally through the NPRA's passive surveillance system, ensuring that the benefits of these treatments and pre-exposure prophylaxis consistently outweigh the risks.

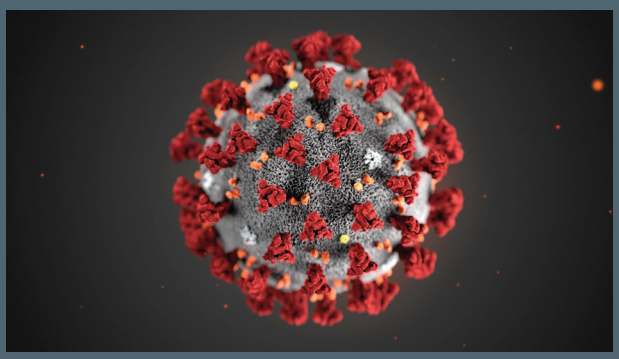


Image of Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2).
Source: https://phil.cdc.gov/Details.aspx?pid=23312

COVID-19 Vaccine Safety Monitoring

The NPRA continues to oversee the safety of all registered vaccines used in Malaysia, including COVID-19 vaccines used under the National COVID-19 Immunisation Programme (PICK), primarily through the passive surveillance of Adverse Events Following Immunisation (AEFI) reported locally. Since the inception of PICK on 24 February 2021 up to 31 December 2022, there were 5 COVID-19 vaccines used for PICK, which are Comirnaty (Pfizer), CoronaVac (Sinovac), Vaxzevria (AstraZeneca), Convidecia (CanSino), and Covilo (Sinopharm). In February 2022, the NPRA also began closely monitoring AEFIs reported in children aged 5 to 11 years who received the conditionally registered Comirnaty 10 mcg Injection under the National COVID-19 Immunisation Programme for children (PICKids).

COVID-19 Vaccine Special Pharmacovigilance Committee (JFK)

Established in early 2021, the COVID-19 Vaccine Pharmacovigilance Special Committee (JFK—*Jawatankuasa Farmakovigilans Khas Vaksin* COVID-19) play pivotal roles in assessing AEFI reports associated with COVID-19 vaccines, communicate relevant findings to the National Immunisation Policy and Practice Committee (JDAIK), provide advice on vaccine safety and policy revisions, and provide essential information to the Special Financial Assistance on Adverse Effects of COVID-19 Vaccine Committee (BKK—*Bantuan Khas Kewangan Kesan Mudarat Vaksin* COVID-19). Throughout 2022, JFK convened **12 meetings** to fulfill these responsibilities.

Training on AEFI Data Collection and Capacity Building

To strengthen COVID-19 vaccine safety surveillance, NPRA continued to deliver training programs aimed at strengthening HCP's capacity to identify, manage, and report AEFI through passive surveillance. Additionally, substantial focus has been directed towards guiding HCPs in conducting thorough investigations of serious AEFIs by healthcare facilities and communicating risk.

Dissemination of Information on COVID-19 Vaccines

To counteract misinformation during the pandemic, NPRA has been proactively disseminates factual and updated information regarding COVID-19 vaccines. Through various platforms, including NPRA website and direct media engagement, regulatory and safety updates pertaining to COVID-19 vaccines have been consistently provided to the public, healthcare professionals, and industry. Efforts include FAQs, educational materials, safety alerts, media interview, and summary report of data collected and analysed.

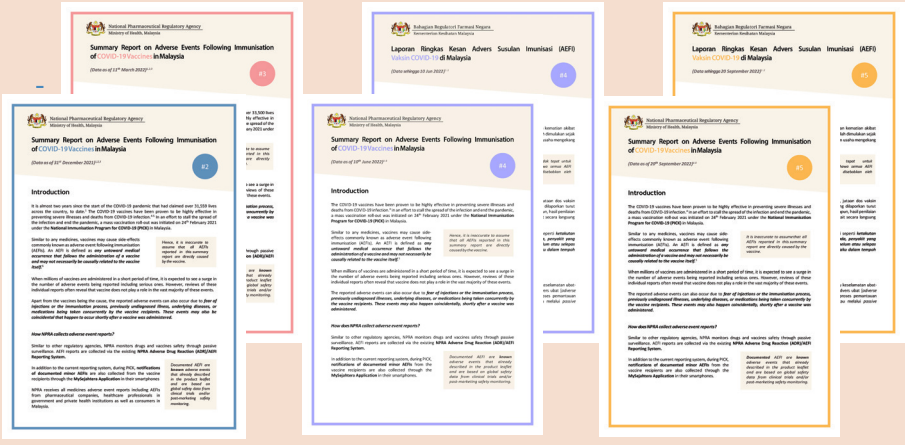
Public Engagements Through Various Media Outlets

Summary Report on Adverse Events Following Immunisation of COVID-19 Vaccines in Malaysia

Since 2021, NPRA started to publish the summary report of AEFI related to COVID-19 vaccines that provides an overview of adverse events that have occurred in individuals who received COVID-19 vaccines in Malaysia. The purpose is to provide transparency and information to the public, healthcare professionals, and relevant authorities regarding the safety profile of COVID-19 vaccines administered in Malaysia. It allows healthcare professionals and the public to stay informed about the safety of COVID-19 vaccines and ensures that any necessary actions are taken to address potential risks.

In 2022, the NPRA has published and distributed **4 Summary Report on AEFI following Immunisation of COVID-19 vaccines** and **2 *Laporan Ringkas Kesan Advers Susulan Imunisasi (AEFI) Vaksin COVID-19 di Malaysia***, which are available on the NPRA website via Summary Reports on AEFI of COVID-19 Vaccines, as follows:

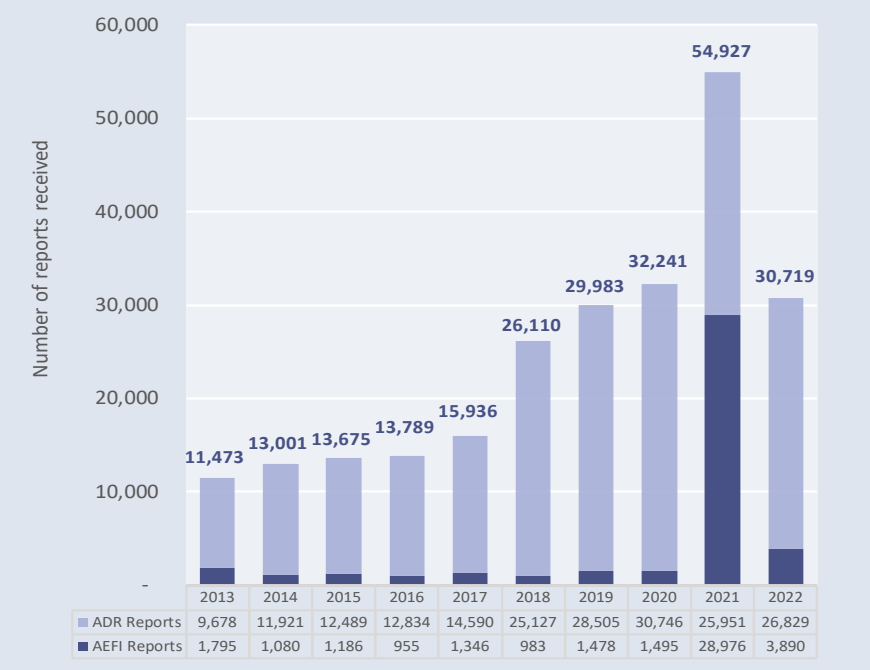
Summary Report #2 (Data as of 31 Dec 2021)
Summary Report #3 (Data as of 11 Mar 2022)
Summary Report #4 (Data as of 10 June 2022)
Laporan Ringkas #4 (Data sehingga 10 Jun 2022)
Summary Report #5 (Data as of 20 Sept 2022)
Laporan Ringkas #5 (Data sehingga 10 Sep 2022)



Analysis of ADR/AEFI Reports

In 2022, the National Centre received **30,719 reports** of adverse events (ADR/AEFI), noting a significant **44.1% decline** compared to the prior year. This downturn was chiefly due to an **86.6% decrease** in AEFI reporting, a phenomenon predominantly related to the earlier influx of reports following the launch of the National COVID-19 Immunisation Programme (PICK) on 24 February 2021. After filtering out duplicates, follow-up reports, rejected reports, or splitting reports as necessary, a total of **30,821 reports** were recorded in the Malaysian Pharmacovigilance Database (QUEST). Subsequent to causality assessments conducted during MADRAC meetings, in 2022, **54,921 viable new reports* (excluding unregistered/food products)** were submitted to the World Health Organisation (WHO) Collaborating Centre for International Drug Monitoring in Uppsala, for inclusion into the VigiBase—the WHO global database of individual case safety reports (ICSRs). The collected data are being continuously monitored for not only changing patterns and trends in any adverse event but also for new safety signals that warrant further evaluation and confirmation.

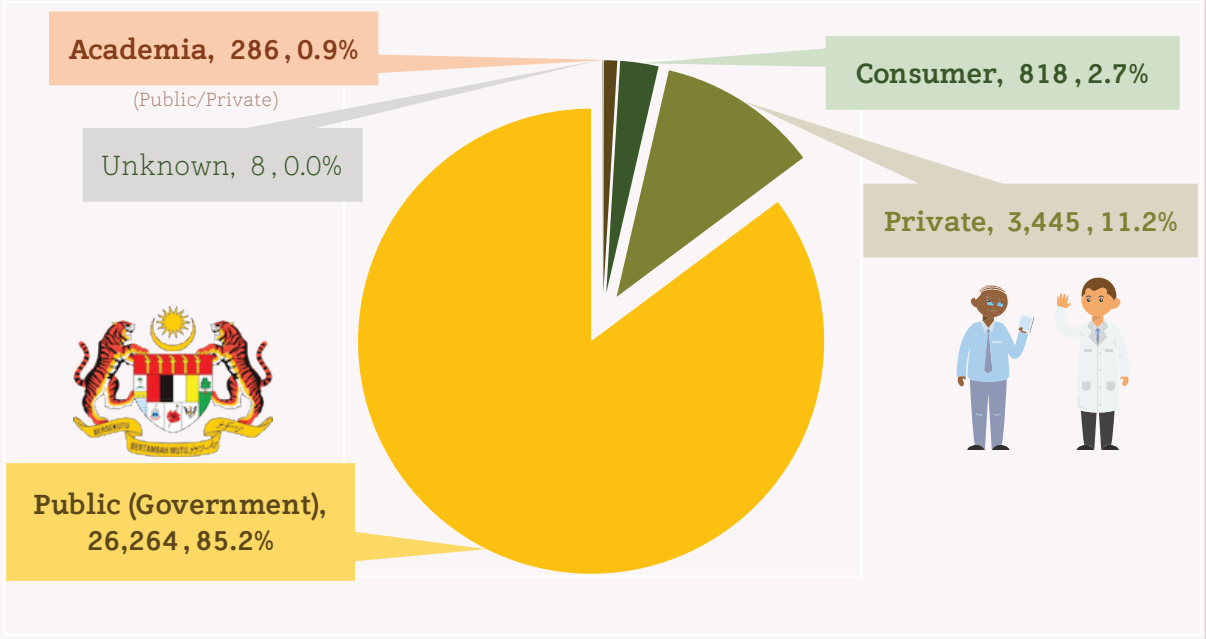
Total Number of ADR and AEFI Reports Received in Malaysia 2013-2022



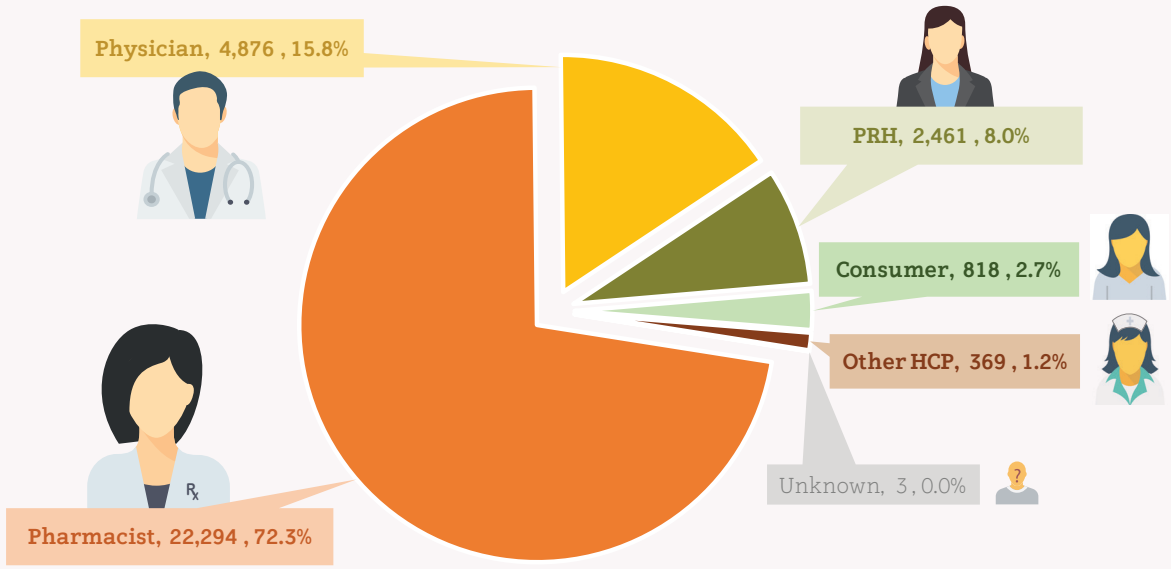
	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022
ADR Reports	9,678	11,921	12,489	12,834	14,590	25,127	28,505	30,746	25,951	26,829
AEFI Reports	1,795	1,080	1,186	955	1,346	983	1,478	1,495	28,976	3,890

**This included reports received by the NPRA in 2021. Due to meticulous assessment and processing, followed by causality assessment by the MADRAC at quarterly intervals, reports received in one year may be submitted to VigiBase the following year.*

Distribution of ADR/AEFI Reports Recorded by Sector, 2022*



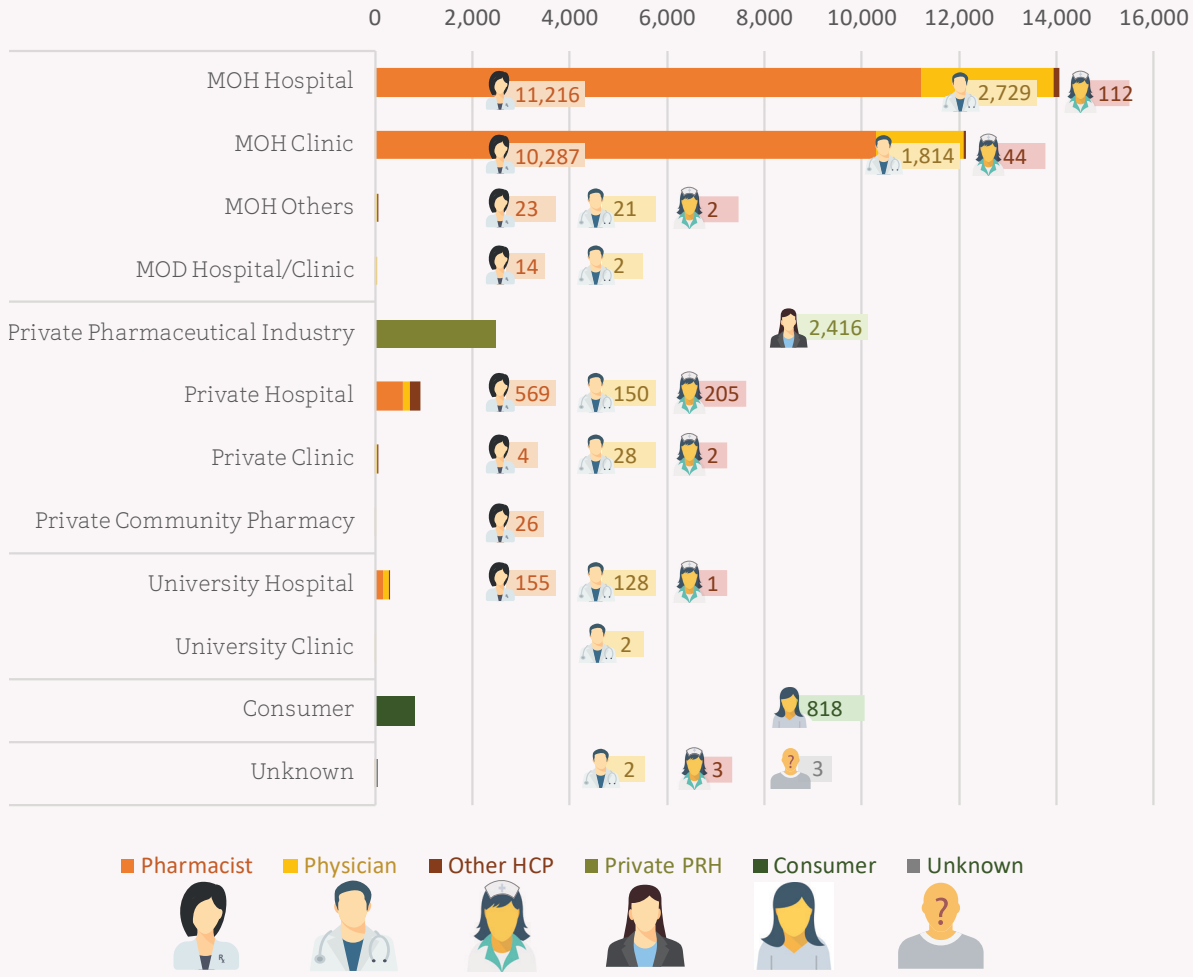
Distribution of ADR/AEFI Reports Recorded By Reporter Qualification, 2022*



HCP: Healthcare professionals; PRH: Product registration holders

*Based on total 30,821 processed ADR/AEFI reports

Distribution of ADR/AEFI Reports Recorded by Institution Type/Reporter Qualification, 2022*

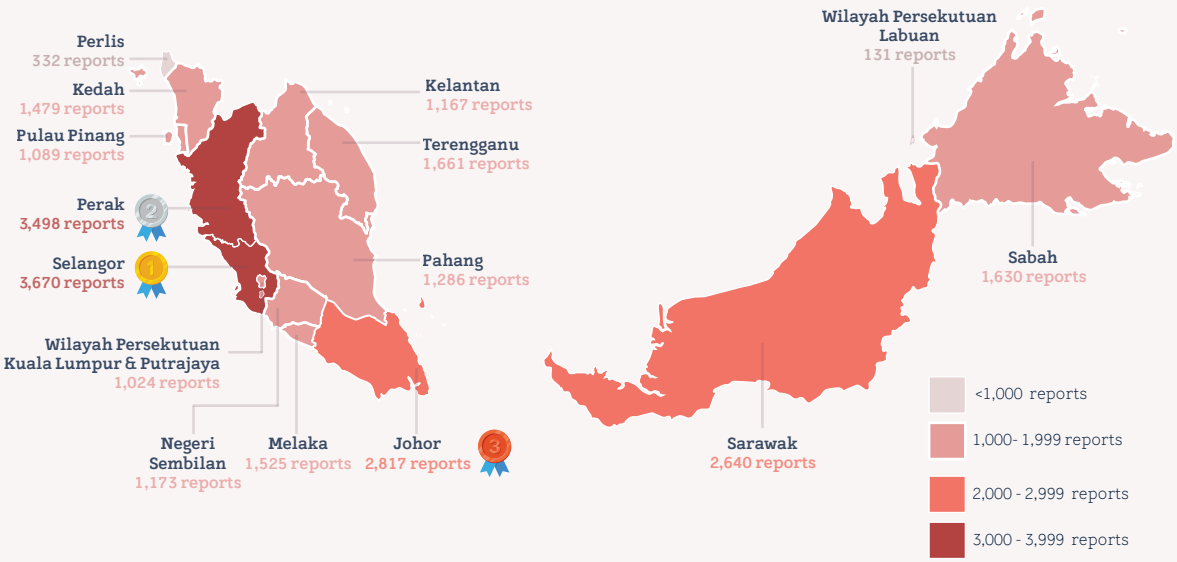


	Government				Private				Academia				
	MOH Hospital	MOH Clinic	MOH Others	MOD Hospital	Pharmaceutical Industry	Hospital	Clinic	Community Pharmacy	University Hospital	University Clinic	Consumer	Unknown	**Total**
Pharmacist	11,216	10,287	23	14		569	4	26	155				**22,294**
Physician	2,729	1,814	21	2		150	28		128	2		2	**4,876**
Other HCP	112	44	2			205	2		1			3	**369**
Private PRH					2,461								**2,461**
Consumer											818		**818**
Unknown												3	**3**
Total	**14,057**	**12,145**	**46**	**16**	**2,461**	**924**	**34**	**26**	**284**	**2**	**818**	**8**	**30,821**

HCP: Healthcare professionals; MOD: Ministry of Defence; MOH: Ministry of Health; PRH: Product registration holders

*Based on total 30,821 processed ADR/AEFI reports

Distribution of ADR/AEFI Reports Recorded from Ministry of Health (MOH) Facilities, 2022*



Hospital Kuala Lumpur
763 reports

Respiratory Medicine Institute
174 reports

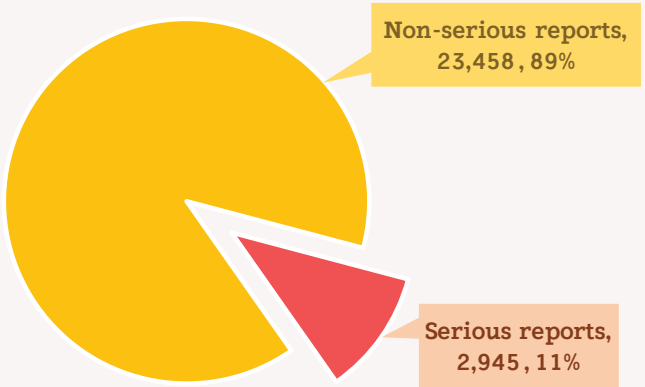
National Heart Institute
114 reports

National Cancer Institute
53 reports

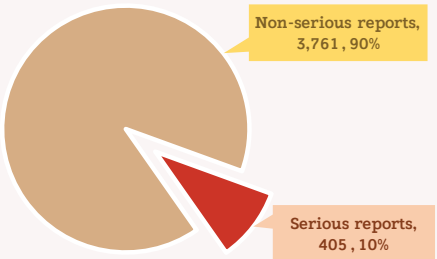
Vaccination Centres (PPV)
22 reports

Distribution of ADR/AEFI Reports Recorded by Case Seriousness, 2022*

ADR Reports



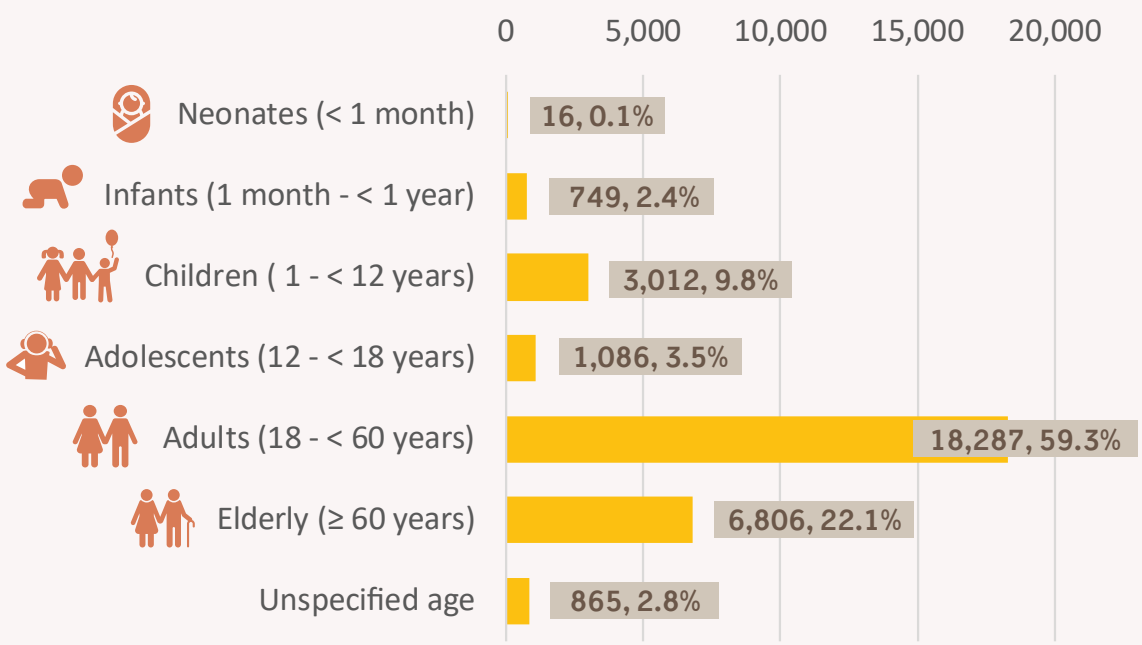
AEFI Reports



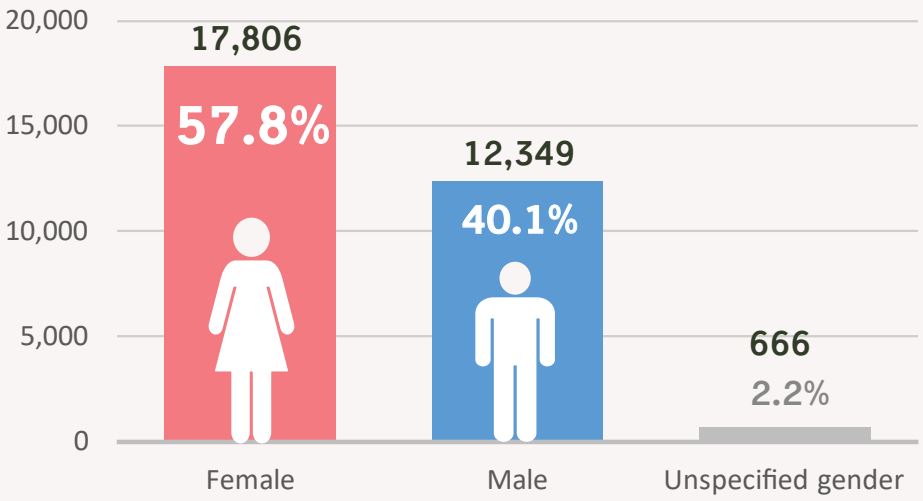
Serious cases include those that require hospitalisation, prolonged existing hospitalisation, are life-threatening, cause persistent or significant disability/incapacity, a congenital anomaly/birth defect, or suspected to cause death

*Based on total 30,821 processed ADR/AEFI reports

Distribution of ADR/AEFI Reports Recorded by Patient's Age Group, 2022*



Distribution of ADR/AEFI Reports Recorded by Patient's Gender, 2022*



*Based on total 30,821 processed ADR/AEFI reports

Number of Products Involved in ADR/AEFI Reports, 2022#

30,653 (94.3%)
Poisons & prescription items

1,630 (5.1%)
Non-poisons

42 (0.1%)
Natural products

167 (0.5%)
Unregistered/Food products

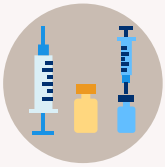
Top 10 Most Reported Route of Administration of the Products Involved, 2022#

Route of Administration	Number (%)
	**20,240 (62.3%)**
 Intramuscular	**4,556 (14.0%)**
 Intravenous (not otherwise specified)	**4,233 (13.0%)**
 Subcutaneous	**750 (2.3%)**
 Intravenous drip	**484 (1.5%)**
 Intravenous bolus	**321 (1.0%)**
Intraperitoneal	**181 (0.6%)**
 Inhalation	**112 (0.3%)**
 Topical	**76 (0.2%)**
 Rectal	**73 (0.2%)**
Unknown	**1,148 (3.5%)**

#Based on total 32,492 products involved in 30,821 processed ADR/AEFI reports
Note: A report may involve one or more medicinal products

Top 10 Most Reported Pharmacological Group of the Products Involved, 2022#

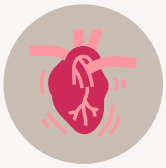
1



Anti infectives

6,496 (19.9%)

2



Cardiovascular

4,318 (13.3%)

3

Vaccines

4,243 (13.1%)

4

Analgesics

4,215 (13.0%)

5

Others

1,728 (5.3%)

6

Anti neoplastics

1,358 (4.2%)

7

Anti diabetics

1,321 (4.1%)

8

Anti hyperlipidaemic

669 (2.1%)

9

Anti tuberculosis

501 (1.5%)

10

Anti epileptics

475 (1.5%)

#Based on total 32,492 products involved in 30,821 processed ADR/AEFI reports
Note: A report may involve one or more medicinal products

Top 10 Most Reported MedDRA System Organ Class of the Adverse Drug Reactions (ADR) Recorded, 2022+

1

Skin and subcutaneous tissue disorders
14,168 (31.3%)

2

Gastrointestinal disorders
6,048 (13.4%)

3

Nervous system disorders
5,877 (13.0%)

4

General disorders and administration site conditions
5,295 (11.7%)

5

Eye disorders
4,157 (9.2%)

6

Respiratory, thoracic and mediastinal disorders
4,151 (9.2%)

7

Investigations
1,254 (2.8%)

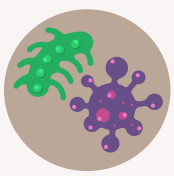
8

Musculoskeletal and connective tissue disorders
692 (1.5%)

9

Cardiac disorders
510(1.1%)

10



Immune system disorders
456 (1.0%)

+Based on total 45,216 adverse events involved in 26,655 processed ADR reports.
Note: A report may involve one or more adverse events.

Top 10 Most Reported MedDRA System Organ Class of the Adverse Events Following Immunisation (AEFI) Recorded, 2022^

1

General disorders and administration site conditions
3,550 (37.3%)

2

Skin and subcutaneous tissue disorders
1,311 (13.8%)

3

Nervous system disorders
1,245 (13.1%)

4

Gastrointestinal disorders
704 (7.4%)

5

Respiratory, thoracic and mediastinal disorders
696 (7.3%)

6

Musculoskeletal and connective tissue disorders
527 (5.5%)

7

Cardiac disorders
362 (3.8%)

8

Psychiatric disorders
240 (2.5%)

9

Eye disorders
197 (2.1%)

10

Infections and infestations
157 (1.6%)

^Based on total 9,524 adverse events involved in 4,166 processed AEFI reports.
Note: A report may involve one or more adverse events.

Safety Signal Detection and Risk Management

Detecting Local Safety Signals

The year 2022 marks the beginning of a new chapter in Pharmacovigilance Section with the **newly incorporated quantitative signal detection** into our routine drug safety monitoring activities. Previously, our signal detection primarily relied on information from external sources such as safety updates from reference agencies and notifications by product registration holders. Our newly established procedures and workflow aim to identify local safety signals based on adverse drug reactions (ADR) and adverse events following immunisation (AEFI) reports received in Malaysia. For a detailed explanation, refer to *MADRAC Bulletin Vol. 40 > Highlights > Venturing into Quantitative Signal Detection.*

The process consists of four main steps: signal triage, signal validation and prioritisation, signal assessment, and signal endorsement.

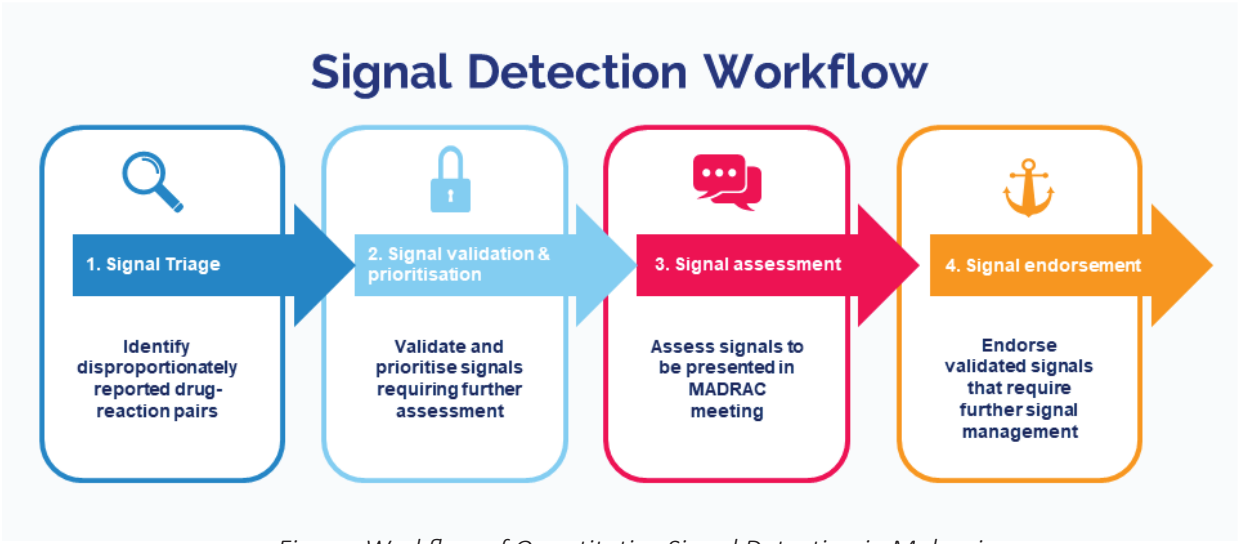


Figure. Workflow of Quantitative Signal Detection in Malaysia.

In 2022, the MADRAC endorsed a total of **7 signals**, resulting in **updates of package inserts / consumer medication information leaflets (RiMUP)** for **2 signals** and **risk communication** via MADRAC Bulletin and NPRA website for **4 signals**. **One signal** was **closed** with no regulatory actions required.

6

Signals resulted in risk minimisation measures

2 **Updates of package inserts / RiMUPs required**

Polymyxin B
Skin hyperpigmentation

Phenobarphital
Stevens-Johnson Syndrome (SJS)

4 **Risk communication issued**

Cefepime
Acute Generalised Exanthematous Pustulosis (AGEP)

Cefazolin
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Efavirenz
Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Aloe Vera
Acute Kidney Injury

1 **Signal closed with no regulatory actions required**

Monitoring Drug Safety Issues

In 2022, a total of **312 drug safety issues** were proactively identified through the environmental screening of published information on reference agencies' websites. Additionally, **203 notifications of drug safety issues** were received from the product registration holders (PRHs). Following review, **27 safety issues were presented at MADRAC meetings** to determine the appropriate risk minimisation measures (refer to page 22–23). The majority of these led to updates to the product safety information, including the addition of details related to newly identified safety concerns, harmonisation of product information across all products registered in Malaysia, or strengthening existing product information. **Twelve recommendations for mandatory regulatory action** were proposed to the DCA, resulting in directives issued to ensure package inserts and consumer medication information leaflets (RiMUP) of all products containing the affected active ingredients are updated with the crucial safety information.

4
MADRAC meetings

27
Safety issues presented

12
Safety issues required mandatory updates of package inserts/ consumer medication information leaflets

3
Direct Healthcare Professional Communication (DHPC) letters reviewed

253
Products involved in regulatory action

MADRAC 181 24 February 2022	DCA Directive	DHPC Letter	PI/RiMUP Update	Safety Alert	Further Review	Others
Betamethasone (Systemic) Risk of Pheochromocytoma Crisis				●	●	
Amoxicillin Risk of Aseptic Meningitis				●	●	
Tenofovir Alafenamide (TAF) Risk of Renal Adverse Effects				●	●	
Sulfamethoxazole & Trimethoprim (Co-Trimoxazole) Risk of Acute Respiratory Distress Syndrome (ARDS)	●		●	●		
Warfarin Risk of Anticoagulant-Related Nephropathy (ARN)	●		●	●		
Hydrochlorothiazide, Chlorthalidone, Indapamide and Acetazolamide Risk of Choroidal Effusion, Acute Myopia & Acute Angle-Closure Glaucoma	●		●	●		
MADRAC 182 26 May 2022						
Olmesartan Risk of Autoimmune Hepatitis				●	●	
Empaglifozin Risk of Tubulointerstitial Nephritis				●	●	
Loperamide: Risk of Acute Pancreatitis				●	●	
Mavenclad® (Cladribine) Risk of Serious Liver Injury and New Recommendations About Liver Function Monitoring		●	●	●		
Corticosteroids (Systemic) Risk of Pheochromocytoma Crisis	●		●	●		
Azathioprine Risk of Erythema Nodosum	●		●	●		
Chloroquine and Hydroxychloroquine Risk of Psychiatric Disorders	●		●	●		

MADRAC 183 25 August 2022	DCA Directive	DHPC Letter	PI/RiMUP Update	Safety Alert	Further Review	Others
Metformin Risk of Vitamin B12 Deficiency				●	●	
Nirmatrelvir/Ritonavir (Paxlovid®) Risk of Anaphylaxis dan Hypersensitivity Reactions				●	●	
COVID-19 Vaccines Risk of Tinnitus				●	●	
Alectinib (Alecensa®) Risk of Haemolytic Anaemia (New Warning and Precaution and Dose Modification Guidance)		●	●	●		
Brolucizumab (Pagenax®) Risk of Intraocular Inflammation, Including Retinal Vasculitis and/or Retinal Vascular Occlusion (Updated Recommendations to Minimise the Known Risks)		●	●	●		
Methadone Risk of Hypoglycaemia	●		●	●		
Iodinated Contrast Media Risk of Hypothyroidism (Particularly in Newborns and Young Children)	●		●	●		
Piperacillin (Including Combination P roducts) Risk of Haemophagocytic Lymphohistiocytosis (HLH)	●		●	●		
Sertraline Risk of Microscopic Colitis	●		●	●		
Labetalol Risk of Nipple Pain and Raynaud's Phenomenon of the Nipple	●		●	●		
MADRAC 184 11 November 2022						
Sorafenib Risk of Thrombotic Microangiopathy (TMA)				●	●	
Pneumococcal Polysaccharide Vaccine (23-Valent) Risk of Extensive Swelling of Vaccinated Limb				●	●	
Hydroxychloroquine Risk of Hepatic Impairment				●	●	
Donepezil Risk of QT Prolongation and Torsade de Pointes	●		●	●		

Assessment of Drug Safety Documents

Periodic Benefit-Risk Evaluation Report (PBRER)/ Periodic Safety Update Report (PSUR)

For the first five years of post-registration, product registration holders (PRHs) are required to submit Periodic Benefit-Risk Evaluation Reports/ Periodic Safety Update Reports (PBRERs/PSURs) on newly registered products, namely New Drug Products (NDPs) and Biologic products. PBRERs/PSURs contain information on the product safety profile in countries where it is registered, and any changes or new findings related to product safety. Besides, new COVID-19 vaccines and treatment were also required to submit Monthly Safety Summary Report (MSSR).

In 2022, assessment was conducted on **297 PBRERs** and **MSSRs** pertaining to **198 products**, including **115 new drug products** and **83 biologics products**. Thereafter, **20% (39/198) of these products underwent package insert updates** to incorporate the latest safety information.

Risk Management Plan (RMP)

A Risk Management Plan (RMP) is a detailed description of the risk management system. An updated RMP post-registration for New Drug Products (NDPs) and Biologic products is required to be submitted by product registration holder when there is a significant change in the safety specification.

In 2022, a total of **107 RMPs** were received. Additional risk minimisation measures mainly in the form of educational materials targeted for healthcare professionals and patients were also reviewed. In 2022, there were **29 educational materials** reviewed and approved as additional risk minimisation measures for healthcare professionals and patients.

Drug Safety Communication

Publications

MADRAC Bulletin

MADRAC Bulletin features articles based on local adverse drug reactions/adverse events following immunisation information of a particular drug, followed by discussion and advice to healthcare professionals. These articles are aimed to capture the interest of healthcare professionals in the clinical setting to help identify adverse drug events, practise caution when prescribing, dispensing or counselling of medicines to patients as well as to encourage ADR/AEFI reporting. MADRAC Bulletin also keeps its readers up to date with new directives issued to communicate recent drug safety issues, changes in drug prescribing information as well as new warnings and precautions.

NPRA has published and distributed **three (3) MADRAC Buletin** issued in 2022, which are available on the NPRA website via MADRAC Bulletin, as follows:

MADRAC Bulletin, Issue 01/2022, Vol. 37

MADRAC Bulletin, Issue 02/2022, Vol. 38

MADRAC Bulletin, Issue 03/2022, Vol. 39

Safety Alerts

Safety Alerts are concise drug-related articles published in the NPRA website which are intended to alert healthcare professionals on new drug safety issues that arise as a result from drug safety reviews by NPRA and other international regulatory agencies. This communication is a form of risk minimisation measure taken to reduce the risk of adverse events of new and existing registered products in Malaysia.

In 2022, NPRA has published **25 safety alerts** to highlight drug safety issues. The full list of safety alerts in 2022 is available on the NPRA website via Safety Alerts.

Direct Healthcare Professional Communication (DHPC) Letter

In addition to the publications listed above, Direct Healthcare Professional Communication (DHPC) letters, previously known as "Dear Doctor letters", are used to communicate recent safety information to healthcare professionals. Such instances include important new or emerging risks, important changes in prescribing information, new contraindications, suspension or withdrawal of product registrations, and product quality or availability issues that may possess potential detrimental effects on patient care. DHPC letters submitted by the product registration holders are carefully reviewed and approved by NPRA before being distributed.

In 2022, a total of **three (3) DHPC letters** were reviewed and approved by NPRA.

Electronic Mailing List

The **NPRA Safety Information Mailing List**, an electronic mailing list, was established in 2014 for healthcare professionals in an effort to ensure wider and faster spread of information. This mailing list is managed by the Pharmacovigilance Section and currently consists of **more than 2,350 individuals**, including doctors, dentists, pharmacists, nurse, assistant medical officers, assistant pharmacists, regulatory affairs professionals, academicians, and journal editors.

Consumer Medication Information Leaflets

Consumer Medication Information Leaflets, otherwise known as ***Risalah Maklumat Ubat untuk Pengguna*** **(RiMUP)** are a source of information for consumers, containing advice on how to use the medicines as well as important warnings/precautions in more layman and easy-to-understand terms. RiMUPs are prepared in *Bahasa Malaysia* and English by product registration holders, and to be reviewed and approved by the NPRA.

In 2022, a total of **220 RIMUPs** were approved by the Pharmacovigilance Section in NPRA and is available on the NPRA website via Product Search.

Training, International Participation & Collaborations, and Other Pharmacovigilance Activities

Highlights of Training & Local Collaborations

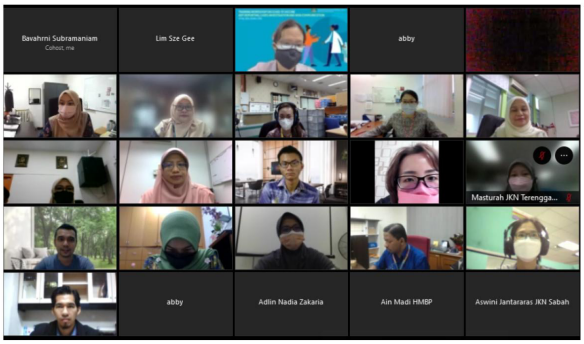
Over the years, the NPRA has consistently provided training or sharing sessions on a wide range of pharmacovigilance topics to various stakeholders. These initiatives have reached healthcare providers in both the public and private sectors, pharmaceutical companies, authorities, and university students.

In 2022, the Pharmacovigilance Section of NPRA successfully hosted 3 national pharmacovigilance training sessions for over 600 healthcare providers across Malaysia. Besides, numerous esteemed agencies graciously extended invitations to pharmacovigilance officers to share their expertise through talks, presentations, or interviews on medication safety. Throughout the year, these efforts resulted in a commendable total of **36 training and sharing sessions**, serving to enlighten and inform target audiences on vital aspects of pharmaceutical and natural product vigilance. Selected highlights from these engaging sessions are as follows.

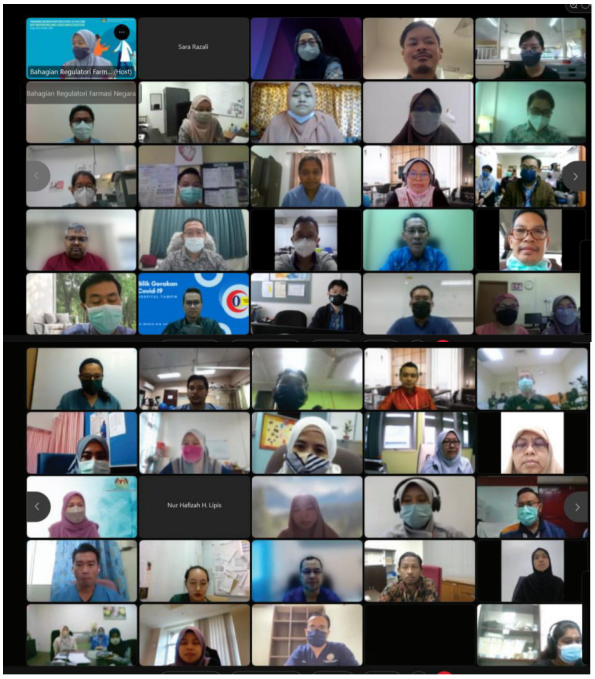
NPRA's Training Workshops on COVID-19 Vaccine AEFI Reporting, Case Investigation and Risk Communication

In 2022, the Pharmacovigilance Section of NPRA organised 2 significant virtual training workshops focused on adverse events following immunisation (AEFIs) related to COVID-19 vaccines.

The first workshop on 17 February 2022 was attended by 90 medical doctors and pharmacists, and provided in-depth training on enhancing COVID-19 vaccine-specific AEFI reporting and case investigations. It also covered the vital role of effective risk communication and its impact on public health.



The second workshop on 21 April 2022, attended by 284 physicians, pharmacists, and medical assistants from public health facilities, focused on investigating death reports potentially linked to COVID-19 vaccines. This session clarified common misconceptions about AEFI investigations and causality assessments pertaining to death cases, highlighted the importance of forensic pathologists, and involved participants in forensic case discussions.



Pharmacovigilance Seminar: Pharmacovigilance for Safer Use of Medicines

On 4 October 2022, over 250 pharmacists participated in a virtual Pharmacovigilance Seminar organised by the NPRA, aimed at enhancing patient safety by deepening their understanding of the Malaysian Pharmacovigilance System. The seminar highlighted four critical areas: management of adverse drug reactions (ADR) and adverse events following immunisation (AEFI), safety signal detection, risk assessment, and risk communication.

In this seminar, participants learnt about the importance of of producing high-quality ADR/AEFI reports, procedures for investigating serious cases, and causality assessments. The seminar also discussed how safety signals are detected from accumulated reports, the steps involved in evaluating and managing safety issues, and the processes underpinning Good Pharmacovigilance Practices (GVP) Inspection. The seminar wrapped up with a focus on effective risk communication strategies and the mechanisms in place for promoting the safer use of medicines in Malaysia.

Visit from Final-Year Pharmacy Students at MAHSA University to NPRA

On 30 June 2022, the NPRA hosted a half-day visit from final-year students of the Faculty of Pharmacy at MAHSA University. The visit involved a total of 20 students accompanied by a lecturer and featured a comprehensive sharing session at Anggerik Hall. The goal of the session was to familiarise B. Pharm students with various regulatory activities and operations within Malaysia. NPRA representatives enthusiastically provided an overview of the agency's roles and responsibilities, covering topics on product registration, cosmetic notification, good manufacturing practice (GMP), and pharmacovigilance system in Malaysia.

Briefing Session on Pharmaceutical Services for the National Pharmacy Call Centre (NPCC) and Medicine Information Service (PMU) in Malaysia

A meeting organised by the Pharmaceutical Services Division (PPF) that engaged pharmacists from the National Pharmacy Call Centre (NPCC) and Medicine Information Service (*Perkhidmatan Maklumat Ubat*—PMU) committee members from all states in Malaysia was held on 13–14 September 2022.

The primary objective of this meeting was to clarify the job scopes and functions of each centre within the PPF and the NPRA. This meeting also aimed to provide updates on current issues related to COVID-19 and to serve as a national communication platform for pharmacists from the NPCC and PMU, fostering information and idea sharing among the attendees. Speakers at the event included pharmacists from both the NPRA and PPF.

An officer from the Pharmacovigilance Section of the NPRA was invited to deliver a talk on 'Pharmacovigilance of COVID-19 Vaccines in Malaysia'. This presentation provided valuable insights into the overview of pharmacovigilance, adverse event following immunisation (AEFI) reporting, ongoing monitoring, and the compilation of summary reports of AEFIs following COVID-19 vaccinations in Malaysia.

World Patient Safety Week & World Pharmacy Week Workshop at Hospital Al-Sultan Abdullah UiTM, Puncak Alam

From 27 until 30 September 2022, Hospital Al-Sultan Abdullah UiTM (HUITM) in Puncak Alam hosted the World Patient Safety Week & World Pharmacy Week Workshop. The event featured several key activities, including a "Medication Without Harm" workshop, an "Incident Reporting and Root Cause Analysis" workshop, and various side activities. The workshops aimed to enhance awareness of Medication Without Harm, support the goals of the Malaysia Patient Safety Goals and the WHO Global Patient Safety Challenges, and empower patient involvement in safety issues at UiTM.

A pharmacovigilance officer from the NPRA was invited to deliver a plenary talk titled "Adverse Drug Reaction (ADR) / Adverse Event Following Immunisation (AEFI) – How to Improve Patient Safety". This talk provided insights into ADR and AEFI reporting in Malaysia, focusing on the quality and impact of these reports.

World Patient Safety Day at National Heart Institute (IJN): CME Session on Adverse Drug Reaction Reporting & Quality

On 28 September 2022, in conjunction with World Patient Safety Day, the National Heart Institute (IJN) hosted a virtual Continuous Medical Education (CME) session titled "Adverse Drug Reaction (ADR): Reporting and Quality". A pharmacovigilance officer from the NPRA was invited to lead the session. The session, attended by IJN staff including pharmacists, nurses, and other healthcare professionals, aimed to enhance understanding of the importance of reporting high-quality reports. It covered topics such as ADR and adverse events following immunisation (AEFI) reporting protocols, report quality, and strategies for preparing high-quality reports. Specifically, this session featured case studies of cardiovascular-related ADRs, providing relevant and practical insights for the IJN audience.

Pharmacovigilance Talk at Tuanku Mizan Armed Forces Hospital

On 7 October 2022, the Pharmacy Department of Tuanku Mizan Armed Forces Hospital (HATTM) hosted a Continuous Medical Education (CME) hybrid event, featuring a pharmacovigilance officer as one of the distinguished speakers. The talk, titled "Pharmacovigilance: Its Importance, Role, and Impact on National Healthcare" was well-attended by healthcare professionals and support staff from HATTM. This session sparked significant interest among the audience, where participants enthusiastically engaged with questions and discussions about various aspects of pharmacovigilance and its critical influence on healthcare practices.

International Participation & Collaborations

Malaysian NPRA-Australian Therapeutic Goods Administration (TGA) Seminar on Safety Signal Management

The NPRA continuously takes steps to strengthen and refine regulatory control processes through collaboration with other regulatory agencies. Since 2021, NPRA has participated in the Regulatory Strengthening Programme conducted by the Australian Therapeutic Goods Administration (TGA). Among the activities included technical assistance and collaborations in pharmacovigilance areas.

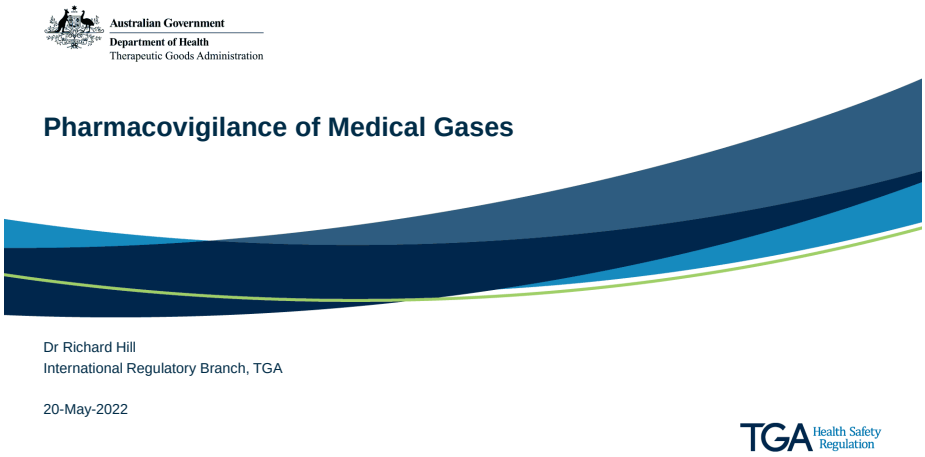
On 30–31 March 2022, a seminar on safety signal management was conducted for all NPRA pharmacovigilance staff, featuring speakers from both NPRA and TGA. During the session, TGA shared their experiences in signal investigations, covering signal detection, signal prioritisation, and signal assessment for medicines and vaccines. NPRA's pharmacovigilance team also presented our current signal management process, receiving valuable input from TGA for further refinement. Various strategies to enhance local safety signal management were discussed.

Additionally, on 18 March 2022, a session on Effective Communication of Safety Risks was held. TGA shared their expertise in effective risk communication, particularly in conveying information on COVID-19 vaccine safety to the public.

Training on Medical Gases by the Australian Therapeutic Goods Administration (TGA)

On 20 May 2022, the NPRA Medicinal Gas Task Force (MG-TF) organised a virtual training on Medical Gases for NPRA officers, with participation from 69 officers, including 3 from the Pharmacovigilance Section. This training, facilitated by the Australian Therapeutic Goods Administration (TGA), underscored a global commitment to enhancing regulatory oversight on medical gases.

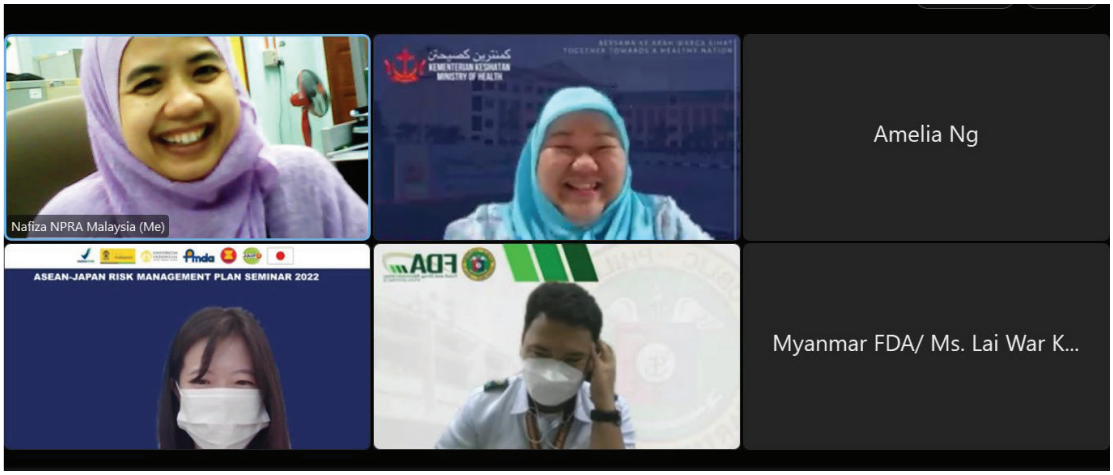
The training session covered aspects of the regulation and control of medical gases in Australia, including good manufacturing practice (GMP) and post market surveillance activities (PMS). Additionally, it delved into the pharmacovigilance practices specific to medical gases in Australia, providing valuable insights into their safety oversight.



ASEAN-Japan Risk Management Plan Symposium and Seminar 2022

On 23 May 2022, the ASEAN-Japan Risk Management Plan Symposium took place virtually, co-hosted by the Indonesian Food and Drug Authority (BPOM), the Pharmaceutical and Medical Devices Agency (PMDA), and the University of Indonesia. Supported by the Japan-ASEAN Integration Fund (JAIF), the symposium aimed to deepen the understanding of Risk Management Plans (RMP) among regulators from ASEAN Member States (AMS). The event targeted regulators, industry professionals, and academicians from AMS, attracting 283 participants. Six pharmacovigilance officers from NPRA were among the attendees.

The following days, 24 and 25 May 2022, saw the continuation of discussions at the ASEAN-Japan Risk Management Plan Seminar 2022, virtually co-hosted by the same organisations. The seminar focused specifically on ASEAN regulators, attracting 72 participants, including 44 observers, with 2 pharmacovigilance officers from NPRA in attendance. During the seminar, PMDA staff from the Office of Pharmacovigilance I/II and representatives from the Japan Pharmaceutical Manufacturers Association (JPMA) delivered insightful lectures on RMP and labelling. Additionally, interactive group work on RMP development further enhanced the collaborative learning experience, allowing participants to actively exchange opinions and gain a deeper understanding of the subject.



WHO Global Benchmarking Tool: Training Course for Assessors in Turkey

In 2022, the World Health Organisation (WHO) organised face-to-face workshops in Istanbul, Turkey for selected members from the National Drug Regulatory Authorities (NDRA) worldwide. These workshops targeted assessors of all experience levels and were considered a necessary step for the involvement in future benchmarking missions. The WHO extended an invitation to Madam Norleen Mohamed Ali, senior pharmacovigilance officer from NPRA to participate in the workshop held from 1 to 3 June 2022. This workshop saw participation from 28 assessors.

The objectives of the workshop were to enhance the consistency of assessors' approaches during benchmarking missions, increase the quality of benchmarking outputs, and provide training on the WHO Regulatory System Strengthening (RSS) programme's benchmarking process. Additional objectives included practising the use of computerised Global Benchmarking Tool (GBT) and managing the conduct of benchmarking missions—covering interviews, investigation skills, correct behaviour, communication skills, and team working. The workshop also aimed at strengthening the preparation of effective

reports, including recommendations and results presentation, as well as acquiring basic elements of the WHO-Listed Authority (WLA) framework and the performance evaluation process.

The workshop provided a comprehensive overview covering challenges, common mistakes, good investigation practices, correct reporting, formulation of recommendations, soft skills, and communication styles. It included hands-on training with interactive exercises on electronic platforms and role-playing to reinforce the integration of theoretical knowledge with practical sessions. Participants actively engaged in individual and group exercises, conducted reviews of benchmarking documents, and evaluated daily sessions with warm-ups emphasising the significance of body language and teamwork in benchmarking activities. The successful execution of the workshop provided participants with a robust foundation for effectively implementing benchmarking skills.

Notably, as a certified WHO GBT assessor, Madam Norleen later participated as a team member in the WHO GBT assessment of the Saudi Food and Drug Authority (SFDA), conducted from 27 November to 1 December 2022.

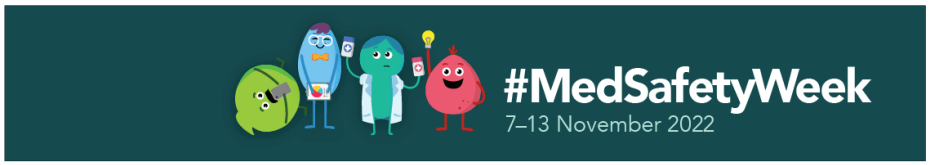
The 2nd Malaysia -Japan Symposium

The 2nd Malaysia-Japan Symposium on Medical Product Regulation was successfully held on 14 July 2022, continuing the collaborative efforts initiated in 2015. Hosted by the NPRA and Pharmaceutical and Medical Devices Agency (PMDA) Japan, this symposium aimed to enhance mutual understanding of each country's regulatory systems, particularly in the context of the COVID-19 pandemic, and to promote the advancement of pharmaceutical regulations and development.

This virtual symposium attracted 420 participants, including regulators and representatives from the pharmaceutical industries not only from both countries but also from Singapore, Taiwan, Indonesia, Hong Kong, and Cuba, reflecting a shared commitment to enhancing regulatory standards and ensuring the safety and efficacy of medical products in the region.

YBrs. Madam Norhaliza binti A. Halim, Senior Director of Pharmaceutical Services at the Ministry of Health Malaysia, and Dr. Yasuhiro Fujiwara, Chief Executive Officer of PMDA, delivered the opening remarks and officially commenced the symposium. Both agencies shared country experiences on expedited reviews, challenges in e-labelling, and pharmacovigilance of COVID-19 vaccines. Participants gained valuable insights into the regulatory landscapes of Japan and Malaysia, fostering stronger ties and promoting the advancement of pharmaceutical regulations.

#MedSafetyWeek 2022: How Patients and Healthcare Professionals Make Safety Work



From 7 to 13 November 2022, NPRA actively engaged in the global #MedSafetyWeek campaign initiated by the World Health Organisation (WHO)-Uppsala Monitoring Centre (UMC), joining forces with national medicines regulatory authorities from over 81 countries and various non-governmental organisations worldwide. In 2022, the focus of this collaborative social media campaign was to highlight the crucial role that healthcare professionals, patients, and carers play in reporting suspected side effects and contributing to medicines safety.

Various communication materials in English and Malay languages, including infographics, animation videos, and posters, were collaboratively prepared and disseminated through diverse channels during the campaign week.

#MedSafetyWeek posters displayed at the pharmacy dispensing counter at Hospital Mesra Bukit Padang, Sabah, showing support for the #MedSafetyWeek campaign.

WHO-International Regulatory Cooperation for Herbal Medicines (IRCH) Network: Workshop on Adverse Drug Reactions (ADRs) for Herbal Medicines

The 14th Annual Meeting of the WHO-International Regulatory Cooperation for Herbal Medicines (IRCH) Network was convened virtually from 23 to 25 November 2022. This meeting gathered regulatory experts, healthcare professionals, and stakeholders worldwide to collaboratively address issues related to herbal medicine regulation. Among the 31 member countries, Malaysia, Argentina, China, Cuba, and Japan were selected to deliver 15-minute presentations during the third day of the conference, focusing on a workshop on adverse drug reactions (ADRs) for herbal medicines.

Malaysia's presentation highlighted significant challenges in reporting ADRs for herbal medicines, notably the substantial underreporting by consumers and product holders, which leads to gaps in data quality and completeness. Other challenges included difficulties in assessing unregistered traditional products with multiple ingredients, as well as unlabelled products and adulteration issues that further complicate regulatory efforts.

Specific safety issues shared by Malaysia included adverse reactions associated with ganoderma ("Lingzhi" in Chinese or "Reishi" in Japanese) products, noting an increase in adverse reactions linked to kidney and liver functions. Recommendations were made for patients to seek medical advice if experiencing signs or symptoms of related adverse reactions.

*Figure: Image of Ganoderma lucidum**

**Image source: https://www.researchgate.net/publication/360619209_Ganoderma_lucidum_and_Antimicrobial_Activity/figures*

Another safety concern shared by Malaysia involved red yeast rice products, which have been linked to muscle pain due to its naturally occurring lovastatin. Malaysia responded by imposing safety measures such as capping the daily dosage at 10mg or less and mandating labels to warn about the lovastatin content to improve consumer awareness and safety.

Figure: Image of red yeast rice

**Image source: https://www.nccih.nih.gov/health/red-yeast-rice*

During the Meeting, Malaysia further recommended strengthening regulations for herbal medicine vendors, promoting research into herbal products, addressing challenges posed by online sales of herbal products, and sustaining efforts to assure the effectiveness and safety of the herbal medicine industry worldwide. These actions are deemed essential for establishing a robust regulatory framework for the safety and efficacy of herbal medicines on a global scale.

Publications

Research Articles

In 2022, the National Centre collaborated with two institutions, namely the National Institutes of Health (NIH) and University Malaya Medical Centre (UMMC), on three research studies.

During the first quarter of the year, the collaboration with UMMC yielded two publications. The first article was titled "**Incidence of Antiseizure Medication-Induced Severe Cutaneous Adverse Reactions (SCARs) in Malaysia**".

This retrospective analysis observed an upward trend in reported antiseizure medication-induced SCAR cases from 28 cases in 2006 to 92 in 2016. The incidence of carbamazepine (CBZ)-induced SCARs increased from 7.5 per 1000 person-years (2006) to 17.8 per 1000 person-years (2016) but later dropped to 7.2 per 1000 person-years (2019). Concurrently, there was an increase in the incidence of SCARs secondary to phenytoin and lamotrigine. The prevalent users of CBZ reduced from 22.8% (2006) to 14.1% (2016), whereas the levetiracetam and sodium valproate users increased by 5.5% and 4.8%, respectively. The incidence of CBZ-induced SCARs had reduced since 2016, probably related to the implementation of human leukocyte antigen-B*1502 screening in Malaysia or substitution of CBZ with other antiseizure medications. However, this was accompanied by an increase in SCAR incidence related to phenytoin and lamotrigine.

Fong SL, Lim KS, Hariraj V, Lee SC, Wo WK, Ramli A, Ho JH, Lai PSM, Ng WL. Incidence of Antiseizure Medication-Induced Severe Cutaneous Adverse Reactions in Malaysia. J Clin Pharmacol. 2022 Aug;62(8):983-991. Available from: https://doi.org/10.1002/jcph.2040

The second article "**Incidence of allopurinol-induced severe cutaneous adverse drug reaction in Malaysia**" analysed cases reported to NPRA from 2015 to 2019, showing an average 2.5 cases per 1000 new users, with a decreasing trend from 3.2 per 1000 new users in 2015 to 2.25 per 1000 in 2019; despite the increasing number of adverse drug reaction cases being reported over the years. Stevens–Johnson syndrome was the most common form of allopurinol-induced SCAR reported, at 143 cases (46.8% of total SCAR reported). Among Malaysia's 3 main ethnicities, the Chinese had the highest percentage of allopurinol-induced SCAR when compared to Bumiputera and Indians (3.18×10^{-4} %).

The estimated incidence of allopurinol-induced SCAR in Malaysia from 2015 to 2019 was 2.5 cases per 1000 new users. This figure is consistent with the incidence reported in other Asian countries, namely Taiwan and Thailand.

Ng WL, Lim KS, Hariraj V, Lee SC, Wo WK, Ramli A, Lai PSM, Fong SL, Lim JR. Incidence of allopurinol-induced severe cutaneous adverse drug reaction in Malaysia. Br J Clin Pharmacol. 2022 Aug;88(8):3782-3788. Available from: https://doi.org/10.1111/bcp.15327

As a part of the SAFECOVAC (Case-Based Monitoring of Adverse Events Following COVID-19 Vaccination) study group led by NIH, the first journal article entitled "**Risk of serious adverse events after the BNT162b2, CoronaVac, and ChAdOx1 vaccines in Malaysia: A self-controlled case series study**" was published in 2022.

This self-controlled case-series study found no increase in the risk formyocarditis/pericarditis, Bell's Palsy, stroke, and myocardial infarction in the 21 days following either dose of BNT162b2, CoronaVac, and ChAdOx1 vaccines. A small increased risk of venous thromboembolism (IRR 1.24; 95% CI 1.02, 1.49), arrhythmia (IRR 1.16, 95% CI 1.07, 1.26), and convulsion/seizure (IRR 1.26; 95% CI 1.07, 1.48) was observed among BNT162b2 recipients. No association between CoronaVac vaccine was found with all events except arrhythmia (IRR 1.15; 95% CI 1.01, 1.30). ChAdOx1 vaccine was associated with an increased risk of thrombocytopenia (IRR 2.67; 95% CI 1.21, 5.89) and venous thromboembolism (IRR 2.22; 95% CI 1.17, 4.21). Overall, the study concluded acceptable safety profiles for these vaccines.

[1]Ab Rahman N, Lim MT, Lee FY, Lee SC, Ramli A, Saharudin SN, King TL, Anak Jam EB, Ayub NA, Sevalingam RK, Bahari R, Ibrahim NN, Mahmud F, Sivasampu S, Peariasamy KM; SAFECOVAC study group. Risk of serious adverse events after the BNT162b2, CoronaVac, and ChAdOx1 vaccines in Malaysia: A self-controlled case series study. Vaccine. 2022 Jul 30;40(32):4394-4402. Available from: https://doi.org/10.1016/j.vaccine.2022.05.075

CPD Points for Adverse Event Reporting by pharmacists

As part of efforts to increase the quantity and quality of adverse event (AE) reports, in particular from private sector healthcare professionals, beginning January 2016, pharmacists are eligible to claim Continuing Professional Development (CPD) points for the submission of quality AE reports.

The Pharmacy Board Malaysia has agreed to award one (1) CPD point under category A4 for every AE report submitted to the NPRA which fulfills certain mandatory criteria [Ref: KKM-55/BPF/101/001/01 JLD 29 (20) and KKM.600-16/1/6(57)].

In 2022, a total of **135 reports received** from pharmacists in the private sector were evaluated and **121 reports** were approved for CPD points claim (89.6% approval).

--- The End ---

Editorial Team

Ministry of Health Malaysia
National Pharmaceutical Regulatory Agency