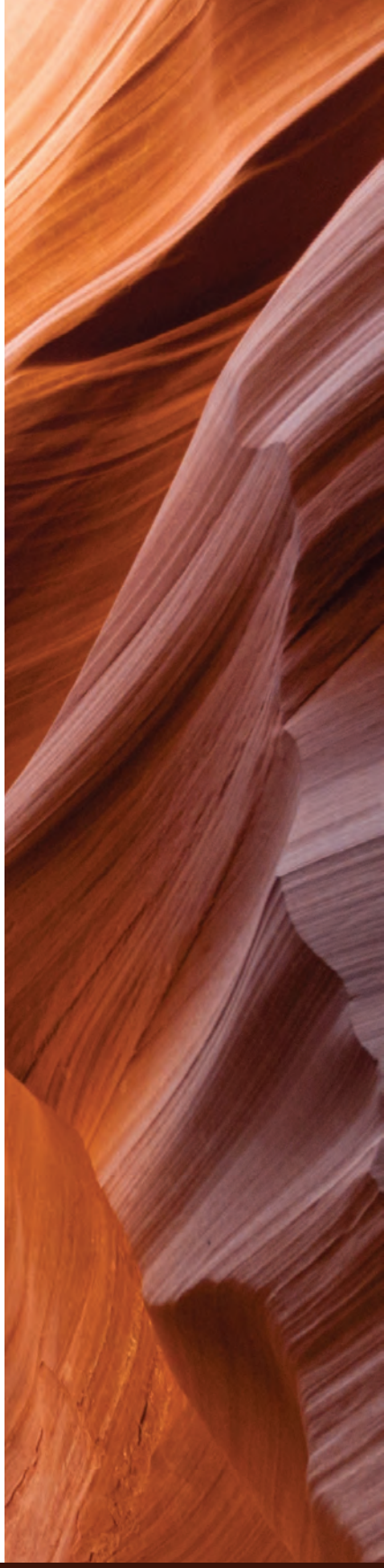
Ministry of Health Malaysia
National Pharmaceutical Regulatory Agency

2021
ANNUAL REPORT
NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING



Ministry of Health, Malaysia

NATIONAL CENTRE FOR ADVERSE DRUG REACTIONS MONITORING: ANNUAL REPORT 2021

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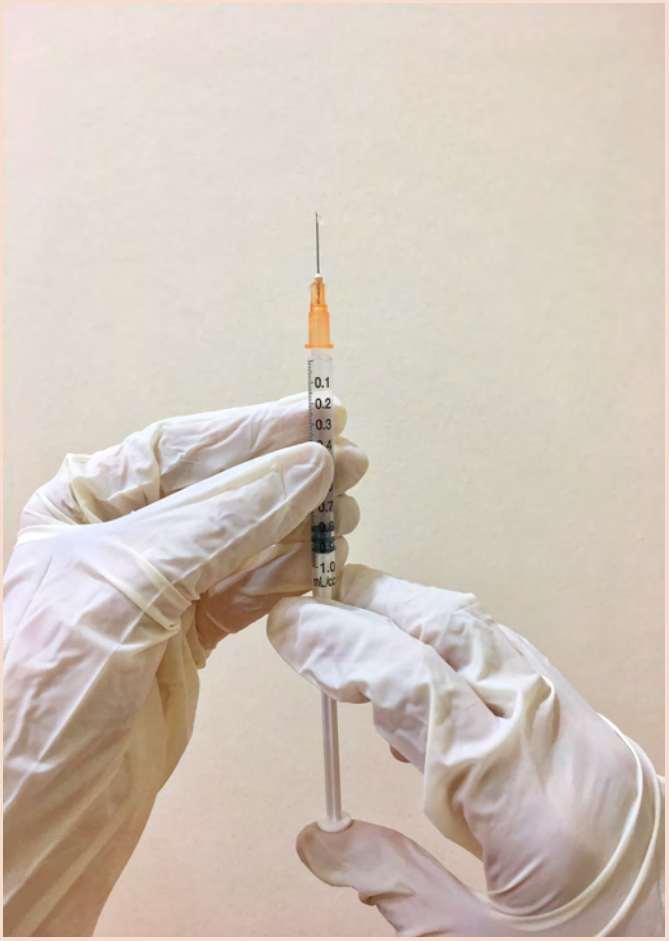
Website: www.npra.gov.my

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.



Inside this report

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 drugs 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 2021.

Table 1: Members of MADRAC Session 2019-2021

Ex-officio	Chairman **YBhg. Datin Dr. Faridah Aryani Md. Yusof / YBrs. Dr. Hasenah Ali** Director of NPRA
	Secretary to MADRAC **YBrs. Dr. Roshayati Mohamad Sani** 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** Senior Medical Consultant Hospital Kuala Lumpur *(Dr. Marzilawati Abdul Rahman)*
	Dr. Mollyza Mohd. Zain National Head of Rheumatology and Senior Medical Consultant (Rheumatology), Hospital Selayang *(Dr. Liza Mohd. Isa)*
	Dr. Suganthi Thevarajah National Head of Dermatology and Senior Consultant Dermatologist, Hospital Kuala Lumpur *(Dr. Tang Min Moon)*

Commitee Members

(Alternate members)

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

Dr. Ramli Ali
Senior Consultant Psychiatrist
Hospital Tunku Azizah
(Dr. Uma Visvalingam)

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

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

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

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

Dr. Adliah Mhd. Ali
Faculty of Pharmacy
Universiti Kebangsaan Malaysia
(Pn. Kamaliah Md. Saman)

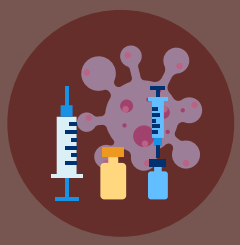
Rozita Mohamad
Deputy Director
Pharmaceutical Care Subdivision
Pharmacy Practice & Development Division
(Rohana Hassan)

Dr. Thirunavukarasu Rajoo
Malaysian Medical Association (MMA)
(Dr. Sivanaesan Letchumanan)

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

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

Harpreet Kaur Darshan Singh
Malaysian Pharmaceutical Society (MPS)
(Charmaine Tan Shwu Fen)



Highlights:
Pharmacovigilance Work During the COVID-19 Pandemic

Malaysian Pharmacovigilance Framework for COVID-19 Vaccines

2021 was a year of intense learning and development, as the world battled the COVID-19 pandemic. In an effort to stall the spread of the infection in Malaysia, a mass vaccination roll-out was initiated on 24th February 2021 under the National Immunisation Program for COVID-19 (PICK). Five (5) COVID-19 vaccines were used in Malaysia – Comirnaty (Pfizer), CoronaVac (Sinovac), Vaxzevria (AstraZeneca), Convidecia (Cansino) and Covilo (Sinopharm). These vaccines have been granted conditional registration by the Drug Control Authority (DCA) as they met NPRA's high standards for quality, safety and efficacy.

The rapid roll out of mass COVID-19 vaccination demands a strong and all-encompassing safety monitoring system to ensure that the benefits of the COVID-19 vaccines remain greater than the associated risks. The Malaysian Pharmacovigilance Framework for COVID-19 Vaccines is, therefore, essential in ensuring all new safety data or information to be promptly reviewed and shared with all the stakeholders in a timely and transparent manner.

The main objectives of this Pharmacovigilance Framework include:

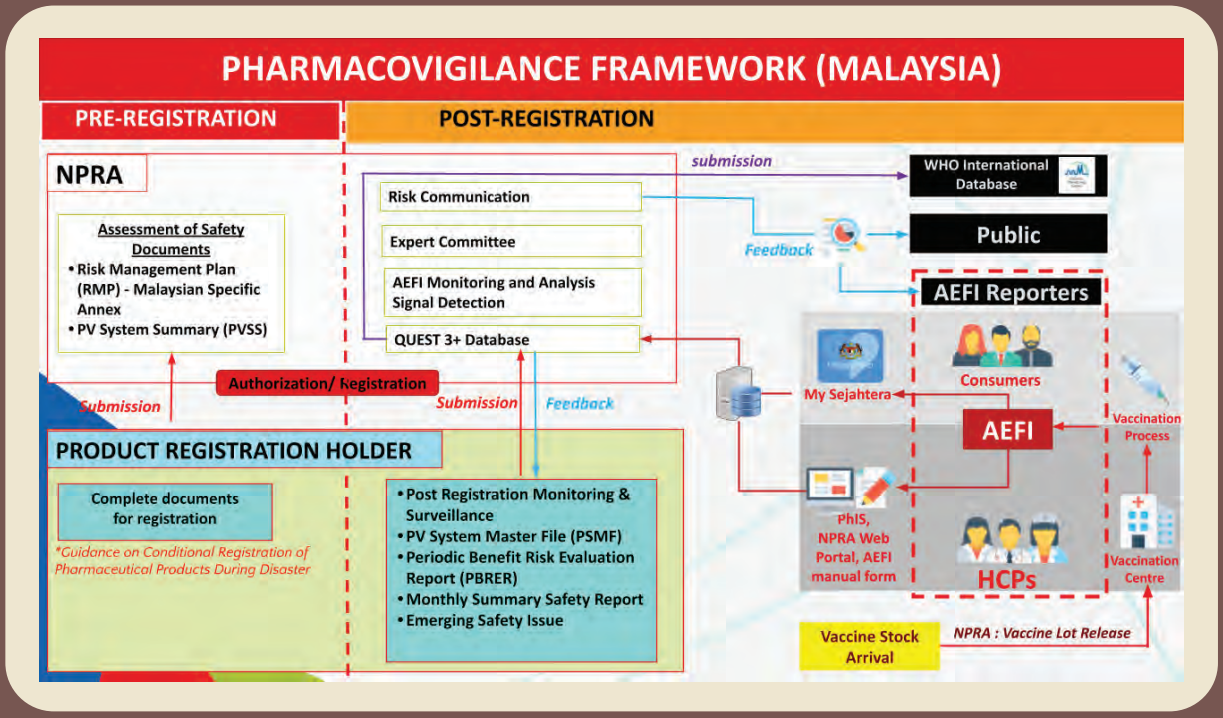
(i) Collaboration among all identified stakeholders to ensure that COVID-19 vaccine safety data and information are properly collected, analysed, and communicated;

(ii) Rapid detection of possible safety signals for COVID-19 vaccines from various sources;

(iii) Thorough evaluation of detected safety issues to assess COVID-19 vaccines' benefit-risk balance;

(iv) Prompt and effective communication of emerging safety information about COVID-19 vaccines.

The national pharmacovigilance strategies for COVID-19 vaccines in Malaysia are outlined in the Pharmacovigilance Framework as follows:



New Pharmacovigilance Activities for COVID-19 Vaccines

(I) COVID-19 Vaccine Safety Monitoring

Pre-Registration The Product Registration Holders (PRH) are required to provide NPRA with safety related documents including the company's Pharmacovigilance System Summary (PVSS) and the Risk Management Plan (RMP) with a Malaysia Specific Annex (MSA). These documents are thoroughly reviewed by NPRA to mitigate any identified and potential risks of the vaccines.

Post-Registration Besides submitting AEFI reports for COVID-19 vaccines via the established NPRA Reporting System, vaccine recipients had the option to self-notify mild and documented adverse events by using MySejahtera Application. This data enabled NPRA to monitor the incidence and trends of known adverse events among vaccine recipients. Apart from passive surveillance by NPRA, the Institute of Clinical Research (ICR), MOH, also conducted active surveillance of selected adverse events of special interest (AESI) as a research project.

(II) COVID-19 Vaccine Special Pharmacovigilance Committee (JFK)

In early 2021, the Ministry of Health (MOH) set up the COVID-19 Vaccine Pharmacovigilance Special Committee (JFK - Jawatankuasa Farmakovigilans Khas Vaksin COVID-19). This committee was established as part of the pharmacovigilance preparedness for the National Immunisation Program for COVID-19 (PICK) in Malaysia. The first JFK meeting was held in April 2021, then scheduled to be held virtually once a month.

JFK is chaired by the Director of NPRA. The members comprise medical specialists from various fields, and representatives from relevant MOH departments, universities and private association. The medical specialities covered include cardiology, immunology, haematology, neurology, internal medicine, pathology, infectious diseases, geriatrics, dermatology and forensics.

The functions of JFK include:

(i) evaluating the causality of serious AEFI reports specific to COVID-19 vaccine,

(ii) communicating insights from AEFI reporting to the National Immunisation Policy and Practice Committee (JDAIK - *Jawatankuasa Dasar dan Amalan Imunisasi Kebangsaan*)

(iii) making recommendations on COVID-19 vaccine safety issues, including any necessary policy changes

(iv) providing essential information to the Special Financial Assistance on Adverse Effects of COVID-19 Vaccine Committee (BKK - *Bantuan Khas Kewangan Kesan Mudarat Vaksin COVID-19*).

Training on AEFI Data Collection and Capacity Building

To strengthen COVID-19 vaccine safety surveillance, NPRA has planned and delivered 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 and assessing causality.

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

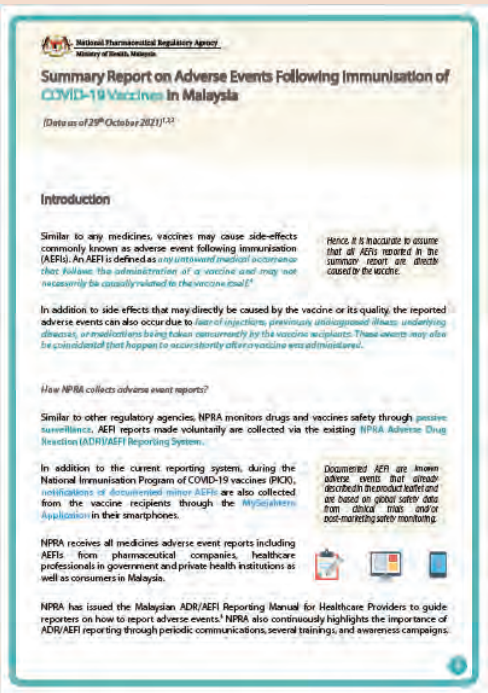
National Centre for Adverse Drug Reactions Monitoring
Annual Report 2021

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

In 2021, NPRA started to publish the first 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.

Updated summary reports will be published periodically on the NPRA website via Summary Reports on AEFI of COVID-19 Vaccines, as follows:

Summary Report #1 (Data as of 29th October 2021)



National Pharmaceutical Regulatory Agency
Ministry of Health, Malaysia

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

(Data as of 29th October 2021)[1,2]

Introduction

Similar to any medicines, vaccines may cause side-effects commonly known as adverse event following immunisation (AEFIs). An AEFI is defined as *any untoward medical occurrence that follows the administration of a vaccine and may not necessarily be causally related to the vaccine itself.*[3]

Hence, it is inaccurate to assume that all AEFIs reported in the summary report are directly caused by the vaccine.

In addition to side effects that may directly be caused by the vaccine or its quality, the reported adverse events can also occur due to *fear of injection, previously undiagnosed illness, underlying diseases, or medications being taken concurrently by the vaccine recipients. These events may also be coincidental that happen to occur shortly after a vaccine was administered.*

How NPRA collects adverse event reports?

Similar to other regulatory agencies, NPRA monitors drugs and vaccines safety through passive surveillance. AEFI reports made voluntarily are collected via the existing NPRA Adverse Drug Reaction (ADR)/AEFI Reporting System.

In addition to the current reporting system, during the National Immunisation Program of COVID-19 vaccines (PICK), notifications of documented minor AEFIs are also collected from the vaccine recipients through the MySejahtera Application in their smartphones.

Documented AEFI are known adverse events that already described in the product leaflet and are based on global safety data from clinical trials and/or post-marketing safety monitoring.

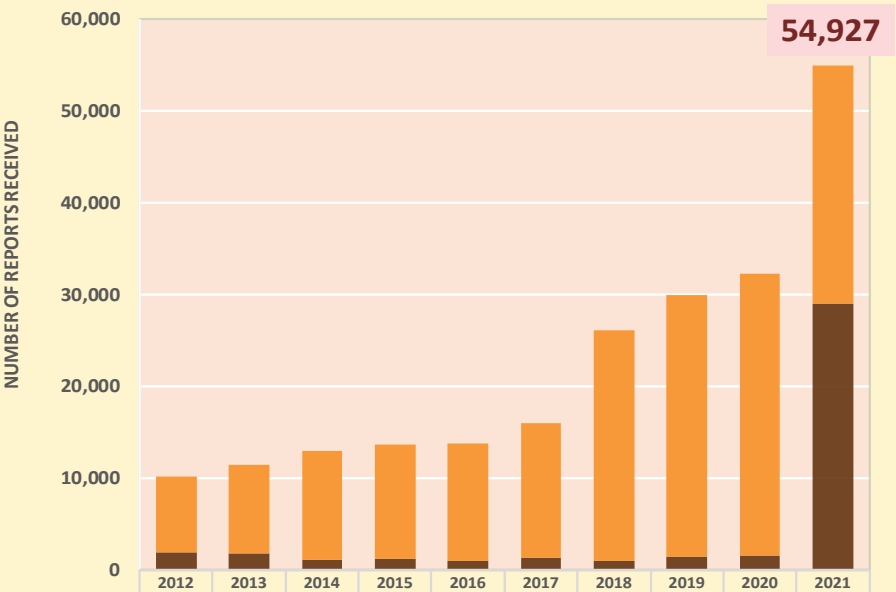
NPRA receives all medicines adverse event reports including AEFIs from pharmaceutical companies, healthcare professionals in government and private health institutions as well as consumers in Malaysia.

NPRA has issued the Malaysian ADR/AEFI Reporting Manual for Healthcare Providers to guide reporters on how to report adverse events.[3] NPRA also continuously highlights the importance of ADR/AEFI reporting through periodic communications, several trainings, and awareness campaigns.

Analysis of ADR/AEFI Reports

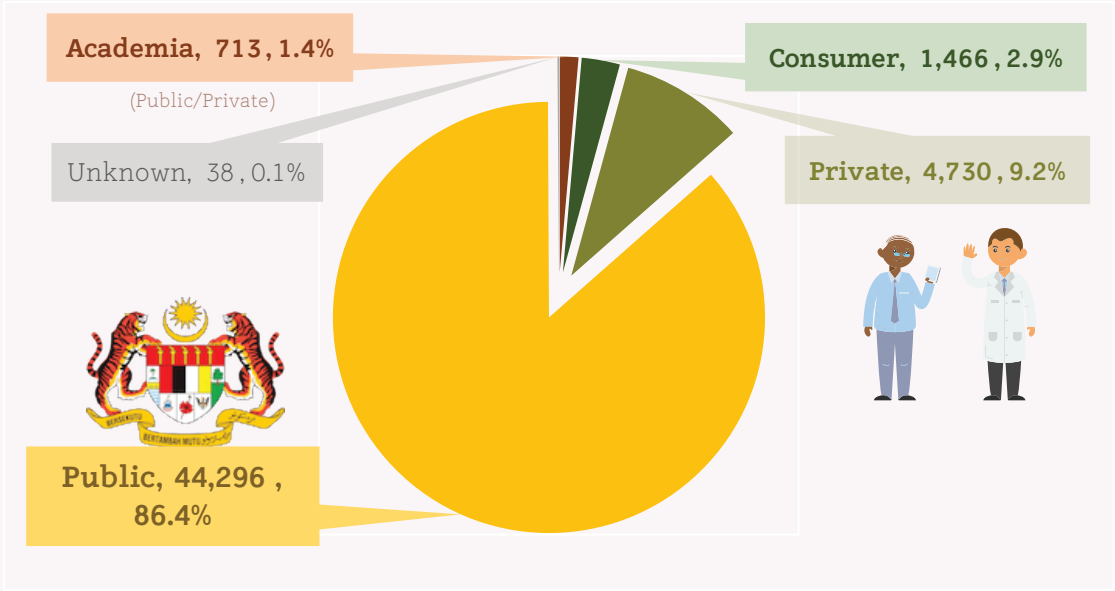
In 2021, the National Centre received **54,927 adverse event (ADR/AEFI)** reports, marking a **70.4% increase** from the previous year, with a notable **1838.2% increase** in AEFI reporting. This substantial surge is largely attributed to COVID-19 vaccinations, aligning with the launch of the National COVID-19 Immunisation Programme (PICK) on 24th February 2021. Of these, **24,042** were AEFI reports specific to COVID-19 vaccines. Once these reports were processed to exclude duplicates/follow-up reports/rejected reports, a total of **51,243 reports** were recorded in the Malaysian Pharmacovigilance Database (QUEST). Following causality assessment at MADRAC meetings, **51,194 viable new reports (excluding food/unregistered 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 2012-2021

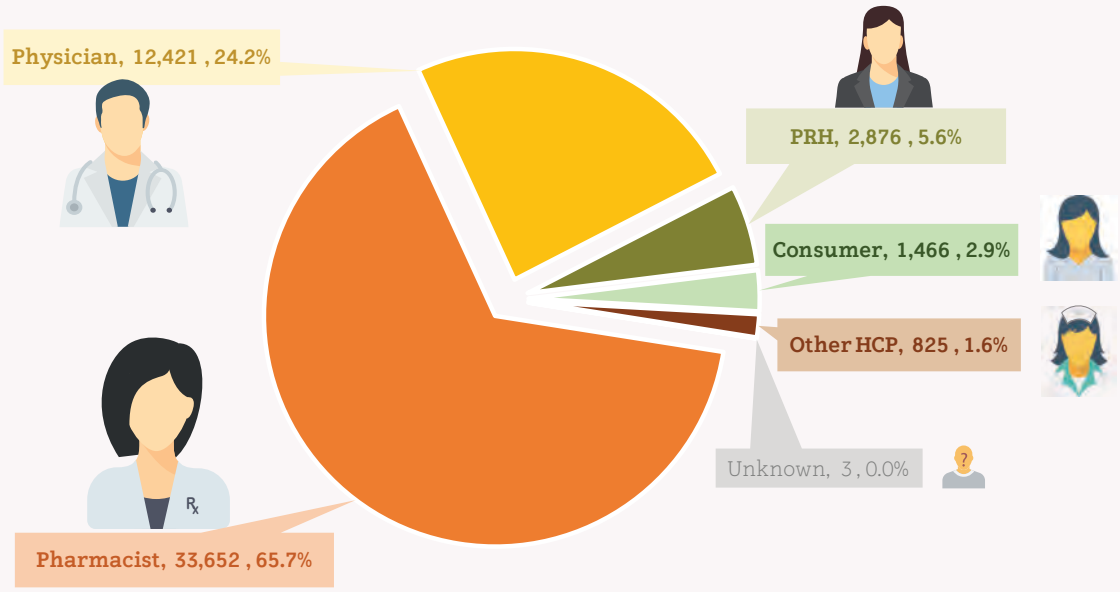


	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
ADR Reports	8,199	9,678	11,921	12,489	12,834	14,590	25,127	28,505	30,746	25,951
AEFI Reports	1,903	1,795	1,080	1,186	955	1,346	983	1,478	1,495	28,976

Distribution of ADR/AEFI Reports Recorded by Sector, 2021*



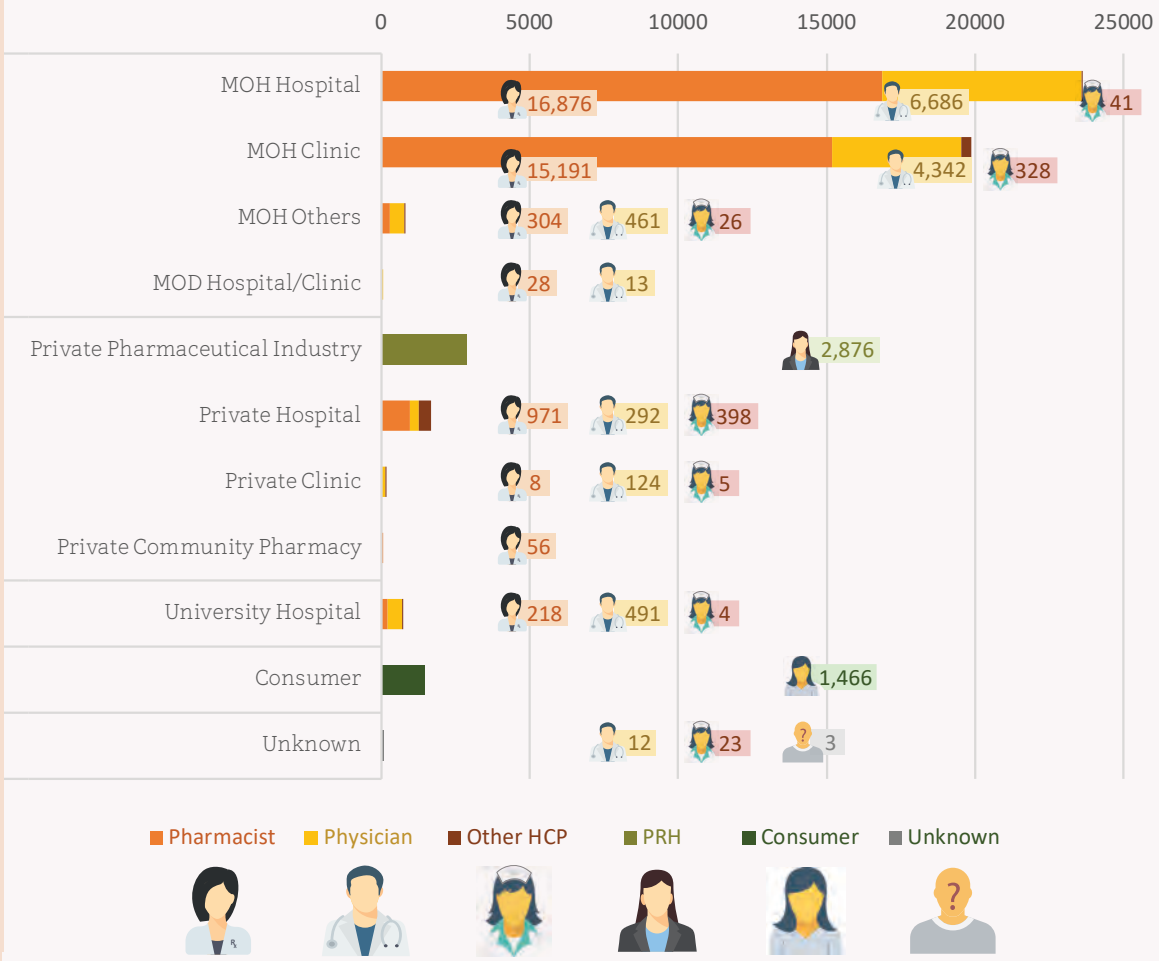
Distribution of ADR/AEFI Reports Recorded By Reporter Qualification, 2021*



HCP: Healthcare professionals; PRH: Product registration holders

*Based on total 51,243 processed ADR/AEFI reports

Distribution of ADR/AEFI Reports Recorded by Institution Type/Reporter Qualification, 2021*

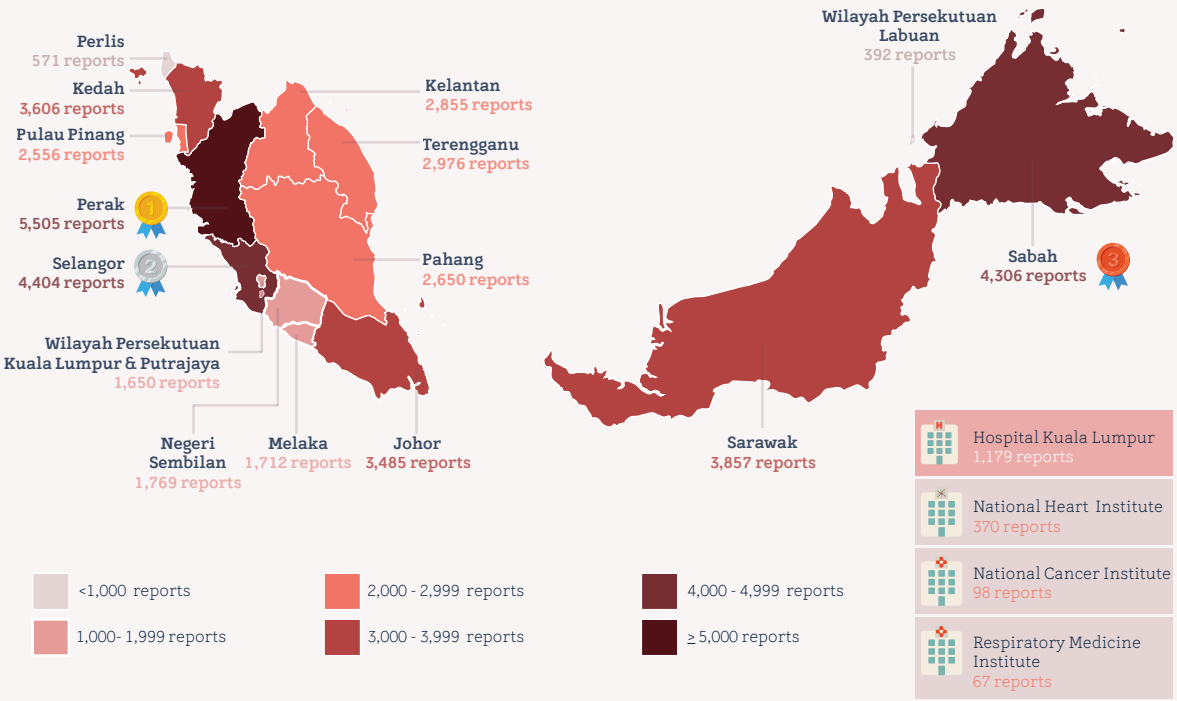


	Government				Private			Academia				
	MOH Hospital	MOH Clinic	MOH Others	MOD Hospital	Pharmaceutical Industry	Hospital	Clinic	Community Pharmacy	University Hospital	Consumer	Unknown	**Total**
Pharmacist	16,876	15,191	304	28		971	8	56	218			**33,652**
Physician	6,686	4,342	461	13		292	124		491		12	**12,421**
Other HCP	41	328	26			398	5		4		23	**825**
PRH					2,876							**2,876**
Consumer										1,466		**1,466**
Unknown											3	**3**
Total	**23,603**	**19,861**	**791**	**41**	**2,876**	**1,661**	**137**	**56**	**713**	**1,466**	**38**	**51,243**

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

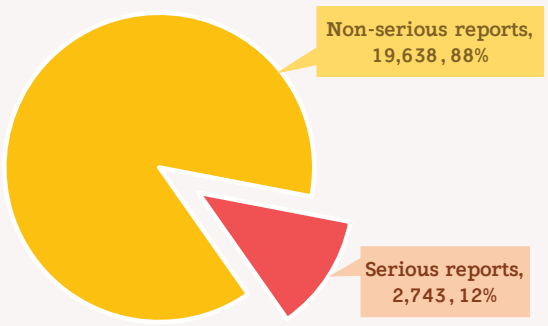
*Based on total 51,243 processed ADR/AEFI reports

Distribution of ADR/AEFI Reports Recorded from Ministry of Health (MOH) Facilities, 2021*

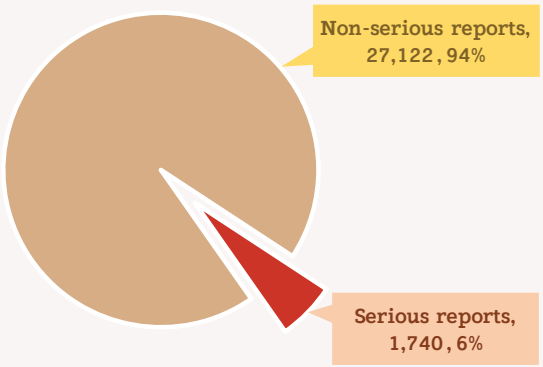


Distribution of ADR/AEFI Reports Recorded by Case Seriousness, 2021*

ADR Reports



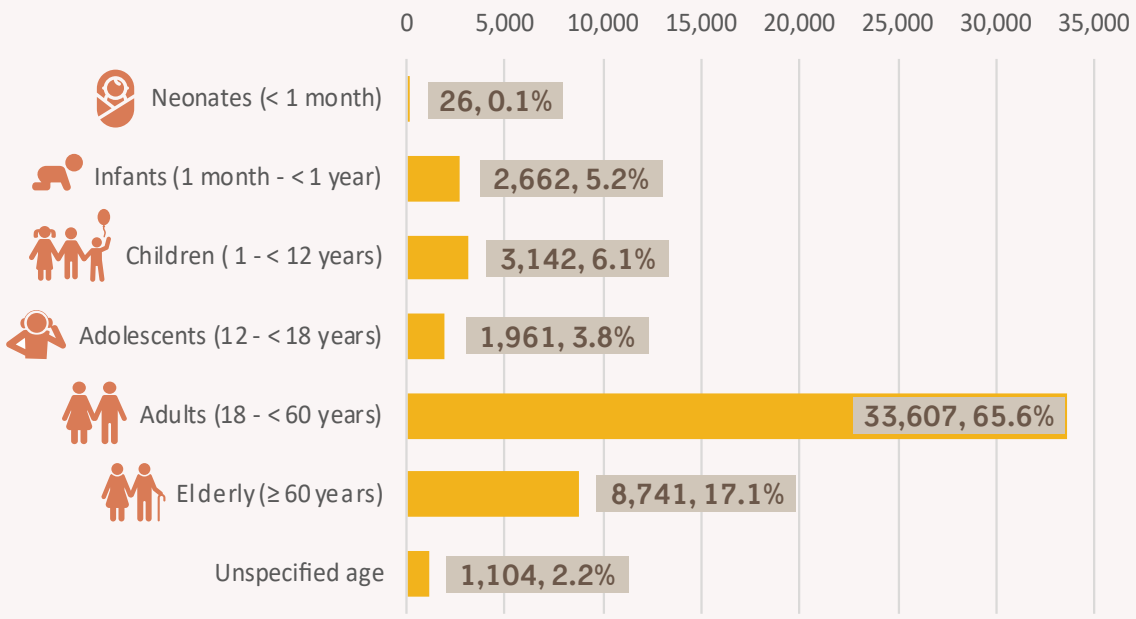
AEFI Reports



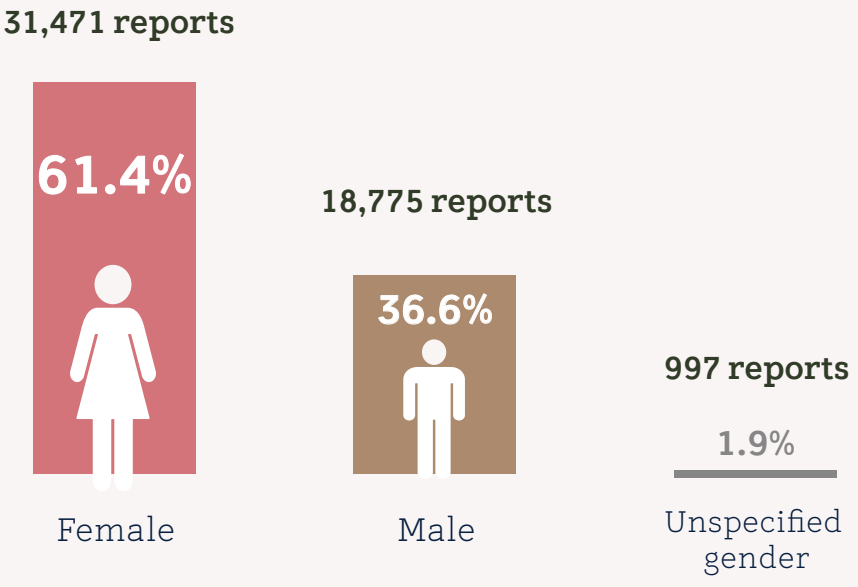
Serious cases include those that require hospitalisation, prolonged existing hospitalisation, are life-threatening, cause persistent or significant disability/incapacity, a congenital anomaly/birth defect, or suspected to cause death

*Based on total 51,243 processed ADR/AEFI reports

Distribution of ADR/AEFI Reports Recorded by Patient's Age Group, 2021*



Distribution of ADR/AEFI Reports Recorded by Patient's Gender, 2021*



Based on total 51,243 processed ADR/AEFI reports

Number of Products Involved in ADR/AEFI Reports, 2021#

51,305 (96.1%)
Poisons & prescription items

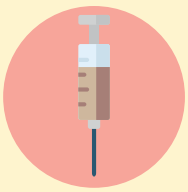
1,838 (3.4%)
Non-poisons

81 (0.2%)
Traditional products

41 (0.1%)
Food products

131 (0.2%)
Unregistered products

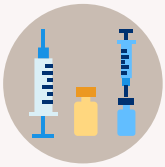
Top 10 Most Reported Route of Administration of the Products Involved, 2021#

Route of Administration	Number (%)
1  **Intramuscular**	29,195 (54.7%)
 Oral	16,646 (31.2%)
 Intravenous (not otherwise specified)	3,605 (6.8%)
 Subcutaneous	927 (1.7%)
 Intravenous drip	472 (0.9%)
 Intraperitoneal	285 (0.5%)
 Intravenous bolus	229 (0.4%)
 Topical	95 (0.2%)
 Ophthalmic	88 (0.2%)
 Inhalation	66 (0.1%)
Unknown	1,439 (2.7%)

#Based on total 53,396 products involved in 51,243 processed ADR/AEFI reports
Note: A report may involve one or more medicinal products

Top 10 Most Reported Pharmacological Group of the Products Involved, 2021#

1



Vaccines

29,114
(54.5%)

2

Anti infectives

5,299
(9.9%)

3

Cardiovascular agents

4,889
(9.2%)

4

Analgesics

3,469
(6.5%)

5

Others

1,666
(3.1%)

6

Anti neoplastics

1,643
(3.1%)

7

Anti diabetics

1,457
(2.7%)

8

Anti hyperlipidaemic

707
(1.3%)

9

Anti tuberculosis

460
(0.9%)

10

Anti epileptics

422
(0.8%)

#Based on total 53,396 products involved in 51,243 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, 2021+

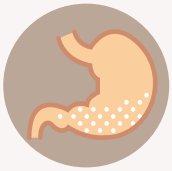
1

Skin and subcutaneous tissue disorders
12,153 (32.1%)

2

General disorders and administration site conditions
4,925 (12.6%)

3



Gastrointestinal disorders
4,833 (12.4%)

4

Respiratory, thoracic and mediastinal disorders
4,028 (10.3%)

5

Eye disorders
3,572 (9.2%)

6

Nervous system disorders
3,246 (8.3%)

7

Investigations
1,402 (3.6%)

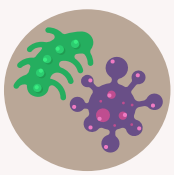
8

Musculoskeletal and connective tissue disorders
678 (1.7%)

9

Cardiac disorders
615(1.6%)

10



Infections and infestations
558 (1.4%)

+Based on total 39,000 adverse events involved in 22,381 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, 2021^

1

General disorders and administration site conditions
20,867 (33.3%)

2

Nervous system disorders
8,168 (13.0%)

3

Psychiatric disorders
7,703 (12.3%)

4

Skin and subcutaneous tissue disorders
7,528 (12.0%)

5

Gastrointestinal disorders
4,904 (7.8%)

6

Respiratory, thoracic and mediastinal disorders
4,237 (6.8%)

7

Musculoskeletal and connective tissue disorders
3,718 (5.9%)

8

Cardiac disorders
1,389 (2.2%)

9

Eye disorders
1,082 (1.7%)

10

Investigations
867 (1.4%)

^Based on total 62,691 adverse events involved in 28,863 processed AEFI reports.
Note: A report may involve one or more adverse events.

Monitoring Drug Safety Issues

In 2021, a total of **68 drug safety issues** were proactively identified through the enviromental screening of published information on reference agencies' websites. Additionally, **119 notifications of drug safety issues** were received from the product registration holders (PRHs). Following review, **21 safety issues were presented at MADRAC meetings** to determine the appropriate risk minimisation measures (refer to page 21–22). The majority of these issues resulted in updates to the product safety information, such as tightening of indications or additional contraindications. **Ten 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

21
Safety issues presented

10
Safety issues required mandatory updates of package inserts and consumer medication information leaflets

2
Direct Healthcare Professional Communication (DHPC) letters reviewed

237
Products involved in regulatory action

MADRAC 177 4 March 2021	DCA Directive	DHPC Letter	PI/RiMUP Update	Safety Alert	Further Review	Others
Ceftriaxone Risk of Encephalopathy				●	●	
Antidepressants (Citalopram, Desvenlafaxine, Escitalopram, Fluoxetine, Fluovoxamine, Paroxetine, Sertraline, Venlafaxine, Vortioxetine): Risk of Postpartum Haemorrhage (PPH)				●	●	
Atezolizumab (Tecentriq®): Risk of Severe Cutaneous Adverse Reactions (SCARs)		●	●	●		
Vascular endothelial growth factor (VEGF) inhibitors for systemic use (except application on eyes) Risk of Artery Dissections and Aneurysms	●		●	●		
Rocuronium: Risk of Kounis Syndrome	●		●	●		
Mirtazapine: (i) Risk of Amnesia (ii) Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)	●		●	●		
MADRAC 178 27 May 2021						
Mycophenolate mofetil (MMF) and Myocophenolic acid (MPA): Risk of De Novo Purine Synthesis Inhibitors-Associated Acute Inflammatory Syndrome				●	●	
Oseltamivir: Risk of Haemorrhages				●	●	
Ceftriaxone: Risk of Encephalopathy	●		●	●		

MADRAC 179 26 August 2021	DCA Directive	DHPC Letter	PI/RiMUP Update	Safety Alert	Further Review	Others
Sacubitril/Valsartan: Risk of Psychiatric Events				●	●	
Non-Vitamin K Antagonist Oral Anticoagulants (NOACs): Risk of Abnormal Uterine Bleeding				●	●	
Sulfamethoxazole & Trimethoprim (Co-Trimoxazole): Risk of Acute Respiratory Distress Syndrome (ARDS)				●	●	
Insulin (including combination): Risk of Cutaneous Amyloidosis	●		●	●		
Mycophenolate mofetil (MMF) and Myocophenolic acid (MPA): Risk of De Novo Purine Synthesis Inhibitors-Associated Acute Inflammatory Syndrome	●		●	●		
Bortezomib: Risk of Guillain-Barré Syndrome and Demyelinating Polyneuropathy	●		●	●		
Anastrozole: Risk of Depression	●		●	●		
Iclusig [Vascular endothelial growth factor (VEGF) inhibitors]: Risk of Artery Dissections and Aneurysms		●	●	●		
MADRAC 180 10 November 2021						
Clindamycin: Risk of Acute Renal Failure				●	●	
Janus Kinase (JAK) Inhibitors in Rheumatoid Arthritis Patients: Risk of Major Adverse Cardiovascular Events (MACE) and Malignancies [Excluding Non-Melanoma Skin Cancer (NMSC)]				●	●	
Antidepressants (Citalopram, Desvenlafaxine, Escitalopram, Fluoxetine, Fluovoxamine, Paroxetine, Sertraline, Venlafaxine, Duloxetine & Vortioxetine): Risk of Postpartum Haemorrhage (PPH)	●		●	●		
Decitabine: Risk of Differentiation Syndrome	●		●	●		

Safety Monitoring of New Products

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

For the first five (5) 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, specifically New Drug Products (NDPs) and Biologic products. Each PBRER/PSUR presents the safety profile of the product in countries where it is registered, and include any updates or new findings concerning product safety. During the COVID-19 pandemic, PRHs for new COVID-19 vaccines and treatments were also required to submit Monthly Safety Summary Reports (MSSRs). In 2021, a total of **218 PBRERs** and MSSRs involving **188 registered products** were assessed, resulting in implementation of **51 safety-related package insert changes (23.4%, 51/218)** to ensure that they contain the latest safety profile information.

Risk Management Plan (RMP)

A Risk Management Plan (RMP) provides a detailed description of the risk management system. When a significant change in the safety specification for NDPs and Biologic products occurs post registration, an updated RMP is required to be submitted by PRHs. In 2021, to address challenges of the COVID-19 pandemic and to expedite the registration of COVID-19 vaccines and treatments, relevant pre-registration RMPs were also evaluated. Throughout 2021, a total of **73 RMPs (both pre- and post-registration)** were reviewed, accounting for **60 registered products.** This includes **eight (8) products for COVID-19 vaccines and one (1) product for COVID-19 treatment**. In addition, **16 COVID-19-related and 27 other product-related educational materials**, encompassing information for healthcare professionals and patients, were reviewed and subsequently approved.

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 2021, which are available on the NPRA website via MADRAC Bulletin, as follows:

MADRAC Bulletin, Issue 01/2021, Vol. 34

MADRAC Bulletin, Issue 02/2021, Vol. 35

MADRAC Bulletin, Issue 03/2021, Vol. 36

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 2021, NPRA has published **24 safety alerts** to highlight drug safety issues. The full list of safety alerts in 2021 is available on the NPRA webiste 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 2021, 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 2,100 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 pharmacy officers in NPRA.

In 2021, a total of **204 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 and Trainings Activities

Over the years, NPRA has conducted a variety of training sessions for stakeholders in Malaysia, including healthcare professionals from both public and private health institutions, university students, pharmaceutical companies, and overseas regulators. The majority of the training sessions focused on spontaneous reporting and causality assessment; other topics of pharmacovigilance covered included risk assessment, risk management, risk communication, and implementing pharmacovigilance in pharmaceutical companies.

In 2021, a total of **13 training sessions** were held/attended by NPRA pharmacovigilance officials as speakers in physical seminars and workshops.

Adverse Drug Reaction (ADR) Training Course: Reporting and Causality Assessment

On 14th June 2021, the Pharmaceutical Services Division of the Selangor State Health Department organised a training course on ADR reporting and causality assessment, engaging pharmacists from MOH Selangor healthcare facilities. NPRA contributed three (3) pharmacovigilance officers who enriched the session by imparting their expertise on an array of topics, encompassing an overview of the pharmacovigilance system in Malaysia, ADR reporting, advice for enhancing report quality, as well as methodologies for ADR causality assessment. Additionally, a medical officer from the University Malaya Medical Centre shared insights on drugs and post-vaccination allergic reactions in clinical settings. This training course was conducted virtually and spanned one entire day.

International Participation & Collaborations

PMDA-ATC Pharmacovigilance Webinar 2021

From 1st to 4th February 2021, PMDA hosted the "PMDA-ATC Pharmacovigilance Webinar 2021", aligned with its role as the Center of Excellence (CoE) Workshop under the auspices of the Asia-Pacific Economic Cooperation, Life Sciences Innovation Forum, Regulatory Harmonization Steering Committee (APEC-LSIF-RHSC). The webinar saw participation from 26 regulators responsible for pharmacovigilance in in their respective countries, including three (3) pharmacovigilance officers from Malaysia and others from countries such as Azerbaijan, India, Indonesia, Korea, Myanmar, Nigeria, Philippines, Saudi Arabia, Singapore, Sri Lanka, Taiwan, Tanzania, Thailand, and Uganda.

The objectives of the webinar were to empower regulators with the knowledge and skills to bolster the pharmacovigilance systems in their respective countries. Recorded lectures covered diverse topics: from pharmacovigilance considerations, PV systems in the US, EU, and Japan and international harmonisation, benefit/risk balance evaluation, pharmacoepidemiology, end-to-end labeling, to safety risk information communication. The first two days combined lectures with live Q&A sessions, fostering active discussion among attendees. During the final two days, attendees split into five (5) groups to delve deeper into case studies using mock data on safety specifications and risk minimisation activities. Guided by facilitators, attendees drew from their own expertise to discuss the scenarios and each group's conclusions were presented.

Workshop on Pharmacovigilance by Saudi Food and Drug Authority (SFDA)

The Saudi Food and Drug Authority (SFDA), in collaboration with the Organisation of Islamic Cooperation (OIC), hosted a series of virtual training workshops on medical device regulation and pharmacovigilance (PV) for OIC Member States. Pharmacovigilance officers from the National Pharmaceutical Regulatory Agency (NPRA) attended two pivotal sessions: the Basic PV Workshop session on 9th March 2021, followed by the Advanced PV Workshop from 22nd to 23rd March 2021.

Intended to promote expertise exchange among National Medicine Regulatory Authorities (NRAs) from OIC Member States, the workshops aimed to enhance the knowledge and skills of NRAs from OIC Member States in the domain of PV and medical device regulation. Such advancements are anticipated to improve the safety and efficacy of medical products across OIC countries, ultimately benefiting healthcare professionals and patients.

The Basic PV Workshop, streamlined into a day, addressed essentials ranging from adverse drug reaction (ADR) reports processing, pharmacoepidemiology, periodic safety update reports (PSUR), to PV inspections. During the subsequent two-day Advanced PV Workshop, attendees delved into a broader scope of topics, including risk communication from regulatory perspectives, signal management, proactive drug safety monitoring initiatives, medication errors, cosmovigilance, qualified person responsible for pharmacovigilance (QPPV), and causality assessment.

ORGANISATION OF ISLAMIC COOPERATION

SFDA

PMDA-ATC Regenerative Medicinal Products Review Webinar 2021

In a collaborative endeavor, the Pharmaceuticals and Medical Devices Agency (PMDA), Japan, and the NPRA, Malaysia, concluded the PMDA-Asia Training Center for Pharmaceuticals and Medical Devices Regulatory Affairs (PMDA-ATC) Regenerative Medicinal Products Review Webinar 2021. Tailored especially for NPRA, this session took place on 19th March 2021 and witnessed the enthusiastic participation of 53 NPRA regulators. This webinar provided introduction to regulatory framework of regenerative medicines in Japan as well as the review process of products or treatments using regenerative medicines, with a special focus on human somatic cell-processed products and plasmid vector products. The NPRA also shared information on the current framework for regulation of Cell and Gene Therapy Products (CGTPs) in Malaysia.

2021 International Society of Pharmaceutical Engineering (ISPE) Vaccine Conference and Exhibition

The ISPE Malaysia Vaccines Conference and Exhibition took place virtually on 24th, 25th, and 27th May 2021. The virtual conference and exhihibition, graced by the Minister of Science, Technology and Innovation, featured several keynote speakers with virtual factory tours and exhibition booths throughout the 3-day event.

On the first day, discussions centered around the regulatory and certification of vaccines, while the second day delved into supply chain management. Key focus areas encompassed new vaccine development areas, emerging landscapes, technology advancements, and regulatory milestones including pharmacovigilance and post-marketing surveillance of vaccines.

An officer from the Pharmacovigilance Section, NPRA was invited to deliver a plenary talk on “Vaccine Pharmacovigilance in Malaysia”. This talk provided a timely opportunity to share insights with the industry to highlight the dynamic changes in Adverse Event Following Immunisation (AEFI) monitoring for COVID-19 vaccines in Malaysia, following the release of the NPRA Guidance and Requirements on Conditional Registration for Pharmaceutical Products during Disaster. Additionally, the conference served as an excellent platform for exchanging perspectives on vaccine pharmacovigilance in Malaysia amidst the ongoing COVID-19 pandemic.

ISPE®
Connecting Pharmaceutical Knowledge

The Indian Siddha Regional Research Institute (SRRI)'s National Webinar on the Pharmacovigilance of Ayurveda, Siddha, Unani, and Herbal (ASU & H) Drugs

On 2nd September 2021, the Siddha Regional Research Institute (SRRI) from Thiruvananthapuram, India organised a National Webinar on the Pharmacovigilance of Ayurveda, Siddha, Unani, and Herbal (ASU & H) Drugs. Held virtually from the SRRI conference hall, the event attracted 282 participants comprising a diverse group of healthcare professionals (HCPs), including government and private doctors, pharmacists, nurses, other HCPs, and undergraduate ayurveda medical students. The presence of such a varied group underscores the importance of pharmacovigilance across different fields and specialties within healthcare.

There were three (3) sessions, and a pharmacovigilance officer from the NPRA was invited to deliver the first session, titled "Drug Safety: Everyone's Responsibility". Adverse Drug Reaction (ADR) reporting was emphasised as fundamental to ensure medication safety, and a collective role of HCPs, patients, and pharmaceutical companies to improve the overall quality of healthcare was highlighted.

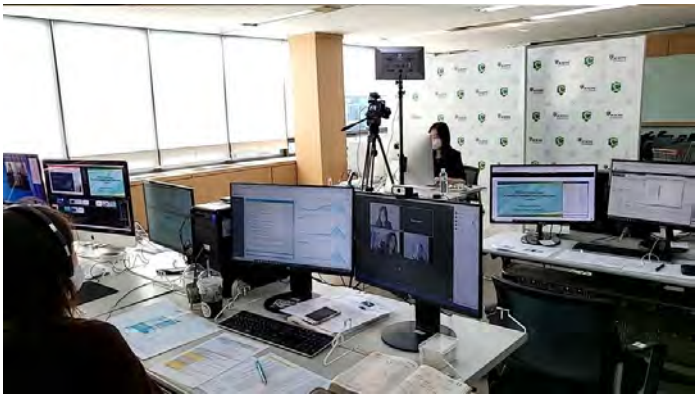
2021 KIDS-APEC Pharmacovigilance Centre of Excellence Training

The Korea Institute of Drug Safety and Risk Management (KIDS) – Asia-Pacific Economic Cooperation (APEC) Pharmacovigilance Centre of Excellence Training Program took place virtually from 8th to 10th September 2021. Serving as a professional pharmacovigilance (PV) training program for regulators, this program aimed at facilitating understanding between economies on current PV activities, implementing an effective PV system, and strengthening the in-field capacity of regulators within the APEC region and beyond.

This program featured esteemed speakers from various regulatory agencies, including the United States Food & Drug Administration (US FDA), the Ireland Health Products Regulatory Authority (HPRA), KIDS, as well as representatives from Bayer, the International Society of Pharmacovigilance (ISoP) and the Uppsala Monitoring Center (UMC). Participating delegates hailed from national regulatory agencies (NRAs) in countries like Malaysia, Azerbaijan, Thailand, Philippines and Indonesia. Four (4) pharmacovigilance officers from the NPRA attended this virtual training programme, with Pn. Nafiza Ismail standing out as a chosen presenter for a hands-on exercise on Benefit-Risk Assessment discussion.

Topics covered spanned a wide range of PV concerns: the Korean PV system, PV automation, opioid medication risk management and risk minimisation strategies, the use of Medical Dictionary for Regulatory Activities (MedDRA) as the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) terminology standard for safety information coding, signal management from both regulatory and industry perspectives, vaccines causality assessment, and PV inspections from a regulatory perspective. Participants also engaged in discussions and presentations on benefit-risk assessments, as well as vaccine safety and risk management.

This program was designed to empower regulators to expand their PV knowledge and proficiency, ultimately improving the safety and efficacy of medical products in their respective countries. On the whole, this training proved an invaluable platform for APEC region regulators—and those beyond—to exchange insights, learn collaboratively, and enhance their PV competencies.



Training Workshop on AEFI Cases Investigation and Causality Assessment

On 28th September and 6th October 2021, the NPRA hosted a virtual Training Workshop on Adverse Events Following Immunisation (AEFI) Cases Investigation and Causality Assessment virtually. The workshop saw active participation from 118 dedicated healthcare professionals (HCP), encompassing medical officers and pharmacy officers representing each state as well as members of the COVID-19 Vaccine Special Pharmacovigilance Committee (JFK). The opening ceremony was graced by Dr. Roshayati Mohamad Sani, Director of NPRA, and Dr. Lo Ying-Ru Jacqueline, the World Health Organization (WHO) Representative to Malaysia, Brunei Darussalam, and Singapore.

Central to this workshop was the objective of equipping HCP with in-depth knowledge and practical skills to conduct investigation and causality assessment of AEFI cases, particularly those linked to COVID-19 vaccines. It was stressed that providing such adequate information for each case is fundamental to assist the NPRA, as the regulatory body responsible for handling AEFI monitoring, in performing reliable causality assessments.

During the first session on 28th September, WHO consultants delivered latest updates on COVID-19 vaccine safety and the investigation of safety events following COVID-19 vaccinations. This was followed by a group work session where the Investigation Team presented case reviews and a plenary discussion aimed at enhancing AEFI investigations.

The second session on 6th October commenced with a group work session where the Investigation Team presented case reviews and a plenary discussion aimed at enhancing AEFI investigations. This was followed by the Pharmacovigilance Section Head addressing causality assessment in Malaysia. Next, the JFK experts discussed and reviewed AEFI cases, with workshop participants closely observing their methodologies. The participants then benefited from a knowledge-sharing session steered by the WHO consultants on methodologies used to assess the causality of COVID-19 related adverse events of special interest (AESI). The workshop concluded with a comprehensive plenary discussion, zooming in on the findings from the causality assessment within the Malaysian context.

MedSafetyWeek November 2021: Help Make Vaccines Better for Everyone

From 1th to 7th November 2021, 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 65 countries and various non-governmental organisations worldwide. This collaborative social media campaign was focused on elevating public awareness about the critical importance of reporting any suspected side effects associated with vaccines.

Throughout #MedSafetyWeek, NPRA specifically called upon healthcare professionals, especially those administering vaccines and staff involved in national immunisation programs, as well as vaccine recipients and their caregivers, to diligently report any side effects observed post-vaccination.

Publications

Guidance documents

In August 2021, NPRA published two guidance documents related to pharmacovigilance. One was targeted to the pharmaceutical companies, and the second to healthcare providers. These two documents replace the Malaysian Pharmacovigilance Guidelines 2nd Edition, 2016. Further description of each document is provided below.

The Malaysian Guidelines on Good Pharmacovigilance Practices (GVP) for Product Registration Holders - First Edition, August 2021

As part of efforts to ensure drug safety, pharmaceutical companies are required to establish a robust pharmacovigilance system within their organisations as any shortcomings in these systems may directly impact patient safety. In view of this requirement, NPRA developed this detailed guideline to provide guidance for the pharmaceutical companies in setting up good pharmacovigilance systems. This guideline outlines the requirements and procedures for Good Pharmacovigilance Practice (GVP) which include activities such as:

(i) appointing the responsible person for pharmacovigilance
(ii) managing Adverse Drug Reaction (ADR)/ Adverse Events Following Immunisation (AEFI) reports
(iii) submitting Periodic Benefit-Risk Evaluation Reports (PBRER) or Risk Management Plans (RMP).
(iv) preparing the Pharmacovigilance System Master File
(v) handling emerging safety issues
(vi) conducting safety communication

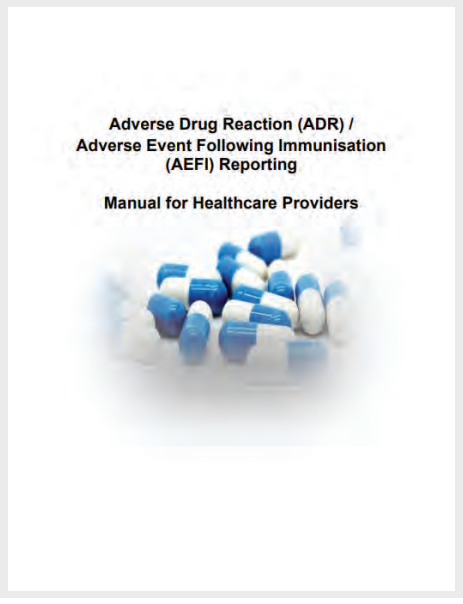
This guideline may be viewed on the NPRA website via Malaysian Guidelines on GVP for Product Registration Holders.

Adverse Drug Reaction (ADR)/ Adverse Event Following Immunisation (AEFI) Reporting Manual for Healthcare Providers - First Edition, August 2021

Spontaneous ADR/AEFI reports submitted by healthcare professionals are the backbone of post-marketing safety monitoring. Good quality ADR/AEFI reports play an important role in helping NPRA identify safety issues or safety signals, and take action to optimise the benefit-risk balance of a medicinal product. Therefore, NPRA published this manual to guide healthcare providers on submitting high quality ADR and AEFI reports.

This manual encompasses an introduction to pharmacovigilance, followed by the procedures to submit an ADR/AEFI report. The reporting and investigation of AEFIs are covered in detail, including updates on the latest causality assessment categorisation. The requirements outlined in this manual will help improve the quality and standard of ADR/AEFI reporting in Malaysia.

The manual may be viewed on the NPRA website via Manual for Healthcare Providers.



Research Articles

In 2021, the National Centre has published a research article entitled "**Allopurinol-Induced Severe Cutaneous Adverse Drug Reactions: An Analysis of Spontaneous Reports in Malaysia (2000–2018)**" in the Therapeutic Innovation & Regulatory Science journal.[1] The study found that predictors of allopurinol-induced severe cutaneous adverse reactions (SCARs) were elderly females (65 years and above), patients with underlying renal disease, high allopurinol dose (300 mg/day or higher), and the use of allopurinol for unspecified hyperuricaemia and off-label indications. The study also assessed the impact of allopurinol-induced SCARs on fatality and found that it was associated with older age and a diagnosis of Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) overlap or TEN. The study recommended that these patients need close monitoring and must be educated to stop allopurinol at the first signs of rash. The outcomes of the study were also presented at the 11th National Pharmacy R&D Conference 2021, which was held virtually from 27th to 30th September 2021.[2]

[1]Lee SC, Wo WK, Yeoh HS, Mohamed Ali N, Hariraj V. Allopurinol-Induced Severe Cutaneous Adverse Drug Reactions: An Analysis of Spontaneous Reports in Malaysia (2000–2018). Therapeutic Innovation & Regulatory Science. 2021 May;55:514-22. Available from: https://doi.org/10.1007/s43441-020-00245-w

[2]Pharmaceutical Services Programmes [Internet]. 11th National Pharmacy R&D Conference 2021 [cited 2023 Feb 28]. Available from: https://www.pharmacy.gov.my/v2/en/events/11th-national-pharmacy-rd-conference-2021.html.

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 (maximum of 10 points per year) 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 2021, a total of **234 AE reports** received from pharmacists in the private sector were evaluated and approved for CPD points claim. This is a 12% increment from the previous year.

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Editorial Team

Ministry of Health Malaysia
National Pharmaceutical Regulatory Agency