REVIEW ARTICLES

COVID-19 VACCINES AND ITS ADVERSE EVENTS FOLLOWING IMMUNIZATION(AEFI) IN INDONESIA

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ABSTRACT

Background: The Indonesian government has begun to administer vaccines en mass and is planned in stages as an effort to prevent and control Covid-19 by immunity. To reduce the negative impact of immunization on individual health and the implementation of vaccination itself, it is best to know Covid -19 vaccines in Indonesia and their AEFI. The purpose of this article is to discuss Covid-19 vaccines in Indonesia and their AEFI

Methods: Systematic review of studies about Covid-19 vaccines that have been and will be used in Indonesia along with an overview of AEFI

Results: There are 5 Covid-19 vaccines manufacturer that has been and will be used in Indonesia. The types of antigens used in the Covid-19 vaccine include a whole virus, protein subunits, and nucleic acid. An allergic reaction happens because of the vaccine components (antigen, adjuvant, stabilizer, antibiotic, preservative, culture media) that bring to AEFI. AEFI reaction can be divided into a minor reaction that settles on its own (10%) and a severe reaction that requires clinical management (0,01%)

Conclusion: Covid-19 vaccines are relatively safe and can rarely cause AEFI. It is very important to detect AEFI early, to respond quickly and accurately that will determine the success of the immunization program by increasing public confidence in the benefits and safety of immunization.

Keywords: vaccine, Covid-19, AEFI, Indonesia

INTRODUCTION

Covid-19 (Coronavirus Disease 2019) was first reported in the Wuhan area, Hubei Province, China. The disease is caused by a novel coronavirus, SARS-CoV-2, which can cause the severe acute respiratory syndrome. WHO (World Health Organization) declared Covid-19 as a global pandemic in March 2020. Since the Covid-19 disease was declared a pandemic by WHO, until the time this article was written, it has caused a mortality rate of 3.4% or 0.34 per 100,000 population in Indonesia and a mortality rate of 2.3% at the global level. The Indonesian Government through the Ministry of Health in dealing with the Covid-19 disease has been conducting vaccination since 13 January 2021 in addition, to actively intensify the promotion of health protocol since the early days of the pandemic. In the first quarter of 2021, the use of the Sinovac vaccine has taken place with strict AEFI supervision and reporting. The pandemic forces vaccination programs to be carried out as quickly as possible without compromising the safety, effectiveness, and immunogenicity of a vaccine. Vaccination is carried out after the issuance of an Emergency Use Authorization (EUA) permit from the National Agency of Drug and Food Control (NADFC) as well as a Halal Fatwa from the Indonesian Ulema Council (IUC) regarding vaccine products entering Indonesia.[5, 6]

Vaccine production is done by modern biotechnology that is expected to produce good quality vaccines though none could be perfect. The use of large quantities of vaccines requires monitoring of Adverse Event Following Immunization (AEFI) –WHO, better known as Kejadian Ikutan Pasca Imunisasi (KIPI) in Indonesia.[7]

VACCINES

Vaccines are biological products that contain antigens which when administered to an individual will establish specific immunity against disease, while immunization is an effort to build immunity through vaccines.[8] Vaccine development is an expensive and a long time-process. The traditional vaccine can take years from design exploratory pre-clinical studies to distribution. The SARS-Cov-2 vaccine development is following an accelerated timeline because an existing process of vaccines for SARS-Cov and MERS-Cov makes the studies phase shorter.[8, 9] Clinical trial stages are running in parallel by initiating phase III trials when the interim analysis of phase I/II comes out with results. In the meantime, vaccine producers are at risk for producing a large-scale vaccine. The vaccine candidates then will be licensed and reviewed by emergency use authorization.[8]

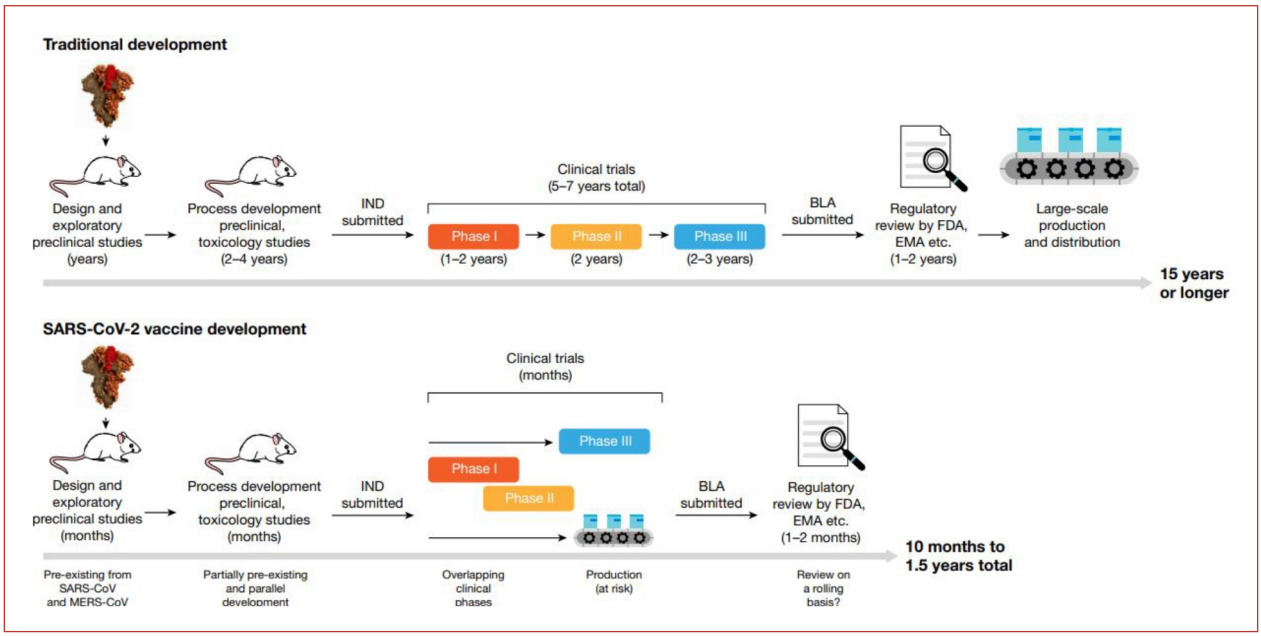

Figure 1. Traditional and Accelerated Vaccine-development Pipelines[8]

Investigational New Drug (IND), Biologics Licence Application (BLA), Food and Drug Administration (FDA), the European Medicines Agency (EMA)

Table 1. Type of Covid-19 Vaccine [8,9,10,11,12,13]

Type of Covid-19 Vaccine	Subtype	Definition	Example	Advantage and Disadvantage
Whole virus	Live attenuated vaccines	Vaccines use a weakened form of the virus, which can still grow and replicate, but does not cause illness	Vaccines : Yellow fever, Measles, Tuberculosis, Polio	Well-established technology, strong immune response, immune response involves B cells and T cells, relatively simple to manufacture, unsuitable for people with compromised immune systems, may trigger disease in very rare cases, relatively temperature sensitive, so careful storage necessary
	Inactivated vaccines	Vaccine use viruses whose genetic material has been destroyed by heat, chemicals or radiation so they cannot infect cells and replicate, but can still trigger an immune response	Vaccine : Influenza, hepatitis A, Covid-19	Well-established technology, suitable for people with compromised immune systems, no live components, so no risk of the vaccine triggering disease, relatively simple to manufacture, relatively stable, booster shots may be required
	Viral vector vaccine	Vaccine uses a safe virus to deliver specific sub-parts – called proteins – of the germ of interest so that it can trigger an immune response without causing disease	Vaccine against Ebola, Zika, Flu, HIV, Covid-19	Well-established technology, suitable for people with compromised immune systems, no live components, so no risk of the vaccine triggering disease, relatively stable, relatively complex to manufacture, adjuvants and booster shots may be required, determining the best antigen combination takes time

The subunit approach	Protein subunit	Vaccines use fragments of protein from the disease-causing virus to trigger protective immunity against it	Vaccines : Hepatitis B, Pertussis, Tetanus, Diphteria, Meningitis, Covid-19	Well-established technology, suitable for people with compromised immune systems, no live components, so no risk of the vaccine triggering disease, relatively stable Relatively complex to manufacture, adjuvants and booster shots may be required, determining the best antigen combination takes time
The genetic approach	Nucleid acid vaccine (RNA or DNA)	Vaccines use genetic material from a disease-causing virus to trigger protective immunity against it	Relatively new technology. being developed : HIV, Zika, Covid-19	Immune response involves B cells and T cells, no live components, so no risk of the vaccine triggering disease, relatively easy to manufacture, some RNA vaccines ultra-cold storage, never been licensed in humans ,booster shots may be required

During this Covid-19 pandemic year, around 170 types of vaccines had been developed and some have been through the stage 2 or 3 of clinical trials [10]. The vaccine consists of several ingredients which include:[11]

1. Antigen is a component derived from the structure of disease-causing organisms and is known as a "foreign object" by the immune system to form an immunity. The types of antigens used in the covid-19 vaccine include whole virus, protein subunits, and nucleic acid.[10]
2. Adjuvants are added in vaccines to stimulate, increase and prolong the formation of antibodies against antigens, especially for inactivated vaccines. Currently, several hundred types of adjuvants had been used and researched in vaccine technology and there are large variations in how they affect the immune system and an adverse reaction caused by the immune system's hyperactivation.
3. The stabilizer is used to keep the vaccine stable during storage. Instability can lead to loss of antigenicity and reduce infection of live vaccines. The factors that influence vaccine stability are temperature and pH, while stabilizers used are MgCl2, MgSO4, lactose-sorbitol and sorbitol-gelatin.
4. Small amounts of antibiotics are used in the vaccine manufacturing process to prevent bacterial contamination of cell cultures when the virus is developed. People who are known to be allergic to the antibiotic component must be strictly observed after vaccination.
5. Preservatives are added to multidose vaccines to prevent the growth of bacteria and fungi. Several types of preservatives are thimerosal, formaldehyde and phenol derivatives which can cause minor reactions such as redness and swelling at the injection site.
6. Culture media is used to grow the antigen. Examples of culture media are egg, yeast, horse serum.

Similar to drugs, an allergic reaction can happen because of the vaccine component that brings to AEFI. However, vaccine availability is needed to achieve the goal of immunization including lowering morbidity and mortality, achieve immunity group (herd immunity), strengthening the overall health system and to maintain productivity and minimize the socio-economic impact.[14]

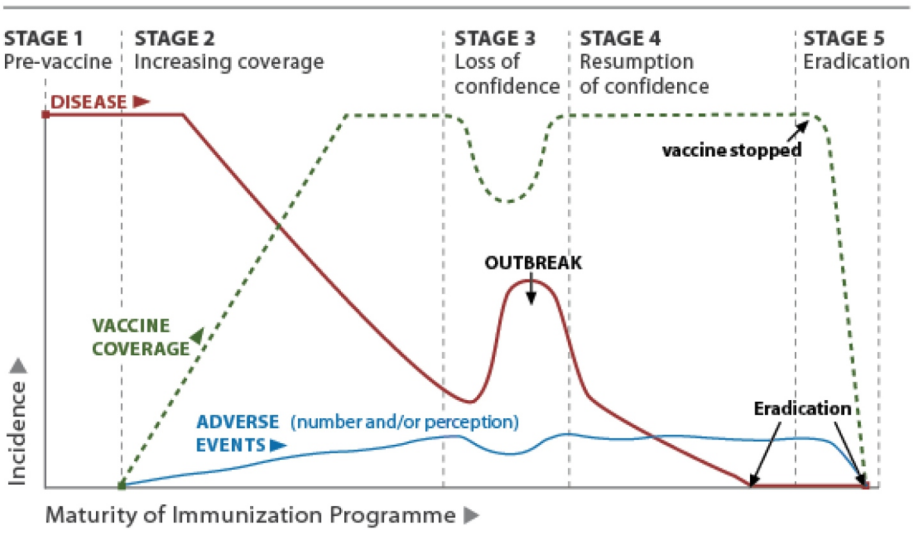

Figure 2. Immunization Program Maturation[15,16]

Immunization maturity is needed to achieve immunization goals. Several stages in the maturity of the immunization program include:

Stage 1 or Pre-Vaccine is the stage where the vaccine has not been introduced to the public and new diseases are discovered.

Stage 2 or Increasing coverage is the stage where an effective vaccine has been used and is circulating in the market, thereby reducing the incidence of disease along with the emergence of AEFI which is the concern of the public.

Stage 3 or Loss of confidence is the stage where public confidence in immunization decreases due to the mass media raising AEFI cases so that immunization coverage will decrease and can cause another outbreak.

Stage 4 or the Resumption of confidence is the stage where the people feel the need for immunization because of the increase in outbreaks and accompanied by the availability of more effective vaccine alternatives so that disease eradication can be carried out.

Stage 5 or Eradication is the stage where vaccine administration can be stopped because herd immunity has occurred.

Herd immunity is a condition when most of the people in a group have immunity to certain diseases, making it more difficult for the disease to spread. One way to achieve herd immunity is by immunization. To qualify for the establishment of herd immunity required target of 181.5 million people in Indonesia who have to be vaccinated, or about 70% of the total Indonesian population. The Indonesian Government through the Ministry of Health has embarked on Covid-19 immunization activities by ordering the vaccine product as many as 400 million units from several vaccine producers. [17] Manufacturers of the vaccine in clinical trials reporting local events that occur such as pain, swelling, redness, itching at the injection site, and some also experienced systemic events such as fatigue, diarrhea, muscle aches, nausea, vomiting, fever, headache, and changes in appetite. Severe AEFI was extremely rare and was almost the same occurred in the placebo group with tracking for coincidental events (Table 1).

Table 2. List of Vaccines Planned for the Implementation of Covid-19 Vaccination in Indonesia

Manufacturer	Type	Storage	Day of Injection	Efficacy	Subject age	Safety Concern	Planning to enter Indonesia
Sinovac [18]	Inactivated virus	Stored, transported and handled at 2-8 C	0,14 0,28	91,25%	18 years or older (including > 55 years)	In elderly : Local events : Vaccine (11-13%) vs placebo (4%) Systemic events : Vaccine (10-15%)vs placebo (16%)	Q1 2021
Novavax [19]	Protein subunit	Stored, transported and handled at 2-8 C	0,21	89,3 % in UK 60 % in South Africa	18-59 years	Local events 4-16% Systemic events 4-32% Severe reaction 0%	Q3 2021
Astrazeneca [20]	Viral vector	Stored, transported and handled at 2-8 C	0,28	62,1-90%	18 years or older (including >55 years)	Adverse events : myelitis	Q2 2021
Pfizer[21]	mRNA	Stored, transported at -60 s.d -80 Celsius Handled at 2-8 Celsius	0,28	95%	18 years or older (including >55 years)	Local events : Vaccine (66-83%) vs Placebo (8-14%) Systemic events : Vaccine (39-59%) vs Placebo (14-24%) Severe event Vaccine (0.6%) vs placebo (0.5%)	Q3 2021
Moderna [22]	mRNA	Stored, transported and handled at 2-8 C	0,28	94,5%	18 years or older (including >55 years)	Local events: Vaccine (84-89%) vs placebo (18-20%) Systemic events : Vaccine (55-80%) vs placebo (37-42%) Severe event Vaccine (0.6%) vs placebo (0.6%)	Q3 2021

AEFI

Each product of the vaccines used must meet the requirements of safe and effective even so no vaccine is one hundred percent free of adverse effects, although extremely rare. AEFI could happen particularly if the vaccine is used widely. AEFI is any unwanted medical event in a person that occurs after immunization, due to a vaccine reaction or not (coincidental). The classification is divided into reactions related to vaccine components, vaccine quality defects, procedural errors, anxiety due to fear of being injected, and coincidental (Table 3). [15]Reactions to vaccine usually limited to the injection site (pain, swelling, redness) or non-specific activation of the inflammatory system (fever) and seldom can be a form of allergic reaction.

Based on symptoms, AEFI is divided into mild and severe symptoms (Table 4). The symptoms also can be divided in to acute setting such as local, systemic and allergic reactions.[11] Mechanism of allergic reaction due to vaccines are : [23, 24]

1. Ig-E-mediated hypersensitivity reaction Type I. The reaction occurs within minutes to 4 hours after exposure with common symptoms like urticaria, angioedema, nasal congestion, cough, stridor, wheezing, shortness of breath, vomiting, abdominal pain, diarrhea and hypotension. Anaphylaxis also can occur as a severe life-threatening reaction but very rare.
2. T cell-mediated hypersensitivity reaction Type IV. The onset usually begins 48 hours to 96 hours after vaccination with common symptoms like maculopapular exanthema, eczema, acute generalized exanthematous pustulosis, erythema multiforme.
3. Immune complex-mediated hypersensitivity reaction Type III. The reactions are mediated by Ig-G, Ig-M and protein complement. Vasculitis and myocarditis are the most common symptoms.
4. Autoimmune. The reactions create autoantibodies that are induced by the molecular similarity between vaccine antigen and endogenous epitope. Frequent clinical manifestations are thrombocytopenia, vasculitis, polyradiculoneuritis, macrophagic myofasciitis, bullous pemhigoid, rheumatoid arthritis, Guillain-Barre syndrome, polymialgia.

Table 3. AEFI Classification[15,25,26,27,28,29]

Classification	Reaction
Vaccine (product-related and quality defect) reaction. An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties and quality defect of the vaccine product including its administration device as provided by the manufacturer.	Minor reaction: occur within a few hours of injection, resolve after short period of time and pose little danger, local (includes pain, swelling or redness at the site of injection) systemic (fever, malaise, muscle pain, headache or loss of appetite). Severe reactions : usually do not result in long term problems, can be disabling, can be life threatening but rare, include allergic and autoimmune reactions caused by the body's reaction to a particular component in a vaccine (anaphylaxis, thromboembolism/blot clot)
Immunization error-related reaction An AEFI that is caused by inappropriate vaccine transport, storage or handling (exposure to excess heat or cold and its diluents, use of a product after expiry date), error in prescribing or administration and thus by its nature is preventable (failure to adhere to vaccine indications, prescirption or contradiction)	Non-sterile injection : local infection at side injection, sepsis, toxic shock syndrome, blood-borne transmission of disease, death Reconstitution error: local abscess, vaccine ineffective, effect of drug, toxic shock syndrome, death. Injection at incorrect site : local reaction or abscess, sciatic nerve damage
Immunization anxiety-related reactions or Immunization stress-related respons An AEFI arising from anxiety about the immunization	Fainting, dizziness, headache, vomiting, hyperventilation, convulsion
Coincedental events An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety	Example: A fever occurs at the time of the vaccination (temporal association) but is in fact caused by malaria. Coincidental events reflect the natural occurrence of health problems in the community with common problems being frequently reported

Table 4. Frequency of AEFI Occurrence and Management[15,25,26,30,31,32]

Frequency	Percent occurrence among vaccinated person	Severity	Treatment
Very common	≥ 10%	Common and usually minor reactions : - are part of the immune response to vaccine - Reactions settle on their own, Example include : fever, malaise, diarrhoea, cough, vomiting, flu like syndrome, headache, myalgia	Local reactions: cold cloth at injection, extra oral fluid, paracetamol (symptomatic treatment)
Common	≥ 1% and < 10%		
Uncommon	≥ 0.1% and < 1%	Rare, usually more severe reactions: 1. Usually require clinical management, 2. Examples include : - severe allergic reaction (e.g., anaphylaxis) including an exaggerated response to the vaccine antigen or component, - vaccine specific reactions, such as BCG osteitis - autoimmune, such as thrombotic thrombocytopenia	Anaphylaxis: - adrenaline (epinephrine) 1:1000 Under 6 months -6 years 150 micrograms IM (0.15ml) Over 6 to 12 years 300 micrograms IM (0.30ml) Over 12 years including adults 500 micrograms IM (0.5ml) and Dexametasone 1 ampule Thrombotic thrombocytopenia : - consult thrombosis expert - Intravenous imunoglobulin therapy, steroid, non heparin anticoagulant
Rare	≥ 0.01% and < 0.1%		
Very rare	< 0.01%		

From January to February 2021, the Government has implemented vaccination program with vaccine from Sinovac for health workers and public service providers with coverage of one million people and until now reported mild AEFI incidents that did not cause serious reactions such as soreness, pain at the injection site, redness, fever, nausea, and changes in appetite.[33,34]

AEFI monitoring consists of finding, tracking, incident analysis, follow-up, reporting and evaluation (Figure 2). [15,35] The types and reports consist of serious and non-serious AEFI. Serious Adverse Event (SAE) or serious AEFI is any medical event after immunization that causes hospitalization, disability, and death and which causes unrest in the public, it is reported every time an incident occurs and, equipped with an investigation to be carried out by Regional Commitee and / or National Committee of AEFI. A non-serious or mild AEFI is a medical event that occurs after immunization and does not pose a potential risk to the health of the recipient. It is reported regularly every month along with the results of immunization coverage.[35]

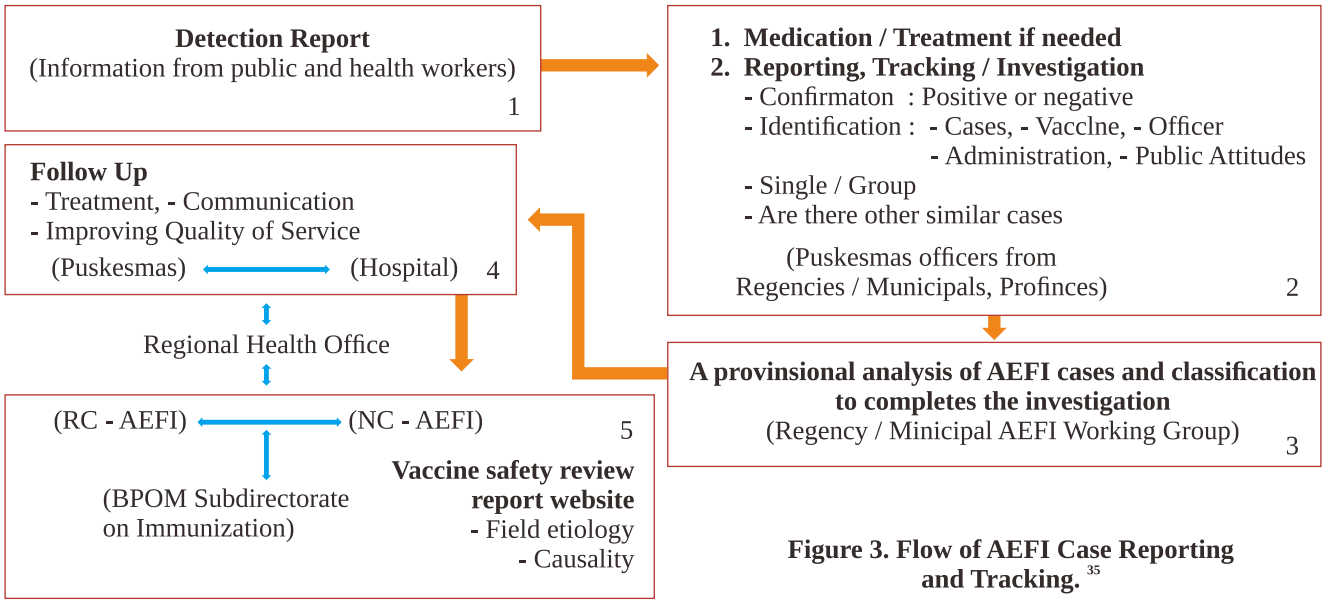

Figure 3. Flow of AEFI Case Reporting and Tracking. [35]

In an AEFI event that raises public attention, the AEFI must be tracked, recorded, and responded to by the immunization administrator and can be done directly independently through the vaccine safety website to the Ministry of Health, in this case Sub Directorate on Immunization/Komnas PP KIPI (National Committee – AEFI) (Figure 3).[35,36] Immunization administrators must also report to the higher administrative level that it can be investigated and evaluated for improvement of immunization. The central and regional governments are also responsible for AEFI handling and its budget in their regions.[35]

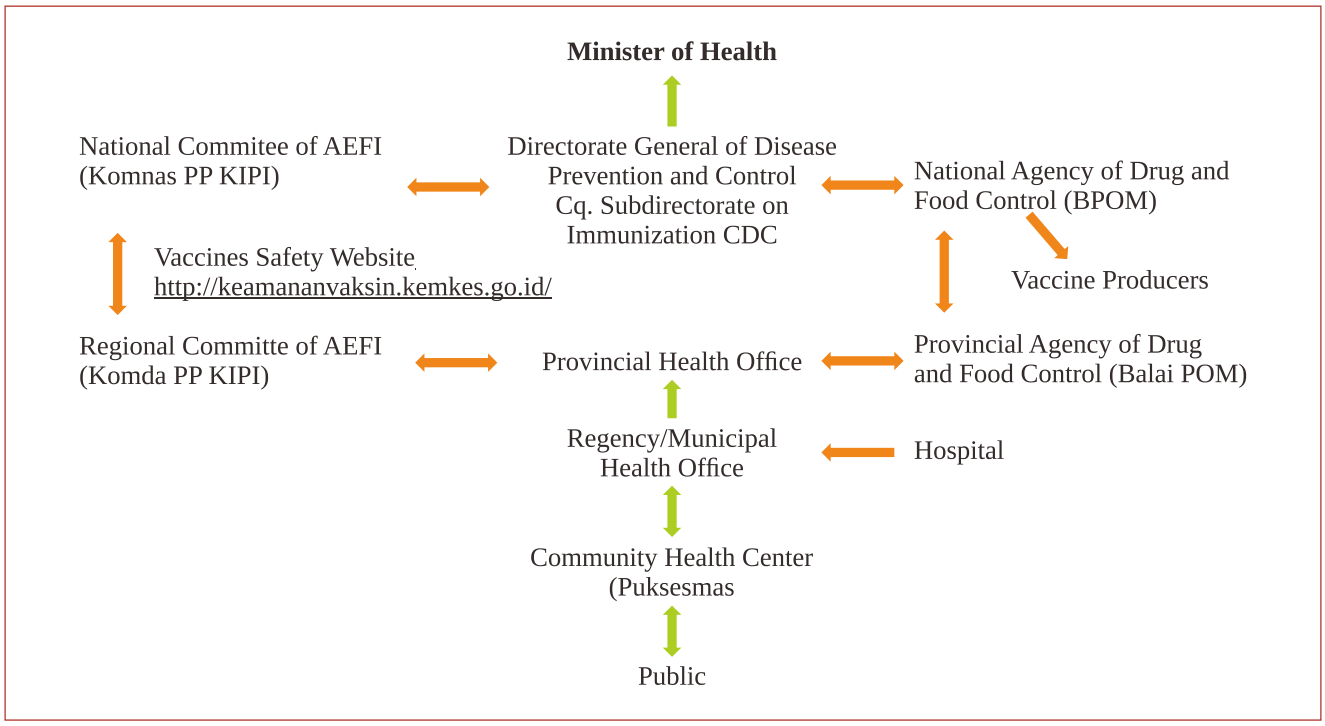

Figure 4. Flow of AEFI Reporting and Assessment [35]

The main purpose of this monitoring is to detect AEFI early, to respond quickly and accurately, and to reduce the negative impact of immunization on individual health and the implementation of vaccination itself. The Public has a low tolerance for AEFI because vaccines are given to healthy people to prevent disease, that good surveillance is needed to detect and manage AEFI.[15, 35]

CONCLUSION

Prevention and control of Covid-19 in Indonesia have been carried out with health and vaccination protocols. Vaccines are relatively safe and can rarely cause AEFI. AEFI may occur during immunization campaigns in large populations or when new vaccines are produced. However, severe AEFI events are extremely rare. Surveillance and good management of AEFI will determine the success of the immunization program by increasing public confidence in the benefits and safety of immunization.

Acknowledgements

This work is supported by Department of Internal Medicine, Faculty of Medicine UIN Syarif Hidayatullah

Conflict of Interest

All authors declare no competing interests.

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Print ISSN: 2716-3628, Online ISSN: 2720-9563