Adverse Event Following Immunization Monitoring System in Japan

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Abstract: Although immunization is essential for maintaining public health, adverse events following immunization (AEFI) occur at a certain rate. Therefore, it is extremely important to conduct postimmunization safety monitoring and relief systems to ensure the safe implementation of immunizations for the public. This article summarizes the monitoring system of AEFI and the unique compensation system (so-called relief system) in Japan. In addition, current problems and issues on the AEFI monitoring and relief system will be specified, and immunization-related systems planned to be built in the future in Japan will be introduced.

Key Words: safety monitoring, adverse event following immunization, the relief system, Japan

(*Pediatr Infect Dis J* 2024;43:e52–e56)

THE MONITORING SYSTEM OF ADVERSE EVENTS FOLLOWING IMMUNIZATION IN JAPAN

Monitoring the safety of immunization is essential for the national immunization program. In Japan, there are 2 data sources for monitoring immunization safety. The first is individual case safety reports (ICSRs) from the healthcare professionals of the medical institutions, and the other is ICSRs from marketing authorization holders (MAHs) (Fig. 1). It was established in 2013 that if a physician suspects adverse events following immunization (AEFI), they are obligated to report the event to the Ministry of Health, Labour and Welfare (MHLW) in accordance with the Immunization Act.[1] Meanwhile, ICSRs from MAHs are regulated based on the Act on Securing Quality, Efficacy, and Safety of Products, including Pharmaceuticals and Medical Devices.

The reporting criteria for physicians to report AEFI are in Article 5 in the Order of MHLW (Table 1).[1] It defines the reporting criteria of symptoms to be reported in each vaccine if they are observed during a specified period after which the vaccine is administered, regardless of a clear causal relationship. In addition, even if the defined duration and symptoms are not met for each vaccine, a physician may report a case that requires hospitalization, has residual complications or results in death if they think it might be associated with vaccination. Table 2 lists the items of information collected in the report of AEFI. If the event to be reported is diagnosed as acute disseminated encephalomyelitis (ADEM), Guillain-Barré syndrome (GBS), thrombosis including thromboembolism but limited to those with thrombocytopenia (TTS), myocarditis and pericarditis, the respective survey forms[1] have to be submitted to evaluate the diagnosis by using the Brighton Classification[2] if available. On the other hand, the report from MAHs does not define when and what symptoms are to be reported. In addition, there is another path whereby the vaccinated person or the family reports the symptoms after immunization to the municipality, which is reported to the MHLW through the prefecture government.

The ICSRs from the healthcare professionals and MAHs are submitted to the Pharmaceuticals and Medical Devices Agency (PMDA). PMDA and external experts organize and analyze the ICSRs and evaluate the causal relationship between the vaccine and the symptoms. The documents are submitted to the joint council, and the council discusses whether there are any serious concerns that require immediate action such as suspension of vaccination[3] (Fig. 1). The joint council consists of an adverse reaction review subcommittee positioned under the Health Science Council for Immunization and the Pharmaceutical Affairs and Food Sanitation Council, held usually every 3 months.

In addition, a health status survey monitors relatively frequent symptoms (fever, swelling of immunization site, seizure, vomiting, diarrhea, cough/runny nose, etc.) for a certain period after routine immunization.[4] Managed by MHLW, physicians distribute questionnaires to vaccinated persons or their guardians, and they are asked to observe and record their health status from the date of vaccination. The observation period is 28 days (4 months for the BCG vaccine), and reporting is requested even if no adverse reactions are observed. Results are analyzed annually and evaluated by the Joint Council. This relatively small cohort survey system was launched to inform the public about common adverse effects and ensure safe immunization practices and it was also utilized when the COVID-19 vaccine was introduced.

THE RELIEF SYSTEM FOR INJURY TO HEALTH WITH VACCINATION IN JAPAN

Overview

The unique compensation system (so-called Relief System) for injury to health with vaccination in Japan is based on the no-fault compensation scheme stipulated in Article 15 of the Immunization Act of 1976.[5] This system is independent of the aforementioned monitoring system of AEFI.

The person who has suffered after the immunization or their family/guardian can request relief from the municipality in which the certificate of residence was registered at the time of vaccination.[6] The external experts at the municipality investigate the case

Accepted for publication October 30, 2023

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Supported by the Ministry of Health, Labour, and Welfare Program, Grant No JPMH21HA1004.

S.K.'s institution has received funding from SK and reports research support to his institution from Pfizer, Emergent BioSolutions, Meissa, CDC, and NIH. Dr. A.S. has received honoraria from MSD, Pfizer, Moderna, Tanabe-Mitsubishi Pharmaceuticals, and Biken Co. Ltd. for lectures. Other authors have no conflicts of interest to disclose.

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ISSN: 0891-3668/24/432-e52e56
DOI: 10.1097/INF.0000000000004184

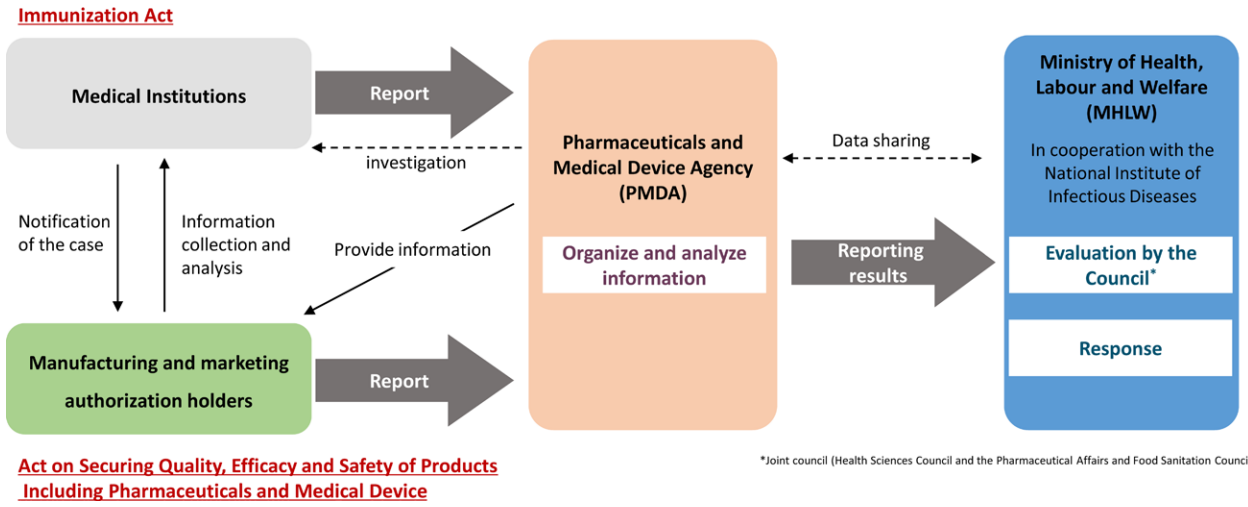

FIGURE 1. Evaluation structure for vaccine safety monitoring.

and submit the application form to the prefecture government, and the prefecture government checks the contents and submits it to the MHLW. At the MHLW, the causal relationship is examined by the Examination Committee for Certification of Sickness and Disability. The committee thoroughly reviews each case, considering both medical and legal perspectives, to ensure the symptoms are medically plausible and temporally related, with no other evident cause. This review is guided by the principle that certification does not necessitate a strict medical causal relationship. Still, it covers cases where it is undeniable that immunization has led to the symptoms. Based on the examination results, the applicant will be notified whether the municipality will provide the compensation (Figure 2). Between February 1977 and December 2021, 3,522 cases were certified by MHLW for routine vaccines other than the COVID-19 vaccine.[7,8] In 2018, 46% of certified cases were approved as undeniably attributable to immunizations.[9]

BENEFIT TYPE AND AMOUNT

The types of benefits for the relief system for AEFI include medical expenses, medical allowance, pensions for rearing children with disabilities, disability pensions, lump-sum benefits for death, survivors' pensions, lump-sum benefits for survivors, funeral expenses, and additional amounts for nursing care.[6] However, the amount of money paid as relief depends on the category to which the administered vaccine belongs. The Immunization Act categorizes routine vaccines into 2 categories (A and B) based on the purpose of the vaccine.[10] Diseases included in category A are diphtheria, pertussis, tetanus, poliomyelitis, hepatitis B, hemophilus influenza type B, pneumococcal (PCV13), tuberculosis (BCG), measles, rubella, varicella, Japanese encephalitis, human papillomavirus and rotavirus, and category B is seasonal influenza and pneumococcal (PPSV23) for older people or those with underlying medical conditions. The vaccine in category A is vaccinated to prevent the outbreak and spread of the disease because the disease is contagious and can cause severe outcomes. Therefore, category A vaccines are strongly recommended to prevent the disease in the majority of the population acquiring immunity. Routine immunization for children is classified as category A. On the other hand, vaccines in category B can prevent disease onset or its severity in individuals. The amount of relief differs between categories A and B, but the amount is higher for category A. For example, as of June 2023, if a disability pension (Class 1) is approved, 5,175,600 yen (about $40,000) per year is paid for category A and 2,875,200 yen (approximately $22,000) for category B annually. If the death due to illness caused by vaccination is approved, lump-sum benefit for death of 45,300,000 yen (approximately $350,000) is paid in category A. In category B, survivors' pensions of 2,514,000 yen (approximately $19,000) annually (limited to 10 years maximum) are paid if the person died was the financial provider for the bereaved, and 7,542,000 yen (approximately $58,000) are lump-sum benefits for survivors are paid if the person died was not the financial provider for the bereaver.[7] The relief system for voluntary vaccines other than routine vaccines is provided by the Relief System for adverse reactions to drugs which is stipulated in the Act of PMDA, Independent Administrative Agency.[11] The benefit amount for category B is set with reference to the benefit amount of adverse reactions to drugs.

FUTURE PROSPECTS OF SAFETY ASSESSMENT OF IMMUNIZATION IN JAPAN

The current monitoring system of AEFI in Japan is a passive reporting system similar to the United States. Vaccine Adverse Event Reporting System, which is useful for the early detection of adverse reaction cases and accumulating unusual events. However, data on individuals without AEFI is not reported, and denominator information is not available, making it challenging to determine the causal link between immunization and adverse events and estimate the incidence of the events by doses given. In addition, the systematical challenge exists, such as immunization history and medical records are stored separately by municipalities and medical institutions, and no readily accessible immunization registry is available. Under such a system, there was concern that people's confidence in the safety assessment of vaccines could be reduced. Therefore, the MHLW revised The Immunization Act in 2022, which includes plans to establish a nationwide digital immunization registry. It is stated that the future goal is to connect immunization-related information, including immunization registers, a national database of health insurance claims and ICRS, to establish a database that will allow us to better assess the causal relationship between vaccination and adverse reactions than the current system. We expect that this change will lead to more robust safety monitoring and assessments.

TABLE 1. Reporting Criteria for Suspected Adverse Event Following Immunization under the Japanese Immunization Act

	Disease	Symptom	Period to Onset	Symptoms
Reporting criteria	Diphtheria	1 Anaphylaxis	4 hours	If "others" is selected on the left
	Pertussis	2 Encephalitis/encephalopathy	28 days	
	Polio myelitis	3 Seizure	7 days	a Apnea
	Tetanus	4 Thrombocytopenic purpura	28 days	b Bronchospasm
		5 Others	-	c ADEM
	Measles	1 Anaphylaxis	4 hours	d Multiple sclerosis
	Rubella	2 Acute disseminated encephalomyelitis (ADEM)	28 days	e Encephalitis/encephalopathy
		3 Encephalitis/Encephalopathy	28 days	f Myelitis
		4 Seizure	21 days	g Seizure
		5 Thrombocytopenic purpura	28 days	h Guillain-Barré syndrome
		6 Others	-	i Optic neuritis
	Japanese encephalitis	1 Anaphylaxis	4 hours	j Facial nerve palsy
		2 ADEM	28 days	k Peripheral nerve palsy
		3 Encephalitis/encephalopathy	28 days	l Abnormal perception
		4 Seizure	7 days	m Thrombocytopenic purpura
		5 Thrombocytopenic purpura	28 days	n Vasculitis
		6 Others	-	o Impaired liver function
	Tuberculosis (BCG)	1 Anaphylaxis	4 hours	p Nephrotic syndrome
		2 Disseminated BCG infection	1 year	q Asthma attack
		3 BCG osteitis (osteomyelitis/periostitis)	2 years	r Interstitial pneumonia
		4 Skin tuberculosis-like lesions	3 months	s Mucocutaneous ocular syndrome
		5 Pyogenic lymphadenitis	4 months	t Uveitis
		6 Meningitis (only caused by BCG)	-	u Arthritis
		7 Others	-	v Cellulitis
				w Vasovagal reaction
				x If other than a-w, list symptom name
	Haemophilus Influenzae type b	1 Anaphylaxis	4 hours	
	Pneumococcal (Child)	2 Seizure	7 days	
		3 Thrombocytopenic purpura	28 days	
		4 Others	-	
	Human papilloma virus	1 Anaphylaxis	4 hours	
		2 ADEM	28 days	
		3 Guillain-Barré syndrome	28 days	
		4 Thrombocytopenic purpura	28 days	
		5 Vasovagal reaction (accompanied by syncope)	30 minutes	
		6 Various Symptoms, mainly pain or movement disorders	-	
		7 Others	-	
	Varicella	1 Anaphylaxis	4 hours	
		2 Thrombocytopenic purpura	28 days	
		3 Aseptic meningitis (accompanied by herpes zoster)	-	
		4 Others	-	
	Hepatitis B virus	1 Anaphylaxis	4 hours	
		2 ADEM	28 days	
		3 Multiple sclerosis	28 days	
		4 Myelitis	28 days	
		5 Guillain-Barré syndrome	28 days	
		6 Optic neuritis	28 days	
		7 Peripheral neuropathy	28 days	
		8 Others	-	

(Continued)

TABLE 1. (*Continued*)

Disease	Symptom	Period to Onset	Symptoms
Rotavirus	1 Anaphylaxis	4 hours	
	2 Intussusception	21 days	
	3 Others	-	
Influenza	1 Anaphylaxis	4 hours	
	2 ADEM	28 days	
	3 Encephalitis/encephalopathy	28 days	
	4 Seizure	7 days	
	5 Myelitis	28 days	
	6 Guillain-Barré syndrome	28 days	
	7 Optic neuritis	28 days	
	8 Thrombocytopenic purpura	28 days	
	9 Vasculitis	28 days	
	10 Impaired liver function	28 days	
	11 Nephrotic syndrome	28 days	
	12 Asthma attack	24 hours	
	13 Interstitial pneumonia	28 days	
	14 Mucocutaneous ocular syndrome	28 days	
	15 Acute generalized exanthematous pustulosis	28 days	
	16 Others	-	
Pneumococcal(Older people)	1 Anaphylaxis	4 hours	
	2 Guillain-Barré syndrome	28 days	
	3 Thrombocytopenic purpura	28 days	
	4 Necrosis or ulceration at the injection site	28 days	
	5 Cellulitis (symptoms similar to this, including those. extending from the upper arm to the forearm)	7 days	
	6 Others	-	
Coronavirus Disease 2019 (COVID-19)	1 Anaphylaxis	4 hours	
	2 Thrombosis (including thromboembolism) (limited to those with thrombocytopenia) (TTS)	28 days	
	3 Myocarditis	28 days	
	4 Pericarditis	28 days	
	5 Febrile seizure	7 days	
	6 Others	-	

Table 2. Reporting Items

Vaccine Categories	Routine Vaccine Temporary Vaccine/Voluntary Vaccine
Patient information	Name or initials/sex/age at time of vaccination/address/date of birth
Information about the reporter	Name of medical institution/phone number/address
Vaccinated location	Name of medical institution/address
Vaccine information	Vaccine types/lot number/ marketing authorization holders/vaccine doses
Situation at the time of vaccination	Date of vaccination/birth weight/body temperature before vaccination Family history/points of concern of Prevaccination Screening Questionnaire
Information about the symptom	Symptoms/date of onset/causal relationship with vaccines/possibility of other factors
Severity of symptoms	Severe (death, disability, hospitalization, etc)/not severe
Outcomes	Recovered/recovering/not recovered/sequelae/death/unknown
Opinion of the reporter	
Number of reports	1st report/2nd report/3rd report or more

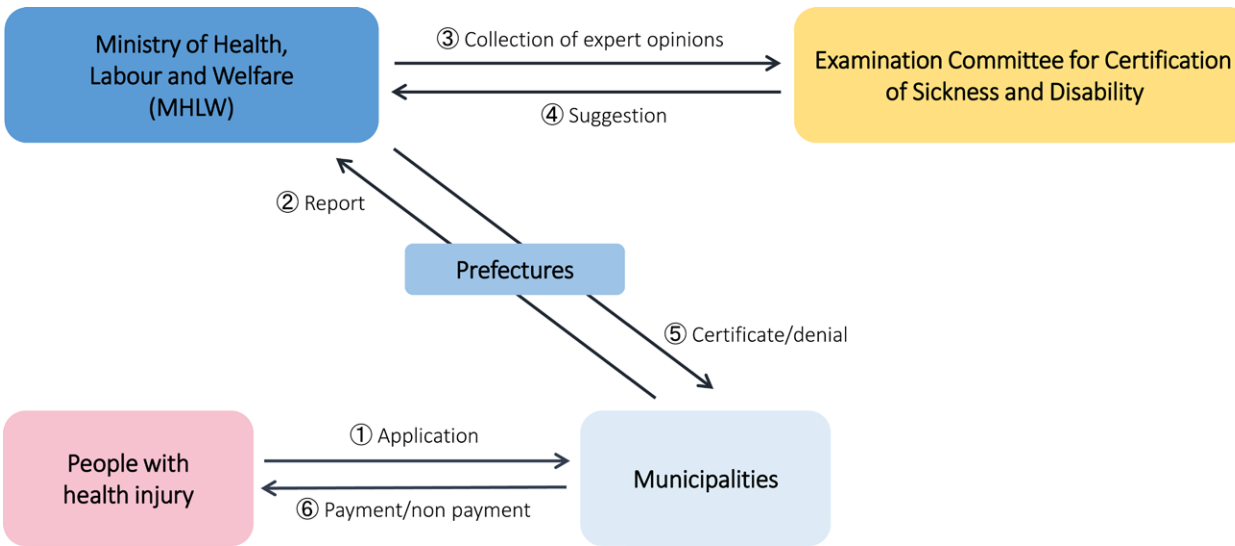

FIGURE 2. Structure of relief system for injury to health with vaccination.

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