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Health and Global Policy Institute

Immunization and Vaccination Policy Project

Recommendations on the Development of Information Infrastructure and System Maintenance for Long-Term Safety Assessment of Immunizations and Vaccines

Health and Global Policy Institute (HGPI)

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HGPI Health and Global Policy Institute

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Introduction

■ About Health and Global Policy Institute (HGPI)

Health and Global Policy Institute (HGPI) is a Tokyo-based independent and non-profit health policy think tank, established in 2004. Since our establishment, HGPI has been working to help citizens shape health policy by generating policy options and bringing together stakeholders as a non-partisan think-tank. Our mission is to enhance the civic mind along with individuals' well-being and to foster sustainable, healthy communities by shaping ideas and values, reaching out to global needs, and catalyzing society for impact. We commit to activities that bring together relevant players from various fields to deliver innovative and practical solutions and to help interested citizens understand available options and their benefits from broader, global, long-term perspectives.

■ The significance of safety assessment within immunization and vaccination policy

Immunizations and vaccines have been called "the greatest invention in the history of medicine," and in the context of infectious disease control, they are considered the most cost-effective public health intervention. The Coronavirus Disease 2019 (COVID-19) pandemic has enabled people in Japan and around the world to reaffirm the value of immunizations and vaccines. For example, by preventing infectious diseases, they lighten burdens placed on families and are particularly effective at helping children do better in school. Considering this from a society-wide perspective, they can decrease and optimize healthcare spending and lead to productivity gains, helping to stabilize economies and governments as a result. In addition, reaching a common understanding toward the benefits of immunizations and vaccines as a society helps to further promote R&D, which leads to even greater reductions in infectious diseases. In this manner, immunizations and vaccines are social interventions that create virtuous cycles for individuals and for society, and they are essential for protecting the health and daily lives of every citizen from Vaccine Preventable Diseases (VPDs) and for maintaining socioeconomic activities.

In medical terms, vaccination is the act of building immunity against an infectious disease by injecting a foreign substance (a vaccine) into the body to induce an immune response. In addition to eliciting an immune response, vaccines can also result in adverse reactions. Therefore, the need for a vaccine must be determined using a comprehensive assessment regarding its potential risks and benefits. However, there are multiple aspects to the ability of vaccines to prevent infectious diseases and the onset or exacerbation of symptoms, or to directly or indirectly start virtuous cycles, which makes their benefits difficult to understand intuitively. Therefore, those benefits must be scientifically evaluated and shared throughout society so they can become common knowledge.

Immunizations and vaccines are administered to citizens in various states of health, which naturally includes people with comorbidities and people who are healthy, with the intended result of achieving herd immunity. This means vaccination programs are extremely large in scale. Looking at the ongoing COVID-19 pandemic, for example, the total number of COVID-19 vaccines administered in Japan exceeded 280 million by June 30, 2022. As this figure suggests, the scope of impact of immunizations and vaccines surpasses the individual to affect all of society. In addition to understanding the medical value of immunizations and vaccines, it is important for us to also grasp their value for society and public health.

As of June 2022, most of the COVID-19 vaccines that have been approved and are now being administered in Japan are mRNA vaccines. The fact that vaccines using this new modality were deployed for the first time during a pandemic and administered in multiple doses must not be overlooked when considering how to assess immunization and vaccine safety. In May 2022, the "Act for the Partial Revision of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices" was revised, and an emergency regulatory approval system was established. Now that legislation establishing an emergency approval system has been enacted, it has become possible for pharmaceuticals and vaccines to be granted accelerated regulatory approval during emergencies, specifically when their usage "is urgently required to prevent the spread of a disease that may have severe impacts on lives and health of citizens or other hazards to health, and when there is no other alternative to using said pharmaceutical." This system is also likely to serve as a mechanism that encourages domestic companies to pursue rapid vaccine deployment. On the global level, the "100 Days Mission" was backed by G7 leaders at the G7 Summit 2021 with the goal of developing vaccines within 100 days after a new epidemic or pandemic threat has been identified. Research and development for new modalities is also progressing in Japan. In this manner, we see that expectations for new vaccines continue to grow.

On the other hand, there is enormous social impact when safety concerns emerge after a vaccine is approved, demonstrating that post-approval safety measures are all the more important for preventing confusion in society. This point was also pointed out in the "Joint Statement by Four Societies on Ensuring the Safety of Novel Coronavirus Vaccines" issued by the Japanese Society for Pharmacoepidemiology, the Japan Epidemiological Association, the Society for Clinical Epidemiology, and the Japanese Society for Vaccinology in November 2020, when the deployment of COVID-19 vaccines was close at hand. Immunizations and vaccines are large-scale public health interventions, so in addition to promoting R&D, we should also position safety assessment as a safety net in immunization and vaccination policy and systematically promote the establishment of a safety assessment system.

■ The purpose of these recommendations

In April 2013, before the COVID-19 pandemic, a revision to the Immunization Act made it mandatory to report suspected adverse reactions. After legislation on that system was passed, an application for reporting suspected adverse reactions after vaccinations was created. Although this served to promote the digitalization of suspected adverse reaction reports, those reports still had to be converted to PDF, printed, and submitted to authorities by fax. Then, about one year before the COVID-19 pandemic began, the Ministry of Health, Labour and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA), and the National Institute of Infectious Diseases (NIID) began holding meetings on revising this system, including allowing reports to be submitted electronically. These efforts were successful, and a system that allows suspected adverse reaction reports to be entered and submitted using the internet was in operation by April 2021, in time to contribute to the domestic COVID-19 response. Suspected adverse reaction report data is now being gathered day by day by the MHLW, the PMDA, and NIID, where it is analyzed and submitted to a joint committee of the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council and the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council.

The fact that a system which was built up steadily over the course of a decade during a period of non-emergency was able to function properly in 2021, during the COVID-19 pandemic, is deserving

of high praise. This was the fruit of efforts to incorporate issues encountered during the 2009 H1N1 pandemic into law and to establish a system to address those issues. Next, we should look back on issues that surfaced during the COVID-19 pandemic and the system that was rapidly constructed during the pandemic to prepare for the next infectious disease outbreak. At the same time, we should make steady and swift progress on establishing systems needed for immunization and vaccine safety assessment during non-emergency periods.

On June 17, 2022, the Cabinet Secretariat presented the "Directions on Measures to Prepare for the Next Infectious Disease Crisis Based on Past Efforts for COVID-19." Some specific measures that will be considered under those directions include the establishment of an infectious disease crisis management agency in the Cabinet Office, a new headquarters for infectious disease countermeasures at the MHLW, and what could be called a Japanese version of the United States Centers for Disease Control and Prevention (CDC) by merging NIID and the National Center for Global Health and Medicine. The need to strengthen infectious disease countermeasures including necessary legal amendments has also been recognized, as demonstrated by the perspective of further enhancing the effectiveness of each measure included in the "Overall Picture of Measures to Ensure Security Against the Next Spread of Infections" presented on November 12, 2021. On June 7, 2022, the Basic Policy on Economic and Fiscal Management and Reform 2022 included the establishment of a Headquarters for the Promotion of Digital Transformation (DX) (tentative name). The "Priority Policy Program for Realizing Digital Society" was formulated that same day. At the same time, the establishment of the Next Infectious Disease Surveillance System (tentative name) in 2025 is also under consideration, and it will be necessary to include items related to immunization and vaccine safety assessment to make improvements based on a comprehensive review of the COVID-19 pandemic response.

Given these circumstances, in these recommendations, we have summarized discussions held by volunteer experts with a shared recognition for the need for safety assessment for immunization and vaccination policies, and have organized discussion points regarding necessary future efforts. To help policies for immunizations and vaccinations, which are public health interventions, start virtuous cycles for individuals and in society through these recommendations, it will be necessary for safety assessment to be positioned as a safety net within immunization and vaccination policies, to expand discussions on advancing the systematic creation of systems for safety assessment among industry, Government, academia, and civil society, and to implement concrete measures for creating those systems.

In June 2021, HGPI presented, "A Life Course Approach to Immunization and Vaccination Policy – Five Perspectives and Recommended Actions," which was based on discussions held in FY2020 as part of our Immunization and Vaccination Project. These recommendations were created as an FY2022 initiative undertaken in accordance with those five perspectives.

Executive Summary

1 Establishing a Common Understanding of Immunization and Vaccine Safety Assessment

1.1 Establishing a common understanding of the necessary information for and current systems of immunization and vaccine safety assessment

- Establish a common understanding of the epidemiological information required to quantitatively and scientifically evaluate the safety of immunizations and vaccines and the systems required to collect such information

2 Enhancing the Function of Passive Surveillance and Institutional Design of Active Surveillance

2.1 Enhancing the function of the suspected adverse reaction reporting system

- Promote use of the suspected adverse reaction reporting system for the prompt detection of adverse events and abnormal signals that should be examined for causal relationships with immunizations and vaccines
- Enhance the function of passive surveillance through effective use of the suspected adverse reaction reporting application, electronic reporting system, etc.

2.2 Institutional design of active surveillance to complement the functions of passive surveillance

- Make appropriate and prompt use of information based on the functional limitations of passive surveillance
- Implement institutional designs for active surveillance based on the functional limitations of passive surveillance

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- Design and establish an active surveillance system that is aligned with the domestic healthcare system
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- Adopt the VRS to provide statistical information
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3.3 Building a cooperative system among the national Government, local governments, and other related organizations

- Construct a cooperative system between the national Government and local governments for linking National Health Insurance and other insurer databases with vaccination information to contribute to immunization and vaccine safety assessments
- Promote efforts from local governments for information sharing among insurer databases, to develop good practices, and to accelerate efforts to examine personal information handling
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4.1 Establishment of a system for comprehensive policy decisions

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- Promote human resource development and the dissemination of relevant and correct information, terminology, and the understanding of systems to contribute to effective communication with citizens regarding comprehensive policy decisions

Policy Recommendations

1. Establishing a Common Understanding of Immunization and Vaccine Safety Assessment

1-1. Establishing a common understanding of the necessary information for and current systems of immunization and vaccine safety assessment

Establish a common understanding of the epidemiological information required to quantitatively and scientifically evaluate the safety of immunizations and vaccines and the systems required to collect such information

For immunization and vaccination policies to start a virtuous cycle for individuals and society, vaccine safety should undergo quantitative and scientific evaluation. The information and verification methods needed to conduct those evaluations should be shared among specialists in infectious diseases and relevant fields, and throughout society. Current systems and the necessary information can be organized as follows.

	With adverse event	Without adverse event
Vaccinated group	A	B
Non-vaccinated group	C	D

Immunization and vaccine safety can be assessed by comparing risk in the vaccinated and non-vaccinated groups. Risk can be calculated using A/(A+B) for the vaccinated group and C/(C+D) for the non-vaccinated group. However, the information needed for these calculations and comparisons is somewhat scattered among different administrative bodies that use different collection methods. For example, the Japanese National Database of Health Insurance Claims and Specific Health Checkups (NDB) does not currently include information from registries of the insured, so the number of people in the “D” category cannot be counted accurately. Only when the public has an accurate, broad understanding of the necessary information and the characteristics of existing systems will it be possible to hold discussions to assess immunization and vaccine safety.

	Information gathered	Collection method	Managing entity
Some of A	Those with adverse events among vaccinated group	Suspected adverse reaction reports	National Government
Total number of A+B	Total number of people in vaccinated group	Vaccination ledgers	Municipal governments
Total number of C+D	Total number of people in non-vaccinated group	Vaccination ledgers	Municipal governments
Total number of A+C	Number of people with adverse events reported and recorded	NDB, medical claims data, insurer database	National Government or insurer
Some of B+D	Number of people without adverse events reported and recorded	NDB, medical claims data, insurer database	National Government or insurer

Information related to A and B	Information related to vaccinated group	Post-vaccination health survey	National Government
Partial information related to A through D	Health and medical information	Medical records	Healthcare institutions

2. Enhancing the Function of Passive Surveillance and Institutional Design of Active Surveillance

2-1. Enhancing the function of the suspected adverse reaction reporting system

Promote use of the suspected adverse reaction reporting system for the prompt detection of adverse events and abnormal signals that should be examined for causal relationships with immunizations and vaccines

Substantial revisions were made to the system for reporting suspected adverse reactions when the Immunization Act was amended in April 2013, when it became mandatory for healthcare institutions to make such reports to the MHLW under Article 12 of that act. This system was built up steadily over the course of around ten years during a non-emergency period and functioned as intended in 2021, during the COVID-19 pandemic, for which it deserves high praise. In practice, the suspected adverse reaction reporting system detects signals in real time and at a high frequency using reports of suspected adverse reactions to COVID-19 vaccines, which have provided an enormous amount of reference materials to be publicized and discussed at the joint committee of the Side Effect Subcommittee of the Immunization and Vaccine Section Meeting in the Health Science Council and the Subcommittee on Drug Safety of the Committee on Drug Safety in the Pharmaceutical Affairs and Food Sanitation Council.

This system is a passive surveillance system and is not limited to direct reports made from physicians and other healthcare professionals to the MHLW (addressed to the PMDA), as vaccinated people or their guardians can also make voluntary reports to the MHLW through local public organizations. This system for reporting suspected adverse reactions based on voluntary reports has the potential to detect highly rare adverse reactions and also helps the rapid detection and identification of abnormal signals that should be examined for causal relationships with immunizations and vaccines, so it should be further promoted.

Enhance the function of passive surveillance through effective use of the suspected adverse reaction reporting application, electronic reporting system, etc.

To broadly gather information of interest and minimize the possibility of under-reporting, which is unavoidable given the nature of the system, steps should be taken to improve awareness toward the suspected adverse reaction reporting application as well as the electronic reporting system. Coincidentally, a system called the Vaccination Record System (VRS) was established to facilitate the COVID-19 vaccine rollout. As part of that system, the Government distributed tablet PCs for registering information to many local or municipal governments, who are responsible for managing that information. Although the tablet PCs for the VRS are on short-term loan and with usage limited to COVID-19 vaccines, the MHLW and the Digital Agency should maximize on the opportunities they provide by pre-installing the suspected adverse reaction reporting application and displaying the electronic reporting system URL where users will see it to spread awareness toward both tools. Expectations are particularly high for efforts to more strongly recommend usage of the electronic reporting system because it allows users to complete reports entirely online without having to fax them.

Suspected adverse reaction reports tend to be submitted several days after a vaccination, and by the 28th day after a vaccination, diseases outside of reporting criteria tend to not even be reported. While it is necessary to be cautious toward the influence of reporting bias no matter what tools are used due to the nature of the passive surveillance system, trials should be held

on creating mechanisms for detecting diseases without overly relying on reporting from healthcare institutions or other institutions.

2-2. Institutional design of active surveillance to complement the functions of passive surveillance

Make appropriate and prompt use of information based on the functional limitations of passive surveillance

Two challenges the suspected adverse reaction reporting system should overcome is that it lacks information on non-vaccinated people and that the number of vaccinated people is unknown. In addition, it does not provide the capacity to conduct quantitative risk assessment or scientific evaluation on the causal relationships between vaccines and suspected adverse reactions after excluding sources of reporting bias, such as reports that focus on high-profile events or incidental health problems.

Using the existing system alone, symptoms for which a causal relationship between a vaccination and a suspected adverse reaction can be identified include those that are clearly related to a vaccination, such as redness or pain at the injection site; vaccine-related symptoms when attenuated vaccines like BCG or rotavirus are administered to children with congenital immunodeficiencies; and the three types of anaphylaxis, where a causal relationship is clear from the time course. Despite these functional limitations, passive surveillance was the primary source of data used in discussions on myocarditis caused by COVID-19 vaccines. At the same time, the fact that making the best possible use of the existing system enabled the rapid detection of suspected adverse reaction signals while the information was constantly changing during the pandemic is worthy of recognition. For COVID-19 vaccines, which were administered on an enormous scale, the non-vaccinated group is naturally limited, so those discussions were based on disease incidence data from 2019, before the pandemic. Although those discussions advanced with every possible effort being made, further improvements will be necessary in the future.

Implement institutional designs for active surveillance based on the functional limitations of passive surveillance

Japan's suspected adverse reaction reporting system is equivalent to the Vaccine Adverse Event Reporting System (VAERS) in the U.S. However, the U.S. also has an active surveillance framework called Vaccine Safety Datalink that anonymizes and links vaccination- and disease-related information to complement the passive surveillance system and to assess safety based on medical evaluations. Japan should also establish an active surveillance system while referring to systems like VSD to be prepared for the next infectious disease threat and to make it possible to conduct safety assessments to inform immunization and vaccination policy during both emergency and non-emergency periods.

2-3. Utilizing insurer databases and developing medical information for active surveillance

Design and establish an active surveillance system that is aligned with the domestic healthcare system

In Japan, vaccinations are not conducted within the health insurance system, so immunization and vaccine information is rarely included as health and medical information in medical records and medical claims data. At the same time, in Japan, citizens' health insurance information is comprehensively managed through the universal health insurance system, although databases

are split among insurers. There is plenty of room for reconsidering the pros and cons of conducting vaccinations (which are called “the greatest invention in the history of medicine” and are considered the most cost-effective public health intervention within infectious disease control) outside of the health insurance system, but considering the existing health insurance system, it is desirable that the institutional design and best methods of operating an active surveillance system using insurer databases is taken under consideration.

With active surveillance, it is not necessary to cover the entire population; information from a subset of the population is sufficient. However, large databases are needed when assessing suspected cases of infrequent adverse reactions, such as Guillain-Barre syndrome. On the other hand, disease incidence trends can be assessed using medical claims data, so it is desirable that an active surveillance system using insurer databases including medical claims data is taken under active consideration for assessing items like rare diseases.

Promote active surveillance systems that use insurer databases that are based on medical claims data

As others have pointed out, the primary function of medical claims data is processing insurance claims. This means there are slight discrepancies in terminology between the names of actual diseases and those listed in claims data. These sorts of biases have been the subject of active studies in the area of real-world databases in recent years, but there are still lingering concerns regarding integrity. In the future, it will be necessary to consider measures such as relaxing conditions for using the NDB and adding registries of the insured to the NDB in a flexible, continuous manner, based on their feasibility. One specific proposal is to create an environment in which an anonymized vaccine database is linked to the NDB and other databases so diseases and other conditions among both vaccinated and non-vaccinated people can be compared, including for frequency. VSD covers about 10 million people, so one encounters limitations when attempting to use it to assess rare diseases like myocarditis, which must be assessed by detecting one excess case out of one million. Linking such a database to the NDB in Japan will enable users to be able to gather highly complete information on as many as 100 million people. Even if that were to happen, however, the information available would still only be based on medical claims data, so while recognizing the limitations of assessments using medical claims data, it will be necessary to carefully discuss the nature and purpose of usage of data collected and, while building social consensus, to strategically engage in this over the long term.

Examine analysis methods including self-controlled study designs to make effective use of active surveillance

Although the situation is still developing, even if an active surveillance system is built, there are limits to fully encompassing the background elements for each different population among methods of examining adverse reaction frequency among groups of vaccinated and non-vaccinated people. Generally speaking, vaccinated groups tend to include people with high health awareness or who have health concerns, or are children or elderly. Characteristics of those in non-vaccinated groups tend to include vaccine hesitancy and good health. Study designs and analysis methods that take into account the possibility of various biases due to population characteristics should be considered.

In the U.S., VSD provides the option to not use data from non-vaccinated groups to conduct safety assessments using a self-controlled study design developed to examine the frequency of adverse reactions among vaccinated groups. That self-controlled study design requires a target disease, the date that disease was diagnosed, and the date the vaccine was administered, making it highly compatible with medical claims data and appropriate for circumstances in Japan. A self-controlled study design is especially useful for assessing acute diseases that recover quickly with treatment, like thrombosis, instead of chronic diseases.

In Japan, self-controlled methods were used by an MHLW research group that examined risk of intestinal complications for rotavirus vaccines with findings that contributed to policy decisions regarding the addition of rotavirus vaccines to the routine vaccination schedule. In the future, expectations are high for the continued examination and adoption of analysis methods that are appropriate for the information collected and its objective.

Accelerate discussions on linking vaccination information and medical information in a manner that uses insurer databases to go beyond active surveillance for more adequate safety assessments

More adequate safety assessments that can be used to inform immunization and vaccination policies should be conducted continuously by conducting active surveillance and utilizing appropriate methods on information collected to construct analyses. While it is a long-term, ambitious goal, because the main purpose of active surveillance is to evaluate signals from the voluntary reporting system, it is highly desirable that vaccination information is eventually linked with health and medical information, such as medical records.

3. Supporting Surveillance Through Information Infrastructure Development During Non-emergency Periods and Collaboration With Local Governments

3-1. Maintenance and further promotion of vaccination ledgers

Promote the digitalization and compilation of vaccination ledgers in databases within information-sharing networks

Vaccination ledgers are records of immunizations and vaccinations retained by municipalities. In the past, vaccine ledgers (both paper documents and electronic data) were managed by each municipality and were not transferred across municipalities. This made it impossible to grasp vaccination information linked to people in the form of data. However, by 2018, over 95% of municipalities had converted this information to electronic data, while about 88% of them have entered it into databases stored on information-sharing networks. As a result of these efforts, citizens can now use their My Number to view their vaccination records on Mynaportal, regardless of time or where they are registered as residents. Furthermore, personal information can now be provided to third parties using applications and other tools through API links. Every citizen including those who are healthcare professionals should be educated on the mechanisms of the My Number system and how to utilize it effectively. However, because these records are based on vaccination ledgers, the rate of digitalization and database conversion should be further accelerated while taking the integrity of vaccination records into account.

In addition, the Order for Enforcement of the Immunization Act currently stipulates that vaccination ledgers must be retained for five years. This means information older than five years cannot be confirmed, even using Mynaportal. Information regarding voluntary vaccinations also cannot be confirmed because it is not recorded in vaccination ledgers. Originally, a framework should have been built that enabled individuals to have lifetime access to their own vaccination information regardless of time or registered place of residence. Regardless of management method (be it paper or electronic data), retention times and content of records should be reexamined and gaps in information should be filled.

3-2. Utilization of information-sharing network systems

Consider how to balance decentralized management as a security measure for information-sharing network systems and the sharing of statistical information that contributes to immunization and vaccine safety assessments

Accessing vaccination-related information is classified as a “Process Using an Individual Number” and said information can be provided using information-sharing network systems. As a security measure, the system is designed so officials access that information online with public personal authentication using codes instead of a My Number. In addition, officials are obligated to follow security measures for “Processes Using an Individual Number,” so data is also managed in a decentralized manner. Therefore, the only information linked to information-sharing network systems is limited to vaccination status and date. Decentralized data management also means statistical information and other such information cannot be obtained for the entire population. The fact that sufficient consideration is being given to personal information and safety management is worthy of recognition, and the current environment allows individuals to inquire about their own vaccination information. However, the environment is not sufficiently prepared to allow population-wide vaccination information to be used for immunization and vaccination policy to contribute to all of society, which should be seen as an issue.

Adopt the VRS framework to provide statistical information

The VRS provides centralized management for COVID-19 vaccination data and contains such records as basic information (including My Number, name, date of birth, gender, and registered municipality of residence) and vaccination records (date of first vaccination, vaccination site, healthcare institution, vaccine manufacturer, lot number, and name of physician who administered vaccine), so it can be used to obtain complete statistical information. The information-sharing network system provides vaccine data on: the 4-in-1 vaccine (diphtheria, pertussis, tetanus, polio (DPT-IPV)); the diphtheria-pertussis-tetanus vaccine (DPT); the diphtheria-tetanus vaccine (DT); inactivated polio vaccine (IPV); BCG; Hib; pneumococcal vaccine; human papillomavirus (HPV; both bivalent and quadrivalent); hepatitis B; pneumococcal vaccination for older adults; rotavirus (monovalent and pentavalent); the combined measles-rubella (MR) vaccine; measles; rubella; varicella; and Japanese encephalitis. Vaccines for COVID-19 were added in June 2022. The VRS framework should be applied to immunizations and vaccines other than COVID-19 vaccines to create an environment in which anonymized statistical information can be provided in a standardized format nationwide to contribute to easier and more appropriate safety assessments.

Providing anonymized statistical information in a standardized format nationwide is likely to make contributions beyond safety assessments. While it will be necessary to make special considerations for protecting personal information, building a system that allows parties like healthcare institutions or healthcare providers to check, for example, rubella vaccination status for men born between April 2, 1962 and April 1, 1979 (which corresponds to the fifth period of routine vaccinations for rubella in Japan) will help prevent vaccination errors and enable those parties to take concrete measures, such as providing catch-up vaccinations. This should be addressed in a manner that follows developments in establishing the health crisis management agency currently under consideration by the Cabinet Office and the Next Infectious Disease Surveillance System (tentative name) which is currently set to launch in 2025.

When considering how to accelerate better future practices for data linking and digitalization as well as specific and effective measures based on those practices, in addition to implementing security measures, it will be necessary to unify IDs attached when consolidating multiple databases. Expectations are high for further development and penetration of a Government Interoperability Framework (GIF).

Accelerate better information coordination and digitalization practices in the future based on a review of lessons learned in response to past emergencies

The VRS underwent accelerated development to enable rapid data linkage to respond to the COVID-19 pandemic. Originally, linking specified personal information among municipalities was supposed to be conducted using a highly-secure information-sharing network system. A special exception was made for the VRS in accordance with Article 19, Paragraph 16 of the Act on the Use of Numbers to Identify a Specific Individual in Administrative Procedures, which provides exceptions “If it is necessary for protection of the life, body or property of humans, and the consent of the Person is obtained or it is difficult to obtain the consent of the Person.” Under this exception, the VRS is being used to confirm past vaccination records when vouchers for the third dose of COVID-19 vaccines are sent to people who have changed residence. The VRS was also linked to My Numbers themselves without using codes, which was conducted without consent from each individual. Furthermore, while the data is scattered among

municipalities, it is stored in the public cloud, so it can be inferred that municipalities cannot confirm which safety management measures are in place. On the other hand, the fact that making maximum use of the current system and the limited information provided by that system allowed for a nationwide vaccination system to be rapidly established is deserving of high praise.

As previously discussed, data linkage using the information-sharing network for COVID-19 vaccines began in June 2022, but it is not too late for both national and local governments to examine, in a comprehensive manner, if processes related to COVID-19 vaccines could be considered "necessary for protection of the life, body or property of humans," if it is "difficult to obtain the consent of the Person," or if the public cloud can provide sound safety management. At the same time, in the future, the adoption of better information linking and digitalization practices should be accelerated during non-emergency periods to enhance information management systems using lessons learned during the pandemic.

3-3. Building a cooperative system among the national Government, local governments, and other related organizations

Construct a cooperative system between the national and local governments for linking National Health Insurance and other insurer databases with vaccination information to contribute to immunization and vaccine safety assessments

The Guidelines for the Implementation of Routine Vaccination instructs local governments to "Create vaccination ledgers based on resident ledgers and similar records proving the residence of vaccinated people." This obligates local governments to manage vaccination ledgers as part of their responsibilities in administering vaccines. However, local governments are not legally obligated to perform duties related to linking vaccination information and information in insurer databases including that of the National Health Insurance system. It can be extremely difficult to actively encourage duties that were not originally assigned, but if doing so is perceived as a condition for promoting active surveillance that uses insurer databases based on medical claims data, it will be extremely effective to assign these tasks to local governments and similar bodies. This should be taken into active consideration.

For example, because statistical information in vaccination ledgers is reported by local governments to the national Government, one method might be to request additional information regarding National Health Insurance managed by local governments as part of those reports. If the MHLW were to request this information with a basis in law or through other frameworks, local governments could work on gathering it as part of their duties. In addition to making information more complete, it would also greatly increase the possibility that nationwide statistical information can be published in a similar manner to vaccination ledgers and statistical information using tools like e-Stat, which is the general resource for government statistics. When doing so, steps should be considered, at least at the national Government, to create an anonymous database that includes suspected adverse reaction reports and vaccination program progress which could be provided to universities and other research institutes for conducting surveys and research on vaccine safety and similar topics.

Promote efforts from local governments for information sharing among insurer databases, to develop good practices, and to accelerate efforts to examine personal information handling

According to ordinances on the protection of personal information enacted in each municipality, matters related to the handling of personal information by local governments fall under the responsibility of governing councils on personal information. However, these ordinances differ by municipality, hindering efforts to link information among them. This is known as the "2000 problem," and the Act on the Protection of Personal Information was revised in 2020 to address it. It appears that it will be difficult to standardize ordinances on the protection of personal information across Japan, so expectations are high for efforts to gradually make it easier to link vaccination information, National health Insurance, and the Late-Stage Medical Care System for the Elderly.

In fact, a number of municipalities are engaged in research for immunization and vaccine safety assessment by building active surveillance systems with the intention of linking vaccination information, National Health Insurance, and health and medical information. There is little data concerning children in the National Health Insurance system, so social insurance, mutual aid, and other forms of health information will be needed regarding vaccines administered to children. Even if assessments are conducted using only data from National Health Insurance, they would require information on a national scale, but any form of research progress should be welcomed and all concerned parties should voice strong support for the promotion of such efforts. In addition, although limited to COVID-19 vaccines, there are also high expectations for certain medical groups like national research groups and research centers to actively engage in active surveillance, safety assessment for immunizations and vaccines, and other such topics by utilizing databases related to COVID-19 infections, which are currently on the rise.

Utilize combined information from vaccination information and health information and return such information to citizens through data visualization

Cooperation from the public will be essential for conducting immunization and vaccine safety assessments. To promote understanding toward safety assessments and convey the risks and benefits of immunizations and vaccines more effectively, it is desirable that information is utilized and visualized in a more integrated manner so information can be used to give back to the public. For example, Toda City is working to visualize information regarding COVID-19 vaccines using a tool called the "Vaccine Meter." By allowing the public to visually confirm the progress of vaccinations and by updating it daily, the Vaccine Meter can provide a sense of security and encourage non-vaccinated citizens to get vaccinated. Using the VRS, it is currently possible to issue proof of COVID-19 vaccination using a smartphone application. The Digital Agency also uses the VRS to compile a vaccination status dashboard which includes total number of vaccinations nationwide, changes in the vaccination rate by date and time, and vaccination rate by prefecture.

In addition, in cooperation with the MHLW, NIID publishes measles and rubella vaccination rates by prefecture and municipality. For vaccines other than measles and rubella, vaccination rates can be estimated based on the number of people vaccinated in a given year and the number of the people who become eligible for vaccination that year, but creating an environment that enables centralized assessments of vaccination rates based on age group or by target population will make it possible for more effective measures to be implemented.

Under Article 23 of the Immunization Act, which states, "In order for the citizens to be vaccinated having the proper understanding, the national Government is to strive to educate

and disseminate knowledge regarding vaccinations," the Government must take a leading role in establishing active surveillance while taking into account all research findings and pilots. Safety assessment is the root concept of risks and benefits for immunizations and vaccines, and is a key item on which people should possess an accurate understanding.

4. Making Comprehensive Policy Decisions Based on Safety Assessments

4-1. Establishment of a system for comprehensive policy decisions

Promote human resource development and the establishment of an assessment institution so comprehensive policy decisions on immunization and vaccine policy can be made on a permanent basis

Surveillance involves both safety and effectiveness assessments, so it is necessary to make comprehensive decisions based on information from both and actually link them to countermeasures. At the same time, the possibility that major health problems can be caused by a VPD outbreak must be recognized when making policy decisions, such as whether to suspend or modify vaccination programs or recommendations for the routine vaccination schedule.

For example, Osaka University has projected that discontinuing active recommendations for the HPV vaccine may have resulted in 4,000 annual cases of cervical cancer and 1,000 annual deaths. These could have been prevented if a system which enabled rapid safety assessments had been in place. In the past, reports of aseptic meningitis and other adverse reactions to the measles, mumps, and rubella (MMR) vaccine led to the discontinuation of MMR vaccinations. Since then, the measles and rubella (MR) vaccine has continued to be a routine vaccination and mumps vaccines have been available as voluntary vaccinations, but a nationwide survey found at least 359 people had hearing loss due to mumps after the infectious parotitis outbreak in 2015 and 2016. Although effective treatments for mumps-associated hearing loss have yet to be identified, its incidence can be reduced if people are vaccinated.

Political decisions related to vaccine safety must be made in a comprehensive manner that encompasses not only continuous epidemiological information and information regarding effectiveness, but that also takes into account items like case definitions of adverse events, projections of VPD prevalence, the availability of alternative vaccines, and public health impact in the event a vaccination program is discontinued. In the past, there have been cases when the active recommendation of a vaccine was withheld due to reports of side effects but was later resumed. This occurred with Japanese encephalitis, for which active recommendation was revoked due to reports of acute disseminated encephalomyelitis (ADEM) occurring as a side effect, but was later resumed because there was no clear causal relationship between vaccination status and the number of ADEM reports. We must note this policy decision may have been influenced by the development and approval of a new Japanese encephalitis vaccine, which was derived from tissue culture cells (Vero cells) instead of mouse brain cells. Differences in objectives mean there are differences between safety assessments conducted as a form of academic research and safety assessments that are reflected in immunization and vaccination policy. When it is time to make policy decisions, decision-makers must be willing to take those differences into account. Being able to make comprehensive decisions on a permanent basis will require continuous efforts to develop human resources in many related fields. These include epidemiologists and technicians who can conduct database analysis, specialists in vaccine and pharmaceutical safety, and healthcare professionals with detailed knowledge on clinical symptoms. In addition, vigorous efforts should be taken to establish a central base or institution for analysis or assessment that can gather cross-disciplinary human resources and expertise from these fields and related fields.

From the perspective of implementing countermeasures based on information like safety assessment results, the decision whether to add a vaccine to the routine vaccination schedule is

also important. While it is already necessary to reexamine the distinction between routine and voluntary vaccinations from the perspective of preventing VPDs, the existing system has frameworks for non-statutory vaccinations, and there are cases in which the national Government entrusts vaccine deployment to each local government, such as when subsidies are granted to provide the aforementioned mumps vaccines or influenza vaccines for children. After self-controlled methods were used to analyze the rotavirus vaccine, and after the risk of developing intestinal complications among those who receive it was examined, a study on disease burden was conducted that led to it being added to the routine vaccination schedule. However, it took some time to arrive to that policy decision. Vaccines are only effective when people receive them. Adding a vaccine to the routine vaccination schedule can also expand the effects of immunizations and vaccines, so to enable rapid and appropriate discussions, it will be necessary to promote and advance safety assessments in a more systematic manner.

4-2. Achieving effective communication strategies for comprehensive policy decisions

Promote human resource development and the dissemination of relevant and correct information, terminology, and the understanding of systems to contribute to effective communication with citizens regarding comprehensive policy decisions

Final decisions that are comprehensive and based on safety assessments should be communicated to the public by regulatory authorities in an easy-to-understand manner. To achieve that, regulatory authorities must educate specialists who communicate that information during periods of non-emergency. In particular, for the mass media to accurately convey information regarding immunizations and vaccines from regulatory authorities to the public, sufficient attention should be paid to the fact that communication is only possible when the definitions and mechanisms of terms like “adverse event,” “adverse reaction,” “suspected adverse reaction,” “routine vaccination,” and “voluntary vaccination” are understood correctly. We must never forget that the only method of demonstrating the risks and benefits of immunizations and vaccines is to accurately convey information related to safety assessment.

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These recommendations were compiled based on working group meetings, expert hearings, and related meetings hosted by the HGPI Immunization and Vaccination Policy Promotion Project in FY2021, as well as on discussions held under the Chatham House Rule and policy trends and other developments in this area as of June 30, 2022.

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