<The Fifth Recommendation>

Recommendation on the Reporting System of Adverse Reactions to Vaccines and the Development of Infrastructure related to Vaccine Risk Management in Japan

Introduction

The vaccination policy is a key to the primary prevention of infection-related diseases in Japan. However, the approach to vaccination in Japan has long been conservative since the 1990s. During that period, various novel vaccines have been developed in foreign countries, and the vaccine gap between Japan and foreign countries has become a problem. In recent years, however, vaccines introduced on the market in foreign countries have at last come to be approved in Japan, and since the revision of the Vaccinations Act in 2013, vaccines that are used for regular vaccination in foreign countries have also come to be used for the same purpose in Japan.

However, although the "types" and the "product lineup" of vaccines have been improved to nearly the same level with that of foreign countries, the environment relating to the risk management of vaccination has hardly been established. There is still room for improvement in establishing a mechanism for efficient collection, evaluation, and provision of immunization-related information, and thus we are still experiencing unnecessary confusion. With regard to the handling of spontaneous reports and the framework of safety evaluation in particular, during the period when Japan' attitude toward vaccination was still conservative, foreign countries have established various environments and infrastructures in accordance with the changes in the social landscape and the development of information technology. Thus, compared to foreign countries, Japan still has a lot of unsolved problems.

It is extremely important that robust infrastructures related to risk management are established when introducing new vaccines. Therefore, we would like to make the following recommendations to citizens in general including healthcare providers, vaccine specialists, administrative authorities and healthcare educators.

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Recommendation on the Reporting System of Adverse Reactions to Vaccines and the Development of Infrastructure related to Vaccine Risk Management in Japan <Recommendation Excerpt>

1. Legal matters

1-1 Use of correct terms

As our Foundation described in the Fourth Recommendation (Aiming at More Scientific Drug Risk Management in Japan—A Recommendation to the Regulatory Authority and Industry), the definition of "adverse drug reactions" in Japan and that stipulated in the ICH E2D are different, and by definition, the case reports made spontaneously to the industry or the regulatory authority actually refer to "suspected adverse drug reactions." Similarly, the term "adverse reactions to vaccines" when reported in the case reports in accordance with the Vaccinations Act means "suspected adverse reactions to vaccines."

The evaluation of safety information regarding vaccines is discussed, in principle, publicly at the Adverse Reactions to Vaccines Reviewing Committee of the Ministry of Health, Labour and Welfare. However, although what are reviewed here are actually not "adverse reactions to vaccines" but are "suspected adverse drug reactions" stipulated in the Pharmaceuticals and Medical Devices Act, and "adverse events" according to the Vaccinations Act, they are treated as "adverse reactions to vaccines" in the publicly available documents. When reported by the media etc., however, all the cases reviewed by the committee are treated and communicated as "adverse reactions to vaccines," causing unnecessary anxiety and misunderstanding to the general public and also confusion regarding risk management activities.

It is important to prevent confusion related to risk management activities by considering again appropriate wordings including descriptions in public documents and the naming of the Committee itself, and thereby to help healthcare providers and the general public understand the information correctly.

1-2 Clarification of the objective of the reporting systems

Currently, the criteria for unsolicited reporting are different between Preventive Vaccinations Act and Pharmaceuticals and Medical Devices Act. The Preventive Vaccinations Act requires that all cases of specific events associated with regularly inoculated vaccines that occur during the risk period be reported irrespective of seriousness or the assessment of causal relationship by physicians; thus, these reports are actually the reports of adverse events. In addition, the definition of the events concerned is given in the report form; thus, the reporting system for spontaneous reports (which should be "unsolicited" reports by nature) can be

interpreted as the reporting system for solicited reports rather than unsolicited reports. On the other hand, with regard to the adverse drug reaction reports by physicians etc. in accordance with the Pharmaceuticals and Medical Devices Act, the objects to be reported are the events for which causal relationships are suspected and for which reporting was considered necessary by the reporter in order to prevent the occurrence or escalation of harm to public health. Thus, the nature of information obtained from these two reporting systems is naturally very different.

With regard to regular vaccinations (including those changed from voluntary vaccinations), case reports based on two different systems are accumulated; thus, the integration and comparison of the data are impossible, and the possibility of overlapped cases cannot be ruled out. Actually, reported data to the Adverse Reactions to Vaccines Reviewing Committee cannot be integrated, and thus by necessity individual data are aggregated and presented. This kind of data presentation is hard to understand for the general public. Therefore, due to various misunderstandings, multiple and different numerical data are reported through the media; thus, the general public cannot know the true figures. This situation has caused unnecessary confusion, doubts, and anxiety.

If unification of the two systems with two different data collection objectives is difficult, then evaluations according to the objectives should be made individually after explicitly explaining the objectives of the two systems. Regarding the regular vaccination, one of the objectives of the "report of suspected adverse reactions to vaccines" under the Vaccinations Act would be to comprehensively grasp the symptoms beforehand that are concerned about. The data from the spontaneous (unsolicited) report system based on the Pharmaceuticals and Medical Devices Act are the key to safety monitoring in that the data broadly reflect safety signals. Thus, the conduct of more scientific and appropriate monitoring is considered critical in the risk management of vaccination. In order to disseminate information which is medically clear and easy to understand for healthcare providers and the general public, it is essential that the objectives of these two systems are explicitly explained.

1-3 Construction of the system for managing vaccination history

The efficiency of preventing the epidemic of infectious diseases by vaccination is closely associated with the vaccination rates; therefore, in view of public health, the vaccination coverage and the vaccination history are important information. In addition, although vaccination is conducted by local governments, the responsibilities of risk management of vaccination should mainly be borne by the institutions of the central government and not by the local governments. Thus, the

vaccination rate of residents in Japan is important information for the central government institutions. The information of vaccination rate and vaccination history is also important for medical institutions etc.; in addition, this information should also be provided to the general public in a timely manner.

However, currently, no appropriate database of the records of vaccination has been developed. Although the ledgers of the preventive vaccination which is subsidized publicly are managed by individual local governments, their formalities, media, etc. are varied. In order for the central government to know the vaccination rate, it needs to be provided with the data by the local governments etc., and thus it is difficult for the central government to grasp the nationwide vaccination rate automatically and in a timely manner.

To grasp and manage the vaccination records in an integrated fashion and for a long time, the central government should develop a "Registry of Vaccination Records" which manages the electronic vaccination records collectively, by using the national identity number (nicknamed "MY NUMBER") system [note], for example. Even under the current design, usefulness, such as (a) the coverage of regular vaccination of individual age groups in individual local governments can be grasped real time through the linkage with the information of the resident card etc., and (b) vaccinated individuals can confirm the information by themselves, are conceivable. The personal-level vaccination history management such as this can be the background information of adverse reactions to preventive vaccination; in addition, it will make the long-term post-vaccination follow-up outcomes available. Thus, it will also play an important role in the comparison of the frequencies of the occurrences of adverse reactions to vaccines etc. before and after the implementation of the policy. On the other hand, under the current design, the information of voluntary vaccination and the information of adverse events cannot be managed. Therefore, taking into consideration the linkage with other information, such as making it possible to link with clinical records by using the My Number system, the value of the Registry of Vaccination Records should be maximized as an infrastructure that is involved in scientific risk management.

Note) This is planned to be introduced in October 2015. It is the number assigned to each person holding a resident card and tie personal information owned by different organizations.

1-4 Enrichment and effective use of health survey following vaccination (omitted)

1-5 Enrichment of relief service system for adverse health effects

Enrichment and operation of the safety net are important for "peace of mind" of the people. The relief system for sufferers from adverse drug reactions serves as a safety net for voluntary vaccination, and the relief system for adverse health effects

following vaccination serves as a safety net for regular vaccination. However, it is hard to say that these systems are used to their full capacity and are satisfactory for the general public. One of the reasons for this is their low degree of recognition, and another reason may be that it takes a long time from the application for relief to the decision of provision of benefits.

In addition, currently, the amount and the range of benefits to be provided are different between the two relief systems. Therefore, even if the same vaccine is used, the amount and the range of benefits to be provided are different depending on whether their national positioning is voluntary vaccination or regular vaccination. That the amount and the range of benefits to be provided are different depending on whether or not there is an obligation to make efforts to receive certain vaccinations as a national policy, even if the vaccines are the same, may be understandable to persons who know that there are two different relief systems in accordance with two different acts. However, it may be difficult for the general public who receive vaccination. In view of the understanding of the general public, it may be desirable to eventually unify the two systems; however, if it is difficult, information provision activities should be performed before vaccination so that the individuals receiving vaccination and their guardians are fully explained about the relief systems to gain their understanding.

2. Enrichment of information provided by the central government

2-1 More flexible operation of the Adverse Reactions to Vaccines Reviewing Committee

Accumulated data are mainly explained at Adverse Reactions to Vaccines Reviewing Committee meetings, with the Ministry of Health, Labour and Welfare serving as the secretariat; however, because the amount of the data dealt with at the committee meeting is large, there seems to be room for improvement with regard to time allocated to the explanation of data and actual discussion. When details of some data are asked, it happens that the secretariat has to ask a relevant company for confirmation, and thus the matter is postponed until the next meeting. This kind of things decreases the efficiency of the committee meeting, leading to delayed decision making. Thus, it may be said that the maximum safety of the people is hardly secured.

The secretariat should consider more efficient operation of the meeting. It would be possible to operate the Adverse Reactions to Vaccines Reviewing Committee, which is open to the public, as a place for substantial discussion by, for example, disclosing the data of a briefing session and explaining the data to the members of the committee meeting beforehand, and then encouraging them to ask questions about the data, if there are any, before the meeting. In addition, rapidity would be

secured by taking measures, such as inviting relevant companies to the Adverse Reactions to Vaccines Reviewing Committee meeting as references and have them respond to questions on the spot or before the next committee meeting at the latest, as necessary.

Furthermore, it should be noted that the data for deliberation at this committee meeting are public information. For example, when risks are deliberated at an Advisory Committee on Immunization Practices (ACIP) meeting in the U.S., the information regarding benefits are also publicly presented. Thus, the data of the results of benefit-risk comparison, which can be easily understood by even a third party, are often used. However, in the case of the Adverse Reactions to Vaccines Reviewing Committee meeting in Japan, only the information of risks is recorded as data, and only the data that do not contain clear conclusion of the committee meeting are presented to the public. Part of the conclusion may be supplemented by reading the minutes of the meeting; however, the information regarding the committee meetings reported by the media etc. include contents which more or less generate misunderstanding.

2-2 Provision of appropriate information

In Japan, people are required to make an effort to receive vaccination, but ultimately, the decision is up to vaccinees. However, it is hard to say that the government is making sufficient effort to provide information which is necessary for the general public to make judgement and the validity of which is guaranteed by the government through multiple and various media in a clear and easy-to-understand way.

To prevent information lacking sufficient evidence from spreading, the government should quickly and timely issue clear information, the validity of which is sufficiently guaranteed. With regard to the validity of scientific data related to safety and efficacy, it is important that the government provides neutral and easy-to-understand information quickly.

For example, the Centers for Disease Control and Prevention (CDC) of the U.S. is presenting on its website an easy-to-understand and concise explanation of the benefits and risks of vaccines for vaccinees and their parents. In addition, if information with insufficient evidence is reported by the media etc., the CDC issues an information article with clear evidence to raise awareness as necessary. It is very important in Japan as well that, following this example, the National Institute of Infectious Diseases and other public institutions take the lead to create a site through which the general public can acquire and understand information about the efficacy and safety of vaccines at one stop. At the same time, it is also important for risk communication that the media, which play an important role in

communicating information, understand the information provided by these public institutions scientifically and appropriately. It is desirable that the National Institute of Infectious Diseases as a leading organization appointing a spokesperson and actively "provide appropriate information, including background information" to the media so that correct information is provided to the general public.

In addition, it will be one of the important responsibilities of the Japanese regulatory authorities, as one of the trilateral members of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), to issue and globally disseminate on the web "information with clear evidence" from the summary of the material of the Adverse Reactions to Vaccines Reviewing Committee meetings in English, a common language of the world.

3. Improvement of education

3-1 Ensuring that healthcare providers are fully aware of Preventive Vaccinations Act and Pharmaceuticals and Medical Devices Act

Reporting of suspected adverse reactions to vaccines is essential for improving healthcare and is an important responsibility of healthcare providers.

It is important to have healthcare providers to recognize that they are playing an important role in gathering information of adverse reactions to vaccines and that they are also responsible for providing the information. In the case of regular vaccination, in particular, reporting is clearly described as an "obligation;" however, in view of the fact that provision of information is sometimes refused by healthcare providers on the ground that they are too busy, it has to be said that practicing healthcare providers are not well informed about the obligation.

Whether or not healthcare providers have had sufficient opportunities to receive education about Preventive Vaccinations Act and Pharmaceuticals and Medical Devices Act should be reviewed. Knowledge about these Acts is important for quick reporting of safety information and for making use of the accumulated data of the information. In this respect, it is necessary to construct a framework which ensures that practicing healthcare providers be given education at least at the timing of legal revisions, for example, as part of career-long education and that they are well informed about the reporting system and its significance.

3-2 Cultivation of experts on evaluation of adverse reactions to vaccines and their use

Different skills are needed for evaluating individual cases and accumulated data. When investigating whether or not a certain event is an adverse reaction to

vaccines, medical, chronological, and geographic validities need to be considered.

Both the main effects and adverse reactions to vaccines occur via immune response; therefore, molecular biological and physiological knowledge about these reactions is necessary for evaluating the medical validity of adverse reactions to vaccines.

It is hard to say that there is sufficient number of experts in the field of epidemiology in Japan. The government should not only cultivate experts in the field of epidemiology but also positively foster "epidemiologists well versed in vaccinology with knowledge of immunology, molecular biology, and physiology" as specialists of "the study of adverse reactions to vaccines" with a long-term perspective.

3-3 Enriching vaccine education at school

By enriching the education of vaccines in compulsory education for the general public and specialized education for healthcare providers, the general public will be able to correctly understand the "information regarding the benefits and risks of vaccines" issued by the government.

Provision of solid basic knowledge necessary for judging the benefits and risks of vaccines (personal and societal significance of preventive vaccination, risks associated with vaccination, and the fact that drugs or vaccines are not free from risks) should be one of the policies that the government needs to implement. Particularly, establishing a system in which this basic education is firmly provided in the compulsory education at elementary schools and junior high schools should be an important policy to implement.

In addition, whether or not vaccine education is sufficiently provided to healthcare providers should be once again reviewed. Healthcare providers need to deeply understand the information about personal and societal significance of preventive vaccination, basic action mechanisms of vaccines, preventive vaccination systems, and the mechanisms and frequencies of occurrences of adverse reactions to vaccines, bearing in mind that these items are inter-related.

The Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare are encouraged to collaborate in this endeavor.