Section 5　Vaccination

1 Purpose of vaccination etc.

(1) Efficacy and safety of vaccine

From Section2 to Section4 we mentioned management of novel influenza （A／H1N1) in aspects of public health and medical care etc. Besides them, influenza vaccination is no less important to reduce as many fatal or serious cases as possible focusing on persons with basic diseases that easily lead to serious complications, infants, mothers-to-be, and the elderly.

The efficacy of novel influenza vaccine is expected to basically match seasonal influenza vaccine which is manufactured in similar method. Though seasonal influenza vaccine is confirmed to be to a certain extent effective in prevention of death and severe complications, it does not guarantee 100％ of efficacy, and has not proven to be effective in prevention of infection or epidemic. Furthermore, though rarely, it causes serious adverse event. Vaccination has to be proceeded with under comprehensive judgments, with such situation being taken into consideration.

(2) The aim of vaccination

Based on the “basic guidelines for vaccination of novel influenza （A／H1N1)” which was established on 1 October 2009, vaccination against novel influenza started in some areas on 19 October of the same year already.

The Ministry of Health, Labour and Welfare informed the public that:

・ Current vaccination has not proven to be effective in prevention of influenza virus “infection” (invasion into and proliferation in organism), therefore, this is not aimed at “infection” prevention of the person who received the vaccination.

・The vaccination is aimed at ① reducing as many fatal or serious cases as possible, as well as ② controlling as much as possible the confusion in medical institutions caused by intensive occurrence of “onset” cases in particular districts.

Chart 1-5-1　Efficacy of vaccine against seasonal influenza

As for seasonal influenza, by its vaccination

- ○Incidence of influenza in healthy persons dropped 70-90%
- ○Hospitalization of general elderly persons with pneumonia and influenza dropped 30-70%
- ○Deaths of elderly facility residents from influenza dropped 80%
- ○Cases of fever in infants dropped 20-30%

Target persons	Result indicators	Efficacy ratio (%)
Healthy persons (under 65)	Onset	70-90
General elderly persons (65 and over)	Hospitalization with pneumonia/influenza	30-70
Elderly facility residents (65 and over)	Onset	30-40
	Hospitalization with pneumonia/influenza	50-60
	Death	80
Infants (1-6)	Fever	20-30

Material: Morbidity and Mortality Weekly Report (MMWR) 2007 vol56, CDC
*For infants, see "On influenza vaccination for infants (under 6) – View of Japan Pediatric Society –" Japan Pediatric Society, 31 October 2004

Chart 1-5-2　Side reactions of influenza or other vaccines

Number of reported cases of side reactions in routine vaccination based on Preventive Vaccination Act

Vaccine	Number of vaccine recipients	Number of reported cases of side reactions	Frequency (per 10,000people)
DPT	4,222,082	168	0.33565
DT	783,059		
Measles	11,300	6	5.30973
Rubella	61,209	5	0.81687
MR	1,937,568	58	0.29934
Japanese encephalitis	141,421	3	0.21212
Poliomyelitis	2,054,380	9	0.0438
BCG	987,075	98	1.00196
Influenza	13064354	25	0.01913
Total	23253448	372	

Material: Excerpt from material formulated on the basis of "totaling report of reports on post-vaccination side reactions" by member of committee, Tashiro, which was presented at "8/20, 8/27 Opinion Exchange Meeting on novel influenza vaccine"

Side reactions of influenza vaccine

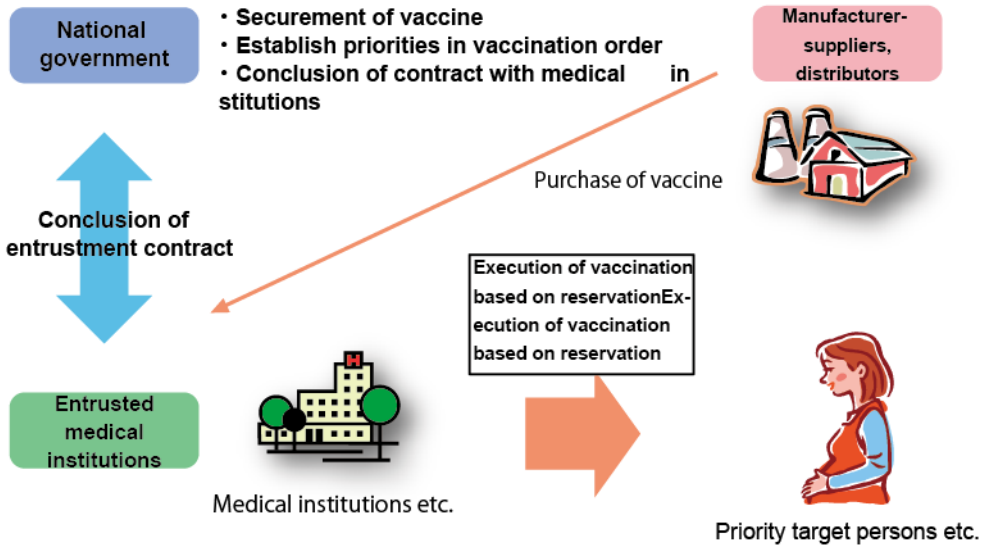
Reported side reactions	Ratio (%)
Immediate systemic reactions	9.0
Anaphylaxis	2.7
Generalized urticaria	6.3
Encephalitis encephalopathy	2.7
Spasm	1.4
Mobility impairment	1.8
Other neurological disorders	7.2
Local abnormal swelling (extending beyond the elbow)	3.2
Generalized rash	10.4
Fever of 39°C and over	14.5
Other abnormal reactions	11.8
Irregular reports	38.0
Local reactions (rubor, swelling etc.)	8.1
Systemic reaction (fever etc.)	11.8
others	18.1

*What is side reaction?: When reactions other than the aim of vaccination, "bestowal of immunity" occur, then they are called side reactions. Side reactions of influenza include local reactions (rubor, swelling, pain etc.) and systemic reactions (fever, chill, headache, lassitude, vomiting, etc.), which disappear within a couple of days. Side reaction reports in routine vaccination based on Preventive Vaccination Act count side reaction cases reported due to the above-mentioned symptoms etc.

(3) The role of responsible organization for each program

As shown in Chart 1-5-3, vaccination was conducted in a basic outline where the State（the Ministry of Health, Labour and Welfare）and medical institutions make entrustment contract, the entrusted medical institutions purchase vaccine based on the contract and conduct vaccination. As certain amount of vaccine was to be provided in order, the State turned to emergency and integrated securement of vaccine as well as decision of priority order.

Chart 1-5-3　　The Scheme of Vaccination



2　Priority target persons for vaccination。

In vaccination it was expected to be unable to achieve total and prompt preparation of necessary quantity of vaccine, therefore, decision of priority order in vaccination existed as task from the start. In this regard, the Minister of Health, Labour and Welfare and experts held a public meeting for an exchange of ideas on 26 August 2009, where opinion hearing was conducted of members of patient groups and group of victims of harmful effects of medicines as well as clinical experts followed by meeting for an exchange of ideas in public places on 20 and 27 of the same month with experts and members of patient groups. Based also on the results of these meetings, plan of priority order was officially announced on 4 September, being submitted for public comment for a week starting 6 September. At the same time meetings for an exchange of ideas were held on 9 and 11 September.

After hearing of opinion in such places and discussion in several experts meeting, we decided on starting such preferential vaccination as shown in Chart 1-5-4:

①　"Medical care providers directly engaged in medical treatment of influenza patients (including ambulance team members)"

②　"Mothers-to-be and persons with basic diseases (of them, preferential vaccination is applied for persons aged between 1 year and that corresponding to children in the lower grades of elementary school)"

③　"Children aged between 1 year and that corresponding to the lower grades of elementary school"　* [1]

④ “Guardians of children under 1 year and guardians etc. of some priority target persons who are unable to receive vaccination for physical reasons” * [2] and persons aged corresponding to pupils in the upper grades of elementary school, junior and senior high school, and the elderly

Chart 1-5-4 Target persons of preferential vaccination

	Target persons		Number of people
Priority target persons	①Health care providers directly engaged in medical examination of influenza patients (including ambulance team members)		about 1 million people
	②	Mothers-to-be	about 9 million people
		Persons with pre-existing diseases	about 1 million people
	③Persons aged between 1 year and that equivalent to the 3d grad elementary school		about 10 million people
	④ ・Guardians of children under 1 year ・Guardians etc. of some priority target persons who are unable to receive vaccination for physical reasons		about 2 million people
Others	Persons aged equivalent to pupils in the 4 - 6th grades of element school, junior and senior high school		about 10 million people
	Elderly persons (aged 65 and over)(excluding those with pre-exist diseases)		about 21million people
			about 54 million people

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*1 As for infants under 1 year, considering the difficulty in their immunization with vaccine, we switched to the principle of vaccination of their protectors. Additionally, in the plan submitted to public comment this item was specified as “children from 1 year to preschool age” along with “(As for children at age corresponding to the lower grades of elementary school) considering some cases of serious complications under 10 years, pupils under 10 in (the lower grades of) elementary school, in particular, shall, if possible, be treated similarly to priority target persons for vaccination”. Due to upward revision of initial estimate for production output of vaccine ensuring management, “persons at age corresponding to the lower grades of elementary school” were specified to be added.

3 The scheme of vaccination (sharing of costs)

Considering the aim of current vaccination, we decided on nationwide uniform charge of 3,600 yen for the first service and 2,550 yen for the second*[4] as amount equivalent to actual cost (vaccine prices plus cost of transportation and vaccination) via entrusted medical institutions from vaccine recipients or their protectors in accordance with “routine vaccination”*[3] of seasonal influenza conducted to the elderly etc. Additionally, as alleviation measures for low-income households it was decided that municipalities

shall take measures for subsidization of the cost with emphasis on untaxed households exempted from inhabitants tax (about 20% of population) (source of revenue: the State 1／2, prefecture/municipality, each 1／4) *5

4 Securement of vaccine

(1) Securement of domestic vaccine

In Japan since middle July 2009 all manufacturers successively began manufacturing vaccine. According to the "basic guidelines for vaccination of the novel influenza (A／H1N1)" established on 1 October of the same year, "domestic vaccine for about 27 million people(two shots for one person in principle) was to be secured by the end of this fiscal year".

(2) Securement of imported vaccine

Based on the fear that production output of domestic vaccine in Japan is too limited for securement of necessary quantity, the "basic guidelines" of 1 October specified that "Considering the possibility of future infection spread and mutation of virus, <Omitted> severe cases can happen besides priority targets, therefore, from the perspective of risk management of health, secure vaccine by urgently importing it in addition to domestic products" and "Import vaccine for about 50 million people from overseas entrepreneurs".

Additionally, the procedure of "Special Approval"*6 in the Pharmaceutical Affairs Law was adopted because if all the procedures and testing usually necessary for the approval of imported vaccine for domestic use were followed, it would be too late for the autumn/winter 2009 vaccination, and based on the results of consideration at Sub-committee II of Pharmaceutical Affairs and Food Sanitation Council as well as of public comment, opinion was formulated at pharmaceutical subcommittee of the same Council held on 15 January 2010 to the effect that application of "Special Approval" is appropriate, which was specially approved by the Minister of Health, Labour and Welfare on 20 January of the same year.

It was specified that on that occasion such conditions as shown in Chart 1-5-5 shall be attached with safety being strictly watched. Furthermore, because imported vaccine was added to domestic vaccine through Special Approval, vaccination for healthy adults was scheduled to start at 15 January of the same year by the judge of prefectures based on the confirmed feasibility of vaccination for all applicants of citizens.

*2 While in the plan submitted to public comment this item was specified as "parents of infant under 1 year", there may be such cases when their protectors are not parents or when, despite being priority target person for vaccination aged 1 year and older, they cannot receive it owing to egg allergy etc. used in vaccine manufacturing, therefore, in such cases similarly to the cases of infant under 1 year, protectors etc. were specified to be immunized.

*3 Based on Preventive Vaccination Act, municipalities are specified to conduct "routine vaccination" of diphteria, pertussis, poliomyelitis (polio), measles, rubella etc. for target persons. Additionally, influenza and the rest of these diseases are different in that target persons of the latter are obliged to make effort to receive vaccination while those of the former are not.

*4 In case of receiving the second vaccination at another medical institution, it costs￥3,600 because of required reaffirmation of basic state of health etc. Imported vaccine and domestic vaccine cost as much per one round of vaccination.

*5 While the State secured 21.35 billion yen in reserves for miscellaneous expenses and summed up 20.72 billion yen in the second supplementary budget for fiscal 2002 to execute the above-mentioned burden relief measures, further burden relief measures were enabled by independent judgement of and fiscal burden on local governments, therefore, specific cost-sharing of recipients of current vaccination may differ by districts.

*6 If "Medicine or medical equipments are necessities specified to be urgently used to block the spread of health damage including spread of diseases capable of seriously influencing lives and health of the citizens, and except for the use of which there are no adequate alternatives" and "Regarding their uses, medicine or medical equipments are specified to be approved in foreign countries (limited to those countries <Omitted> where, in terms of securement of quality, efficacy and safety of medicine or medical equipments, systems can be recognized as equivalent to that of Japan <Omitted>) of their sales, donation, as well as storage and exhibition for the purposes of sales or donation" apply the case (Article 14-3 of the Pharmaceutical Affairs Act), approval may be granted after hearing opinions of Pharmaceutical Affairs and Food Sanitation Council and without following procedures specified for approval of manufacture and sales by the Pharmaceutical Affairs Act. Additionally, list of target medicines and " " are specified to be determined by government ordinance on each occasion.

Chart 1-5-5 Conditions of approval imposed on the special approval of imported vaccine

① Because the vaccine has been specially approved pursuant to Article 14.-3 of the Pharmaceutical Affairs Act, and has limited experiences in domestic use, it shall be required to conduct post-marketing surveillance, to grasp the background information of recipients, to collect data as soon as possible concerning safety and take necessary measures for its proper use. Additionally, information obtained in post-marketing surveillance of the vaccine shall be reported routinely.
② It shall be conducted the earliest possible domestic post-marketing surveillance for verification of safety and immunogenicity of the vaccine in elderly persons and promptly reported the results.
③ Medical doctors shall be requested to give recipients a satisfactory explanation that the vaccine is specially approved and that further data on safety/efficacy of the vaccine are being gathered, in addition to the presently acquired information, thereby to obtain informed consent when vaccinating.
④ Regarding scheduled and ongoing clinical tests, the test result and its analysis shall be reported as promptly as possible.
⑤ (Specially approved vaccine manufactured by GlaxoSmithKline) regarding coagulation recognized in antigen vials, report shall be required as promptly as possible in case of obtaining new safety information suggesting relation with coagulation.
⑥ The equivalence of seed virus at the period of cell culture (of specially approved vaccine manufactured by Novartis) and residual BPL concentration in vaccine substance shall be confirmed.
⑦ Because of the special approval for the public vaccination program, manufacture and sale thereof shall be limited to purchase by the government.

[1] Ability to induce immune response

[2] A medicine bottle

[3] Virus used as material for pharmaceutical preparation

[4] Abbreviation for β-Propiolactone. It is used in inactivation process of virus. Though this is a mutation inducing and carcinogenic substance, it is to be hydrolyzed in manufacturing process according to explanation. As conditions for approval, Novartis was required to confirm its concentration.

5 Verification of efficacy/safety of vaccine, and course of policy making based upon it

(1) Revision of frequency of vaccination rounds

As mentioned in 4(1), frequency of vaccination rounds was specified as twice for all citizens, however, based on results of subsequent clinical studies one round was newly specified as satisfactory except for persons under 13 years and some of those with basic diseases, who have extremely decreased immune function.

The results of clinical studies leading to such a decision are reported in three parts (For the course concerning revision of vaccination rounds, see Chart 1-5-6)

(2) Safety of vaccine and relief of vaccine-induced sufferings

1) Prompt gathering of information on side reaction and management

Novel influenza （A／H1N1）vaccine is manufactured by similar method to that of seasonal influenza vaccine, and basically equivalent safety may be expected of it, only with different virus strain being used in manufacturing process. And as for imported vaccine, in addition to the difference in used virus strain from the traditionally used seasonal influenza vaccine, in order to pay close attention to safety in the difference in manufacturing method, ingredient, and vaccination method from the traditional domestically used vaccine as well as the use of adjuvant（immune auxiliary substance）*7 that never experienced domestic use etc. such conditions for approval as shown in

Chart 1-5-5　were added.

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*7　Substance, mixture of which with vaccine can enhance the efficacy of vaccine. While this enables the same amount of vaccine to inoculate more persons with, it is pointed out that this increases possibility of side reactions (vaccination-induced side effect).

Chart 1-5-6　On revision of the dosage of novel influenza vaccination (with vaccine made in Japan) (Summary)

○ Since it was assumed that most citizens did not have immunity against novel influenza, initially vaccination was conducted twice for all.
○ Based on interim results etc. of clinical tests in healthy adults, it was revised as follows on 20 October
○ Based on results of clinical tests conducted after the second dose and overseas situation etc., it was revised as follows on 11 November
○ Based on interim results etc. of clinical tests in junior and senior high school students and mothers-to-be, it was revised as follows on 16 December

Target persons	Revision on 20 October (officially contacted on 22 October)	Revision on 11 November (notification on 17 November)	Revision on 16 December (Notification on 16 December)
Health care providers directly engaged in medical treatment of influenza patients (healthy adults)	Vaccination conducted once ※ Healthy adults in their 20s-50s	same as on the left ※ Vaccination shall be conducted once for persons aged 19 and over 60	
The following persons	For the present, .vaccination shall be conducted twice for each person. Revision shall be considered based on domestic] data, overseas information, expert opinions	—	—
Guardians of children under 1 year and priority target children who are unable to receive vaccination for physical reasons	Revision shall be considered based on the results (approxi-mately in mid-November) of second dose of vaccination in healthy adults in clinical tests. Persons under 13 shall receive vaccination twice.	**Vaccination conducted once**	same as on the left
Persons with pre-existing diseases		**Vaccination conducted once** Those with significantly suppressed immune reaction may take a second dose after individual consultation with a medical doctor.	same as on the left
Elderly persons aged 65 and over		**Vaccination conducted once**	same as on the left
Mothers-to-be	• Revision shall be considered based on the results (approxi-mately in mid-November)of second dose of vaccination in healthy adults in clinical tests, and • the results (approximately in mid-December)of first dose of vaccination in mothers-to-be in clinical tests.	**Vaccination conducted once** Additionally, verification shall be conducted based on results coming out in mid-December of clinical tests in mothers-to-be	**Vaccination conducted once** (Revision on November 11 shall be applied)
Persons aged equivalent to students of junior and senior high school (13 and over)	• Revision shall be considered based on the results (approximately in mid-November) of second vaccination in healthy adults in clinical tests、and • the results (approximately in the end of December) of first vaccination in junior and senior high school students in clinical tests.	**Vaccination conducted twise** Revision shall be considered based on the results of first dose of vaccination in persons aged equivalent to junior and senior high school	**Vaccination conducted once**
Persons under 13	**vaccination conducted twice**	same as on the left	same as on the left

Because of extensive inoculation of many people with such vaccine , The Ministry of Health, Labour and Welfare not only requested to medical institutions for direct reports, promptly gathered serious side reaction etc. and released the situation, but also, as the occasion demands, conducted study of safety etc. measure by experts.

2）“Act on Special Measures concerning relief of health hazard induced by novel influenza vaccination”

As mentioned above we are endeavoring to ensure the safety of vaccine, still, because certain extent of side reaction is inevitable, adequate relief measures should be taken. Persons who have suffered health hazard from inoculation with novel influenza （A／H1N1） vaccine, however, do not become the object for the scheme of health damage relief of the present Preventive Vaccination Act because the current program for novel influenza vaccination is not placed in the said Act. Therefore, relief measures for those persons were being required along with formulation of governmental compensation system for the loss suffered by manufacturers/dealers in compensation for health hazard induced by the use of specially approved vaccine, considering that current Special Approval was adopted in response to a state emergency caused by novel influenza.

Chart 1-5-7　The management system for side reactions after novel influenza (A／H1N1) vaccination (Outline)

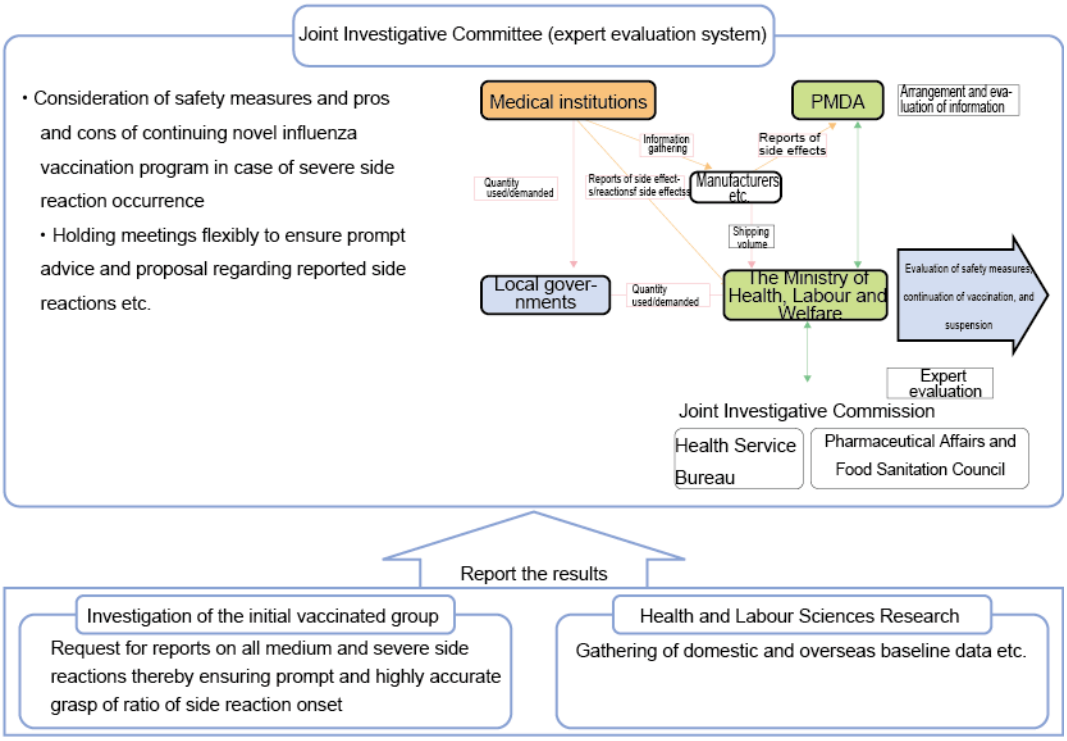


Chart 1-5-8　The outline of Act on Special Measures concerning Relief etc. of Health Hazards of Novel influenza Vaccination

New legislative measures shall be taken in order to ensure prompt relief of health hazards of novel influenza vaccination executed by the Minister of Health, Labour and Welfare as well as to conduct the government's compensation for losses of enterprises regarding side effect induced hazards etc. with the aim of importing necessary portion of overseas products.

1. Arrangement of relief measures prepared for occurrence of health hazards

○ The Minister of Health, Labour and Welfare shall take relief measures for the recipient of novel influenza vaccination in case of occurrence of health hazards caused by the said vaccination.

○The sum of benefits etc. shall be determined on the basis of measures related to benefits concerning routine vaccination of Category II diseases specified by the Preventive Vaccination Act (as for Relief Benefits based on Act on Pharmaceutical and Medical Device Agency).

2. Response to contents of contract with importing enterprises (government's compensation for losses for enterprises regarding side effect induced hazards etc.)

○With the manufacturers and distributors of the specially approved novel influenza vaccine being the opposite party, the Government shall be able to make a contract guaranteeing compensation for losses etc. incurred by the said manufacturers and or distributors as a result of reparations etc. for losses related to health hazards resulting from vaccine use

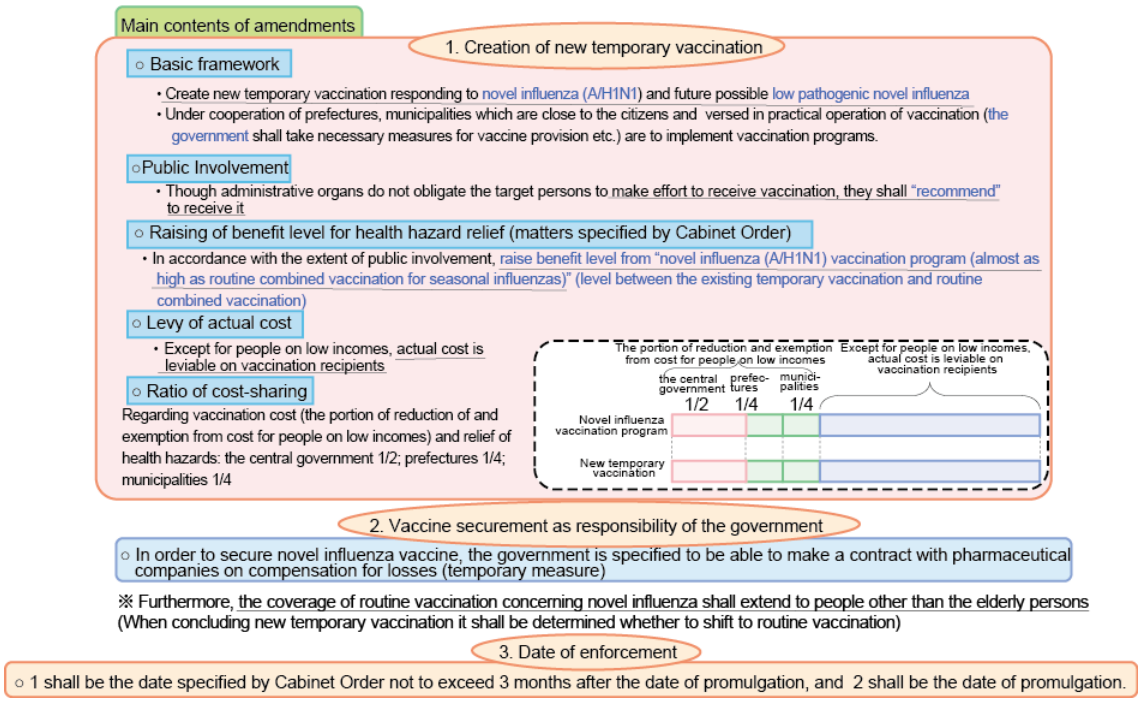
3. Date of enforcement

○The said Act shall be enforced at the promulgation date. Provisions concerning relief measures for health hazards shall be also applied to those who received novel influenza vaccine prior to the enforcement date.

4. Regulation for consideration

○The government shall take into account the state of execution of novel influenza vaccination conducted by the Minister of Health, Labour and Welfare and the results etc. of study and research concerning efficacy and safety of novel influenza vaccination, discuss on how to conduct vaccination programs for infectious diseases including novel influenza which are likely to happen in the future, as well as on relief measures for health hazards concerning the said vaccinations, and based on the results thereof take necessary measures.

Chart 1-5-9　The summary of reform bill of Preventive Vaccination Act etc.



Therefore, "Act on Special Measures concerning relief of health hazard induced by novel influenza vaccination" was presented to the 173rd extraordinary session of the Diet, being approved and established at the plenary session of the House of Councilors on 30 November 2009, and enforced since 4 December of the same year.*8

3) Revision of Preventive Vaccination Act

We managed the relief measures for the current health hazard induced by novel influenza (A/H1N1) with special legislation. However, in order to ensure flexible management of future similar cases within the scheme of Preventive Vaccination Law without legislating on each occasion, after consideration at Vaccination Section of the Infectious Diseases Control Panel of the Public Health Council we presented on 12 March 2010 " Partial Revision of the Act on Special Measures concerning relief of health hazard induced by novel influenza vaccination" to the 174th ordinary session of the Diet, which was, however, submitted to continuous consideration till the next Diet. Additionally, existing novel influenza (A/H1N1) vaccination programs are scheduled to continue until the establishment of the said bill.

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*8　For details of target persons of benefit and method of receiving benefit, see home

page of the Ministry of Health, Labour and Welfare （http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou04/inful_06.html）.

(3) Study on drastic revision of Preventive Vaccination Act

The revision bills of Preventive Vaccination Act etc. currently presented at the Diet are simply temporary countermeasures for current novel influenza （A／H1N1） and similar influenza without high pathogenicity. And along with them we will also conduct study on drastic revision of the said Act aiming at revision of target diseases and vaccine etc. in response to the indication by related personnel of necessity of revising whole policy concerning vaccination. Hearing of expert opinions etc. is currently underway at Vaccination Section of the Infectious Diseases Control Panel of the Public Health Council.

Chart 1-5-10 Vaccination Sectional Meeting of the Infectious Diseases Control subcommittee, the Health Science Council

■ State of holding the meeting

- The 1st December 25, 2009
  Agenda: ○ Vaccination system
- The 2nd -4th January 15 and 27, February 9, 2010
  Agenda: ○ Cases in which measures against novel influenza are needed to be taken urgently
- The 5th February 19, 2010
  Agenda: ○ Compilation of "The 1st proposal"
- The 6th March15, 2010
  Agenda: ○Subcommittee interim report on Japanese encephalitis
  ○ Future promotion (draft)
- The 7th April 21, 2010
  Agenda: ○ Hearing of experts (・Acceleration of research and development of vaccine and securement of production base)
  ○How to promote discussion on the diseases and the vaccine that the Preventive Vaccination Act prescribes
- The 8th May19, 2010
  Agenda: ○ Hearing of experts
  ・Reports on side reactions related to vaccination
  ・Evaluation on health economics of vaccination and epidemic surveillance
  ○Future policy on pre-pandemic vaccine
- The 9th June16, 2010
  Agenda: ○ Hearing of experts
  ・System for evaluation/consideration of vaccination
  ・How to provide information on vaccination
  ○ Aggregation of opinions on revision of vaccination
- The 10th June23, 2010
  Agenda: ○ Hearing of experts
  ・System for execution of vaccination
  ・Relief of health hazards related to vaccination
- The 11th July7, 2010
  Agenda: ○The diseases and the vaccines that the Preventive Vaccination Act prescribes
  ○How to share vaccination cost