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Review

Development of Vaccination Policy in Japan: Current Issues and Policy Directions

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CONTENTS:

SUMMARY: Until November 2001, eight vaccinations had been offered to Japanese children on a routine basis; namely, diphtheria-tetanus-pertussis, polio, measles, rubella, Japanese encephalitis, and BCG. The 2001 amendment of the Immunization Law introduced an influenza vaccine for the elderly population. This paper reviews the progress of the immunization program in the broader context of infectious disease control in Japan. There are two recent major policy changes in the field of infectious disease control in Japan. One is the strengthening and revitalization of the infectious disease control program, particularly surveillance, by the enactment of new 1999 legislation entitled "Law concerning the Prevention of Infectious Diseases and Patients with Infectious Diseases". The other major policy change is a review of existing immunization programs and the amendment of the Immunization Law in 2001. In this article, the present routine vaccination program, as well as the recent amendments to the law, are described. Current policy issues are then discussed, including polio vaccination after the WHO "Zero Polio" announcement in the Western Pacific Region in 2000; strategies for changes in measles, rubella, tuberculosis, and influenza control; as well as adverse reaction monitoring/surveillance and feedback for improving vaccine safety. Finally, the future prospects of intended/planned changes in the vaccination policy are considered.

1. Introduction

The history of vaccination in Japan started with the smallpox vaccination in 1849, and the first legislation concerning the smallpox vaccination was enacted in 1910. After the end of World War II, the government decided to more actively promote vaccination against many infectious diseases that caused serious health burdens at that time, and the Immunization Law was enacted in 1948. That law still provides the legal framework for the immunization program in Japan. However, recently, two major changes have been implemented. The first change involves the strengthening and revitalization of the infectious disease control program, particularly as regards surveillance, by the enactment of new legislation in 1999; the other change involves a review of existing immunization programs and the resulting amendments. This paper reviews the progress of the immunization program in the broader context of infectious disease control in Japan.

1-1. Law concerning the Prevention of Infectious Diseases and Patients with Infectious Diseases

New legislation, i.e., the "Law concerning the Prevention of Infectious Diseases and Patients with Infectious Diseases" (hereafter referred to as the new Infectious Diseases Control Law) was enacted and became effective as of 1 April 1999. This law defines the role of the public sector at various levels and authorizes the Prefecture Governors to conduct preventive measures according to the legal procedures mandated by the law. For the purpose of enforcement, infectious diseases are classified into Categories I to IV, according to the level of restriction of patients' rights, the judgment of which is based on the potential seriousness of the infectious disease in question.

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For example, five serious infectious diseases including Ebola hemorrhagic fever and Lassa fever are classified as Category I diseases, in cases of which the Governors are authorized to enforce hospitalization. Diseases targeted by the expanded program on immunization (EPI) are classified in Categories II or IV. For example, polio is a Category II disease that requires hospitalization as necessary, and measles is a Category IV disease that requires only weekly physician's reports at sentinel institutions for surveillance and public health intervention, as necessary. The specific infections belonging to each category are shown in Table 1. Needless to say, physicians are expected to immediately report patients with diseases in Categories I to III; reports are submitted such that appropriate clinical and administrative action can be taken, e.g., isolation or limitation of food handling in cases involving Category III disease, in which only enterohemorrhagic *Escherichia coli* infection is designated. All of the information collected through the surveillance system is submitted to the Ministry

Table 1. Target diseases of the Infectious Control Law

Target diseases of the new Infectious Disease Control Law
(Reportable infectious diseases of categories I to IV)

Category I infectious diseases
(to be hospitalized in principle)

Crimean-Congo hemorrhagic fever
Ebola hemorrhagic fever
Lassa fever
Marburg disease
Plague

Category II infectious diseases
(to be hospitalized depending upon the conditions)

Cholera
Shigellosis
Typhoid fever
Paratyphoid fever
Diphtheria
Acute poliomyelitis

Category III infectious diseases
(requiring restriction on working in particular kinds of occupation)

Enterohemorrhagic *Escherichia coli* infection

Category IV infectious diseases
(requiring collection and analysis of information on occurrence of the infectious disease and publication of the results)

a. Diseases required notifying all the cases (to be reported by all physicians)

Acute viral hepatitis
Acquired immunodeficiency syndrome*
Amebiasis*
Anthrax*
Brucellosis*
Coccidioidomycosis*
Congenital rubella syndrome*
Creutzfeldt-Jakob disease*
Cryptosporidiosis
Dengue fever*
Echinococcosis*
Epidemic typhus*
Giardiasis
Hantavirus pulmonary syndrome*
Hemorrhagic fever with renal syndrome*
Herpes B virus infection*
Infant botulism*
Japanese encephalitis*
Japanese spotted fever*
Legionellosis*
Lyme disease*
Malaria
Meningococcal meningitis*
Psittacosis*
Q fever*
Rabies*
Relapsing fever*
Severe invasive streptococcal infections (Streptococcal toxic shock-like syndrome)*
Scrub typhus (Tsutsugamushi disease)*
Syphilis
Tetanus*
Vancomycin-resistant *Enterococcus* infection
Yellow fever*

b. Diseases to be reported by the sentinel clinics and hospitals

Influenza*

<Pediatric diseases>
Chickenpox
Erythema infectiosum
Exanthem subitum
Group A streptococcal pharyngitis*
Hand, foot, and mouth disease*
Herpangina*
Infectious gastroenteritis*
Measles*
Mumps*
Pharyngoconjunctival fever*
Pertussis*
Rubella

<Eye diseases>
Acute hemorrhagic conjunctivitis*
Epidemic keratoconjunctivitis*

<Sexually transmitted diseases (STD)>
Condyloma acuminatum
Genital chlamydial infection
Genital herpes
Gonorrhea

<Target diseases at sentinel hospital>
Acute encephalitis (excluding Japanese encephalitis)*
Aseptic meningitis*
Bacterial meningitis*
Chlamydial pneumonia (excluding psittacosis)
Measles in adults
Methicillin-resistant *Staphylococcus aureus* infection
Multi-drug-resistant *Pseudomonas aeruginosa* infection
Mycoplasmal pneumonia
Penicillin-resistant *Streptococcus pneumoniae* infection

*Target disease of infectious agent surveillance in category IV

(Source: Infectious Disease Surveillance Center, NIID http://idsc.nih.go.jp/index.html)

of Health, Labour and Welfare (MOHLW), and then the Infectious Diseases Surveillance Center of the National Institute of Infectious Diseases (IDSC/NIID) publishes the Infectious Diseases Weekly Reports (IDWR), which are available through an Internet Website: http://idsc.nih.go.jp/index-j.html, for a summary in Japanese, and http://idsc.nih.go.jp/index.html, for an English summary. Based on this information, the Minister of the MOHLW may recommend local authorities to provide additional measures, including non-routine vaccination according to the Immunization Law.

1-2. Amendment of the Immunization Law

The other new development is the review of existing immunization programs based on the Immunization Law (enacted in 1948 and amended in 1976, 1994, and 2001) mandating that local mayors offer residents of defined age groups in the community the opportunity of vaccination. The names of the vaccine-preventable diseases according to the Immunization Law are listed in the major body of the law, but the target populations are provided by the Cabinet Order (1); details covering both technical and practical aspects as regards compensation for vaccine-associated injuries are further provided by the Ministry Order (2,3) and by the Director-General's Memoranda (4). Furthermore, detailed practical guidelines for health professionals (5) and informational brochures (6) have been prepared and distributed by the non-governmental organization, Immunization Research Center.

Recently, there have been two major amendments to the Immunization Law. The 1994 amendment included three major elements, i.e., to change the target diseases for vaccination, to expand the compensation for accidental vaccine-related adverse reactions, and to change vaccination from a compulsory basis to an informed-consent basis, as conferred by the target population or by their parents. Furthermore, the amendment eased the level of citizen obligation to receive vaccination from "is the duty of every citizen" to "should make an effort to be immunized". In accordance with this trend, more emphasis has been placed on parental decision as regards vaccination, with an understanding of the advantages and disadvantages of vaccination, as a part of the attempt to reduce adverse reactions. In the clinical setting, the Director General's Memorandum on the Practical Implementation of Immunization enacted in 1996 urged individuals to seek vaccination from their attending physicians, which clearly discouraged the type of mass campaign-type vaccination implemented in the past.

The 2001 amendment was based on the recommendation submitted to the Minister by the Public Health Council in January 2000, which urged the enhancement of measures against influenza among the elderly population. This recommendation was made because of the record high mortality observed among the elderly population at that time. According to the Vital Statistics Report of the Ministry of Health and Welfare during the period of December 1998 to March 1999, there were 1,350 of deaths due to influenza, more than 85% of which were in people over 65 years of age. This recommendation urged the MOHLW to amend the Immunization Law in order to introduce routine influenza vaccinations for people over 65 years of age and for those with specific health risks who were over 60 years old. Routine vaccinations were then categorized into two groups. Vaccinations for Category I diseases aimed at preventing the transmission of infections in the community. For this purpose, citizens are now strongly urged to receive seven vaccinations, namely, those against diphtheria, Japanese encephalitis, measles, pertusiss, polio, rubella, and tetanus. In contrast, vaccinations against Category II diseases aim at reducing morbidity and mortality. In such cases, informed consent should be more eagerly sought; currently the Immunization Law defines only influenza under this category. The amendment was supported by an absolute majority of parties in Parliament and was passed on 31 October, becoming effective as of 7 November 2001. On a practical level, it is very important to promote the education of citizens regarding vaccination; MOHLW encourages the translation of the information brochure into foreign languages, e.g., Korean, Chinese, Portuguese, etc., prepared by local authorities (7-9) in prefectures with a significant number of non-Japanese residents.

In addition to the above vaccinations, the Tuberculosis Control Law stipulates the use of BCG vaccination. Therefore, a total of nine vaccinations are publicly offered to residents. The current vaccination schedule appears in Fig. 1. It should be noted that the administration of vaccination is recommended during the period indicated by the black bar, but that vaccinations are also provided during the period indicated by the white bar. This arrangement is designed to maximize the window of opportunity for vaccination. Also, prior to 1994, the rubella vaccination was offered to female students in junior high school before they reached reproductive age. However, this policy was changed to include both males and females between 12 months to 90 months of age, with transitional arrangements to urge junior high school boys and girls to be immunized. Eventually, all Japanese children will have received the rubella vaccine.

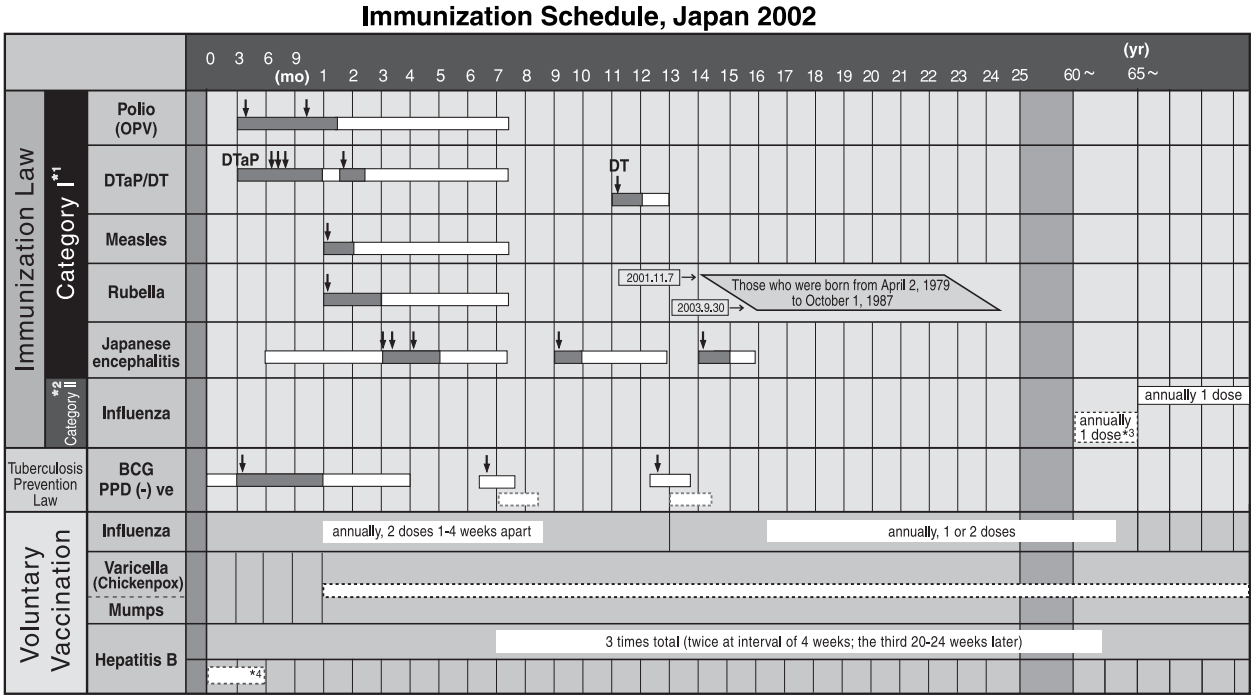
2. Routine vaccination

2-1. Vaccination coverage

The trends of vaccination coverage are collected by the MOHLW, and are shown in Fig. 2. It should be noted that alleged cases of aseptic meningitis among children who received measles, mumps, and rubella (MMR) vaccine contributed in particular to the low coverage of measles during the period from 1989 to 1993. More specifically, the MMR vaccine were introduced starting in April 1989, and the first report of aseptic meningitis at an incidence of 1 in 100,000-200,000 vaccinations was submitted to the Public Health Council in September 1989. The Council responded by strengthening relevant information gathering procedures, obtaining consent from the parents, and disseminating information, but the official cessation of MMR vaccine was enforced in April 1993. Reflecting the public concerns about adverse reactions to vaccines, the amendment to the Immunization Law in 1994 decreased the level of obligation to vaccinate and made a clear shift to an individualized approach to vaccination. The public health community was concerned about the possibility of a decrease in the rate of immunization, but the abovementioned Panel reviewed the progress of immunization programs in 1999 and expressed satisfaction with the maintenance of high immunization rates, as shown in Fig. 2. In addition, a national epidemiological surveillance of vaccine-preventable diseases has been conducted by the MOHLW and the IDSC/NIID. This national report (10) includes the respective antibody levels of different age groups in the Japanese population.

2-2. Reported cases of EPI disease

The disease burden due to the EPI target diseases is of public concern; the number of reported cases of each disease appears in Table 2. However, it should be noted that these



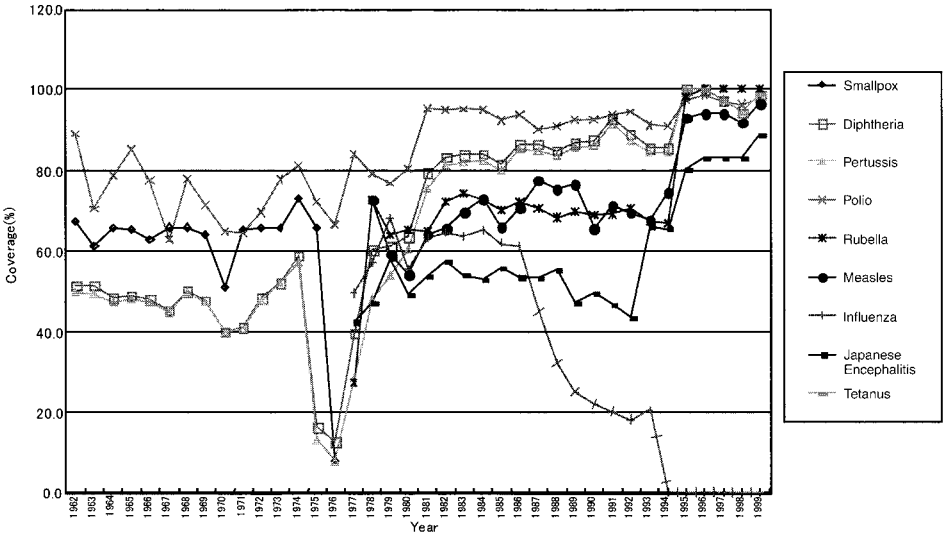
(Source: Infectious Disease Surveillance Center, NIID http://idsc.nih.go.jp/index-j.html)

Fig. 1. Immunization schedule

shot — age regularly vaccinated — age vaccination is regulated — age vaccinated — revaccination of PPD (-) ve — program of prevention of mother-to-child infection — temporary schedule (until 9/30/2003)

*1 **Category I** : The objective is to protect the public health. Immunization is strongly recommended by law.
*2 **Category II**: The objective is to protect the individual's health. This is available on request.
*3 60-64 year-old persons who have severe disorders of the heart, kidney, respiratory organs, or from the human immunodeficiency virus
*4 Newborn babies from HBs antigen positive mothers should receive anti-HBs human immunoglobulin (HBIG) and HB vaccine. HBIG is intramauscularly injected to the neonates within 48 hr and 2-3 months after birth, followed by hepatitis B vaccine starting at the time of the second immunoglobulin injection. The vaccine is given three times; the first two doses at one month apart and the third one in three months after the first dose. This is covered by health insurance.

OPV: oral poliovirus
DTaP: diphtheria and tetanus toxoids and acellular pertussis vaccine
DT: diphtheria and tetanus toxoids
BCG: bacille Calmette-Guérin
PPD: purified protein derivative



(Source: Ministry of Health, Labour and Welfare)

Fig. 2. The trends of immunization coverage.

numbers depended on voluntary reporting according to the administrative guidelines of the MOHLW, but reporting has now become the legal responsibility of the diagnosing doctors, according to by the new Infectious Diseases Control Law implemented after April 1999. This change resulted in an increase in the number of reported cases. Measles and pertussis are still reported by sentinel institutions, and thus these values do not represent the total number of the cases, but instead show trends of infection. During the debate about the new Infectious Diseases Control Law, this level of information collection was considered appropriate for assessing the adequacy of local control measures. The new sentinel reporting

Table 2. Reported cases of EPI diseases 1998-2000

	Measles[2]	Pertussis[2]	Tetanus		Diphtheria
			ALL	NNT[1]	
1998					
No.cases	761	43	47	0	3
Population	125,252,000	125,252,000	125,252,000	1,203,147	125,252,000
Rate per 100,000	N.A.	N.A.	0.04	0	0.002
1999 (Apr-Dec)*					
No. cases	5,958	2,653	65	0	2
Population	125,432,000	125,432,000	125,432,000	1,177,669	125,432,000
Rate per 100,000	N.A.	N.A.	0.05	0	0.002
2000 (Jan-Dec)					
No. cases	22,978	3,804	91	0	1
Population	125,588,787	125,588,787	125,588,787	1,190,560	125,588,787
Rate per 100,000	N.A.	N.A.	0.07	0	0.0008

(Source: 1998; Statistics on Communicable Diseases, 1999 (Apr-Dec), 2000; Annual Report of Surveillance for Infectious Diseases)

[1] NNT: Neonatal tetanus

[2] No. of cases reported from designated pediatric institutions (3,000) and general hospitals (500).

* Law concerning the Prevention of Infectious Diseases and Patients with Infectious Diseases became effective as of April 1999.

N.A.: cases reported from sentinel points, therefore not applicable.

system has the following features:

(1) Cases of measles and pertussis are collected from approximately 3,000 collaborating pediatric sentinels;
(2) Measles cases among the adult population are reported separately from approximately 500 general hospital sentinels;
(3) The selection of collaborating sentinels is based on the likelihood of covering as many patients in the respective geographic areas as possible;
(4) In order to ensure the quality of reporting, clinical guidelines taking relevant the World Health Organization (WHO) criteria into consideration were developed and distributed jointly by the MOHLW and the Japan Medical Association.

2-3. Improvements and problems regarding quality of services

In response to two alleged cases (one death and one paralysis) of severe adverse reaction due to oral polio vaccine (OPV) within a Prefecture in April and May 2000, the Infectious Diseases Control Panel of the Public Health Council established a task force and conducted a comprehensive laboratory and epidemiological investigation. The conclusion of the investigation rejected a positive causal relationship between health hazards and the OPV. However, even before the investigation began, the Prefecture had ceased OPV immunization until safety was ensured. Eventually, the use of the same lot of OPV vaccines was stopped nationwide and all OPV vaccinations were suspended temporarily. Since the decision of this Prefecture had such a wide impact, the decision-making process itself was also reviewed. Taking advantage of this case, a standard response protocol for dealing with such alleged cases of vaccine-derived reactions was developed and endorsed by the Panel in August 2000 (11). The vaccination rate of OPV recovered in the autumn session of the vaccination schedule, but the provisional figure of annual coverage for the year 2000 was approximately 89%, i.e., about 10% lower than in the previous years. Whether or not those who had not received the OPV were eventually vaccinated until now is of current concern.

3. Specific issues

Despite the overall progress of the immunization program in Japan, some issues remain that deserve further improvement.

3-1. Poliomyelitis

Polio has been eliminated in Japan, and a special WHO meeting to celebrate "Zero Polio" in the Western Pacific Region of the WHO was held in Kyoto in 2000 (12).

After this declaration, four issues remained, i.e., maintenance of a high level of surveillance and monitoring to ensure the zero-polio status, maintenance of a high level of immunization coverage, the possible switch from the OPV to an inactivated polio vaccine (IPV), and laboratory containment of polio virus, as was undertaken in the case of smallpox.

3-1-1. Poliomyelitis eradication: surveillance monitoring

All physicians are required to immediately report poliomyelitis cases as Category II infectious diseases designated under the new Infectious Diseases Control Law. Active surveillance for polio and polio-like diseases is conducted by the National Certification Committee of Japan (J-NCC) at all hospitals, clinics, local public health laboratories (PHLs), and local health centers (LHCs). This surveillance system includes searches for all clinical conditions that may represent poliomyelitis infection. For such cases, adequate stool specimens are collected and forwarded to the PHL network.

Supplementary surveillance activities for certification of poliomyelitis eradication were also conducted by the J-NCC. Six study sites were selected in Hokkaido, Fukushima Prefecture, Yokohama City, Mie Prefecture, Osaka and Hyogo Prefectures, and Fukuoka Prefecture. In this investigation, the total percentage of children under 15 years of age covered by the catchments area of the hospitals investigated was 20% of the total population of Japanese children under 15. The supplementary surveillance activities were divided into two categories: 1) retrospective record review and 2) prospective acute flaccid paralysis (AFP) surveillance study. The retrospective study of medical records was conducted covering the period from January 1 to December 3, 1998, for pediatric cases of AFP less than 15 years of age. The study was

conducted in six prefectures and 327 institutions (pediatric departments of hospitals in coordination with PHLs). A standard questionnaire was sent to all of the pediatric hospitals or pediatric departments in the general hospitals in these regions. No cases of poliomyelitis had to be reported as zero cases. As regards active surveillance for polio and polio-like diseases, 11 polio-like cases were reported and investigated between April 1998 and March 2000. In four cases, poliovirus vaccine (type: Sabin strain) was isolated. All cases were reviewed by an Expert Committee of the MOHW and subsequently discarded as not indicative of wild-type poliovirus infection.

A prospective study was conducted from 1 January 1999 to 31 March 2000 to identify cases of AFP at the same 327 institutes in the six regions mentioned above. Whenever a pediatric patient under 15 years of age was suspected of AFP, including poliomyelitis, the pediatrician who diagnosed the case of AFP was required to obtain two stool specimens within 14 days of onset of paralysis, and the samples were sent to the PHLs in the region for virological examination. If poliovirus was found, the specimens were forwarded to the Section of Enteroviruses, Department of Virology II, NIID for confirmation and intratypic differentiation. Completion of the same standard questionnaire mentioned above was also required as a record of the AFP case in question. Zero cases of AFP also had to be reported, if no patients at a particular site presented with AFP symptoms.

3-1-2. Poliomyelitis eradication: routine vaccination

The OPV has been used and the national coverage remained as high as 97.8% in 1999 (13). Regarding the issue of whether OPV, IPV, or a combination of the two should be used, it is generally acknowledged that although the incidence of vaccine-associated paralytic poliomyelitis (VAPP) has been within the expected range (one per 4.4 million doses of the first vaccination and one per 5.8 million doses of the second) (14), the possibility of developing polio due to vaccine-derived polioviruses is of public concern. Therefore, it is necessary to discuss this issue, taking into account safety, efficacy, as well as administrative and financial feasibility.

3-1-3. Poliomyelitis eradication: laboratory containment

In July 2000, a national commission for wild-type poliovirus containment was established, consisting of most of the members of the existing National Certification Commission for Polio Eradication. The following actions were undertaken by the commission.

(1) Based on materials from the WHO, documents were prepared to explain four items, as follows: i) what polio is, ii) the progress of polio eradication initiatives in Japan and in the Western Pacific Region, iii) the purpose of containment, and iv) a provisional schedule for global polio eradication.
(2) Using the above documents, an explanation was given to those governmental authorities considered to be in positions of responsibility relevant to this matter.
(3) Moreover, the same information was distributed via non-governmental channels; for example, an announcement in the Journal of Japanese Society for Virology (December 1999) was issued, and a detailed presentation was given at academic meetings.
(4) Documents for notification of request for the survey were prepared for appropriate universities, laboratories, and companies, with the agreement of the authorities concerned.
(5) The notification request documents were sent to the appropriate institutions.
(6) A website was concurrently prepared, covering the same information as that described in item (3).
(7) The initiative was announced in the Japanese Society for Virology and continues to be periodically announced (See section 3, "Non-governmental Promotions").
(8) The initiative was publicized through the mass media.
(9) Replies to the survey were collected.
(10) Follow-up activities are being carried out.

As regards the Wild Poliovirus Laboratory Containment Survey, the results as of July 2001 were as follows.

A total of 6,880 responses were received.

- 5,604 replies were received via fax.
- 1,276 replies were received via the website.
- 45 laboratories responded that they possessed the wild poliovirus.
- 3,169 laboratories responded that they did not possess the wild poliovirus.
- 7 laboratories responded that there was a possibility that they possessed the wild poliovirus, but that they were not certain.
- 1,848 institutes and organizations responded that they did not have a laboratory that could possibly possess the wild poliovirus.

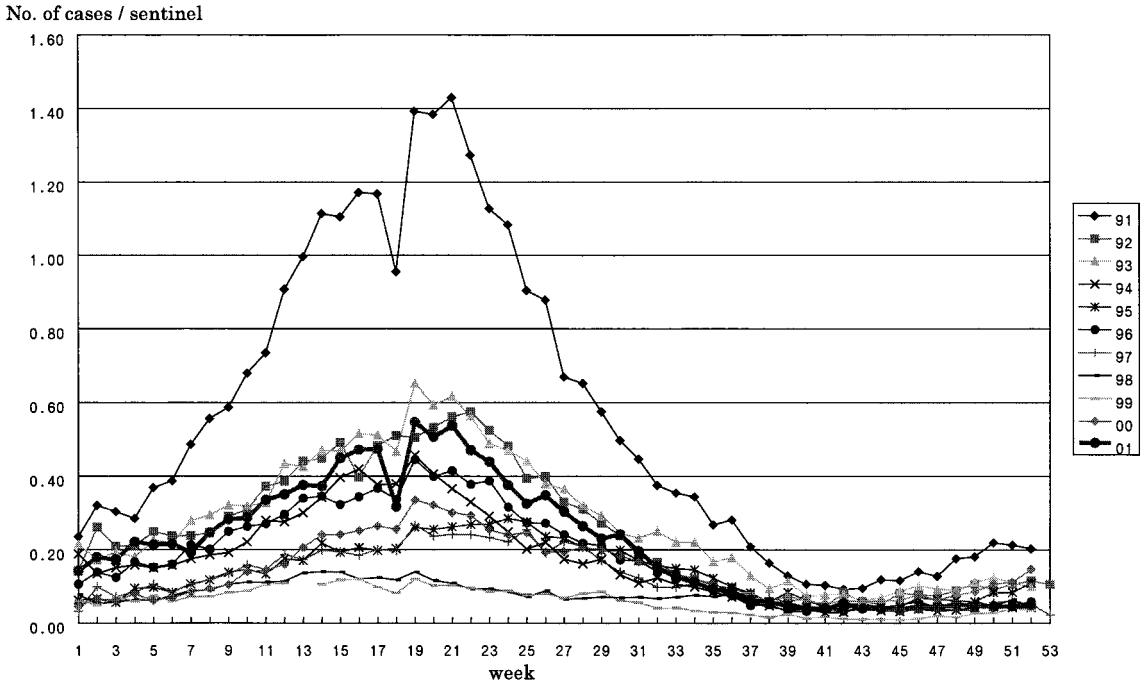
3-2. Measles control

3-2-1. History

Outbreaks of measles have been observed from time to time. The largest outbreak in the last decade was observed in 1991 when 68,980 cases were reported from 2,407 collaborating institutions, and the demographic census filed 39 deaths. The numbers of cases under 5 years of age was 46,531, with 23 deaths. Vaccination of children had been completely voluntary before 1978, but the Immunization Law provided vaccination of children aged 12 months to 72 months (now extended to 90 months, with a recommendation of vaccination at ages between 12 to 24 months) since 1978. The large number of cases generated public awareness, and the seriousness of the infection was gradually recognized. For example, the Japan Pediatric Association, the Japan Child Health Association, and the Japanese Association of Pediatricians jointly appealed to the Minister of MOHLW to promote vaccination against measles in July 2001.

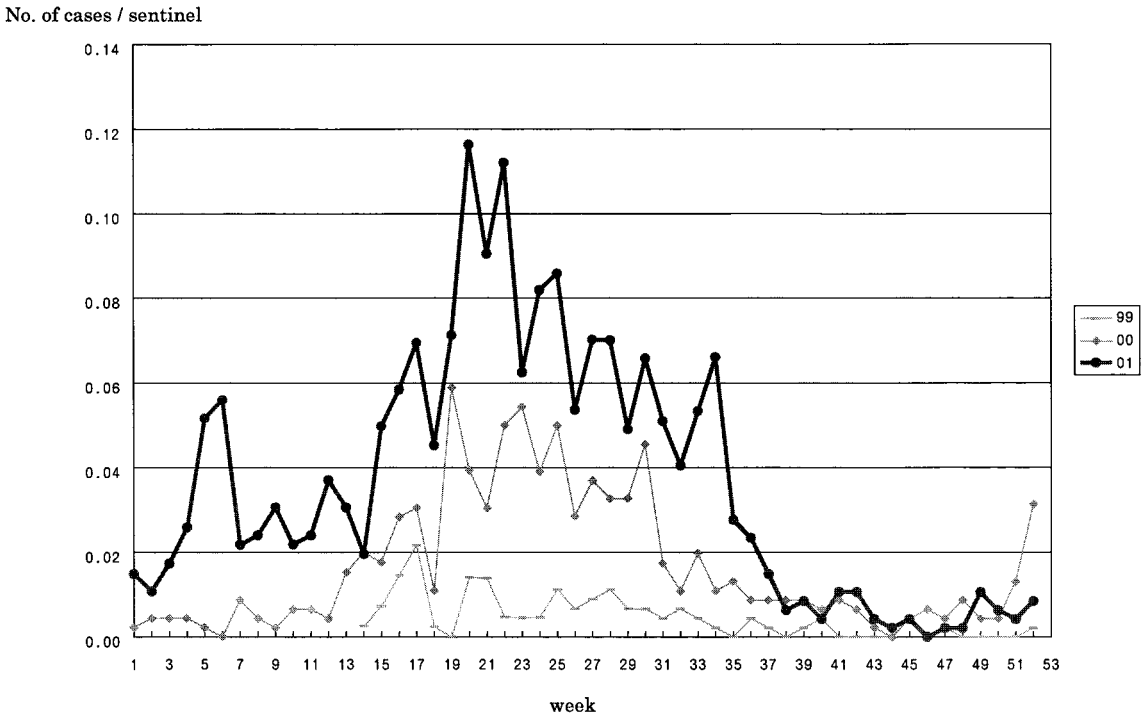
3-2-2. Incidence by age and prefecture

Sentinel surveillance was started as early as 1980, but the new Infectious Diseases Control Law systemically established sentinel surveillance in April 1999. Since then, some 3,000 collaborating institutional sentinels have been reporting the weekly incidence of measles among children; in addition, 500 general hospital sentinels have reported the incidence of measles in the adult population. Current figures of comparison with previous years appear on the Internet (Figs. 3 and 4). The age distribution of reported cases is shown in Fig. 5, which illustrates that the dominant age group affected was less than 2 years old. Furthermore, one study group revealed that 94.3% of the measles cases, occurred in people with a clear vaccination history who had not yet received the measles vaccination (15). However, the cases were distributed widely among various age groups, despite a fair level of anti-measles antibody revealed by the national sero-surveillance of the Japanese population (Fig. 6). If one acknowledges the number of cases reported in 2000 by sentinels, 22,978, and the estimation of total cases, 181,000 to 213,000 (16), then the possibility is revealed that the actual number of cases is nearly 10 times greater than the number reported by the surveillance.



(Source: Infectious Disease Surveillance Center, NIID http://idsc.nih.go.jp/kanja/weeklygraph/measles.html)

Fig. 3. Reported pediatric cases of measles per sentinel point (excluding cases of adults).

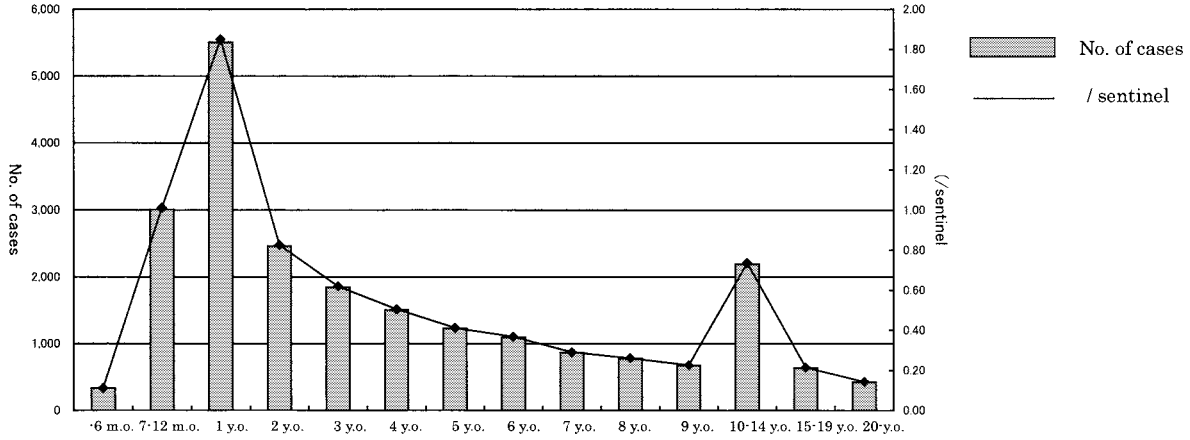


(Source: Infectious Disease Surveillance Center, NIID http://idsc.nih.go.jp/kanja/weeklygraph/adultmeas.html)

Fig. 4. Reported adult cases of measles per sentinel point.

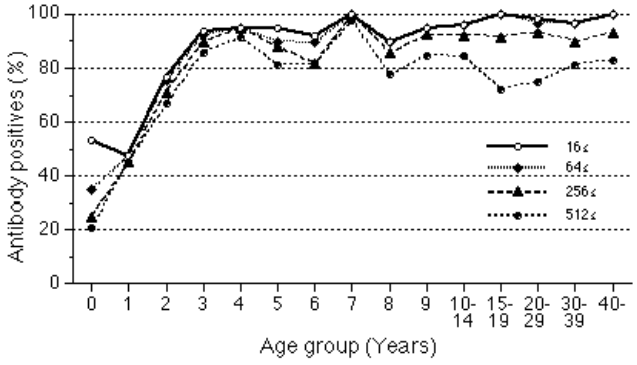
3-2-3. Immunization services

Measles vaccination is a part of the immunization program stipulated by the Immunization Law, and is administered to children between 12 months to 90 months of age. The original vaccination period was between 12 to 72 months, but this range was expanded to 90 months in 1994 with the intention to increase coverage. By including measles in the Immunization Law, the cost of vaccination is publicly supported and health hazards would be compensated for under the law. At present, the overall coverage exceeds 95%, but there is some concern that this figure does not show the coverage rate among the most vulnerable population, i.e., that under 2 years of age. A calculation factor may also have contributed to an overestimation of the coverage rate. At present, the coverage rate



(Source: Infectious Disease Surveillance Data in Japan 1999/4-2000/12)

Fig. 5. Number of measles cases by age group, 2000.



(Source: Infectious Disease Surveillance Center, NIID http://idsc.nih.go.jp/index.html)

Fig. 6. Age distribution of measles PA antibody-positive cases, 1997.

is calculated by the following formula: total number of persons vaccinated per year divided by the total number of children between 12 to 24 months. This means that children aged 24 to 90 months who received the vaccine are duly included in the number of vaccinated persons. The contribution of this fraction to the present coverage figure cannot be ignored, because the coverage by the measles vaccination dropped sharply during the period of 1989 to 1994, when the adverse reactions of the MMR vaccination came to be of public concern; those who failed to be immunized at that point in time may now seek vaccination under the Immunization Law. It has been estimated that the current coverage in the population under 3 years old is around 80% (10), and that there are particular communities with extremely low coverage rates.

3-2-4. National plan

Measles is considered as a significant health problem in Japan. Hence, there is much interest in strengthening our efforts as regards the measles vaccine, in particular after polio transmission has been interrupted for so many years in Japan. For the time being, steady implementation of the existing immunization program will be advocated, with special emphasis on increasing coverage among younger children. The MOHLW is committed to "control" measles, but no clear decision has been made as regards whether to "eliminate" or "eradicate" measles. A study team has been established and supported by the MOHLW to acquire first-hand evidence for a policy review. The terms of reference of the team include full epidemiological investigation, sero-surveillance of the Japanese population, investigation of immunization coverage, and recommendation of possible changes in the measles vaccination program, including the timing of vaccination, frequency, and safety measures. The team is expected to submit its final report by March 2003, and an interim report was submitted to the MOHLW in April 2002. The report (15) highlights the age distribution of measles cases and it urged early vaccination within the scope of the present Immunization Law. This recommendation served as the basis of a Memorandum (17) from the Director of Tuberculosis and Infectious Diseases Control; this memorandum addressed the March 2002 issue of early vaccination against measles. The group is now working to develop a strategy to reduce the incidence of measles, which may include changes in the present vaccination schedule. However, to ensure wide support from the public health community, as well as from the general public, any changes in the vaccination schedule need to be discussed at the Health Science Council (formerly the Public Health Council), which is an advisory organ for the Minister of MOHLW. In this context, the Council may discuss more fundamental and broader policy issues.

In considering these issues, we first need to learn about the experiences of other nations and we must be in agreement with the global response. Through the experience gained in Japan and also by the international contribution to polio eradication, we firmly believe that all countries need to be united toward a common goal and schedule; otherwise, our efforts will be always disturbed by frequent importations and an extremely high measles re-transmission rate. Currently, the WHO and the United Nations Children's Fund (UNICEF) have endorsed a global target (18) to reduce morbidity due to measles by 50%, but the WHO has not yet declared whether the ultimate target is the "elimination" or "eradication" of measles. However, the American Region and some countries in the Asia/Pacific Region (i.e., Australia and the Republic of Korea) have adopted more active policies towards the elimination of measles.

Second, there are two general opinions regarding strategies to support vaccination; one is support of a mass campaign and the other advocates intensification of routine immunization. Mass campaigns were very successful in Japan 40 years ago when vigorous effort was made to stop polio transmission.

However, in the present environment, individual vaccinations at physicians' offices has become common practice. It is important for us to decide which method is more realistic from the viewpoint of logistics, sustainability, and social acceptability. Routine immunization is easy to maintain, but with this option it difficult to assure coverage, especially in specific target age groups, unless the public is adequately motivated. Once successful, though, this method will give us a good chance of sustainability. In the case of Japan, after the amendment of the Immunization Law in 1994, mass campaigning has become legally and administratively unfeasible. The question of booster vaccinations also needs to be reconsidered. The optimal timing of vaccination is an additional issue that should be studied in view of the low antibody transmission from mothers to neonates and the high frequency of febrile convulsion among Japanese young children. For example, according to the national survey of self-reported health problems after measles vaccination, 13.4% of the subjects claimed to have a fever over 38.5°C, and 0.2% of all subjects developed convulsion with a fever of over 37.5°C (sample size, 2,827) (19). In addition, efforts to reduce possible adverse reactions should be strengthened in order to ensure public support. Needless to say, the first priority should be to strengthen surveillance and increase laboratory confirmation, whenever possible. In an international venue, the Technical Advisory Group of the WHO Western Pacific Region recently (2001) discussed the measles control strategy and declined to adopt the elimination target until full technical, administrative, and political assessments are completed (20).

3-3. Rubella control

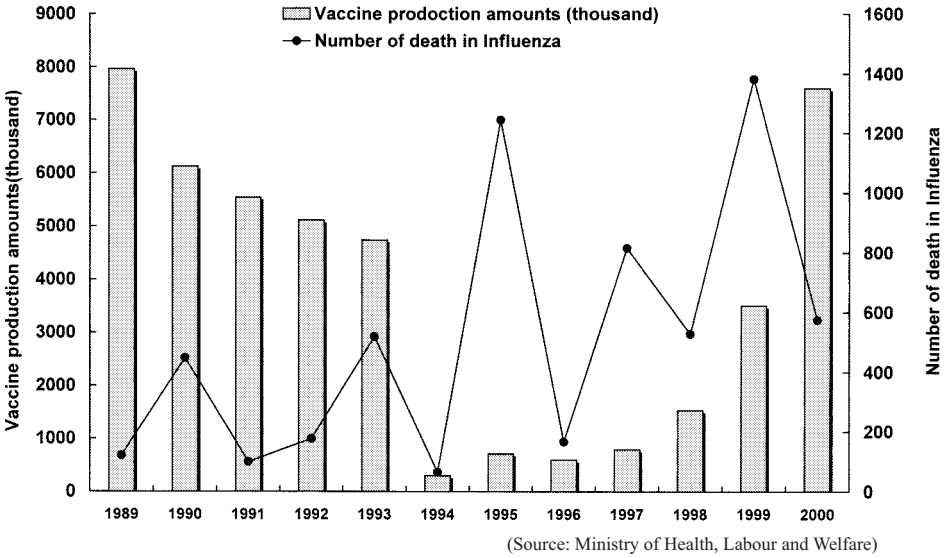
The timing of and subjects for vaccination were changed in 1994 (from junior high school females to both males and females between 12 months to 90 months of age, preferably 12-36 months), with transitional arrangements to urge junior high school boys and girls (the age group no longer covered by the new vaccination schedule) to receive the vaccination. Coverage of the new target group is satisfactorily high, but coverage of the transitional group is estimated to be as low as 50% (13). Hence, the MOHLW has collaborated with the Japan Medical Association to organize an active campaign to increase coverage of unvaccinated children and young adults.

3-4. Tuberculosis

Currently, BCG is given to children under 4 years of age (with a recommendation for vaccination at ages between 3-12 months), at primary school entrance and junior high entrance with preceding tuberculin testing. This practice has been reviewed, but the recent up-turn trend of the incidence and prevalence of tuberculosis (TB) since 1997 has caused a resurfacing of more fundamental questions regarding the existing TB control programs, including those regarding BCG vaccination. A nationwide ad hoc survey was conducted in 2000 and the TB Advisory Panel has started a comprehensive policy review (21). In its report to the Health Science Council (22), the Panel adopted the recommendation of ceasing BCG revaccination in both primary school and junior high school students.

3-5. Influenza

Vaccination against influenza was offered to school children before 1994, but this practice was ceased due to the debate over the lack of hard evidence supporting the effectiveness of influenza vaccine for that population, and due to clear existence of adverse reactions. Although the Infectious Control Panel of the Public Health Council acknowledged the potential contribution of the vaccine to prevent fatal cases, especially in the elderly population, the panel finally endorsed the position of "no hard evidence in support of the prevention role of the vaccination for the community as a whole" (23). Still, there remain diverse views on the pros (24) and cons (25) of immunizing school children. However, due to an outbreak of influenza in geriatric institutions in the 1998/99 seasons, the MOHLW established a study group which confirmed the reduction of relative risk of mortality by influenza vaccine (26), as stated in the Centers for Disease Control and Prevention (CDC) report (27). This finding served as the basis for the 2001 amendment of the Immunization Law to introduce routine influenza vaccination for those over 65 years of age and those over 60 years with specific health risks. Also, the reduced vaccine production capability was of concern to the public health community in terms of preparedness against new types of influenza virus. Furthermore, statistics tend to show that vaccine production and coverage both tend to have a negative correlation with mortality (Fig. 7), although this aspect was rejected at the time of the 1994



(Source: Ministry of Health, Labour and Welfare)

Fig. 7. Vaccine production and number of death in influenza.

amendment. Of note, a recent article has demonstrated the usefulness of vaccinating children to achieve a lower mortality among the general population (24). Yet, during the debates at Parliament, numerous questions were raised regarding whether or not alternative control measures other than vaccination would be desirable in the prevention of influenza (28). Therefore, it is hoped that more vigorous study of influenza vaccination policy will be conducted to determine the real efficacy of influenza vaccination at mortality prevention.

3-6. Adverse reaction monitoring/surveillance and feedback for vaccine safety

With great improvements made in the control of infectious diseases, the awareness of adverse reactions of vaccination has increased and information has been collected through three channels, namely, i) sentinel reporting of all health problems after vaccination (regardless of causative relationship with vaccination) in vaccinated individuals, ii) formal reports of vaccine-related injuries from local authorities (highly probable causative relationship), and iii) appeals to the vaccine injury compensation committee (seeking judgement of the causative relationship). The annual reports are prepared and shared among those concerned, with hopes of to utilizing the data for improving the overall safety of vaccination. However, it should be stressed that compensation for vaccine-related injury is granted unless firm evidence rejects the causative relationship, which is often difficult to establish. This practice stems from the notion that vaccinations are administered to protect against infection of particular individuals as well as of the community as a whole. In other words, if an accident does occur, this is understood as the result of a sacrifice of the individual for the good of the community, and therefore should be compensated generously. This viewpoint has resulted in a compensation rate higher than the international standard (29). However, a review of the compensated cases revealed different levels of causal relationship with the vaccination in question, ranging from "clear evidence" to "no evidence, but circumstantially probable" and "no evidence but circumstantially not rejectable". This generous coverage policy is beneficial for the individuals and families affected, but may be misleading to the public because a relatively high compensation rate is often interpreted as a high adverse reaction rate.

4. Future directions

In general, there remain rather skeptical views on vaccination in general. The benefits and contributions of vaccination against vaccine-preventable diseases are not well-covered by the media, whereas rare adverse reactions are commonly highlighted. This media practice is largely a result of the fact that many infectious diseases are no longer serious disease burdens to the Japanese population, especially among children. However, this practice also urges more extensive application of measures to ensure vaccination safety. Moreover, further review and modification of routine vaccination programs and schedules is required.

Currently, the following vaccines are available in Japan, in addition to the vaccines covered by the Immunization Law: freeze-dried live attenuated mumps vaccine, freeze-dried live attenuated varicella vaccine, freeze-dried inactivated tissue culture hepatitis A vaccine, adsorbed hepatitis B vaccine (recombinant), freeze-dried inactivated tissue culture rabies vaccine, cholera vaccine, pneumococcus vaccine, Weil's disease and Akiyami combined vaccine, absorbed habuvenom toxoid, and yellow fever vaccine.

In a 1999 report (30), the Vaccination Subcommittee of the Public Health Council identified four possible vaccinations for further consideration. These vaccines are influenza for the elderly population, chickenpox, mumps, and pneumococcal pneumonia. Out of the four, the influenza vaccine has been included in the Immunization Law since 2001, and the remaining three vaccinations will be continuously studied, though no timeline has been established. Furthermore, the vaccination schedule for measles and the possible switch from OPV to IPV are issues that need to be addressed before considering new vaccinations. Also, review and revision of the guidelines for health professionals are required to improve the safety of vaccination under an environment of growing public concern over the adverse reactions of vaccination. The public conception is that many infectious diseases appear to be less harmful in the present context in Japan, whereas the alleged adverse reactions are perceived as serious, unnecessary, and unreasonable sacrifices. Hence, any changes to a vaccination program need solid scientific justification and demonstration of clear benefit overriding the possible disadvantages of adverse reactions. Every effort to enhance the safety of vaccines should continue to be made; otherwise, it will be extremely difficult to gain public support. One typical example is the introduction of acellular pertusis vaccine (aP), developed in Japan in 1981, which resulted in a marked decrease in adverse reactions after its introduction.

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