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Review

Rubella and Congenital Rubella Syndrome in Japan: Epidemiological Problems

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CONTENTS:

SUMMARY: Rubella virus infection can lead to problems with congenital rubella syndrome (CRS) in the next generation due to fetal infection, but these problems are preventable with vaccination. In other words, rubella epidemics and the occurrence of CRS can be eliminated by vaccination. In Japan, until recently, rubella epidemics occurred every 5 years, and there were at least 1,600 CRS cases between 1965 and 1985. Following the 1994 revision of the Preventive Vaccination Law, national surveillance from approximately 3,000 clinics has shown that the number of rubella cases has dramatically decreased to a few thousand and the occurrence of CRS has decreased to only a few cases. However, the vaccination rate during a transitional period from 1995 to 2003 has been unsatisfactory. This has been especially true for junior high school students, because individual vaccination has replaced mass immunization in urban areas. As a result, the negative antibody rate in females below 18 years of age has increased to approximately 27%. If this trend continues, there is likely to be an increase in rubella epidemics and occurrence of CRS in the near future. Vaccination is not compulsory under Japanese law, and vaccination campaigns alone have proved unsuccessful in promoting vaccination. Another system of motivating individuals to seek vaccination will be needed in order to maintain a high vaccination rate without such campaigns.

1. Introduction

Rubella is a relatively mild viral infection. Its clinical features are a maculopapular rash, lymphadenopathy, arthralgia, and pyrexia. The symptoms are often mild, with 30-50% of cases being subclinical or going unnoticed. Its complications are arthritis, thrombopenic purpura, and encephalitis, but its prognosis is generally favorable. However, the rubella virus can induce problems in the next generation due to fetal infection. Rubella virus infection in susceptible women during the early stage of pregnancy may induce congenital defects, known as congenital rubella syndrome (CRS). The major defects are deafness, cataracts, congenital heart disease, microcephaly, and mental retardation. However, since rubella is a vaccine-preventable disease, epidemics and the occurrence of CRS can potentially be eliminated. Accordingly, I here analyze the present epidemiological and clinical problems and suggest future measures to assist in the prevention of CRS and rubella in Japan.

2. History of rubella vaccination in Japan

Between 1977 and 1994, the goal of the Japanese government was only to prevent the occurrence of CRS rather than to eliminate epidemics of rubella. Therefore, rubella vaccine was administered only to female junior high school students during that period. However, the epidemics have been accompanied by CRS cases. Vaccination with measles-mumps-rubella (MMR) vaccine, which was started in 1989, was suspended in 1993 because of the occurrence of many cases of aseptic meningitis caused by the mumps vaccine virus (1,2). Since the suspension, it has not been possible to administer the rubella vaccine as an MMR or as a measles-rubella (MR) vaccine, on which a phase III study was recently finished in Japan. Within a few years, it should again be possible to administer the MR or MMR vaccine in Japan.

The Japanese Supreme Court judged from fatal adverse reaction cases after vaccination that mass vaccination – i.e., group immunization without physical examination – was not safe. It recommended that a physical examination, followed by attainment of informed consent from one of the parents, be required. A revised law for vaccination, mainly based on recommendations and data regarding epidemics and the occurrence of CRS, was passed in 1994 (3). With regard to rubella, it indicated that, to prevent CRS through the elimination of epidemics, both boys and girls of 12 to 90 months of age should be vaccinated. At the same time, individual vaccination replaced mass immunization at each high school in order to make vaccination safe. The government decided that children between 90 months of age and junior high school

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age should provisionally be administered the vaccine during their junior high school years during a transitional period from 1995 to 2003.

3. Characteristics of vaccination in Japan

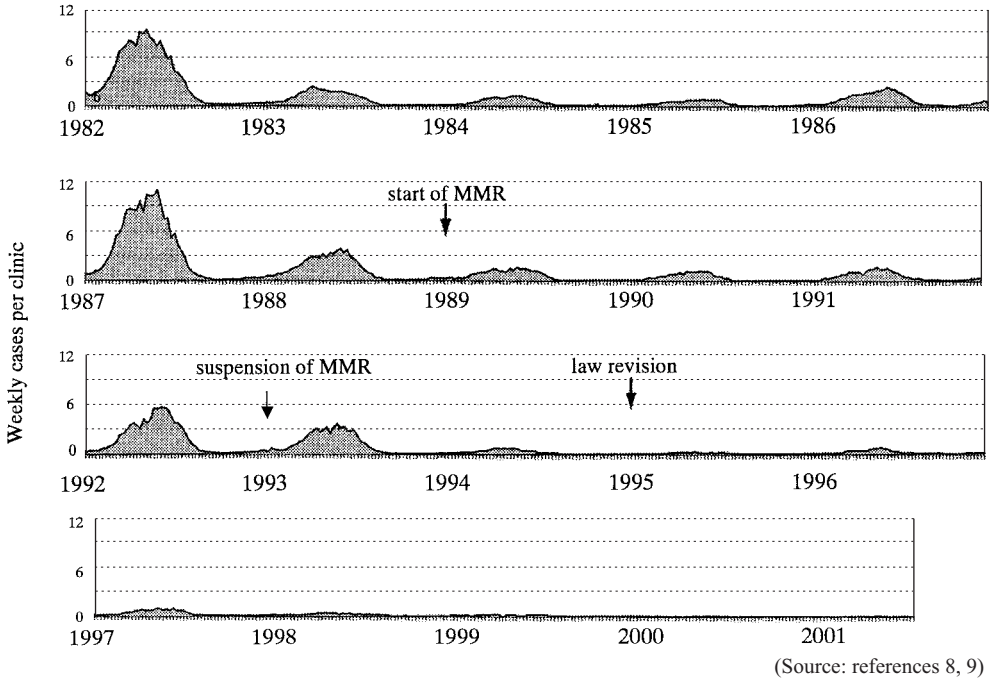
In Japan, rubella vaccination is performed using a monovalent rubella vaccine, and is given only once during the lifetime of the individual. The incidence of reinfection on exposure to a wild virus has been reported as 3 - 10% among those with a history of rubella and 14 - 18% among those immunized with the RA27/3 vaccine (4). There have been some reports of CRS due to reinfection (5 - 7). The focus of vaccination changed from junior high school students to young children in 1995, but we do not know whether the vaccine's effect can be maintained for more than 20 years by only a single dose without a boosting effect of the wild virus by epidemic. Therefore, from this point forward, changes in the epidemiology of rubella, the occurrence of CRS, and the positive rate and antibody titer must be watched over the long-term. In addition, I propose that two doses of the vaccine should be administered at appropriate intervals in Japan.

Five rubella vaccine strains have been developed, and four of these – the Matsuba, Takahashi, TO-366, and Matsuura strains – are still being administered in Japan. These differ from the RA27/3 strain, which is used elsewhere in the world. These Japanese rubella vaccine strains are considered to be effective and to have a low adverse reaction rate. However, differences in the efficacy and adverse reactions of the Japanese strains and/or RA27/3 strain are known a little.

4. Changes in the incidence of epidemics and occurrence of CRS

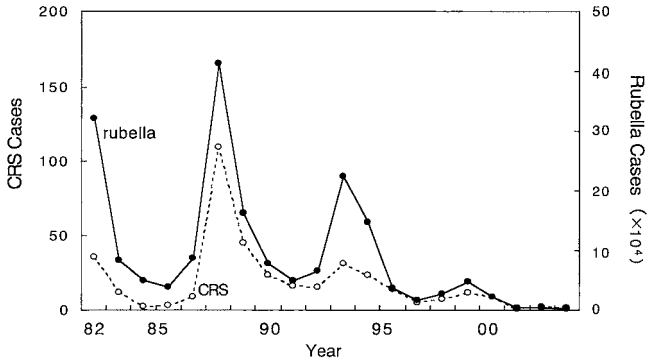
National Epidemiological Surveillance of Infectious Diseases, including rubella, by approximately 3,000 collaborating clinics throughout Japan was begun in 1981, but surveillance for CRS was not included until 1999. Each week, the occurrence of specific infectious diseases has been analyzed and reported. The diagnosis is generally made clinically, but it is not necessarily confirmed serologically or by polymerase chain reaction (PCR). The results of the surveillance (8,9) indicate that, in the past, rubella epidemics occurred every 5 years, i.e., in 1982, 1987, and 1992, as shown in Fig. 1. Although administration of MMR vaccine was started in 1989, the peak of incidence in 1992 was only slightly lower than those in 1982 and 1987 due to suspension of the vaccine's use. Epidemics have been on the decrease since the revised law went into effect in 1995, because approximately 50 - 70% of young children between 12 and 90 months of age have been immunized, but the vaccination rate is still not sufficient to control rubella infection. The total number of rubella cases reported by the 3,000 clinics was 35,883 - 411,772 cases per year for each of the years between 1982 and 1994. The number decreased to 4,385 cases in 1999, 3,123 cases in 2000, and 2,252 cases in 2001.

In 1964 and 1965, 408 CRS cases occurred due to the epidemic of rubella in Okinawa (10,11), which was returned to Japan in 1972 after having been administered by the United States since the end of World War II. The number of CRS cases in Japan before 1999 is not precisely known, but it is estimated that there were at least 1,600 CRS cases between 1965 and 1985 based on a survey of schools for the deaf in Japan (12). In addition, according to a survey sent in questionnaire form to 923 hospitals in Japan having more than 300 beds, there were 301 CRS cases between 1978 and 1993 (13). The occurrence of CRS was compatible with the occurrence of epidemics, as shown in Fig. 2. The new Infectious Diseases Control Law, by which infectious diseases are classified into categories I to IV according to a decision based on their potential seriousness, went into effect in 1999. CRS has been classified as a category IV infectious disease in order



(Source: references 8, 9)

Fig. 1. Changes in rubella epidemics in Japan.
The numbers are the mean reported cases per hospital or clinic every week from approximately 3,000 collaborating hospitals or clinics by national surveillance.



(Source: references 8, 9)

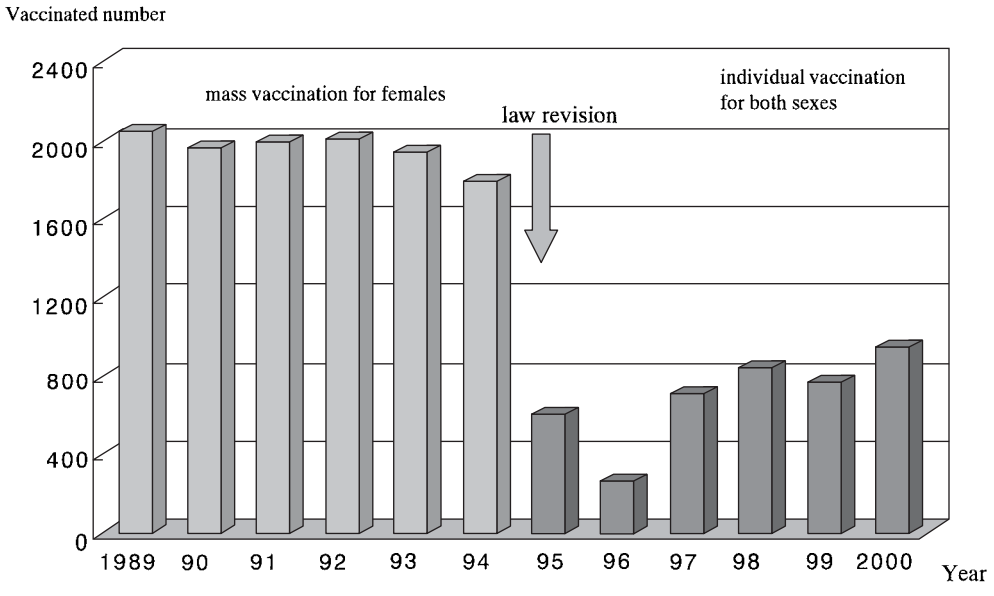
Fig. 2. Alterations in cases of rubella and congenital rubella syndrome (CRS) in Japan.
CRS cases had been estimated before the new Infectious Diseases Control Law went into effect in 1999, and then CRS was classified as a category IV infectious diseases in order to record the occurrence of all cases. Rubella cases have been reported by national surveillance.

to assure that all cases be recorded; category IV diseases must be reported to the local health department within 1 week. One CRS case was reported in 1999, three were reported in 2000, and two cases were noted in 2001. However, the reported rubella cases were not confirmed serologically or by PCR, although the diagnosis of CRS is strictly based on those criteria. The reported number of rubella cases may not necessarily reflect the actual number of cases. Rubella, unlike measles, is characterized by mild and self-limited symptoms lasting a few days, especially in children. After disappearance of the epidemic conditions, it is difficult to make a diagnosis of rubella in locally scattered cases without serological tests or PCR.

5. Alterations in the vaccination rates

Generally, vaccination rates in Japan tend to be overestimated. This is because public health centers have conventionally reported the annual vaccination rate in a region as the annual number vaccinated divided by the annual number of births without the addition of those unvaccinated. The possible period of vaccination was not 1 year and the annual vaccinated number included those after the second year. Therefore, it becomes necessary to choose the most reliable data. Governmental research is presently being done to find a good method for determining the correct vaccination rate or coverage rate.

The vaccination rate in female junior high school students was approximately 70% before passage of the revised law for vaccination in 1994 (14). Because individual vaccination replaced mass immunization in 1995, junior high school students must visit their family doctors in order to be vaccinated. However, generally these students are busy with school club activities and other after-school activities. In addition, they have no desire to be vaccinated. Thus, as a typical result of the revised law, the vaccination rate for junior high school students in Kurashiki City, Okayama Prefecture decreased from approximately 70% to 6% in 1996 (15). Since then vaccination has been promoted through lectures, schools, medical societies, and regional mass media, but the result has been only a 3.6-fold increase, which is still far from satisfactory, as shown in Fig. 3 (16). This decreasing tendency in the rubella vaccination rate has been observed in most areas in Japan since 1995. Changes in the vaccination rate based on national surveys (14,17-21) administered by a governmental study group, which are considered the most reliable, are shown in Fig. 4. The vaccination rate among junior high school students ranged from 44.4% in 1995 to 55.8% in 1999, but this was because mass vaccination was still being used in 61.4-77.4% of cities or towns. The vaccination rate for mass vaccination ranged from 67.1% in 1995 to 76.4% in 1999, while it was 17.3-34.4% for individual immunization during that period. Most of the areas using mass vaccination are rural areas, because there is a shortage of pediatricians in these



(Source: reference 16)

Fig. 3. Changes in rubella vaccination numbers for junior high school students in Kurashiki City.
The rubella vaccine was administered to female junior high school students by mass immunization at each school before 1995, but this was changed to vaccination of both sexes between 12 and 90 months of age. The vaccine has been provisionally administered to junior high school students during a transitional period from 1995 to 2003.

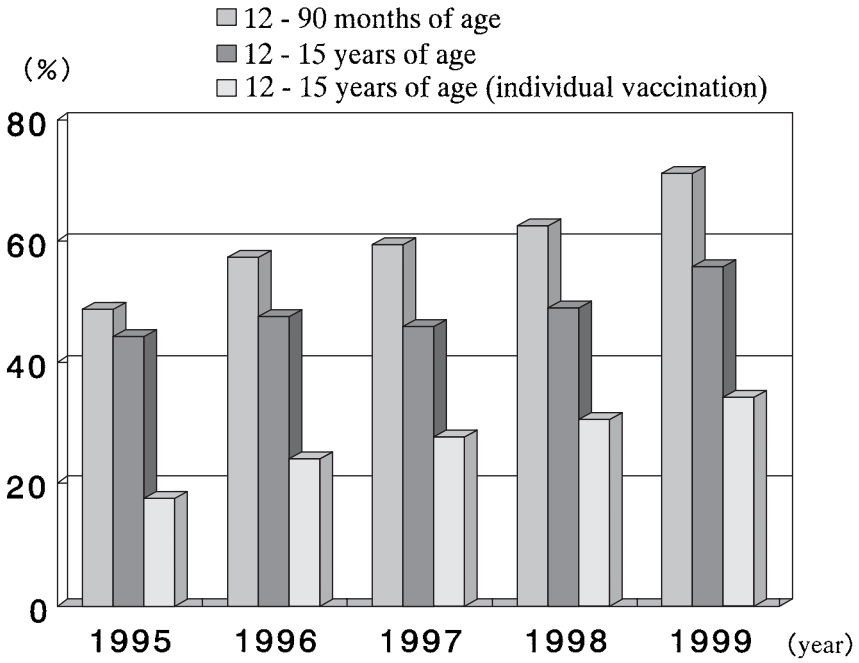


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Fig. 4. Alterations in the vaccination rate in young children and junior high school students.
Although individual vaccination replaced mass immunization after a revision of the law in 1995, mass vaccination is still carried out in rural areas because of the shortage of pediatricians. There has been a strong tendency for junior high school students to avoid vaccination, so their vaccination rates have been very low.

regions. The vaccination rate is likely to be lower in urban areas. Therefore, there should be more concern about epidemics or the occurrence of CRS in densely populated urban areas in the future.

The vaccination rate in young children between 12 and 90 months of age increased from 48.7% in 1995 to 71.2% in 1999. Our survey (22) of Kurashiki City in 2001 showed the vaccination rates to be 80.4%, 63.2%, and 33.1% at entry to kindergarten, primary school, and junior high school, respectively. The vaccination rate inversely decreases with age and will result in a lower positive antibody rate in the future, unless an epidemic takes place. At present, the rate is approximately 95% in female adults older than 23 years of age.

6. Changes in susceptibility based on antibody surveys results

Since the revised law for vaccination went into effect in 1995, the number of rubella cases has decreased. A comparison of the positive antibody rates in each age group in 1995 and 2001 (9,23), as shown in Fig. 5, suggests that this reason is due to a decrease in epidemics changes in the vaccination rate. For example, the positive antibody rate for children 3 years of age increased from approximately 30% in 1995 to 80% in 2001.

Every year, our group has measured the rubella antibody levels in nursing students using an enzyme immunoassay in order to prevent nosocomial infection. The results (24) showed the negative antibody ratio to be 4/116 (3.4%) in students born in 1977 or 1978, who were vaccinated by mass immunization, but 37/267 (14.1%) in students born between 1980 and 1983, who were immunized by individual vaccination. A national antibody survey of 8,000 pregnant women by obstetricians and gynecologists (25), the results of which are shown in Fig. 6, revealed that, in women younger than 22 years, age

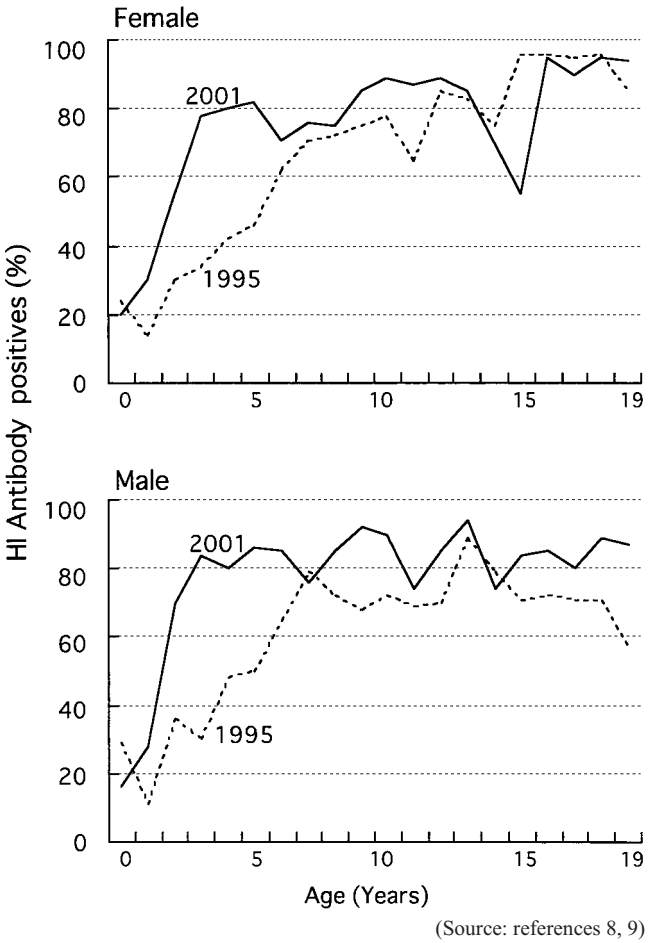

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Fig. 5. Comparison of positive rubella antibody rates in each age group in 1995 and 2001.
Approximately 2,000 subjects were measured using a HI assay.

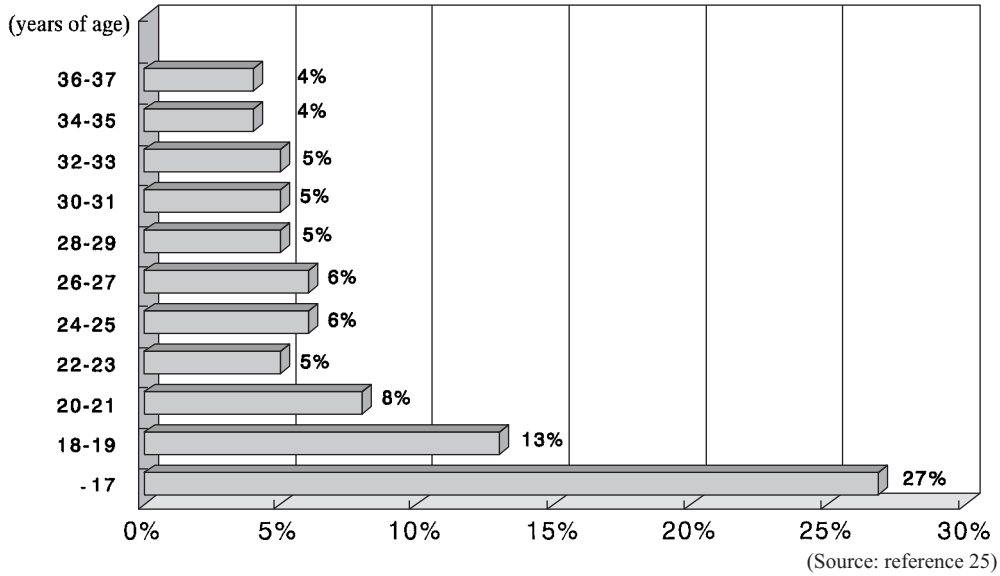

Fig. 6. Negative rubella antibody rates for pregnant women.
This national survey of rubella antibody titers in 8,000 pregnant women was performed in 2002 by obstetricians and gynecologists using the HI assay.

was proportional to the negative antibody rate as measured by hemagglutination inhibition assay. These increases in susceptibility to rubella are related to the decreased vaccination rate in junior high school students and the decreased number of epidemics after 1995.

7. Effectiveness of measures taken in Okayama Prefecture

Since the report of the remarkable decrease in the vaccination rate for junior high school students in Kurashiki City, vaccination has been promoted through lectures, schools, medical societies, and regional mass media. However, the results have been unsatisfactory. The students are apparently avoiding injection. Although we deliver a note about rubella vaccination to students through their teachers to be given to their parents, a recent survey indicated that many parents had not read or, in some cases, had not received it. Even when parents had read the note, many found it difficult to make their sons or daughters see a doctor for vaccination. As a potential method to overcome this problem, our study group showed an educational videotape to all of the junior high schools in Okayama Prefecture. The result, however, was that only 11.5% of those who are susceptible were vaccinated after watching the videotape (26). This increased rate is compatible with the conjoint analysis-based estimate of an increase following a strong educational campaign (27), and with our own campaign experience in a hospital in the past (28,29). I believe that many kinds of campaigns are necessary but still may be insufficient, and that their effects may frequently be temporary. Since vaccination is not compulsory under Japanese law, a new system is required to develop motivation for vaccination. Since 2002, we have advocated checking children for susceptibility, recommending vaccination, and then asking for certificates of vaccination upon school entry in Kurashiki City, and we feel there have been good results with this new system.

8. Changes in vaccinated numbers after a new law revision in 2001

The government made a revision to the Preventive Vaccination Law in 2001 to improve the vaccination rate among junior high school students. Rubella vaccination is available to all subjects who were born between April 2, 1979 and October 1, 1987 for a transitional period between 1995 and 2003. However, most people, including doctors and parents, are not aware of this revision, since no national campaign was carried out in conjunction with this revision. In our hospital the number of newly vaccinated subjects was only three during 10 months, and the total vaccinated number was 99 in Kurashiki City, which was estimated at best to be 1.6% of the subjects who should be vaccinated (24). A survey in Okayama Prefecture for a tentative period of 7 years showed the vaccination rate to be 14.5% (26). Mass vaccination is still used in 16.7% of the towns in Okayama Prefecture, where the vaccination rate is approximately 80%. This tentative period will end on September 30, 2003. Therefore, the government should promote major vaccination campaigns as soon as possible.

9. Problems in the future

There have been no rubella epidemics in Japan since 1995. This situation may continue until the number of susceptible subjects reaches epidemic proportions. However, the vaccination rates in junior high school students have been less than 35%, especially in urban areas, where individual vaccination has replaced mass immunization. These children are at risk for passing on CRS even now, because they are from 15 to 23 years of age and some of them are of childbearing age, and because they live in densely populated urban areas. Two separate strategies will be needed to reach subjects who did not receive vaccination during the transitional period and to reach young children. We hope that it will become possible to vaccinate subjects twice for rubella with either the MR or MMR vaccine in the future.

10. Conclusion

1) The reported vaccination rates in Japan have been incorrect.
2) National surveillance for rubella is performed by clinical diagnosis. However, rubella is difficult to diagnose in scattered cases. Rubella cases should be confirmed serologically or by PCR, because there have been no rubella epidemics since 1995.
3) There are four rubella vaccine strains in Japan, but the differences in their efficacy and adverse reaction rates have not been adequately clarified.
4) Rubella vaccination is performed using a monovalent vaccine, and is given only once during the lifetime of the individual in Japan. Vaccination should be done twice at appropriate intervals.
5) The vaccination rate for junior high school students has been very low, especially in urban areas where individual immunization has replaced mass vaccination.
6) The vaccination rate in young children is currently unsatisfactory.
7) There has been no significant increase in vaccination since a revision of the Preventive Vaccination Law in 2001.
8) Vaccination campaigns are necessary but have been insufficient. A new system of motivating individuals to seek vaccination will be needed in order to maintain a high vaccination rate without campaigns.

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