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Changes in the prevalence of the measles, rubella, varicella-zoster, and mumps virus antibody titers in Japanese pregnant women

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ABSTRACT

In the present study, immunity against infectious diseases, which are capable of influencing both the mother and fetus during pregnancy and the infant in the postnatal period, were assessed in pregnant women to elucidate the necessity of vaccination during the childbearing age. It was determined that there was a trend of increases in the proportion of patients that had low antibody titers observed at a young age. Overall, after adjusting for age, low antibody titers of measles (≤4 via the neutralization test [NT]), rubella (≤16 via the hemagglutination inhibition [HI]), and varicella and mumps (plus minus or negative on the enzyme-linked immunosorbent assay [EIA]) indicated that the rates of necessity for vaccination against measles, rubella, varicella, and mumps were 27.6%, 16.1%, 3.9%, and 23.8%, respectively. In Japan, acquired immunity for measles, rubella, and mumps was dependent on vaccination, whereas acquired immunity for varicella was dependent on natural infection. We recommend that women be vaccinated after delivery, as these vaccines are live, and thereby, are contraindicated during pregnancy.

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1. Introduction

Understanding the seroprevalence of viral antibodies is important not only for preventing viral infections in the local area, but also several infectious diseases that are capable of influencing the mother and fetus during pregnancy and the infant in the postnatal period. Viral infections during pregnancy can aggravate the mother, and lead to abortion, preterm delivery, growth retardation, malformation, and/or congenital infection of the fetus. Acquired immunity, transferred from the mother to the fetus though the placenta, continues to protect the baby from infections up to approximately 6 month after delivery [1,2]. Furthermore, acquired immunity in the mother protects against child-to-mother infections during nursing and provides protection and stability following pregnancy.

Antibody titers against viruses are affected by the patient's history of both natural infections and immunizations, and are country dependent. With respect to the history of immunizations in Japan (Table 1), the measles vaccine was initiated in 1966 and adopted into the regular national immunization program from 1978 onwards. In Japan, a single-antigen, live attenuated vaccine is inoculated only once in children aged 12–72 months, with an approximately 70% coverage rate. The measles vaccine has been incorporated into the measles, mumps, and rubella (MMR) vaccine since 1989; however, the MMR vaccination was terminated in 1993 due to the adverse effects of aseptic meningitis resulting from the mumps vaccine. In 1994, the vaccination policy was changed from being compulsory to becoming voluntary, and consequently, the coverage rate thereafter has been lower than that of other countries [3,4]. In 2006, the measles–rubella (MR) vaccine, a two-dose vaccination administered at 1 and 5–6 years of age, was introduced [5]. Moreover, the rubella vaccination program was initiated for women aged 12–<16 years (junior high school students) in 1977, and then the MMR vaccination for children was initiated in 1989 [6]. The MMR vaccination was terminated in 1993, as described above, and the rubella vaccination was then continued as a monovalent rubella vaccine until 1994. Thereafter, the rubella vaccination was no longer administered to junior high school students, but instead to children. Although the coverage rates of MMR and monovalent rubella vaccines are unclear, it appears that these rates have been sufficient in preventing outbreaks of rubella among children, and no significant epidemics have been observed since 1999. However, a local outbreak of rubella among young adults was observed in recent years, with 10 cases of congenital rubella syndrome reported in 2004 [6,7]. The varicella-zoster vaccine was started in 1987 as a voluntary vaccination, and currently has a coverage rate of

Abbreviations: NT, neutralization test; HI, hemagglutination inhibition; EIA, enzyme-linked immunosorbent assay.

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Table 1
The history of the immunization of measles, rubella, varicella-zosters and mumps vriuses in Japan.

Vaccine	Start		Target age group	Progress	Compulsory	Dose[a]	Coverage rate (approximately %)
	Year	Birth year					
Measles and rubella	1966	1960–1965	12–72 months	Measles vaccination was started	No	1	–
	1977	1962–1965	12–<16 yesrs	Routine rubella vaccination program for junior high school girls was started	Yes	1	70%
	1978	1972–1977	12–72 months	Routine measles vaccination program for children was started	Yes	1	70%
	1989	1983–1988	12–72 months	MMR vaccination program for children was started	Option	1	–[b]
	1993	1987–1992		MMR vaccination program was terminated because of an adverse effect (aseptic meningitis) of the mumps vaccine			
	1994	1986–1993	12–90 months	Measles and rubella vaccinations were continued as monovalent vaccines and the targeted age group for the rubella vaccination was changed from junior high school students to elementary school students.	Yes	1 1	Measles 70–80% Rubella 50–60%
	2006	2005	1st: 1 year 2nd: 5 to <7 years	MR vaccine was started	Yes	2	95%
Varicella-zosters	1987	–1986	12 months or later	Varicella-zosters vaccine was started	No	1	30% (present)
Mumps	1981	–1980	12 months or later	Mumps vaccine was started	No	1	–
	1989	–1988	12 months or later	Mumps vaccine was incorporated into the MMR vaccination program	Option	1	–[b]
	1993	–1992	12 months or later	Discontinued for the same reason as mentioned above for the MMR vaccination program, and continued as a voluntary vaccination	No	1	30%

[a] All vaccines were used to perform in single dose before MR vaccine was introduced as two doses in 2006.
[b] Coverage rate of MMR vaccine was unclear because the vaccination program was started from 1989 as an option in parallel with each monovalent vaccine.

approximately 30% [8]. The mumps vaccine was initiated in 1981, and incorporated into the MMR vaccine program between 1989 and 1993. After discontinuing the MMR vaccine program, the mumps vaccine became a monovalent vaccination [9,10].

In the present report, we analyzed the titers of antibodies against measles, rubella, varicella-zoster, and mumps viruses of pregnant women, who later delivered children at our institute located in Japan, and evaluated the changes in the prevalence of antibody titers according to the birth years of the mothers.

2. Materials and methods

2.1. Study design

We retrospectively surveyed the prevalence of measles, rubella, varicella-zoster, and mumps virus antibody titers of 13,924 Japanese pregnant women, who sought antenatal care at the National Center for Child Health and Development in Tokyo, Japan.

2.2. Neutralization test for determining the measles antibody titer

The measles antibody titer was determined via a neutralization test (NT). Virus suspensions containing the 100 median tissue culture infectious dose ($TCID_{50}$) were added in serially double-diluted serum, and the mixtures were incubated at 37 °C for 60 min while shaking. The virus-serum mixtures were inoculated onto monolayers of VERO cells in 96-wells plate (NUNC, Thermo Fisher Scientific Inc., Penfield, NY, USA), incubated at 35 °C for 3 days, and then the cytopathic effect (CPE) was assessed. The antibody titer was determined as the highest dilution of serum that produces a 50% or more inhibition in CPE. Measles NT antibody titers of 1:8 are approximately equivalent to >500 mIU/ml [11].

2.3. Hemagglutination inhibition (HI) test for measuring the rubella antibody titer

The rubella HI test was performed on U-bottom microtiter plates (Corning, Corning, NY, USA) with goose erythrocytes and the Baylor strain as the antigen. Serum were pretreated with 12.5% of kaolin in PBS at 15–25 °C for 20 min, and adsorbed into 25% of goose erythrocytes at 4 °C for 60 min with occasional shaking. Two-fold serial diluted sera were incubated in 4 U of hemagglutinin and 0.125% of goose erythrocytes at 15–25 °C for 60 min. The titers of the specific antibodies were determined at the final dilutions that completely inhibited hemagglutination. Rubella HI antibody titers of 1:16 are approximately equivalent to 30 IU/ml [12].

2.4. Enzyme-linked immunosorbent assay for measuring the varicella-zoster and mumps antibody titers

Varicella-zoster and mumps antibody titers were measured using an enzyme-linked immunosorbent assay (EIA). 96-Well

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