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WEEKLY EPIDEMIOLOGICAL SURVEILLANCE REPORT

วัคซีน

RUBELLA
Vaccination during pregnancy

UNITED STATES OF AMERICA. — From January 1971 through December 1986, the Centers for Disease Control (CDC) received reports of 1 176 pregnant women who were given live attenuated rubella vaccine either within 3 months before or 3 months after their presumed dates of conception. These women were followed prospectively to determine the risk of fetal abnormalities after exposure to 3 types of licensed vaccine.

Cendehill and HPV-77 vaccines. Before April 1979, data were collected on 538 women vaccinated during pregnancy with either Cendehill or HPV-77 rubella vaccines. None of the 290 infants born to these women had defects indicative of congenital rubella syndrome (CRS); however, 8 infants had serological evidence of intrauterine infection. Three other women who received unknown strains of rubella vaccine delivered healthy infants who appeared normal.

RA 27/3 vaccine. Since licensure of the RA 27/3 rubella vaccine in January 1979, CDC has received reports of 635 women who were given this vaccine during pregnancy *(Table 1)*. Two hundred and twenty-four of these women had negative serological testing for rubella within 12 months of vaccination and were, therefore, susceptible at the time of vaccination. Outcomes of pregnancy are known for 211 (94%) of these susceptible women. Of the 211 women, 170 (81%) delivered 172 living infants. An additional 30 immune women and 319 women of unknown immune status delivered 350 living infants. All of these 522 infants were free of defects indicative of CRS. Outcomes of the 116 pregnancies that did not result in known live births are presented in *Table 1*.

The dates of vaccination and estimated dates of confinement were known for all of the 170 susceptible women who had full-term pregnancies. Fifty-five women (32%) were vaccinated within 1 week before to 4 weeks after conception, the period of presumed highest risk for viraemia and fetal malformations.

Serological evaluations were performed on 136 (79%) of the 172 infants whose mothers were susceptible. Three (2%) of the 136 infants had normal examinations but measurable titres to rubella-specific IgM in cord blood, initially suggesting a subclinical infection. Prior to July 1985, the CDC laboratory performed haemag-

glutination inhibition (HI) tests for both rubella-specific IgM antibody and total rubella antibody titres. Such testing revealed that 1 infant who appeared normal had a rubella-specific IgM antibody titre of 8 in cord blood and a corresponding total rubella antibody titre of 128. The mother's total rubella antibody titre was also 128. Simultaneous retesting of cord blood and testing of a follow-up specimen taken when the infant was 2 months old showed a decrease in the titre of maternally derived antibody from 64 to 16 over the 2-month period, suggesting that subclinical infection may not have occurred. The infant had no evidence of defects indicative of CRS either at birth or at the 18-month and 29-month follow-up examinations. Sera could not be obtained for further follow-up testing to measure HI antibodies.

Since July 1985, the CDC laboratory has tested for rubella-specific IgG antibody using an indirect enzyme-linked immunosorbent assay (ELISA). Rubella-specific IgM antibodies were detected by ELISA using the same antigen-coated plates, but with an enzyme-conjugated anti-human IgM serum. For IgM testing, sera were adsorbed with staphylococcal protein A to remove IgG and to eliminate interference by rheumatoid factor. An IgM index was calculated for each serum using a known low-positive IgM serum as a reference standard. An IgM index ≥ 1.0 was considered positive, with increasing values indicating higher antibody levels. Using these tests, it was found that 2 additional infants who appeared normal had cord sera that were positive for rubella IgM.

Table 1. **Pregnancy outcomes for 635 recipients of RA 27/3 vaccine, United States of America, January 1979-December 1986**

Prevaccination immunity status	Total women	Live births	Spontaneous abortions and stillbirths	Induced abortions	Outcome unknown
Susceptible . . .	224	172[a]	11	30	13
Immune . . .	32	30	1	—	1
Unknown	379	320[b]	8	24	28
Total	**635**	**522**	**20**	**54**	**42**

[a] Includes 2 twin births.
[b] Includes 1 twin birth.

Serological studies were also obtained on 156 of the 320 infants *(Table 1)* born to mothers whose immune status was unknown at the time of vaccination. Subclinical infection was documented in 2 infants. One infant had a rubella-specific HI IgM antibody titre of 16 in cord blood. Both mother and infant had titres of 32 by HI at the time of birth; the infant still had a titre of 32 at 4 months of age. This infant had no evidence of defects indicative of CRS at birth or at the 10-month and 17-month examinations. A serum specimen was not obtained at subsequent follow-up visits. The second infant had a persistent HI titre of 8 at 3 months of age, suggesting that there had been subclinical infection. This infant was diagnosed as normal at the 3-month follow-up examination.

While none of the 172 infants born to susceptible women had defects indicative of CRS, 2 infants did have asymptomatic glandular hypospadias. However, both had negative rubella-specific IgM titres (< 4) in cord blood at birth. Serum taken at the 6-month follow-up examination was available for one of the infants; he had a rubella-specific HI antibody titre of < 8 (i.e., a negative titre).

Thirty susceptible women elected to have induced abortions *(Table 1)*. Products of conception were available for viral isolation studies from 19 of these women, from 2 women who spontaneously aborted, and from 13 women whose case histories have been reported in the literature. Rubella virus has been isolated from the products of conception of 1 (3%) of these 34 susceptible women.

MMWR EDITORIAL NOTE: Since 1971, CDC has maintained a register to monitor and quantitate the risks to the fetus of exposure to live attenuated rubella vaccine virus. Data are obtained through reports from physicians and state and local health departments as well as directly from women vaccinated either within 3 months before or 3 months after conception. Follow-up study is conducted to determine the outcome of each pregnancy. In 1979, when RA 27/3 rubella vaccine replaced the other rubella vaccines, there was concern that it might have greater fetotropic and teratogenic potential than earlier vaccines. Data collected so far show that the RA 27/3 rubella vaccine, like the other vaccines, has not caused defects compatible with CRS.

Fifty-five (32%) of the 170 susceptible mothers were vaccinated with RA 27/3 vaccine during the highest risk period for viraemia and fetal defects (1 week before to 4 weeks after conception). Neither the infants born to these high-risk women nor those born to any of the other women had CRS. Therefore, the observed risk of CRS following rubella vaccination continues to be zero *(Table 2)*. However, based on the 95% confidence limits of the binomial distribution, the theoretical maximum risk for the occurrence of CRS in this group of 172 children could be as high as 2.1%. If the 95 infants exposed to other rubella vaccines are included, the maximum theoretical risk is 1.4% *(Table 2)*. This overall maximum risk remains far less than the 20% or greater risk of CRS associated with maternal infection with wild rubella virus during the first trimester of pregnancy and is no greater than the 2%-3% rate of major birth defects in the absence of exposure to rubella vaccine.

Table 2. **Maximum theoretical risks of congenital rubella syndrome (CRS) following rubella vaccination, by vaccine strain, United States of America, 1971-1986[a]**

Vaccine strain	Susceptible vaccinees	Normal live births	Risk of CRS	
			Observed	Theoretical
RA 27/3	170	172[b]	—	0%-2.1%
Cendehill or	94	94	—	0%-3.8%
Unknown	1	1	—	—
Total	**265**	**267**	—	**0%-1.4%**

[a] Through 31 December 1986. No women entered after 1980 in CDC's register of those receiving rubella vaccine within 3 months before or after conception were vaccinated with Cendehill or HPV-77 vaccine.

[b] Includes 2 twin births.

These favourable data are consistent with the experiences in the Federal Republic of Germany and the United Kingdom. The vaccine has not been associated with the occurrence of CRS among infants born to susceptible mothers who had been vaccinated in either country. In the Federal Republic of Germany, 98 susceptible women vaccinated with either the Cendehill or RA 27/3 strain of vaccine gave birth to infants without CRS. In the United Kingdom, none of 21 infants born to susceptible mothers (not all of whom were prospectively followed) had defects compatible with CRS.

The occurrence of any congenital defect following maternal vaccination deserves careful analysis and follow-up. In the United States, 2 infants born to susceptible mothers had asymptomatic glandular hypospadias. While hypospadias has been noted in CRS cases, there are no data to suggest that glandular hypospadias should be considered a CRS-associated defect. In any case, neither of the 2 infants in question had serological evidence of rubella virus infection. Eight other infants born to mothers of unknown immune status and 2 born to mothers known to be immune at the

time of vaccination had some type of defect. However, none of the defects were compatible with CRS, and serological testing, when done, did not confirm rubella virus infection.

While no CRS-like defects have been noted, it is clear that rubella vaccine viruses, including the RA 27/3 strain, can cross the placenta and infect the fetus. Approximately 1%-2% of infants born to susceptible vaccinees had serological evidence of subclinical infection, regardless of vaccine strain. On the other hand, while the rubella virus isolation rate from the products of conception of women who have received the RA 27/3 vaccine is only 3% (1 out of 35), the rate of virus isolation from the products of conception of those receiving Cendehill and HPV-77 vaccines is 20% (17 out of 85). These data indicate that the risk of placental or fetal infection for RA 27/3 vaccine is low.

Recognizing that no amount of data collection can absolutely rule out a theoretical risk to the fetus, however small, the Immunization Practices Advisory Committee (ACIP) continues to state that: *(1)* pregnancy remains a contraindication to rubella vaccination because of the theoretical, albeit small, risk of CRS; *(2)* reasonable precautions should be taken to preclude vaccination of pregnant women, including asking women if they are pregnant, excluding those who say they are, and explaining the theoretical risks to the others; and *(3)* because the risk of CRS is so small as to be negligible, rubella vaccination of a pregnant woman should not ordinarily be a reason to consider interruption of pregnancy, even if vaccination does occur within 3 months of conception.

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สถานการณ์โรค

		โรคติดต่ออันตราย อหิวาตกโรค ป่วย	ตาย
เอเชีย			
สิงคโปร์	8 - 14 พ.ย.	1	0
อิหร่าน	9 - 15 พ.ย.	67	1

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