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Rubella in the United States: toward a strategy for disease control and elimination

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INTRODUCTION

More than 25 years have passed since the last rubella epidemic in the United States. The rubella pandemic of 1964–5 demonstrated clearly the extraordinary teratogenic potential of the rubella virus. In the United States alone, it is estimated that more than 12500000 cases of rubella occurred during the winter and spring of 1964–5. Congenital rubella infection occurred in an estimated 30000 pregnancies, 10000 resulting in fetal death or therapeutic abortion and 20000 resulting in infants born with congenital rubella syndrome (CRS) [1]. In contrast, during 1988, only 225 cases of rubella were reported to the Centers for Disease Control (CDC) in Atlanta, the lowest annual total since rubella became a nationally notifiable disease in 1966 [2]. However, in 1989, this downward trend of reported cases was interrupted, with the number of reported rubella cases in the United States increasing nearly twofold, and in 1990, the total increased another threefold (to more than 1000 cases) [3]. Although the 1990 reports represent the highest total since 1982, the overall incidence of rubella in the United States has still declined by more than 98% since 1969, the year rubella vaccine was licensed (Fig. 1).

EPIDEMIOLOGIC PATTERNS OF RUBELLA AND CRS

Before the licensing of rubella vaccine, rubella was a common childhood rash disease in the United States. Presently it can often be overlooked or misdiagnosed because its signs and symptoms are usually mild and variable. The common postauricular and suboccipital lymphadenopathy, transient erythematous and sometimes pruritic rash, and low-grade fever may not be recognized as rubella. Similar exanthematous illnesses are caused by adenoviruses, enteroviruses, parvovirus, and other common respiratory viruses. Moreover, up to 30% of rubella infections are subclinical and many go undetected.

Prior to the widespread availability and use of rubella vaccine in the 1970s, rubella in the United States was episodic, with epidemics occurring at roughly 6- to 9-year intervals. Major epidemics occurred in the United States in 1935, 1943, and 1964, with periods of high incidence in 1952 and 1958 (Fig. 2). Since the initiation of rubella immunization in 1969 there have been no rubella epidemics in the United States although the provisional 1990 reports to CDC indicate a moderate resurgence of rubella, particularly in young-adult age groups.

Many of the rubella outbreaks in 1990 occurred in settings in which adolescents

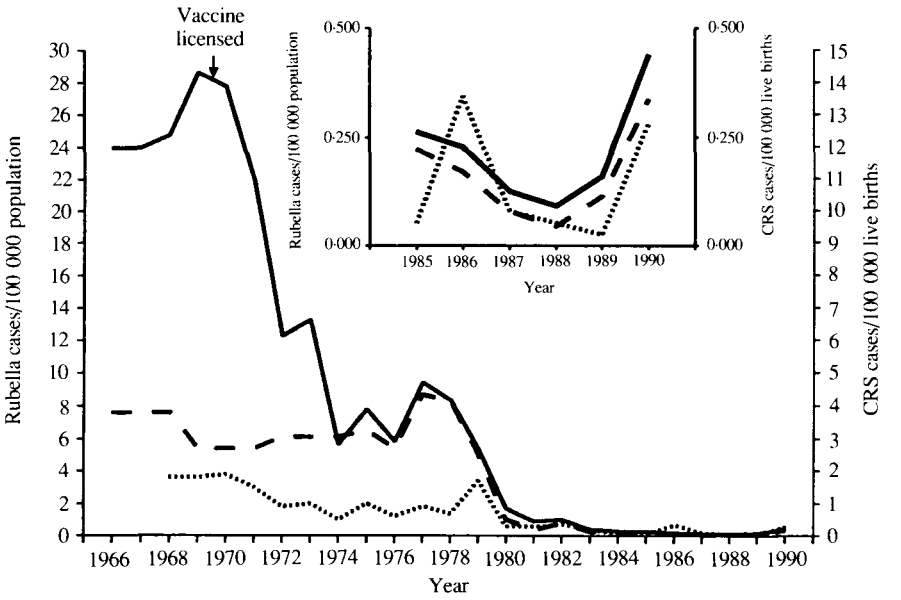

Fig. 1. Incidence rates of reported rubella and congenital rubella syndrome (CRS), United States, 1966–90. All cases were reported to the National Congenital Rubella Syndrome Registry; data for 1990 are provisional. ....., CRS; ---, Rubella, ⩾ 15-year-olds; ——, Rubella, total.

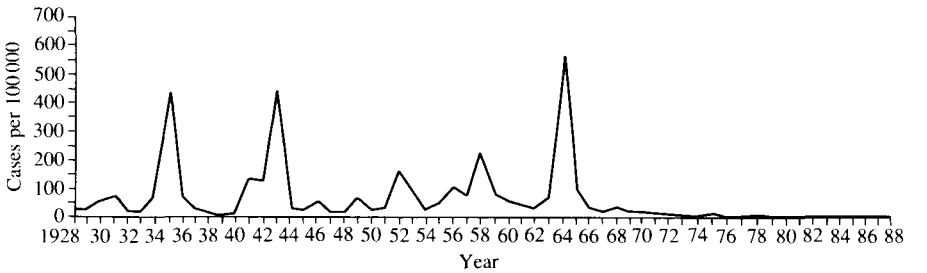

Fig. 2. Rubella incidence in 10 selected areas, United States, 1928–88. Areas are Maine, Rhode Island, Connecticut, New York City, Ohio, Illinois, Wisconsin, Maryland, Washington and Massachusetts.

and adults congregate and transmission to susceptible persons can occur. Because a substantial proportion (6–25%) of women of childbearing age in the United States are still susceptible, the observed patterns of rubella disease and transmission in 1990 cause particular concern.

STRATEGY FOR RUBELLA ELIMINATION

Rubella immunization programmes are designed to prevent maternal rubella infection and its teratogenic effects on the unborn fetus. When rubella vaccine was licensed in 1969, strategies to control congenital rubella were based on the existing understanding of the epidemiology of rubella. Prior to vaccine licensing, most rubella cases in the United States occurred among young school-aged children. The initial strategy for rubella control as recommended by the Committee on

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Infectious Diseases of the American Academy of Pediatrics [4] and the Immunization Practices Advisory Committee (ACIP) of the U.S. Public Health Service [5] was to interrupt rubella transmission by vaccinating all preschool and elementary school children of both sexes. It was reasoned that vaccination would protect children both immediately and through the childbearing years, as well as greatly reduce the circulation of the virus. Susceptible pregnant women would be protected indirectly by virtually eliminating the risk of exposure. Secondary emphasis was placed on vaccinating susceptible adolescents and young adults, especially females. By 1977, vaccination of children > 12 months of age had resulted in a marked decline in the reported rubella incidence among children and had interrupted the characteristic 6- to 9-year rubella epidemic cycle. This vaccination strategy, however, had less effect on reported rubella incidence among persons > 15 years of age, which included the childbearing ages for women. This age group subsequently accounted for more than 70% of reported rubella cases. Rubella outbreaks continued to occur in settings where young adults congregated. Approximately 10–25% of young adult women continued to be susceptible. This proportion was similar to that of prevaccine years, and reported CRS continued at a low but relatively constant endemic level (an annual average of 32 reported confirmed and compatible* cases between 1971 and 1977).

LIVE RUBELLA VIRUS VACCINE

The live rubella virus vaccine (official name: rubella virus vaccine, live) currently distributed in the United States is prepared in human diploid cell culture. In January 1979, this vaccine (RA 27/3) replaced the HPV-77 DE-5 vaccine grown in duck embryo cell culture because of higher seroresponse, greater resistance to reinfection, and a lower reaction rate. Clinical efficacy and challenge studies have shown that more than 90% of vaccinees can be expected to have protection against both clinical rubella and viraemia for a period of at least 15 years [7–10]. Based on available follow-up studies, vaccine-induced protection is long-term, probably lifelong; therefore, a history of vaccination can be considered presumptive evidence of immunity.

General recommendations

Live rubella virus vaccine is recommended in the United States for all children and susceptible adults older than 12 months of age. Vaccine should not usually be given to infants because persisting maternal antibodies may interfere with seroconversion. Initial rubella vaccination of children is commonly given in combination with measles and mumps vaccines as MMR vaccine at age 15 months.

Because a clinical history of rubella illness is not a reliable indicator of immunity, older children and young women who have not received rubella vaccine but report a history of rubella-like illness should be vaccinated unless there are contraindications. Persons can be considered immune to rubella only if they have

* A confirmed case has at least one defect in categories (A) or (B) and laboratory confirmation of rubella infection. A compatible case has any two complications listed in (A) or one from (A) and one from (B), without laboratory confirmation. (A) Cataracts, congenital glaucoma (either or both count as one), congenital heart disease, loss of hearing, pigmentary retinopathy. (B) Purpura, splenomegaly, jaundice, microcephaly, mental retardation, meningoencephalitis, radiotranslucent bone disease.

Table 1. *Pregnancy outcomes for 1241 recipients of rubella vaccine – United States, January 1971 through April 1989*

Prevaccination immunity status	Total women	Live births	Spontaneous abortions and stillbirths	Induced abortions	Outcome unknown
RA 27/3 vaccine					
Susceptible	289	229*	15	31	17
Immune	32	30	1	0	1
Unknown	379	320†	8	24	28
Subtotal	700	579	24	55	46
Cendehill or HPV-77 vaccine					
Susceptible	149	94	6	43	6
Immune	25	22	0	3	0
Unknown	364	174	18	140	32
Subtotal	538	290	24	186	38
All vaccines‡					
Susceptible	439	324	21	74	23
Immune	58	53	1	3	1
Unknown	744	495	26	164	60
Total	1241	872	48	241	84

* Includes three twin births.
† Includes one twin birth.
‡ Includes three women (one susceptible, one immune, and one of unknown immune status) who received an unknown strain of rubella vaccine; all three women gave birth.

documented (1) laboratory evidence of rubella immunity or (2) immunization with at least one dose of rubella vaccine on or after the first birthday.

Vaccination of women of childbearing age

The ACIP has weighed several factors in developing recommendations for vaccinating women of childbearing age against rubella [11]. Although there may be concern about giving rubella vaccine during pregnancy, data on previously and currently available rubella vaccines indicate that the risk of teratogenicity from live rubella vaccines is small. From January 1971 to April 1989, CDC collected data on 324 infants born to 321 susceptible women who had inadvertently received rubella vaccine up to 3 months before conception or during the first trimester of pregnancy (Tables 1 and 2). Ninety-four of the mothers had received the previously used Cendehill or HPV-77 vaccines, one received vaccine of unknown strain, and 226 received RA 27/3 vaccine. None of the infants born had defects indicative of CRS. Three of the infants born to mothers who had received Cendehill or HPV-77 vaccines and two of those born to RA 27/3 vaccine recipients had laboratory evidence of subclinical fetal infection, but none of the five had illness or defects. Although the observed risk of congenital malformations after rubella vaccination with RA 27/3 is zero, the theoretical risk may be as high as 1·6% (Table 2). The risk is substantially less than the estimated 20–50% risk of CRS associated with natural rubella infection of women during the first trimester of pregnancy [12]. Reasonable precautions, however, should still 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. The ACIP, which recommends immunization policy in the United

Table 2. *Maximum theoretical risks of congenital rubella syndrome (CRS) following rubella vaccination in known susceptible women, by vaccine strain, United States, January 1971–April 1989**

Vaccine strain	Susceptible vaccinees	Normal live births	Risk of CRS	
			Observed	Theoretical
RA 27/3	226	229†	0	0%–1.6%
Cendehill or HPV-77	94	94	0	0%–3.8%
Unknown	1	1	0	—
Total	321	324	0	0%–1.2%

* No women entered in the register after 1980 were vaccinated with Cendehill or HPV-77 vaccine.

† Included three twin births.

States, has stated that the inadvertent vaccination of a woman within 3 months before or after conception should not ordinarily be a reason in itself to consider interruption of pregnancy, since the risk of CRS is so small as to be negligible. The pregnant patient and her physician should make the final decision.

Side effects and adverse reactions to rubella vaccination

More than 180 million doses of rubella vaccine have been distributed in the United States since licensing of the vaccine in 1969. Reports to CDC of significant adverse reactions to the vaccine have been rare. After receiving rubella vaccine, mild rubella-like symptoms such as low-grade fever, rash, and lymphadenopathy are not unexpected. More severe or lasting adverse side reactions such as severe joint pain or transient arthritis with visible joint swelling and redness have rarely been reported after rubella vaccination. Early experience in the United States with the HPV-77 DK12 strain vaccine revealed such an increase of postvaccination rubella-like symptoms, including arthralgia and frank arthritis, resulting in its voluntary withdrawal from the market in 1970. The RA 27/3 strain vaccine replaced all HPV-77 vaccines in the United States market in 1979 because it was more immunogenic and caused relatively fewer adverse side reactions [13].

When joint symptoms do occur following rubella vaccination, they generally have been observed to begin 1–3 weeks after vaccination, persist 1 day to 3 weeks, and rarely recur. Adults with joint symptoms after rubella vaccination usually have not had to alter their work activities. On rare occasions, such vaccinees reportedly have developed chronic or recurrent arthralgias, sometimes with arthritis or neurologic symptoms, including paraesthesias, carpal tunnel syndrome, and blurred vision [14]. One group of investigators in Canada has reported that the incidence of persistent or recurrent frank arthritis following rubella vaccination is as high as 5–11% in small studies of adult female vaccinees [15, 16]. This rate is higher than the background annual rate of chronic arthritis in adult women due to all causes; data from the National Health Interview Survey conducted by the National Center for Health Statistics, CDC, indicate that 2% of persons younger than age 34 years and 11% of persons aged 35–44 years have consulted a physician within the last year for arthritis [17]. Passive surveillance systems in the United States have to date failed to show an association of chronic

joint problems with rubella vaccination. However, to investigate the Canadian reports more definitively, a prospective study of persistent or recurrent arthropathy and other potential adverse events following rubella vaccination of adult women is being initiated by the U.S. Public Health Service.

ONGOING EFFORTS TO ELIMINATE RUBELLA AND CRS

The strategy to eliminate rubella in the United States continues to depend on the combined efforts of paediatricians, family practitioners, obstetricians, internists, hospital administrators, school administrators, and public health workers. To succeed, this strategy requires (1) the achievement and maintenance of high immunization levels from preschool through young adulthood, (2) the development of strong surveillance programmes, and (3) aggressive outbreak control. Knowledge accumulated since 1969 indicates that previous concerns about possible waning of immunity after childhood vaccination and about vaccinating postpubertal women are no longer warranted. Recent rubella outbreaks in the United States have occurred primarily among unvaccinated children and young adults. Transmission has generally been associated with places where children and young adults congregate, such as day-care centres, schools, and places of employment. Hospitals and prisons have also been the focus of recent rubella outbreaks. Intensified efforts must be made in coming years to reach these undervaccinated populations if we are to be successful in eliminating rubella and CRS in the near future.

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