RUBELLA VACCINATION[1]

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Campaigns for vaccination against rubella vary considerably from place to place. Several different vaccines are widely used, different population groups are often vaccinated, and the campaigns themselves frequently have different goals.

Introduction

The public health importance of rubella has been established since 1941, when the late Sir Norman Gregg found a link between congenital defects and history of maternal rubella. These findings were subsequently confirmed by many other investigators. In 1962 the rubella virus was isolated by Parkman et al. (*1*) and by Weller and Neva (*2*) in cell cultures, which made possible the development of vaccines against the disease. Since then rapid progress has been made in this field.

Several live vaccines are currently licensed in the United States of America and in various European countries, while others have undergone study. In the United States alone more than 50 million children have already been immunized with one or another of four vaccine preparations.

Vaccines

HPV 77 DE 5. This vaccine, started from African green monkey kidney (GMK) cell culture at the 77th passage level, has been produced through five additional passages in duck embryos (*3*). It has been widely used in the United States and other countries.

Cendehill. The virus was isolated in GMK, propagated three times in the same cell, and then transferred to primary rabbit kidney (PRK), in which 50 serial passages were performed for attenuation (*4*). Cendehill vaccine is licensed in many countries and is widely used.

RA 27-3. The virus was cultured on an explant of human embryonic tissue obtained from an infected fetus and then serially passed 25 times in a human diploid cell line (WI-38), including a limiting dilution passage. The vaccine was first licensed in the United Kingdom and other European countries and later in the United States.

To-336. The virus was isolated by GMK cell culture from a case of German measles in Japan, where the congenital rubella syndrome is rarely found. It was attenuated through serial passages, including limiting dilution passages, in primary guinea pig kidney cells and then transferred to PRK (*6*, *7*). The final vaccine preparation is produced on PRK after three passages. It has been tested in about a thousand children and adults and will soon be licensed in Japan.

Leningrad 8/23. The virus was attenuated by 23 passages in PRK. The vaccine has been used in the USSR (*8*), but little information about it is available to the author.

Immunogenicity and Side Effects

All the vaccines listed above are considered satisfactory with regard to seroconversion and low frequency of adverse side

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effects. The results of many comparative field trials (*7*, *9*) have shown Cendehill vaccine to produce a lower geometric mean titer of hemagglutination-inhibition antibody than the vaccines HPV 77 DE 5, RA 27-3, or To-336. The incidence of rash, lymphadenopathy, and joint involvement is somewhat greater with HPV 77 DE 5 and RA 27-3.

The RA 27-3 vaccine has been reported to elicit an IgA antibody response in nasal secretions, especially when administered intranasally. It has also been found to prompt the production of rubella complement-fixing and precipitating antibodies in vaccines just as a natural infection does—a result which has not been obtained with the HPV 77 DE 5 or Cendehill vaccines (*10*).

Reactions in the joints, most frequently in the knee, usually arise two to four weeks after vaccination and may last from one to seven days. Such reactions are generally experienced by 5 to 10 per cent of the vaccinees. It is well known that reactions in the joints occur most frequently in adult women, and the small joints of the hand are especially likely to be involved. Long-term reactions in the joints, lasting over a year, are rarely seen. Peripheral neuropathy has been known to occur, starting four to seven weeks after vaccination, but its frequency is very low—approximately one case in 10,000 vaccinations.

Vaccination Programs

General Strategy

So far two main approaches have been adopted in the national programs:

- Protection of females between the ages of 10 and 14, together with susceptible women of childbearing age who have no detectable rubella HI antibody.
- Routine immunization of all children from one to 12 years of age (antibody responses are poorer among infants under 10 months of age) with a view to ultimately eliminating the disease entirely (*11*), as well as of susceptible women of childbearing age who have no detectable rubella HI antibody.

The first approach is designed to utilize immunity acquired by natural infection along with that stemming from vaccination. It has been adopted by many European countries.

The second method, which appears to have been successful, has been used in the United States. So far, an epidemic rise in the incidence of rubella, which was predicted to occur in that country in the 1970's, seems to have been suppressed, and the reported incidence of congenital rubella has been declining since 1969. However, some criticims have also been voiced. For one thing, several authors have proposed that the concept of herd immunity is invalid and that recent outbreaks of rubella among adolescents and adults in the United States demonstrate the inadequacy of childhood vaccination programs. For another, replacement of a permanent immunizing agent (natural rubella) with an artificial nonpotent immunogen could create future nonimmune populations among women of childbearing age.

The first approach may be reasonable in a country where no rubella epidemic exists at present. The second is justified in the case of nationwide rubella epidemics such as the one that occurred in the United States in 1964.

Vaccination of Adult Women

Immunization of susceptible women of childbearing age is a most logical approach, although there is always a risk of inadvertently immunizing women in early pregnancy. It has been reported that a vaccinelike virus was recovered from a cataract in the eye of an aborted fetus whose mother was immunized with HPV 77 DE 5 seven weeks

before conception (*13*). Consequently, attenuated rubella virus is considered to retain teratogenicity, and for this reason immunization of women during or shortly before pregnancy is strictly contraindicated. Two approaches can be taken to avoid such risk: either postpartum vaccination immediately after delivery while the mother is in the hospital (*14*), or vaccination of nonpregnant susceptible women. In either case strict precautions are necessary to avoid conception for two months thereafter.

Duration of Immunity and the Problem of Reinfection

In a seven-year follow-up (the longest to date) of institutionalized children, Mayer and Parkman observed a pattern of antibody persistence after administration of HPV 77 DE 5 vaccine, although it was of lower magnitude than that following natural infection (*15*). Similar findings were obtained in studies done three and four years after vaccination on subjects who received Cendehill vaccine. With regard to reinfection, antibody boosts have been reported in 2.5 to 10 per cent of children with natural immunity, compared with boosts in 3.5 to 80 per cent of children and young adults naturally exposed to wild rubella virus at varying intervals after vaccination (*16*).

Reinfection was induced by artificial challenge with wild virus less frequently in RA 27-3 vaccinees than in subjects immunized with other vaccines (*10*). Virus shedding from the pharynx of reinfected children was documented over a short period of time; the titers of virus shed were very low and viremia was not demonstrated. Reinfection of pregnant women was rarely seen, although one report states that placental transmission of virus resulted in fetal abnormality (*17*).

Recommendations

- Continuing surveillance of rubella and the congenital rubella syndrome should be encouraged in order to clarify their epidemiology, which is not fully understood.
- The choice of vaccination strategy should depend on the epidemiologic circumstances.
- Follow-up testing should be conducted on the immunity acquired from vaccination in order to determine its duration.
- Different methods of immunization (via the respiratory route, with combined vaccines, etc.) need to be studied.
- The teratogenic potential of attenuated rubella vaccine virus in pregnant women vaccinated inadvertently should be thoroughly explored.
- Experimental animal models of congenital rubella virus infection should be established for purposes of testing vaccine safety and understanding the pathogenesis of malformation.
- Further studies on fetal pathology are needed.

SUMMARY

Various attenuated live rubella vaccines now in use are considered generally safe and immunogenic, but to date the longest that vaccinal immunity has been shown to endure is seven years. Subclinical reinfection is not uncommon among vaccinees, but its effect on pregnancy and fetal development is not yet fully known. At present two mass immunization strategies are used: vaccination of all children under 12 years of age or protection only of females 10-14 years of age. In either case susceptible women of childbearing age who have no detectable rubella HI antibody are immunized as well. Such women may receive the vaccine during the postpartum period or at any other time when they are not pregnant, but strict precautions must always be taken to make sure they do not conceive for at least two months thereafter.

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