The History of Rubella and Rubella Vaccination Leading to Elimination

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Congenital rubella syndrome (CRS) was discovered in the 1940s, rubella virus was isolated in the early 1960s, and rubella vaccines became available by the end of the same decade. Systematic vaccination against rubella, usually in combination with measles, has eliminated both the congenital and acquired infection from some developed countries, most recently the United States, as is confirmed by the articles in this supplement. The present article summarizes the clinical syndrome of CRS, the process by which the vaccine was developed, and the history leading up to elimination, as well as the possible extension of elimination on a wider scale.

The importance of congenital rubella infection was recognized in the United States and elsewhere in 1941, after the ophthalmologist Norman Gregg linked epidemic congenital cataracts in Australia to intrauterine rubella [1]. Landmark articles by Greenberg et al. [2] in the United States, Manson et al. [3] in the United Kingdom, and Lundstrom in Sweden [4] established congenital rubella as a prevalent and serious disease, changing rubella from a minor rash disease to a major threat in pregnancy.

At first, cataracts, deafness, and congenital heart disease were the only identifying characteristics of congenital rubella, but, in the spring of 1963, an epidemic of rubella started in Europe and subsequently spread to the United States in 1964 and 1965, leaving thousands of damaged infants in its wake [5]. Studies of these infants revealed that congenital rubella syndrome (CRS) has many manifestations and affects virtually all organ systems [6, 7]. In addition to affecting 3 core organs—the optic lens, the cochlea, and the heart—CRS was recognized as a cause of pathology in the brain, lungs, liver, spleen, kidney, bone marrow, bones, and endocrine organs. This anatomic pathology was associated with encephalitis, mental retardation, pneumonia, hepatitis, thrombocytopenia, metaphyseal defects, diabetes mellitus, and thyroiditis. Moreover, although cataracts, cochlear atrophy, and patent ductus arteriosus were prevalent in typical CRS, other manifestations in the eye, ear, and heart were found to occur frequently, including glaucoma, central auditory perception, and peripheral pulmonic stenosis [7].

Those of us who were practicing pediatrics or obstetrics during those years remember with poignancy the many tragedies we witnessed as families struggled with decisions about therapeutic abortions and severely damaged infants. In Philadelphia, I calculated that at the height of the epidemic 1% of all births were affected [8].

Meanwhile, the cell culture revolution that began after the Second World War was applied to the study of rubella in the early 1960s. Two laboratories succeeded in detecting the presence of rubella virus: that of Weller and Neva [9] in Boston and that of Parkman, Buescher, and Artenstein [10] in Bethesda. In Boston, rubella virus was isolated by detecting subtle changes in human amnion cells, whereas in Bethesda the workers used a novel technique of viral interference. When samples containing rubella virus were inoculated on cultures of African green monkey kidney (AGMK) cells, the virus grew without cytopathic effect, but the cells secreted interferon. Challenge of the AGMK cultures with enteroviruses such as echovirus 11 revealed interference with their readily detectable cytopathic effect. This technique became widely used in virology laboratories.

Fortunately, the isolation of rubella virus came just before the 1963–1965 rubella epidemic, permitting ac-
curate virologic and serologic diagnosis and elucidation of disease pathogenesis. Many key features of rubella and CRS were recognized, including the following [7, 11]:

1. Replication of the virus in the throat for periods of 2–3 weeks
2. Viremia at high levels, particularly during the second week of infection, terminated by the appearance of antibodies
3. Clinically inapparent rubella virus infection in as many as a one-third of infected individuals
4. Correlation between the presence of serum antibodies and resistance to rubella virus infection
5. Viral infection of the placenta
6. Panembryonic infection of fetuses after viremic infections in their mothers
7. Confirmed rubella during the first trimester of pregnancy resulted in damage to 50%–90% of fetuses, with declining percentages through the second trimester [12, 13]
8. Cell death found in key organs of the fetus, together with inhibition of cellular mitosis and vascular endothelial damage
9. Excretion of virus at birth by babies with CRS, who continued to excrete virus for months, serving as vectors of transmission to others
10. Seronegativity in ∼15% of American women of child-bearing age, with higher or lower percentages in other parts of the world, depending on social conditions and population density. Thus, in crowded urban areas, rubella virus infection was relatively continual in children, but women were usually immune, whereas in some island populations epidemics were sporadic, and a high proportion of women were susceptible.

The devastating consequences of the rubella epidemic left no doubt that a vaccine was needed, and many groups set to work. The common denominator was attenuation by passage in cell culture, since it had become clear with other viruses that such passage usually resulted in selection for lower virulence in vivo. Parkman, Meyer, and colleagues [14] attenuated rubella virus in AGMK cell cultures (HPV-77), Hilleman et al. [15] in duck embryo cells (HPV-77/DEV), Prinzie et al. [16] in rabbit kidney (Cendehill), and I and my colleagues [17] in a human diploid fibroblast cell strain. The HPV-77 virus developed by Parkman was also adapted for commercial use in dog kidney cell cultures.

One feature of the human diploid fibroblast vaccine (RA 27/3) that differed from the others was the adaptation of the strain to growth at 30°C [18–20]. The idea behind this was to rapidly induce attenuation, on the basis of my previous experience with attenuated poliovirus strains [21], following the work of others showing that replication at low temperatures selected against virulence. By the 25th passage in a human diploid cell strain, RA 27/3 had clearly become attenuated for humans.

All of the live attenuated vaccines except RA 27/3, the human diploid cell vaccine, were licensed in 1969 and 1970 in the United States. At the same time, RA 27/3 was licensed in Europe. The reason for this difference is of historical interest. At the time, there was a prejudice in the American regulatory agency against a human cell strain, on the grounds that it might contain some hypothetical contaminating agent [22]. Some what illogically, primary cultures from animals were thought to be preferable. Ironically, over the years, human diploid cell strains (first developed by Leonard Hayflick and Paul Moorhead [23] at the Wistar Institute) have become the reference standard for fully characterized cells free of contaminants.

Over the next decade, accumulating evidence led to changes in the United States. First, the duck embryo and dog kidney vaccine strains caused significant joint reactions [24–27]. Second, reinfection on exposure to wild rubella virus was demonstrated frequently with all strains except the RA 27/3 vaccine [28–30]. Third, the good safety record of the RA 27/3 vaccine in Europe, plus the majority opinion of scientists, led the US Food and Drug Administration to license RA 27/3. Important pressure for this decision came from Dorothy Horstmann at Yale, who was convinced by her comparative studies of rubella vaccines [31], and by Maurice Hilleman at Merck, who sought a better rubella strain for measles-mumps-rubella (MMR) vaccine.

Over the past 30 years, the properties of the RA 27/3 vaccine have been well documented. Seroconversion is regularly induced in >95% of vaccinees after subcutaneous injection [32–34], and the strain can also be given intranasally [35, 36]. Data on protection against natural rubella matches the antibody data. Persistence of protection has been somewhat controversial, because some studies have shown >90% presence of antibodies in subjects vaccinated many years before [37–39], whereas other studies show eventual loss of antibodies in as many as one-third of vaccinees [40]. Although rubella vaccine is now commonly given twice in MMR vaccine and a second dose effectively boosts vaccinees who have become seronegative [41], it is not clear how important this is for rubella control. No doubt, the sensitivity of antibody detection is an important factor in the evaluation of antibody persistence, but in any case, there is no evidence yet that vaccinated populations lose protection with time. That said, it will be necessary to continue evaluation of the duration of protection to cope with possible reintroductions of rubella into vaccinated populations. Anamnestic responses may protect even if serum antibodies disappear, and, additionally, RA 27/3 vaccine induces IgA secretory antibodies in the nasopharynx [36].

With regard to safety, seronegative adult women are prone to acute transient arthalgia and arthritis after vaccination [28, 42], but the idea that such reactions lead to chronic joint problems has not been supported by controlled studies [43, 44]. Subclinical thrombocytopenia may occur after vaccination [45]. Of great importance is the fact that extensive postvaccination surveillance has not turned up any instance of teratogenic effect.
by RA 27/3 administered inadvertently to pregnant women [11, 46, 47].

With the availability of virologic and serologic tools, it became possible to elucidate the epidemiological profile of rubella and CRS [5]. Transmission occurs from respiratory secretions, and implantation of the virus probably occurs in the nasopharynx [7]. The average number of transmissions from a case of rubella in developed countries is between 3 and 8 [48, 49]. In developed societies, infection occurs in collectivities of children, who may infect their parents. However, adult-to-adult transmission is also common, as is experienced among military recruits, on cruise ships, and even among Wall Street traders [50]. Seropositivity in women of childbearing age varies between 85% and 95%, depending on when rubella disease was last introduced. In urban areas, epidemics occur with a certain periodicity, averaging 7 years [51].

When rubella vaccination became feasible, both the United States and the United Kingdom embarked on vaccination programs. In the United States, the strategy was to vaccinate infants, so that eventually the reservoir in childhood would be abolished [52]. In contrast, the United Kingdom decided on a program of vaccinating adolescent girls [53]. Both strategies were partial successes, in that CRS incidence began to decrease. However, both were also partial failures, because in the United States pregnant women were still being exposed to rubella in children and adults, and in the United Kingdom unvaccinated girls who refused vaccination were still exposed to rubella cases because of circulation of virus in the male population and children. Each country revised its strategy to include both universal immunization of infants and targeted vaccination of adolescent girls and adult women. Military recruits and health care workers were also singled out for vaccination [54].

Meanwhile, a second dose of MMR vaccine became standard, and the Scandinavian countries began systematic efforts to eliminate rubella. Finland was a leader in this respect and, by maintenance of high coverage and monitoring by serologic testing, succeeded in eliminating rubella completely [55].

Elimination of rubella and CRS is now a goal throughout the Western Hemisphere, promoted by the Pan American Health Organization [56]. The importance of rubella and CRS elimination became obvious when laboratory studies of rash disease incident to measles elimination campaigns revealed the high prevalence of rubella virus infections.

More recently, EURO (European Region of the WHO) has chosen to attempt elimination of rubella [57]. Whereas northern Europe has already done the job, low vaccination rates in southern and eastern Europe have resulted in persistent disease. However, increasing pressure put on the countries in those areas will inevitably result in elimination.

Rubella vaccination is also beginning in developing countries, where the incidence of CRS is also thought to be considerable [58]. The high immunogenicity of RA 27/3 vaccine was confirmed in Oman [59]. The former Soviet states of Central Asia are adopting vaccination [60]. Thailand and Malaysia have introduced MMR vaccine into their vaccination schedule. Japan has recently decided to make rubella a target through the use of measles-rubella vaccine. Rubella vaccine production is just beginning in China.

Sub-Saharan Africa remains a problem, both for epidemiological and economic reasons. The incidence of CRS is poorly documented, except for data from Ghana [61] and South Africa [62]. The cost of vaccines is also an issue. However, at this point, rubella-containing combinations are being manufactured in the developing world and can be purchased for <50 cents/dose. Results of cost-benefit analyses favor vaccination, particularly since there are no additional costs of administration when rubella vaccine is used in combination with measles vaccine [63]. Moreover, aerosol administration of measles and rubella combinations in mass campaigns has been shown to be feasible in Mexican studies [64].

An important strategic issue concerns a possible paradoxical effect, in which vaccinating only infants reduces infection of nonpregnant women by circulating rubella virus and, therefore, results in an increase in their susceptibility to residual exposures during later pregnancy [48]. Although the issue is only temporary—because with time the infants become immunized adults—it can be dealt with by a single mass campaign of vaccination of women (or both sexes) up to 39 years of age. Catch-up vaccination of children up to 15 years of age will also greatly reduce the risk of a paradoxical effect.

The articles in this supplement recount the elimination of rubella and CRS from the United States. After a brief recrudescence in the early 1990s, elimination became possible through increased vaccination coverage, the institution of a universal second dose of MMR vaccine, and the efforts of Mexico and other Latin American countries to vaccinate against rubella. The latter efforts reduced the introduction of rubella virus into the United States by immigrants. At this point, the major sources of importation are Asia and Europe.

On 29 October 2004, the Centers for Disease Control and Prevention convened the meeting at which the accompanying papers were presented, against the background of few or no reports of rubella activity from the 50 states and the virtual absence of reported CRS. It seemed propitious to examine the situation to determine whether rubella virus was or was not still circulating. The clinical, laboratory, and epidemiological evidence supported the absence of rubella virus. A committee of experts then decided on the basis of the evidence that rubella is no longer endemic in the United States. There are reasons to be optimistic about the eventual elimination of rubella from the world. We have the tools to do it, and only the political will is required. Elimination now has been accomplished in the
United States and in several other developed countries. One hopes that elimination will succeed in more and more regions, eventually resulting in the eradication, once and for all, of a threat to the birth of healthy infants.

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