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Review

Rubella eradication

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Abstract

The virulence of rubella virus for the fetus was fully defined between 1963 and 1965 when an epidemic of rubella occurred in Europe and the US, followed by a wave of damaged babies. Attenuated live virus vaccines were developed in our and other laboratories and their use has already considerably changed the epidemiology of rubella. Nevertheless, only about half of the world's countries vaccinate against rubella. We argue for the combination of rubella vaccine with measles vaccine in all campaigns for the control of measles, and will discuss the strategies by which congenital rubella syndrome could be eradicated at little additional cost.

1. Introduction

Rubella is one of the major exanthemata of childhood, together with measles, varicella and scarlet fever. Although recognized since the 18th century, rubella was considered a relatively benign infection until the discovery of its teratogenicity by the ophthalmologist Norman McAlister Gregg [1] in Australia during the early days of the Second World War. Gregg was asked to see many babies with congenital cataracts whose mothers shared a history of rubella during early pregnancy.

The virulence of rubella virus for the fetus was not fully defined until the early 1960s, when methods were discovered to cultivate the virus and to accurately diagnose infection in pregnant women. Between 1963 and 1965 a pandemic of rubella occurred in Europe and the US which confirmed beyond doubt that rubella during the first trimester of pregnancy carried with it a very high risk of fetal damage [2]. The need for prophylaxis was thus confirmed.

I witnessed the toll of that epidemic, both in the UK and the US. Even 18 yr later, one still recognized patients with sequelae of the epidemic, including those who were blind, deaf and mentally retarded.

Attenuated live virus vaccines have been commercially available since about 1970 [3], and as we shall see, the epidemiology of rubella has already changed considerably. Nevertheless, only about half of the world's countries use rubella vaccine [4], and the question before is what should our worldwide goals be for control of rubella-reduced incidence, elimination or eradication?

2. Clinical

Although acquired rubella infection does cause encephalitis, arthritis and thrombocytopenia, the rarity of these manifestations would probably be insufficient to justify vaccination. It is rather the proclivity of the virus to injure the fetus that is the main medical problem associated with rubella. The pathogenesis of congenital rubella syndrome (CRS) starts with maternal viremia (Fig. 1), which then infects the placenta, and subsequently, probably by migration of infected cells, infection rapidly passes to the fetus. In the fetus all organs are infected, but their response varies, and is dependent on the stage of organ maturation, with early infection causing the greatest damage [5].

Basically, there are two mechanisms of damage: one by cellular deletion through mitotic arrest and apoptosis, and the other by damage to the endothelium of small vessels, leading to maldevelopment of specific organs. The prominent clinical findings in congenital rubella are listed in Table 1, which testifies to their variety [6].

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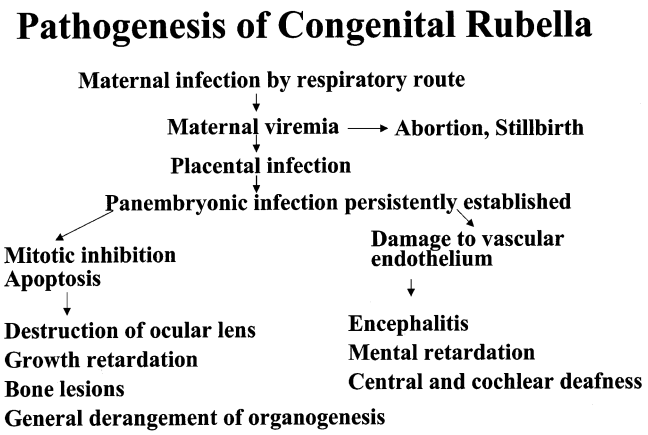

Fig. 1. Pathogenesis of congenital rubella.

The precise risk to the fetus of maternal rubella was in dispute until virologic diagnosis became available. Now, it is known that confirmed rubella in the first 8 weeks of gestation leads to fetal abnormality more than two-thirds of the time (Fig. 2); that the incidence drops to one-third during the 9th to 16th weeks; and that fetal abnormality is uncommon afterwards [7,8].

In the US between 1964 and 1965, the rubella pandemic was catastrophic. Over 30000 pregnancies were marred as a result ([2]; Table 2) and in some areas at the height of the epidemic, such as Philadelphia, 1 of every 100 births was affected. Lest anyone think that the 1963–1965 experience was unusual, the data from a recent epidemic in Poland (Table 3) should correct that idea [9].

Table 1
Prominent clinical findings of congenital rubella syndrome

Encephalitis
Microcephaly
Mental retardation
Autism
Cochlear deafness
Central auditory imperception
Retinitis
Cataracts
Microphthalmia
Glaucoma
Patent ductus arteriosus
Peripheral pulmonic artery stenosis
Intrauterine growth retardation
Metaphyseal rare factions
Hepatosplenomegaly
Interstitial pneumonitis
Thrombocytopenic purpura
Diabetes
Hypothroidism

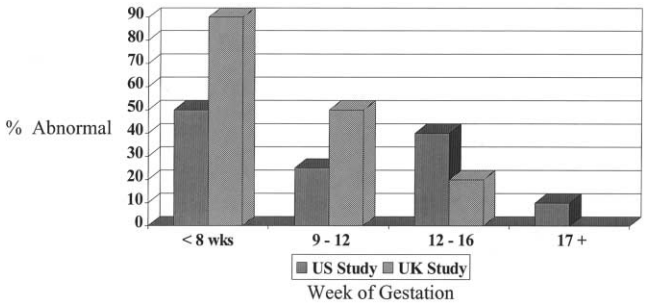

Fig. 2. Fetal abnormality induced by confirmed rubella at various stages of pregnancy.

3. Epidemiology

Rubella is a ubiquitous infection and occurs throughout the world. However, epidemiologic patterns differ, as can be inferred from seroepidemiology. (Table 4). The pattern known in many developed countries such as the US, the UK and Scandinavia, is one of relatively low incidence of infection until the school years and a seroprevalence in women of child-bearing age that is in the range of 5–20%. The reproduction number, that is the number of secondary infections of susceptibles caused by a single case of rubella varies between 3.4 and 7.8 in European countries, indicating a relatively moderate contagiousness [10].

A second epidemiologic pattern, found in island countries and some rural areas of developing countries, is a low seroprevalence between epidemics, with 50% or more of women remaining seronegative. When rubella enters these countries, large outbreaks occur.

The third pattern is found in populous developing countries, where childhood infection is common and

Table 2
Estimated morbidity associated with the 1964–1965 rubella epidemic in the US

Clinical events		
Rubella cases		12 500 000
Arthritis–arthralgia		159 375
Deaths		
Excess neonatal deaths	2100	
Other deaths	60	
Total deaths		2160
Excess foetal wastage		6250
Congenital rubella syndrome		
Deaf children	8055	
Deaf–blind children	3580	
Mentally retarded children	1790	
Other congenital rubella syndrome	6575	
Total congenital rubella syndrome		20 000
Therapeutic abortions		5000

Table 3
Outcome of pregnancy in rubella-infected women in Poland

Trimester of pregnancy	No. of infected women observed	Consequences of infection		Still-birth	Termination abortion	% Abnormal
		None	Present			
I	22	5	9	1	7	77
II	12	8	2	2	–	33
III	2	2	–	–	–	–

where women have a low rate of seronegativity. However, it must be understood that in these areas rubella may not be present every year, and that therefore, even in developing countries susceptible women may accumulate, to be discovered only by random serologic surveys or by the introduction of rubella virus. A good example of this variation is found in the wide differences in seropositivity among women from different Indian cities [11,12].

4. Surveillance

How can we survey for rubella and for CRS? A number of methods are now available (Table 5), all of which are valuable in the diagnosis of individual cases. However, for epidemiologic purposes the detection of IgM antibodies to rubella in serum is the best. Salivary assays for IgM antibodies have also been developed, but unfortunately are not commercially available [13]. The use of the IgM technique has, for example, enabled the Pan American Health Organization to determine that 20% of samples sent for measles diagnosis were positive for rubella IgM, thus confirming the importance of the virus as a cause of rash disease [14].

The diagnosis of CRS would be simple if blood specimens were always available from birth. In the absence of such a sample one may still attempt laboratory confirmation of CRS albeit with less sensitivity. Thus, clinical criteria in addition to laboratory criteria are necessary. Major and minor findings in CRS are listed in Table 6 [15]. The most sensitive is probably detection of cochlear hearing loss by otoacoustic emissions or auditory evoked brainstem responses. However, the easiest criterion to use in the field is the presence of congenital cataracts. About 25–35% of CRS cases will have congenital cataracts [15], and although the presence of cataract has poor sensitivity for the detection of CRS [16], it should lead to attempts to confirm CRS by laboratory test. Confirmation of rubella in infants with congenital cataracts should enable one to estimate the likely total number of CRS cases by multiplying cataract cases by four.

Confirmation of CRS can be obtained in clinically compatible cases by positive virus culture or PCR; by positive IgM rubella antibodies; or by persistence of rubella IgG antibodies beyond the time passive antibodies would still be present. A probable CRS case is one with two major or one major plus one minor clinical sign of CRS (Table 7). Only 13% of CRS cases have a single abnormality, so in principle over 80% can be detected by clinical definition [15].

5. Vaccination

Rubella vaccination is accomplished by parenteral injection of live attenuated rubella strains grown in human diploid fibroblast cells. With the exception of Japan, the vaccine in use is the RA 27/3 virus [3], attenuated and produced in cultures of human diploid fibroblast cell strains during the early 1960s in my laboratory [17]. The immunogenicity of the RA 27/3 virus is high, leading to seroconversion in close to 100% of vaccinees [18], and although mean antibody titers are lower after vaccination, the immunity produced seems to be similar to that after natural infection. The quality of immunity was ascertained by simulating natural infection by intranasal challenges with attenuated virus (Table 8). Even when their serum antibody titers were low, vaccinees resisted challenge [19], perhaps because vaccination often induces secretory antibodies. As is also the case in measles, reinfection does occur in vaccinees when antibody titers are low, and may even be transmitted to a fetus [20], but reinfection seems to play an unimportant role in the epidemiology of rubella and CRS.

It is important to note that RA 27/3 is available in combination with measles and with measles and mumps, as well as in a monovalent form. Combination

Table 4
Patterns of rubella epidemiology

Areas	Peak age of infection	Prevalence of seronegative women
Developed countries	School age	5–20%
Islands	All ages during outbreaks	20–50%
Developing countries	Pre-school	$<5\%$

Table 5
Diagnosis of rubella

Virus culture	Acquired	Congenital (post-natal)
RT-PCR	NP swab	NP swab, urine, blood
IgM Ab	Present 1–2 months	Present 6–12 months
IgG Ab	Low avidity 30–40 days	Low avidity, but persistent

with the other valences does not reduce its immunogenicity.

Data concerning persistence of antibodies after vaccination are somewhat variable, but the majority of studies seem to show maintenance of antibodies for at least 20 yr [21,22]. Nevertheless, a second dose of rubella vaccine at 4–12 yr of age is routinely recommended in many developed countries, primarily to immunize the few primary vaccine failures but secondarily to provide a booster to those whose titers have fallen to low levels [23,24]. The efficacy and effectiveness of rubella vaccine have been extensively documented, as in the case of a French school outbreak (Table 9).

As with any vaccine, reactions do occur (Table 10). In pre-pubertal children these are remarkably few, essentially fever and rash [25,26]. In adolescents, arthralgias may be seen at a low rate [27]. However, in adult women significant arthralgia and arthritis are common. Rates of about 25% have been reported in many studies [28]. Although retrospective studies from one group gave evidence for chronicity [29], prospective data show that chronic arthritis following vaccination is rare, if it occurs at all [30–32]. Nevertheless, joint reactions may be temporarily disabling, and the risk clearly rises with age of the vaccinees.

The principal safety concern about live rubella vaccine is the possibility that it might cause CRS if administered during pregnancy. An extensive experience (Table 11) has shown that although the attenuated virus infects the fetus at a rate of $< 5\%$ [33–35], the outcome of that infection is asymptomatic because of the attenuation of the vaccine strain. Nevertheless, pregnancy remains a contraindication to rubella vaccination, if not a reason for medical abortion [36].

Table 6
Clinical criteria of CRS

Major	Minor
Cataracts	Purpura
Glaucoma	Hepatosplenomegaly
Retinopathy	Microcephaly
Heart disease	Developmental delay
Central deafness	Meningoencephalitis, radiolucent bone lesions

Table 7
US CRS definition

Confirmed: CRS compatible defect and laboratory confirmation
Probable: Two major defects or one major and two minor

6. The use of rubella vaccine until the present

Initially in the US rubella vaccination was recommended for children. The idea was to decrease the circulation of the virus and thus to protect pregnant women by reducing their exposure. No doubt this policy had some success, as rates of CRS decreased by about half [37]. However, disease incidence in individuals above the age of 15 yr did not fall rapidly, and it became clear that much of the transmission was adult to adult. Thus, in 1979 greater emphasis was placed on vaccination of adolescent girls and adult women, taking advantage of school-based programs, matriculation to college, gynecologic visits and post-pregnancy visits.

Moreover, the recrudescence of measles in 1989–1991 in the US led to a recommendation for a second dose of measles vaccine [38]. In the occurrence, this is given almost exclusively as MMR. Thus, a second dose of rubella vaccine became standard without much in the way of epidemiologic data to support it.

Nevertheless, this policy had a marked effect [39]. Endemic rubella essentially has disappeared from the US, where rubella and CRS are now diseases of immigrants (Table 12). Unvaccinated immigrants have come predominantly from Latin America [40,41], but with the establishment of new vaccine programs in Mexico, Central America and the Caribbean, introductions of rubella have come increasingly from Europe and Asia.

On the other hand, originally British policy was to vaccinate school girls and to create a cohort of immune women [42]. This policy was also a partial failure, because acceptance of the vaccine was incomplete, and because exposure to infected children was undiminished. Accordingly, in 1988, Britain started routine MMR immunization of infants [43], and in 1994 a mass campaign with measles–rubella vaccine was conducted [44]. There was a marked decrease in CRS, but safety concerns caused by claims of a putative association between MMR, autism and inflammatory bowel disease has produced a decline in vaccination and a resurgence of rubella and CRS.

Table 8
Viremia and virus excretion in volunteers after nasal challenge with RA 27/3 virus

	Viremia	Excretion
Seronegatives	70%	100%
Seropositives	0%	5%
Vaccinated	0%	5%

Table 9
Efficacy of RA 27/3 vaccine according to different case definitions[a]

Case definition	% Efficacy (confidence limits)
Clinical only	95% (84–98)
Clinical+lab	100 (83–100)

[a] Primary school, Chomerac, France January–March, 1997.

The most successful experience with rubella vaccination has been accumulated in Scandinavia, notably Sweden [45] and Finland [46]. In those countries, a two-dose regimen was adopted already in 1982. Rubella and CRS have disappeared as indigenous diseases. Continuous surveillance of serology and disease has been conducted in Finland. As successive cohorts have been immunized, seropositivity has attained high levels [47] because at first boys were not given the second dose, disease persisted longer in them, but now has disappeared. In effect, eradication of rubella has already taken place in Scandinavia.

The picture for the rest of continental Europe is not so rosy. Although MMR is recommended in every European country, immunization rates are suboptimal in many of them, and CRS continues to occur [48].

Latin America and the English-speaking Caribbean have recently become bright spots in the picture of rubella prevention. Under the leadership of the Pan American Health Organization, more and more countries have added rubella to measles vaccination in recognition of the wide circulation of rubella infection reaching 100% this year [49]. Goals have been set for the eradication of rubella from the Caribbean and for the control of rubella elsewhere. Assuming success in measles eradication from the Western Hemisphere, there is no reason why rubella cannot be eradicated at the same time, with however, some special problems that are considered below.

The situation in Asia and Africa is mixed. Japan, Korea, Thailand, Singapore, Hong Kong and Malaysia all use rubella-containing combinations. Other countries, including almost all of Africa, have not yet made the decision [50]. Part of the problem, as might be imagined, is the lack of data concerning CRS in particular countries, but perhaps the more accurate way to state the problem is the lack of systematic data, for

Table 10
Adverse events following rubella vaccination

(1) Usually mild, increase with age in susceptible individuals
(2) Low grade fever, rash and lymphadenopathy of short duration occur occasionally
(3) Transient pain in joints 7–21 days after vaccination mostly in post-pubertal females (<1% of children versus one in four adult female; arthritis in only 10% of adult females). Chronic arthropathy not demonstrated

Table 11
Summary of data on accidental vaccination before pregnancy and during early pregnancy of women in the US and Germany[a]

Study location	No. vaccinated women	Mother known susceptible	Outcome for live births			Products of conception positive when tested for rubella	Theoretical risks CRS defect
			Liveborn to susceptible mothers	Asymptomatic infection	CRS defect		
United States	Cendehill & HPV-77 538	149	94	8	0	17/85	0–3.8
	RA 27/3 683	272	226	3	0	1/35	0–1.6
Germany	Cendehill 340	130	107	2	0	1/34	
	RA 27/3 25	16	12	0	0		

[a] From MMWR 38/289–293, 1989; MMWR 39"RR-15, 1990 and Ref. [34].

Table 12
Rubella in US 1994–1997

(1) 567 cases 85%⩾15 yr 54% hispanic (68% in 1996)
(2) Origin imported cases Mexico, Japan, Kenya, Columbia, England, Germany, Korea and Switzerland
(3) Possible interruption transmission, 1996

scattered information exists (Table 13). Two particular experiences should be cited, for they occurred in areas with reasonably well-functioning health systems. One was in Vellore, India, where Dr. R. Samuel conducted a 4 yr survey for CRS, and found over 200 cases possible [51]. Another experience was in Kumasi, Ghana, where an epidemic of rash disease turned out to be mixed measles and rubella, and was followed by the birth of CRS babies ([52]; Table 14). Serologic surveys in Africa also show local variation in seropositivity down to 70% in women of child-bearing age [53,54].

Incidence data are also available from a number of developing countries, indicating that between 1 in 500 and 1 in 2500 infants, averaging about 1 in 1000, develop CRS. Moreover, Cutts and Vynnyky [55] have attempted to estimate the global total of CRS cases per year. Although their confidence limits were wide, their best estimate (Table 15) came to over 100000 cases per year. Such disease burdens are not negligible, all the more so because most CRS babies survive to become burdens on their families and their health systems. Despite this burden, 50% of the world's countries, including the most populous, do not use rubella vaccine [56].

Table 13
Rates of CRS per 1000 live births in seven developing countries prior to the introduction of rubella vaccine

Country	Year (s)	Rate of CRS per live births
Israel	1972	1.7
Jamaica	1972–1981	0.4
Oman	1988	0.5
	1993	0.7
Panama	1986	2.2
Singapore	1969	1.5
Sri Lanka	1994–1995	0.9
Trinidad and Tobago	1982–1983	0.6

Table 14
Rubella in Kumasi, Ghana

Epidemic "measles" February–May 1995	30 000 reported cases in Ghana
Eighteen cases CRS October 1995–February 1996	Minimum incidence 0.8/1000 births

7. Possible strategies for eradication

What are the reasons for thinking that rubella or CRS could be eradicated (Table 16)? First, the infection is carried by humans only; second, the only human reservoir, CRS babies, excrete virus transiently; third, we have an effective vaccine; and fourth, the effort could be incorporated into measles virus eradication.

However, there are a number of impediments (Table 17). There will be an additional cost if rubella is added to measles vaccine, although a combined vaccine is unlikely to cost more than $0.50 per dose to UNICEF [57]. Moreover, there is no additional cost of administration, which has always been the major part of the expense of immunization. Incidentally, rubella vaccine can be given as early as 9 months of age in the form of MMR, thus facilitating its use in the prevention of measles [58].

The issue of vaccine supply is as usual a circular one. At least eight manufacturers produce RA 27/3, including some in developing countries. The strain is no longer under patent and is available from the Wistar Institute. As long as no demand is made for additional vaccine supply, it will remain insufficient. Serious discussions with manufacturers are needed.

The third issue is the most problematical. Mathematical modeling predicts that if rubella vaccine coverage of infants is less than 80%, there will be a paradoxical increase in CRS, because the decrease in virus circula-

Table 15
Estimated incidence rate of CRS per 100 000 live births and number of cases of CRS by WHO region [55]

WHO region	Incidence rate of CRS per 100 000 live births	No. of CRS cases
Africa	104	22 471
Americas		
Island	171	
Mainland	175	
Total		15 994
Eastern Mediterranean	77	12 080
South East Asia	136	46 621
Western Pacific	173	12 634
Global total		109 800

Table 16
Reasons to consider eradication of rubella and CRS

(1) No animal reservoir
(2) Human reservoir is transitory
(3) Effective vaccine, available in combination with measles
(4) Could be incorporated into measles eradication programs

tion will be sufficient so that more girls will reach child-bearing age without having contracted rubella or received the vaccine [59]. On the other hand, at coverage levels of above 80%, the effect is outweighed by the markedly reduced circulation of the virus. Therefore, the WHO has recommended combining universal vaccination of infants with attempts to vaccinate adolescent and adult females [60].

The reality of this paradoxical effect may have been demonstrated recently in Greece, where an increase in reported CRS followed sporadic and uncoordinated use of MMR in infants [61]. Although the interpretation of the Greek results may be debatable [62], they serve as a warning. Moreover, in some developing countries, immunity is so prevalent that only extremely high vaccine coverage would avoid increasing CRS [63].

However, vaccination of adolescents and adults is notoriously difficult to organize, and there is no infrastructure for it in developing countries. Moreover, the more vaccination is done in post-pubertal subjects, the more reactions there will be to vaccine, the more negative publicity, and the more inadvertent vaccination during pregnancy. Nevertheless, inability to do adult vaccination should not be used as an excuse to retard the introduction of rubella vaccine in infant. We must take into account the annual toll of CRS that will occur if we do nothing.

There is a third way, pioneered by Dr. Massad and his collaborators in Sao Paolo, Brazil (Table 18), and now incorporated into PAHO's strategy [64,65]. That is to combine the introduction of MMR or MR into routine vaccination during the second year of life, with mass vaccination campaigns involving all children up to puberty. Of course, mass vaccination of the population through the child-bearing ages would be even better, but such an endeavor introduces practical and theoretical problems, including a magnification of costs.

Table 17
Impediments to rubella/CRS eradication

(1) Cost of vaccine
(2) Supply of vaccine
(3) Concern regarding paradoxical enhancement of susceptibility of pregnant women
(4) Inapparent rubella

Table 18
Reported number of cases of congenital rubella syndrome in Sao Paolo [64,66]

	1992	1993	1994
Confirmed	16	1	0
Suspected	13	5	0
Total	29	6	0

Admittedly, this third approach is not perfect, but in both the short- and the long-term it seems to me to be most likely to succeed, as it takes advantage of the simultaneous desire to eradicate measles from childhood populations. The main risk, already experienced in Sao Paolo, is the creeping reintroduction of rubella from outside [66]. However, since measles eradication is likely to require more than one mass vaccination, all that is needed is to make sure a combined vaccine is used in measles campaigns. In any case, the repeated vaccination of pre-pubertal children will eventually produce a population of immune adults, particularly the young adults who are the most likely to bear CRS babies.

I would also urge that our goal be first to eradicate CRS rather than rubella. Since there is much inapparent rubella infection, eradication of the virus will be more difficult to attain and more difficult to confirm. Eradication of CRS is a well-defined goal that can be easily measured, and should be the interim target before attempting more ambitious eradication. Tables 19 and 20 give the author's recommended strategies for the eradication of CRS.

It is customary to talk about opportunity costs, which are the things you would be doing if you were not doing what you are doing. In this context, it seems to me that opportunity costs are those that will accrue if advantage is not taken of measles control, to simultaneously deal with rubella.

Table 19
Recommended strategy for eradication of CRS

Developed countries
(1) Universal MMR at 12–18 months and 4–12 yr
(2) Vaccination of adolescents and adults at any opportunity

Table 20
Recommended strategy for eradication of CRS

Developing countries
(1) Increase universal immunization with MR or MMR at 9–12 months of age
(2) Mass vaccination campaigns of children 1–14 yr of age with MR or MMR
(3) Vaccination of female adolescents and adults when opportunities arise

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