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# Theoretical Aspects of Rubella Vaccination Strategies

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The theoretical epidemiologic basis for an appropriate vaccination strategy for the prevention of congenital rubella syndrome is outlined and reviewed. The main choice lies between a direct strategy, in which adolescent girls and women are protected against the effects of being exposed, and an indirect strategy, in which children of both sexes are vaccinated and in which women are protected through the interruption of rubella transmission and are not exposed at all. The direct strategy produces a slow response but is free from substantial hazard. The indirect strategy produces a more rapid response but carries hazards, which arise from either shortfall in uptake, decay of vaccine-induced immunity, or from combinations of the two. In unfavorable circumstances, an indirect strategy produces paradoxical responses that increase rather than decrease the incidence of congenital rubella syndrome either immediately or as a "rebound phenomenon" after some years. A rational choice of policy depends chiefly on the transmission rate in the population concerned and on an estimate of the achievable level of uptake.

The literature relating to the prevention of congenital rubella syndrome (CRS) — and the proceedings of this conference — display a worldwide unity of purpose but a gross variance of strategy. Countries and regions have of course differed in the internal coherence of their preventive policies, but it is even more striking that some of those countries with well-organized preventive programs have adopted entirely different policies.

One approach is to vaccinate adolescent girls to protect those who have escaped natural infection. Natural infection before the age of vaccination remains the principal source of protection in the community, and vaccine-induced immunity for those who have escaped infection is supplementary. Since protection is conferred on the child of the woman who had been vaccinated as a schoolgirl, we refer to this as the "direct" method. The other policy is to vaccinate preschool children of both sexes. This policy also provides protection for the vaccinated girls, but not until many years have passed. Short- to medium-term protection is achieved through interruption of the spread of rubella, so that unvaccinated women are protected from exposure itself rather than the effects of exposure. Consequently, we refer to this as the "indirect" method.

The direct method has been adopted especially in the United Kingdom and Europe, and the indirect method, in the United States and Canada. Some countries have applied both methods simultaneously. Some have not really thought the choice of strategy through and have no coherent policy at all.

A variety of questions concern the choice of vaccination policy. Which policy is best? Which is most cost-effective and which reduces CRS most rapidly? How do the two methods respond to different levels of vaccination acceptance and vaccine efficacy? What hazards are attached to each policy? Does it really matter which of the policies is adopted or whether any policy is adopted? Is a combined policy to be preferred? Is systematic vaccination of adults a necessary supplement to either policy or both policies? Do the answers to these questions differ in different countries and in different circumstances? What information is required to determine the best policy in any particular situation?

The basic principle on which answers to these questions hinge can be set out in qualitative common-sense terms. Simply, although vaccination against rubella benefits those who are vaccinated, it does positive harm to those who are not vaccinated unless the infection is eradicated. The reduction of the spread of the disease postpones the age of first exposure among the nonvaccinated to early adult life. These hazards are more intrusive when vaccination

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is performed early and when children of both sexes are vaccinated. The greater potential benefits of the indirect method, which include the prospect of eradication, must therefore be balanced against the greater risk that such a program carries if eradication is not achieved. The balance between the harm and the benefit of each of the two basic strategies is likely to vary in different circumstances, and the problem is to identify those circumstances that lead us to prefer one approach to the other. Quantitative assessments are needed not only for long-term but also for short-term predictions and for demonstrating the effects of interim changes of policy and uptake, changing maternal-age distributions, socially and demographically mediated alterations in transmission patterns, and possible decay of vaccine-induced immunity. Solutions to these complex problems lie beyond the boundaries of reliable intuitive interpretation. Mathematical and computer-simulation approaches, together with the data necessary for the setting of parameters, are necessary for further progress.

## Aspects of a Theoretical Approach

*Simple models.* A homogeneous population suffers a constant rate of exposure to rubella, such that the number of rubella-susceptible persons declines by a fixed proportion ($a$) with each additional year of age. The proportion of susceptible persons ($s$) in a population can then be described in terms of the classical "die-away" model of exponential decay, with $s$ at age $t$ described in the terms:

$$s = e^{-at} \qquad (1)$$

If, through a serologic survey, we find the value for $s$ at a given age $t$, we can estimate a value for $a$:

$$a = \ln(1/s)/t \qquad (2)$$

If our serologic survey did not directly supply the proportion of susceptible persons at the mean age of childbearing ($b$), we can obtain an estimate by substituting the estimated value for $a$ into equation 1, and substituting $b$ for $t$. The result then indicates the size of the problem of CRS in our population. The proportion ($i$) of fetuses exposed to rubella infection is the product of three values, namely, the proportion of susceptible persons at age $b$ ($e^{-ab}$); the annual rate of attack by rubella among those susceptible persons ($a$); and the duration of the teratogenic period, say 0.1 to 0.2 years ($g$). The fetal exposure rate ($i$) is estimated thus:

$$i = gae^{-ab} \qquad (3)$$

The incidence of CRS itself is a fraction of $i$, representing the proportion of exposed infants who are in fact affected and who were not spontaneously or therapeutically aborted as fetuses. Data from several countries suggest that this fraction is in the range of 0.1 to 0.3. These and other basic mathematical relationships have been set out in previous work by the present author and by others [1-7].

*Practical consequences.* The relationship expressed in equation 3 is demonstrated graphically in figure 1. The incidence of CRS is low both when $a$ is small and when $a$ is large. CRS is relatively frequent when the value for $a$ is intermediate and is indeed maximal when $a = 1/b$. Thus, for a population with a mean age at delivery of 25 years, the worst possible situation would be that $a$ should be ~0.04. Such a value applies to a population of which 67% are seronegative at age 10 and of which 45% are seronegative at age 20. In practice, most societies have transmission rates of $>1/b$ and have lower proportions of seronegative persons at these ages. The approximate position for the United Kingdom at the present time is indicated in figure 1.

It is clear that countries with transmission rates higher than the rate in the United Kingdom and positioned further to the right on the curve of figure 1 present a less serious initial problem. The scope for benefit from a vaccination program is therefore smaller; the scope for harm among the nonvaccinated, through the reduction of exposure and postponement of infection, is greater. Different initial circumstances therefore present different prospects for both achieving benefits and creating hazards. Even for a given efficiency of implementation, different solutions might be required for different places. Clearly, the first step in determining an appropriate policy for a given population is to carry out a serologic survey so that the population's position on this curve can be determined.

*Effects of vaccination.* The administrative efficacy of a vaccination program can be expressed in terms of a fraction ($f$), which represents the proportion of the target population at age $v$ that is immunized. The fraction $f$ is the product of the proportion accepting vaccination and the procedural efficacy of the vaccine itself when administered to susceptible persons. The relationship between efficacy ($f$) and the effectiveness of the program in preventing CRS can be calculated through extensions of the formulas already given. Vaccination at age $v$

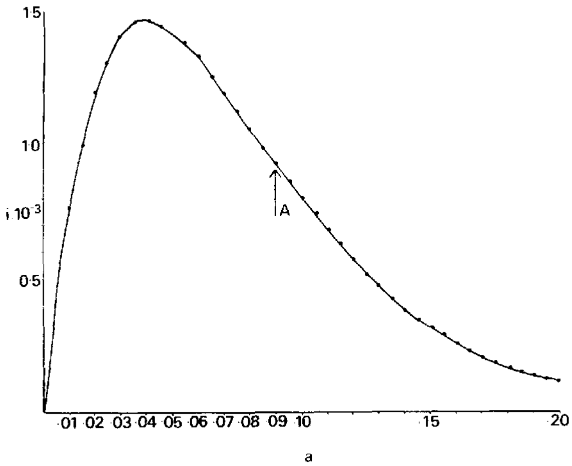


**Figure 1.** The incidence of fetal exposure ($i$) in relation to the transmission rate ($a$) for rubella. $A$ indicates the position in the United Kingdom.

produces a sharp downward step in the declining curve of the percentage of the population who are susceptible, expressed in equation 1, but it also alters $a$, which has to be recalculated. This calculation in turn alters the whole shape of the curve, as well as the downward step. Repeated recalculation is demanded until the new curve and its downward step reach stable values. Direct mathematical approaches that short-circuit the need for these iterative calculations have recently been devised [3]. The results of both types of calculations are concordant and are as follows.

In general, the direct strategy gives a result in terms of reduced CRS that is almost linearly proportional to the administrative efficacy; but the equivalent relationship for the indirect strategy is highly nonlinear. For low values of $f$, the direct method is always more effective than the indirect method, while for high values the reverse applies. Typically, the break-even point is approximately at $f = 0.7$ to 0.8. In the United Kingdom, for the initial position expressed in figure 1, an indirect strategy gives almost no net benefit for values of $f$ of <0.3. With increasing uptake the benefits improve and overtake the existing direct policy at an uptake of between 70% and 80%. For populations with higher values for $a$ than those obtained in the United Kingdom, low values for $f$ are not only not beneficial, they actually make matters worse, so that the incidence of CRS at first increases and may not decline to the initial level—and subsequently show a net benefit—until $f$ is approximately >0.6. The exact values depend on the initial value for $a$. The results of these studies consistently indicate that a combination of a high initial transmission rate, the choice of an indirect strategy, and a shortfall on acceptance targets is dangerous and can lead to disaster.

*Approaches to reality.* The homogeneous model on which these deductions are based is highly unrealistic. To generate some confidence in such predictions, it is necessary to suppose, and to provide for the supposition, that the population is stratified in terms of its transmission rates, that the age of delivery is distributed over a range of ages rather than represented by a single age $b$, and that the transmission rate might over a period of years alter spontaneously. In addition, we should examine the effects of possible decay in levels of vaccine-induced immunity and the possibility that such decay might be arrested through the "booster" effects of exposure to wild virus where wild virus still existed. Our pragmatic interests also go beyond the long-term, steady-state end results that the simpler formulas represent; we require an indication of intermediate results and of the rate with which a preventive program approaches its maximum predicted benefits.

These kinds of complexities are not easily represented through simple mathematical formulas. They require instead the construction of computer-simulation models that systematically manipulate a population on a step-by-step basis. Such models have been constructed, and initial results have been published [1]. In general, these dynamic simulation models have confirmed the long-term predictions of the simpler models and have revealed other properties of the alternative strategies. First, direct strategies provide their maximum benefits slowly, taking perhaps 20 years. Indirect strategies, provided that the efficacies are high (e.g., $f$>0.9), approach their targets more rapidly and almost eliminate CRS in ~10 years. They also reduce the incidence of rubella itself to levels at which total extinction might occur or might be engineered through the intensive containment of localized outbreaks. However, whereas the pattern of convergence on the end point is nearly linear for the direct strategy, whatever the value for $f$, an incompletely implemented indirect strategy can induce oscillations in the incidence of rubella. The oscillations are especially powerful when the uptake of the vaccine is between 40% and 60%. A minimum incidence of CRS is achieved after ~10 years but is followed by an upward swing. Approximately 20 years after the onset of the program, the incidence of CRS can substantially exceed the prevaccination level, although the incidence later falls. The upward swing is induced by the presence of those women who were too old for vaccination when the program was instituted, who moved into childbearing age without having been exposed to the wild virus, and who then suffered from the fact that the virus had not been completely eradicated. Decay of vaccine-induced immunity at a rate of, say, 1% per annum is also capable of inducing or seriously exaggerating oscillations of these kinds.

The effects of combined strategies, in which vaccination is offered to both adolescent girls and young children of both sexes, have also been examined. Such programs offer substantial insurance against shortfalls on acceptance targets but are less successful in providing insurance against the effects of decay of vaccine-induced immunity. Similar approaches are possible in relation to proposals to combine either the direct or the indirect strategy with vaccination of adults, but the outcomes have not yet been fully explored.

## Discussion

The main conclusion from these theoretical studies is that vaccination for the prevention of CRS must be handled within each country and region within the terms of an explicit and coordinated choice of strategy. It is dangerous to permit individual clinicians to follow their own inclinations or different institutions or district authorities to pursue their own strategies. Nothing could be more harmful than for one area to pursue a policy that depended on the maintenance of the existing pattern of rubella transmission while an adjacent area adopted a policy of eradication or reduction. As in the question of driving on the left or driving on the right, any policy is better than no policy!

The choice of a policy as optimal, which differs in different circumstances, depends on two main factors: (*1*) the rate of rubella transmission observed before vaccination is introduced, and (*2*) the administrative, regulatory, or educational feasibility of achieving an adequate uptake target. A population that has already been persuaded of the benefits of universal vaccination or whose politicians have been persuaded that vaccination should be compulsory provides the best opportunity for attempting eradication of rubella infection. A population that cannot be persuaded or compelled in these terms is a candidate rather for the direct strategy, especially if the preexisting transmission rate is high.

Two recent developments have modified previous constraints on the choice of policy. First, the safety of the vaccine for pregnant women has now been established to a degree that permits the adoption of a supplementary policy of vaccinating women in general, possibly after screening for the presence of antibodies. This policy permits enhancement of the rapidity with which a direct strategy attains its maximum effectiveness. It can also be used to supplement an indirect policy to insure a program against the rebound that will occur if the uptake rate falls short of the targets. Finally, it provides a means for protecting those isolated (e.g., island) communities where rubella has undergone spontaneous extinction and where a high-risk population of susceptible persons now extends into the adult age groups. The second development relates to the question of decay of vaccine-induced immunity. This problem no longer holds the threat that it did, although it has not entirely disappeared. The possibility of low annual rates of decay, say between 0.2% and 0.4%, still exists and should still be taken into account in the making of theoretical predictions, but the effects of decay are likely to be marginal. The basis of choice between strategies therefore depends almost entirely on the two primary factors, namely, the initial levels of transmission and a realistic assessment of the levels of vaccine uptake that can be attained and maintained.

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