Is post partum rubella vaccination worthwhile?

PD GRIFFITHS, C BABOONIAN

From the Virology Department, St Bartholomew's Hospital, West Smithfield, London EC1

SUMMARY This study was designed to determine whether a program of screening for rubella antibodies during pregnancy, coupled with selective vaccination after delivery, could effectively increase herd immunity. One thousand women were studied when they returned for further antenatal care after having been screened, and possibly vaccinated, during an earlier pregnancy. Overall, the program was shown to be 83% effective since 108 women were truly seronegative in their initial pregnancies and 90 of them had been rendered immune by the time of their next pregnancy. The 18 failures of the program were attributed to the haemagglutination inhibition test employed (eight cases), failure to administer vaccine (seven cases) and true vaccine failures (three cases). Five pregnant women became infected with rubella virus during the study but all were in their initial pregnancies. All seronegative women were shown to follow the instruction not to become pregnant within three months of vaccination. We conclude that a program of screening for immunity, together with selective vaccination post partum, can significantly reduce both the number of susceptible women and the number who experience rubella infection during pregnancy. Such programs should be vigorously encouraged as a means of helping to prevent congenital rubella.

Congenital rubella is a potentially preventable disease. Vaccination policy in this country is currently aimed at two main target populations; all peripubertal schoolgirls, irrespective of their serological status, and women of child-bearing age known to be seronegative to rubella. Many women in the latter group are identified by General Practitioners or by Occupational Health Clinics, but the largest group is undoubtedly represented by pregnant women who should be vaccinated immediately after delivery to protect them from rubella infection during a subsequent pregnancy. Despite the large amount of effort currently devoted to screening such women during pregnancy and vaccinating those found to be seronegative, remarkably little is known about the overall ability of this program to prevent congenital rubella.

Multiple difficulties for the successful operation of such a program can be envisaged. First, 40% of congenitally infected babies are born to primiparas so that vaccination post partum could, at best, be expected to eliminate only 60% of cases. Second, no screening test is currently available which combines 100% sensitivity with a complete absence of false-positive reactions so that occasional laboratory errors are inevitable. Third, some susceptible women may fail to be given vaccine due to administrative errors, especially if they wish to return home only a few hours after delivery.

Given these varied theoretical problems, the present study was undertaken to identify pregnant women who had been screened for rubella antibodies during a previous pregnancy. The aim was to determine whether this program had resulted in a significant reduction in the number of women running the risk of contracting rubella infection during a subsequent pregnancy.

Patients and methods

DETECTION OF ANTIBODIES AGAINST RUBELLA

As previously described antibodies were measured in sera diluted 1/16 by haemagglutination inhibition (HI) after treatment with kaolin to remove non-specific inhibitors, using overnight incubation to increase sensitivity.

PATIENTS

As part of a continuing prospective study which began in 1975, all women attending the antenatal clinic of this hospital are being followed serologically, from the time of booking until delivery, for evidence of infection with rubella or cytomegalovirus. Booking sera are tested for the presence of antibodies against rubella and the patients are reported simply as being “susceptible” or “immune.” When these laboratory
reports are received by the antenatal clinic the medical notes of the susceptible patients are stamped with the words “rubella vaccine” on the pages reserved for the midwives’ labour notes. In addition, a preprinted sheet of paper explaining the need for rubella vaccine is attached to the postnatal pages. This sheet contains the words “rubella vaccine required post partum” and has space for the midwife to indicate her name and the date and time that she administers the RA27/3 vaccine. This sheet is completed after informed consent has been obtained and the lower half, containing a reminder not to become pregnant again for at least three months, is given to the patient. As an additional means of ensuring good vaccine uptake, sisters on the postnatal wards are asked to be particularly vigilant in checking that vaccine has been given to women previously reported to be susceptible to rubella infection.

For the present study, patients were identified from our records when they rebooked at this hospital for antenatal care during a subsequent pregnancy. Women were recruited prospectively in this manner until 1000 had been enrolled consecutively. The first woman was recruited in March 1977 and delivered in August of that year. The last woman was enrolled in January 1981. All eligible women were included in the study, irrespective of the outcome of their initial pregnancy.

It should be noted that the term “initial pregnancy” is used to denote the first time that a particular woman was studied by us; it does not necessarily mean that she was, at that time, a primigravida.

Results

The results presented in Table 1 show that 895 (89.5%) of the 1000 women were reported to be immune to rubella in their initial pregnancies. When they returned for further antenatal care 887 (99.1%) of these women were still immune. Sera taken during the initial pregnancies were still available from five of the eight women giving discordant results. When retested, none of these sera contained HI activity suggesting that the earlier results had been false-positive reactions attributable to the presence of non-specific inhibitors rather than to low concentrations of true antibody. This conclusion was subsequently confirmed when two of the sera were tested by single radial haemolysis and were found not to contain rubella-specific antibody. It was assumed that false-positive reactions had likewise been given by the three further sera mentioned above which were not available for retesting by HI or by single radial haemolysis.

One hundred women were initially reported to be susceptible but only 10 (10%) of them remained so when they were tested in a subsequent pregnancy. The medical records of these 10 women were examined and it was found that vaccine had been administered to only three of them. For the purposes of the present analysis, it was assumed that all initially susceptible women who subsequently produced antibodies had gained their immunity from vaccination. However, since fairly extensive rubella epidemics occurred in 1978 and 1979, it cannot be ruled out that a few of the women failed to respond to the vaccine and became naturally infected after delivery. Five women were in fact known to have been infected with rubella virus during pregnancy; all five infections occurred during the initial pregnancies of the women concerned.

All of these results were further analysed to determine the efficacy of each stage of the screening and selective vaccination program. As shown in Table 2, the true proportion (excluding laboratory false-positive reactions) of seropositive women was 88·7% (887/1000) initially which increased significantly to 98·2% (977/995) when the same women were tested during a subsequent pregnancy (p < 0·001). The efficacies of the vaccine and laboratory were 96·8% and 92·6% respectively while the midwives managed to administer vaccine to no less than 93·9% of those women reported to be susceptible. Overall, 108 women had been truly susceptible initially and immunity was subsequently induced in 90 of them; an efficacy for the whole program of 83·3%. The total number (18) of therapeutic failures could readily be classified into one of three main categories. The largest group (eight cases) resulted from false-positive HI results so that truly seronegative women were not identified as requiring vaccine after delivery. The second group (six cases) were susceptible women who had not been given vaccine. Two of these women delivered as emergencies at other hospitals (one had a normal baby, one a spontaneous abortion). Two women required urgent surgical intervention around the time of delivery (emergency caesarean section, evacuation of retained products of conception after an inevitable abortion). One further woman had aborted spontaneously. Thus, of the six women in this second

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Results of testing for immunity against rubella virus in initial and subsequent pregnancies of 1000 women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initially reported to be immune*</td>
<td>895</td>
</tr>
<tr>
<td>Still immune in a subsequent pregnancy</td>
<td>887 (99·1%)</td>
</tr>
<tr>
<td>Presumed false-positive HI results</td>
<td>8 (0·9%)</td>
</tr>
<tr>
<td>Initially reported to be susceptible*</td>
<td>100</td>
</tr>
<tr>
<td>Still susceptible in a subsequent pregnancy</td>
<td>10 (10%)</td>
</tr>
</tbody>
</table>

*Five women who were initially susceptible but who seroconverted during pregnancy have been excluded.
Table 2  Efficacy of serological testing for immunity against rubella during pregnancy coupled with selective vaccination post partum

<table>
<thead>
<tr>
<th>Efficacy of serological testing</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of women truly seropositive initially</td>
<td>887/1000† = 88-7</td>
</tr>
<tr>
<td>Proportion of women seropositive subsequently*</td>
<td>977/995† = 98-2</td>
</tr>
<tr>
<td>Efficacy of vaccinea</td>
<td>90/93 = 96-8</td>
</tr>
<tr>
<td>Efficacy of obstetric practiceb</td>
<td>93/99 = 93-9</td>
</tr>
<tr>
<td>Efficacy of laboratory screeningc</td>
<td>100/108 = 92-6</td>
</tr>
<tr>
<td>Efficacy of whole programd</td>
<td>90/108 = 83-3</td>
</tr>
<tr>
<td>Eighteen program failures attributed to:</td>
<td></td>
</tr>
<tr>
<td>Laboratory error</td>
<td>8 = 8</td>
</tr>
<tr>
<td>Obstetric practice</td>
<td>6 = 6</td>
</tr>
<tr>
<td>Vaccine failure</td>
<td>3 = 3</td>
</tr>
<tr>
<td>Vaccine contraindication</td>
<td>1 = 1</td>
</tr>
</tbody>
</table>

* Five women who seroconverted during pregnancy have been excluded.
† χ² = 73-2; p < 0-001.

a No susceptibles rendered immune/No vaccinated.
b No vaccinated/No in whom vaccination recommended.
c No initially reported to be susceptible/No truly susceptible.
d No subsequently rendered immune/No originally truly susceptible.

group, only one had had an uncomplicated delivery at this hospital. In contrast, all of the three women in the third group (true vaccine failures) had had normal deliveries (p = 0-048). In one woman, live rubella vaccine was contraindicated because she was a renal allograft recipient being treated with prednisolone and azathioprine.

Finally, since each woman had been advised to avoid becoming pregnant for at least three months after vaccination, it was of interest to determine if this advice had been followed. The time taken for the 93 vaccinated women to return with a subsequent pregnancy was calculated and only one woman reported her subsequent LMP to be within 12 weeks of her previous delivery. The precise timing was 11-6 wk so she can be said to have obeyed the instruction not to conceive within three months. To determine whether this reassuring finding for the group of vaccinated women had resulted from the advice given, or was merely a manifestation of natural puerperal subfertility, the same calculation was performed for a group of 93 control women. Each control was chosen because she had been immune to rubella initially and had been entered into the prospective study at the same time as a vaccinated woman. The mean time (86-9 wk) taken to become pregnant again was longer for the 93 vaccinated women than for the 93 controls (76-9 wk) but the
is post partum rubella vaccination worthwhile?

difference (Figure) did not reach statistical significance (p = 0.15).

Discussion

This study has clearly shown that a program of screening for rubella antibodies, coupled with selective vaccination post partum, is of benefit to those it is intended to help, namely initially seronegative women who become pregnant again. In a group of 1000 consecutive women, 11-3% were initially susceptible to the infection but this proportion had fallen dramatically to only 1.8% when the same women returned for further antenatal care (p < 0.001). This increase in herd immunity would be expected to reduce the incidence of rubella infection during pregnancy, and this was indeed the case. During the study, two moderately extensive rubella epidemics occurred in 1978 and 1979. Five of the women described here were infected while pregnant but, in each case, this occurred during their initial pregnancies, not their subsequent ones (p = 0.033).

Although these results are encouraging, it must be admitted that the rubella screening program was not completely effective since 18 failures were identified at three distinct stages. Firstly, the laboratory test employed (HI) produced eight false-positive reactions so that only 99.1% of women were initially identified as requiring vaccination post partum. These eight women therefore remained unprotected throughout their subsequent pregnancies. The false-positive reactions were presumably produced by failure to remove completely non-specific inhibitors, a problem with the HI test which is well recognised.\(^7\)\(^8\)\(^9\)\(^10\) As a result we have now changed our screening program to utilise single radial haemolysis, a technique which is not affected by such non-specific factors, and we hope virtually to eliminate false-positive laboratory errors.\(^5\)\(^7\)\(^8\)\(^16\)

Secondly, seven women were identified as being susceptible but were not given vaccine post partum. In one woman, vaccination was contraindicated for medical reasons but the remaining six cases were admitted lapses in obstetric practice. Only one of these six women had a normal delivery so it seems probable that their medical attendants had been understandably preoccupied with acute clinical problems when the vaccine should have been given. In practice, it may be difficult to improve upon the already excellent 93.9% efficacy of the midwifery staff but, in theory, this could be achieved by paying particular attention to the vaccine requirements of clinically demanding cases, particularly those women who deliver, or abort, as emergencies at distant hospitals.\(^10\) Finally, the vaccine itself failed to induce immunity in three women. These cases were not clustered in time and so cannot be explained by deterioration of a particular batch of vaccine. Such sporadic examples of true vaccine failure have been well recognised by others.\(^17\)\(^18\)

As part of the program described here, each seronegative woman was asked to sign a standard form stating that the need for rubella vaccination had been explained to her and that she understood she should not become pregnant again for at least three months.\(^19\) In practice, the mean time from delivery to subsequent conception was shown to be 10 weeks longer for the group of women who were vaccinated than in a control group. Whether or not this delay in conception was the result of the medical advice offered to such women is a matter for conjecture, but the important point is that all of the 93 vaccinated women followed the instruction.

In summary, we have shown that screening pregnant women for the presence of antibodies against rubella, coupled with selective vaccination post partum, can effectively increase herd immunity. We believe this to be an important means of helping to eliminate congenital rubella infection and, since it is simple to organise, one which should be vigorously encouraged.

We wish to thank the medical and nursing staff of the Obstetric Department for their enthusiastic cooperation and members of the Virology Department for technical assistance. Financial support was provided by the Wellcome Trust.

References

3 Department of Health and Social Security. 1976 Circular 4/76.
5 Goldwater PN, Quiney JR, Banatvala JE. Maternal rubella at St Thomas' hospital: is there a need to change British vaccination policy? Lancet 1978;ii:1298-300.


Requests for reprints to: Dr PD Griffiths, Virology Department, St Bartholomew’s Hospital, West Smithfield, London EC1A 7BE, England.