RUBELLA VACCINATION IN THE PUERPERIUM

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Horstmann, Liebhaber, and Kohorn (1970) reported on the administration of Cendehill rubella vaccine to seronegative and seropositive women in the puerperium. Their study was conducted in New Haven, Connecticut.

This paper gives the results of a similar but smaller study made on women delivered at Queen Charlotte's Maternity Hospital. It was undertaken to ascertain whether it is safe, effective, and practicable to give Cendehill vaccine in the puerperium, and to provide figures for estimating the costs of vaccination against rubella in the postpartum period.

Following extensive trials with living attenuated rubella virus vaccines, the Department of Health and Social Security stated in January 1970 that the Cendehill vaccine was available for use in Britain (Leading article, 1970); in pursuance of public policy, the vaccine will be given to adolescents, that is, to girls between their 11th and 14th birthdays (Leading article, 1970). It will be some years before the full effects of a policy to vaccinate schoolgirls will be evidenced by a reduction in the number of children born with congenital rubella, and meanwhile some fertile women remain at risk of German measles, especially during early pregnancy.

Although the Cendehill vaccine has side effects, it is safe. It has the disadvantage of having to be given parenterally, but it does not carry the hypothetical risk of transmission of human genetic material, as does the intranasal RA 27/3. The virus may be excreted by the individual, after vaccination, but it is not communicated to others, even in closed communities (Dudgeon *et al.*, 1969), and thus is not a hazard to other susceptible women in early pregnancy. Its side effects, which include pyrexia and sore throat, adenopathy, and allergic rashes, are transient and mild, and its use is less frequently complicated by arthralgia than are other parenteral rubella vaccines. Successful vaccination does not preclude reinfection with rubella virus (Detels *et al.*, 1969) and should such infection occur during pregnancy there is risk of damage to the fetus. However, in these circumstances, virus replication is likely to be confined to the nasopharynx, and serum antibody

should prevent viraemia and transmission to the fetus. Thus, the vaccine should protect against congenital rubella. There is no evidence that attenuation of the virus is associated with a reduction in teratogenicity, and preliminary findings suggest that the vaccine is transmitted across the placenta to the fetus (Vaheer *et al.*, 1969). It must not be given if there is any possibility of the recipient becoming pregnant within eight weeks of vaccination, and, if vaccination is inadvertently given during pregnancy, termination must be considered. For these reasons, rubella vaccine is unpromising in women of childbearing age unless pregnancy can be avoided.

The chances of conception are least in the immediate puerperium, which is probably the safest time to attempt rubella vaccination on a large scale in adult women.

This paper presents the results of a pilot study undertaken to assess the practicability, safety, and costs of offering vaccination with the Cendehill virus to women at risk, during the puerperium.

METHODS

Two hundred and forty-five consecutive sera sent for booking tests (serological tests for syphilis) were screened for rubella antibodies using a haemagglutination inhibition technique (Stewart *et al.*, 1967) as modified by the Central Public Health Laboratory, Colindale. Sera were inactivated at 56°C for 30 minutes and were pretreated with heparin and manganous chloride, since this method provides a reliable means of removing serum inhibitors (Mann, Rossen, Lehigh, and Kasel, 1967).

Four H.A. units of rubella virus haemagglutinin (Burroughs Wellcome, or Colindale) and a 0.25% suspension of 1-day-old chick cells were used in the tests, which were done in WHO perspex plates. Known positive and negative human control sera were included in each batch, and the end point was taken as the highest dilution of serum showing complete inhibition of agglutination. Booking sera were screened at dilutions of $\frac{1}{16}$ and $\frac{1}{64}$, and patients with a titre less than $\frac{1}{16}$ were regarded as seronega-

tive. Titration up to at least 1/512 was performed on postnatal sera.

Although patients had already been examined in the booking clinic, they were again interviewed by one of us (M.F.R.), and very careful enquiries were made about past history of rubella. If the woman was foreign, these enquiries were couched in appropriate words from her own language.

Seronegative patients were offered vaccination during the first seven days of the puerperium. Their vulnerability to German measles and the potential risk of the disease to future pregnancies were explained. The minor illness which might follow vaccination was described, including the possibility of a mild arthralgia. Reassurance was given that vaccination would not interfere with breast feeding, or make them infectious to others (Martin Du Pan *et al.*, 1968), and they were warned that, as a living virus was used, pregnancy within eight weeks of injection was contraindicated.

Women volunteering for vaccination received, if their health was good, a subcutaneous injection of a suspension of the Cendehill strain of live attenuated rubella virus vaccine. They were asked to report any subsequent malaise to us, or to their general practitioners, but no attempt was made by us to assess side effects by direct questioning.

An appointment was made for each vaccinated patient to be seen at the postnatal clinic, when a venous blood sample was taken and examined for rubella antibodies.

RESULTS

A rubella HAI titre of $\frac{1}{16}$ or greater was found in 82.5% (202/245) patients who were regarded as immune.

TABLE I

RELATION BETWEEN HISTORY OF RUBELLA AND SEROLOGICAL TESTING

History of German Measles (no. of patients)	Antibodies Present (Titre $\frac{1}{16}$)	No Antibodies (Titre $\frac{1}{16}$)
Positive 75	70	5
Negative 129	95	34
Unknown 41	37	4
Total 245	202	43

Table I analyses the relationship between history of rubella and serological testing. Only 7% (5/75) of women with a positive history of rubella were seronegative, compared with 22% (38/170) of women with a negative or doubtful history.

Vaccination was performed in 29 of 43 seronegative (susceptible) women and the reasons for not vaccinating 14 subjects are given in Table II.

TABLE II
OUTCOME OF OFFERING POST-PARTUM VACCINATION
TO 43 PATIENTS WHO WERE SERONEGATIVE ON
SCREENING

Vaccinated	29
Not vaccinated	14
Vaccination declined	2
Vaccination declined, family complete	2
Rubella infection during pregnancy	1
Puerperal illness prevented vaccination	3
Abortion or defaulted	6

All the vaccinated subjects who were retested (22) developed rubella antibody subsequent to vaccination. One patient (case 22) was found on retesting to be seropositive, and seven patients did not attend the follow-up clinic (Table III).

TABLE III

Case	Rubella HAI Titres		Time (days) between Date of Vaccination and Date of Retesting
	Prevaccination	Postvaccination	
1	> 1/16	1/64	37
2	> 1/16	1/32	36
3	> 1/16	1/128	43
4	> 1/16	1/128	44
5	> 1/16	1/256	43
6	> 1/16	1/128	43
7	> 1/16	≥ 1/512	47
8	> 1/16	1/1024	36
9	> 1/16	1/32	36
10	> 1/16	1/128	36-39
11	> 1/16	1/128	40
12	> 1/16	1/64	41
13	> 1/16	1/256	39
14	> 1/16	1/128	40
15	> 1/16	1/128	41
16	> 1/16	≥ 1/512	34
17	> 1/16	1/32	39
18	> 1/16	1/256	35
19	> 1/16	1/128	55
20	> 1/16	1/164	37
21	> 1/16	1/64	37
22	< 1/64	1/128	37

Cases 23 to 29 did not attend for postvaccination testing.

No significant ill effects were reported by the vaccinated patients.

DISCUSSION

In this study, 82.5% of patients were shown to have a significant titre of circulating rubella antibodies. The figure is in agreement with the findings of a large survey conducted by the Public Health Laboratory Service Working Party (1970).

A history of German measles is thought to be unreliable evidence of past infection with rubella, and, indeed, Banatvala *et al.* (1970) have emphasized that a clinical diagnosis of rubella is itself inaccurate in a high proportion of cases. Brown, Hambling, and Ansari (1969) reported that only 71% of patients who gave a history of German measles had rubella antibodies. The high correlation

(93%) between positive history and positive serological findings in our series is remarkable. It is probably attributable to the care of the interviewer and is unlikely to be reproducible in the average, busy, antenatal clinic. Only 7% of women with a positive history were susceptible, whereas 22% of women with negative or unknown histories were without protection.

Not all patients at risk require vaccination, since no further pregnancies may be envisaged. Two of our 43 susceptible patients declined vaccination for this reason. Vaccination may also be considered undesirable by reason of illness during the puerperium, and it may be refused when offered. About 70% of patients at risk were finally vaccinated.

No ill effects were reported by the 29 vaccinated subjects. Although Horstmann *et al.* (1970) reported mild adverse effects in 30% of their seronegative vaccinated subjects, it is probable that information on these effects can be elicited only on direct questioning. They were not reported by any of our patients. Seroconversion (detectable antibody $\frac{1}{32}$ minimum) occurred in all cases. This compared favourably with the findings of Dudgeon *et al.* (1969) and Horstmann *et al.* (1970) using the same vaccine.

We undertook this study to ascertain whether it is safe, effective, and practical to vaccinate women in the puerperium. We are satisfied that the vaccine is safe and effective. Since it is also safe to give vaccine to seropositive subjects (Dudgeon *et al.*, 1969), the policy of the vaccination programme will probably be determined on cost and availability of personnel, and four schemes are possible:

(1) *Vaccination of all puerperal patients without preliminary serological testing*

This involves offering treatment to the total population to protect the 15–20% at risk (17.5% in our series).

(2) *Vaccination of those with negative or doubtful history of rubella, without preliminary serological testing*

This means treating 60–70% of puerperal patients (69% in our series), and presupposes most careful enquiry into the history of the antenatal clinic to separate those with a positive history. This scheme will leave unprotected about 7% of susceptible patients; these are women with a positive history, who are negative on serological testing.

(3) *Screening (HAI) all patients antenatally; vaccination of seronegative patients*

This involves investigation of the total population to detect 15–20% at risk (17.5% in our series), who will be offered vaccination.

(4) *Screening (HAI) patients with negative or*

unknown history of rubella; vaccination of seronegative patients

Again, this scheme will leave untreated the women who are seronegative but give a positive history. Thus vaccination will not be offered to 7% of susceptible women.

We have costed vaccine, reagents and apparatus, and the labour of laboratory, administrative, and other personnel required for each of the above schemes for a population of 5,000 pregnant women using the figures derived from our sample (Table IV). Where HAI is done, the costing applies only to work done on samples already collected and sent to the laboratory for the antenatal booking tests. The cost will be greatly increased if separate specimens are collected. Only major items of expenditure, including medical and nursing time, and total cost of HAI test are detailed. Thus the comparative costs are approximate, and items such as time spent by supplies department and pharmacy are excluded.

If protection on a large scale is to be undertaken, vaccination in the puerperium offers the most

TABLE IV
COMPARISON OF COSTS OF MAJOR ITEMS OF EXPENDITURE, AND OF MEDICAL AND NURSING TIME*, FOR FOUR SCHEMES FOR POSTPARTUM VACCINATION AGAINST RUBELLA
(Total population 5,000 parturient women)

<i>Scheme 1: Vaccination of all puerperal patients without preliminary serological testing</i>			
Vaccination of 5,000 women	£3,833		
Midwife's time to explain need and to obtain consent	£ 489	833 hours	
Doctor's time to vaccinate	£ 753	583 hours	
Approximate total cost	£5,075		
<i>Scheme 2: Vaccination of those with negative or doubtful history of rubella, without preliminary serological testing</i>			
Vaccination of 3,450 women	£2,645		
Midwife's time to elicit history in ANC, and to explain need and obtain consent	£ 434	741 hours	
Doctor's time to vaccinate	£ 519	402 hours	
Approximate total cost	£3,698		
<i>Scheme 3: Screening (HAI) all patients antenatally; vaccination seronegative patients</i>			
Serological testing of 5,000 women	£2,198		
Vaccination of 900 women	£ 690		
Midwife's time to explain need and obtain consent	£ 88	150 hours	
Doctor's time to vaccinate	£ 136	105 hours	
Approximate total cost	£3,112		
<i>Scheme 4: Screening (HAI) patients with negative or unknown history of rubella; vaccination of seronegative patients</i>			
Serological testing of 3,450 women	£1,511		
Vaccination of 759 women	£ 582		
Midwife's time to elicit history in ANC, and to explain need and obtain consent	£ 171	292 hours	
Doctor's time to vaccinate	£ 115	89 hours	
Approximate total cost	£2,379		

*Average costs are given, allowing 2 minutes to elicit history, 1 minute to explain benefit of vaccination, and 7 minutes for vaccination.

The costs are based on findings of the survey reported here, viz. 17.5% (43/245) of total population are seronegative (taken at 18%); 69% (170/245) of total population have negative or doubtful history of rubella; and 22.3% (38/170) of the latter are seronegative (taken at 22%).

reasonable alternative to vaccination of prepubertal girls, but whichever way it is done, it is costly. However, it is cheaper than the cost of vaccinating girls between 11 and 14 years, for general practitioners are paid fees for vaccination, whereas, since it is not public policy, hospital doctors are not. The costs need not be viewed too pessimistically. The cost of the HAI can probably be reduced greatly, if the test is performed in large centres, and if automation can be introduced.

Schemes 1 and 2 are impracticable in our view, because of the heavy expenditure of medical manpower entailed. It thus seems that serological screening, extensive or limited, is a desirable preliminary to the offering of rubella vaccine in the postnatal period. Perhaps it is pertinent to add that vaccination of fertile patients between pregnancies in no way minimizes costs and may increase demand for termination of pregnancy.

SUMMARY

The Cendehill vaccine is safe and effective when given to puerperal patients. The probable costs of organizing full-scale vaccination programmes in such women are discussed, and it is suggested that serological screening should be undertaken before vaccination is offered. Any other arrangement proves too costly of medical manpower.

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