Papers and Originals

Studies of the Effect of Immunoglobulin on Rubella in Pregnancy

Report of the Public Health Laboratory Service Working Party on Rubella*

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Summary: Studies were done on 5,447 pregnant women given immunoglobulin after exposure to rubella and on 652 adult women similarly at risk but not pregnant and therefore not given immunoglobulin. The amounts of immunoglobulin, of known antibody content ranged from 750 mg. to more than 1,500 mg.; in a few second doses were given. Preinoculation blood samples from both groups showed that about 15% were still susceptible. Second blood samples were obtained from many of the women and nasal and throat swabs from as many index cases as possible. In the development of rubella by susceptible women a major factor was an index case in the same household. Whether judged on the serological evidence alone, or as a result of exposure to a confirmed index case, immunoglobulin in the amounts given did not appear to affect the incidence of rubella by comparison with the uninoculated group. Suppression of clinical manifestations attributable to immunoglobulin was possible in a few instances, but this could also have been an example of natural variation.

Introduction

An interim account of an investigation into passive protection against maternal rubella (P.H.L.S., 1968a) reported on the effect of human normal immunoglobulin given to unselected pregnant contacts of rubella as soon after known exposure as could be arranged. From the preinoculation blood samples tested about 85% were known already to be immune. Among those still susceptible was a subgroup who were contacts of laboratory-confirmed index cases of the disease. For comparison a small group of adult women were included who were rubella contacts but not given immunoglobulin because they were not pregnant at the time. The preliminary results of the investigation showed that immunoglobulin in the dosage used, and the rubella antibody content of which was known, did not appear to be protective against rubella. More information being desirable, the study was continued for a further period and the amount of immunoglobulin being given was also increased to at least 1,500 mg. to see whether a larger dose was more effective.

Schiff (1969) has shown once again that immunoglobulin of high titre, given to susceptible volunteers within 24 hours after inoculation with rubella, will prevent an attack. Experimental conditions in his study differed from the natural course of events in that the lack of immunity of recipients had been ascertained, a single known dose of virus was given in challenge, and the batch of immunoglobulin used was very potent, had been specially prepared, and was immediately available. In more usual circumstances an infected person may excrete rubella virus for up to a week before the illness becomes apparent (McCarthy and Taylor-Robinson, 1967). The chances of a household contact being given immunoglobulin within 24 hours of first exposure must therefore be small, and outside the household a number of days may for various reasons elapse after a clinical diagnosis has been made in the index case before action is taken. Infection is also much more likely to occur when repeated exposure is possible. A much increased incidence of rubella has been noted in susceptible persons who were contacts of an index case in the same household (P.H.L.S., 1968a). Though special high-titre antirubella immunoglobulin may well be effective, its preparation on an adequate scale presents difficulties.

The basic problem has been whether the available immunoglobulin given after exposure to rubella, provides any protection against infection. If it should do so, even to the extent of suppressing the disease clinically, will such protection be sufficient to prevent fetal abnormality? To try to answer this, the investigations have been concentrated on whether immunoglobulin, given in different amounts to women chiefly in the first trimester of pregnancy who have been in contact with rubella, has reduced the incidence of the disease compared with its development in susceptible women contacts also exposed to rubella but not given immunoglobulin because they were not pregnant at the time. The results, part of which have already been published (P.H.L.S., 1968a), form the basis of this report.

Laboratory Methods

The methods used in these investigations have, in the main, been described previously (P.H.L.S., 1968a). Preinoculation blood samples and in many instances, particularly from those initially without antibody, second blood samples were collected, the latter mostly between 5 and 10 weeks later. Nasal and throat swabs were also procured from as many of the reported index cases as possible. Virus isolation and serum neutralization techniques remained unchanged, but the haemagglutination-inhibition test (Stewart *et al.*, 1967; Field *et al.*, 1967) was introduced during the last phase of the study. For this test most sera were pretreated with kaolin to remove the non-specific inhibitors of rubella virus haemagglutinin, but in some laboratories the alternative method with manganese chloride and heparin (Dold and Northrop, 1968) was in use. The haemagglutination-inhibition test appeared as reliable an indicator of past infection as did the neutralization test, and the more rapid availability of results was an advantage. In a small number who lacked antibody such results made possible the administration of a further dose of immunoglobulin. For assessment of the effect of immunoglobulin on rubella, patients whose sera had titres of less than 1/4 by neutralization or less than 1/8 by haemagglutination-inhibition test were regarded as lacking antibody and therefore fully susceptible.

The co-ordination of all aspects of the study by the Epidemiological Research Laboratory, including the col-

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lection and tabulation of information has previously been referred to (P.H.L.S., 1968a). Similarly, the haemagglutination-inhibition titres of batches of human normal immunoglobulin used, ranging from 1/3,200 to 1/12,800, have been reported (P.H.L.S., 1968b).

Results

A total of 5,447 pregnant women received immunoglobulin in varying amounts as a result of contact with a clinically diagnosed case of rubella; 2,258 (41·5%) were household contacts of a case, 2,992 (55%) were in contact outside their household, and for the remaining 197 the type of contact was not reported. The duration of pregnancy and the susceptibility of the contacts at the time of inoculation is shown in Table I and the distribution by area in Table II. (For their age range see Table IX). Despite the geographical scatter the proportion susceptible was fairly consistent, being overall 15·8%. A total of 860 were found susceptible—337 (16·3%) out of 2,069 tested by neutralization and 523 (15·5%) out of 3,378 tested by haemagglutination-inhibition. These findings indicated that the area of residence and the method of testing the sera did not provide any distinguishing feature in women joining the study.

Of the 5,447 women, 1,079 were given a larger initial dose of immunoglobulin than 750 mg.; 1,066 of whom 171 (16%) were found to be susceptible, received 1,500 mg.; two received 2,250 mg., and 11 received 3,000 mg. Also, 164 women, of whom 137 were susceptible, received a second dose of immunoglobulin, the amount recommended being 1,500 mg.

Rubella in Susceptible Pregnant Contacts

Of the 860 women classed as susceptible, 695 (81%) provided second samples of serum; 119 (17%) of these showed a fourfold or greater rise in titre, indicating infection with rubella in the intervening period. Of the 860, 340 were household contacts; 270 of these provided second sera and 70 (26%) developed rubella. From the remainder 425 provided paired sera and 49 (11·5%) developed rubella. The number with serological evidence of rubella despite receiving immunoglobulin (Table III) did not vary significantly for the different amounts given, though in 19 women the dose received was not recorded. Clinical rubella with manifestations including rash, lymphadenopathy, fever, and arthritis occurred in 68; the attack was subclinical in 48, and in three the information was lacking. As shown in Table IV even the larger amounts of immunoglobulin used appeared to have little effect in suppressing clinical rubella. Again, six cases had to be omitted from the table for lack of information on type of illness or on dosage.

A serious difficulty in this study of prophylaxis against rubella was the interval between the first contact with an index case and inoculation of the pregnant woman with immunoglobulin. The overall median time was three to four days, but the range was from the first day of contact to more than 20 days after. This variation, as it affected 115 women who developed rubella, is shown in Table V.

TABLE I.—*Duration of Pregnancy and Susceptibility of Contacts.*

Duration of Pregnancy (weeks)	No.	No. Susceptible to Rubella		
		N.T.	H.I.T.	Total
1–4	461	22	39	61
5–8	2,105	123	186	309
9–12	1,847	117	187	304
13–16	612	46	61	107
17+	107	8	6	14
Not known	315	21	44	65
Total	5,447	337	523	860

N.T. = By neutralization. H.I.T. = By haemagglutination-inhibition.

TABLE II.—*Pregnant Contacts According to Area.*

Laboratory	No. Examined	Susceptible	
		No.	%
Bedford	209	43	20·6
Bristol	797	114	14·3
Coventry	515	64	12·4
Leeds	560	74	13·2
Liverpool	456	58	12·7
London (Colindale)	2,773	479	17·3
Newcastle	137	28	20·4
Total	5,447	860	15·8

TABLE III.—*Occurrence of Serologically Confirmed Rubella in Susceptible Pregnant Contacts Given Immunoglobulin.*

Dose of Immunoglobulin Given	Antibody Titre		Total
	Unchanged	Fourfold or Greater Rise	
750 mg. or less	451	91 (17%)	542
1,500 mg. or more	109	25 (23%)	134
Not known	16	3	19
Total	576	119	695

TABLE IV.—*Immunoglobulin Dose and Type of Rubella.*

Dose of Immunoglobulin Given	Serologically Positive Rubella (Fourfold or Greater Rise in Titre)		Total
	Subclinical	Clinical (with Rash)	
750 mg. or less	35	54 (61%)	89
1,500 mg. or more	12	12 (50%)	24
Total	47	66 (58%)	113

TABLE V.—*Interval between Contact and Inoculation with Immunoglobulin in Women Who Developed Rubella.*

Rubella	Days							Total
	0–1	2	3	4	5–6	7–10	11–20+	
Clinical	14	6	7	8	12	10	8	65
Subclinical	6	10	13	3	5	8	5	50
Total	20	16	20	11	17	18	13	115

Virus Isolation from Index Cases

In studying the effect of immunoglobulin it was considered essential to have at least a small group of treated susceptible pregnant women who had been in contact with an index case of rubella from whom virus was isolated. When at all possible, therefore, nasal and throat swabs from the index cases were examined. The varying circumstances in which these index cases came to light made it unlikely that a high proportion would be swabbed, or that a high isolation rate would be attained. Ultimately, swabs taken from 1,932 cases yielded 402 strains of rubella virus. In 331 (82%) instances virus was recovered from both nose and throat and 97% of the isolations were made from patients with clinical rubella, including a rash. Most isolations were made from the specimens collected within 48 hours of the appearance of the illness (Table VI). Successful virus isolation also varied with the age of index cases (Table VII), the proportion being much lower in young children.

Among the 402 pregnant contacts of index cases from whom rubella virus was isolated 75 were found to be still susceptible, and paired samples of serum were obtained from 66 of these. Despite the immunoglobulin which was given, rubella occurred in 31 of the 66, 19 having clinical manifestations. The type of contact is shown in Table VIII; 40 were of the same household as the index case and 26 of them de-

veloped serological evidence of rubella; 22 were not household contacts of an index case and only three developed rubella. This indicates a highly significant difference between infection rates for household and non-household susceptible contacts ($P<0.001$). Again, 179 of the 402 were known to have received 750 mg. of immunoglobulin. From 29 of these, initially susceptible, 26 paired samples of sera were obtained and in 18 rubella had developed. Another 83 were known to have received 1,500 mg. of immunoglobulin; of these, 17 were initially susceptible, 14 had provided paired samples of serum, and eight had developed rubella. Despite the small numbers it is evident that the attack rates give little support to the possibility of either dose of immunoglobulin affording protection.

As already stated, of 164 women given a second dose of immunoglobulin 137 were shown to be susceptible. Paired samples of serum were obtained from 102 of them and 23 were found to have developed rubella. Only 12 out of the 102 were contacts of a confirmed index case, but among these 12 rubella developed in seven compared with 22 out of 50 similar contacts given a single dose. Though the timing varied, 90% of recipients received their second dose within 13 days of the first, yet this mode of giving immunoglobulin also failed to reveal any protective effect.

TABLE VI.—*Isolation of Rubella Virus from Index Cases.*

	Days after Rash on which Swabs Taken					Total
	0–2	3–4	5–6	7–10+	N.S.	
No. examined	864	620	213	152	83	1,932
No. positive	228 (26)	113 (18)	33 (15)	21 (14)	7 (9)	402 (21)

Percentages given in parentheses.
N.S. = Not stated.

TABLE VII.—*Isolation of Rubella Virus According to Age of Index Case.*

	Age of Index Case (Years)						Total
	0–2	3–5	6–9	10–15	16–20+	N.S.	
No. examined	780	480	347	71	127	127	1,932
No. positive	57 (7)	130 (27)	127 (37)	22 (31)	54 (43)	12 (9)	402 (21)

Percentages given in parentheses.
N.S. = Not stated.

TABLE VIII.—*Rubella in Susceptible Pregnant Contacts with Known Exposure.*

Type of Contact	No. Giving Paired Sera	No. with Fourfold Rise
Household	40	26
Non-household	22	3
Not known	4	2
Total	66	31

Indication of Possible Reinfection

Because reinfection might constitute a risk to the fetus, a check was made of the occasions on which a fourfold or greater rise in rubella antibody was found in treated pregnant contacts whose first serum contained some antibody. This occurred in 28 (1·8%) of 1,549 contacts from whom paired samples of serum had been obtained. In 20 tested by neutralization the initial serum titre did not exceed 1/16, and in six out of eight tested by haemagglutination-inhibition it did not exceed 1/32, the others being 1/64 and 1/128 respectively. Though it may not be correct, the most likely explanation is that in at least 26 these were primary infections and that the first sera were taken at the stage when circulating antibody was beginning to appear.

Rubella in Susceptible Adult Women not Pregnant

As has been described (P.H.L.S., 1968a) an additional though not a strictly matched control group of women of child-bearing age was included in the study. These women, 652 in number, were not pregnant at the time and had not received immunoglobulin despite possible contact with rubella. Serum samples were collected in similar fashion to the pregnant contacts, together with information on the development of rubella and nasal and throat swabs from index cases. Though drawn from within the same age range as the pregnant contacts (Table IX) these non-pregnant women had an average age of 32 compared with 27 for the former because for the most part they were mothers who sought medical advice as a result of the appearance of rubella in their families. For the same reason a greater proportion, 569 out of the total of 652, were household contacts of an index case. On account of their greater age the 12·7% (83 out of 652) who lacked antibody was somewhat less than the overall 15·8% among the pregnant contacts but within the scatter found in the different areas (Table II). Among those found susceptible the age difference is less, averaging 29 years for those not pregnant and 27 for those pregnant.

Second serum samples were obtained from 62 (75%) of the 83 women initially susceptible and 25 were found to have had rubella in the interval, an incidence of 40%. Twenty-three, of whom 22 had clinical manifestations, were household contacts of an index case, and it may be noted that 569 (87%) of the non-pregnant contacts were members of the same household as an index case, compared with only 2,258 (41·5%) of those who were pregnant. The chance of a susceptible household contact developing rubella has already been shown to be considerably greater. Among this group also, rubella virus was isolated from 258 (52·4%) of the 492 index cases swabbed, one reason for this better isolation rate being that specimens tended to be collected at an earlier stage of the illness. It is possible that diagnosis of the index case was more exact. With a potential risk to the fetus in pregnancy the benefit of the doubt must be given when exposure of the mother to rubella is suspected.

TABLE IX.—*Age Range and Numbers of Pregnant and Non-Pregnant Contacts.*

Contacts	Age Range in Years							Total
	< 20	20–24	25–29	30–34	35–39	40+	N.S.	
Pregnant	236	1,598	1,969	1,076	330	65	173	5,447
Non-pregnant	38	79	135	172	117	92	19	652

N.S. = Not stated.

Exposure to rubella, confirmed by virus isolation from an index case, had occurred in 41 of the adult women without antibody. Paired samples of serum were obtained from 35, 34 of these being contacts of a case in the same household; 17 such household contacts developed rubella, 16 of them with clinical manifestations including a rash. Comparison of susceptible adults exposed to a laboratory-confirmed case of rubella in the same household (Table X) showed no significant difference in the proportion of cases in non-pregnant untreated adults and in pregnant adults given immunoglobulin. The actual attack rate observed was higher among the inoculated pregnant women. In the smaller group of non-pregnant untreated adults 88% of the cases of rubella had clinical manifestations compared with 57% in the larger group of pregnant adults given immunoglobulin. Whether this variation in the proportion of clinical cases is a natural phenomenon or whether the reduction can be attributed to the immunoglobulin is uncertain. If due to the latter the effect cannot be claimed to be more than minimal.

TABLE X.—*Rubella in Women Exposed to a Confirmed Case in the Same Household.*

Group of Women	No. Susceptible	No. Developing Rubella
Non-pregnant	34	17 (50%)
Pregnant*	40	26 (65%)

*All these women had been given immunoglobulin.

Outcome of Pregnancies

Though prevention was the main object of the study, details were sought on the outcome of pregnancies in which the mother had developed rubella. Of the 119 mothers concerned, 42 out of 68 who had a clinical attack and 42 out of 51 with an inapparent infection were reported to have continued their pregnancy. Information was provided on 70 babies born subsequently. A cardiac abnormality was detected at birth in one baby, and rubella virus was isolated from this baby and also from two other babies who were without obvious defects at birth. A follow-up investigation of as many of these babies as possible is being done by Dr. Catherine Peckham and her colleagues at the Hospital for Sick Children, Great Ormond Street, London.

Discussion

In this country the prophylactic use of immunoglobulin against maternal rubella has reached considerable proportions and is based on premises that now appear largely unsound. Antibody studies of different population groups have consistently shown that in about 85% of women of child-bearing age there is evidence of past infection with rubella. In these the injection of immunoglobulin can make only a marginal difference to the circulating antibody, and if it is antibody which protects the fetus from harm the immunoglobulin is not needed. For those without circulating antibody experience has shown they are very liable to develop rubella on exposure, particularly in a residential community (Reid *et al.*, 1970) or when there has been an index case in the same household. It being accepted that high-titre immunoglobulin if given early enough and in sufficient amount may prevent rubella, can the available immunoglobulin have a similar protective effect when used on a considerable scale under the general conditions of medical practice? The finding in this whole study, which confirms that of the preliminary report (P.H.L.S., 1968a), is that immunoglobulin does not protect to any appreciable extent.

There are disadvantages in any procedure which has to provide a cover of immunity after the event. No systematic rubella antibody tests are yet done on sera from women of child-bearing age, so that no advance knowledge is available of the immune state of a pregnant woman who realizes she may have been in contact with a case of rubella. Apart from delays for various reasons before the immunoglobulin can be given, there is the knowledge that index cases are infectious before the illness becomes manifest. There are limits, including economic and of supply, to the amounts of immunoglobulin that can be made available. In the women who took part in the study, when serological conversion by itself was used as an indicator of the development of rubella it did not appear that those who had received immunoglobulin were protected to any significant extent. Nor when the conversion was supported by laboratory confirmation of rubella in an index case did the results appear any less clear-cut, and increasing the amounts of immunoglobulin given was of no obvious benefit.

No investigation of this nature can avoid imperfections such as the gaps between exposure to rubella and inoculation with immunoglobulin, but great care has been taken by many persons over both the epidemiological and laboratory aspects and in securing the co-operation of doctors and patients. It seems clear, however, that immunoglobulin has little effect in preventing maternal rubella and cannot therefore be expected to protect against the possibility of fetal abnormality. Such protection could better be provided for susceptible women by active immunization before the stage of pregnancy is reached.

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