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RUBELLA: REINFECTION OF VACCINATED AND NATURALLY IMMUNE PERSONS EXPOSED IN AN EPIDEMIC*

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Abstract The protective efficacy of vaccine-induced and naturally acquired immunity was compared in a prospective study of a rubella epidemic among military recruits. The population consisted of 190 men in the following categories with respect to immunity to rubella: 26 who were susceptible, 15 vaccinees who had been immunized two to three months previously and 149 who were naturally immune. As a result of the epidemic all 26 susceptible men were infected; rubella virus was recovered from the throats of 11. On the basis of hemagglutination-inhibiting and complement-fixing antibody responses, 80 per cent of those vaccinated and 3.4 per cent of those who were naturally immune were reinfected. Virus was recovered from the throat of one vaccinee, but from none of the reinfected naturally immune men. If precipitin antibody results are included, 100 per cent of vaccinees responded serologically. None of those reinfected became ill; among the susceptible men the ratio of inapparent to apparent infections was approximately 2:1.

A CRITICAL question in immunization against rubella concerns the quality of immunity induced by attenuated-virus vaccines as compared with that achieved through natural infection with wild rubella virus. We have investigated this problem, along with quantitative aspects of the immune response, by comparing reinfection rates in vaccinated and naturally immune persons exposed in the same rubella epidemic.

MATERIALS AND METHODS

Study Population and Procedures

The subjects were military recruits from Hawaii, chosen because of the known high susceptibility rates among young adult residents of the Hawaiian Islands[1,2] and the regular occurrence each year of rubella among recruits of the All-Hawaiian company at Ford Ord, California.[3]

The first phase of the study took place in Hawaii in April and May, 1969. It consisted of collection of blood specimens and administration of rubella vaccine (Cendehill)† subcutaneously to 54 of the men who with 136 others eventually made up the All-Hawaiian company.

The second phase began during the first week of July, when the company formed and proceeded to Fort Ord. The total company consisted of 190 men, of whom 151 were actually from Hawaii. The 39 additional recruits from the continental United States who were assigned to the company were distributed throughout the four platoons.

Abbreviations Used	
CF:	complement fixing
GMK:	green monkey kidney
GMT:	geometric-mean titer
HAI:	hemagglutination inhibiting

During the approximately nine weeks of basic training, all the men were observed for clinical evidence of rubella. Blood specimens were collected from the entire company during the first, sixth and ninth weeks, and throat swabs during the first, fourth, sixth and ninth weeks. In addition, blood samples and throat swabs were obtained from men hospitalized for rubella or other illnesses, and throat swabs were collected from those reporting to sick call for any reason.

Handling of Specimens

Throat swabs were placed in 3 ml of Hanks's balanced salt solution containing 0.2 per cent bovine serum albumin. Blood specimens were separated promptly, and both serums and throat swabs were

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stored at −20°C. All specimens were transported to New Haven on dry ice.

Serologic Tests

Serum specimens were examined for hemagglutination-inhibiting (HAI) and for complement-fixing (CF) antibodies, all specimens from each individual being run in the same test. For the HAI test, nonspecific inhibitors were removed by treatment with dextran sulfate and calcium chloride, according to the method of Liebhaber.[4] The CF antigen was prepared by extraction of rubella infected Vero cells with glycine at pH 9,[5] which yielded antigens with CF titers of 8-16. In the CF test, 2 full U of complement and 4 U of antigen were used.

In addition, the serum samples of some of the men were tested by the immunodiffusion method for antibodies to rubella precipitinogens theta and iota.[6]

Virus Isolation

Throat swabs were examined for rubella virus by inoculation of continuous-line Vero-cell cultures,[7] 0.2 ml per tube, three tubes per specimen. After 12 days' incubation at 35°C, the fluids were harvested, pooled, and inoculated into primary green monkey-kidney (GMK) cells. The presence of rubella virus was detected by the interference method, challenging the GMK cultures with ECHOvirus 11 between the 10th and 12th days after inoculation.[8] In addition, some of the specimens were inoculated as above into JR-GMK cells, a continuous line developed in this laboratory from primary GMK cells. After 12 days, two of the cultures were challenged with ECHOvirus 11, the fluids and cells of the third being harvested and used for a second passage.

Results

Responses to Rubella Vaccine

Fifty-four men were given rubella vaccine in Hawaii two to three months before arriving at Fort Ord, California. Fifteen of them were antibody negative at the time of vaccination, and in all, HAI and anti-theta antibodies developed as a result of vaccination. On arrival at Fort Ord the levels of HAI antibody in this group ranged from 1:16 to 1:128 (Table 1). CF antibodies developed in six of the men who showed seroconversion by HAI test, whereas none had detectable levels of anti-iota antibody in response to vaccine. The 39 men who were antibody positive when vaccinated did not exhibit an appreciable change in HAI, CF or precipitating antibodies after vaccination.

Immune Status of the Population before Exposure to Rubella

When serial blood specimens from the total company were tested for HAI antibodies, it became apparent that on arrival at Fort Ord, the 190 men could be divided into two groups: 26 susceptible (23 of them Hawaiians), and 164 immune men (Table 2). Of the latter, 15 were the vaccinees who had been antibody negative when given the Cendehill strain in Hawaii, and had shown seroconversion. They were classified as *vaccine immune*. The 149 designated as *naturally immune* included the 39 who had been antibody positive and failed to respond to vaccination, and the remaining 110 who were antibody positive at the time the company was formed, as a result of previous infection.

The Epidemic

As in previous years, the Hawaiian recruits experienced an epidemic of rubella while at Fort Ord. The first case developed approximately 17 days after the company was formed, and in the following five days, there were eight more (Fig. 1). There was no second wave. The clinical patterns of illness exhibited by the men were typical: a prodrome of malaise, fever, headache, sore throat, lasting for one to four days and followed by the appearance of a maculopapular eruption on the face, which spread over the trunk and extremities. Temperatures on admission to hospital were between 98 and 102°F, and all but one patient had enlarged posterior cervical or posterior auricular lymph nodes. All recovered without complications and were discharged within three to five days.

The nine cases occurred in seronegative men; no vaccinees or naturally immune men experienced rash disease compatible with rubella.

Table 1. Antibody Responses of 54 Young Adult Hawaiians to Rubella Vaccine (Cendehill Strain).

Group	No. of Men	Time	HAI Antibody			CF Antibody		
			No. Positive	No. Tested	Geometric-Mean Titer	No. Positive	No. Tested	Geometric-Mean Titer
Susceptible	15	Before vaccination	0	15	<8.0	0	15	<8.0
		After vaccination	15	15	34.6	6	15	12.5*
Immune	39	Before vaccination	39	39	82.6	16	33	10.1*
		After vaccination	39	39	89.1	16	33	10.1*

*Antibody-positive men only.

†In calculations, actual values obtained were given numerical assignments as logarithms to base 2: 1/4U = 1; 1/2U = 2, etc.

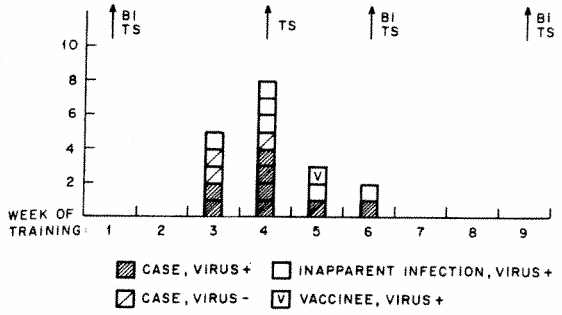

Figure 1. Course of the Epidemic and Times of Collection of Blood Specimens (BI) and Throat Swabs (TS) from the Entire Company.

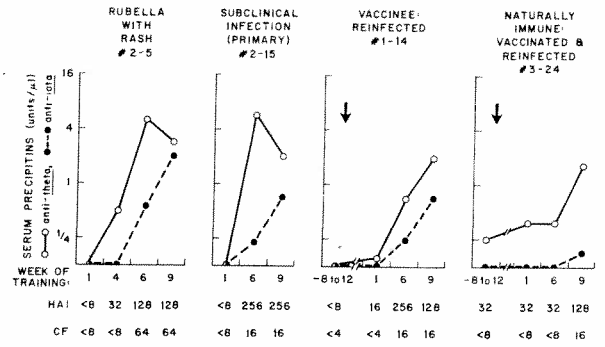

Figure 2. Representative Precipitin Responses in Susceptible Men, Vaccinated Men, and Naturally Immune Men after Infection or Reinfection with Rubella Virus during an Epidemic.

Arrows indicate time of administration of live, attenuated rubella-virus vaccine.

Virus Isolation

From six of the nine patients hospitalized with clinical rubella, virus was recovered from the admission throat swab (Table 3). One patient was still shedding virus one week later, and another 15 days after onset. Specimens from men who had subclinical infection were taken without knowledge of when infection occurred, and therefore many were probably not obtained at optimum times for recovery of the agent. Nevertheless, the three groups with inapparent infection (those with primary subclinical infection, and reinfected men who were vaccine and naturally immune) were comparable in this respect. Virus was recovered from five of the 17 susceptible men with inapparent infection, and from one of the vaccinees. The isolation rate in those with primary subclinical infection was thus 29.3 per cent, as compared to 6.2 per cent for reinfected vaccinees, and zero for reinfected naturally immune men. The amounts of virus recovered were low, second passages being required to obtain a positive result with all but one specimen. The JR-GMK line yielded a few more isolations than the Vero-primary GMK system, but the numbers tested were not sufficient to allow conclusions about its superiority in primary isolation.

Serologic Results

Serologic responses of susceptible and immune men in terms of HAI, CF and precipitating antibodies are summarized in Table 4, and representative antibody patterns are compared in Figure 2. Infection and reinfection rates, based on fourfold or greater rises in HAI or CF antibody levels, are presented in Table 5.

Susceptible men. Examination of the three to five serum specimens from each of the 26 men who had been antibody negative on arrival at Fort Ord revealed that every one had been infected during the course of the epidemic. The conversion rates were 100 per cent for HAI, CF and anti-theta and anti-iota antibodies. With nine cases of clinical rubella and 17 subclinical infections, the ratio of inapparent to apparent infections was approximately 2:1.

Vaccine immune men. Among the 15 men in whom rubella HAI antibody had developed after vaccination, 10 responded to exposure to rubella with fourfold or greater HAI titer rises. Three of the six with vaccine-induced CF antibody also showed substantial boosts, and all nine in whom CF conversions had failed to develop after vaccination did so on exposure to natural rubella. Thus, on the basis of HAI or CF antibody responses, 12, or 80 per cent, of the vaccinees were reinfected (Table 5).

The patterns of response in terms of precipitating

Table 1 (Continued).

Group	Precipitins					
	No. positive for anti-theta	No. tested	Geometric-mean concentration (U/μliter)†	No. positive for anti-iota	No. tested	Geometric-mean concentration (U/μliter)†
Susceptible	0	15	<0.1	0	15	<0.1
	15	15	2.7	1	15	2.0*
Immune	20	20	10.0	10	20	3.0*
	20	20	10.0	10	20	3.0*

*Antibody-positive men only.

†In calculations, actual values obtained were given numerical assignments as logarithms to base 2: 1/4U = 1; 1/2U = 2; etc.

Table 2. Composition of Recruit Company According to Platoon, Place of Residence and Immune Status before Exposure to Rubella.

Platoon No.	No. of Men	Number		HAI-Antibody Status		
		Men from Hawaii	Men from continental US	Susceptible men*	Immune men†	
					Vaccinees	*naturally immune*
1	48	39	9	3	7	38
2	48	40	8	10	2	36
3	48	40	8	8	3	37
4	46	32	14	5	3	38
Totals	190	151	39	26 (13.7%)	15	149
					(86.3%)	

*HAI titer < 1:8.

†HAI titer ≥ 1:16.

antibodies were even more striking. In all vaccinees some anti-theta (but no anti-iota) antibodies had developed as a result of vaccination. After exposure to wild rubella virus, 100 per cent had sharp increases in anti-theta, and all but one showed anti-iota antibodies.

Naturally immune men. Evaluation of the antibody patterns of the 149 men who were HAI antibody positive as a result of previous natural infection revealed the presence of CF antibodies in 65 per cent of the 125 with satisfactory tests. Of the 57 whose serums were tested for precipitins, all possessed anti-theta, and 32 (57 per cent) had anti-iota antibodies.

Table 3. Results of Virus Isolation from Throat Swabs Collected before, during, and after the Epidemic.

Wk of Training	Men with Clinical Rubella		Men with Inapparent (Primary) Infections		Vaccine-Immune Men		Naturally Immune Men	
	No. with virus isolation	No. tested	No. with virus isolation	No. tested	No. with virus isolation	No. tested	No. with virus isolation	No. tested
1-2	0	8	0	15	0	15	0	39
3-4*	6	9	4	16	0	16	0	19
5-6	2	8	2	18	1	16	0	5
7-9	0	8	0	16	0	16	0	18

*Onset of all cases.

Table 4. Antibody Responses on Infection or Reinfection with Rubella Virus.

Type of Infection	HAI Antibody			CF Antibody			Precipitins					
	No. positive	No. tested	Geometric-mean titer	No. positive	No. tested	Geometric-mean titer	No. positive for anti-theta	No. tested	Geometric-mean concentration (U/μ liter)‡	No. positive for anti-iota	No. tested	Geometric-mean concentration (U/μ liter)‡
Clinical rubella:												
Before exposure*	0	9	<8.0	0	9	<8.0	0	9	<0.1	0	9	—
After exposure	9	9	168.0	9	9	42.9	9	9	21.5	9	9	7.95
Subclinical infection (primary):												
Before exposure	0	17	<8.0	0	17	<8.0	0	17	<0.1	0	17	<0.1
After exposure	17	17	154.0	17	17	24.8	17	17	25.7	17	17	6.05
Vaccine-immune men:												
Before exposure	15	15	34.6	6	15	12.5	15	15	2.74	1	15	2.0†
After exposure	15	15	166.0	15	15	20.9	15	15	21.8	15	15	3.0
Naturally immune men (reinfected):												
Before exposure	5	5	27.6	0	5	<8.0	5	5	2.63	0	5	<0.1
After exposure	5	5	128.0	4	5	16.0	5	5	7.95	4	5	2.82
Naturally immune men (not reinfected):												
Before exposure	144	144	101.0	81	125	13.0†	52	52	13.0†	32	52	3.0†
After exposure	144	144	99.6	81	125	12.5†	52	52	14.4†	34	52	3.31†

*Before & after exposure refer to 1st & 9th wk of training respectively.

†Refers to antibody-positive men only.

‡See footnote† in Table 1.

Table 5. Clinical and Subclinical Rubella Infections* According to Immune Status on Exposure.

Platoon No.	Total No. of Men	Susceptible Men			Immune Men			
		No. Exposed	Cases of Clinical Rubella	Cases of Subclinical Infection	No. of Vaccinees Exposed	No. with Subclinical Infection	No. of Naturally Immune Men Exposed	No. with Subclinical Infection
1	48	3	0	3	7	4	38	2
2	48	10	6	4	2	2	36	0
3	48	8	2	6	3	3	37	2
4	46	5	1	4	3	3	38	1
Totals	190	26	9	17	15	12 (80%)	149	5 (3.4%)
			(100%)					

*Based on appreciable HAI or CF responses.

On exposure to rubella during the epidemic, five, or 3.4 per cent, experienced reinfection. Four men exhibited substantial HAI antibody titer boosts, and a fifth, who had other serologic evidence of reinfection, showed a consistent twofold rise. None of the five had been CF positive during the first week of training, but four of them acquired CF titers of 1:16 during the epidemic.

The precipitin responses of the 57 men tested were similar: all five with CF or HAI responses had appreciable increases in their low level anti-theta, and four of the five went from negative to positive with respect to anti-iota antibodies. In addition, three of the 52 other men who had neither CF nor HAI rises, showed modest increases in anti-theta or anti-iota antibodies (or both).

As had previously been demonstrated, the risk of reinfection was shown to be greater in men with low HAI levels than in those with higher titers. The pre-exposure geometric-mean titer (GMT) of the five naturally immune men who were reinfected was 27.6, which is comparable to the 34.6 GMT of the vaccinees. In contrast, the GMT of naturally immune recruits who resisted reinfection was 101.0. None of the reinfections occurred in persons with HAI levels greater than 1:64 except for one vaccinee whose titer was 1:128. Table 6 shows that in those with comparably low HAI titers, the presence of CF antibody was correlated with a higher degree of resistance to reinfection in naturally immune as well as in vaccinated men.

Table 6. Relation of CF Antibody Status to Reinfection Rates in Recruits with HAI Titers of 1:64 or Less.

Status at Time of Exposure	Vaccinees	Naturally Immune Men
CF positive (≥1:8)	3 of 6* (50%)	0 of 30 (0%)
CF negative (<1:8)	9 of 9 (100%)	5 of 34 (15%)
Totals	12 of 15 (80%)	5 of 64 (8%)

*1 vaccinee had HAI titer of 1:128.

Magnitude of antibody responses after primary infection and after reinfection. The data presented in Figure 3 show that after the epidemic of rubella had gone through the company, the GMT of HAI antibodies of the 15 vaccinees had risen so that it was similar to that of the 26 men who had experienced primary infection, either clinical or subclinical, and also similar to the levels shown by the naturally immune group, whose titers remained stable throughout. CF antibody responses on the other hand (Table 7) were somewhat lower in those with

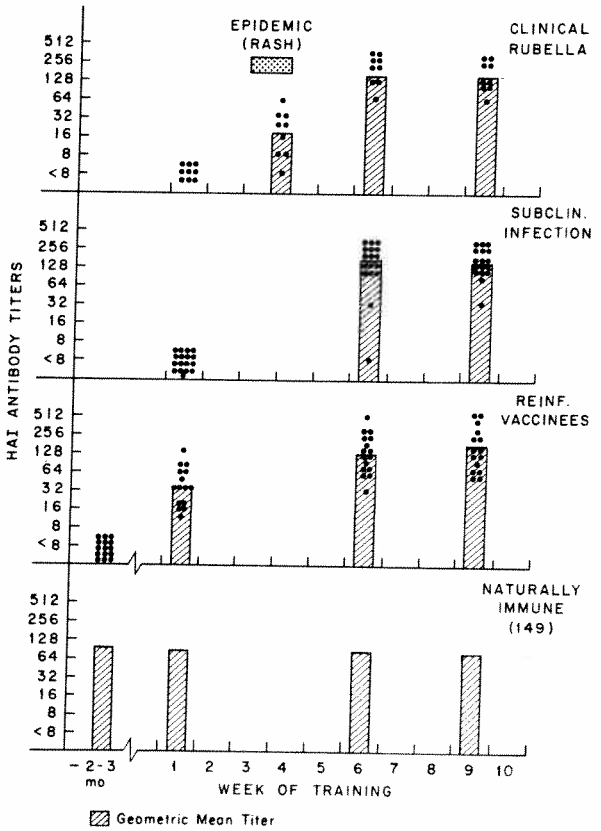

Figure 3. Comparison of Antibody Responses on Infection or Reinfection with Rubella Virus during an Epidemic.
Each dot represents one recruit, and the bars the geometric-mean titers for the group. —2-3 mo represents the prevaccinal titers of the 15 vaccinees and 39 of the 149 naturally immune recruits who were vaccinated.

Table 7. Comparison of CF Responses of Men with Primary Infections and Those with Reinfection.

WK OF TRAINING	MEN WITH CLINICAL RUBELLA			MEN WITH INAPPARENT (PRIMARY) INFECTIONS			VACCINE-IMMUNE MEN*			NATURALLY IMMUNE MEN†		
	NO. POSITIVE	NO. TESTED	GEOMETRIC-MEAN TITER‡	NO. POSITIVE	NO. TESTED	GEOMETRIC-MEAN TITER‡	NO. POSITIVE	NO. TESTED	GEOMETRIC-MEAN TITER‡	NO. POSITIVE	NO. TESTED	GEOMETRIC-MEAN TITER‡
1	0	9	—	0	17	—	6	15	12.5	0	5	—
6	9	9	42.9	13	17	32.0	15	15	16.6	3	5	12.6
9	9	9	42.9	17	17	24.8	15	15	22.0	4	5	16.0

*No positive responses in 15 tested before vaccination. †No positive response in 1 tested before vaccination. ‡CF = positive men only.

inapparent infection, whether in susceptible or in reinfected vaccinated men. The precipitin levels achieved, like the HAI, were of the same magnitude in infected and reinfected persons.

DISCUSSION

The results of this study point up marked differences in resistance to reinfection between persons who have acquired their immunity to rubella by vaccination and those who have experienced natural infection with wild rubella virus at some time in the past. That reinfection can occur in both groups has been well documented by other investigators. Thus, Meyer et al.[9] first demonstrated HAI antibody rises in two of five vaccinees challenged with wild virus. More extensive studies by Wilkins, Leedom and Portnoy,[10] working with children living in an institution for the retarded, demonstrated reinfection in four of eight who were vaccine immune, on intranasal challenge with wild virus, and in seven of eight exposed to natural rubella. Schiff et al.[11] reported similar results with adult vaccinees. Detels and his colleagues[12] examined the effect of vaccine in preventing reinfection during an epidemic among schoolchildren in Taiwan. They found that although the several vaccines used had a 90 to 95 per cent protective effect against clinical rubella, inapparent reinfection rates were high among the vaccinees, as measured by virus shedding from the throat.

Reinfection of persons who have experienced natural infection in the past has also been demonstrated.[13,14] Parkman[15] reported that 2 per cent of antibody-positive Army recruits showed booster responses during a rubella epidemic, and Meyer et al.[9] observed antibody boosts in two of 20 naturally immune persons exposed to rubella.

In the present study reinfection rates in the men with vaccine-induced immunity and those with antibodies resulting from previous natural infection were compared when both groups were exposed to the same sources of infection at the same time. The results confirm and extend the observations of others. On the basis of marked HAI and CF responses, 80 per cent of recently vaccinated young adults were reinfected when exposed during a rubella epidemic, in contrast to less than 5 per cent of naturally immune persons. If results of precipitating-antibody determinations are taken into account, 100 per cent of the vaccinees were reinfected. Furthermore, the magnitude of the antibody responses of vaccinees suggests that they must have experienced extensive virus multiplication and not simply limited replication at the portal of entry.

The evidence in the present study, and in several previously reported,[10-12,16] is that reinfection rates are correlated in a general way with HAI antibody levels at the time of exposure. If the titer is 1:64 or less the risk of reinfection is greater than if it is 1:128 or higher. There is considerable imprecision in these figures owing to the variations in technic and the consequent wide range of titers obtained in HAI tests in different laboratories. Nevertheless the trend is clear. It is recognized that CF antibody responses are much reduced in vaccinees as compared to those with natural infection, and are detected in postvaccinal serum only if sensitive antigen preparations are used.[16] Similarly, anti-iota antibodies have previously been detected rather infrequently after vaccination,[17] and then only at minimal concentrations and in children. In the present study, out of 15 susceptible and 20 naturally immune subjects, low levels of anti-iota precipitin were evoked by vaccine only in one of the susceptible men.

Analysis of the serologic results shown in Table 5 suggests that there is some correlation between possession of CF antibody and resistance to reinfection. Among the 15 men immunized in Hawaii, CF antibody developed in only six (40 per cent), and the three who resisted reinfection with wild virus (as determined by HAI and CF tests) were all in this group. A similar relation held with the naturally immune men who were reinfected: considering only those with HAI titers of 1:64 or below, the reinfection rate in the 30 who were CF positive was zero, whereas it was five of 34 (15 per cent) in the CF-negative group. These results illustrate the quantitative aspects of immunity and resistance, but they also suggest that there may well be *qualitative* differences between vaccine-induced and naturally acquired immunity, since, as indicated in Table 5, the reinfection rate of vaccinees was 10 times greater than that of naturally immune men with comparably low antibody levels.

The importance of these findings depends on how

they relate to several crucial questions. The first of these is whether or not a vaccinee who is reinfected is capable of transmitting the infection to others. There are some data on this point, but the question is far from settled. Wild virus has been recovered from throat swabs of reinfected vaccinees by Wilkins et al.,[10] by Schiff and his colleagues[11] and by Meyer, Parkman and Hopps.[18] In comparison with primary infection of susceptible persons, the amount shed by reinfected vaccinees has been less, and the duration of virus excretion shorter. Our results are similar to those of others, and taken together the data point to the probability that the risk of contagion from such reinfected persons recently vaccinated is greatly reduced, but whether or not it is eliminated is unknown.

Related to this problem is another, even more difficult one: if vaccinees can be readily reinfected a few months after successful immunization, what are the long-term prospects for durable protection of the young woman in the childbearing age who was successfully vaccinated at the age of six? Serologic surveys of normal populations have shown that naturally acquired neutralizing, HAI and CF antibodies tend to decrease in titer with increasing age,[19,20] and CF levels fall to undetectable levels after approximately 10 to 20 years.[21] If the rate of decline in antibody after natural and after vaccine-induced infection is similar, a substantial proportion of vaccinees (provided they have not experienced reinfection in the meantime) might be expected to have low titers or absent HAI and CF antibody 10 or more years after immunization. When reinfection occurs in persons who have lost *naturally acquired* immunity, the epidemiologic evidence is that they experience inapparent infection rather than clinical rubella, but they respond with virus shedding and antibody rises in a manner similar to that of the patient with primary infection.[22] Occasionally, however, even frank clinical rubella occurs in reinfected persons.[14,15] If naturally immune subjects can loose detectable HAI and CF antibody, vaccinees would seem to be more vulnerable to this eventuality. If reinfection with wild virus occurred in a young woman in early pregnancy, the hazard to the fetus would depend on the presence of appreciable viremia. There are data suggesting that, in general, if a rubella infection is inapparent, the degree of viremia is less than in the presence of clinical signs,[23] presumably as a reflection of less extensive virus multiplication. Fetal damage after inapparent infection has been well documented, but it is not known whether it might occur if the maternal infection is in a woman who has lost serologic evidence of immunity.

Another point for consideration is how the results presented are related to the current rubella-vaccine program in the United States. The objective of this program is to immunize the childhood population and thus to achieve a barrier to spread of the agent, which will in turn protect susceptible pregnant women from exposure. If this is achieved to the extent that circulation of wild virus is virtually eliminated, as with polioviruses, one might question the degree and quality of protection that the young population with vaccine-induced immunity alone might have in 10 to 15 years. Furthermore, we now have an 80 to 85 per cent immune population in the childbearing age group; is it possible that reduction of virus circulation, coupled with the logistic problems of reaching all susceptible persons with vaccine in childhood, would result in a shift so that a far lower proportion of young adults would be immune in the future than is now the case? Such susceptible persons would include those who had not been vaccinated and who did not have the benefit of natural infection. Under these circumstances the potential risk of fetal rubella might be *increased* rather than *decreased*.

On the other hand, if rubella virus can spread rapidly through a population in which 86 per cent possess specific HAI antibodies — as in the present study — the prospects for eliminating circulation of wild virus are not bright. Although a disadvantage to susceptible pregnant women, this failure may be a blessing as far as vaccinated children are concerned. If they are reinfected their immunity would be enhanced and would measure up to that naturally acquired in terms of quantity and quality.

With so many "ifs" in the picture, one is tempted to re-examine the priorities for vaccination, and consider whether a main target should not be the susceptible adolescent or young adult woman. Here, there are also difficulties, including the identification of susceptible persons and the risk that the vaccine might accidentally be given in the presence of early pregnancy. If these problems can be circumvented, there would be an advantage in inducing immunity in young women whose serum antibody might then be expected to have a greater chance of persisting at high enough levels during the childbearing period to block viremia should reinfection occur. One possibility that deserves attention is the development of a purified noninfectious subunit vaccine in which the antigen responsible for inducing protective antibodies has been concentrated. Such a product could probably be given without risk to adult women whether or not they were pregnant.

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HEPARIN THERAPY IN SEPTICEMIA WITH DISSEMINATED INTRAVASCULAR COAGULATION*

Effect on Mortality and on Correction of Hemostatic Defects

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Abstract Of 26 children with septic shock studied for coagulation defects, 24 received heparin in addition to standard therapy. Disseminated intravascular coagulation was diagnosed in 96 per cent. Of the heparin-treated patients 58 per cent died in shock; laboratory evidence of improvement in the coagulation defects occurred in all who survived and in three who died in shock. The presence of hypofibrinogenemia indicated a very poor prognosis but did not necessarily mean that shock was irreversible. Thus, heparin does not appear to improve survival in patients with septicemia and associated hypotension but may improve the coagulation defects. Improvement in the hypotension probably has a major role in abolishing disseminated intravascular coagulation.

THE mortality rate in patients with septicemia and associated hypotension is high, ranging from 50 to 80 per cent in reported series.[1-5] The syndrome of disseminated intravascular coagulation (DIC) or consumption coagulopathy occurring with septicemia has been well documented and is found almost exclusively in cases associated with hypotension or shock.[6-8] Since these findings suggest a causal relation between DIC and shock, the purposes of the present investigation were to determine the frequency of DIC in 26 children with septic shock, and to show if heparinization improved not only these coagulation defects but also the mortality rate.

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MATERIALS AND METHODS

Clinical Material

Twenty-six children with septicemia and clinical shock with documented systolic blood pressures below 80 mm of mercury admitted to the Grady Memorial Hospital and the Henrietta Egleston Hospital for Children, Atlanta, Georgia, between September, 1966, and January, 1970, are the subject of this investigation. Some data on 11 of these cases were reported in an earlier study.[6] Organisms were isolated from the blood in 19; six had sterile cultures, of whom three were treated with antibiotics before cultures were obtained, and one case of leptospirosis was diagnosed serologically.

All patients were treated with one or more antimicrobials, intravenous isotonic saline solution and plasma expanders consisting of plasma, whole blood or 6 per cent clinical dextran. In addition, three patients received isoproterenol hydrochloride, and two corticosteroids. Twenty-four patients were