The Use of Vaccinia Hyperimmune Gamma-Globulin in the Prophylaxis of Smallpox*

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This paper records an attempt to assess the prophylactic value of immune gamma-globulin, prepared from the serum of recently vaccinated adults, in the protection of close contacts of smallpox in Madras. The results serve to confirm findings of a previous study made in Madras in 1953, and show that the incidence of smallpox in close contacts given immune gamma-globulin prophylactically was about a quarter of that in the control contacts who received no such passive immunization—a statistically significant difference. Because of the limited supply of immune gamma-globulin, it is likely that its prophylactic use will be restricted to those especially at risk, for example, close unvaccinated family contacts, newborn infants and pregnant women.

In a previous field trial of hyperimmune gamma-globulin for the prevention of smallpox¹¹ the number of cases involved was insufficient to give conclusive evidence of prophylactic value, although the results were highly suggestive. For this reason, the experiment was repeated in a co-operative venture involving the Department of Pediatrics of the University of Colorado School of Medicine, the Department of Bacteriology of the University of Liverpool; the World Health Organization, the Indian Council for Medical Research; the Madras State Government and the Corporation of Madras.

STUDY METHODS

Index cases were gathered from the admission roster of the Infectious Diseases Hospital, Tondiarpet, Madras. The criteria for selection of index cases were the following:

1. No previous cases of smallpox had occurred in the particular family within the past month and the index case had to be the reason for the revaccination of family contacts.
2. The patient resided within the city limits of Madras.

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¹¹ Kempe, C. H., Berge, T. O. & England, B. (1956) *Pediatrics*, 18, 177.

3. The patient had a stable and verifiable address.

When two cases of smallpox were admitted to the Infectious Diseases Hospital at the same time from the same family and at approximately the same stage of disease, they were accepted for inclusion in the study and treated as a single index case.

When the index case hospital number ended in an even number all contacts were placed in the gamma-globulin group and were also vaccinated. On the other hand, if the index case hospital number ended in an odd number, all family contacts were placed in the control group and received vaccination only. Family contacts who refused vaccinia immune gamma-globulin (VIGG) administration or were not found until after the probable incubation period were treated as controls. There were nine such controls (see Table 3). Newborn infant contacts received vaccinia immune gamma-globulin regardless of group.

The definition of family contact was based on the following criteria :

1. Intimate room contact, i.e., family members and others who shared the same room unit for eating and sleeping.
2. Individuals joining the family after the index case was admitted to the hospital but exposed upon visiting the hospital frequently.
3. No proven history of clinical smallpox in the past; persons were not excluded who reported having smallpox in the past but showed no visible scars.

In instances where index cases were admitted to the hospital with fever only and left the hospital before the onset of rash, only frequent visitors to the hospital were accepted as contacts, as these had mass exposure during their frequent hospital visits and were to be included in our daily visit routine.

DOSAGE OF VACCINIA IMMUNE GAMMA-GLOBULIN

The vaccinia immune gamma-globulin employed was prepared as previously described,^{1, 2} and was used as a 12% solution. A fixed dose was used depending on age. Children under 5 years of age received 5 ml intramuscularly and adults received 10 ml. Swedish, British and United States products were employed. These were essentially of equal potency.

METHOD OF FOLLOW-UP OF CONTACTS

Preliminary visit

Each contact was seen as soon as possible after the admission of the index case to the Infectious Diseases Hospital. Where the index case was a mother, this visit usually occurred on the day of admission. In other cases, the visit was made the day following admission. At the time of the first visit a complete record of name, age, sex, and relationship to index case was obtained. The vaccination history of the contact was determined; each contact was checked for symptoms of disease; and vaccinia immune gamma-globulin was administered to all contacts in the vaccinia immune gamma-globulin group, provided this visit was made before the end of the probable incubation period. This date was generally determined as 12 days following the day preceding the onset of rash in the index case. In general, a vaccination or revaccination of all contacts was performed at approximately the same time by the Sanitary Inspector.

Second follow-up visit

A check for symptoms of disease was begun in each contact on the twelfth day following the known exposure to the index case, or on the twelfth day following the day preceding the onset of rash in the index case. Fever, systemic symptoms of illness, or skin eruptions were sought for. In a number of instances conjunctivitis was a presenting finding in otherwise afebrile or minimally ill contacts. In general, revisits to contacts were again made on the following two days—the thirteenth and fourteenth days following the onset of rash in the index case. Visits were then repeated at two- or three-day intervals until discharge from the study. All contacts were discharged from the study on the fourteenth day after the admission of the index case to the hospital. Whenever possible each contact was seen for the last time on this last day. Some contacts however, had to be discharged without being seen on a last visit provided the examiner could be certain that they were well.

POTENCY OF VACCINIA IMMUNE GAMMA-GLOBULIN USED IN THE STUDY

Vaccinia immune gamma-globulin from three sources was employed in this study. All three products were found to be of essentially the same potency by neutralization test. They had all been prepared from the plasma of recently vaccinated

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young adult donors and the vaccinia immune gamma-globulin was in a 12% solution. The respective neutralization titres of the products were as follows:

<i>VIGG product</i>	<i>Neutralization titre*</i>
Swedish (KABI-Royal Medical Board)	256
British (Central Public Health Laboratory, Colindale)	512
American (American Red Cross-Cutter Laboratories)	512

* The neutralizing end-point by the pock-counting technique is that dilution of serum which results in reduction of greater than 50% of the pock-count of control eggs.

DESCRIPTION OF POPULATION STUDIED

The following tabulation shows the number of index cases and their contacts as well as the division between the control and vaccinia immune gamma-globulin groups:

<i>Number of index cases</i>		<i>Number of contacts</i>	
Having contacts not receiving VIGG	111	Controls	379
Having contacts receiving VIGG	97	Receiving VIGG	326
Total	208	Total	705

TABLE 1
ANALYSIS OF INDEX CASES OF SMALLPOX COMPARED AS TO SEX AND AGE IN CONTROL AND VACCINIA IMMUNE GAMMA-GLOBULIN GROUPS

Age (years)	Control			VIGG			Total
	Male	Female	Total	Male	Female	Total	
<1	2	3	5	2	3	5	10
1-4	13	5	18	7	11	18	36
5-9	6	6	12	4	6	10	22
10-14	3	5	8	1	5	6	14
15-19	3	7	10	2	5	7	17
20-24	13	5	18	4	11	15	33
25-59	13	3	16	8	6	14	30
30-34	3	9	12	4	3	7	19
35-39	2	3	5	2	2	4	9
40-49	4	—	4	5	1	6	10
50+	1	2	3	2	3	5	8
Total	63	48	111	41	56	97	208

TABLE 2
INDEX CASES COMPARED AS TO NUMBER OF CONTACTS PER CASE

No. of contacts	Control	VIGG	Mixed	Total
1	17	10		27
2	24	26		50
3	28	21	1	50
4	18	18	1	37
5	11	5	1	17
6	4	6		10
7	3	2	1	6
8	5	2	1	8
9	1		1	2
10				
11		1		1
Total	111	91	6	208

Table 1 shows the comparable nature of the index cases in the respective groups as regards sex and age.

Table 2 compares the index cases as regards the number of contacts for each case. For six index cases, contacts were divided between both groups. This occurred either when a member of a family assigned to the vaccinia immune gamma-globulin group refused an injection and thereby became a control case or when, as in the case of newborn infants, vaccinia immune gamma-globulin was routinely given even though the rest of the family members were in the control group.

TABLE 3
SIX INDEX CASES WITH MIXED CONTROL AND VACCINIA IMMUNE GAMMA-GLOBULIN CONTACTS

Index case	No. contacts in family	Group	
		Control	VIGG
1	3	1	2
2	4	1	3
3	5	1	4
4	7	1	6
5	8	4	4
6	9	1	8

Table 3 lists the index cases with mixed control and vaccinia immune gamma-globulin contacts as regards the number of such contacts, and Table 4 compares the contacts in both groups as regards sex and age.

TABLE 4
CONTACTS IN CONTROL AND VACCINIA IMMUNE
GAMMA-GLOBULIN GROUPS COMPARED AS TO SEX
AND AGE

Age (years)	Control			VIGG			Total
	Male	Female	Total	Male	Female	Total	
<1	7	6	13	10	10	20	33
1-4	22	25	47	20	20	40	87
5-9	28	22	50	20	14	34	84
10-14	22	21	43	21	16	37	80
15-19	7	21	28	8	15	23	51
20-24	16	16	32	10	14	24	56
25-29	17	25	42	23	18	41	83
30-34	18	11	29	13	14	27	56
35-39	9	17	26	6	9	15	41
40-44	20	5	25	13	7	20	45
45-49	10	8	18	8	7	15	33
50+	7	19	26	11	19	30	56
Total	183	196	379	163	163	326	705

A review of the vaccination histories of the contacts in the two groups (Table 5) reveals that, while the vast majority of contacts had been vaccinated, there were seven in the vaccinia immune gamma-globulin group who had received neither primary

TABLE 5
VACCINATION HISTORIES OF CONTACTS IN CONTROL
AND VACCINIA IMMUNE GAMMA-GLOBULIN GROUPS

	Control	VIGG
No primary vaccination, no revaccination	3	7
Primary vaccination on admission to study		
Take	19	20
No take	12	12
Primary vaccination in infancy, revaccination not done	34	28
Primary vaccination in infancy, revaccination on admission to study	150	123
Primary vaccination in infancy, past history of revaccination	152	126
History unknown	9	10
Total	379	326

TABLE 6
SMALLPOX IN CONTACTS RECEIVING VACCINIA IMMUNE GAMMA-GLOBULIN

No.	Age (years)	Sex	Vaccination status ^a	Duration of known exposure (days)	Interval from VIGG administration to onset of smallpox (days)	Vaccination at time of VIGG administration	Clinical classification of smallpox ^b	Laboratory confirmation ^c
1	10	F	PV at 1 year	14-17	11	Yes	Mild disc.; 30 lesions	+
2	40	F	PV at 1 year	8-14	7	Yes	Mild disc.	ND
3	5	M	0	13-19	11	No	Mod. disc.	ND
4	23	F	PV, 2 scars	0-17	11	Yes	Mild disc.	+
5	20	F	PV, 2 scars	0-11	9	Yes	Mild disc.; 20 lesions	+

^a PV = primary vaccination.

^b Mild disc. = mild discrete; Mod. disc. = moderate discrete.

^c ND = not done.

TABLE 7
SMALLPOX IN CONTROL CONTACTS

Series No.	Age (years)	Sex	Vaccination status before admission to trial	Vaccination or revaccination at time of study	Clinical classification	Laboratory confirmation			Remarks
						Focal lesions		Mouth washings culture CAM	
						Microscopy	Culture CAM		
13-1	23	F	PV (2)	ND	Mild disc.	ND	ND	+	Confirmed, C.H.Kempe
37-4	1½	F	Unvacc.	PV (4) 8 days before admiss.	Severe disc.	ND	ND	ND	
52-1	35	M	PV (4)	RV on admiss.; no take	Mild disc.; conj.	+	+	—	
52-7	25	F	PV (2)	No take?	2 lesions; conj.	ND	ND	ND	
76-6	25	M	PV (4)	No take?	Mod. disc.	Dbtfl.	+	+	
76-4	1½	M	Unvacc.	PV take 4 days before onset	Mild disc.	ND	ND	—	Confirmed, A.W.Downie
90-5	17	F	PV (4)	RV; not seen	Severe disc.	ND	ND	ND	
116-5	26	M	PV (4)	RV; not seen	Mild disc.	ND	ND	ND	
135-2	30	F	PV (4)	RV; take 7 days before onset	Mild disc.	Dbtfl.	+	+	
135-8	15	M	PV; not seen	RV; no take	Severe disc.	ND	ND	ND	
135-5	2½	M	Unvacc.	PV; take 8 days before onset	1 lesion in forearm	+	+	ND	
135-6	5	M	Unvacc.	PV; no take	Mild disc.	+	+	ND	
159-1	16	F	PV (3)	RV 4 days before onset of fever	Mild disc.; conj.	ND	ND	+	
163-1	21	F	PV (2)	ND	Mod. disc.	+	+	+	
171-1	30	F	PV (4)	RV on day of onset	Mild disc.	+	ND	+	
178-3	2	M	Unvacc.	?	Mild disc.	ND	ND	ND	
178-4	11/12	F	Unvacc.	PV; no take?	Mild disc.	+	+	ND	
206-6	9	F	Unvacc.	PV; take 6 days before onset	Mild disc.	+	+	—	
206-5	3	M	Unvacc.	PV; take 6 days before onset	Severe disc.	+	+	+(swab)	
201-2	3	M	Unvacc.	PV; take 7 days before onset	Mild disc.	+	+	+(swab)	
201-3	½	F	Unvacc.	PV; take 7 days before onset	Mild disc.	—	+	ND	

Key:

Unvacc. = unvaccinated.	CAM = chorio-allantoic membrane.
RV = revaccination.	ND = not done.
PV = primary vaccination.	+ = positive
disc. = discrete.	— = negative.
conj. = conjunctivitis.	Dbtfl. = doubtful.

vaccination nor revaccination as contrasted with three contacts in the control group, weighing the odds for contracting smallpox slightly towards the vaccinia immune gamma-globulin group.

Among 379 controls there were 21 cases of smallpox. Tables 6 and 7 provide more detailed information.

Two groups not included in the above summaries may now be discussed separately.

RESULTS

LATE OCCURRENCE OF SMALLPOX AMONG CONTACTS OF INDEX CASES

Among 326 contacts receiving vaccinia immune gamma-globulin during the follow-up period described there were five cases of smallpox identified.

Table 8 gives details regarding three individuals in the vaccinia immune gamma-globulin group as

TABLE 8
LATE OCCURRENCE OF SMALLPOX AMONG CONTACTS

No.	Age (years)	Sex	Vaccination status ^a	Known exposure (days)	Interval from VIGG administration to onset of smallpox (days)	Successful revaccination	Clinical classification of smallpox	Laboratory confirmation
6	50	F	0	22-27	19	No	Severe discrete	+
7	9/12	M	0	0-30	28	No	Mild discrete	
8	30	F	PV at 4	34-38	32	No	Mild discrete	
22	5	M	0 PV after exposure	23-33	No VIGG	No	Confluent; fatal	

^a PV = primary vaccination.

TABLE 9
NEWBORN INFANTS RECEIVING VACCINIA IMMUNE GAMMA-GLOBULIN FOLLOWING EXPOSURE

No.	Relationship of contact	Smallpox severity in contact	Newborn				
			Breast-fed	Fever rash	Smallpox severity	Age at time of onset of rash (days)	Comment
1	Mother	Haemorrhagic; died	No	0			Died of malnutrition
2	Mother	Haemorrhagic, died	No	+	Mild discrete	13	Died
3	Mother	Mild discrete	No	+	Mild discrete	9	Died
4	Mother	Haemorrhagic; died	No	0			Died
5	Mother	Confluent; died	No	+	Mild discrete	8	Died
6	Mother	Confluent; died		0			Survived
7	Mother	Confluent; survived	No	+(?)	2 lesions (?)	12	Died of prematurity
8 ^a	Sister (patient in smallpox ward)	Not smallpox		0			Survived
9 ^b	Patient (in smallpox ward)	Patient suspected, but not smallpox	Yes	0			Survived

^a Baby 2 weeks old when exposed in hospital. Sister did not have smallpox.

^b Baby is patient; 2 months old when exposed in hospital.

well as one in the controls who contracted smallpox at a considerable time after known exposure, presumably from a case other than the index case. It will be seen that in none of these four cases was successful revaccination carried out. In the absence of successful revaccination, the protection passively conferred by vaccinia immune gamma-globulin had probably vanished after two to three weeks, leaving the patient again susceptible to the disease.

It is clear that the period of intensive supervision having extended only over 14 days after the admission of the index case to the Infectious Diseases Hospital, discovery of subsequent later cases, particularly among the control group, was largely fortuitous. It is for this reason that the additional information of later occurrence of smallpox among contacts previously discharged from the study is included for consideration.

NEWBORN INFANTS

Nine newborn infants exposed to smallpox infection *in utero* (cases 3 and 5 in Table 9), at birth or shortly thereafter are considered separately. All of these infants received 5 ml of vaccinia immune gamma-globulin and information about these is shown in Table 9. It will be seen that mild clinical smallpox occurred in three of these infants. Chances of survival in this group, regardless of the appearance of smallpox, were poor because of the death of the mother. It is our impression on clinical grounds that the majority of these infants being deprived of maternal breast milk succumbed to dehydration and malnutrition. The expected death-rate in newborn infants infected *in utero* or at birth by their own mothers is exceedingly high and it is likely that the appearance of clinical smallpox in only three of the nine infants is a significant finding.

DISCUSSION

The findings of the present investigation support suggestive data gathered in a previous study in Madras in 1953.^{1, 2} Combined figures of the two studies show 29 cases of smallpox among control contacts as compared to eight in the vaccinia immune gamma-globulin group. The groups are sufficiently similar in sex, age, vaccination history

and numbers for the results to be regarded as significant, in the sense that a reduction in the incidence of smallpox of the order of 70% can be expected in contacts given immune gamma-globulin.

The four cases of smallpox occurring late in contacts illustrate the importance of prompt successful vaccination or revaccination regardless of whether vaccinia immune gamma-globulin is administered upon known exposure or not. It can be assumed that if vaccination had been successfully carried out at the time of the first known exposure, these contacts would have been protected by their active immunization.

It must be recalled that the vaccinia immune gamma-globulin used for these studies was obtained from recently vaccinated young adult donors bled 4-6 weeks after revaccination. The neutralizing titres of plasma obtained at the time of such donation was of the order of 1:25 using the standard egg neutralization test. It was known from previous studies that the neutralizing titre of smallpox convalescent serum is 10 to 20 times greater than that obtained after successful primary vaccination or successful revaccination.³ The greater antibody concentration of smallpox convalescent serum is also shown in another paper in this issue, entitled "Studies of Smallpox Antibody Levels of Sera from Samples of the Vaccinated Adult Population of Madras".⁴ For this reason, it is entirely logical to predict that even better protection could be obtained from an immune gamma-globulin made from plasma from convalescent smallpox patients. As long as smallpox continues to be endemic in India it will be possible to make such a product.

Although this method of prophylaxis has been shown to be of value under the conditions of test in Madras, it is obvious that it is not a method that could be used as a general procedure throughout India, especially in large towns where the disease is endemic. None the less, even in those areas it might be particularly valuable in contacts exposed to a high risk of contracting severe disease, for example, in pregnant women or in unvaccinated infant contacts. On the other hand, it might be of particular value in smaller communities or villages where the disease is not endemic but is liable to recur every few years in epidemic form. In such villages the vaccination rate is frequently low. Consequently, when an epidemic occurs the mor-

¹ Kempe, C. H., Berge, T. O. & England, B. (1956) *Pediatrics*, **18**, 177.

² Kempe, C. H. (1960) *Pediatrics*, **26**, 176.

³ Downie, A. W. & McCarthy, K. (1958) *J. Hyg. (Lond.)*, **56**, 479.

⁴ See page 55 of this issue.

tality rate tends to be high. In such a situation, vaccinia immune gamma-globulin given to the contacts, particularly unvaccinated contacts of early cases in an outbreak, might well limit the spread as well as lessen the mortality from the outbreak. In countries where smallpox is not endemic, but into which it may be imported occasionally, and in which epidemics tend to be localized effectively by public health measures, vaccinia immune gamma-globulin might have special usefulness. This is particularly so in those few countries where vaccination is no longer compulsory, for example, in the

United Kingdom. Here the vaccination rate of the general population is somewhat less than 50% and, because of the country's commerce, particularly with parts of the world where the disease is endemic, importations of disease are not infrequent. When the first cases occur and are recognized, the spread of infection is usually limited by quarantine, and by vaccination and supervision of contacts. In spite of this a few fatal infections among the unvaccinated contacts frequently occur. For such unvaccinated contacts vaccinia immune gamma-globulin might be life-saving.

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RÉSUMÉ

Dans le cadre des études sur la variole, entreprises à Madras, Inde, les auteurs ont évalué expérimentalement la protection conférée aux contacts de varioliques par la gamma globuline à forte teneur en anticorps, prélevée sur des adultes récemment vaccinés, préparée en Suède, en Angleterre et aux Etats-Unis d'Amérique. Les contacts de cas admis à l'hôpital pour variole sont vaccinés; c'est là une mesure de routine. Dans les études décrites dans cet article, la gamma globuline a été administrée à des contacts au moment de l'admission à l'hôpital du cas avéré. Un groupe de contacts non traités par la gamma globuline servait de témoin.

Parmi les 326 contacts qui reçurent la gamma globuline, il y eut 5 cas de variole, contre 21 dans le groupe témoin. Cette différence est statistiquement significative. Tous les nouveau-nés, contacts de varioliques, ont reçu de la gamma globuline. Sur 9 de ces enfants, 3 contractèrent la variole. En outre, la maladie apparut chez 4 des sujets, 19 jours après l'admission à l'hôpital du cas avéré. Trois d'entre eux avaient reçu de la gamma globuline, mais la vaccination, pratiquée en même temps, n'avait pas réussi. Il semble donc que la protection temporaire conférée par la gamma globuline (2-3 semaines) n'a pas pu empêcher la contagion. Ces faits mettent en évidence

la nécessité de procéder à la vaccination active ou à une revaccination — que l'on administre ou non de la gamma globuline — au moment où un cas avéré crée un risque pour les contacts.

L'administration de gamma globuline, n'est évidemment pas applicable sur une vaste échelle dans l'Inde entière, surtout dans les grandes villes où la variole est endémique. Cependant, même dans ces conditions, elle peut être d'un grand secours pour protéger les contacts brusquement exposés à un grand risque de contagion — tels que les femmes enceintes et les nouveau-nés non vaccinés. Elle peut avoir une grande valeur aussi dans les petites collectivités et les villages, où la variole n'est pas endémique, mais peut survenir sous forme épidémique, après quelques années de silence. Dans ces villages, le nombre des vaccinés est en général faible et la mortalité élevée, en cas d'épidémie. La gamma globuline administrée aux contacts des premiers cas peut contribuer à limiter la mortalité et la propagation de l'épidémie. C'est le cas dans les pays où la vaccination n'est plus obligatoire. La gamma globuline peut sauver la vie des contacts non vaccinés d'un cas importé, surgissant dans une collectivité non vaccinée.