mothers under his care; to Dr. J. G. Cunningham and his Directors for providing facilities for the study of factory controls; and to Dr. D. D. Reid for statistical assistance.

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REPORT ON THE USE OF GAMMA GLOBULIN AND ADULT SERUM FOR MEASLES PROPHYLAXIS IN ENGLAND AND WALES, 1949-53

BY

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Gamma globulin prepared by the method of Kekwick and Mackay (1954) was shown in a Report to the Medical Research Council (Report, 1950) on a series of controlled trials in day nurseries to be superior to adult serum for measles prophylaxis. Since 1949 gamma globulin produced on behalf of the Medical Research Council and Ministry of Health at the Lister Institute has been distributed, mainly for measles prophylaxis, by the Public Health Laboratory Service. It is issued in ampoules containing 250 mg. of protein, 96% of which is gamma globulin. The contents of each ampoule are derived from the fractionation of approximately 40 ml. human serum or about 48 ml. human plasma, and are dissolved in 3 ml. of sterile distilled water before injection.

During the same period irradiated adult serum—that is, serum from normal adults which has been exposed to ultra-violet light—has also been distributed for measles prophylaxis. Until February, 1951, the adult serum was

issued at normal strength in 5-ml. or 10-ml. doses; thereafter it was concentrated to one-third its original volume, so that a 5-ml. ampoule contained the equivalent of 15 ml. of normal serum.

All doctors using the three prophylactics—gamma globulin, unconcentrated adult serum, and concentrated adult serum—were asked to complete a standard form reporting the results they obtained. During the period October 1, 1949, to December 31, 1953, report forms were returned for 82% of the 12,408 doses of globulin and 67% of the 3,931 doses of adult serum issued. These forms were analysed with three aims in view: (1) to obtain information on how measles prophylactics were used, so that the demand might be more satisfactorily met in future; (2) to determine the incidence of local and general reactions to inoculation; and (3) to gain some indication of the influence of dosage, the age of the person injected, and the period between exposure and inoculation on the prophylactic effect.

In the analysis all forms returned were used in the study of the distribution of measles prophylactics and of reactions to inoculation, but only those relating to 4,080 home contacts under 5 years of age were used to study the prophylactic effect. Full details of dosage and result were available for 3,846 of these, 2,760 of whom had received gamma globulin, 375 unconcentrated adult serum, and 711 concentrated adult serum.

Home contacts were selected because they were almost certainly exposed to infection, and if untreated most of them would have been attacked. The incidence of measles among susceptible children of different ages exposed to infection in another member of the same family has, in past studies, been remarkably constant. Family secondary attack rates noted by various observers are set out in Table I for children at different ages under 5 years and averages calculated from them. In the absence of any untreated but otherwise similar control group these average rates give the best available estimate of what might have been expected if no prophylactic had been used. On this basis about 9% of susceptible children under 6 months of age, about 70% over 6 months and under 1 year, about 88% over 1 year and under 3 years, and about 89% over 3 and under 5 years would have been expected to develop measles when exposed to another case in the same family.

As gamma globulin and adult serum were not allocated to contacts at random it is possible that those who received gamma globulin differed in some relevant respect from those who received adult serum. This should be borne in mind when the results with gamma globulin and adult serum are compared. It is also possible that if all the forms had been returned instead of 80% different results might have been obtained.

Distribution of Measles Prophylactics

In relation to population and to incidence of measles, London and the South-east of England received much more gamma globulin than other parts of the country. In London and the South-east about 10 contacts were inoculated for every 1,000 cases notified, compared with about 3 contacts for every 1,000 cases in other regions. Steps have now been taken to ensure a more uniform distribution throughout the country. Three-fifths of the gamma globulin was used in hospitals and two-fifths in general practice. These proportions were roughly reversed for adult serum. Of the gamma globulin used in general practice 77% was administered to children less than 3 years of age, so it is already being used in the main for young children, and little further

economy in this direction is possible; only in hospital was an appreciable amount of gamma globulin given to children over 3 years of age.

Reactions to Inoculation

Local and general reactions were recorded as nil, mild, moderate, or severe. Moderate or severe local reactions were noted in 0.3% of children given gamma globulin, 1.2% of children given concentrated adult serum, and 1.0% of children given unconcentrated adult serum. Moderate or severe general reactions were noted in 0.8% of children given gamma globulin, 0.9% given concentrated adult serum, and 1.4% given unconcentrated adult serum. The smaller volume of the gamma globulin dose may have been partly responsible for the relatively smaller incidence of reactions.

Several doctors added a brief description of the reactions which occurred. None was severe enough to cause any anxiety. Twenty-nine of the 76 moderate or severe general reactions following gamma globulin were described—11 as rash and coryza, 14 as fever, 2 as vomiting, 1 as abdominal pain, and 1 as vertigo. It was not possible to determine when these reactions occurred in relation to the time of injection, and some of these illnesses were possibly modified measles.

Results in Relation to Age of Contact and Dose

Prevention

Measles attack rates among home contacts of different ages under 5 years treated with varying doses of the three preparations are shown in Table II. At all ages over 6 months an increase in dose of gamma globulin was accompanied by a fall in attack rate, the dose required to produce a given level of protection rising with age. When these rates are compared with the secondary attack rates in Table I it will be seen that a marked reduction was produced by less than 2 ml. of gamma globulin in children over 6 months and under 1 year, by 2 to 4 ml. in children over 1 year and under 3 years, and by 4 to 8 ml. in children over 3 and under 5 years. The doses required to produce

attack rates of about 25% were 2 to 4 ml. in children over 6 months and under 1 year, 4 to 8 ml. in those over 1 year and under 3 years, and more than 8 ml. for those over 3 and under 5 years.

Few babies under 6 months of age developed measles, but only about 9% would have been expected to do so. These rates are not comparable, however, because for the most part babies of this age are given a prophylactic injection only if their mothers are thought not to have had measles and, if untreated, the attack rate among them might have been higher than 9%. The proportion of children over 1 year and under 5 years of age who developed measles after being given adult serum, whatever the dose or preparation used, was hardly lower than would have been expected if they had not been treated. Adult serum appeared to have some protective value, however, for children over 6 months and under 1 year of age, of about the same order as the lowest dose of gamma globulin.

Modification

In Table III the results of analysis of the severity of measles in treated home contacts are shown. It is difficult to interpret these findings without knowing in what proportion of cases of measles in uninoculated children the disease is as mild as in those where modification was described as "good." Good modification was recorded in about three-quarters of cases given gamma globulin and in about half those given adult serum. The proportion of well-modified measles in those who received gamma globulin appeared to vary with the dose used. It is possible that adult serum modified some of the attacks, particularly in children under 1 year of age, but its effect in children between 1 and 5 years of age was clearly much less than that of gamma globulin. The proportions of children in different age groups in which measles was neither prevented nor well modified are set out in Table IV. Nine out of 10 children over 6 months and under 5 years of age exposed to measles in the home and given one bottle (250 mg.) of gamma globulin were protected completely or had only a mild attack.

TABLE I.—Secondary Attack Rate of Measles Among Susceptible Family Contacts Under 5 Years of Age, According to Different Observers

Age of Children at Risk	Butler (1912-13) in Willesden		Chapin (1925) in Providence, Rhode Island		Top (1938) in Detroit		Wilson <i>et al.</i> (1939) in Providence, Rhode Island		Stillerman and Thalhimer (1944) in New York		Average Attack Rates Based upon All Observers	
	No. at Risk	Attack Rate (%)	No. at Risk	Attack Rate (%)	No. at Risk	Attack Rate (%)	No. at Risk	Attack Rate (%)	No. at Risk	Attack Rate (%)	No. at Risk	Attack Rate (%)
Under 6 months	174	10.2	1,208	47.0	193	45.6*	247	7.3*	21	19.0*	442	9.0
Over 6 months and under 1 year	209	77.0			194	91.2*	245	65.3*	30	63.3*	484	70.0
1 year	242	84.3					490	83.5	43	86.0	4,087	87.5
2 years	248	89.1					545	86.6	26	92.3		
3	323	90.1			328	93.9*	577	86.3	33	87.9		
4	316	83.2	1,055	89.5	279	91.4*	635	87.4	30	83.3	4,691	88.6

* Rates calculated from published figures.

TABLE II.—Effect of Dosage of Gamma Globulin and Adult Serum on the Measles Attack Rates in Home Contacts Under 5 Years of Age

Prophylactic	Dose	Under 6 Months		Over 6 Months and Under 1 Year		Over 1 Year and Under 3 Years		Over 3 Years and Under 5 Years	
		No. at Risk	Attack Rate (%)	No. at Risk	Attack Rate (%)	No. at Risk	Attack Rate (%)	No. at Risk	Attack Rate (%)
Gamma globulin	Less than 2 ml.	34	3	29	34	44	70	15	67
	More than 2 and less than 4 ml.	333	10	664	25	1,128	55	254	64
	More than 4 and less than 8 ml.	29	3	77	10	89	29	40	50
	More than 8 ml.	1	—	6	—	8	25	9	22
Unconcentrated adult serum	More than 3 and less than 9 ml.	18	0	23	43	67	75	36	69
	More than 9 ml.	21	0	49	35	115	80	46	70
Concentrated adult serum	More than 3 and less than 9 ml.	96	17	162	43	339	80	109	87
	More than 9 ml.	0	—	3	—	2	—	0	—

TABLE III.—Doctors' Estimate of Severity of Measles in Home Contacts Over 6 Months and Under 5 Years of Age.

Prophylactic	Dose	Over 6 Months and Under 1 Year		Over 1 Year and Under 3 Years		Over 3 Years and Under 5 Years	
		No. of Cases of Measles	Percentage with Good Modification	No. of Cases of Measles	Percentage with Good Modification	No. of Cases of Measles	Percentage with Good Modification
Gamma globulin	Less than 2 ml.	10	60	31	61	10	60
	More than 2 and less than 4 ml.	163	79	626	78	163	72
	More than 4 and less than 8 ml.	8	88	26	88	20	75
	All doses	181	78	683	77	193	72
Unconcentrated adult serum	More than 3 and less than 9 ml.	10	70	50	54	25	44
	More than 9 ml.	17	35	92	52	32	31
Concentrated adult serum	More than 3 and less than 9 ml.	70	63	272	42	95	32
Concentrated and unconcentrated adult serum	All doses	97	59	414	46	152	34

TABLE IV.—The Proportion of Home Contacts Under 5 Years of Age in Which Measles Was Neither Prevented nor Well Modified

Prophylactic	Dose	Under 6 Months		Over 6 Months and Under 1 Year		Over 1 Year and Under 3 Years		Over 3 Years and Under 5 Years	
		No. at Risk	Percentage Neither Prevented Nor Well Modified	No. at Risk	Percentage Neither Prevented Nor Well Modified	No. at Risk	Percentage Neither Prevented Nor Well Modified	No. at Risk	Percentage Neither Prevented Nor Well Modified
Gamma globulin	Less than 2 ml.	34	3	29	14	44	27	15	27
	More than 2 and less than 4 ml.	333	2	664	5	1,128	12	254	18
	More than 4 and less than 8 ml.	29	0	77	1	89	3	40	13
	All doses	135	3	237	17	523	43	191	53
Concentrated and unconcentrated adult serum	All doses	135	3	237	17	523	43	191	53

Interval between Exposure and Inoculation

It is generally believed that measles prophylactics should be given as soon as possible after exposure to infection and that if given more than six days after first contact complete prevention is unlikely. Report forms for 1,719 home contacts over 6 months and under 5 years of age who had received more than 2 ml. and less than 4 ml. of gamma globulin were used to investigate this question. Doctors were not asked to state the date of first exposure on the record form until December, 1950, and only forms completed since then were suitable for this analysis.

As the inoculated children were home contacts the date of first exposure was almost always the day of onset of prodromal symptoms—that is, about three days before the appearance of the rash in the primary case. The attack rates for children inoculated at varying times after first exposure are shown in Table V. The effect of delay was not apparent in those under 1 year, not great in those between 1 year and 3 years, but clearly present in those over 3 years

TABLE V.—Relation of Attack Rate to Interval Between Exposure and Inoculation in Home Contacts Over 6 Months and Under 5 Years of Age Treated with More than 2 and Less than 4 ml. of Gamma Globulin

Exposure to Inoculation. Time in Days	Age Group					
	Over 6 Mths and Under 1 Yr.		Over 1 Yr. and Under 3 Yrs.		Over 3 Yrs. and Under 5 Yrs.	
	At Risk	Attack Rate (%)	At Risk	Attack Rate (%)	At Risk	Attack Rate (%)
Under 3 days	51	25	84	37	17	47
Over 3 and under 6 days	315	24	473	55	113	60
Over 6 and under 9 days	196	26	322	61	57	79
Over 9 days	22	18	58	55	11	91
Total	584	25	937	55	198	66

of age. It is possible that higher dosage would have offset the effect of delay in older contacts, but sufficient information was not available to test this.

Discussion

A report by Greenberg *et al.* (1944) on the results of the prophylactic effect of gamma globulin in children exposed to measles in their own homes can be compared with those in this study if allowance is made for differences in strength of the gamma globulin preparations used. Greenberg and his colleagues gave 2 ml. from a phial containing 2.2 ml., to allow for waste, to each of 814 household contacts aged more than 6 months and less than 6 years. Their preparation contained between 153 and 224 mg. of protein per ml., 85 to 99% of which was gamma globulin. Thus 2.2 ml. would have contained between 286 and 488 mg. of gamma globulin. Almost all children who received more than 4 ml. and less than 8 ml. in our study were given the contents, less wastage, of two bottles each containing about 240 mg. of gamma globulin—that is, 480 mg. in all. The measles attack rates in children who received over 4 ml. and less than 8 ml. in the three age groups, over 6 months and under 1 year, over 1 year and under 3 years, and over 3 and under 5 years, were in our series 10, 29, and 50% respectively: whereas the corresponding rates calculated from the figures of Greenberg *et al.* were 5, 21, and 31%. The rates in both series are of the same order, and though the American gamma globulin, despite rather lower dosage, appears to have given better results, this may be due to many factors other than differences in methods of manufacture.

The findings of Stokes *et al.* (1944) and Ordman *et al.* (1944), though very similar to those of Greenberg and his colleagues, cannot be compared with our figures because of differences in the age grouping.

In the doses used adult serum was clearly inferior to gamma globulin for both prevention and modification, and

in all age groups no better results were obtained with more than 3 ml. and less than 9 ml. of concentrated adult serum than with the same dose of unconcentrated serum. The poor protection obtained from unconcentrated adult serum is easily understood when the gamma globulin content of the small doses is considered. The doses most frequently employed, 5 ml. and 10 ml., contain only about 40 and 80 mg. of gamma globulin respectively. Though there have been many reports on the use of adult serum, only in one, that of Morales and Mandry (1930), were there records of results in more than a very small number of the inoculated children exposed to measles in another member of the same family. In that study 10 to 40 ml. of adult serum was given, and a steep rise in attack rate was observed with doses less than 20 ml. Insufficient details of age and dose were supplied for a direct comparison of their results with those in Table II. The degree of protection obtained, however, seemed to be of about the same order.

Though there was evidence in a previous report (Cockburn *et al.*, 1951) that gamma globulin was probably free from the risk of transmitting serum hepatitis, recent surveys carried out on behalf of the Ministry of Health, the Medical Research Council, and the Department of Health for Scotland (Report, 1954) have shown that exposure of plasma to ultra-violet light did not prevent subsequent cases of the disease. In view of this serious potential danger and of the small degree of protection obtained it would appear wise to abandon the use of pooled adult serum for measles prophylaxis. Convalescent measles serum is of well-established value, and, if taken from a single donor to minimize the risk of hepatitis, would seem to be the best alternative when gamma globulin cannot be obtained.

A Suggested Dosage Scale for Gamma Globulin

A scale of dosage based upon the results of this investigation is set out in Table VI. It aims at being simple, economical, and practical, and at providing good protection for the greatest possible number of children. Slightly greater pro-

TABLE VI.—A Suggested Dosage Scale for Gamma Globulin

Aim	Age of Child		
	Under 1 Year	Over 1 Year and Under 3 Years	Over 3 Years
Prevention ..	3 ml. (250 mg.)	6 ml. (500 mg.)	9 ml. (750 mg.)
Modification ..	3 ml. (250 mg.)	3 ml. (250 mg.)	3 ml. (250 mg.)

tection could probably be obtained from higher dosage, but as the demand for gamma globulin exceeds the supply this would seem justifiable only in exceptional cases.

The two scales, one for prevention and one for modification, suggest a more precise association between dosage and result than was actually demonstrated. In the younger age groups a high probability of modification is unfortunately accompanied by a substantial risk of preventing measles altogether.

The same modifying dose of 3 ml. (250 mg.) is at present recommended for all age groups. It should be sufficient to prevent measles or to ensure a mild attack in an infant less than 1 year old; the degree of protection of older children would be less, but so would be the need for it. It is possible that a smaller dose of gamma globulin would be effective in modifying the disease, and studies on this point are being planned.

As gamma globulin may be required in special circumstances for the protection of contacts of infective hepatitis, poliomyelitis, and other diseases the amount available for measles prophylaxis may be insufficient to meet all requests, and it should be used mainly for children suffering from an intercurrent illness and for children whose general health or environment indicates that a serious outcome may be

expected from an attack. Babies under 6 months of age as a general rule seem to require no protection unless their mothers have no past history of measles or are suffering from the disease. In conjunction with other measures, gamma globulin has proved useful in preventing outbreaks in children's wards where a case of measles has occurred, and its use for this purpose seems justifiable. It is probably better to give a sufficiently large dose to prevent the disease to children occupying beds near the measles case than to give a small dose to all children in the ward.

Summary and Conclusions

The use of measles prophylactics in a series of cases is reported upon.

Confirmatory evidence was obtained of the superiority of gamma globulin over adult serum in measles prophylaxis.

Measles, though not invariably prevented by larger doses, was usually prevented or modified by relatively small doses of gamma globulin.

Within limits the prophylactic effect of gamma globulin varied directly in proportion to the dose used and inversely with the age of the child inoculated and the length of time between exposure and inoculation. The effect of delay between exposure and inoculation was not apparent in children under 1 year of age and was only slight in children between 1 year and 3 years of age.

The use of gamma globulin for measles prophylaxis should be restricted to weakly children or children suffering from an illness, to children living in bad home or institutional environments, and for preventing the spread of measles in children's wards in which a case occurs. It should only be given to babies under 6 months of age whose mothers have not had measles.

It is suggested that adult serum has not sufficient value in measles prophylaxis to justify the risk of serum hepatitis which its use entails.

We wish to thank those doctors in all parts of Britain who have so conscientiously completed the report forms sent to them with measles prophylactics.

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The Central Midwives Board last year was continually facing problems arising out of the increase in institutional confinements, according to its report for 1953-4. But, in view of statistical estimates of future population trends and the expected increase in women between 18 and 30 years old in 1961, the board thought it important to maintain a well-organized domiciliary service even if the service were under-employed for a year or two. The number of midwives on the Roll increased by 129 to 56,807 on March 31, 1954, and in the twelve months to January 31, 17,513 midwives notified their intention to practise—an increase of 42 over the previous year's figure.