The Distribution and Use of Gamma Globulin

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During the past few months, wide publicity has been given to the results of studies indicating that a fraction of human plasma, known as gamma globulin, has some value as a prophylactic agent for paralytic poliomyelitis. As a result of this publicity, an overwhelming demand for the material may be anticipated in the coming months. The purpose of the present document is to outline the steps that have been taken to meet this situation and to discuss briefly the principles on which current plans for the distribution of gamma globulin have been based.

The supply of gamma globulin is severely limited. It is estimated that the maximum amount available this summer will not exceed 10,000 liters. Even if this were all used for the prophylaxis of poliomyelitis in children, it would provide less than one and a half million average doses. Moreover, the dose would be large enough only to give protection for 4 to 5 weeks. How inadequate is this supply to meet the demand will be evident when it is recalled that there are some 40 million children in the United States of America under 15 years of age.

The situation is even less favorable than these figures indicate. Gamma globulin contributes to the public health in ways other than in the prophylaxis of poliomyelitis. It is well established as a valuable agent in the control of measles and of infectious hepatitis. It is proving its effectiveness in the treatment of the rare condition of hypogammaglobulinemia. Provision must be made to reserve amounts of gamma globulin adequate to meet these needs. Furthermore, since gamma globulin is a product derived from human blood, consideration must be given to the requirements of military and civilian services for whole blood, plasma and albumin. To maintain a well-balanced National Blood Program, blood collected by the American National Red Cross must be wisely apportioned between these varied needs.

Shortly after the outbreak of the Korean War, it was recognized that the competing demands of several Government agencies for blood and the derivatives of blood might become acute. To assure an equitable distribution, the Office of Defense Mobilization was assigned the task of coordinating the National Blood Program. Late in 1952, the evidence for the value of gamma globulin in the prophylaxis of poliomyelitis was first published. Realizing that this new development would lead to an extreme demand for gamma globulin during the next poliomyelitis season, the Office of Defense Mobilization turned to the National Research Council for advice. In response, the Council appointed a panel of experts in public health services, epidemiology and poliomyelitis to study the problem. There was general agreement that the equitable and effective use of available supplies of gamma globulin could be achieved only by the adoption of a system of controlled distribution. In consultation with the foremost authorities on poliomyelitis, an allocation program was devised and submitted to the Office of Defense Mobilization. The recommendations of the panel were approved in principle by the Health Resources Advisory Committee, Office of Defense Mobilization, on April 15, 1953. The plan, in the form which has been communicated to all health authorities, appears on pages 666–668 of this issue of *Public Health Reports.* The discussion that follows is a brief review of the nature of gamma globulin,

the amounts that are expected to be available this summer and the criteria on which the effective use of the material should be based.

Gamma Globulin

Gamma globulin is the name given to one of several fractions of the protein component of human plasma. It is comparable with the product officially known as immune serum globulin. Gamma globulin is prepared commercially by a method involving a series of precipitations with varying concentrations of alcohol under controlled conditions of acidity and low temperature. An average donation of blood (500 cc.) yields 7 cc. of a 16-percent solution of gamma globulin. This represents a single recommended dose for the prophylaxis of poliomyelitis in a 50-pound (6–7-year-old) child.

The production capacity of existing fractionating plants is limited.

The Administration of Gamma Globulin

Gamma globulin is available as a 16-percent solution. This solution is opalescent and somewhat viscous, necessitating injection through a No. 18 or 20 needle for quantities required for the prophylaxis of poliomyelitis. Injections should be made intramuscularly, using a separate syringe and needle for each subject. Gamma globulin should never be given by the intravenous route.

The use of separate syringes is recommended because of the danger of contamination of the syringe with blood containing the virus of homologous serum hepatitis. This may occur when one attempts to withdraw blood in order to be certain that the needle point is not in a vein. It is for this reason that the repeated use of the same syringe carries the hazard of the transmission of homologous serum jaundice. No instance of hepatitis has been recorded following the use of gamma globulin which has been prepared and administered in the manner described above.

The intramuscular injection of gamma globulin is not accompanied by any significant reactions. The danger of local or systemic reactions must, however, be considered if repeated injections are contemplated.

Measles

A dose of 0.1 cc. per pound body weight, when given soon after exposure, will prevent infection in most cases. When given later in the incubation period, this dose will result in modification of the disease. A dose of 0.02 cc. per pound body weight will usually modify the severity of the attack if given soon after exposure to infection.

In general, modification is to be preferred to prevention. Because of the seriousness of the disease in the younger age group, it is suggested that modification be attempted in all children below the age of 3 years who have been exposed to infection.

Prevention rather than modification may be warranted in hospital situations involving debilitated children and in individual cases where there is concurrent serious disease such as clinically active childhood tuberculosis.

The selection of exposed children rarely presents difficulties since the contact is almost always a frank clinical case and the time of exposure can frequently be determined. A history of a previous attack of measles should suffice to distinguish immune from susceptible children, and thus determine the need for prophylaxis following exposure.

Infectious Hepatitis

Evidence for the effectiveness of gamma globulin in the prophylaxis of epidemic infectious hepatitis is of recent origin. The dose recommended at the present time is 0.02 cc. per pound body weight. There is evidence that lower doses will modify the disease. Further studies are in progress to determine the optimum dose range.

The indications for use are less sharply delineated than they are with measles. Inapparent infections may occur and may contribute to the spread of the disease and to the difficulty in identifying susceptible individuals. Moreover, the infection may be spread by means other than direct contact. In food-borne and water-borne outbreaks, control measures directed at the vehicle of transmission should be imposed and may be supplemented by the prophylactic use of gamma globulin.

Gamma globulin should be most useful in the control of sharp outbreaks in the armed forces and in civilian groups where adequate hygienic measures cannot readily be imposed. In the general population, prophylaxis with gamma globulin among the family and intimate contacts of cases would appear to be desirable. At the same time, hygienic controls and the typhoid-type of isolation of nonicteric as well as jaundiced cases should be instituted.

Hypogammaglobulinemia

This clinical entity has only recently been described (*1*). It is a rare anomaly characterized by a deficient ability to form antibodies. The essential clinical manifestation is the frequent recurrence of severe infections. Laboratory evidence of the condition may be obtained from electrophoretic analyses of the gamma globulin content of the plasma of the patient and from immunological assays. In this condition, the regular repeated administration of gamma globulin is required to maintain the resistance of the patient to infection. As yet there has been little experience with this treatment and dosages have not been adequately established. The physician must be prepared to adjust the dose to the individual response.

Poliomyelitis

Two reports (*2*, *3*) by Dr. W. McD. Hammon and his associates are available on the epidemiological studies which form the basis for the use of gamma globulin in the prophylaxis of paralytic poliomyelitis. The children investigated ranged in age from 1 to 11 years and the doses used were 4, 7, or 11 cc. depending on the weight of the child. The average dose approximated 0.14 cc. per pound body weight.

Significant protection was demonstrated from the second through the fifth week following injection and diminishing protection was evident from the sixth to the eighth week. There was no significant difference in the number of cases of poliomyelitis in the treated and control groups in the week following injection, but there was evidence of mitigation of paralysis in the cases occurring in the children who had received gamma globulin. This evidence is the basis for the conclusion that gamma globulin will be most effective if given shortly before or as soon as possible after infection. It is of no value after clinical symptoms of the disease have become apparent (*4*).

Criteria for Diagnosis

It will be noted that the basis for allocation to the States is dependent upon the reported incidence of the disease, with the suggestion that the incidence of paralytic cases may be used as a control in making additional and supplemental allocations.

To insure uniform reporting it is suggested that physicians and health departments adopt criteria for diagnosis similar to those formulated by the National Conference on Recommended Practices for the Control of Poliomyelitis (*5*). The following is an excerpt from the above document.

"Diagnostic criteria of paralytic or nonparalytic poliomyelitis should generally include three or more of the following:

1) history compatible with poliomyelitis,
2) fever,
3) stiff neck and/or stiff back,
4) 10 to 500 cells per cc. of spinal fluid taken during the acute or early convalescent period of the disease,
5) spinal fluid protein elevated above normal limits,
6) demonstrable muscle weakness or paralysis.

"Cases which present only (1) history compatible with poliomyelitis, and (2) fever, should be classified as presumptive (abortive) poliomyelitis.

"Paralytic cases are defined as those in which definite weakness or paralysis has been detected and persisted during at least two examinations made at intervals of at least several hours. Results of an examination for paralysis of muscles of the extremities or trunk may be very unreliable during the period of muscle tenderness or 'spasm'."

Community Prophylaxis

Community prophylaxis of age groups at the greatest risk is indicated only in areas in which the incidence is exceptionally high and the onset

of the epidemic is abrupt. In Hammon's studies in Harris County, Texas, where the epidemic rate was 82/100,000, only 0.4 cases were prevented per 1,000 injections. The effectiveness rose to 3.4 per 1,000 in the Iowa study where the epidemic rate was nearly 400/100,000. A further difference between these two epidemics lay in the fact that the former was prolonged over many months whereas the majority of the cases in Iowa occurred in a period of 2 months. The effectiveness of mass prophylaxis is proportional to the incidence of the disease in the selected age group during the few weeks following injection and is influenced by the intensity of the outbreak as distinct from its ultimate rate. Mass prophylaxis is most effective if instituted about 3 weeks prior to the peak of an unusually intense epidemic.

Unfortunately, the prediction of the course and duration of poliomyelitis outbreaks in the population size exposed to the greatest risk is difficult and is subject to large error. It is suggested that an area qualifies for initial consideration for community prophylaxis only if it achieves a rate of 40 per 100,000 within a period of not more than 1 or 2 months and has a sharply rising weekly incidence, calculated by dates of onset at the time the selection is made. Other factors useful in selecting epidemic areas are high paralytic rates with relatively increased percentages of respirator cases and deaths. Urban populations exceeding 100,000 will seldom achieve rates justifying mass prophylaxis and populations of less than 15,000 are unlikely to have enough cases, after recognition of epidemic incidence, to make this type of prophylaxis profitable. Areas most likely to qualify are those with predominantly urban populations of 15,000–100,000. In addition to these, camps, schools, and other captive populations are favorable situations for community prophylaxis.

It should be remembered that only 60–70 percent of the expected cases will be influenced, because the rates among older persons are unlikely to be high enough to justify inclusion of all ages in the treated group. It must also be remembered that, if the recommended dose is used, only a 5- to 8-week segment of the epidemic will be affected. In a few instances, it may be necessary to consider a second injection in the course of an outbreak.

Consideration must also be given to the administrative problems involved in the setting up and staffing of clinics and in the administration of gamma globulin to large numbers of children in a short period of time. The viscosity of the solution and the need for large numbers of 10 cc. and 20 cc. syringes present problems.

It is anticipated that the selection of areas and age groups for community prophylaxis will be made by the State health officer or the State allocation authority. If a request for a special allocation be made to the National Allocation Office, the State health officer will be expected to supply information on the case incidence by week of onset, the number of deaths and of respirator cases, and the ratio of paralytic to total reported cases in the area.

Household Contacts of Clinically Diagnosed Cases

During epidemics, the incidence of secondary cases in families is five to twenty times the rate of poliomyelitis in the general population. That is to say, the members of a family in which a case occurs are subject to a much higher risk than are individuals in the community at large. On the basis of risk alone there would appear to be good reason to give priority to the prophylaxis of family contacts. There are, however, no controlled studies of the effectiveness of gamma globulin in the protection of household contacts of diagnosed cases. There is much evidence to indicate that infection is often widespread in families at the time the first case is recognized. If gamma globulin were effective only when given prior to infection, the case for household prophylaxis would be prejudiced. Hammon's results suggest, however, that inoculation after infection but prior to the onset of symptoms may be expected to modify the disease although it may not prevent it. This view bears significantly on the interpretation of the data in the table in which the incidence and chronological distribution of secondary cases of poliomyelitis in families are summarized.

It will be observed that 60 percent of secondary cases occur within 5 days of the diagnosis of the first case. Even if gamma globulin is

administered promptly to the household contacts, it will not be expected to prevent or modify the severity of disease in these cases. An additional 30 percent of the secondary cases will occur within a few days of inoculation. Hammon's results suggest that this group of cases may be mitigated in severity.

Table 1. Chronological distribution of poliomyelitis cases in families following index case

[A summary of data from several sources (*6*)]

Days interval between onset of first and subsequent cases	Number of secondary cases	Percent	Possible prophylaxis
0–5	242	60. 0	None.
6–12	120	29. 6	Modification.
13–30	42	10. 4	Prophylaxis.
Total	404	100. 0	

The final 10 percent of secondary cases will occur in the period in which the protective effect of gamma globulin is maximal and it is this fraction of cases that one may hope to prevent by the use of household prophylaxis. This would, at first sight, appear to be a poor return on the investment were it not a fact that the rates for this small fraction of delayed cases are comparable with the rates among all children in epidemic areas. On this basis, household prophylaxis may be expected to be as effective (cases prevented per 1,000 doses of gamma globulin) as community prophylaxis in the prevention of epidemic poliomyelitis and may be more effective if weight is given to modification as well as prevention of the disease. In areas in which epidemic proportions have not been attained, there will be no justification for general community prophylaxis.

There are a number of administrative advantages associated with household prophylaxis. The population that is to receive gamma globulin is easily defined. Distribution can be carried out through established public health channels and can be made in advance of the poliomyelitis season because allocations do not depend on the precarious prediction of epidemic incidence. Moreover, the cooperation of private physicians is assured since on them will rest the responsibility for the diagnosis of cases, and the identification and inoculation of contacts.

There is one subjective disadvantage which should not be overlooked. Some 60 percent of secondary family cases will be neither prevented nor modified by the use of gamma globulin. Unless physicians and the public are fully informed of this situation, an unjustifiably critical attitude toward the value of gamma globulin may develop. The public will see the failures of prophylaxis; the successes will be hidden from it.

Intimate Contacts of Clinically Diagnosed Cases

This is simply an extension of household prophylaxis to include individuals who are judged to have been as intimately associated with the diagnosed case as were the members of the household. The extension is logical but raises the difficulty of defining the criteria of intimacy. The method is likely to be most useful in rural and in self-contained suburban communities in which the number of intimate contacts of an individual is limited.

The extension of prophylaxis from household contacts to equally intimate contacts must be used with restraint; otherwise, the allocations to States will be rapidly depleted. It is anticipated that the responsibility for the definition of extra-household contacts and the areas within the State in which this method of prophylaxis may be used to advantage will rest with the State health officer.

Household Contacts of Suspected Cases

The immunization of household contacts of suspected cases may be viewed as a selective form of community prophylaxis which is specifically directed toward those individuals in the community subject to the most intimate exposure to the virus of poliomyelitis at the time that prophylaxis is undertaken. The use of this method is advocated only in intense epidemic situations. It may be particularly valuable in sparsely populated areas in which sporadic cases lead to extremely high rates of incidence but which are not suited to mass prophylaxis.

The method has the merit of giving protection to individuals who may be exposed to infection several days earlier than would be possible were the injections delayed until the phy-

sician could make a more certain diagnosis. There is a further hypothetical advantage which is of quite undetermined value although it may be most significant. Infection with the poliomyelitis virus is much more likely to be abortive than paralytic. It follows that the first invasion of a family by the virus is probably evidenced only by a case of minor illness. Should the case actually be one of poliomyelitis, immunization of the family at this time may prevent any paralytic case from developing.

The prophylaxis of contacts of suspected cases has serious disadvantages. Its efficacy is just as dependent as is that of community prophylaxis on the accurate prediction of epidemic conditions. If it is used in other than epidemic areas, much gamma globulin will be squandered on contacts of minor illnesses, a negligible proportion of which are poliomyelitis infections.

The method has been described as a selective form of community prophylaxis. It differs in that the office of every physician in the area will become a prophylactic clinic. From one point of view, this will simplify administration by avoiding the problems that are associated with the organization of centralized clinics. On the other hand, if a significant fraction of the total population in the area is involved, it may overtax the physicians and result in undesirable delay in completing the required number of injections.

Summary

It is estimated that about 1,000,000 average doses of gamma globulin will be available for the prophylaxis of poliomyelitis during 1953. The selection of the group of individuals in which this limited supply of material can be used most effectively presents many epidemiological and administrative problems. Four alternative methods have been recommended by the division of medical sciences, National Research Council, and have been incorporated in the allocation plan adopted by the Office of Defense Mobilization. The advantages and disadvantages of these methods in particular situations are reviewed. The allocation plan is based on the principle that it is the local health officer who is in the best position to decide which method of prophylaxis will most effectively meet each local situation as it arises.

The household contact plan would appear to be the most effective in areas of low or moderate incidence, with possible extension to include intimate contacts other than family members. With high epidemic incidence in a community with an intense outbreak, either community prophylaxis of age groups particularly susceptible or extension of the household contact plan to include contacts of suspected cases may be suitable. Factors such as community size, expected severity and duration of the epidemic, facilities for the injection of large numbers of individuals and the availability of gamma globulin may influence the decision as to the plan for emphasis in a particular area.

The plans are of sufficient latitude, however, to apply to almost any situation, and appear to offer some hope of restricting the use of the scarce material to the groups at greatest risk.

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