

Proceedings of
**A SYMPOSIUM ON
IMMUNIZATION
IN CHILDHOOD**

held in
**THE WELLCOME BUILDING
LONDON**

4th to 6th May 1959



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FOREWORD

By BRIGADIER SIR JOHN BOYD, O.B.E., F.R.S.

A number of diseases resulting from bacterial or viral infection can now be prevented by means of vaccines and toxoids, and the problem of administering these to the best advantage, and with the least inconvenience to the recipients, has become complex and difficult. The time has come to assess all the evidence which has accumulated, and to attempt to reach agreement on certain basic principles which must be observed in all inoculation schedules. The Symposium was organized with this object in view.

Taking part in the Symposium were representatives of all sections of the profession interested in the subject—medical officers of health, school medical officers, general practitioners, paediatricians, epidemiologists, statisticians, representatives from infectious diseases hospitals, from the laboratories, from interested departments overseas, and, casting a paternal eye on the proceedings, from the Ministry of Health.

The first session was devoted to consideration of the complications and side-effects which occasionally result from one or other of the immunization processes, such as provocation poliomyelitis, encephalopathy occurring after the administration of pertussis vaccine, and generalized vaccinia and encephalitis resulting from smallpox vaccination. Other relevant problems such as the sterilization of syringes were also discussed.

In subsequent sessions, dealing with the different procedures which are now recommended and commonly practised, opening and supporting papers were presented by those having special and in many cases unique experience. The advantages and disadvantages of combining the different prophylactics so as to reduce the number of inoculations and visits to the clinic were enumerated, and the difficult but extremely important problem of maintaining records of inoculation, and in particular personal records kept by the individuals concerned, was given due consideration. At all sessions ample time was given for discussion, and indeed one of the main objects of the Symposium, and one which was successfully achieved, was to draw out as wide an expression of opinion as possible, so that, when a final assessment came to be made, a clear picture would exist of all the advantages and disadvantages of the different procedures.

In the interval between the last two sessions it became the task of the Steering Committee, augmented by the Chairmen of the earlier sessions, to draw up

one or more schedules embracing as far as possible the proposals which had been made. It was found possible to define certain fundamental requirements, and on this basis to build up two schedules, one avoiding the use of mixed prophylactics and so calling for a greater number of injections, the second admitting the use of mixed prophylactics and so cutting down the number of inoculations.

At the final session, these tentative proposals were presented to the Symposium, and under criticism were modified in some minor details. In the end, however, it was unanimously agreed to recommend the modified schedules, a recommendation which, in view of the status of those who took part in the Symposium, must be regarded as giving authoritative guidance to those concerned.

A final recommendation, well worthy of implementation, was that a representative body be set up to keep the problems of immunization under review and to make from time to time such recommendations as might be rendered necessary by advancing knowledge.

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NOTE.—A short account of the first two sessions of the Symposium, and the authorized text of the Recommendations agreed upon at the Fifth Session, including the two Schedules, were published in the "British Medical Journal", May 23rd, 1959, vol. 1, p. 1342. For reasons of space the Third and Fourth Sessions were omitted from this report. An Editorial on "Immunization Schedules" was published in the same issue (p. 1336).

FIRST SESSION

(Chairman: Professor R. CRUICKSHANK)

THE RISKS OF IMMUNIZATION

PROVOCATION POLIOMYELITIS

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If within a short period of inoculation a person developed poliomyelitis with paralysis affecting the inoculated limb, the association was striking. A number of occurrences of this kind were reported from time to time, but too rarely and too spasmodically to suggest that they were a major problem. In 1949, however, three independent reports had appeared which brought wide recognition to provocation poliomyelitis. McCloskey (1950) as Poliomyelitis Officer in the State of Victoria reported on cases seen in a large epidemic in Melbourne; Martin (1950) reported on children seen in the Hospital for Sick Children, Great Ormond Street; and Geffen (1950) as Medical Officer of Health of the Borough of St. Pancras reported on cases notified in his area. The common finding was that a number of patients with paralytic poliomyelitis had received inoculations of diphtheria and pertussis antigens in the previous few weeks and that the paralysis was confined to, or concentrated mainly on, the limb last inoculated. When their Department had been asked for advice on this problem, they had suggested that the apparent association, the double event of paralysis and recent inoculation in the same individual, might often be coincidental. At about the first birthday a high proportion of children received their primary inoculations, and in the summer months in particular some of these would get paralytic poliomyelitis without their illness being influenced at all by previous injections. The question was whether the number of such double events was greater than might be expected by chance association alone, or whether there was some qualitative characteristic which distinguished provoked paralysis from coincidental paralysis. To answer this an inquiry was conducted in the autumn of 1949 through the Medical Officers of Health of thirty-three areas in England and Wales, chosen because these had been most severely hit up to that time by the current epidemic. This study (Hill and Knowelden, 1950) confirmed that provocation poliomyelitis was a true entity by two findings:

- (1) Paralysis in children who had been inoculated within twenty-eight days

of the onset of their illness involved the last inoculated limb in a much higher proportion than in children inoculated at longer periods before onset.

(2) Children with paralytic poliomyelitis had received prophylactic inoculations within twenty-eight days of onset more frequently than children of the same age and sex who were not suffering from this illness.

As suggested by the earlier reports, the association seemed particularly strong with the alum precipitated mixed diphtheria-pertussis prophylactic, but A.P.T. could not be exonerated. Experience of other antigens was insufficient to determine if they held any risk at all.

Two main questions arose from these reports. Although inoculations had been shown to provoke poliomyelitis, the frequency of this hazard, whether one case per 1,000 or one case per million injections, was unknown. Furthermore, the relative risks attached to different prophylactics were required. Consequently, the Medical Research Council sponsored a large investigation in Britain. In the years 1951-55 Medical Officers of Health provided reports of all notified cases of poliomyelitis stating whether there had been any prophylactic inoculations within twelve months prior to the onset of symptoms. By personal investigations the history of the injections given and of the clinical and general epidemiological findings were obtained for the group of patients who had inoculations within three months of onset. For large urban areas, mainly London, Middlesex and the County Boroughs, the Medical Officers of Health in addition gave details of the number of children of different ages inoculated in their clinics with the separate prophylactics week by week for a period of two and a half years from May 1951 to December 1953.

Combining the two sources of data from urban areas in this two and a half year period, poliomyelitis case reports and returns of the number of children inoculated, it was possible to calculate attack rates to show the frequency with which paralytic poliomyelitis developed within the first month after the last inoculation, i.e. 1 to 28 days; within the second month, 29 to 56 days; and within the third month, 57 to 84 days. The rates for the second and third months were very similar and there was little difference in the rates for these periods from one prophylactic to another. Therefore, a combined rate for all prophylactics for the whole period 29 to 84 days after inoculations was obtained and this was 1.3 cases per 100,000 inoculations (Table I). This rate was very similar to the paralytic notification rate per 100,000 of the general child population of corresponding age in England and Wales at the time of the study. Against this 29 to 84 day rate in Table I are set the rates for the first month, the 1 to 28 day period, for each of the prophylactics separately. For all prophylactics the 1 to 28 day rate of 4.0 per 100,000 exceeded the 29 to 84 day rate. The difference, shown in the third column, 2.7 per 100,000, represents the risk of getting paralytic poliomyelitis directly attributable to inoculation. In the fourth column the risk is shown in the inverse form, viz. the number of inoculations to provoke one case; for all prophylactics the figure was 37,000. The risk thus calculated confirmed that provocation poliomyelitis was not merely an alteration in the site

of paralysis in persons who would have been paralysed anyhow, but a real increase in the number of paralysed patients. This increase was observed in each of the three epidemic years of the study and was maximal in the second and third quarters of the year.

Table I

PARALYTIC POLIOMYELITIS AFTER INOCULATION
C.B. Clinics England and Wales 1951-53

Prophylactics	Rates per 100,000 per month			Inoculations to provoke 1 Case
	1-28 Days	29-84 Days	Diff.	
Mixed with alum	8.0	1.3	6.7	15,000
Mixed without alum	6.5		5.2	19,000
P.T.A.P.	6.0		4.7	21,000
A.P.T.	3.4		2.1	48,000
Pertussis vaccine	1.9	1.3	0.6	170,000
F.T. and T.A.F.	1.4		0.1	1,000,000
All prophylactics	4.0		2.7	37,000

Turning to individual prophylactics, the 1 to 28 day rate for each exceeded the 29 to 84 day rate, but the difference, the provocation rate, varied considerably. The provocation rate was highest for the mixed prophylactic with alum, 6.7 per 100,000, but was not much less for the mixed without alum, 5.2, or for the P.T.A.P., 4.7. A.P.T., with a rate of 2.1, occupied an intermediate position, while plain pertussis vaccine and F.T. and T.A.F. had relatively low risks with rates under 1.0 per 100,000. The rates for the first four prophylactics were significant at the 0.05 level, while the last two were not. Smallpox vaccination, which is not shown in the table, gave no evidence of provocation as there were no cases at all in the 1 to 28 day period.

Although these rates were based on an experience of over three million inoculations, the provocation risks were quite small and the total number of children developing paralysis within 1 to 28 days of injection was only 68. It would be appreciated, therefore, that divided into the separate prophylactics, the numbers were far too small to give precise estimates of risk. Figure 1 shows not only the provocation rates listed in the previous table but also their 95 per cent. confidence limits. For the mixed prophylactic with alum, for example, where the estimated risk was 6.7 per 100,000, it was unlikely that the true risk was less than 3.2 (i.e. 1 case in 31,000 injections) or more than 10.5 (1 case in 9,500 injections).

The estimate for this mixed prophylactic with alum was relatively precise, compared with that for the mixed without alum. Here the smaller experience produced very wide limits, from 0.7 (1 in 142,000) to 12.4 (1 in 8,000). The A.P.T.

estimate had the narrowest limits of all, but clearly set at a lower level than the mixed with alum; there was, in fact, a significant difference between these two. The lower limits for plain pertussis vaccine and for F.T. and T.A.F. were zero, another way of expressing that there was no significant provocation with these antigens. Summarizing this picture, it was possible to say that the mixed with alum was more dangerous than A.P.T., but that it was impossible to distinguish between the mixed without alum, P.T.A.P. and A.P.T. or rank them with any confidence.

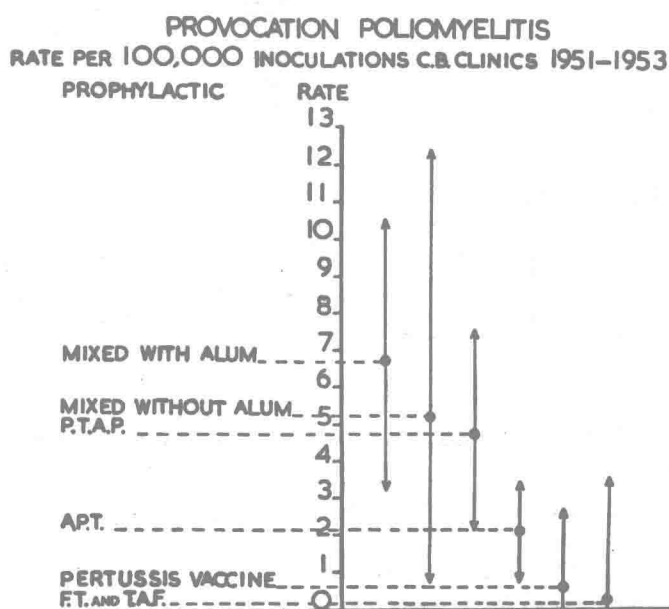


Fig 1.

In their investigation of patients with provoked poliomyelitis Dr. Cockburn, Dr. Thomson and the speaker had found that the most characteristic pattern was that a child with a history of inoculation in an arm about 8 to 14 days previously had complete paralysis of the muscles around the shoulder, severe or complete paralysis of muscles affecting elbow movement, and less severe involvement of wrist and finger movement. This severe disability was commonly the only detectable paralysis, all other regions being unaffected. One method of assessing provocation was therefore to determine in what proportion of patients the last inoculated limb was the one and only site of paralysis. The proportion could be obtained for patients inoculated in the upper or lower limbs (i.e. thigh or buttock), but the two must be kept distinct since the normal distribution of paralysis affected legs several times more often than arms, and because inoculation into the arm was commoner than into the leg. The advantage of this method of looking at the data, which was used in the early 1949 study and was very similar to Dr. Holt's method, was that it was