No satisfactory explanation is given for success or failure with this drug, but it is pointed out that all patients in this series who showed no response had previously received insulin.

Ketosis may develop rapidly on the substitution of insulin by BZ 55 in patients who require the former for their control.

We wish to acknowledge our indebtedness and thanks to Mr. A. P. Kenny, of the Biochemical Department, Victoria Infirmary, Glasgow, for undertaking the blood-sugar and urine-sugar estimations, and to British Insulin Manufacturers, who kindly provided us with the A and B tablets.

REFERENCE

Bertram, F., Bendfeldt, E., and Otto, H. (1955). *Dtsch. med. Wschr.*, **80**, 1455.

A WARNING NOTE

In view of a recent report from America of a small number of cases of severe agranulocytosis and also of several cases of thrombocytopenia in this country, it is the considered opinion of the authors of the papers on BZ 55 appearing in this issue of the "British Medical Journal" that the drug in question should at present be used only under careful hospital supervision.

This view is shared by the majority of those who have had experimental and clinical experience of the use of BZ 55 in this country.

L. J. P. DUNCAN, Edinburgh Royal Infirmary.
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VACCINATION AGAINST WHOOPING-COUGH

RELATION BETWEEN PROTECTION IN CHILDREN AND RESULTS OF LABORATORY TESTS

A REPORT TO THE WHOOPING-COUGH IMMUNIZATION COMMITTEE OF THE MEDICAL RESEARCH COUNCIL AND TO THE MEDICAL OFFICERS OF HEALTH FOR CARDIFF, LEEDS, LEYTON, MANCHESTER, MIDDLESEX, OXFORD, POOLE, TOTTENHAM, WALTHAMSTOW, AND WEMBLEY*

In a previous report (Medical Research Council, 1951) the results were given of a series of controlled trials made to assess the prophylactic value of pertussis vaccine in children 6 to 18 months old. Five batches of vaccine from three different manufacturers were tested. Each batch gave substantial protection, but the two batches supplied by the Michigan Department of Health gave much greater protection than the others.

In 1948, before the previous trials were completed, further field investigations were begun in conjunction with laboratory studies to determine whether the protective effect of vaccines in children could be assessed by a laboratory test. Two series of trials were made—one from October, 1948, to March, 1951, using British vaccines, and the other from early 1951 to mid-1954, using British and American vaccines. The second series was planned not only to give information on the relation between field and laboratory results, but also to determine whether British manufacturers could produce good vaccines by methods similar to those of the Michigan Department of Health and to determine whether a vaccine prepared from culture in liquid medium was as effective as one from culture on solid medium. A description of all the vaccines used in the two series of trials is given in Table I.

INVESTIGATIONS IN THE FIELD

General Plan

The previous trials (M.R.C., 1951) were made on a strictly controlled basis to investigate whether pertussis vaccines were of any value in protecting against the disease. Half the children whose parents volunteered to have them injected were given vaccine and the rest were given injections of an inoculum which looked like pertussis vaccine but which did not contain *Haemophilus pertussis*. This procedure could not be continued after it was known that each of five different batches of vaccine used gave substantial protection, and it was decided that in all subsequent trials every child should be given pertussis vaccine, and that the results with one batch of vaccine should be compared with those with other

**Whooping-cough Immunization Committee:* Sir Samuel Bedson, F.R.S. (chairman), Dr. P. Armitage, Dr. W. C. Cockburn, Dr. E. T. Conybeare, Professor R. Cruickshank, Professor A. W. Downie, F.R.S., Professor A. Bradford Hill, F.R.S., Dr. J. O. Irwin, Dr. Pearl Kendrick, Dr. J. Knowelden, Professor J. W. McLeod, F.R.S., Dr. H. J. Parish, Mr. A. F. B. Standfast, Dr. G. S. Wilson, Dr. J. Ungar, Dr. D. G. Evans (secretary).

Medical Officers of Health: Dr. J. Greenwood Wilson and Dr. W. Powell Phillips, Cardiff; Dr. I. G. Davies, Leeds; Dr. A. W. Forrest, Leyton; Dr. C. Metcalfe Brown, Manchester; Dr. A. C. T. Perkins, Middlesex; Dr. J. F. Warin, Oxford; Dr. G. Chesney and Dr. J. Hutton, Poole; Dr. G. Hamilton Hogben, Tottenham; Dr. A. T. W. Powell, Walthamstow; Dr. E. Grundy, Wembley.

Field Workers: Dr. I. A. Bolz and Miss M. R. Elliott, Cardiff; Dr. G. R. Baxter and Mrs. E. R. Beard, Leeds; Dr. A. R. Fox and Miss R. M. Edward, Leyton; Dr. B. J. Griffiths and Miss O. I. Howell, Manchester; Dr. Beryl Anscombe, Dr. A. M.-M. Payne, and Miss C. H. Rudkin, Oxford; Dr. Joan Moignard, Miss M. D. Smith, and Miss W. E. Bennett, Poole; Dr. A. T. W. Powell and Mrs. H. M. Johnston, Walthamstow; Dr. J. C. McDonald, Miss M. M. Wall, and Miss E. E. Wilden, Tottenham and Wembley.

Laboratory diagnostic tests were made by: Dr. G. J. G. King and Mr. E. C. Young, Bournemouth; Dr. J. Marks and Professor Scott Thomson, Cardiff; Dr. H. D. Holt, Mr. G. V. Heimer, and Mr. J. Hollingsworth, Colindale; Professor J. W. McLeod, F.R.S., Dr. D. E. Nicholson, Dr. G. C. Turner, and Miss B. B. Waller, Leeds; Dr. W. W. Walther and Mr. K. R. Podger, Leyton; Dr. Mary O. Adams and Mr. A. G. Harbour, Manchester; Dr. W. H. H. Jebb, Oxford; Dr. F. Marsh, Mr. E. F. Browning, Mr. P. Lovell, and Mr. G. Hoy, Walthamstow.

Laboratory tests for antigenic potency were made by: Mr. A. F. B. Standfast, Lister Institute; Dr. Margaret Pittman, U.S. National Institutes of Health, Bethesda; Dr. Pearl Kendrick and Dr. Grace Eldering, Michigan Department of Health; Dr. A. E. Francis and Mr. H. Proom, Wellcome Research Laboratories; Dr. D. G. Evans and Dr. F. T. Perkins, M.R.C. Laboratories; Hampstead; Dr. J. Ungar, Glaxo Research Laboratories, Dr. Mary O. Adams, Manchester; Dr. Naomi Datta, Colindale.

The field trials were put in train and supervised by Dr. W. C. Cockburn.

The analysis of the field and laboratory results were made and the report prepared by Dr. P. Armitage, Dr. W. C. Cockburn, Dr. D. G. Evans, Dr. J. O. Irwin, Dr. J. Knowelden, and Mr. A. F. B. Standfast.

batches tested at the same time in the same area. There were therefore no unvaccinated control groups, but in some of the trials records were kept of the incidence of pertussis in the siblings of vaccinated children when the vaccinated children and the siblings were known to be exposed to infection by a primary case in the family. This was the main difference between the new and the earlier studies; otherwise the procedure in the field was similar to that described in the 1951 Report.

Children in the 1948–51 trials were allocated to a vaccine group in succession as their names were received. In the 1951–4 trials, when only two vaccines were tested in each area at one time, children born on *odd* days of the month were allocated to one group and children born on *even* days to the other. After the injections had been completed, arrangements were made for each child to be visited monthly for about 24 months. Special visits were paid when it was known that a child was being exposed to pertussis or had symptoms which might be those of the early stages of the disease. Swabs were taken from vaccinated children with coughs and also so far as possible from infective cases to which vaccinated children were exposed. The doctors and nurse-investigators visiting children during the follow-up period did not know which vaccine a child had received.

Trials Made Between 1948 and 1951

Seven separate trials were made in six areas—Cardiff, Leyton, Manchester, Oxford, Poole, and Walthamstow; two were made in Manchester and one in each of the other areas. The vaccines used—V1, V2, V3, V3b, V4, V5, V5a, V6, and V7—were prepared by different methods from the same strains of *H. pertussis* (Table I). In each trial three vaccines were tested in parallel. Vaccines V1, V2, and V3 were tested in Cardiff, Poole, Leyton, and Walthamstow, vaccines V3b, V4, V5a, V5, V6, and V7 in Manchester, and vaccines V2, V3b, and V4 in Oxford.

Children 6–18 months old were given three doses of vaccine intramuscularly with an interval of one month between injections. The first two doses were each 0.5 ml., the third 1 ml., and the total dose, in terms of the U.S.A. opacity standard, was approximately 70,000 million organisms. Consent forms were received from the parents of 11,093 children in all areas; 9,794 (88%) of the children completed the course of three injections.

Reactions and Untoward Sequelae

In the trials with plain suspension vaccines—V1, V2, and V3—940 children, about 20% of the total, were visited 24–48 hours after each injection, and degrees of redness, swelling, and general malaise, and other reactions were estimated. According to the trial area, one-half to one-third of the children had no local or general reaction. Of those who had reactions, all but nine had mild malaise of 24–48 hours or redness or swelling about an inch (2.5 cm.) in diameter. Three of the nine children with more serious reactions had malaise severe enough for them to be kept in bed for 24–48 hours and six had screaming attacks in the evening of the day of injection; between the screaming attacks the children were said to be pale and limp. These episodes were not confined to any one of the three injections; some occurred after the first, some after the second, and some after the third. Three of the nine children were given subsequent injections without ill effect. In the Manchester trial with the alum-precipitated vaccines V3b, V4, and V5a, 194

TABLE I.—*Vaccines and Dosage Schedule*

Vaccines									Dosage Schedule	
Batch No.	Date of Prep.	Medium for Growth	Killing Agent and Concentration	Alum-precipitated or Plain	Preservative and Concentration	Strains of *H. pertussis*	Other Details of Preparation	No. of Organisms (Millions/ml.)	Doses at Monthly Intervals (ml.)	Total Dose in Millions of Organism
V1	Sept., 1948	BG with horse blood	Formalin 0·5%	Plain	Phenol 0·5%	2128	48-hr. growth	35,000	0·5, 0·5, 1	70,000
V2	,, ,,	,, ,,	,,	,,	,, ,,	2128	Similar method to V1	35,000	0·5, 0·5, 1	70,000
V3	,, ,,	,, ,,	,,	,,	Thiomersalate 0·01%	2128	24-hr. growth	35,000	0·5, 0·5, 1	70,000
V3b	,, ,,	,, ,,	,,	Alum pptd.	,,	2128	Same batch as V3 but alum pptd.	35,000	0·5, 0·5, 1	70,000
V4	July, 1948	Cohen and Wheeler	,,	,, ,,	,,	2128	Whole fluid from 20-hr. growth; culture shaken	35,000	0·5, 0·5, 1	70,000
V5	April, 1949	BG with horse blood	,,	,, ,,	Phenol 0·5%	2128	Same method as for V1 but alum pptd.	35,000	0·5, 0·5, 1	70,000
V5a	Oct., 1948	,, ,,	,,	,, ,,	,, ,,	2128	,, ,,	35,000	0·5, 0·5, 1	70,000
V6	April, 1949	,, ,,	,,	,, ,,	Thiomersalate 0·01%	2128	Same method as for V3 but alum pptd.	35,000	0·5, 0·5, 1	70,000
V7	Mar., 1949	Cohen and Wheeler	,,	,, ,,	,,	2128	Same method as for V4	35,000	0·5, 0·5, 1	70,000
V8	Dec., 1949	BG with sheep blood	Thiomersalate 0·01%	Plain	,,	18925; 16945; 10536; 18334	Michigan method	20,000	1 1 1	60,000
V9	June, 1950	,, ,,	,,	,,	,,	83E; 252; L46; C26573; 2891; 2893	,, ,,	20,000	1 1 1	60,000
V10	Nov., 1950	,, ,,	,,	,,	,,	83E; 252; L46: C26573; 2891; 2893	,, ,,	20,000	1 1 1	60,000
V11	Aug., 1950	Cohen and Wheeler	,,	,,	,,	18925; 16945; 10536; 18334	Whole fluid from 72-hr. growth; culture not shaken	30,000	1 1 1	90,000
V12	Sept., 1951	BG with human blood	Thiomersalate 0·02%	,,	Thiomersalate 0·013%	293; 324; 360; 357; 358; 332; 343	Michigan method but with human blood in BG	20,000	1 1 1	60,000

BG = Bordet–Gengou medium.

TABLE II.—1948–51 *Trials. Similarity of Groups*

	Areas and Vaccines											
	Cardiff, Poole, Leyton, Walthamstow			Manchester			Manchester			Oxford		
	V1	V2	V3	V3b	V4	V5a	V5	V6	V7	V2	V3b	V4
No. of children followed up	1,709	1,701	1,648	910	943	941	414	396	417	230	241	244
Percentage of males	**50**	**50**	**51**	**52**	**51**	**51**	**54**	**54**	**51**	**53**	**55**	**54**
Average age (months)	13	13	13	15	15	14	15	15	15	14	14	14
Average duration of observation per child (months)	20	20	20	27	27	27	23	23	22	25	25	25
Infectious diseases* during follow-up:												
Total No. of illnesses	644	584	629	483	528	492	161	139	151	71	126	84
Average No. of illnesses per child	0·38	0·34	0·38	0·53	0·56	0·52	0·39	0·35	0·36	0·31	0·52	0·34
Average No. of other children per household under 14 years of age	0·93	0·93	0·98	0·76	0·84	0·77	0·89	0·85	0·90	0·99	1·15	0·98

* Measles, chicken-pox, mumps, rubella.

children, 7% of those followed up, were similarly visited after each injection. One severe reaction was noted, in a child who developed extensive redness and swelling after the third injection.

Particular attention was paid to the occurrence of convulsions in all children vaccinated in all areas. Four children had convulsions within 72 hours after an injection. One of these children was given a subsequent injection without ill effect. None of the children showed evidence of permanent cerebral damage.

None of the children developed poliomyelitis within four weeks after injection.

Similarity of Groups

To determine whether the vaccine groups in each trial were essentially alike certain attributes were examined.

TABLE III.—1948–51 *Trials. Number of Cases of Pertussis and Attack Rates per* 1,000 *Child-months of Observation*

Area	Vaccine	No. Followed Up	Duration of Observation (Child-months)	Cases of Pertussis	Attack Rate per 1,000 Child-months
Cardiff, Poole, Leyton, Walthamstow	V1	1,709	34,850	247	**7·1**
	V2	1,701	34,359	276	**8·0**
	V3	1,648	33,234	190	**5·7**
Manchester	V3b	910	25,002	101	**4·0**
	V4	943	25,692	164	**6·4**
	V5a	941	25,667	112	**4·4**
,,	V5	414	9,420	35	**3·7**
	V6	396	9,003	36	**4·0**
	V7	417	9,304	37	**4·0**
Oxford	V2	230	5,741	55	**9·6**
	V3b	241	6,023	28	**4·6**
	V4	244	6,143	44	**7·2**
Totals		9,794	224,438	1,325	**5·9**

Table II records the results of the tests for similarity; it is clear that with each set of three vaccines the groups were similar.

Incidence of Pertussis

The results of all trials are given in Tables III and IV. Altogether 1,325 cases of pertussis were diagnosed, and in 68% the diagnosis was confirmed bacteriologically. By all three methods of comparing the vaccines—the attack rate per 1,000 child-months (Table III) and the percentage attack rates for "home exposures" and "other exposures" (Table IV)—no striking differences in protective effect were seen. Some slight differences did, however, exist, and these are referred to later.

Since there were no unvaccinated control groups in these trials, an absolute estimate of the value of the vaccines could not strictly be made. In the previous trials (M.R.C., 1951) the attack rate in "home exposures" in the unvaccinated control groups was 87%. Similar high attack rates in susceptible children exposed in their own homes have been reported by others (Wheeler, 1936; Kendrick and Eldering, 1939; Court *et al.*, 1953). In the present study, taking all vaccines together, 547 children were exposed in their own homes; of these, 379 (69%) developed the disease. This attack rate is much nearer the 87% in the unvaccinated than the 18% in the vaccinated groups in the previous study. Furthermore, only one vaccine, V3b in the Oxford trial, gave a home exposure attack rate of less than 50%, and this was based on only 18 home exposures (Table IV). All the vaccines in this new series of trials were therefore poor.

Trials Made Between 1951 and 1954

11 trials were made in this series, in Cardiff, Leeds, Manchester, Oxford, Poole, Tottenham, and Wembley (Tottenham and Wembley were considered as a combined area). The Michigan Department of Health provided a vaccine—V8—in

TABLE IV.—1948–51 *Trials. Number of Cases of Pertussis and Percentage Attack Rates by Type of Exposure*

Area	Vaccine	Home Exposures			Other Exposures			No. of Cases After No Known Exposure	Total Cases
		No. of Exposures	No. of Cases	Attack Rate (%)	No. of Exposures	No. of Cases	Attack Rate (%)		
Cardiff, Poole, Leyton, Walthamstow	V1	93	73	**78**	197	62	**31**	112	247
	V2	88	75	**85**	203	57	**28**	144	276
	V3	109	66	**61**	216	46	**21**	78	190
Manchester	V3b	47	28	**60**	178	31	**17**	42	101
	V4	54	42	**78**	184	51	**28**	71	164
	V5a	51	31	**61**	190	35	**18**	46	112
,,	V5	18	11	**61**	44	10	**23**	14	35
	V6	21	12	**57**	40	10	**25**	14	36
	V7	16	9	**56**	42	11	**26**	17	37
Oxford	V2	14	14	**100**	51	13	**25**	28	55
	V3b	18	7	**39**	70	6	**9**	15	28
	V4	18	11	**61**	76	10	**13**	23	44
Totals		547	379	**69**	1,491	342	**23**	604	1,325

sufficient quantity for it to be used as a reference vaccine against which the other vaccines could be compared. In each trial half the children were given the reference vaccine V8 and the remainder were given either one of three British vaccines—V9, V10, or V12—made by methods similar to those used by the Michigan Department of Health, or vaccine V11, which was prepared by the State of New York Department of Health from liquid medium culture (Cohen and Wheeler, 1946) using the same strains of *H. pertussis* as were used in the preparation of V8 (Table I). In each area except Oxford, two trials were made. Each vaccine except V9 was tested in parallel against V8 in two areas; V9 was tested against V8 in all areas except Oxford (Table V).

In all the areas the parents of 36,811 children 6 months to 3 years old agreed to have them vaccinated. Three intramuscular or subcutaneous injections were given at monthly intervals. Each dose was 1 ml., and the total dose consisted of 60,000 million organisms (U.S.A. opacity standard). Because of reports that convulsions might occasionally occur after pertussis vaccine, particularly in children with a personal or family history of convulsions or epilepsy, children with such a history were not vaccinated, and on account of this 1,601 children were not accepted. In addition, 2,108 children failed to arrive at the clinics for the first injections. Of the 33,102 who had their first injection, 31,557 (95%) completed the course.

When the trials began it was not known how many children might be presented for vaccination, as vaccination was becoming popular in the trial areas, and hence there was some difficulty in deciding whether all or only a portion of the children could be followed up. At first it was thought that it might suffice to follow only vaccinated children in families where there was also an unvaccinated child with no history of pertussis, such potential "home exposure" families being the ones from which it was known by experience that the most accurate information could be obtained. However, the proportion of children from such families was not more than 10%, and to avoid jeopardizing the studies by having too few children under observation it was decided to increase the numbers taken into the follow-up. After the first few weeks of the trial, approximately all the children were followed up in Cardiff, Oxford, Poole, Tottenham, and Wembley, and approximately half the children in Leeds and Manchester. The total number of children followed up was 19,005. In the areas where half the children were followed up, every second child presented for vaccination was chosen, and the others, though not followed up, were given a full course of vaccine.

Reactions and Untoward Sequelae

Local and General

One child in five from the follow-up groups was visited 48 hours after each injection to determine the incidence of local and general reactions. Children chosen for visiting after the first injection were also visited after the second and third injections. Nearly 10,500 visits were made. There was considerable variation in recording between areas, presumably due to observer differences, but very little difference within areas between vaccines and between the first, second, and third dose. Redness more than 2 in. (5 cm.) in diameter was noted on 6% of visits (not of children) and the child appeared "obviously disturbed by the tenderness" on 0.4% of visits. Other reactions noted were that three children were kept in bed for more than 24 hours, 99 vomited once or oftener within 48 hours after an injection, and 72 were described as "fretful," "didn't sleep," or "had lost their appetites." Local and general reactions were therefore not serious.

Convulsions

As in the 1948–51 series of trials, special notes were kept of children who developed convulsions after vaccination. Children not in the follow-up were visited after the first and second injections if they failed to return to the clinic for the next injection, and convulsions in these children were recorded if they occurred. The children not in the follow-up, however, were not visited after the third injection. All children known to have had convulsions, whether or not in the follow-up group, were visited at intervals until May, 1955.

A report by Byers and Moll (1948) indicated that in cases of encephalopathy associated with vaccination the first convulsion occurred within 72 hours after an injection. In this series of trials eight children had their first recorded convulsion within 72 hours after one of the three injections. It is impossible to say whether or not the number of cases observed was greater or less than might be expected to occur by chance in this period. Thirty-four children had their first recorded convulsion 4 to 28 days after injection. There is no reason to consider their convulsions were precipitated by the vaccine. Of them, 11 (32%) had more than one convulsion during the period of observation. Of the eight children who had convulsions within 72 hours after injection, three (38%) had more than one attack. The proportions of the two groups are similar and, though based on small numbers, suggest that serious cerebral damage, as manifested by repeated convulsions, did not occur as a result of the injections. None of the children with repeated convulsions showed evidence of gross cerebral damage such as was noted by Byers and Moll, but one child had five convulsions during the period of observation and two had four. These three children had their initial convulsions 12, 17, and 20 days after injection.

In over 30,000 vaccinated children, therefore, there was no definite evidence that convulsions or encephalopathy were directly related to vaccination. As previously stated, children with a personal or family history (the family for the purpose was taken to include only father, mother, sisters, and brothers) of convulsions, epilepsy, hydrocephalus, mental defect, or similar conditions were not accepted in the trial. In addition, children were not injected within a month after attacks of measles, mumps, influenza, chicken-pox, and similar diseases, or smallpox vaccination. These precautions may account for the freedom from cerebral accidents, but it may also be that the risk of

TABLE V.—1951–4 *Trials. Similarity of Groups*

	Areas and Vaccines							
	All Except Oxford		Leeds, Tottenham, Wembley		Oxford, Poole		Cardiff, Manchester	
	V8	V9	V8	V10	V8	V11	V8	V12
No. of children followed up	3,342	2,975	2,397	2,311	1,254	1,195	2,835	2,696
Percentage of males	51	51	51	54	52	49	53	52
Average age (months)	22	21	18	18	15	16	17	17
Average duration of observation per child (months)	25	25	22	22	22	23	22	22
Infectious diseases* during follow-up: Total No. of illnesses	892	795	372	392	108	115	545	501
Average No. of illnesses per child	0·27	0·27	0·16	0·17	0·09	0·10	0·19	0·19
Percentage of children with previous history of measles	18	20	8	8	4	5	10	9
Average No. of other children per household under 14 years of age	1·1	1·2	0·92	0·93	0·83	0·92	1·2	1·2

* Measles, chicken-pox, mumps, rubella.

encephalopathy is so remote that a group of over 30,000 children was not large enough to show that it existed.

Poliomyelitis

Twenty-four children developed paralytic poliomyelitis during the study. Three children became ill less than 28 days after an injection, and all three were paralysed in the injected limb and nowhere else. Twenty-one children became ill 29 days to 26 months after injection. Five had paralysis only in the injected limb, six had paralysis in the injected limb as well as at other sites, and in 13 there was no association between the site of paralysis and the site of injection. The fact that the three children who developed poliomyelitis within a month after injection had paralysis only in the injected limb suggests, in view of the published evidence, that there was a causal relationship between the injection and the site of paralysis.

Similarity of Groups

In each trial there were two groups of children, those given the reference vaccine V8, and those the vaccine under test. In Table V trials made in the different areas with the same pair of vaccines are combined; it is clear that with each pair of vaccines the groups were similar in all respects for which information was obtained. In each separate trial also the groups were similar.

Incidence of Pertussis

The results of the trials are given in summary form in Tables VI and VII. Altogether 231 children were diagnosed as cases of pertussis, and 59% of these were confirmed bacteriologically. Bacteriological evidence of exposure to infection was also obtained in many cases. Of the 801 vaccinated children exposed in their own homes to infection, *H. pertussis* was isolated from the sibling—or siblings—to whom the vaccinated child was exposed in 64%. Of the 1,967 "other exposures," *H. pertussis* was isolated from the infecting child in 43%.

When chloramphenicol was introduced for the treatment of pertussis it was thought that, if it lessened the period during which infection was dispersed by cases, and was used for the treatment of siblings to whom vaccinated children were exposed, it might reduce the home exposure attack rate and make it impossible to compare rates in the pre- and post-chloramphenicol periods. Records were kept of the use of chloramphenicol in the siblings of vaccinated children. It was found that the attack rate in 128 vaccinated children exposed to chloramphenicol-treated siblings with pertussis was 20% and that the attack rate in 673 vaccinated children exposed to infection by siblings not treated with chloramphenicol was 13%. Thus the use of chloramphenicol for the siblings of vaccinated children did not reduce the risks of the vaccinated children developing the disease.

By all three methods of comparing the vaccines—attack rate per 1,000 child-months (Table VI) and percentage attack rates in "home exposures" and "other exposures" (Table VII)—no outstanding differences in protective effect were evident. The test vaccines were of the same order of potency as the Michigan reference vaccine.

As mentioned earlier, the studies were made to compare vaccines and not to ascertain their absolute value. Some information on absolute values can, however, be deduced. Taking all vaccines together, the attack rate in 801 home exposures was 14%, ranging from 4 to 29% (Table VII). In the controlled trials reported previously (M.R.C., 1951) the attack rate in the control unvaccinated groups was 87%. The evidence, along with the previously mentioned observations of Wheeler (1936), Kendrick and Eldering (1939), and Court *et al.* (1953), suggests that the vaccines used in the 1951–4 series of trials were highly potent unless the disease had recently changed its character and had become less infectious. There is evidence that such a change had not occurred. In the course of the trials there were 56 households in the three largest trial areas—Manchester, Leeds, and Cardiff—in which vaccinated children and unvaccinated children up to 7 years of age were exposed to infection from another case in the family and in which the size of the family at the time of exposure was accurately known.

In the 56 households there were 69 vaccinated and 62 unvaccinated children. Fourteen (20%) of the vaccinated developed pertussis compared with 51 (82%) of the unvaccinated. The diagnosis of pertussis was confirmed bacteriologically in eight (57%) of the vaccinated, in 37 (73%) of the unvaccinated, and in 34 (61%) of the initial cases providing the sources of infection in the households. Eleven per cent. of the vaccinated were under 1 year of age compared with 29% of the unvaccinated, and 16% of the vaccinated were 4 years old or more compared with 48% of the unvaccinated. These differences were mainly due to the ages at which vaccination was offered (6 months to 3 years).

TABLE VI.—1951–4 *Trials. Number of Cases of Pertussis and Attack Rates per* 1,000 *Child-months of Observation in Areas Testing the Same Two Vaccines*

Area	Vaccine	No. Followed Up	Duration of Observation (Child-months)	Cases of Pertussis	Attack Rate per 1,000 Child-months
Cardiff, Leeds, Manchester, Poole, Tottenham, Wembley	V8	3,342	84,463	46	**0·54**
	V9	2,975	74,984	29	**0·39**
Leeds, Tottenham, Wembley	V8	2,397	52,907	33	**0·62**
	V10	2,311	50,392	48	**0·95**
Oxford, Poole	V8	1,254	28,025	21	**0·75**
	V11	1,195	27,440	13	**0·47**
Cardiff, Manchester	V8	2,835	63,329	26	**0·41**
	V12	2,696	59,548	15	**0·25**
Totals		19,005	441,088	231	**0·52**

TABLE VII.—1951–4 *Trials. Number of Cases of Pertussis and Percentage Attack Rates by Type of Exposure in Areas Testing the Same Two Vaccines*

Area	Vaccine	Home Exposures			Other Exposures			No. of Cases After No Known Exposure	Total Cases
		No. of Exposures	No. of Cases	Attack Rate (%)	No. of Exposures	No. of Cases	Attack Rate (%)		
Cardiff, Leeds, Manchester, Poole, Wembley, Tottenham	V8	172	24	**14**	409	11	**3**	11	46
	V9	132	17	**13**	352	5	**1**	7	29
Leeds, Tottenham, Wembley	V8	84	17	**20**	181	10	**6**	6	33
	V10	85	25	**29**	172	10	**6**	13	48
Oxford, Poole ..	V8	58	3	**5**	159	7	**4**	11	21
	V11	52	2	**4**	163	4	**2**	7	13
Cardiff, Manchester	V8	114	15	**13**	270	2	**0·7**	9	26
	V12	104	9	**9**	261	1	**0·4**	5	15
Totals		801	112	**14**	1,967	50	**3**	69	231

The groups were exposed to infection at the same time in the same families, and the high attack rate in the unvaccinated is so near the rate one would have expected to find on the basis of previous experience that it is justifiable to suppose that no change had occurred recently in the facility with which pertussis spreads in unprotected susceptible children in families and that the vaccines used were uniformly of high potency.

An analysis was made which showed that during the period of observation there was no waning in the degree of immunity afforded by the vaccines. Taking all the vaccines together, the attack rates in "home exposures" at six-monthly intervals after vaccination showed no evidence of increasing two and a half to three years after vaccination (Table VIII).

TABLE VIII.—1951–4 *Trials. Attack Rates in Home Exposures at Six-monthly Intervals after Vaccination in all Trials*

Period After Third Injection	No. of Exposures	No. of Cases	Attack Rate (%)
0–5 months	218	23	11 } 14
6–11 ,, ...	188	35	19 }
12–17 ,, ...	184	22	12 } 14
18–23 ,, ...	123	20	16 }
24–29 ,, ...	79	12	15 } 14
More than 29 months ..	9	—	0 }

In summary, the field trials showed that the vaccines in the first series were poor and in the second series good.

INVESTIGATIONS IN THE LABORATORY

The Mouse-Protection Test

Tests were made in the laboratory to compare the ability of vaccines to protect mice against experimental *H. pertussis* infection. Two methods were first explored—one in which the level of protection of immunized mice was determined by injecting a challenge dose of *H. pertussis* intracerebrally, and the other in which the challenge dose was given intranasally. It was shown (Standfast, 1954) by testing a number of vaccines in parallel by both methods that the intranasal method did not distinguish between the protective power of the vaccines in mice as well as did the intracerebral method. For this reason it was decided to employ only the intracerebral method.

In all, 18 vaccines were tested; four of those used in the previous field trials—D231, O87860, G61, and G174—and all 14 of those in the present trials. The details of the method are fully described in the W.H.O. Report (1953). Groups of 15 mice were injected intraperitoneally with graded doses of vaccine and challenged intracerebrally 10 to 14 days later with a suspension of virulent *H. pertussis*, strain 18-323. The mice were observed for 14 days after challenge, and from the proportion of deaths occurring in each group the dose of vaccine required to protect 50% of mice (ImD_{50}) was calculated. In each test at least two vaccines were compared, one of which was a reference vaccine, usually G61, V3, or V8.

From preliminary studies it became evident that the errors of the tests were large and that, in spite of standardization of reagents and procedures and the use of mice from an inbred stock, many mice would be needed to detect significant differences in potency between vaccines. Two series of tests were therefore made in which three vaccines, V1, V2, and V3, were tested in parallel on 14 occasions in each of two different laboratories. From the results of these tests it was calculated that it was necessary to test any two vaccines in parallel eight times (720 mice) in order that an apparent twofold potency-ratio between them should be significant ($P=0.05$). As a result of this statistical analysis, which will be published in full elsewhere (Irwin and Standfast, 1956), it was decided to test all vaccines at least eight times in one laboratory (Lister Institute) and as often as possible in other laboratories. Some more recent results in the mouse-protection test suggest that the same degree of precision may often be achieved with a smaller number of mice (Irwin and Standfast, 1956; Ungar and Basil, 1956).

Comparison of Vaccines by the Mouse-Protection Test

The comparison of vaccines was made from the results of 118 assays by Mr. Standfast, 21 Dr. Pittman, 12 by Dr. Ungar, 11 by Mr. Proom, and 2 by Dr. Kendrick. It is convenient to divide the vaccines into three groups according to which of three reference vaccines was normally used as a standard of comparison in the laboratory tests. Group 1 consisted of D231, O87860, G61, and G174 (G61 as the reference vaccine), group 2 consisted of V1, V2, V3, V3b, V4, V5, V5a, V6, and V7 (V3 as the reference vaccine), and group 3 consisted of V8, V9, V10, V11, and V12 (V8 as the reference vaccine).

For each vaccine in each assay, the ImD_{50} was estimated by the Reed–Muench method, or, where this was inapplicable, by a rough probit method, and the analysis was performed on the logarithms of the ImD_{50} values. The relative potency of each vaccine in terms of the appropriate reference vaccine was calculated entirely from comparisons made on the same day, since the ImD_{50} has been observed to fluctuate markedly from one day to another. The estimates of the log potency-ratios, with their standard errors, are shown in Table IX. The results from the different laboratories were consistent with each other, and have been pooled. The relative potencies of the three reference vaccines were obtained in the same way, and, finally, each of the 18 vaccines is compared with the vaccine G61. These relative potencies are given in the last two columns of Table IX.

TABLE IX.—*Relative Potencies of Vaccines by Mouse-protection Test*

Vaccine	Log Potency-ratios (±Standard Errors) in Terms of Reference Vaccine			In Terms of G61	
	G61	V3	V8	Log Potency-Ratio	Potency-ratio
Group 1:					
D231	0·594±0·146			0·594	3·93
O87860	0·300±0·219			0·300	2·00
G61 (ref.)	—			**0**	**1·00**
G174	−0·944±0·155			−0·944	0·11
Group 2:					
V4 ..		0·365±0·155		0·030	1·07
V7 ..		0·347±0·180		0·012	1·03
V3b ..		0·290±0·167		−0·045	0·90
V6 ..		0·240±0·179		−0·095	0·80
V5a ..		0·176±0·158		−0·159	0·69
V3 (ref.)	−0·335±0·120	—		−0·335	0·46
V5 ..		−0·140±0·180		−0·475	0·34
V1 ..		−0·494±0·062		−0·829	0·15
V2 ..		−1·169±0·098		−1·504	0·03
Group 3:					
V11 ..			0·172±0·095	1·023	10·55
V9 ..			0·107±0 066	0·958	9·08
V12 ..			0·077±0·071	0·928	8·47
V8 (ref.)	0·851±0·129		—	0·851	7·10
V10 ..			−0·269±0·094	0·582	3·82

It should be emphasized that these relative potencies are properties of the vaccines when tested at the same time. For example, V8 is shown as being about seven times as potent as G61. When these two vaccines were tested together, however, V8 was new and G61 was some two to three years old. If each vaccine gradually deteriorated it may be that V8, when new, had about the same potency as G61 when new. In the absence of a standard vaccine known to be stable, the possible deterioration of these vaccines cannot be measured with certainty. However, for almost every vaccine which was tested over a period of more than a year, the ImD_{50} values showed a gradual trend upwards. On the average, this was equal to about 0.2 logarithmic unit a year, equivalent to a loss of potency of 40% per annum. This trend may have been due to a gradual change in the test conditions or to a real deterioration of the vaccines, or both. When comparing the mouse-protection results with those of the field, it has been assumed that the trend was due entirely to deterioration of the vaccines.

The Mouse-Agglutination-Production Test

A number of vaccines were also tested for their ability to produce agglutinin in mice, using the method described by Evans and Perkins (1953, 1954). Groups of mice were given two spaced injections of vaccine separated by an interval of 14 days, and the geometric mean agglutinin titre of the sera was determined 10 days after the second dose. Since the method was introduced late during the field studies, it was not possible to test all vaccines extensively. However, 13 vaccines were tested—one from the previous trials and 12 from the new series. With each vaccine the agglutinin response to a total dose of 10×10^9 organisms was determined, and in the case of five of the vaccines the response to two additional smaller doses, 2.5×10^9 and 0.625×10^9, was also obtained. Each vaccine was tested in parallel with a reference vaccine which gave only a slight variation in response in the different tests. The detailed results have already been reported (Evans and Perkins, 1953, 1954).

A rough comparison of the vaccines may be made from the results shown in Table XII, in which the response obtained with each of the 13 vaccines to a total dose of 10×10^9 organisms is given.

Production of Agglutinin in Children

Tests were made with 13 of the vaccines to determine their ability to produce specific agglutinin in children. Two independent studies were made. In the first, tests were made by Dr. Mary O. Adams on the sera of children immunized with vaccines V1 to V8 and V12. These sera were taken from children aged 6 to 18 months 2 to 10 months after their third inoculation, and the titrations were made using as antigen a suspension of living *H. pertussis* according to the method described by Evans and Adams (1952). In the second study the tests were made by Dr. Naomi Datta on the sera of children immunized with vaccines V8, V10, V11, and V12. These sera were from 2- to 5-year-old children, and were taken 6 to 10 weeks after the third dose of vaccine. The titrations were made by a method similar to that used by Dr. Adams, except that a killed suspension of *H. pertussis* was used as antigen. Similar results were obtained by both workers in testing sera from children immunized with vaccines V8 and V12; more than 90% of the sera with these two vaccines gave titres of 16 or more in both studies. It was therefore considered justifiable to compare the vaccines by grouping the results of all the tests in spite of the fact that the tests had not all been made by a standard method (Table X).

TABLE X.—*Comparison of Vaccines by the Agglutinin Response in Children*

Vaccine	No. of Sera Tested	Sera with Titre of 16 or More		Geometric Mean Titre
		No.	%	
V1	55	2	3·6	4
V2	61	1	1·6	4
V3	52	2	3·8	4
V3b	45	5	11·1	6
V4	39	3	7·7	7
V5	9	0	0·0	4
V5a	30	7	23·3	12
V6	10	1	10·0	5
V7	9	1	11·1	5
V8	267	251	94·0	211
V10	81	73	90·2	208
V11	60	58	96·7	291
V12	126	120	95·2	279

COMPARISON OF FIELD AND LABORATORY TESTS

Field Trials and Mouse-Protection Tests

A comparison of the prophylactic effect of vaccines in the field is most safely made when the vaccines are tested at the same time in the same centres, otherwise the comparison may be distorted by changes in the field conditions or deterioration of the vaccines. These strict comparisons, made on the home-exposure attack rate for reasons given in the first section of this report, are presented in Table XI alongside the corresponding potencies estimated in the laboratory. Differences in either field or laboratory results which are significant at the 0.05 level of probability are also indicated.

Though field and mouse-protection test results occasionally put vaccines in different orders of potency, there are no definite contradictions; on no occasion was a significant

TABLE XI—*Comparisons of Field and Mouse-protection Results for Vaccines Tested in the Field at the Same Time and in the Same Centre*

Vaccine	Results of Field Trials				Results of Mouse-protection Tests	
	Centres	Home Exposures		Significant Differences	Potency in Terms of G61 by Mouse-protection Test	Significant Differences
		Cases/Exposures	Attack Rate (%)			
Group 1:						
D231	Manchester*	2/20	10	None	3·93	None
O87860		8/36	22		2·00	
G174	Leeds*	7/29	24	None	0·11	G61 better than G174
G61		7/23	30		1·00	
Group 2:						
V3	Cardiff, Poole, Leyton, Walthamstow	66/109	61	V3 better than either V1 or V2	0·46	V3 better than V1
V1		73/93	78		0·15	V1 better than F2
V2		75/88	85		0·03	
V3b	Manchester	28/47	60	V3b and V5a pooled better than V4	0·90	None
V5a		31/51	61		0·69	
V4		42/54	78		1·07	
V3b	Oxford	7/18	39	V3b and V4 both better than V2	0·90	V3b and V4 both better than V2
V4		11/18	61		1·07	
V2		14/14	100		0·03	
V7	Manchester	9/16	56	None	1·03	None
V6		12/21	57		0·80	
V5		11/18	61		0·34	
Group 3:						
V9	All areas except Oxford	17/132	13	,,	9·08	,,
V8		24/172	14		7·10	
V8	Leeds, Tottenham, Wembley	17/84	20	,,	7·10	V8 better than V10
V10		25/85	29		3·82	
V11	Oxford, Poole	2/52	4	,,	10·55	None
V8		3/58	5		7·10	
V12	Cardiff, Manchester	9/104	9	,,	8·47	,,
V8		15/114	13		7·10	

* These vaccines were not used at the same time, but a large part of the subsequent follow-up periods overlapped.

difference found in one direction in the field and in the opposite direction by the mouse-protection test. Furthermore, in certain comparisons, both field and mouse-protection test results gave significant differences in the same direction. These were: (*a*) that V3 was better than both V1 and V2, and (*b*) that both V3b and V4 were better than V2.

The results of Table XI may be supplemented by a rather less rigorous comparison of the field and mouse-protection test results for all vaccines. Table XII shows, for each vaccine; (*a*) the home-exposure attack rate for all children inoculated with that vaccine, and (*b*) the estimated potency-ratio by the mouse-protection test of the vaccine, at about the middle of the period during which it was used in the field, in comparison with the potency of G61 at the beginning of 1947. The assumption has been made here that each vaccine deteriorated at a rate of 0.2 log unit of potency each year. Thus vaccine V5a was used during a period centred at about the beginning of 1949. Its log-potency-ratio in comparison wth G61 *when tested simultaneously* is given in Table IX as −0.159. We assume that G61 declined in potency by 0.2 log unit during each of the years 1947 and 1948. Then the log-potency-ratio of V5a at the beginning of 1949, in terms of G61 at the beginning of 1947, will be estimated at $-0.159-2(0.2)=-0.56$.

TABLE XII.—*Comparison Between Results of Field Trials and Laboratory Tests*

Vaccine	Results of Field Trials			Results of Laboratory Tests			
	Mean Year* of Inoculation in Children	Home Exposures		Potency by Mouse-protection Test in Terms of G61 in 1947·0		Mean Agglutinin Titre	
		Cases/ Exp.	Attack Rate (%)	Log Ratio	Ratio	In Mice	In Children
V11	1952·3	2/52	4	−0·04	0·91	1,259	291
D231	1947·4	3/41	7	0·51	3·24	1,125	NT
V12	1952·4	9/104	9	−0·15	0·71	1,990	279
V9	1951·5	17/132	13	0·06	1·15	2,820	NT
V8	1952·0	59/428	14	−0·15	0·71	708	211
O87860	1947·1	8/36	22	0·28	1·91	NT	NT
V10	1952·2	25/85	29	−0·48	0·33	644	200
G61	1947·5	7/23	30	−0·10	0·79	NT	NT
G174	1948·7	14/47	30	−1·28	0·05	,,	,,
V3b	1949·0	35/65	54	−0·44	0·36	,,	6
V7	1949·5	9/16	56	−0·49	0·32	16	5
V6	1949·5	12/21	57	−0·60	0·25	49	5
V3	1949·5	66/109	61	−0·89	0·13	13	4
V5	1949·5	11/18	61	−0·98	0·10	14	4
V5a	1949·0	31/51	61	−0·56	0·28	NT	12
V4	1949·0	53/72	74	−0·37	0·43	17	7
V1	1949·5	73/93	78	−1·33	0·05	15	4
V2	1949·5	89/102	87	−2·00	0·01	10	4

* 1952·3 means 0·3 of the way through 1952, and so on.
NT = Not tested.

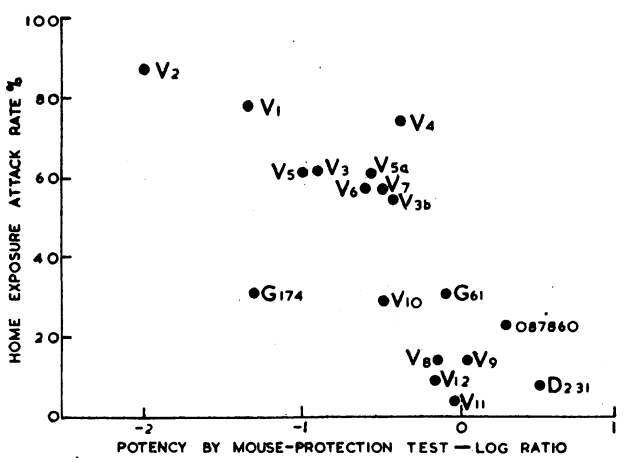

Chart showing the relationship, with 18 pertussis vaccines, between home exposure attack rate in the field and potency as estimated by the mouse-protection test.

The relationship between the home-exposure attack rates and the potency-ratios, estimated by the mouse-protection test, is shown in the Chart. There appears to be good correlation. In interpreting these results it should be remembered that both the attack rates and the potencies are subject to sampling errors which may have exaggerated or detracted from the true correlation, that attack rates are possibly subject to variations from one area or one period of time to another, and that the assumptions that the vaccines deteriorate at a constant rate of 0.2 log unit a year may be invalid. However, as the second column of Table XII shows, the different vaccines within each of the three groups were used in the field over fairly short periods of time. Consequently, a false assumption about the rate of deterioration would affect principally the relative potencies between the three groups rather than those within the groups. Even when attention is restricted to fluctuations within the three groups of vaccines, the correlation between the home-exposure attack rate and the potency-ratio is still significant. These results suggest that the mouse-protection test is of some value in predicting field results.

Field Trials and Agglutinin Tests

Table XII also shows for a number of vaccines the relationship between (*a*) the home exposure attack rate, (*b*) the agglutinin produced in mice to a dose of 10×10^9 organisms, and (*c*) the agglutinin produced in children to their course of immunization. It is evident that there is a close correlation between the production of agglutinin in mice and in children; of the 11 vaccines tested by both methods, 7 gave a poor response and 4 a decidedly higher response in both cases.

It is also evident that there is a general correlation between protection in the field and agglutinin response. Six vaccines which showed substantial protection each gave a good agglutinin response in mice, and four of these also gave a good response when tested in children. On the other hand, nine vaccines which showed poor protection each gave a poor agglutinin response in children, and seven of these also gave a poor response when tested in mice.

CONCLUSIONS

Two series of field trials were made in which 28,799 children were followed up for an average of two years after inoculation with pertussis vaccines. Severe local or general reactions were not encountered and there was insufficient evidence to show that pertussis vaccine precipitated repeated convulsions or initiated serious cerebral damage. In three cases of poliomyelitis which occurred within 28 days after injections, the site of paralysis was confined to the injected limb.

Fourteen batches of vaccine were used; their protective effect was assessed mainly on the basis of home-exposure attack rates. The nine batches of vaccine used in the first series of trials were poor, but the five batches used in the second series gave substantial protection.

As is shown in Table I, the vaccines in the first series were all made from the same strain of *H. pertussis*. They were prepared from 24- or 48-hour cultures on Bordet–Gengou medium containing horse blood or from culture in liquid medium. In all of them formalin was used as the killing agent, but some were preserved with phenol and others with thiomersalate. Between initial isolation and use in the vaccines, the strain had been repeatedly subcultured in the laboratory. The vaccines in the second series were made from a mixture of four, six, or seven freshly isolated strains which had been subcultured on very few occasions before being freeze-dried. Three vaccines were made using Bordet–Gengou medium containing sheep's blood, one using Bordet–Gengou medium containing human blood, and one using liquid medium. All were killed, and preserved with thiomersalate.

It is clear that the vaccines in the first series differed in many ways from those in the second series, but it is not

possible to say which of the differences were responsible for the widely divergent results.

The field studies showed that in the second series three vaccines (V9, V10, and V12) made in this country from strains of *H. pertussis* isolated here were as effective as the reference vaccine (V8) made with American strains and supplied by the Michigan Department of Health, and that the vaccine prepared by the State of New York Department of Health (V11) from the same American strains as the reference vaccine, but grown in liquid medium, was, in a preliminary trial, also as effective as the reference vaccine.

At the same time as the field trials were in progress, laboratory tests were made in which the vaccines were extensively tested for their ability to protect mice against intracerebral pertussis infection. Some of the vaccines were tested for their ability to produce agglutinin in mice, and sera from a number of vaccinated children were titrated for agglutinin.

There was a correlation between protection in children and three laboratory tests : (*a*) protection of mice against intracerebral infection with *H. pertussis*, (*b*) production of specific agglutinin in mice, and (*c*) production of specific agglutinin in children. Though the three laboratory tests gave results parallel with those obtained in the field, it does not necessarily follow that the laboratory tests measure directly the factor or factors responsible for the production of immunity in children. Pillemer and his colleagues (1954) have prepared from *H. pertussis* an antigenic fraction which protects mice against intracerebral infection, but which produces a very poor agglutinin response in mice (Evans and Perkins, 1955). The protective potency of this fraction in children is being tested at present in Liverpool and preliminary results suggest that it is giving protection. The mouse-agglutinin-production test therefore may not be a reliable guide to the value of all vaccines in children. Agglutinin production in children has been accepted by some workers as evidence of protective potency, and the tests reported here support this conclusion. Production of agglutinin, however, is only one of the properties of *H. pertussis* and may be different from, and not always run parallel with, protective potency. In any event it would scarcely be practicable to estimate the agglutinin response in children before each batch of vaccine produced commercially was issued for general use.

Of the three laboratory tests, therefore, the mouse intracerebral challenge test is considered, on the basis of present evidence, as the most satisfactory. It is correlated with protection in children, and in mice it measures protection from infection with a virulent strain of *H. pertussis*. A British standard pertussis vaccine has been established in terms of which the potency of other vaccines may be assayed by means of comparative tests. The standard has been prepared from vaccine V12 (Table I), which gave substantial protection in the field, by freeze-drying in 6% dextran. No instability has been detected in the dried standard, and its use in comparative tests will be the subject of a separate communication (Armitage and Perry, 1956).

In view of these results it would seem wise before the issue of a vaccine for use in children to submit it to the mouse intracerebral protection test to ensure that it has an adequate potency in relation to the British standard vaccine. It is also clear that a vaccine need not necessarily be made by the Michigan method ; the results of the present trials show that one produced from cultures made in a liquid medium can give equally good results.

SUMMARY

In two series of field trials, 14 pertussis vaccines were tested for their protective potency in 28,799 children. The vaccines used in the first series of trials were poor, but those in the second series gave substantial protection, which was maintained for at least two and half to three years after vaccination.

At the same time as the field trials were in progress, laboratory tests were made in which the vaccines were tested for their ability to protect mice against intracerebral pertussis infection. Some of the vaccines were also tested for their ability to produce specific agglutinin in mice and in children.

A comparison between the field and laboratory results showed some correlation between the potency of vaccines in protecting children and their ability to protect mice against intracerebral infection. There was also evidence of a correlation between protection in children and ability to produce agglutinin in both mice and children.

It is concluded that in future only those pertussis vaccines which have been shown, by the intracerebral mouse-protection test, to have an adequate potency in relation to the British standard pertussis vaccine should be issued for use in children.

The Whooping-cough Immunization Committee of the Medical Research Council and the medical officers of health in the areas where the trials were made are grateful to the parents who consented to have their children injected. They wish to thank Glaxo Research Laboratories, the Lister Institute of Preventive Medicine, the Michigan Department of Health, the State of New York Department of Health, and the Wellcome Research Laboratories for the free supply of the pertussis vaccines, and the World Health Organization for its interest and for some financial help towards the cost of the second series of trials. They particularly wish to record their indebtedness to Dr. Pearl Kendrick, corresponding member of the Committee, who gave help and advice on the preparation of the vaccines during visits to this country and also by correspondence. The vaccine for the preparation of the British standard pertussis vaccine was generously provided by Glaxo Laboratories.

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Medical Memorandum

Repeated Delayed Splenic Bleeding Into the Lesser Sac

Spontaneous rupture of a normal spleen is a rare occurrence, and only about 100 cases have been reported in the world's literature. The case described below appears to be the first recorded instance where haemorrhage took place almost entirely into the lesser sac of the peritoneum, and is the first example of spontaneous splenic rupture in a case of arterial hypertension.

CASE REPORT

A woman aged 29 was admitted to hospital on April 14, 1951. Two days previously she had been discharged from another hospital, having had an operation there about six weeks before "for bleeding from a mesenteric vessel." On the day of admission she took a laxative for constipation, after which generalized abdominal pain and vomiting began and continued up to the time she was examined (3 p.m.). On direct questioning she admitted that about 24 hours