Toxicity of pertussis vaccine: frequency and probability of reactions

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SUMMARY From a file of 1127 children in whom signs of brain damage were reported after injections of vaccines containing pertussis antigen, the first 197 cases with good documentation of events were chosen for further study. In these children, 291 reactions had been reported, usually of screaming attacks (68), convulsions (87), collapse (17), or one or more of these signs (99), within 24 hours of injection. Subsequently 165 children became mentally defective and 102 had further convulsions. In 129 (65%), contraindications to vaccination were present *ab initio* and in 25, subsequent injections were given despite reactions to a previous injection or injections.

From a mathematical model constructed from data in published reports, it is calculated that the frequency of convulsions appears to be higher by 2 : 1 in vaccinated than in unvaccinated infants. In children subject to febrile or other convulsions, the frequencies may be of the same order but a second convulsion occurring only after a second or subsequent injection of vaccine is unlikely to be due to chance.

The pattern of reactions and sequence of events observed in the present study and in published reports suggest an association between certain reactions to pertussis vaccine and subsequent severe brain damage, the incidence of which appears to be not less than one per fifty thousand children vaccinated during the last 20 years of mass vaccination in the United Kingdom.

The present debate about pertussis vaccine concerns its efficacy or lack of efficacy no less than its toxicity. If it is effective and if, as the Department of Health and Social Security and its chief medical advisers maintain (DHSS, 1972; Joint Committee on Immunisation and Vaccination, 1977), the menace of whooping cough is held at bay only by vaccinating almost every infant from three months after birth onward, then there could be a case for accepting some risks of adverse reactions in individuals for the sake of the community. If, on the other hand, the claims for efficacy are spurious and the decline in whooping cough since 1880 and especially since 1920 is attributable to other factors such as improvements in living standards and child care (Bassili and Stewart, 1976), then it is timely to question the continuing use of the vaccine. If, in addition, the hazard of toxicity begins to approach the hazards of the disease itself to life and health, then it may be time to stop using the vaccine unless it can be improved and be shown to be effective in controlling an outbreak under present-day conditions.

I have attempted to review the balance of evidence for and against vaccination in reports published elsewhere (Bassili and Stewart, 1976; Stewart,

1977a; 1977b; 1977c; 1977d; 1977e), and in contribution to a debate organised by the Royal Statistical Society (RSS, 1978). This study describes the present state and antecedents in children who were diagnosed in hospital paediatric units as having brain damage after the injection of vaccines containing pertussis antigens.

Method

Since 1974, I have been receiving the examining reports of toxicity from various quarters. My investigation began with a few cases reported to me locally but expanded rapidly after publication of a paper (Stewart, 1977a) in 1977 when cases dating from the 1950s were brought to my attention. The work of Wilson and his colleagues (Kulenkampff *et al.*, 1974) and a preliminary analysis of cases reported to me (Stewart, 1977b) suggested that in many though by no means all of these cases, the association between injection of vaccine and severe neurotoxic sequelae was strong, and not easily explained by other occurrences or lesions. From this point onward, investigation has been more systematic. Any case notified to me from any quarter

is entered into a File (File A) stored in the University of Glasgow's computer. Cases suggestive at first reading of an adverse reaction to the vaccine are then investigated more closely by sending a questionnaire to parents or guardians and, with their consent, by writing to doctors and hospitals for information. This additional information is coded for entry into File B, also stored in the computer. A search has been made also via hospital records, for cases notified as 'Encephalopathy' and 'Post-vaccinal encephalitis' in the Scottish Hospital In-Patient Statistics (SHIPS), in the Hospital In-Patient Enquiry (HIPE) and in other official statistics published by the Office of Population Censuses and Surveys and the Scottish Home and Health Department. In 1976 preliminary findings were communicated to the Department of Health and Social Security for the attention of the Joint Committee on Immunisation and Vaccination, and were also published (Bassili and Stewart, 1976; Stewart, 1977a; 1977b; 1977c; 1977d; 1977e). Since July 1977, Files A and B have been passed to the Committee on the Safety of Medicines in collaboration with whom the continuing investigation is now proceeding. This committee will report separately in due course. The present report and any opinions expressed are my own.

To date, File A contains identifying data on 1127 children notified or detected from these various sources. All of these children are reported as having had reactions to triple vaccine (DPT) or, rarely, to pertussis vaccine given alone, followed by severe brain damage. During the same period 17 children have been notified as having had reactions followed by brain damage after receiving other vaccines (seven smallpox, four measles, three rubella, three diphtheria-tetanus).

File B, with 110 variables each with up to nine sub-variables, is built up as independent medical and other evidence is obtained. The present report deals with 197 cases in which the evidence is reasonably complete.

Results

The 197 children received a total of 435 injections of DPT (one injection only, 54; two injections, 57; three, 77; four, 9). The first injection of DPT was followed by a reaction in 123 children. A total of 121 children reacted to one injection only, 47 to two injections, 25 to three, and four to four injections. The majority (90%) of reactions occurred between 1961 and 1977, and this is the pattern also in the larger series in File A.

Reactions are described mainly as attacks of uncontrollable screaming or convulsions occurring five to 24 hours after injection of a first or subsequent DPT (Table 1). In most cases, these reactions were reported to GPs, health visitors, or clinics during or soon after the incidents, but in 52 children in whom the reaction subsided, reports were not made until the next injection was due. Many children were taken to hospital as emergencies; others were referred to paediatricians or paediatric neurologists later, when it was apparent that the child was not recovering.

Of the 123 children who reacted badly to their first injections, 63 received one or more subsequent injections to which all but three reacted again, similarly or more severely. The immediate outcome of the reactions was, in 84 cases, the continuation of convulsions, diagnosed in 20 cases as epilepsy. Discontinuation of normal development (64); altered responses to parents (7); paralysis (7); hyperkinesis (5); and various combinations of these and other signs (70) were also recorded as sequelae of reactions.

According to their parents, 52 children subsequently improved appreciably in behaviour and physical performance although only four became 'normal'. The remainder showed no improvement or deteriorated to a point where they were helpless or unmanageable (Table 2).

The present state of these 197 children is that 165 are mentally handicapped or defective and 117

Table 1 Time of original reaction by type of reaction in children with brain damage after receiving vaccines containing pertussis antigen (271 reactions in 197 children with permanent brain damage)

Time	Type of reaction				Total
	Screaming	Convulsions	Collapse	Other signs†	
0-4 hours	19	18	3	29	69
5-24 hours	25	35	5	39	104
1-3 days	4	13	1	7	25
> 4 days	8	17	3	6	34
Uncertain	12	4	5	18	39
	68	87	17	99†	271

† Including one or more of named reactions.

Table 2 *Present state of 197 children with brain damage reported after receiving vaccines containing pertussis antigen*

Convulsions	Mental handicap		
	Yes	No.	
Yes	88	14	102†
No	77	18	95
	165	32	197‡

† Uncontrollable by drugs in 49.

‡ Helpless or unmanageable 41.

physically handicapped. More than half (100) are grossly defective, mentally and physically, 33 being completely paralysed, totally unresponsive and vegetative. Convulsions occur regularly in 102, uncontrollable by medication in 49. Ten have died.

Only 21 of the children are in institutions. The remainder (166) are at home, attending special schools (110), regular schools (17), or in day care.

CONTRAINDICATIONS TO VACCINATION

The following are defined as contraindications by the Department of Health and Social Security (1972): 'A history of seizures, convulsions or cerebral irritation in the neonatal period. A history or family history of epilepsy or other diseases of the nervous system. Children with neurological defects. Any febrile illness, particularly respiratory, until the patient is fully recovered'.

Table 3 *Contraindications to vaccination in 197 children receiving vaccines containing pertussis antigen*

Reacting to:	Family or personal history		
	Any contraindication	None	Total
1st injection only	43	18	61
One injection only excluding first	35	25	60
2 or more injections	51	25†	76
	129	68	197

† Vaccination contraindicated in these children also by occurrence of reaction.

A severe reaction of any kind to a first or second injection is usually regarded as a contraindication to a third. There is evidence in the literature (Hannik, 1970; Sen *et al.*, 1972) and in the package notice of at least one manufacturer that allergy in the child or the family is also a contraindication, but not in the view of the Department of Health and Social Security (1972). If all these conditions are included, the list of potential contraindications is considerable and indicates (Table 3) that initiation or completion of vaccination was justifiable in fewer than 68 of the 197 children in the present series. If the contraindications are subdivided into their various categories (Tables 3 and 4), the number of children in whom pertussis vaccine was contraindicated from the start is 129 (65%), to which must be added 25 who, having no contraindications at the time they received their first dose of vaccine, reacted adversely to that or to subsequent doses. Of the 143 children receiving more than one injection, seven were reported to have tolerated a subsequent injection without adverse effects; the remainder (136, 95%) were stated to have had a similar or more severe reaction. Even so, 25 children received three injections and one child four injections, reacting adversely to each, while 76 who had failed to react to their first injection reacted to one or more subsequent injections. In 31 cases, reaction was noted only after the third injection and in three cases only after a fourth (booster) injection, but in 14 of these, pertussis vaccine was already contraindicated on grounds of personal or family history. Vaccination was discontinued or pertussis vaccine withheld after reactions in 125 children, in 42 of whom second reactions had already occurred.

The main dependent variables, that is, time, type, and outcome of reactions were tabulated against the main independent variables: family history of convulsions, neurological or mental disorder; mother's obstetric history; perinatal events; child's milestones and history of illness. There was no significant interaction between any of these variables as tested by χ^2 . The main independent variables—family and personal history of the child and perinatal events—were also tested against each other and against the occurrence of convulsions,

Table 4 *Contraindications to vaccination in children receiving vaccines containing pertussis antigen*

Reacting to:	Contraindications					Total
	Family history	Obstetric or perinatal	Other disease	More than one	None	
1 injection only	12	17	15	34	31	109
2 or more	5	12	6	28	37	88
	17	29	21	62	68	197

mental handicap, and other signs in the children, again without significant interaction. A family history of convulsions, for example, was not significantly higher in the 101 children with convulsions than in those whose reaction patterns did not include convulsions. Severe mental handicap was not significantly more prevalent in children with convulsions (Table 5).

Table 5 *Mental handicap by convulsions in children reacting adversely to vaccines containing pertussis antigen*

Convulsion	Mental handicap		Total
	Mild or none	Severe	
Yes	25 (33)†	77 (69)	102
No	38 (30)	57 (65)	95
	63	134	197

† Expected numbers in brackets.
0.1 > P > 0.05.

OPINION OF CONSULTANTS

Documented evidence of the opinions of consultants, and of hospital investigations, is available for all cases in File B of this investigation. Each of the 197 children reported here was considered by paediatricians or paediatric neurologists to have brain damage, and in 103 cases this was attributed unequivocally (34), or as a possibility (69), to

pertussis vaccine. Birth injury (4), genetic or congenital defects (10), and infection (4) were offered as explanations of damage in the other cases, of whom eight only were unequivocally stated to be unconnected with vaccination. But in 76 children who reacted adversely to vaccine on two or more occasions, the cause of reaction was stated to be unknown in 28, including 11 out of 29 children who reacted to each of three or four injections (Table 6).

These opinions were compared with evidence of family history, birth trauma, and other disorders given by parents or in hospital or other records (Table 7), and also with contraindications and types and times of reactions. While there is some correlation between assignment of a causal role to the vaccine and absence of any antecedent abnormality or other explanation, vaccine as a possible cause of reaction was excluded in 30 cases in which vaccination was contraindicated by pre-existing or concomitant disease.

Discussion

These results suggest that the main signals of an adverse reaction to pertussis vaccine are convulsions, continuous screaming, and collapse, with or without apnoea, in that order. In all but a few of the cases studied here, these signs were followed in a few days or weeks by arrest or loss of mental development and by varying degrees of physical handicap ranging from spasticity to complete paralysis of all but the vital

Table 6 *Consultants' opinions on children with brain damage after vaccines containing pertussis antigen*

No. of children reacting to:	Consultants' opinions on causes					Total
	Genetic	Perinatal	Infection	Pertussis vaccine	Unknown	
1 injection only	7	2	4	60	48	121
2 injections	3	2	0	25	17	47
3 or more	0	0	0	18	11	29
	10	4	4	103	76	197

Table 7 *Antecedent disorders and consultants' opinions in cases of brain damage*

Medical record	Consultants' opinions on causes					Total
	Genetic	Perinatal	Infection	Pertussis vaccine	Unknown	
Genetic disorder	0	0	0	0	4	4
Perinatal problems	0	3	0	4	4	11
Infection	1	0	0	0	0	1
Other disease	4	0	2	21	12	39
No antecedent abnormality	5	1	2	78	56	142
	10	4	4	103	76	197

reflexes. From observations in clinics, it is obvious that local and systematic reactions to vaccines containing pertussis antigen are very common indeed in 25% or more recipients, but severe neurological or cardiorespiratory signs are much less common. The question raised by this study is whether these signs can be explained by occurrences other than vaccination. Of the various signs observed after vaccination, convulsions or minor seizures are the most frequent (33%), with screaming fits (25%) and rigidity or hypotonia with or without apnoea (10%) next. Most of the children failed to progress or actually regressed thereafter in behaviour and development, sometimes becoming epileptic and showing hypsarrhythmic tracings electroencephalographically, conforming to the non-specific neuropathic states described by Lennox (1960) and Jeavons and Bower (1964) among others. Convulsions with such sequelae can occur symptomatically for other reasons, so it is of critical importance to investigate the possibility that the convulsions reported here might have occurred by coincidence after vaccination.

INCIDENCE OF CONVULSIONS
AFTER VACCINATION

The total number of severe adverse reactions after vaccination, including convulsions, notified from all parts of Great Britain over the 20-year span of the national vaccination programme (1957–76) is about 1000. To date, medical and other supportive evidence indicates that at least 250 of these reactions

are strongly associated with the administration of pertussis vaccine, and that at least 100 more might reasonably be added to this total when investigations are complete. During this time 11 811 923 children received complete courses of DPT (Joint Committee on Immunisation and Vaccination, 1977) while an additional (estimated) total of 1·2 million received only one or two out of the three injections because of adverse reactions to first and/or second injections or for other reasons. The denominator of children at risk may be taken as 13 000 000. The incidence of reactions with severe neurological signs ranges therefore from one per 52 000 children vaccinated at the lowest, to about one per 17 000 at the highest notification figure (Table 8). These figures may be an underestimate. Data released recently by the Committee on the Safety of Medicines (Table 9) suggest that severe neurotoxic reactions might occur much more often, since its yellow card system is unlikely at present to register much more than 10% of reactions.

Within the lower range (1 : 17 000 to 1 : 52 000) the neurotoxic reactions reported here were followed by permanent cerebral and neuromuscular damage in all but a few cases. It is probable from the figures for withdrawal from the vaccine programme that, for every child with permanent damage, there are many more who have similar signs but recover. On this basis, the incidence of neurotoxicity (Table 8) would be at least one per 6500 children, a figure very close to that of the World Health Organisation (Ounsted, 1952); Dick (Haire *et al.*, 1967); Strom (1967); some PHLS studies (Perkins *et al.*, 1970); and the incidence suggested by the incomplete register of the Committee on the Safety of Medicines.

In the cases reported here, contraindications to vaccination, or other lesions that might have contributed to brain damage, were often present. There is no way at present of establishing the causal role of any one mechanism of brain damage with certainty except in the proportion of cases (about 40%) which show a consistent pattern of reactions with increasing severity after second or third injections. The fact that the great majority of infants tolerate DPT without obvious damage to the CNS

Table 8 *Estimated incidence of brain damage in children in Great Britain who received vaccines containing pertussis antigens between 1957 and 1976*

Level of notification		Corresponding incidence
250	Confirmed	1 : 52 000 (19 per million children)
350	Under investigation	1 : 37 142 (26 per million children)
500		1 : 26 000 (38 per million children)
750		1 : 17 333 (57 per million children)
2000	Total reported (all sources)	1 : 6 500 (154 per million children)

Table 9 *Reports† on reactions to vaccines containing pertussis antigen*

	1966-1974	1974-1978	Total	Deaths
Neurotoxic reactions	132	167	299	10
Other reactions	445	195	640	5
Total reactions	577	362	939	15
Total no. of children vaccinated	6 347 445	1 360 000	7 707 445	—
Approximate incidence	1 : 11 000	1 : 3750	1 : 8200	1 : 513 829

† By doctors to Committee on the Safety of Medicines; estimated at 10% of total.

suggests that those who do react are predisposed to do so by other factors, several of which are specified as contraindications by health authorities (DHSS, 1972; Joint Committee on Immunisation and Vaccination 1977) and manufacturers.

In 25% of cases, the pattern of convulsions corresponded closely to clinical descriptions of West's syndrome or infantile myoclonic seizures in which, according to Jeavons and Bower (1964), about 17% of cases are strongly associated with injections of DPT.

The most obvious overlapping condition, and also the commonest single condition associated with convulsions, is pyrexia. Febrile convulsions—so-called—are likely to occur because of infections incubating or established at the time of injection, or because of the pyrexia caused by the vaccine itself. The risk of coincidence for this reason is considerable; among the 18 500 children aged 5 and under studied by Van den Bergh and Yerushalmy (1969), 2% experienced febrile convulsions, twice the rate of those with non-febrile convulsions. But the proportion occurring in infants (see below) is much lower, while the frequency in the months of the first year of life seems to vary in different countries (Someya, 1972; Lennox-Burchal, 1973; Melchior, 1977). The situation in infancy is complicated further by the occurrence of salaams, absences, and other types of seizure, for example, of infantile spasms at a modal age of five months (Jeavons and Bower, 1964), head nodding, lightning fits, and various myoclonic syndromes (Jeavons and Bower, 1964). These syndromes can be classified on the basis of genetic, traumatic, metabolic, and other lesions, but since there are no epidemiological data on the individual frequencies of these lesions and of the relevant symptoms, the only approach at present is to compare best estimates of overall frequencies with actual observations in the present study and to calculate the probability of coincidence at different levels of incidence.

PROBABILITY OF A CONVULSION IN INFANCY

Estimates vary widely. A comparison of the data of Spence *et al.*, (1948) in Newcastle upon Tyne in the late 1940s with recent data indicates that convulsions are now much less common, presumably because of the decline in perinatal insult and severe childhood infections. The survey in general practice in the United Kingdom assessed cumulative incidence at 3.5/1000 children per year aged 0–4 (Royal College of General Practitioners, 1960). Kurland's survey (1960) in Rochester, New York, suggests a lower figure (2/1000 per year) over the same age span, but Van den Bergh and Yerushalmy (1969) gave a higher

figure of 6.9/1000 per year in the first year of life of children in California. Nelson *et al.* (1976) in the NIH Collaborative Perinatal Project in the United States of America found an incidence of two febrile seizures per 1000 children in the first six months of life and estimated afebrile seizures at about half of that rate. In Harker's recent survey in Oxford (Harker, 1977) 59/160 seizures in a population of 6617 children aged 0–5 were in children less than 16 months old, which suggests cumulative incidence by that age of about 15/1000, very much higher than in other recent surveys. Very few convulsions occur before two months of age but the reported frequencies between two and six months in American studies are higher than in British studies.

The problem here is to compute the probability that a seizure occurring after any one of three injections of DPT is one that was going to occur anyway, in other words that it was a coincidence; given this coincidence, what then is the probability of a second and third coincidence? To calculate this, let x = the number of convulsions occurring between two and 14 months of age in any child. If we then assume also that convulsions occur independently of each other—which may be unlikely but allowance can be made for this, as below—then x can be assumed to follow a Poisson distribution with mean Θ . From the data quoted above, a wide estimate of the range of Θ would be 0.003–0.015. A coincidence can be defined for our purpose here as being the occurrence of a convulsion within three days of vaccination, caused by something other than vaccination. We can then calculate approximately from this model the probability of exactly one coincidence (Θ_1), of two coincidences (Θ_2) and so forth, as follows:

with $\Theta = 0.003$

$$P(x_1) = 7.39 \times 10^{-5} \text{ or } 1 : 13\ 500$$

$$P(x_2) = 7.32 \times 10^{-9} \text{ or } 1 : 136\ 000\ 000$$

with $\Theta = 0.01$

$$P(x_1) = 2.47 \times 10^{-4} \text{ or } 1 : 4000$$

$$P(x_2) = 1.96 \times 10^{-7} \text{ or } 1 : 5\ 000\ 000$$

This means that, if spontaneous convulsions occur at the generally observed rate of 0.003, the chance of a convulsion unrelated to vaccination occurring within three days of vaccination (1 : 13 500) is about half of the rate observed by Strom (1967), and by Haire *et al.* (1967) and also of the estimated rate of 1 : 6500 in the PHLS reports. If spontaneous convulsions occur at the highest end of the range ($\Theta = 0.01$), which is much higher than any observed frequency in the first year of life except in Harker's data, then a coincidence after a first DPT cannot be excluded because the probability (1 : 4000) is well within the observed range of such occurrences. For clinical as

well as epidemiological and possibly medicolegal purposes, it is important to identify the sub-population of children who may be in this category because of what Ounsted (1952) calls a 'low convulsive threshold'.

Convulsions recurring after a second or subsequent DPT are highly unlikely to be coincidences because, whatever the frequency of spontaneous convulsions, the chance of a coincidence is one in several millions.

In the majority of children, that is, those presumed to have a normal convulsion threshold, even one convulsion within three days of DPT would be beyond normal expectation. At either frequency, a second convulsion after a second DPT would be well beyond the bounds of coincidence and would be expected to occur in only about eight of the 13 million children vaccinated—far less than the observed frequency of at least 25 cases out of 197 fully investigated in the present series, many more of whom had repeated convulsions after only one injection. A second convulsion following a first is highly unlikely even if the probabilities are conditional, that is, if the occurrence of a first convulsion in a normal child increases the likelihood say tenfold in the second. In practice, such cases should not receive pertussis antigen, but the fact is that it was given to many children in the present series in the face of strong contraindications. Apart from this, and even at the lowest estimate, the incidence of severe neurotoxic reactions is clearly far higher than can be explained by coincidence, except in so far as there would be in the series a group of children with a low convulsive threshold and no obvious contraindication to receiving their first DPT. Such children would constitute an unidentifiable high-risk group.

In this series, as in the literature, there is no evidence of comparable neurotoxicity with DT or any other vaccine excluding pertussis. Notifications of 'Encephalitis' from all sources for all other vaccines combined amounted only to 17 and lacked the early signs of severe neurological damage observed with vaccines containing pertussis antigen.

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