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How are the sub-unit pertussis vaccines to be evaluated?

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SUMMARY

Although an effective whooping cough vaccine has been available in the UK since the 1950s, its current association with neurotoxicity has resulted in poor uptake: as a consequence major epidemics (with significant morbidity and mortality) are still being experienced.

Component (sub-unit) vaccines, which incorporate those antigens thought to be concerned with generating a protective effect, have been developed and are now available for field testing. This paper addresses how such a vaccine might be evaluated, the organization of a trial and the difficulties to be expected.

INTRODUCTION

Immunization against whooping cough has been routinely available in many countries since the 1950s. Current policy has a twofold rationale. It provides individual protection with a high degree of efficacy and by generating *herd immunity* also indirectly protects the unimmunized population (Mortimer & Jones, 1979; Preston, 1979; PHLS, 1982; Expanded Programme of Immunisation, 1986).

Current vaccines contain a suspension of killed *Bordetella pertussis* (whole-cells) in a concentration of $\geqslant 4$ IU per 0·5 ml.; preparations include a monovalent plain form, and both plain and adsorbed (with aluminium hydroxide) forms in combination with diphtheria and tetanus antigens.

Controversy during the early 1970s about possible major neurological sequelae led to a serious decline in pertussis vaccine acceptance rates with the inevitable consequence that major epidemics recurred e.g. in the UK starting in 1977, 1981 and 1985. The attendant morbidity and mortality reinforced the need for an effective vaccine with minimal toxicity and stimulated the development of component (or sub-unit) vaccines. Their availability raises the problem of field testing and this paper will examine the approaches to, and the feasibility of, such evaluation.

Component vaccines

The whole-cell vaccine suspension contains a large number of antigens, not all of which are required to generate a protective response. Since the frequency of adverse reactions presumably relates to this multiplicity of antigens, it is important to identify those concerned with protection and exclude all others. Although the nature of the host-agent interaction is not completely understood,

lymphocytosis promoting factor, filamentous haemagglutinin and agglutinogens 1, 2 and 3, are thought to be important antigens and various combinations have been incorporated in the new component vaccines, the development of which has recently been reviewed (Miller, 1986).

Vaccine evaluation

Whatever other benefits are claimed for these new vaccines, their advantages should include a reduced toxicity, an enhanced level of protective efficacy or preferably both.

Toxicity

Minor side effects following immunization are frequent and vary with the dose number and type of vaccine preparation (Waight *et al.* 1983). Plain preparations generally cause more problems than absorbed ones (Pollock *et al.* 1984).

Major adverse neurological reactions have also been reported (Berg, 1958; Strom, 1967; Stewart, 1977) and an association between pertussis immunization and certain neurological syndromes was demonstrated in the National Childhood Encephalopathy Study (NCES) (Miller *et al.* 1981; Report, 1981). The results gave an estimate frequency for acute neurological sequelae within 7 days of DPT administration of 1 in 110000 immunizations (95% confidence interval (C.I.) 1 in 360000 to 1 in 44000), and for permanent neurological sequelae, 1 in 310000 immunizations – 95% C.I. – 1 in 5310000 to 1 in 54000 (Report, 1981).

The occurrence of either minor or major side effects may be used in clinical trials as indicators of pertussis vaccine toxicity. Since, however, no direct relationship between these two types of effect has been demonstrated, and because we are more concerned with the latter, then serious neurological disorders (either acute or chronic) should be used as one of the markers of toxicity.

Efficacy

Efficacy describes the ability of the vaccine to prevent disease and requires the correct administration of the appropriate antigen(s) to an immunologically responsive individual (Expanded Programme of Immunisation, 1985). Absolute protective efficacy (APE) measures the percentage reduction in disease attack rates between vaccinated and non-vaccinated persons, and is calculated according to a standard formula*: using bacteriological confirmation of disease, APE for current pertussis vaccine is 95% (Preston, 1986). Relative protective efficacy† (RPE) measures performance of the new vaccine against the current vaccine preparation.

When the disease concerned is serious and where an effective vaccine exists, it is unethical to use non-immunized controls and RPE only should be measured. An

* Absolute protective efficacy is calculated from the following formula:

$$VE = \frac{ARU - ARV}{ARU} \times 100,$$

VE = vaccine efficacy; ARU = attack rate in the non-vaccinated population; and ARV = attack rate in the vaccinated population (Expanded Programme of Immunisation, 1985).

† RPE is calculated from a similar formula except that ARU is replaced by ARPV, i.e. the attack rate in persons immunized with the previous vaccine.

estimate of APE might be derived by using historical controls or vaccine non-consentors, but such approaches should be discouraged on the following methodological grounds. Historical controls are unsatisfactory because exposure to whooping cough may have changed since the data were originally collected and also criteria for establishing a correct diagnosis are still subject to some disagreement (Preston, 1986). Vaccine non-consentors are unsuitable because they are not representative of the general population, thus limiting the wider application of conclusions based on the results.

Clinical Trials

What then will be the required features of a clinical trial designed to evaluate whether component vaccines confer advantages in these two areas? Four possible approaches should be considered:

(i) Case-control;
(ii) Serological;
(iii) Post-marketing surveillance;
(iv) Prospective;

Approaches (i), (iii) and (iv) are more suitable for evaluating toxicity, whereas (i), (ii) and (iv) are more useful for efficacy studies.

Each has advantages and disadvantages. The case-control approach for toxicity is relatively quick and inexpensive and in the UK could utilize the existing British Paediatric Surveillance Scheme where previous experience of the NCES would be undoubtedly beneficial. A disadvantage, however, relates to methodological problems inherent in the case-control design: it being argued that such an approach can only show association, with no direction. Whilst there is some validity to this criticism, it should be realized that decisions regarding causality are not made in isolation, e.g. a strong association supported by other evidence would be highly persuasive of causality. Problems do arise, however, where the association is weak and this situation would most likely recur if this methodology were again used to evaluate the new sub-unit vaccines since (if they are an improvement) the demonstrated association will be even weaker than was shown in the NCES. Doubt would still then be expressed about whether pertussis immunization causes serious neurological sequelae, with the inevitable effects on uptake rates. It can be argued that there is a need to resolve this issue not least because it has important consequences for brain damaged children and the approach to compensation.

Serological markers cannot currently be used to assess efficacy because it is not yet conclusively established which of them are related to clinical efficacy (hence the differing sub-unit preparations now available).

Post-marketing surveillance relies on practitioners forwarding details of side effects and serious reactions. This system must be included in the continuing evaluation scheme, but reporting bias and the known incompleteness of reporting systems limit its use for field trials.

Prospective studies of groups exposed to the sub-unit vaccines have the advantage that they are far more likely to demonstrate conclusively whether pertussis preparations are indeed associated with neurological sequelae, and if so at what rate. Such a study would need to have the following features.

Table 1. *Numbers of volunteers required to demonstrate significant* differences between the sub-unit vaccine and the current whole-cell preparation using neurological sequelae as markers of toxicity*

Assumed level of toxicity of sub-unit vaccine in comparison with the whole-cell vaccine (%)	Acute neurological sequelae	Chronic neurological sequelae
0	2732010	7698580
25	5704280	16074200
50	14725100	41494000
75	66419700	187165000
125	81378800	229319000
150	22208000	62580400
175	10697000	30143300
200	6481500	18264400

* Significant at 0·05, with a power of 0·9.

(1) Informed consent would be a pre-entry requirement and only volunteers should enter; this is a disadvantage since unknown selection factors, that are associated with volunteering, may bias the results (Cockburn, 1955).

(2) Ideally the study should be based on the existing immunization programme – the results would then relate to current practice rather than the somewhat artificial situation of vaccine trials.

(3) Subjects must not have had the disease nor been previously immunized. This will be achieved mainly by limiting immunization to younger children (see (6) below), although a confirmed diagnosis of pertussis should exclude a child.

(4) There will be a need to ensure standardization of administration and potency of the vaccines throughout the trial.

(5) Since the new vaccine may be worse than the whole-cell preparation i.e. more toxic or less effective (or indeed both), two-tailed significance tests should be used in planning the trial and analysing the results.

(6) The upper age limit for entry into the trial should be determined by the local epidemiological pattern but two points should be born in mind as age at entry increases: firstly it becomes more likely that children will have had undiagnosed (or misdiagnosed) natural disease and this will reduce the apparent efficacy of the vaccine. And secondly though the complication rate (and hence risk) of natural disease declines, vaccine side-effects appear to remain constant: hence there is a reduction in the vaccine's apparent benefit. As a consequence we suggest that only children in the first year of life (the time when whooping cough vaccine is usually administered) be entered into the trial.

(7) It will be necessary to ensure strict comparability between the groups given the two vaccines. This might be achieved by matching or randomization. As discussed later, the practical difficulties of a large scale trial preclude matching and we recommend therefore that subjects be serially allocated on a random basis to either vaccine at entry into the trial.

(8) Continued observation of these children will be required for a period of time (not less than 2 years). During this period it will be necessary to ensure accurate recording of all pertussis-associated morbidity and mortality (including that for children who have moved out of the area) with biological confirmation where appropriate. This has major implications for both clinical and laboratory support services. Drop-out and lost to follow-up will be a problem, but has not been allowed for in the sample size calculations (see later).

(9) The trial should be double blinded. It is reasonable to expect that the participants should not know the particular vaccine they received as subjective expectations may well influence disease recognition. Similar considerations would extend to the investigators.

A double-blind prospective trial with randomization of subjects at entry using acute and chronic neurological end points would thus be required to establish whether toxicity was reduced and protective efficacy was enhanced.

Using accepted statistical techniques (see Appendix), the numbers required for such a study may be calculated. Table 1 gives the estimate sample sizes required under differing assumptions of the sub-unit vaccine's rate of neurological sequelae.*

How are these figures to be interpreted? If the sub-unit vaccine has no acute neurological sequelae (i.e. 0% assumed toxicity), a study population of 2732010 (half given the new vaccine and half given the old vaccine) is required to have a 90% chance of demonstrating this at a significance level of 0·05. Were the new vaccine to double the risk (200% assumed toxicity) of acute effects, then nearly 6500000 children would be needed to demonstrate it with the same chance of success as above.

What do these numbers mean in practice? Consider the situation in the United Kingdom. There are approximately 550000 births annually and assuming 70% of these were volunteered, then 385000 children in the first year of life could enter the trial. Probably 2% of these might be excluded because of genuine contra-indications so that 377300 would actually be eligible. Thus even assuming that the new vaccine has no acute neurological effects, it would take just over 8 years to recruit sufficient children into a study. To detect a doubling of acute neurological sequelae would take at least 19 years in the UK. The numbers that would be involved if chronic neurological sequelae were used to evaluate the vaccine would be even greater (see Table 1).

Where the sub-unit vaccine has a toxicity level 25% less than the whole cell vaccine, a study population of nearly 6 million children is required: and to detect a corresponding increase in toxicity requires just over 10·5 million children. Given the professional, political and commercial pressure that will be exerted to use these new vaccines, shorter reporting times and hence multi-national cooperative studies will be required.

* (*a*) The true rate of acute neurological syndromes following within 7 days of the whole cell (old) vaccine is 1 in 110000 immunizations. (Report, 1981). (*b*) The true rate of permanent neurological syndromes following within 7 days of the whole cell (old) vaccine is 1 in 310000 immunizations. (Report, 1981). (*c*) The trial will be undertaken on the basis of a concurrent control group, with equal numbers receiving the new and old vaccine. (*d*) The alternative to the null hypothesis in the statistical analysis is that the component or subunit vaccine (new) may be more or less toxic, significance tests will thus be two-tailed.

Table 2. *Numbers of volunteers required to demonstrate significant* differences between the sub-unit vaccine and the current whole-cell preparation using neurological sequelae as markers of toxicity. Sensitivity analysis assuming that neurological sequelae have declined by 25%*

Assumed level of toxicity of sub-unit vaccine in comparison with the whole-cell vaccine (%)	Acute neurological sequelae	Chronic neurological sequelae
0	3642690	10264800
25	7605720	21432300
50	19633400	55325600
75	88559700	249555000
125	108505000	305761000
150	29610700	83441000
175	14262700	40191300
200	8642030	24352700

* Significant at 0·05, with a power of 0·9.

Table 3. *Numbers of volunteers required to demonstrate significant* differences in protective efficacy between the sub-unit vaccine and the current whole-cell preparation assuming different annual disease incidence rates*

Assumed level of protective efficacy in comparison with the whole cell vaccine (RPE)	Annual incidence rate (per thousand)		
	4	2	0·5
+100	606	1227	4952
+75	1263	2559	10337
+50	3248	6594	26672
+25	14575	26669	120233
−25	17630	36133	147094
−50	4780	9827	40108
−75	2286	2559	19302
−100	1374	2847	11685

* Significant at 0·5, with a power of 0·9.
Assuming all natural disease occurs in children aged 0–5 years, i.e. a population of 2·5 million.

The values in Table 1 may be an underestimate since there are two reasons for thinking that the risk is now lower than was calculated from the 1977–8 NCES. Firstly, adherence to the contra-indications identified in that study should have led to higher risk children being excluded. Secondly, West's and Reye's syndromes were assumed in the study to be related to pertussis immunization, which is probably incorrect, and their exclusion would reduce the overall risk. Table 2 shows calculated sample sizes based on the assumption that neurological risks have reduced by an arbitrary 25%. To detect a 50% change in toxicity requires a study population of nearly 30 million; this would be practically very difficult but significant differences could be detected with a sample of just over 8·5 million.

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Protective efficacy (PE) could be reliably determined using much smaller study populations. Comprehensive follow-up of subjects, with bacteriological confirmation of disease, would of course be needed. Table 3 contains estimated sample sizes assuming differing disease incidence rates and a 2 year follow-up. We suggest a study population of approximately 5000 to detect a 50% change in PE. If there is more than one sub-unit preparation, then correspondingly more volunteers would be needed.

DISCUSSION

The existing whole-cell vaccine is a highly immunogenic preparation which unfortunately causes minor intrinsic reactions at an undesirably high level; the postulated (but unconfirmed) association with major neurotoxicity has further eroded public confidence in the vaccine.

Any new preparation must therefore demonstrate an improvement over existing vaccines, especially in the area of major side-effects. Whilst theoretical support for a lack of toxicity is useful it must be supported by evidence from clinical trials. Community acceptance of immunization programmes is dependent on the use of safe and highly effective vaccines.

There are a number of approaches that might be used to evaluate the new vaccines, but we advocate a prospective randomized control. A study population of just over 8·5 million children would be required to demonstrate important differences in toxicity: much smaller numbers are needed to evaluate protective efficacy.

Such a study is technically feasible but the numbers involved make multinational involvement (W.H.O.) essential. The enormous cost is justified by the existing global mortality and morbidity, but participating countries in the trial might find it less easy to justify their own individual expenditure.

It is rare for major public health intitiatives to be effectively evaluated before their implementation. The reliance of all countries on prophylactic immunization demands that at least in this area all feasible measures be undertaken to assess these new vaccines.

If these arguments are accepted, then the interesting situation will soon arise of whether such a trial will be undertaken, or will 'lack of resources' prevail. Is there indeed a commitment to evaluate medical therapies before their widespread use, or will authorities, as so often in the past, simply implement and rely on expert opinion that there is no risk? This raises interesting ethical issues which should be resolved.

REFERENCES

Berg, J. M. (1958). Neurological complications of pertussis immunisation. *British Medical Journal* **2**, 24–27.

Casagrande, J. T. (1978). An improved approximate formula for calculating sample sizes for comparing two binomial distributions. *Biometrics*; **34**, 483–486.

Cockburn, W. C. (1955). Large-scale field trials of active immunizing agents. *Bulletin of the World Health Organization* **13**, 395–407.

Expanded Programme on Immunisation (1985). Field evaluation of vaccine efficacy. *Weekly Epidemiology Record* **18**, 133–140.

Expanded programme of Immunisation (1986). Pertussis vaccine efficacy; *Weekly Epidemiological Record* **10**, 73–4.

MILLER, D. L., ROSS, E. M., ALDERSLADE, R., BELLMAN, M. H. & RAWSON, N. S. (1986). Pertussis immunisation and serious acute neurological illness in children. *British Medical Journal* **282**, 1595–1599.

MILLER, E. (1986). Progress towards a new pertussis vaccine. *British Medical Journal* **292**, 1348–50.

MORTIMER, E. A. & JONES, P. K. (1979). An evaluation of pertussis vaccine. *Review of Infectious Diseases* **1**, 927–934.

PUBLIC HEALTH LABORATORY SERVICE (1982). Epidemiological Research Laboratory: efficacy of pertussis vaccination in England. *British Medical Journal* **285**, 357–9.

POLLOCK, T. M., MILLER, E., MORTIMER, J. & SMITH, G. (1984). Symptoms after primary immunisation with DTP and DT vaccine. *Lancet* ii, 146–149.

PRESTON, N. W. (1979). Whooping cough in Hertfordshire. *Lancet* ii, 645.

PRESTON, N. W. (1986). Recognising whooping cough. *British Medical Journal* **292**, 901–2.

REPORT (1981). *Whooping Cough*. Report of the Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunisation. London: Her Majestys Stationery Office.

STEWART, G. (1977). Vaccination against whooping cough. *Lancet* i, 234–237.

STROM, J. (1967). Further experience of reactions, especially of a cerebral nature, in conjunction with triple vaccine: a study based on vaccination in Sweden, 1959–1965. *British Medical Journal* **4**, 320–323.

WAIGHT, P., POLLOCK, T. M., MILLER, E. & COLEMAN, E. M. (1983). Pyrexia after diphtheria/tetanus/pertussis and diphtheria/tetanus vaccines. *Archives of Diseases of Childhood* **58**, 921–3.

Appendix. Calculation of sample size for toxicity studies

In calculating sample size the corrected χ^2 modification has been used. This was developed by Casagrande (1978) and the relevant formulae are shown below.

Let

p_1 = risk of neurological reaction of whole cell vaccine;

$q_1 = (1-p_1)$;

p_2 = risk of neurological reaction to the new sub-unit vaccine;

$q_2 = (1-p_2)$;

$$\bar{p} = \frac{p_1+p_2}{2};$$

$$\bar{q} = (1-\bar{p}).$$

Equations (1) and (2) allow calculation of the sample size required.

$$n = \frac{A\left[1+\sqrt{\left(1+\frac{4(p_1-p_2)}{A}\right)}\right]^2}{4(p_1-p_2)^2}, \tag{1}$$

$$A = [Z_{1-\alpha}\sqrt{(2\bar{p}\bar{q})}+Z_{\beta}\sqrt{(p_1q_1+p_2q_2)}]^2, \tag{2}$$

where $\alpha = 0{\cdot}05$ and $\beta = 0{\cdot}9$: then $Z_{1-\alpha} = 1{\cdot}96$ and $Z_{\beta} = 1{\cdot}28$ from tables of the standard normal distribution.