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REVIEW ARTICLE

Bordetella Pertussis Whole Cell Vaccines—Efficacy and Toxicity

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ABSTRACT. Trollfors B. (Department of Infectious Diseases, University of Göteborg, Göteborg, Sweden). *Bordetella pertussis* whole cell vaccines–efficacy and toxicity. Acta Paediatr Scand 73: 417, 1984.

The literature concerning efficacy and side effects of pertussis vaccines is reviewed. With few exceptions, most vaccines induce a protective immunity lasting for 2 to 5 years. The large-scale use of pertussis vaccines has markedly contributed to the decrease in pertussis morbidity in small children but in some countries the incidence has increased in older children. Not even countries with immunisation rates of 90–95 % have managed to eradicate pertussis or prevent disease in infants below the age of immunisation. The pertussis-associated mortality is currently very low in the industrialised countries and no differences can be discerned when countries with high, low and zero immunisation rates are compared. Local and benign systemic reactions are commonly seen after immunisation. The vaccines also sometimes cause convulsions, a shock-like state and, rarely, serious neurological reactions. *Key words: Pertussis vaccine, pertussis immunology, pertussis mortality, immunisation programmes.*

Among currently available vaccines, the pertussis vaccines are probably the most controversial. They have been debated in the medical press by experts with widely differing views on their benefits and disadvantages. The attitude of the authorities and the public acceptance of pertussis vaccines vary considerably from country to country. In the United States, Japan and most European countries, vaccination is strongly recommended by the authorities (1–6). In some countries, e.g. the United States, France, Finland and the Netherlands, more than 90% of all infants are vaccinated (1, 5–7) while in other countries, e.g. Japan and Great Britain, the public has not been convinced of the benefits of immunisation (2, 8). In West Germany and Sweden the authorities have judged that the toxicity of the vaccines outweighs the benefits and recommend them only for certain high-risk groups (9, 10).

Difficulties to be considered in the evaluation of pertussis vaccines

Heterogeneity of the vaccines. Most of the industrialised countries produce their own whooping cough vaccines and some countries, like Great Britain, France and the United States, use or have used vaccines from more than one producer. The different vaccines may contain varying numbers of killed organisms per dose. The procedure for culture and killing of the organisms may also differ, as may the use of aluminium as adjuvant and the agglutinogen composition of the vaccine strains (11). The potency of a vaccine is measured by the "mouse protection test", the relevance of which can be questioned (11). Data on efficacy or toxicity of one pertussis vaccine might therefore not be applicable to others. The difficulties in vaccine testing are emphasised by a report showing that in the USA 15–20% of vaccine lots considered to be of sufficient potency by the producers failed confirmatory tests performed by the Bureau of Biologics (12). Vaccine standardisation might be better performed in the future, since it now seems possible to determine the

vaccine content of two immunogenic components, fimbriaehemagglutinin (FHA) and lymphocytosis promoting toxin (LPT), by enzyme-linked immunosorbent assay (13).

Comparisons of vaccines are also rendered difficult by the *different immunisation schedules* practised in different countries. Up until 1979, Sweden had an immunisation programme that differed from those of most other countries. Only three injections were given within the short time period of 3 months. Great Britain and Denmark also give three injections but spaced over the first year of life (8, 14). In the United States, France, Finland and Norway basic immunisation is achieved with three monthly injections followed by a booster dose 10–18 months later (1, 5, 7, 15). In Hungary, Czeckoslovakia and the Soviet Union, two booster doses are given at intervals of 3–4 years after the primary immunisation (16–18). In most countries, the first injection is given at the age of three months (5–8, 15–18) but in Denmark immunisation is started at the age of five weeks (14). In view of the recent finding that antibodies to LPT and FHA pass the placenta and interfere with the active antibody response (19), it is not impossible that remaining maternal antibodies might impair the development of protective immunity if the immunisation is started too early.

Insufficient knowledge of pertussis immunology. The efficacy of several currently available vaccines, e.g. the attenuated morbilli, parotitis and rubella vaccines, the purified HBsAg vaccine and the capsular polysaccharide vaccines, can be evaluated by measurements of protective serum antibodies in the vaccine recipients. Until very recently, this has not been possible with pertussis vaccines. It has now been shown that serum antibodies against FHA develop after naturally acquired infection (20) and that serum antibodies against both FHA and LPT are induced by American and British vaccines (13, 19).

The decline in pertussis-associated morbidity and mortality during the 20th century. Reports from several countries show that the mortality from pertussis decreased markedly during the decades preceding the introduction of vaccines. In the United States the average annual age-specific mortality rates for pertussis in children less than 1 year decreased from 4.34/1 000 in 1900–1904 to 0.86/1 000 in 1940–1944. In children aged 1–4 years, the average annual mortality rates decreased from 0.87/1 000 to 0.09/1 000 during the same period (21). In England and Wales the annual mortality decreased from more than 550 to less than 50/1 000 000 total population from the early twenties to the beginning of the fifties. There was also a decrease in hospital admissions during the decades preceding the use of vaccines (22). In Sweden the age-specific pertussis mortality in children less than 5 years decreased from 1.2/1 000/year to 0.2/1 000/year between 1911 and 1945 (23). There was also a decrease in pertussis morbidity (24). Similar figures have been reported from other countries, e.g. the Netherlands (6) and Finland (25).

There is, thus, no doubt that the pertussis-associated mortality had decreased before the introduction of the vaccines to about 10–20% of the levels seen at the beginning of this century. This decline continued after the introduction of vaccines. There is, however, disagreement between supporters and opponents of the pertussis vaccines as to whether the decline in morbidity and mortality from the fifties to the present day is the result of the use of vaccines or due to a continuation of the decline which had started several decades earlier (8, 21, 22, 26). The personal opinion of the reviewer is that both factors are of importance and that the full truth concerning the relative importance of the vaccines, social factors, the development of antibacterial agents, improved hospital facilities etc, can never be obtained.

Prolongation of vaccine-induced immunity by "natural booster doses". Two British studies concerned with the duration of vaccine-induced immunity against whooping cough published in the same year, 1979, gave somewhat different results. In one study (27),

performed in the Shetland Islands, where whooping cough had been absent for several years, the vaccine-induced immunity seemed to have disappeared completely after 3 years. In the other study (28), performed in a region with endemic pertussis, a protection rate of 85% was seen in children immunised five years earlier. Although not proven, it must be considered probable that a short-lasting vaccine-induced immunity may have been prolonged by natural exposure to *B. pertussis* in the latter population. The efficacy of pertussis vaccines might therefore appear different in different areas depending on variations in pertussis epidemiology.

Efficacy of pertussis vaccines

Early prospective trials. Several trials were performed with different vaccines in the United States and Europe during the thirties and forties. The most valuable were performed in Great Britain (29). In a comprehensive publication, the results of 10 studies using 5 different vaccines from 3 different producers are described. All studies were randomised, double-blind and performed according to the same protocol, so it seems permissible to report them together. Three injections of vaccine or placebo were given at monthly intervals to children aged 6 to 18 months. Whooping cough occurred during the observation period of 23–30 months in 149 of 3801 vaccinated children and in 687 of 3757 controls. The incidence among the immunised children was 1.45/1000 child-months and among the controls 6.72/1000 child-months.

A prospective study was performed in America during the thirties in children aged 8 months to 6 years. Four injections were given at weekly intervals. Among 1815 vaccinated children, 52 cases of whooping cough occurred, compared to 348 cases in a control-group of 2397 children matched for age and district (30). In a Swedish study, 315 children received 3 or 4 injections of a pertussis vaccine. During the observation period of on average 51 months, nine whooping cough cases occurred. In an age-matched control group of 289 children 55 whooping cough cases occurred (31).

Duration of vaccine-induced immunity. In Michigan, USA, it was calculated during the sixties that the protection from a vaccine was about 80% 0–3 years after the last dose. Individuals immunised 4–7 years prior to exposure were protected to about 50%. If more than 11 years had passed the protection was virtually absent (32).

Basic immunisation with the Finnish vaccine seems to offer protection for about one year, while a fourth booster dose prolongs the duration by 2–3 years (25).

In Denmark the vaccine has been estimated to offer 70–80% protective immunity during the first four years of life; thereafter protection is virtually absent (14).

In the Soviet Union a vaccine-induced protective immunity of about 80% lasted for two years. During the third year after immunisation the protective effect was halved (33).

As previously mentioned, the duration of the immunity induced by the British vaccine differed in an area with endemic pertussis and a relatively isolated rural area. In the former population a high rate of protection was evident 5 years after immunisation (28). In the latter area the vaccine-induced immunity had dissappeared after 3 years (27).

Even though the methodology of retrospective studies of this kind can almost always be criticised, it may be concluded that several of the currently available pertussis vaccines offer about 80% protection against clinical whooping cough for 2 to 5 years. There are, however, vaccines which are less efficient. Much of the vaccine used in Great Britain before 1968 was in retrospect shown to have been ineffective (34, 35), which is acknowledged both by supporters (8, 36) and opponents (22) of pertussis immunisation. It has been suggested that changes in serotypes of *B. pertussis* in the community rendered the vaccines ineffective (26, 35). The Swedish vaccine given from the late sixties until 1977 also induced very little or possibly no protective immunity, as evidenced by the epidemics

occurring in the country during the seventies, which hit vaccinated and non-vaccinated individuals of all ages (37–39). The failures of the British and Swedish vaccines were not appreciated until after they had been used for several years. It is to be hoped that the newly developed methods of determining the antigen content of pertussis vaccines (13) can prevent such misfortunes in the future.

Whooping cough situation in countries with different immunisation programmes

Northern Europe—Denmark (population 5 million), Finland (5 million), Norway (4 million) and Sweden (8 million): In Denmark, Norway and Finland the immunsation rates against pertussis are 85–88% (14), 90% (15) and 95–99% (5, 25, 40), respectively. Sweden, on the other hand, can be considered to have had a virtually non-vaccinated population since 1970, since a vaccine with little or no efficacy was administered during the seventies and since the vaccine was administered over the short time period of three months, without the addition of booster doses. Towards the end of 1979 pertussis immunisation was stopped completely. During the years 1980–1982 Denmark has reported 1 400–4 700 cases yearly (14), Norway 2 000 cases yearly (15) and Sweden 2 200–5 200 cases yearly (41). Since only certain doctors in Sweden are obliged to notify whooping cough, the figures from Sweden must be considered gross underestimations, but under-reporting is also considered likely in Norway and Denmark (14, 15). Reports from Finland have not been available for this review but judged from recent publications whooping cough epidemics occurred during the end of the seventies and beginning of the eighties (5, 25, 42). Provided that notified or culture-verified cases have a representative age-distribution, Swedish children seem to be attacked by pertussis at an earlier age than children in the other countries. The median age of 100 culture-verified cases in Umeå, Sweden, was 2.5 years and that of 2819 culture-verified cases in Gothenburg, Sweden, 4 years (unpublished data) while the median age of 522 cases in Turku, Finland, was 7 years (5). In an epidemic in another part of Finland, 42 out of 49 patients were older than 6 years (25). In Denmark the peak incidence occurs in the age-group 4–6 years (14). Morbidity from pertussis in infants below one year of age is reported from all countries. About 8% of the cases from Umeå and Gothenburg, Sweden, were of that age, as were 10% of the cases from Turku, Finland (5) and 3% of the cases reported from Denmark (14).

Hospitalisation of infants is reported from all countries (5, 14, 15, 38). From Sweden about 350 hospitalised cases/year were reported 1981 and 1982 (41). From Finland it was recently stated that "many young patients have required hospital admission for a severe paroxysmal cough and vomiting" (5).

Other European countries—England and Wales (population 49 million), France (54 million), West Germany (62 million): Pertussis immunisation rates differ markedly between these three countries. In France basic immunisation followed by one or two booster doses is recommended and the immunisation rate is estimated to be about 95% (7, 8). In Britain immunisation is also recommended by the authorities but the immunisation rate was not higher than 70–80% before 1974 and thereafter fell to only 40% following a report (43) of vaccine-associated brain damage (7, 8, 22, 44). In West Germany pertussis immunisation is (since 1975) only recommended for certain risk groups (9) and the immunisation rate has gradually fallen from about 60% in 1970–1972 to less than 10% in 1978 (45). Judged from notifications, pertussis has become exceedingly rare in France, with only 66–372 cases reported yearly from 1975 to 1982 (7). Britain and West Germany, in contrast, have had major epidemics of pertussis. During the epidemic years 1978 and 1982, England and Wales reported 66 000 cases per year, and even between epidemics there have been more than 10 000 cases per year (7). In West Germany the number of pertussis cases was estimated to be about 90 000 during the epidemic year 1980 (46). Surprisingly, however, there is no difference in reported mortality from pertussis in the three countries. France reported 56 deaths during the 7-year period 1975–1981 while England and Wales reported 52 deaths (7) and West Germany 66 deaths during the same period (47). It is difficult to know how to interpret the discrepancies in notified cases and deaths from pertussis in the three countries. Provided the case fatality rate is not as high as 1 in 14 in France, massive under-reporting of pertussis must be considered likely (7) and it is difficult to draw conclusions concerning the benefits of pertussis vaccination from these figures. Neither in England and Wales nor in West Germany has the decline in pertussis immunisation been accompanied by increases in pertussis associated mortality (7, 47). In fact, both countries reported more fatal cases during 1970, when the immunisation rate was relatively high, than during the latter half of the decade, when the immunisation rates had fallen (7, 47).

Studies from Hamburg, West Germany, where mass vaccination against pertussis was stopped as long ago as in 1962, with subsequent immunisation rates of about 15%, indicate that whooping cough has taken a somewhat milder course during the last two decades. There has been a decline in both the number of whooping cough cases and hospital admission due to pertussis (45).

The United States (population 230 million): In 1980 95% of all children had received basic immunisation by the time they entered school. According to current recommendations, all children should receive three injections by six months of age and a fourth dose one year later. Despite this, pertussis has not been eradicated. In the three-year period 1979–1981, 1 277 cases were reported to the Centers for Disease Control from 42 states. Forty-nine per cent of the patients were younger than six months. There were seven deaths (1).

Japan (population 117 million): The situation in Japan has been similar to the situation in Britain. After having had an immunisation rate of about 80% from 1955 to 1974, pertussis vaccination was stopped for a short time due to reports of two vaccine-associated fatalities. During the rest of the seventies the immunisation rate varied from 14 to 65%. The number of reported pertussis cases increased from a few hundred per year during the first years of the seventies to 13 000 in 1979. In contrast to Britain, there was also an increase in the number of notified fatal cases, from 2–5/year in 1970–1975 to 20–41/year in 1976–1979, but it should be noted that the surveillance of pertussis was intensified from 1976 (2).

Low-endemic pertussis is also reported from Eastern Europe, despite very high immunisation rates and administration of two booster doses after basic immunisation (16–18, 48).

Conclusions. There can be no doubt that the drastic decline in pertussis notifications in several countries observed after the large-scale introduction of vaccines (2, 5–7, 20, 21) can be largely attributed to the vaccines. During the beginning of the vaccination era the herd immunity must have been very good, since older children and adults had a naturally acquired immunity while younger children had a vaccine-induced immunity. However, several countries now report problems with pertussis, probably since the herd immunity declined when *B. pertussis* almost ceased to circulate. As can be expected when pre-school children are protected by a relatively short-lasting vaccine-induced immunity, pertussis affects older children in some countries with high immunisation rates (5, 14, 33), but also infants too young to be vaccinated (1, 5, 14, 15). No country has managed to eradicate pertussis or prevent exposure of infants (1, 5–7, 14, 15). To what extent immunisation now affects the morbidity from pertussis is not possible to assess, at least not from comparisons of countries with different immunisation policies, since the methods of pertussis surveillance differ so much and the degree of under-reporting cannot be estimated. The mortality figures are presumably more reliable. From these figures it can be deduced that the mortality in France, Britain and West Germany is almost identical despite immunisation rates of 95%, 40% and 10%, respectively (7, 8, 47).

To achieve better protection of infants, two approaches can be discussed: The immunisation programme can start at an early age, but this might not be successful since passively transferred maternal antibodies may impair the active immune response (19). The other possibility is to improve the heard immunity by administration of repeated booster doses as is done in some countries in Eastern Europe. The advantages of this policy must be carefully weighed against the side effects and probable difficulties in convincing the public to accept this procedure.

Side effects

Administration of pertussis vaccines to laboratory animals gives rise to several physiological and biological changes, e.g. changes in cardiac rhythm, an increase in plasma insulin, increased sensitivity to histamine and blocking of the epinephrine response (49–54). One of these effects, the increase in plasma insulin, has also been demonstrated in humans (55).

Local reactions and less serious systemic reactions. Local reactions, fever, vomiting, irritability and other benign side effects are seen relatively often after pertussis immunisation. In a randomised, double-blind, American study (56) including 195 children receiving diphtheria-tetanus-pertussis (DTP) vaccine and 110 children receiving diphtheria-tetanus (DT) vaccine, redness, swelling and pain occurred at a rate of 31, 36 and 47%, respectively, after DTP vaccination and at a rate of 6, 9 and 11%, respectively, after DT vaccination.

Fever above 38°C was noted in 40% of DTP and 12.5% of DT patients. Other systemic reactions like drowsiness, fretfulness, vomiting, anorexia and persistent crying were also seen more often in DTP than in DT patients. Other studies have shown similar rates of local and systemic reactions after pertussis or DTP vaccine injections (55, 57–59). From Britain a lower incidence of side effects is reported. Only 19% of 897 vaccinerecipients developed any kind of side effect (60).

Neurological side effects. Convulsions without permanent sequelae were seen with an incidence of 1/1 750 injections in a prospective American study (56). Retrospective studies from the Netherlands, West Germany and Sweden have yielded estimated rates of 1/2 200–1/6 500 completely immunised children (6, 61, 62). These convulsions have usually been shortlasting and not associated with permanent brain damage. They have often occurred in connection with high fever.

Almost all countries in Europe, North America and Japan have reported serious neurological reactions after pertussis immunisation (56, 63) but it is impossible to determine in retrospect whether the vaccine or other factors have been the cause of the individual reactions. In Great Britain and Japan the publicity around these neurological reactions has markedly contributed to the decrease in vaccine acceptance (2, 8).

Of all studies of serious neurological reactions, the most reliable is the much-cited National Childhood Encephalopathy Study in Great Britain (64), since that study is the only one including a control group. It was performed as a case-control study and included all cases of encephalitis, encephalopathy, unexplained coma, convulsions lasting more than 30 minutes or followed by persisting complications, infantile spasms and Reye's syndrome occurring in the whole country during a three-year period. A significant correlation between serious neurological illness and pertussis immunisation was found. The risk of developing serious neurological reactions for previously normal children was estimated to be 1/110 000 injections. The risk of developing neurological sequelae persisting after one year was 1/310 000 injections. According to a later report from the same investigation (65) and studies from Denmark and Japan (66, 67), infantile spasms are not caused by pertussis vaccines.

Despite the unique quality of the National Childhood Encephalopathy Study, it has been criticised on the grounds of the possible omission of some vaccine-associated cases of brain damage, bias of controls and short observation period (8). However, it is probably not possible to get closer to the true incidence of reactions which occur with such rarity. It must be emphasised, though, that the results of the study are only valid for the British vaccine. Whether other pertussis vaccines give rise to serious neurological reactions with a higher or lower frequency is not known.

Shock. A state of shock or collapse occurs occasionally after pertussis immunisation. The affected infants are limp, pale and unresponsive. The episodes can last from a few minutes to several hours (21, 56). In a prospective American study of 15 000 vaccine recipients, the incidence was estimated to be 1/1 700 (56). The incidence after the Dutch vaccine was retrospectively estimated to be 1/2 700 vaccinated children (6). Other estimates have varied between 1/200 injections and 1/9 500 completely immunised children (62, 68, 69). The condition is self-limiting and not associated with permanent damage (6, 20, 48, 62, 68, 69). During the early trials of pertussis vaccines a few fatal cases were reported (70, 71).

Sudden infant death. In a study from Los Angeles, a significant clustering of cases of sudden infant death was found following the administration of pertussis vaccines (72). Six cases of sudden infant death within 24 hours after immunisation were found by retrospective scrutiny of autopsy records. The expected number of cases, provided no temporal association had existed, would only have been 0.96 ($p<0.0005$). During the second to

seventh day after immunisation 11 cases were found compared to the expected 5.76 ($p<0.05$). However, despite the statistical significance, the results cannot be taken as proof that pertussis vaccines may cause sudden infant death (73), mainly because only 38% of all registered cases of sudden infant death could be evaluated.

Final comment

Despite the lack of knowledge on certain important aspects of pertussis immunisation, it is clear that pertussis vaccines, with some exceptions, induce a protective immunity, but that this immunity lasts for only 2 to 5 years. The large-scale use of pertussis vaccines has significantly decreased the pertussis morbidity in the pre-school age-groups, but no country has eradicated the disease. The very low, but not negligible, mortality from pertussis in the industrialised countries today does not seem to be markedly affected by the immunisation programmes. Most vaccines are associated with a high rate of local reactions, fever and other benign systemic reactions. Convulsions and shock are uncommon and serious neurological reactions with permanent brain damage seem to be rare, but a significant correlation to pertussis vaccination has been demonstrated. As is evident from the debate in the medical press, there is major disagreement about the interpretation of these facts and it is doubtful whether the full truth concerning the merits and disadvantages of the whole cell vaccines will ever be obtained. There is definitely a need for improved vaccines.

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