

Brain damage following whooping cough vaccination - is it time to lay the myth to rest?

Victor E Grech*, Ray Busuttil**

ABSTRACT: Whooping cough causes significant morbidity and mortality, especially in early infancy. Although an effective vaccine exists, vaccine uptake in Malta was previously disappointing due to the general public's and the medical community's doubts regarding vaccine efficacy and safety. The aim of this study was to review population-based studies which have analysed the potential short and long term neurological sequelae following pertussis and pertussis vaccination, to describe vaccine uptake globally and in Malta over the past 15 years, and to analyse the effect of vaccine uptake on pertussis epidemics in Malta. This study found that pertussis vaccine uptake has only become satisfactory in recent years, with a resulting attenuation in the most recent pertussis outbreak. Uptake has increased progressively all over the world, and no study has ever incriminated pertussis vaccination as a cause of permanent neurological disability, both locally and abroad. This should encourage the present continuing trend of pertussis uptake.

* Department of Paediatrics, St Lukes Hospital, Gwardamangia, Malta.

** Department of Primary Health Care, Floriana, Malta.

Correspondence: Dr. VE Grech, Department of Paediatrics, St. Luke's Hospital, Guardamangia, Malta. email: vgrech@mail.link.net.mt

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Introduction

Whooping cough is a bacterial infection caused by *Bordatella pertussis*, which can cause significant morbidity and mortality. Infants between 1 and 2 months of age are at highest risk for pertussis, along with the highest rates of hospitalisation (82%), pneumonia (25%), seizures (2-4%), encephalopathy (0.3-1%), and death (0.2-1%)^{1,2}.

Neurological symptoms may be caused by endotoxin release due to bacterial lysis, asphyxia, CO₂ retention, loss of cerebral vascular autoregulation, or a combination of these factors². Seizures, encephalopathy and other neurological manifestations are complications that also occur in adults³.

A widespread impression that Diphtheria-Tetanus-Pertussis (DTP) vaccine can cause brain damage was initially based on historical precedent. Smallpox and rabies vaccines were recognised as occasionally causing devastating neurological complications, and in the minds of the lay public and the medical community, this analogy was extended to pertussis. In addition, anecdotal case reports of a syndrome of pertussis vaccine encephalopathy began to be reported over 60 years ago⁴. This study reviews the literature regarding pertussis and pertussis vaccine related complications, with emphasis on neurological complications, reviews the literature regarding pertussis vaccine uptake, and compares this with the situation in Malta.

Methods

Medline was searched using the keywords 'whooping cough' and 'encephalopathy'. Population-based studies which analysed cases of encephalopathy occurring in association with pertussis or pertussis vaccination were identified. For the estimation of pertussis vaccine uptake, since the pertussis vaccine is almost invariably given as a combined **DTP vaccine**, the statistics for the combined vaccine were used. Pertussis vaccine uptake was defined as percentage of infants surviving the first year of life, who have received three doses of combined vaccine (DTP3). Unless stated otherwise, DTP/DTP3 refer to the whole-cell pertussis vaccine, which does not include vaccination with acellular preparations of pertussis vaccine.

DTP3 data for Malta was obtained from statistics maintained by the Department of Primary Health Care, while DTP3 statistics for individual countries - such as the United Kingdom - and for global regions, were obtained from World Health Organisation publications^{5,6}.

Annual Maltese figures for whooping cough were obtained from 1980 to 1996⁵. Annual population estimates⁷ were then used to calculate Maltese pertussis rates per 100,000 population.

Excel was used for data entry and for charting. SPSS was used for non-parametric correlations of vaccine uptake and pertussis rates with time (Kendall's t test). A p value of 0.05 was taken to represent a statistically significant result.

Results

Globally

DTP3 uptake has increased significantly in all of the World Health Organisation regions ($p \leq 0.001$ - Table 1). WHO global statistics show DTP3 uptake has more than doubled in the past 15 years, from approximately 35% to almost 80% (Figure 1). Analysis of DTP3 for developed regions shows >80% uptake for the UK and America (Figure 1). Although uptake is not as high in developing regions, the trend is persistently upwards (Figure 2).

Locally

DTP3 uptake in Malta has increased significantly (Table 1), climbing rapidly since the mid-1990s to reach the 80% level (Figure 3). Pertussis outbreaks in Malta show classical 4-yearly peaks (Figure 3). The last classical outbreak was in 1991, and the effect of DTP3>40% is instantly discernible, with attenuation of the next expected outbreak in 1995. There have been no cases of permanent neurological sequelae definitively attributable to DTP vaccination.

Discussion

Historical background to DTP vaccination

The development and extensive uptake of an effective DTP vaccine (taken in three doses in infancy) in the United States in the 1930s led to a decline in the incidence of pertussis in this region, and instilled confidence in a vaccination programme which continues to this day. This contrasts with the turbulent history of pertussis vaccination in the United Kingdom, where doubts as to the efficacy of pertussis vaccines delayed their active national promotion until the late 1950s, after which various reports reinforced the medical community's and the general public's doubts regarding DTP vaccine efficacy and safety⁴.

In 1974, the media were deeply embroiled in the issue when the National Hospital for Sick Children case series of neurological events was aired in a television documentary. This study allegedly identified patients with neurological sequelae which had occurred after DTP vaccination.

The Courts were also involved when a claim for damages in the High Court of Justice in London in 1989 (Loveday vs Renton and The Wellcome Foundation) dealt with the issue of whether pertussis vaccine could cause permanent neurological sequelae. The foundation of this claim was the apparent clustering of neurological disorders within the first 24 to 48 hours after DTP vaccination. One of the findings of the National Childhood Encephalopathy Study (NCES) which came to light in court, was that permanent brain damage did not occur within 48 hours of DTP vaccination in any child in England, Scotland and Wales from mid-1976 to mid-1979, when two million doses of vaccine had been given, although an excess of febrile convulsions in the first 24 hours was noted. All temporally associated cases with permanent sequelae had either viral encephalitis or Reye's syndrome, and no cases were unexplained⁸. The High Court's judgement was that there was no evidence that DTP vaccination causes permanent neurological sequelae⁸.

A reduction of DTP uptake, or even discontinuation,

Table 1 - Correlation of percentage uptake of 3 doses of combined diphtheria, tetanus, pertussis and polio vaccine by 1 year of age with time

	Year	t	p
Malta	1984-96	0.87	<0.0001
UK	1981-94	1	<0.0001
<i>WHO regions</i>			
Europe	1980-96	0.75	<0.0001
America	1980-96	0.88	<0.0001
E. Mediterranean	1980-96	0.82	<0.0001
Africa	1980-96	0.71	<0.0001
S.E. Asia	1980-96	0.67	<0.0001
W. Pacific	1980-96	0.63	0.001
Global	1980-96	0.86	<0.0001

Fig. 1 - Percentage uptake of 3 doses of combined diphtheria, tetanus, pertussis and polio vaccine by 1 year of age in WHO developed regions (UK and America), the UK and globally

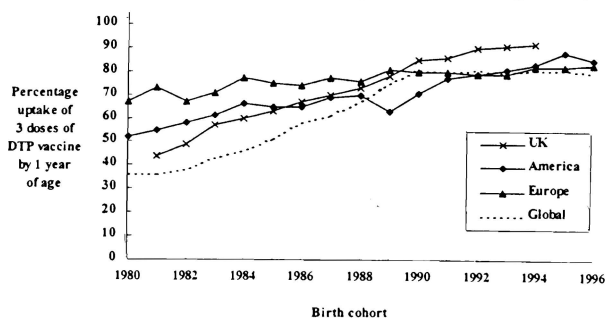


Fig. 2 - Percentage uptake of 3 doses of combined diphtheria, tetanus, pertussis and polio vaccine by 1 year of age in WHO developing regions

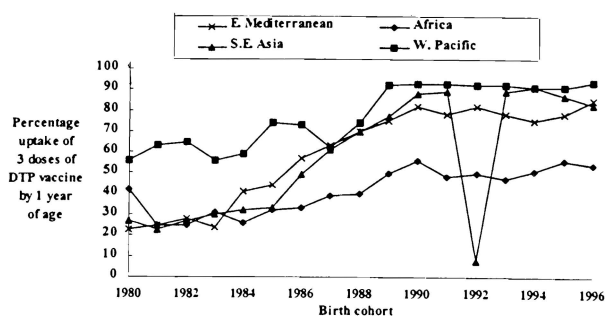
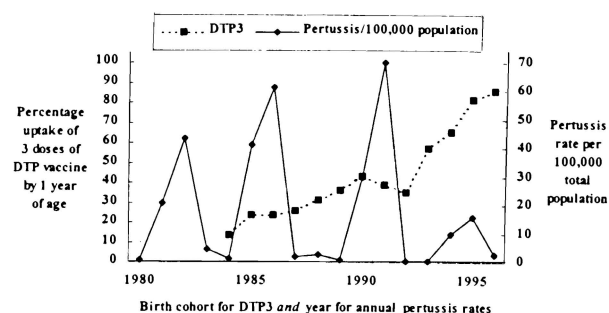


Fig. 3 - Percentage uptake of 3 doses of combined diphtheria, tetanus, pertussis and polio vaccine by 1 year of age in Malta and pertussis rates



was also observed in other countries, including Sweden, Japan, the USSR, Ireland, Italy, the former West Germany and Australia, leading to a sharp rise in the number of reported cases of pertussis during epidemics⁹. On the other hand, countries which maintained a high or compulsory uptake of DTP, including Hungary, the former East Germany, Poland and the United States, had reported rates of pertussis which were 10-100 times lower⁹. In the United Kingdom, confidence in DTP was enhanced by introducing the vaccine at an earlier age, which is associated with a decreased incidence of reactions. This practice was also followed in Malta.

Known complications of DTP vaccination

DTP vaccination may cause various reactions within 48 hours of administration, which include hypotonic-hyporesponsive episodes, seizures and fever $\geq 40.5^{\circ}\text{C}$ ¹⁰. Children with seizures tend to have a high rate of personal and family histories of seizures, and fever occurring in association with DTP vaccination ($\geq 38^{\circ}\text{C}$)¹⁰. Persistent crying (≥ 3 hours) is generally noted in association with painful local reactions¹⁰. A rare association has also been described between DTP vaccination and anaphylaxis¹¹.

Large, population-based studies have concluded that combined DTP vaccine may, on rare occasions be associated with the development of severe acute neurological illnesses, with only the potential for severe, long-term sequelae. Some of the cases of severe acute neurological illnesses observed may have occurred due to chance alone, or may have had other causes. It is impossible to determine retrospectively the role of the pertussis component of the vaccine in these cases, as a primary or secondary factor¹²⁻¹⁵.

It is important to emphasise that no population studies have ever implicated DTP vaccination as a cause of permanent neurological sequelae, and this must be weighed against the known morbidity and mortality that occurs in association with pertussis itself. DTP vaccination is given at the age of emergence of primary neurologic disease, and a temporal link between DTP vaccination and the recognition of such problems may be established in the minds of parents and doctors alike, and a causal link inferred.

Also, no evidence has been found to link DTP vaccination with infantile spasms, hypsarrhythmia, Reye's syndrome, aseptic meningitis, Guillain-Barre syndrome, peripheral mononeuropathy, or indeed, any form of chronic neurologic damage including learning disabilities and attention-deficit disorder¹¹. Furthermore, no link has been found with sudden infant death syndrome, erythema multiforme or other rashes, haemolytic anaemia, juvenile diabetes, or thrombocytopenia¹¹.

The following are the modern contraindications to pertussis vaccination¹⁶:

Severe local reactions:

- More than half the limb involved.

Severe generalised reactions:

- Marked febrile reactions ($> 39.5^{\circ}\text{C}$) within 48 hours of vaccination
- Allergic reactions: Anaphylaxis, bronchospasm or laryngeal oedema

- Generalised collapse
- Prolonged unresponsiveness
- Prolonged screaming (> 4 hours)
- Convulsions or encephalopathy within 48 hours of vaccination

Failure to vaccinate must be weighed against the known morbidity and mortality of pertussis itself. Vaccinators should be strongly discouraged from the inappropriate deferral of pertussis immunisation due to mild illness, or the omission of vaccine because of non-existent contraindications. This is especially important in children who have underlying conditions which may place them at greater risk of acquiring pertussis infection and its potential complications.

Locally

Malta has followed the rest of the world in increasing the uptake of pertussis vaccination over the past decade. The effect of a high herd immunity limiting the spread of pertussis, which has been brought about by a high uptake of DTP3, is readily apparent (Figure 3), with a marked drop in the number of reported cases in the most recent pertussis outbreak, when compared to previous outbreaks. Increased uptake is attributed to a number of factors including the effective allaying of misguided public fears by the Department of Primary Health Care with regard to vaccine safety, and an increasing number of local paediatricians who follow logical guidelines in pertussis vaccination practice. A further stimulus to vaccination would also include morbidity and mortality observed locally¹⁷.

Conventional DTP consists of killed whole organisms (whole-cell vaccine). A new acellular pertussis vaccine, containing partially purified protein antigens, filamentous hemagglutinin, and lymphocytosis-promoting factor hemagglutinin has been developed for use, and was initially tested in Japan in a randomised double-blind trial, vaccinating children at the appropriate time. Acellular pertussis vaccine was found to be significantly less reactogenic for fever, pain, fretfulness and local reactions at the vaccine administration site¹⁸. The role of this vaccine is uncertain, and the World Health Organisation continues to recommend use of whole-cell vaccine.

Conclusions

Pertussis is a dangerous and potentially lethal illness, immunisation is effective in protecting against the disease, and should therefore be strongly encouraged. There is no proof that the incidence of complications from DTP whole-cell vaccination of children with seizure disorders or other pre-existing stable neurologic abnormalities is higher, and therefore the balance of possible risk against known benefits of pertussis immunisation supports continued use of the DTP vaccination even under such circumstances.

There is overwhelming evidence to show that the occasional neurological illness following whole-cell DTP vaccination has a temporal, rather than a causal relationship, as the vaccine is given at the age of emergence or recognition of primary neurologic disease.

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