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Scientific panel on childhood immunisation schedule: Diphtheria-tetanus-pertussis (DTP) vaccination

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Table of contents

Abbreviations

D	diphtheria toxoid
DTP	combined diphtheria, tetanus, pertussis vaccine
dTpa	combined DTPa vaccines with reduced content of diphtheria toxoid (d) and pertussis component (p)
ECDC	European Centre for Disease Prevention and Control
eIPV	enhanced inactivated polio vaccine
EU	European Union
HBV	hepatitis B vaccine
Hib	vaccine against *Haemophilus influenzae* type b
IPV	inactivated polio vaccine
MS	Member States
Pa	acellular pertussis vaccine (vaccine component)
Pw	whole-cell pertussis vaccine (vaccine component)
SAU	Scientific Advice Unit
SPaCIS	Scientific Panel on Childhood Immunisation Schedule
T	tetanus toxoid
VENICE	Vaccine European New Integrated Collaboration Effort
WWI and WWII	World War I and World War II

Scientific Panel on Childhood Immunisation Schedule

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Conflict of interest

No conflict of interest was declared by the panel members.

Executive summary

The quality of vaccination programmes in Europe is on average very high. Childhood vaccination programmes have shown a tremendous impact in all Member States, bringing to elimination or to a fairly good control of many serious communicable diseases.

All childhood immunisation schedules have been shown to work well both in terms of safety and effectiveness.

Current vaccination schedules are the result of historical tradition, compliance with provision of health services and national vaccine registration. They have been designed on the basis of different needs related to how the healthcare system – but also the education system – is organised at national level.

During the last decade, the availability of new combined vaccine products registered at EU level through the EMEA centralised procedure has allowed some convergence of the use of those vaccines.

According to the information provided by the VENICE and EUVAC projects, the current schedules for vaccination below 24 months of age in Europe with acellular pertussis-containing vaccines can be divided into few distinct groups (variants of 3-5-11, 2-3-4, 2-4-6 months). There is greater variation in the number of booster doses for children at school age or during adolescence.

In order to facilitate the scientific discussion on such issue, the European Centre for Disease Prevention and Control (ECDC) in Stockholm asked a panel of experts for their scientific opinion on the use of the DTP vaccine.

The ECDC's Scientific Panel on Childhood Immunisation Schedule (SPACIS) reviewed the current scientific knowledge focusing on three questions:

- What is the best age (or age range) to start the basic immunisation scheme for a combined diphtheria-tetanus-pertussis (DTP) vaccine?
- What is the minimum number of doses and what are the best immunisation intervals to provide sufficient protection against DTP in infants younger than two years of age?
- What is the minimum number of booster doses that should be administered between two and 18 years of age, and what are the best intervals between doses?

Unfortunately, the quality of the available evidence in this area is very variable. Many studies on DT, for instance, were conducted in 1950s and 1960s according to the methods available at that time.

Nevertheless, SPACIS managed to develop its expert opinion on the basis of the current available knowledge also building up on the lessons learnt in some EU countries on the basis of epidemiological observations. As a consequence, SPACIS highlighted a number of knowledge gaps and areas of scientific uncertainty that still exist in this field and that should be covered by future research.

The result of SPACIS's work – widely illustrated in this document – may inform decisions in those MS where the immunisation schedule would be under revision.

The full SPACIS guidance paper on childhood immunisation is available at www.ecdc.europa.eu.

Preface

It has become increasingly apparent that there is a need for Member States (MS) to discuss childhood vaccination schedules. The work done by the EU-funded VENICE and EUVAC projects has shown marked variation in vaccination schedules around Europe (Table 1). This variation in vaccination schedules is encountered worldwide and — up until January 1999 — might have been governed partly by national traditions and historical vaccine registrations at the Member State level. Moreover, the use of various combined vaccines (trivalent, tetravalent, pentavalent, and hexavalent) and concomitant administrations provide so many choices that an impact on the timing of vaccinations is very likely.

The objectives of this document are:

- to address the need for an effective minimum vaccination schedule in childhood and to draw up a minimum schedule that represents what is considered to be good practice;
- to provide a vaccination framework for children with migration backgrounds; due to the free movement of individuals in EU Member States, the increasing migration of families with children has led to great difficulties in ensuring optimum protection against vaccine-preventable infectious diseases that affect children; furthermore, a wide acceptance of individual protection contributes to high coverage rates which lead, depending on the vaccine, to herd immunity, which is also beneficial for the community at large; and
- in addition, this document aims, if possible, at decreasing the number of schedules in which new vaccines and concomitantly administered vaccines need to be tested, in order to reduce the number of unnecessary clinical trials and to minimise the amount of testing on infants.

This guidance was developed by the European Centre for Disease Control (ECDC) Scientific Panel on Childhood Immunisation Schedule (SPaCIS), a group of experts appointed by the Head of ECDC's Scientific Advice Unit (SAU).

Members were selected from scientists who had applied and were accepted as expert advisors to ECDC.

The group is independent of ECDC itself, although ECDC provides administrative support.

The group based its work on an overview of the scientific literature.

The time scale and available resources precluded carrying out a systematic review of the topic, but several third-party reviews were consulted. The documents addressing each question were prepared by literature searches and through consultations. They are intended as a starting point for a discussion that could potentially highlight questions that may require more systematic reviews.

The first vaccine assessed was the combined diphtheria-tetanus-pertussis (DTP) vaccine. The panel chose to address DTP vaccination by asking three questions:

- What is the best age (or age range) to start the basic immunisation scheme?
- What is the minimum number of doses, and what are the best intervals to provide a sufficient protection in infants less than 24 months of age?
- What is the minimum number of booster doses that should be administered between 24 months and 18 years of age, and what are the best intervals between doses?

The evaluation of the merits and drawbacks of the different schedules was based primarily on protection against pertussis since neither tetanus nor diphtheria represent a threat to newborn infants in Europe today. Pertussis is a disease that is most severe in infants, especially under six months of age, when the highest rates of hospitalisation and mortality occur.

Not discussed in detail were the following issues:

- the use of whole cell pertussis (Pw) versus acellular pertussis (Pa) vaccine; although some European countries continue to use Pw vaccine, there is largely agreement that the possible marginal reduction in protective efficacy caused by Pa vaccine is more than counter-balanced by its reduction in adverse events;
- the number and types of Pa vaccines components, since effectiveness data have not shown any significant differences;
- the immune correlates of protection in pertussis, due to conflicting and controversial data in the literature;
- the role of combined or concomitantly administered vaccines, e.g. inactivated polio (IPV), *Haemophilus influenzae* type b (Hib), hepatitis B (HBV), except where it directly impinges on DTP administration policy.

The Panel found that current schedules, both empirical and theoretical, are mostly based on data from Pw-containing vaccines. Thus, the Panel had to assume that the same findings also apply to Pa vaccine.

Furthermore, the Panel considered the epidemiology of pertussis to be rather homogeneous in all EU countries, despite possible differences in notification that could well be due to surveillance issues.

Introduction: A historical perspective

While this document is clearly not a comprehensive history of a century of vaccination programmes, some historical aspects that are still relevant today need to be emphasised. The first vaccine in general use was against tetanus and was used for the vaccination of military recruits during WWI [1]. The promising results were confirmed during WWII, when French, American and British troops were vaccinated, while most of the German troops were not (with the exception of the *Luftwaffe*, the German air force).

The tetanus vaccine was at first plain, non-adsorbed tetanus toxoid (T), and it was shown early on that three doses for priming were needed. In the 1930s, several scientists independently found that precipitation of the tetanus toxoid with aluminium phosphate or hydroxide yielded a vaccine that with only two doses induced as good a response (or even higher responses) than the non-adsorbed, plain vaccine. French and American troops received additional regular booster doses while the British troops received no booster. A marked difference was observed between the UK and the US troops: the UK troops suffered more cases of tetanus, including deaths, while the US only reported a few mild cases. Based on these findings, the UK introduced a booster dose in 1942. Shortly after WWII, the immunisation of parts of the civilian population was started in most countries. In general, two doses were given, with a two-months interval for priming.

Vaccination efforts against diphtheria were started with the vaccination of children. Diphtheria vaccination was introduced in France and in Hungary in 1938, and in 1941 in the UK, to give a few examples. At first the vaccine was a plain, non-adsorbed vaccine but later an aluminium salt-adsorbed toxoid was used. In Europe, natural immunity to diphtheria was widespread, but natural immunity to tetanus was non-existent. Consequently, the tetanus vaccination of adults caused no adverse reactions, while the vaccination of adults with a natural immunity to diphtheria resulted in frequent and severe reactions. The antigen content of the toxoids therefore differs in all vaccines, with tetanus toxoid being vastly overdosed in comparison to diphtheria toxoid (D).

Combined diphtheria and tetanus (DT) toxoid was first introduced in France, thanks to the pioneering work of Ramon. The combination of vaccines also included (whole-cell) vaccines against typhoid and paratyphoid, and the combination was claimed to enhance the responses to the D and T vaccines. Other studies with only combined tetanus and diphtheria toxoids indicated a decreased immunogenicity when compared to each monovalent vaccines, but the decrease was slight and viewed as acceptable considering the convenience of vaccinating against both diseases at the same time.

Immunisation against whooping cough was first studied on the Faroe Islands. The vaccine was found to have a good protective clinical effect once it was understood that vaccination had to be made prior to exposure. These encouraging results led to numerous smaller vaccine trials, with doses of 80–120 x 10^9 bacteria per full vaccination in a child, mainly in the US. Because of the well-known side effects of whole-cell vaccines these large doses could not be administered in less than 4–6 injections, given weekly. Whole-cell pertussis vaccine was also alum-adsorbed and the dose reduced to 60 x 10^9 bacteria, given in three injections.

Combined diphtheria-tetanus-pertussis (DTPw) vaccines were first developed and more widely used in the US. Combining whole-cell pertussis vaccine with diphtheria-tetanus vaccine was invariably found to increase the immunogenicity of the latter vaccines. The age of vaccination was from the beginning governed by the fear of interference with the response to diphtheria toxoid from maternal antibodies. For this reason, the start of vaccination was deferred to the second half of the first year of life. During the late 1940s, however, several authors argued that the change of the epidemiology of diphtheria in the US made the conclusions of strong interference less relevant, and studies were carried out showing that the rate of mothers with immunity to diphtheria (as measured by the Schick test) had decreased.

Urged by a need for early protection against pertussis, several studies were carried out to vaccinate young infants [2]. The most elegant series of studies, conducted by Di Sant'Agnese [3-6], showed that good antibody responses to DTPw vaccine were obtained in children as young as three months, and that the efficiency of priming could only be fully observed after the booster dose, administered at least six months after the last of three priming doses.

In the US, the efficacy of the whole cell pertussis vaccine was generally recognised, while less encouraging results were found in smaller European trials. To settle the issue, the British Medical Research Council [7, 8] started a series of large studies in the late 1940s, including different types of vaccines from several manufacturers. The

studies included children with no history of pertussis from six months of age up to 18 months of age. The results showed that (some) vaccines were highly effective in preventing pertussis [7]. Also, the protective efficacy was correlated to the mouse protection assay, when the most favoured laboratory assay —measurement of agglutinin response — gave a discrepant result for the Pillimer vaccine, the first acellular type of pertussis vaccine [8]. As a result of these trials, most European countries introduced the general vaccination with DTPw vaccine in the 1950s. The age for the first dose was initially three months in most countries, which later was decreased to two months of age in many countries, in order to induce earlier protection against pertussis.

In summary, the various immunisation schedules in Europe for DTPa vaccines evolved from experiences gained from immunisation with whole-cell pertussis-containing DTP vaccines (2, 3, 4 and 2, 4, 6 months schedules), where the need for three doses was governed by the Pw component while the D and T components — immunogenic and less reactogenic — could be given in two doses. The two doses (3, 5 months schedule), on the other hand, evolved from the vaccination schedule for DT vaccine. This priming schedule was introduced first in Italy in 1981 and in Sweden in 1986. This two-doses schedule was kept when Pa vaccine was added to DT.

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1 Age at first dose

The basic assumption is the acceptance of six weeks of age as the minimum age to start DTPw/DTPa vaccination as recommended by WHO [1]. This section therefore examines the available evidence for an earlier vaccination, including neonatal vaccination.

In this regard, several issues need to be taken into account: what impact has the relative immaturity of the immune system in the newborn, particularly during the early weeks of life? What is the role of transplacental maternal antibodies? Does it have the same effect on diphtheria, tetanus and pertussis? What is the impact of these immunological issues on age at first dose of DTP in terms of benefits (both immunogenicity and clinical protection)?

1.1 The rationale in industrialised European countries

- All industrialised countries have introduced D, T, P vaccination in their schedules. All of them benefit from combined DTP (either Pw or Pa) vaccines.
- In Europe, diphtheria and tetanus are no longer a risk for young infants (high coverage rates achieved by vaccination in the population; maternal antibodies are transferred to their newborns during pregnancy).
- Most of the countries, having achieved 90% vaccination coverage, have considerably diminished the burden of the three diseases, in particular whooping cough in young children. The purposes of the vaccination programmes are mostly achieved: vaccination safety is ensured; protection is provided in the targeted population with the greatest needs.
- In the 1990s, epidemiological data [2] from many developed countries demonstrated an age shift of pertussis towards adolescents and young adults with an increase in incidence (although now the disease is better diagnosed due increased awareness and improvement in diagnostic techniques). This shift is partly due to a waning of immunity post vaccination and partly to a limited impact of pertussis vaccines on the circulation of *B. pertussis* — even in countries with high vaccination coverage. Increased numbers of susceptible adolescents and adults may serve as a reservoir for the infection, leading to occasional outbreaks.
- As a consequence, due to high infectivity in households with up to 90% of secondary cases, there has been an increase in incidence in very young infants not yet or not fully immunised.
- Due to a possible suboptimal compliance with recommended vaccination schedules during infancy, the window of susceptibility to pertussis infection may be enlarged [3].
- Pertussis remains an important cause of death in very young infants, with up to 3.9% of all deaths [4] in developing countries.
- In European Union (EU) countries, on one hand, all the national schedules have introduced a primary series with three doses starting at the earliest at two months of age (adding doses at least one month apart, at three and four months of age), or two doses starting at three months (adding one dose at five months of age). On the other hand, all EPIs countries follow WHO recommendations with a three-doses primary series starting at six weeks of age and adding two doses at 10 and 14 weeks of age. One or several boosters have been introduced at different older ages, the first booster mostly given in the second year of life throughout European countries.

The situation in 2008 could thus be summarised as follows:

- The necessity of giving diphtheria and tetanus toxoids to newborns does not appear to be a public health priority. Moreover, as will be shown later, the question of the effectiveness of the immune response to diphtheria toxoid is raised due to the presence of transplacentally acquired antibodies against diphtheria toxin.
- The issue of protecting newborns and infants under three months of age against pertussis has to be raised again. This need has led to various recent strategies: adolescent or young-adults booster, maternal immunisation, selective immunisation of close contacts of neonates, or even the idea of universal adult immunisation. As no monovalent pertussis vaccine has been licensed in Europe so far, the use of a combined DTPw or DTPa at the youngest age is a source of concern. Some recently published data on monovalent Pa vaccines administered in newborns are challenging [5].

1.2 General comments regarding immune responses in the neonatal period

Neonates are immunologically less mature than a few months later during infancy and functionally deficient in their adaptive immune responses [6] as expressed by a diminished T-cell function and T-cell help for B-cell differentiation. Essential differences distinguish early-and later-life antibody responses, both qualitatively and quantitatively.

Qualitatively, immune system maturation is progressive and includes a switching from Th2 responses (expressed by a predominance of IgM, IgG1, IgA and IgE with B cell proliferation and eosinophil activation) to Th1 responses (IgG2 production, cytotoxic T cell activation and macrophage activation) to conventional vaccine antigens [7, 8].

Quantitatively, the capacity to raise antibody responses to an antigenic stimulus (live and inactivated vaccines) is acquired early in life [9]. During the first months of life, a large proportion of infants fail to respond to 'weak antigens'. For example, Di Sant'Agnese [10] demonstrates a difference between two age groups for pertussis, although no maternal antibodies are transmitted, and concludes that the immaturity of the immune response mechanism is responsible. Antibody responses to common vaccine antigens in children < 12 months of age, even when satisfactory (important differences between antigenic stimuli are reported in the literature), are usually transient and low or undetectable in the second year of life [7, 8]. A strong and rapid response post-booster vaccination is a key component of a primary vaccination series.

1.3 Inhibition of vaccine responses by transplacental maternal antibodies to antigens administered early in life

The phenomenon has been reported for DTP [11] but not for DTPa vaccines [12, 13]. Interference may occur, especially for diphtheria toxoid, which does not mean that early immunisation has no effect. The antibody response may exist still, masked initially, confirmed later on by a strong, rapid antibody response post-booster dose [14]. This demonstrates that maternal-acquired antibodies do not affect priming for most antigens.

Although early studies exploring DTPw in neonates resulted in a concept of a so-called 'immune tolerance' in infants, there is no further evidence of this immune tolerance after post-neonatal immunisation with protein antigens or protein-conjugate antigens [15].

Transplacental transmission

Maternal antibodies against both tetanus and diphtheria toxins have been found in cord sera during the first weeks of life (with some discrepancies in the literature), varying from a prevalence of 15% for tetanus and 58.5% for diphtheria [16] down to none for tetanus and 20% for diphtheria [17].

The percentage of women of childbearing age carrying *B. pertussis* serum antibodies varies from community to community. It is mostly less than 50%. In infants from seropositive mothers, maternal antibodies (pertussis agglutinins) ranged from 63% [18], 54% [19], 22% and 37% [20] to only 2% [16]. Regardless of the method employed — complement fixation reaction for *B. pertussis* [21], opsonocytophagic index [22, 23], opsonins [24], mouse protective antibodies [25] in past and recent times [12, 26-28] — transplacental transmission was demonstrated across the same wide range. Therefore probably no more than 25% of infants are born with circulating antibodies. Most often, transplacentally transferred antibodies (IgG antibodies pertussis agglutinins) are at lower titre compared with their mothers (half titres) and disappear within the first six months of life [19] (half-life of approximately six weeks in infant sera) [12]. This rapid decay leaves infants with little protection against whooping cough [29].

The impact of transplacental transmission: interference?

Several studies detailing the interference between transplacental antibodies and early-life vaccination response demonstrate that some vaccine antigen components may be suppressed while others are not.

For tetanus toxoid, most authors [14, 30, 31] found no neonatal interference with maternal transmitted antibody for tetanus toxoid when given soon after birth; some, however, reported disparate results [32].

For pertussis agglutinins (antibodies), no relation between their presence or absence in cord blood and immune response to vaccination was apparent. For example, the antibody rise in serum was similar in groups receiving either four or three doses, with almost identical percentages of high titre (≥ 1:320) in infants for whom cord blood was positive or negative [11]. In view of these findings it seems unlikely that transplacentally acquired antibodies can be present in sufficient concentration to block vaccine-induced immune responses [18, 33].

For diphtheria toxoid, some interference is probable between maternal antibody and vaccine immune response. Although no constant quantitative relationship was found between the amount of transmitted toxin antibody and the inability to develop a post-vaccine immunity [17], a striking defect of the latter was observed in cases of transmitted antibody. Infants under three months of age respond poorly when transplacental transmission occurs, resulting in lower diphtheria titres. The presence of recognisable transplacental antibody (even in small amounts) leads to a combination of vaccine toxoid antigen with the antitoxin antibody. The resulting neutralisation prevents the vaccine antigen exerting its usual stimulus. The higher the level of maternal antibody titre, the more difficult it is to overcome [14, 16, 34], suggesting an inverse relationship of two factors: the amount of maternal antibody present and the duration and intensity of the antigenic stimulus [17]. After six months of age, immune response was good in up to 95% of infants. However, the similarity of post-booster response in cord blood-positive and -negative infants means that neutralisation of vaccine toxoid by transmitted maternal antibodies is partial. If enough vaccine antigen reaches the immune tissues, it is able to induce antibodies resulting in a satisfactory response after a booster dose.

1.4 Age at first dose and immune responses after DTP/DT/P primary series

In the 1940s, vaccination programmes were proposed from six months of age. Several authors then demonstrated that earlier immunisation achieved some immune response.

Age appears to be a major factor in the serologic response to pertussis immunisation. When immunised older than six months with a pertussis vaccine (at that time, whole cell, 80 x 10^9 saline-suspended *B. pertussis* adsorbed or precipitated), over 60% of infants maintained high titres for four years [18]. When injections started at 4–8 weeks of age, fewer infants produced high titres of agglutinins and titres were not equally well maintained. Less serologic protection was achieved when immunisation started at one week of age. Agglutinin response was significantly better when the first dose was given at ≥ 3 months of age (with four doses, fourth dose at six months plus booster dose at one year) [34]. Other authors subsequently confirmed this fact [10, 16, 18, 19, 33, 35-38]. The poor response related to age is mainly attributed to physiological immaturity of the immune system. Nevertheless, neonates immunised against pertussis with Pw at one week of life and receiving two more doses at one and two months of age had good agglutinin responses; after a booster dose given at 6–7 months of age, the immune response was similar to that obtained in infants vaccinated at 2, 3, 4, and 6–7 months of age [39].

Age at first dose of tetanus toxoid is not critical, due to its great antigenic capacity. An equally good immune response is achieved regardless of the age at first dose [10, 14, 16, 30, 34, 40].

For diphtheria toxoid, higher titres were found in older children but no significant difference persisted after the booster dose [14, 16]. The role of transmitted maternal antibody is likely in infants but overcome by a high antigenic stimulus.

In summary, several authors agreed that antibody titres are generally higher with increasing age of immunisation [18, 19, 33, 38, 41] and are consequently cautious about neonatal immunisation [20] when utilising a DTPw vaccine.

1.5 Strength of antigenic stimulus to overcome constraints

The need for stronger (due to high concentration) pertussis antigens became evident at the end of the 1940s. Adjuvanted (alum-precipitated) pertussis whole-cell vaccines were associated with longer duration antibody when immunisation was started as early as the second month of life [35]. Miller [18], comparing two *B. pertussis* whole-cell vaccines — alum-precipitated or saline-suspended up to 100 x 10^9 cells — found higher titres which lasted longer than the former after the third dose. Similar results from Di Sant'Agnese confirmed a slow decline of titres over the next two years after administration of an aluminium hydroxide-adsorbed DTPw vaccine [16].

Tetanus toxoid is a sufficient antigen stimulus to overcome immune immaturity [17].

The antigenicity of diphtheria toxoid overcomes the negative impact of transmitted maternal antibody in young infants. This explains the absence of significant difference — after a booster dose — between early- and late-start immunisation, although higher titres are achieved in older children after the primary series.

In summary, the role of variable maternal antibody is greatest with vaccines of borderline potency and can be overcome by more potent antigen [31]. However, for pertussis [5, 41] antibody response may not be the only basis for immunity, and protection is at least partly dependent on cell-mediated immunity.

1.6 Limitations of the studies in the 1940s, 1950s and 1960s

Methodology has changed over the past 50–60 years:

- Whole-cell vaccines were the only vaccines used in the 1940s. These vaccines were either a fluid formulation or adjuvanted. The whole-cell pertussis vaccines used at that time were made from fresh clinical isolates while today's vaccines are based on seed-lot strains. Furthermore, numerous European countries now recommend acellular pertussis vaccines for the primary series.
- No randomised prospective trials compared early and late vaccination. Children were not of the same age for early- and late-vaccination schedules at the time of boosting (due to boosters given with the same interval after the end of the series). Finally, small effects were frequently found, which was particularly unfortunate since loss to follow-up was often high, reaching 70% in some studies.
- For pertussis antibodies, the immune correlates used in the 1940s are no longer accepted because of the identification of the major toxins and surface proteins of *B. pertussis* [42] in the 1970s.
- One remaining issue is to identify — with a reproducible laboratory test — a reliable immune correlate of clinical protection against pertussis. The mouse protection test reproducibly measures vaccine potency. Although it was not established that the mouse and human protective antigens were identical, the results of this test were shown to correlate well with protective efficacy in humans. The mouse protection test allows reliable standardisation of pertussis whole-cell vaccines. In 1956, the Medical Research Council (MRC) [43] established some correlation between laboratory tests (mouse protection test, agglutinins produced in mice and in infants) and infants' home exposure attack rates in field trials that included more than 28,700 children that were followed up for two years post vaccination. The MRC acknowledges that in spite of this correlation, none of these factors can be demonstrated as directly related to protective immunity. The protective value of other antigens such as FHA or pertactin is still questionable. It is generally recognised that no sound immune correlate of protection in term of seroprotective antibody concentration can currently be identified for pertussis despite the demonstrated effectiveness of routine pertussis vaccination at a population level.
- In contrast to diphtheria and tetanus toxoids, immune thresholds of protection are now well established.

1.7 Immune response to neonatal DTPa

So far, only three randomised, controlled, (double) blind studies have been published [5, 44, 45] on this topic. One study [44] from Italy was designed to evaluate immunogenicity of an acellular pertussis vaccine given at birth. Forty-five infants fulfilled the inclusion criteria (gestational age between 37 and 42 weeks, an appropriate weight for their gestational age, and no major illness) and were immunised with a three-component acellular pertussis vaccine — combined with diphtheria and tetanus toxoids — on the fourth day of life (Pa group). The control group of 46 infants did not receive this dose (control group). Both groups were given further DTPa vaccinations at 3, 5, and 11 months of life, according to the current Italian vaccination schedule. At three months of age, before any further dose, approximately 10% of the infants vaccinated at birth reached a fourfold increment in antibody levels against pertussis toxin (PT), filamentous hemagglutinin (FHA), and pertactin (PRN), compared with pre-vaccination titres. Nevertheless, no statistically significant differences in the antibodies geometric mean titres GMT were observed for the three antigens between groups. One month after the dose received at five months of age (dose three for the infants vaccinated at birth; dose two for the control group), the percentage of infants with at least a fourfold increase of pre-vaccination anti-PT, anti-FHA, and anti-PRN antibodies titres was significantly higher in those vaccinated at birth compared with the control group infants (first dose of vaccine at three months of age). Although anti-PT GMTs were significantly higher in the Pa group than in the control group after the dose given at five months, the opposite was found one month after the last dose given at 11 months of age.

In a second study [5] from Germany, 121 healthy neonates were randomly assigned to receive either a single dose of an investigational stand-alone three-component Pa vaccine (Pa group) or hepatitis B vaccine (controls) between two and five days of age, followed by primary series with DTPa-HBV-IPV/Hib given at 2, 4 and 6 months of age. There was no evidence of hyporesponsiveness to the pertussis antigens at any time point in infants who received Pa at birth compared with control infants. One month after the first dose of hexavalent vaccine, infants vaccinated with Pa at birth had significantly higher antibody responses to the three pertussis antigens compared with controls. At seven months of age, GMTs against pertussis antigens were similar in both groups. Neonatal immunisation with a stand-alone Pa vaccine negatively interfered with Hib. Due to the four HBV vaccine doses received it was not possible to define an interference with HBV valences.

The third study [45] from the US yielded controversial results with a combined DTPa vaccine including a 5-component pertussis administered at birth concomitantly with HBV. The antibody response to PT, *fimbriae*, PRN, and diphtheria antigen was significantly lower after the primary series. A persistent reduced response to pertussis antigens after a booster dose was achieved.

1.8 Safety of DTP/DTPa administered neonatally

DTPw and DTPa vaccines administered in clinical trials very early in life were generally well tolerated.

After DTPw vaccination very few adverse events were noted post injections: 8% develop cysts related to adsorbed pertussis vaccine [37]; 1% sterile abscesses [37]; 5% local reactions [20]; 3% moderate or marked febrile reactions without convulsions [18]. Di Sant'Agnese [10] confirmed that systemic reactions (fever 38.5–40°C) were more frequent in older vaccinees compared with the youngest and less frequent after the first dose. In addition, when whole-cell pertussis vaccine was administered neonatally, much less local and systemic reaction occurred when compared with administration at older ages [39]. Neonatal immunisation is not prone to increased systemic or local reactions when further doses are given, compared with infants starting immunisation at two months of age [40].

Regarding neonatal DTPa vaccination, either no significant difference in adverse events rates compared with HB vaccine [5] or no side effects were observed [44].

1.9 Conclusions

- Vaccination of newborns against pertussis is a critical point for their individual protection. The factors of major importance regarding neonatal immunisation are: the physiologic maturity of antibody-producing mechanisms, although they are only part of immunity; the potency of antigen given; the age at first dose; the number and spacing of doses; and the adverse events risk.
- Adverse events, especially systemic reactions, appear to be rare in newborns and do not seem to increase with the subsequent doses of the primary series. Local reactions are noted with an equal frequency compared with a later start of vaccination.
- Age appears to have an impact on the serologic response to immunisation. As infants grow older, the immune system matures and transmitted maternal antibodies disappear. This leads to the usual postponing of the start of the primary series at least until 6–8 weeks of age or even up to three month of age, although DTP vaccines given at birth or in the first week of age show some antibody response.
- The potency of antigenic stimulus is reflected by the strength of the response and may overcome both the immune immaturity and the transmitted maternal antibody. Tetanus and diphtheria toxoids give good results in early vaccination after birth. Some negative interference with transmitted maternal antibody is observed with diphtheria antigen although it becomes negligible after the booster dose.
- The potency of pertussis antigens has a positive direct impact on the strength of immune response (e.g. alum-precipitated whole-cell vaccines were more potent than saline vaccines; within the saline vaccines, 80 x 10^9 cells were more potent than the 40 x 10^9 cells). The concept of 'immune tolerance' has to be reviewed in regard to the results of recent studies in newborns with acellular pertussis vaccines, either combined or stand-alone.
- From a practical point of view, in case of a first dose given before six weeks of age, the level of immune immaturity may be such that for some non-responding newborns the immune response will rely only on the two further doses — with the risk of lower response. Thus, it remains uncertain whether the rather poor immediate results of immunisation in very young infants afford any immediate, short-term protection in the new-born period. Further research is needed, for instance to determine whether increasing the antigen stimulus potency might lead to better results.
- Finally, based on the available data, there is still not enough evidence to support initiation of immunisation schedule in newborns especially for pertussis. There is a need for studies with stronger vaccine antigens in the youngest infants, both full term and premature.

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2. Priming schedule and early booster

2.1 Introduction

The current schedules for vaccination below 24 months of age in Europe with acellular pertussis-containing vaccines can be divided into three major groups for the priming doses (variants of two-doses scheme at 3, 5 months of age and variants of three-doses schemes at 2, 3, 4 months or 2, 4, 6 months).

A booster dose is given in all countries before the age of 24 months except in the UK and Ireland. As noted above, the various immunisation schedules in Europe for DTPa vaccines evolved from experiences gained from immunisation with whole-cell pertussis-containing DTP vaccines (2, 3, 4 and 2, 4, 6 months schedules), where the need for three doses was governed by the Pw component that needed to be administered in three doses. The 3, 5 months schedule, on the other hand, evolved from the vaccination schedule for DT vaccine, where this priming schedule was introduced first in Italy in 1981 and in Sweden in 1986. The schedule was kept when Pa vaccine was added to DT.

2.2 Acellular *versus* whole-cell pertussis vaccine-containing vaccines

The majority of European countries have now switched to, or are in the process of introducing, DTPa vaccine (mostly in penta- and hexa-valent combinations). For tetanus, the minimal amount required in priming vaccines is at least 40 IU, without an upper limit. With whole cell combinations, hundreds if not thousands of IU were measured in animal models, well above the amount needed for efficient priming. For diphtheria, on the other hand, the adjuvant effect of whole-cell vaccine was important in order to easily exceed the minimal requirement of at least 30 IU. Thus, with the strong adjuvant effect of whole-cell pertussis vaccine having been removed, the immunogenicity of the diphtheria toxoid component of DTPa vaccines needs to be particularly carefully monitored.

Negative interference of acellular vaccine with the response to DT was documented with a mono-component acellular pertussis vaccine (40 µg of pertussis toxoid), when the same lot of vaccines and of aluminium adjuvant in the DT and the DTPa vaccine were used [1]. The decrease in response to D and T was highly significant after priming at three and five months of age, after the booster dose (at 12 months of age) and at three years of age. Since antibody concentrations to T are always higher than to D, no child had fallen below the minimal protective level of 0.01 IU/ml to tetanus in either group, but in terms of diphtheria — 2% (in the DT group) and 4% (in the DTPa group) — they had done so at three years of age. A study with doubled PT and FHA content in a 5-component pertussis vaccine showed a decrease to half of the GMT to diphtheria toxoid in the high dose vaccine, but no effect on the response to the tetanus toxoid [2].

In summary, when extrapolating results from studies with whole-cell pertussis vaccine-containing DTP vaccines, it has to be kept in mind that both the disappearance of the strong adjuvant effect of whole-cell vaccine and the direct interference of Pa has affected the other two components, particularly the weaker immunogenicity of the diphtheria toxoid.

2.3 Interference with DTPa by other components of combined vaccines

Most European countries using DTPa vaccine do so in penta- or hexavalent combinations. For this reason, conclusions drawn from studies with DTPa vaccines, e.g. efficacy trials of the pertussis component and the duration of protection, will have to be viewed in the light of the possibility of negative interference with the additional antigens.

The enhanced inactivated polio vaccine (eIPV) has been shown to have the most profound effect on the immunogenicity of D, T and Pa. The effect has been noted for a majority of combined vaccines but the most elegant study was conducted by Lagos et al. [3] with five trial groups: DTPa vaccine (plus oral polio vaccine), DTPa and IPV given in different limbs, combined DTPa-eIPV, DTPa-eIPV and *Haemophilus influenzae* type b vaccine given in different limbs, and DTPa-IPV used to reconstitute Hib. Concomitant but separate administration of eIPV had no effect on the response to PT and FHA in this two-component Pa vaccine. Combining DTPa with eIPV resulted in a highly significant decrease of the immune response to PT and a significant decrease of the response to FHA. Adding Hib vaccine did not decrease the response further. In addition, mixing DTPa with eIPV

resulted in a highly significant decrease of the response to diphtheria, which was not further decreased by Hib. The decrease in the response to tetanus was also highly significant and decreased further when the tetanus-conjugated Hib was given concomitantly and even more so when Hib was given in the same vaccine.

The eIPV represents a large quantity of protein, and negative interference was thus not unexpected. The strong negative effect of eIPV was already documented on the whole-cell pertussis vaccine from Connaught [4, 5]. When eIPV was given concomitantly but in separate limbs, a significant decrease of the antibody responses to PT, FHA, pertactin and *fimbriae* were noted. In the case of the response to PT it was decreased to 1/6 of the GMT, as compared to DTPw being administered with OPV. The response was completely abrogated when the whole-cell DPT was given mixed with eIPV: none of the children in the group given the mixed DTw-IPV showed a seroconversion to PT or FHA.

Vaccine against *Haemophilus influenzae* type b (Hib) has had a less consistent effect on DTPa vaccines and the effect varied with the carrier protein. With the most widely used tetanus as carrier, Eskola et al. [6] saw some decrease of the response to tetanus and FHA. Also Schmitt et al. [7] reported a decrease in the response to T, PT, FHA and pertactin when Hib was reconstituted in DTPa vaccine. Richie et al. [8] reported a highly significant decrease in the responses D, T, PT. In another study, Hoppenbrouwers et al. [9] found a significant decrease of the response to PT but neither to FHA nor D or T. Knutsson et al. [10] reported a highly significant increase in the response to T and a significant decrease in the response to D. Pichichero et al. [11], on the other hand, found an increase in the response to D and FHA but a decrease in the response to T.

In summary, DTPa vaccine in further combinations has become less immunogenic due to negative interference, mostly from eIPV. The clinical relevance of the lower antibody response is not completely ascertained, as correlate of protection for Pa vaccines is not clear.

Tetra-, penta- and hexavalent combined vaccines might necessitate a booster dose sooner than can be deduced from studies with DTPa alone. If no booster dose is given then clinical efficacy failures could be more likely to occur sooner with those combined vaccines than with DTPa and concomitant but separate administration of monovalent vaccines.

2.4 Comparison of European priming schedules

Three different priming schedules are used in Europe (Table 1): three doses at 2, 3 and 4 months of age, three doses at 2, 4, 6 months of age, and two doses at 3 and 5 months of age. All three of them have been shown to accomplish their primary goal, i.e. to induce immunological memory against diphtheria, tetanus and pertussis in 100% of vaccinated infants. Therefore, the answer to the question on the minimum number of doses needed for priming is ‘two doses’. However, in addition to inducing an immunological memory, the priming doses also induce an antibody response that reinforces protection. The level of this additional protection will vary by the number of doses given and by the interval between the doses.

Immunological memory, i.e. the ability to mount a B and T cell response upon exposure, represents a main component of protection against disease. For this reason, the age at which the different schedules induce an immunological memory would be the most relevant basis for comparison. For robust protection, presence of antibody is also of importance. When relying on immunological memory alone, expanding the pool of memory cells and mounting a measurable antibody response takes three to five days. With large infective doses, as in household exposures, the incubation period of pertussis may be as short as three days, implying that breakthrough cases can occur [12]. On the other hand, these cases of pertussis will be mild since the disease will be mitigated by the immune response.

From the perspective of the earliest possible priming, the 2, 3, 4 months schedule would seem to give the earliest priming and therefore the best protection. This conclusion might be modified if it were shown that the two first doses of the 2, 4, 6 months schedule also induce an immunological memory (thus inducing a long-term immune response), but so far studies are lacking. If these two doses do not induce an immunological memory in infants, or not in all infants — and premature babies represent a group that would be immunologically very immature — then the 2, 4, 6 months schedule is the least apt to fulfil the important criteria of inducing an early immunological memory. The 3, 5 months schedule would then be an intermediate.

From the point of view of antibody responses, a comparison across studies indicates that the 2, 3, 4 months and the 3, 5 months schedules seem to induce about the same response rates and antibody concentrations, although direct comparisons between the schedules are lacking. On the other hand, both have repeatedly been compared in studies to the 2, 4, 6 months schedule, which is used in the US and some European countries. This schedule shows both lower antibody response rates and concentrations than the 2, 4, 6 months schedule. However, the higher response rates and concentrations of the 2, 4, 6 months schedule are reached during the second half of the first year of life, when pertussis is less life-threatening than in the first six months. Also from this aspect, the 2, 3,

4 months schedule seems to provide the earliest, most robust protection, with the 3, 5 months schedule as an intermediate.

The only caveat with the 2, 3, 4 months schedule is the possibility of interference by maternal antibody. The high dosage of tetanus toxoid in priming vaccines renders it unlikely that significant interference would occur. Diphtheria toxoid, on the other hand, has a much lower concentration and has further been weakened by interference in combined vaccines. Thus, it is important that the number of booster doses during adolescence and adulthood, as well as the timing of the booster doses in relation to childbearing age, is taken into account. The same applies to pertussis antigens in case such combined vaccines would be given in the national vaccination programme or recommended in a 'cocooning strategy'.

In summary, all three schedules induce an immunological memory, the most important component of protection against pertussis (and tetanus-diphtheria). With the 2, 3, 4 months schedule, protection will be achieved one month earlier then with the 3, 5 months schedule but at the price of an additional dose. The merits of the 2, 4, 6 months schedule are more difficult to ascertain due to a lack of studies showing possible priming after the two first doses at two and four months of age. If such priming does not occur in 100% of infants then the 2, 4, 6 months schedule would seem to fulfil the need for early protection against pertussis less well.

2.5 Additional considerations

From the above discussion, it seems clear that all three primary schedules used in Europe accomplish the goal of inducing priming. Also, the European experience shows that priming can be accomplished by two doses given at three and five months. There is, however, the remaining problem that with current knowledge the first dose in a two-dose priming schedule can be given no earlier than at three months of age, resulting in a one-month loss of protection against pertussis, as compared to the accelerated three-dose priming schedule. The schedule that would best combine a need for early protection with the least number of priming doses would be a two-dose vaccination at two and four months of age, followed by an early booster at 10 to 11 months of age.

Starting vaccination at two months of age instead of three months of age in the two-dose priming schedule might not seem like much of a difference but could make a major difference in the maturity of an infants' immune system. Introducing a two- and four-months priming instead of a three- and five-months priming cannot be done without clinical trials that show that that all infants were primed under this new schedule. Such trials represent a major need in the paediatric field since they could improve protection and decrease costs.

The diversity of the European schedules has also other implications since all new vaccines and concomitant administrations will have to be tested in all three variants. The costs for all these trials will eventually be paid by the end-users, as the manufacturers will recover them through higher vaccine prices. Last, but not least, the diversity and the need to test all possible combinations and concomitant administrations lead to tests in many infants, which could be viewed as unnecessary testing in children.

In summary, even if EU Member States wish to keep their own variants of the priming schedule, a 2, 4 and 10–11 months schedule could be a possible model for vaccine trials. Since priming at two and four months would certainly represent the least robust variant, any vaccine or concomitant administration that works (e.g. assures immunologic priming and a non-inferior level of antibodies/seroprotection rate) in this schedule will also work in the other three variants.

2.6 Booster dose after the priming doses

From the previous discussion it is clear that one of the main functions of the priming doses is to induce an immunological memory. A measurable antibody response will not develop in all children after the priming doses and the level of the antibody responses may be low. The booster dose will 1) induce measurable antibody responses in 100% of children; and 2) result in much higher antibody levels than after the priming doses.

No booster dose is given in the WHO's current EPI programme, in the UK and in Ireland, but in these two countries a booster dose is given at school entry, from three years and four months to five years of age. All other vaccination schedules include a booster dose prior to 18 months of age, both in Europe and in the US. It may be relevant to review the experiences made with vaccination programmes that do not include a booster dose in the primary series.

The EPI programme has been very successful in reducing notified pertussis in developing countries (Figure 1). It may thus seem that a booster dose might not be needed. However, pertussis in a vaccinated population is atypical, with protracted cough as a cardinal symptom. Bacteria are excreted in low numbers, rendering culture more difficult than in unvaccinated individuals. Pertussis in vaccinated individuals is more readily diagnosed by serology, as noted already in the combined Scottish study [13]. PCR will represent a valuable complement to culture. All

three diagnostic methods (culture, PCR and serology) are needed in order to obtain optimal diagnostic sensitivity in the diagnosis of the disease. In many developing countries, culture for *Bordetella pertussis* may not be available; even fewer have access to serology and PCR. It is therefore likely that the decrease in the WHO notifications of disease represents a decrease in mortality rather than morbidity.

The Swedish decision to interrupt pertussis vaccination in 1979 was based more on a weakened vaccine than on a fear of severe side effects to the whole-cell vaccine. At the time, Sweden had a vaccination programme of three priming doses at 3, 4 and 5 months of age, but no booster dose(s) at all. The vaccine undoubtedly had lost immunogenicity in the early 1970s, but children who had been vaccinated and still contracted the disease had a secondary antibody response by ELISA. The vaccine had thus been able to induce priming. The situation and measures would most probably have been different if booster doses had been given.

The reasons for not giving any booster doses in Sweden — and for not administering early booster doses in some other European countries — probably emanate from observations of long-term protection after only giving priming doses in efficacy trials. The first such observation of two years of protection with Pw vaccines comes from the British Medical Research trial [14] and was later repeated for a five-year period by Rabo in Sweden [15]. Similar reports of long-term protection for DTPa after only the priming doses of vaccine come from trials conducted in Italy and Sweden [16, 17].

The epidemiological situation during these trials was, however, quite unique and is not representative of the need for booster doses once general vaccination is introduced. The vaccinated trial children live among the remaining child population that is unvaccinated and thus represent a source of constant natural boosters for the trial cohort. In addition, if they do develop pertussis, the disease is likely to be mild and may not be recognised and diagnosed. Once general vaccination is introduced, the source of natural boosters wanes and needs to be replaced by vaccine boosters. The validity of this assumption has been shown in the Swedish long-term follow-up of Pa vaccines [17]. Despite the fact that the Swedish schedule of 3, 5 and 12 months contains an early booster dose, waning immunity in the first cohorts of general DTPa vaccination led to pertussis being diagnosed as early as age five to six. As a consequence, a further DTPa booster dose at school-entry was introduced, a need that will be discussed in answer to the third question, i.e. timing of booster doses after 24 months of age.

The timing of a booster dose for DTPa has to consider the weaker immunogenicity of combined vaccines. Also, antibody responses to the priming doses wane over time, irrespective of the priming schedule. Therefore there seems to be no scientific reason for delaying the booster, which will give a more robust protection than provided by the priming doses alone. A booster dose given at the earliest opportunity between 12 and 18 months of age would therefore seem optimal.

The need for a booster dose to *Haemophilus influenzae* has recently been shown in the UK with the re-emergence of *Haemophilus influenzae* meningitis among children between one and four years of age. The failure led to the introduction of a booster dose against Hib in the national vaccination programme. An investigation into the causes indicated a reduced immunogenicity of Hib component of the DTPa/Hib vaccine [18, 19], waning of the catch-up campaign with a loss of herd immunity [20], one-month interval between doses [21], prematurity [22], and the lack of a booster dose [23]. The same number of doses, the same type of combined vaccine and starting the programme at the same time, but in a 3, 5, 12 months schedule, have not led to any comparable increase of Hib in other European countries. The basic problem seemed thus to have been the lack of a booster dose.

In summary, there is some evidence from current and past vaccination programmes about the need for a DTPa booster dose before 24 months. On the other hand, with the waning of antibody over time and the weaker immunogenicity of the combined vaccines, it would seem preferable to propose a DTPa booster dose as early as possible in the second year of life, irrespective of the type of priming schedule used.

2.7 Conclusions

- The main objective of the DTP primary series is to induce early protection by priming of the immunological memory in all vaccinated infants.
- An early start of the immunisation schedule is particularly important for providing protection against pertussis. Starting at three months of age, with two doses given at eight-week intervals, achieves the goal of priming.
- All three primary series schedules (at 2, 3, 4; 2, 4, 6; and 3, 5 months) used in the EU induce priming.
- Starting vaccination earlier would provide earlier protection by priming. A three-dose priming schedule at 2, 3, 4 months of age induces priming against pertussis one month earlier than the 3, 5 months schedule, but at the price of an additional dose.
- A priming schedule at 2, 4 months may achieve the goal of priming all infants at an earlier age with only two doses. Since data on this schedule are lacking, studies to investigate this possibility are needed.
- Regardless of the used priming schedule, antibody levels will wane within a few months.

- A booster dose induces a strong antibody immune response in all children previously primed, thereby providing more robust protection against the disease than immunological memory alone.
- Thus, one booster dose should be administered to infants or toddlers. In order to minimise the period of under-protection, an early booster before 15 months of age is needed after a two-dose primary series. After a three-dose primary series, the benefits of a booster dose between 12 and 18 months are based on a solid rationale.
- Active surveillance of pertussis is needed in all European countries in order to assess the specific epidemiological situation.

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3 Booster doses between 24 months and 18 years of age

3.1 Introduction

European vaccination schedules all call for at least one booster dose and up to four doses between the ages of two and 18 years (Table 2). Such a variation creates problems in mobility since parents and physicians will have to face difficult decisions on how to adopt or supplement vaccinations when families move from one European country to another. The wide variation in the number of doses implies also that some programmes might be less suitable, either by causing insufficient protection or over-immunisation, which may cause unnecessary side effects and/or may interfere with the antibody response of infants if given close to childbearing age.

3.2 Need for a pre-school, early school-age booster

Tetanus

Cases of tetanus continue to occur in Europe but mainly in unvaccinated older individuals, as illustrated by a review of the epidemiology of tetanus in Italy [1]. The number of doses needed for long-term protection has been an issue of debate, with proposals ranging from four doses claimed as sufficient for life-long protection [2] to recommended booster doses every 10 years, as promoted in most European countries. Due to the robustness of the tetanus toxoid antigen and the quality of immune response achieved by priming (reinforced by the early second-year booster dose) one additional booster dose would probably be sufficient before the end of adolescence. Since vaccination programmes are based on combined vaccines, the need for the weaker immunogens (i.e. the diphtheria and pertussis valences) govern the need and timing of the booster doses — the reason why two tetanus boosters between two and 18 years are given in most European countries.

Diphtheria

The residual circulation of the bacteria in Europe has generated cases due to the weakened immunity in the general population [3, 4]. This is partly due to: 1) insufficient coverage in adolescents and adults; 2) weaker dosage and immunogenicity of diphtheria toxoid than that of tetanus toxoid (as discussed previously); and 3) further weakening by negative interference in hexa-, penta-, and tetravalent combined DTPa based-vaccines. A large sero-survey of immunity to diphtheria across Europe revealed low antibody levels in school children in countries that did not give a pre-school booster dose [5], despite differences in sample collection and applied methods. It does thus seem that a pre-school or early-school age booster dose, e.g. at five or six years of age, is needed. Also, it seems reasonable to give a further booster dose during adolescence to achieve individual protection as well as elimination of this vaccine-preventable disease in Europe. For safety and tolerance reason, ‘d’ valence in the combined vaccines is preferable for this older age group.

Studies have addressed the difference in responses to a paediatric dose of diphtheria toxoid (D) and a reduced dosage (d). An Italian study compared DT vaccine and dT vaccine in a booster dose at six years of age, finding geometric mean titres (GMT) of diphtheria antitoxin twice as high after DT than after dT, while the side effects were comparable [6]. Another study compared a DTPa-IPV vaccine to a dTpa vaccine and a dTpa-IPV vaccine [7]. Again, the response in terms of GMT was twice as high for the paediatric tetravalent vaccine containing a full dose of D as compared to the tetravalent combination containing the reduced dose of diphtheria toxoid (d). Side effects were the same or lower for the full-dose tetravalent combination vaccine. It thus seems that a full dose diphtheria toxoid will induce a higher response in 4–6-year-olds than a reduced dose without increasing the rate of side effects, provided that a tetravalent combination is used and that sufficient spacing between the booster dose after the priming doses and the second booster is maintained.

Pertussis

In the US and several other European countries, a Pa booster with trivalent or tetravalent vaccine has been introduced at school-entry, mainly based on an expected need for reinforcement of immunity against pertussis. Scientific evidence for a need for such a booster has now been presented by the Pertussis Surveillance Project in Sweden, the follow-up of Pa vaccine effectiveness, a part of the commitment that manufacturers of Pa vaccine were required to make for licensure in the EU [8]. The survey has confirmed the protective effectiveness of Pa vaccines during the nine-year period after the introduction of DTPa-containing vaccines in Sweden, with a

reported incidence of laboratory-confirmed global pertussis incidence 80% to 90% lower than before the reintroduction of pertussis immunisation. The reduction of incidence in the unvaccinated infants by indirect protection is less marked than in the fully vaccinated older age groups. In the 3–5-months age group, i.e. after the first dose, the incidence also remains high, although hospitalisation due to pertussis has been significantly reduced.

The Pertussis Surveillance Project data indicate that the Pa vaccines appear to be effective from the second dose administered at five months of age, and a third booster dose of vaccine at 12 months of age further reduces disease incidence. The reduction in disease was more pronounced during the first year following vaccination, but seemed to remain fairly stable for four to five years following the completion of the full 3, 5, 11–12 months vaccination schedule. As a consequence of these findings, the Swedish vaccination schedule was revised to replace the previously given DT booster at 10 years of age by a DTPa booster in 2006. After a more complete revision for 2007, the Swedish vaccination schedule recommended a pre-school booster at five to six years of age with tetravalent vaccine and a dTpa booster at 15 to 16 years of age.

Further epidemiological data are needed in order to optimise the timing for the second booster in countries with a three-dose primary schedule and a booster in the second year of life.

Side effects of DTPa vaccines have been shown to increase with each dose, while the pattern was the opposite for DTPw vaccines [9, 10]. It was also noted early on that children primed with Pa vaccine have a higher rate of local side effects to a Pa booster than children primed with Pw-containing vaccines [11]. Increased side effects at four years of age, mainly large local reactions, were noted in an American study with a DTPa vaccine [9]. A large Italian study in 4–6-year-olds compared the reactogenicity of two DTPa vaccines to that of DT vaccine and found a higher reactogenicity with DTPa vaccine but no difference for large local reactions > 5 cm [12]. Good booster responses to all antigens were noted in the subset of children sampled.

A French study with a tetravalent combination vaccine for the booster dose showed a good immune response to all antigens and a favourable safety profile [13]. Similarly favourable results were obtained in Swedish and Italian children boostered with another tetravalent combined vaccine [14]. The difference between the reactogenicity in the US study and the European studies with lower rates of local side effects could be due to a shorter period between the last priming dose and the booster in the US study, and perhaps also to the fact that this study used DTPa vaccines while the other used tetravalent combinations, where the interference between components leads not only to a decrease in immunogenicity but also of reactogenicity [7, 15].

In summary, there seems to be a need for a second booster dose at four to six years of age in order to sustain immunity to diphtheria. To ensure a solid protection against pertussis during childhood, a second pertussis booster dose is important. Its timing from four to six years of age up to 11 to 13 years relies in particular on taking into account the quality of national surveillance systems, the epidemiological background and past history of vaccination programmes in the countries. Earlier pertussis booster doses could result in increased side effects while a later booster increases the risk of pertussis in school-aged children, also representing a source of infection for the youngest infants. Full dose diphtheria toxoid results in higher antitoxin levels than reduced-dose vaccines without higher rate of side effects, for which reason full-dose paediatric tetravalent vaccines seem to be preferable to reduced-dose vaccines.

3.3 Need for further booster doses

Ad hoc studies and findings from various surveillance systems in Europe show that the epidemiology of pertussis has changed over the past two decades, with the highest increase of cases seen among adolescents and adults in countries with high vaccine-coverage rates in younger children [16–18]. The reasons for this change are not entirely clear but part of the increase could be due to higher awareness of pertussis as an atypical disease in this age group combined with better diagnostic methods. A further explanation could be the previous use of whole-cell vaccine that was considered contraindicated for older children and adults, with a consequent accumulation of a large pool of susceptible individuals in these age groups [19]. This shift in age groups has led to outbreaks in schools and adolescents who now represent an important source of pertussis infection to the youngest, most vulnerable infants [20, 21].

dTpa vaccine trials

New combined vaccines with reduced content of diphtheria toxoid (d) and pertussis component (pa) have been developed for vaccination of adolescents and adults [22–26]. These vaccines do not seem to induce large local reactions, irrespective of the type of vaccine that has been given for the previous doses [27]. In a uniquely large trial of adolescent vaccination it has been shown that dTpa vaccines are protective [28]. Although the confidence limits were wide, the vaccination of adolescents seems to result in a point estimate of vaccine efficacy that was in the same range as seen in Pa vaccine trials in infants [29]. The study also allowed for a conservative estimate of disease incidence in this age group, indicating much higher rates than could be seen in notifications.

Vaccination recommendations for adolescents

The recommendation to introduce a pertussis booster dose at adolescence is supported by most experts and accepted in most industrialised countries. Vaccination with dTpa vaccines is recommended [30–33] in several countries' national immunisation programmes, e.g. in Canada and the US. Many European countries (e.g. Austria, Finland, Germany, Iceland, Ireland, Italy, Luxembourg, and Sweden) also recommend the vaccination of adolescents with dTpa vaccine in their national programmes. The new Swedish vaccination schedule, implemented in 2007, will include such a booster dose for the cohorts that will have received a booster at 5–6 years of age. Catch-up strategies in adolescents are also under consideration in some EU countries.

Type of vaccine and interval between doses for adolescent vaccination

In countries that have implemented adolescent vaccination in their national programmes, the vaccine of choice seems to be a dTpa vaccine rather than a full-dose vaccine. The choice of dTpa vaccines seems reasonable if a previous booster dose with DTPa was given before adolescence. The age for recommended vaccination in the US was at first 11–12 years but then was extended to 18 years of age for adolescents who have only received Td vaccine as a booster. A recent study from Canada implies that the reduced dTpa vaccine can be given as early as 18 months after a previous dose of either DT/Td vaccination without increase of side effects [34]. The purpose of the Canadian study was to encourage catch-up vaccination with dTpa vaccine in children and adolescents who had already received a dose of Td vaccine in previous years, especially in the context of pertussis outbreaks, a situation somewhat different from the planning of national immunisation programmes.

At present, there are still no certain data for the duration of immunity induced by DTPa vaccination at 4–6 years of age. As a general practice, most European countries' recommendations call for revaccination every 10 years with Td vaccine; in some countries Td vaccine was recently replaced by dTpa vaccine (at least once in adulthood). A first step toward adult vaccination is the recommendation of one dTpa booster dose given to healthcare workers. Some European countries use the cocooning strategy. One aspect discussed in this manuscript is the risk of interference by maternal antibody to the infants' immunisation regime, in particular with responses to the diphtheria component, but perhaps also with the pertussis component(s). This risk is not much discussed in the recommendation to vaccinate up to 18 years of age (i.e. childbearing age), and no studies are available on the levels of maternal antibody induced by the repeated booster doses.

3.4 Conclusions

- Booster vaccinations after 24 months of age are needed.
- As indicated by the Pertussis Surveillance Project in Sweden, one dose of DTPa vaccine at pre-school or early school age, i.e. at 4–6 years of age, seems to be needed.
- Epidemiological data from other countries utilising different priming schedules might indicate that the second booster dose could be postponed.
- A further booster dose with a reduced diphtheria and pertussis component (dTpa) vaccine later on (from 11–13 up to 16–18 years of age) would be needed to maintain protection in adolescents and thereby also ensure indirect protection to infants.
- Catch-up vaccinations against pertussis are needed but are hampered by a lack of monovalent pertussis vaccines. Instead, dTpa vaccines should replace Td vaccines in national adolescent vaccination schedules.
- Pertussis vaccination might probably be needed also for adults to maintain herd immunity and for protection of the youngest infants.

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Annex

Synopsis. DTP vaccines studies. Summary table of evidence

Authors	Valence	Age Schedule	Methods	Results	Remarks
Sauer L Am J Pathol 1941	Pertussis alone	60 10^9 cells doses: 1cc / Wk / 6 WK Deep SC or IM.	> 1000 children/cohort	Illness Unvaccinated children: 14.84%; Children injected < 3m of age: 8.19% ('cradle'); children vaccinated after 6m of age: 2.48%. ('Edmonston' private clinics); vaccinated > 7m of age: 1.44%	Adverse events: local and systemic reactions to vaccine were negligible.
Sako W J Am Med Assoc 1945	Pertussis Alum-precipitated	Start at 2m 3 doses 1-month interval	3793 infants; 1834 received a total dose 40 10^9 cells.	Agglutinins > 1:320 50.5% post Dose 3 plateau up to 36 ms 308 familial exposures during a period of 27 ms. Secondary familial attack rate: 18.9% in 159 exposed vaccinated infants. 85.2% in 149 unvaccinated infants.	Statistically significant
Waddell W J Pediatr 1946	Pertussis alone	40 10^9 cells/cc Group 1 Start at 1 week (0.5cc) followed by 1 cc at 1m and at 2m with booster at 6–7m of age. Group 2 Same dose and interval starting at 2m of age with booster at 6–7m of age. Deep SC	129 infants in group 1 with booster dose in 50 infants; 44 infants in group 2.	Agglutinins Group 1 After primary series: 38%, 12%, 7%, and 13% positive in a dilution of 1:3.200, 1:1.600, 1:800, and 1:400, respectively. After booster: 74% and 24% positive in a dilution of 1:3.200 and ≥1:400, respectively. Group 2 After booster dose 84% and 14% positive in a dilution of 1:3.200 and ≥1:400, respectively.	No transfer of maternal agglutinins in 6 of 22 unvaccinated infants born of mothers with a previous attack of pertussis.
Adams J Am J Dis Child 1947	Pertussis alone Cutter®	40 10^9 cells/cc Control: mothers and infants not immunised. Group 1 Infants given 3 weekly shots within the first month of life (0,5, 1 and 1 cc). Group 2 Infants given 3 monthly shots prior to the fourth month of life (42% completed series before third month of life) (0,5, 1 and 1 cc). Group 3 Mothers immunised during last trimester of pregnancy with 3 doses (100 10^9). Titre of the infant's serum determined at intervals up to six months.	Control: 7 infants. Group 1 21 infants. Group 2 19 infants. Group 3 16 mothers.	Agglutinins Control Nearly all determinations were negative when followed at monthly intervals (last determination at 12m of age). Group 1 28% failed to show any rise in titre (followed at monthly intervals) 71% (15 subjects) showed definite rises in titre with 5 of 9 subjects with good titres at 1m of age. Group 2 26% failed to show any rise in titre followed at monthly intervals The remainder showed titres but at a much slower rate but more permanent rise than group 1. Group 3 Mean titre of the mothers at term: 1:320. Mean titre on cord blood: 1:160. 3 infants (19%) with no agglutination titre. Mean titre at 2m: 1:80.	

Cooke J J Pediatr 1948	DT Alhydrox Cutter®	2 doses 2m interval	284 children 1–14m	Tetanus threshold 0.01 unit/ml. Pre-vac: no antitoxin in blood. Post dose 2: 188 tested 181/188 > 1 unit/ml < 1% (2/188): 0.01–0.03 5/188: 0.03–1 children < 6m (n=127) >95% (122/127) > 1 unit/ml Diphtheria Pre-vac: 284 tested. 80% (228/284) < 0.03 unit/ml > 0.03 unit/ml: < 3m: 1/3 ; 3–6m: 1/5 ; > 6m: 4% Post vac (191 tested) protective titre > 0.1 unit/ml < 3m (n=75) 66.6% n=52* 82.7% 3-6m (n=55) 89.3% n=46* 87% 6-14m (n=60) 95% n=60* 95% *: 158 infants with no passive immunity Post vac: 33 infants with passive immunity & titre > 0.1 < 3m (n=23): 30.4% 3-6m (n=10): 90%	Transplacental transmission of antibody Ab Tetanus: no Diphtheria: 20% 1-3m of age: 33%
Miller J Pediatrics 1949	Pertussis Cutter Saline-suspended vaccine Alum-precipitated vaccine	0–4 m 5D, 1m, 2m, 6m (4 doses) 4–8W, 3m, 4m 4–8W, 3m, 4m	Agglutinins 108 pairs maternal sera/cord 41 infants total dose: 50 10^9 cells 145 infants total dose: 100 10^9 cells 134 infants total dose: 80 10^9 cells 151 infants total dose: 40 10^9 cells	maternal sera + , n=54 (half) cord sera: 34 offspring/54 women. Agglutinins > 1:320 4/26 (15.4%) 29/115 (25.2%) cord blood+=cord blood – 48.5% 36–40% of infants in following 6m older age group, > 60% of infants maintained high titres for 4 yrs 62.6% 63% of infants maintained high titres/1 yr	Transplacental transmission of antibody Ab 63 % of infants from sero + mothers. Adverse events 11 (3 post 1st inj, 4 post 2nd inj & 3 post 3rd inj) moderate or marked febrile reactions. No convulsions.

di Sant' Agnese P Amer J Pub Health 1950 Pediatrics 1949	DTP Alum-precipitated	1W, 5W, 9W Booster at 6m or 12m of age	198 infants 20 109/dose	Pertussis agglutinins > 1:400 pre-vac: 98% (144 tested) no agglutinins post Dose-3: (125 tested) 30% negative titre 54.4% titre > 1:400 26% titre > 1:600 – 1:3200 post booster (N tested ?) protective titre: no significant change/dose 3 16% negative Tetanus antitoxin 'protective' lowest titre 0.1 unit/ml pre-vac: (156 tested) 15% > 0.1 post dose 3 (128 tested) 100% titre > 0.1 unit/ml 92% > 1 unit/ml post booster ? Diphtheria antitoxin protective lowest titre 0.03 unit/ml Pre-vac (168 tested) 58.5% seropositive 12% titre > 1.0 unit/ml Post dose 3 (123 tested): 84.6% seropositive ; 20% > 1.0 unit/ml Post-booster: (N tested ?) 100% (but one) seropositive Ab raise 20–50% Duration of Ab up to 9m Tetanus: > 0.1: all > 1: 73% Diphtheria: > 0.03: 77% > 1: 'steady decline' Pertussis: > 1:400 50% High level: 'steady decline'	Transplacental transmission of antibody Ab Pertussis: 2% Tetanus: 15% Diphtheria: 58.5%

di Sant' Agnese P Pediatrics 1949 Duration of Ab	DTP Alhydrox Cutter®	Group 1 1W, 5W, 9W Group 2 3 doses 1m apart >3m, most > 6m & < 1yr	N=128 N=82 Remark 10–14m later N= 57 & 27 after booster dose N= 29 & 19 for early & older vac respectively	Tetanus 'protective' titre 0.01unit/ml 100% both groups High titre >1.0unit/ml Post primary group 1 2 1m after 92% 95% 4–6m after 83% 91% 10–14m after 73% 67% 1m post-booster 97% 95% Diphtheria antitoxin 'protective' titre 0.03 unit/ml Post primary group 1 2 1m after 85% 99% 4–6m after 70% 100% 10–14m after 77% 85% 1m post-booster 100% 100% High titre > 1.0 unit/ml Post primary group 1 2 1m after 20% 84% 4–6m after 12% 41% 10–14m after 57% 27% 1m post-booster 70% 93% Pertussis agglutinins protective titre > 1:400 Post primary group 1 2 1m after 54% 86% 4–6m after 33% 82% 10–14m after 34% 50% 1m post-booster 63% 92% high titre > 1:3200 Post primary group 1 2 1m after 17% 38% 4–6m after 9% 46% 10–14m after 0.3% 31% 1m post-booster 23% 92%	Adverse events Older vac > early vac Early vac: D1<D2=D3 (fever 38.5–40°C) local reactions early=older 5 cysts in early vac
du Pan M J Pediatr 1958	DTP Alum-precipitated Alhydrox Cutter®	3 doses, 1m interval	N children ? 3 groups 1–15D 1m of age 6–26m of age	Pertussis agglutinins Pre-vac At birth mean titre 1:40 1 & 6-26: quasi inexistent Post dose 3 At birth: 1:320 1 & 6–26: 1:500	
Gaisford W J Pediatr 1960	DTP Alum-precipitated	3 doses at 1, 5, and 9 weeks of life.	31 infants	Pertussis agglutinins Diphtheria & tetanus antitoxin levels Six weeks after the 3-dose series 90% (28/31) agglutinin response 100% and 80% responders to tetanus and diphtheria, respectively	Better diphtheria levels in infants whose cord blood titres were <0.05 units

Butler N N Eng J Med 1962	Plain P 20 10^9 cells P alum adsorbed 10 10^9 cells	1st W, 6W & 12W plain P 1ml x 3 or adsorbed P 0.5ml x 2 & 1ml x 1 booster plain P 1ml 12–15m	 N= 381 N= 352 N= 324 N= 121 N= 106 N= 108	Pertussis aqgglutinins GMT (Ungar) + GMT Post primary 69% 28 Pre-boost 54% 19 Post-boost 83% 82 Post primary 90% 131 Pre-boost 86% 76 Post-boost 95% 278	Cohort control 1/1 unvaccinated 2-yr follow-up 136 pertussis cases: 34 vaccinated (13 ads P, 21 plain P)/102 unvaccinated after home exposure unvaccinated: 24 cases/24 exp plain P: 2/13 ads P: 5/14 Adverse events 8% 'cysts' post ads P
Barrett C Pediatrics 1962	DTPpolio Trigene® Quadrigen®	D1/2, 1m, 2m, 3m (4 doses) 4W apart +booster at 9m	633 infants 1D–6m 4 groups: at birth 1–2m of age 3–4m of age 5–6m of age	Pertussis agglutinins titre > 1:25 Pre-vac newborn 47%; 1m 0%; 1–6m < 6% 2W post dose 4 median titre at birth start 1:50 1–2m 1:100 3–4m & 5–6m 1:500 Post booster (460/633 tested) median titre 1:50 post birth primary 1:100 for primary 1–2m 1:250 for primary 3–4m & 5–6m Diphtheria Pre vac 12.4% newborn > 0.1 unit/ml Post 4 doses same responses regardless of age at 1st dose Tetanus Pre-vac 5/177 newborn > 0.1 unit/ml Post 4 doses same responses regardless of age at 1st dose, even newborns	

Provenzano R N Eng J Med 1965	Pertussis (P) alone or DTP	1st dose within D1 (6–24h of life)	2 groups Group 1: n=22 3 doses Pertussis 0.5ml, 1ml, 1ml 3W interval + 2 doses DTP 0.5ml 1m interval Group 2: n=8 3 doses DTP 1m interval Boosters in 2 groups 1yr post primary series + 2yr post 1st booster	Agglutinins titre negative < 1:20 Protective > 1:160 16/22 received vaccine series post dose 3, P alone: 16/16 < 1:20 0/16 > 1:160 post dose 2 DTP: 5/16 > 1:160 6/16 < 1:20 pre-booster 1: 2/12 > 1:160 post booster 1: 7/12 > 1:160 pre-booster 2: 4/9 > 1:160 post-booster 2: 9/9 > 1:160 8/8 received 3 doses post dose 3 DTP: 3/8 > 1:160 pre-booster 1: 6/8 > 1:20 0/8 > 1:160 post-booster 1: 6/8 > 1:160 pre-booster 2: 4/7 > 1:160 post booster 2: 7/8 > 1:160	Transplacental transmission of Ab Group 1:17/22 (78%) negative Group 2: 5/8 (63%) negative Adverse events 95%: none
Baraff LJ 1984 Pediatrics	DTP adsorbed Wyeth +polio oral	Early vac 1W, 2, 4, 6m Control 2, 4 & 6m of age	91 newborns recruited: 45 early vaccine, 46 controls	FHA titres IgG & IgM IgM rise significantly in early vac /controls at 9m IgG fell at 4m, rise at 9m (early vac=control) IgG titre lower in early vac at 9m when low cord titres to LTP LPT IgG & IgM Fall at 4m; rise at 9m early vac=control Pertussis agglutinins Fall at 4m ; rise at 9m early vac = control IgG anti-LPT titres > 1:40 Control group sero cord+: low Ab titres sero cord -: high Ab titres ($p<0.05$) Early vac sero cord -: lower Ab titres/control at 9m	Transplacental transmission of Ab Cord IgG anti-LTP titres > 1:40 18/46 controls 6/18 high Adverse events No significant difference (vaccine/controls)
Lieberman J J Pediatr 1995	DT and DTP Connaught	Early vaccination: DT or HbOC at birth (72h?) and DTP plus HbOC or PRP-T at 2, 4 & 6m of age Control group: DTP and HbOC or PRP-T at 2, 4 & 6m of age	Early: 150 newborns Control: 100 infants	Anti-tetanus Ab: Tetanus antibody levels at 7m of age similar among early vaccination and controls. Anti-diphtheria Ab: Significantly lower diphtheria antibody levels at 7m of age in early vaccination.	Adverse events: DT vaccination in the newborn period not associated with any immediate adverse event nor with reactions after subsequent immunisations

Belloni C Pediatrics 2003	DTPa Acelluvax® Biocine PT: 5 mcgs FHA: 2.5 mcgs PRN: 2.5 mcgs	Group 1 Immunisation at 4D of life with acelluvax and again at 3, 5, and 11m Group 2 Immunisation at 3, 5, and 11m of age	Randomised, controlled, blind study Group 1: 45 newborns Group 2: 46 infants	Measurement of Anti-PT, anti-FHA, and Anti-PRN At 3m: Group 1: ~10% reached a 4-fold increment of pre-vaccination antibody levels to the 3 antigens. No statistically significant differences in GMTs to any antigen between both groups for the 3 antigens. At 5 m: Significantly higher % of infants with at least 4 fold/pre-vaccination levels to the 3 antigens in group 1. Antibodies (GMT) to the 3 antigens significantly higher in group 1. At 6m: No differences in % of infants with at least 4-fold increment in the two groups. No difference in Anti-PT GMTs in the 2 groups. Antibodies (GMT) to FHA and PRN significantly higher in group 1. At 12m: No differences in % of infants with at least 4-fold increment in the two groups. Anti-PT GMT significantly higher in group 2. Anti-FHA GMT significantly higher in group 1.	At birth all infants (91) had detectable antibodies to PT, FHA, and PRN. No correlation between maternal antibody levels at delivery and infant antibody levels at 3, 5, and 6 m in both groups.
Knuf M J Pediatr 2008	Pa investigational vaccine. GSK PT: 25 mcgs FHA: 25 mcgs PRN: 8 mcgs	Group Pa Immunisation at 2–5 days of life and again at 2, 4, and 6m with hexavalent vaccine Controls Immunisation at 2–5 days of life with HBV and again at 2, 4, and 6m with hexavalent vaccine.	Phase II double-blind, controlled study Group Pa: 60 newborns Group control: 61 newborns	Measurement of Anti-PT, anti-FHA, and Anti-PRN before first dose and again at 3, 5, and 7m of age. At 3m: 100%, 100%, and 98% seropositive to PT, FHA, and PRN, respectively in Pa group 46.9%, 95.9%, and 93.9% to PT, FHA, and PRN, respectively in controls. At 5 at 7 months: No differences in % seroposivity among groups. Antibody GMCs for all three antigen pertussis significantly higher at 3 months in Pa group. Significantly higher Anti-FHA antibody GMCs at all time points in infants in Pa group.	Birth dose of Pa was as well tolerated as the birth dose of HBV without statistically differences between groups. Over all doses % of subjects with adverse events were similar between groups.

Halasa N J Pediatr 2008	DTPa (Daptacel, Sanofi Pasteur) PT: 10 mcgs FHA: 5 mcgs PRN: 3 mcgs FIM 2,3: 5 mcgs	Group Pa Immunisation at 2–14 days of life and again at 2,4,6 and 17m with DTPa, at 2–14 days of life and again at 2 and 6m of life with HB, at 2, 4 and 17m of life with IPV and at 2, 4, 6 and 17m with Hib Controls Immunisation at 2, 4, 6, and 17m of life with DTPa, at 2–14 days of life and again at 2 and 6m of life with HB, at 2, 4 and 17m of life with IPV and at 2, 4, 6 and 17m with Hib	Prospective, randomised, controlled pilot study Group Pa: 25 newborns Control: 25 newborns	Venous blood samples were obtained before administration of birth dose and again at 6, 7, 17, and 18m of life to determine antibodies to PT, FHA, PRN, fimbriae 2/3, PRP, pneumococcal serotipes 6B,14 and 23F, diphtheria and tetanus. At 7m: Less GMT´s to PT, PRN, fimbriae and diphtheria in group Pa. At 18m: Less GMT´s to PT, PRN, fimbriae and FHA in group Pa.	No statistically significant differences were noted in local or systemic reactions, fever, use of concomitant medications, or serious adverse events between the experimental and control groups after any vaccine doses.

Table 1. Vaccination schedules and type of pertussis vaccine used across the European Union for children below 24 months of age (Source: VENICE and EUVAC.NET)

Country	Priming doses (months)	1st booster dose (months)
Austria	2,4,6 Pa	12–24 Pa
Belgium	2,3,4 Pa	13–18 Pa
Bulgaria	2,3,4 Pa or Pw	24 Pa or Pw
Cyprus	2–3,4–5,6–8 Pa or Pw	15–20 Pa or Pw
Czech Republic	13 weeks, 17 weeks–1 year, 21 weeks–1 year Pa	11–18 Pa
Denmark	3,5 Pa	12 Pa
Estonia	3,4.5,6 Pa	24 Pa
Finland	3,5 Pa	12 Pa
France	2,3,4 Pa	16–18 Pa
Germany	2,3,4 Pa	11–14 Pa
Greece	2,4,6 Pa	18 Pa
Hungary	2,3,4 Pa	18 Pa
Ireland	2,4,6 Pa	0
Italy	3,5 Pa	11–13 Pa
Latvia	3,4.5,6 Pa	18 Pa
Lithuania	2,4,6 Pa	18 Pa
Luxembourg	2,3,4 Pa	12 Pa
Malta	6–8 weeks, 3,4 Pa or Pw	0
Netherlands	2,3,4 Pa	11 Pa
Poland	2,3–4,5–6 Pw	16–18 Pw
Portugal	2,4,6 Pa	18 Pa
Romania	2,4,6 Pa	13–15 Pa
Slovakia	3,5, Pa	11 Pa
Slovenia	3,4–5,6 Pa	12–24 Pa
Spain	2,4,6 Pa	15–18 Pa
Sweden	3,5 Pa	12 Pa
UK	2,3,4 Pa	0
For comparison		
Iceland	3,5 Pa	12 Pa
Norway	3,5 Pa	12 Pa
Australia	2,4,6 Pa	0
Canada	2,4,6 Pa	18 Pa
USA	2,4,6 Pa	15–18 Pa

Figure 1. **Pertussis global annual reported incidence and DTP3 coverage, 1980–2005**

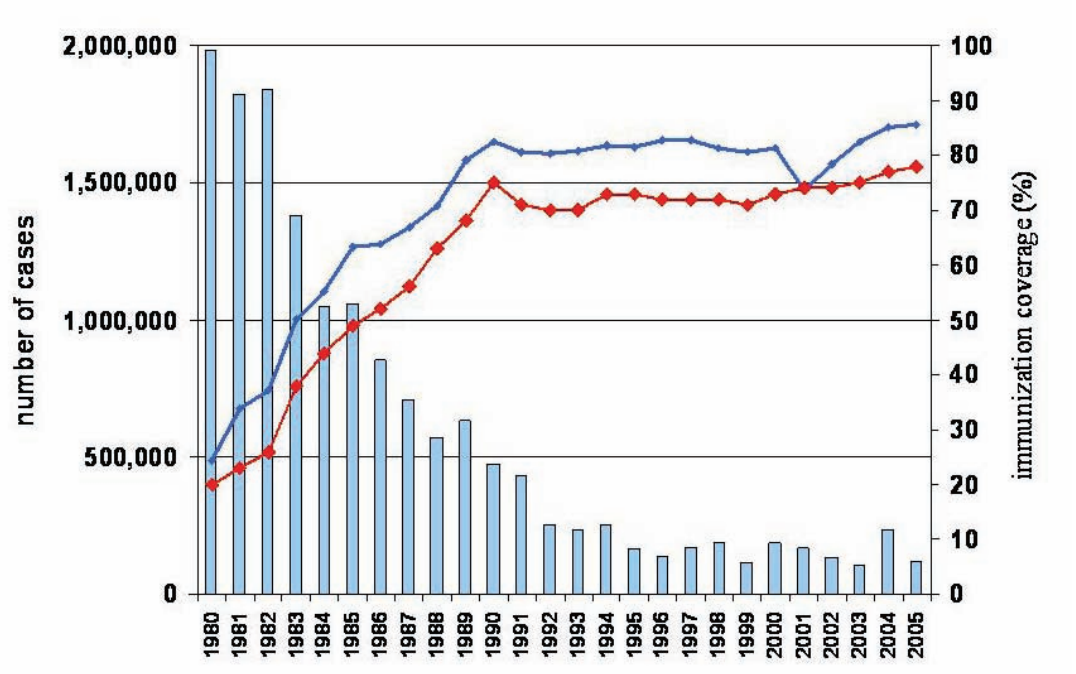

Table 2. Overview of DTP schedules in EU countries up to 18 years of age

		Year of age																			
Country	**No. of DTP doses 2–24 months**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**Total no. of DT con-tain-ing vac-cine doses**	**Total no. of w/aP con-taining vaccine doses**
Austria	4					dT-IPV							dTpa							6	5
Belgium	4				DTPa										dT					6	5
Bulgaria	3	DTPw/a					DT					dT					dT			7	4
Cyprus	4			DTPw/a										dT						6	5
Czech Republic	4				DTPa									T						6	5
Denmark	3				DTPa															4	4
Estonia	3	DTPa				DTPa									dT					6	5
Finland	3			DTPa										dTpa						5	5
France	4					DT					DTPa					dT				7	5
Germany	4				dTpa				dTpa											6	6
Greece	4			DTPa							dT									6	5
Hungary	4					DTPa					dT									6	5
Iceland	3				DTPa									dTpa						5	5
Ireland	3			DTPa							dTpa									5	5
Italy	3				DTPa						dTpa									5	5
Latvia	4						DT							dT						6	4
Lithuania	4					DT									dT					6	4
Luxembourg	4				DTPa										dTpa					6	6
Malta	3		DT													dT				5	3
Netherlands	4			DTPa					dT											6	5
Norway	3						DTPa								dT					5	4
Poland	4					DTPa								dT					dT	6	5
Portugal	4				DTPa					dT										6	5
Romania	4			DTPa										dT						7	5
Slovakia	3	DTPw			DTPw							dT								6	5
Slovenia	4							dT										T		6	4
Spain	4			DTPa										dT						6	5
Sweden	3				DTPa									dTpa						5	5
UK	3		DTPa										dT							5	4
For comparison purposes																					
Australia	3			DTPa											dTPa					5	5
Canada	4			DTPa											dTpa					6	6
USA	4			DTPa							dTpa									6	6