Whole-cell and Acellular Pertussis Vaccines

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Whole cell (wp) vaccines have been used for more than 60 years, and acellular (ap) vaccines were developed in the 1980s. The WHO Technical Report series for wp (WHO 2007) and ap (WHO 1998) vaccines requires for wp that strains should be well characterized and have a fully documented history, that strains should be chosen in order that the final vaccine contains predominantly phase I bacteria, which may be controlled by its haemolytic activity. Strains should express both fimbriae 2 and 3, which could be controlled by standard reagents, and they should be maintained by methods preserving their activity, which could be done by freeze-drying or in liquid nitrogen. Different producers, however, use different strains, and the "genealogy" of sources is only partly known publicly, and these strains are not in a public repository (Njamkepo et al, 2002) Few requirements are made for ap vaccines: Strains should be well characterized and have a fully documented history, and some manufacturers use the *B. pertussis* strain Tohama. It is not known, to which extent the polymorphisms in the PT, PRN and FIM genes can influence vaccine effectiveness.

Culture of wp and ap vaccines is recommended to be done in a seed lot system, various media are possible and no human blood is allowed in culture media. Production now is mostly done with synthetic media.

The inactivation of toxins in wp vaccines can be done by various methods, but no active heat-labile toxin should be detectable in the final product. In wp vaccines, the role of varying amounts of biologically active PT, lipopolysaccharide, TCT and/or ACT is unclear. Similarly, various inactivation methods are allowed for ap vaccines, and formaldehyde, glutaraldehyde, hydrogen peroxide and genetic inactivation are being used.

As for the content of wp vaccines, they are standardized to Opacity Units using a WHO reference preparation (IU), and one vaccine dose should not contain >20 IU. However, the number of bacteria per IU may differ depending on the production process, and it is unclear whether the bacterial number or the antigen content is more relevant for effectiveness.

The content of ap vaccines is defined by protein antigen contents measured by physicochemical, immunological and biological methods. Besides the declared antigens, traces of other antigens may be present. Irrespective on many clinical trials, the exact contribution of the different antigens to protection is not fully clear and only some antigens (PT, FHA, PRN, FIM) are available for industrial production (Edwards & Decker, 2008).

The quality control of wp vaccines is done by comparing them to an International Standard of Potency (IU), and they should have not less than 4.0 IU per dose. This comparison is done by a mouse intracerebral (IC) challenge assay with *B.pertussis* strain 18323. It is, however, not clear, what immunological mechanisms are measured by the IC challenge of mice (Canthaboo et al., 1999; Corbel & Xing, 2004, Preston, 1966). Vaccines that passed the IC challenge without problems were found to have a significantly reduced efficacy (Gustafsson et al., 1996) or effectiveness (de Melker et al., 2000; de Serres et al., 1996; Krantz et al., 1989) after being tested in clinical trials or when surveillance data showed that effect. Thus, the IC challenge is unable to predict effectiveness of vaccine lots.

Quality control of ap vaccines may be done by their immunogenicity evaluated in mice, or by an intra-nasal challenge in mice. This model is able to detect differences between vaccines or vaccine lots. A modified intracerebral challenge in mice has also been proposed. However,

also for ap vaccines, the optimal method for reliably controlling potency and detecting small differences in effectiveness is not clear.

The human immune response against wp vaccines is directed against an array of antigens of the whole bacterial cells. Some antigens i.e. active PT may also serve as immune response modifiers, and significant differences in immune responses to various antigens between different vaccines have been observed (WHO, 1993).

The human immune responses against ap vaccines are directed against purified protein virulence factors. Significant differences in immunogenicity per µg protein between different vaccines have been observed (Decker & Edwards, 1995).

Wp vaccines have effectively controlled pertussis in infant and toddlers in many countries for prolonged periods. However, changes in effectiveness have occurred without being noticed in the production or lot release process. Ap vaccines were also able to effectively control pertussis in infant and toddlers in many countries, and may also be used in adolescent and adults. Irrespective of changes in the genetic makeup of circulating *B. pertussis* strains, significant changes in effectiveness of ap vaccines have not been documented yet.

Both wp and ap vaccines are normally used in combination with other antigens, and, for the time being, combinations with wp vaccines are sold at a significantly lower price than combinations with aP vaccines.

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Adolescent and Adult Boosters

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Despite high pertussis childhood immunization coverage rates, surveillance data from developed countries have shown an increase in reported pertussis incidence among adolescents and adults[1,2,3,4]. While it is unclear if these reported increases are real or reflect changes in diagnostic testing patterns or increased physician awareness, waning immunity has likely led to increased susceptibility in adolescents and adults[5].

Source of infection studies suggest that adolescents and adults serve as a reservoir for the pathogen and transmit infection to susceptible infants too young to have completed the primary immunization series[6,7,8,9,10]. Adolescents and adults, particularly those in the household, are a significant source of transmission to unvaccinated infants, especially in areas with high childhood coverage rates[11,12]. An international study conducted in France, Germany, U.S. and Canada provide data indicating for infant cases that had a primary case identified, 55% of the primary cases were parents and 16% were siblings[10].

Morbidity and societal cost data indicate a significant burden of pertussis in adolescents and adults[13,14,15,16,17]. This increasing burden of disease in adolescents and adults, and the role of adolescents and adults in the continued transmission of pertussis, led multiple countries (e.g., U.S., Canada, Germany and France) to recommend a single dose pertussis booster for adolescents and adults given as a combined tetanus, reduced-dose diphtheria and acellular pertussis vaccine (Tdap). Regulatory approval of Tdap was based on serological bridging studies comparing the adolescent and adult immune responses to Tdap to the infant immune response to DTaP[18]. A multicenter randomized controlled trial in healthy 15 to 65 year olds estimated the vaccine efficacy (VE) of a three component acellular vaccine to be 92% (CI: 32-99%)[19]. More recently, a post-licensure study has estimated the VE of an adolescent pertussis booster (Boostrix, GlaxoSmithKline, Rixensart, Belgium) at 78% (95% CI: 60.7-87.6%) using the screening approach[20]. Pre- and post-licensure data support the safety of Tdap in adolescents and adults[21]

Results from an analysis using U.S. national surveillance data support an early impact of the Tdap adolescent program on disease incidence in adolescents[22]. This analysis did not reveal any significant indirect effects on infant disease, but coverage rates were likely too low to realize the full indirect benefit of the program.

Currently there is a lack of evidence showing a reduction in severe infant disease and mortality following the implementation of an adolescent or adult pertussis vaccination program. Continued surveillance in countries that have implemented adolescent and/or adult boosters is needed to demonstrate an indirect impact on infant disease before a universal recommendation can be considered.

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Childhood Boosters

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A number of different schedules are currently in use for the primary pertussis vaccine series. The WHO recommends a 6, 10, 14 week 3-dose series. Other schedules that have been used are 2, 3, 4 months, 3, 4, 5 months and 2, 4, 6 months. A number of countries use a 3, 5, 12 month schedule of which the 3 and 5 month doses have the characteristics of a primary series while the 12 month dose has the characteristics of a booster dose. Although higher antibody levels are achieved by 2, 4, and 6 month primary series than either more compressed 3 dose schedules or 2 dose primary series schedules, antibody levels after all of the primary series schedules drop rapidly after the primary series and boost equally well (1-6).

Using acellular pertussis vaccine, a variety of schedules have been shown to be efficacious including a two dose primary series at 3 and 5 months with a booster at 12 months (7) and a 3 dose primary series at 2, 4, and 6 months (8). There are no data demonstrating the efficacy of a 3, 5 month primary series without a booster. Protection after a 3 dose primary pertussis vaccine given at 2, 4, 6 months of age has been shown to last at least until school entry (9). If a 2 dose primary series is used with a booster at 12 months of age, a second booster is also required at school entry (10-11). With a 3-dose primary series and a booster in the second year of life, duration of protection appears to be longer, with a booster not required for as many as 10 years later (12-13).

Given the variable efficacy of whole-cell pertussis vaccines and demonstration of improved whole-cell pertussis vaccine efficacy after a booster in the second year of life (7, 8, 14, 15), there is a case for recommending a booster during the second year of life unless the epidemiology in a country provides compelling evidence that a booster is not needed until preschool. This early booster would prevent accumulation of susceptibles and would provide additional protection in situations where the effectiveness and duration of protection of the vaccine in use is less than optimal. The timing of this booster would also provide an opportunity for catch-up vaccination and would allow for the use of a combination vaccine containing both pertussis and Hib antigens.

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Cocooning (Maternal and Family/Household Vaccination)

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There are numerous studies that indicate household contact-type adults are an important source of pertussis infection in non immune infants in regions where vaccine coverage is high[1-9]. Rationale for the cocooning strategy is demonstrated by studies showing that up to 75% of infants are infected from a household contact, and 30% from the mother[4,10,11]. Computer simulations and cost-effectiveness analyses indicate cocooning would be cost-effective[13,14,19,20,21], but a critical review of the models is needed.

In 2004 cocooning was introduced in France based on a computer simulation that estimated that 2.7 deaths and 150 hospitalizations would be avoided if cocooning was implemented with 100% coverage and vaccine efficacy of 90% for 10 years[12]. Coverage has been low (around 4% in 2008) and educational barriers exist[22,23]. A survey conducted one year after the cocooning recommendation was implemented in France indicated that very few mothers (1%) and roughly half of general practitioners (GP) were aware of the cocooning recommendations, but over 92% found the recommendations to be justified[22]. Additionally, 21% of GPs indicated that the recommendations were difficult to apply. In 2007, three years after the program was implemented, 80% of GPs knew of the recommendations, but 69% indicated they had difficulties with implementation (personal communication Lasserre).

While implementing a cocooning strategy in addition to childhood and adolescent vaccination is beneficial for newborns and may maintain low levels of pertussis, data are currently limited to some developed countries. The timing of dose administration may also be problematic with a GP delivered system providing the doses too late. The rapid antibody response of Tdap is promising, but at this time there is little outcome data to support a universal cocooning recommendation and further cost-effectiveness assessments for developing countries are needed.

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Pertussis-containing Combination Vaccines

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There are a number of potential advantages of delivering vaccines in combination rather than as separate antigens at the same or multiple visits. These include:

- Reduced number of visits (personal/health system costs, pressure on primary health care)
- Reduced number of injections (cost of consumables, storage, sharps disposal, infection risks)
- Reduced patient (parent and health worker) discomfort
- Increased compliance
- Earlier optimal protection (Kalies et al, PID, 2006)

However, before preferring this approach it is necessary to ensure equivalent effectiveness of the combination, ideally against the diseases in question but if this is not ethically or logistically feasible, then immunogenicity may be used with the goal of demonstrating non-inferiority. It is also necessary to confirm the safety of the combination. A further consideration is the relative cost of the combination vaccine and its storage and delivery.

A Cochrane review was recently conducted to assess the effectiveness and safety of combination DTP-HBV-HIB vaccines (Bar-On ES et al). Combined DTP-HBV-HIB vaccine versus separately administered vaccines or placebo, administered to infants aged up to two years, were included. DTP-HBV and HIB vaccines for primary prevention of diphtheria, tetanus, pertussis, hepatitis B and Haemophilus influenzae B (HIB). *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art.No.: CD005530. DOI: 10.1002/14651858.CD005530.pub2) with the objective of comparing the effectiveness of the combination vaccines with compared with separate vaccines or placebo, administered to infants aged up to two years. Eighteen RCTs or quasi-RCTs, nine using acellular pertussis (DTPa) and nine using whole cell pertussis (DTPw) were included. In five studies IPV was combined with DTP-HBV-HIB vaccine (Aristegui 2003; Avdicova 2002; Gabutti 2004; Mallet 2000; Schmitt 2000), while in three OPV vaccine was administered to all vaccinees in both groups concurrently (Nolan 2001; Omenaca 2001; Pichichero 1997).

No data on clinical outcomes for the primary outcome (incidence of diphtheria, tetanus, pertussis, hepatitis B and *H. influenzae* type B) post-vaccination was available and all studies reported on immunogenicity, ie. the antibody responses to tetanus, diphtheria, pertussis, hepatitis B and *H. influenzae* type B.

In evaluating the immunogenicity of vaccines the data following the last dose of the vaccines, excluding a booster dose was used, because of differences in number of doses administered. In two immunological responses the combined vaccine achieved lower responses than the separate vaccines: anti-PRP (*H. influenzae* type B), both for the threshold of 0.15 μg/ml (RR 2.73, 95% CI 1.19, 6.22), and for the threshold of 1.0 μg/ml (RR 2.09, 95% CI 1.20, 3.64); and anti-hepatitis B. The anti-PRP comparison was influenced by one study with a large number of events (Pichichero 1997), which used pure (and not conjugated) PRP vaccines (polyribosylribitolphoshate). The anti-hepatitis B comparison was influenced by one large DTPw containing study (Nolan 2001) with a total of 26 serological failures and when this study was excluded, no

significant difference was found between DTPw-HBV-HIB combined and separate vaccines (RR 0.54, 95% CI 0.24 to 1.22).

For the other responses (pertussis, diphtheria, polio and tetanus) no significant differences were found, but the number of responses below the serological threshold were relatively low with large confidence intervals.

Systemic and local adverse events, including fever, pain, redness, swelling, irritability, drowsiness, loss of appetite, vomiting and more generalized and severe signs were investigated. The combined vaccine did not result in a significant increase in the incidence of serious adverse events (RR 0.91, 95% CI 0.56, 1.48), but caused more minor reactions. A significant difference between combined and separate DTPa-HBV-HIB vaccines was found for pain (RR 1.20, 95% CI 1.06 to 1.37) and redness (RR 1.12, 95% CI 0.96, 1.30).

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Vaccination of Healthcare and Childcare Workers

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There are two main reasons to consider vaccination of healthcare workers (HCWs) against pertussis; to reduce transmission from HCWs to susceptible care-takers including young infants, and to reduce morbidity in the HCWs[1].

It is well known that pertussis may represent a life-threatening disease in the youngest and still unvaccinated infants[2], but also other vulnerable groups such as immunocompromised persons are at substantial risk for severe disease. In HCWs the clinical manifestations are similar to in other adults and disease is rarely severe even though complications do occur[3]. Pertussis in HCWs may nevertheless cause severe consequences, because of unrecognised transmission from mild and moderate cases[4], and nosocomial transmission of pertussis often requires extensive and expensive control measures[5]. Antibiotic treatment of the HCW, and furlough from work, may imply economic consequences also at individual level.

The true global burden of pertussis disease in HCWs is not known. Estimates of pertussis in adults in general range from 1-8% in industrialised countries[6,7], with some data indicating higher incidence in care workers (1.7 times higher in one study[8]). Disease transmission within health care settings is, however, well documented in numerous outbreak reports from maternity wards, neonatal care, paediatric emergency or other paediatric wards, haematology-oncology wards, general hospitals and other care settings[9,10,11,12,13,14,15,16,17]. Most outbreak reports from developed countries describe labour intensive infection control management including contact-tracing, extensive testing and generous post-exposure prophylaxis with antibiotics, nowadays often azithromycin[12,13,18,19]. The tolerability and compliance is favourable in comparison with erythromycin but treatment is still costly[20].

Several of these reports provide examples of the costs attributed to the outbreak control measures, concluding that prevention of such extensive work would be preferable, and that there is now an opportunity to vaccinate[21,22,23]. The Tdap vaccines (full antigen tetanus toxoid, reduced antigen diphtheria toxoid and reduced antigen acellular pertussis vaccines) have high efficacy in adults[24], can be safely given to HCWs[25] as early as 18 months after a previous dose of dT[26], and there are studies documenting stable antibody levels 2-4 years following the initial decay after vaccination of HCWs[27,28]. Noteworthy is a rapid antibody response after vaccination, indicating a possible use as part of outbreak control measures[29].

Cost-benefit and cost-effectiveness evaluations from developed countries suggest that vaccination of HCWs would be cost effective (in these settings) if high coverage rates were obtained[30,31,32,33,34,35,36]. One study explored the probability of secondary transmission within a neonatal unit. A reduction in transmission (from 49 to 32%) from HCW vaccination was predicted already at coverage 25%, with further substantial reduction (to 2%) at 95% coverage. Vaccination also resulted in smaller sizes of the outbreaks. Without vaccination the model predicted outbreaks with up to 37 cases (22 HCW, 15 infants), but the sizes were 1-13 cases at coverage 25% and 3 cases at coverage 95%[37].

Data is needed to determine if boosted HCWs can be exempt from control interventions such as mandatory furloughs and chemoprophylaxis.

There are national recommendations to vaccinate HCWs in some countries including the US[38,39,40], and there are also occupational health recommendations[41] or legislation that may

apply[42]. Implementation including obtaining high coverage rates has been problematic. Some attitude studies indicate unawareness of the risk of pertussis[43] or inappropriate attitudes towards vaccination[44,45]. Others found that a majority of HCWs was willing to get immunized but only a minority showed up when offered the vaccine[46,47].

In summary, pertussis transmission in healthcare settings is well documented and control measures are costly and labor intensive. Infants and immunocompromised persons are at substantial risk for severe disease. There are safe and effective aP vaccines that can be used to vaccinate HCWs and thereby reduce their morbidity as well as transmission to vulnerable groups[48]. On the other hand there is an ethical dilemma in using different vaccines for different segments of the population since wP is currently used for vaccination of children in most developing countries.

Overall, HCW vaccination is a small component of a total package of measures to control pertussis and prevent severe infant cases and mortality. The advantages and disadvantages should be evaluated in comparison to, or in addition to, other pertussis vaccination strategies. Additionally, the epidemiology of disease and evidence of nosocomial transmission in middle income countries should be assessed.

Vaccination of HCWs is not mentioned in the current position paper. Working Group members agreed that countries with increasing adult pertussis, and/or nosocomial transmission, are encouraged to include vaccination of HCWs (at least maternity and childcare workers) in their pertussis infection control strategy, if economically and logistically feasible.

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Maternal Pertussis Immunisation in Pregnancy –
Role in Preventing Severe Infant Morbidity

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Introduction

Whooping cough as a clinical syndrome and *Bordetella pertussis* as the causative organism were recognized as an important cause of infant deaths in the pre-vaccine era. Due to this significant disease burden, studies of maternal immunization were undertaken using crude whole cell pertussis vaccine preparations from the 1930s. These studies have been recently summarized; (1,2) only immunologic endpoints were available except for one study. (3) No studies are available for acellular pertussis vaccines, but post-marketing safety data is accumulating. (1)

Issues considered below which are relevant to the role of maternal immunization against pertussis in pregnancy include the pattern of infant deaths due to pertussis, antibody response to pertussis vaccine antigens in pregnancy and levels required for protection of the newborn, duration of this protection and whether high maternal antibody levels interfere with infant responses to pertussis or other vaccine antigens.

Burden and pattern of infant deaths

Data from the United States show that although there has been an enormous decrease in infant deaths from pertussis, those currently occurring are shifted to the left, with sharp increases in the proportion of deaths among infants <1 to 2 months of age over the past two decades. (1) The most recent data, to 2006, show that some 25% of infant deaths occur under 28 days of age and another 60% between one and two months of age, with evidence of an absolute increase in incidence in the youngest age group compared with historical data. Rates of hospitalization of young infants have been reported as increasing in the Netherlands. (2) It is likely that this pattern is reflected in other countries with long-standing pertussis immunization programs. Data from poor countries are scant, and detail on age at death unavailable, but pertussis is estimated to account for some 300,000 infant deaths worldwide.(4) The earlier after birth death and severe disease occurs, the more impact maternal immunization during pregnancy would be expected to have.

Trials of pertussis vaccines in pregnant women

A total of 5 trials of killed, whole cell pertussis vaccines conducted between 1938 and 1951 were identified in the report of Murphy et al (1). The vaccines used in these trials contained variable but large numbers of killed organisms and were administered on multiple occasions during the third trimester. Substantial rises in agglutinating antibodies were found in all studies, but only one study evaluated clinical outcomes. (3) This study compared 100 babies born to trial participants with 100 opportunistic controls. No cases of pertussis occurred after recognized exposures for 8 infants of vaccinated mothers whereas 3/6 exposed comparison infants developed clinical pertussis. No clinical trials of

immunization with acellular pertussis vaccines have been reported, but enrolment is ongoing in a study in Nova Scotia, Canada. (S Halperin, personal communication)

Duration of antibody protection and interference with infant responses

The available data on persistence of transplacentally acquired antibody suggest that it is still detectable at least up to the age at which the first infant pertussis-containing vaccine is due, at 6 to 8 weeks of age. (1) The level of antibody or antibodies required for protection against various degrees of severity of pertussis in newborn infants is unknown, but it seems likely that maternal immunization in the third trimester with either whole cell or acellular vaccine would provide some protection. Following adult immunization with acellular vaccines, antibody levels decline quickly in the first 12 months but remain above baseline for at least 5 years. (5) This means that administration of pertussis-containing vaccine would be required in each subsequent pregnancy to provide indirect protection to the infant.

Interference with antibody responses to pertussis-containing vaccines from maternal antibody has been demonstrated for infants receiving whole cell vaccines, but seems to be less of an issue for acellular vaccines. (1) However, current studies pertain to antibody levels in unimmunised mothers, and immunized mothers are likely to have substantially higher antibody levels. Responses to vaccines among infants whose mothers have been recently immunized with acellular pertussis vaccine is unknown.

Adverse event profile

No data are available during pregnancy, but two manufacturers have established voluntary registries to record the experience of pregnant women who are inadvertently immunized. (1) Experience with immunization of adult women with acellular vaccines in clinical trial settings has not found any clinically significant increase in adverse events.

Public and professional acceptability

In rich countries, acceptance of maternal immunization during pregnancy has been low for the only recommended vaccine (influenza) until recently. There is anecdotal evidence of a substantially higher uptake in the context of pandemic H1N1 vaccination in the light of both data on significant maternal morbidity and emerging data on the potential infant protection. Similar data for pertussis might also translate into increased uptake. In poor countries, uptake of maternal immunization against tetanus during pregnancy has been high and has resulted in large reductions in the occurrence of neonatal tetanus. In general, acceptance of such a recommendation would appear likely to be more straightforward than it has been in rich countries.

Current recommendations of advisory groups

The US Advisory Committee on Immunisation Practices (ACIP) does not recommend routine use of acellular pertussis vaccines in pregnancy but has stated that this could be considered in special situations of significantly increased risk of pertussis disease. (1) No other national advisory group recommends routine pertussis immunization.

Summary

The available evidence strongly suggests that pregnant women mount antibody response to pertussis-containing vaccines which would be expected to provide at least partial protection against clinical pertussis to full term newborns for at least 3 months. This is the peak period for pertussis deaths and hospitalizations in rich countries with long-standing immunization but similar data for poor countries are unavailable.

Uncertainties include the degree of interference with infant responses to vaccines in the presence of very high levels of transplacentally acquired antibody and the duration of protection.

Recommendations

There is insufficient evidence to recommend routine maternal pertussis immunization during pregnancy, both with respect to proven protection of the infant against pertussis and the potential for interference with infant vaccine responses. It is a promising strategy for implementation in rich and poor countries, and would benefit from availability of acellular pertussis-containing vaccines without diphtheria and tetanus antigens.

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Pertussis Vaccines: Are they Interchangeable?

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The United States NIH funded comparison studies of thirteen different acellular pertussis vaccines made in both North American and Europe and comparing their safety and immunogenicity with two US made whole cell pertussis vaccines in a primary vaccination schedule at 2, 4, and 6 months of age. When these children reached the age for booster doses at 15-20 months and 4-6 years, respectively, many of them also participated in booster dose comparisons. A number of children who had received whole cell vaccine were randomized to receive different acellular products, and several of the acellular vaccines administered in the primary series study were no longer available, so different acellular vaccines had to be administered to children previously primed with other acellular products. These booster studies were the first "mix and match" or interchangeability studies performed with the whole cell and acellular vaccines. Both of these studies will be summarized in the tables below. Only those vaccines that are still available or the predecessors of the currently licensed vaccines will be presented.

Safety and Immunogenicity Comparison of Acellular and Whole Cell Vaccines Given as a Fourth Dose to 15-20 Month Old Children
(Reference 1: Pichichero et al. Peds 1997)

MAPT Vaccine Antigens (micrograms)

Vaccine	PT	FHA	Fim	PRN
PM-2	25	25		
SKB-3	25	25		8
CL-4*	10	5	5	3

*Currently licensed comparable vaccine contains 20 PT, 20 FHA, 5 Fim, 3 PRN.
Note: PM-2 and SKB-3 are composed of bacterial proteins purified separately and after co-adsorbed on Aluminium hydroxide. FHA from PM-2 is not detoxified whereas FHA from SKB-3 is. Bacterial proteins from CL4 are co-purified and adsorbed on aluminium phosphate.

GMT After 4th Dose Vaccine

Vaccine	PT	FHA	Fim	PRN
PM-2/PM-2	54.4	193.0	2.6	3.2
SKB3/SKB3	92.9	275.6	3.8	533.3
CL4/CL4	43.3	32.3	308.2	182.4
WCL*/WCL*	68.6	5.8	265.7	60.8

*Whole cell vaccine produced by Lederle Laboratories

These studies clearly showed that local and systemic reactions to the vaccines were less frequent after DTaP than after DTwP. For children vaccinated with a fourth dose of DTaP, which was the same DTaP as received in the primary series, fever and injection site redness, swelling, and pain increased in prevalence compared with the third dose in the primary series. No DTaP was consistently most or least reactogenic or immunogenic. Although serologic correlates of pertussis immunity are not defined, it is clear that most

DTaP vaccines can stimulate comparable or higher serum antibody responses than DTwP for those antigens contained in the vaccines. The administration of DTaP as the fourth dose in children previously primed with DTwP was also safe and immunogenic, indicating that these vaccines could be interchangeable.

When these same children reached 4-6 years of age, a number of them also participated in booster studies comparing various mixed vaccine schedules. The immune responses to only those vaccines that are currently available or to those that are predecessors of current vaccines are presented.

GMT After 5th Dose Vaccine
(Reference 2: Pichichero et al. Peds 2000)

Vaccine	PT	FHA	Fim	PRN
PM-2/PM-2	180	68.2	2	6
SKB3/SKB3	105	86	0	86
CL4/CL4	61	59	583	444
WCL*/ WCL*	92	36	56	80

*Whole cell vaccine produced by Lederle Laboratories

These studies showed that all the DTaP vaccines performed similarly with regard to reactions, whether given as a fifth sequential dose of the same vaccine, a mix of different DTaP vaccines in the 5-dose sequence, or after 3 DTwP and 1 DTaP vaccinations. Large injection site reactions occurred more frequently after the fifth dose of DTaP than after the previous 4 doses. A fifth dose of all DTaP vaccines induced an antibody response to those antigens contained in the vaccine. No DTaP was consistently most or least reactogenic or immunogenic. The administration of DTaP as the fifth dose in children previously primed and boosted at 15-18 months of age with DTwP was also safe and immunogenic, indicating that these vaccines could be interchangeable.

Several additional studies were then conducted where different acellular pertussis vaccines were used interchangeably in primary vaccination schedules (3,4,5,). These studies demonstrated that the safety and immunogenicity of the different acellular vaccines were not compromised when administered in an interchangeable schedule. Finally, studies of the combination vaccines, containing several additional vaccines with DTaP, showed that they too could be administered interchangeably (6).

In summary, interchanging different DTaP vaccines does not interfere with the safety or immunogenicity of the individual vaccines. There are no studies assessing the interchangeability of whole cell vaccines. Interchanging different combination vaccines does not interfere with safety or immunogenicity of the individual vaccines

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