Whole Cell Pertussis Vaccines: Summary of evidence relevant to schedules

1a. Burden and epidemiology
- Pertussis is still a major public health problem
  - Approximately 16 million new cases occurred in the world in 2008, 95% in low and middle income countries
  - Estimated responsible for c. 195,000 (?) deaths in children annually; most deaths in infants and very young children
  - Case-fatality rate highest in very young infants
  - Prior to vaccination, nearly 80% children were infected with Bordetella pertussis by age 5 years, and an appreciable proportion (>50%) with clinical disease. Surveillance difficult and good data are sparse in the literature
  - Since vaccines introduced, dramatic decline in number of cases.

1b. Issues relevant to choice of schedule
Decisions on optimal vaccination schedules should take several factors into consideration:
- Age distribution of pertussis disease and pertussis attributable deaths in the population
- Implications of age at vaccine initiation, number of doses, interval between doses, waning of protection, reactogenicity, expected vaccine coverage and timeliness of vaccination for vaccine use, effectiveness and impact
- Pertussis vaccine given as a combined vaccine, thus must consider implications for other antigens and target diseases

1c. Vaccine immunogenicity
- Whole-cell pertussis vaccines (wP) induce a complex immune response to many bacterial antigens, including production of antibodies against Bordetella pertussis main virulence factors (PT, FHA, ACT, LPS, DNT, PRN, FIM2/3 and BrkA).
- No good serological correlate of protection identified
- No good data comparing immunogenicity of three primary vaccination doses given in the first year of life in either 3p+0 or (2+1)p schedules

1d. Vaccine effectiveness
- Consistent evidence from low and moderate quality studies (including 4 RCTs) that wP given in infancy as three primary doses at intervals of 4 to 8 weeks (3p schedules) protects against severe pertussis disease in the first 5 years of life.
- Consistent evidence, though from lower quality studies, that vaccination in infancy using (2+1) schedules (around age 3, 5 and 10-13 months) is effective in the first 5 years of life.
- No good data to compare schedules in term of effectiveness
- Limited evidence of incremental protection in the first 5 years of life with number of vaccine doses received.
  **Note:** Heterogeneity between studies makes comparisons difficult:
  - Different vaccine strains and case definitions
  - Different duration of follow-up
  - (2+1)p VE estimates do not include 1st year of life when disease most severe
  - Limited data on effectiveness of 2p in infants under 12 months

1e. Current vaccines and safety data
- 64% countries currently use wP containing vaccines (including 96% in WHO AFR and 100% WHO SEAR);
- 86% of countries with wP vaccines use pentavalent DTwPHibHepB (91% in WHO AFR and 77% in WHO SEAR)
- Most common adverse reactions within 7 days of vaccination are fever (up to 59%), local swelling (up to 57%) and local pain (up to 65%).

1f. Current schedules, coverage and timeliness
- All wP countries give three doses in infancy, typically at 6-10-14 weeks or 2-4-6- months.

1g. Predicted impact of different schedules
- Depends on several assumption (see 1b above)
- Impact against mortality determined in particular by protection in early infancy, and thus vaccination at an early age
- Modelling suggests 6-10-14 week preferable to 6w-10w-9m schedule for reduction of pertussis deaths, except under assumptions of high effectiveness of second dose and rapid waning of vaccine-induced protection.
2a. Burden and epidemiology of pertussis

Pertussis (whooping cough) remains a major public health problem, especially in low and middle income countries (LMIC). The disease is caused by infection with *Bordetella pertussis*, a bacterium that is ubiquitous in human populations. The most severe manifestations of the disease include a protracted cough lasting several weeks, often accompanied by paroxysms that end with a characteristic inspiratory whoop. The disease can be fatal, especially in infants and younger children (Edwards 2013).

WHO estimates that there were approximately 16 million cases of pertussis in the world in 2008, of which 95% occurred in developing countries, and that it was responsible for about 195,000 deaths. There is considerable uncertainty over these estimates.

Formalin-killed whole-cell pertussis vaccines (wP) were introduced widely in developed countries in the mid-20th century, and included in the Expanded Program for Immunization (EPI) in 1974. Their introduction has been credited with the steep decline in pertussis morbidity and mortality in children worldwide (Figures 1 and 2). Many high-income countries (HIC) introduced acellular pertussis vaccines (aP), containing 2 to 5 purified antigens, since 2000 (Von Konig 2009, Pertussis Vaccines WHO Position Paper).

Whole-cell vaccines remain the most widely used pertussis vaccines in the world. In the majority of countries where they are employed, vaccination is given as a course of three primary doses administered at various intervals within the first year of life, followed in some countries by one or two boosters between 15 months and 5 years of age. Two schedules are most commonly used to deliver the primary immunisation course. In one, all three doses are given at approximately equal intervals of 4 to 8 weeks (referred to in this document as “3p”, while in the other, two doses are given at short interval of about 2 months, with a longer interval (4-6 months) before the third dose (named “(2+1)p” in this document).

Fig 1. Pertussis reported global annual incidence and DTP coverage 1980-2013 (WHO pertussis Database 2015)

Note: only a small proportion (<5%) of actual cases are reported globally.
Figure 2. Notified pertussis incidence and whole cell vaccine coverage in England and Wales, 1940 – 2000. The vaccine was introduced in 1950s, and became national in 1957. Note cyclical epidemics and resurgence of disease after decline in vaccine coverage in 1970s.

**Pattern in pre-vaccination era**

Limited data on the distribution of pertussis in unvaccinated (pre-vaccine) populations indicate that infection was ubiquitous, with most individuals infected in childhood, of whom an appreciable proportion, > 50 %, exhibited classical disease. Approximately 80% cases occurred in children under 5 years in some parts of the USA, and less than 3% cases in persons aged 15 years or above (Fales 1928). Case fatality rates were also high, in particular in infancy. Similar patterns were observed in other countries, including in Africa (e.g. Senegal, Kenya and South Africa) and South Asia (India). Examples of age distribution of pertussis disease and deaths in the pre-vaccination era are provided in figures 3 and 4.

**Patterns in post-vaccination era**

The introduction of effective infant vaccination with high coverage was accompanied by a steep decline in the number of pertussis cases and deaths in children worldwide. Pertussis surveillance remains difficult and in need of strengthening.

A shift toward pertussis in older age groups (adolescents and young adults) has been reported in recent years in some high income countries, in particular those which now use acellular pertussis vaccines. The age shifts may, in part, be explained by an increasing awareness and recognition of less typical disease manifestations in older subjects, as well as more sensitive laboratory testing. It has also been suggested that waning of vaccine-derived immunity, combined with lower naturally-acquired immunity and boosting (as a result of lower community transmission) may play a role in increased susceptibility in adolescents and adults.

Several high income countries which introduced dTP vaccines experienced resurgence of pertussis in recent years, including relatively large numbers of cases in adolescents and adults. The reasons for these resurgences are not yet clear.
Figure 3: Pertussis notification rates, by age, in England and Wales pre (1953-56) and post (>1957) vaccination. Four year averages to cover epidemic cycles.

Figure 4: Examples of the age distributions of pertussis deaths reported in various settings in the pre-vaccine era (Note that these are curves fitted to observed data (number of observations in each study in bracket), and represent relative frequencies. Details of observed data for each curve are presented in appendix 1. Note also the very small numbers of deaths in the studies in India, Kenya and Senegal, reported under conditions which may not be representative of the entire countries)

Variation in the age distribution of pertussis deaths <5yrs in the pre-vaccine era: curves fitted to available datasets
2b. Issues relevant to choice of optimal pertussis vaccination schedule

Several factors need to be considered when choosing an optimal vaccine schedule, e.g.: 
- Age distribution of pertussis disease and deaths 
- Implications of age at vaccine initiation, number of doses and dose interval on VE 
- Possible waning of vaccine derived (and natural) immunity especially in absence of boosting 
- Reactogenicity and safety of the vaccine 
- Expected vaccine coverage and timeliness of vaccination 
- Vaccine-derived herd immunity 
- Implications for other antigens and target diseases included in the combined vaccine 
- There appears to be considerable heterogeneity between populations and between studies in disease patterns, and in vaccine effects, some of which is attributable to differences in case ascertainment and definition (see Appendix 2).

2c. Immunogenicity of primary course of vaccination

Immunogenicity data are difficult to interpret and compare for whole-cell Pertussis vaccines. There is no established immunological correlate of protection against pertussis disease (Von Konig 2009). Different wP vaccines may have different antigenic content, leading to variations in post-vaccination immune response. There are limited data in the literature, and much of the available information refers to vaccine formulations no longer in use. However, patterns of immune response may contribute insights on vaccine effectiveness.

Limited evidence from a systematic review (Mueller et al. 2014) suggests that the short-term immune response (few weeks to months post-vaccination) increases with the number of doses, and appears to be stronger with longer intervals between primary doses. Observational studies report higher antibody titres 6-8 weeks following the 3rd dose when given after ~6 months [i.e. (2+1)p schedule] than when given 1-2 months after the 2nd dose (i.e. 3p schedule).

Whole-cell pertussis vaccine induces a complex immune response to many bacterial antigens, including the production of antibodies against B. pertussis key virulence factors (PT, FHA, ACT, LPS, DNT, PRN, FIM2/3, BrkA). For details, see (Von Konig, 2009).

Despite the standardization of some aspects of the vaccine production process, considerable variation has been noted in the strain and quantity of bacterial material, and hence in the antigenic content of different wP vaccines. Consequently, it is difficult to directly compare the immunogenicity of different wP vaccines. Furthermore, the absence of any known correlate of protection implies that comparison of immunogenicity may not translate into differences in clinical effectiveness.

The assay used to assess whole-cell Pertussis vaccine lot potency for licensure remains the intracerebral mouse challenge test introduced in the 1940s, although it remains unclear what specific immune response is being assessed.

Immune response and age at initiation of vaccination
The evidence is limited. Wilkins et al (1987) reported an increasing trend in the proportion of children achieving a titre ≥1:80 when the 1st dose was given respectively at age 4-11, 12-19 and 20+ weeks. An RCT by Baraff et al (1984) found no evidence that a 1st dose at birth led to different immune response (anti-FHA IgG) after subsequent doses.

Immune response and number of doses
Using serum antibody titres a few weeks to months post-vaccination as the proxy-measure, there is limited but consistent evidence (Baraff 1984, Barkin 1985, Wilkins 1987) of increasing immune response with the number of doses received, compatible with a boosting effect of each additional dose.
Immune response and interval between of doses
The evidence suggests that a longer interval between doses is associated with a stronger immune response. In a US study (Wilkins 1987), a higher proportion of children with intervals between doses of 8 weeks or more achieved antibody titres $\geq 1:80$ than did those with 3-7 week intervals, irrespective of age at vaccine initiation. A trial conducted by Barkin et al (1985) reported higher antibody titres 1-2 months after the 2nd dose given at a 4-month interval compared to 2 months.

Immune response and vaccination schedules
A systematic review found 4 observational studies with direct comparison of immunogenicity attributable to 3p and (2+1)p schedules within similar timeframe after vaccination, providing evidence of very low to low quality. Two studies (Olin 1998 & Booy 1992) contrasted immune response about 4 weeks after the 3rd dose, the third (Miller 1995) about 6 weeks after, and the fourth (Miller 1997) at 6 weeks and then at 12-18 months after the 3rd dose. All but one of the studies were based on the comparison of unrelated cohorts. Olin (1998) compared subjects randomised to the wP arm of a trial, but in which both schedules were used. There is some suggestion from Miller (1995) and Miller (1997), and marginally from Olin (1998) that post-vaccination anti-FHA and anti-PT are titres slightly higher 4-6 weeks after the 3rd dose in children who received (2+1)p (3rd dose at $\approx 11-13$ m) compared to 3p (3rd dose at $\approx 6$m). This is consistent with the other studies that found apparent associations between intervals between doses and immune response.

There was no difference between schedules when antibody titres were compared at age 12-18 months, except for anti-FIM. Key results from these 4 studies are summarised in figure 5 below, showing the ratio and 95%CI of antibody Geometric Mean titres (GMTs) in (2p+1)/3p.

**Type of evidence:** Observational studies  
**Quality of evidence:** Very low to Low  
**Caution:** Various limitations and potential for bias in different studies. Also, difficult to separate effect (on immune response) of interval between doses to that of age (e.g. 3p children receive 3rd dose at age 4-6 months whereas (2+1)p children do so at 11-13 months).

**Fig 5.** Comparison of three different anti-pertussis antibodies induced by (2+1)p versus 3p schedules, in terms of ratios of GMTs. *Age or time since last dose given in parentheses. (Note: ratio $>1$ means post-vaccination antibody Geometric Mean Titres (GMT) higher after (2+1)p compared to 3p)*
2d. Vaccine effectiveness against pertussis disease

The evidence summarised here (figure 6) is derived from an update to a systematic review (Mueller et al. 2014) of controlled trials, observational studies, and surveillance estimates using the screening method. Note that there are several complexities and sources of heterogeneity that may affect direct comparisons of estimates between studies, including:

1. **Vaccine strain and batch used:** variability in vaccine strain, antigenic content, batch and immunogenicity. There are relatively few data on vaccine formulations currently in use.
2. **Specificity of case definition:** This varies between studies from clinical diagnosis only to culture-confirmed cases only. A further complication is that the vaccines may protect best against severe disease (more typical and easier to diagnose clinically), with implications for VE measurement.
3. **Differences in follow-up time:** Disease is most severe early in life, so dose timing and VE in infancy is very important. 3p schedules are typically completed between ages 4 to 6 months, whereas the 3rd dose in (2+1)p is given later at 11-13 moths.
4. **Trends in vaccine-derived protection:** Evidence suggests VE may decline with time after vaccination, so it is necessary to compare schedules over similar follow-up times.
5. **Context:** Most studies are relatively old, and the majority were conducted in high income countries where whole cell pertussis vaccines are no longer used. There are limited data from LMIC countries where community transmission rates may be higher with implications for age at infection, naturally-acquired immunity and boosting.

**Note:** Assessment and Ranking of Quality of evidence from the systematic review used the GRADE approach (GRADE working group, BMJ 2004):

- **High** = Further research unlikely to change confidence on estimates of effect;
- **Moderate** = Further research likely to have an important impact on confidence in estimates of effect and may change estimates;
- **Low** = Further research very likely to have an important impact of confidence in effect estimates and is likely to change estimates;
- **Very low** = Any estimate of effect is very uncertain.

### Comparison of vaccine effectiveness by schedules

- **Very low to moderate quality evidence** (including 4 controlled trials) that 3p schedules are effective against pertussis disease in the first 5 years of life.
- **Very low to low evidence** (no data from RCTs) that (2+1)p schedules are effective against pertussis at age 1-5 years (protection in under 1 year old not included). Limited data on VE of 2 doses in infants under 1 year old.
- **Very limited data** on direct comparison of 3p and (2+1)p schedules; No direct evidence that either schedule is superior or inferior to the other.

### 3p vs 0: Moderate evidence that 3p schedules are effective against pertussis disease

Four trials measured the efficacy of wP given in 3 primary doses at 4-8 weeks intervals. Two trials [MRC (UK) 1951 and Blennow (Sweden) 1988] using the UK-Wellcome and the Sauer strains respectively found high VE up to 20-27 months after the 3rd dose (respectively 80% [95%CI 74-84] and 71% [95%CI 37-86]). Two later trials [Gustafsson (Sweden) 1996 and Giuliano (Italy) 1998] reported lower VE (48% [95%CI 37-57] and 31% [95%CI 9-45]). These later trials used a particular Connaught vaccine, and it has been suggested that the lower efficacy may have been due to the vaccine strain or to poor quality vaccine batches.

Evidence from observational studies is mostly consistent with the two older trial estimates and further suggest good protection in children up to age 5 years.

**Type of evidence:** RCTs and observational studies

**Quality of evidence:** Very low (3 screening and 3 case-control studies) to moderate (4 controlled trials)
There is no published controlled trial measuring the effectiveness of (2+1)p schedules. The available data come from 6 UK-based observational studies with moderate to high risk of bias. All studies except the two old household-cohort* studies found high effectiveness (ranging from 72% to 90%) of the (2+1)p schedule up to 4-5 years of age. VE estimates were lower in household cohort studies, respectively 24% [95%CI 11-35] (PHLS 1969 & 1973) and 53% [95%CI 45-60] (PHLS 1982). Note that VE estimates of completed (2+1)p by definition does not include protection in 1st year of life, given the 3rd dose is given at 11-13 months. The evidence on VE of 2 doses in children aged under 12 months is limited.

### Type of evidence: Observational studies;
### Quality of evidence: Very low to low

#### Caution:
1. Two of the four studies with relatively high VE are estimates using the screening method. This approach is highly dependent on assumptions regarding population vaccine coverage, has limited control for confounding by age and secular trends, and is vulnerable to other biases.
2. “Old’ household-cohort studies used retrospective ascertainment of cases among household contacts of confirmed cases, which could lead to lower specificity of case detection and underestimation of VE. Also note that poor quality batches suspected as a contributing factor to lower wP VE in the UK in 1960s.

### 3p vs (2+1)p: Limited evidence to conclude whether schedule 3p or schedule (2+1)p has greater effect on risk of disease

There are no controlled trial data that provide direct comparison of 3p against (2+1)p schedules. Olin et al (1998) contrasted VE of 3 doses at 2-4-6 months to 3-5-12 months for participants in a Swedish pertussis vaccines trial who were randomised to the wP arm. They found that this 3p schedule was marginally more effective (11% relative VE) than the (2+1)p schedule, but the difference was not significant (95%CI -89% to 57%). Limitations to the study include:

- follow-up was not comparable as the (2+1)p follow-up started much later than 3p, after age 1 year; and
- The study was underpowered to evaluate this hypothesis, which was not its primary objective.

More generally, the direct evidence supporting effectiveness of 3p schedules appears stronger (2 trials) than that of (2+1)p schedules. However, in settings where both schedules were used and VE measured using similar methods (e.g. UK estimates using screening method and case-control study) and with similar case definitions, the effectiveness of 3p and (2+1)p appear comparable.

### Vaccine effectiveness against pertussis-attributable death

The literature search did not identify any study that measured wP effectiveness against pertussis deaths. However, a review of the evidence by the WHO SAGE committee looked at severe pertussis morbidity and hospitalisation in infants less than 1 year of age. Given that the disease is likely to be more severe or fatal in infants, vaccine-induced protection against severe disease may apply to pertussis death. The review concluded that there was consistent evidence that a single dose of vaccine in infancy provided around 50% protection against severe disease, hospitalisation and death (ref SAGE background doc March 2014).

### Effect on vaccine effectiveness of interval between 1st and 2nd dose

- No within-study data available. Limited evidence from between-study comparisons that VE is no different with 3p at monthly or 2-monthly intervals
- No data on interval other than 2-monthly between 1st and 2nd doses for (2+1)p

### 3p schedules:
Studies with data on effectiveness of 3p typically used 4-8 weeks intervals between primary doses. There was no study directly comparing the effect of different intervals on effectiveness. A total of seven studies used 4-weekly doses, including 2 RCTS (MRC 1951 & Blennow 1988), one
cohort (Laurell 1957), 2 household cohort (Brink 1982 & Schmitt 1996), and 2 screening (White 1996 & Campbell 2012) studies.

Nine studies used 6 to 8 weeks intervals, including two RCTs (Gustafsson 1996 & Giuliano 1998), 1 cohort (Stehr 1998), 2 household cohort (Onorato 1992 & Simondon 1997), 3 case-control (Izurieta 1996, Liese 1997 & Bigsard 2005) and 1 screening (Guris 1997) studies. Between-study comparisons do not suggest that the vaccine effectiveness systematically differs between schedules with 4-week intervals versus 6-8 weeks intervals between doses.

(2+1)p schedule:
All studies measuring effectiveness of (2+1)p schedules used the same interval (about 2 months) between the 1st and 2nd dose.

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**Figure 6:** Summary of published data on whole-cell vaccine effectiveness against clinical pertussis

*(Note: Vaccine abbreviations: Be=Behring Co = Connaught, Gx=Glaxo, Me = Pasteur-Merieux, Sa=Sauer, We = Burroughs-Wellcome, Wy=Wyeth-Lederle, ? = not mentioned in paper)
Note (figure 6): For studies reporting estimates using more than one case definition, the one included in the figure was chosen using the following hierarchy [Culture confirmed > New WHO/CDC confirmed > Old WHO > Clinical + culture/serology > Clinical + Epi-link > Clinical Only] in order to present the most specific (See appendix 2 for most commonly used case definitions).

### Age at initiation of first dose and vaccine effectiveness

- Data on effectiveness are only available for schedules initiated around 2-3 months, not earlier.
- There is no within study comparison of VE of similar regimens starting at 2 months versus later age. Between-study comparisons provide no evidence on whether wP vaccine efficacy is different when the 1st dose is given at 2 or 3 months.
- There is low grade evidence (1 small RCT) that antibody response to a primary vaccination course is similar whether or not an additional dose is given at birth.

In all studies measuring wP VE, the vaccination schedules were initiated at around 2 to 3 months of age, except the MRC trial (1951) in which the 1st dose was given between 6 and 18 months.

**3p schedules:** All but 2 studies initiated vaccination in infants at around 2 months old, and there is low to moderate Grade evidence (from 3 trials, 2 cohort, 3 household cohort, 3 case-control and 3 screening studies) of vaccine protection after 3 doses, with VE estimates of up to 80% (95%CI 58-90) in one RCT (Blennow 1988). One household cohort study (Schmitt 1996) evaluated a 3p schedule with initiation at 3 months, and estimated VE at 97.6% (95%CI 83-99.7) up to age 2 years. The other study (MRC RCT, 1951) in which vaccination was initiated between 6-18 months of age found VE = 80% (95%CI 74-84) after ~27 months follow-up.

**3p+1 vs 3p+0:**

3p schedules [3p+1 vs 3p+0]:

No RCT directly compared primary vaccination with and without booster in children under 5 years. Three studies (2 household cohort [Brink 1982 & Heininger 1998] and 1 screening [Guris 1997]) reported higher VE in children <5 years who had been given a booster. Three other studies (1 cohort [Stehr 1998], 1 household cohort [Onorato 1992] and 1 case-control [Bisgard 2005]) measured similar VE in children with and without booster.

**3p+1 vs 3p+0:**

3p+1 schedules [(2+1)p+0 vs (2+1)p+1]:

A single (2+1)p study (PHLS 1969 household cohort) reported on the effect of a childhood booster. The interval between the last dose and booster dose was not reported, and there was no evidence of better protection in children <5 years who received the booster compared to those with complete (2+1)p vaccination (31% [95%CI 0-72%] higher attack rate in group with booster compared to those with no booster).

### Childhood boosters

- (2+1)p: No evidence relating to additional effectiveness of booster dose in children under 5 years.

**Type of evidence:** RCTs and observational studies  
**Quality of evidence:** low to moderate

Caution:

(1) It is not clear from most studies if complexities linked to follow-up were considered, notably whether follow-up and estimates were restricted in both groups (with and without booster) to the period after booster was given.

(2) Most observational studies were not designed to measure effect of booster doses, so likely underpowered.
Number of doses and vaccine effectiveness

There is some low quality evidence from one cohort (Onorato), one case-control (Bisgard et al. 2005) and one Screening study (Campbell et al. unpublished) that a single dose is associated with some clinical protection against pertussis.

The evidence (e.g. Walker 1981, Broome 1981, Onorato 1992, Bisgard 2005, Campbell 2014 Unpublished) is consistent with incremental protection with increasing number of doses received up to the 3rd dose, although the data are weak.

The evidence on effectiveness by number of doses is summarised in figure 7.

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Figure 7: Dose specific Vaccine Effectiveness of whole cell pertussis vaccines against pertussis disease
(NB: using VE estimates for shortest and earliest reported follow-up since last dose in order to approximate maximum vaccine-induced protection immediately after the dose.)
Vaccine effectiveness and duration of protection

**Duration/Waning of protection (figure 8)**

- There is limited evidence on how wP VE changes with time since vaccination in children up to 10-16 years old. However, the data are consistent with decline of VE in time.
- Duration of immunity acquired after wP vaccination is estimated to range from 4-12yrs.
- The actual rate of decline in VE remains unclear, as well as the explanation. It could be due to waning in vaccine-derived protection, or by progressive acquisition of natural immunity by the unvaccinated population, or both.
- The reasons for the decline have implications for estimation of vaccine impact.

**3p schedules:**
Six observational studies (MRC 1965, Blennow 1988, White 1996, Gustafsson 1996, Van Buyden 1999, Campbell 2012) with some data on VE by time since vaccination suggest progressive decline over time, starting as soon as 1-2 years after the 3rd dose. The most dramatic decline is reported in data from Gustafsson (1996) with a drop of VE from ~75% 0-6 months after the 3rd dose to ~34% after 18-24 months follow-up. However the decline in VE appears more modest in other studies, and only three report VE beyond 60 months (5 years).

**(2+1)p schedules:**
Five observational studies (Bassili 1976, Church 1979, PHLS 1982, Jenkinson 1988, Ramsay 1993) consistently suggest decline in VE starting between 1-2 years after third dose. For example Jenkinson (1988) report a decline from around 90-100% in 1-2 years old to about 50% VE in 5-6 years old. But the decline is less dramatic in other studies.

**Caution:**
Although the overall pattern is consistent, the evidence is weak; studies contributing data are of very low to low quality, with several limitations and high risk of bias. Interpretation is unclear (see above).

**Effect of booster vaccination in children older than 5 years and adolescents:**
There are no data on the effectiveness of booster vaccination (using whole-cell or acellular pertussis vaccine) in children aged over 5 years.

Until recently, pertussis disease in adolescents and adults was not considered an important problem, and the risk of adverse reactions precluded any routine use of a booster wP in older children (Van Konig 2009). As a result there are very few data on the efficacy of booster vaccination in children over 5 years and adolescents.
Figure 8: Data on apparent decline in observed effectiveness of pertussis vaccines with time since last dose, after three different schedules: (2+1)p; 3p+0; or 3p+1.
2e. Reactogenicity and safety of whole-cell pertussis vaccines

- Whole-cell pertussis vaccines are associated with systemic (e.g., fever, vomiting) and local (e.g., swelling, redness, pain/tenderness) adverse reactions in the days following vaccination.
- There is limited evidence that the risk of adverse events after the third vaccine dose is higher in children using the (2+1)p schedule than those using a 3p schedule.
- There may be considerable differences between vaccines in this respect.

Overview of evidence on absolute reactogenicity of whole-cell pertussis vaccines

The reactogenicity and safety profile of whole-cell pertussis vaccines has been summarised in several reviews (Von Konig, 2009). There is good evidence that WP vaccines are associated with a relatively high rate of systemic (fever, vomiting) and local reactions (swellings, redness, warmth, pain/tenderness etc.). Comparisons of multi-component vaccines with and without WP (e.g., DTwP vs DT) suggest that WP is the most reactogenic component and responsible for the majority of immediate post-vaccination adverse reactions.

Three trials using the 3p schedule (Gustaffson 1996, Greco 1996 & Long 1990) reported high incidence of systemic (up to 7 to 12 times more fever), and local reaction (including local tenderness, redness and/or swelling) as soon as 24-48 hours after each dose of DTwP, compared to DT only. Findings from observational studies were consistent with these results.

The association of WP vaccines with less common post-vaccination reactions (hypotonic hyporesponsive episodes and seizures) is less certain. The trial by Greco et al (1996) found no significant difference in the rate of these two adverse events up to 48 hours following the administration of any dose of either DTwP or DT in infants.

Vaccination schedules and reactogenicity

Two cohort studies (Ramsay 1992 & Miller 1997) compared the reactogenicity of WP given in 3p monthly versus (2+1)p (3, 5 and 9-11 months) schedules, with data presented for each vaccination dose in the study by Ramsay (1992). The risk of fever, local redness and swelling seemed to increase after the third dose in the (2+1)p schedule, compared to the 3p schedule in which the frequency of adverse reactions appears similar after all three doses. Children vaccinated using the 3p schedule had 56% less fever, 50% less redness and 40% less local swelling after the third dose than children vaccinated in the (2+1)p schedule.

An RCT (Wong 2008) compared 3p schedules at 4 weeks (3,4,5 months) and 6-8 weeks (1.5,3,5months) intervals respectively, and reported broadly similar risks of adverse reactions.

Method: Systematic review Type of evidence: RCTs and observational studies Quality of evidence: Low to moderate Caution: No trial or purposely designed study available to compare reactogenicity of 3p and (2+1)p schedules

2.f. Currently used WP vaccines and safety data from manufacturers

- Sixty-four (64%) countries currently use WP containing vaccines, including 45/47 (96%) in WHO AFR region and all 13 countries in WHO SEAR region (see Figure 9).
- Pentavalent DTwPHibHepB is the most widely used WP containing vaccine (~86% countries using WP vaccines), with respectively 43/47 (91%) countries in WHO AFR and 10/13 (77%) countries in WHO SEAR regions.
- The Serum Institute of India’s DTwPHibHepB (Pentavac) is used in over 50% countries using pentavalent WP vaccines, including two-thirds of WHO AFR countries.
- Evidence suggests that whole-cell pertussis is the most reactogenic component of WP containing vaccines, thus responsible for most of the adverse reactions.
- The most common adverse reactions within 7 days of vaccination include fever (up to 59%), local swelling (up to 57%) and local pain (up to 65%).
- Acellular pertussis (aP) vaccines are less reactogenic than whole-cell.
Currently used wP containing vaccines

Across the world, 142/223 (64%) countries currently use wP containing vaccines, with 122/142 (86%) of them using pentavalent DTwPHibHepB vaccines*. Nearly half of countries using wP containing pentavalent vaccines employ the Serum Institute of India brand (Pentavac), including two-thirds (29/43) of countries in the WHO AFR region.

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<tr>
<td>WHO region (N)</td>
<td># (% of A) Using wP containing vaccines</td>
<td># (% of A) Using pentavalent DTwPHibHepB</td>
<td># (% of C) Using SII Pentavac</td>
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<td>AFR (n=47)</td>
<td>45 (96%)</td>
<td>43 (91%)</td>
<td>29 (67%)</td>
</tr>
<tr>
<td>AMR (n=39)</td>
<td>28 (72%)</td>
<td>27 (69%)</td>
<td>8 (30%)</td>
</tr>
<tr>
<td>EMR (n=26)</td>
<td>21 (81%)</td>
<td>16 (62%)</td>
<td>5 (31%)</td>
</tr>
<tr>
<td>EUR (n=64)</td>
<td>15 (23%)</td>
<td>9 (14%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>SEAR (n=13)</td>
<td>13 (100%)</td>
<td>10 (77%)</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>WPR (n=34)</td>
<td>19 (56%)</td>
<td>17 (50%)</td>
<td>7 (41%)</td>
</tr>
</tbody>
</table>

*Note: some countries use more than one schedule/vaccine (e.g. for specific sub-groups)

Fig 9.Number of countries using each type of DTP combination, grouped by region

Manufacturer safety data

The most commonly reported post-vaccination adverse effects are systemic (fever, drowsiness, and vomiting) and local (pain, redness, and swelling). Local reactions within 7 days after vaccination appear to be more common with wP containing than acellular vaccines, and the rates seem to decrease with subsequent vaccination doses.

Fever is frequently reported in the 7 days following vaccination with either aP (range between studies = 29-59%) or wP (range between studies = 12-48%) containing vaccines, although the incidence of grade 3 or more severe fever is higher after wP (up to 27%).

Studies also reported between 4-65% local pain (with up to 24% grade 3 or more severe) after receipt of wP containing vaccines, and 2-57% local swelling (with up to 49% grade 3 or more severe). The reported rate of most common adverse reactions after SII’s Pentavac, the most...
widely used pentavalent wP containing vaccine, are given in the table below.

<table>
<thead>
<tr>
<th>Adverse reaction rate (%) up to 7 days after DTwPHibHepB from SII (Pentavac) vaccination* (grade 3 or more severe)</th>
<th>1st dose (6 weeks)</th>
<th>2nd dose (10 weeks)</th>
<th>3rd dose (14 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>41.2 (17.5)</td>
<td>41.2 (17.5)</td>
<td>28.6 (13)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3.7</td>
<td>2.4</td>
<td>1.6</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>2.3</td>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Swelling</td>
<td>41.2 (39.1)</td>
<td>36.3 (35.1)</td>
<td>29.8 (28.9)</td>
</tr>
<tr>
<td>Pain</td>
<td>57.6 (22.4)</td>
<td>51.8 (21.6)</td>
<td>41.6 (15.5)</td>
</tr>
<tr>
<td>Redness</td>
<td>21.2 (19.6)</td>
<td>17.1 (15.5)</td>
<td>14.7 (13)</td>
</tr>
</tbody>
</table>

*Data from Phase III multicentre RCT in India (Sharma 2011)

2g. Current schedules, coverage and timeliness

The table below summarises typical pertussis vaccine schedules currently in use. For further details, see Appendix 5. Note that most high income countries currently use acellular pertussis containing vaccines, while the majority of LMICs use whole cell pertussis containing vaccines.

<table>
<thead>
<tr>
<th>Income level</th>
<th>WHO region</th>
<th>DTP visits</th>
<th>Typical vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low / Middle</td>
<td>Africa South East Asia Western Pacific</td>
<td>6w 10w 14w</td>
<td>- - -</td>
</tr>
<tr>
<td></td>
<td>Eastern Europe</td>
<td>2m 3m 4m 18m</td>
<td>- -</td>
</tr>
<tr>
<td></td>
<td>Eastern Mediterranean Latin America</td>
<td>2m 4m 6m 18m</td>
<td>~5yrs -</td>
</tr>
<tr>
<td>High</td>
<td>North America Western Europe Western Pacific</td>
<td>2m 4m 6m 12m -18m ~5yrs 15yrs (few)</td>
<td></td>
</tr>
</tbody>
</table>

All except 3 countries using wP containing vaccines currently administer primary vaccination using a 3p schedule. In most countries in WHO AFR (39/43), WPR (11/16) and SEAR (5/9) primary pertussis vaccination is given at 6,10 and 14 weeks, whereas the majority in AMR (24/26) and EMR (12/18) administer the vaccine at 2,4 and 6 months. In WHO EUR, 7/14 wP countries give primary vaccination at 2, 3 and 4 months.

Three countries report using a long interval between the 2nd and 3rd dose, including Jamaica (6,10 weeks and 9 months), Tunisia (2,3 and 6 months) and Poland (4,8 weeks and 7 months). At least one childhood booster dose is administered (between age 15 and 24 months) in 69/127 (54%) countries using wP vaccines [respectively AFR (6) AMR (24) EMR (15) EUR (14) SEAR (5) WPR (5)].
Coverage and timeliness of wP containing vaccines vary considerably between countries. Figure 10 shows coverage and timeliness of primary DTP vaccination doses in Kenya, Senegal and India from DHS survey data, and in England from Public Health England data. Grey/blue lines in the Kenya, Senegal and India figures refer to measles vaccine, which achieved coverage greater than DTP3 but less than DTP2 in the second year of life in each of these countries.

Figure 10. Examples of coverage and timeliness of DTP vaccination in three LMIC (Senegal, Kenya and India) and one high income (England) countries.
Impact prediction requires several assumptions, in particular on the background pattern of disease and on vaccine effectiveness by number of doses received, as well as on any decline in VE-induced protection with time since vaccination. Figure 11a shows an example of a set of assumptions on effectiveness by dose, based upon data in Figure 7. Figure 11b shows an example of a set of assumptions on waning protection, based upon data in Figure 8.

**Figure 11. Scenarios of vaccine protection after each dose of wP using studies that report on all 3 doses (11a) (with VE expressed as the highest reported VE for studies with multiple follow-up points) and relative clinical protection by time since the 3rd dose of wP (11b)**

(a) Vaccine protection after each wP dose*

(b) Relative clinical protection**

* Note (11a). Studies were restricted to those reporting on all three doses. The relationship between the VE reported for each dose within the same study was maintained in each scenario. The high VE scenario is based on unpublished screening data from a wP cohort aged 9w-6m in England (see Campbell 2012). The mid scenario is based on children aged 6-23m in a case control study in the USA (Bisgard 2005) and the low scenario is based on children aged 1-4yrs in a cohort study in the USA (Onoratu 1992). It is assumed there would be a 2 week period before vaccine protection starts and waning vaccine-induced protection begins.

** Note (11b). For example, if a study reported 90% VE after 3m and 45% after 60m, this would be expressed as 1.0 at 3m and 0.5 at 60m.

Model results are shown in Figures 12 and 13. Figure 12 shows how the impact on deaths due to pertussis of whole cell pertussis vaccination, at 6w-10w-9m is estimated. The baseline age distribution of deaths from pre-vaccination era – see Figure 4 and appendix 1 – is in red. Coverage and timeliness from DHS data for Senegal, 2008 (Figure 10) are used to estimate the proportions of deaths “covered” by successive doses, represented by blue shading (b). The proportions of deaths prevented are based on vaccine effectiveness of 36%, 49% and 83% (for doses 1, 2 and 3 respectively) with 2% waning per year after administration of each dose.
Figure 12. Example of modelled coverage (a), coverage of pertussis deaths (b) and direct impact* against pertussis deaths (c) of wP vaccination (6w-10w-9m) in Senegal.

(a) Coverage by age

(b) Coverage of deaths by age

(c) Direct effectiveness by age

Timeliness by age and dose:
DHS 2008

Current coverage by dose:
WUENIC 2011

Age distribution of deaths:
Preziosi et al, Am J Epi 2002

Protection after each dose (wP):
Mueller/Djomo review, 2015

Duration of clinical protection (wP):
Mueller/Djomo review, 2015

*Note (12c). The blue shaded areas on chart 12c represent the number of pertussis deaths that could be prevented by each dose, accounting for the dose-specific coverage, effectiveness and duration of vaccine-induced protection among wP vaccine recipients, excluding herd immunity considerations.

Figure 13 shows the percentage point difference in direct impact of 6w-10w-9m schedule compared to the current 6-10-14w schedule used in India, Kenya and Senegal under different assumptions relating to effectiveness by dose (see Figure 7), age distribution of deaths (see Figure 4) and magnitude of waning per year (see Figures 8 and 11b). The direct impact of the 3p schedule is subtracted from the direct impact of the (2+1)p schedule to estimate the absolute difference in direct impact. Thus, positive differences indicate better direct impact with the (2+1)p schedule. Negative differences indicate better direct impact with the current 3p schedule. A major determining factor of the difference is the assumed protection level immediately after the second dose, here illustrated as 49 % versus 80% and 92 %.

A low VE scenario with limited waning would favour the existing 6-10-14w (3p) schedule in all countries. A 6w-10w-9m ([2+1]p) schedule is slightly favoured if the second dose VE is high (>80%) and protection wanes rapidly (13% per year). There are subtle differences between the three countries, which reflects differences in the age distribution of deaths (earlier in India see figure 4 and appendix 1) and differences in the coverage of each dose (higher and more timely in Kenya and Senegal – see figure 10), highlighting the need to account for local circumstances where possible.

Other variations (e.g. in age distribution of deaths and timeliness) were explored in further models using Senegal as an example (see appendix 4).
Figure 13. Percentage point difference* in direct impact against pertussis deaths in children <5yrs: (2+1)p [6w-10—9m] compared to 3p [6-10-14w] in Senegal, India and Kenya

<table>
<thead>
<tr>
<th>Some waning (2% per year)</th>
<th>Low VE scenario (36%--49%--&gt;83%)</th>
<th>Mid VE scenario (40%--&gt;80%--&gt;92%)</th>
<th>High VE scenario (70%--&gt;92%--&gt;92%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low VE scenario</td>
<td><img src="chart1.png" alt="Bar Chart" /></td>
<td><img src="chart2.png" alt="Bar Chart" /></td>
<td><img src="chart3.png" alt="Bar Chart" /></td>
</tr>
<tr>
<td>Mid VE scenario</td>
<td><img src="chart4.png" alt="Bar Chart" /></td>
<td><img src="chart5.png" alt="Bar Chart" /></td>
<td><img src="chart6.png" alt="Bar Chart" /></td>
</tr>
<tr>
<td>High VE scenario</td>
<td><img src="chart7.png" alt="Bar Chart" /></td>
<td><img src="chart8.png" alt="Bar Chart" /></td>
<td><img src="chart9.png" alt="Bar Chart" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High waning (13% per year)</th>
<th>Low VE scenario (36%--&gt;49%--&gt;83%)</th>
<th>Mid VE scenario (40%--&gt;80%--&gt;92%)</th>
<th>High VE scenario (70%--&gt;92%--&gt;92%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low VE scenario</td>
<td><img src="chart10.png" alt="Bar Chart" /></td>
<td><img src="chart11.png" alt="Bar Chart" /></td>
<td><img src="chart12.png" alt="Bar Chart" /></td>
</tr>
<tr>
<td>Mid VE scenario</td>
<td><img src="chart13.png" alt="Bar Chart" /></td>
<td><img src="chart14.png" alt="Bar Chart" /></td>
<td><img src="chart15.png" alt="Bar Chart" /></td>
</tr>
<tr>
<td>High VE scenario</td>
<td><img src="chart16.png" alt="Bar Chart" /></td>
<td><img src="chart17.png" alt="Bar Chart" /></td>
<td><img src="chart18.png" alt="Bar Chart" /></td>
</tr>
</tbody>
</table>

Some waning (2% per year)
- Low VE scenario (36%--49%-->83%)
- Mid VE scenario (40%-->80%-->92%)
- High VE scenario (70%-->92%-->92%)

High waning (13% per year)
- Low VE scenario (36%-->49%-->83%)
- Mid VE scenario (40%-->80%-->92%)
- High VE scenario (70%-->92%-->92%)

**Note (fig 13).** The direct impact of the 3p schedule is subtracted from the direct impact of the (2+1)p schedule to estimate the absolute (percentage point) difference in direct impact. Thus, positive differences indicate better direct impact with a (2+1)p schedule. Negative differences indicate better direct impact with the current 3p schedule.
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who received either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the
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Wong SL, Soosai P, Teoh YL, Han HH, Lefevre I, Bock HL. Four is better than nine. A combined diphtheria-
tetanus-pertussis-hepatitis B – Haemophilus influenza type B vaccine for routine immunization in
Appendix 1: Example of observed age-distribution of pertussis deaths in pre-vaccine era

Age distributions of pertussis deaths in the pre-vaccine era

2 high income countries

England 1922-39 (pre-vaccine)

Source: Registrar General’s Statistical Review of England and Wales, 1922-39 pooled

USA 1938-40 (pre-vaccine)

Source: Sako et al, JAMA 1945

4 lower income countries

Senegal 1986 (pre-vaccine)

Source: Preziosi et al, Am J Epidemiol 2002

South Africa 1939-47 (pre-vaccine)

Source: Ordman D, SA Medical Journal 1945

India 2007 (<5% DTP coverage)

Source: Takum T et al, Indian Pediatrics 2009

Kenya 1974-76 (pre-vaccine)

Source: Mahieu et al, WHO Bulletin 1978

Appendix 2: Some commonly used case definitions in wP vaccine efficacy studies

<table>
<thead>
<tr>
<th>Case definition</th>
<th>Clinical</th>
<th>Culture</th>
<th>PCR</th>
<th>Serology</th>
<th>Epi-link</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO Old</td>
<td>&gt;21 days</td>
<td>AND ANY OF</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>WHO New</td>
<td>&gt;14 days</td>
<td>AND ANY OF</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>CDC Clinical</td>
<td>&gt;14 days</td>
<td>AND ANY OF</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>CDC Confirmed 1 (CDCC1)</td>
<td>&gt;14 day</td>
<td>AND ANY OF</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>CDC Confirmed 2 (CDCC2)</td>
<td>&gt;1 day</td>
<td>AND ANY OF</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Laboratory confirmed (LC)</td>
<td>Varied</td>
<td>AND ANY OF</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

*Clinical include cough + characteristic signs depending on study (paroxysm, inspiratory whooping, post-tussive vomiting)
Appendix 3: Details of studies with estimates of Vaccine Effectiveness

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Study</th>
<th>Year</th>
<th>Setting</th>
<th>Strain</th>
<th>Design</th>
<th>Timing</th>
<th>Age gp</th>
<th>F/up</th>
<th>VE (%) by Case definition (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3p</td>
<td>MRC</td>
<td>1951</td>
<td>UK</td>
<td>Sa/We</td>
<td>1.RCT</td>
<td>3 monthly</td>
<td>~27m</td>
<td>78 (74-82)</td>
<td>80 (74-84)</td>
</tr>
<tr>
<td>3p</td>
<td>Blennew</td>
<td>1988</td>
<td>Sweden</td>
<td>We</td>
<td>1.RCT</td>
<td>2-3-4m</td>
<td>6-23m</td>
<td>~20m</td>
<td>80 (58-90)</td>
</tr>
<tr>
<td>3p</td>
<td>Greco</td>
<td>1996</td>
<td>Italy</td>
<td>Co</td>
<td>1.RCT</td>
<td>2-4-6m</td>
<td>6-23m</td>
<td>~17m</td>
<td>27 (5-43)</td>
</tr>
<tr>
<td>3p</td>
<td>Gustafsson</td>
<td>1997</td>
<td>Sweden</td>
<td>Co</td>
<td>1.RCT</td>
<td>2-4-6m</td>
<td>~18m</td>
<td></td>
<td>41 (30-51)</td>
</tr>
<tr>
<td>3p</td>
<td>Laurell</td>
<td>1957</td>
<td>Sweden</td>
<td></td>
<td>2.Coh</td>
<td>2-3-4m</td>
<td>&lt; 5yr</td>
<td>88 (75-94)</td>
<td></td>
</tr>
<tr>
<td>3p</td>
<td>Stehr</td>
<td>1998</td>
<td>Germany</td>
<td>Wv</td>
<td>2.Coh</td>
<td>2-3.5-5m</td>
<td>0.5-3yr</td>
<td>78 (62-88)</td>
<td>84 (77-89)</td>
</tr>
<tr>
<td>3p</td>
<td>Broome</td>
<td>1981</td>
<td>USA</td>
<td></td>
<td>3.CCa</td>
<td>2-3-4m</td>
<td>1-4yr</td>
<td>94 (53-99)</td>
<td></td>
</tr>
<tr>
<td>3p</td>
<td>Brink</td>
<td>1982</td>
<td>USA</td>
<td></td>
<td>3.CCa</td>
<td>2-3-4m</td>
<td>0-4yr</td>
<td>38 (-47-74)</td>
<td></td>
</tr>
<tr>
<td>3p</td>
<td>Onorato</td>
<td>1992</td>
<td>USA</td>
<td></td>
<td>3.CCa</td>
<td>2-4-6m</td>
<td>1-4yr</td>
<td>83 (52-94)</td>
<td></td>
</tr>
<tr>
<td>3p</td>
<td>Schmitt</td>
<td>1996</td>
<td>Germany</td>
<td>Be</td>
<td>3.CCa</td>
<td>3-4-5m</td>
<td>0.5-5yr</td>
<td>98 (83-100)</td>
<td></td>
</tr>
<tr>
<td>3p</td>
<td>Simondon</td>
<td>1997</td>
<td>Senegal</td>
<td>Me</td>
<td>3.CCa</td>
<td>2-4-6m</td>
<td>1-4yr</td>
<td>74 (55-85)</td>
<td>92 (81-97)</td>
</tr>
<tr>
<td>3p</td>
<td>Storsaeter</td>
<td>1997</td>
<td>Sweden</td>
<td>Co</td>
<td>3.CCa</td>
<td>2-4-6m</td>
<td>~24m</td>
<td>29 (2-48)</td>
<td></td>
</tr>
<tr>
<td>3p</td>
<td>Storsaeter</td>
<td>1997</td>
<td>Sweden</td>
<td>Co</td>
<td>3.CCa</td>
<td>2-4-6m</td>
<td>~24m</td>
<td>37 (0-60)</td>
<td></td>
</tr>
<tr>
<td>3p</td>
<td>Heiningen</td>
<td>1998</td>
<td>Germany</td>
<td></td>
<td>3.CCa</td>
<td>2-3.5-5m</td>
<td>4-5yr</td>
<td>76 (45-90)</td>
<td></td>
</tr>
<tr>
<td>3p</td>
<td>Izurieta</td>
<td>1996</td>
<td>USA</td>
<td></td>
<td>4.CCo</td>
<td>2-4-6m</td>
<td>&lt;7m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3p</td>
<td>Hese</td>
<td>1997</td>
<td>Germany</td>
<td>Be</td>
<td>4.CCo</td>
<td>2-4-6m</td>
<td>&lt;7m</td>
<td>95 (81-99)</td>
<td>96 (71-100)</td>
</tr>
</tbody>
</table>

Legend:
- **Clin ± lab**: Clinical diagnosis ± laboratory confirmation
- **Clin only**: Clinical diagnosis without laboratory confirmation
- **Culture**: Culture isolation
- **Old WHO**: Old World Health Organization
- **New WHO**: New World Health Organization
- **CDC Conf**: CDC Confirmed
<table>
<thead>
<tr>
<th>p</th>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Type</th>
<th>Age, Duration</th>
<th>Duration</th>
<th>% Confirmed</th>
</tr>
</thead>
<tbody>
<tr>
<td>3p</td>
<td>Campbell</td>
<td>2012</td>
<td>UK</td>
<td>5.Scr</td>
<td>2-3-4m</td>
<td>40-59m</td>
<td>96 (92-98)</td>
</tr>
<tr>
<td>3p</td>
<td>Campbell</td>
<td>2012</td>
<td>UK</td>
<td>5.Scr</td>
<td>2-3-4m</td>
<td>5-yr</td>
<td>93 (89-95)</td>
</tr>
<tr>
<td>3p</td>
<td>Campbell</td>
<td>2012</td>
<td>UK</td>
<td>5.Scr</td>
<td>2-3-4m</td>
<td>10-16yr</td>
<td>82 (41-93)</td>
</tr>
</tbody>
</table>

**(2+1)p + Booster**

| (2+1)p+1 | PHLS | 1969 | UK | Gx/We | 4.CCo | 3-5m (+10) (+/- B) | 0-4 yrs | 24 (11-35) |
| (2+1)p+1 | PHLS | 1969 | UK | Gx/We | 4.CCo | 3-5m (+10) (+/- B) | 5-10 yrs | 25 (-10 to 49) |

**3p + Childhood Booster**

| (3+1) | Kenyon  | 1997 | USA | 2.Coh | 2-3-4m (+12/18) | 19-47m | 76 (29-92) |
| (3+1) | Stehr   | 1998 | Germany | Wy | 2.Coh | 2-3.5-5m (+15/18) | 0.5-3yr | 85 (78-90) |
| (3+1) | Broome  | 1981 | USA | 3.CCa | 2-3-4m (+12/18) | 1.5a | 55 (28-71) |
| (3+1) | Brink   | 1982 | USA | 3.CCa | 2-3-4m (+12/18) | 0.5-4yr | 81 (66-89) |
| (3+1) | Onorato | 1992 | USA | 3.CCa | 2-3-4m (+12/18) | 1-4yr | 78 (44-91) |
| (3+1) | Heininger| 1998 | Germany | 3.CCa | 2-3.5-5m (+15/18) | 4.5yr | 91 (66-98) |
| (3+1) | Bisgard | 2005 | USA | Co/Wy | 4.CCo | 2-4-6m (+12/18) | 0.5-5yr | 97 (92-99) |
| (3+1) | Guris   | 1997 | USA | 5.Scr | 2-3-4m (+12/18) | 7-47m | 92 (90-93) |
| (3+1) | Baron   | 1998 | France | Me | 5.Scr | 2-3-4m (+16-18) | 2-6yr | 92 (81-100) |
| (3+1) | Baron   | 1998 | France | Me | 5.Scr | 2-3-4m (+16/18) | 6-12yr | 93 (85-100) |

**Vaccine strains abbreviations:**

Be=Behring Co = Connaught, Gx=Glaxo, Me = Pasteur-Merieux, Sa=Sauer, We=Burrough-Wellcome, Wy=Wyeth-Lederle

**Study design:**

1. RCT = Controlled trial; 2. Coh = Cohort; 3. Cca = Case-contact (household); 4. Cco = Case-control; 5. Scr = Screening Method

**Case definition:** CDC Conf = CDC confirmed case; Clin only = Clinical only; Clin ± lab = combination of Clinical and laboratory other than WHO/CDC classic
Appendix 4: Further details on the models and additional scenarios

Methods

Whole-cell pertussis (wP) vaccines are used, and will continue to be used (WHO WER July 2014), in most low and middle income countries (LMICs) where the greatest pertussis disease burden exists. A modelling approach previously used to inform optimal schedules for Hib vaccination (WHO WER April 2013) was used to infer simple estimates of the benefits of alternative wP vaccination schedules in selected LMICs, namely India, Kenya and Senegal. The 3p (6-10-14w) schedule currently used in all three countries was compared to two alternative (2+1)p schedules, 6w-10w-9m and 6w-14w-9m. The 9m option was evaluated because all three countries currently administer the first dose of measles vaccine at this age, and data are available on the coverage and timeliness of this visit. The modeled outcome was the direct impact of wP vaccination, defined as the predicted percent reduction in all pertussis deaths <5 years, accounting for the coverage, effectiveness and duration of vaccine-induced protection among wP vaccine recipients. Pertussis deaths were the modelled outcome of interest since mortality reduction is the main priority for pertussis vaccination schedules in LMICs. Herd immunity considerations were not included in these estimates because the available data from these settings are of insufficient quality to accurately capture the age-specific incidence of infection, duration of natural protection, wP vaccine effectiveness vs natural infection, social contact patterns etc.

Best-fitting age distributions of pertussis deaths <5yrs were used to estimate the proportion of pertussis deaths occurring in each week of age <5yrs, assuming no deaths could occur in the first week of life (van Hoek AJ et al, Euro Surveillance 2013). Pre-vaccine era age distributions were based on 30 deaths in India (Takum T et al, Indian Pediatrics 2009), 24 deaths in Senegal (Preziosi et al, Am J Epidemiol 2002) and 12 deaths in Kenya (Mahieu et al, WHO Bulletin 1978).

Estimates of the coverage and timeliness of the first three doses of DTP (scheduled at 6, 10 and 14 weeks) and the first dose of measles vaccine (scheduled at 9 months) were based on dates reported on vaccination cards in large household surveys (India DHS 2005; Kenya DHS 2008; Senegal DHS 2010)(Figure 12a). In each week of age, the number of deaths potentially covered by each dose was calculated (Figure 12b). This was converted into direct impact (Figure 12c) by assuming different scenarios of vaccine protection after each dose (assumed to start 2 weeks after dose administration) and different scenarios of waning clinical protection after each dose (Figure 11). The estimates used in these scenarios were based on wP studies identified in reviews by Mueller (2014) and Nguipdop-Djomo et al. (2015). The effectiveness of each dose against pertussis cases was assumed to be a conservative proxy for effectiveness against pertussis death.

Additional Scenarios

Several additional scenarios were also evaluated (Figure below):

(i) Firstly, given the small numbers involved in fitting the age distributions in India, Kenya and Senegal, a conservative scenario was run based on the pre-vaccine era age distribution in the USA (Sako et al, JAMA 1945). This was the most heavily skewed distribution to
younger ages of all the pre-vaccine era distributions identified in the review (Figure 4). In this scenario, labeled ‘6w-10w-9m (age shifted left)’ there was limited advantage of the 6w-10w-9m schedule, even under assumptions of high VE and rapid waning;

(ii) Secondly, it has been postulated that changing the schedule from 6-10-14w to 6w-10w-9m could adversely affect the coverage and timeliness of the existing 10w dose. If the timeliness and coverage were assumed to be similar to the 14w dose, only shifted 4 weeks earlier, then there would be a detrimental effect of changing to the 6w-10w-9m schedule – see scenario labeled ‘6w-10w-9m (10w coverage / timing worsens)’;

(iii) Thirdly, one of the main reasons to delay the 3rd primary dose is to achieve a more durable immune response, and thus less waning. If a 25% lower waning rate were to be assumed after the 9m dose (vs the doses administered at 6-14w) then the 6w-10w-9m schedule would generally be preferable to the 6-10-14w schedule if 2 dose VE is high and waning is rapid – see scenario labeled ‘6w-10w-9m (lower waning after 9m dose)’. However, there is currently no evidence to support such an advantage, and indeed limited evidence that waning clinical protection occurs irrespective of whether a 3p or (2+1)p schedule is used – see Figure 11b;

(iv) Fourth, a 6w-14w-9m schedule was evaluated. This schedule generally had lower estimated direct impact than the 6w-10w-9m option because the 14w visit has worse coverage and timeliness than the 10w visit. However, with high VE and rapid waning this option could be slightly preferable to the 6w-10w-9m option; and,

(v) Finally, the 6w-14w-9m schedule was run under the assumption that timing and coverage of the 14w visit could be improved to reflect the coverage and timing of the 10w visit, labeled ‘6w-14w-9m (14w timing / coverage improves)’. In this scenario there was limited difference between the 6w-10w-9m schedule and the 6w-14w-9m schedule. Thus, the 6w-14w-9m option is unlikely to be a practical alternative to the current 6-10-14w schedule unless: a) there are substantial improvements in the coverage and timeliness of the 14w visit; and/or, b) there is a very significant clinical advantage of increasing the interval from 4 to 8 weeks. There is currently very limited evidence to support either of these assumptions.
In conclusion, there are large uncertainties around highly influential parameters included in the model (e.g. the rate of waning clinical protection) as well as uncertainties about the potential role of parameters that were not included (e.g. herd effects). In most scenarios which assume at least 80% protection after the 2nd dose (the midpoint assumed in this evaluation), a 6w-10w-9m schedule is likely to achieve better or similar direct impact to the existing 6-10-14w schedule. Thus, current evidence is not strong enough to preclude a move to a 6w-10w-9m schedule should this be advantageous for other antigens administered as part of the same combined vaccine. However, moving to a 6w-10w-9m schedule could be detrimental if 10w coverage and timeliness are adversely affected. Finally, 6w-14w-9m is likely to be inferior to 6w-10w-9m unless dramatic improvements can be achieved in the coverage and timing of the current 14w dose visit.
Appendix 5: Current Pertussis vaccine schedules in the world

Variation in DTP schedules: **30 largest birth cohorts**

<table>
<thead>
<tr>
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**Age (months)**  **Age (years)**
Variation in DTP schedules: Africa
## Variation in DTP schedules: **Americas**

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### Age (months)
Variation in DTP schedules: Eastern Mediterranean

Variation in DTP schedules: South East Asia
Variation in DTP schedules: **Europe**

Variation in DTP schedules: **Western Pacific**