Report from the SAGE Working Group on Pertussis vaccines
26 - 27 August 2014 meeting
Geneva, Switzerland

Participants of the meeting:

Pertussis Working Group Members:

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External experts:

Andrew Clark, Paul Fine, Colin Sanderson, (LSHTM); Judith Mueller (EHESP), Martha Roper, Karla Soares (Enhance Reviews), Tej Tejpratap (US CDC), Richard Wood, (AMP)

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Background

In March 2013, in the light of a recent increase in reported pertussis cases from some countries, which was in some instances associated with an increase in infant deaths, SAGE and WHO agreed that a new working group on pertussis vaccines would be established to prepare for a SAGE review of the evidence that would lead to updating as needed the 2010 WHO position paper on the use of pertussis vaccine[1] .This also provided an opportunity to review newly available data on effectiveness of various vaccination strategies aimed at reducing infant mortality, as well as the pertussis-related outcomes of the vaccine schedule optimization project.

The terms of reference for the SAGE pertussis vaccines working group were to:

1. Review epidemiological data on pertussis from selected countries using acellular pertussis (aP) and/or whole cell pertussis (wP) vaccines and evaluate the evidence for resurgence of pertussis, with an emphasis on severe pertussis in very young infants. In countries where the evidence supports resurgence, evaluate the evidence for the hypothesis that resurgence is due to shorter lived protection from aP relative to wP vaccines;

2. Review the evidence on effectiveness of 1 or 2 doses of pertussis vaccines against severe disease and death in young infants;

3. Review the evidence on effectiveness of three key strategies aimed at reducing severe disease and death from pertussis in very young infants (cocooning, maternal immunization during pregnancy, and immunization of newborns);

4. Review the evidence for optimal primary vaccination scheduling and timing of booster dose(s);

5. Review the evidence that changes in circulating pertussis strains have had an adverse impact on the effectiveness of aP or wP vaccines;

6. Propose updated recommendations for SAGE consideration on the use of pertussis vaccines.

The working group completed its review in relation to points 1, 2, 3, and 5, of its terms of reference in February 2014 and presented to SAGE on those points at the April 2014 SAGE meeting.

The review of the optimal primary immunization schedules as per point 4 of the terms of reference was, at that time ongoing, so the initial plan was that this would be presented at the October 2014 SAGE meeting. This review entailed a 4-component framework (epidemiology of the diseases, systematic review of the effectiveness and safety of the various schedules, operational considerations, and modelling) following the model already applied to pneumococcal conjugate, rotavirus and *Haemophilus influenzae* type b (Hib) vaccines. The initial intent was that both combined diphtheria, tetanus toxoid and pertussis vaccine (DTP) and tetanus toxoid vaccine (TT) schedules be reviewed by the pertussis working group, in view of the challenges of disentangling the primary vaccination schedule for pertussis from that of diphtheria and tetanus and the interrelation of the TT and DTP schedules. Point 6 of the terms of reference was to be fully completed only after completion of point 4.

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[1] Pertussis vaccines: WHO position paper. WER 2010, 85, 385–400.
http://www.who.int/wer/2010/wer8540.pdf).

As a result of SAGE's review of the evidence in April 2014, a brief revised guidance note on choice of pertussis vaccines was published in July 2014[2], with a plan to update the full position paper on the use of pertussis vaccines after the review of the evidence for optimal primary vaccination scheduling and timing of booster dose(s) would have been presented to SAGE.

Purpose of the August 2014 meeting and content of this report

The aim of the August 2014 meeting of the pertussis working group was to present the various components of the systematic reviews completed under the aegis of the schedule optimization project and to explore the implications of different vaccination schedules for diphtheria, tetanus and pertussis, recognizing that one single schedule would be unlikely to fit all settings.

Discussions focused mostly on the revision of the current ideal schedule for DTP with some discussions of TT and DT boosters.

The rationale for the pertussis working group being appointed for this task was first, that pertussis is an important driver of the schedules second, as stated above, it is hard to disentangle the primary vaccination schedule for pertussis from that of diphtheria and tetanus and third the interrelation of the TT and DTP schedules.

The key questions to be addressed were the number and timing of primary pertussis doses and their interval. Although during the meeting the pertussis working group and additional invited experts looked at the broader life course with much discussion on diphtheria and tetanus, the current report focuses on children and pertussis. It only presents diphtheria and tetanus related information that is essential to understand the drivers of the pertussis vaccine containing schedules in the context of the main aim of pertussis control at global level i.e. to reduce the risk of severe pertussis in infants and children.

Discussions on the overall duration of protection induced by adolescent and adult boosters, and how to ensure durable protection for tetanus and diphtheria are very complex. During the meeting, none of the data presented were informative in relation to booster schedules necessary to ensure continuous protection as compared to current recommendations/practices. Work will continue, to retrieve and interpret additional data, acknowledging the major limitations of the currently available data.

This report is to be read in conjunction with the "wP pertussis vaccines: research evidence on effects of various immunization schedules" produced by the London School of hygiene and Tropical Medicine (LSHTM) and inserted in the Yellow Book. This latter document contains more specific information related to the wP vaccine, which remains the priority for developing countries. The LSHTM report reflects any updated information related to wP that has become available since the August 2014 meeting of the pertussis working group. This report only briefly alludes to evidence with respect to wP vaccines, and refers to the LSHTM report for more detailed information.

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[2] Revised guidance on the choice of pertussis vaccines: July 2014 WER 2014, 89, 337-344.

SAGE members are also invited to refer to the full systematic reviews shared at the August 2014 meeting and available on the SAGE password protected website. They are further advised to refer back to the report prepared for SAGE by the pertussis working group on 14 March 2014 and also available on the SAGE website[3].

Methods and information presented to the working group

Andrew Clark provided an overview of the current DTP schedules and the vaccines in use by country and WHO region.

Colin Sanderson reported on the actual age of vaccination and age-specific, coverage-related issues, as well as on the number of maternal Tetanus Toxoid (TT) vaccine doses received. A total of 66 Demographic Health Surveys (DHS) as well as 36 Multiple Indicator Cluster Surveys (MICS), mostly from lower and middle income countries within all WHO regions, were assessed, using only the most recent surveys from each country and only if the date of vaccination was reported for at least 40% of doses given. The data were mainly collected via interviews with mothers as well as assessments of their children's vaccination cards (data from cards preferred). In total 102 surveys were reviewed and 56 included. The 56 included surveys contained data on about 236,000 children aged 24 months and older. Age-specific coverage as an indicator of vaccine delay was assessed for time-points of receipt of BCG, DTP1-3 and measles containing vaccines (MCV).

Colin Sanderson also reported on the pre-vaccine and post-vaccine era distribution of pertussis cases by age. Relevant studies were identified through PubMed/Medline, the Cochrane Library, Embase, Web of Science and Scopus databases. In total 15 studies that contained age-specific data were identified. These covered 9 countries, 3 of them low income countries, during the post-war pre-vaccine). In some cases it was possible to present country specific data from both the pre and post vaccine era. Data were presented as a distribution of percentage of cases or deaths per week, versus age from the following countries: Sweden (pre- and post), Denmark (pre- and post), UK (pre- and post), Romania, Kenya (pre- and post), Senegal, South Africa, USA (pre- and post) and India.

Tejpratap Tiwari presented a review of historical data from the pre and post vaccine introduction era of industrialized countries. The objective of this review was to evaluate the age trend of diphtheria during the pre- and post- vaccine era and examine the evidence of age-group shifts in disease notifications. English-language databases (Web of Science Core Collection, Virtual Health Library, The Cochrane Library and WHOLIS) were searched without restriction in years. Historical national data were available from developed countries for the pre-vaccine era but data including age distribution was limited to studies from England and Wales, Germany, Scandinavian countries, the United States of America and Canada.

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[3] WHO SAGE pertussis working group. Background paper. SAGE April 2014. Available at http://www.who.int/immunization/sage/meetings/2014/april/1_Pertussis_background_ FINAL4_web.pdf?ua=1; accessed June 2014.

Martha Roper presented a summary of key points on the epidemiology of tetanus, with focus on age- and sex- specific differences in neonatal tetanus (NT) and non-neonatal tetanus (nNT) between the pre- and post-vaccine eras.

Judith Müller presented a systematic review of data on the comparative efficacy/effectiveness, immunogenicity and reactogenicity of DTP infant schedules (available on the SAGE web site). The objectives were to provide the best evidence on primary series vaccination with DTP vaccines among children <18 months and to compare the effect on outcomes of the number of doses, the age at initiation of vaccination, the length of vaccine dosing intervals and any schedule compared to no vaccination. Further objectives were to provide best evidence on booster vaccination with DTP vaccines among children <5 years and to compare the effect on outcomes of age at booster as well as any booster compared to no booster.

The systematic review was conducted according to Cochrane processes. Literature in English, French and German were taken into consideration. Relevant outcomes were clinical efficacy or effectiveness, immunogenicity and reactogenicity. Randomized controlled trials (RCTs) as well as observational studies (cohort or case control; surveillance) comparing ⩾2 different schedules, vs. no vaccination, vaccine without DTP, or placebo, using the same immunization schedule or incidences before and after introduction or change in DTP schedule were taken into consideration. Comparisons between groups were only analyzed when they had the same surveillance protocol (or reasonably comparable groups) or the same vaccine product. Additional evidence from studies which were not-per-protocol contributed relevant evidence with regard to the study objectives but did not fulfil inclusion criteria for case definitions or serological methods. GRADE was used to assess the quality of the evidence. For diphtheria and tetanus vaccines, a total of 15 references were included (6 RCTs and 9 observational). An additional 9 not-per-protocol studies (3 RCTs and 6 observational) informed the review. These studies did not meet any exclusion criteria, contributed relevant evidence with regard to the study objectives, but did not fulfill all inclusion criteria, mainly those relating to outcomes i.e. case definitions and serological methods. .

Immunological correlates of protection were considered. Single, validated correlates based on threshold antibody levels, are available for tetanus and diphtheria disease[4]. No agreed threshold for antibody-mediated protection against pertussis disease is available, although antibody against pertussis toxin is generally deemed necessary for protection against severe pertussis disease in naïve infants.

A systematic review conducted by Karla Soares et al. on the absolute reactogenicity of pertussis vaccines compared various vaccines on the outcomes of redness, persistent crying, temperature ⩾38°C, hypotonic, hypo-responsive episode, local pain/tenderness, swelling/nodule, seizures and any other systemic symptoms of aP and wP containing vaccines.

Andy Clark reported on his group's modelling efforts in estimating the direct impact of wP schedules on pertussis deaths among children aged <5years. The aim of these efforts was to use nationally relevant data (vaccine coverage by age, deaths by age as presented

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[4] Vaccines, 6th Edition Edited by Stanley Plotkin, Walter Orenstein, and Paul A. Offit. Philadelphia, PA: Elsevier, 2013. 1392 pp.

earlier by Colin Sanderson) to estimate the direct effectiveness of two alternative wP schedules (2p+1 and 3p+0 i.e. a 6, 10 (or 14) and 9 month schedule versus a 6, 10, 14 schedule) on pertussis deaths <5 years. Parameters entering the model derived from national and international data sources: the distribution of pertussis deaths by age in weeks (pre-vaccine era) and the coverage of DTP1, DTP2 and DTP3 and first dose of measles containing vaccine (MCV1) (as a proxy for a 9 month DTP coverage) by age in weeks as well as the vaccine efficacy by dose and the duration of vaccine-induced protection. The focus on mortality was chosen due to the high severity in younger infants which had been consistently observed, irrespective of country. Age distributions of pertussis deaths in the pre-vaccine era were chosen from 2 high income countries (USA and England) as well as 4 low-income countries (Senegal, India, Kenya, South Africa). In addition the national estimates of vaccine coverage and timeliness by dose as presented by Colin Sanderson were fed into the model. The first estimate taken from the model was the number of potential deaths prevented by each dose, based on the pre-vaccine era distribution. The meeting participants provided feed-back that was then used to adjust the modelling of age curves and other parameters used in the model to adjust impact estimates. This report benefits from this revised modeling work completed since the meeting and from the updating of the systematic review of the immunogenicity, effectiveness and reactogenicity of wP vaccination scheduled performed by LSHTM and particularly by Patrick Nguipdop-Djomo and Riya Modley under the leadership of Paul Fine.

Current WHO schedule recommendations and current schedules in use

WHO recommendations on the use of pertussis vaccines

As stated in the 2010 WHO position paper on the use of pertussis vaccines[1], WHO currently recommends a 3-dose primary series, with the first dose administered at age 6 weeks; subsequent doses should be given 4–8 weeks apart, at age 10–14 weeks and 14–18 weeks. It is also recommended that the last dose of the recommended primary series be administered by the age of 6 months. WHO recommends that all infants, including those who are HIV-positive, should be immunized against pertussis.

Considering that the duration of protection following primary immunization varies considerably depending upon factors such as local epidemiology, immunization schedule and choice of vaccine, a booster dose is recommended for children aged 1–6 years, preferably during the second year of life. The stated rationale for this preferred earlier boosting during the second year of life, is that this will improve protection following the primary immunization should a less effective vaccine (wP or aP) be used, thus preventing early accumulation of susceptible individuals. The timing of this booster would also to provide an opportunity for catch-up vaccination and allow for the use of a combination vaccine containing both pertussis and Hib antigens. The booster should be given ⩾6 months after the last primary dose.

Completion of this schedule (primary series plus booster) is expected to ensure protection against pertussis for ⩾6 years i.e. past the period of highest risk for serious pertussis.

Although vaccination can prevent pertussis in adolescents and adults, the WHO position paper states that there is insufficient evidence to support the addition of booster doses in these age groups in order to achieve the primary goal of reducing severe pertussis in infants. Decisions concerning such programmes should be based on both incidence and cost-effectiveness data; embarking on a strategy to vaccinate adolescents and adults

presupposes there is high coverage of routine immunization in infants. Only aP-containing vaccines should be used for vaccination in those aged >6 years.

In the Revised guidance on the choice of pertussis vaccines published in August 2014[2] as a result of the April 2014 SAGE recommendations, it is stated that "available evidence indicates that licensed aP vaccines have lower initial efficacy, faster waning of immunity, and possibly a reduced impact on transmission relative to currently internationally available wP vaccines." This is likely ascribed to the fact that aP vaccines induce a different type of immune response (higher Th2-promoting antibody responses but lower Th1 and Th17 responses), which is less effective at clearing mucosal infections. Individual protection against severe or fatal pertussis in infancy and early childhood is acquired after a primary series of vaccination with either wP or aP vaccine in healthy infants." Based on the SAGE recommendations, WHO advises that "countries where <5 doses of pertussis vaccine (only 3 primary doses, or 3 primary doses plus 1 booster) are used/affordable should continue to use wP vaccines for primary pertussis infant vaccination. " "When considering a switch from wP to aP vaccines, countries need to consider the overall goal of their immunization programme. Disease-related mortality in the first year of life can be significantly reduced using a primary series of either wP or aP vaccination, whereas the protection of older children or adults requires repeated boosting with aP vaccines. "

The revised guidance acknowledged that the main aim of pertussis vaccination was to reduce the risk of severe pertussis including death in infants and young children. All children worldwide should be immunized against pertussis, and every country should seek to achieve early and timely vaccination, initiated >= 6 weeks and no later than at 8 weeks of age, and maintain high levels of coverage (≥90%) with at least 3 doses of assured quality pertussis vaccine.[5]
Individual protection against severe or fatal pertussis in infancy and early childhood is acquired after a primary series of vaccination with either wP or aP vaccine in healthy infants.

Evidence suggests that ≥90% coverage with effective vaccines leads to high levels of protection in children in the <5 year age group and that any reduction in overall coverage can lead to an increase in cases of pertussis.

Guidance on the prevention of mortality in the very young infants too young to be immunized is not included in this updated guidance document, although it was discussed

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[5] Vaccines of assured quality include vaccines produced in a country with a functional national regulatory authority (NRA), including vaccines prequalified by WHO. WHO defines a vaccine of assured quality as one that consistently meets appropriate levels of purity, potency, safety and efficacy, as judged through an independent review system competent to make an evidence-based decision on the product for a specific population in a specific context. Such a review system makes use of all available information, such as licensing dossiers, surveillance of field performance, lot-by-lot scrutiny, appropriate laboratory testing, current Good Manufacturing Practice, inspection of manufacturers, and evaluation of clinical trials. This definition therefore depends on the existence of a competent and functional regulatory authority (NRA) to regulate the product, as assessed by an external expert team using widely agreed indicators. This definition also indicates clear pathways to improve vaccine quality by strengthening national regulatory authorities, which WHO is actively engaged in doing. Only vaccines of assured quality should be considered for use in national immunization programmes.
http://www.who.int/entity/immunization/global_vaccine_action_plan/GVAP_secretariat_report_2013.pdf?ua=1

by SAGE in April 2014. This guidance will be included in a full updating of the pertussis position paper

Current national immunization schedules
Based on the analysis of the 2014 UNICEF/WHO joint reporting, there are many variations in country specific schedules, with 87 different schedules among the 194 WHO Member States. In addition to this variation, there is much evolution within countries, with changes of schedule from one year to another relatively frequent.

Notwithstanding, the coverage levels achieved with the booster dose(s) which are rarely measured and likely suboptimal in many countries, less than 30% (62/194) of the countries rely only on 3 doses of pertussis vaccine. Many countries offer a booster dose in the second year of life and/or at between the age of 6 and 13 years. The two following tables provide a summary of current schedules broken down by region.

WHO regions (N of countries)		Number of doses for <7 years			>7 years or adult doses	N of countries using aP	N of countries using ap in primary
		3	4	5 or more			
AFR	(47)	40	7	0	0	2	2
AMR	(35)	2	9	24	12	12	6
EMR	(21)	5	8	8	2	6	6
EUR	(53)	0	35	18	23	42	41
SEAR	(11)	6	3	2	0	0	0
WPR	(27)	9	13	5	7	13	13
Total	**(194)**	**62**	**75**	**57**	**44**	**75**	**68**

WHO regions (N of countries)		2, 3, 4 months	2, 4, 6 months	6, 10, 14 weeks	other with all 3 doses given <=6M	2+1 schedule	other
AFR	(47)	2	2	39	4	0	0
AMR	(35)	0	29	1	4	0	1
EMR	(21)	1	11	6	3	0	0
EUR	(53)	10	18	0	15	9	1
SEAR	(11)	1	4	6	0	0	0
WPR	(27)	2	5	11	9	0	0
Total	**(194)**	**16**	**69**	**63**	**35**	**9**	**2**

The African region (AFR) and the South-East Asian region (SEAR) and low/middle-income countries (LMIC) in Western-Pacific region (WPR) share the DTP schedule of 6, 10 and 14 weeks, without administration of a booster, using the DTwPHibHepB combination vaccine. This vaccine is also used mainly in Eastern Europe as well as low-income countries in the Eastern-Mediterranean region (EMR) and Latin America in a schedule of 2, 3, 4 months and ~18 month booster or 2, 4, 6 with 18 and 60 month boosters, respectively. High income countries in North America, Western Europe and the Pacific Region use the combination DTaPHibIPV vaccine, with or without hepatitis B, with schedules varying from 4 to 6 doses between two and 60 months of age.

The European region (EUR) is currently the only region where the majority of countries use an aP-containing vaccine for primary immunization. In WPR close to 50% of countries (13/27) use aP for primary immunization.

60% of countries use DTwPHibHepB, 12% use DTaPHibIPV, 12% use DTaPHibHepIPV, 3% use DTwP and 5% use DTaP. 8% use a different combination than these that are listed.

In AFR, all but 2 countries (Mauritius and South Africa) use a wP containing vaccine with a booster dose of aP or wP administered in 7 countries.

In the Americas, the primary vaccination schedule is more uniform at 2, 4 and 6 months in most countries and all countries but two (Haiti and Guyana) administer booster doses. All but 5 countries use wP containing vaccines for the primary course and an additional 3 countries use aP for older age groups. Ten countries have introduced TdaP for older age groups.

In EMR, four countries use mixed aP/wP schedules for their primary and/or booster doses, the other countries use a wP containing vaccine. Only one country (Saudi Arabia) uses exclusively aP. The poorest five countries (Afghanistan, Pakistan, Somalia, Sudan, and Yemen), use a three-dose schedule starting at 6 weeks of age without administration of booster doses.

In EUR, there is a lot of variations between country schedules. All countries use boosters and most use aP containing vaccines. Low and middle income countries are mainly using a 4 dose schedule with a booster before two years of age.

In SEAR, only wP containing vaccines are used, and 5 out of 9 countries administer booster doses.

WPR has a mixed picture both in terms of aP or wP use and in terms of schedules and this is related to the income level of countries. About half of the countries use wP, the other use aP vaccines, including China. Eighteen of the 27 countries administer an aP or wP containing booster.

Globally, of the 30 countries with the largest birth cohorts, 22 are exclusively using wP containing vaccines for their primary immunization and 14 of those countries only rely on a 3 dose primary vaccination course.

The combination DTwPHibHepB is the most popular vaccine across all WHO regions used in over 120 countries (60%), followed by DTaPHibIPV and DTaPHibHepIPV which are used predominantly in Europe and the Americas (12% of countries for each) . In addition 3% of countries use DTwP and 5% use DTaP, while 8% use a different combination.

The largest supplier of the DTwPHibHepB is the Serum Institute of India. Over 50 countries use this vaccine exclusively. Other manufacturers' products are used to a much lesser extent.

It is to be noted that the above mentioned information relates to administration of vaccines as part of the national immunization programmes. In some settings, the administration of the vaccine by the private sector, which may be significant, relies on the use of different vaccines and schedules.

Further all the above relates to the recommended age for vaccination and not to the actual age of vaccination and delays in vaccination are experienced for DTP1-3.

More specific information can be found in the LSHTM report.

In conclusion, there was a great variation in the schedules used globally with more consistency noted in relation to income (Higher income = 3p+1, DTaPHibIPV; Lower income = p3+0 or p3+1, DTwPHibHepB). All countries using aP employed a booster 1-6yrs. The specific product most widely included in national programmes is the pentavalent combination DTwPHibHepB vaccine manufactured by the Serum Institute of India.

Framing of the policy questions

The main incentives for countries to change the schedule would be an increase in vaccine impact in line with a greater control of the specific disease or reduced costs of the program (i.e. ideally by reducing the total number of doses administered or the administration cost per dose).

The pertussis working group and invited experts first discussed the specific criteria to be taken into consideration for specific vaccines/ schedules, including the age at first dose and interval between doses and related gains or trade-offs. The following priority/high level criteria to be taken into consideration during the deliberations to inform the policy questions were agreed upon:

- Maternal antibodies (conferring initial protection / interfering with early infant responses)
- Pertussis- diphtheria –tetanus epidemiology and particularly the epidemiology of pertussis in young infants
- Disease control objectives for all three diseases
- Coverage (at a given age)
- Regulatory approval of the vaccine
- Correlates of protection (circulating antibodies, memory, intervals between priming and boosting)
- Degree and duration of protection
- Reactogenicity in infants when spacing primary doses and booster
- Safety
- Potential co-administration of other vaccines (Hib, Hep B, IPV)
- Availability /licensed vaccines and licensing conditions
- Number of contacts/ number of shots per visit
- Number of doses needed with a specific schedule.
- How criteria differ for wP vs aP-based vaccines
- Cost-effectiveness
- Costs of changing schedules

The stated key policy questions were:

> Is there enough evidence to support the preferential use of different DTP-(X) immunization schedules?
> How does this differ for wP and aP-based vaccines?
>
> Is there enough evidence to identify criteria supporting the preferential use of different DTP- (X) immunization schedules?

Current schedules in use to be considered and then selected/ dismissed by the working group based on the available/not-available evidence included the following:

Age at first dose:
- 6 weeks
- 8 weeks
- 12 weeks and onwards

Number and timing of primary infant doses
- 3 doses using an accelerated schedule (6-10-14 weeks or 2-3-4 months)
- 3 doses using an extended schedule (2-4-6 months)
- 2 doses using an extended schedule (2-4 months and 3-5 months)
- 2 doses using an accelerated schedule (2-3months and 3-4months)

Infant-toddler booster
- None
- <9 months
- 9-11 months
- 12-14 months
- ≥15 months

Preschool booster
- None
- < 4years
- 4-5 years
- ≥6 years

Epidemiology of pertussis, diphtheria and tetanus

Age distribution of pertussis in the pre and post vaccine area
The discussions of the working group evolved around the presented figures, noting there were some for which only very few time points were available. The working group agreed that pertussis mortality would be seen only at 7 days minimum post-birth. The group also agreed that each age distribution curve should normally have only one peak and that a two peak distribution like that shown for Kenya would be more likely to be an artefact of the limited data in the context of an extended tail of the age distribution.

The importance of the case-definition and diagnostic tests used, which may differ throughout countries, was flagged.   It was questioned whether the evidence was

sufficient to demonstrate disparity between the countries is attributable to the different schedules used in the countries. Unfortunately the data do not supply information on these disparities.

Limited data on the distribution of recognised pertussis in unvaccinated (pre-vaccine) populations indicate that most individuals were infected in childhood, with > 50 %, exhibiting 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). This was based on typical clinical cases and in the absence of laboratory diagnosis. Similar patterns were observed in other countries, including in Africa and South Asia. Case fatality rates were high, in particular in infancy.

For the developing country-specific patterns of the pre-vaccine era appreciable mortality was reported also in older age-groups whereas in the US and England and Wales, most deaths occurred in the younger age-group. In developed countries the case fatality in younger age-groups was higher than in older age groups.

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, and a shift in the age distribution of pertussis to older ages, in particular in industrialized countries. The age shifts may, in part, be explained by an increasing awareness and recognition of the less typical disease manifestations in older subjects, as well as more sensitive surveillance and laboratory testing, and surveillance covering the entire life span, not only in children. Waning of the infant vaccine-derived immunity, combined with lower naturally-acquired immunity and boosting (as a result of lower community transmission rates) is likely to play a role in increased susceptibility in adolescents and adults.

Specific age distribution graphs are provided in the LSHTM companion document.

In conclusion, the prevention of infant pertussis is a key driver requiring DPT immunization to be initiated as early in life as possible.

Age distribution of diphtheria in the pre and post vaccine area

Prior to the introduction of diphtheria antitoxin and its widespread use, and to the development of diphtheria toxoid vaccines in the 1920s, diphtheria was widespread in most countries in Europe and in the USA and Canada. However, around the mid-1940s, many countries started to report rapid declines in notifications. Diphtheria declined to near elimination by 1980 when globally 97,164 cases were reported from all WHO regions. But beginning in the late 1980s, massive outbreaks occurred in the Russian Federation and newly independent states. In 2013, about 67% of 4679 cases were reported from India. Overall there has been a steady decline in the number of reported diphtheria cases to the WHO from 1980 to 2013 by every country (except the years of the Russian Federation epidemic). Diphtheria is now exceptional in many of the industrialized countries. The vast majority of cases in the industrialized countries represent importations from other countries where diphtheria transmission is still occurring.

From 1990 to 1997, a total of 115,088 cases of diphtheria were reported in Russia and Newly Independent States, including 3078 fatalities. During this period, 27–32% of the annually reported cases occurred among children (<14 years); 6–8% among adolescents

(14–17 years), and 58–68% in adults (18–19, and 40–49 years). Of 99,861 cases seen at the Gabrichevsky Institute, Moscow during this period, 32% of cases were in individuals aged <15 years old. Despite this massive outbreak, few related cases, exclusively among adults, were reported from other neighboring European countries (including the Netherlands, Belgium, Germany, Finland, Greece, and the United Kingdom) during this period.

A few other relatively small outbreaks have occurred in the past decade in countries such as Afghanistan, Ecuador, Paraguay, Haiti, Dominican Republic, Indonesia, Lao and Nigeria predominantly in children <14 years and most cases occurring in unvaccinated individuals. An outbreak of diphtheria in Thailand in 2012 revealed an unusual pattern, with most cases being 5-14 and 20-44 years of age. This age-grouping could be explained by changes in the schedule over time, and by cohorts 20-44 years having received less doses whereas in the younger group the outbreak mostly affected Hmong communities where vaccine acceptance is low.

Interpretation of data needs to be done with caution. Although WHO has a standard case definition, this is not uniformly implemented across WHO regions and countries. As no standard case-definition is implemented and it is unclear whether confirmed or clinical cases only are reported. It is further uncertain what is reported as a case of diphtheria (all types, carriers, close contacts) and toxic vs non-toxic *C. diphtheria.*

The underlying cause of the outbreaks was questioned, in particular for cases in mid-adulthood, (except the one occurring in the Russian Federation) i.e. in Yemen and Jordan i.e. was it a lack of booster doses or a lack in coverage? The overarching question being: Does diphtheria only occur in unimmunized?

The discussions of the working group evolved around the possible environmental burden, the waning of immunity, and the immunization coverage. The working group concluded that with circulation of the disease, in most cases, despite low diphtheria antibody levels in adults outbreaks of diphtheria do not occur. One probable explanation for the discrepancy between serological findings of low antibody levels at distance of the last booster and the rarity of cases in previously immunized individuals is that protection still persists despite undetectable levels of antibodies (or below the threshold considered for protection). The risk of acquiring diphtheria is hence not an issue at the population level but rather at an individual level.

Immunization protects against mortality but immunized individuals do acquire and transmit the disease. Maintaining high levels of antibodies, especially among children who are the vectors/amplifiers of disease, is crucial to protect against transmission and disease.

Both during the Russian Federation outbreak as well as the Indonesia outbreak government vaccination coverage rates were reported to be high, though a case-control study revealed that the coverage rates were very low for the cases.

Diphtheria would not be the main driver for the DTP schedule. The data demonstrated that the disease is well-controlled even if no booster is applied. There might not be individual-level protection but disease control was ensured with the current schedules, even if not including boosters.

In conclusion, the incidence of diphtheria was high in the pre-vaccine era in many countries and it affected young children but spared very young infants. With the introduction of routine childhood immunization in many industrialized countries during the late 1940s, diphtheria notifications steadily declined to record lows in 2012. Although immunity wanes over time, serologic studies show an expanding protective immunity to older age groups, most likely related to a greater Td coverage. Unfortunately, recent outbreaks in populations with low vaccination coverage were observed which mainly affected children <15 years of age.
In industrialized countries sporadic cases occur in older individuals mainly related to importations of diphtheria disease, e.g. in Australia.
The prevention of diphtheria does not require immunization to be initiated very early in infancy, nor repeat boosters, but to achieve a high coverage through infant immunization.

Age distribution of tetanus in the pre and post vaccine area

Data are very limited as surveillance is generally passive and even higher income country systems capture only 20-60% of the cases. In many LMIC, non-neonatal tetanus (nNT) is not notifiable and under-reporting is common.

nNT is defined as tetanus occurring at 29 days of age or older. Over half of nNT cases (47-82%) are associated with acute wounds, most commonly punctures and lacerations, but also including abrasions, burns and excoriations. nNT also is associated with a wide variety of non-traumatic conditions. Up to 30% of tetanus cases in published series have no known associated cause.

In the pre-vaccine era, the burden of nNT was as unclear as that of NT. Modeled estimates suggest that as many as 500,000 nNT cases occurred annually in the 1980s. 50-70% of nNT cases occurred in children who also had the highest age-specific incidence of the disease. Starting around 5 years of age, the number and incidence of cases in boys tended to be greater than those for girls.

In higher income (industrialized) countries, tetanus was relatively rare even before tetanus toxoid-containing vaccines (TTCV) were introduced. Incidence and mortality had slowly declined in association with urbanization, higher living standards, modern concepts of hygiene and other factors unrelated to vaccination.

The highest burden of tetanus in the pre-vaccine era occurred in neonates followed by children ≤15 years of age. After introduction of DTP in infancy, the incidence of paediatric tetanus has declined, as has NT and tetanus in adult women in association with TT administered to women of reproductive age (WRA). In countries where DTP and TTCV boosters have been in use for decades, an upward age shift in numbers and rates of nNT has been observed and tetanus has become increasingly rare. The upward age shift has been less striking in countries where only infants and women of reproductive age are targeted for vaccination with TTCV, however high coverage with the primary series was achieved only relatively recently in such countries. Pediatric tetanus (cases in children< 15 years) is very rare and usually occurs in unvaccinated children. The numbers of cases, incidence and mortality are all highest in older adults. Current susceptibility to tetanus (not being addressed by the maternal and neonatal tetanus elimination (MNTE) program is in

those who are inadequately immunized with TTCV, mainly adolescents and adult males in LMIC.

No new evidence was presented that would challenge the current evidence presented in the WHO Immunological Basis of Immunization series - Module 3: Tetanus Update 2006 and Module 2: Diphtheria update 2009 (available on the SAGE website) .

Vaccine immunogenicity, efficacy and effectiveness including of alternative and reduced schedules

Diphtheria and tetanus containing vaccines

Number of doses
Five studies compared 2 vs. 3 primary doses. Outcomes were assessed with low or very low level of evidence (limitations, imprecision; but includes evaluations on correlate of protection), suggesting that for both diphtheria and tetanus, 2 doses resulted in substantially lower antitoxin mean titers (factor down to 0.5) than three doses, one to seven months post primary vaccination. Data at one month after a booster dose are inconsistent for diphtheria, with 1 of 2 studies reporting lower titers for diphtheria and little or no difference for tetanus. Differences did not translate into a substantially decreased prevalence of putatively protective or otherwise dichotomized antitoxin levels. Appropriate not-per-protocol studies supported lower antitoxin titers after 2 compared to 3 doses soon after the primary series, and, for diphtheria, at age 3 years.
Among children aged 0-2 years during a diphtheria outbreak, the results suggest that vaccine effectiveness is >90% for one, two or three primary diphtheria doses given during the first 12 months of life; and among children aged 3-5 years, vaccine effectiveness >90% for two or three primary doses, or ≥99% after a fourth dose at age 2 years. Tetanus toxoid neutralizing titers were 20-fold higher one month after a 2nd dose in 6-mo interval, compared to no vaccination. Previous reviews provide further evidence[6], that 1 dose does not confer significant protection against DT but 2 doses result in protective titers in close to 100% in infants. Even higher titers and longer duration can be elicited following 3 doses.

Age at primary vaccination
Two studies on birth dose and two on other schedules addressed the effect of age at initiation of vaccination. A birth dose prior to a 2, 4, 6 month schedule did not provide higher antitoxin GMC against diphtheria or tetanus between age 6 through 9 months or after a booster in the second year or life(*Very low level of evidence*).Furthermore,   one study suggested that 3, 4, 5 vs. 2, 3, 4 month schedule provides similar antitoxin seroprevalence above a threshold of 0.01 IU/ml (ELISA) or GMC against diphtheria and tetanus, at one month post third primary or booster dose (*Low level of evidence*: indirect evidence as not using putatively protective levels, only one moderately large study). A single study suggested that initiation of vaccination with 3 primary doses at age 9-23 months compared to age 3-8 months does not provide higher antitoxin titers against diphtheria or tetanus (assay not per protocol) (*Very low level of evidence:* cohort with limitations, indirectness, imprecision). Appropriate not-per-protocol studies support the absence of a substantial effect from age at primary series initiation.

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[6] Orenstein WA, et al.Diphtheria and tetanus toxoids and pertussis vaccine, combined. In: Recent advances in immunization: a bibliographic review. Scientific pub no. 451. Washington: PAHO, 1983:30-51.

Intervals between doses

Three immunogenicity studies addressed the effect of length of interval on the outcomes with an overall very low level of evidence (limitations, indirectness, imprecision). Results suggest that an accelerated schedule results in lower level of antibodies (factor 0.5) after the third dose or during the second year of life, when compared to a schedule with an interval of around 6 months between 2nd and 3rd doses. One appropriate not-per-protocol study is compatible with higher antitoxin titers after accelerated schedule which is different from other available data. Higher D and T titers were observed after a 2 versus 1 month interval though no difference was found 1 year later.

Two studies with overall very low level of evidence (one single case control study with low sample size and large confidence intervals per number of doses; one small clinical trial with unclear allocation procedure) addressed the effect of any vaccination on the outcomes.

Impacts of boosters

The effect of any booster vaccination on the outcomes was addressed by one study, with overall very low level evidence (one single small RCT with unclear limitations, indirectness). The result suggests substantial increase in diphtheria and tetanus antibody due to booster vaccination at 18 months, following an initial 3, 4, 5 month schedule. The results suggest that delaying booster vaccination against diphtheria or tetanus to age 18 months, compared to 12 or 15 months, may yield higher antitoxin concentrations, while the differences likely do not translate into higher prevalence of putatively protective concentrations.

Overall very low level of evidence as most studies were relatively small, each question was addressed by only one or two studies, the outcomes (mean titers per group) were mainly indirect and the studies showed risk of biases (design, blinding, confounding).

With respect to the minimal interval between priming and booster doses it was noted that there were no data on intervals shorter than 6 months. Additional research on the minimal interval would be needed if shorter intervals were to be recommended.

In conclusion, there is some evidence available for all questions on DT primary or booster schedules, with limited level of confidence. Only one study evaluated vaccine effectiveness (VE).
- Concerning 2 vs. 3 primary doses there was a substantially lower mean antitoxin titer after primary series, but the difference did not persist during the 2nd year of life (rapid antibody decline regardless of the number of primary doses) and after boosting and did not clearly translate into a difference in clinical protection *(overall low quality of evidence[7]).*
- A long interval (6 months) between 2nd and 3rd dose provides substantially higher antitoxin titers for the 2nd year of life (*very low quality of evidence*).
- The birth dose (in addition to a 3-dose primary series) does not provide higher antitoxin titers (*very low quality of evidence*).

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[7] GRADE level 1 indicates very low quality of evidence, GRADE level 2 indicates low quality of evidence, GRADE level 3 indicates moderate quality of evidence, GRADE level 4 indicates high quality of evidence (http://www.gradeworkinggroup.org/)

-The age of initiation of a 3-dose primary series does not substantially impact on resulting antitoxin titer levels, (*very low quality of evidence*).
- Booster vaccination at age 18 months yields slightly higher antitoxin concentrations than earlier boosting, but does not offer better protection, (*low quality evidence*). Booster vaccination during the 2nd year of life after a 3-dose primary series substantially increases antitoxin titers.

Pertussis containing vaccines (wP and aP)

Whole cell pertussis vaccines (wP)
This section only presents summary information as extracted and copied from the companion LSHTM document on the wP vaccine schedules. Much more detailed and contextualized information appears in this document.

Immunogenicity data are difficult to interpret and compare for whole-cell Pertussis vaccines. There is no established immunological correlate of protection against pertussis disease[8], although PT is believed to play a critical role in protection against severe infant disease. Different wP vaccines may have different antigenic content and ways of production and controls, 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[9] suggest 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).

With respect to vaccine effectiveness by schedule, there is:
*   Moderate quality evidence (including 4 controlled trials and 3 screening and 3 case-control studies) that 3p schedules are effective against pertussis disease in the first 5 years of life.
*   Low grade evidence (no data from RCTs) that (2+1)p schedules are effective against pertussis at age 1-5 years (protection in under 1year old not included). Limited data on VE of 2 doses in infants under 1years 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.

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

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[8] Wirsing von König C. *Module 4: Pertussis*. Geneva: World Health Organization; 2009. Available at: http://whqlibdoc.who.int/publications/2010/9789241599337_eng.pdf
[9] Mueller J, Koutangni T. Comparative efficacy/ effectiveness of schedules in infant immunization against pertussis, diphtheria and tetanus: Systematic review and meta-analysis. Part 2: Whole-cell pertussis vaccine. Unpublished report to WHO. August 2014. (available on the SAGE website)

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.

Childhood boosters:
- 3p: Very low grade evidence on effect of booster dose in children under 5 years. Limited evidence of benefit.
- (2+1)p: No evidence relating to additional effectiveness of booster dose in children under 5 years

In the companion document information is also presented on vaccine effectiveness and duration of protection.

The literature search did not identify any study that measured wP effectiveness against pertussis death. However, a review of the evidence by the SAGE working group that was presented to SAGE in April 2014 (see Report of the SAGE pertussis working group, March 2014) looked at severe pertussis morbidity and hospitalization in infants less than 1 year of age as a proxy, given that the disease is likely to be more severe or fatal in infants, thus any vaccine-induced protection against severe disease may apply to pertussis death. The following table is extracted from this report and summarizes vaccine effectiveness against infant disease and hospitalization both for aP and wP vaccines.

Country/ Vaccine	Single dose	Two doses	Full primary schedule
Australia aP	VE hospitalization: 55% (95%CI: 43-65%)	VE hospitalization: 83% (95%CI: 70-90%)	VE hospitalization: 85% (95%CI: 75-91%)
England aP or wP	VE against infant pertussis disease: 62% (95%CI: 53-69%)	VE against infant pertussis disease: 85% (95%CI: 77-91%)	VE against infant pertussis disease: 95% (95%CI: 86-99%)
France wP	VE against infant pertussis disease: 58%	VE against infant pertussis disease: 87%	VE after 4 doses against infant pertussis disease: 84%- 100%
Germany aP	VE hospitalization: 68.0% (95%CI: 45.6-81.1)	VE hospitalization: 91.8% (95%CI: 84.7-95.7)	
USA DTaP/ Tdap			VE after 5 doses of DTaP, approx. 98% in first year after vaccination but declining to approx. 75% >5years after vaccination. VE of Tdap: 75% in the first year declining to 40% after 2-4 years.
USA DTwP/DTaP	VE against pertussis disease in ages 6-23mo: 50.5% (95% CI: -71.1-86.3)	VE in ages 6-23mo against pertussis disease: 80.1% (95% CI: 41.3-93.2)	

Based on this in April 2014 SAGE concluded that there is increasing and consistent evidence both from observational and analytical studies from a number of industrialized countries using aP and wP to show that a single dose of either pertussis vaccine in infancy has around 50% effectiveness in preventing severe disease, hospitalization, and death and that 2 doses of either pertussis vaccine offers higher protection (83%-87%).

The group concluded that timely delivery of the first dose as soon as possible after 6 weeks of age is critical, but the age at which the first dose is recommended should depend on the local epidemiology and vaccine delivery system. While on-time vaccination is crucial regardless of the schedule, the group reinforced that 1 or 2 doses are not sufficient and that completion of the entire recommended number of doses is needed to protect older age groups, which might not be at risk of death but still at risk for increased morbidity and who may contribute to transmission of the disease to unvaccinated young infants.

Acellular pertussis vaccines (aP)

For aP vaccines, 33 studies were retrieved by the systematic review (19 RCT and 14 observational) along with 11 not-per-protocol studies (7 RCTs, 2 observational). The section below just focusses on the studies that are informative in relation to the comparative schedule question.

For information on the effectiveness of one versus two doses of vaccine against death please refer to the previous section on wP vaccine and previous discussions from SAGE on this issue. SAGE concluded that evidence is not sufficient to assess a significant difference in vaccine effectiveness using different component aP vaccines; there is no evidence pointing to the superiority of one aP vaccine over another. The systematic review did not add additional robust information on the effectiveness of 1 or 2 doses but was used to generate the upper and lower bounds around the existing effectiveness estimates for the modelling by LSHTM.

The effect of initiation of a 3+1 schedule at 3 vs. 2 month of age was addressed by one RCT (1-month intervals) and one cohort study (2-month intervals). The proportions of seroconverters or Geometric Mean Titers (GMTs) after the 3rd dose or a booster are similar (*Low and moderate quality of evidence*). Delaying the initiation of a 3+1 schedule from 3-8 months to 9-23 months does not substantially increase immunogenicity (*Very low quality of evidence*).

The comparison between accelerated (3+0) and long (2+1) schedules was addressed by three studies (*Very low quality of evidence*). Schedules assessed were 2, 3, 4 months versus 3, 5, 9 months; 2, 4, 6 months versus 3, 5, 11 months) and 2, 4, 6 months versus 3, 5, 12 months. Only one study using the latter comparative schedule[10] looked at clinical effectiveness. This latter study indicated a lower risk of pertussis from 9 months after the first dose with the 3, 5, 12 months than the 2, 4, 6 month schedule indicating that this extended schedule with a late 3rd dose (acting as a booster) provides better clinical protection after the first year than one without a booster. No comparative efficacy data

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[10] Olin P et al. Measuring protection: a case study of pertussis vaccines – Swedish Trial II: secondary non randomized comparisons between two schedules of infant vaccination. Develop Biol Standard 1998:95211-20.

were available for other schedules considered by the working group (WG). In the immunogenicity study comparing 2, 4, 6 months versus 3, 5, 11 months antibody responses were higher at 7 months of age in the former group who had received 3 doses than in the 3, 5, 11 months group who had received only 2 doses by this age. Post dose 3 antibody responses were higher to two pertussis antigens in the 3, 5, 11 months than in the 2, 4,6 month group. In the immunogenicity study comparing 2, 3, 4 months and 3, 5, 9 months antibody levels after 3 doses in the accelerated schedule were similar to those after 2 doses in the extended schedule with no consistent differences between schedules after the third dose.

The comparison of 1-mo versus 2-mo intervals within a 3-dose primary schedule was addressed by 2 studies (*Very low quality of evidence).* The proportion of seroconverters and GMT are similar one month after the third dose. Of note is that the shorter schedule in one study implied later initiation.

The effect of any vaccination on outcomes was addressed by in total 13 studies on clinical efficacy/ effectiveness and 2 studies on immunogenicity.

Across various study designs, schedules and outcome definitions, absolute VE of 3 doses (3+0 or 2+1) is 59-95% (*Moderate to high quality of evidence*) and of 2 doses, 35-86% (*High quality of evidence*). The lower bound refers to a 2 component vaccine that did not proceed to licensure.

Using 3-dose schedules, VE tended to be lower in randomized studies (60-85%) than in purely observational (excluding unblinded RCT) studies (83-95%). In a single RCT using the old WHO definition and studying children <3years of age, a 1-component vaccine used in a 3, 5, 12 month schedule had slightly lower VE (95%CI 71-73%) than a 3-component vaccine used in a 2, 4, 6 month schedule (95%CI 78-84%).

Titers against included antigens after 3 primary doses of any vaccine compared to no vaccination are at least 50-fold higher one month after primary schedule and 4-fold higher 15 months later (*Moderate quality of evidence*).

The effect of booster schedule on the immunogenicity outcomes   was addressed by one study (*Moderate quality of evidence*). After a 3-dose primary series before age 8 months, timing of booster between age 15 and 18 months did not result in consistent or significant differences in immunogenicity.

The effect of any booster vaccination on the outcomes was addressed by one RCT (*Moderate quality of evidence*).

A previous review[11] deemed all tested pertussis vaccines efficacious. No data on 2- vs. 3-dose schedules at six months (GMT data or seropositivity) are available. Due to high levels of heterogeneity, summary statistics for efficacy of aP vaccines derived from meta-analysis were not appropriate[12] (only RCTs included).

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[11] Jefferson T. Systematic review of the effects of pertussis vaccines in children. *Vaccine*. 2003;21(17-18):2003-2014. doi:10.1016/s0264-410x(02)00770-3.
[12] Zhang L et al. Acellular vaccines for preventing whooping cough in children. Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD001478. DOI: 10.1002/14651858.CD001478.pub5.

In summary:
- 2 vs. 3 primary doses possibly result in substantially lower clinical protection and titers during 1st year of life, until the 3rd dose is given *(Very low to low quality of evidence).*
- 2+1 provides better clinical protection than 3+0 from 3rd dose on, unclear difference before this dose. No meaningful difference in immunogenicity. (*Very low quality of evidence*)
- The age of initiation and length of intervals of 3-dose primary schedule do not substantially impact on immunogenicity *(Very low to moderate quality of evidence).*
- There are inconsistent findings and variability of study design on relative immunogenicity of birth dose (before 3-dose primary series) *(Low to moderate quality of evidence).*
- No serological impact of timing of booster between 15 and 18 months (after 3 primary doses) was observed (*Moderate quality of evidence*)

Of particular relevance is that good level of control of severe pertussis in children and good individual protection was achieved in different countries using different aP primary schedules (i.e. different starting age, different interval between doses as well as different number of doses i.e. 2+1 versus 3 doses and different timing of booster doses). However, a resurgence of pertussis was observed in some countries a number of years after the switch from wP to aP (Australia, Portugal ,USA, UK) leading to an increased risk in unprotected infants including in those too young to be immunized[3]. Countries experiencing a resurgence had used different schedules to each other.

Reactogenicity of pertussis containing vaccines in children with focus on comparative reactogenicity for different schedules

DTwP: 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 quite large differences between different wP products. More detailed information is provided in the LSHTM report.

DTaP accelerated schedule vs. DTaP long schedule
Three RCTs, two of low[13][14], one of moderate risk of bias [15]; and two cohort studies, one of moderate[16] and one of moderate-high risk of bias[17] , conducted in Europe, the Middle East and East Asia were included. Mostly, there were no significant differences in reactogenicity between the accelerated and longer DTaP schedules. For some of the time

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[13] Li R et al, Immunogenicity and safety of a pentavalent acellular pertussis combined vaccine including diphtheria, tetanus, inactivated poliovirus and conjugated *Haemophilus influenzae* type b polysaccharide for primary vaccination at 2, 3, 4 or 3, 4, 5 months of age in infants in China *Vaccine*. 2011;29(10):1913-1920. doi:10.1016/j.vaccine.2010.12.103.

[14] Hoppenbrouwers K et al. Priming effect, immunogenicity and safety of an *Haemophilus influenzae* type b-tetanus toxoid conjugate (PRP-T) and diphtheria-tetanus-acellular pertussis (DTaP) combination vaccine administered to infants in Belgium and Turkey. *Vaccine*. 1999;17(7-8):875-886. doi:10.1016/s0264-410x(98)00273-4.

[15] Carlsson R et al, Safety and immunogenicity of a combined diphtheria-tetanus-acellular pertussis-inactivated polio vaccine-*Haemophilus influenzae* type b vaccine administered at 2-4-6-13 or 3-5-12 months of age. *The Pediatric Infectious Disease Journal*. 1998;17(11):1026-1033. doi:10.1097/00006454-199811000-00013.

[16] Kamiya H. Immunogenicity and Reactogenicity of Takeda Acellular Pertussis-Component Diphtheria-Tetanus-Pertussis Vaccine in 2- and 3-Month-Old Children in Japan. *Archives of Pediatrics & Adolescent Medicine*. 1992;146(10):1141. doi:10.1001/archpedi.1992.02160220027015.

[17] Acellular vaccines may enhance spread of whooping cough. *Reactions Weekly*. 2013;1482(1):1-1. doi:10.1007/s40278-013-7676-4.

points for erythema/redness, swelling/nodule, any systemic symptoms, and irritability there was a lower risk of adverse events with the accelerated schedule.

There were no significant differences in reactogenicity between the accelerated and longer (DTwP or DTaP) schedules.

Using modelling to explore the impact of different strategies in different epidemiological settings

This section presents the revised estimated resulting from the further work by A. Clark following the August 2014 meeting of the pertussis Working Group

The modelling efforts focused in estimating the direct effectiveness of wP schedules on pertussis deaths <5years. Aim of these efforts was to use nationally relevant data to estimate the direct effectiveness of two alternative wP schedules (2p+1 and 3p+0) on pertussis deaths <5years.   The focus on wP was justified by the fact that current WHO recommendations are that developing countries continue with wP for the primary vaccination series and that developing countries have most of the mortality burden from pertussis.

Parameters entering the model derived from national and international data sources: the distribution of pertussis deaths by age in weeks (pre-vaccine era) and the coverage of DTP1, DTP2 and DTP3 and first dose of measles containing vaccine (MCV1) (as a proxy for the DTP booster) by age in weeks as well as the vaccine efficacy by dose and the duration of vaccine-induced protection.

A modelling approach previously used to inform optimal schedules for Hib vaccination [18] 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 is 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. More detailed information on the parameters used for the modelling work is provided in the companion LSHTM paper.
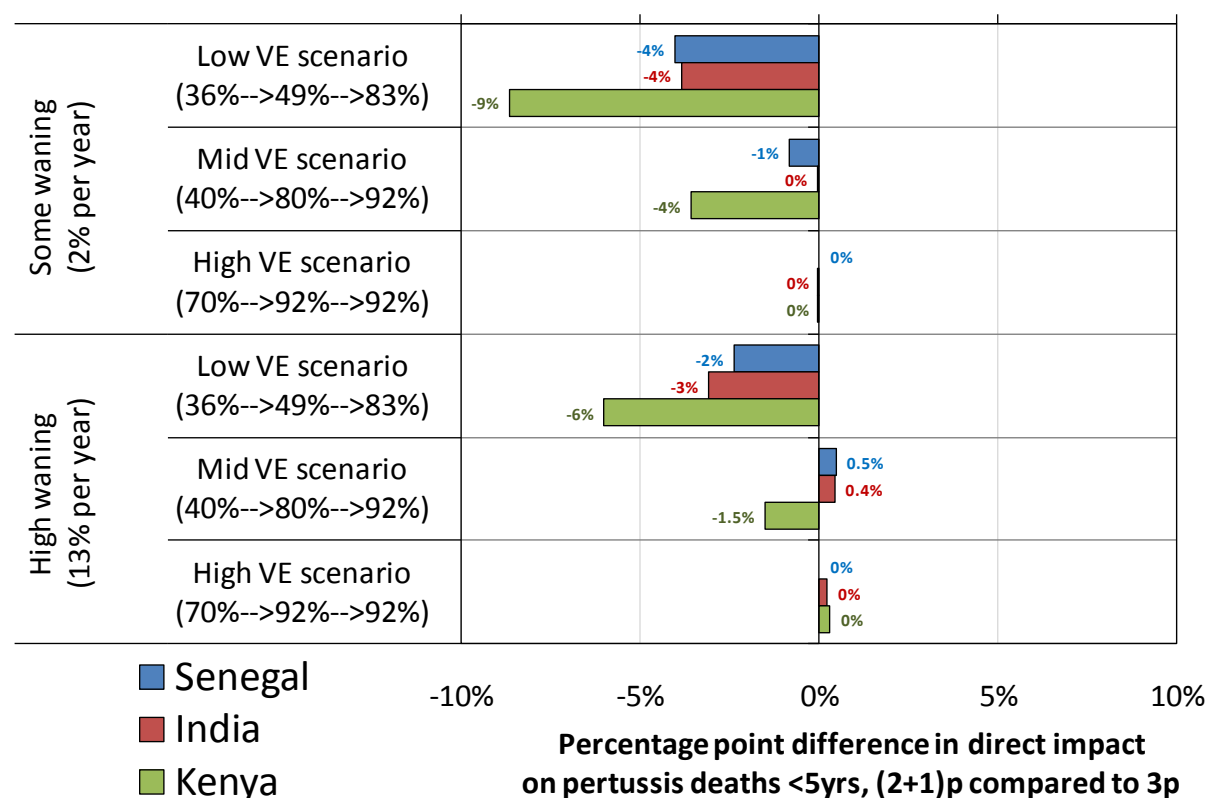
Figure 1 shows the percentage point difference in direct impact of 6w-10w-9m schedule compared to the current 6-10-14w schedule used in India, Kenya and Senegal. The direct impact of the 3p schedule is subtracted from the direct impact of the (2+1)p schedule to estimate the absolute difference in direct impact. Thus, positive differences indicate better direct impact with the (2+1)p schedule. Negative differences indicate better direct

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[18] *Haemophilus influenza* type b vaccination position paper – July 2013 Wkly Epid Rec 2013;88:413-428.

impact with the current 3p schedule. A low VE scenario would favor the existing 6-10-14w schedule in all countries. A 6w,10w,9m schedule is slightly favored only if the second dose VE is high (>80%) **and** if protection wanes rapidly. There are subtle differences between the three countries, which reflects differences in the age distribution of deaths (earlier in India) and differences in the coverage of each dose (higher and more timely in Kenya and Senegal), highlighting the need to account for local circumstances where possible.

Figure 1: Percentage point difference* in direct impact vs pertussis deaths <5yrs: (2+1)p compared to 3p in Senegal, India and Kenya

* Note. 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.

A number of additional scenarios were also evaluated (Figure 2):

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[19]. This was the most heavily skewed distribution to younger ages of all the pre-vaccine era distributions identified in the review. 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)';

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[19] Sako W. Early immunization against pertussis with alum precipitated vaccine. *Journal of the American Medical Association*. 1945;127(7):379. doi:10.1001/jama.1945.02860070011004.

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 ;

iv.   Fourthly, 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 6w, 10w, 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.

Figure 2. Percentage point difference* in direct impact vs pertussis deaths <5yrs: (2+1)p compared to 3p in <u>Senegal</u> – alternative scenarios

Percentage point difference in direct impact on pertussis deaths <5yrs, (2+1)p compared to 3p
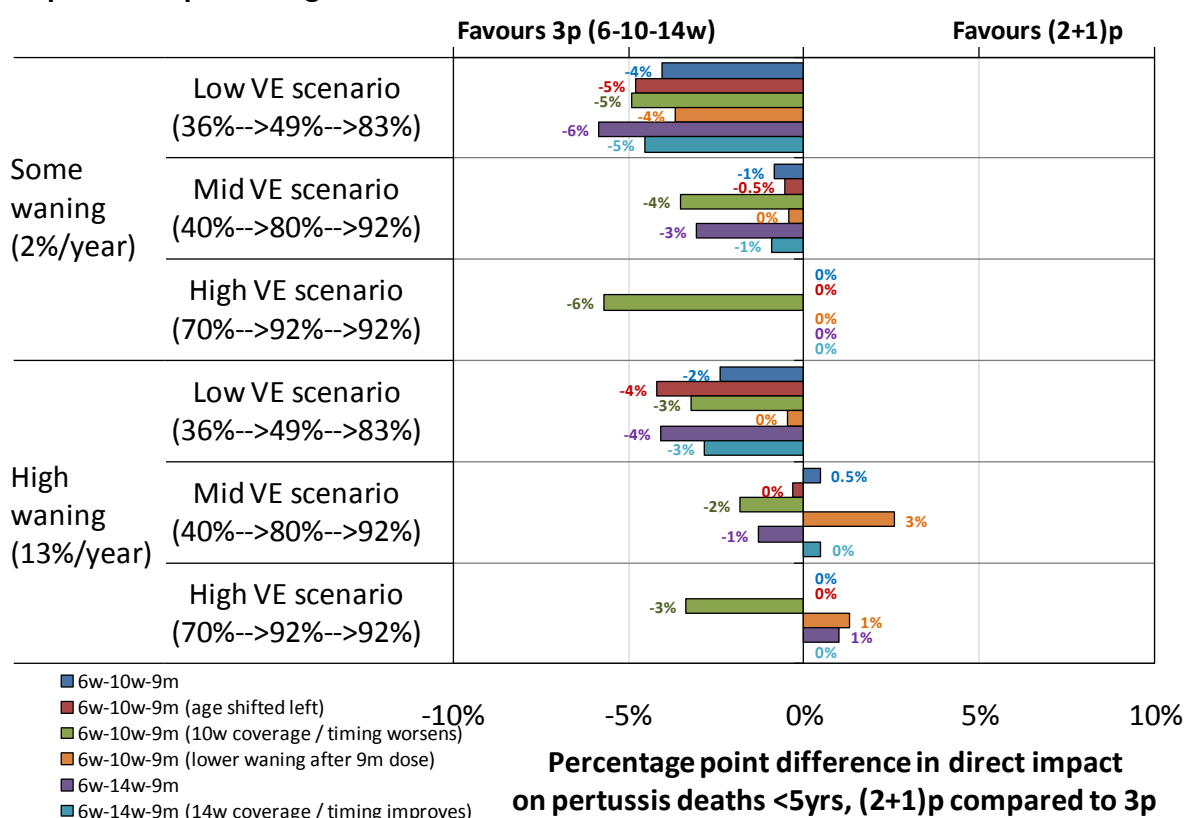
In conclusion, there are large uncertainties around highly influential parameters included in the model (e.g. the rate of waning clinical protection) as well as uncertainties about the potential role of parameters that were not included (e.g. herd effects). In most scenarios which assume at least 80% protection after the 2nd dose (the midpoint assumed in this evaluation), a 6w,10w,9m schedule is

likely to achieve 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.

Conclusions and recommendations

The following summarizes the working group's considerations on the available evidence for each previously framed question. Working group members first reflected on the available evidence in support/against DTwP/DTaP schedules and the evidence on timing of booster doses (aP and wP) before moving to the deliberations on the conclusions and recommendations.

Evidence to support/prevent the use of following DTwP schedules:

Age at first dose
Should be as early as possible ≥6 weeks, thus late schedules not considered further.

2p+0 primary schedule at 6,10 weeks/ 6,14 weeks
No evidence supporting either schedule without additional doses

2p+1 primary schedule at 6,10 weeks plus infant booster (<1 year)
No clinical data from LMIC
Concerns that this schedule would create a window of vulnerability for pertussis between the 2nd dose and the booster as seen in the UK when a 3, 5, 10 month schedule was used before the change to a 2,3,4 months schedule .

2p+1 primary schedule at 6, 14 weeks plus toddler booster
Lower responses against T and D until boosting
Concerns that this schedule would create a window of vulnerability for pertussis between the 2nd dose and the booster

3+0 primary schedule at 6, 10, 14 weeks
High VE in 1st year of life
Booster doses for tetanus needed to maintain circulating antibodies (though the number and intervals need to be defined)

3p+1 primary schedule plus infant booster (<1 year)
3 primary doses already ensure protection against DTP for the first year of life, so no infant booster required.

3p+1 primary schedule plus toddler boosting (1-6 years, preferably in 2nd year of life)
This schedule ensures protection for at least 6 years.

3p+1 primary schedule plus preschool booster
Greater reactogenicity of the booster dose than with aP; prefer aP for preschool booster

3p+1 primary schedule plus adolescent/adult booster
wP not licensed for the use in adolescents/ adults; aP should be used for adolescent / adult booster

Evidence to support/preventing the use of following DTaP schedule:

Age at first dose:
As early as possible ≥6 weeks.

3+0 primary schedule (none of the evidence has been assessed with a 6, 10, 14 weeks schedule)
High VE against pertussis in 1st year of life
Tend to be lower VE in 1st year of life than wP (although may not apply to all vaccines),) faster waning, lower boostability with increasing doses
Boosters doses for tetanus needed to maintain circulating antibodies (though the number and intervals to be defined)
No clinical evidence available (only seroresponses)

2p+0 primary schedule at 6, 10 weeks/ 6, 14 weeks
No evidence supporting either schedule without additional doses
Immunogenicity will most likely be insufficient
Concerns that this schedule would create a window of vulnerability for pertussis

2p+1 primary schedule at 6, 10 weeks plus infant booster
No evidence available to support this schedule (accelerated priming)
Immunogenicity will most likely not be sufficient
Concerns that this schedule would create a window of vulnerability for pertussis between the 2nd dose and the booster

2p+1 primary schedule at 6, 14 weeks and infant booster (9-12 months) :
No data from LMIC
Demonstrated efficacy of 2 doses of aP against hospitalisation/mortality (Scandinavian countries, Italy – though with later initiation of the schedule) but later protection is questionable
Risks of this schedule:
Tendency for lower VE than effective wP and faster waning.
Limited boostability with increasing doses?
Reduced coverage and delayed DTP3 coverage may lead to less protection in children having received only 1 dose for many months
Transient reduction of infant Ab responses in presence of maternal antibodies (significance?)

6-14 weeks and toddler booster (2nd year of life):
Waning efficacy after two doses of aP containing vaccine (P and D)

3p+1 primary schedule plus infant booster (<1 year)
No evidence available

3p+1 primary schedule plus toddler boosting (1-6 years, preferably in 2nd year of life) / preschool booster
Proven effective to prevent infant pertussis mortality
Booster dose should be based on the local epidemiology
Booster dose should be based on the aim of the immunization program

3p+1 primary schedule plus adolescent/adult booster
No evidence available

Evidence on timing of boosting (aP and wP):

Toddler booster (2nd year of life)
Useful after 3 primary doses of aP vaccine to reduce morbidity in young children and reduce exposure of infants (based on epidemiology)
Lower reactogenicity with aP than wP

Preschool booster (4-6 years)
Useful to reduce pertussis morbidity in school children (based on epidemiology)
The pre-school boosting is also beneficial for sustained protection against tetanus and diphtheria

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Pertussis vaccine was considered to be the main driver of the deliberations on the use of different schedules, given its relative importance in particular in light of protecting infants against pertussis-related mortality. It was reemphasised that the recommended immunization schedules should ensure a maximum of flexibility to countries in order to tailor immunization schedules based on their local epidemiology, the objective of their immunization program as well as to programmatic issues. There are gaps in knowledge for the timing of diphtheria and tetanus boosters in order to rationalize the optimal schedules to achieve long term or lifelong protection

The working group underlined the recommendation that the first primary DTP dose should be given **as early as possible ≥6 weeks of age**. Thus, later schedules (e.g. 3, 5, 11 months) were not further discussed.

In terms of the data on the different schedules, the working group concluded that there was no evidence in support of any 2p+0 primary schedule, 2p+1 primary schedule at 6-10 weeks plus infant booster, or 3p+1 primary schedule plus adolescent/adult booster.

Concerning a 2p+1 schedule at 6-14 weeks plus an infant booster (9-12 months), even given the high effectiveness of 2 doses of wP and aP against pertussis death, the main risk was assessed to be related to excess deaths if DTP2 dose was only given at 14 weeks (or later, in real life) as this would lead to an increased risk in children having received only 1 dose until the age that they are given DTP2. A primary series at 6, 10, 14 weeks would likely lead to a higher coverage of children with DTP2 at an earlier age.

On a 3p+0 primary schedule at 6, 10, 14 weeks, the high vaccine effectiveness against pertussis infant mortality was underlined. Protection against diphtheria seems to be sufficient with 3 primary doses in most settings. For tetanus, boosters would be needed to ensure circulating antibodies i.e. continuous protection.

A 3 primary doses plus toddler boosting (1-6 years, preferably in 2nd year of life) / preschool booster schedule demonstrated duration of protection and high vaccine effectiveness against pertussis for 6 years. Dependant on the aim of the immunization program and the local epidemiology, administration of a booster would a) reduce pertussis morbidity in children, b) reduce exposure of infant siblings to pertussis, c) ensure continued protection against tetanus and diphtheria beyond the first year of life.

Implication for Hib vaccine

Further the working group discussed the possible impact and implications for Hib vaccines particularly for countries using pentavalent vaccines. For Hib vaccines the two key factors are the need for an 8 weeks interval between dose 1 and dose 2 when a 2 primary doses plus a booster (2+1 schedule) is used; and if a 6,10,14 weeks schedule is used the uncertain need for a booster to ensure longer term protection. As stated in the *Haemophilus influenza* type b vaccination position paper – July 2013[18], there is currently insufficient information to determine whether or not there is a need for a booster dose, which may be influenced by local epidemiology, co-administered vaccines, and the potential for natural boosting as well as other factors.

Hence, when using a Hib containing pentavalent vaccine is used, this would advocate against a 6w, 10w, 9m 2p+1 schedule. The working group acknowledged that the 4th dose of hepatitis B within the pentavalent vaccine was administered essentially for programmatic issues, though it is assumed that administering the third dose later within this schedule would be rather beneficial.

A 3 primary doses plus toddler booster and d) when using a pentavalent vaccine, ensure continued protection against Hib beyond the first year of life

The working group concluded that concerning the timing of the pertussis booster dose, no revisiting of the current statement was needed, as it was clearly phrased and there was no new information regarding this schedule. The pertussis booster dose should be administered at 1-6 years preferably in 2nd year of life (booster 6 months after primary doses). This contact could further be used as catch-up for other vaccines. This schedule should ensure protection for at least 6 years for countries using wP vaccine. For countries using aP, protection may not last as long as evidenced in the USA and Australia.

In conclusion the WG recommended the following:

1. **That on the grounds of protection against pertussis, diphtheria and tetanus the current schedule remains the preferred option for countries where it is currently used as there is no compelling evidence to recommend a change to a 2+1 schedule (e.g . 6w, 10w, 9m or 6w, 14w, 9m).**

    This is because:
    Epidemiological evidence does not suggest that current wP and aP vaccines induce rapid waning within the first year of life which might favour a late dose at 9 months.

    Overall the epidemiological evidence indicates that there is additional benefit for pertussis from the 3rd dose and delaying its administration until 9 months may impact on course completion and, without rapid waning, would reduce overall protection against severe disease in the first year of life

    For pentavalent Hib-containing vaccines there is benefit for the Hib component from the 3rd priming dose if given with one month intervals between doses. If pentavalent DTPHepBHib vaccine is given as a 2+1 schedule then there needs to be 8 weeks between doses (i.e. this would require a 6w, 14w, 9m schedule). Delaying the second dose to 14 weeks of age would likely have deleterious effects on its coverage and on the protection against pertussis in the first year of life.

2. **That the pertussis booster dose should be administered at 1-6 years preferably in the 2nd year of life (booster 6 months after primary doses).**
This contact could further be used a as catch-up for the administration of other vaccines.

3. **That countries which are currently successful using alternate primary vaccination schedules as witnessed by adequate surveillance, can continue doing so.**

4. **That before contemplating a move from a 3+0 to a 2+1 schedule, countries should seriously consider their current epidemiological situation, and the potential implications in terms of potential impact on pertussis and Hib in the context of the vaccination coverage achieved at different ages, as well as timeliness of immunization.**

5. **That given the costs inherent to any change, a change in vaccination schedule and strategy should be informed by data.**

6. **That it is important for countries to try to reach the highest coverage possible with the current vaccination strategy, and to implement disease surveillance.**