Preamble
In 2004, pertussis was responsible for an estimated 18.4 million cases globally with infant mortality rates as high as 4%. At least 90% coverage with 3 doses of the diphtheria-tetanus-pertussis vaccine (DTP3) remains an immunization program priority worldwide; however, there are still an estimated 23.5 million infants without DTP3. Pertussis has not received sufficient attention in recent years and difficulties with pertussis disease surveillance have resulted in an under-recognized disease burden. Given these concerns, as well as increasing pressure on countries to use acellular pertussis vaccine (aP) or additional vaccination strategies particularly in Europe and North America, the SAGE Pertussis Working Group on Vaccines was formed to review the current recommendations on vaccine use and disease surveillance.

Meeting Proceedings
The first in-person meeting of the SAGE Working Group on Pertussis was held on September 2-3, 2009 at the WHO Headquarters in Geneva, Switzerland. The meeting agenda and list of participants can be found in annexes 1 and 2, respectively. A pertussis session is planned for the 27-29 October SAGE meeting. The objective of this Working Group meeting was to review the current evidence and prepare evidence and recommendations for SAGE review and decision.

Session 1: General Issues

Introduction to WHO vaccine position papers and role of Working Group
Liz Miller opened the meeting and presented the main tasks for the working group which include:

- Review evidence and prepare for a SAGE review of impact of current vaccination strategy and surveillance efforts
- Review recommendations on vaccine use (as per 2005 pertussis vaccine position paper) and surveillance strategies, and identify important information gaps

She identified the following key questions to be considered by the working group:

1. Surveillance, burden and impact
   - Should control goals be established for pertussis at the regional or global levels? And if so, how should these goals be formulated?
   - Is current surveillance sufficient to properly monitor progress and inform policies? And if not, what additional efforts are required?

2. Primary vaccination schedule
   - What is the optimal primary immunization schedule (age of 1st dose, number of doses and interval between doses) for pertussis?
   - Is there a need for a birth dose?

3. Supplementary vaccination activities
   - Is there a need to change the current recommendation on use of pertussis vaccine boosters? If yes,
     i. What should be the recommended age for the booster dose?
     ii. Should more than one booster dose be recommended?
     iii. Should additional booster doses be recommended (adolescents, adults)?
   - What is the optimal vaccination strategy to prevent early infant deaths?
• What should be the recommended use of vaccines in response to periodic epidemics?

4. Vaccine Issues
• Should WHO change its recommendation when it comes to use of whole-cell (wP) and aP vaccines?
• Are vaccines including aP and wP interchangeable for primary series and booster doses?
• Are there any issues with combined vaccines?
• What are the vaccines that can be co-administered with pertussis/DTP vaccines?

Philippe Duclos reviewed the developmental process for WHO position papers and gave an outline of the expected format. Position papers must fit the Weekly Epidemiological Record format, and this format recently underwent some changes. These changes include the removal of a summary, referencing, word limit (4000-6000 words), and inclusion of grading of evidence. The GRADing scheme was reviewed, as well as specific issues and limitations relevant to vaccine recommendations (including its emphasis on randomized clinical trials). He explained that the role of the Working Group is to identify the key evidence, propose recommendations, identify key recommendations that require a systematic review and grading of evidence, and review of final grade tables.

The timeline for Working Group activities was presented as follows: WG review of scientific evidence (occurring now), SAGE meeting presentation of a first set of draft recommendations for decision by SAGE in October 2009. This will be followed by another face to face meeting of the working group in preparation for a final review by SAGE at its April 2010 meeting. This will then lead to the updating of the pertussis vaccine position paper with a publication date in the summer of 2010.

During the discussion following these first two presentations, members of the Working Group expressed concern that the GRADing scheme was not flexible enough for vaccine evaluations and that randomized trials do not take into account the public health value of the indirect effects of vaccination. SAGE has made recommendations based on evidence even with low levels of quality of evidence according to the GRADE approach but that this is indeed raising communication challenges.

The possible need for a cost effectiveness evaluation was raised. Philippe mentioned that the work could be commissioned as needed and that IVR has a document defining criteria for doing cost effectiveness analysis (QUIVER). Additionally, it was mentioned that tools exist that allow individual countries to input their own data and modify parameters to see the impact on cost effectiveness.

Current WHO recommendations: 2005 pertussis vaccine position papers and current immunization schedules
Philippe presented all key recommendations from the 2005 pertussis vaccine position paper and reviewed current pertussis immunization schedules as per information communicated by countries on the 2008 UNICEF/WHO joint reporting form.

The primary aim of pertussis vaccination is to reduce pertussis mortality of infants and to decrease the incidence of pertussis among young children. The programme priority is to obtain at least 90% coverage with 3 doses of DPT in infancy. The optimal schedule is not well defined
and the 2005 position paper acknowledges the great variability of schedules and gives flexibility. The recommendations state that the need and timing of additional booster doses should be assessed by national programs and based on epidemiological situation. No preference is given towards aP vaccines and no interchangeability issues are mentioned. Surveillance is encouraged as well as outbreak investigations. Philippe also presented summary data from an LSHTM study highlighting that children are not receiving timely vaccinations.

Session 2: Surveillance, burden, and impact of current vaccination strategies

Global pertussis surveillance: WHO guidelines and global picture

Peter Strebel gave an overview of the current state of global pertussis surveillance. Most of the recommendations from the WHO pertussis surveillance meeting that occurred in 2000 were implemented except for the recommendation calling for the establishment of a regional pertussis laboratory network linked to sentinel hospitals and integrated with other existing or developing bacteriological networks and the recommendation that operational targets for reductions in pertussis morbidity and mortality be developed and presented for discussion at the World Health Assembly. The 2003 WHO surveillance guidelines, in which the routine surveillance recommendations differ according to high versus low coverage settings, have not been implemented in many member states. For example, in 2008 when all 193 WHO member countries were expected to have pertussis cases, only 109 (56%) of countries reported 1 or more pertussis cases and 43 (22%) countries reported laboratory-confirmed cases. In addition few outbreaks have been the object of proper investigations. The IVB laboratory manual for the diagnosis of whooping cough was published in 2004 and revised in 2007 and a generic protocol for estimating the burden of pertussis in young children was published in 2005. While the content of both manuals is current (except for the need to adjust the general considerations on use of serology), very few locations have implemented the recommendation approaches to pertussis surveillance or disease burden estimation. The reasons for not using the available guidelines include low awareness of pertussis among health professionals, lack of capacity for laboratory diagnosis, and the absence of pertussis champions (both at the national and at international level) to advocate for greater financial resources for pertussis control.

The challenges of pertussis laboratory diagnosis and absence of a laboratory network to support clinical diagnosis remain a major hurdle to improving surveillance. Some countries have implemented PCR, but the costs of reagents and transportation of specimens as well as major problems of false positive as well as false negative results and quality control have limited its usefulness.

The discussion revolved around the pros and cons of using sentinel sites as a means of establishing some laboratory-supported surveillance for pertussis in developing countries. While sentinel sites may be limited to larger cities and would not be representative of the entire country, they would provide laboratory capacity to confirm the endemic nature of pertussis in the catchment population of the sentinel site and the opportunity to document outbreaks in other parts of the country. The need to investigate outbreaks was also stressed. The possibility to use lymphocytosis as part of the diagnosis was also discussed.

Surveillance in the American region

Mauricio Landaverde presented an overview of coverage and disease surveillance data from the PAHO region. He also discussed the partial cocooning strategy (vaccination offered to mother and another member of the family/household) that was introduced in Costa Rica in response to a
reported increase in cases and deaths. A small decline in incidence has been seen since the implementation of cocooning, however the strategy has not been fully implemented and a direct relation with the decline in cases cannot be established. The PAHO region has an established case definition for pertussis, but reports are accepted without verification of compliance with the case definition and without laboratory confirmation or a completed case investigation form.

Pertussis control was on the agenda of the August 2009 PAHO TAG meeting. The TAG concluded that the epidemiology of pertussis must be properly studied in Latin America to guide the decision-making process, and that PAHO must support countries in this initiative. The joint CDC/Sabin Vaccine Institute/PAHO project aimed at strengthening the pertussis surveillance system in 3 countries is a way of creating evidence that can facilitate the decision-making process in pertussis control. The TAG made the following recommendations relating to surveillance and programme monitoring:

- Countries must consider pertussis control as a priority and strengthen their surveillance system and control measures.
- Changes in immunization policies and control measures should only be justified with adequate documentation and analysis of the basic causes of outbreaks.
- The current emphasis on PCR for pertussis diagnostics in the field makes obtaining cultures seem less important. However, since PCR can result in false positive results due to contamination or false negative results due to poor specimen collection, it should be stressed that obtaining specimens for culture is still essential for confirming the diagnosis, especially in neonates.

During the discussion the importance of outbreak investigations was emphasized. Representatives from the Eastern Mediterranean and Western Pacific Regions indicated that they learn about outbreaks when assistance is needed and that pertussis outbreaks are generally not considered to be significant public health issues unless they are accompanied by infant deaths. Laboratory confirmation of outbreaks is a recurring challenge.

With respect to establishing pertussis control goals or other measurable targets for monitoring programme performance, three approaches were mentioned:

1. Using the existing 2010 GIVS coverage target of DTP3 coverage of 90% at national level and 80% in every district
2. Tracking the contribution of pertussis to achieving the GIVS target of reducing mortality due to vaccine preventable diseases by two-thirds by 2015 compared to 2000 levels (this will require an acceptable mathematical model that can be used to generate annual estimates of country-specific pertussis deaths)
3. Establishing a quantifiable target for reduction in pertussis incidence (this would be difficult because improvements in pertussis surveillance would likely confound any real reductions in disease incidence)

**Burden estimation model: methods and results**

Dr. Hélène Broutin presented the approach the NIH group is taking to update and improve on the current model published by Crowcroft et al. in 2003. The key innovations in the NIH approach are: 1) inclusion of burden estimates for age-groups greater than 15 years of age; 2) a protective effect after receipt of 2 doses of vaccine; 3) waning immunity following natural disease and following vaccination; and 4) use of country-specific CFRs.
There was significant concern that the model did not distinguish between infection and clinical cases. Working Group members agreed that the purpose of the model was to estimate the burden of pertussis cases (i.e., clinically relevant disease) and pertussis-related deaths. Hence, the assumptions and parameters used in the model should be appropriate for this purpose.

The coverage data used in the example seemed incorrect. The modelers agreed to confirm they were using the latest (2008) WHO/UNICEF coverage estimates.

The parameter for vaccine efficacy was also believed to be too low and it was suggested that they change it to 80% efficacy after 3 doses. In addition there was discussion as to whether different vaccine effectiveness estimates should be used for protection against disease vs. protection against death.

The choice of an on/off variable for waning immunity was strongly felt to be problematic because it led to sudden jumps in the estimated number of cases that tremendously undermine the model credibility. Working Group members encouraged the modelers to model waning immunity using existing data (e.g., the Jenkinson paper). A possible approach to waning immunity may be to assume protection remains constant for the first 5 years after vaccination or 15 years after natural infection and then wanes in a linear manner over the subsequent 10 years (i.e., protection against clinical disease has fully waned by 15 years after vaccination and 25 years after natural disease).

The model has yet to be validated using real data. Working Group members requested that they at least use available data from Sweden and Senegal (if available) to test the model. The data from Sweden is available online and it is in a publication in press. Also, it was suggested that the modelers consider country specific force of infection parameters since mixing patterns may differ substantially between countries and that data from Senegal could be used to evaluate this.

In response to many of the concerns raised by Working Group members, the modelers explained that the purpose of the models is not to give answers but to define the questions and that putting too much emphasis on the results may not be a useful approach.

Working Group members asked to see estimates of mortality from the model.

**Session 3: Primary Immunization Schedule**

**Results of rapid reviews**
Nicola Low presented the findings from the commissioned rapid review of published literature that focused on three key questions:

1. How many doses of pertussis vaccine are required for primary immunization?
2. What is the optimal age for the first dose and
3. What is the optimal interval between primary doses?

The rapid review utilized Embase.com, WHO clinical trials portal and expert opinion and was restricted to Jan 2002 to the present. Eligible study designs included randomized and quasi-randomized and two reviewers screened all abstracts. Overall conclusions from the 19 studies included in the qualitative synthesis were as follows: no evidence to support an optimal schedule; limited new evidence; evidence was based on immunological outcomes only; studies did not address number of doses or intervals and they did not include a safety assessment. The Working
Group was asked to consider whether a full systematic review was warranted that could include a broader search strategy.

During the discussion, many of the Working Group members expressed concern that excluding observational studies unnecessarily ignored relevant data and that generally speaking it would be very difficult to design a randomized trial that would answer the questions posed. However, without some exclusion criteria the quantity of studies to review would make a systematic review of observation studies impossible. The Working Group members were encouraged to define the relevant outcomes and to specify the types of observational evidence that could be considered credible. The consensus of the group was that a more detailed systematic review would probably not yield additional useful information; however they identified several key observational studies from Sweden, UK, USA and Australia that should be reviewed.

Session 4: Supplementary Vaccination Activities

Need and timing of booster dose(s)
Scott Halperin covered the need and timing of pertussis booster doses. Primary immunization can be defined as one or a series of exposures to antigens that result in an initial IgM antibody response that transitions to an IgG response over time with the induction of memory B cells. Booster doses are a subsequent exposure to vaccine antigen to re-stimulate a waning immune response or reinforce a primary immune response. The booster response is characterized by a rapid IgG antibody response as a result of pre-existing memory B cells. Currently WHO recommends that a booster should be administered 1-6 yrs after the completion of the primary series, but before 7 yrs. The recommendations also state that the need for additional booster doses should be assessed by the individual national immunization programs. The first booster is given because antibody levels drop quickly after the primary series and the pre-school booster is given in some countries to address cases in school-aged children and the rapidly diminished antibody levels following the 18 months booster. It is difficult to address the question of whether both the 18 months and pre-school booster are necessary, but there are examples of both or one or the other being recommended in developed countries. Consideration should also be give to how elimination of one of the pertussis boosters impacts the other antigens contained in combination vaccines.

The adolescent and adult booster was recently recommended in some countries (e.g., Canada, France, Germany and the US) to address an increased incidence in these age groups and the concern that they are the source of infection for young infants. The adult booster is also used in a few countries that have implemented the cocooning strategy to protect infants.

The discussion focused on the largely undetected burden of pertussis among adolescents and adults and the role they play as a source of infection and severe disease among infants. As countries strive to achieve higher levels of pertussis control, the addition of adolescent and adult booster doses are a rational approach to the prevention pertussis among infants. However, although the effectiveness and cost-effectiveness of these approaches begin to be well analyzed in developed countries, they need to be better documented, in developing country settings.

With respect to administration of the first dose at or shortly after birth, concern was raised that if the first dose of the primary series was given prior to 6 wks the other antigens would need to be removed and that aP may need to be given to prevent immunologic interference. It was unclear whether a standalone pertussis vaccine (monovalent) was feasible. There was consensus that
there was insufficient data to support the recommendation of the birth dose, that currently there isn’t an appropriate vaccine to use and that manufacturers have not expressed interest in conducting the necessary studies. Studies using a birth dose of either aP or wP vaccines are needed to evaluate immunogenicity and safety, however, better justification for such studies will depend on demonstration of the burden of infant disease and mortality especially in developing countries.

Optimal strategy to prevent early infant deaths including the role of vaccination of parents in disease prevention in neonates

Carl-Heinz Wirsing von König gave a presentation outlining possible strategies to prevent early infant deaths. He provided results from studies indicating that adults and parents are often the source of infection for unvaccinated infants. The proposed strategies are summarized in Table 1. A more in depth discussion of the pros and cons of each strategy was deferred until a later time.

Table 1. Strategies to prevent early infant deaths from pertussis

<table>
<thead>
<tr>
<th>Strategies</th>
<th>Primary Objective</th>
<th>Secondary Objective</th>
<th>Motivation</th>
<th>Experience</th>
</tr>
</thead>
<tbody>
<tr>
<td>Universal immunization of adults</td>
<td>Morbidity in adults, herd immunity</td>
<td>Reduce transmission to under vaccinated infants</td>
<td>Source of infection studies; herd immunity demonstrated; modeling data</td>
<td>Implemented in several countries; effect on infants not documented; need for epidemiological studies</td>
</tr>
<tr>
<td>Immunization of pregnant women</td>
<td>Morbidity and mortality in neonates and infants</td>
<td>Morbidity in women</td>
<td>Maternal antibodies protect against disease; low concentration in maternal sera; high agglutinin titers associated with protection</td>
<td>Not routinely recommended; ongoing studies; safety and immunogenicity documented</td>
</tr>
<tr>
<td>Immunization of newborns</td>
<td>Morbidity and mortality in neonates</td>
<td></td>
<td>Data suggests 1 dose may prevent severe disease; birth dose may alter immunogenicity of subsequent doses</td>
<td>Safety in small studies; variable vaccine composition; effect unknown</td>
</tr>
<tr>
<td>Cocooning</td>
<td>Reduce transmission to young infants</td>
<td>Reduce morbidity in adults and adolescents</td>
<td>Source of transmission data</td>
<td>Implemented in several countries; theoretical basis well documented; difficult to implement</td>
</tr>
<tr>
<td>Healthcare and childcare workers</td>
<td>Reduce transmission to pts and young infants</td>
<td>Reduce morbidity in healthcare workers</td>
<td>Healthcare worker contact with newborns; rates may be increased in HCW; outbreak documented</td>
<td>Implemented in several countries; effect not documented</td>
</tr>
<tr>
<td>Reinforce/improve current schedule</td>
<td>Morbidity and mortality in infants, toddlers and children</td>
<td>Herd immunity</td>
<td>Delay/missed doses prolongs period at risk</td>
<td>Reduced period at risk</td>
</tr>
</tbody>
</table>

Impact of vaccination during outbreaks
Stacey Martin presented on the use of pertussis-containing vaccines during outbreaks. She presented U.S. data highlighting that pertussis outbreaks occur in settings with high-vaccine coverage rates. Four possible vaccine options were presented, including: catch-up vaccination for those not up-to-date, accelerated immunization schedule in infancy, target booster vaccination and mass vaccination campaigns. The pros and cons of each were discussed and the supporting data was presented. Recently published data on the rapid booster response to the adult and adolescent booster was also presented, suggesting its potential usefulness in outbreak control.

During the discussion it was mentioned that it is important to distinguish between routine doses and additional doses that may be given during outbreaks. Also the type of vaccine and its indications for use (e.g. age limits) may limit its use during an outbreak. Working Group members generally agreed that during periods of elevated risk, catch-up campaigns are warranted and consideration could be given to the accelerated schedule.

**Session 5: Vaccine Issues**

*Comparative evaluation of wP and aP vaccines*

Kathryn Edwards presented a comparative evaluation of wP and aP vaccines with focus on both safety and effectiveness. The estimated efficacy of current wP vaccines is 70%-90% after 3 doses, depending on the vaccine type and protection is expected for 5-10 yrs. Data showing significant differences in antibody responses to wP vaccine was presented making the point that there is not one wP vaccine. This suggests that between wP vaccines there may be marked differences in their effectiveness in preventing pertussis. aP vaccines consist of one or more specific antigens and serologic responses to each antigen are measured by ELISA and functional assays. aP vaccines are less reactive than wP vaccines and may be better characterized and have more reproducible titers. Effectiveness of aP vaccine is estimated to range from 76%-89% and generally interference is not seen with other antigens in combination vaccines with the exception of Hib. In the discussion it was stressed that aP vaccines could not be considered to result in better protection than wP. The age cut off (6 years) generally put forth to no longer administer the wP vaccine was based in part on programmatic considerations and has no scientific basis.

*Interchangeability of vaccines*

Nicole Guiso presented on the interchangeability of pertussis vaccines. For wP vaccine strains are similar in terms of genomics but the expression of virulence factors depends on growth conditions used by manufacturers. Differences in wP and aP vaccines can have consequences at the level of human population and at the level of pathogen population. Furthermore adjuvants, combination with other vaccines, vaccine schedule and strategies can induce different consequences and therefore caution is needed in interpreting epidemiological data according to the country. Efficacious wP vaccines were demonstrated to induce a humoral and cellular response in humans against bacterial proteins and induce immunity targeting all constituents of the bacterium. Efficacious aP vaccines induce a humoral and cellular response against their components and induce immunity targeting the virulence of the bacterium hence vaccine induced immunity by the two categories of products is different. Following introduction of wP, the isolates corresponding to the vaccine type strains are no longer circulating but other types are being detected with similar virulence to vaccine strains and for which the vaccine afford a similar level of protection. Now aP are replacing wP vaccines and the immunity they induce is targeting the virulence of the bacterium and might directly control the virulent isolates. Using France as a model, she evaluated the hypothesis of whether aP vaccine might impact expression
of vaccine antigens. *B. pertussis* isolates in France expressed all four primary antigens until 2007 when isolates were observed that did not express pertussis toxin (PT) or pertactin (PRN). If the virulence of the isolates decreases it will be followed by a decrease in hospitalization rates, which is our major goal. However, it will be (i) difficult to collect isolates if their virulence decreases, (ii) no longer possible to diagnose disease using anti-PT antibodies, and (iii) introduction of specific real-time PCR for other *Bordetella* organisms will be necessary to evaluate their real incidence.

The relative merits of aP versus wP will be discussed more thoroughly at a later Working Group meeting.

**Combination vaccines and co-administration**

Peter McIntyre presented on the issues associated with combination vaccines and co-administration. Concomitant antigens in combination vaccines with DTP include hepatitis B, Hib, IPV, Men A/C. Using several examples he highlighted how increasing the number of combined or co-administered antigens can lead to an increased chance of bystander effects and unanticipated adverse events. For example, in a study looking at the immunogenicity of Pentavax, significant differences were seen in the antibody responses to hepatitis B between study groups and the difference persisted after the booster dose. Hib and pertussis vaccine interactions have also been documented although the clinical implications of these diminished Hib responses are likely minimal.

**Pertussis vaccine supply and cost**

Adam Sabow and Graegar Smith from Oliver Wyman shared some of the findings from their recently-completed assessment of the supply landscape and economics of inactivated polio vaccine-containing (IPV-containing) combinations. The assessment was commissioned by the Bill & Melinda Gates Foundation, in close collaboration with WHO, and built upon an evaluation completed last year on the supply and demand for IPV in the post-polio eradication era. Oliver Wyman analyzed the current and potential IPV-containing combination vaccine supply base as well as the underlying economics of different combination vaccine manufacturing configurations. The assessment included an in-depth look at the pertussis antigen, though it did not evaluate all sources of pertussis vaccine supply, but rather only those that currently have, or potentially could have IPV-containing combination vaccines. The assessment included extensive consultations with current and potential combination vaccine manufacturers.

As context, the underlying cost of acellular pertussis (aP) has historically been higher than whole-cell pertussis (wP) due to inherent differences in the manufacturing efficiency, differences in the scale of production, and royalties paid by aP manufacturers to the intellectual property holders. However, current and potential aP manufacturers are taking steps to improve the manufacturing efficiency of aP production. Some manufacturers are seeking to further optimize “traditional” methods of production while others are exploring entirely new methods of production - for example, using genetically-modified *B. pertussis* to improve pertussis toxin expression and potency or *E. coli* or baculovirus systems to express pertactin/69k. As a result, it is possible for the manufacturing cost difference between aP and wP to narrow considerably in the future, particularly when aP is produced at high scale and as royalties disappear with patent expiry. It is important to note, however, that on-going manufacturing costs are only one input into manufacturers’ vaccine pricing equation – manufacturers will also consider the significant investments required for new aP products and broader market dynamics.
Given current portfolios and new development timelines, the potential exists for the supply of wP and aP-based IPV-containing combination vaccines to increase significantly by 2013 to 2015. Some manufacturers are making specific choices around their products and others are delaying until further clarity is provided around demand. Providing guidance to the manufacturers soon on three dimensions will be critical to ensure that supply is ultimately matched to demand: 1) the desired antigen composition (i.e., pentavalent or hexavalent); 2) the characteristics of the pertussis component (e.g., aP or wP); 3) volumes of demand over time. This information will enable manufacturers to assemble their business cases and make the required investments. Lastly, since public policy will impact demand, it is important that the various antigen-specific policy bodies act in a coordinated fashion - policy on one antigen can impact the availability and affordability of combination vaccines as a whole.

**Session 6: General Discussion around Priority Questions**

*Proposed recommendations and planning for October SAGE Meeting*

The objective of this final session was to focus on the first two key questions to determine whether any clear recommendations could be made for presentation to SAGE in October.

1. Surveillance, burden and impact

   - Should control goals be established for pertussis at the regional or global levels? And if so, how should these goals be formulated?

     - The main emphasis should remain to reduce the severe burden of disease and mortality in young children and this should drive the WHO recommended vaccination strategies.

     - The existing GIVS immunization coverage and mortality reduction targets should be reflected in the revised position paper. Additional control goals could be established at country or regional levels depending on the performance of the immunization programme, quality of surveillance, and resources. These additional goals would result in an extended vaccination schedule/strategy

     - Pursuing a stand alone pertussis control goal at the World Health Assembly was unlikely to succeed; WHO efforts should rather be directed at supporting surveillance projects (pilots) in select areas similar to the approach taken by PAHO, CDC and the Sabin Vaccine Institute.

   - Is current surveillance sufficient to properly monitor progress and inform policies? And if not, what additional efforts are required?

     - Clearly not. A critical first step is to expand the laboratory capacity for diagnosis of pertussis in developing countries. This could be achieved through establishment of demonstration projects in selected countries. Linking these with the expanding network of laboratories funded by GAVI to support diagnosis of invasive bacterial diseases should be explored. Advocacy and funding to support these projects is urgently needed.
Because the highest risk of death from pertussis is in the first months of life, on-time vaccination can have a major impact on reducing pertussis deaths. It is important that monitoring of vaccination coverage focuses not only on coverage among infants (i.e., by 12 months of age) but also on on-time coverage.

2. Primary vaccination schedule

- What is the optimal primary immunization schedule (age of 1st dose, number of doses and interval between doses) for pertussis?

- After careful consideration of other possible schedules the WG members did not think there was enough supporting evidence to change the current flexibility allowed by the current vaccine position paper and privilege one schedule over another; however consideration should be given to combination vaccinations and co-administration. Where the risk of pertussis is high there is value in starting vaccination at 6 weeks. All agreed that the diversity of schedules needed to be taken into account and that the inclusion of other antigens will influence the decision making regarding optimal schedules. Pertussis may no longer be the sole driver of the EPI schedule and flexibility in the schedule may be needed; however the motivation for these other antigens and schedules should be apparent and changes should be carefully evaluated to assess possible impacts on pertussis.

- Possible alternative primary immunization schedules in early infancy should be better described to allow more systematic evaluation of the immunogenicity, safety, impact on disease reduction, and cost-effectiveness of competing schedules

- Is there a need for a birth dose?

- There was no evidence to support the inclusion of the birth dose. Further studies using both aP and wP vaccines are needed to evaluate effectiveness, safety and possible impacts on other vaccines.

Additional conclusions, discussion on Working Group activity plan till May 2010 and need for additional research

Within the next 5 years it is unlikely that the price of aP vaccines would be significantly reduced. There is currently no rationale to promote the use of aP vaccines and change the drive of the current vaccine position paper in this respect. However, considering that aP vaccines may reach a price comparable to that of wP vaccines in a 5-7 years range, more information on the comparative advantages of both products should be collected should be fostered including in developing countries.

The Working Group should consider the booster dose recommendation and what evidence is required to support the recommendation. It was agreed upon that countries that have the ability to look at doses received by age should determine who is currently receiving the later doses and
whether these doses given at older ages are booster doses or delayed doses. Also, the age at first
dose should be evaluated.

There is a significant need for new research, additional data and an improved understanding of
pertussis disease burden in countries using vaccine. SAGE could advocate for this new
research. SAGE should consider advocating for expanding current research platforms (Child
Health Epidemiology Reference Group (CHERG) and Pneumonia Etiology Research for Child
Health (PERCH)) to obtain additional information on disease burden and mortality estimates.
This is important to address lack of awareness and recognition that pertussis causes severe
disease and mortality in countries with limited surveillance.

There is a need to follow up with QSS on need for new clinical trials when new generations aP
vaccines (genetic deregulation) will become available.

The draft immunological basis module produced by Carl is a very useful background document.
It should be finalized pending receipt of comments from selected members of the WG and then
made available as a background document for the SAGE meeting.