Report from the Pertussis Working Group

Elizabeth Miller
SAGE Member and Chair of the Pertussis Working Group

29 October 2009

Geneva
Working Group Members

- **Elizabeth Miller** (chair), Health Protection Agency, England
- **Zulfiqar Ahmed Bhutta**, The Aga Khan University, Pakistan
- **David Durrheim**, Newcastle University, Australia
- **James Southern**, Medicines Control Council, South Africa (regulatory)
- **Joyce Ducusin**, Philippines (EPI Manager)
- **Kathyrn Edwards**, Vanderbilt University School of Medicine, USA (vaccines)
- **Rose-Marie Carlsson**, Swedish Armed Forces, (epidemiology)
- **Nicole Guiso**, Institut Pasteur, France (microbiology)
- **Scott Halperin**, Dalhousie University, Canada (clinical trials, epidemiology)
- **Peter McIntyre**, Children’s Hospital at Westmead, Australia (epidemiology, vaccines)
- **Carl H. Wirsing von Konig**, Institut für Hygiene and Laboratoriums Medezine, Germany (author of WHO Immunological Basis of Pertussis Immunisation)
Tasks for Pertussis WG

- Surveillance, burden and impact:
  - Update burden of disease estimates (model reviewed by QUIVER)
  - Do we need control goals?
  - Is current surveillance adequate?

- Optimal primary immunisation schedule
  - Age at 1st dose, interval between & number of doses (overlap with P Fine group)
  - Birth dose?

- Supplementary vaccination activities
  - Number of boosters and at what age
  - Outbreak response

- Vaccine issues
  - wP vs aP
  - Combination vaccines
  - Co-administration/interchangeability issues

- WHO pertussis position paper for SAGE to discuss April 2010
Focus for Today’s Session

- Update on the progress of the Working Group

- Requesting a SAGE decision with respect to the following:
  1. Programme goals and surveillance
     - Should control goals be established for pertussis at regional and/or global level?
     - Are current surveillance efforts sufficient, and if not, what additional efforts should be recommended?
  2. Recommendations for the primary schedule
     - What should be the recommendation for the primary immunization schedule?
     - Is there a need for a birth dose?
Primary aim of vaccination is to reduce incidence and severity among young children

At least 90% coverage with 3 doses of DPT in infancy remains the first priority
  – First dose may be given as early as 6 weeks of age
  – Optimal primary schedule and number of immunizations not well defined
  – Acknowledges the great variability of schedules (2 or 3 primary doses)

In countries where the incidence has been considerably reduced by immunization, 1 booster dose 1-6 yrs after primary series is warranted

Need and timing of additional booster doses should be assessed by national program and based on epidemiological situation

No preference for either aP or wP

No interchangeability issues are mentioned
First in-person meeting of the Working Group was held on September 2-3, 2009

- A detailed report from this meeting is included in the Yellow Book
- Presentation of updated burden of disease model (QUIVER)
- Review of pertussis situation in Americas (PAHO presentation)
- Results presented from a rapid review concerning the optimal schedule for primary immunization
- Review of evidence on birth dose
- Oliver Wyman presented an assessment of supply landscape and likely costs of aP containing combinations
Priority Area 1: Surveillance, Burden and Impact

- Since the pertussis surveillance meeting in 2000 the following have been achieved:
  - Revised case definition and case classification
  - Lab manual
  - Burden of disease tool
  - Estimate global disease burden

- Not achieved were:
  - Regional laboratory networks linked to sentinel hospitals
  - Operational targets for reductions in pertussis morbidity and mortality
Careful epidemiological surveillance of pertussis is encouraged worldwide to monitor diseases burden as well as the impact of immunization.

- Of particular interest are surveys comparing age specific incidences of pertussis in countries with different vaccine booster policies.

Detailed outbreak studies should be encouraged.
Reported pertussis incidence rate per 100,000 population, 2008

Source: IVB database

193 WHO Member States. Date of slide: 31 August 2009
Current Guidelines

- Surveillance Guidelines, 2003
  - Rationale for surveillance
  - Case definitions and case classification
  - Types of surveillance and data elements

- IVB Laboratory Manual, 2004 (revised in 2007)
  - Diagnostic approach depends on age and immune status

- Generic Protocol, 2005
  - Primary objective: to estimate incidence and disease burden in children <5 yr
    - Ongoing enhanced passive surveillance
    - Community-based surveys
    - Outbreak investigations
  - Secondary objective:
    - Incidence, hospitalization, CFRs among infants
    - VE of single dose against infant death
Pertussis Programme Goals

- No stand alone global goal for pertussis control

- Global Immunization Vision and Strategies
  - 2010 vaccination coverage target:
    - ≥90% nationally and ≥80% in every district
  - 2015 target for morbidity and mortality reduction:
    - 2/3 reduction in morbidity and mortality from vaccine-preventable diseases compared to 2000 level
Priority Area 2: Primary Immunization Schedule
# Pertussis immunization schedule by WHO region, 2008

<table>
<thead>
<tr>
<th>WHO regions (N of countries)</th>
<th>Number of doses</th>
<th>adolescent or adult doses</th>
<th>N of countries using aP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>4</td>
<td>5 or more</td>
</tr>
<tr>
<td>AFR (46)</td>
<td>35</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>AMR (35)</td>
<td>3</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>EMR (21)</td>
<td>5</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>EUR (53)</td>
<td>1</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>SEAR (11)</td>
<td>9</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>WPR (27)</td>
<td>11</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td><strong>Total (193)</strong></td>
<td>64</td>
<td>69</td>
<td>60</td>
</tr>
</tbody>
</table>

1\textsuperscript{st} booster (4\textsuperscript{th} dose) administered between 11 months and 7 years
2\textsuperscript{nd} & 3\textsuperscript{rd} booster (5\textsuperscript{th} or 6\textsuperscript{th} dose) administered between 18 months and 28 years

Source: WHO/IVB database, August 2009
Primary Immunization Schedule – Rapid Review

Questions to be addressed
- How many doses of pertussis vaccine are required for primary immunization?
- What is the optimal age for the first dose?
- What is the optimal interval between primary doses?

Eligible study designs
- Randomized and quasi-randomized
- 19 studies included in qualitative synthesis

Summary
- No evidence to support an optimal schedule
- Limited new evidence
- Immunological outcomes only
- Studies did not address number of doses or intervals
- No safety assessment
- Further systematic review not warranted
Birth Dose

Administration of first dose at or shortly after birth may protect infants at highest risk for disease and death

- If given prior to 6 weeks a monovalent aP may be needed to prevent immunologic interference
- No appropriate vaccine currently available
- Studies using a birth dose of both aP and wP are needed to evaluate immunogenicity and safety
  - Better justification for studies will depend on demonstration of the burden of the infant disease and mortality
Priority Area 3: Supplementary Vaccine Activities
Booster Doses

- First booster is given because antibodies drop quickly following the primary series.

- Pre-school booster is given in some countries to address cases in school-aged children and rapidly diminished antibody level following first booster.

- Limited evidence to suggest whether (or not) both boosters are necessary.
  - but there are examples of both or one or the other being recommended in developed counties.
Adolescent and Adult Booster

- Adolescent and adult booster was recently recommended in US, Canada, Germany and France
  - To address increased incidence in these age groups and concern that these age groups are the source of infection for young infants
  - Used in a few countries for cocooning strategy

- Effectiveness and cost-effectiveness need to be evaluated, especially in developing countries

- Additional uses of adolescent and adult booster included
  - Immunization of pregnant women
  - Targeting healthcare workers
  - Vaccination during outbreaks or in response to periodic epidemics
Priority Area 4: Vaccine Issues

- **Whole cell (wP) vaccines**
  - Induces immunity targeting all constituents of the bacterium
  - Efficacy is 70% to 90% after 3 doses depending on vaccine type
  - Protection expected for 5-10 yrs
  - Between wP vaccines there may be marked differences in effectiveness

- **Acellular (aP) vaccines**
  - Induces immunity targeting the virulence of the bacterium
    - Might directly control the virulent isolates
    - Isolates that don’t express PT or PRN have been observed in France
  - Effectiveness is 76% to 89% after 3 doses and interference is generally not seen with other antigens in combination vaccines
  - Less reactive than wP vaccines
  - Better characterized and have more reproducible titers
  - aP vaccines are not considered to result in better protection than wP
Combination Vaccines and Co-Administration

- Concomitant antigens in combination with DTP include
  - Hepatitis B, Hib, IPV, Men A/C

- Consideration should be given to combination vaccines and co-administration to assess possibly bystander effects and unanticipated adverse effects
  - Examples include
    - Hib and pertussis vaccine interactions
      - although clinical implications of diminished Hib responses are likely minimal
    - Pentavax hepatitis B immunogenicity
Pertussis Vaccine Supply and Cost
Oliver Wyman Assessment

- Affordability of wP vs aP
- Key cost drivers and ability to influence
- Supply of wP vs. aP
- Impact of antigen-focused policy bodies on the broader combination vaccine landscape
Proposed Recommendations
Should control goals be established for pertussis at regional and/or global level?

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

- There is no need for a stand alone global goal for pertussis control. Existing GIVS coverage and morbidity/mortality reduction targets can be applied to pertussis and 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.
Are current surveillance efforts sufficient?

- Clearly not, a critical first step is to expand the laboratory capacity in developing countries
  - Establishment of demonstration projects in selected countries and linking these with the expanding network of laboratories funded by GAVI to support diagnosis of invasive bacterial diseases
  - Advocacy and funding to support these efforts is urgently needed

- Monitoring of vaccination coverage not only on infant coverage, but also on-time coverage
  - Risk of death is greatest during first few months of life
What should be the recommendation for the primary immunization schedule?

- Not enough supporting evidence to change the current flexibility allowed by the current paper and privilege one schedule over another
  - Where the risk of pertussis is high there is value in starting vaccination at 6 weeks

- Pertussis vaccine may no longer be the sole-driver of the EPI schedule and flexibility is needed
  - But any potential negative impact on pertussis should be carefully evaluated
Additional Conclusions

- There is a considerable need for new research, additional data and improved understanding of pertussis disease burden in countries using vaccine
  - SAGE could advocate for this new research
    - Expand current research platforms including CHERG\(^1\) and PERCH\(^2\) to obtain disease burden and mortality data
    - Address lack of awareness and recognition that pertussis causes severe disease and mortality in countries with limited surveillance

- aP vaccines may reach a price comparable to wP in 5-7 yrs
  - more information on the comparative advantages of both products is needed

- Efforts should be made to track the contribution of pertussis to achieving the GIVS target of reducing mortality due to VPDs by 2/3 by 2015 compared to 2000 levels
  - requires further revision of burden estimation model to generate annual estimates of country-specific pertussis deaths

\(^1\)Child Health Epidemiology Reference Group
\(^2\)Pneumonia Etiology Research for Child Health
Next Steps

- Address remaining priority questions
  - Supplementary vaccination activities
    - Booster doses
    - Prevention of early infant deaths
    - Response to epidemics/outbreaks
  - Vaccine issues
    - aP vs. wP
    - Interchangeability issues
    - Combination vaccines
    - Co-administration