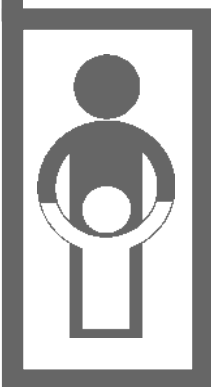


Informal consultation on the control of pertussis with whole cell and acellular vaccines

Geneva, 18-19 May 1998



**DEPARTMENT OF VACCINES AND
OTHER BIOLOGICALS**



*World Health Organization
Geneva, 1999*

CHILDREN'S VACCINE INITIATIVE



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Glossary

AEFI	adverse events following immunization
CBER	Center for Biologics Evaluation and Research
DT	diphtheria and tetanus vaccine
DTP	diphtheria-tetanus-pertussis vaccine
DTaP	diphtheria, tetanus and acellular pertussis vaccine
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FHA	filamentous haemagglutinin
HHE	hypotonic hypo-responsive episode
Hib	<i>Haemophilus influenzae</i> type b
IPV	inactivated poliomyelitis vaccine
PCR	polymerase chain reaction
PT	pertussis toxin
SDS-PAGE	sodium dodecyl sulphate - polyacrylamide gel electrophoresis

Executive summary

The global burden of pertussis is approximately 45 million cases and 409 000 deaths per year, with the highest incidence rates and major risk of deaths and complications occurring in the developing world. Current global coverage levels of 82% using three doses of DTP avert approximately 760 000 deaths each year due to whole cell pertussis vaccines, which have been shown to be efficacious in past and recent clinical studies. However, local and systemic side effects are known to be associated with their use. In addition, many uncommon and rare adverse events have been purported to be causally associated with whole cell vaccines. These concerns about vaccine safety led to the development of acellular pertussis vaccines. With the licensure and increasing use of acellular pertussis vaccines in many countries recently, the Children's Vaccine Initiative (CVI) and the World Health Organization (WHO) convened an informal consultation to discuss the global use of available whole cell and acellular pertussis vaccines in the years to come. Experiences with pertussis vaccines in several developed and developing countries were presented. It was concluded that the cost-benefit of the use of different vaccines will vary by country and by the whole cell and acellular pertussis vaccines in question. Whole cell vaccines will continue to be used by the vast majority of public health authorities for routine infant immunization for many years to come. The use of high quality vaccines is of utmost importance.

The meeting participants agreed the following major conclusions.

Pertussis epidemiology and surveillance

- In developed countries, control of reported pertussis is generally good but variable, and the morbidity and mortality of disease in under-vaccinated children indicates continuing circulation of *Bordetella pertussis*. Considerable variation exists in schedules of vaccination against pertussis. Many developed countries plan to continue to use whole cell vaccines for routine use in infants.
- Global surveillance data cannot currently reveal much more than general trends. This is due to problems in standardization of reporting systems, case definitions, varying diagnostic methods to confirm cases, and other inherent limitations of pertussis surveillance.
- The global burden of pertussis remains substantial, with approximately 45 million cases and 409 000 deaths per year by 1997 estimates. The highest incidence rates and major risk of deaths and complications occur in the developing world. Nonetheless, approximately 760 000 deaths are averted each year due to whole cell vaccination, currently at global coverage levels of 82% (strong regional variation) for three doses of DTP.

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- Further improvements in pertussis vaccination coverage will require addressing inappropriate contraindications and drop-out rates following the first DTP dose, as well as infrastructure improvements in some regions.
 - There are also limitations in interpreting selected regional or national data, which may be influenced by age-specific incidence, notification efficiencies, or regional epidemiology. Specific difficulties may relate to changes in surveillance methods, limited availability of laboratory confirmation, or problems in physician awareness and inherent impediments to diagnosis such as modified disease in vaccinated individuals and relatively insensitive standard laboratory methods. There may be considerable variation in the sensitivity of reported disease by age groups, with a higher proportion of reporting for young infants who are hospitalized.
 - Recent studies have suggested a significant occurrence of pertussis disease and infection in adult and adolescent populations. This is consistent with the continued cyclic variation of pertussis in countries with high immunization coverage, the clinical observation of many infants with pertussis evidently being infected by adults and older siblings in the household, and increasing proportions of illness reported in persons ten years and above in some countries. The actual rates of disease in older persons remain incompletely defined.
 - The experience in pertussis control and use of vaccines was presented for England and Wales and the United States as examples of developed countries. Public and professional loss of confidence in the whole cell vaccine led to very low coverage and increased morbidity and mortality in England and Wales. In contrast, while the concerns in the United States led to increased strength of anti-immunization groups, no change in vaccine coverage could be detected.

Acellular pertussis vaccines

- Several clinical trials and other studies have indicated the safety and efficacy of acellular pertussis vaccines administered with DT. The frequency of local reactions, fever, seizures and hypotonic hyporesponsive episodes (HHE) was lower following DTaP vaccination compared with the whole cell vaccines. These studies also indicated high observed efficacy of four of the five whole cell DTP vaccines studied.
- Acellular pertussis vaccines are in current wide-scale use for routine infant vaccination and booster doses in approximately ten countries around the world and their wide-scale use for booster doses is being considered or implemented in others.
- Recent data from two household contact studies using pre-exposure serologic specimens (Stockholm II and Erlangen trials) have suggested a correlation of protection with antibody to pertactin and fimbria type 2, while no significant correlation with antibody to FHA and PT was observed. The reasons for antibody to PT not being predictive may include its rapid decline following vaccination. Cellular immune responses were not evaluated in these analyses. Data correlating protection with serology are not likely to be available from any other future study. Comparison of immunogenicity data from the Swedish trials I (1992-95) and II (1993-96) indicated marked differences in responses to the whole cell vaccines studied. Following the randomized clinical trial in Gothenburg, children with the highest antibody to PT had half the attack rate of the other children.

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- Animal models suggest that all of the protective effect of acellular vaccines may not be due to antibody; these animal models show the protective effect of pertactin.
 - In Japan, which experienced marked increases in incidence following an increase in age of vaccination and declining immunization coverage, surveillance data reveal a return to low incidence with the exclusive use of several acellular pertussis vaccines. There has been a marked decline in compensation claims for neurologic illnesses following pertussis vaccination with acellular vaccines.
 - Although patents and proprietary rights limit serious consideration of immediate wider scale use of acellular vaccines in many countries, these patents are time limited. Collaboration of vaccine producers in developing countries with commercial manufacturers may be one way to increase access to these products.

Regulatory issues

- The Netherlands experienced a marked increase in the incidence of pertussis in 1996-97, predominantly in children two to ten years of age with relatively mild symptoms. The vaccine meets European Pharmacopoeia potency requirements, but responses to PT and pertactin are low. One observation was the variation over time in antigenic types of pertactin and PT in isolates obtained during 1949-96 in this population. However, this variation is probably not the major reason for the recently increased observed incidence.
- WHO guidelines have been written for the control of acellular pertussis vaccines, with the emphasis on ensuring the consistency of product characteristics. Many regulatory authorities consider each manufacturer's product as distinct, requiring full characterization, particularly given major differences in how the vaccines are prepared. Consistency extends to the manufacturing process, the physical characteristics of the product, and immunogenicity in animal models. Lots to be released should share these characteristics with reference vaccines shown to be efficacious.
- In Brazil, a recent episode occurred which compromised the national immunization programme for a time when the reporting of adverse events following immunization (AEFI) raised concern about some lots of imported vaccines. Questions were raised about vaccine toxicity test results of these lots. In many countries, the potential exists for rapid erosion of the public trust in immunization programmes unless preparation is made to monitor AEFI and interpret the reported data using international experience and the medical literature.

Factors influencing choice of pertussis vaccine

- With the change of immunization schedule in England and Wales in 1990 to younger ages, at two, three and four months, and increased coverage, fewer adverse events have been reported. Disease is under better control and, particularly given the result of the Sweden II efficacy study, acellular vaccines are currently being considered for future use only for booster doses, as is currently the case in France (at 11 years).
- In the United States, there is a clear transition to total use of DTaP vaccine following infant immunization with three vaccines which began in 1996-97. With fewer physician visits for adverse events following immunization, the use of the acellular vaccine is only slightly less cost-beneficial than use of the whole

cell pertussis vaccine in DTP. The gradual increase in reported cases, which is mostly due to an increase in the proportion of cases over age ten years, is thought to primarily reflect increased awareness of disease in older individuals.

- Whole cell pertussis vaccines have been used in all countries of the European Region, with high levels of disease control in many. Several of these countries are now in economic transition. Whole cell vaccines will continue to be used for routine infant immunization in the vast majority of countries of the Region for many years, although acellular vaccines are increasingly being used in some countries because of low coverage with whole cell vaccines.
- China has effected pertussis control using whole cell DTP, and has recently explored limited use of locally-produced DTaP vaccines. Currently, the crude incidence of pertussis is below 1 per 100 000 and the surveillance of disease was said to be estimated at 30-40% efficient in reporting of diagnosed pertussis. Safety concerns have not been raised about the whole cell vaccine. The current cost of acellular vaccines, accounting for under 0.5% of all pertussis vaccines used in China, prevents any consideration of wider use.

Recommendations

The following recommendations were agreed:

1. Whole cell vaccines of documented quality have proved to be highly effective tools for preventing pertussis. Acellular pertussis vaccines are valuable alternatives to whole cell vaccines for primary immunization in infancy. Because of the safety profiles, acellular vaccines may be a preferred alternative in industrialized countries where pertussis vaccination with whole cell vaccines is not widely accepted. In each country, recommendations for use of pertussis vaccines will be based on local risk-benefit and cost-benefit analyses.
2. Use of acellular vaccines can be considered for booster doses (fourth and fifth doses) to improve pertussis control after evaluation by local authorities of the epidemiological, cost and programmatic issues. Additional data on the potential benefit of booster doses using acellular pertussis vaccines in adolescence or older ages are needed.
3. A WHO working group may be helpful in addressing some aspects of pertussis epidemiology, including the three points below:
 - WHO is encouraged to develop and promulgate new case definitions for pertussis for surveillance purposes with consideration of all available information on the sensitivity and specificity of clinical and laboratory case criteria in children.
 - In developed countries with diagnostic capabilities, special surveillance studies are encouraged to examine the extent and relative importance of *B. pertussis* infection in adolescents and adults in various settings, and the field effectiveness of the various vaccines and schedules in use.
 - WHO should consider the development of new models to estimate the current burden of pertussis and disease averted at global, regional, and national levels.

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4. WHO should support a strong collaborating laboratory or laboratory network for the characterization (antigenic heterogeneity, antibiotic sensitivity) of *B. pertussis* isolates from around the world. The laboratory could also handle long-term storage of isolates.
 5. The current control requirements and recommendations for pertussis vaccines (whole cell and acellular) need review in light of recently available scientific data, following which revisions should be made where appropriate.
 6. National immunization programmes should be made aware that with the use of all vaccines, but particularly with the use of whole cell pertussis vaccines, the opportunity exists for AEFI to be reported. These events may be coincidental or caused by the vaccine due to programmatic errors or to its inherent properties. Surveillance of adverse events following immunization can be useful for detecting rare serious adverse events to monitor overall vaccine safety, but are particularly useful to monitor functioning of the immunization programme. Programme personnel first need full preparation for such surveillance. This preparation includes:
 - Public education on expected common and uncommon adverse events;
 - Training in investigation of reported illnesses after vaccination and collection of additional information;
 - Advice on clinical management of anaphylaxis and other rare medical events;
 - Appropriate public health responses; and
 - Appropriate responses to the public, medical personnel and the media.
 7. Manufacturers are encouraged to continue and further collaborative relationships with local producers for technology transfer, quality control and issues in the manufacturing process, with full involvement of the relevant national regulatory authority.

Summary of discussions

Introduction

An informal consultation of invited epidemiologists, infectious disease clinicians, immunologists, representatives of regulatory agencies for biological products and other scientists and public health officials was held in Geneva on 18-19 May 1998 on the control of pertussis using whole cell and acellular pertussis vaccines. The consultation was jointly called by the Children's Vaccine Initiative (CVI) and the World Health Organization's Global Programme for Vaccines and Immunization (WHO/GPV)¹. The meeting was opened by Dr Jong Wook Lee (Director WHO/GPV and Executive Secretary CVI), followed by introductory comments by Dr Mark Kane (WHO/GPV) and Dr Roy Widdus (Coordinator CVI). Dr James Cherry chaired the meeting and Dr Steven Wassilak was elected Rapporteur. The programme and the list of participants are attached as Annexes 1 and 2 respectively.

Scope and purpose

The main objectives of the meeting were to review:

- the current data available on the global epidemiology and surveillance of pertussis;
- possible correlates of immunity to clinical efficacy and the potential impact of antigenic variation on efficacy;
- issues in evaluating quality, safety, and efficacy of pertussis vaccines;
- current control of pertussis in selected developed and developing countries; and
- economic implications of vaccine choice for vaccine supply in developing countries.

Background

Increasing concerns about the effectiveness, and especially the safety of whole cell pertussis vaccines led to decreased public and professional confidence in their use in the 1970s and 1980s in Germany, Italy, Japan, and the United Kingdom. When routine use of whole cell pertussis immunization declined in these countries, the resulting epidemics of disease accelerated attempts to develop, license and use acellular pertussis vaccines. Concerns about vaccine safety threatened to reduce pertussis vaccine use in many other countries.

¹ GPV has since been restructured and a new WHO Department of Vaccines and Other Biologicals has been formed under the Health Technology and Pharmaceuticals cluster.

Several acellular vaccines were used in Japan beginning in 1981, and subsequently many studies have been conducted on the safety and efficacy of acellular vaccines. Data from these clinical trials and from post-licensure surveillance have indicated their overall improved safety over whole cell vaccines. Several acellular vaccines have been shown to be effective in protecting against pertussis, with the most rigorous data on efficacy arising from randomized clinical trials.

Public health control of pertussis has been achieved in most areas following routine use of whole cell vaccines over many years. Furthermore, review of the data in the medical literature supporting the safety of whole cell vaccines has supported their overall safety profile. Because recent data from clinical studies demonstrated high observed efficacy of several whole cell pertussis (DTP) vaccines, they remain strong tools for disease control and prevention. However, recent concerns have been raised about the changing epidemiology of pertussis in developing countries.

Epidemiology and surveillance

In 1997, an estimated 45 million cases of pertussis occurred, leading to approximately 409 000 deaths. In industrialized countries, the reported crude incidence (100-1000 per 100 000 total population) in the pre-vaccine era has fallen by 95-99%. The case-fatality ratio is currently reported to be less than 0.5% in developed countries. In developing countries, the annual incidence of clinical disease in children may be 4-15% depending on season and age group, but generally more than 90% of susceptible children experience pertussis by 15 years of age. The case-fatality ratio in developing countries approaches 3% in community-based studies and 15% in hospital-based studies.

Only 1-2% of cases are estimated to be reported globally, due to under-awareness, clinical diagnosis (incomplete or absent bacteriologic testing), and focus on hospitalized illness. Even in areas where diagnostic tests for *B. pertussis* are available, problems in recognition and reporting exist. In Nova Scotia (Canada), with active surveillance, up to 14-fold higher incidence was observed compared to passive surveillance areas. Up to 50% of cases reported in the United States are in infants. Over the last several years, however, many countries have reported an increased number of cases in older children. Adults and adolescents may serve as a dynamic reservoir source of infection for younger children.

Given the approximate global coverage with three doses of DTP of 80% over the last several years, approximately 760 000 deaths are estimated to be prevented each year. Barriers to higher vaccine coverage include high drop-out rates after DTP1 in some countries, extensive inappropriate contraindications and the increasing effect of anti-immunization pressure groups.

Dr Cherry indicated that study of persons at the early stage of cough indicates 18-25% of serologic or culture proven illness will have cough duration of less than three weeks. Persistence of the two to five year cyclic variation in pertussis incidence from the pre-vaccination to the post-vaccination era strongly suggests continued wide circulation of the organism.

The hypothesis that many cases of pertussis in adults are routinely occurring is based on observations that the apparent source of infection of many hospitalized infants is a coughing parent or other adult. Dr Cherry also stated that IgA antibody to pertussis antigens is nearly ubiquitous in adult sera. Serologic diagnosis has been proposed using single-serum levels that are set by comparison with the antibody level distribution in the general population. Using change in antibody titer or diagnostic methods based on various single-serum levels, studies of adult attendees of outpatient clinics with prolonged cough (more than six days to one month, varying by study) have indicated 12-26% with evidence of recent infection.

Studies in Germany similarly suggest 31-32% of persons with prolonged cough (>7-21 days) had such serologic evidence of infection. German studies also suggest one-fourth to one-third of adult infections were in persons with evidence of prior infection. If true, this would indicate that protection from past disease is not long lasting. With several large outbreaks in the US, a larger proportion of reported cases has been seen in 10-14-year-olds and older. Discussion by participants indicated that the data from studies using single-serum diagnosis have not fully validated its use and that questions of specificity remain, particularly given immune responses in previously vaccinated individuals. Data in France from several studies supports a relatively high incidence of atypical infections.

The sensitivity and specificity of clinical pertussis diagnosis varies by age group (since incidence varies by age group), and incidence (cyclic peak or not). Problems with pertussis disease reported to WHO include major changes in surveillance systems over time, lack of case definitions with known specificity, and use of sentinel systems from limited areas to generalize an estimated incidence. Data reported to WHO with inconsistent approaches to surveillance are yielding unclear global estimates, including coverage data. Surveillance data with constant surveillance systems are useful to examine trends and geographic variability, and could suggest changes in age-specific incidence rates, but problems remain in differential reporting by area and age.

Discussants suggested that special studies are needed to address changing epidemiology and vaccination strategies, issues that cannot be appropriately addressed using surveillance data alone. Data from the recent clinical trials were cited to demonstrate the differences in observed incidence by routine surveillance or by special studies. Based on existing data, clinical symptoms can be helpful for surveillance in many settings, but these may be difficult to apply universally.

The surveillance systems recommended by WHO include a minimum of routine monthly aggregate number of suspected and confirmed cases; in areas with higher vaccine coverage and evidence of disease control, case-based surveillance is recommended, or at least aggregate data collection by age group and immunization status. Alternatively, sentinel systems can be applied, or special time-limited studies. The data collected should allow review of objectives at the national level by examining monthly and annual incidence by geographic area at a minimum. Currently, WHO is reviewing how its estimates of pertussis incidence are made.

Recent scientific issues in vaccine use

Dr Patrick Olin presented recent data from the clinical trials of pertussis vaccines from investigators in Erlangen and Stockholm (Sweden). Because earlier attempts to find a serologic correlate of vaccine immunity, comparing post-vaccination serum specimens from cases of pertussis versus non-cases, failed, the design of the 1992-1995 clinical trial in Sweden and the trial in Germany included routinely collected serum specimens to serve as pre-exposure specimens if the child became ill. By following children in households of confirmed cases who became ill with cough of ≥ 7 days a fixed period of days after onset in a confirmed household contact (7-42 days in Germany, 5-56 in Sweden), and comparing to specimens of all other children (no relevant antibiotic exposure in Germany study), comparisons were made. In this way, 209 appropriately exposed infants were studied in Sweden, 87 in the German study.

In Sweden, using log regression analysis and each antibody result classified as high (≥ 5 units) or low (< 5 units), the greatest negative correlation was with anti-pertactin and there was some effect with anti-fimbrial (type 2 tested) antibodies. The lowest attack rate was observed when both of these antibody levels were high (with or without high antibody to PT); the highest rate was observed with low levels of antibody to PT, fimbria and pertactin.

In the German study, the significant negative correlation was with anti-pertactin, and again anti-fimbrial (2) antibody had a substantial negative correlation.

In the Erlangen study, there was a suggestion (not statistically significant) that there might be interference in protection if high antibodies were observed to both fimbria 2 and PT.

The conclusions were that anti-pertactin is the most important antibody, that FHA is probably not a major antigen contributing to protection, and that there are data to support inactive pertussis toxin and fimbriae 2 and 3 as incrementally additive antigens. The antibody responses to the vaccines in the trials in Sweden (as evidenced by reverse cumulative distribution curves) showed the superior responses following Wellcome whole cell vaccine to pertactin and fimbriae (and PT) compared to the whole cell vaccine from Connaught Laboratories, Inc. (CLI), consistent with the higher efficacy of the former relative to the latter. PT ELISA responses to the Wellcome vaccine were lower than to the two-component SmithKline vaccine (SB) in both studies, although higher than following the CLI vaccine.

Discussion concerned opinions on which components of acellular vaccines are essential. Dr Taranger noted preliminary serologic correlate studies from Gothenburg that indicated that the higher the response to PT, the lower the attack rate. The very low level of observed pertussis following the demonstration project in Gothenburg also caused those investigators to question the added value of other components. These were countered with arguments that active surveillance and surveillance over a more protracted period is needed to address questions of real and lasting changes in incidence/transmission of the agent. Dr Mills suggested that not all PT antigens are the same, as evidenced by differing responses in the mouse aerosol challenge model, and that antibody and cellular immune responses can be additive. However, others noted that cellular immune responses can be difficult to quantitate and are

currently measured as proliferative response to antigen or by cytokine responses. Additionally, using only the pre-exposure titers ignores issues on the differential kinetics in the loss of antibody, which may confound the observations for PT, for example (against which antibody quickly falls).

Dr Kreeftenberg presented data from the Netherlands, which had controlled pertussis with locally made whole cell DTP vaccine given at three, four, five and eleven months of age. During 1996-1997, a marked increase in pertussis incidence occurred, primarily among children two to ten years of age. The whole cell vaccine in use evokes little PT response but meets European Pharmacopoeia and WHO requirements. The characteristics of the PT and pertactin antigens from strains isolated from 1949 to 1996 were investigated. They showed increasing predominance of types 'B' and 'C' pertactin, although the vaccine contains only 'A'. Also, the S1 subunit of PT was found to alter in prominence over the years among the four identified types. The conclusion reached by investigators was that S1 and pertactin had drifted in predominance to be more antigenically distant from vaccine components. Participants noted that this drift has been seen in other countries, but was not associated with increase in disease, nor necessarily with vaccine use.

Conclusions of studies were also discussed by Dr Xing in which UK vaccine (containing type 'A' pertactin) was protective in the mouse aerosol challenge model against strains isolated in UK producing any type of pertactin.

The consensus of the participants was that the observed increase in cases in Netherlands is not adequately explained by antigenic variation in pertactin given these other observations. Further animal studies using more available acellular and whole cell vaccines may be helpful. Dr Robbins stated that the systematic collection of *B. pertussis* strains for antigenic variation and antibiotic sensitivity should be encouraged by WHO.

Vaccine quality issues

Dr Griffiths presented the role of WHO in defining standards in biologicals control which has led to international reference materials, requirements and guidelines. Quality control of biological products involves control of starting materials, the production process and the final product. There are existing WHO requirements for agreed procedures in the control of whole cell pertussis vaccines, and guidelines have been written for acellular vaccines. There is a lack of consensus about the antigenic composition of acellular pertussis vaccine, no unequivocal immunological correlates of protection and no generally accepted animal model validated to predict clinical protection. The quality control procedures recommended by WHO for acellular pertussis vaccines therefore emphasize physical characterization of the antigens, and strict adherence to production and formulation processes used in the manufacture of vaccine lots used to prove efficacy and safety in clinical trials.

Dr Schild stated that for the control of acellular vaccines, the modified mouse intracerebral challenge assay needs further evaluation, but there is agreement that immunogenicity in mice is one way to control the consistency of the DTaP products. Official international standards for antigens and antiserum are in preparation. As recommended in the WHO guidelines, the basis for current registration is that the characteristics of released lots of vaccine are consistent with lots studied in clinical trials and show consistency in manufacture.

Dr Meade noted that CBER/FDA standards in the United States are in line with this approach. Currently in the US, several multiple-component acellular vaccines combined with DT are licensed for infant use, and some for fourth and fifth doses. Given the absence of properties which are validated predictors of safety and efficacy, CBER/FDA evaluates acellular vaccines for licensure and lots for release in a similar manner: important issues are consistency in the manufacturing process, the physical characterization of the product, and consistency in immunogenicity in animal models. For licensure, CBER/FDA requires data on immunogenicity in humans for lot consistency and for consistency with vaccines shown to be safe and effective. With some allowances, this approach can also be used to evaluate combination vaccines. If validated immunologic correlates are established, testing for them may or may not be relevant for lot release, but may be relevant for validation assays (following changes in manufacturing or with combination vaccines). Correlates of immunity might also be helpful in establishing mechanisms of protection.

Dr Dellepiane indicated that WHO provides a service to UN agencies to evaluate the acceptability in principle of vaccines offered for purchase by pre-qualifying manufacturers on a global basis, with continual review. Review of a product file consists of examination of the production process, quality control testing to confirm lot consistency and relies on the national regulatory authority of the producing country. As other speakers noted, regulation of acellular vaccine is complicated by the absence of validated immunologic correlates and direct methods for assessment of potency, and because each manufacturer's vaccine is prepared and formulated differently, but questions about some whole cell vaccines have also been raised by recent data from clinical trials and surveillance. Problems with standardization of pertussis vaccines continue. Similarities and differences with tetanus and particularly diphtheria toxoids were discussed. Dr Olin pointed out that much has been learned since planning for acellular vaccine trials began in 1984, including the impact of active surveillance and diagnostic methods on observed results, and how the use of different antigens results in different findings, although direct comparisons for each antigen have not been possible.

Control of pertussis in industrialized countries

Dr Salisbury indicated the importance of public confidence in vaccines by discussing the United Kingdom experience when whole cell vaccine use was questioned. Vaccine use fell in England and Wales from 80% to 30%, with three major epidemics before high coverage (to 95% in 1997) has again resulted in low levels of reported disease. Surveillance in England and Wales is based on physician notifications, sentinel surveillance in primary care clinics for 10% of the population, and laboratory surveillance. Using sentinel surveillance, vaccine efficacy estimates for three doses of vaccine vary by age from 98% in children 6-11 months to 90% in children of 5-14 years of age. With the vaccine schedule changed from three, five and 8.5-11 months of age to two, three, and four months of age in 1990, the absolute number of reported cases in children under three months of age has not decreased substantially since 1982, although cases in other age groups have. Vaccinating earlier has contributed to increased coverage by reducing drop-out attributed to adverse events. A recent study using hospital discharge data linked with immunization data found no significant association of whole cell DTP with febrile convulsions in children under six months of age.

Current directions in surveillance are that all culture-positive pertussis cases will be thoroughly investigated, all hospital admissions for pertussis will be analysed regarding outcome and PCR, and serologic diagnosis will be offered to general practitioners and hospitals. Acellular pertussis vaccines are not being considered for routine primary immunization, but are being considered for booster doses. Any change in immunization policy must be determined to be cost-effective before being implemented.

Dr Livengood indicated that the United States is clearly in transition to exclusive use of acellular pertussis vaccines. Although the US avoided a major decrease in vaccination coverage, questions of AEFI and questions over the effectiveness of some whole cell vaccines (i.e., from Connaught Laboratories, Inc.) have propelled public policy in this direction. Liability issues forced many manufacturers to drop DTP vaccine production and distribution until only two remained on the open market.

Surveillance in the US is based on passive reporting, with an estimated 10% reporting efficiency. The reported incidence has fallen from 150/100 000 to 1.2/100 000 in the 1980s. A clinical case definition for summary of statistics is cough of ≥ 2 weeks duration plus paroxysms, inspiratory whooping or post-tussive vomiting. A confirmed case is any illness with isolation of *B. pertussis* or a clinical case with PCR-positive result or epidemiologically linked with a laboratory-confirmed case. From 1991-1998, the incidence during three-yearly peaks has increased, as has inter-peak incidence. Vaccine effectiveness estimates ('field method') have suggested an efficacy of 82% for whole cell vaccines in general, without an indication of decreasing effectiveness over several years. There has been an increase in the proportion of cases in persons over nine years of age, reaching 50% in 1996, including culture-proven cases. The 10-19-year age group displayed a 120% increase in reported incidence over 1990-1996, and cases in persons ≥ 20 years of age increased 100%; the age-specific incidence remained stable for children under one year of age, while timely immunization coverage increased slightly over this time.

The interpretation of the increase in reported disease is increased attention to illness and diagnosis in the older age group. Surveillance data analysis will be augmented by enhancing the collection of vaccine histories and quantifying the burden of disease in adolescents. For publicly-funded vaccine, the total number of AEFI reports following pertussis vaccination has decreased as acellular vaccine use has increased. Although the costs of vaccines are higher than whole cell vaccines, the decrease in AEFI is estimated to have saved US\$20 million in physician visits and antipyretic use.

Dr Sakai presented the experience in Japan. Acellular pertussis vaccines were introduced in 1981 and vaccination recommended for children aged under two years of age in 1988. Currently, three doses are recommended at < 12 months of age. Over 18 million doses of various acellular vaccines are distributed per year. In children 0-15 years of age with reported pertussis in a 1988-1992 outpatient study, a high proportion was predominantly unvaccinated (95%) or had received only a single dose (4%) compared with a smaller proportion in a 1972-1975 study (61% with 0 or 1 dose) when whole cell DTP vaccine was used. From this, public health authorities have inferred that the acellular vaccines in use are more effective than the whole cell vaccines. There is a compensation system for adverse events

following immunization that had more than 37 claims for neurologic illnesses per 10 million doses of whole cell DTP in 1970-1974; in 1995-1997 there were fewer than seven claims for neurologic illness per 10 million doses of acellular pertussis vaccines (and about two per 10 million doses in 1981-1988 when vaccine was administered only after two years of age). The overall rate of reported anaphylaxis is 13 per million doses distributed; the majority have been related to third or fourth doses of vaccine containing gelatin from production of diphtheria toxoid.

In discussion, Dr Cherry pointed out that in Japan also the reported pertussis incidence in children under three months of age has not declined substantially with return to a high vaccination coverage. There was much discussion about various reported observations on the frequency of hypotonic, hyporesponsive episodes (HHE). The United Kingdom has noted a marked decrease of reported HHE following the change in vaccination schedule, whereas in the 1993-1997 Trial II in Sweden, the observed frequency of HHE was significantly higher among Wellcome whole cell DTP recipients, generally at the first dose at three months of age, than in recipients of acellular vaccines. Therefore, distinctions must be made in discussing data from passive surveillance and active surveillance experiences. Also, in this trial, parents of participants were warned to look for these events so that overall increases in reported HHE (for acellular vaccines) may have represented a form of observer bias. All children in the study also received simultaneous *Haemophilus influenzae* type b (Hib) and inactivated poliovirus vaccines.

In the United Kingdom, antipyretics are in wide use, and minor AEFI following DTP are generally accepted. In the United States, common minor reactions and uncommon serious events attributable to DTP are apparently less acceptable to parents and clinicians, perhaps because there has been no recent history of marked increases in disease as in the UK. Administering the Wellcome whole cell vaccine for primary immunization is followed by a relatively low frequency of AEFI. It was noted that in the Netherlands, children with HHE following whole cell DTP go on to receive further doses without episodes. In France, a booster dose of licensed DTaP has been approved for reimbursement. Dr Guiso indicated that strong surveillance is important where changes in vaccination are being introduced, since use of acellular vaccines could improve the rate of completing primary immunization on schedule compared to use of whole cell vaccines.

Control of pertussis in developing countries and countries in transition

Dr Dittmann presented pertussis control in the European Region. In the 51 countries of the Region with 850 million people, more than half are developing countries or countries in transition following the political and socioeconomic changes of the early 1990s. Most countries have an overall incidence of pertussis disease of 3-10/100 000 total population.

Although reporting efficiency and surveillance systems differ greatly among the countries of the Region, some countries have reported (in 1991-1996) fewer than one case per 100 000 population (Belgium, Bulgaria, Czech Republic, Hungary, Iceland, Luxembourg, Portugal) suggesting strong disease control. Incidence rates higher than 10 per 100 000 have been reported in the Russian Federation, Spain, Switzerland, and Tajikistan; high rates were reported in Italy, Germany and Sweden, where acellular vaccines are now licensed and in routine or widening use. In 1991-1996, 10 of 47 reporting countries had a DTP3 coverage rate under 80%.

Vaccination schedules vary widely within the Region, in three to five dose schedules (most with four-dose schedules). Increases in incidence were noted in 1996-1997 in Denmark, Ireland, Norway, Netherlands and Switzerland, with a shift in age to older children, adolescents and adults, prompting many to consider the addition of booster doses. Currently, four European countries are producing DTaP vaccines, and at least six are importing and using acellular vaccines, particularly in combination with Hib (mixing), hepatitis B vaccine and/or IPV.

The European Advisory Group has recommended that whole cell pertussis vaccines be the “mainstay” of national immunization programmes until the effectiveness of acellular vaccines in routine use is shown, as well as their cost-effectiveness. Many countries have begun use of acellular vaccines because of low coverage (or no coverage, in the case of Sweden) with whole cell vaccines. Some countries, particularly those of central and eastern Europe, will continue to produce and use whole cell vaccines.

Discussion among participants was vigorous on the topic of criteria used for switching from whole cell to acellular products, but nonetheless public health authorities in most European countries are satisfied with pertussis control using whole cell DTP vaccines. Local production of whole cell vaccines will continue in several European countries.

Dr Yu presented the pertussis control situation in the People’s Republic of China. DTP vaccination began in the 1950s and expanded in 1978. Up to 120 million doses of whole cell DTP are manufactured per year by six biological manufacturers within China for an annual birth cohort of 20 million. Vaccine is given to children at three, four, five, and 18-24 months of age. Coverage of DTP3 at one year has exceeded 90% since 1988 and currently exceeds 95%. The incidence of reported pertussis varied from 90 to 280 per 100 000 total population before EPI was initiated, fell below 10 per 100 000 by 1986 and has remained at or below one per 100 000 since 1991, with geographic variation by province over time (ranging approximately 0.5-10 per 100 000). An increase from 5000 cases in 1996 to 8000 cases in 1997 could reflect cyclic variation/ accumulation of susceptibles and/or improved reporting efficiency of surveillance with the polio eradication programme.

In addition to statutory reporting, there is a sentinel surveillance system with 145 sites collecting more accurate and precise data for 1% of the population, chosen to be statistically representative of the country. Using capture-recapture methods and these two reporting systems, the reporting efficiency was estimated to be 30-40% in 1994-1995. For AEFI, there is no national monitoring system, but staff at the periphery are instructed to monitor adverse events as a supervision tool. Concerns about adverse events/common reactions have not affected immunization coverage. Studies of common events following immunization have revealed a frequency of local redness of 2-34%, fever of 1.4-6.1% with wide variation by study. Sterile abscesses have been reported in 0.02-1.1% of doses. Since 1996, payment of vaccine costs has been the responsibility of the local rather than provincial governments, and prices of vaccine have increased.

Dr Lei presented experience on the use of acellular pertussis vaccines in China. Copurified PT/FHA vaccines (inactivated by peroxide or glutaraldehyde) are made by all six manufacturers as pilot or licensed products, but amounted to fewer than

500 000 doses in 1997 (under 0.5% of pertussis vaccines produced). Control of the vaccine is performed using the modified mouse intracerebral challenge test as well as SDS-PAGE for purity, mouse weight-gain test for toxicity, and toxicity assays in mice of histamine sensitization and leukocyte induction. Comparison testing for immunogenicity and safety has indicated higher anti-PT and anti-FHA responses following DTaP than after the whole cell vaccine studied. Fever following DTaP occurred at the same frequency in placebo recipients (and up to 13% in whole cell DTP recipients). Local erythema and induration were found in recipients of <2% of doses administered. Use of DTaP as a booster was also associated with a lower frequency of local reactions and higher anti-FHA and anti-PT. The cost of the vaccine is ten times that of whole cell DTP.

Dr Homma presented the experience in Brazil. The incidence of reported pertussis has fallen from 44 per 100 000 total population in 1982 when DTP3 coverage was 56% to less than two per 100 000 since 1995 when immunization coverage has been around 80%. DTP is given at two, four, and six months of age and in the second year of life. There are 25 states in Brazil with a total population of 160 million. Sao Paulo State has had a passive monitoring system for AEFI for many years, and noted a general increase in reporting of HHE and convulsions following DTP over that time (from 1 per 650 000 doses in 1984 to 1 per 54 000 in 1995 for HHE; from 1 per 435 000 in 1984 to 1 per 38 000 in 1995 for convulsions). In November 1996, within two days, following use of one lot of vaccine, nine convulsions and 12 HHE were reported (1/3386 doses and 1/2539 doses respectively). After further investigation in several states, other lots of vaccines were found to be associated with events at one per 2000 doses, suggesting a variance for the lot in question from the usual under-reporting in passive surveillance. The number of reports varied for the same lots by state from 0 to 169 reports per million doses.

In the interim, there was disruption in the routine administration of the immunization programme. The national regulatory authority, which controls importation and local production of DTP, found wide variance in mouse weight-gain testing on DTP from five manufacturers, but investigation by a team of WHO consultants found that inappropriate testing methods were being applied, and, in fact, all lots met WHO standards for toxicity. Vaccination coverage levels have again increased, but only with much effort to restore public confidence. The results of this episode were efforts to improve 1) safety testing methods of vaccines, 2) AEFI surveillance, and 3) laboratory and epidemiological surveillance of pertussis. Current costs of DTaP vaccines imported for special purposes are almost 100 times the price of whole cell DTP, but Dr Homma believes DTaP vaccines could be used in the future if appropriate technology transfer were applied.

On discussion, the strong apparent control of pertussis despite sub-optimal DTP3 coverage was questioned. The response was that the highest density areas have very high coverage, even though a high percentage of the population is rural. Dr Salisbury noted that in evaluating serious AEFI, consideration must be made of the background rate of illnesses (estimating expected number of reports if events are occurring by chance alone), to guide judgement of the significance of the reports; the reported frequency of such coincidental events may vary by the efficiency of surveillance reporting. Additional comments from several participants indicated that, because more public and press attention is being paid to vaccine safety—often negatively and with misrepresentation and misinterpretation of the facts—ministries

of health and health care workers need the background data and information to address all contingencies. This includes enhancing the monitoring systems for AEFI and the training of health staff and epidemiologists to interpret AEFI monitoring data using international experience and the medical literature.

Patent issues and perspective of industrialized country manufacturers

Ms Fuller presented information about current, published and enforced patents on acellular pertussis vaccines. North American Vaccines has filed with the Office of Technology Transfer a patent with 4% royalty fees which will expire August 2011 for high yield production and peroxide inactivation of PT (the product was not yet licensed at the time of the meeting). Massachusetts Public Health Laboratories has filed for a PT/FHA vaccine using tetranitromethane inactivation, without royalties (no license as yet). SmithKline Beecham (SB) has a world-wide, exclusive product patent for pertactin until 17 August 2010 (applied as a function of the number of other components) obtained in 1991 from Medeva/Evans after original patent applied by Novotny; Evans and SB are known to be assertive in enforcement.

The Technology Board of the European Office has provisionally opined that enforcement of this is not valid in Europe.

Connaught Laboratories, Ltd. (CLL) has several patents for purification of components and inactivation, valid in Canada only (and has the right to market its pertactin-containing vaccine in Canada). Biken has patents for PT/FHA fixed ratio vaccine to year 2009 (in US and Japan, no royalties accruing) and for PT vaccine (ratio to FHA not controlled). Takeda has patents for the purification process for its vaccine (expiring 2007) and for modification of PT (expiring 2000); there is a 0.3% royalty for NIH, Japan. Because this process was patented before the Novotny application, attempts to block US application of the product under the pertactin product patent were unsuccessful. Chiron has applied for patents in Europe and the US on the isolation and characterization of the promoter for fimbriae (expires 2008) and cloning of PT (expires 2009).

There are also patents for fermentation for several parties (with low or no royalties, including one for the National Institutes of Health, Bethesda), and gene mutation.

Discussion centred on the implication of patents on local production of acellular vaccines in developing countries. Dr Olin stated that it appears that the patent and proprietary issues are more important in the current use of available acellular vaccines than the results of scientific studies. In the future, however, the primary question of local production of acellular vaccines in developing countries may likely be one of expense in production. This is possible since the production methodologies are published and patents may have limited applicability; many patents for acellular products/methods have less than 12 years to expiration.

Dr Gust from vaccine producer and distributor CSL (formerly Commonwealth Serum Laboratories) presented the current situation in Australia, which has controlled pertussis well for over 50 years using CSL whole cell vaccine at two, four, six and 18 months of age. Recent years have shown a slight decline in coverage, particularly in the fourth dose, and increase in reported disease incidence. A fifth dose at four to five years of age had been the routine for a number of years, and coverage for this

dose also has decreased. The Ministry of Health has responded with incentives for physicians to give the vaccine and disincentives for parents to allow children to miss doses by enforcing school entry requirements.

Two DTaP products have been licensed in Australia (CLL and SB; only one in use thus far). Because the cost of acellular vaccines is US\$12-13 compared to US\$3 for whole cell DTP, the health authorities have retained use of DTP for the first three doses (and funds have been applied to additional hepatitis B vaccine). In surveys of parents with children not given boosters, convenience and logistics were cited as primary reasons—concern about vaccine reactions was cited as only eighth in priority. However, authorities viewed vaccine safety concerns as predominantly responsible for the coverage drop-off when deciding to use DTaP for fourth and fifth doses.

Dr Pètre indicated that whole cell vaccines will continue to be used in most of the world for many years, but given the overall atoxic biologic properties of the genetically-inactive PT, wondered if there was a place for whole cell vaccine using the mutant PT-producing *B. pertussis* strain. Drs Schild and Mills cited the improved immune responses to genetically-modified PT over chemically-inactivated PT; Dr Mills also commented on the animal models on active toxin in vaccines. Results of intracerebral assays showing potency have been published. Mr Holst questioned whether inactivation or chemical treatment would be necessary for stabilization.

There were several opinions expressed about how rigorous testing of such vaccine would need to be, as a new preparation of whole cell vaccine. Dr Meade indicated that prior US standards in pertussis vaccines are no longer applicable, as the relevant portion of the Code of Federal Regulations has been removed, but clearly stability and extensive immunogenicity and safety data would be necessary. The discussion ended as it began, with questions remaining of the added benefit of using such vaccine over available acellular vaccines if the reasons for consideration were vaccine safety issues. Dr Taranger indicated continued study of the North American Vaccines single component PT vaccine in wider community use and booster studies, and in DTaP-IPV combinations. Drs Olin and Cherry again indicated the importance of interpreting the data in light of the methods of surveillance and following long-term surveillance.

Production issues in developing countries

Dr Milstien noted that there were currently 33 countries where whole cell pertussis vaccines were produced, compared to eight producing acellular pertussis vaccines. Any decision by WHO to recommend use of acellular vaccines would have impact on both the quantity and the quality of available pertussis vaccines. She agreed with the concept of joint ventures for transfer of technology for production of acellular vaccines by local producers, if done with total involvement of the relevant national regulatory authority.

Dr Mehta commented on the difficulties of theoretical application of methodologies in production of acellular vaccines in India. The issues are not only the costs of licensing fees, but government regulations in vaccine production and the application of intellectual property rights. Currently, there is increased use of technology in quality control procedures in vaccine production, and training programmes are increasing in the use of alternative production procedures. Dr Poeloegan commented

on BioFarma vaccine production efforts in Indonesia. BioFarma, RIVM, Netherlands and Kitasato Institute, Japan are cooperating in vaccine production. BioFarma now produces 19-47 million doses of whole cell vaccine per year (capacity of 50 million). This vaccine has been successfully used for many years in the country's EPI.

Discussion included recognition by Dr Arita of the bilateral assistance and existing means of collaboration by governmental and commercial entities of developed countries with developing countries, with examples from Japan. The future will likely include more and stronger partnerships with commercial entities. The consensus of the discussion was that further collaboration between commercial biologics manufacturers and developing country vaccine producers should be encouraged, with the involvement of the relevant national regulatory authority.

Criteria for consideration of use of acellular pertussis vaccines in developing countries

The discussion aired many current opinions on use of whole cell DTP or DTaP in developing world settings. With estimates of the cost of acellular vaccines to be more than \$1 per dose compared to the whole cell vaccine DTP UNICEF cost of \$0.08, much will have to change to overcome the potential economic burden of any wide-scale DTaP vaccine use. The current UNICEF estimate of vaccine costs for a fully vaccinated child with traditional EPI antigens is \$0.65 per child, but this would be almost \$4 per child using DTaP at current estimates. This would add \$250 million to the current UNICEF cost of \$100 million to purchase a billion doses of all EPI vaccines.

Arguments about adding hepatitis B with or without *Haemophilus influenzae* type b vaccine could be more strongly made for overall disease control and prevention of deaths and disability. Since developed countries have already financed vaccination against these latter diseases, the use of acellular vaccines because of improved overall safety is more easily considered, but national immunization programme managers in developing countries have more constraints. On the other hand, one problem with continued use of whole cell vaccines is that current standards for the production and testing of whole cell DTP allow the use of some vaccines that are not highly efficacious. The incomplete picture on the burden and effect of adverse events following immunization in most developing countries further complicates decisions on considering the use of DTaP vaccines.

Several participants indicated that public support for immunization programmes depends on trust in the overall efficacy and safety of the products used. Mr Holst and Dr Schild stated that the continued use of whole cell DTP vaccines of high quality is desirable and appropriate in developed and developing countries. Drs Kane and Widdus reminded participants that there are occasions in which events can suddenly erode public confidence in vaccines, and the circumstances allowing such rapid erosion in public support exist in most countries; therefore, there must be constant monitoring of public confidence as well as disease burden and adverse events following immunization.

The example of concerns about tetanus toxoid use in women leading to sterility was cited. Dr Yu pointed out that even with a high priority programme for hepatitis B vaccine use in China, national coverage has not exceeded 40% because of cost

considerations. The implications of contemplating a change in pertussis vaccines are vast in large countries and convincing arguments are not present to currently consider it, even with improved safety for common reactions to whole cell DTP. Some discussion took place on the use of acellular pertussis vaccines for boosting in pre-adolescence or adolescence, which is under consideration in several developed countries where data might suggest an added benefit in disease control.

The consensus of the discussion was that the standard for use of pertussis vaccines—whole cell or acellular—should be that they be of high quality, and that the decision for the use of one type be made locally based on the situation, including cost-benefit considerations and public acceptance, with appropriate monitoring systems for disease and adverse events following immunization.

Eradication of pertussis

The possibility of eradication of pertussis was raised by Dr Robbins, citing the experience in Gothenburg and Japan. The experience in Japan was not considered as strong evidence by some, given the continued incidence in children under the age of immunization. Previous deliberations on the eradication of pertussis concluded that it would be difficult, i.e. requiring very high vaccination coverage, given the high infectivity of the agent and incomplete efficacy of all available vaccines. This, plus issues of transient colonization impeding bacterial disease control, the practical aspects, and current and past eradication experiences have led participants at a recent meeting in Atlanta on disease eradication to recommend avoiding serious consideration of the eradication of any bacterial diseases. Dr Olin and others reemphasized that reported disease does not reflect actual disease and infection, and that surveillance artifacts can introduce a false sense of confidence towards consideration of eradication. Dr Bogaerts indicated that with wider use of acellular vaccines in Europe, especially with future combination vaccines, there will be a greater experience to judge the effect on reported disease.

Drs Gupta and Kole of Wyeth-Lederle commented on the vaccines the company is licensing in the US. Dr Sabouraud of Pasteur Mérieux-Connaught suggested that technology transfer for local production is the key, with collaboration in quality control and upgrading the manufacturing process.

Annex 1: Agenda

Day One - Monday 18 May

Introduction and overview

09.00-09.15 Opening of meeting - *Dr Jong Wook Lee, Director, WHO/GPV and Executive Secretary, CVI*

Purpose of the meeting:

09.15-09.30 WHO view - *Dr Mark Kane, WHO/GPV/EPI*

09.30-09.45 CVI view - *Dr Roy Widdus, Coordinator, CVI*

Epidemiology and surveillance

09.45-10.00 Global epidemiology of pertussis - *Dr Mark Kane*

10.00-10.15 Epidemiology of pertussis in children and adults - *Dr James Cherry, UCLA School of Medicine, USA*

10.15-10.30 Pertussis surveillance - *Dr Maureen Birmingham, WHO/GPV/EPI*

10.30-11.00 Coffee break

11.00-11.30 Discussion on epidemiology and surveillance

Scientific issues

11.30-11.45 Correlates of immunity - *Dr Patrick Olin, Swedish Institute for Infectious Disease Control, Sweden*

11.45-12.00 Do pertussis mutants pose a threat? - *Dr Johannes Kreeftenberg, RIVM, Netherlands*

12.00-12.30 Discussion on scientific issues

12.30-14.00 Lunch break

Quality issues

14.00-14.15 WHO role - *Dr Elwyn Griffiths, WHO/BLG*

14.15-14.30 National role - *Dr Geoffrey Schild, NIBSC, UK*

14.30-14.45 National role - *Dr Bruce Meade, FDA/USA*

14.45-15.00 Pre-qualification of suppliers on a global basis - *Dr Nora Dellepiane, WHO/GPV/VSQ*

15.00-15.30 Discussion on quality issues

Day One - Monday 18 May (continued)

15.30-16.00 Coffee break

Control in industrialized countries

- 16.00-16.15 United States of America - *Dr John Livengood, NIP, CDC*
16.15-16.30 United Kingdom - *Dr David Salisbury, Department of Health*
16.30-16.45 Japan - *Dr Harumi Sakai, NIID*
16.45-17.00 Discussion on control in industrialized countries
17.15-17.30 Introduction of GPV position paper on acellular pertussis -
Dr Julie Milstien, WHO/GPV/VSQ

Day Two - Tuesday 19 May

Control in developing countries and countries in transition

- 09.00-09.30 People's Republic of China - *Dr Yu Jingjin, MOH/EPI;*
Dr Lei Dianliang, National Institute for the Control of
Pharmaceutical and Biological Products
09.30-09.45 Brazil - *Dr Akira Homma, Fundacao Oswaldo Cruz*
09.45-10.00 Europe - *Dr Sieghart Dittmann, WHO/EURO*
10.00-10.30 Discussion on control in developing countries and
countries in transition
10.30-11.00 Coffee break
Perspective of industrialized country producers
11.00-11.15 Intellectual property issues - *Ms Liz Fuller, Triskel Consulting*
11.15-12.30 Perspectives of industrialized country producers
Discussion on industrialized country production
12.30-14.00 Lunch break
Production issues in developing countries
14.00-14.15 Overview - *Dr Julie Milstien, WHO/GPV/VSQ*
14.15-15.30 Perspectives on technology transfer and production issues
in developing countries
15.30-16.00 Coffee break
16.00-16.30 Discussion on developing countries production issues
Criteria for considering use of ACP in developing countries
16.30-17.30 Discussion on GPV position paper for ACP,
conclusions and recommendations
17.30 Closure of meeting

Annex 2:

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