Pertussis surveillance

A global meeting
Geneva, 16-18 October 2000

DEPARTMENT OF VACCINES
AND BIOLOGICALS

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<th>Full Form</th>
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<td>AFP</td>
<td>acute flaccid paralysis</td>
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<tr>
<td>AFRO</td>
<td>WHO Regional Office for Africa</td>
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<td>AMPT</td>
<td>active mouse protection test</td>
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<td>AMRO/PAHO</td>
<td>WHO Regional Office for the Americas/Pan American Health Organization</td>
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<td>ARI</td>
<td>acute respiratory infection</td>
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<td>CDC</td>
<td>Centers for Disease Control and Prevention (USA)</td>
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<td>CDSC</td>
<td>Communicable Disease Surveillance Centre</td>
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<td>CI</td>
<td>confidence interval</td>
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<td>CIDA</td>
<td>Canadian International Development Agency</td>
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<td>DTP</td>
<td>diphtheria-tetanus-pertussis vaccine</td>
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<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
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<td>EMRO</td>
<td>WHO Regional Office for the Eastern Mediterranean</td>
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<td>EPI</td>
<td>Expanded Programme on Immunization</td>
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<td>ESEN</td>
<td>European Seroepidemiology Network</td>
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<td>EURO</td>
<td>WHO Regional Office for Europe</td>
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<tr>
<td>FHA</td>
<td>filamentous haemagglutinin</td>
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<td>FIM</td>
<td>fimbriae</td>
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<tr>
<td>Ig</td>
<td>immunoglobulin (IgA, IgG)</td>
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<td>MICS</td>
<td>Multiple Indicator Community Survey</td>
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<td>PCR</td>
<td>polymerase chain reaction</td>
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<td>PHLS</td>
<td>Public Health Laboratory Services (UK)</td>
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<td>PRN</td>
<td>pertactin</td>
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<td>PFGE</td>
<td>pulsed-field-gel electrophoresis</td>
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<td>PT</td>
<td>pertussis toxin</td>
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<td>Pw</td>
<td>whole-cell pertussis vaccine</td>
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<td>RSV</td>
<td>respiratory syncytial virus</td>
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<td>SEARO</td>
<td>WHO Regional Office for South-East Asia</td>
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<td>WPRO</td>
<td>WHO Regional Office for the Western Pacific</td>
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Executive summary and recommendations

Summary

Bordetella pertussis is the causative agent of whooping cough, a major cause of childhood morbidity and mortality. An estimated 50 million cases and 300,000 deaths occur every year; case-fatality rates in developing countries may be as high as 4% in infants. Despite these figures neither WHO nor UNICEF has established specific disease reduction targets for pertussis. High immunization coverage with either diphtheria–tetanus–pertussis (DTP) or DtaP vaccines are the cornerstones of prevention. The rationale for pertussis surveillance is to monitor the impact of the immunization system, identify high-risk areas and detect outbreaks to be investigated. In moderate to low coverage countries (<50% DTP3), pertussis surveillance should function as an adjunct to improve coverage and lower the incidence of pertussis. Once immunization coverage is high (>90%) and pertussis incidence is low, surveillance should be enhanced in order to better understand changes in the epidemiology of the disease and to guide vaccination policy. Because Bordetella parapertussis causes milder disease it is not a priority for surveillance at this time.

Recommendations

1) Case definition

Clinical case definition

A case diagnosed as pertussis by a physician, or

A person with a cough lasting at least two weeks with at least one of the following symptoms:

- paroxysms (i.e. fits) of coughing
- inspiratory “whooping”
- post-tussive vomiting (i.e. vomiting immediately after coughing) without other apparent cause

Criteria for laboratory confirmation

- Isolation of Bordetella pertussis, or
- Detection of genomic sequences by polymerase chain reaction (PCR), or
- Positive paired serology
Case classification:
- Clinical case: A case that meets the clinical case definition, but is not laboratory confirmed.
- Laboratory confirmed case: A case that meets the clinical case definition and is laboratory confirmed.

2) Types of surveillance

Routine surveillance (where DTP3 coverage is <90%)
Routine monthly reporting of aggregated data of clinical cases from peripheral to intermediate and central levels is recommended. All levels should be encouraged to report cases by age group (<1 year, 1–4 years, ≥5 years) and immunization status. Zero reporting should be required at all levels.

Routine surveillance (where DTP3 coverage is ≥90%)
When coverage reaches 90%, case-based surveillance is recommended. Information on age, immunization status and mortality should be collected.

Investigation of outbreaks
A pertussis outbreak should be reported immediately to the WHO Regional office, confirmed by culture and investigated epidemiologically. Case-based information should include: date of onset, age, immunization status, address and final outcome (i.e. alive or dead).

Sentinel surveillance
Sentinel surveillance is recommended in a few major hospitals to collect more detailed information including: date of onset, immunization status, age, laboratory confirmation, other cases at home and final outcome (i.e. alive or dead). Surveillance at sentinel facilities should include appropriate microbiologic studies.

3) Minimum data elements

Aggregate data for reporting (when coverage is <90%)
- Number of cases by age group (<1 years, 1–4 years, ≥5 years) and immunization status
- Number of first and third doses administered to infants of DTP
- Number of DTP booster doses given (if part of the country schedule)

N.B. If possible, coverage surveys should collect and analyse data on the timeliness of DTP doses since doses given on time (versus late) can have a substantial impact on mortality reduction.
Case-based data (when coverage is >90%; also for sentinel surveillance and outbreak investigation)

- Unique identifier
- Address (city/town/village, district and province)
- Date of birth
- Date of onset
- Total number of DTP vaccine doses
- Date of latest DTP vaccine dose
- Outcome (alive, dead or unknown)
- Classification (clinical, laboratory confirmed).

4) Data analysis, presentations, reports

Aggregate data

- Incidence rate by month, year, age, and geographic area
- Proportion of cases immunized, partially immunized and not immunized
- DTP3 coverage by year and geographic area
- DTP booster by year and geographic area
- Drop-out (DTP1–DTP3) by year and geographic area
- Completeness / timeliness of monthly reporting by geographic area.

Case-based data – same as aggregate data plus the following:

- Case fatality ratio
- Age-specific case fatality ratio.

5) Develop a community-based method to measure pertussis disease burden, particularly in countries with low (<50% DTP3) coverage

6) Encourage the development of regional laboratory networks to improve diagnostic capabilities

7) Targets

Burden of disease estimates must guide public health strategies. That is, operational targets for reductions in pertussis morbidity and mortality should be developed and presented for discussion at the World Health Assembly.

8) Training

Training material needs to be developed by WHO and made available for education of physicians (both under- and post-graduate), nurses, paramedics and other health care workers. Such material should include audio-visual aids (videos, slides, CD-ROM) and should be included in resource materials produced by WHO.
1. Introduction

Dr F. Marc LaForce

Pertussis has not received sufficient emphasis in recent years, although globally millions of cases and tens of thousands of deaths occur annually despite the wide availability of effective vaccines. Pertussis surveillance is difficult, hence disease burden due to pertussis goes largely unrecognized. To raise the profile of pertussis, more effective surveillance tools are needed, particularly in developing countries, if pertussis is to be brought under control.

Pertussis: the ultimate challenge - Dr Jean-Marc Olivier

Although estimates of the incidence and mortality of pertussis vary greatly, there is consensus that the burden is considerable. Surveillance is difficult to carry out and surveillance performance varies widely. Many countries do not report cases at all. For example, in the African region 25% of countries did not provide any pertussis data to WHO during 1999 and 19% reported 0 cases.

In 1991 the following pertussis case definition was developed for the purpose of interpreting data from the acellular vaccine trials. A pertussis case was defined as a patient with a cough lasting at least 21 days and one or more of the following:

(i) positive culture for B. pertussis;
(ii) serological evidence of Bordetella-specific infection by a significant rise in antibody;
(iii) household contact with a B. pertussis bacteriologically confirmed case occurring within 28 days before or after the onset of illness in the trial child.

However, the definition is overly specific and not well suited for routine surveillance. Case definitions are always a balance between specificity and sensitivity. Infants may meet the WHO clinical trials case definition at some point in their illness but often do not at the time they are first seen. Adults often have milder diseases and do not often meet these case definitions.

The type of surveillance that should be implemented depends partly on the degree of pertussis control achieved through vaccination. When high levels of coverage with low incidence rates are achieved special studies are often needed to better understand the pertussis epidemiology in a given country. The paucity of surveillance data from countries with low DTP coverage is a major public health issue because pertussis may be relatively hidden as a major cause of respiratory morbidity and mortality.
2. Objectives of the meeting

The meeting focused on surveillance of pertussis as a fundamental component for the development of effective control strategies. It addressed surveillance problems in countries with low and high coverage with DTP. Specific goals of the meeting included:

- Review current surveillance data received at WHO
- Determine what are the surveillance needs to inform and adjust control strategies
- Discuss the role of laboratory diagnosis in the surveillance of pertussis
- Update current WHO pertussis surveillance standards
- Determine ways to improve pertussis burden estimation methods
3. Presentations and discussions

3.1 Clinical manifestations of pertussis and parapertussis

Clinical presentation and severity of pertussis in different age groups - Dr Scott Halperin

Pertussis affects all age groups and clinical manifestations vary by age. Pertussis can occur in previously immunized and infected individuals, but immunization and prior infection attenuate the clinical picture. In highly immunized populations most morbidity and nearly all mortality occur in infants under one year, whereas, in unimmunized populations morbidity and mortality also occur in older children and infants. In a Nova Scotia study, immunized children who were culture-positive for B. pertussis were presented, for the most part, with typical whooping cough; 88% met the WHO case definition but none was hospitalized. Early erythromycin treatment decreased the duration of cough and paroxysms. Half of all household contacts developed a cough illness and 37.5% of these met the WHO case definition for pertussis, findings that underscore the infectivity of this disease.

In countries with sustained high coverage like Australia, Canada, Germany, Italy, New Zealand and the USA, an increasing proportion of cases has been documented in adolescents and adults. In adults there is a wide spectrum of disease from mild respiratory infection to paroxysmal cough episodes with apnoea. However, there is less information about the spectrum of disease in adolescents and adults than in children because there is less awareness of the diagnosis. Both adults and adolescents can give pertussis to young infants who are at the highest risk of death or complications.

Most hospitalizations occur in children less than five years of age. Duration of hospitalization is greatest in children under six months of age and they are also much more likely to require hospitalization in intensive care units. Complications include pneumonia, atelectasis, seizures, encephalopathy, weight loss, hernias and death.

Pertussis mortality is generally estimated using case fatality rates in hospitalized cases. In Canada mortality has been recorded at 0.37 pertussis deaths per 100,000 infants under one year of age. Underreporting of pertussis affects estimates of mortality and incidence. Only about one third of cases are reported to the Centers for Disease Control and Prevention (CDC) and deaths from pertussis are possibly being reported as other respiratory illnesses or sudden infant death syndrome (SIDS). Previous global burden of disease estimates have assumed an overall case fatality rate of 1% in developing countries and 0.04% in developed countries. However, it is important to understand the effect of age on mortality. Virtually all deaths occur
in infants under one year of age. Improved surveillance is necessary to delineate the full spectrum of disease and to better estimate the impact of immunization programmes. There are no good estimates of pertussis morbidity in adults. Surveillance data from the African region are almost non-existent and DTP3 coverage for many countries range from 23 to 60%. Pertussis is particularly serious in malnourished children, and in large areas of Africa and Asia malnutrition is common in infants under one year of age. A cough lasting for three weeks can significantly exacerbate malnutrition. Better data are needed from such regions before an accurate assessment of the burden of disease from pertussis can be made.

**The role of adults and adolescents in pertussis transmission - Dr Scott Halperin for Dr Kathy Edwards**

Adults can transmit pertussis to infants. The relationship between severity of clinical symptoms and infectivity needs to be better understood in order to properly assess the role of older children and adults in maintaining transmission of pertussis. For example, how infectious are people with asymptomatic or mild infections?

**Bordetella parapertussis - Dr Jussi Mertsola**

Clinically it can be very difficult to distinguish B. parapertussis from B. pertussis. Epidemiologically, B. parapertussis cases peak in the two to six year age group which is generally later than for pertussis. Cases of parapertussis are rare in infants under six months old accounting for the low mortality in that age group. Most pertussis vaccines do not protect against parapertussis, although there is some degree of protection with the Dutch whole cell pertussis vaccine. Pertussis fimbriae (FIM) seem to be the important cross protective antigens. The acellular pertussis vaccines used in Italy had no protective efficacy against parapertussis. Broad clinical case definitions used for pertussis surveillance may easily include cases of parapertussis. Parapertussis does not produce pertussis toxin (PT) and so there is no opportunity for cross reaction in serosurveys measuring antibody to toxin.

**3.2 Pertussis vaccines**

**Vaccination schedules - Dr Luis Barreto**

Both whole cell and acellular pertussis vaccines are widely used. Some countries use the whole cell vaccine for the primary vaccination schedule and acellular vaccine for booster doses in older age groups, while other countries, like Germany and Sweden, use acellular pertussis vaccines for the primary schedule as well as for boosting. Many countries including Finland, Hungary, India, Netherlands, Poland and Romania produce whole cell vaccines that meet WHO standards. Most countries follow the three dose Expanded Programme on Immunization (EPI) schedule and many recommend boosters at 18 months, and some at 4 years of age.
Effectiveness of current whole cell /acellular vaccines against B. pertussis as measured in animal potency assays. Report of the WHO working group on standardization and control of pertussis vaccines - Dr Dorothy Xing

Potency of whole-cell pertussis vaccine varies between and within batches. Immunogenicity in mice is variable and difficult to correlate with human immunogenicity or with vaccine efficacy. The active mouse protection test (AMPT) is used for assessing potency of whole cell vaccines against a challenge strain but is not suitable for assessing protection against naturally occurring strains. An improved aerosol challenge system can be used for assessing protection pertussis vaccine protect against any B. pertussis isolate. However, there is no agreed official test of potency for acellular vaccines and the WHO pertussis working group is studying different approaches.

3.3 Reports from WHO regions

Region of the Americas (AMRO/PAHO) - Dr Mauricio Landaverde

In the Region of the Americas the incidence of pertussis has fallen as DTP coverage has risen. Overall coverage is close to 90%, however there are many districts that have coverage rates below 80%. Peru and Chile have noted an increase in the incidence of pertussis but mortality has remained low. Some of this increase may be due to changes in the case definition. In Chile surveillance of whooping cough syndrome started in 1992, and in 1996 a new case definition was introduced whereby infants under three months with respiratory infection or recurrent apnoea would be reported as suspected pertussis, even if respiratory syncytial virus (RSV) was confirmed as the diagnosis. There is no information available as to whether the increase in cases has occurred predominantly in low coverage districts.

European Region (EURO) - Dr Steve Wassilak

It has been difficult to obtain accurate immunization coverage estimates at 12 months of age. Most European countries report coverage over 80% now, and at least 90% coverage is reported in most Western European countries, the Newly Independent and Baltic States. Pertussis surveillance in many counties is weak, and often there are no standard clinical or laboratory case definitions. Use of pertussis vaccine boosters is also variable. Denmark, Sweden and the United Kingdom do not use booster doses, but Norway and Sweden are re-considering using them. Germany is boosting at 10 years of age and is considering boosting adults as well.

Eastern Mediterranean Region (EMRO) - Dr Taky Gaafar

Coverage in EMR is 90% or more in 14 countries, 70-90% in 6 countries and below 40% in 3 (Afghanistan, Djibouti and Somalia). Iraq and Jordan have experienced a drop in coverage between 1998-1999, the latter due to publicity surrounding adverse events. Regional coverage is estimated by EMRO to be at 83%. In Egypt, high coverage has been followed by low pertussis incidence, but there are questions about the quality of case reporting. In Kuwait, good data shows that the number of cases has fallen, but the cyclical pattern of pertussis incidence has been maintained. In Oman the number of cases has fallen to just a few hundred since the early 1980s when thousands of cases were reported. In Pakistan coverage has been
reported between 70% and 80% for about four years, but reports of pertussis cases are not consistent with reported coverage levels. In Sudan, reported cases have been falling but the estimated coverage is low; the fall in cases probably reflects a weak surveillance system.

There are no standards for pertussis surveillance and case management, neither are there accepted training materials or standardized educational material for medical students. As a result, case management and reporting are not satisfactory, laboratory confirmation is not done and clinical diagnosis is the only basis for reporting. Surveillance data from most countries are difficult to interpret since both underestimates and overestimates occur.

The DTP immunization schedule is at 6, 10 and 14 weeks plus booster doses during the second year of life in most countries, though some countries follow a 2, 4 and 6 month immunization schedule, and some have no booster dose (e.g. Pakistan). Surveillance activities currently do not guide immunization strategies in most countries, and there is no feedback or follow-up. Larger countries could institute sentinel surveillance to provide more detailed information.

**South-East Asia Region (SEARO) - Dr Abdulaziz Adish**

Reported DTP coverage is inaccurate, and in India, Bangladesh and Nepal reported coverage levels were found to be 10% to 20% higher than survey results. In Bangladesh, India and Indonesia, reported coverage appears to have fallen, however, this may be secondary to the use of survey data instead of administrative data. In Sri Lanka where coverage is between 80% and 90%, cases are measured in hundreds rather than 10 thousands as they are in India. Surveillance for pertussis is generally poor in the Region and contrasts sharply with the achievements in acute flaccid paralysis (AFP) surveillance. Polio has received strong outside funding and good systems have been developed, but as countries do not receive external funding to strengthen surveillance for pertussis and they remain in need of advice on how to improve pertussis surveillance.

**African Region (AFRO) - Dr Mac Otten**

Only limited information on pertussis is collected. Surveillance of pertussis is scant and pertussis is not included in the current integrated surveillance module or the bacteriology network. This may be because clinical reports are hard to interpret and, like PAHO, the region lacks any clear policy.

3.4 Country reports

**Changing epidemiology with sustained high coverage; lessons from the UK - Dr Natasha Crowcroft**

The UK serves as a model for the best control that can be achieved with three doses of whole cell vaccine. UK pertussis surveillance indicates that a three dose vaccination schedule at two, three and four months can control pertussis well in a country with good coverage, a healthy population and a reasonable health service. However, hospitalizations remain quite common in young infants, and there are about 10 pertussis deaths annually in England.
Impact of high vaccination coverage, the French experience – Dr Nicole Guiso

France has used the same whole cell pertussis vaccine for thirty years and has achieved high coverage rates using a four-dose schedule. Good coverage appears to be associated with proportionally more disease transmission from adults to infants, or among adults. In regions of France with lower coverage, such as Marseilles, there is more transmission to infants coming from their siblings or other children aged under 10. Resurgence of pertussis must be controlled with adequate boosting and supported by improved clinical and laboratory surveillance. Vaccine-derived immunity lasts at least eight years and waning immunity is critical in determining clinical severity of disease and chains of transmission.

3.5 Laboratory related issues

Diagnosis of pertussis – Dr Carl Wirsing von Konig

Culture is currently the gold standard for the diagnosis of pertussis. However, culture depends on the duration of the patient’s cough and their age, adults being much less likely to be culture positive. PCR is much more sensitive especially in the later stages of the disease and is highly specific. Both depend upon the correct specimens being taken. Nasopharyngeal aspirates are the best samples to diagnose pertussis but health care workers are often reluctant to take them.

Enzyme-linked immunosorbent assay (ELISA) serologic methods for pertussis toxin (PT), filamentous haemagglutinin (FHA) and pertactin (PRN) have been well studied and are the most commonly used methods. Commercially available ELISAs, however, require further validation. Single point serology evaluated against population and age-specific reference values can be useful for children who have been coughing for a long time, but in acute illness is not so helpful.

Further work needs to be done to clarify the role of IgA. Culture needs to be made more efficient and PCR tests need to be standardized, automated and made affordable. Diagnostics would be helped greatly by the availability of a standardized commercial serologic assay. Reference values are needed for different populations and the role of mixed infections in causing pertussis-like cough should be clarified.

Adaptation of B. pertussis to vaccination: a cause for its re-emergence? – Dr Frits Mooi

In the Netherlands, post-vaccine bacterial adaptation of B. pertussis was proposed to have occurred. At the gene level, several small changes were observed particularly in relation to the genes that code for pertactin and pertussis toxins. For example, the vaccine pertactin was less likely to be found in isolates from vaccinated individuals than unvaccinated individuals. Similar findings have been reported from other countries. This observation may imply some immune selection. Variation in pertactin is important since pertactin is an important determinant of whole cell pertussis vaccine efficacy. Animal studies indicate that variation in pertactin type affects vaccine efficacy. Continued strain surveillance is important, particularly if whole-cell vaccines are replaced by acellular vaccines.
Changes in circulating B. pertussis isolates: possible effect of immunization pressure and impact on vaccine effectiveness and disease severity - Dr Nicole Guiso

The same pertussis whole-cell vaccine has been used in France since 1957. Circulating strains of B.pertussis differ from vaccine strains in a variety of ways indicating that the vaccination programme may have induced variation. However, these changes have had no observable impact on vaccine efficacy. Variability of the structural gene encoding pertactin in Bordetella sp. affects two immunodominant regions, I and II. In B.pertussis, vaccination appears to have induced variation only in one of the two immunodominant regions (I). Natural disease does not seem to induce immune selection hence it is not entirely clear why these changes should occur as a result of vaccination programmes. Changes in pertactin type that affect transmissibility will be of critical importance in determining the survival of new clones, irrespective of the impact on vaccine efficacy. Good surveillance is required to evaluate the impact of these molecular changes on the epidemiology of pertussis.

Global standardization of strain differentiation methods and the establishment of a collaborating laboratory network for the characterization of B. pertussis isolates - Dr Hans Hallander

B. pertussis is complex organism with 80 different patterns found on gel electrophoresis. The 80 different patterns can be aggregated into three clusters that broadly correspond to pertactin types. Much more information is needed to better define the relationship between strain profiles and vaccination programmes. A database on strain variation and strain differentiation should include clinical information and vaccination history to enable interpretation of shifts in transmission patterns related to vaccination. An important international collaborative effort of standardization for strain differentiation has begun.

Is there a need for a global laboratory network? - Dr Ray Sanders

Laboratory networks can work at different organizational levels:

- Methodology (minimum level)
- Reporting structures
- Proficiency test/accreditation schemes
- Reagent supplies
- Training support
- Financial support

Laboratory networks (both virological and bacteriological) have or are being developed to guide immunization systems in regions and countries. Pertussis could be integrated into such networks.
Discussion

Good surveillance requires laboratory support. So-called sentinel hospitals must be able to reliably culture for *B. pertussis*. However, given the well known difficulties with culture of *B. pertussis*, serologic tests for pertussis toxin IgG are another possible diagnostic approach. Standardized diagnostic criteria could be perfected as kits are developed. However, nine years of experience in Senegal aimed at providing laboratory services showed a lack of diagnostic demand in West Africa; external financial support was needed to maintain the laboratory. If more detailed strain identification were required, more financial support would be needed. Currently, only a small number of centres type strains because the public health significance of typing is unclear. Clearly more research is needed before broad laboratory recommendations beyond isolation are recommended. In special settings more refined laboratory studies should be linked with epidemiological data. Regional networks like the European Seroepidemiology Network (ESEN) offer solid benefits but secure funding for these initiatives is not at all clear.

3.6 Pertussis surveillance

Is there a role for serosurveillance? The European seroepidemiology network - Dr Anna Giammanco

ESEN has studied epidemiological patterns of different diseases using standardized serologic techniques. Single point serology for pertussis is estimated to have sensitivity of 80–95%, and specificity of 95% in younger children and 87% in older children. However, antibody responses may differ significantly in different regions. For example, after pertussis vaccination there appears to be a higher antibody response in populations in African countries than those in Europe. Therefore standardization studies such as those done by ESEN may need to be repeated in other regions. Vaccination history may also need to be taken into account particularly where programmes use acellular pertussis vaccines that can induce very high levels of PT IgG compared to whole cell pertussis vaccines. Seasonality and epidemic cycles also need to be considered if comparisons are to be made across regions.

Surveillance of pertussis in a country with high coverage: Japan - Dr Kuno-Sakai

Japan has used only acellular pertussis vaccine in recent years. Very low rates of infection are observed from surveillance data and almost all children in Japan become immune by vaccination only. Diagnosis is made by ELISA methods. Quite high levels of local reactions are seen after the fourth dose (35%) of DTaP vaccine, but this may be accounted for by the DT component. In the 1990s, cases of anaphylaxis following measles vaccine were linked to gelatin content in vaccines. All DTP vaccines used in Japan are now gelatin-free.
Surveillance of pertussis in a country with low coverage: Ethiopia - Dr Amha Mekasha

Ethiopia is a country of 62 million people, of which 85% live in rural areas and almost half of the population are children under 16. Like many other countries in the region, diarrhoea, acute upper respiratory tract infection and bronchopneumonia are the dominant causes of morbidity and death. In one study, pertussis was diagnosed in 5% of acute respiratory infections (ARI). DTP coverage fell below 50% in 1991 because of social and political unrest. In 1998 there was another fall in coverage because of financial problems. A verbal autopsy study identified pertussis in 4.7% of all community deaths. Although the disease is known locally many mothers do not know that the vaccine can protect their children. Coverage is currently about 60% but varies between districts. Most pertussis diagnoses are made clinically and standard case definitions are needed. There is no clinical impression that HIV and pertussis interact.

Surveillance in Sweden - Dr Patrick Olin

Sweden represents a natural experiment where an effective whole cell pertussis vaccine was replaced by a poor whole cell vaccine, followed by interruption of the vaccination programme and reintroduction of an acellular pertussis vaccine. Since the implementation of the acellular programme there has been an increase in the age of pertussis cases. Last year there were 2200 cases and 2 deaths from pertussis in Sweden. Surveillance data come from compulsory notification; laboratory reports from pertussis cases are more detailed.

Can surveillance demonstrate an improvement in pertussis control in Canada? - Dr Eleni Galanis

A cellular pertussis vaccine has been in widespread use in Canada since 1997-1998 when it replaced the whole cell vaccine that was first licensed in 1943. The incidence of pertussis dropped dramatically after the introduction of pertussis vaccine but since the late 1980’s reported cases increased again to a peak of 34.7/100 000 in 1994. Possible explanations include antigenic change, problems with the vaccine, increased awareness of pertussis with better reporting, increased use of PCR and a change in the case definition. The likeliest explanation for the high incidence observed in Canada was probably a poor whole cell vaccine. It is too early to accurately estimate the impact of the new acellular programme. However, comparing epidemic years, the incidence has fallen in children under 5 years of age. There has been no observable fall in incidence in 5-9 year olds, so there remains the possibility that the acellular is not as effective as anticipated or that the surveillance system is not sensitive enough to detect a change.
Pertussis surveillance in the USA - Dr Melinda Wharton

The voluntary passive reporting system in the US has detected an increase in pertussis in older children (10–14 years) and adolescents in the United States from 1980–2000. A low incidence of disease in infants appears to be associated with a high incidence of disease in adolescence and adults. There is some evidence that seasonality differs by age group as well, with children under five years and adults showing late summer seasonality and 5–19 year olds peaking later in the year, perhaps suggesting an amplification of transmission within schools. Since 1991 there has been an increase in pertussis incidence in infants under four months of age (i.e. unvaccinated infants). Reports in older infants and children 1–4 years have not increased. The increasing incidence in adolescents and adults may be due to several factors, including improved case ascertainment and the increased recognition of school-based outbreaks. Items still to be resolved include the need for a better definition of the incidence and health impact of pertussis in adolescents and adults, and the potential impact of vaccinating this age group on disease both within the age group and in young children.

The epidemiological situation in Australia - Dr Peter McIntyre

In the past decade pertussis notifications in Australia have increased 5–10 fold. This may be related to increased ascertainment, with the implementation of the Australian National Notifiable Diseases Scheme which allows cases to be reported by culture, PCR or epidemiologically linked clinical case definition and by serology. Diagnosis by serology began in the 1980s in Australia, and is now one of the most common methods of diagnosis. Since the 1990s laboratory reporting has been mandatory, also contributing to the observed increase. There is clear periodicity with four year cycles and hospitalizations greatly exceed notifications. Three quarters of all cases are diagnosed by serology but for children under five years old, culture and PCR account for most cases. Hospitalization rates have changed little in the 1990s in infants and the greatest increase is accounted for by serological diagnoses in adults and older children. In 1997, a fifth dose was added to the routine vaccination schedule for 4–5 year olds and incentives have been given to increase coverage. There is a substantial disease burden in adolescence and adults and a booster dose at 12–13 years is being considered.

The epidemiological situation in Oman: the 1997 outbreak - Dr Salah Al Alwaidy

Oman is a good example of a country where surveillance is being used to inform and guide vaccination policy based on the changing epidemiology of pertussis. The population is 2.3 million with 14% of the population under five years. Since 1981, DTP has been administered at 3, 5, 7 and 9 months of age. Pertussis has been notifiable within seven days of detection using a standard clinical laboratory case definition since 1992. The epidemic threshold is five or more suspect cases. There were two major outbreaks in 1997 and 1998 in which 90% of the cases were infants 0–3 months and 34% of cases were over 4 years of age. As a result of these data, booster doses were added to the schedule at 4–6 years of age. Very few cases were laboratory confirmed. Only three laboratory confirmed cases out of 200 clinically reported were found, but this may be due to problems with the transport of specimens.
Lessons from Senegal - Dr Francois Simondon

A population health project started in 1962 involving 30 villages and 1800 compounds in a small area of Senegal has provided data on pertussis. Between 1984 and 1986 pertussis vaccination coverage increased and the number of cases fell, but the epidemic cycles continued. The crude incidence rate for pertussis during the pre-vaccination era was 180 per thousand child-years under five years of age with a 2.6% case fatality ratio based on verbal autopsy data. After the introduction of vaccination, pertussis incidence dropped rapidly and dramatically. The decline in incidence involved all age groups, but was most substantial in children under five years of age. The surveillance activities are expensive to maintain, but provides probably the best data on pertussis in the African region in recent years.

Discussion

Surveillance is carried out in some countries, but is not done in any meaningful way in three quarters of the world. Surveillance data and coverage data are both unreliable. Reliable surveillance data are needed to check coverage and vaccine efficacy; both surveillance and coverage data are needed to monitor immunization programmes. What could be done differently? Specific policies and targets for pertussis would be very useful drivers to improve surveillance. Funding for new vaccines from UNICEF include requirements of data and quality standards all in one package. The idea of funding for vaccines being linked to the provision of surveillance data is attractive.

The real question is what do we want to do with the data? If clear targets cannot be defined then the purpose of surveillance will also be unclear. If the data are not going to be used or it is not feasible to collect useful surveillance data, then consideration should be given to discontinuing surveillance altogether. Why collect surveillance data at all if the data are of no use?

3.7 Models to predict disease burden due to pertussis

Why do we need burden estimates? - Dr Maureen Birmingham

Estimates of the burden of diseases are necessary to inform Ministries of Health and enable priority-setting among public health initiatives. At WHO, credible pertussis burden estimates (defined as estimates of cases and deaths) are needed for the following reasons: 1) fulfill WHO’s responsibility as the principle UN technical agency on health; 2) set priorities and advocate; 3) influence research and development of appropriate vaccines; 4) guide vaccination policies and strategies; and 5) assess impact and performance.

There are two principal methods of estimating burden: the natural history method and the proportional mortality method. The general approach used by WHO to estimate disease burden is to start with an expert consultative process in order to develop a sound approach. The methodology should aim to use the best data available and seek to validate results with existing data. Sensitivity analysis and continuous critical review are the only guarantees that the approach is as sound as it can be.
The estimates continue to be refined as new information becomes available. The final product is a database of cases and deaths by age, sex, country and year, as well as a careful documentation of methods, assumptions, and data sources. The process should result in recommendations on how to improve the precision, robustness and usefulness of the estimates.

Factors that affect the estimates are epidemiologic, demographic and programmatic, as well as co-factors such as HIV prevalence and nutritional status. Other practical issues include the quality and generalizability of the input data. Validation of the estimates is always important. The process is often messy since reliable data may be lacking, broad extrapolations or generalizations are made, or there is a heavy reliance on "expert opinion".

**Methods for pertussis burden estimation - Dr Peter Strebel**

Various methods have been used in the past, one of which was based on the proportion of acute respiratory infection that might be pertussis. Using such a model it is possible to show that increasing pertussis vaccination coverage from 80% to 90% would prevent 11 million pertussis cases and 144,000 pneumonia deaths in the 1990 birth cohort. The mortality rate from pertussis is age specific and concentrated in the first six months of life. Consequently a large impact on mortality can be achieved by improving timeliness of vaccination without increasing coverage. In fact, more deaths will be prevented by achieving on-time immunization at four months of age with a coverage of 80% than will be achieved with a coverage of 90% by 12 months of age without attention to timeliness of vaccination.

**Proposed methods for pertussis burden estimation - Dr Natasha Crowcroft**

The quality of existing data does not allow for complex modelling of pertussis globally although such exercises have been done for Canada, the UK and the USA. Nonetheless, estimates can be generated using a simple model that includes coverage, vaccine efficacy from clinical trials, and case fatality estimates from the literature. Important assumptions are as follows: 1) vaccination has minimal impact on age distribution of infection in unvaccinated individuals; 2) all susceptible individuals will be infected by the time they are 15; and 3) infections after 15 will be either re-infections or infections in vaccinated individuals with waning immunity and will be mild. Using these assumptions it is possible to generate a static model which estimates the mean number of infections, but does not account for epidemic cycles. The results represent the average number of infections per year over an epidemic cycle. Since epidemic cycles are not synchronized over large regions the estimates would be reasonable when aggregated by large administrative categories. Using such an approach generated preliminary estimates of 34 million cases and 250,000 deaths worldwide in children under 5 years of age in 1999.
Discussion
Participants were broadly supportive of this approach taken to estimate the global burden of pertussis. Several suggestions were made for improving the estimates. In particular, the number of deaths generated for some countries was considered to be higher than anticipated. Vaccine efficacy against death is probably higher than infection, and this could be incorporated into the estimates, using a suggested level of 95%. Better data is needed on many aspects of pertussis, but good coverage data is particularly important for this model. Coverage data for some countries can be improved by replacing reported coverage with levels obtained from surveys. Partial vaccination has partial efficacy that is not reflected in DTP3 coverage figures, so levels of DTP1 coverage would help in refining the estimates. Giving vaccinations on time is very important because the highest risk period is in the first 6 months to 1 year of life, but this is information that is not routinely collected at present. Finally, a sensitivity analysis could be carried out to evaluate the robustness of the model and the impact of each assumption. All these factors will be considered in further developing the estimates in consultation with an expert advisory group.
During the discussion it was pointed out that neither WHO nor UNICEF have disease reduction targets for pertussis despite the high disease burden. Routine surveillance even in some countries with high DTP coverage is at best spotty and incomplete. In low coverage countries surveillance is for the most part non-existent. Several priorities and areas to be further developed were discussed:

1) Emphasizing the importance of the burden of disease from pertussis.
2) Developing a community-based methodology to measure pertussis disease burden. These results could provide essential data to help reinvigorate routine immunizations. A method(s) should first be developed for high incidence and low coverage countries. Focus groups of mothers would be another approach. The Multiple Indicator Community Survey (MICS) or healthcare seeking study of children with acute respiratory infection might be adaptable to pertussis.
3) Investigating outbreaks and reporting them to WHO.
4) Standardizing laboratory diagnostic techniques, and establishing sentinel sites and bacteriology training networks. These should include pertussis, such as that being developed in the African region for Vibrio cholerae, Shigella, Haemophilus influenzae type b and pneumococcal disease.
5) Monitoring booster-dose policies.
6) Improving routine surveillance. Reporting systems should be standardized and the WHO case definition simplified. There should also be syndrome reporting of typical whooping cough. For use at country level, age-specific information should be collected for children under one, one to four years, and five years and over in cases of whooping cough.
7) Developing a better understanding of pertussis in adolescents and adults and the role of adult disease in relation to chains of infection in young infants. These data are important when considering options to immunize during pregnancy and adolescence.
8) Testing the utility of hospital-based sentinel surveillance. Sentinel surveillance might be a cost-effective approach and may be particularly useful to monitor the introduction of new vaccines. PAHO already has a sentinel system. A number of health facilities, for example, could be chosen to monitor selected vaccine-preventable diseases in different definitions. Sentinel facilities could also investigate children who die from pertussis as they often eventually come to a health facility and could be identified if a clear policy and appropriate facilities for investigation were in place. The problem of sentinel systems is that their results may not be generalizable and surveys have to be carried out periodically to validate findings elsewhere.
5. Recommendations

Pertussis continues to be an important public health priority, particularly in countries with DTP3 coverage rates less than 50%. Although the evidence is limited, there are data to suggest that pertussis is responsible for at least 300,000 deaths annually. Respiratory disease from B. parapertussis is not responsible for significant mortality and should not be considered a priority at this time.

**Burden of disease survey tool**

A simple reliable survey tool designed for developing countries must urgently be developed to measure morbidity and mortality of pertussis in the community.

**Case definitions**

The following modifications to the WHO case definitions should be considered:

**Clinical case definition:**

- A case diagnosed as pertussis by a physician, or
- A person with a cough lasting at least 2 weeks with at least one of the following symptoms:
  - paroxysms (i.e. fits) of coughing
  - inspiratory “whooping”
  - post-tussive vomiting (i.e. vomiting immediately after coughing) without other apparent cause.

**Criteria for laboratory confirmation:**

- Isolation of Bordetella pertussis, or
- Detection of genomic sequences by PCR, or
- Positive paired serology.

**Case classification:**

- Clinical case: A case that meets the clinical case definition, but is not laboratory confirmed
- Laboratory confirmed case: A case that meets the clinical case definition and is laboratory confirmed.
Reporting

Countries developing national plans of action for improving immunization systems should incorporate plans for pertussis surveillance. Surveillance recommendations are different for low and high coverage countries.

Routine surveillance (where DTP3 coverage is <90%)

The focus of surveillance should be on severe disease and deaths from pertussis. Routine monthly reporting of aggregated data of clinical cases from peripheral level to intermediate and central levels is recommended. All levels should be encouraged to report cases stratified by age group (e.g. <1 year, 1-4 years, ≥ 5 years) and immunization status. Zero reporting should be required at all levels.

Routine surveillance (where DTP3 coverage is ≥90%)

When coverage reaches 90%, case-based surveillance is recommended. Information on age, immunization status and mortality should be collected. More detailed studies may be needed to examine the changing epidemiology in adolescents and adults.

Monitoring coverage

The quality of DTP coverage data should be improved and monitored by dose. Countries should be encouraged to record and report administration of booster doses. Timeliness of vaccination should be evaluated and field surveys should pay particular attention to the age of the vaccination.

Outbreaks

Pertussis outbreaks should be promptly investigated and reported to WHO regional offices. Guidelines to investigate outbreaks should be developed, including the dates of onset, age of patient, immunization status, geographic location and outcome (alive or dead) for each case.

Sentinel surveillance

Sentinel surveillance sites should be developed in a few major hospitals to collect more detailed clinical information including laboratory confirmation.

Laboratory standardization and networks

Guidelines are needed to standardize specimen collection, transport and processing (culture, serology etc). A field laboratory diagnostic test would be enormously useful and should be developed.

Regional laboratory networks should be developed following other successful models (e.g. ESEN). These should be linked to sentinel hospitals. Laboratory networks for pertussis should be integrated with other existing or developing bacteriological networks (e.g. meningococcal, Hib).
Training

Training material needs to be developed by WHO and made available for the education of physicians (both under- and post-graduate), nurses, paramedics and other health care workers. Such material should include audio-visual aids (videos, slides, CD-ROM) and should be included in resource materials produced by WHO.

Estimation of global disease burden

Better data on disease burden in developing countries are urgently needed to validate disease burden estimates. The impact of partial vaccination and timeliness of vaccination should be taken into account. Within two years the disease burden estimates should be better defined especially in countries with low to moderate coverage.

Targets

Burden of disease estimates must guide public health strategies. That is, operational targets for reductions in pertussis morbidity and mortality should be developed and presented for discussion at the World Health Assembly.
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Monday 16 October 2000

08:00–08:30 Registration

08:30–08:50 Welcome and opening session

Welcoming remarks Dr Bjorn Melgaard
Objectives of meeting Dr Marc Laforce

08:50–10:30 Pertussis disease and its control strategies

- Pertussis: the ultimate challenge Dr Jean Marc Olivé
- Pertussis, a serious disease with a variable presentation and severity in the different age groups (to include updated figures on pertussis mortality)
- Different vaccines and vaccination schedules Dr Luis Barreto
- Regional experiences with respect to vaccination strategies and vaccination coverage
  - EURO
  - AMRO/PAHO
  - SEARO

- Discussion

10:30–11:00 Coffee break

11:00–12:45 Pertussis disease and its control strategies (contd)

- Changing epidemiology with sustained high coverage Dr Natasha Crowcroft
- The role of adults and adolescents in transmission Dr Kathy Edwards
- Impact of vaccination on infants susceptibility Dr Nicole Guiso
- Bordetella parapertussis and its importance Dr Jussi Mertsola

- Discussion
12:45-14:00 Lunch break

**14:00-15:30 Laboratory related issues and molecular epidemiology**

- Laboratory diagnosis  
  Dr. C. Wirsing von König
- Is there a role for serosurveillance?  
  Dr. Anna Giammanco
- Changes in circulating strains: possible effect of immunization pressure and impact on vaccine effectiveness and disease severity  
  - the Netherlands  
    Dr. Fritz Mooi
  - France  
    Dr. Nicole Guiso

- Discussion

**15:30-16:00 Coffee break**

**16:00-17:30 Laboratory related issues and molecular epidemiology (contd)**

- Global standardization of strain differentiation methods and establishment of a collaborating laboratory network for the characterization of B. pertussis isolates  
  Dr. Hans Hallander
- Effectiveness of current whole cell/acellular vaccines against new strains as measured in animal potency assays. Report of the WHO working group on standardization and control of pertussis vaccines  
  Dr. Mike Corbel
- Is there a need for a global laboratory network?  
  Dr. Ray Sanders

- Discussion
Tuesday, 17 October 2000

08:30-10:30  Is current surveillance contributing to the understanding of the situation and interpretation of epidemiologic changes?
- Is there a good match between surveillance and coverage data?
  - The experience of AFRO
  - The experience of EMRO
  - The experience of WPRO
- Can surveillance demonstrate an improvement in pertussis control in Canada? Dr Eleni Galanis
- Epidemiological situation in Sweden Dr Patrick Olin
- Surveillance of pertussis in a country with low coverage - Ethiopia Dr Amha Mekasha
- Surveillance of pertussis in a country with high coverage - Japan Dr Kuno-Sakai

Discussion

10:30-11:00  Coffee break

11:00-12:00  Is current surveillance contributing to the understanding of the situation and interpretation of epidemiologic changes? (contd)
- Discussion (contd)

12:00-13:30  Lunch

13:30-15:00  Is pertussis on the raise and why?
- The epidemiological situation in the USA Dr Melinda Wharton
- The epidemiological situation in Australia Dr Peter McIntyre
- The epidemiological situation in Oman: the 1997 outbreak Dr Salah Al Awaidy

Discussion

15:00:15:30  Coffee break

15:30-17:30  General surveillance issues
(open discussion around the following themes)
- Should disease in adolescents and adults be monitored in all or certain countries?
- Clinical diagnosis and case definitions. What surveillance in the absence of laboratory support?
• How much could we learn through outbreak investigation versus regular surveillance?
• What surveillance do we need at the global level to adjust vaccination strategies (acellular versus whole cell vaccine, schedule, need for booster doses)?
• The WHO recommended surveillance standards for pertussis: do they need changes?

Wednesday, 18 October 2000

08:30-09:30 Synthesis: next needed steps for WHO (research activities, strategies, ...)
Open discussion

9:30-10:15 Pertussis burden estimation
- WHO’s approach Dr M. Birmingham
- Why do we need burden estimates and how do we obtain them?
- Methods previously used for pertussis burden estimation Dr Peter Strebel
- Discussion

10:15-10:45 Coffee break

10:45-12:30 Pertussis Burden Estimation (contd)
- Proposed methods for pertussis Dr Natasha Crowcroft burden estimation
- Discussion

12:30-14:00 Lunch break

14:00-15:30 Review of recommendations and discussion
Closure
Annex 3: Abstracts

The following are abstracts taken from presentations made at this meeting. These abstracts appear here in order of presentation according to the agenda.

Pertussis: A Serious Disease with Variable Presentation and Severity in Different Age Groups Dr Scott A. Halperin

Pertussis is an upper respiratory infection caused by the Gram-negative coccobacillus Bordetella pertussis. Pertussis affects persons of all ages and can occur in previously immunized, unimmunized or infected individuals. Immunization (and previous infection) moderates the severity of the clinical manifestations. In immunized populations, most morbidity and virtually all mortality occurs in infants under one year of age. In unimmunized populations, morbidity and mortality is also seen in older infants and children. Symptoms of pertussis (paroxysmal cough, whoop, vomiting with cough) are reported less frequently and are of shorter duration in immunized individuals, although classic pertussis is still the norm. In the industrialized world, adolescents and adults are accounting for an increasing proportion of reported cases of pertussis. Reported cases are associated with symptoms not unlike those seen in infants and young children, although seroepidemiology studies suggest that asymptomatic and mildly symptomatic infections are more common. Symptomatic adolescents and adults are the likely source of infection in young infants; the role of asymptomatic infection in transmission has not been established. The global burden of disease, case fatality rates and infant mortality from pertussis are not known because of inadequate collection of epidemiological data. Infant pertussis deaths may be misdiagnosed or not reported. The burden of illness in adolescents and adults is also unknown. Improved surveillance is necessary to understand the full spectrum of disease and to better estimate the morbidity, mortality and effect of immunization programmes.

Pertussis Immunization Schedules Dr Luis Barreto

Pertussis immunization schedules vary from country to country, both in types of vaccines and in timing of vaccine administrations (Tables 1 and 2). Two types of vaccines are licensed for use: whole-cell pertussis vaccines, used in some industrialized countries, and in wide use in public programmes in developing countries; and acellular pertussis vaccines, now used exclusively, or in part, in several industrialized countries. North America and Japan, for instance, now use acellular pertussis vaccine (DTaP), or combinations, exclusively. Countries in Western Europe either use acellular, whole cell, or schedules with both pertussis vaccines. A cellular vaccines are also available in the private markets (5–10% of populations) of developing countries, but public programmes in developing countries typically use whole-cell vaccine.
North America uses a 5-dose schedule, and a 6th dose adolescent/adult booster has been licensed for use in Canada. Other countries have 3, 4 or 5 dose-schedules; France and Germany using acellular vaccines as a 5th dose adolescent booster.

Timing of administration varies greatly from country to country with earliest dose at six weeks of age (e.g. EPI) and oldest age for first dose 3–12 months (Japan). In many developing countries, infants can have completed a primary series by 3.5 months of age, with no further booster, whereas in some European countries a primary series may not be complete until 12 months of age, and an additional two boosters given at older ages.

Given the variability in schedules, the type of vaccine used and the number of doses administered, epidemiological assessment would help to evaluate the impact of immunization schedules on pertussis morbidity and mortality, especially in countries with early 3-dose schedules, no further boosters, and low vaccination coverage.

**Pertussis in the Region of the Americas**

**Dr Mauricio Landaverde**

The incidence of pertussis in the Region of the Americas has been going down during the last twenty years while the coverage with DTP3 in children under one year of age has been consistently over 80% over the last six years. That coverage was over 80% in 64% of the districts in 1995. In 1998, 40% of the districts had DTP3 coverage better than 95% for children under one year of age.

The incidence of pertussis has remained low and stable in most countries of the Region, with the exception of local outbreaks confined mainly to small and rural districts as those reported by Peru.

Chile has also reported a clear increase in the incidence since 1995. In that country a case definition that included the Whooping Cough Syndrome was started in 1992; the Direct Fluorescent Antibody technique was implemented in most of their regional laboratories during 1995; and in 1996 a new case definition was introduced that requested that any case under three months of age with respiratory infection and apnoea was to be reported as pertussis. The increase in reported cases has been in infants under 12 months of age.

**Changing epidemiology of pertussis with sustained high coverage in the United Kingdom**

**Dr Natasha Crowcroft, Dr Liz Miller, Dr Nigel Gay**

The UK pertussis vaccination schedule comprises three doses of whole cell vaccine given as DTP Hib at 2, 3 and 4 months of age. The UK serves as a model for the level of control that can be achieved with a three-dose schedule when high coverage is sustained. The history of pertussis vaccination in the UK is dominated by the vaccine scare of the 1970s when coverage fell to 30%. Large epidemics of pertussis followed with up to 70,000 cases per year. It took 15 years for coverage to return to an acceptable level of over 90%, which has been sustained for the decade 1990–2000. Epidemic cycles have continued but with many fewer cases.
Notifications have now fallen to their lowest level on record, with 2,989 notifications during the most recent epidemic year of 1997. The rate of disease in young infants may be at its lowest possible level with the existing UK schedule.

Although there is little reported pertussis, notifications have been shown to underestimate the true burden of disease. Rates of disease in infants are higher than notifications when measured using data from hospital admissions. Pertussis is also under-reported on death certificates. Using capture-recapture methods there are an estimated 10 deaths per year from pertussis in England. Seroprevalence data have been modelled to look for age-specific rates of infection and these indicate highest rates of infection in pre-school children, followed by children 5–9 and 10–14 years of age. Annual rates of infection have been found to be as high as 3–5% in children 1–3 years of age. These estimates based on serological evidence of infection do not include the proportion of such infections that cause severe or symptomatic disease in the child.

An ongoing study in London paediatric intensive care units has found that pertussis is under-diagnosed using routine diagnostic methods, and that adults may play a significant role in transmitting infection to young infants. The decision facing those responsible for the UK vaccination programme is whether the level of pertussis warrants addition of boosters to the programme. If it does warrant this, which is the best age to boost?

**Pertussis burden estimation: Proposed methods**

Dr Natasha Crowcroft, Dr Jean-François Aguilera, Dr Nigel Gay

WHO has developed a new approach to estimate the global burden of diseases and this technique has been followed to produce preliminary estimates of the burden of pertussis. Estimating the number of deaths is the simplest part of the task conceptually. However, routine mortality statistics are incomplete and inaccurate, even in high-income countries, and especially in the first year of life where deaths are concentrated. The youngest infants with pertussis do not always present with typical whooping cough, and in the event of death from apnoea it is possible that it may be misdiagnosed as sudden infant death syndrome.

Measuring burden of disease due to pertussis is even more problematic. Estimates could include all infections, all symptomatic infections, all severe infections (WHO case definition for clinical trials), or all infections but only in young children. Routine surveillance data are not adequate. Notifications have been used to estimate disease burden in the past by applying an arbitrary multiplier to allow for underreporting by countries. However, there is no objective method for estimating the multiplier. A proportional mortality method has been applied to estimate disease burden from ARI, but estimates of proportions of pertussis to ARI will vary making this approach also problematic, especially for estimating trends.

The epidemiology, natural history and transmission dynamics of pertussis are quite complex. At this stage, routinely available data do not allow dynamic models to be developed that can be applied globally. A good model should be transparent, simple and generate believable estimates.
The proposed model is static and assumes the following:

- Percentage protected = 1 - (coverage * efficacy)
- 100% of susceptibles are infected by the age of 15 years
- Infections in those protected do not contribute significant morbidity
- Infections in older children and adults are not important (they only affect transmission)
- Vaccination does not significantly affect transmission in the unvaccinated
- The age distribution in unvaccinated cases is stable

The critical parameters are:

- Vaccine efficacy - 80%
- Case fatality ratio - from literature
- Age distribution of the proportion of susceptibles infected by one year, and by five years of age - from literature
- Pertussis vaccination coverage
- Population estimates

A detailed literature search has been carried out using Ovid Medline, WHO EPI office, the Public Health Laboratory Services (PHLS), Communicable Disease Surveillance Centre (CDSC), and WHO regional office libraries. 376 papers so far have been evaluated and disease parameters extracted. This collection of papers and Refman bibliography is a resource for EPI. Unfortunately very little literature has been found on case fatality in developing countries.

Draft estimates are of 34 million pertussis infections in 0–4 years, 250 000 deaths, 8 million hospitalizations, 4 million pneumonias, 0.7 million convulsions and 250 000 cases of acute encephalopathy. As this is a static model, the estimate represents the average number of cases over an epidemic cycle, which is appropriate for aggregation over large territories where epidemic cycles are unlikely to be synchronized. Ongoing tasks include incorporating additional literature, modifying estimates for countries with sustained high coverage, allowing for demographic change and gender difference, refining estimates of mortality and complications, and applying a 95% vaccine efficacy against death from pertussis. Further considerations include allowing for epidemic cycles, trends, the impact of vaccination on transmission, and validation against reported mortality rates.
The role of adolescents and adults in pertussis transmission
Dr Kathryn M. Edwards

Several lines of evidence support the hypothesis that adolescents and adults play a major role in the transmission of pertussis. As early as 1918 Luttinger reported "Pertussis Pete", who was an adult who spread pertussis among three community families. Then in 1925 Madsen described transmission of pertussis to infants from grandmothers with persistent cough. As early as 1972 two separate outbreaks of pertussis were reported within a three month period in a large paediatric hospital. Secondary cases occurred in the housestaff treating children with pertussis, in their families, and among additional paediatric patients admitted for other illnesses. The important role of adults in the transmission of pertussis to infants was demonstrated by Nelson in 1978. He evaluated two periods (1965-1971 and 1971-1977) and found less than half the number of cases in the second period. However, there was no decline in the number of cases in infants <12 weeks of age throughout the two study periods. During the first period an adult was the source of the infection in 3/14 infants; during the second period an adult was the source in 14 infants, 12 of them were the mothers of the infants. In Finland in 1983 cases of intrafamilial spread of pertussis were demonstrated in 21 families with pertussis. Serologic studies in family members demonstrated 83% acquired infection in the household, however, only 46% were symptomatic with cough. Also infants often acquired disease from vaccinated siblings or parents, therefore documenting a waning immunity with vaccination or with natural disease.

Other data to support transmission of adults to children was proved by an outbreak in central Wisconsin in 1985. This outbreak involved 161 culture-confirmed cases and occurred in three rural counties. To determine risk factors for pertussis, 61 households with pertussis were compared with 120 control households without disease. These studies demonstrated that transmission of the organism to adolescents and adults in the community occurred and that it was associated with prolonged and paroxysmal cough. In addition, transmission from adult relatives or babysitters was demonstrated in 6 of 8 primary cases in infants (< 6 months of age).

Another similar study was reported by Long in 1990. Four infants with classic culture-confirmed pertussis and 18 family members were evaluated by pertussis culture and serology. Although pertussis cultures were positive in only 20% of family members, serologic rises were seen in 83% with at least one symptomatically infected contact per family. The infant cases were secondary to primary infections in adult family members.

Finally, peripartum transmission of serious disease was shown when coughing mothers infected their infants with pertussis during the peripartum period. Some of the infants died.

In summary, increasing evidence exists from countries with pertussis vaccination programmes that documents adults and adolescents, particularly if they have symptomatic cough, often serve as the source of infection for infants and children. Pertussis immunity wanes with time from both vaccination and natural disease. Thus, immunization of older individuals with acellular vaccines is likely to reduce spread.
The French experience with pertussis vaccine
Dr Nicole Guiso

Following the introduction of a whole-cell pertussis vaccine (Pw) in France in 1957 and the generalized use of a combined vaccine (DTPw) in 1966 a dramatic decline of pertussis mortality and morbidity was observed. In addition, adolescents and adults were shown to be the source of infection for non or incompletely vaccinated infants. Nonetheless, after thirty years of generalized vaccination a resurgence of pertussis was observed. This resurgence could be due to a decrease in the acceptability of the vaccine, a decrease in the coverage, a low efficacy of the vaccine or waning of immunity with a 4 dose vaccination schedule (doses at 2, 3, 4 and 18 months). Results from a study in the Hôpital Trousseau in 1991, a national study in 1993–1994 and a clinical trial in Senegal (1990–1994), showed that despite high vaccination coverage B. pertussis was still circulating. The Pw used in France was shown to be efficacious in France and Senegal and the resurgence was mainly attributed to a lack of vaccine and natural boosters.

Furthermore, in a study comparing two departments in France with high (Paris – 91%) and low (Marseille – 61%) vaccine coverage, it was shown that the proportion of adults as a source of contamination was higher in the high coverage department (Paris).

A serological study performed in the Paris area, where the coverage is very high, demonstrated that vaccinated children become susceptible to infection 6–7 years after their last vaccination at 18 months. For this reason, a booster dose with acellular pertussis vaccines at 11–13 year old was introduced in France in 1998.

In 1997, a surveillance net that included 43 paediatricians, 43 bacteriologists, the National Center of Reference of Bordetellosis (Institut Pasteur) and the Institut de Veille Sanitaire (Ministry of Health), RENACOQ, was established in France.

Laboratory diagnosis of pertussis
Dr Carl Heinz Wirsing von König

The laboratory diagnosis of pertussis can be made directly by detecting Bordetellae with conventional culture or their nucleic acid by PCR, or indirectly by assessing the antibody response of the host.

The quality of the clinical material (i.e. nasopharyngeal aspirates, nasopharyngeal swabs) critically influences the sensitivity of culture. Further variables include transportation time, the duration of clinical symptoms, the age of the patient, the vaccination status of the patient, and his antimicrobial therapy. Use of enrichment media should be considered when plates cannot be directly inoculated and transportation time is more than one day. Various PCR formats have been described for detecting Bordetella DNA and most techniques are more sensitive than culture, especially in the later stages of the disease. Thus, PCR is especially useful in diagnosing the disease in adults, in vaccinated individuals and in patients receiving antimicrobial therapy. PCR is on its way to standardization and real-time detection of amplicons will increase its speed and robustness.
Serology can be done with in-house ELISA s, commercial ELISA s, immunoblotting and various other serological methods, but ELISA s are most widely used. ELISA s using purified pertussis toxin, filamentous heamagglutinin and pertactin have been intensively evaluated and standardized during vaccine studies. Many commercially available ELISA still need improvement concerning their comparability with validated ELISA s, their reproducibility and their sensitivity. Single sample serology can help in diagnosing pertussis when age-specific reference values have been established for the population in which the test is being used.

The role of other microorganisms in producing pertussisform coughts and the frequency of mixed infections in pertussis still needs clarification.

Changes in circulating strains: possible effect of immunization pressure and impact on vaccine effectiveness and disease severity - Netherlands data.

Dr Fritz Mooi

In the Netherlands, like in many other western countries, pertussis vaccines have been used intensively for more than 40 years and it is conceivable that vaccine-induced immunity has affected evolution of B. pertussis. Consistent with this notion, pertussis has re-emerged in the Netherlands, despite high vaccination coverage. To investigate the cause for the re-emergence of pertussis we studied changes in the population structure of B. pertussis in the Netherlands in the period 1949–1996. A significant change in the population structure of B. pertussis was observed subsequent to the introduction of the vaccine in the 1950s. A large decrease in genotypic diversity was observed after the introduction of vaccination, suggesting a decrease in population size or clonal expansion. The decrease in genotypic diversity was followed by a gradual increase to pre-vaccination levels, suggesting adaptation of the bacterial population. Changes in the B. pertussis population were also studied at the gene level. We observed antigenic divergence between clinical isolates and vaccine strains, particularly with respect to the surface-associated proteins pertactin and pertussis toxin.

An important question to address is whether adaptation of the B. pertussis population has affected vaccine efficacy, i.e. contributes to the re-emergence of B. pertussis. Animal experiments have indicated that variation in pertactin affects vaccine efficacy (our unpublished data). Furthermore, we found vaccine-type pertactin variants in lower frequencies among vaccinated people compared to unvaccinated people, which would be expected if the vaccine protects differentially against strains with distinct pertactin types. However, the extent in which polymorphism affects vaccine efficacy is probably dependant on the vaccine used. Further studies are required to assess the effect of the observed adaptations on the efficacy of pertussis vaccines. In this period, where whole-cell vaccines are replaced by acellular vaccines in many countries, continued strain surveillance is of paramount importance.
Changes in circulating *Bordetella pertussis* isolates: possible effect of immunization pressure and impact on vaccine effectiveness and disease severity - French data

Dr Nicole Guiso

*Bordetella pertussis* isolates circulating in France during the past decade have been compared to vaccine strains and to isolates collected before 1966 when general DTP vaccination was introduced. Analysis included biochemical identification, serotyping, DNA analysis by pulsed-field-gel electrophoresis (PFGE), and sequencing of genes encoding the S1 subunit of pertussis toxin (PT) and the pertactin (PRN).

The same pertussis whole-cell vaccine produced by Aventis-Pasteur, (Pw), has been used in France since 1957. It is composed of two strains differing at least in the expression of fimbriae (FIM) (one is expressing FIM 2 and the other is expressing FIM 2 and FIM 3) and in the gene encoding the S1 subunit of PT (one is expressing type B and the other is expressing type D). The *B. pertussis* isolates circulating in the last ten years in France differ from vaccine strains by serotype (the majority express FIM 3), PFGE analysis, the gene sequence encoding S1 subunit of PT (all isolates express a type A) and the gene sequence encoding PRN (the majority of the actual isolates express type 2 and 3 prn genes, whereas vaccine strains and isolates circulating before the introduction of the vaccination express type 1 prn gene). These data suggest that thirty years of vaccination may have induced variation, although there is no proof of vaccine failure due to circulation of these variants.

The change from whole cell to acellular vaccines (Pa) composed of purified bacterial proteins is worrisome given the limited number of antigens contained in the acellular vaccine. Furthermore, the PT is of type B and the PRN included is of type 1, whereas actual clinical isolates express type A PT and type 2 or 3 PRN.

However, the variability of the structural gene encoding PRN concerns mainly two regions (I and II) composed of repeated sequences which were shown to be immunodominant. Comparison of these two regions showed that *Bordetella parapertussis* PRN is invariant, whereas *B. pertussis* PRN varies mostly in region (I) and *Bordetella bronchiseptica* mostly in regions (II), a region that was shown to induce protective immunity. The lack of cross-protection between *B. pertussis*, *B. parapertussis* and *B. bronchiseptica* PRN is consistent with this observation because the major differences between these proteins occur in this region. No variation in this region was observed for the PRN produced by *B. pertussis* isolates. Thirty years of vaccination may have induced variation in one immunodominant region (I) but not in the other (II).

These observations indicate that a strategy of continuous surveillance of antigens expressed by *B. pertussis* isolates is prudent. Different techniques such as animal models and standardization of *B. pertussis* typing have been established to meet these surveillance goals.
Global standardization of strain differentiation methods and establishment of a collaborating laboratory network for the characterization of B. pertussis isolates

Dr. Hans Hallander


When acellular vaccines are introduced it is important to monitor the polymorphism of critical vaccine antigens. If implemented in a multi-site surveillance programme such an approach would offer the opportunity to determine the extent of polymorphism and to compare genetic structures of variants between regions with different vaccination practices.

The proposed standard methodology includes serotyping, gene typing of pertactin and the pertussis toxin subunit S1 and, finally, fingerprinting of chromosomal DNA by means of PFGE with two restriction enzymes (OH 2).

Determination of pertussis serotypes requires specific antisera, which is a major standardization issue. Before 1996 we used slide agglutination and a polyclonal antiserum obtained after immunization of rabbits with heat killed bacteria. Since 1997 we have used monoclonal antibodies in microplates. To avoid artefacts the monoclonals were validated in collaboration with Nicole Guiso and Fritz von König.

Gene typing is based on the work by Frits Mooi and collaborators in Bildthoven. Nine pertactin alleles have been identified. This relatively high degree of polymorphism is due to the presence of two regions which harbour repeats. Most polymorphism is observed in region 1 (OH 4 upper part) with the globally most frequent types: 1, 2 and 3. The sequencing technique is straight forward and reproducible. Reference strains are needed ensure that the tests are correct. There are four subtypes of PT localized to subunit 1 which has the toxic function. The toxin sequence is long 935 bp (OH 4, lower part). Type B and D are those present in vaccines.

To increase the capacity of gene typing and reduce the costs it is necessary to develop and implement new molecular techniques which have been successfully adopted for allele specific genotyping in other microbial systems. One model that can be used as an example comes from the Uppsala group working with rotavirus. There are G- and P-types, both coding for proteins inducing neutralizing antibodies. Multiple PCR products are captured by specific oligonucleotides and detected by fluorescence labelling.

Cluster technique is also applicable to epidemiological typing of B. pertussis and would compare combinations of properties; it may be too difficult to analyse the different markers one by one. For example, in Sweden the serotype2/pertactin2 variant which was predominant during our 17 vaccine free years is now decreasing since general vaccination against pertussis was reintroduced in 1996, and is successively replaced...
by serotype3/pertactin2 (OH 6). Furthermore, a new cluster, serotype3/pertactin3, has appeared since 1996. Pertactin 1 which is present in the vaccine has almost disappeared.

As part of a subtyping effort it would also be possible to add oligonucleotides specific for other microbes causing pertussis-like syndromes, thus improving etiological laboratory diagnosis. The most important ones are B. parapertussis, Mycoplasma pneumoniae and adenovirus (OH 7).

The most difficult method to standardize is the PFGE. In this method chromosomal DNA is cleaved with restriction enzymes and the fragments separated by gel electrophoresis. Our studies of 168 isolates from vaccinated individuals with pertussis show that it is possible to identify up to 80 different patterns. When the bands are organized by the Gel Compare programme three main clusters may be identified at a level of approximately 80% identity. These clusters fit well with the serotype/pertactin combinations. A special problem with PFGE is that patterns may be modified according to the equipment used. To make results comparable between laboratories and to attain a common terminology it is necessary to introduce adequate internal controls.

Also, without a fine tuned analysis PFGE does allow for the selection of representative isolates from the main clusters for further studies (OH 10). These same isolates can be used for challenge experiments in mice or functional tests demonstrating adhesion or invasiveness.

In summary, potential reference laboratories should offer testing with the reference methods. They should also organize external quality assessment programmes with defined panels to assure traceability, in addition to arranging training for other laboratories within their region. Data bases with strain profiles related to vaccination programmes, regions, time periods should be set up.

Can surveillance demonstrate an improvement in pertussis control?
D r E l e n i G a l a n i s , D r A r l e n e K i n g , D r G a s t o n D e S e r r e s

A cellular pertussis vaccine has been touted as significantly more effective than whole-cell pertussis vaccine (80–95% vs. 70–90%) and is believed to lead to better control of the disease. In Canada, whole cell vaccine was first licensed in 1943 and the first acellular vaccine was licensed in 1996. The latter was in widespread use by 1997–98. The objective of this paper is to assess whether the introduction of acellular pertussis vaccine in Canada has had an impact on age-specific incidence rates of pertussis and whether the pertussis surveillance system permits such an impact to be observed.

Pertussis has been a nationally notifiable disease in Canada since 1924. The latest case definition, in use between 1991 and 2000, was: A confirmed case of pertussis is a case with compatible symptoms and isolation of B. pertussis. A clinical case is either 1) a paroxysmal cough and one of the following associated symptoms: apnoea, vomiting or whoop; or 2) a cough lasting more than 2 weeks and epidemiologically-linked to a laboratory-confirmed case. Health providers and laboratory personnel report cases of pertussis to local health authorities who submit
the information to provincial/territorial Ministries of Health, who in turn submit monthly reports to Health Canada. All 13 provinces and territories report cases in an aggregate manner, while 7 of them have begun submitting case-by-case data.

The incidence of pertussis dropped dramatically since the introduction of pertussis immunization, from 181.6 cases/100 000 in 1934 to 4.3/100 000 in 1988. Since the late 1980s, reported cases have increased again to a peak of 34.7/100 000 in 1994 with epidemics every three to four years. The highest age-specific rates continue to be seen among infants. Starting in 1997, the age group one to four years has seen a decrease in pertussis incidence rates as compared to the rest of the population. From 1997 to 1999, incidence rates increased in all age groups, whereas they decreased by 19% in the one to four year age group. This age group has received the greatest number of doses of acellular pertussis vaccine (0 to 4 doses) since its introduction.

The increase in pertussis incidence since the late 1980s has not yet been explained and may be due to poor vaccine effectiveness, changes in the circulating strains of B. pertussis or to increased awareness and/or testing. Since the introduction of acellular vaccine in Canada, there has been a small relative decrease in national pertussis incidence rates among one to four year olds. In conclusion, it is still too early to determine whether acellular pertussis vaccine has had or will have a significant impact on pertussis incidence in Canada. Next steps include improving the passive surveillance system and conducting enhanced surveillance of the laboratory and epidemiologic aspects of pertussis.

Is current surveillance contributing to the understanding of the situation and interpretation of epidemiological changes? Epidemiological situation in Sweden

Dr Patrick Olin

Surveillance of pertussis in Sweden during the last century was based on reports to National Bacteriological Laboratory (SBL, later SIIDC) from the community medical officers (GP reports), from 1900 to 1988, when pertussis was removed from the list of notifiable communicable diseases. Since 1980 voluntary laboratory reports of B. pertussis confirmed by culture or serology, and in recent years also PCR were collected by SBL/SIDI C. In 1997 the new Communicable Disease Act required compulsory notification from laboratories and clinicians.

During the pre-vaccination period, pertussis was endemic in four-year cycles. Introduction of whole-cell vaccination in the 1950s reduced incidence to a low level. A poor vaccine was inadvertently used in the 1970s and led to a return of whooping cough. Interruption of vaccination led to further increase of the rate of endemic pertussis. A cellular vaccine was introduced in January 1996, leading to a drastic reduction of whooping cough with milder illness in vaccinated children.

The passive surveillance methods used in Sweden, albeit representing large underreporting, have detected gross changes in the incidence of pertussis reflecting changes in the use of vaccines. When acellular pertussis vaccine was introduced in 1996 at 3, 5 and 12 months of age, the age specific incidence of culture confirmed pertussis could be shown to decrease, not only in the recently vaccinated young age groups but also in older children. Furthermore, the main reservoir of reported cases
was shown to be in 5–9 year old children. In 1997, a surveillance project was started in order to assess the effect of the introduction of acellular vaccines. This included additional data on vaccination history and clinical course in culture confirmed cases among children born 1992 or later, as well as vaccine specific coverage data. Only crude rates of cases among unvaccinated and vaccinated children have been reported, indicating that cases among vaccinated children constitute a small fraction of notified pertussis cases. Hospitalizations due to culture confirmed pertussis is common among unvaccinated cases 0 to 3 months of age before the first dose of DTP IPV Hib vaccine, and the duration of hospital stay is longer for unvaccinated infants than for vaccinated infants.

In summary, compulsory notification of pertussis by laboratories and clinicians in combination with good demographic data will detect gross changes in the pertussis incidence and may generate age specific incidence rates. Analyses of vaccine effectiveness require that laboratory confirmed cases are documented regarding vaccination status and clinical course in order to estimate immediate effects of the vaccination programme. In the long term this will also enable the assessment of potential differences between vaccines and waning immunity.

Analyses of effectiveness of individual vaccines would benefit from a vaccination registry with batch specific information and linked data bases for demography, disease surveillance (including strain collections) hospitalizations, deaths and adverse events.

**Pertussis in Ethiopia**

**Dr Amha Mekasha**

The Ethiopian population is estimated at 61.7 million of which 85.3% live in rural areas. Children below 16 years of age constitute about 48% of the total population. Children under the age of five years are about 18% and infants are 3.5% of the total population.

An estimated 60–80% of the health problems are due to infectious diseases and nutritional problems. The system is underdeveloped and is able to provide health service only to about half of the population.

Statistics on morbidity are collected from health institutions by the Ministry of Health. The EPI unit collects monthly reports of immunization performed for the purpose of monitoring. Pertussis is one of the epidemic diseases included in the monthly reports, but it is not among the 17 diseases under surveillance system.

In 1999, a national report of epidemic diseases (based on reports from regions), which included pertussis, reported 640 cases with only 3 deaths.

EPI coverage is increasing steadily in spite of the difficulty in reaching the inaccessible areas. Some of such areas are covered by out-reach programmes, but due to budgetary problems the coverage remained low. Although the pertussis trend may be on the decline, it is likely that there are further unreported cases in the community as well as in health facilities. Hence, the surveillance must be strengthened and the EPI programme accelerated.
National data in a rural survey revealed that 4.4% of all the illnesses were due to pertussis and other coughs. Pertussis is well known by the people, and is called "Tik Tik". In a community based study it was found that all mothers knew about its main feature, a cough of long duration, and about a third of them reported that it is associated with vomiting. However, none of these women recognized vaccination as a means of prevention.

Pertussis accounted for about 5% of deaths in a verbal autopsy study. Thus, it is a recognized cause of death and morbidity in the community.

**Surveillance of pertussis in a country with high coverage, Japan**

Dr Harumi Kuno-Sakai

In 1981, acellular pertussis vaccines totally replaced whole cell vaccines, beginning immunization at two years of age. The national surveillance started in 1981 and 2400 sentinel doctors throughout Japan are making weekly reports on pertussis. The surveillance revealed a dramatic decrease in the number of pertussis cases aged one to four years since 1981. However, epidemics of pertussis among infants could not be fully controlled. In December 1988 DTP started to be given to children below two years of age, and after amendment of the preventive immunization law in October 1994 (active as of April 1995), most of first three doses of DTP are being given to 3-24 months old infants. We developed the ELISA methods using polystyrene ball (PS Ball method). Since surface areas of balls were constant, reproducibility and sensitivity of the PS Ball method were much better than those of ELISA using a plate. With the latter, the surface for reaction fluctuate when fluid levels changes. The PS Ball method has been used for the population survey conducted by the government in collaboration with NIH and Prefectural Institutes of Public Health. In April 1996 the Ministry of Health and Welfare started nationwide prospective studies on adverse reactions to DTP. Ten thousand cases per year have been studied and the results have been reported every six months. Since DTP is an adjuvant vaccine, local reactions to DTP are more commonly observed than plain vaccine, and become more marked when DTP are administered repeatedly. Although frequencies of local reactions differ from one manufacturer’s product to another, the study showed that local reactions over 1cm in diameter during 28 days after administration of DTP were 11-29% for the first dose, 24-40% for the second dose, 19-30% for the third dose, 38-54% for the fourth dose, and 27-37% for 0.1 ml dose of DT given to 11-12 year olds.

A research team organized by the Ministry of Health and Welfare and chaired by Kimura M, Tokai University, revealed that a minute amount of gelatin (which had been one of the ingredients of DTP of some of the manufacturers) sensitized infants who then developed allergic reactions to subsequent administrations of gelatin-containing live vaccines. This resulted in the recommendation of the Ministry of Health and Welfare to withdraw gelatin from vaccines. Current DTP vaccines in Japan do not contain even trace amounts of gelatin.
Epidemiology of pertussis in the United States
Dr Melinda Wharton, Dr Lynn Zanardi, Dr Masahiro Tanaka, Dr Kristine Bisgard, Dr Brian Pascual, Dr Jacqueline Tate, Dr Trudy Murphy

Introduction and widespread use of diphtheria and tetanus toxoids and whole cell pertussis vaccines (DTP) in the United States led to a dramatic decrease in reported cases of pertussis. In the early 1990s, acellular pertussis vaccines (DTaP) were licensed for use as the fourth and fifth dose of the five dose series (at 15–18 months and 4–6 years, respectively) and, in 1996, for use as the primary series at two, four and six months of age.

National pertussis surveillance is conducted through a voluntary passive reporting system operated at the state level. Key clinical, laboratory and epidemiological data are collected. Underreporting is substantial. In 1996 the PCR assay was added to the case definition as an accepted method for laboratory confirmation.

During the 1990s, reported cases of pertussis continued to increase, a trend that began in the 1980s. In 1996, 7796 cases were reported, the most in any year since 1967, and in 1999, 7298 cases were reported. Although incidence increased in most age groups, the most dramatic increases were seen among adolescents and adults. Incidence rates remain highest in infants <1 year of age (57 per 100 000 in 1999), but the second highest rates are reported among children 10–14 years of age (7 per 100 000). Outbreaks of pertussis in junior high and high schools (attended by students 12–18 years of age) are now increasingly recognized. Reported rates vary markedly among states, and the variation is largely due to differences in reported rates among adolescents and adults. Since 1990, rates of disease have increased among young infants (<4 months of age) while remaining stable among those 4–11 months of age and among children 1–4 years of age. In 1998, 96% of children 19–35 months of age had received three or more doses of DTP, DTaP, or diphtheria and tetanus toxoids, and 84% had received four or more doses. Using the screening method, the US pertussis vaccination programme during the period 1992–1994 was found to be highly effective in prevention of culture-confirmed pertussis (3 doses, 79% (95% confidence interval (CI) 74%–83%), 4+ doses 90% (95% CI 88%–92%)).

Reported pertussis incidence has increased among adolescents and adults. Increased awareness of the occurrence of pertussis in these age groups and increased recognition of school-based outbreaks has contributed to the increases observed. Recent increases among young infants <4 months of age suggest that the observed increases are not only due to improved reporting but may reflect a real increase in the incidence of disease. However, disease rates have remained stable during the 1990s among young children four months to four years of age, consistent with an effective vaccination programme. Decreases in pertussis in the United States will require new strategies to prevent disease in those age groups currently not protected by vaccination - young infants, adolescents, and adults.
The epidemiological situation in Australia
Dr Peter McIntyre, Dr Siranda Torvaldsen, Dr Michelle Cagney, Dr Raina MacIntyre

There has been a large increase in pertussis notifications in Australia over the past decade, from rates (per 100 000 population) of 5–10 to rates of up to 50. There were also nine infant deaths recorded in 1996–1997, equal to the number in the decade 1986–1995.

Several factors have contributed to this increase in notifications. Firstly, a national notifiable diseases surveillance scheme (NNDSS) was introduced in 1991, which coincided with enhancements in public health infrastructure, including infectious diseases. Secondly, pertussis serology, based on a whole cell antigen and produced by an Australian manufacturer became widely available in the early 1990s. Also in the early 1990s mandatory notification by laboratories of positive diagnostic tests for pertussis including serology was introduced. Nevertheless, epidemics occurred in most parts of the country in 1993 and 1997, prompting the addition of a fifth dose of pertussis vaccine at four to five years of age to the national immunization schedule.

The significance of this increase in notifications and the impact of immunization initiatives has been evaluated in a number of ways. These include:

1) Examination of hospitalization rates in infants (believed to be less susceptible to changes in diagnostic and public health practice)
2) Examination of the impact of serologic diagnosis on notifications
3) Examination of changes in patterns of age-specific incidence
4) The Australian Childhood Immunization Register (ACIR) has recorded all vaccines given to children under the age of seven years since 1996
5) There have been a number of parental and provider incentives to maximize immunization coverage since 1998
6) Studies to measure the effectiveness of the Australian-made whole cell pertussis vaccine were set up in 1997–1998
7) A cellular vaccines have been introduced for the fourth and fifth doses in 1998 and all doses from 1999
8) A sample of Australian pertussis isolates from the 1970s to 1998 has been tested for emergence of new pertactin variants by RIVM in the Netherlands
9) The validity of serologic diagnosis based on single high titre IgA to whole cell antigen has been studied
10) Population-based studies to examine the degree of under-notification of pertussis have been set up, using reported symptoms with serologic validation.
Results of the above initiatives indicate that hospitalization rates in infants have changed little in the 1990s compared with the previous decade, with the greatest increase in notifications accounted for by serologic diagnoses in adults and older children. These notifications appear valid, as serologic diagnosis as practised in Australia (based on a single high titre) has high specificity but is not very sensitive, characteristics desirable in this context. The effectiveness of the locally manufactured whole cell vaccine as measured by the screening method appears satisfactory, therefore problems with pertussis in young children appear more related to previous inadequate immunization coverage. Immunization coverage is now above 90% nationally. Pertactin mutant strains were found for the first time after 1989. Age specific incidence has changed since the introduction of a fifth dose, and the highest notification rates are now seen in 10–14 years old children, with evidence that notification is more than 10-fold lower than the true disease burden.

Current attention in Australia is focused on improvements in surveillance and the potential role of acellular vaccines formulated for adults in pertussis control. Options under consideration include replacing the currently recommended diphtheria–tetanus booster at 15–19 years with DTaP at high school entry (12–13 years), possibly initiated following a once-off national DTaP vaccination of high school students to the age of 17 years.

Epidemiology of Pertussis in Oman
Dr Salah Al Awaidy

The EPI programme was established in 1981, and pertussis vaccine introduced as DTP immunization. Between 1981 and 1997 the DTP was given at 3.5 and 7 months with a booster at 19 months. Pertussis is a recognisable disease under group B. The standard clinical and laboratory case definitions (1992) are used by all health institutions, including those in the private sector. The suspect case is defined as having a history of severe cough in addition to a cough persisting 2 weeks, paroxysm coughing or a cough followed by vomiting. A confirmed case is a suspect case and positive culture. Both standard case and outbreak investigation are being followed throughout the country.

During the pre-immunization era about 6000 cases were reported annually. However, with the introduction of vaccine (DTP), there has been a dramatic reduction from 2236 cases in 1981 to around 73 cases in 1996. The immunization coverage with DTP3 among >12 months has been maintained ≥ 95 for the last 10 years. However, there were major outbreaks in the Northern region in 1997/98.

The outbreak started in Batina in February 1997 and spread to the interior region (interior and Dhatmia) and ended up in July 1998.

Nineteen per cent of the cases were among <3 months unvaccinated and 19% were partially immunized. 34% were between 2–6 years and 13% were ≥ 6 years. Among infants, 90% were <7 months.
As far as symptoms were concerned, 24% had a duration of cough <2 weeks, 29% for 2–3 weeks and 27% for more than 3 weeks. 100% had paroxysmal cough. The laboratory investigation revealed that 91% had lymphocytosis and 76% had leukocytosis. We were able to isolate B. pertussis in 3 cases in 1997 and 2 cases in 1998.

In conclusion, the clinical and laboratory findings of a majority of the notified pertussis cases satisfy the clinical and laboratory criteria for diagnosis. The analysis indicated the age group most affected to be <7 months, those most susceptible to pertussis. A cluster of cases was also observed after two years indicating a waning immunity. The high immunization coverage has led to a modified and a milder clinical presentation in the majority of cases.

There was no mortality associated with pertussis. As a result of this outbreak a decision was made to change the DTP schedule, the vaccine would be given at 6, 12 and 20 weeks followed by 2 boosters at 15 months and 4 years of age.

Pertussis burden estimation
Dr Maureen Birmingham

At WHO, credible pertussis burden estimates (defined as estimates cases and deaths) are needed for the following reasons: 1) WHO’s responsibility (as the principle UN technical agency on health); 2) priority setting and advocacy; 3) to influence research and development of appropriate vaccines; 4) To guide vaccination policies and strategies; and 5) to assess impact and performance.

In short, credible pertussis burden estimates would help reverse the apparent complacency in developing countries regarding the burden of this disease.

Within WHO, estimations of burden are made by syndrome as well as by specific etiology, and the two must be coherent with each other. There are two principle methods of estimating burden, the natural history method and the proportional mortality method. The general approach by WHO is to get the best available data, use the best methods, develop a consultative process with experts, use the best assumptions/probabilities, conduct a sensitivity analysis, validate or check consistency with existing data, document the methods, assumptions and data sources, and subject the estimates to expert review. As further information becomes available, these estimates must continue to be improved.

The final product is a database of cases and deaths by age, sex, country and year, as well as documentation of methods, assumptions, and data sources. The process should also result in recommendations on how to improve the precision, robustness and usefulness of the estimates.

Factors that affect the estimates are epidemiologic, demographic and programmatic, in addition to co-factors such as HIV prevalence and nutritional status. Some of the practical issues that we deal with include the quality of the input data, the generalizability of data, assumptions to other geographic areas where data are non-existent, the degree of precision needed, the frequency and periodicity of update needed, and how to validate (or at least check for coherence and consistency) the estimates.
The process is often “dirty” since data may be lacking, extrapolations or generalizations are made, or there is too heavy a reliance on “expert opinion”. Sometimes crude methods are used since refined data are not available to use more refined methods. In summary, WHO makes estimates using the best available information, methods and assumptions which are documented and explicit to enable improvements over time.

Methods for estimating global pertussis disease burden
Dr Peter Strebel

Prior to 2000, at least four methods for estimating global pertussis mortality have been used. This presentation reviews these methods and their results.

In the 1980s, pertussis deaths were estimated by the World Health Organization (WHO) Expanded Programme on Immunization (EPI) as one-third of measles deaths. Working with WHO/EPI, Dr Artur Galazka developed two additional methods. The “proportion susceptible” method assumed a vaccine efficacy after 3 doses of 80%, a case-fatality ratio of 1% in developing countries and 0.04% in industrialized countries, and that the proportion susceptible equalled one minus the product of vaccination coverage times vaccine efficacy. The “underreporting” method was based on estimates of the extent of underreporting for cases in each WHO region and published estimates of case-fatality ratios. The ARI method estimated the number of pertussis deaths in developing countries only. Community-based field studies conducted in developing countries provided estimates of the age-specific probability of pertussis and its ARI-related complications (pneumonia and death from pneumonia). Calculations were based on a birth cohort of 125 million and vaccine efficacy of 85% after 3 doses.

The estimated annual number of pertussis deaths using these four approaches ranged from 296 000 to 392 000 deaths. Using the ARI method and an immunization coverage of 80%, an estimated 34 million cases of pertussis and 358 000 pertussis-related pneumonia deaths occur annually among children <5 years of age in developing countries. By increasing vaccination coverage to 90% with doses administered on time at 6, 10 and 14 weeks of age, an additional 11 million pertussis cases and 144 000 pneumonia deaths could be prevented.

Uncertainty remains about current global pertussis mortality. Estimates could be improved by more accurate DTP3 coverage information, more current measures of the age-specific risk of pertussis, pertussis pneumonia and death due to pertussis from community-based studies, and refinement of the ARI model assumptions. On time vaccination against pertussis is especially important because of the increased risk of pertussis death among infants <3 months of age.