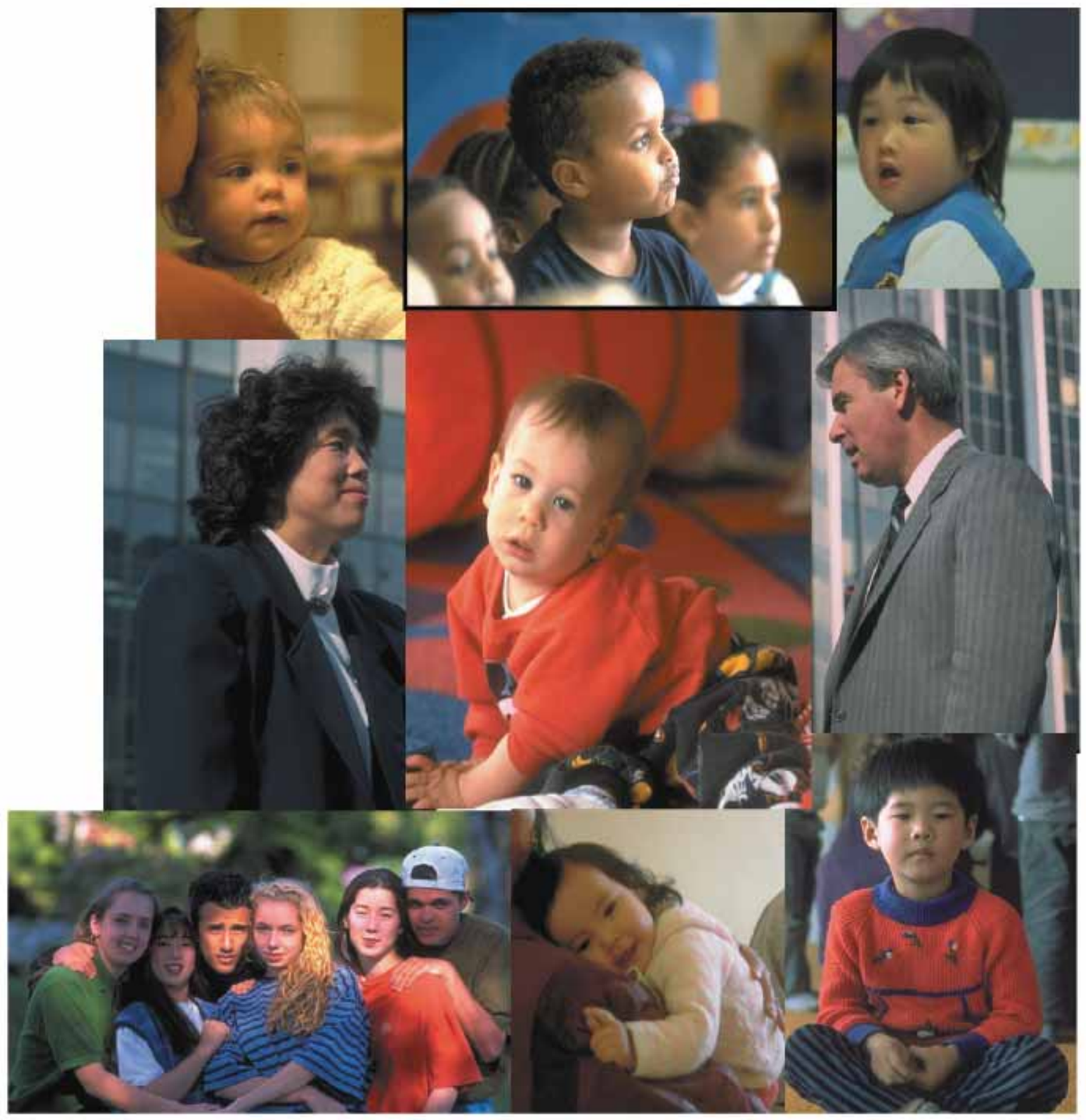
CCDR
Canada Communicable Disease Report
ISSN 1188-4169
Volume: 29S3 April 2003

National Consensus Conference on Pertussis



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National Consensus Conference on Pertussis

Toronto

May 25-28, 2002

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EXECUTIVE SUMMARY

Pertussis: Clinical Features and Diagnosis

The most serious pertussis disease occurs in young infants, who may experience complications such as pneumonia, seizures and encephalitis and who are at the greatest risk of dying from pertussis. The symptoms are milder in older children and adults but include the characteristic whoop after paroxysmal cough, and possibly vomiting. Several tests are available for diagnosis: culture, direct fluorescent antibody testing, polymerase chain reaction (PCR) and serologic testing. Although culture has been the gold standard in the past, its sensitivity is affected by many factors. There is evidence that PCR is more sensitive, although the laboratory methods in use need to be standardized.

Epidemiology

The number of reported cases in Canada has increased from the early 1990s with peaks every 4 years. The greatest incidence has been among infants < 1 year of age, and the second highest rate at present is among children aged 10 to 14. There are epidemiologic data showing that the cohort of children and teenagers immunized between 1980 and 1992 with Connaught whole cell adsorbed vaccine is currently at greater risk of pertussis, because this vaccine provided poor protection and no acellular pertussis vaccine booster dose was given. The vulnerability of this cohort is reflected in the increasng age of cases over time. Waning immunity is an additional factor in this group.

There is evidence from those provinces that introduced the acellular vaccine into their immunization program several years ago that it is having a positive impact on the number of cases reported. In British Columbia, the incidence of pertussis in infants and preschool children fell substantially after the vaccine came into use in 1997, as did rates of hospital admision in these groups. The incidence trends in that province over the 1990s have shown increases in mid-childhood, and by 2000 the proportion of cases reported in 10 to 14-year-olds was greater than that among infants or preschool children. Molecular surveillance of *Bordetella pertussis* strains in Alberta and Quebec indicates that new strains are emerging in these provinces, and there is a move away from the "old" vaccine types.

In the U.S. there have also been increases in reported cases of pertussis in the last decade, and since the late 1990s the number of deaths, mainly in infants, has risen as well. The age groups to be affected by the greater burden of disease are 10 to 19 year olds and, to a lesser extent, adults aged 20+. Among infants who had received at least two doses of the acellular vaccine there was a levelling off in incidence rates in the mid 1990s. In a large, prospective randomized controlled trial in the U.S. the incidence rate of pertussis among subjects aged 15 to 65 was estimated to be between 370 and 860 cases per 100,000. A French study carried out to estimate incidence among adults reported a similar rate, at 884 cases per 100,000. In France, there is evidence of a shift in the spread of disease, from child-child to adult-infant transmission. Increases in reported cases in the U.K. have been most evident in those aged < 3 months, but it is believed that there is significant under-reporting. In a community study of patients aged 5 to 92 years with cough of > 3 weeks' duration, the incidence rate was estimated to be 330 per 100,000, whereas the official notification rate for that period was < 4 per 100,000. In Australia, the number of deaths rose sharply from 1986-95 to 1996-2002, and

hospitalization data for 2001 indicate that the majority of serious illness occurred in infants < 8 weeks of age, i.e. the unimmunized.

Immunization

Although used in Japan for over 20 years, acellular pertussis vaccines have figured only relatively recently in the immunization schedules of other countries. In the U.K., a whole cell vaccine is used for the primary series, and a preschool booster dose of acellular vaccine was added in 2001. A whole cell vaccine is also given during infancy in France, but booster doses of acellular vaccine are now administered at 16 to 18 months and 11 to 13 years of age because of changing epidemiologic patterns. In Sweden, doses in the primary series and the booster dose (at 6 to 10 years) all make use of acellular vaccine. The immunization schedule in Canada consists of a primary series at 2, 4, and 6 months of age, and booster doses at 18 months and 4 to 6 years. Studies on the immune response to pertussis vaccines have shown that although the antibody response to vaccine wanes over time before being boosted by a further dose, the T cell count increases and remains elevated between vaccine doses. Acellular pertussis vaccines provide a better, longer lasting cellular immune response than whole cell vaccine.

The efficacy of the acellular pertussis vaccine currently used in Canada, as estimated from clinical trials, is 85%. Hospital data from the IMPACT surveillance system in Canada provide evidence of the greater efficacy of the acellular vaccine: after 1998, when the vaccine was introduced, the ratio of hospitalized infants < 3 months of age to infants aged 6 months to 1 year (i.e. those who had received three doses of the new vaccine) increased dramatically. Patterns in reported cases among older children in Quebec since 1998 also support its efficacy. In international trials, acellular vaccines with three or more pertussis antigens have been found to be more effective than those with one or two antigens, but acellular vaccines have not been uniformly superior to whole cell vaccines in efficacy. Although they are associated with fewer adverse events than whole cell vaccines, acellular vaccines give rise to injection site reactions, such as swelling and tenderness, that increase substantially with the first booster dose given and again with the second. Whole limb swelling has also been reported.

In a survey of provincial/territorial immunization programs in Canada, all jurisdictions were found to offer publicly funded Td (tetanus and diphtheria) vaccine between the ages of 14 and 16. With the new adolescent/adult formulation of acellular pertussis vaccine (Tdap), the hope is that universal immunization – possibly as a piggyback onto the existing Td schedule – would not only reduce morbidity in these age groups but would also increase herd immunity and reduce transmission to young infants. However, issues of timing and safety need to be resolved. Newfoundland and Labrador incorporated the adolescent pertussis vaccine into their tetanus/diphtheria booster dose in 1999-2000, but it is too soon as yet to gauge the effects.

A modelling study of the cost-benefit of immunizing adolescents reported results favourable to the use of the vaccine, but given the caveats concerning the methodology it was recommended that the study be redone. With the use of a dynamic mathematical model and epidemiologic data from Quebec, it has been estimated that immunization of adolescents would lead to an overall reduction in disease of 15%, affecting primarily the age group 15-25 years rather than infants.

Management of Pertussis

The recommended therapy for pertussis in Canada has been erythromycin 40-50 mg/kg daily for 10 days to a maximum of 1 g, started within 3 weeks after onset of cough. Because of the side-effects of erythromycin, reduction in the duration of treatment and the use of alternative macrolides have been explored. Seven days have been found to be as effective (bacteriologic cure) as 14 days of treatment with erythromycin and give rise to fewer adverse events. Both clarithromycin and azithromycin have been shown to have equivalent effectiveness to erythromycin and fewer adverse events, but are more costly. Because pertussis is spread by close contact with the respiratory secretions of an infected person,

chemoprophylaxis with erythromycin is usually instituted for household contacts and has been found to have a 67% efficacy in preventing bacteriologically confirmed secondary cases in that setting. However, its success in preventing clinical cases has been limited. Outside of closed settings, it is unlikely to be effective. Achieving outbreak control through chemoprophylaxis is hindered by the cost of the antibiotics and by the lack of understanding and appropriate action by general practitioners, who may not realize that pertussis in adults needs to be taken seriously for a variety of reasons.

Recommendations

After small group discussions, a number of recommendations were developed and presented for adoption in the plenary session. They covered several aspects of pertussis control: objectives of a pertussis control strategy, diagnosis, surveillance, treatment and chemoprophylaxis, and outbreak management. See page 20 for the full recommendations.

BACKGROUND

Pertussis, or whooping cough, results from an acute infection of the respiratory tract by *Bordetella pertussis*. Its main features are a paroxysmal cough ending in an inspiratory whoop and vomiting. The disease can lead to serious complications in young infants, and most of the deaths that occur are in this age group. Since the introduction of pertussis vaccine in Canada in the late 1940s, the number of reported cases has dropped dramatically, from 160 cases per 100,000 just before the introduction of the vaccine to < 20 cases per 100,000 in the 1980s. However, there has been an increase in the reported incidence during the 1990s and an emerging pattern, evident in several provinces (and in other countries), of a greater burden of disease in older age groups (10-14 years) and adults. As well, it is likely that pertussis is considerably under-reported in adults, who constitute an important source of transmission to infants and children.

Acellular pertussis vaccine was introduced in Canada in 1997-98 and has replaced the previous whole cell vaccine. The immunization schedule consists of a primary series at 2, 4, and 6 months of age, and booster doses at 18 months and 4 to 6 years. An adolescent/adult formulation of the acellular vaccine has a lower antigen content and is recommended as the booster dose for adolescents (*Canadian Immunization Guide* 2002).

The last consensus conference on pertussis was held in 1993. Because of the changes in pertussis incidence over the last decade, a shift in strategy may be required to improve control of the disease. This invitational meeting, organized by the Canadian Public Health Association in collaboration with the Centre for Infectious Disease Prevention and Control, Health Canada, was held to define national objectives on the prevention and control of pertussis. This report is an account of the proceedings of that meeting.

Participants heard presentations from experts in various fields and subsequently broke into small groups to discuss specific aspects of pertussis, including objectives of a pertussis control strategy, diagnosis, surveillance, treatment and chemo-prophylaxis, and outbreak management. The recommendations that emerged were brought back for further discussion by the whole group and were adopted by a consensus process (agreement by 90%+). They are not necessarily endorsed by Health Canada, the Canadian Public Health Association or provincial/territorial governments.

Unrestricted education grants from Aventis Pasteur Inc and GlaxoSmithKline helped make this meeting possible.

INTRODUCTORY REMARKS

Dr. Arlene King

The first mention of whooping cough (later called pertussis, meaning violent cough) in the medical annals was in 1540; the first epidemic was reported in 1578, and widespread epidemics followed in the 17th and 18th centuries. The memorable feature of the disease, the whoop, occurs during a paroxysm of coughing, when several powerful coughs following quickly one after the other hinder inspiration and produce the characteristic sound. In Canada, a whole cell pertussis vaccine became available in the 1940s, and the number of reported cases per annum has decreased by 71% since then; acellular vaccine was introduced in 1997.

Participants will be asked to consider a number of issues that have recently arisen with regard to pertussis, such as the use of the acellular vaccine for infants and children, the new adolescent/adult acellular pertussis/tetanus/diphtheria vaccine that will replace the booster Td dose, and changing incidence trends over the last 10 years. All of these will have implications for pertussis control goals, immunization and surveillance strategies, treatment, and prophylaxis.

PRESENTATIONS

Pertussis: Clinical Features and Diagnosis

Clinical Spectrum of Pertussis Across the Ages

Dr. Jussi Mertsola

Pertussis may be categorized according to stage: the catarrhal stage, when there is cough, rhinorrhea and possible fever; the paroxysmal stage, during which the whoop and vomiting after cough occur; and the convalescent stage, consisting of gradual recovery with possible set-backs. Complications are most common in infants. In the U.S., 63% of infants < 6 months of age required hospitalization; complications included pneumonia (11.8%), seizures (1.4%), and encephalopathy (0.2%), and the mortality rate was 0.8%[1]. In one U.S. study, 98% of infants who died had pneumonia, and 78% had not been vaccinated[2]. Heininger et al[3] found that in 18% of 51 cases of sudden infant death syndrome the results of polymerase chain reaction (PCR) testing were positive for *B. pertussis*.

In Finland, there were 164 laboratory confirmed pertussis cases admitted to university hospitals in the 1990s. About 70% were < 4 months old, 22% were admitted to the intensive care unit (ICU), and 8% required assisted ventilation. Comparison of pertussis symptoms in immunized and unimmunized children indicated that the whoop was present in 39% of immunized as compared with 56% of unimmunized children, vomiting in 49% versus 65%, and apnea in 8% versus 15%[4].

There is good evidence that vaccine efficacy decreases with time, possibly from 100% at 1 year down to 46% at 7 years[5]. This is why there was a trend toward increased pertussis incidence among older children, adolescents, and adults in the 1990s. In Finland, the whole cell pertussis vaccine has been available since 1952 and is given at 3, 4, 5, and 24 months, with about 98% coverage. In the 1990s there was a 5-fold increase in the incidence of pertussis among infants, who get the disease mainly from adolescents and adults. In 1999, 29% of laboratory confirmed cases in Finland were aged 20 years or older. Symptoms in adolescents and adults have included paroxysms (83% and 87% respectively), whoop (30% and 33%), vomiting (45% and 41%), and apnea (19% and 37%)[6].

The State of the Art in Diagnosis of Pertussis: the Positive Predictive Value of Symptoms in Children, Adolescents and Adults, and Laboratory Confirmation

Dr. Kathryn Edwards

Diagnostic methods for *B. pertussis* consist of direct detection, i.e. culture, direct fluorescent antibody (DFA) testing, PCR, and indirect detection, i.e. serologic methods using paired sera (from early and later in the course of the illness), a single elevated antibody titre, or high titres in family members. In the past, culture was the gold standard, but many factors influence its sensitivity. DFA provides rapid results, but it has low sensitivity. PCR methods are not consistent across laboratories in terms of sample preparation, primer selection, detection systems and selection of controls. Enzyme linked immunosorbent assay (ELISA) is the basis for serologic methods.

Validation of PCR against serology, culture and symptoms was carried out by Heininger et al[7] in a large pertussis vaccine efficacy trial (among children) in Germany. Using a positive serologic result for *B. pertussis* as the standard, the overall sensitivity of PCR was found to be 61% and the specificity 88%; PCR was more sensitive than culture. Comparison of PCR results and clinical symptoms revealed that duration of cough, presence of paroxysms, whooping

and/or vomiting, and clinical diagnosis of probable or definite pertussis were all significantly less pronounced in children with negative PCR as compared with positive PCR results. In a community-based study of the prevalence of pertussis among 442 adolescents and adults it was found that 20% had either laboratory confirmed pertussis or laboratory evidence of pertussis, the latter based primarily on serologic criteria[8]. The use of paired serum samples may be problematic, in that the specimen from the acute stage is often obtained late; use of a single specimen relies on cut-off levels that may be arbitrary. Information on levels of antibody to pertussis antigens in a large sample of the general population could be used as age-specific reference values for serologic diagnosis. The CDC has carried out such a survey to determine these levels.

Epidemiology

Epidemiology of Pertussis in Canada

Dr. Eleni Galanis

As measured from data obtained from the National Disease Reporting System and the Canadian Institute for Health Information, the incidence of pertussis in Canada has increased since the beginning of the 1990s, with peaks every 4 years. The average number of reported cases across Canada in the 1990s was 6,000 or 10 to 35 per 100,000 per year, the highest incidence being found among infants < 1 year of age and the second highest currently among children aged 10 to 14. Possible reasons for the increasing incidence are

- a change in circulating strains of *B. pertussis*
- waning vaccine immunity
- a decrease in vaccination coverage
- low efficacy of the whole cell vaccine
- increased awareness and reporting.

The stable or decreasing hospital separation rates in all age groups during the same period suggests that at least part of the increase in pertussis incidence is due to increased awareness and reporting of the disease. Not all provinces/territories reported an increased incidence in the early 1990s, but in all jurisdictions there were large pertussis outbreaks during different years; this may have led to an overall increase in pertussis incidence in Canada.

With respect to the acellular vaccine, introduced in 1997, data from British Columbia, Alberta, Saskatchewan and Ontario show a positive impact, as illustrated by a decreasing incidence since 1998 among 1 to 6-year-olds as compared with infants < 1 year and 7 to 9-year-olds; the dip in 2000 among 7-year-olds (2 years after their booster dose of acellular vaccine); and the fact that the lowest incidence is in the cohort that has received the most doses of the new vaccine.

Epidemiology of Pertussis in British Columbia

Dr. Danuta Skowronski

In British Columbia, the gradual increase in reported pertussis since the 1990s has been accompanied by outbreaks of the disease occurring in 1990, 1993, 1996 and 2000, each with a higher peak incidence than the previous outbreak. In 1990, the highest proportion of cases occurred in children < 5 years of age; in 1993, the pattern was similar, but the proportion among 5 to 9-year-olds had increased substantially; in 1996, there were further increases in this age group and also among 10 to 14-year-olds; and by 2000, the largest proportion occurred among 10 to 14-year-olds. In 2000, both the proportion of pertussis cases reported and the incidence were greater among 10 to 14-year-olds than among infants or preschool children.

Although requests for laboratory confirmation of pertussis rose during 2000 in the 10-14 year age group, so too did the proportion of positive test results, suggesting that increased awareness and indiscriminate laboratory requests were not responsible for the greater incidence of disease. Neither is PCR testing likely to be the sole reason for recent trends: even though this laboratory method increased the proportion of positive results across all age groups, the greatest proportion by either culture or PCR was reported among pre-teens and teens. The protective effect of pertussis immunization wanes with time, and individuals aged 10 to 14 might be expected to be more vulnerable to infection than younger children. However, the increasing rates in the same age group over each outbreak, together with a declining incidence after age 12 during 2000, argue against waning immunity as an explanation for the epidemiologic pattern. On the other hand, a vaccine that was suboptimal in its efficacy 10 years ago would be expressed through a persistent cohort effect such as the one noted.

The results of introducing the more efficacious acellular vaccine in 1997 have been beneficial. The incidence of pertussis among infants and preschool children fell appreciably between 1996 and 2000, as did rates of hospitalization (by half among infants and one-quarter among preschool children).

Epidemiology of Pertussis in the U.S

Dr. Trudy Murphy

The National Notifiable Diseases Surveillance System in the U.S. is a passive system that has been in operation since the 1960s, in which individual States send data on confirmed and probable cases of notifiable disease, including pertussis, to the Centers for Disease Control and Prevention (CDC). A confirmed case is defined as one in which *B. pertussis* has been isolated, or as a clinical case with either a positive PCR result or a link with a laboratory confirmed case; a probable (clinical) case is defined as 14 days or more of cough with paroxysms, whoop or vomiting, with no other cause.

From the early 1990s there has been an increase in the number of reported pertussis cases, ranging from < 5,000 cases per year in 1990 to 7,867 cases in 2000, and yet rates of immunization – vaccine given at 2, 4, 6, 15 to 18 months and 4 to 5 years – have remained high, in the 90%+ range for at least three doses of either acellular or whole cell vaccine. As well, the number of deaths (which occur predominantly in infants) has been increasing since the late 1990s.

The acellular pertussis vaccine has been available for the fourth and fifth doses in the immunization program since 1992 and for the primary series since 1996. Overall, the incidence or reported number of cases has remained fairly stable among 1 to 4 and 5 to 9-year-old children. Among infants 4 to 11 months who received at least two doses of the acellular vaccine there was a levelling off in rates from the mid-1990s, whereas among younger infants with fewer doses this occurred later. The incidence of reported cases among 10 to 19-year-olds and, to a lesser degree, among adults aged 20+ has increased during the 1990s. It is unclear how much of the increase among adolescents represents a real increase or improvements in recognition, diagnosis and reporting.

The APERT Study

Dr. Joel Ward

The APERT study[9], sponsored by the National Institutes of Health, was a prospective, randomized controlled trial (double blind) that was carried out at eight sites in the U.S. to assess the incidence and clinical spectrum of pertussis in adolescents and adults as well as the efficacy and safety of the acellular vaccine in these individuals. One dose of vaccine was administered to 2,781 subjects aged 15 to 65, recruited between 1997 and 1999. Acellular pertussis vaccine was given in the experimental group and hepatitis A in the control group. All subjects were prospectively followed and contacted every 2 weeks for 2 years. If they reported a cough of 5 days' duration or longer this was evaluated clinically and by culture, PCR, and serologic testing (acute versus convalescent specimens). Each subject

provided three to 10 blood specimens for serologic evaluation during the study to detect asymptomatic infections.

Cough illness was found to be very common in both groups (about half of all subjects reported a cough lasting 5 or more days per year), with a mean duration of 24.4 days. There was no significant difference between the vaccine groups in incidence of cough illness. There were 10 cases of well-confirmed pertussis detected during the trial, as determined by positive results on culture or PCR or by increases in antibody titres; all but one of the cases occurred in the control group. The overall efficacy of the pertussis vaccine was estimated to be 92%. Pertussis cases as a proportion of reported cough illness increased significantly the longer the duration of cough, i.e. the longer the cough continued the higher the proportion of pertussis cases. Risk factors for pertussis were young age (< 30 years) and duration of cough. Culture and PCR were relatively insensitive in diagnosis, even early in the illness at day 5 of cough.

The incidence of disease as determined in the unimmunized controls was 4 cases per 1,000 subjects per year. This represents up to 1 million cases per year in older individuals in the U.S. No serious adverse events from the vaccine were reported, although local reactions were experienced, more commonly by women than men.

Epidemiology of Pertussis in France

Dr. Nicole Guiso

In France, the whole cell pertussis vaccine, combined with diphtheria and tetanus toxoid and polio vaccine, has been in use since 1966, given at 3, 4, and 5 months with a booster at 16 to 18 months; *Haemophilus influenzae* type B vaccine was added in 1995. In 1985, only 86 cases of pertussis were reported, therefore the disease was discontinued as a notifiable disease and surveillance ceased. In 1991, however, a study carried out in a pediatric hospital reported that the number of infants hospitalized for pertussis had increased and that there was a change towards adult-infant rather than child-child transmission[10].

In a subsequent national study[11], in 1993-1994, involving 22 pediatric hospitals (20% of the total number in France), 316 index cases were reported, of which 204 (65%) were aged < 1 year and 99 (33%) were < 3 months. Of 314 index cases, 230 (73%) had not been vaccinated, 98 because they were < 3 months old. The resurgence of pertussis was not felt to be due to decreased vaccination coverage or vaccine efficacy. Since 1996, surveillance carried out in 43 pediatric hospitals across France has shown similar trends. In 1998, the immunization schedule was changed to a primary series of whole cell vaccine at 2, 3, and 4 months, a first booster dose of acellular vaccine at 16 to 18 months, and an additional booster dose of acellular vaccine at age 11 to 13 years.

A 1999 study to estimate the incidence of pertussis in adults recruited 217 patients aged ≥ 18 years who complained of cough lasting > 7 but < 31 days[12]. A diagnosis of pertussis was confirmed by culture, PCR or serologic detection of increased or decreased anti-pertussis toxin IgG (by a factor of at least 2) between acute and convalescent serum samples. A total of 70 confirmed cases were found (32%), for an estimated incidence of 884 cases per 100,000. Antibiotic treatment did not modify the duration of cough.

Booster vaccination doses given to adolescents and adults regularly throughout life would be the ideal strategy for reducing the burden of pertussis, but this is not feasible for a number of reasons. Vaccination of targeted groups, such as adolescents, adults in contact with infants, and vulnerable adults with other health problems, is more likely to succeed.

Epidemiology of Pertussis in the U.K.

Dr. Natasha Crowcroft

In the U.K., a whole cell pertussis vaccine is given in a combined vaccine at 2, 3, and 4 months, and since 2001 a booster dose of acellular vaccine has been added at age 3.5 to 5 years. Although there was widespread concern among the public about the adverse effects of the vaccine in the late 1970s, vaccination coverage has since recovered and has been over 90% for the last decade. The last epidemic

occurred in 1997, when 2,989 cases were reported; in 2000 there was an all-time low of 712 cases. The proportion of cases among infants < 3 months increased during the 1990s. The number of deaths observed varies according to the data source but has been estimated at 9 per year from 1994 to 1999.

It is believed that the disease is substantially under-reported – for instance, there are two to three hospital admissions for pertussis for every one case reported – thus enhanced surveillance and special studies are needed to improve data collection. A community study conducted in 1996-97 investigated patients (age range 5-92) who presented with acute tracheitis or spasmodic cough of > 3 weeks' duration[13]. Of 356 such patients, 58 were identified as having serologic and/or bacteriologic evidence of pertussis, 32 (55%) of whom were known to have been fully vaccinated. This is equivalent to an incidence rate of 330 cases per 100,000 per year. (The official notification rate for the period under study was < 4 per 100,000.) Of those aged 5 to 14 years, 45% had evidence of recent pertussis infection, and of those 15 to 44 years old the proportion was 28%. In a further study, carried out in a pediatric ICU, it was found that 25 of 127 infants (20%) admitted had pertussis, only 3% of whom had been suspected of having the disease[14]. In 44% of cases the parents were responsible for transmitting the infection, and in 32% it was a sibling. Taken together, these results indicate that the pertussis notification rate is a vast underestimate, and that older children and adults are becoming infected and passing the infection on to infants.

Epidemiology of Pertussis in Australia

Dr. Peter McIntyre

In Australia, there has been an increase in the pertussis notification rate from the early 1990s to the present, as recorded by the National Notifiable Disease Surveillance Scheme. The last epidemic occurred in 1997, when the incidence rate reached almost 60 cases per 100,000 population.

With regard to the burden of disease, in a study of 140 infants hospitalized for pertussis in the year 2001 through the Australian Paediatric Surveillance Unit, the average hospital stay was 8 days, 18% required ICU admission, and 3% died[15]. Aboriginal babies were over-represented. In a group of adults with reported pertussis[16], the median duration of cough was 60 days, median number of visits to the general practitioner 3.7, and the median number of days in work lost was 4 (equivalent to 15,000 lost work days overall in Australia). With regard to deaths, the annual rate rose sharply from 1986-95 to 1996-2002. From 1993 to 2001 there were 16 deaths, for an estimated annual mortality rate of 0.70 per 100,000 (as compared with 0.60 in the U.K. during 1994-99 and 0.32 in the U.S. during 1997-2000).

The proportion of reported cases in which serologic results were positive has increased during the 1990s (New South Wales data). Clinical diagnosis is much more common in children < 5 years, whereas in those aged > 5, serologic methods have a greater impact on the number diagnosed. Laboratory and notification studies have indicated that symptoms of pertussis in adults match the finding of high whole cell antibody levels[17].

A primary series of pertussis vaccine is given at 2, 4, and 6 months and boosters at 18 months and 4 to 5 years. Immunization with acellular vaccine has been funded for the primary series since 1999 and for the booster doses since 1998. Hospitalization data for 2001 show that more than a third of cases occur before 6 weeks of age and more than a half before 8 weeks, i.e. in unimmunized infants. Since the introduction of the preschool booster dose in 1995, 5 to 9-year-old children showed a decline in notification rates after the 1997 epidemic, close to the rates for 1 to 4-year-olds, whereas since 1999 and for the first time in Australia the notification rate among 10 to 14-year-olds has become higher than among infants. Possible options to address the high incidence rates among adolescents and the increasing number of infant deaths are to eliminate the fourth (18 month) booster dose so that the first dose after the 2, 4, 6 months primary series is at 4 years, but introduce an adolescent booster; and to encourage

pertussis immunization in mothers, and possibly fathers, at or shortly after the birth of a baby ("cocooning").

Molecular Surveillance of Pertussis

Dr. Mark Peppler

Molecular surveillance is an essential tool to determine trends in strain types and their relation with disease and vaccines, for example, whether the use of vaccines over time leads to the development of resistant organisms. Three methods of molecular surveillance are serotyping of isolates using monoclonal antibody to fimbrial antigens; pulsed-field gel electrophoresis (PFGE), used to generate a genomic fingerprint of an isolate; and gene typing by PCR, particularly on pertussis toxin S1 subunit and pertactin.

There are two types of fimbriae produced by *B. pertussis*, Fim2 and Fim3, and isolates may express one or the other, or a combination of both, on their surface. There are some problems with the expression of fimbriae in culture, but they are an important antigenic marker: in the past, vaccine has had to be modified to address the type of fimbriae produced by circulating strains of *B. pertussis*. PFGE is used to separate genomic DNA fragments that can vary in size from 50 to 200,000 kilobases. The technique was used to analyze 3,700 isolates from Alberta and Quebec between 1985 and 1994. On the basis of the pulsed field results, 98 different patterns were identified, of which 80% were represented by 15 different types. Although PFGE showed that the most common strains were different in the two provinces (strains designated 1 and 2 in Alberta, strains 1 and 3 in Quebec), it cannot define the characteristics of the strains. Information from gene typing must be added to explore these characteristics.

Pertactin and pertussis toxin S1 subunit are the genes that have been investigated by gene typing in relation to virulence. Of the top 30 PFGE types from Alberta and Quebec, estimated numbers and proportions of the old and new pertactin and pertussis toxin combinations show that 47% overall represented new types, 36% represented old types, and 17% were in transition. Thus, in Alberta and Quebec at least, there is a trend away from the old vaccine types, although it is debatable whether this is a result of vaccine pressure.

Immunization

Pertussis Schedule in the U.K.

Dr. Natasha S. Crowcroft

Children in the U.K. are given the whole cell pertussis vaccine in a combined form, DTwP-Hib, with meningococcus C and oral poliovirus vaccine (OPV) at 2, 3, and 4 months, and a booster dose of acellular pertussis vaccine, DTaP, at the age of 3.5 to 5 years (with MMR and OPV). Before 1990, the primary vaccine schedule was 3, 5, and 9 to 10 months. The new "accelerated" schedule was introduced in the interests of increasing coverage and reducing adverse events.

The preschool booster dose was included from 2001 onward because of evidence of continuing hospitalizations and deaths in young children. The decision to opt for a 4-year rather than a 15-year booster was based on a modelling (dynamic) exercise, whereby the cost-benefits of the two interventions were compared using a variety of assumptions about direct and indirect costs, vaccine efficacy, herd immunity, incidence, hospitalization data and deaths. It was felt that if indirect protection through herd immunity was more than 60% to 70% then a 15-year booster would be the appropriate choice; when indirect protection is low, then the booster dose is more beneficial at 4 years. The effects of the booster dose at 4 years will be monitored, and if necessary that decision will be revisited.

Pertussis Schedule in France

Dr. Gaston De Serres (on behalf of Dr. Nicole Guiso)

A whole cell pertussis vaccine is used in France. In 1998 the schedule was switched from a primary series at 3, 4, and 5 months with a booster between 16 and 18 months to the primary series being given at 2, 3, and 4 months, a booster dose of acellular vaccine at 16 to 18 months and a second acellular booster dose at 11 to 13 years. Vaccine coverage in infants is 96% and the efficacy is 94%.

Pertussis Schedule in Sweden

Dr. Patrick Olin

When the whole cell vaccine used in Sweden lost its potency in the 1970s, routine vaccination of infants against pertussis was discontinued. This was followed by a resurgence of the disease in the country. The current schedule for immunization against pertussis consists of three doses in infancy of DTaP-Hib-polio at 3, 5 and 12 months (the third administered as a matter of policy after at least a 6 months' interval), and a late fourth dose at 6 to 10 years of age. It is felt that there is a better antibody response if the interval between the first two doses is 2 months rather than 1 month. There has been high vaccination coverage, at about 98%, for the first three doses, and a dramatic reduction in the number of pertussis cases since acellular vaccination programs began. The counties in Sweden are using a variety of different acellular vaccines, and this makes surveillance and estimation of efficacy problematic.

Perspectives on the Immune Response to Acellular Pertussis Vaccines, Including Cell- Mediated Immunity

Dr. Fred Zepp

The usefulness of a vaccine may be gauged by its clinical efficacy, the generation of antibody responses to it, and the cell-mediated immune response, achieved primarily through T cell helpers and/or cytotoxic T cells. Modern vaccine development strongly concentrates on the interaction of the various components of the human immune system (mainly T cells, B cells and antigen presenting cells). The antigen-presenting cells (i.e. dendritic cells, B cells) present antigen (e.g. vaccine antigen) to T cells. Depending on the type of antigen and the antigen-presenting cell, different patterns of T cell function will be activated, leading to the recruitment of various other T cells having helper, suppressor and cytotoxic functions. These activated cells then produce cytokines (various interleukins and gamma interferon) that further amplify T cell reactivity, activate macrophages, facilitate immunoglobulin production, or enhance the action of cytotoxic T cells (killer cells).

To explore cell-mediated immunity in the laboratory, T cells are cultured from peripheral blood and then challenged with the antigens of interest. In response, the T cells proliferate and produce cytokines. The cytokine production pattern of T cells can be measured by means of ELIspot analysis, ELISA or RT-PCR (reverse transcriptase PCR). These laboratory studies have shown that unvaccinated infants do not have specific antibodies to pertussis antigens[18]. After the primary immunization course the infants develop antibodies, which wane through the second year of life. Booster vaccination reactivates B cell memory and leads again to an increased concentration of pertussis-specific antibody. The antigen-specific proliferative T cell response increases with the first dose of vaccine and, in contrast to B cell responses, remains elevated even during the time when there are low levels of circulating antibodies. Booster vaccination further potentiates the antigen-specific T cell response. The findings suggest that pertussis-specific T helper responses control immunologic memory, thus providing protection between vaccinations. The T cell response after natural infection is very similar to vaccine induced responses[19].

Comparison of immune responses in infants to acellular and whole cell pertussis vaccines shows that acellular vaccines provide a better, longer lasting cellular immune response than whole cell vaccine. Overall, they are highly immunogenic for B and T cells; they induce high concentrations of

antigen-specific antibodies and high rates of seroconversion, as well as long-lasting pertussis-specific T cell responses.

Impact of the Acellular Pertussis Vaccine on Canadian Children Since 1997-1998

Dr. Gaston De Serres

The estimated efficacy of the adsorbed whole cell pertussis vaccine used in Canada has ranged between 28% and 60%, whereas that of three doses of the acellular pertussis vaccine given in clinical trials was 85%. The proportion of pertussis cases by age during the 1990s, when the whole cell vaccine was being used, shows a shift in peak incidence, from the highest incidence among infants in 1990 to a peak among those aged 3 to 4 years in 1993 and, again, among children approximately 3 years older than this in 1996. This has been taken to represent a cohort effect resulting from the lack of protection in a proportion of infants vaccinated in 1990.

With regard to the acellular vaccine, data from IMPACT (the pediatric hospital-based surveillance system) for 1990 to 2001 indicate that, for infants admitted to hospital because of pertussis, the ratio of those aged < 3 months (i.e. not vaccinated) to those 3 to 5 months of age did not change after the acellular vaccine had been introduced, in 1998. However, the ratio of infants < 3 months to infants 6 months to 1 year (i.e. those who had received three doses of vaccine) did increase dramatically after 1998. Thus it appears that with the use of the new acellular vaccine the number of older infants hospitalized has been reduced. Data from Quebec on the number of pertussis cases reported according to age also show this change in ratios after 1998. In terms of older children, the reported rates per 100,000 in Quebec were considerably higher among 3 to 5-year-old children than 9 to 11-year-olds up to about 1997, but after 1998 the rates tended to converge, and from 2000 onward the rates among 3 to 5-year-olds have been lower, as would be expected from the booster dose of acellular pertussis vaccine they received in 1998.

The use of acellular pertussis vaccine has reduced the risk of pertussis in infants and children. The group protected by this vaccine will be moving into adolescence in the next few years and may still be at decreased risk. The group that received only whole cell vaccine remains vulnerable now and would benefit the most from an adolescent booster dose of acellular vaccine. This cohort is currently aged from 10 to 17-22 years, depending on the year of introduction in the different provinces.

Efficacy of Acellular Pertussis Vaccines in Infants and Duration of Protection

Dr. Patrick Olin

Many different types of acellular pertussis vaccine with from one to five antigen components have been evaluated in efficacy trials and compared with whole cell vaccines. Although the overall antigen level may be similar among vaccine types, the amounts of individual antigens – for instance, pertussis toxoid – vary widely. The conclusions of a Cochrane review of randomized controlled trials (RCTs) were that acellular pertussis vaccines with three or more pertussis antigens were more effective than those with one or two antigens[20]; they were more effective than one whole cell vaccine but less effective than two others; and they showed fewer adverse effects than whole cell vaccine. It is important to note that there are a few whole cell vaccines with high efficacy. The greater efficacy of multicomponent over single component vaccines has been questioned by some authors, who argue that the result is an artifact of the serologic criteria used[21].

With regard to duration of protection, active surveillance in an Italian trial of two types of three-component acellular vaccine showed no difference between the vaccines during the first 6 years of life, and it was concluded that efficacy was maintained over 5 or 6 years[22]. In a comparison of a four-component acellular pertussis vaccine and a whole cell vaccine given at 3, 4.5, 6 and 18 months of age in German trials[23], overall cough rates were similar in both groups, and the calculated efficacy over 6 years of follow-up was 89% for the acellular vaccine and 92% for the whole cell vaccine.

The incidence of pertussis in Sweden rose to high levels after the discontinuation of routine vaccination in 1979. With the introduction of acellular pertussis vaccine in 1996 there was a rapid drop in culture-confirmed cases from 1996 to 1998. Before the vaccine was in use, most of the disease burden occurred in 2 to 4-year-old children, whereas peaks were evident in the higher age groups after its introduction. Analysis of vaccine failures shows that at 6 to 7 years of age there is a clear increase in the number of failures particularly with the three-component and five-component acellular vaccines, suggesting that there is waning immunity after the primary dose and a possible need for a preschool booster dose.

Vaccine Safety: Risk with Multiple Doses of Acellular Pertussis Vaccine

Dr. Scott Halperin

Although the rate of adverse events during the primary series of pertussis vaccination does not increase with succeeding doses, it has been found that the risk of injection site reactions is higher with subsequent booster doses.

After the booster dose at 18 months, redness, swelling and tenderness have been found to increase substantially as compared with reactions to the vaccine in the primary series[24]. Systemic reactions, such as fever, crying, irritability and drowsiness, on the other hand, tended to decrease with the booster dose. The fifth consecutive dose, at 5 years of age, resulted in further increases in local reactions over the 18 month dose, from 35% to 60% of recipients for redness and 18% to 70% for swelling, although there was a reduction in tenderness[25]. A study of 356 children given a variety of vaccine types found that although five doses of acellular vaccine and five doses of whole cell vaccine resulted in similar proportions of cases reporting redness at the injection site, the acellular vaccine gave rise to fewer systemic adverse events[25]. A U.S. study has also shown increased redness and pain with the fifth dose of a variety of acellular pertussis vaccines[26]. Whole limb swelling after three doses of DTaP has been reported in Germany and subsequently in a solicited adverse event cohort (2.5%) and an unsolicited adverse event cohort (0.5%)[27]. With regard to adolescent and adult studies, although redness and swelling occur with administration of Td vaccine, addition of the acellular pertussis component does not lead to higher rates of these reactions[28].

The mechanism of injection site events remains unclear, but may be related to IgG antibody levels and cell-mediated immunity. Further research is required on this issue as well as on optimal scheduling and dosage.

Td Coverage in Adolescents and in Adults: Could Pertussis Piggyback on the Td Booster Program?

Dr. Karen Grimsrud

Acellular pertussis vaccine is currently combined with tetanus and diphtheria toxoids in the childhood immunization schedule. One way of increasing protection against pertussis in adolescents and adults might be to include acellular pertussis vaccine with the Td booster dose that these groups receive.

A survey of provincial/territorial immunization programs revealed that all jurisdictions offer publicly funded Td or TdaP between the ages of 14 and 16 years, either as a school program (10 provinces/territories) or given primarily by a physician (Ontario), or both. Newfoundland and Labrador, Nunavut and the Northwest Territories use TdaP. Information on coverage rates is collected only in Newfoundland/Labrador and Nova Scotia (95% and 96% respectively); other jurisdictions' estimated coverage ranges from 75% to 95%.

The results of two surveys (Aventis Pasteur, 2002, and the BC Centre for Disease Control, 2002) of adult tetanus coverage indicate that an estimated 64% of adults had been vaccinated, about half within the previous 10 years, primarily because of recent injury (64%) or for anticipated travel (12%). Adults received information about immunization from the media (51%) and their family doctor (43%), and 92% agreed that they would be vaccinated if this was recommended by their doctor. Other factors likely to influence their decision were knowledge about the severity of

the disease in adulthood, and exposure and transmission patterns; the low risk of side effects of the vaccine; the protection it would afford young infants with whom they might be in contact; and recommendation by a doctor or public health nurse.

Provision of a booster dose of acelullar pertussis vaccine, therefore, would fit well with the usual Td booster dose in adolescence (and in some jurisdictions already does). In adults, uptake could be increased by public awareness through the media, encouraging physicians to recommend and provide vaccine, and offering vaccine during routine contact with public health, e.g. during infant immunization.

The Newfoundland Experience in Implementing the Adolescent Program

Ms. Cathy O'Keefe

Because of the recommendation of the National Advisory Committee on Immunization (NACI) supporting adolescent acellular pertussis vaccination and the apparent shift to older age groups of reported pertussis cases, Newfoundland and Labrador introduced TdaP into its immunization program for grade 9 children in 1999-2000. Since 1999, 18,000 have been immunized, for an overall rate of coverage of 95%.

A survey of public health nurses (n = 82) in 2000 revealed that 67 (82%) had previous experience with the TdP program and 67 had administered 25 or more doses. In 2002, seven communicable disease coordinators, with input from public health nurses, reported that most of the staff were pleased with the information materials on TdaP provided for parents and that the post-immunization tear-off sheet was useful. It was felt that better communication, for example, through the media, would have helped in implementing the program in the community. Experienced nurses reported spending more time in preparing information in the first, but not subsequent, years of the program; they also needed to explain the program to other health care professionals.

The adverse effects of the vaccine have consisted of two official reports of adenopathy, which were deemed not to be associated with the vaccine, seven official reports of swelling and discomfort at the injection site, and one sterile abscess.

Since the number of pertussis cases reported has decreased from the peak incidence in 1994, it is difficult to demonstrate any effect of the new program at this time. Enhanced surveillance of pertussis will continue, with review particularly once the cohort immunized with acellular pertussis vaccine during childhood reaches the age of 15.

Various Strategies for Adolescent and Adult Immunization

Dr. Scott Halperin

With the increased incidence of pertussis among older children and adults in many jurisdictions, the goal of pertussis control – to reduce its incidence and severe morbidity among young children – as articulated by NACI[29] may need to be revised. The current immunization strategy does control the disease in young children but does not address the problem in older age groups and in unimmunized infants < 2 months of age.

An alternative strategy is to provide universal immunization for adolescents and adults. Ideally, this would not only reduce morbidity in these age groups but also develop herd immunity and reduce transmission to young infants. Problematic areas with this strategy are the appropriate timing of the immunization, the lack of a monovalent acellular pertussis vaccine, and the safety of administering a sixth dose of the vaccine.

Selective immunization aimed at protecting very young infants would target pregnant women, close contacts of newborns, and health care and child care workers. The challenge associated with vaccinating pregnant women is that the safety of acellular pertussis vaccine in pregnancy is unknown, as is the duration of protection and the effect of women's

increased antibody levels on their infants' immune response to subsequent vaccination. Targeting close contacts of newborns, or "cocooning", may not be easy to implement, particularly as the target group would be difficult to define. Protection of health care and child care workers carried out to benefit young infants and children might run into objections to mandatory immunization from organized labour, particularly as there are few data to support such a move.

In summary, there are many unknown variables in the choice of a different immunization strategy. It has to be decided which are the most important variables requiring further information before the choice can be made.

Cost Benefit of Adolescent and Adult Immunization

Dr. Philippe De Wals

There have been a number of studies to evaluate the economic effect or cost-benefit of the new acellular pertussis vaccine in Canada. The most recent one, by Hemels et al, modelled the epidemiologic and economic consequences of an additional booster dose of acellular pertussis vaccine for adolescents in Ontario[30].

The model followed a cohort of 144,000 adolescents aged 12, who were given a booster dose of acellular pertussis vaccine (combined with diphtheria and tetanus toxoids) at the same time as hepatitis B vaccine and were followed over the course of the next 10 years. The current practice is to give three doses of hepatitis B vaccine at the age of 12 years and diphtheria-tetanus vaccine at the age of 14 years. All subjects had received five doses of whole cell pertussis vaccine in childhood. Estimates of the burden of disease were taken from Canadian studies carried out during 1994 to 1998. An under-reporting factor of 9 was used. Productivity losses were given as an average of 5 days' work lost by parents of hospitalized children and 8 hours of work lost by parents of non-hospitalized children. Vaccine efficacy was assumed to be 85% over 10 years, and program coverage was predicted to be 95%.

From the Ministry of Health perspective, it was found that the new program would result in a yearly additional cost of $0.20 per child and a cost of $62.40 per pertussis case avoided. The overall outcome in terms of vaccine purchase was an estimated increase in costs of $2.1 million. However, there was a reduction in the costs associated with vaccine administration (–$1.1 million), disease burden (–$0.7 million) and productivity lost (–$2.5), resulting in a net saving of $2.3 million from a societal perspective; 4,500 cases of pertussis would be prevented.

The study methodology had many problems, and it appears that a new cost-effectiveness analysis should be done. Among other problems, the model underlying the study described is a linear, deterministic one that takes no account of the cyclical nature of pertussis, the possible indirect effect of the vaccine in reducing transmission, or the waning of immunity after vaccination. A dynamic model might better mimic the long-term epidemiology of the disease and evaluate the economic consequences of adolescent vaccination.

Expected Impact of the Different Strategies to Immunize Adolescents and Adults: Mathematical Approach

Dr. Babak Pourbohloui

The dramatic recent increase in reported cases of pertussis in Quebec along with the increased incidence of the disease among adults prompted a mathematical modelling approach to assess different immunization strategies for adults and adolescents. It was decided to start the investigation by looking at the pre-vaccine era, when the population acquired immunity through exposure to *B. pertussis*, and to challenge the standard assumption that such immunity lasted for 20 years. Data from the pre-vaccine era indicate that only a small proportion, < 2%, of reported cases were adults, whereas if acquired immunity lasted for only 20 years there should be many more adults with symptomatic disease for a second time.

The mathematical model assumes that in the pre-vaccine era infants are fully susceptible until they become infected, and at the end of the episode of pertussis they move to the fully protected category. However, their immunity wanes with time, and they move to a lower level of immunity in which they are susceptible to boosting by infection; they lose immunity again and again in this way until they become fully susceptible once more. With the assumption that acquired immunity lasts for 20 years, 50% of the infected population would be expected to be adults. In order to achieve a result closer to the 2% actually observed it is necessary to increase the duration of immunity as well as the number of intermediate loops of lower immunity followed by boosts from infection. This was accomplished by adding new compartments to the model in order to better simulate the different levels of immunity occurring after disease. With the assumptions of 50 years of acquired immunity and 10 intermediate loops of mild infection, the model simulates results consistent with the pre-vaccination notification data. The model also incorporates post-vaccine compartments and vaccine-related waning immunity.

The overall conclusions were that the resurgence of pertussis in the 1990s was largely due to a poorly protective vaccine, although even with an effective vaccine there will be a shift to higher age groups because of the intrinsic properties of the dynamics of pertussis, rather than because of vaccine properties. Remaining with the current schedule and vaccine will result in continued decreases in the number of cases. Immunization of adolescents would lead to an overall reduction of 15%, affecting primarily the age group 15-25 years rather than infants. Introduction of adult immunization based on the current Td booster schedule would have little impact.

Management of Pertussis

The Treatment of Pertussis: Old and New Macrolides

Dr. Scott Halperin

Antibiotics eradicate *B. pertussis* from the nasopharynx but have no effect on the clinical symptoms or course of pertussis unless given in the early stages. They are therefore prescribed more for control of transmission than for individual benefit. Erythromycin (preferably estolate) 40-50 mg/kg daily for 10 days to a maximum of 1 g (for 14 days to a maximum of 2 g in the U.S.) is the recommended macrolide in Canada, and this should be started within 3 weeks after onset of cough. Cotrimoxazole can be used if erythromycin is not tolerated.

The efficacy of erythromycin has been demonstrated[31]. However, it is not well tolerated, and adverse gastrointestinal effects are reported more often after 14 than 7 days of treatment. In an RCT of 7 days versus 14 days of erythromycin estolate for children (and their household contacts) with culture confirmed pertussis, it was found that 7 days of treatment were as effective as 14 days in terms of bacteriologic cure (negative culture after treatment)[32]. Adverse events were less common with the 7-day course of treatment; however, there was no difference in compliance rates between the two schedules.

Two newer macrolides, clarithromycin and azithromycin, have been compared with erythromycin in two RCTs. In the first, culture positive subjects (n = 62) were given either clarithromycin (15 mg/kg daily) for 7 days or erythromycin estolate (40 mg/kg daily) for 14 days[33]. The two drugs were found to be equally effective, but clarithromycin was better tolerated and resulted in higher compliance rates. In the second study, comparing the same schedule of erythromycin estolate with 5 days of azithromycin (10 mg/kg on the first day and then 5 mg/kg daily for 4 days) in 114

subjects, the results were similar, i.e. compliance with azithromycin was better because of fewer adverse events, although it was no more effective than erythromycin in treating pertussis (unpublished data: Halperin S, Langley JM, Boucher F for PICNIC). The comparative cost of the drugs – erythromycin being two to four times cheaper than clarithromycin and azithromycin – may be a factor in the treatment of choice.

Effectiveness of Prophylaxis

Dr. Gaston De Serres

Pertussis is spread by close contact with the respiratory secretions of an infected person, and within households the secondary attack rate tends to be higher in younger age groups. An RCT[34] has shown a 67% efficacy of erythromycin prophylaxis in preventing culture positive pertussis in household contacts, but its clinical impact was very limited. Epidemiologic studies also suggest that chemoprophylaxis provides some benefit. However, it must be started as soon as possible after the onset of cough in the primary case: the secondary attack rate has been found to increase from 11% when prophylaxis was initiated within 21 days of cough onset to 29% if prophylaxis was delayed beyond 21 days[35]. When delayed by 21 days or more the secondary attack rate was similar in those with and without prophylaxis.

There may be delay in the use of prophylaxis if the time to diagnosis is long, either because the primary case did not consult a physician straight away, the physician did not consider a diagnosis of pertussis, or laboratory results were not available quickly. Deeks et al. found that even in the presence of four symptoms of pertussis, physicians diagnosed the disease in only 44% of cases[36]. Even after diagnosis, household contacts may not willingly undergo chemoprophylaxis if the cost of a new macrolide is high (e.g. clarithromycin) or the drug carries the risk of adverse events.

There is little evidence for the efficacy of prophylaxis outside household and closed settings – for example, in the classroom. However, household contacts should be targeted and possibly children in home day care settings, particularly if there are very young infants present in both cases.

Prophylaxis may prevent some cases, but it should be used selectively because of the its limited positive impact.

Current Status and Problems with Outbreak Management: Perspective from the Field

Ms. Karen Pielak

A survey of public health nurses and medical officers of health has highlighted several areas of frustration that these health professionals experience when following up pertussis cases and contacts. Respondents were consistent in stating that 30 to 60 minutes was the time required for each index case, and 15 to 30 minutes per close contact. With an average of 10 to 12 contacts per case the process can take up to 4 hours altogether. Getting in touch with contacts is very time-consuming, and maintaining confidentiality (with regard to the name of the case) can be difficult.

Other delays are those arising from laboratory investigation – either because of constraints on resources or because general practitioners do not consider pertussis in their differential diagnosis and do not order the appropriate tests at an early stage – and case reporting. Delays are likely to result in increased transmission, until contacts are given chemoprophylaxis. The drugs used for chemoprophylaxis are a high cost for some families, and many individuals are not willing to take antibiotics when they have no symptoms, particularly if there are side effects. With regard to immunization, it is difficult to ascertain the status in certain children without an immunization registry in place. Updating the immunization schedule for contacts of pertussis

cases may be complicated by the fact that there is only a combined acellular pertussis vaccine at present, and extra doses of diphtheria and tetanus toxoid may not be warranted. A further source of frustration is the lack of understanding on the part of some community physicians that pertussis is a health concern for adults as well as children, particularly as adults may be the ones most likely to transmit the infection.

Suggestions for improved outbreak control include covering the cost of chemoprophylaxis in order to increase compliance, using prescriptions for antibiotics pre-signed by medical officers of health as a means of expediting chemoprophylaxis, and reserving chemoprophylaxis for individuals at greater risk of the complications of pertussis or those who are in contact with unimmunized children or infants.

RECOMMENDATIONS

Goals

It was agreed that, given the information presented during the last 2 days, the goals of the pertussis control strategy, as formulated at the 1993 consensus conference, are inadequate for the present circumstances and should be changed to the following.

1. The goal of the pertussis control strategy is to decrease morbidity and mortality from pertussis across the entire life span.
    - Given the current state of knowledge, it is unclear whether elimination is achievable.
2. Protection of adolescents and adults is a worthy goal for the benefit of these cohorts themselves.
    - It is not clear whether a collateral benefit of protection of infants would be achieved.

Priorities, Methods and Conditions

3. It is necessary to prioritize efforts to control disease in various cohorts.
    - Improve control in infants and young children.
    - Control pertussis in adolescents (by use of universal adolescent immunization).
    - Develop and implement effective strategies for control of pertussis in adults.
4. There is a priority to ensure that the pertussis immunization schedule maximizes safety, effectiveness and efficiency.
    - number of doses
    - interval between doses

Factors that must be taken into account in making changes to the immunization schedule in order to improve pertussis control are the possible adverse events associated with multiple doses, the duration of immunity, other antigens given concurrently, the cost and logistics.

If the primary dose were to be accelerated in order to protect infants at an earlier age, then the effect of this on other vaccines now given at the same time would need to be considered. The lack of a monovalent acellular pertussis vaccine limits the choices. The World Health Organization has a recommendation not to immunize until after the first month.

Routine immunization of adolescents with the new adolescent form of acellular pertussis vaccine has been recommended by NACI. One possibility would be to provide the adolescent booster dose with the tetanus and diphtheria boosters, another would be to give it with hepatitis B vaccine. The best way of achieving pertussis control in adults, for instance through immunization of new parents, is a subject for research.

Targets and Measurable Outcomes

The difficulty in setting quantifiable targets for a cyclical disease like pertussis was acknowledged.

5. The ultimate target should be decreased disease outcome.
    - Improved surveillance may affect achievement of pertussis control outcomes.
    - Decrease the number of deaths from pertussis to zero.

- Decrease rates of hospital and ICU admission among young infants.
  - Precise targets and timing to be determined by future research, with the goal of having a strategy in place by 2008.
- Reduce the reported incidence of pertussis among older children and adolescents to at least the levels present in preschool-aged children.

6. Process outcomes: immunization should be delivered on time.
   - At least 95% of infants should receive the first dose of pertussis vaccine before 3 months of age.
   - At least 95% of infants should receive two doses of pertussis vaccine by 5 months of age.
   - At least 95% of children should receive other recommended pertussis vaccine doses at the recommended age (within 3 months).

Laboratory Diagnosis

7. Polymerase chain reaction (PCR) should be established as the new gold standard for diagnosis within 3 years.
   - Two sets of primers should be used.
   - External proficiency testing should be in place to ensure quality control.
8. A system should be established for selective performance of culture for strain typing, antibiotic sensitivity testing, and identification of *Bordetella parapertussis* and *B. holmseii*.
9. There should be support for the development of criteria for serologic diagnosis.
10. International reference sera and reference antigens should be available.
11. An international consensus conference on pertussis diagnostic methods should be held.
    - PCR
    - serology
    - pulsed-field gel electrophoresis
    - specimen collection, handling and transport

Surveillance

Surveillance was defined as follows:

> The timely collection, analysis and dissemination of information that leads to public health action and/or hypothesis generation.

General

12. Data fields submitted nationally should be standardized and applied consistently across Canada (i.e. there should be harmonization).
    - Required parameters are age, sex, onset, outcome, method of confirmation, clinical presentation.
    - Ideally, there should also be information on vaccine status.
13. Data fields should be specific enough to allow valid and useful analysis and interpretation.
    - i.e. non-aggregated age information in years and/or months
14. Support for infrastructure for local public health is required in order to ensure that there is adequate case investigation and data entry.
15. Linked disease and vaccine registries are a priority for development and implementation (e.g. to connect with individual level vaccine status).

Routine Disease-related Surveillance

The purpose of routine disease surveillance is to monitor age-related trends in incidence, morbidity and mortality and to permit outbreak recognition.

16. Pertussis should be notifiable in all provinces and territories by both laboratories and clinicians.

17. The 2000 revised case definition* should be adopted, except for reporting of only laboratory confirmed cases (see next item).
18. National reporting of pertussis should be of clinical and confirmed cases, with an indication of the method of confirmation.
19. The case definition should be revised to include approved laboratory methods that have been validated and standardized as developed.
20. Intermittent statistical review of hospitalization and mortality data should be carried out routinely.
21. IMPACT (Immunization Monitoring Program – Active) should be recognized and supported as an important component of routine pertussis surveillance.

Routine Vaccine-related Surveillance

22. A system for accurately monitoring annual vaccine coverage should be established and maintained in each jurisdiction.
    - minimum at 24 months and other ages specified in the objectives
    - additional age groups to be added according to changes in vaccine schedule
23. Standards and data fields for assessing vaccine status should be developed and applied consistently across Canada (e.g. What does "up to date" mean?)
24. IMPACT surveillance and routine vaccine-associated adverse event reporting on a timely basis should be maintained to effectively monitor vaccine safety and ensure public confidence.

Special Disease-related Surveillance

25. Active surveillance initiatives should be established in selected jurisdictions to assess the duration and effectiveness of the entire pertussis immunization program (including the new adolescent program).
26. Surveys or enhanced surveillance projects should be conducted to calibrate the sensitivity of the passive surveillance system.
27. Enhanced surveillance projects should be implemented to assess the impact and consequences of pertussis in adults and adolescents.
28. Periodic enhanced mortality tracking from multiple sources should be implemented to better gauge this indicator (e.g. using capture-recapture methods).
29. All undiagnosed deaths in infants and SIDS (sudden infant death syndrome) cases should be investigated for pertussis.
30. Circulating/outbreak strains should be characterized to monitor the evolution of the organism.
31. Special studies should be established to assess particular vaccine-related risks in adolescents and adults (e.g. to monitor injection site reactions) and the cumulative effect of multiple doses.
32. An initiative to monitor knowledge, attitudes and beliefs among members of the public and health care workers should be established both before and after the introduction of an adolescent/adult program, related to
    - pertussis disease
    - immunization against pertussis

* Confirmed case:
Isolation of *B. pertussis*
Positive PCR for *B. pertussis*
Epi link with laboratory confirmed case and
paroxysmal cough or
cough with vomiting or apnea or
cough with inspiratory whoop

Treatment and Prophylaxis

Treatment

33. Any of the following should be used for treatment of pertussis:
    - azithromycin 10 mg/kg once daily for 1 day and then 5 mg/kg once daily for 4 days
    - clarithromycin 15 mg/kg twice daily in a divided dose for 7 days
    - erythromycin 40 mg/kg three times daily in a divided dose for 7 days
      - choice based on cost, side effects, etc.
34. Antibiotics should be administered as soon as possible after onset of illness; there is no limit to the start date for treatment of symptomatic, untreated cases of pertussis whose culture or PCR results are positive.
35. Patients should no longer be considered infectious after 5 days of therapy.
36. Infants < 2 months of age who are receiving macrolide antibiotics should be monitored for symptoms and signs of pyloric stenosis.

Chemoprophylaxis

37. For confirmed cases (culture, PCR, serology or epidemiologic link) or clinically diagnosed cases occurring during an outbreak, chemoprophylaxis should be given to the following:
    - household contacts (including attendees at family day care centres) where there is a vulnerable person (an infant < 1 year of age [vaccinated or not] or a pregnant woman in the third trimester)
    - for out of household exposures, vulnerable individuals who have had face-to-face exposure and/or have shared confined air for > 1 hour
38. For chemoprophylaxis, the same antimicrobials and schedule should be used as outlined under Treatment.
39. When used, chemoprophylaxis should be implemented as soon as possible.
    - Efficacy is related to early implementation and is unlikely to be of any benefit after 21 days have elapsed since the first contact.
40. Antibiotics recommended for the control of pertussis where household chemoprophylaxis is indicated (index cases, household contacts) should be supplied by public health.

Notification and Early Treatment

41. There should be notification (see Appendix 1 for notification procedures) of other contacts of confirmed cases in the following settings:
    - other households
    - non-family day care centres
    - schools
    - health care settings
    - work places
42. Treatment should be based on symptoms suggestive of early pertussis (coryzal stage).
43. The same antibiotics and schedule should be used as outlined under Treatment.
44. The settings listed in recommendation 41 should be assessed for special circumstances that might warrant chemoprophylaxis.

Outbreak Management

45. If there is a confirmed case in a household the following apply:
    - vaccination is not recommended for outbreak management, but the opportunity should be taken to update the immunization status of contacts if required.
    - exclusion is not a proven effective strategy; however, in high risk situations (where there are vulnerable individuals – for instance, infants) exclusion until 5 days after the start of antibiotic therapy or, if no treatment is

given, until after 21 days and with negative results from culture or PCR should be at the discretion of the medical officer of health.

46. If there are two or more confirmed cases epidemiologically linked in a non-household setting (school, day care centre without infants < 1 year old) the following apply:
    - Chemoprophylaxis is not indicated.
      - In household-like settings use individual judgement.
      - Alert parents to signs and symptoms of pertussis so that early diagnosis and treatment can be initiated when needed; inform community physicians of increased pertussis activity.
    - Use the opportunity to update routinely scheduled immunizations in school or day care contacts as required.
      - Catch up immunization of other cohorts can be considered by public health authorities.
      - All parents of contacts should be notified of the possibility of purchasing vaccine from the family physician.
    - Exclusion criteria are the same as in recommendation 45.
47. Public health nurses should obtain training and gain expertise in taking nasopharyngeal swabs.

Research Agenda

Topics to be included on the research agenda are as follows.

- Evaluation of each change recommended by this consensus conference upon implementation.
- Assessment of the population effectiveness of such strategies as immunization of new mothers, immunization of household contacts of a newborn, immunization of other close contacts of a newborn.
- Methods to reduce mortality and morbidity (hospitalization) in young infants.
- Use of acellular pertussis vaccine in outbreak control.
- Schedule issues
  - 5th dose
  - primary series
  - accelerated schedules
  - newborn immunization
- Efficacy of vaccine in adolescents (and adults)
  - This should not delay implementation.
- Seroepidemiology in new Canadian adolescents.
- Evaluation of single dose of azithromycin.
- Monitoring of macrolide resistance.
- Duration of protection of children fully immunized with acellular vaccine.
- Cost-effectiveness of different strategies.
- Investigation of the point at which patients receiving treatment are no longer infectious.
- Source of infection of young infants.
- Mechanisms of transmission related to
  - culture/PCR positive results
  - symptoms
- Effect of maternal immunization on infant disease.
- Immunization during pregnancy.
- Role of maternal antibody (transplacental and via breast milk) in the protection of infants in the first few months of life.
- The effect of the interval between booster immunization and childbirth on the production of antibody titres that do or do not protect infants.

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APPENDIX 1

Notification and Early Treatment of Contacts

(See Recommendation 41)

- The notification of individuals exposed to confirmed cases of pertussis in the settings covered by Recommendation 41 should comprise
  - notification that a case of pertussis has been diagnosed in the setting
  - a brief description of the case of pertussis, its symptoms, incubation period and period of communicability
  - advice to seek medical attention if symptoms develop
  - the request to notify public health.
- To this notification should be attached a letter to the physician, which should provide information on pertussis and its diagnosis, and recommendations for
  - physician assessment
  - nasopharyngeal swab for pertussis, and other diagnostic modalities
  - early treatment, listing the recommended antibiotics and their schedules
  - notification of public health.

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