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Re-emergence of pertussis in Slovenia: Time to change immunization policy

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Summary The introduction of childhood vaccination has dramatically reduced morbidity and mortality of pertussis in Slovenia. However, despite high vaccination coverage for many decades, reported incidence has increased recently, to the highest incidence of 27.5/100,000 in 2006, a 6.5-times increase in comparison to the previous year. Marked shift in age distribution among reported cases was observed in recent years. In 2006, reported age-specific incidence was relatively high in children 8–12 years old, the highest among 9 years old. Similar to other countries, where children are given pre-school boosters, we also have to consider the revision of the national vaccination policy. A booster dose at school entrance or latest at 8 years of age should be introduced to decrease the transmission of disease among school children and to further reduce the burden of disease among infants.

Introduction

Whooping cough or pertussis, which is caused by *Bordetella pertussis*, is a highly communicable infectious disease with epidemic peaks occurring every 2–5 years [1]. Before the vaccination era, pertussis was a common cause of childhood morbidity and mortality. Dramatic decline in the incidence occurred after vaccination against pertussis was introduced. Despite high vaccination coverage for decades, pertussis re-emerged as a public health problem in many countries during the last decade [2–5]. Different explanations were proposed as possible reasons for the increase in the incidence of pertussis, waning of vaccine-induced immunity being one of them [4,5]. As a consequence, many countries introduced booster vaccination for pre-school children and some countries have been considering the introduction of additional booster vaccination for adolescents and adults [6].

In Slovenia, mandatory vaccination against pertussis with the basic vaccination schedule of three doses in the first year of life was introduced in 1959. In 1961 a booster in the second year was added. In 1969, the second booster was introduced at the age of 4. Combined vaccine against tetanus, diphtheria and pertussis was used. In 1990 the second booster was dropped, mainly to reduce the total number of doses against tetanus and diphtheria (from 8 to 7), while no adverse impact on pertussis incidence was expected. In 1999, whole-cell pertussis vaccine was replaced with acellular vaccine. Current Slovenian immunization programme recommends three doses

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of acellular pertussis vaccine in the first year (combined diphtheria—tetanus—pertussis—polio—Hib vaccine at 3, 4—5 and 6 months of age) followed by a single booster in the second year of life.

In Slovenia, pertussis has been a notifiable disease for more than 50 years and reported data show that Slovenia also experienced an increased incidence of pertussis in recent years. This paper presents Slovenian pertussis surveillance data, recent increase in reported incidence, and explores changes in reported age-specific incidence, with the aim to consider the need for, and to inform the revision of our national vaccination policy.

Methods

Notification of pertussis cases as well as death cases due to pertussis has been mandatory in Slovenia since 1946. The case definition was based on clinical diagnosis. Laboratory confirmation was not required. Individual cases were reported. Data have been collected in the Centre for Communicable Diseases, Institute of Public Health of the Republic of Slovenia (IPH). In 2005, EU surveillance case definition for pertussis was widely publicised and general practitioners and paediatricians who most often notify pertussis cases were actively encouraged to confirm every possible case of pertussis (except for close contacts of confirmed cases) with appropriate laboratory diagnosis. However, we continued to include in our surveillance data base cases that were not laboratory confirmed. Thus, the surveillance case definition for pertussis has not changed.

We analysed surveillance data on reported cases of pertussis for the period from 1957 to 2006. Proportion of laboratory-confirmed cases during 2004—2006 ranged from 80.9% (in 2006) to 89% (in 2005); while in 2001 it was only 35%. Overall and age-specific reported incidence rates as well as proportional age distribution were calculated. We used the following age groups: <1, 1—4, 5—9, 10—14 and >14 years. Data from the last 4 years, the years with increased incidence, were compared according to age distribution.

Data on national vaccination coverage were available from mandatory recording of all vaccinations within the Slovenian national immunization programme, and for the period from 2003 to 2006, estimated by surveys on vaccination coverage.

Results

Reported cases and incidence rates

Before vaccination against pertussis was introduced in Slovenia in 1959, thousands of cases were reported every year, with the peak of nearly 7000 cases in 1958 (350/100,000 population). In addition, a few deaths due to pertussis were reported every year, with the peak of 30 deaths in 1955 (1.5/100,000).

After the introduction of vaccination against pertussis, reported incidence started to decline (Fig. 1). After 1963 it fell below 1000 cases (<50/100,000) reported annually and during the 1990s it stabilized below 100 cases (<5/100,000), with smaller outbreaks every 3—4 years (in 1990, 1994, 1997 and 2001). Since 2003 the reported incidence of pertussis has increased again and 551 cases were reported in 2006 (27.5/100,000), which represented a 6.5-times increase in comparison to the previous year. During the 1960s, a few deaths due to pertussis were reported every year (ranging from the lowest number 1 in 1961 and 1965, to the highest number 7 in 1963). After 1970, there were only two additional deaths (in 1995 and 2004).

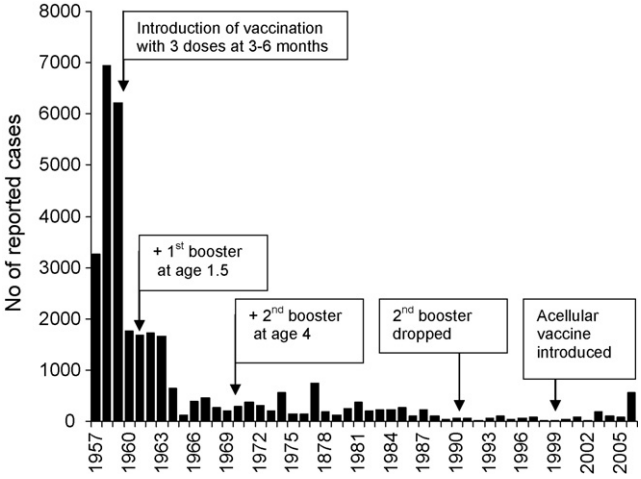

Figure 1 Reported cases of pertussis, Slovenia, 1957—2006.

Age distribution

Recently, there was a marked shift in the age distribution of reported cases (Fig. 2). During 2003—2006, children and teenagers 10—14 years old represented the largest proportion of reported cases, ranging from 35% in 2003 to 47% in 2005, while during the 1990s the corresponding proportions ranged from 2% (in 1991) to 17% (in 1993). In contrast, the proportion of reported cases in infants (<1 year) decreased from approximately 50% in the 1990s to only 5% in 2006. Nevertheless, the incidence in infants, which used to be the highest age-specific incidence until 2005, remained high (Fig. 3). In 2006, for the first time, 10—14 years old children had the highest age-specific incidence rate of pertussis (220/100,000), followed by 5—9 years old

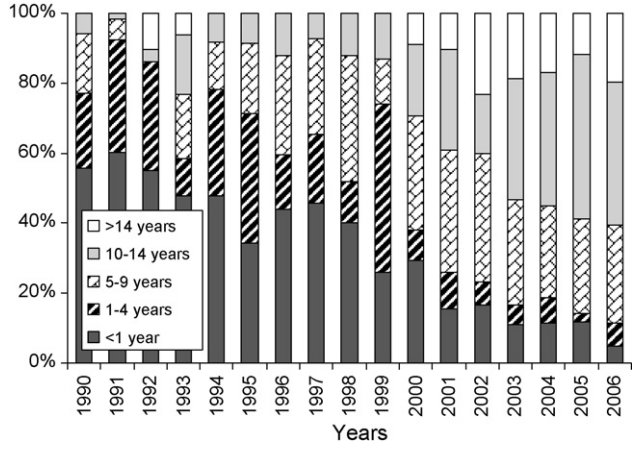

Figure 2 Age-specific proportions of reported pertussis cases, Slovenia, 1990—2006.

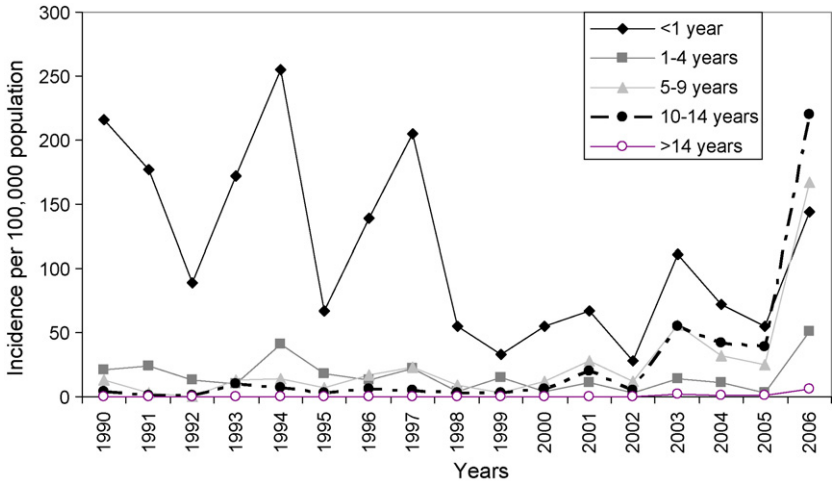

Figure 3 Reported annual incidence rates of pertussis by age groups, Slovenia, 1990—2006.

children (167/100,000) and by infants (144/100,000). In the 1990s age-specific incidence rates were mostly decreasing with increasing age, but from 2000 to 2003, age-specific incidence rates were second highest in 5—9 years old, and from 2004 to 2005 in 10—14 years old (Fig. 3).

During the period 2003—2005, except for infants, the age-specific incidence rates were the highest in children 8—14 years old, with peaks occurring in 8 years old in 2003, and in 11 years old in 2004 and 2005. In 2006, the highest age-specific incidence rates were observed at similar ages (8—12), with the peak of 365.5/100,000 at the age of 9 (Fig. 4).

Vaccination coverage

During the last 20 years vaccination coverage against pertussis remained relatively high and stable. Coverage for the third dose (at 12 months of age) ranged from the lowest 89.5% (in 1998) to the highest 96.8% (in 1993), while the coverage for the first booster during the same period ranged from the lowest 85.1% (in 1998) to the highest 93.5% (in 1996).

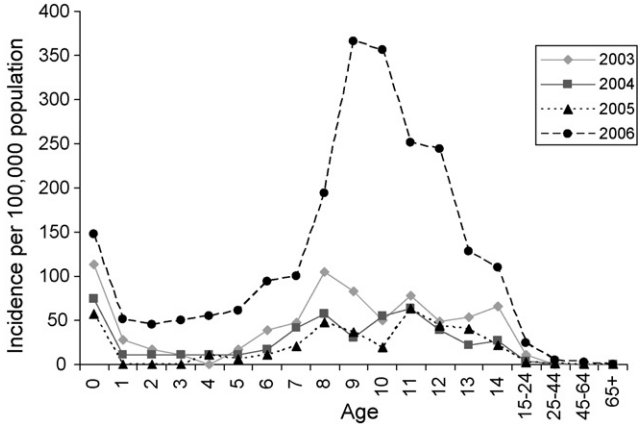

Figure 4 Age-specific incidence rates of pertussis, Slovenia, 2003—2006.

Discussion

Our results show that although the overall reported pertussis incidence rates have become very low, pertussis is still endemic in Slovenia, with small outbreaks occurring every 3—4 years despite the high vaccination coverage. As in many other countries, an increase in reported pertussis incidence rate was observed after the year 2002, with the highest overall incidence rate in 2006, and the highest age-specific incidence rate in 9-year-old children.

Though pertussis may occur at any age, in the pre-vaccine era it was a disease of pre-school children. After the introduction of vaccination the overall incidence declined but epidemics still occurred, and age-specific incidence was the highest in infants followed by pre-school children. More recently, in countries with high vaccination coverage, the age distribution of pertussis has changed markedly (1). Such changes were also observed in Slovenia. As numbers of reported cases of pertussis were getting lower during 1980s, it was perceived safe to drop the second booster against pertussis in 1990. Reported numbers were even lower in the 1990s (<5/100,000 population), but peaks were still observed every 3—4 years. After 15 years of very low incidence rates, when there was an impression that pertussis was under control, a rising incidence was first observed in 2003, rising further to the highest in 2006 with the rate 27.5/100,000 population. Surprisingly, in 2006, reported incidence rate in infants was lower than during many other peak years in the 1990s, when the annually reported numbers of pertussis cases were very low. The peak incidence occurred in older children, suggesting greater susceptibility in older age groups, as reported by others [3,7]. Since the vaccination coverage in Slovenia remained high and stable, other possible explanations for re-emerging of the disease were considered.

Waning of vaccine-induced immunity was suggested as an explanation for re-emergence of pertussis [5,8]. However, with waning immunity, one would expect incidence rates to increase with longer delay after the last dose. Increased rates of pertussis in older children in the last years could also be explained by lower possibility of natural boosting

due to reduced circulation of *B. pertussis* after long-term vaccination [4]. Waning immunity among infrequently naturally boosted adolescents and adults might thus result in a reservoir and a source of infection for infants.

Data from Netherlands supported the hypothetical role of antigenic changes in *B. pertussis* during the 1996 outbreak [2]. Also, in Poland, occurrence of epidemics was thought to be in part due to a genetic shift in *B. pertussis* strains [4]. There could also be some other reasons for re-emergence of pertussis in Slovenia. The second booster against pertussis at the age of 4 was dropped in 1990, which may have contributed to the recently increased incidence rates.

In contrast, in Italy the lowest levels of incidence were observed in recent years due to increase in vaccination coverage [9]. However, decreased incidence was most obvious in children below age 10, while less clear in older age groups, where significant circulation of pertussis, due to the waning immunity in adolescents and young adults, was still going on. Also, in Sweden, declining incidence rates of pertussis followed the introduction of acellular pertussis vaccine in 1996, 17 years after the withdrawal of the whole-cell vaccine [10]. Similarly, in Austria, the incidence of hospitalised children during the transition period from the whole-cell to the acellular pertussis vaccine decreased for all age groups but less in older children as a result of steadily increasing vaccination coverage since the introduction of acellular vaccine in 1998 [11].

From the US and Canada they reported of increasing incidence among adolescents and adults, which constituted the main source of infection in infants [12,13]. Although a shift in the age distribution of pertussis cases in the last years is evident in Slovenia, reported incidence among older adolescents and adults remained low and probably hampered by the non-specific symptoms in adolescents and adults or lower awareness among physicians of the clinical presentation of pertussis in these age groups, as suggested by others [14].

An important finding from Canada indicates that after childhood, the risk of complications due to pertussis increases with age. Therefore, in addition to young infants, adolescents and adults emerged as groups at higher risk of disease [15].

Many countries that observed similar changes in epidemiology of pertussis as we have in Slovenia, already implemented additional booster doses to their immunization programmes (http://www.euvac.net/graphics/euvac/vaccination/pertussis.html). Most of them introduced additional boosters before entering school [4,6]. In Sweden, the first signs of waning immunity were observed at 6—7 years of age [10] and their data suggested a booster dose at the age of 5—7 years [16]. A teenage pertussis booster is currently recommended in Austria, France, Germany and Malta [6]. Recently, in Austria a recommendation for a booster vaccination every 10 years has been issued [11]. Since pertussis is most severe in infants and often requires hospitalization, the role of booster doses of pertussis vaccines is primarily an indirect protection of vulnerable infants [17]. However, a study from Denmark evaluating the impact of pre-school booster vaccination on pertussis hospitalization in infants only showed a modest effect [18]. The indirect effect of a booster on epidemiology of pertussis over time would probably be an increased average age at infection. The authors suggested that this would result in increased transmission to infants from adolescents and adults [18].

Describing the epidemiology of pertussis from case reported data can be hampered by changes over time that may influence the completeness of reporting, such as awareness of physicians, changes in case definition and laboratory confirmation of cases. We cannot exclude the possibility that the reported incidence partially increased as a result of increased awareness of physicians after numerous reports on outbreaks of pertussis from other countries and our active promotion for laboratory confirmation of cases. On the contrary, reporting of laboratory-confirmed cases only would have increased the specificity of the surveillance system that could result in partially decreased reported rates. In recent years about 80—90% of reported cases were laboratory confirmed in Slovenia in comparison to 35% in 2001. However, we have no reason to believe that the reported incidence trends were substantially distorted by these factors.

High immunization coverage in Slovenia was very important in reducing reported pertussis incidence rate from more than 300/100,000 in pre-vaccination era to less than 5/100,000 in the 1990s. Nevertheless, in recent years the reported rates increased again and it is evident that with current immunization schedule the endemic situation cannot be improved. Pertussis outbreak in 2006 clearly indicates that an additional booster is needed to decrease the transmission of disease among school children and to further reduce the burden of disease among infants, too young to be vaccinated. Other possible strategies to improve disease control were also suggested, as selective immunization of mothers and close family contacts of newborns, or selective immunization of health care workers [19,20]. Our data suggest the need for the introduction of a booster dose at school entrance or latest at 8 years of age. Therefore, a booster was proposed to be added into national immunization programme at the age of 8 in the year 2008, together with the second booster (fifth dose) against diphtheria and tetanus. The effect of a booster vaccination on the epidemiology of pertussis will have to be monitored to evaluate the effect of this change in the immunization programme over time and to further improve (by considering booster doses for adolescents and adults) the national strategy of controlling this re-emerging communicable disease.

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