Pertussis in Poland

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Background Since 1997, an unexpected 2–5-fold increase in the incidence of pertussis has been reported in Poland in comparison with the previous 10 years, although the introduction of the diphtheria-tetanus-pertussis (DTP) vaccination in 1960 reduced the incidence of pertussis approximately 100-fold in the 1980s. The aim of the study was to analyse all available data on pertussis in Poland to identify the risks associated with its re-emergence.

Methods Available data on notification, incidence, mortality, hospitalization, geographical distribution, incidence according to age, and diagnosis of pertussis were collected from national surveillance monographs and statistically evaluated.

Results Analyses performed in the study found two periods of rising and falling trends: in the incidence before and after 1989, respectively. Moreover, after 1989, the age-specific incidence among children aged 0–4 years decreased, and among 5–9, 10–14, and 15–19 year olds increased in comparison to the previous decade. The incidence rate of pertussis among infants was similar in both decades analysed. Clustering of pertussis incidence increase in provinces along a line from North East to South West was observed.

Conclusions As vaccination coverage did not decrease and diagnostics have not been improved since the 1980s, it is possible that waning immunity and the appearance of Bordetella pertussis vaccine escape mutants are involved in the changing pertussis epidemiological parameters. Further monitoring studies, together with improving diagnostics, might allow more precise epidemiological data to be obtained. An additional booster dose of acellular pertussis vaccine at age 6 years has been included in the current vaccination schedule.

Keywords Pertussis, DTP, Poland

Pertussis has been controlled successfully by routine mass immunization of infants and children with whole-cell vaccine for nearly 50 years. However, in many countries considerable media interest has been mixed with a fear of the possible re-emergence of pertussis.1–3 In some of countries recrudescence or persistence of pertussis has been recognized as being due to permanent or temporary exclusion of diphtheria-tetanus-pertussis (DTP) immunization from vaccination schedules, because of an underlying fear of possible local and general adverse events following immunization (AEFI) in vaccinated children.5 In some other countries, however, pertussis rates have increased despite the high vaccination coverage achieved over the course of many years.6–8 In these countries, changes in the surveillance system, a decrease in vaccination coverage and in vaccine quality, waning of vaccine-induced immunity, and the emergence of vaccine resistant strains (escape mutants) are proposed as possible factors for the increased incidence of pertussis.9–12 Reasons for the increase in pertussis have been studied intensively in the US12 and The Netherlands,13 but they are still not fully elucidated. In 1997–1998 in Poland—a country with a population of 38.6 million14,15—despite a 98% level of vaccination coverage with whole-cell pertussis vaccine, pertussis incidence rates were found to be similar to the rates registered 30 years earlier. In 1997 and 1998, 2082 and 2871 cases of pertussis were reported, accounting for an incidence/100 000 population of 5.4 and 7.4 respectively. Available national surveillance data on pertussis were collected and analysed in order to describe epidemiological changes in pertussis in Poland 1963–2000, and to identify factors of possible significance for the recent pertussis rates increase.
Material and methods

Data
To recognize pertussis trends in Poland, epidemiological parameters of pertussis were collected from available sources. A legally obligatory system of notification of infectious diseases is handled by the Ministry of Health (MOH) through the Department of Epidemiology at the National Institute of Hygiene (NIH), Warsaw. Routinely, cases of pertussis diagnosed by physicians are registered in the Provincial Public Health Laboratories, and are reported twice a month to the Department of Epidemiology, NIH. Collected aggregated data are analysed and published every 2 weeks in the ‘Meldunki o zachorowaniach na choroby zakaźne i zatrucia chemicznymi w Polsce’ (Bi-weekly Reports on Infectious Diseases and Intoxications with Chemical Compounds in Poland; www.pzh.gov.pl/epimeld/index_p.html).

Data of yearly notification, hospitalization, mortality, and incidence/100 000 population were collected for 1950–2000 using data published in the Bi-weekly Reports on Infectious Diseases and Intoxications with Chemical Compounds bulletin—of the MOH for 1958–1968; the MOH together with the Public Health Laboratory, Warsaw for 1969–1983; and the Department of Epidemiology at NIH and the MOH for 1984–2000. Population-based incidence and incidence according to age refers to the number of recorded pertussis cases in correlation with specific census data, which is evaluated annually and published by the governmental Central Office of Statistics (CSO; www.stat.gov.pl).

Vaccination coverage data were collected from ‘Szczepienia ochronne w Polsce’ (Vaccinations in Poland) monographs published yearly by NIH, MOH, and CSO. Vaccine coverage of pertussis with locally produced whole-cell pertussis (DTP) vaccine (Sera and Vaccines Manufacture ‘BIOMED’ SA, Krakow, Poland) is routinely assessed by NIH. They determine the proportion of 2 year olds who received three or four doses of DTP, using obligatory yearly reports from Provincial Health Laboratories on all vaccinations performed at Health Institutions in each province.

Additionally, case-surveillance on collected case-standardized epidemiological questionnaires collected from Provincial Health Laboratories is performed by the Department of Epidemiology, NIH, and results of these are published yearly in ‘Przegląd Epidemiologiczny’ (Epidemiological Review—a Polish scientific journal published quarterly since 1920). The incidence rate according to age has been calculated by NIH using Polish CSO data. Data on specific incidence rate according to age and vaccination status on 12 174 cases 1976–2000 (no data 1982) were collected from Epidemiological Review publications.

The distribution of notifications of pertussis and incidence rates within 49 provinces from 1980–1998 were collected from Epidemiological Review publications and Vaccinations in Poland monographs.

Pertussis definition
Pertussis is defined by the presence of the following symptoms: cough with whooping lasting for >2 weeks or cough followed by vomiting in combination with such symptoms as apnoea, cyanosis, subconjunctival bleeding, leukocytosis, lymphocytosis, or contact with a confirmed or suspected pertussis case during the previous 3 weeks. For confirmation of clinical diagnosis, bacteriology, immunofluorescence, or serology tests are recommended. Serological confirmation of clinical diagnosis of pertussis is based on a passive haemagglutination test (PHT) with pertussis endotoxin or ELISA assay with pertussis toxin and whole Bordetella pertussis cells as antigens. PHT performed on patient sera at 2-weekly intervals is used to correlate specific antibody level dynamics with clinical features of pertussis, onset of clinical symptoms, or vaccination status. The ELISA test is considered positive when a high titre of IgA against B. pertussis in a single serum or 100% rise of IgG antibodies against pertussis toxin in the second of the paired serum sample is seen.

Statistical analysis
Incidence rates in 0–4 (0, 1, 2, 3, 4), 5–9, 10–14, and 15–19 age groups within the periods 1976–1989 and 1990–2000 were analysed using linear regression. Pooled estimate of slope for each group incidence was obtained by averaging age group specific incidence estimates with inverse variance as a weight. Averages of pertussis incidence/100 000 population calculated for the periods 1980–1989 and 1990–1998 in 49 provinces were compared using a t-test, and the significance of incidence increase found in 11 provinces was calculated after application of the Bonefferoni correction. The Bonefferoni correction was applied to avoid problems associated with multiple comparisons. Notification averages within particular months were calculated from 1990 to 2000. All calculations were performed using the statistical package Splus 2000.

Results
Notification and incidence
During 1950–2000, a total of 995 857 cases of pertussis were reported by Provincial Health Laboratories to NIH. From 1960, when DTP vaccination was introduced in Poland, the number of recorded pertussis cases per year steadily decreased: from approximately 58 000–29 551 to a few thousand in the 1970s and a few hundred during the 1980s. The lowest notification rates, 122 and 174 cases, were noted in 1986 and 1988, respectively.

The reported yearly incidence generally decreased over time from >100–200 cases/100 000 population in the pre-vaccine decade (1950–1960) to <1 case/100 000 population within the 1981–1990 period (Figure 1). The number of deaths fell from approximately 1000 in the 1950s to single cases in the 1980s with the last death from pertussis occurring in 1991.

The decrease in pertussis notification and incidence rates commenced from 1989. In 1992 the increase in pertussis incidence in comparison to 1991 and 1989 was twofold and fivefold, respectively. In 1997, a sixfold increase in comparison to 1996 was noted (Figure 1). Within the period of 1997–2000 the yearly incidence/100 000 population was 5.4, 7.4, 2.3, and 5.9, respectively.

Although the highest increase in morbidity/year has been noted since 1997, analysis of notification rates/month within the last 10 years evidently shows that pertussis has been on the increase since June 1995. Arithmetic means of the monthly registered cases within the last 10 years show that pertussis cases were periodically more prevalent from September to March (Figure 2). Analysis of quarterly registered case rates

In the period 1974–2000 similar shape curves were obtained for pertussis notifications and hospitalization rates. However, for 1991–2000, higher hospitalization rates/year and similar notification rates/year, in comparison to the period 1972–1990, were recognized (Figure 1).

**Figure 1** Summary of epidemiological parameters of pertussis in Poland during 1950–2000

**Vaccination coverage**

Children in Poland have, from 1960, been continuously immunized with three primary doses and 1 booster dose at the ages of 2, 3–4, 5, and 16–18 months with a locally manufactured DTP vaccine. Vaccination coverage with three and four doses of the DTP vaccine for children born in particular years between 1979–1999, oscillated in ranges of 98.2–99.5% and 94.9–98.7%, respectively.

**Figure 2** Pertussis cases monthly registered within 1990–2000. Each horizontal line in the graphs related to the particular months represents the average of the notification rates during a period studied. Each vertical line in the graphs related to the particular months represents notification rate in the particular year in relation to the average.
Vaccination status

Analysis of the vaccination status of 12,174 registered cases patients between 1976–2000 revealed, from 1990 onwards, an increase in the incidence of pertussis in those vaccinated in comparison to the non-vaccinated. However, there were no major changes observed in the proportions of children vaccinated with one, two, or three doses of DTP vaccine, who got pertussis.

Pertussis distribution within 49 provinces (1980–1998)

Among 49 provinces, 20 during 1980–1989 and 22 during 1990–1998 have maintained an average incidence of <1/100,000 population. Moreover, 18 provinces reported no changes in the average incidence at a level <1, 16 provinces at a level lower than 1–2, and one province at a level lower than 2–5/100,000 population. Five provinces in both periods recorded fluctuations between ≤1 and 1–2. Thus, in 30 provinces the incidence remained at ≤2/100,000. Among 19 others there were incidence increases in 1990–1998 observed in comparison with 1980–1989, and in 11 it was statistically significant (P < 0.05). However, statistical significance of the incidence increase after application of the Bonferroni correction has been found only in a single province. A clustering of pertussis incidence increase has been observed along a line from North East to South West (Figure 3).

Age distribution

Looking at the notification data, since 1990, a slow but continuous shift of pertussis infections towards older age groups has been found. Children <1 year and children aged 0–4 accounted for the highest proportion of cases (37.0% and 73.9%, respectively) reported during 1976–1989. However, the proportion of cases in both these groups decreased from 24.0% and 65.9% (1990–1996) to 7.7% and 24.5% (1997–2000), respectively.

The frequency of pertussis cases among 5–9 and 10–14 year olds increased threefold and sevenfold, respectively, when comparing 1985 and 1998. There was a 33% increase in infections among those >10 years old out of the total number of pertussis cases registered in 1997. Generally, the frequency of pertussis increased 0.5, 3, and 6 times for 5–9, 10–14, and 15–19 year olds when comparing 1990–1996 to 1997–2000. In 1985–1992 only a few pertussis cases were registered in the age group 15–19 years. However, in 1997 and 2000 as many as 77 and 158 cases, respectively, were registered.

A significant decrease (P = 0.028) and increase (P = 0.045) in pooled incidence rates calculated from data relating to all age groups compared between 1976–1989 and 1990–2000 respectively, were found.

A non-statistically significant downward trend between 1976 and 1989 in the age group <1 year old was found in comparison with a statistically significant decrease found when 1 (P = 0.001), 2 (P = 0.002), 3 (P = 0.001), and 4 (P = 0.001) year old children within the total 0–4 age group were analysed (Figure 4A). During 1990–2000, in the total 0–4 age group, a statistically significant incidence increase was found only for 3 (P = 0.009) and 4 year old (P = 0.008) and not for 0, 1, and 2 year old children (Figure 4B).

A statistically significant morbidity decrease within 1976–1989 was seen in all age groups analysed (P ≤ 0.003) (Figure 5A). Among individuals in the four age groups analysed, a significant increase in incidence rates was found between 1990–2000 for 5–9 (P = 0.006), 10–14 (P = 0.005), and 15–19 (P = 0.016) year olds, but not in the 0–4 year old age group (Figure 5B). Regressive analysis of the data revealed that the most aggressive slopes for morbidity increase have been found for 5–9 and 10–14 year olds, and for 3 and 4 year old children among the 0–4 group as a whole (Figures 4B and 5B).

Discussion

Currently, several European countries, the US, and Canada have been reporting an increased rate of incidence of pertussis, although DTP vaccination has been included in vaccination schedules for approximately 50 years.2,3,6,8,10 In this study, general trends in the epidemiology of pertussis in Poland are described which may supplement data on the pattern of pertussis in European countries. Collected data are discussed from the point of view of pertussis epidemiological changes observed among highly immunized populations.

In Poland, before the introduction of pertussis immunization to the vaccination programme, pertussis was mainly registered in 2–4 year old children. As little as 10 years after the introduction of DTP, when incidence was lowered in groups covered by vaccination, a decrease of incidence rates in all age groups as an effect of increased herd immunity was notified. The rise in incidence registered in Poland since 1997, after 36 years of continuously successful DTP immunization, was unexpected for the following two reasons. Firstly, the DTP vaccination programme has been performed with success continuously since 1960. Secondly, the success of this programme has been easily seen since the 1970s, when cycles with epidemic and endemic peaks every 3–5 years were recognized, but generally pertussis incidence during 1982–1991 was <1/100,000.

Average vaccine coverage in the period 1985–2000 has not changed, reaching 96–98% for children aged 1 year,8 and thus a possible role of the occurrence of a large pool of susceptible
individuals in the population can be excluded. Vaccination coverage was maintained thus at a high stable level even in the 1980s; much higher than registered in the US in the 1990s.\textsuperscript{12}

The increased rate of pertussis found among 5–9, 10–14, and 15–19 year olds in Poland in the last decade may be related to the reduced circulation of \textit{B. pertussis} due to long-term vaccination with subsequent less frequent exposure to the bacteria, and therefore a lower possibility of natural boosting. The risk of pertussis among infants, many of whom may be too young to receive primary doses of DTP, remained at similar levels during 1976–1989 and 1990–2000. Additionally, the incidence of pertussis in children aged \( \leq 4 \) years old also remained stable within both periods analysed. A similar picture was found in the US, where the average incidence for children \( \leq 5 \) years has not increased, but among those aged 5–9, 10–19, and older the increase was pronounced.\textsuperscript{12,20} In The Netherlands, a decrease in the proportion of pertussis cases among infants \(<1\) year old was also found. However, an

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure4}
\caption{(A) Pertussis morbidity trends in 0–4 year old children during 1976–1989. (B) Pertussis morbidity trends in the 0–4 years old children within 1990–2000}
\end{figure}
increase of pertussis cases among children aged 1–4, and adults, together with a decrease in cases among 5–9 year old children was observed. No changes were observed among 10–14 and 15–19 year old children. As the pertussis incidence rate among the whole 0–4 year old group has not increased, the recent increase in the incidence of pertussis in Poland is related neither to a decrease in vaccination coverage nor to a significant reduction in DTP efficacy. The whole-cell vaccine produced in Poland meets international standards and there was no sign of a gradual deterioration of the vaccine quality as determined for product release using a mouse-protection test. However, our unpublished data show lower potency levels (but still fulfilling accepted lower limits) in the DTP lots released 1992–1997 correlated to the lower IOU number/single human dose in comparison with vaccine lots produced in another periods. It could be suspected that lower vaccine immunogenicity might cause a lower protective immunization level than previously achieved, resulting in higher incidence rates among 3, 4, and 5–9 year old children, as observed in the study. However, the increase of pertussis incidence rates observed among >10 year olds suggests the involvement of other factors. The increase in pertussis rates in vaccinated people, with

Figure 5 (A) Pertussis morbidity trends within 1976–1989. (B) Pertussis morbidity trends within 1990–2000
a subsequent decrease in the pertussis rate among the non-vaccinated from 1990 onwards, might be related to an increase in infections among children of school age and older. Such a trend is to be expected when there is a high proportion of vaccinated people in a population together with no significant decrease in vaccine efficacy. In the study, an expected association between school opening and a peak in pertussis (similar to data from the US) was seen since pertussis is spread by the airborne route. However, we could not specify differences in monthly recorded prevalence according to age. American data correlated increased prevalence among infrequently naturally immunized populations. Waning immunity among frequently immunized populations. However, the laboratory aspects of pertussis diagnosis present several drawbacks and improving these is essential for real estimation of the burden of pertussis.

Changes in the epidemiology of pertussis observed in Poland are similar to other highly vaccinated populations. Waning immunity among infrequently naturally boosted adolescents and adults who may get only a mild form of the disease, might thus create a reservoir and a source of infection for under immunized children. Moreover, it has been suggested that vaccinated people become susceptible to pertussis 5–10 years after vaccination, depending on the type or brand of vaccine. Strebel et al. and De Serres et al. indicated that a booster dose for 11–12 year olds might be an effective strategy to prevent pertussis among US adolescents. In Europe, France and Germany implemented additional reinforcing booster doses of acellular pertussis vaccine at age 11 years. Pertussis seroprevalence studies in Poland determined protective antibody levels against pertussis in 70%, 58%, and 45% of children aged 6, 7, and 8, respectively. It shows that a decrease in immunity may cause an increase in the number of pertussis cases among children > 5 years. An additional booster (fifth) dose of acellular pertussis vaccine before entering school has now been introduced in Poland.

In Poland, contrary to the US, underestimation of the true incidence due to surveillance and diagnostic improvements resulting from increased awareness of pertussis in adolescents and adults has not been suspected. However, under-reporting might be involved, similar to the pertussis increase in 1996 in The Netherlands, due to improved compliance with the notification system. Pertussis cases in Poland were reported based on clinical definition up to 1980, and still are. However, after 1980, because of the availability of serological tests, many of them were laboratory confirmed. Following a current WHO Expert Committee case definition, laboratory confirmation of pertussis is advised in Poland. Recently as many as 90% of registered pertussis cases have been laboratory confirmed. However, only half have used methods according to the WHO recommendations. The remaining half has unfortunately been confirmed with an old-fashioned PHT method, frequently performed only once.

Although there are some weaknesses in surveillance influencing absolute validity of the data, epidemiological trends of pertussis in Poland are similar to other highly vaccinated populations. However, the laboratory aspects of pertussis diagnosis present several drawbacks and improving these is essential for real estimation of the burden of pertussis.

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Commentary: Is pertussis disease increasing?

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Over the past two decades, several countries have reported increasing rates of pertussis disease. In the 1980s the UK and Japan documented increased pertussis illness associated with the decreased uptake of the reactogenic whole-cell pertussis vaccine.1 In the 1990s Canadian epidemiologists reported increased pertussis cases resulting from the administration of an ineffective whole-cell vaccine.2 In the past several years investigators in the US and France have suggested that pertussis is increasing in adolescents and adults.3–5 Although some have argued that the increase is simply a function of improved diagnostic methods...