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# Epidemiological shift in the prevalence of pertussis in Taiwan: implications for pertussis vaccination

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In Taiwan, routine pertussis immunization has been implemented for more than 40 years and a low incidence of pertussis was maintained until an 80-fold increase in cases occurred in 1992. The unexpected increase emphasized the significance of pertussis. This study evaluated a total of 2452 reported cases of pertussis during 1993–2004 and surveillance data on incidence, age distribution and seasonality. The highest morbidity was in infants aged <1 year, and upward trends in the incidence of pertussis were significant for infants aged <1 year and adolescents aged 10–14 years. The highest mean number of cases was observed in August and upward trends were in colder months. This study indicates that the epidemiology of pertussis may have been changed by waning immunity in Taiwan. Increased surveillance activities, especially in older age groups, and additional booster doses of acellular pertussis vaccine for children aged 6–8 years and adolescents/young adults aged 15–20 years are necessary to control and prevent pertussis.

## INTRODUCTION

Pertussis, caused by the Gram-negative bacterium *Bordetella pertussis*, was a severe disease of children in the pre-vaccination era (Bass & Zacher, 1989). After the introduction of whole-cell pertussis vaccines in the 1950s, the incidence of pertussis declined substantially. Since the 1990s, a resurgence in pertussis has been reported in many countries with high vaccine coverage (Centers for Disease Control and Prevention, 1993; Celentano *et al.*, 2005; Mooi *et al.*, 2001). Despite the fact that pertussis vaccines are highly effective against pertussis, immunity from immunization is known to wane in the decade following the last pertussis vaccine dose (He *et al.*, 1994). Hence waning immunity may play a crucial role in the increase in reported pertussis cases in older age groups (Guris *et al.*, 1999; Halperin, 2005).

In Taiwan, routine mass immunization of infants and children with diphtheria–tetanus–pertussis (DTP) vaccine has been implemented since 1954. From 1996 on, acellular pertussis (DTaP) vaccines were introduced gradually (Lin *et al.*, 2006). Low incidence was retained until an 80-fold increase in reported pertussis cases occurred in 1992 in comparison with 1991. This unexpected increase again emphasized the significance of pertussis. In this study, we analysed the epidemiology of pertussis in Taiwan between 1993 and 2004 based on national surveillance data on reported pertussis cases, and discuss the probable reasons for the increased incidence in pertussis in recent years.

Abbreviation: DTP, diphtheria–tetanus–pertussis.

## METHODS

**Case definition.** The clinical and laboratory definitions of pertussis cases were used as recommended previously (Centers for Disease Control and Prevention, 1997). The clinical case definition was a coughing illness lasting for at least 2 weeks with one of the following: paroxysms of coughing, inspiratory whoop or post-tussive vomiting without other apparent cause. A probable case was one that met the clinical case definition but was not laboratory-confirmed or epidemiologically linked to a laboratory-confirmed case. A confirmed case was one that met the clinical case definition and was laboratory-confirmed or epidemiologically linked to a laboratory-confirmed case. Culture of *B. pertussis* from a clinical specimen was the laboratory criterion for diagnosis. All clinical specimens from probable pertussis cases were collected and sent by hospitals located in different areas of Taiwan to the Center for Disease Control, Taipei, Taiwan. All isolates were laboratory-confirmed as *B. pertussis* using Gram staining, oxidase tests and slide agglutination tests with *B. pertussis* antiserum (Difco, BBL). *B. pertussis* strains were grown on Bordet–Gengou agar supplemented with 15 % defibrinated horse blood at 37 °C for 4–5 days.

**Data and statistical analysis.** Epidemiological parameters for pertussis cases were collected from the National Reporting System for Communicable Diseases in the Center for Disease Control, Taiwan. A total of 2452 reported cases of pertussis were obtained between 1993 and 2004 from different parts of Taiwan. The data analysed included the case reporting date and age at the time of the report. The incidence rate of each age group over the years was calculated using population numbers from statistical information released by the Ministry of the Interior.

All calculations were performed using SPSS, version 10.0.7 (SPSS). The changes in incidence in each age group over the years and trends in seasonality between 1993 and 2004 were analysed using linear regression. All $P$ values were two-tailed and $P<0.05$ was considered to be significant.

## RESULTS

### Pertussis incidence

The annual incidence of pertussis for the period 1955–2004 in Taiwan is shown in Fig. 1. Since the DTP vaccine was introduced in 1954, the incidence of reported pertussis cases per year has declined significantly from 77 cases per million in 1955 to less than 1 case per million in 1970, and this low incidence was retained from 1971 to 1991. An unexpected increase of 226 reported pertussis cases occurred in 1992 and the incidence of pertussis increased significantly from less than 1 case per million in 1991 to 11 cases per million in 1992.

Between 1993 and 2004, a total of 2452 cases of pertussis were reported by hospitals located in different areas of Taiwan to the Center for Disease Control, Taiwan (63 in 1993, 51 in 1994, 86 in 1995, 146 in 1996, 477 in 1997, 283 in 1998, 276 in 1999, 312 in 2000, 168 in 2001, 203 in 2002, 195 in 2003 and 192 in 2004) (Fig. 1). In 1997, compared with 1996, a threefold increased incidence of pertussis from 7 to 22 cases per million was noted. The period 1997–2000 was characterized by a higher number of reported cases, with an incidence of pertussis of 13–22 cases per million. However, after 2000, the incidence of pertussis decreased and was maintained at $<10$ cases per million during 2001–2004.

### Vaccine coverage

In Taiwan, routine vaccination of the primary series is given at 2, 4 and 6 months of age, with a booster dose at 12–18 months. The rates of vaccine coverage with three doses of DTP or DTaP for infants between 2001 and 2003 were 98.1, 97 and 94.8 %, respectively. The DTaP was offered at the patient's own expense. However, due to its low adverse reaction and amenability of combination with other vaccines such as inactivated polio vaccine, *Haemophilus influenzae* B (Hib) and hepatitis B virus as a multivalent vaccine, the rate of usage of DTaP has increased from $<1$ % before 2002 to 55.3 % in 2004.

### Age distribution

The incidence trends per 100 000 person-years for each of five age groups over the period 1993–2004 are shown in Fig. 2. The incidence of pertussis decreased with increasing age. Infants aged $<1$ year accounted for the highest proportion (mean of 56.4 %) of all reported cases, with a significant increase in incidence (120–605 cases per million; $P=0.014$). The increase in incidence in children aged 1–9 years was lower (2–67 cases per million) than in the $<1$ year age group and the incidence showed no trend in the years 1–4 ($P=0.112$) or 5–9 ($P=0.944$) age groups. In adolescents aged 10–14 years, the increase in incidence from less than 1 case per million in 1994 to 15 cases per million in 2004 was significant ($P=0.03$). The incidence in adults aged $\geqslant 15$ years showed no statistically significant trend ($P=0.804$). When excluding the incidence of pertussis in 1997 (epidemic year), the upward trend in incidence was more significant for infants and adolescents ($P<0.01$), and the highest slope for incidence increase was found in adolescents aged 10–14 years.

### Seasonality

The number of reported pertussis cases in each month between 1993 and 2004 was calculated (Fig. 3). The highest mean number of reported cases was in August. Three upward trends by year were found in February ($P=0.018$), March ($P=0.046$) and November ($P=0.034$). When 1997 was omitted from the analyses, significant upward trends were found in February ($P=0.025$), March ($P<0.01$), November ($P<0.01$) and October ($P<0.001$).

## DISCUSSION

In recent decades, an increased incidence of pertussis has been reported in many countries with routine vaccination

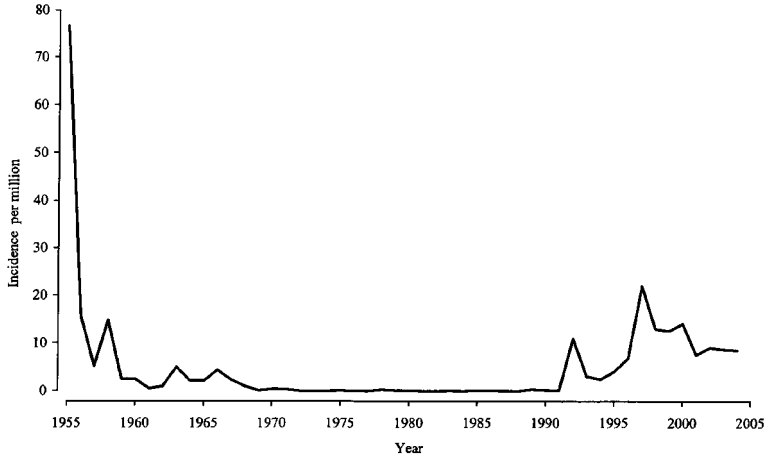


**Fig. 1.** Incidence trend of reported pertussis cases per million in Taiwan during 1955–2004.

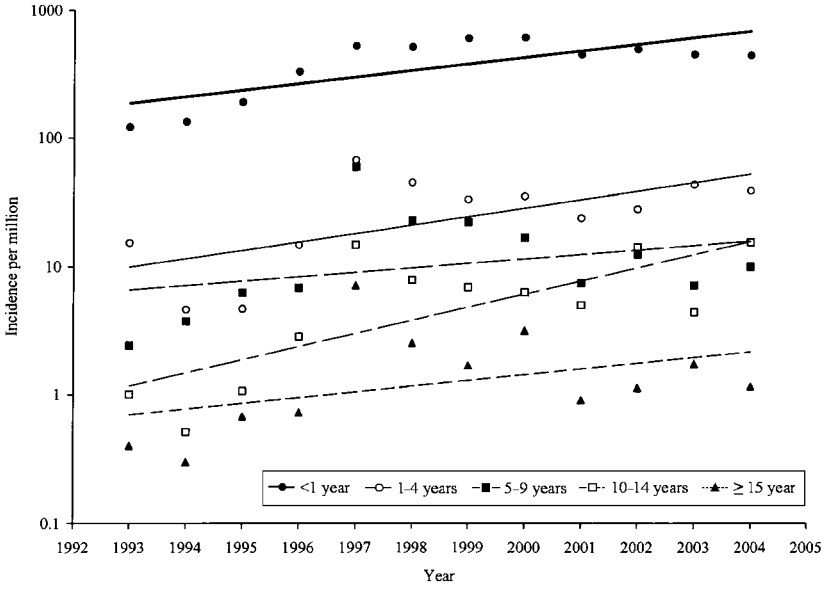


**Fig. 2.** Incidence trends of reported pertussis cases per million by age group in Taiwan during 1993–2004.

and high vaccination rates, including the USA (Centers for Disease Control and Prevention, 1993), Canada (Skowronski *et al.*, 2002), Poland (Gzyl *et al.*, 2004) and several other European countries (Celentano *et al.*, 2005; Mooi *et al.*, 2001). There are probably multiple reasons for this increase. Long-term vaccination with effective pertussis vaccine significantly decreased the prevalence of *B. pertussis*, but caused populations to be exposed less frequently to natural boosters of *B. pertussis* (Gzyl *et al.*, 2004). Furthermore, protection against reinfection from vaccination is not life-long; thus waning immunity may gradually increase the incidence of pertussis among older people (von Konig *et al.*, 2002). Another suggestion to explain the increasing incidence of pertussis in the 1990s is that antigenic shift of *B. pertussis* may have caused a loss of vaccine efficacy (Mooi *et al.*, 1998). In Taiwan, as in other countries, an epidemic trend in pertussis has in part been attributed to the antigenic divergence in *B. pertussis* strains due to vaccine-driven selection as a result of using whole-cell pertussis vaccines for long periods (Lin *et al.*, 2006; Yao *et al.*, 2005). It has been suggested that antigenic divergence in *B. pertussis* might lead to escape from vaccine-induced immunity, resulting in an increased incidence of pertussis. However, even though the shift of *B. pertussis* virulent alleles has continued for years, it is too early to expect vaccine-driven antigenic divergence to compromise the efficacy of vaccination.

In Taiwan, the upward trends in the incidence of pertussis in all age groups between 1993 and 2004 may be due to the intensification of recognition and reporting systems. Generally, infants aged $<1$ year accounted for the highest

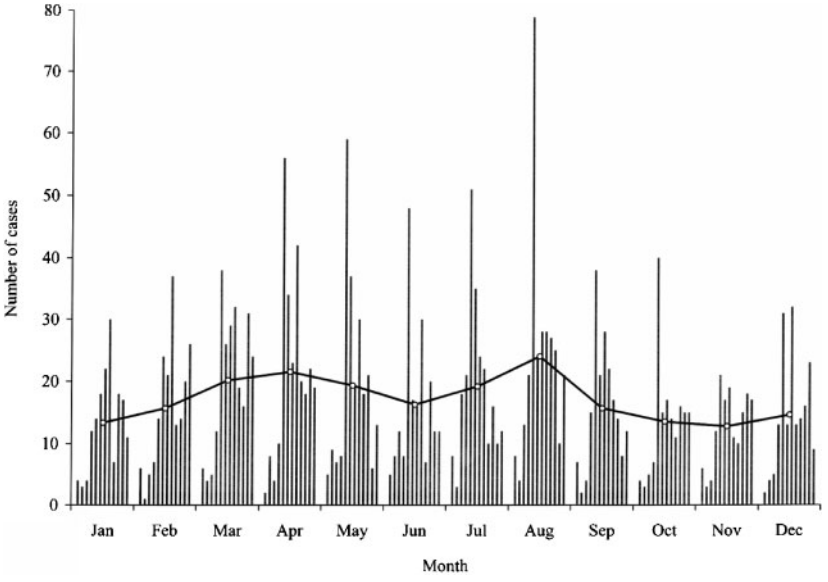


**Fig. 3.** Number of pertussis cases reported each month. Each vertical line represents the number of reported cases for each year during 1993–2004 by month. The open circles indicate the mean number of reported cases of each month.

incidence of pertussis, and most (84 %) of the infants in this age group were younger than 6 months and yet to be immunized or had not completed the primary series with three doses of pertussis vaccine. Furthermore, the greatest morbidity was found in infants younger than 2 months, i.e. infants too young to receive any pertussis vaccine, accounting for 28 % of all reported cases during 1993–2004 (data not shown). This age group continues to give the greatest disease burden and mortality (Centers for Disease Control and Prevention, 2002).

Between 1993 and 2004, a significant increase in the incidence of pertussis was found in adolescents in the age group 10–14 years in Taiwan. A similar phenomenon was observed in the USA, where the mean reported incidence of pertussis among persons aged 10–19 years increased by 106 % between 1990 and 1996 compared with data from 1990 to 1993 (Guris *et al.*, 1999). The data available on the duration of pertussis vaccine-induced immunity suggest that vaccinated adolescents and adults become susceptible to pertussis about 5–10 years after vaccination (He *et al.*, 1994; Jenkinson, 1988). For Taiwanese adults aged $\geqslant$15 years during the study period, no statistically significant upward trend was identified. This may be due to underreporting of pertussis cases in this age group. A significant amount of underreporting could occur, with the possibility of five to six times more cases than those reported. Underreporting of pertussis cases may be even higher for adolescents and adults than for young children (Edwards, 2005). Mild symptoms, such as a prolonged and non-distinctive cough, may be the only clinical features of pertussis in adolescents and adults, and these often go unrecognized, in part because clinicians continue to see pertussis as a childhood disease (Deeks *et al.*, 1999; Orenstein, 1999). Even when symptoms are typical of pertussis, the diagnosis is often not considered in adolescents and adults because of a low awareness of the existence of the disease in these age groups (Rothstein & Edwards, 2005). Following vaccination, the epidemiology of *B. pertussis* has changed such that adolescents and adults have replaced children as the main source of infection (Hewlett & Edwards, 2005). Hence the major source of infection for unimmunized infants may be the unrecognized older population, such as parents, siblings and healthcare workers (Baron *et al.*, 1998; Linnemann *et al.*, 1975). A recent serological study in Taiwan also suggested that an increase in the number of pertussis cases was attributable to an increase in the number of cases in older people with waning immunity (Hu *et al.*, 2006).

The highest mean number of reported pertussis cases was in August, which is a summer month in Taiwan with higher temperatures. However, upward trends were observed in February, March, October and November, when temperatures were lower. This phenomenon was similar to that in Cincinnati in the USA, where a seasonal predominance in July–September in epidemic years changed to October–December and January–March in the post-epidemic period (Bisgard *et al.*, 2001). It was assumed that the symptoms of pertussis were difficult to differentiate and confounded by the existence of other respiratory infections. Symptoms of pertussis experienced by adolescents and adults often include influenza-like symptoms (Rothstein & Edwards, 2005), and respiratory diseases such as those caused by chlamydia and influenza usually start in November and circulate in the winter in Taiwan (Hsieh *et al.*, 2005).

Currently, a pertussis booster for persons aged 6 years or older is not yet included in the routine vaccination programme in Taiwan. As immunity wanes after vaccination early in life, repeated vaccination has been proposed and the suggestion has been made that acellular pertussis vaccines be used for adolescents and adults (Halperin, 2005; Kuno-Sakai & Kimura, 2004). Several countries, such as Germany, France and Canada, now recommend the routine vaccination of adolescents with acellular pertussis vaccine boosters (Tan *et al.*, 2005). A study in Taiwan aimed at evaluating the immunogenicity and reactogenicity of a reduced-antigen-content diphtheria–tetanus–acellular pertussis (dTaP) vaccine has suggested that dTaP may be administered safely and effectively as a booster dose to children aged 6–8 years and adolescents/young adults aged 15–20 years who were previously primed with the DTP vaccine (Huang *et al.*, 2005).

In conclusion, to comprehend the true incidence of pertussis in adolescents and adults, active surveillance is needed in different areas of Taiwan, and in particular enhanced surveillance activities are needed for older age groups. New acellular pertussis vaccines may be licensed in Taiwan for use in older people in the future and these may provide protection to control the transmission of pertussis in adolescents and adults.

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