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ARTICLE

Recent findings on pertussis epidemiology in Turkey

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Abstract The World Health Organization (WHO) reports that pertussis remains one of the least well-controlled vaccine-preventable diseases. It is supposed that the incidence of reported pertussis among adolescents, adults, and young infants has increased over the past decade. The aim of this study is to evaluate recent epidemiological data on pertussis in Turkey by regions. Data on vaccination coverage and pertussis incidence between 1986 and 2005 obtained from the Expanded Programme on Immunization national surveillance database of the Ministry of Health of Turkey were analyzed. Age and geographical distribution of the reported cases between 2000 and 2005 were evaluated. It was found that third-dose vaccination coverage increased from 1986 (45%) to 2005 (90%). In 2005, pertussis incidence tended to decrease (0.38 per 100,000) compared to 1986 (2.03 per 100,000). Even though only up to 6.5% of the cases were ≥15 years of age until 2005, 16.9% of them were included in this age group in 2005. It was observed that vaccination coverage rates steadily increased and pertussis incidence decreased by years despite some regional differences. In Turkey, pertussis incidence appears to be reaching the WHO targets, except East Anatolia. It is possible that waning immunity is responsible for the change of the age distribution of pertussis cases. However, priority should be given to strengthening available vaccination efforts throughout the country. A booster dose of pertussis vaccine in adolescence might be required in the future.

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Background

Pertussis is caused by *Bordetella pertussis* and all age groups are susceptible to this respiratory infection. However, the consequences are more severe in young children and infants [1, 2]. In the prevaccine era pertussis epidemics followed a cyclic pattern, with peaks every 2–5 years. With the marked reduction of pertussis by vaccination, the same cyclic pattern still occurs. Studies of prolonged cough illnesses in adolescents and adults reveal that 13–20% are a result of *Bordetella pertussis* infection [3]. Vaccination is effective to prevent the disease. Although the precise time frame remains unresolved, immunity provided by whole cell vaccines appears to persist for at least 3–5 years and then to progressively decline approximately 10 years after vaccination [4]. The data on acellular vaccines suggest that protective immunity persists for >6 years after primary vaccination with three or four doses [5, 6].

The World Health Organization (WHO) initiated the Expanded Programme on Immunization (EPI) in 1974 to provide countries with guidance and support to improve vaccine delivery and to help make vaccines available for all children [7]. A standard immunization schedule was established in 1984 on the basis of a review of immunological data for the original EPI vaccines: bacille Calmette-Guérin (BCG), diphtheria-tetanus-pertussis (DTP), oral polio, and measles vaccines [8]. The Ministry of Health is the main provider of childhood vaccinations and DTP vaccine has been purchased from other countries by Turkey. After participation in the EPI of the WHO, immunization accelerated with Turkey's "National Vaccination Cam-

paign" in 1985. As a result of this campaign, DTP vaccination coverage increased from 20–30% to 83% in 2001, providing evidence for a decrease in pertussis incidence in Turkey, from 21 cases per 100,000 in 1970 to 0.27 per 100,000 in 2001 [9]. However, pertussis still affects all age groups, especially children less than 5 years of age in our country.

It is supposed that the incidence of reported pertussis among adolescents, adults, and young infants has increased over the past decade [3]. This is the first report of a nation-based study on pertussis epidemiology from our country; therefore, its aim is to evaluate recent epidemiological data on pertussis in Turkey by regions.

Material and method

Available data on vaccination coverage rates and pertussis incidence between 1986and 2005 were obtained from the EPI national stores of the Ministry of Health of Turkey. Age and geographical distribution of the reported cases between 2000 and 2005 and gender distribution of the cases for the last 2 years were also evaluated.

Vaccination coverage

Routine childhood immunization with DTP has been launched in Turkey since 1968. Pertussis vaccine is being administered in the 2nd, 3rd, and 4th months of life, in combination with a booster dose administered between the 16th and 24th months. If the booster is delayed, it can be administered afterwards to children if younger than 6 years old.

At the national level, province-specific (total 81) vaccination dose and target population determined based on actual or projected data from the most recent census are consecutively entered in a database (Excel). National estimates of coverage are calculated by weighting each province's coverage estimate according to the enrolled target population. Region-specific (total 7) third-dose DTP coverage rates for children 12 months of age are recalculated from these chart data.

Disease surveillance

Pertussis is most easily diagnosed in young children because they present with whooping cough. Infants often present with cough and apneic episodes. Adolescents and adults may be asymptomatic or present with a cough lasting several weeks. Although reporting of pertussis is obligatory, recognition of illness by physicians is hampered by the nonspecific symptoms in those age groups. Laboratory confirmation of pertussis infection is not as easy as that of many other infectious diseases. Growing in the culture media is considered the "gold standard" for laboratory diagnosis of pertussis. Most local laboratories are not well enough equipped to make the diagnosis of *Bordetella pertussis* infection. The preferred approach is polymerase chain reaction (PCR) testing and culture of the organism from a posterior nasopharyngeal specimen obtained using two separate Dacron swabs. Isolation of the organism is compromised by recent antibiotic therapy effective against pertussis (i.e., macrolide/azalide or trimethoprim-sulfamethoxazole), by delay in specimen collection beyond the first 2 weeks of illness, and in vaccinated persons [10, 11].

A negative culture does not exclude the diagnosis of pertussis [11]. Serology is the most common method for supporting a pertussis diagnosis, especially in the later stages of the infection, making it an important tool in our understanding of disease frequency and there are several studies on standardization [12, 13].

In Turkey, culture of the organism from a posterior nasopharyngeal specimen is available in most laboratories and used to confirm disease. Health care providers are obliged to report all suspected and confirmed cases and deaths due to pertussis to the Provincial Health Directorates, which in turn report to the Ministry of Health on a monthly basis. The Ministry of Health receives collected data clustered by these age groups: 0, 1–4, 5–9, 10–14, 15–24, 25–44, 45–64, and >65 years. Due to the small number of cases, data for cases over 15 years of age were gathered as one group.

Written permission to use the national surveillance database was received from the Ministry of Health of Turkey.

Statistical analysis

All data in Excel files were saved in Statistical Package for the Social Sciences (SPSS) 10.0 format. The Kolmogorov-Smirnov test was used to define normal distribution. Differences among vaccination coverage rates according to the regions and years were analyzed using Student's t and analysis of variance (ANOVA) tests. Two-sided significance tests were used and $p<0.05$ was accepted as the level of statistical significance.

Results

Vaccination coverage

After the National Vaccination Campaigns of the Ministry of Health in 1985, the third-dose DTP (DTP3) coverage rate rose to 80% for Turkey in general in 2000. In the following 5 years, coverage rates steadily increased, reaching 90% in 2005, except two drop points in 1995 and 2003, 67 and 68%, respectively (Fig. 1).

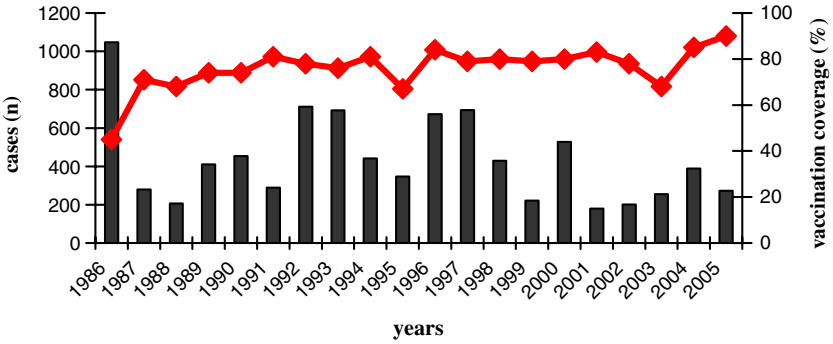

Fig. 1 Vaccination coverages among children <12 months of age (*red line*) and reported pertussis cases (*black bars*), Turkey, 1986–2005

In 2000, two regions (East and Southeast Anatolia) reported a pertussis vaccination coverage of <70%, three regions a coverage of 83−85%, and two regions a coverage of >90%. Coverage rates of East and Southeast Anatolia significantly increased in 2005 compared to 2000 (84 and 85%, respectively) ($p<0.05$, $p<0.05$). In 2005, reported coverage was not <80% in any region and was ≥90 in four regions (Fig. 2).

Pertussis cases

As shown in Fig. 1, the reported number of pertussis cases was 1,048 with vaccination coverage of 45% in 1986. Following this year, pertussis cases dramatically decreased.

Analyzing the last 6 years, it was found that pertussis incidence decreased from 2000 (0.78 per 100,000) to 2005 (0.38 per 100,000). Most of the cases were reported in 2000 ($n=528$) and nearly half (47.9%) of them from the East and Southeast regions. In 2005, pertussis cases decreased to 272, with 47.2% of them from these regions (Fig. 3).

Third-dose vaccination coverage rates and pertussis incidence by regions for 2005 are shown in Fig. 4 and Table 1.

We observed that most cases were <5 years of age for the last 6 years. Even though only up to 6.5% of pertussis cases were ≥15 years of age until 2005, 16.9% of the cases were in this age group in 2005 (Fig. 5).

According to available data of the last 2 years, it was observed that nearly half of the cases were boys (52.4% in 2004 and 53.4% in 2005).

Three children, <5 years of age, died due to pertussis: in 2003 ($n=1$), 2004 ($n=1$), and 2005 ($n=1$). The mortality rate was 0.01 per 100,000 for each year.

Discussion

Since 1974, thanks to the EPI of the WHO there had been significant decreases in the morbidity and mortality of the vaccine-preventable diseases (VPD) in developing countries [14]. Turkey, with 72 million people and an area of 780,000 km^2, is one of the largest countries in the European Region of the WHO. EPI vaccination goals included (1) eradication of poliomyelitis by the year 2000, (2) elimination of neonatal tetanus by the year 1995, (3) control of measles and hepatitis B, and (4) immunization of 90% of the world's children 1 year or younger by the year 2000 [15]. In Turkey, following the National Vaccination Campaigns of 1985, pertussis vaccination coverage has reached a level of about 80% among children and was

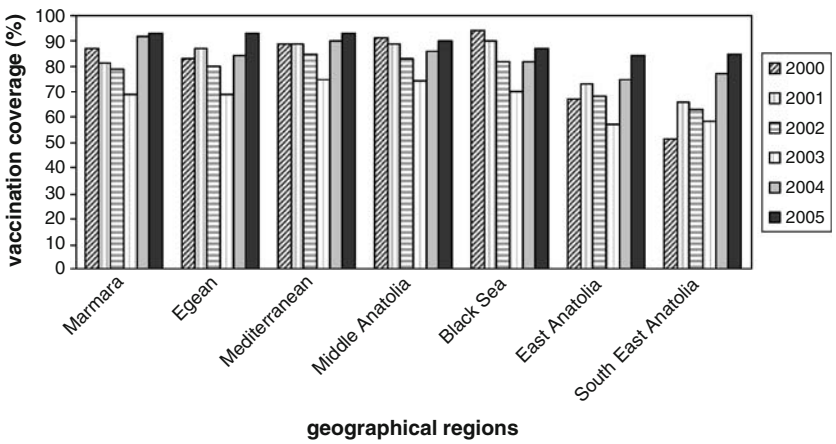

Fig. 2 Vaccination coverages with DTP3 by geographical regions, Turkey, 2000–2005

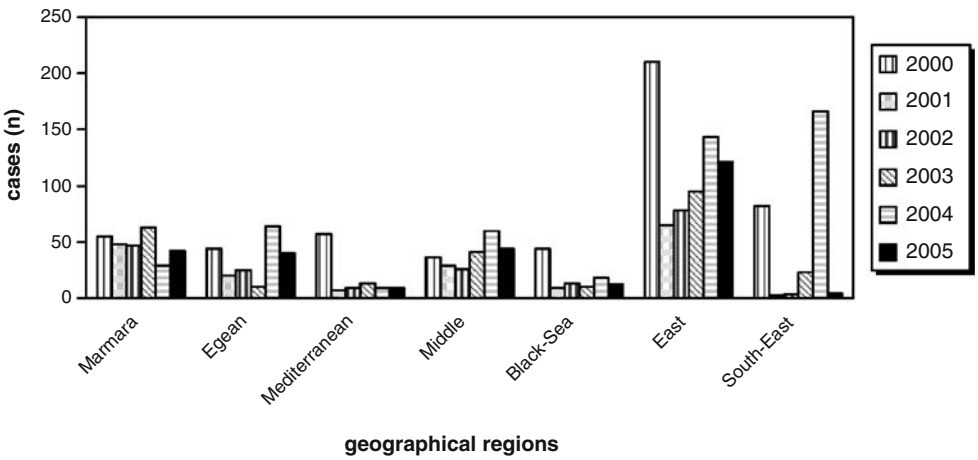

Fig. 3 Pertussis cases by geographical regions, Turkey, 2000–2005

maintained around this level for the following years with improvement in vaccination practices [16]. In the current study, available data on pertussis between 1986 and 2005 years were evaluated. It was observed that vaccination coverage rates nearly reached the EPI aims in 2005 despite some regional differences.

Pertussis occurs endemically with 2- to 5-year cycles of increased disease [3]. It is possible that a decrease in pertussis cases may be caused by the natural cycle. The number of reported pertussis cases was 1,048 in 1986 with a coverage rate of 45%. In 2005, the coverage rate increased to 90% while pertussis cases decreased to 272. We think that increasing coverage rates dramatically decreased the number of the cases. However, it was noticed that the number of cases increased in 1997 and 2004 despite increased coverage. This can be explained by low coverage rates in the previous years due to shortages in the national vaccine supply.

In the medical literature, there are many epidemiological studies on pertussis from different countries. In a study from Australia, Quinn et al. reported that Pertussis was well controlled in the 1–4 and 5–9 year age groups with the highest annual notification rates in infants less than 6 months of age. They determined that adolescents aged 10–19 years had high notification rates in all states and territories. Therefore, they thought that following the introduction of a fifth dose for adolescents, the current focus should be on protecting infants too young to be vaccinated and further defining the true morbidity of the disease in the elderly population [17].

In an epireview, Viney et al. observed that the highest rates of pertussis were consistently found in infants aged 0–6 months and adults. They reported that new strategies were needed to control pertussis in these age groups [18].

Cöplü et al. investigated the existence and the rate of pertussis infection in a village of Turkey. Their data of the

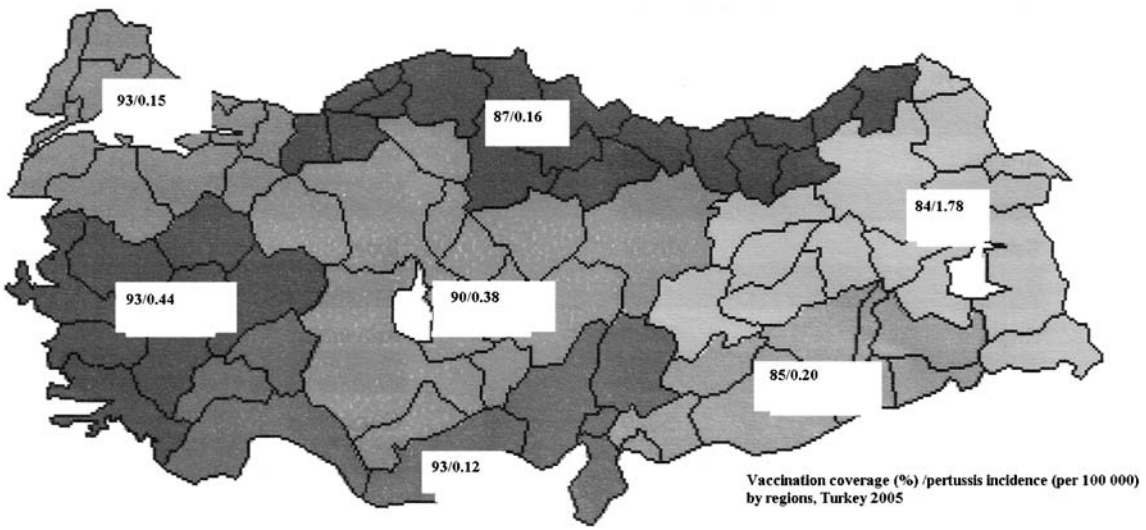

Fig. 4 Vaccination coverages (%) and pertussis incidence (per 100,000) by regions, Turkey, 2005

Table 1 Vaccination coverage rates and pertussis incidence by regions, Turkey, 2005

Regions	Coverage (%)	Pertussis cases (*n*)	Population (n)	Incidence per 100,000
1-Marmara	93	29	19,348,429	0.15
2-Egean	93	42	9,427,675	0.44
3-Mediterranean	93	12	9,884,437	0.12
4-Middle Anatolia	90	47	12,288,126	0.38
5-Black Sea	87	13	8,123,939	0.16
6-East Anatolia	84	114	6,404,473	1.78
7-Southeast Anatolia	85	15	7,492,222	0.20
Turkey (general)	~90	272	72,969,301	0.38

field survey indicated a possible pertussis outbreak in this region [19].

Esen et al. detected anti-pertussis toxin antibody in serum samples from 2,085 healthy subjects ranging in age from 6 months to > or = 60 years. They found that up to half of the expectant mothers lacked a sufficient level of estimated antibody titers. They reported that to protect infants from life-threatening pertussis infection, improving vaccination coverage to ensure herd immunity and uniformly establishing coverage throughout the country and revaccination with acellular vaccine for schoolchildren as well as for the households of pregnant women was necessary [20].

Aksakal et al. investigated the incidence of pertussis among schoolchildren 6–14 years old with prolonged cough in a province of Turkey. They found that pertussis was evident among older children and adolescents in Turkey and recommended booster vaccinations beyond childhood [16].

In another study from Turkey, the authors investigated vaccination coverage in the Southeast Anatolia region between 2001 and 2002. They observed that only 30% of children had received a complete set of vaccines and the vaccination coverage was 62.0% for DTP3 in children aged 12−23 months [21]. In our study, it was observed that DTP3 vaccination coverage rates of East and Southeast Anatolia were <70% in 2000. However, in 2005, these rates significantly rose to >80% with effective and successful vaccination strategies of the Ministry of Health.

The WHO recommended that a pertussis incidence of <1 case per 100,000 population be achieved in Europe by 2000. The incidence of reported pertussis has increased steadily in the USA and many other countries [22]. In 2005, a total of 25,616 cases of pertussis were reported in the USA [23]. According to available data, we did not observe an increase in pertussis incidence in Turkey in the past 20 years. In 1986, >1,000 pertussis cases were reported and this number decreased to 272 in 2005, after the EPI. In this millennium, Turkey appears to be reaching the WHO target with a pertussis incidence of <1 case per 100,000, except East Anatolia.

Immunity against pertussis begins to decline approximately 10 years after vaccination, causing adolescent and adult susceptibility [24]. Tan et al. reported that there was a general shift in age distribution of pertussis towards older groups [22]. In another study de Melker et al. reported that *Bordetella pertussis* circulated even in highly vaccinated populations and mathematical modeling could explore what booster vaccination strategies are most effective in reducing severe disease among not (completely) vaccinated infants. [25]. In this study, we noticed that adolescent cases have been increasingly reported since 2004. However, future studies are needed to determine whether this strategy is cost-effective and will reduce pertussis-related morbidity and mortality in our country.

It had been reported that *Bordetella pertussis* was more frequently isolated in female patients, which is in contrast to most other febrile diseases [26]. In a study from Iraq, 133 pertussis cases were studied during an outbreak in Basra from June to December 1996 and it was observed that most of them were females [27]. However, in Dominguez et al.'s study the authors did not find a statistically significant difference between pertussis cases for gender [28]. In Turkey, gender data of pertussis cases have been reported since 2004 and the gender distribution seems to be equal.

Vaccination against pertussis has resulted in reduction of the infection pressure of *Bordetella pertussis* (partial herd immunity), but the circulation of *Bordetella pertussis* has

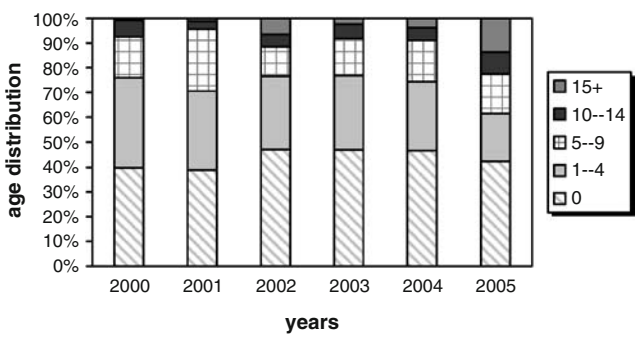

Fig. 5 Pertussis cases by age groups, Turkey, 2000–2005

persisted as a consequence of waning of vaccine-induced and naturally acquired immunity. An increase in the reported incidence of *Bordetella pertussis* infection in older children, adolescents, and young adults has been noted, resulting in a perceived resurgence of the disease in these age groups. [29]. Neonates are susceptible to pertussis infection because they have not yet been immunized and they receive little passive immunity from their susceptible mothers. Tanaka et al. reported that there has been an increase in the number of the cases and deaths reported among infants <4 months of age [30]. Young infants have the greatest risk of secondary bacterial pneumonia, the most common cause of pertussis-related deaths [31]. Moreover, the number of infant deaths due to pertussis may be underreported because of misdiagnosis of pertussis as other respiratory illnesses or sudden infant death syndrome. In the present study, most pertussis cases were <5 years of age and three of them died due to pertussis.

In the majority of countries where pertussis is a notifiable disease, a case-based national surveillance system is in place. Nevertheless, the general consensus is that reported incidences are probably considerably lower than the actual incidence of pertussis [25].

Underrecognition, underreporting, and misdiagnosis are widespread, and these are particular problems with adolescent and adult disease. As laboratory diagnosis of pertussis has improved over the past two decades, it has become possible to maintain more accurate data on pertussis in adults who present without classic symptoms and signs [32]. However, intercountry comparisons and global evaluations are difficult to perform, because countries use different pertussis disease case definitions, diagnostic techniques, surveillance methods, and reporting regulations [33–35]. In Turkey, the surveillance system for pertussis was renewed by the Ministry of Health, using the definitions of both clinically suspected and laboratory confirmed cases established in the "Guideline for Standardized Diagnosis, Surveillance and Laboratory 2004" in 2004. According to this guideline, the definition of a "clinically suspected case" included cough lasting longer than 2 weeks together with at least one of the following symptoms: paroxysms of cough, inspiratory "whooping," and post-tussive vomiting without other apparent cause. The description of a "confirmed case" included culture of the organism from a nasopharyngeal specimen and/or a contact history with a confirmed case. In our country reporting of all suspected and confirmed cases is obligatory. According to the surveillance database of the Ministry of Health, 200 clinically suspected cases and 72 laboratory confirmed cases were reported in 2005. It is possible that to use the culture method for case definition may lead to severe underdiagnosis and hamper reliable epidemiology. Currently, the culture method is being used to maintain the standard case definition, because serologic and PCR tests are not available in most local laboratories in Turkey.

High vaccination coverage is important in control and elimination of VPD in a country. Sociodemographic and socioeconomic factors can be important determining factors for vaccination coverage rates.

There are effective practice-based strategies for improving childhood vaccination coverage and reducing pertussis incidence. Three strategies were recommended by the European participants in the Global Pertussis Initiative that might be adapted to each country's specific needs. They are the reinforcement of implementation of current schedules, the addition of an extra dose of vaccine to current immunization schedules, and the selective immunization of health care workers, which is already included in a European Commission directive. Wirsing et al. reported that the main barriers to the acceptance of these strategies are low awareness of pertussis in immunized populations, poor recognition of the disease in adults and adolescents, lack of standardized diagnostic criteria, and poor access to laboratory confirmation of the diagnosis. They noted that actions to overcome these issues were crucial to the implementation of new or improved immunization strategies to combat pertussis in Europe [36]. Mooi and de Greff also reported that maternal vaccination might be an effective way to decrease morbidity and mortality caused by pertussis in newborn babies [37].

In summary, the findings of this study indicate that pertussis incidence in Turkey appears to be reaching the WHO targets, except in the East region. It is possible that waning immunity is responsible for the change of the age distribution of pertussis cases. However, priority should be given to strengthening available vaccination efforts throughout the country. A booster dose of pertussis vaccine in adolescence might be required in the future.

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