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Estimated and reported incidence of pertussis in Estonian adults: A seroepidemiological study

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ABSTRACT

Objectives: Rates of pertussis immunisation among children in Estonia are high (~95%), but pertussis is still the most common vaccine preventable childhood disease. Adults are suspected to be sources of pertussis in children. We aimed to measure pertussis toxin (PT) IgG in adults to estimate pertussis infection activity and compare estimated and reported pertussis incidences.

Methods: In a cross-sectional serosurvey, consecutive leftover blood sera ($n = 3327$) from subjects aged 20–99 years old were collected at Quattromed HTI laboratories between the 7th January and 27th February 2013. Anti-PT IgG concentration was measured by ELISA (Euroimmun, Lübeck, Germany). Estimated annual pertussis incidence was calculated for 10-year age classes using de Melker et al. (2006. J Infect. 53(2):106–13) formula.

Results: The mean number of samples in each 10-year age class was 466 (SD 20.5), except for 90–99 year olds which contained 65 samples.

More than half of all subjects (58.1%) had anti-PT IgG <5.0 IU/mL, 2.7% had 62.5 to <125 IU/mL and 0.6% ≥125 IU/mL; no differences occurred between 10-year age classes.

Estimated incidence of pertussis infection was 5.8% (95% CI 4.8–7.0) in 2012, with peaks observed in 20–29 year olds (11.0%; 95% CI 7.4–15.6) and 90–99 year olds (10.8%; 95% CI 3.0–26.2). Estimated pertussis incidence rate was 915 times higher than reported.

Of 80 subjects with anti-PT IgG ≥62.5 IU/mL, 25 (31.3%) had complained of coughing to their GP during the previous six months.

Conclusion: The frequency of pertussis infection was similar for all ages, suggesting similar *Bordetella pertussis* activity in adults and children. The wide gap between reported and estimated incidence indicates poor recognition of pertussis, likely owing to it being an asymptomatic or mild disease.

1. Introduction

Accumulating evidence indicates pertussis disease can occur at any age and is not solely a childhood disease [1]. Despite effective immunisation of children, recent increased rates of pertussis disease in many countries worldwide have been associated with circulation of *Bordetella pertussis* [2]. Diagnosis of pertussis disease in childhood was straight forward in the pre-vaccine era, owing to pertussis' classical symptoms [3]. After 60 years of vaccinations the symptoms of pertussis in adults are largely unclear and poorly described [4]. Pertussis in adults is suggested to be mostly mild or results in asymptomatic carriage of *B. pertussis* [5]. Adults are important reservoirs for transmission of pertussis to unvaccinated or partly immunised infants and children [6]. Epidemiological studies that measure specific antibodies are crucial in understanding the spread of pertussis infection among the general population. IgG type pertussis toxin (PT) antibodies should be measured, as they are specific to pertussis and do not interact with other microorganisms [7]. It has also been demonstrated that an increase of anti-PT IgG occurs either after pertussis disease/infection or immunisation, but protective levels are still not defined [8,9]. Therefore we believe that anti-PT antibodies could be reliably used in a seroepidemiological study in adults, as immunisation of adults is extremely rare in Estonia and elsewhere.

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Rates of reported pertussis infection in previous studies ranged from 2.5% to 19% [10–18]. Most importantly, all studies including the one conducted by us in Estonian children demonstrated a significant underreporting of *B. pertussis* infection when seroepidemiological data was compared with nationally reported incidence of the disease [18]. Most previous reports have included children or adolescents [10–12,14,15]. Studies involving adults – especially the elderly – are rare despite decreased immunity in the elderly. Considering the unspecific clinical course and low awareness of pertussis in adults, it is likely that underreporting is more pronounced than for children [19]. We are not aware of any seroepidemiological studies on pertussis in the former Soviet Union, where immunisation schedule and vaccine types were often different of that elsewhere [20].

We aimed to describe the incidence of pertussis infection in Estonian adults ≥20 years old by measuring PT IgG type antibodies, and compare estimated incidence of infection with the official national figures.

2. Methods

2.1. Study population and design

First, a cross-sectional seroepidemiological study was conducted from 7th January to 27th February 2013, where all consecutive leftover sera from subjects aged 20–99 years old were stored at Quattromed HTI laboratories (the largest private medical laboratory in Estonia). Sera from patients with suspected pertussis were not included. The only information available was a subject's age and gender. Next, persons with anti-PT IgG ≥62.5 IU/mL were identified. These subjects' general practitioners (GPs) were contacted and asked whether their patient(s) had complained of coughing during the previous six months.

The official number of pertussis cases, diagnosis information and pertussis immunisation history and rates were obtained from the databases of the Health Board of Estonia (www.terviseamet.ee). The size of the general population was obtained from the databases of Statistics Estonia (http://pub.stat.ee/px-web.2001/Database/Rahvastik/01Rahvastikunaitajad_ja_koosseis/04Rahvaarv_ja_rahvastiku_koosseis/04Rahvaarv_ja_rahvastiku_koosseis.asp).

2.2. Measurement of IgG antibodies

All samples were analysed within 48 h of collection. Anti-PT IgG concentrations were measured using a commercial ELISA kit (Euroimmun, Lübeck, Germany), according to the manufacturer's protocol at Quattromed HTI laboratories, Estonia. The sensitivity and specificity of the assay were 100% and 95.5%, respectively. The anti-*B. pertussis* toxin IgG ELISA calibration curve was linear between 5 and 174 IU/mL.

2.3. Statistics

Statistical analyses were performed using Microsoft Excel 2013 and Stata 12.1 (last accessed 15.12.2014).

As epidemiological data on pertussis prevalence (including seroprevalence) were not available for Estonia, we hypothesised a prevalence of 40% to ensure a large enough cohort. To calculate pertussis prevalence in eight 10-year age classes – with 95% confidence intervals (CIs) and an accuracy of ±5% – the required number of unique blood sera for each 10-year age class was calculated to be ≥369.

To compare the subjects with anti-PT IgG ≥62.5 IU/mL who had complained of a cough to their GP we used 20-year classes to ensure a large enough subjects in each age class.

Anti-PT IgG antibodies were presented as geometric mean concentrations (GMCs) with 95% CIs. To calculate GMC for antibody levels below and above the cut-off value, fixed numbers of 2.5 IU/mL and 175 IU/mL, respectively were assigned. Anti-PT IgG values as described in other studies were used for data interpretation: ≥125 IU/mL (very high) indicates recent (in last 6 month) or active pertussis infection; 62.5 to <125 IU/mL (high) suggests pertussis infection during the previous year; <62.5 IU/mL suggests exposure to pertussis infection/immunisation >12 months previously or never exposed/immunised [18]. The prevalence of different anti-PT IgG values in age classes were compared using chi-squared test or Fisher's test (if assumptions for chi-squared test were not met). Adjustments for potential inter-correlations were made using the Holm–Bonferroni method.

Age-standardised seroprevalence was calculated for the following cut-off values: 50 IU/mL; 62.5 IU/mL; 75 IU/mL; 100 IU/ml; 125 IU/mL. Direct age-standardisation of anti-PT IgG prevalence was calculated using the standard Scandinavian ("European") population age structure (http://www.who.int/healthinfo/paper31.pdf).

To calculate estimated pertussis incidence, a cut-off level of 62.5 IU/mL – as suggested in previous studies [10,12] – was chosen. The average time for high anti-PT IgG after infection to decrease to 62.5 IU/mL was expected to be 208.9 days (95% Cl 195.4–223.3) [10]. Estimated annual pertussis incidence was calculated using de Melker et al.'s [10] formula: 365.25/208.9 × the percentage of the population sera containing anti-PT IgG ≥62.5 IU/mL. Estimated incidence rates were compared using a chi-squared test. Adjustments for potential inter-correlations were made using the Holm–Bonferroni method.

3. Ethics

This study was approved by the Ethics Committee of Tartu University. Informed consent was not required as all sera were collected and analysed anonymously. Additional approval of the Ethics Committee of Tartu University was obtained for the GP-s to inform us about coughing episodes of the coded patients with anti-PT IgG ≥62.5 IU/mL.

4. Results

4.1. Epidemiology of pertussis

According to the Health Board of Estonia during the last 25 years, the epidemic curve of reported pertussis incidence among ≤19 and ≥20 year olds were similar. From 1994 to 2003, the average annual reported incidence of pertussis in ≥20 year olds was 3/100,000, but an increase to 12/100,000 with a peak of 41/100,000 in 2010 was observed during 2004–2013 (data in file of the Health Board of Estonia) (Fig. 1). From 2011 onwards the epidemic cycle again stabilised at low levels. Of all reported pertussis cases, about 40–50% were diagnosed in 20–59 year olds and only 2–3% occurred in those ≥60 years old (data in file of the Health Board of Estonia).

5. Immunisation and rates

Routine childhood immunisation using a whole cell pertussis vaccine combined with diphtheria and tetanus toxoids (DTPw) produced in the Research Institutes of Moscow was introduced in 1957 [20,21]. An adsorbed DTPw vaccine (produced in the Odessa I.I.Mechnikov National University) was used from 1966 and switched to TetrACT-HIB™ in 1992 [20]. From 2008, a combined diphtheria-tetanus-acellular pertussis vaccine (DTPa) with two or three pertussis antigens (Infanrix polio/Infanrix-IPV + HIB