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PERTUSSIS INCIDENCE AMONG ADOLESCENTS AND ADULTS SURVEYED IN GENERAL PRACTICES IN THE PARIS AREA, FRANCE, MAY 2008 TO MARCH 2009

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Since the introduction in 1998 of an adolescent pertussis vaccine booster (for persons aged 11–13 years) in France, the incidence of pertussis in adolescents and adults has been unknown. We therefore undertook a study to estimate the incidence of pertussis in these population groups and to evaluate the feasibility of a real-time electronic surveillance system for pertussis in general practices in France. The general practitioners selected for the study were located in Paris and the surrounding area. Polymerase chain reaction (PCR) or measurement of anti-pertussis toxin IgG levels by enzyme-linked immunosorbent assay (ELISA) was used to confirm the infection. Among the 204 patients enrolled in the study, 46 (23%) were diagnosed as having pertussis: 21 were confirmed cases, 24 were clinical cases and one was an epidemiological case. The median age of the 204 patients was 44 years and 134 (66%) were female. The median duration of the patients' cough at enrolment was 24 days. No clinical difference was observed between those with and without a pertussis

diagnosis. The incidence of pertussis was estimated to be 145 (95% confidence interval: 121–168) per 100,000 population based on the results from the 10-month study period (calculated for 12 months). Problems in sample collection were identified: pertussis sentinel surveillance cannot be developed without training the staff of medical laboratories who take the biological samples. French health authorities were alerted and training procedures were developed.

Introduction

Bordetella pertussis remains in fifth place among the leading aetiologies of vaccine-preventable deaths in children around the world. The majority of hospitalisations, complications and deaths due to pertussis occurs in infants who are too young to have been fully vaccinated, predominantly those younger than two months of age [1,2].

In France, a paediatric hospital-based surveillance network (RENACOQ) was set up in 1996 to monitor the occurrence of pertussis among hospitalised infants and the age of the people who were the source of their infection. The national incidence rate of pertussis in infants younger than three months of age between April 1996 to December 2007 was estimated to be 257 per 100,000 population (95% confidence interval (CI): 213–300 per 100,000 population), with the incidence rate varying from 476 (95% CI: 418–535) per 100,000 population in 2000 to 117 (95% CI: 88–147) per 100,000 population in 2003 and 2007 [2]. Among pertussis cases who were aged younger than six months old and where contact with a pertussis case had been identified, the mean age of the persons who were the source of their infection increased from 19.6 years in 1996 to 31.9 years in 2007 [3]. Data on incidence of the disease in adolescents and adults are limited, as in 1986, pertussis was no longer a notifiable disease in France. The last study using the results of biological sampling to evaluate the incidence of the disease in adults, in those aged over 18 years, was carried out in 1999 in the Paris area, reporting an annual incidence rate of 866 (95% CI: 601–1,199) per 100,000 population [4]. Since then, it has been shown that adults are generally the source of infection of infants who are hospitalised with pertussis [3]. In addition, *B. pertussis* has been shown to be an important cause of nosocomial infection in different hospital services, including neonatal and maternity units [5,6].

Pertussis acellular vaccines were introduced in many developed countries more than 10 years ago, to replace whole-cell vaccines. The acellular vaccines are safer in that they cause substantially fewer side effects [7]. Thirty years after the introduction of pertussis vaccination for infants and young children, transmission of *B. pertussis* is still observed in France [3]. For this reason, an adolescent vaccine booster was introduced in 1998, for those aged 11–13 years and a cocooning strategy was implemented in 2004. This strategy aims to protect newborn infants from becoming infected with *B. pertussis* by administering pertussis booster vaccines to mothers, family members and other contacts of newborn infants, young adults, people who are planning to have children, and childcare and healthcare workers. In this way, mothers, other family members and contacts are protected from getting pertussis and passing *B. pertussis* on to the young infants. In 2008, a further vaccine booster was introduced (in parallel with the cocooning strategy), for adults who had not received a vaccine booster in the previous 10 years [8–10].

Given the lack of data on pertussis incidence in adolescents and adults, we carried out a pilot, prospective study to determine the incidence of the disease in these population groups and to evaluate the feasibility of adding pertussis to the health indicators currently surveyed by the French Sentinelles Network. This network comprises 1,294 volunteer general practitioners (GPs) located throughout France who participate in the ongoing surveillance of 10 health indicators and in *ad hoc* epidemiological studies [11]. GPs have individual access to a web-based platform, to declare the health indicators: seven infectious diseases (influenza-like illness, acute diarrhoea, mumps, varicella zoster virus infection, herpes zoster, male urethritis and Lyme disease), as well as three non-infectious conditions (asthma, suicide attempts and any-cause hospitalisations).

Methods

From May 2008 to March 2009, we carried out a survey of selected general practitioners (GPs) belonging to the French Sentinelles Network. As this was a pilot study, we involved only GPs in the Network who were located in Paris and surrounding areas. The 129 GPs located in this area were invited to participate in this study: of those who accepted (n=69), 44 were selected, in order to be representative of the GPs in the Paris area (according to the GP's sex, age and volume of activity in general practice). An independent ethics committee revised and authorised the study protocol. The survey was anonymous and all patients were informed by their GPs about the nature of the study. All enrolled patients agreed to give a biological sample.

An electronic form was specifically created in which GPs could enter data of pertussis patients. The GPs were asked to report patients with clinical suspicion of pertussis, as they do for the other health indicators. They were asked to: (i) include in the study all patients older than 13 years with a newly occurred cough that persisted more than seven days and with at least one specific sign of pertussis (whooping, paroxysmal cough, vomiting, increased coughing at night); (ii) record on the electronic form the patients' clinical data (age, date of onset of the cough, clinical symptoms, date of last pertussis vaccination or disease history, knowledge of close contact with a pertussis confirmed case, contact with a pet with respiratory symptoms or conjunctivitis (because of possible infection due to *B. bronchiseptica* [11]), whether the patient had asthma, and whether antibiotics were prescribed; (iii) send the patients to a laboratory to have a nasopharyngeal aspirate (NPA) taken if the cough lasted less than 21 days or a blood sample taken if the cough lasted 21 days or longer; and (iv) establish and record on the form their final diagnosis (after having received the laboratory results). If GPs did not enrol any patients, they were contacted regularly by telephone or email to find out why.

Samples were analysed at the Institut Pasteur in Paris, by real-time polymerase chain reaction (PCR) [12] or by measurement of anti-pertussis toxin (PT) IgG by enzyme-linked immunosorbent assay (ELISA) [12]. The minimum level of anti-PT IgG detection was 4 international units (IU)/mL. Infection with *B. pertussis* was confirmed if the PCR was positive or the anti-PT IgG titre was ≥ 100 IU/mL. Titres of anti-PT IgG of between 25 and 100 IU/mL were considered as intermediate. In such cases, GPs were asked to contact the patient in order for a second blood sample to be taken.

Case definition

A confirmed case was defined as a patient with at least one specific sign of pertussis (whooping, paroxysmal cough,

vomiting, increased coughing at night), whose *B. pertussis* infection was confirmed by either PCR or ELISA.

A clinical case was defined as a patient with at least one specific sign of pertussis (whooping, paroxysmal cough, vomiting, increased coughing at night) whose disease was diagnosed clinically by a GP, without laboratory confirmation of *B. pertussis* infection.

An epidemiological case was a patient with at least one specific sign of pertussis (whooping, paroxysmal cough, vomiting, increased coughing at night), without laboratory confirmation of *B. pertussis* infection, but the person had had close contact with a confirmed case in the previous three weeks.

Data analysis

Electronic forms were filled in by the GPs in real time in their personal web-based platform. We monitored these weekly, in order to survey the data entry and match the GPs' data with test results from the Institut Pasteur (to obtain the number of recruited patients, number of samples received and final diagnosis reported by GPs). All the data collected electronically constituted the patient database, which was used for statistical analysis.

Pertussis incidence of the enrolled patients was estimated according to the method of the Sentinelles Network, i.e. multiplying the mean number of cases per participating GP by the total number of GPs in Paris area and then dividing the result by the number of people older than 13 years in the Paris area (9,170,000, according to the national census data of 2007) [13]. As the study was performed during 10 months, the incidence was multiplied by 12 and divided by 10, to obtain a 12-month incidence. To calculate the 95% CI, it was assumed that the number of reported cases followed a Poisson distribution.

Data analyses were performed using the statistical package R, and all statistical analyses were conducted at the 5% level of significance.

Results

Characteristics of the general practitioners in the study

The participating GPs (n=44) had a mean age of 55 years and were mainly men (n=38). Of the participating GPs, 34 enrolled 230 eligible patients while 10 did not enrol any patients. No difference was found between those who enrolled patients and those who did not (by age, sex, years of experience and number of patients seen per year), except in their pertussis vaccination practices. Eight of the 10 GPs who did not recruit patients were following the recommended cocooning strategy, so their patients targeted by the cocooning strategy and in accordance with French guidelines were systematically vaccinated against pertussis.

Sampling results and diagnoses of enrolled patients

A biological sample was obtained for 204 (88.7%) of the 230 enrolled patients but was missing for 26 (11.3%) patients, for the following reasons: 22 patients never went to the laboratory, three samples were lost during the transport between the

laboratory and the Institut Pasteur and a sample was not taken for one patient as NPAs were not standard practice in the laboratory.

The ELISA or PCR results were negative for 127 (62.2%) patients, intermediate for 19 (9.3%), and positive for 22 (10.8%) (Table 1). The results for 36 patients (17.6%) were not interpretable as serological tests were carried out by mistake for patients who had been coughing for less than 15 days ($n=6$) or because NPAs were incorrectly sampled ($n=30$).

Table 1. Test results and diagnoses of enrolled patients, Paris area, France, May 2008–March 2009 ($n=204$)

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Test results and diagnoses of enrolled patients, Paris area, France, May 2008–March 2009 ($n=204$)

Test result	All patients ($n=204$)	Laboratory confirmed ($n=22$)	Clinically diagnosed ($n=23$)	Epidemiologically diagnosed ($n=1$)	Total ($n=46$)
ELISA					
Negative	127	0	0	0	127
Intermediate	19	0	0	0	19
Positive	22	22	0	0	22
PCR					
Negative	107	0	0	0	107
Intermediate	19	0	0	0	19
Positive	22	22	0	0	22
Not interpretable	36	0	0	0	36
Total	204	22	23	1	46

ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; NPAs, nasopharyngeal aspirates.

A final diagnosis was made by GPs based on the laboratory results and the clinical characteristics of each patient. A total of 46 (22.5%) of the 204 enrolled patients were diagnosed as pertussis cases: 22 were laboratory confirmed, 23 were clinically diagnosed and one was epidemiologically diagnosed (Table 1).

Characteristics of enrolled patients

Characteristics of the patients enrolled in the study with or without a pertussis diagnosis are compared in Table 2.

Table 2. Characteristics of enrolled patients from whom suitable samples were obtained, Paris area, France, May 2008–March 2009 ($n=204$)

Table 2

Characteristics of enrolled patients from whom suitable samples were obtained, Paris area, France, May 2008–March 2009 ($n=204$)

Characteristic	Patients without pertussis diagnosis ($n=158$)	Patients with pertussis diagnosis ($n=46$)	P-value
Median age	44 (range 14–89)	44 (range 14–89)	0.93
Female	97 (61.4%)	22 (47.8%)	0.07
Male	61 (38.6%)	24 (52.2%)	
Median duration of cough	13 days	19 days	0.001
History of whooping cough in history	1 (0.6%)	1 (2.2%)	0.50
Whooping cough	10 (6.3%)	10 (21.7%)	0.001
Whooping	10 (6.3%)	10 (21.7%)	0.001
Paroxysmal coughing at night	10 (6.3%)	10 (21.7%)	0.001
Apnea < 1 min	0 (0.0%)	0 (0.0%)	0.99
Cough with a wet sputum	10 (6.3%)	10 (21.7%)	0.001
Cough with a wet sputum > 10 days	10 (6.3%)	10 (21.7%)	0.001
Diagnosis by epidemiological surveillance	0 (0.0%)	1 (2.2%)	0.001
Diagnosis by laboratory surveillance	0 (0.0%)	22 (47.8%)	0.001
Diagnosis by clinical surveillance	0 (0.0%)	23 (49.1%)	0.001
Total	158	46	

ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction; NPAs, nasopharyngeal aspirates.

The median age of patients enrolled in the study ($n=204$) was 44 years (range: 14–89 years) and the majority were female

(66%). The median duration of the patients' cough at enrolment was 24 days, 18 (9%) patients had asthma and 16 (8%) had already had pertussis in infancy. Pertussis vaccination status was reported for 27 patients but was documented for only 12 (in the patient's vaccination booklet). Among those 12, three patients had been vaccinated in the last five years: these patients were diagnosed as not having pertussis by their GP.

The frequency of clinical symptoms (such as vomiting, increasing coughing at night, paroxysmal cough, fever) observed in patients with a diagnosis of pertussis (n=46) was similar to that observed in those who were not diagnosed as having pertussis (n=158).

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Estimated incidence of pertussis among enrolled patients

On the basis of the study data, we estimated that in the Paris area, 723 patients (95% CI: 678–785) per 100,000 population during the study period (calculated for 12 months) would meet the inclusion criteria, giving an incidence of all pertussis cases of 145 (95% CI: 121–168) per 100,000 population (Table 3). The estimated incidence of clinical, confirmed and epidemiological cases is also shown.

Table 3. Estimated incidence of pertussis based on data on enrolled patients, Paris area, France, May 2008–March 2009^a

Table 3
Estimated incidence of pertussis based on data on enrolled patients, Paris area, France, May 2008–March 2009^a

Case definition	Number of patients	Estimated incidence per 100,000 population (95% CI)
All patients meeting the inclusion criteria	723	723 (678–785)
All patients meeting the inclusion criteria and from whom a sample was obtained	546	546 (501–591)
Clinical cases		
All patients with a clinical diagnosis	46	46 (31–61)
Confirmed cases	11	11 (5–17)
Epidemiological cases	11	11 (5–17)
Non-interpretable cases	1	1 (0–2)

^aThe incidence estimates are for a 12-month period on the 12-month study period.

Feasibility of pertussis surveillance

Problems in sample collection were identified: (i) no sample was available for 26 patients (11.3%); (ii) some medical laboratories (n=30), which routinely collect samples, did not know how to collect an NPA. As a result, for 30 patients (14.7%), NPA samples were replaced by expectorations, or saliva or nasal swabs, for which the PCR results were non-interpretable; (iii) some GPs (n=8) arranged for measurement of anti-PT IgG levels too soon after the beginning of the patient's cough. Thus for eight patients, intermediate IgG results were obtained (levels between >25 and <100 IU/mL), which did not allow to a definitive diagnosis to be made. When the patients were asked later for a second blood sample, they did not go to the laboratory.

Discussion

Our study indicates that pertussis is still present among adolescents and adults with a persistent cough in the Paris area, despite the cocooning strategy having been recommended in France since 2004 and the adult booster since 2008 [9,10]. The estimated incidence was lower than that described in 1999 for the same area [4]: 145 cases versus 866 cases per 100,000 population, respectively. This decrease was also observed in a French national observational study conducted in 2006 among people older than 16 years, where the incidence of pertussis was estimated to be 110 cases per 100,000 inhabitants per year [14]. A reduction in the number of pertussis cases was also reported by RENACOQ (the paediatric hospital-based surveillance network) in children below 16 years of age: in 2000, 467 laboratory-confirmed cases were reported, whereas in 2008, there were 138 cases. These observations of hospital-based surveillance indicate that pertussis has a cyclic variation in France (with the number of cases up in 2000 and down in 2008). But it is very difficult to ascertain whether this decrease is attributable to the pertussis cycle or whether it could also be due to the introduction of the adolescent booster (for those aged 11 to 13 years) since 1998 [3]. Surveillance in the coming years will help us to clarify this point. Patients were included in our study if older than 13 years: only four were less than 18 years old and were diagnosed as not having pertussis, suggesting that adolescents are probably more immune than adults.

Countries' case definitions, vaccination strategy and coverage, and surveillance systems differ, making incidence comparisons difficult [15-17]. In our study, 23% of enrolled patients from whom suitable samples were obtained were diagnosed by their GP as having pertussis. The incidence of pertussis in our study population could have been underestimated due to a number of unexpected problems that occurred during sample collection. A surveillance programme, as a part of Sentinelles Network, for pertussis in France will not be possible without training staff in medical laboratories on how to collect NPAs. Consequently, a letter describing the required procedures was sent by the Pasteur Institut to all French medical laboratories. In January 2010, a video demonstrating the procedures was posted on the website of the National Centre of Reference located at the Institut Pasteur, to help to train laboratory staff [18].

The epidemiology of pertussis in adolescents and adults is not well defined because of the broad spectrum of clinical manifestations. In our study, no clinical differences were observed between patients with and without a pertussis diagnosis. It has previously been reported that most (80%) adolescents and adults with pertussis had a cough that lasted more than 21 days and that many were still coughing at 90 days [19]. In our study, patients were not followed to record the number of days that they continued coughing after their visit to the GP, but three confirmed cases had been coughing for more than 40 days when they were enrolled in the study.

The gold standard treatment in French pertussis guidelines [21] is macrolides; however, in our study only 40% of the cases prescribed antibiotics received a prescription for a macrolide. Further medical education in antibiotic therapy is therefore needed.

Some limitations must be considered when interpreting the results of this study. There may have been selection bias because GPs who participated in this study might be more concerned about pertussis than non-responders and their practices might, therefore, differ. Some GPs (n=10) in the study were surveying their patients for pertussis, but did not enrol any patients with a cough. The principal reason given by these GPs for this was that they usually vaccinated all their patients against pertussis (according to the cocooning strategy and French guidelines), thus the chances of them seeing

patients with pertussis in their practices were reduced. Eight of the 10 GPs who did not enrol any patients were following the recommended cocooning strategy. Similarly, the patients enrolled in the study may not be representative of the general population in the area. In addition, women were overrepresented in the study. The overrepresentation of women is often observed in studies conducted in general practices, probably because women visit their physician sooner than men [22].

Taking into account that there are 9,170,000 people older than 13 years in the Paris area, and that the incidence of pertussis is probably underestimated in this area because of the problems identified in this study, it is important to establish robust sentinel surveillance. In order to allow comparison of surveillance data, standardised biological sampling as well as standardised diagnostic techniques is urgently needed.

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