Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Whooping cough surveillance in France in pediatric private practice in 2006–2015

Nicole Guiso [a], Corinne Levy [b,c,d,e,*], Olivier Romain [b,f], Sophie Guillot [a], Andreas Werner [c], Marie Charlotte Rondeau [b], Stéphane Béchet [b], Robert Cohen [b,c,d,e,g]

[a] Institut Pasteur, Molecular Prevention and Therapy of Human Infections Unit, Paris, France
[b] ACTIV, Association Clinique Thérapeutique Infantile du Val de Marne, Saint Maur des Fossés, France
[c] AFPA, Association Française de Pédiatrie Ambulatoire, Villeneuve les Avignons, France
[d] Université Paris Est, IMRB-GRC GEMINI, Créteil, France
[e] Clinical Research Center (CRC), Centre Hospitalier Intercommunal de Créteil, France
[f] Service de pédiatrie et réanimation néonatales, Hôpitaux Universitaires Paris-Sud (HUPS), Antoine Béclère, Clamart, France
[g] Unité Court Séjour, Petits nourrissons, Service de Néonatalogie, Centre Hospitalier Intercommunal de Créteil, France

ARTICLE INFO

Article history:
Received 2 February 2017
Received in revised form 20 September 2017
Accepted 23 September 2017
Available online xxxx

Keywords:
Pertussis
Surveillance
Pediatric practice
Pertussis vaccine

ABSTRACT

Background: Increasing incidence of whooping cough (pertussis) has been reported in many countries, attributed to a switch from whole-cell pertussis-containing vaccine (wPV) to acellular PV (aPV) and circulation of the pertactin non-producing *Bordetella pertussis*. The present study aimed to estimate the duration of immunity conferred by PVs in children in France with data from an ongoing pediatric ambulatory surveillance of pertussis.

Methods: A total of 64 pediatricians throughout France enrolled children with suspected pertussis. A standardized data form was used to collect data on age sex, vaccination status, brand of wPV or aPV and source of infection. Confirmed cases were positive on culture and/or real-time Polymerase Chain Reaction (for *B.-non-classified* or *B. pertussis* or *B. parapertussis*) and/or pertussis serology.

Results: Between October 2006 and December 2015, 149 cases of confirmed *Bordetella* infections were reported, 86 infected with *B. pertussis* and 55 *B. non-classified*. Fifteen children (10.1%) were not vaccinated, and 26 (17.4%) were partially vaccinated. The mean age was greater for children who received 4 doses of wPV (11.3 ± 2.2, $p < 0.001$) or a combination of wPV and aPV (10.5 ± 3.3, $p < 0.001$) than only aPV (7.2 ± 2.4 years). The mean duration of cough before a visit to a pediatrician was longer for children with wPV or a combination of wPV and aPV than only aPV (23.8 ± 10.1 and 25.0 ± 25.6 vs 13.6 ± 10.0 days).

Conclusion: Despite the use of a more sensitive diagnostic method and emergence of pertactin non producing *B. pertussis*, in France context, aPV-induced immunity still protects against pertussis; however, the mean duration of immunity is about 6 to 7 years, compared to 9 years for wPV vaccine, after the primary vaccination and one booster (3 + 1 doses).

1. Introduction

Whooping cough (pertussis) is a severe disease in infants and is responsible for >200,000 deaths annually worldwide and prolonged distressing diseases in older patients [1]. In many developed countries such as Australia, the United States and some European countries, despite adequate vaccination coverage, the incidence of pertussis has increased in the last few years [2–4]. Several explanations for this resurgence include better diagnosis of the disease due to the introduction of diagnostic methods with greater sensitivity (real-time Polymerase Chain Reaction (RT-PCR) with the multicopy IS481 and IS1001 targets), strain variations and the replacement of whole-cell pertussis-containing vaccines (wPVs) used in late 1990s in North America and mid-2000 in Western Europe by acellular PVs (aPVs).

Since the beginning of the aPV development, these vaccines were known to be slightly less efficacious than some wPVs (but not all) [5]. However, the better tolerability and safety of aPVs led to their replacing wPVs. The availability of combination vaccines made it easy. Several years later, aPV-induced immunity was

* Corresponding author at: ACTIV, 27 rue Inkermann, 94100 Saint Maur des Fossés, France.
E-mail address: corinne.levy@activ-france.fr (C. Levy).

https://doi.org/10.1016/j.vaccine.2017.09.072
0264-410X/

found to be shorter than that induced by wPVs and did not seem to protect against disease transmission [6]. These observations have been attributed to the characteristics of immunity induced by the two types of vaccines. Indeed, wPVs induce T helper 1 cells (Th1) and Th17 responses as well as B and T memory cells (including tissue-resident memory cells) after primary vaccination, whereas aPVs mainly induce a Th2 immune response without T memory cells [7].

Another putative cause of the resurgence in these predominantly heavy-aPV vaccinated regions is the emergence of *Bordetella pertussis* and *B. parapertussis* isolates, the agents of whooping cough, which do not produce a vaccine antigen contained in aPVs, mainly pertactin (PRN) [8].

Since 1959 in France, children at age 3, 4, and 5 months have been vaccinated against pertussis with a highly efficacious wPV, with a booster during the second year of life [9]. In 1995, primary vaccination was recommended at age 2, 3, and 4 months with the booster given at age 16 to 18 months. In 1998, because of the waning immunity of wPVs, a vaccine booster with aPVs at age 11–13 years was introduced, reserving wPVs for primary vaccination. However, by 2002, only aPVs were used, and since 2003, wPVs are no more sold in France and in most European countries. In 2013, the strategy was modified and the schedule is now 8 weeks, 4 months, 11 months, 6 years, 11 to 13 years, and 25 years with the cocooning strategy [10].

In France, a hospital-based surveillance of pertussis (Renacoq), including 42 pediatric hospitals, was set up in 1996 to analyze the impact of PV in infants [11]. In 1993–1994, the duration of protection of children with wPV vaccination was estimated at 7 to 9 years of age [12]. However, despite the addition of vaccine boosters, a cyclic pattern of the disease was still observed, as in all other vaccinated regions of the world. In France, five epidemic peaks were observed, in 1993, 1996–97, 2000, 2005, and 2012–2014, but the intervals between the peaks seemed to increase. During this period, the circulation of *B. pertussis* and *B. parapertussis* isolates was evolving in France and the isolates were shown to have less genetic materials and be phylogenetically different than those circulating in countries with low vaccination [13,14]. Therefore, in 2002, the French ambulatory pediatric network has set up a surveillance of pertussis to assess the duration of immunity conferred by PVs and identify changes in epidemiology in a timely manner to help with a public health response if needed. Between 2002 and 2006, our network estimated this duration of immunity to be about 8 years after the booster at age 16–18 months [15]. However, since 2002, only aPVs have been used and vaccine boosters are recommended for adolescents and adults. The estimated duration of aPV-induced immunity with a 3-component aPV was found similar to that induced by the wPV used in France [16]. Since 2012, several reports have shown reduced protection duration during the 5 years after the fifth aPV dose [17–19].

Since 2007, in France, we observed the circulation of *B. pertussis* and *B. parapertussis* isolates not producing PRN, a vaccine antigen [14]. The proportion of the *B. pertussis* isolates reached 15% during the last 2012–2014 cycle and 100% for *B. parapertussis* isolates. This circulation of *B. pertussis* isolates not producing PRN might be one of the causes of the huge epidemic cycle in 2012–2013 in regions using aPV and the reduced duration of immunity induced by these vaccines. However, a recent study in Vermont, with a high proportion of *B. pertussis* isolates not producing PRN, indicated that the effectiveness of aPVs and apVs remained similar as in other regions with a lower percentage of *B. pertussis* isolates not producing PRN [20].

Here we aimed to estimate the duration of immunity conferred by aPV in children in France in light of the switch from wPV and the circulation of *B. pertussis* isolates not producing PRN. We used the data from our ongoing pediatric ambulatory pertussis surveillance between October 2006 and December 2015.

2. Materials and methods

2.1. Network of pediatricians

From October 2006 to December 2015, 64 pediatricians, who are part of a research and teaching network (ACTIV/AFPA) throughout France enrolled infants and children with suspected pertussis (cough illness whether or not the illness were typical of pertussis). The purpose of the surveillance network is not necessarily to capture every case that occurs but rather to assess the duration of immunity conferred by PVs and identify changes in epidemiology. A standardized data form was used to collect data on age, sex, medical history, the precise vaccination status as possible (brand of wPV or aPV, number of doses, date of immunization), clinical signs and symptoms and their duration, and antibiotic treatment.

2.2. Vaccines

Two aPVs are used for children in France: the two-component vaccine from Sanofi-Pasteur (Tetravac and Pentavac) and the three-component vaccine from GlaxoSmithKline (Infanrix tetra, Infanrix quinta and Infanrix hexa). Because the French vaccination schedule recommends the hexa combination vaccine and since the only available combination at the time of the study was Infanrix hexa, the three-component aPV vaccine is mostly used [21]. In adolescents and adults, two aPVs are used: the three-component vaccine from GlaxoSmithKline (Boostrix tetra) and the five-component vaccine from Sanofi-Pasteur (Repevax).

2.3. Definitions of cases

All patients with suspected pertussis were asked to undergo biological confirmation of pertussis. When performed, the diagnosis was obtained by routine laboratory RT-PCR testing. The laboratories in France use the IS481 and IS1001 targets for RT-PCR. These targets allow for very sensitive detection of *Bordetella* DNA but not a specific identification of *Bordetella* species [22,23]. IS481 RT-PCR targets DNA from *B. pertussis*, *B. holmesii* and sometimes *B. bronchiseptica.* IS1001 RT-PCR targets DNA from *B. parapertussis* and sometimes *B. bronchiseptica*. Therefore, we asked the laboratories to send to the Institut Pasteur the DNA from all RT-PCR-positive biological samples and we performed additional RT-PCR to specifically characterize the *Bordetella* species with the *ptx*P, h-IS1001 and *fla* targets specific for *B. pertussis, B. holmesii* and *B. parapertussis*, respectively [23–25]. However, because PCR for *ptx*P and *fla* targets is less sensitive than IS481, h-IS1001 and IS1001, we could not confirm the *Bordetella* species in all biological samples and those samples were assigned as *B*. non-classified. A few cases were also confirmed by ELISA serology with purified pertussis toxin used as an antigen, kindly provided by GlaxoSmithKline [26].

Confirmed cases were thus positive on culture and/or RT-PCR (*B*. non-classified or *B. pertussis* or *B. parapertussis*) and/or serology for *B. pertussis*. Epidemiological cases were defined by a cough lasting 14 days for patients with contacts with confirmed cases and history of all vaccines recorded. We also defined probable cases as persons in contacts with confirmed cases presenting coughing symptoms but no data of pertussis vaccination.

B. parapertussis cases were not included in the analysis of the duration of protection since the PV are not protective against *B. parapertussis* [13]. *B.* non-classified were included since most of the cases were under 11 years of age [23,24], age with no detection of *B. holmesii.*

Please cite this article in press as: Guiso N et al. Whooping cough surveillance in France in pediatric private practice in 2006–2015. Vaccine (2017), https://doi.org/10.1016/j.vaccine.2017.09.072