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COMMENTARY

Pertussis in infants and the resurgence of a vaccine preventable disease: what to do?

Giorgio Fedele and Paola Stefanelli

Dipartimento di Malattie Infettive, Istituto Superiore di Sanità, Rome, Italy

Abstract

Pertussis or whooping cough remains one of the most poorly controlled vaccine-preventable diseases across the world. Universal vaccination has dramatically reduced its incidence but has failed to bring it completely under control. In the last decades, changes in pertussis epidemiology have been noted, likely related to the introduction of acellular pertussis vaccines. Increasing incidence is recorded among adolescents and adults who have become a reservoir for transmission to unimmunized infants, who are at risk of severe disease and death. In Italy, experimental evidences suggest a sustained circulation of *Bordetella pertussis* in the adult population and a significant health burden of pertussis among infants less than six months of age. Public health systems are currently exploring new vaccination strategies, including a cocooning strategy to prevent the transmission of the disease from family members to the newborn and vaccination of pregnant mothers to transmit protective antibodies to the offspring, and neonatal vaccination. An integrated approach for pertussis control and prevention is needed to enhance the current surveillance system and provide an accurate estimate of the real burden of pertussis in our Country, particularly among infants.

Key words

- pertussis
- vaccines
- epidemiology

Pertussis or whooping cough remains a widespread global disease despite the availability of safe and effective vaccines. Estimates suggest that about 16 million new cases of pertussis occurred worldwide in 2008 and that about 195 000 children died from the disease, making pertussis one of the leading cause of vaccine-preventable death in babies under five years of age [1]. The majority of pertussis deaths occur in developing countries; however, pertussis not only has persisted, but also resurged in countries with high vaccination coverage, where epidemic episodes have also been recorded [2-4]. Reemergence of pertussis may be attributed to various factors including greater awareness of pertussis, improved diagnosis due to availability of better laboratory tests, genetic changes in circulating *Bordetella pertussis* strains, and increased bacterial circulation among adolescents and adults related to the waning of vaccine-induced immunity [5-7]. In particular, these epidemiological changes have made adolescents and adults a reservoir for *B. pertussis* and the source of infection to the unvaccinated newborns. While adolescents and adults tend to have a prolonged illness characterized by cough but without other major symptoms, young unimmunised infants represent the most vulnerable group with the highest rates of complications and death. The microorganism is generally transmitted through close direct contact with an infected person [8] and is highly contagious, with up to 90% of household contacts developing the disease [8].

Acellular pertussis (aP) vaccines containing a varying number and quantity of antigens have been licensed in several countries in the last decade of the 20th century. Efficacy studies have shown an equal ability of aP vaccines to protect from the disease as compared to old generation whole cell pertussis (wP) vaccines, constituted by chemically inactivated whole bacteria [9]. However, several years after their introduction, it is becoming apparent that immunity conferred by most currently used acellular pertussis vaccines wanes more rapidly than expected, and vaccinated children are protected against infections only for a period of 5-8 years after their last vaccination [10-12]. Along with waning immunity, another emerging drawback of aP vaccines is represented by the possibility that, even protecting from the disease, they do not prevent colonization and transmission, as inferred from studies in non-human

Address for correspondence: Paola Stefanelli, Dipartimento di Malattie Infettive, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy. E-mail: paola.stefanelli@iss.it.

primate models of infection and mathematical modeling [13, 14]. In the recent years, extensive research efforts allowed to elucidate that natural infection and immunization with wP vaccines predominantly induce IFN-γ secreting T-helper (Th) 1 cells and IL-17 secreting Th17 cells [15-17]. By contrast, it has been shown that aP vaccines induce a qualitatively different immune response, characterized by the induction of Th2 immunity [13, 15, 18]. It is conceivable that this difference, along with the chemical inactivation of the pertussis toxin antigen in aP vaccines, may account for either lack of protection of vaccines from colonization and suboptimal T-cell priming with reduced efficiency in the generation of a immune memory repertoire.

The apparent changing epidemiology of pertussis calls for enhanced disease surveillance. The evaluation of pertussis incidence is a complex task, and several hurdles hamper a precise estimate of the pertussis disease burden. Limited surveillance infrastructures, unavailability of appropriate diagnostic tests and clinical underdiagnosis of the disease may hinder case reporting. In Italy, pertussis is a notifiable disease but the diagnosis of pertussis still relies on clinical symptoms and microbiological confirmation is rarely performed in the country [19, 20]. Underreporting has a significant impact with regard to older children, adolescents, and adults, for whom the cough pattern may be atypical [21]. A recent study on the seroprevalence of anti-pertussis toxin IgG among adult age groups in Italy has shown that *B. pertussis* is circulating widely in the Italian population [22]. These findings confirm previous data [23] and suggest that pertussis is resurging or, at least, still circulates in Italy.

Pediatric populations, too young to be protected by vaccination, experience much more severe disease than children and adults. Data from the Italian Ministry of Health report that, after the introduction of acellular vaccines, infants less than 1 year of age continue to be the age group with the highest incidence rates [24]. A retrospective study reviewing the Italian national hospital discharge form database showed that, in the period 1999-2009, most hospitalizations (57.4%) involved subjects < 1 year of age [25]. Recently, a dramatic resurgence of pertussis has been registered in Tuscan infants [26]. As stated before, the combination of waning vaccine immunity and increased *B. pertussis* circulation among adults may detrimentally contribute to the transmission of the bacteria to young infants. In this regard, it has been recently shown that parents were the main source for pertussis transmission to infants hospitalized in two big pediatric hospitals in Rome [27].

It is worth noting that the clinical diagnosis of pertussis is not easy in early infancy, since clinical manifestations can overlap with several other respiratory infections. Nevertheless, symptoms as paroxysmal cough, apnea, cyanosis, are very often associated with pertussis in babies. In school-age children, the majority of whom have been vaccinated, the disease is less severe, and they are more likely to display the typical symptoms of pertussis, including coughing spasms followed by the inspiratory "whoop" and vomiting [21]. Adolescents and adults may present cough and cold-like symptoms, but without whooping or vomiting. In a minority of adult, pertussis leads to complications such as seizures, pneumonia, and otitis media [28]. Due to different clinical presentations among infants, adolescents, and adults, a differential lab-confirmation diagnosis is required, in order to update the epidemiological situation. Moreover, the molecular characterization of the circulating strains may contribute to identify those harboring variant strains for one or more vaccine antigens possibly due to vaccine pressure.

The resurgence of pertussis as a public health concern, changes in the epidemiology of the disease, and the increasing attitude of parents in delaying or missing vaccination for their children, highlight the urgent need for integrated approaches to prevent this potentially deadly childhood disease. New vaccination strategies have been experimented, such as the "cocooning strategy" and maternal immunization. Cocooning refers to the vaccination of mothers and other contacts of newborns and infants. Cost-effective cocooning is difficult to implement since a successful programme implies very high numbers of contacts to be vaccinated in order to reach a significant impact on severe infant pertussis [29]. Currently, there is a growing evidence for effectiveness of immunization of women during pregnancy, rather than during the immediate postpartum period. This approach has been found to be more cost- effective, and vaccine effectiveness against infant deaths was estimated at 95% [30]. Alongside the vaccination of contacts, an alternative option that could be considered is an early infant vaccination schedule at 6-8 weeks of age. However, even with an accelerated antibody response, infants would remain unprotected during the most vulnerable time window for severe and life-threatening pertussis.

In conjunction with novel immunization approaches, improved pertussis surveillance is required for the control of infant pertussis. Evaluation of vaccine efficacy may help to improve the understanding of how well and how long pertussis vaccines protect in the field. Thus, a targeted surveillance, understanding the epidemiology of the disease, might contribute to better define the burden of disease and facilitate the adaptation of vaccine strategies. At the same time, monitoring the evolution of the bacteria might allow the timely detection of escape mutants, particularly the emergence of strains not expressing the vaccine antigen pertactin [31, 32].

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Conflict of interest statement

There are no potential conflict of interest or any financial or personal relationships with other people of organization that could inappropriately bias conduct and findings of this study.

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